ERBB2 (*HER2/neu*) Gene Amplification by FISH

Indications for Ordering

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

Test Description

- Two-color fluorescence in situ hybridization (FISH) for the determination of *ERBB2* (HER2) copy number
- FDA approved for primary invasive breast cancer and gastric cancer

Tests to Consider

Typical testing strategy

Standard practice for evaluating primary, recurrent, and metastatic breast carcinomas, and gastric or gastroesophageal carcinomas

- Assess *ERBB2* status by IHC or FISH
  - Concordance between the methods can vary due to subjective interpretation and method-specific limitations
- Use alternate test if equivocal results reported on initial test
  - If IHC equivocal (2+), confirm by FISH
  - If FISH equivocal, confirm by IHC and if equivocal (2+), test with an alternate control probe

Primary test

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

- Use to confirm equivocal HercepTest IHC result (2+)

Related tests

Measurement of protein expression

- *ERBB2* (HER2/neu) (HercepTest) with Interpretation by Immunohistochemistry, Tissue 0049174
- *ERBB2* (HER2/neu) (HercepTest) by Immunohistochemistry, Tissue with Reflex to FISH if 2+ 0049178
- *ERBB2* (HER2) (HercepTest) by Immunohistochemistry 2007332

Disease Overview

Incidence – ~234,000 new invasive breast and ~24,500 new gastric cancers (NCCN, 2015) 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 HER2
    - Trastuzumab antibodies are directed against the extracellular portion of HER2 protein
      - Inhibits HER2-overexpressing cancers
    - Due to high drug costs and cardiac toxicity, use of trastuzumab requires identification of tumors that demonstrate *ERBB2* (HER2) gene amplification or protein overexpression (3+ IHC result)
    - New therapies targeting HER2 include pertuzumab (Perjeta), T-DM1 (Kadcyla), and lapatinib (Tykerb)
- A recent study showed that treatment with a combination of trastuzumab and pertuzumab was 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

Results

- Positive – *ERBB2*/CEP17 ratio ≥2.0 **OR** *ERBB2*/CEP17 ratio <2.0 with average *ERBB2* copy number ≥6 signals/cell
  - Predicts favorable response to targeted therapy
- Negative – *ERBB2*/CEP17 ratio <2.0 and average *ERBB2* copy number <4 signals/cell
  - Predicts lack of response to targeted therapy
- Equivocal – *ERBB2*/CEP17 ratio <2.0, and average *ERBB2* copy number ≥4 and <6 signals/cell
  - If equivocal by both *ERBB2*/CEP17 and HercepTest (IHC), confirm equivocal cases with an alternate control probe
  - If equivocal result has been obtained on a biopsy, follow up testing should be performed on the resection specimen

Limitations

- Testing using tissue fixed in alcohol-based or non-formalin fixatives has not been validated using this method
- Specimens placed in decal may have a false-negative result
- This assay has been validated and is FDA-approved for invasive breast carcinoma and gastric cancers only
  - *ERBB2* (HER2) FISH has been validated as a laboratory developed test for other cancer types
- Guidelines for interpretation of HER2 status in non-breast cancers has not been published
  - Testing is interpreted according to ASCO/CAP 2013 Updated Guidelines for breast cancer
- Repeat testing is recommended for discordant results