ERBB2 (HER2/neu) (HercepTest) Testing

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.

Tests to Consider

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
- Confirm equivocal dual ISH or FISH result

ERBB2 (HER2) (HercepTest) by Immunohistochemistry 2007332
Method: Immunohistochemistry
- Measure protein expression

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.

**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**

<table>
<thead>
<tr>
<th>Result</th>
<th>Group</th>
<th><em>ERBB2</em>/CEP17 Ratio</th>
<th>Average <em>ERBB2</em> Copy Number</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Group 1</td>
<td>≥2.0</td>
<td>≥4.0 signals/cell</td>
<td>Predicts favorable response to targeted therapy</td>
</tr>
<tr>
<td>Negative</td>
<td>Group 5</td>
<td>&lt;2.0</td>
<td>&lt;4.0 signals/cell</td>
<td>Predicts lack of response to targeted therapy</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Group 2</td>
<td>≥2.0</td>
<td>&lt;4.0 signals/cell</td>
<td>Perform concomitant HER2 IHC review</td>
</tr>
<tr>
<td></td>
<td>Group 3</td>
<td>&lt;2.0</td>
<td>≥6.0 signals/cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3</td>
<td>&lt;2.0</td>
<td>≥4.0 and &lt;6.0 signals/cell</td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>ASCO/CAP 2018 HER2 IHC Scoring Criteria Used in the Interpretation of the HercepTest for Breast Cancer</th>
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<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0</td>
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<tr>
<td>1+</td>
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<td>2+</td>
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<tr>
<td>3+</td>
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</tbody>
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*aEquivocal results (2+) should be confirmed by ISH testing
bPositive results (3+) indicate possible response to trastuzumab

<table>
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<tr>
<th>Biopsies of Gastric and Gastroesophageal Adenocarcinoma Using ERBB2 IHC Scoring</th>
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<tr>
<td>3+</td>
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Hofmann, 2008

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<th>Resections of Gastric and Gastroesophageal Adenocarcinoma Using ERBB2 IHC Scoring</th>
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<td>1+</td>
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<tr>
<td>2+</td>
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<tr>
<td>3+</td>
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Hofmann, 2008
References


Additional Resources


Related Information

Breast Cancer Biomarkers

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