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Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update

Antonio C. Wolff, MD[1]; Mark R. Somerfield, PhD[2]; Mitchell Dowsett, PhD[3]; M. Elizabeth H. Hammond, MD[4]; Daniel F. Hayes, MD[5]; Lisa M. McShane, PhD[6]; Thomas J. Saphner, MD[7]; Patricia A. Spears, BS[8]; and Kimberly H. Allison, MD[9]

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ABSTRACT

PURPOSE To update ASCO–College of American Pathologists (CAP) recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer. The Panel is aware that a new generation of antibody-drug conjugates (ADCs) targeting the HER2 protein is active against breast cancers that lack protein overexpression or gene amplification.

METHODS An Update Panel conducted a systematic literature review to identify signals for updating recommendations.

RESULTS The search identified 173 abstracts. Of five potential publications reviewed, none constituted a signal for revising existing recommendations.

RECOMMENDATIONS The 2018 ASCO-CAP recommendations for HER2 testing are affirmed.

DISCUSSION HER2 testing guidelines have focused on identifying HER2 protein overexpression or gene amplification in breast cancer to identify patients for therapies that disrupt HER2 signaling. This update acknowledges a new indication for trastuzumab deruxtecan when HER2 is not overexpressed or amplified but is immunohistochemistry (IHC) 1+ or 2+ without amplification by in situ hybridization. Clinical trial data on tumors that tested IHC 0 are limited (excluded from DESTINY-Breast04), and evidence is lacking that these cancers behave differently or do not respond similarly to newer HER2 ADCs. Although current data do not support a new IHC 0 versus 1+ prognostic or predictive threshold for response to trastuzumab deruxtecan, this threshold is now relevant because of the trial entry criteria that supported its new regulatory approval. Therefore, while it is premature to create new result categories of HER2 expression (eg, HER2-Low, HER2-Ultra-Low), best practices to distinguish IHC 0 from 1+ are now clinically relevant. This Update affirms prior HER2 reporting recommendations and offers a new HER2 testing reporting comment to highlight the current relevance of IHC 0 versus 1+ results and best practice recommendations to distinguish these often subtle differences.
Additional information is available at www.asco.org/breast-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

ASCO and the College of American Pathologists (CAP) first published a practice guideline on human epidermal growth factor receptor 2 (HER2) testing in breast cancer in 2007.[1] The guideline was updated in 2013[2] and again in 2018[3] based on targeted literature searching, Panel expertise, and new signals.[4] These guidelines were developed to standardize and ensure accurate detection of HER2 gene amplified or protein overexpressed breast cancers for prediction of benefit from HER2-targeted therapies. The clinical utility of HER2 testing to identify patients for therapy with the HER2 antibody trastuzumab has since expanded to other antibodies (pertuzumab added to trastuzumab, margetuximab), small molecule tyrosine kinase inhibitors (lapatinib, neratinib, or tucatinib), and antibody-drug conjugates (ADCs) (trastuzumab emtansine or trastuzumab deruxtecan).

The impetus for revisiting the ASCO-CAP guideline was the 2022 publication of the DESTINY-Breast04 trial. Modi et al[5] showed in an open-label phase III study a significant improvement in survival in patients with breast cancers without

THE BOTTOM LINE

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Guideline Question

What is the optimal testing algorithm for the assessment of human epidermal growth factor receptor 2 (HER2) status and what strategies can help ensure optimal performance, interpretation, and reporting of established assays?

Target Population

Patients with breast cancer.

Target Audience

Medical oncologists, surgical oncologists, radiologists, pathologists, oncology nurses, patients, caregivers, advocates, and oncology advanced practice providers.

Methods

A systematic review of the literature was performed, and relevant evidence was evaluated for inclusion in this updated clinical practice guideline (Data Supplement, online only).

Recommendations

The 2018 ASCO–College of American Pathologists (CAP) recommendations for HER2 testing are affirmed.

HER2 Immunohistochemistry (IHC) Testing Best Practices Recommendations

- HER2 testing should still be optimized for the predictive purpose of identification of breast cancers with protein overexpression and/or gene amplification who could benefit from therapies aimed at disrupting HER2 signaling pathways.
- While it is premature to change reporting terminology for lower levels of HER2 IHC expression (eg, HER2-Low), pathology labs should include a footnote in their HER2 testing reports (IHC and in situ hybridization [ISH]) with the following recommended comment:
  - *"Patients with breast cancers that are HER2 IHC 3+ or IHC 2+/ISH amplified may be eligible for several therapies that disrupt HER2 signaling pathways. Invasive breast cancers that test 'HER2-negative' (IHC 0, 1+ or 2+/ISH not-amplified) are more specifically considered 'HER2-negative for protein overexpression/gene amplification' since non-overexpressed levels of the HER2 protein may be present in these cases. Patients with breast cancers that are HER2 IHC 1+ or IHC 2+/ISH not-amplified may be eligible for a treatment that targets non-amplified/non-overexpressed levels of HER2 expression for cytotoxic drug delivery (IHC 0 results do not result in eligibility currently)."*
- HER2 IHC 1+ or 0 results are still both interpreted as HER2-negative (HER2 is not overexpressed) using the previously recommended scoring criteria (Fig 1). Importantly, the semiquantitative IHC score must always be reported as well to ensure patients who meet eligibility criteria for trastuzumab deruxtecan can be identified.
  - *Example: HER2-negative for protein overexpression (1+ staining present).*
- Since eligibility for trastuzumab deruxtecan (IHC 1+ or IHC 2+/ISH not-amplified) may hinge around the IHC 0/IHC 1+ threshold (although the clinical validity of this threshold remains untested), pathologists can make best practice efforts to distinguish IHC 1+ results from 0 by the following practices:
  1. Examining HER2 IHC stained slides using standardized ASCO-CAP guidelines scoring criteria (see Fig 1 for interpretation).
  2. Examining HER2 IHC at high power (40×) when discriminating 0 from 1+ staining
  3. Considering second pathologist review when results are close to the 0 versus 1+ interpretive threshold (>10% of cells with incomplete membrane staining that is faint/barely perceptible).
  4. Using controls with a range of protein expression (including 1+) to help ensure the assay has an appropriate limit of detection.
  5. Careful attention to preanalytic conditions of breast cancer tissue samples from both primary and metastatic sites.
- Medical oncologists can also consider HER2 IHC results on prior or concurrent primary samples (or other metastatic sites) because there may be heterogeneity in HER2 expression levels between samples and because metastatic cancer tissue samples may suffer from preanalytic conditions that are not as well monitored as in primary breast tissue samples.

HER2 overexpression or amplification, but with immunohistochemistry (IHC) 1+ or IHC 2+ with in situ hybridization (ISH) not-amplified results, treated with the ADC fam-trastuzumab-deruxtecan-nxki compared with physician's choice of chemotherapy after progression on other therapies for metastatic disease. Participants in the control arm did not have access to trastuzumab deruxtecan after progression, and patients with IHC 0 results were excluded from the trial.

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These data extended the US Food and Drug Administration–approved label indication of this drug and resulted in premarket approval of the monoclonal IHC antibody testing system used in DESTINY-Breast04 (Ventana PATHWAY anti-HER2/neu 4B5 rabbit monoclonal antibody on the BenchMark ULTRA instrument) for a new use as a semiquantitative assay, to identify patients with breast cancer without HER2 overexpression or amplification who could be eligible for treatment with trastuzumab deruxtecan.[6] The implications of these data for the ASCO-CAP breast cancer HER2 testing guideline recommendations were reviewed.

EVIDENCE REVIEW

Although there is clearly a new role for IHC assays to most accurately identify tumors that test HER2 IHC 1+ or 2+/ISH not-amplified, this clinical need is based on DESTINY-Breast04 clinical trial entry criteria rather than the demonstration of a new predictive or prognostic threshold for HER2 IHC test results below overexpression (IHC 3+).[5] As patients whose cancers tested IHC 0 in a central laboratory were ineligible for the trial, and trial data did not identify a differential benefit between patients with IHC 1+ and 2+/ISH not-amplified treated with trastuzumab deruxtecan, no new predictive biomarker threshold for response (yes or no) has been identified among tumors historically classified as HER2-negative for overexpression or amplification. Instead, a new threshold has been artifactually created between a result of IHC 0 and IHC at least 1+ to determine access to the drug based on trial eligibility.

The terminology HER2-Low was used in the trial as shorthand for IHC 1+ or 2+/ISH not-amplified cases. However, other than renaming test results to fit trial eligibility for this new treatment indication, there is no evidence that HER2-Low is a new or reproducibly defined subtype of breast cancer with distinct prognostic or predictive implications.[7-13] HER2 IHC 0 versus Low status also appears to be unstable across patient samples, with close to 40% of cases switching between IHC 0 and IHC 1+ or 2+/ISH not-amplified (HER2-Low) results when paired primary and metastatic are compared.[8]

There are data to suggest that IHC 0 cases may also have low levels of HER2 protein expression by more sensitive testing methods.[11] Higher frequencies of HER2 protein detection in fresh tissue samples also suggest that preanalytic factors during tissue processing likely affect protein detection rates at low levels.[14] Data from one single-arm phase II study (the DAISY trial [ClinicalTrials.gov identifier: NCT04132960] reported in abstract form) suggest that IHC 0 and HER2-Low cancers have similar response to trastuzumab deruxtecan. Although these results require confirmation, they suggest that an IHC 0 result may not truly mean a cancer has no targetable HER2 protein present as HER2 assays are semiquantitative and were optimized to detect overexpression. Additional clinical trial data are needed to determine if IHC 0 samples also include targetable levels of HER2 protein needed for clinical response, to test if new, more sensitive assays can accurately quantify it, and to investigate if there is differential clinical benefit based on protein expression levels. Currently, there is a risk that available IHC assays are suboptimal for detection of these low levels of protein expression and could result in false-negative and false-positive test determinations around the IHC 0/IHC 1+ threshold that would incorrectly influence treatment recommendations and potentially impact data from ongoing clinical trials that still rely on them.

The Panel (Appendix Table A1, online only) also notes that adoption of HER2-Low terminology in IHC reporting is problematic because it would require changing the reporting schema for IHC 2+ results (currently reported as equivocal for protein overexpression with reflex ISH testing required to determine gene amplification status), such that the final IHC result category could not be reported (as HER2-Low *v* HER2-positive) until reflex ISH results are back. Since the DESTINY-Breast04 trial used current standard IHC scoring definitions for 0, 1+, 2+, and 3+, there is also no evidence to support changing these at this time.

Based on the lack of new data to support a change to current HER2 scoring and reporting recommendations, the prior HER2 guideline recommendations for classic anti-HER2 therapies are affirmed, and no new reporting terminology is adopted. However, a new HER2 testing reporting footnote and additional best practices to identify candidates that may be eligible for trastuzumab deruxtecan are offered (The Bottom Line box).

RECOMMENDATIONS

The recommendations in previous (2013 and 2018) ASCO-CAP HER2 testing guideline updates are affirmed for classic anti-HER2 therapies that conventionally target HER2 signaling (Appendix Table A2, online only). Although no changes are made to prior recommendations, there should be awareness that, for metastatic patients without HER2 overexpression or gene amplification, an IHC 1+ or 2+ result may make patients eligible for treatment targeting nonamplified/nonoverexpressed levels of HER2 expression (and IHC 0 results would not), for which trastuzumab-deruxtecan is the only currently available agent. A new HER2 testing reporting footnote and best practices for identification and reporting of IHC 0 versus IHC 1+ results are offered in the bulleted Bottom Line box.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO and the CAP to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it

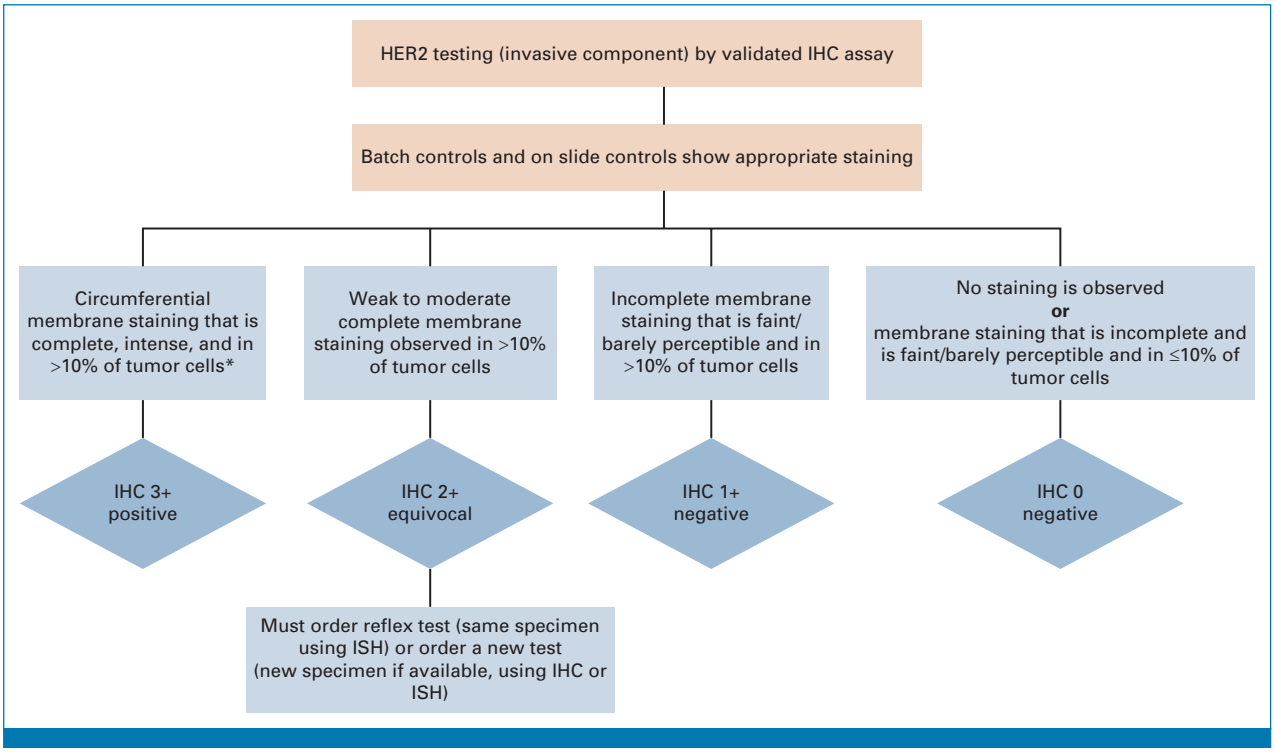

FIG 1. 2018 Algorithm for evaluation of HER2 protein expression by IHC assay of the invasive component of a breast cancer specimen. NOTE. The final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. Unusual staining patterns of HER2 by IHC can be encountered that are not covered by these definitions. In practice, these patterns are rare and if encountered should be considered IHC 2+ equivocal. As one example, some specific subtypes of breast cancers can show IHC staining that is moderate to intense but incomplete (basolateral or lateral) and can be found to be HER2 amplified. Another example is circumferential membrane IHC staining that is intense but within ≤10% of tumor cells (heterogeneous but very limited in extent). Such cases can be considered 2+ equivocal but additional samples may reveal different percentages of HER2-positive staining. *Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population. This algorithm is reprinted from recommendations in *Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO/College of American Pathologists Clinical Practice Guideline Focused Update*.[3] This is a tool based on an ASCO and College of American Pathologists guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool are voluntary. www.asco.org/breast-cancer-guidelines. © 2023 American Society of Clinical Oncology and College of American Pathologists. All rights reserved. For licensing opportunities, contact licensing@asco.org. See reporting "Recommended comment" and "Example" in The Bottom Line box. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice

Guidelines ("Policy," found at www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

AFFILIATIONS

[1]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
[2]American Society of Clinical Oncology, Alexandria, VA
[3]The Royal Marsden NHS Foundation Trust, London, United Kingdom
[4]Intermountain Healthcare and University of Utah School of Medicine, Salt Lake City, UT
[5]University of Michigan, Ann Arbor, MI
[6]National Cancer Institute, Bethesda, MD
[7]Vince Lombardi Cancer Clinic, Two Rivers, WI
[8]University of North Carolina, Chapel Hill, NC
[9]Stanford University School of Medicine, Stanford, CA

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

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EDITOR'S NOTE

This American Society of Clinical Oncology and College of American Pathologists Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/survivorship-guidelines.

EQUAL CONTRIBUTION

A.C.W. and K.H.A. were Expert Panel co-chairs.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care[15] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[16] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Chemotherapy and Targeted Therapy for HER2-Negative Metastatic Breast Cancer[17] (https://ascopubs.org/doi/10.1200/JCO.22.01533)

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AUTHOR CONTRIBUTIONS

Conception and design: Antonio C. Wolff, Mitchell Dowsett, M. Elizabeth H. Hammond, Daniel F. Hayes, Kimberly H. Allison
Administrative support: Mark R. Somerfield
Collection and assembly of data: Antonio C. Wolff, Mark R. Somerfield, Kimberly H. Allison
Data analysis and interpretation: Antonio C. Wolff, Mark R. Somerfield, Mitchell Dowsett, M. Elizabeth H. Hammond, Lisa M. McShane, Thomas J. Saphner, Patricia A. Spears, Kimberly H. Allison
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Antonio C. Wolff
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Mitchell Dowsett
Consulting or Advisory Role: AstraZeneca/MedImmune, Besins Healthcare, Roche, Rovi, Lilly
Research Funding: Lilly (Inst)
Patents, Royalties, Other Intellectual Property: AIR-CIS—a molecular profile for predicting sensitivity of breast cancer patients to CDK4/6 inhibitors among patients resistant to an aromatase inhibitor (Inst), Share of royalties from the invention of abiraterone

M. Elizabeth H. Hammond
Consulting or Advisory Role: Daiichi Sankyo/Astra Zeneca

Daniel F. Hayes
Stock and Other Ownership Interests: InBiomotion
Honoraria: Tempus
Consulting or Advisory Role: Cepheid, Freenome, Epic Sciences, Cellworks, BioVica, Oncocyte, Turnstone Bio, Predictus Biosciences, Guardant Health, L-Nutra, Macrogenics, Tempus, Xilis, Exact Sciences
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Patents, Royalties, Other Intellectual Property: Royalties from licensed technology, Diagnosis and Treatment of Breast Cancer. Patent No.: US 8,790,878 B2. Date of Patent: July 29, 2014. Applicant Proprietor: University of Michigan. D.F.H. is designated as inventor/coinventor, Circulating Tumor Cell Capturing Techniques and Devices. Patent No.: US 8,951,484 B2. Date of Patent: February 10, 2015. Applicant Proprietor: University of Michigan. D.F.H. is designated as inventor/coinventor, Title: A method for predicting progression free and overall survival at each follow-up timepoint during therapy of metastatic breast cancer patients using circulating tumor cells. Patent no.: 05725638.0-1223-US2005008602
Other Relationship: Menarini, UpToDate
Uncompensated Relationships: UpToDate

Patricia A. Spears
Consulting or Advisory Role: Pfizer

Kimberly H. Allison
Consulting or Advisory Role: Mammotome
Expert Testimony: Kaiser Permanente

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APPENDIX

TABLE A1. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-CAP Update Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Kimberly H. Allison, MD (co-chair)	Stanford University School of Medicine, Stanford, CA	Pathology
Antonio C. Wolff, MD (co-chair)	Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD	Medical Oncology
Mitchell Dowsett, PhD	The Royal Marsden NHS Foundation Trust, London, United Kingdom	Molecular Pathology
M. Elizabeth H. Hammond, MD	Intermountain Healthcare and University of Utah School of Medicine, Salt Lake City, UT	Pathology
Daniel F. Hayes, MD	University of Michigan, Ann Arbor, MI	Medical Oncology
Lisa M. McShane, PhD	National Cancer Institute, Bethesda, MD	Biostatistics
Thomas J. Saphner, MD	Vince Lombardi Cancer Clinic, Two Rivers, WI	Community Oncology
Patricia A. Spears, BS	University of North Carolina, Chapel Hill, NC	Patient Advocacy
Mark R. Somerfield, PhD	ASCO, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviation: CAP, College of American Pathologists.

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TABLE A2. Affirmed 2018 ASCO-CAP Recommendations

Topic	Recommendations
Specimens to be tested	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	1. IHC 2+ (equivocal) is invasive breast cancer with weak to moderate complete membrane staining observed in >10% of tumor cells. 2. On the basis of some criteria (including a tumor grade 3), if the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen. 3. If a case has a HER2/CEP17 ratio is ≥2.0 but the average HER2 signals/cell is <4.0, a definitive diagnosis will be rendered based on further workup. If not already assessed by the institution/lab performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH and the slides from both ISH and IHC be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment): a. If the IHC result is 3+, diagnosis is HER2 POSITIVE b. If the IHC result is 2+, recount ISH by having an additional observer count **at** least 20 cells that includes the area of invasive cancer with IHC 2+ staining, blinded to previous ISH results: If reviewing the count by the additional observer alters the result into another ISH category, the result should be adjudicated per internal procedures to define the final category. If the count remains an average of <4.0 HER2 signals/cell and HER2/CEP17 ratio ≥2.0, the diagnosis is HER2 NEGATIVE with a comment.[a] c. If the IHC result is 0/1+, diagnosis is HER2 NEGATIVE with a comment.[a] 4. If a case has an average of ≥6.0 HER2 signals/cell with a HER2/CEP17 ratio of <2.0, formerly diagnosed as **ISH Positive** for HER2, a definitive diagnosis will be rendered based on further workup. If not already assessed by the institution/lab performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH and the slides from both ISH and IHC be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review): a. If the IHC result is 3+, diagnosis is HER2 POSITIVE b. If the IHC result is 2+, recount ISH by having an additional observer count **at** least 20 cells that includes the area of invasion with IHC 2+ staining, blinded to previous ISH results: If reviewing the count by the additional observer alters the result into another ISH category, the result should be adjudicated per internal procedures to define the final category If the HER2/CEP17 ratio remains <2.0 with ≥6.0 HER2 signals/cell, the diagnosis is HER2 POSITIVE c. If the IHC result is 0/1+, diagnosis is HER2 NEGATIVE with comment.[b] 5. If the case has an average HER2 signals/tumor cell of ≥4.0 and <6.0 HER2 signals/cell and HER2/CEP17 ratio is <2.0, formerly diagnosed as ISH equivocal for HER2, a definitive diagnosis will be rendered based on further workup. If not already assessed by the institution/lab performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH and the slides from both ISH and IHC be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review). a. If the IHC result is 3+, diagnosis is HER2 POSITIVE b. If the IHC result is 2+, recount ISH by having an additional observer count **at** least 20 cells that includes the area of invasion with IHC 2+ staining, blinded to previous ISH results: If reviewing the count by the additional observer alters the result into another ISH category, the result should be adjudicated per internal procedures to define the final category If the count remains an average of ≥4.0 and <6.0 HER2 signals/cell with HER2/CEP17 ratio <2.0, the diagnosis is HER2 NEGATIVE with a comment.[c] If the IHC result is 0/1+, diagnosis is HER2 NEGATIVE with a comment.[c]
	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.
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 contiguous 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.
Acceptable (IHC and ISH) tests	Should preferentially use an FDA-approved IHC, brightfield ISH, or FISH assay.

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TABLE A2. Affirmed 2018 ASCO-CAP Recommendations (continued)

Topic	Recommendations
IHC rejection criteria	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)
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 except for changes to reporting requirement and algorithms defined in this table.
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 6-72 hours; cytology specimens must be fixed in formalin. Samples should be sliced at 5- to 10-mm intervals after appropriate gross inspection and margin designation and placed in sufficient volume of neutral buffered formalin. 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
Optimal internal validation procedure	Validation of test must be performed before test is offered
Optimal initial test validation	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.
Optimal initial test validation	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.
Optimal monitoring of test concordance between methods	See text following under "Optimal Laboratory Accreditation" below.
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 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 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 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	On-site 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: CAP, College of American Pathologists; CEP17, chromosome enumeration probe 17; 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]Evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with a *HER2*/CEP17 ratio ≥2.0 and an average *HER2* copy number of <4.0 per cell. In the first generation of adjuvant trastuzumab trials, patients in this subgroup who were randomly assigned to the trastuzumab arm did not seem to derive an improvement in disease-free or overall survival, but there were too few such cases to draw definitive conclusions. IHC expression for HER2 should be used to complement ISH and define HER2 status. If the IHC result is not 3+ positive, it is recommended that the specimen be considered HER2 negative because of the low *HER2* copy number by ISH and the lack of protein overexpression.

[b]There are insufficient data on the efficacy of HER2-targeted therapy in cases with a HER2 ratio of <2.0 in the absence of protein overexpression because such patients were not eligible for the first generation of adjuvant trastuzumab clinical trials. When concurrent IHC results are negative (0 or 1+), it is recommended that the specimen be considered HER2 negative.

[c]It is uncertain whether patients with an average of ≥4.0 and <6.0 *HER2* signals per cell and a *HER2*/CEP17 ratio of <2.0 benefit from HER2-targeted therapy in the absence of protein overexpression (IHC 3+). If the specimen test result is close to the ISH ratio threshold for positive, there is a higher likelihood that repeat testing will result in different results by chance alone. Therefore, when IHC results are not 3+ positive, it is recommended that the sample be considered HER2 negative without additional testing on the same specimen.

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