ERBB2 (HER2/neu) (HercepTest) by Immunohistochemistry

Indications for Ordering

- Aid in prediction of response to HER2-directed therapy [eg, trastuzumab (Herceptin)] in patients with breast or gastric cancer
- Alternate test to confirm equivocal dual in situ hybridization (ISH) or fluorescence in situ hybridization (FISH) result

Test Description

Dako HercepTest test kit in combination with a proprietary polymer detection kit
- Uses a visualization reagent based on dextran technology to locate the human ERBB2 (HER2) protein
- Graded negative (0 or 1+), equivocal (2+), positive (3+)

Tests to Consider

Typical Testing Strategy

Standard practice for evaluating primary, recurrent, and metastatic breast carcinoma, and gastric or gastroesophageal carcinoma
- Assess ERBB2 status by immunohistochemistry (IHC) or ISH/FISH
  o Concordance between the methods can vary due to subjective interpretation
- Use alternate test if equivocal results are reported on initial test
  o If IHC equivocal (2+), confirm by ISH/FISH
  o If ISH/FISH equivocal, confirm by IHC
- Use gene amplification by FISH to resolve discrepancies between IHC and ISH/FISH

Primary Tests

ERBB2 (HER2/neu) (HercepTest) by Immunohistochemistry, Tissue with Reflex to FISH if 2+ 0049178
- Measure protein expression
- Reflex to FISH if IHC is 2+

ERBB2 (HER2/neu) (HercepTest) with Interpretation by Immunohistochemistry, Tissue 0049174
- Measure protein expression

Related Tests

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

ERBB2 (HER2/neu) Gene Amplification by FISH with Reflex, Tissue 2008603
- Aid in prediction of response to HER2-directed therapy [eg, trastuzumab (Herceptin)] in patients with breast or gastric cancer
- Use to confirm equivocal HercepTest of 4B5 IHC result (2+)

Disease Overview

Incidence – ~232,000 new invasive breast and ~21,000 new gastric cancers are diagnosed in the U.S. per year; common causes of cancer-related deaths

Treatment issues

Amplification of the ERBB2 gene occurs in ~15-20% of breast cancers and ~20% of gastric cancers
- Predicts poor prognosis in invasive breast cancer
- Trastuzumab prolongs the overall survival rate in individuals with breast or gastric cancer when tumors overexpress ERBB2
  o Trastuzumab antibodies are directed against the extracellular portion of ERBB2 protein
    ▪ Inhibits ERBB2-overexpressing cancers
  o Due to high drug costs and cardiac toxicity, use of trastuzumab requires identification of tumors that demonstrate ERBB2 gene amplification or protein overexpression (3+ IHC result)

Test interpretation

See tables

Limitations

- Testing using tissue fixed in alcohol-based or nonformalin fixatives has not been validated using this method
- Specimens placed in decal may have a false-negative result
- Repeat testing is recommended for discordant results
### ASCO/CAP 2013 HER2 IHC scoring criteria used in the interpretation of the HercepTest for breast cancer

<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</td>
<td>Circumferential membrane staining that is incomplete, weak, or moderate within &gt;10% of the invasive tumor cells; or complete and circumferential intense membrane staining within ≤10% of invasive tumor cells</td>
</tr>
<tr>
<td>3+</td>
<td>Positive</td>
<td>Circumferential membrane staining that is complete, intense and in &gt;10% of invasive tumor cells</td>
</tr>
</tbody>
</table>

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

### 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 clusters (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>


### Resections of gastric and gastroesophageal adenocarcinoma using ERBB2 IHC scoring

<table>
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<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>
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