ERBB2 (HER2/neu) (HercepTest) Testing

Last Literature Review: April 2019 Last Update: July 2022

Both breast and gastric cancers are common causes of cancer-related deaths. Amplification of the *ERBB2* (*HER2*) gene occurs in 15-20% of breast cancers and approximately 7-38% of gastric 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.

Typical Testing Strategy

Standard practice for evaluating primary, recurrent, and metastatic breast carcinoma, and gastric or gastroesophageal adenocarcinoma:

Breast Carcinoma

- Assess *ERBB2* status by immunohistochemistry (IHC) or in situ hybridization (ISH)/fluorescence in situ hybridization (FISH)
  - Concordance between the methods can vary due to subjective interpretation
  - If IHC equivocal (2+), confirm by ISH/FISH
  - If ISH/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

Gastric Carcinoma

IHC should be performed first, followed by FISH testing for equivocal results

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 prior to the initiation of 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 survival of breast cancer patients.

Featured ARUP Testing

ERBB2 (HER2/neu) Gene Amplification by FISH with Reflex, Tissue 2008603

Method: Fluorescence in situ Hybridization (FISH)

- Aid in prediction of response to HER2-directed therapy [eg, trastuzumab (Herceptin)] in patients with breast carcinoma or gastroesophageal adenocarcinoma
- Confirm equivocal HercepTest (2+) IHC result

ERBB2 (HER2/neu) (HercepTest) by Immunohistochemistry, Tissue with Reflex to FISH if 2+ 0049178

Method: Immunohistochemistry

- Aid in prediction of response to HER2-directed therapy [eg, trastuzumab (Herceptin)] in patients with breast carcinoma or gastroesophageal adenocarcinoma
- Measure protein expression
- Reflex to FISH if IHC is 2+

ERBB2 (HER2/neu) (HercepTest) with Interpretation by Immunohistochemistry, Tissue 0049174

Method: Immunohistochemistry

- Aid in prediction of response to HER2-directed therapy [eg, trastuzumab (Herceptin)] in patients with breast carcinoma or gastroesophageal adenocarcinoma
- Confirm equivocal dual ISH or FISH result
- Measure protein expression

ERBB2 (HER2) (HercepTest) by Immunohistochemistry 2007332

Method: Immunohistochemistry

Measure protein expression

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	*ERBB2*/CEP17 Ratio	Average *ERBB2* 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 • 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 • Repeat scoring consistent with groups 2 and 4 is considered negative while scoring consistent with group 3 is considered positive
	Group3	<2.0	≥6.0 signals/cell	
	Group3	<2.0	≥4.0 and <6.0 signals/cell	

[a]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+)

Gastric

- 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, consider further testing with an alternate control probe or analytic method or follow-up testing on the resection specimen

Limitations

- Testing only validated for 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
- 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

[a]Equivocal results (2+) should be confirmed by ISH testing

[b]Positive results (3+) indicate possible response to trastuzumab

Biopsies of Gastric and 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

Hofmann, 2008[3]

Resections of Gastric and Gastroesophageal Adenocarcinoma Using ERBB2 IHC Scoring		
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

Hofmann, 2008[3]

References

1. 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.

2. Bartley AN, Washington MKay, 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.

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.

Additional Resources

American Cancer Society. How common is breast cancer? Last revised Jan 2019; accessed Apr 2019.

Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119.

Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734.

Wolff AC, Hammond EHale, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *Arch Pathol Lab Med*. 2018;142(11):1364-1382.

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