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 [e.g., 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 [e.g., trastuzumab (Herceptin)] in patients with breast carcinoma or gastroesophageal adenocarcinoma
- Confirm equivocal dual ISH or FISH result
- Measure protein expression
- Reflex to FISH if IHC is 2+

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
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

<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>Score</th>
<th>Interpretation</th>
<th>Microscopic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td>No staining or membrane staining that is incomplete, faint/barely perceptible and within ≤10% of the invasive tumor cells</td>
</tr>
<tr>
<td>1+</td>
<td>Negative</td>
<td>Incomplete membrane staining that is faint/barely perceptible and within &gt;10% of the invasive tumor cells</td>
</tr>
<tr>
<td>2+</td>
<td>Equivocal⁵</td>
<td>Weak to moderate complete membrane staining observed in &gt;10% of tumor cells</td>
</tr>
<tr>
<td>3+</td>
<td>Positive⁶</td>
<td>Circumferential membrane staining that is complete, intense and in &gt;10% of invasive tumor cells</td>
</tr>
</tbody>
</table>

⁵Equivocal results (2+) should be confirmed by ISH testing
⁶Positive results (3+) indicate possible response to trastuzumab

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

Hofmann, 2008³

References


Additional Resources
Related Information

Breast Cancer Biomarkers

