

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

Wolff, et al.

Introduction

- First released in 2007 and updated in 2013, the recommendations by the ASCO/CAP HER2 Testing Expert Panel are aimed at improving the analytic validity of HER2 testing and the clinical utility of HER2 as a predictive biomarker for potential responsiveness to therapies targeting the HER2 protein.
- Based off the signals approach, the Expert Panel reviewed published literature and research survey results on the observed frequency of less common *in situ* hybridization patterns to update the recommendations.
- The HER2 Testing Expert Panel has identified five Clinical Questions that form the core of this Focused Update.

Guideline Development Methodology

The guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO Clinical Practice Guidelines Committee and CAP Independent Review Panel

The full ASCO Guideline methodology supplement can be found at:

www.asco.org/breast-cancer-guidelines



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Clinical Questions

This 2017 Focused Update addresses five Clinical Questions raised following the publication of the 2013 Guideline Update:

Clinical Question 1: What is the most appropriate definition for IHC 2+ (IHC Equivocal)?

Clinical Question 2: Must HER2 testing be repeated on a surgical specimen if initially negative test on core biopsy?

Clinical Question 3: Should invasive cancers with a *HER2*/CEP17 ratio ≥ 2.0 but an average *HER2* copy number < 4.0 signals/cell be considered ISH positive?

Clinical Question 4: Should invasive cancers with an average *HER2* copy number ≥ 6.0 signals/cell but a *HER2*/CEP17 ratio < 2.0 be considered ISH positive?

Clinical Question 5: What is the appropriate diagnostic work-up for invasive cancers with an average *HER2* copy number ≥ 4.0 but < 6.0 signals/cell and a *HER2*/CEP17 ratio < 2.0 and initially deemed to have an equivocal *HER2* ISH test result?

Target Population and Audience

Target Population

Patients with breast cancer.

Target Audience

Medical oncologists, pathologists, surgeons, and radiation oncologists.



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Summary of Recommendations

CLINICAL QUESTION 1

What is the most appropriate definition for IHC 2+ (IHC Equivocal)?

Recommendation 1

The revised definition of IHC 2+ (equivocal) is invasive breast cancer with “Weak to moderate complete membrane staining observed in >10% of tumor cells.” (see Figure 1 in full text)

(Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong)

Summary of Recommendations

CLINICAL QUESTION 2

Must HER2 testing be repeated on a surgical specimen if initially negative test on core biopsy?

Recommendation 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...” (see Table 2 in full text)

(Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong)

Summary of Recommendations

CLINICAL QUESTION 3

Should invasive cancers with a *HER2*/CEP17 ratio ≥ 2.0 but an average *HER2* copy number < 4.0 signals/cell be considered ISH Positive?

Recommendation 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 additional workup. If not already assessed by the institution/laboratory 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, blinded to previous ISH results, count at least 20 cells that includes the area of invasive cancer with IHC 2+ staining:
 - If reviewing the count by the additional observer changes 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.*
- c. If the IHC result is 0 or 1+, diagnosis is *HER2* negative with a comment.*

Summary of Recommendations

*Comment:

Evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with HER2/CEP17 ratio ≥ 2.0 and an average HER2 copy number < 4.0 /cell. In the first generation of adjuvant trastuzumab trials, patients in this subgroup who were randomized to the trastuzumab arm did not appear 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 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 lack of protein overexpression.

(Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong)

Summary of Recommendations

CLINICAL QUESTION 4

Should invasive cancers with an average *HER2* copy number ≥ 6.0 signals/cell but a *HER2/CEP17* ratio < 2.0 be considered ISH Positive?

Recommendation 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 additional 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, blinded to previous ISH results, count at least 20 cells that includes the area of invasion with IHC 2+ staining:
 - If reviewing the count by the additional observer changes 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 or 1+, diagnosis is *HER2* negative with comment*

Summary of Recommendations

***Comment:**

There are insufficient data on the efficacy of HER2-targeted therapy in cases with HER2 ratio <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.

(Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong)

Summary of Recommendations

CLINICAL QUESTION 5

What is the appropriate diagnostic work-up for invasive cancers with an average *HER2* copy number ≥ 4.0 but < 6.0 signals/cell and a *HER2/CEP17* ratio < 2.0 and initially deemed to have an equivocal *HER2* ISH test result?

Recommendation 5

If the case has an average *HER2* signals/tumor cell of ≥ 4.0 and < 6.0 and the *HER2/CEP17* ratio is < 2.0 , formerly diagnosed as ISH equivocal for *HER2*, a definitive diagnosis will be rendered based on additional workup. If not already assessed by the institution/laboratory 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, blinded to previous ISH results, count at least 20 cells that includes the area of invasion with IHC 2+ staining:
 - If reviewing the count by the additional observer changes 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 or 1+, diagnosis is *HER2* negative with a comment*

Summary of Recommendations

***Comment:**

It is uncertain whether patients with ≥ 4.0 and < 6.0 average HER2 signals/cell and HER2/CEP17 ratio < 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 high 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.

(Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong)

Summary of Recommendations

Revised Recommendation

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 > 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.

The remainder of the 2013 guideline recommendations are unchanged and can be read in the full guideline or the summary of recommendations table at

www.asco.org/breast-cancer-guidelines



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Additional Resources

More information, including a Data Supplement, a Methodology Supplement, clinical tools and resources, is available at

<https://capatholo.gy/2IERBBc>

Patient information is available at www.cancer.net



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