

HER2 CISH

DETECTION OF HER-2/NEU GENE AMPLIFICATION BY CHROMOGENIC IN SITU HYBRIDIZATION (CISH) FOR DETERMINATION OF BREAST CARCINOMA REponsiveness TO TRASTUZUMAB (HERCEPTIN[®])

Test Highlights

- *HER2* CISH is an FDA-approved assay that is utilized as an alternative to *HER2* fluorescent in situ hybridization (FISH) for quantitative determination of *HER2* gene amplification in formalin-fixed, paraffin-embedded (FFPE) breast carcinoma tissue.
- Concordance rates between *HER2* FISH and *HER2* CISH are high (95–100 percent).
- Unlike *HER2* FISH, *HER2* CISH is evaluated in the context of tissue morphology, utilizes bright-field microscopy, and is archival.
- Aids in the selection of patients for treatment with trastuzumab (Herceptin).

Disease Overview

- Breast cancer is the second most common cancer (following skin cancer) and second leading cause of cancer death (following lung cancer) in American women.
- *HER2* gene amplification occurs in approximately 18–30 percent of breast cancers and causes the over expression of *HER2* protein, an epidermal growth factor receptor. *HER2* protein overexpression increases signal transduction, which stimulates cell division and growth. Consequently, *HER2* positivity (gene amplification and/or protein overexpression) is associated with more aggressive disease and increased patient mortality.
- Determination of *HER2* status is essential for therapeutic decisions. *HER2*-positive cancers are eligible for targeted therapy with the monoclonal antibody Herceptin. Herceptin binds to the extracellular portion of the *HER2* protein, inhibiting signal transduction and targeting the cell for destruction by the immune system. Clinical trials have shown that Herceptin extends the survival of women with *HER2*-positive breast cancer.
- Assessment of *HER2* status by immunohistochemistry (IHC) and/or FISH has been the standard for the evaluation of newly diagnosed carcinomas of the breast. Given the advantages of CISH and its high concordance with FISH, CISH is well-suited for use as an alternative to FISH for the determination of patient response to Herceptin.

Epidemiology

- It is estimated that 192,370 new breast cancer cases will be diagnosed and 40,170 deaths will occur in 2009.
- The approximate lifetime chance of having breast cancer is one in eight.
- The approximate chance of dying from breast cancer is one in 35.

Indications for Ordering

HER2 testing should be routinely performed on all newly diagnosed cases of invasive breast carcinoma.

Additional Ordering Notes

The biopsy site, fixative used, elapsed time prior to fixation, and fixation time must be included. Only formalin-fixed (10 percent neutral buffered formalin for 6–48 hours), paraffin-embedded tissue samples containing sufficient viable tumor should be submitted. The area of tumor in the submitted tissue must be invasive; ductal carcinoma in situ will not be scored.

Interpretation

The presence of *HER2* gene amplification predicts a favorable response to trastuzumab (Herceptin) therapy.

Limitations

- This assay will not detect the reported 5 percent of breast cancers that overexpress *HER2* protein but are negative for *HER2* gene amplification. Therefore, it should be utilized in conjunction with the HercepTest[®] immunohistochemical stain.
- Results may be compromised if the fixation procedures have not been followed.

Methodology

HER2 CISH utilizes a digoxigenin-labeled DNA probe to determine the amplification status of the *HER2* gene. Since the probe is not fluorescent, it is visualized by sequential staining with a monoclonal digoxigenin antibody, a horseradish peroxidase conjugate, and DAB chromogen. Light counterstaining with hematoxylin allows visualization of tissue morphology while interpreting *HER2* signals. Guidelines for non-amplification and amplification are based on the *HER2* CISH score, which is the average number of *HER2* signals in 30 tumor cells.

Related Tests

- [HercepTest[®] Tissue Assay, Paraffin \(0049174\)](#)
- [HercepTest[®] with Reflex to HER-2/neu by FISH if 2+ \(0049178\)](#)
- [HercepTest[®] with Reflex to HER-2/neu by FISH if 2+ or 3+ \(0049172\)](#)
- [HER-2/neu by FISH \(PathVysion™ HER-2\) \(0049218\)](#)
- [HER-2 Gene Amplification by Monoplex PCR, Paraffin \(0049390\)](#)

References

1. Slamon DJ, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344(11):783–92.
2. Di Palma S, et al. A quality assurance exercise to evaluate the accuracy and reproducibility of chromogenic in situ hybridisation for HER2 analysis in breast cancer. *J Clin Pathol* 2008;61(6):757–60.
3. Gong Y, et al. Chromogenic in situ hybridization is a reliable method for detecting HER2 gene status in breast cancer. *American Journal of Clinical Pathology* 2009;131(4):490–7.
4. SPOT-Light® HER2 CISH Kit [package insert]. Camarillo, CA: Invitrogen; 2008.

Test Information

2002443 HER-2/neu by CISH (SPOT-Light®)

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.