General

Guideline Title


Bibliographic Source(s)


Guideline Status

This is the current release of the guideline.


This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

For all recommendations, evidence quality and recommendation strength are strong, except as noted.

<table>
<thead>
<tr>
<th>HER2 Test Guideline Recommendations</th>
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</thead>
<tbody>
<tr>
<td><strong>Topic</strong></td>
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<tr>
<td>Specimens to be tested</td>
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<tr>
<td>Optimal algorithm for HER2 testing</td>
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<tr>
<td>Topic</td>
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<tr>
<td>HER2 Test Guideline Recommendations</td>
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</table>

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:
- IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within > 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤ 10% of the invasive tumor cells.
- ISH equivocal based on:
  - Single-probe ISH average HER2 copy number ≥ 4.0 and < 6.0 signals/cell.
  - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 4.0 and < 6.0 signals/cell.

Must report a HER2 test result as negative if a single test (or both tests) performed show:
- IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells.
- IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells.
- 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.

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.

**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

Report HER2 test result as indeterminate as per parameters described immediately above.

**ISH interpretation**
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**
Should preferentially use an FDA-approved IHC, bright-field ISH, or FISH assay.
<table>
<thead>
<tr>
<th>Optimal IHC testing requirements</th>
<th>HER2 Test Guideline Recommendations</th>
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<tbody>
<tr>
<td>Test is rejected and repeated or tested by FISH if:</td>
<td>2016 Recommendations expected</td>
</tr>
<tr>
<td>- Controls are not as expected</td>
<td>- Artifacts involve most of sample</td>
</tr>
<tr>
<td>- Sample has strong membrane staining of normal breast ducts (internal controls)</td>
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</tbody>
</table>

| IHC interpretation criteria | 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; Data Supplements 9 and 10 in the original guideline document (see the "Availability of Companion Documents" field) contain information regarding reporting requirement and algorithms defined in this table. |

| Optimal tissue handling requirements | 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 |

<table>
<thead>
<tr>
<th>Optimal internal validation procedure</th>
<th>Validation of test must be done before test is offered.</th>
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<tbody>
<tr>
<td>Data Supplement 12 in the original guideline document lists examples of various external quality assurance schemes.</td>
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<tr>
<th>Optimal initial test validation</th>
<th>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, and who are routinely participating in external proficiency testing for HER2 tests, such as the program offered by the CAP (see Data Supplement 12 in the original guideline document).</th>
</tr>
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<tbody>
<tr>
<td>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 of the original guideline document).</td>
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</table>

| Optimal monitoring of test concordance between methods | See text following under "Optimal Laboratory Accreditation." |

<table>
<thead>
<tr>
<th>Optimal internal QA procedures</th>
<th>Should review and document external and internal controls with each test and each batch of tests.</th>
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<tbody>
<tr>
<td>Ongoing quality control and equipment maintenance.</td>
<td>Initial and ongoing laboratory personnel training and competency assessment.</td>
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<tr>
<td>Use of standardized operating procedures including routine use of control materials.</td>
<td>Revalidation of procedure if changed.</td>
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<tr>
<td>Should perform ongoing competency assessment and document the actions taken as a part of the laboratory record.</td>
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</tbody>
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<tr>
<th>Optimal external proficiency assessment</th>
<th>Participation in and successful completion of external proficiency testing program with at least two testing events (mailings) a year.</th>
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<tbody>
<tr>
<td>Satisfactory performance requires at least 90% correct responses on graded challenges for either test.</td>
<td>Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements.</td>
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</table>

| Optimal laboratory | Onsite inspection every other year with annual requirement for self-inspection. |
**HER2 Test Guideline Recommendations**

**2013 Recommendation**

- Reviews laboratory validation procedures, QA results, and processes, results and reports
- Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method

Refer to Data Supplement 11 in the original guideline document for additional information.

**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.

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 and ISH) on the same specimen, (2) either test on another block (same specimen), or (3) either test on another specimen (e.g., 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.

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

- Observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells.
- Readily appreciated using a low-power objective.
- By counting at least 20 cells within the area.
- Observed in a homogeneous and contiguous population.
- Alternatively, a laboratory accredited by the 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.

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. 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".

**Clinical Algorithm(s)**

The following algorithms are provided in the original guideline document:

- 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
- Algorithm for evaluation 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)
- 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)

**Scope**

**Disease/Condition(s)**

Breast cancer

**Guideline Category**

Diagnosis

Evaluation

Technology Assessment

**Clinical Specialty**
Intended Users
Clinical Laboratory Personnel
Physicians

Guideline Objective(s)
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

Target Population
Patients with invasive breast cancer (early stage or recurrence)

Interventions and Practices Considered
1. Human epidermal growth factor receptor 2 (HER2) testing in breast cancer
   - Immunohistochemistry (IHC)
   - In situ hybridization (ISH)
2. Tissue handling requirements
3. Internal validation procedure
4. Monitoring of concordance between methods
5. Quality assurance procedures
6. External proficiency assessment
7. 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 (FISH) and immunohistochemistry (IHC) 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 the Evidence
Searches of Electronic Databases
Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

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 in the original guideline document (see the "Availability of Companion Documents" field), and a summary of the literature search results is provided in Data Supplement 4 of the original guideline document (see the "Availability of Companion Documents" field).

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+.

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 in situ hybridization (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 in the original guideline document (see the "Availability of Companion Documents" field).

Number of Source Documents

165 articles met selection criteria for data extraction.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Weighting According to a Rating Scheme (Scheme Not Given)

Rating Scheme for the Strength of the Evidence

Not stated

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

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), 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. A detailed rationale for this full 2013 update, as well as additional background information, is available in Data Supplement 1 of the original guideline document (see the "Availability of Companion Documents" field).

In 2012, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive review of the peer-reviewed literature published since 2006 and to revise the guideline recommendations as appropriate.

The HER2 testing Update Committee (see Appendix Table A1 in the original guideline document) 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. Draft manuscripts were circulated by e-mail, and the Update Committee approved the final manuscript.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed a published cost analysis.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The original guideline document was reviewed by external reviewers and approved by the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Committee and relevant College of American Pathologists (CAP) entities.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of human epidermal growth factor receptor 2 (HER2) testing in patients with invasive breast cancer

Potential Harms

Not stated
Qualifying Statements

Qualifying Statements

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Implementation of the Guideline

Description of Implementation Strategy

For information on the American Society for Clinical Oncology (ASCO) implementation strategy, please see the ASCO Web site.

Implementation Tools

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation
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)


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

Date Released
2007 Jan 1 (revised 2013 Nov 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 (ASCO)
College of American Pathologists (CAP)

Guideline Committee
American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Clinical Guideline Update Committee
Composition of Group That Authored the Guideline

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†Affiliation during guideline development.
‡Current affiliation.

Financial Disclosures/Conflicts of Interest

The Update Committee was assembled in accordance with College of American Pathologists (CAP) and American Society of Clinical Oncologists (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.

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about the American Society of Clinical Oncology’s (ASCO) 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 or Leadership Position: Donald C. Allred, Clarient–GE Healthcare (C) Consultant or Advisory Role: Mitch Dowsett, Roche (C); Donald C. Allred, Clarient (U); John M.S. Bartlett, Roche Canada (C), Roche UK (C); Michael Bilous, Roche (C); Wedad Hanna, Roche (C); Michael F. Press, Roche (C); Giuseppe Viale, Roche (C), Genomic Health (C), Dako (C) Stock Ownership: None Honoraria: Mitch Dowsett, Roche, Dako, John M.S. Bartlett, Roche Canada, Roche UK; Michael Bilous, Roche; Wedad Hanna, Roche; Giuseppe Viale, Roche Research Funding: Mitch Dowsett, Roche; John M.S. Bartlett, Roche UK; Wedad Hanna, Roche; Michael F. Press, Roche Expert Testimony: None Patents: None Other Remuneration: John M.S. Bartlett, Roche UK; Wedad Hanna, Roche; Robert B. Jenkins, Abbott

Guideline Status

This is the current release of the guideline.


This guideline meets NGC’s 2013 (revised) inclusion criteria.

Guideline Availability
Availability of Companion Documents

The following are available:


Patient Resources

The following are available:


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. This NGC summary was updated by ECRI Institute on December 20, 2013.

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