

ERBB2 (HER2) (HercepTest) Testing

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Both breast and gastroesophageal cancers are common causes of cancer-related deaths. Amplification of the *ERBB2* gene, alternatively known as the *HER2* gene, produces HER2 protein and occurs in 15-20% of breast cancers and approximately 7-38% of gastroesophageal cancers. Trastuzumab (Herceptin) may improve the overall survival rate in individuals with HER2-positive breast carcinoma or gastroesophageal adenocarcinoma. Laboratory testing can determine *ERBB2* status and aid in the prediction of response to HER2-directed therapy.

Testing Strategy

ERBB2 (HER2) testing workflows vary based on specimen type. Standard practices for primary, recurrent, and metastatic breast carcinoma, as well as gastroesophageal adenocarcinoma, are outlined below.

Breast Carcinoma

- Assess *ERBB2* expression or copy number status by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH), respectively
 - Concordance between the methods can vary due to subjective interpretation
 - If IHC is equivocal (2+), *ERBB2* FISH is indicated
 - If FISH scores fall in groups 2, 3, or 4 (formerly designated as equivocal), confirm by IHC with rescoring in area(s) of highest staining intensity

Gastroesophageal Carcinoma

- Assess *ERBB2* expression status by IHC first
- If IHC is equivocal (2+), reflex to *ERBB2* FISH per recommended guidelines¹

Additional details on ARUP-specific processing of nonbreast tumor specimens are provided in the following section.

Nonbreast Tumor Specimens

At ARUP, *ERBB2* (HER2) FISH processing for **all nonbreast tumor specimens (e.g., colorectal adenocarcinoma, endometrial serous carcinoma)** is performed according to the workflow described in the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for HER2 in gastroesophageal adenocarcinoma¹:

- Perform HER2 IHC initially
- Reflex to *ERBB2* FISH **only** if the IHC result is 2+ (equivocal)
- No FISH testing is required if HER2 IHC is:
 - 0 or 1+ (negative), or
 - 3+ (positive)

To support appropriate processing, please provide the IHC result in the patient report or order ERBB2 (HER2) (HercepTest) by Immunohistochemistry, Tissue with Reflex to FISH if 2+ (0049178).

Featured ARUP Testing

[ERBB2 \(HER2\) Gene Amplification by FISH with Reflex, Tissue 2008603](#)

Method: Fluorescence in situ Hybridization (FISH)

- Aid in prediction of response to HER2-directed therapy (e.g., trastuzumab [Herceptin]) in patients with breast carcinoma or gastroesophageal adenocarcinoma, as well as select other tumor types (e.g., colorectal adenocarcinoma, endometrial serous carcinoma).
- Confirm equivocal HercepTest (2+) IHC result

[ERBB2 \(HER2\) \(HercepTest\) by Immunohistochemistry, Tissue with Reflex to FISH if 2+ 0049178](#)

Method: Immunohistochemistry (IHC)

- Aid in prediction of response to HER2-directed therapy (e.g., trastuzumab [Herceptin]) in patients with breast carcinoma or gastroesophageal adenocarcinoma, as well as select other tumor types (e.g., colorectal adenocarcinoma, endometrial serous carcinoma).
- Measure protein expression
- Reflex to FISH if IHC is 2+

[ERBB2 \(HER2\) \(HercepTest\) with Interpretation by Immunohistochemistry, Tissue 0049174](#)

Method: Qualitative Immunohistochemistry (IHC)

- Aid in prediction of response to HER2-directed therapy (e.g., trastuzumab [Herceptin]) in patients with breast carcinoma or gastroesophageal adenocarcinoma, as well as select other tumor types (e.g., colorectal adenocarcinoma, endometrial serous carcinoma).
- Confirm equivocal dual IHC or FISH result
- Measure protein expression

[ERBB2 \(HER2\) \(HercepTest\) by Immunohistochemistry 2007332](#)

Method: Immunohistochemistry

- Measure protein expression

Disease Overview

Incidence

Breast cancer: ~268,600 cases diagnosed in the U.S.

Gastroesophageal cancers: ~27,510 cases diagnosed in the U.S.

Treatment Issues

Amplification of the *ERBB2* gene occurs in 15-20% of breast cancers and approximately 7-38% of gastroesophageal adenocarcinomas and predicts poor prognosis in invasive breast cancer.^{1,2}

Trastuzumab therapy inhibits HER2-positive cancers by directing antibodies against the extracellular portion of the HER2 protein. Trastuzumab may improve the overall survival rate in individuals with HER2-positive tumors.

Trastuzumab has a potential for cardiac toxicity along with a high drug cost; therefore, tumors that demonstrate *ERBB2* (HER2) gene amplification or protein overexpression (3+ IHC result) must be identified before initiating therapy.

New therapies targeting HER2 include pertuzumab (Perjeta), T-DM1 (Kadcyla), and lapatinib (Tykerb); recent studies have shown that treatment with a combination of trastuzumab and pertuzumab is more effective than trastuzumab alone (in combination with docetaxel) in prolonging the survival of patients with breast cancer.

Genetics

Gene

ERBB2

Function

Amplification of *ERBB2* gene

- Increases membrane expression and activation of the HER2 protein
- Stimulates cell proliferation

Test Interpretation

Gene Amplification

Breast

Result	Group	<i>ERBB2</i> /CEP17 Ratio	Average <i>ERBB2</i> Copy Number	Interpretation ^a
Positive	Group 1	≥2.0	≥4.0 signals/cell	Predicts favorable response to targeted therapy
Negative	Group 5	<2.0	<4.0 signals/cell	Predicts lack of response to targeted therapy
Indeterminate	Group 2	≥2.0	<4.0 signals/cell	Perform concomitant HER2 IHC review
	Group 3	<2.0	≥6.0 signals/cell	<ul style="list-style-type: none">• IHC score of 3+ is considered positive and 0 or 1+ is considered negative• For an IHC score of 2+, additional tumor nuclei are enumerated with FISH from area of highest IHC intensity by an individual blinded to the original results

Result	Group	<i>ERBB2</i> /CEP17 Ratio	Average <i>ERBB2</i> Copy Number	Interpretation ^a
	Group 3	<2.0	≥4.0 and <6.0 signals/cell	<ul style="list-style-type: none"> Repeat scoring consistent with groups 2 and 4 is considered negative while scoring consistent with group 3 is considered positive

^aIt 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+).

Gastroesophageal

- Positive: *ERBB2*/CEP17 ratio ≥2.0 or *ERBB2*/CEP17 ratio <2.0 and average *ERBB2* copy number ≥6.0 signals/cell
 - Predicts favorable response to targeted therapy
- Negative: *ERBB2*/CEP17 ratio <2.0 and average *ERBB2* copy number <4.0 signals/cell
 - Predicts lack of response to targeted therapy
- If results are indeterminate, ARUP will automatically perform reflex testing with the RAI1 alternate control probe to resolve amplification status. Additional analytic methods or follow up testing on the resection specimen may be considered if needed.

Limitations

- Testing is only validated for formalin-fixed paraffin-embedded (FFPE) specimens; specimens fixed in other than 10% neutral buffered formalin have not been validated using this method.
- Specimens placed in decal may have a false-negative result.
- The assay is validated and FDA-approved for invasive breast carcinoma and gastroesophageal adenocarcinoma only.
- Testing is interpreted according to ASCO/CAP 2018 updated guidelines for breast cancer and ASCO/CAP 2017 guidelines for HER2 in gastroesophageal adenocarcinoma.
- Repeat testing is recommended for discordant results.

Immunohistochemistry

ASCO/CAP 2018 HER2 IHC Scoring Criteria Used in the Interpretation of the HercepTest for Breast Cancer

Score	Interpretation	Microscopic Finding
0	Negative	No staining or membrane staining that is incomplete, faint/barely perceptible, and within ≤10% of the invasive tumor cells
1+	Negative	Incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells
2+	Equivocal ^a	Weak to moderate complete membrane staining observed in >10% of tumor cells
3+	Positive ^b	Circumferential membrane staining that is complete, intense, and in >10% of invasive tumor cells

^aEquivocal results (2+) should be confirmed by FISH testing.

^bPositive results (3+) indicate possible response to trastuzumab.

Biopsies of Gastroesophageal Adenocarcinoma Using *ERBB2* IHC Scoring

Score	Interpretation	Staining Pattern
0	Negative	No reactivity or no membranous reactivity in any tumor cell
1+	Negative	Tumor cell cluster (5 cells) with faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained
2+	Equivocal	Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained
3+	Positive	Tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained

Source: Hofmann, 2008³

Resections of Gastroesophageal Adenocarcinoma Using *ERBB2* IHC Scoring

Score	Interpretation	Staining Pattern
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Score	Interpretation	Staining Pattern
0	Negative	No reactivity or membranous reactivity in <10% of tumor cells
1+	Negative	Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane
2+	Equivocal	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells
3+	Positive	Strong complete, basolateral, or lateral membranous in ≥10% of tumor cells

Source: Hofmann, 2008³

References

1. Bartley AN, Washington MK, Colasacco C, et al. [HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology.](#) *J Clin Oncol.* 2017;35(4):446-464.
2. Nitta H, Kelly BD, Allred C, et al. [The assessment of HER2 status in breast cancer: the past, the present, and the future.](#) *Pathol Int.* 2016;66(6):313-324.
3. Hofmann M, Stoss O, Shi D, et al. [Assessment of a HER2 scoring system for gastric cancer: results from a validation study.](#) *Histopathology.* 2008;52(7):797-805.

Related Information

[Breast Cancer Biomarkers](#)

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com