ERBB2 (HER2/neu) (HercepTest) Testing

ERBB2 (HER2/neu) Gene Amplification by FISH with Reflex, Tissue 2008603
Method: Fluorescence in situ Hybridization
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

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

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.
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>ERBB2/CEP17 ratio</th>
<th>Average ERBB2 copy number</th>
<th>Interpretation ^a</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 4</td>
<td>&lt;2.0</td>
<td>≥4.0 and &lt;6.0 signals/cell</td>
<td></td>
</tr>
</tbody>
</table>

^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

<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>Equivocal ^a</td>
<td>Weak to moderate complete membrane staining observed in &gt;10% of tumor cells</td>
</tr>
<tr>
<td>3+</td>
<td>Positive ^b</td>
<td>Circumferential membrane staining that is complete, intense and in &gt;10% of invasive tumor cells</td>
</tr>
</tbody>
</table>

^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

<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, 2008

Resections of Gastric and Gastroesophageal Adenocarcinoma Using ERBB2 IHC Scoring

<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 membranous reactivity in &lt;10% of tumor cells</td>
</tr>
<tr>
<td>1+</td>
<td>Negative</td>
<td>Faint/barely perceptible membranous reactivity in ≥ 10% of tumor cells. Cells are reactive only in part of their membrane</td>
</tr>
<tr>
<td>2+</td>
<td>Equivocal</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumor cells</td>
</tr>
<tr>
<td>3+</td>
<td>Positive</td>
<td>Strong complete, basolateral or lateral membranous in ≥ 10% of tumor cells</td>
</tr>
</tbody>
</table>

Hofmann, 2008

REFERENCES


RELATED INFORMATION

Breast Cancer Biomarkers