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Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

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Editor's note: This article summarizes the Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update and provides the updated recommendations with brief discussions of the relevant literature for each. Additional information, including extensive Data Supplements, used by the Update Committee to formulate these recommendations is available at www.asco.org/guidelines/her2.

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ABSTRACT

Purpose
To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer.

Methods
ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

Results
The Update Committee identified criteria and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

Recommendations
The Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to > 10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (*HER2* copy number or *HER2*/CEP17 ratio by ISH based on counting at least 20 cells within the area). If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity. The Update Committee urges providers and health systems to cooperate to ensure the highest quality testing.

INTRODUCTION

In 2007, a joint Expert Panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for the human epidermal growth factor receptor 2 (*HER2*) gene (also referred to as *ERBB2*),[1,2] which is amplified and/or overexpressed in approximately 15% to 20% of primary breast cancers. Since then, minor clarifications and updates to the ASCO/CAP HER2 testing guideline have been issued.[3-5] A detailed rationale for this full 2013 update, as well as additional background information, is available in Data Supplement 1.

In 2012, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive

THE BOTTOM LINE

ASCO GUIDELINE UPDATE

Recommendations for HER2 Testing in Breast Cancer: ASCO/CAP Guideline Update

Intervention

- Recommendations for HER2 testing in breast cancer

Target Audience

- Medical oncologists, pathologists, and surgeons

Key Recommendations for Oncologists

- Must request HER2 testing on every primary invasive breast cancer (and on metastatic site, if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. This should be especially considered for a patient who previously tested HER2 negative in a primary tumor and presents with disease recurrence with clinical behavior suggestive of HER2-positive or triple-negative disease.
- Should recommend HER2-targeted therapy if **HER2 test result is positive**, if there is no apparent histopathologic discordance with HER2 testing (Tables 1 and 2), and if clinically appropriate. If the pathologist or oncologist observes an apparent histopathologic discordance after HER2 testing, the need for additional HER2 testing should be discussed.
- Must delay decision to recommend HER2-targeted therapy if **initial HER2 test result is equivocal**. Reflex testing should be performed on the same specimen using the alternative test if initial HER2 test result is equivocal or on an alternative specimen (Tables 1 and 2).
- Must not recommend HER2-targeted therapy if **HER2 test result is negative** and if there is no apparent histopathologic discordance with HER2 testing (Tables 1 and 2). If the pathologist or oncologist observes an apparent histopathologic discordance after HER2 testing, the need for additional HER2 testing should be discussed.
- 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). The oncologist should confer with the pathologist regarding the need for additional HER2 testing on the same or another tumor specimen.
- If the HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay (ie, if neither test is unequivocally positive), the oncologist may consider HER2-targeted therapy. The oncologist should also consider the feasibility of testing another tumor specimen to attempt to definitely establish the tumor HER2 status and guide therapeutic decisions. A clinical decision to ultimately consider HER2-targeted therapy in such cases should be individualized on the basis of patient status (comorbidities, prognosis, and so on) and patient preferences after discussing available clinical evidence.

Key Recommendations for Pathologists

- 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 (IHC assay) or *HER2* gene expression (ISH assay) using a validated HER2 test.
- In the United States, the ASCO/CAP Guideline Update Committee preferentially recommends the use of an assay that has received FDA approval, although a CLIA-certified laboratory may choose instead to use a laboratory-developed test (LDT). In this case, the analytic performance of the LDT must be prospectively validated in the same clinical laboratory that will perform it, and the test must have documented analytic validity (CAP guidance document). Bright-field ISH assays must be initially validated by comparing them with an FDA-approved FISH assay.
- Must report **HER2 test result as positive** if: (a) IHC 3+ positive or (b) ISH positive using either a single-probe ISH or dual-probe ISH (Table 1; Figs 1 to 3). This assumes that there is no apparent histopathologic discordance observed by the pathologist (Table 2).
- Must report **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 (Table 1; Figs 1 to 3). This assumes that there is no apparent histopathologic discordance observed by the pathologist (Table 2). Note that there are some rare breast cancers (eg, gland-forming tumors, micropapillary carcinomas) that show IHC 1+ staining that is intense but incomplete (basolateral or U shaped) and that are found to be *HER2* amplified. The pathologist should consider also reporting these specimens equivocal and request reflex testing using the alternative test.
- Must report **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 (Table 1; Figs 1 to 3). This assumes that there is no apparent histopathologic discordance observed by the pathologist (Table 2).

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THE BOTTOM LINE (CONTINUED)

- Must report **HER2 test result as indeterminate** if technical issues prevent one or both tests (IHC and ISH) performed in a tumor specimen from being reported as positive, negative, or equivocal. This may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed. Another specimen should be requested for testing, if possible, and a comment should be included in the pathology report documenting intended action.
- Must ensure that interpretation and reporting guidelines for HER2 testing are followed (Table 1; Data Supplements 7, 8, 9, and 10).
- Should interpret bright-field ISH on the basis of a comparison between patterns in normal breast and tumor cells, because 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.
- Should ensure that any specimen used for HER2 testing (cytologic 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 to72 hours and that routine processing, as well as staining or probing, is performed 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.
- If an apparent histopathologic discordance is observed in any HER2 testing situation (Table 2), 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 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.

Methods

- Systematic review and analysis of the medical literature were conducted by the 2013 Update Committee.

Additional Information

- The revised recommendations and a brief summary of the literature and analysis are provided in this article. Data Supplements including clinical tools and resources can be found at http://www.asco.org/guidelines/her2 and at http://www.cap.org. Patient information is available at http://www.cancer.net. ASCO and CAP believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

review of the peer-reviewed literature published since 2006 and to revise the guideline recommendations as appropriate. Since publication of the 2007 guideline, new diagnostic strategies, like measures of *HER2* amplification by bright-field in situ hybridization, DNA expression by microarray, or mRNA expression reverse-transcriptase polymerase chain reaction, have been introduced into practice, and the Update Committee felt these required evidence-based review. The Update Committee wishes to re-emphasize that it is important that any new test methodology, for the same clinical use, be compared with a reference test that assays for the same analyte and for which there are high levels of evidence that use of the test leads to clinical benefit for the patient (ie, clinical utility). It is the opinion of the Update Committee that there is insufficient evidence to support use of mRNA or DNA microarray assays to determine *HER2* status in unselected patients (Data Supplement 2A).

Further experience with established HER2 assays also led to the identification of unusual *HER2* genotypic abnormalities, like aneusomy of chromosome 17 (polysomy and monosomy), colocalization of *HER2* and CEP17 signals that affect *HER2*/CEP17 ratio in dual-signal in situ hybridization (ISH) assays, and genomic heterogeneity. Limited retrospective data on the clinical significance of these abnormalities in completed prospective trials also guided the discussions that were part of this guideline update.[6-22] Some these issues are discussed in Data Supplements 2B and 2C and in a separate review article by Hanna et al.[23]

During the deliberations, the Update Committee was concerned about false-negative and false-positive HER2 assessments. For example, a false-negative test result could lead to denial of trastuzumab treatment for a patient who could benefit from it. False-positive results could lead to the administration of potentially toxic, costly, and ineffective adjuvant HER2-targeted therapy for 1 year.[24-27] The Update Committee considered mandatory testing of all HER2-negative tests (Data Supplement 2D) and addressed also a narrower set of scenarios that may on occasion be observed with dual-signal ISH assays (Data Supplement 2E; Interpretation Criteria If Using a Dual-Signal *HER2* Assay and Average *HER2* Copy Number $<$ Six Signals Per Cell).

Trastuzumab had previously been shown to improve progression-free survival and overall survival when combined with chemotherapy in the metastatic setting.[28] Since 2005, several of the first-generation adjuvant trials have been updated and have confirmed the disease-free and overall survival benefit offered by 1 year of trastuzumab administered with or after adjuvant chemotherapy.[29-31] Prospective randomized trials, first reported in abstract form in late 2012, seem to suggest that 12 months is the optimal duration of adjuvant trastuzumab therapy.

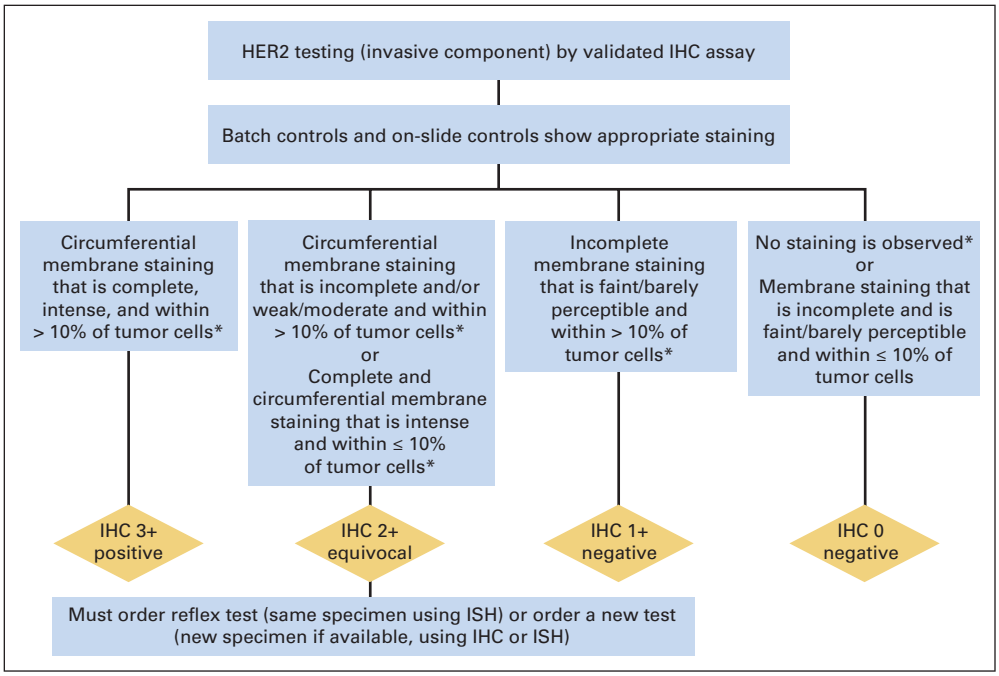

Fig 1. Algorithm for evaluation of human epidermal growth factor receptor 2 (HER2) protein expression by immunohistochemistry (IHC) assay of the invasive component of a breast cancer specimen. Although categories of HER2 status by IHC can be created that are not covered by these definitions, in practice they are rare and if encountered should be considered IHC 2+ equivocal. ISH, in situ hybridization. NOTE: the final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. (*) Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population.

Other HER2-targeted drugs (eg, the kinase inhibitor lapatinib,[32] the antibody pertuzumab,[33] and the antibody-drug conjugate ado-trastuzumab emtansine [T-DM1][34]) have been approved for the treatment of HER2-positive metastatic breast cancer. At the same time, data show that lapatinib (when added to paclitaxel)[35] and pertuzumab (as a single agent)[36] offer no clinical benefit in patients with HER2-negative metastatic disease. These new HER2-targeted drugs are now being tested in the adjuvant setting, including in studies evaluating their adjuvant role alone or in dual-antibody regimens without concomitant or sequential chemotherapy. Compared with regimens already in use, the newer agents are as or more expensive, and they may be associated with other dose-limiting toxicities, such as skin and GI tract toxicities with lapatinib and liver toxicities with ado-trastuzumab emtansine.[37]

Therefore, the need for an updated ASCO/CAP guideline on accurate HER2 testing to ensure that the right patient receives the right treatment is now more critical than ever.[22,24-27,38] Since the publication of the 2007 HER2 testing guideline, CAP has observed a remarkable uptake of proficiency testing (Fig 1),[5] with nearly 1,500 laboratories currently participating. CAP has also observed fewer laboratories experiencing deficiencies on laboratory inspection. Indirect evidence suggests that the performance of laboratories that conduct HER2 testing in the United States and elsewhere is improving.[39-42] Available evidence and experience since 2007 reinforce the importance of robust validation of new assays by laboratories before clinical implementation, as well as their ongoing monitoring, and the value of various external quality assurance schemes adopted in many countries.

METHODS

The HER2 testing Update Committee (Appendix Table A1, online only) met three times via Webinars coordinated by its Steering Committee to review the data published from January 2006 to January 2013 and to revise the recommendations. Additional data were gathered from in-press publications and personal correspondence with researchers to address the issue of mandatory testing if a test result is 0 or 1+. Draft manuscripts were circulated by e-mail, and the Update Committee approved the final manuscript. This guideline was reviewed by external reviewers and approved by the ASCO Clinical Practice Guideline Committee and relevant CAP entities.

Literature Search Strategy

The MEDLINE and the Cochrane Collaboration Library electronic databases were searched with the date parameters of January 2006 through January 2013 for articles in English. The MEDLINE search terms are included in Data Supplement 3, and a summary of the literature search results is provided in Data Supplement 4.

Inclusion and Exclusion Criteria

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, fluorescent ISH (FISH) and immunohistochemistry (IHC) results or other tests; described technical comparisons across various assay platforms; examined potential testing algorithms for HER2 testing; or examined the correlation of HER2 status in primary versus metastatic tumors from the same patients; (2) the study population consisted of patients with a diagnosis of invasive breast cancer; or (3) the primary outcomes included the negative predictive value (NPV) or positive predictive value (PPV) of ISH and IHC assays used to determine HER2 status, alone and in combination; negative and positive concordance across platforms; and accuracy in determining HER2 status and benefit from anti-HER2 therapy and in determining sensitivity and specificity of individual tests. Consideration was given to studies that directly compared results across assay platforms.

Studies were not limited to randomized controlled trials but also included other study types, including cohort designs, case series, evaluation studies, and comparative studies. The Update Committee also reviewed other testing guidelines and proficiency strategies of various US and international organizations, including unpublished data. Letters, commentaries, and editorials were reviewed for any new information. Case reports were excluded. The clinical questions addressed in the update are available in Data Supplement 5.

This information was used to help the Update Committee develop new algorithms (for pathologists and oncologists) for testing, specify testing requirements and exclusions, and facilitate the necessary quality assurance monitoring that will make HER2 testing less variable and ensure more analytic consistency between laboratories. The term ratio, as used in the guideline recommendations and algorithms, always applies to the *HER2*/CEP17 ratio, which means the ratio of *HER2* signals per cell (numerator) over CEP17 signals per cell (denominator).

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Guideline and Conflicts of Interest

The Update Committee was assembled in accordance with CAP and ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (ASCO procedures are summarized at http://www.asco.org/guidelinescoi). Members of the Update Committee completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the procedures, the majority of the members of the Update Committee did not disclose any such relationships.

RECOMMENDATIONS

CLINICAL QUESTION 1

What is the optimal testing algorithm for the assessment of HER2 status?

Literature Update and Discussion

The Update Committee found more than 70 new publications that informed a revision of the testing algorithms contained in the original 2007 guideline. At the time of the original guideline, significant concern existed about false-positive HER2 test results. Guideline recommendations emphasized those changes that would mitigate false positives, particularly relating to issues of specimen fixation and pathologist interpretation.[39,43-47] Preliminary data from an ongoing prospective study seem to suggest that the frequency of false-positive test results may have diminished, in that the concordance between local testing in laboratories throughout the United States and confirmatory central HER2 testing at the Mayo Clinic (Rochester, MN) for the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization HER2 Adjuvant Trial) trial showed that less than 6% of patients initially considered eligible were not subsequently centrally confirmed as being HER2 positive.[48]

On the other end of the spectrum, clinical experience and recent literature have indicated that false-negative HER2 test results must also be considered. The Update Committee was sensitive to the concerns that surfaced after the publication of the 2007 guideline about the very small number of patients potentially affected by the recommendation to consider as HER2 positive only those tumors with more than 30% of cells (or $>$ 10% to $\leq$ 30% if *HER2* amplified by FISH) with diffuse and intense circumferential staining.[49] Therefore, the Update Committee decided to revert to the previously used IHC criterion of more than 10% cells staining for HER2, which had been used as an entry criterion for eligibility for the first generation of prospective randomized trials of adjuvant trastuzumab.[18,22,49-53] The rationale for this recommendation by the Update Committee is detailed in Data Supplement 1. Aside from the very small number of patients affected (as few as 0.15% of all newly diagnosed patients, as previously discussed),[5] the Update Committee was also of the opinion that improvements in analytic performance of HER2 testing in clinical practice since 2007 have further reduced the already small number of patients potentially at risk of receiving a false-negative test result.

Testing is now recommended for primary, recurrent, and metastatic tumors.[19,35,45,54-63,64] Tissue from the primary tumor can be obtained through a core needle biopsy, as well as from an incisional and excisional surgical procedure.[65] Metastases can be biopsied from chest wall, regional lymph nodes, or distant organs.[66-74] It is essential to ensure that time to fixation (cold ischemic time) and time in fixative (which has increased from 6 to 48 hours to 6 to 72 hours in this Update on the basis of available data and to conform with the ASCO/CAP

estrogen receptor [ER]/progesterone receptor [PgR] testing guideline[75,76]) are recorded and considered in defining the test result. More detail about preanalytic issues is available in Data Supplement 6.

In summary, if available, perform the first test in the core biopsy specimen in a patient with newly diagnosed breast cancer. If the test result is clearly positive or clearly negative as defined in Table 1, no retesting is needed. If the test is negative and there is apparent histopathologic discordance (Table 2), or if specimen handling has not been in accordance with guideline recommendations, a section of the tumor from the excisional specimen should be tested. If this result is positive, no further testing is needed. However, if the test is negative and there remains significant clinical concern about the result after consultation between the pathologist and the medical oncologist, it may be appropriate to repeat the test in a different block from the patient's tumor. If all three tests are negative, no additional testing is recommended.

Data Supplement 7 is a table of IHC Interpretation Criteria, and Data Supplement 8 provides ISH Interpretation Criteria. Both of these Data Supplements expand on details provided in Table 1.

The Update Committee clarified several issues in the Update on the basis of recently published literature. The recommendations in Table 1 reflect the Update Committee's interpretation of the new data on polysomy, heterogeneity in ISH, types of assays, and methods of analysis [10-14,19-21,45,67,69,79-135] for inclusion in this Update. See Data Supplement 2 for an extensive discussion of these issues.

A list of US Food and Drug Administration (FDA) –approved assays is available at http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start_search=1&search_term=HER2&approval_date_from=&approval_date_to=07/14/2013&sort=approvaldatedesc&pagenum=10 (last checked July 14, 2013). The product package inserts for trastuzumab and pertuzumab prepared by the FDA indicate that "HER2 testing should be performed using US Food and Drug Administration–approved tests by laboratories with demonstrated proficiency."[77,78]

HER2 Assay Exclusions

Each assay type has diagnostic pitfalls to be avoided. The Update Committee agreed that there were situations in which one assay type was preferred because of assay or sample considerations. Exclusion criteria to perform or interpret an IHC or any ISH assay for HER2 are unchanged but can be viewed in the original guideline.[1,2] The pathologist who reviews the histologic findings should determine the optimal assay (IHC or ISH) for determination of HER2 status.

Algorithms for HER2 Testing by IHC and ISH

Algorithms for evaluation of HER2 protein expression by IHC and *HER2* amplification by single-probe or dual-probe ISH are presented in Figures 1, 2, and 3.

CLINICAL QUESTION 2

What strategies can help ensure optimal performance, interpretation, and reporting of established assays?

Literature Update and Discussion

Testing analytic validation requirements. The Update Committee reviewed new papers and reports on strategies to ensure optimal performance, interpretation, and reporting of assays.[16,22,100,136,137] Most new HER2 assays have been submitted to the FDA for premarket approval review as class III devices in view of their use for therapy selection. Although a new HER2 assay ideally should have its clinical utility validated using specimens from prospective therapeutic trials that tested the effects of anti-HER2 therapy, the Update Committee recognizes that the rarity of these valuable specimens requires that new HER2 assays be approved on the basis of concordance studies comparing them with other established HER2 tests. Consequently, it is important that tissues selected for such concordance studies come from datasets that include a broad representation of patients with breast cancer in whom HER2-positive status will be observed in approximately 15% to 20%.

Ongoing competency assessment. The Update Committee urges ongoing competency assessment as a part of every laboratory's internal quality assessment program. The competency of the laboratory professionals and pathologists interpreting assays must be continuously addressed as required under the Clinical Laboratory Improvements Amendments (CLIA 88). The acceptable performance standard for such competency tests remains the same as in the original guideline.

Reporting requirements. Data Supplements 9 and 10 are tables of reporting elements for IHC and reporting elements for ISH, respectively. Some changes have been made to the reporting elements for IHC and ISH to ensure that they are in accordance with the revised recommendations. In addition, a disclaimer statement is required if the specimen handling requirements are not met.

New interpretation requirements relate to the definition of tumor samples with genomic heterogeneity as well as the examination of specimens and interpretation of results in these samples. No specific requirements were added for designation of polysomy by ISH. Laboratories should maintain documentation of their quality assurance practices and ensure that such documentation is available for inspection.

Regulatory framework. The regulatory framework remains the same as discussed in the original guideline. At the current time, the FDA exercises enforcement discretion over laboratory-developed tests (LDTs) that are generated and performed within an individual laboratory under CLIA 88. CLIA 88 provides stringent quality standards for highly complex tests, which include all predictive cancer factor assays. This legislation also requires biannual surveys of laboratories that perform highly complex tests, with defined criteria and actions required when performance is deficient. However, CLIA certification does not require that the tests performed have been shown with a high level of evidence to have clinical utility.[138,139] Moreover, FDA approval of devices, which includes in vitro diagnostic tests such as those discussed in this guideline, does not necessarily require demonstration that use of the assay results in improved clinical outcomes compared with not using the assay. The Update Committee expresses concern about the need for greater clarity in the regulatory environment with regard to companion diagnostic tests and LDTs for higher-risk tumor biomarker tests, such as HER2. Some of this has been discussed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative and endorsed by the Institute of Medicine Committee in regard to omics-based tests, as well as others,[139] and the Update Committee understands the FDA is developing a risk-based framework to address concerns about test accuracy and clinical utility.

Table 1. Summary of 2007 and 2013 HER2 Test Guidelines and Recommendations

Topic	2007 Recommendation	2013 Recommendation
Specimens to be tested	All primary breast cancer specimens and metastases should have at least one HER2 test performed	All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available.
Optimal algorithm for 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 > 6 signals/nucleus for those test systems without an internal control probe	Must report **HER2 test result as positive for HER2 if:**[a,b] • IHC 3+ based on circumferential membrane staining that is complete, intense[c,d] • ISH positive based on: Single-probe average *HER2* copy number ≥ 6.0 signals/cell[c,e] Dual-probe *HER2*/CEP17 ratio ≥ 2.0[c,e] with an average *HER2* copy number ≥ 4.0 signals per cell Dual-probe *HER2*/CEP17 ratio ≥ 2.0[c,e] with an average *HER2* copy number < 4.0 signals/cell[b] Dual-probe *HER2*/CEP17 ratio < 2.0[c,e] with an average *HER2* copy number ≥ 6.0 signals/cell
	Equivocal for HER2 is defined as: IHC 2+ or FISH *HER2*/CEP17 ratio of 1.8-2.2 or average *HER2* gene copy number 4-6 *HER2* signals/nucleus for test systems without an internal control probe	Must report **HER2 test result as equivocal** and order reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test) if:[a,b] • IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate[f] and within > 10% of the invasive tumor cells[d] *or* complete and circumferential membrane staining that is intense and within ≤ 10% of the invasive tumor cells[d] • ISH equivocal based on: Single-probe ISH average *HER2* copy number ≥ 4.0 and < 6.0 signals/cell[e,f] Dual-probe *HER2*/CEP17 ratio < 2.0 with an average *HER2* copy number ≥ 4.0 and < 6.0 signals/cell[e,f]
	Negative for HER2 is defined as: • IHC HER2 0: no staining • IHC HER2 1+: weak incomplete membrane staining in any proportion of tumor cells or weak, complete membrane staining in < 10% of cells • FISH *HER2*/CEP17 ratio of < 1.8 or average *HER2* gene copy number of < 4 signals/nucleus for test systems without an internal control probe	Must report **HER2 test result as negative** if a single test (or both tests) performed show:[a,b] • IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells[d] • IHC 0 as defined by no staining observed[d] or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells[d] • ISH negative based on: Single-probe average *HER2* copy number < 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio < 2.0 with an average *HER2* copy number < 4.0 signals/cell
	Indeterminate for HER2	Must report **HER2 test result as indeterminate** if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Conditions may include: • Inadequate specimen handling • Artifacts (crush or edge artifacts) that make interpretation difficult • Analytic testing failure Another specimen should be requested for testing to determine HER2 status. Reason for indeterminate testing should be noted in a comment in the report.

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Table 1. Summary of 2007 and 2013 HER2 Test Guidelines and Recommendations (continued)

Topic	2007 Recommendation	2013 Recommendation
ISH rejection criteria	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	Same and report **HER2 test result as indeterminate** as per parameters described immediately above.
ISH interpretation	Interpretation performed by counting at least 20 cells; a pathologist must confirm that counting involved invasive tumor criteria followed	The pathologist should scan the entire ISH slide prior to counting at least 20 cells or use IHC to define the areas of potential *HER2* amplification. If there is a second population of cells with increased *HER2* signals/cell, and this cell population consists of more than 10% of tumor cells on the slide (defined by image analysis or visual estimation of the ISH or IHC slide), a separate counting of at least 20 nonoverlapping cells must also be performed within this cell population and reported. For bright-field ISH, counting requires comparison between patterns in normal breast and tumor cells because 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.
Acceptable (IHC and ISH) tests[g]		Should preferentially use an FDA-approved IHC, bright-field ISH, or FISH assay.[g,h]
Optimal IHC testing requirements	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)	Same
IHC interpretation criteria	Positive HER2 result requires homogeneous, dark circumferential (chicken wire) pattern in > 30% of invasive tumor. Interpreters have method to maintain consistency and competency	Should interpret IHC test using a threshold of more than 10% of tumor cells that must show homogeneous, dark circumferential (chicken wire) pattern to call result 3+, HER2 positive.
Reporting requirements for all assay types	Report must include guideline-detailed elements	Same except for changes to reporting requirement and algorithms defined in this table (Data Supplements 9 and 10).
Optimal tissue handling requirements	Time from tissue acquisition to fixation should be as short as possible; samples for HER2 testing are fixed in 10% neutral buffered formalin for 6-48 hours; cytology specimens must be fixed in formalin. 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	Duration of fixation has been changed **from 6-48 hours to 6-72 hours.** Any exceptions to this process must be included in report.
Optimal tissue sectioning requirements	Sections should ideally not be used for HER2 testing if cut > 6 weeks earlier; this may vary with primary fixation or storage conditions	Same
Optimal internal validation procedure	Validation of test must be performed before test is offered	Same (Data Supplement 12 lists examples of various external quality assurance schemes)
Optimal initial test validation	Initial test validation requires 25-100 samples tested by alternative validated method in the same laboratory or by validated method in another laboratory	Laboratories performing these tests should be following all accreditation requirements, one of which is initial testing validation. The laboratory should ensure that initial validation conforms to the published 2010 ASCO/CAP recommendations for IHC testing of ER and PgR guideline validation requirements with 20 negative and 20 positive for FDA-approved assays and 40 negative and 40 positive for LDTs. This requirement does not apply to assays that were previously validated in conformance with the 2007 ASCO/CAP HER2 testing guideline or to those who are routinely participating in external proficiency testing for HER2 tests, such as the program offered by CAP (Data Supplement 12).
	Proof of initial testing validation in which positive and negative HER2 categories are 90% concordant with alternative validated method or same validated method for HER2	Laboratories are responsible for ensuring the reliability and accuracy of their testing results, by compliance with accreditation and proficiency testing requirements for HER2 testing assays. Specific concordance requirements are not required (Data Supplement 11).

(continued on following page)

Table 1. Summary of 2007 and 2013 HER2 Test Guidelines and Recommendations (continued)

Topic	2007 Recommendation	2013 Recommendation
Optimal monitoring of test concordance between methods	Concordance testing must be performed prior to initiation of testing, optimally as the form of testing validation. If concordance is below 95% for any testing category, that category of test result of either FISH or IHC must be automatically flexed to alternative method before final interpretation	See text under Optimal Laboratory Accreditation.
Optimal internal QA procedures		Should review and document external and internal controls with each test and each batch of tests.
	Ongoing quality control and equipment maintenance	Same
	Initial and ongoing laboratory personnel training and competency assessment	Same
	Use of standardized operating procedures including routine use of control materials	Same
	Revalidation of procedure if changed	Same
	Ongoing competency assessment and education of pathologists	Should perform ongoing competency assessment and document the actions taken as a part of the laboratory record.
Optimal external proficiency assessment	Participation in and successful completion of external proficiency testing program with at least two testing events (mailings) a year	Same
	Satisfactory performance requires at least 90% correct responses on graded challenges for either test	Same
	• 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	Same (Data Supplement 11)
	• Reviews laboratory validation, procedures, QA results and processes, results, and reports	
	• Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method	

NOTE. For all recommendations, evidence quality and recommendation strength are strong, except as noted. Bold font indicates changes in the updated version.

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ER, estrogen receptor; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LDT, laboratory-developed test; PgR, progesterone receptor; QA, quality assurance.

[a]If a reflex test (same specimen/same tissue) ordered after an initial equivocal HER2 test result does not render a positive or negative HER2 test result, the pathologist should review histopathologic features, confer if possible with the oncologist regarding additional HER2 testing, and document it in the pathology report. The pathologist may pursue additional HER2 testing without conferring with the oncologist. This should be accomplished using: (1) the alternative test (IHC or ISH) on the same specimen, (2) either test on another block (same specimen), or (3) either test on another specimen (eg, core biopsy, surgical resection, lymph node, and/or metastatic site). Because the decision to recommend HER2-targeted therapy requires a HER2-positive test result, additional HER2 testing should be attempted in equivocal specimens to attempt to obtain a positive or negative HER2 test result and most accurately determine the HER2 status of the tumor specimen.

[b]See Data Supplement 2E for additional information on rare scenarios.

[c]Observed in a homogeneous and contiguous population and within > 10% of the invasive tumor cells.

[d]Readily appreciated using a low-power objective.

[e]By counting at least 20 cells within the area.

[f]Observed in a homogeneous and contiguous population.

[g]Alternatively, a laboratory accredited by CAP or another accrediting entity may choose to use an LDT, in which case its analytical performance must be documented in the same clinical laboratory that will use the assay, and documentation of analytical validity of the assay must be available.

[h]A list of HER2 assays approved by the FDA as in vitro companion diagnostic devices to aid in the assessment of patients for whom trastuzumab treatment is being considered can be found in the Medical Devices section of the US FDA Web site (http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start_search=1&search_term=HER2&approval_date_from=&approval_date_to=07/14/2013&sort=approvaldatedesc&pagenum=10; last checked July 14, 2013). The product package insert for trastuzumab and pertuzumab prepared by the FDA indicates that "HER2 testing should be performed using FDA-approved tests by laboratories with demonstrated proficiency."[77,78]

Table 2. Histopathologic Features Suggestive of Possible HER2 Test Discordance

Criteria to Consider*
New HER2 test should not be ordered if the following histopathologic findings occur and the initial HER2 test was negative:
Histologic grade 1 carcinoma of the following types:
Infiltrating ductal or lobular carcinoma, ER and PgR positive
Tubular (at least 90% pure)
Mucinous (at least 90% pure)
Cribriform (at least 90% pure)
Adenoid cystic carcinoma (90% pure) and often triple negative
Similarly, a new HER2 test should be ordered if the following histopathologic findings occur and the initial HER2 test was positive:
Histologic grade 1 carcinoma of the following types:
Infiltrating ductal or lobular carcinoma, ER and PgR positive
Tubular (at least 90% pure)
Mucinous (at least 90% pure)
Cribriform (at least 90% pure)
Adenoid cystic carcinoma (90% pure) and often triple negative
If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test must be ordered on the excision specimen if one of the following is observed:
Tumor is grade 3
Amount of invasive tumor in the core biopsy is small
Resection specimen contains high-grade carcinoma that is morphologically distinct from that in the core
Core biopsy result is equivocal for HER2 after testing by both ISH and IHC
There is doubt about the specimen handling of the core biopsy (long ischemic time, short time in fixative, different fixative) or the test is suspected by the pathologist to be negative on the basis of testing error

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PgR, progesterone receptor.
*Criteria to consider if there are concerns regarding discordance with apparent histopathologic findings and possible false-negative or false-positive HER2 test result.

Optimal external quality assurance methods to ensure accuracy in HER2 testing and laboratory accreditation. External proficiency testing is a mandatory requirement for CAP-accredited laboratories, beginning with the 2007 guideline. External proficiency testing challenges failure requires investigation and corrective action before the laboratory can continue to offer HER2 testing.

CAP modified its laboratory accreditation program to include more careful scrutiny of HER2 testing, thus creating a mandatory and expanded proficiency testing program to evaluate laboratory performance. The systematic review revealed many new papers on quality assurance, quality improvement, proficiency testing, and establishment of concordance between local and central laboratories, both in

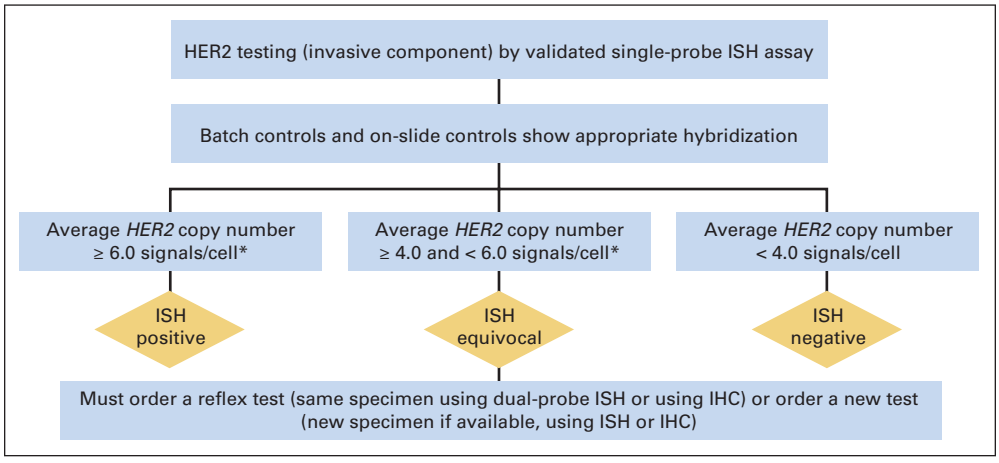


Fig 2. Algorithm for evaluation of human epidermal growth factor receptor 2 (*HER2*) gene amplification by in situ hybridization (ISH) assay of the invasive component of a breast cancer specimen using a single-signal (*HER2* gene) assay (single-probe ISH). Amplification in a single-probe ISH assay is defined by examining the average *HER2* copy number. If there is a second contiguous population of cells with increased HER2 signals per cell, and this cell population consists of more than 10% of tumor cells on the slide (defined by image analysis or visual estimation of the ISH or immunohistochemistry [IHC] slide), a separate counting of at least 20 nonoverlapping cells must also be performed within this cell population and also reported. Although categories of HER2 status by ISH can be created that are not covered by these definitions, in practice they are rare and if encountered should be considered ISH equivocal (see Data Supplement 2E). NOTE: the final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. (*) Observed in a homogeneous and contiguous population.

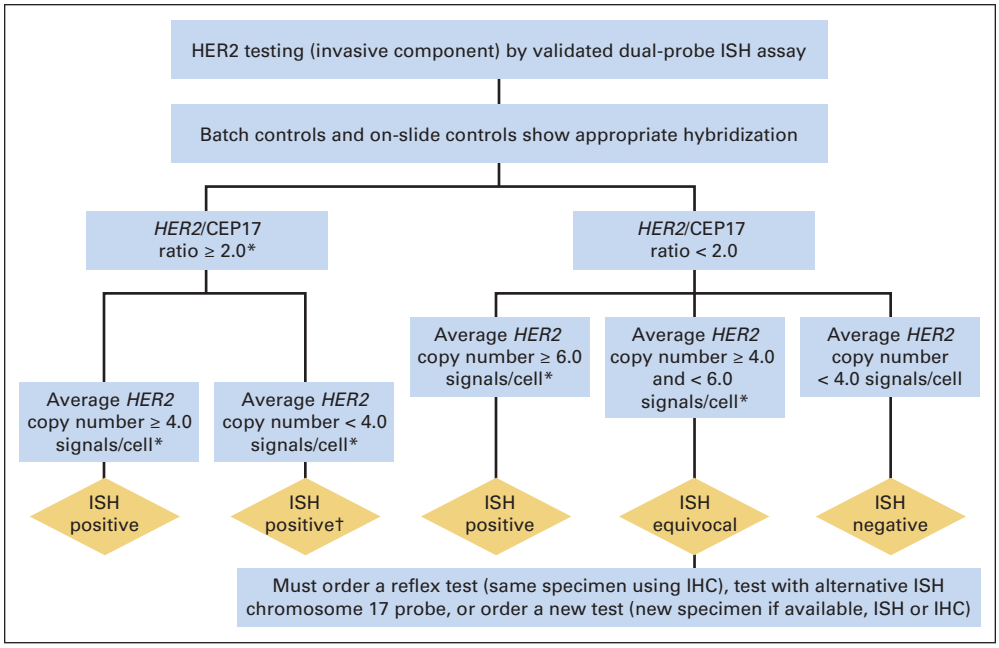


Fig 3. Algorithm for evaluation of human epidermal growth factor receptor 2 (*HER2*) gene amplification by in situ hybridization (ISH) assay of the invasive component of a breast cancer specimen using a dual-signal (*HER2* gene) assay (dual-probe ISH). Amplification in a dual-probe ISH assay is defined by examining first the *HER2*/CEP17 ratio followed by the average *HER2* copy number (see Data Supplement 2E for more details). If there is a second contiguous population of cells with increased HER2 signals per cell, and this cell population consists of more than 10% of tumor cells on the slide (defined by image analysis or visual estimation of the ISH or immunohistochemistry [IHC] slide), a separate counting of at least 20 nonoverlapping cells must also be performed within this cell population and also reported. Although categories of HER2 status by ISH can be created that are not covered by these definitions, in practice they are rare and if encountered should be considered ISH equivocal (see Data Supplement 2E). NOTE. The final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. (*) Observed in a homogeneous and contiguous population. (†) See Data Supplement 2E for more information on these rare scenarios.

the United States and internationally.[40,51,136,140-146] A revised table addressing proficiency testing is contained in Data Supplement 11, which describes statistical requirements for proficiency testing. Examples of international external quality assurance schemas are included in Data Supplement 12.

The number of laboratories participating in predictive marker proficiency testing for HER2 and ER as part of the CAP laboratory improvement program since 2004 is shown in Figure 4, and the program is described at http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=accreditation (last checked July 14, 2013).

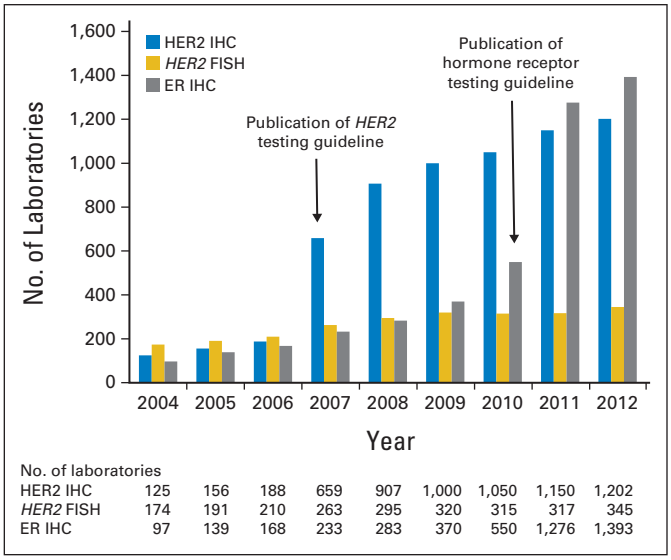
Ongoing Communication, Education, and Evaluation Efforts by CAP

CAP has undertaken comprehensive efforts to educate pathologists about ways to improve laboratory performance of HER2, ER, and PgR assays. Numerous live and online educational offerings are available from CAP and other organizations. Examples in North America include the American Society of Clinical Pathology (ASCP) and United States and Canadian Academy of Pathology (USCAP). CAP provides varied live and online education focused on HER2 and ER/PgR testing elements of relevance to pathologists in meeting the original ASCO/CAP HER2 and ER/PgR guidelines and updates. In follow-up surveys, participants routinely report they made changes to their practice as a result of the educational experience. Many of these learning opportunities have a scored assessment component, allowing participants to test their knowledge as part of completing the courses, and can be used to meet the American Board of Pathology (ABP), the US pathologist certifying organization, Maintenance of Certification requirements. More information can be found at the CAP learning portal (http://www.cap.org) and in the original guideline. CAP has also created a listing of competencies in breast pathology, compiled by experts and available for pathologist self-assessment. After taking this self-assessment, pathologists are prompted to learning offerings that target those areas of self-reported educational deficiency. A listing of the courses is available online at http://www.cap.org via the learning portal.

STUDY QUALITY, LIMITATIONS OF THE LITERATURE, AND FUTURE RESEARCH

Whether in the context of trastuzumab clinical trials or of studies comparing HER2 testing platforms, interpretation of the literature in the field of HER2 testing is still 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. Although FDA-approved assays have been carefully validated, not all LDTs may have, which complicates direct comparisons across trials and platforms, and we maintain that this situation leaves open the possibility that a substantial percentage of some patients with breast cancer could be either over- or undertreated with HER2-targeted therapies.

An important gap in the literature identified by the Update Committee concerns those patients with test results reported as equivocal. The decision to treat with specific therapies like trastuzumab is by necessity dichotomous (yes or no) and will not be informed by an



No. of laboratories									
HER2 IHC	125	156	188	659	907	1,000	1,050	1,150	1,202
HER2 FISH	174	191	210	263	295	320	315	317	345
ER IHC	97	139	168	233	283	370	550	1,276	1,393

Fig 4. Number of laboratories participating in predictive marker proficiency testing for human epidermal growth factor receptor 2 (HER2) by immunohistochemistry (IHC), HER2 by fluorescent in situ hybridization (FISH), and estrogen receptor (ER) by IHC through the College of American Pathologists (CAP) Laboratory Improvement Program. Arrows indicate the years during which the HER2 and hormone receptor testing guidelines were published by the American Society of Clinical Oncology (ASCO)/CAP. The numbers of participating laboratories are shown both graphically and in tabular form. After the publication of the 2007 ASCO/CAP HER2 and the 2010 ASCO/CAP ER/progesterone receptor testing guidelines, there was a significant increase in the number of laboratories in the United States and elsewhere participating in CAP proficiency testing surveys in breast cancer (http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=accreditation; last checked June 14, 2013). CAP has as a core goal to improve the quality of pathology and laboratory services through education and standard setting in order to enhance patient safety, and help laboratories meet or exceed regulatory requirements set by the Centers for Medicare and Medicaid Services, the Joint Commission, and many states in the United States.

equivocal diagnosis with respect to HER2 status without repeat testing, if possible. 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 variability in the reporting definitions of the equivocal ranges for both bright-field ISH and FISH assays.

The literature is lacking evidence on response to HER2-targeted therapy in the subgroup of patients with equivocal results, and there are limited efficacy data in the subgroup tested with both high quality IHC and FISH and found to have a discordant result between these two tests. Patients with such results constitute poorly studied subsets for which there is less confidence in the scores and actual benefit from trastuzumab therapy. Because the retrospective evaluation of the benefit from trastuzumab in patients with apparent discordance between IHC and FISH who were enrolled onto the first generation of trastuzumab trials included only a small number of patients in each of the discordant subsets, patients who would have qualified for enrollment in those trials should be considered for HER2-targeted therapy.

The Update Committee's goal was to address the most common clinical situations encountered by pathologists and oncologists in routine clinical practice. Specifically in regard to ISH assays, it expected that additional but rare categories of HER2 status by ISH could be created that are not covered by the definitions illustrated in Figures 2 and 3. Data Supplement 2E addresses a narrower set of scenarios that may on occasion be observed with dual-signal ISH assays.

For patients with low levels of HER2 expression that do not reach the threshold for HER2-positive disease, the Update Committee encourages enrollment of such patients, if eligible, onto prospective clinical trials that aim to address the value of adjuvant HER2-targeted therapies in patients whose breast cancers show low levels of HER2 expression, like the NSABP B-47 (National Surgical Adjuvant Breast and Bowel Project B-47) trial (NCT01275677). The Update Committee also supports participation in studies evaluating other cutoffs and other technologies to optimize eligibility for HER2-targeted therapies.

PATIENT AND CLINICIAN COMMUNICATION

Patients (and family members or caregivers) should be educated about the results of pathology tests and how they are used to develop a treatment plan tailored to the biology of their cancers. Because many newly diagnosed patients are under emotional stress and/or may be unaccustomed to complex medical terminology, the use of easily understood language (at an educational level that the patient can understand) is key to clear communication. Asking patients to repeat back key pieces of information, providing written or recorded notes, and using visual aids can help ensure information is effectively communicated.

Patients should be given a copy of their pathology report and HER2 test results. The clinician should review the results with the patient, discuss any issues with the test interpretation or performance, and ask if he or she has any additional questions about the results.

Key Points for Clinicians to Discuss With Patients Regarding HER2 Status

Explain the importance of determining the biologic characteristics of breast cancer. Patients should understand that the most common biologic tests are those for ER, PgR, and HER2 and that testing for these markers is important to select an appropriate treatment. The overall percentage of patients with HER2-positive breast cancer is between 15% and 20%. Observed numbers may vary depending on the population being tested by individual laboratories.

Explain the importance of HER2 testing. Patient should understand that HER2 status determines whether certain drugs (eg, trastuzumab, lapatinib, pertuzumab, T-DM1) are recommended. They should also understand that the *HER2* gene is important in tumor cell growth and that tumors that have increased levels of HER2 (as measured by *HER2* gene amplification or HER2 protein overexpression) usually have a higher growth rate and a more aggressive clinical behavior.

Explain the type of tissue used for HER2 testing. Patients should understand the type of tissue used for HER2 testing (eg, core biopsy, excisional biopsy).

Explain the types of tests used to determine HER2 status. Patients should understand that there are different FDA-approved testing methods that detect HER2 protein overexpression or the presence of *HER2* gene amplification.

Explain the interpretation of the HER2 test results. Patients should understand that although most HER2 test results are definitively positive or negative, there are equivocal results that require

additional testing using an alternative test or using the same or alternative test on a different portion of the same specimen (different block). Sometimes, the oncologist or pathologist may recommend additional testing using a different type of tumor specimen (eg, surgical excision *v* core biopsy), if available. Patients should be informed about which test or tests were performed and the expected turnaround time for these tests. Unfortunately, some results remain indeterminate or inconsistent with other histopathologic findings. In such cases, a final treatment decision to consider treatment with HER2-targeted therapy should be made after consultation between the pathologist and oncologist and a discussion with the patient.

Explain the importance of retesting HER2 status in new, metastatic tumors. Patients should understand that HER2 status may occasionally be different (discordant) when comparing a previous primary tumor and a site of recurrence or in the setting of multiple simultaneous metastatic sites. In some cases, it is not possible to fully differentiate between a true biologic change, tumor heterogeneity, or variability in the performance of the assay.

Explain that HER2 testing guidelines exist. Patients should be assured that HER2 testing guidelines were followed. Refer patients to the ASCO/CAP guideline update at www.asco.org/guideline/her2 and/or http://www.cap.org and to www.cancer.net for additional patient-focused information.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines present recommendations on the best practices in diagnosis and disease management to provide the highest level of cancer diagnosis and care, it is important to note that some racial/ethnic minority patients have limited access to optimal medical care and/or accredited pathology laboratories. At the same time, some Medicaid or uninsured patients may have access to accredited pathology laboratories by virtue of receiving some or all of their care in an academic medical center.[147-150]

Disparities clearly exist in the likelihood of receiving HER2 testing. In the United States, Lund et al[151] used data from the National Cancer Institute Metropolitan Atlanta SEER Registry in conjunction with the Georgia Comprehensive Cancer Registry to examine HER2 testing among all cases of primary invasive breast cancer diagnosed among female residents during 2003 to 2004. Overall, 90.1% of women had evidence of HER2 testing. Rates of HER2 testing did not vary significantly based on socioeconomic status (based on the percent living below the federal poverty level) and were similar between black (91.3%) and white (89.8%) women. This is in agreement with other reports showing similar or greater rates of HER2 testing among black versus white women with breast cancer.[152] However, in the Lund et al study, Hispanic women were significantly less likely to receive HER2 testing (79.3%), as were women diagnosed with stage IV (80.7%) or unknown stage (71.7%) disease. In addition, the mean age of women who received HER2 testing (58.8 years) was significantly younger than that of women who did not receive testing (61.3 years). Other studies have also reported that older women[153,154] and those with distant disease are significantly less likely to have documentation of HER2 testing. Stark et al[155] also reported that women with capitated insurance (*v* fee-for-service insurance) were significantly more likely to be tested for HER2 status. Awareness of possible disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

ADDITIONAL RESOURCES

Data Supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/her2. Information for patients is available at http://www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Update Committee Members

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