MEDICAL POLICY

Excellus

SUBJECT: HER-2 TESTING IN INVASIVE BREAST OR GASTRIC CANCER USING FLUORESCENCE IN SITU HYBRIDIZATION (FISH) OR IMMUNOHISTOCHEMISTRY (IHC) ASSAYS	**EFFECTIVE DATE: 07/20/06** **REVISED DATE: 10/18/07, 10/23/08, 10/29/09, 10/28/10, 03/17/11, 02/16/12, 01/17/13, 01/16/14, 01/22/15, 03/17/16, 05/18/17, 03/15/18**
POLICY NUMBER: 2.02.31	
CATEGORY: Laboratory Test	**PAGE: 1 OF: 7**

- ***If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.***
- ***If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.***
- ***If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.***

POLICY STATEMENT:

I. Based upon our criteria and review of the peer-reviewed literature, testing of breast cancer biopsy samples for determination of HER-2/neu gene status in newly diagnosed invasive breast cancer has been medically proven to be effective and therefore **medically appropriate** when the following methods are used:
   A. Fluorescence in situ hybridization (FISH) testing; or
   B. Immunohistochemistry (IHC) testing.

II. Based upon our criteria and review of the peer-reviewed literature, testing for determination of HER-2/neu gene status is considered **medically appropriate** prior to initiation of treatment with the monoclonal antibody Trastuzumab (Herceptin®) in patients with advanced gastric cancer or gastroesophageal (GE) junction adenocarcinoma who have not received prior treatment for metastatic disease.

III. Based upon our criteria and review of the peer-reviewed literature, validation of an equivocal (e.g. inconclusive) HER-2 result via FISH or IHC testing is **medically appropriate** as follows:
   A. IHC score of 2+ should be subjected to reflex testing by a validated complementary (e.g. FISH) method;
   B. FISH result of an average HER2 gene copy number of greater than 4 to less than 6, or a gene amplification ratio of 1.8 to 2.2, or should undergo:
      1. Counting of additional cells; or
      2. Retesting by FISH; or
      3. Reflex testing by a validated IHC method.

POLICY GUIDELINES:

I. Per American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) guidelines:
   A. A positive HER-2 result is:
      1. IHC score of 3+; or
      2. FISH result of greater than or equal to 6.0 HER-2 gene copies per nucleus or ~~a FISH gene amplification ratio~~ dual-probe *HER2*/CEP17 ratio greater than or equal to 2.0.
   B. A negative HER-2 result is:
      1. IHC score of 0 or 1+; or
      2. FISH result of less than 4.0 HER-2 gene copies per nucleus or a dual-probe *HER2*/CEP17 ratio of less than 2.0.
   C. An equivocal (e.g. inconclusive) HER-2 result is:
      1. IHC score of 2+; or
      3. FISH result with a dual-probe *HER2*/CEP17 ratio of less than 2.0 and an average HER2 copy number of greater than 4.0 and less than 6.0 gene copies per nucleus.

II. This policy does not address the use of Herceptin® in the treatment of breast cancer.

DESCRIPTION:

The human epidermal growth factor receptor 2 (HER-2/neu) oncogene is found in high concentrations on the cell surfaces of various cancers. Each cell should have only two copies of the HER-2/neu gene. If it has more than two copies, the cell produces too much of the HER-2/protein. Excessive amounts of this protein (overexpression) causes cells to reproduce uncontrollably. Although the HER-2/neu protein is overexpressed in several epithelial cancers including breast, ovarian, thyroid, lung, salivary gland, stomach, colon and prostate cancer, it has been reported that approximately one-third of breast cancer patients overexpress HER-2/neu. This overexpression appears to be associated with more aggressive disease and usually results from amplification (multiple extra copies) of the HER-2/neu gene in malignant cells.

HER-2/neu testing is used to assist with the selection of breast cancer candidates for treatment with the monoclonal antibody Trastuzumab (Herceptin®). It has been proven by multiple Phase III studies that patients with HER-2/neu overexpressing breast cancer will benefit from therapy with Herceptin®, which may be indicated either as first line therapy or in combination with chemotherapy. Additionally, knowing a tumor's HER-2/neu level may give information about the nature of the cancer and the expected outcome, which can help in the selection of appropriate treatment.

HER-2/neu testing is used to assist with the selection of gastric cancer candidates for treatment with the monoclonal antibody Trastuzumab (Herceptin®). As reported in the NCCN 2011 Gastric Cancer Practice Guidelines, the ToGA study was the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-positive gastric cancer in combination with cisplatin and a fluoropyrimidine. The results of this study confirmed that trastuzumab plus standard chemotherapy is superior to chemotherapy alone in patients with HER2-positive advanced gastric cancer. Five hundred and ninety four patients with HER2-positive gastroesophageal (GE) and gastric adenocarcinoma (locally advanced, recurrent, or metastatic) were randomized to receive trastuzumab plus chemotherapy (5-fluorouracil or capecitabine and cisplatin) or chemotherapy alone. There was a significant improvement in the median overall survival with the addition of trastuzumab to chemotherapy compared to chemotherapy alone (13.5 vs. 11.1 months, respectively.) Safety profiles were similar with no unexpected adverse events in the trastuzumab. There was also no difference in symptomatic congestive heart failure between arms. This establishes that trastuzumab plus chemotherapy as a new standard of care for the treatment of patients with a HER2-expressing advanced gastric and GE cancers.

Two distinct methods are used for detection of the HER-2/neu oncogene in breast and gastric cancer patients. Both methods can be performed on archived or current specimens.

Immunohistochemistry (IHC) is performed on breast tumor tissue removed at surgery and measures protein expression of the HER-2/neu gene. Results are reported as a range from 0 to 3+. 1+ is negative, 2+ is indeterminate or weak (may be positive or negative), and 3+ is positive. An example of an IHC HER-2/neu test is the HercepTest®.

The *fluorescence in situ hybridization* (FISH) technique for detection of HER-2/neu gene amplification is also performed on breast cancer tissue removed at surgery, and measures HER-2/neu gene amplification present in cells. It directly tests DNA in the cancer cell to determine HER-2/neu status at the genetic level and reflects the number of HER-2/neu and 17 chromosome centromere FISH signals enumerated in 50-100 cells. Results are reported as a ratio of the number of HER-2 signals to 17 chromosome centromere signals. A ratio of less than 1.8 is within normal limits, a ratio of 1.8-2.0 is equivocal and requires further testing, a ratio of greater than 2 is consistent with amplification of HER-2/neu gene sequences. An example of a FISH HER-2/neu test is the PathVysion™ test.

RATIONALE:

U. S. Food and Drug Administration (FDA) premarket approval has been given for kits using the FISH technique for quantifying HER-2/neu gene amplification in formalin-fixed, paraffin-embedded breast cancer tissue specimens. These include but are not limited to the PathVysion™ HER-2 DNA Probe Kit (Vysis, Inc.) approved in 2001, the INFORM® her-2/neu test kit (Ventana Medical Systems, Inc.) approved in 2000, and the DakoCytomation *Her*2 FISH pharmDx™ kit (Denmark) approved in 2005. However, only the PathVysion™ FISH test kit has been further indicated by the FDA as an aid in the assessment of patients for whom Herceptin® (Trastuzumab) treatment is being considered. In April 2005 the FDA approved the Ariol HER-2/neu FISH software application (Applied Imaging Corp.) that allows the Ariol automated scanning microscope and image analysis system to detect amplification of the HER-2/neu gene via fluorescence in situ hybridization (FISH) in human breast cancer biopsy samples. The application and system are intended for use with a DNA probe kit (PathVysion HER-2/neu, Vysis, Inc.). The IHC HercepTest® (DAKO, Glostrup, Denmark) and the IHC Pathway® HER2 test (Ventana Medical Systems, Tucson, AZ) have FDA approval for determining the HER2 status of breast cancer tumors.

In 2013, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) published the updated results of an expert panel which conducted a systematic review of the literature and developed recommendations for optimal HER2 testing performance and included new guidelines for consistent handling of samples. The guideline was reviewed by selected experts and approved by the board of directors for both organizations. The panel recommended HER2 status should always be tested for on all newly diagnosed invasive breast cancers (primary site and/or metastatic site). Ensure that at least one tumor sample is tested for either HER2 protein expression (immunohistochemistry [IHC] assay) or (in situ hybridization [ISH assay]) for *HER2* gene amplification. The role of HER2-targeted therapy should be discussed when the HER2 test result is positive and if there is no apparent histopathologic discordance with HER2 testing. The decision to recommend HER2-targeted therapy should be delayed if the HER2 test result is equivocal. Mandatory retesting should be done on the same specimen using the alternative test if the initial HER2 test result is equivocal or on an alternative specimen. If the HER2 test result is negative, HER2-targeted therapy should not be administered. If there is apparent histopathologic discordance with the HER2 test result, additional HER2 testing should be considered. A HER2 test result should be reported as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being done in a tumor specimen, or prevent the test (or tests) from being reported as positive, negative, or equivocal. Confirm that the testing laboratory conforms to standards set for accreditation by CAP or an equivalent accreditation authority.

A retrospective study evaluated the concordance between HER2 gene amplification determined by FISH and HER2 protein overexpression previously determined by IHC in breast cancer tissue specimens from women screened for three pivotal clinical trials, including one international trial, of trastuzumab (Herceptin®) at 54 centers. 5,998 breast cancer tissue specimens were divided into two groups: IHC score of 0/1+ and IHC score 2+/3+. 300 specimens from each group were randomly selected to determine HER2 amplification using the FISH assay. Assay agreement between FISH and specimens with IHC scores were 0 = 97%, 1+ = 93%, 3+ = 89%. Only 24% of specimens with 2+ IHC showed HER2 amplification by FISH (76% disagreement in this IHC subgroup).

A randomized, controlled, multi-center clinical trial evaluated the predictive value of HER2 in a population of advanced breast cancer patients randomly treated either with single-agent doxorubicin or with single-agent docetaxel. Of 326 patients in the trial, tumor samples were available for 176 patients (54%). Different cohorts of patients identified by HER2 were examined to assess a possible relationship between HER2 status and treatment effect. In this trial, all positive IHC cases received FISH to confirm HER2-positive status. HER2 positivity was observed in 20% of the study population. A statistically significant interaction was found between response rates to the study drugs and HER2 status.

Numerous studies with small sample sizes support that HER-2/neu status with an immunohistochemistry (IHC) score of 2+ should be confirmed with FISH testing, and that 3% to 7% of patients who are negative by IHC are found to be positive by FISH testing.

The 2017 National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology for Breast Cancer recommend determination of HER2 status for all newly diagnosed invasive breast cancers. They state that HER2 status can be assessed by measuring the number of HER2 gene copies (FISH assay) or by a complementary method in which the number of HER2 cell surface receptors is evaluated (IHC assay). The NCCN Breast Cancer Panel recommends selecting patients for trastuzumab (Herceptin) therapy who have tumors either positive for HER2 by FISH, or 3+ by IHC. Patients with tumors IHC 0, or 1+ for HER2, or FISH not amplified have very low rates of trastuzumab response and therefore therapy with trastuzumab is not warranted. Additionally either an IHC assay or a FISH assay can be used to make an initial assessment of HER2 tumor status, and all HER2 assays must be validated. Borderline IHC samples (e.g. IHC 2+) should be subjected to reflex testing by a validated complementary (e.g. FISH) method. Borderline FISH samples (e.g. an average HER2 gene/chromosome 17 ratio of 1.8-2.2 or an average HER2 gene copy number of greater than 4 to less than 6) should undergo: counting of additional cells, retesting by FISH, or reflex testing by a validated IHC method. A validated FDA-approved version of the FISH assay is recommended as the "gold standard" for confirmatory testing, when necessary. The NCCN panel endorses the use of College of American Pathologists protocols for reporting the pathological analysis of all breast specimens.

The 2017 National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology for Gastric Cancer recommend determination of HER2 status for patients with inoperable, locally advanced, recurrent or metastatic adenocarcinoma of the stomach or EGJ for whom trastuzumab therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended. The NCCN panel recommends that cases showing 2+ expression of HER2 by immunochemistry should be additionally examined by FISH or other in situ hybridization methods.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

CPT:	88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (list separately in addition to code for primary procedure)
	88344	Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure
	88360	Morphometric analysis, tumor immunohistochemistry (e.g. HER-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
	88361	using computer-assisted technology
	88364	In situ hybridization (e.g., FISH), per specimen; each additional single probe stain procedure (list separately in addition to code for primary procedure)
	88365	In situ hybridization (e.g. FISH), per specimen; initial single probe stain procedure
	88367	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative); using computer-assisted technology, per specimen; initial single probe stain procedure
	88368	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), manual, per specimen; initial single probe stain procedure
	88369	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), manual, per specimen; each additional single probe stain procedure (list separately in

		addition to code for primary procedure)
	88373	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each additional single probe stain procedure (list separately in addition to code for primary procedure)
	88374	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
	88377	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative), manual, per specimen; each multiplex probe stain procedure
	0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified (DEPArray™ HER2, PacificDx) (effective 8/1/2017)

HCPCS:	No code(s)	
ICD10:	C16.0-C16.9	Malignant neoplasm of stomach (code range)
	C50.0-C50.9	Malignant neoplasm of breast (code range)
	C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
	C78.80	Secondary malignant neoplasm of unspecified digestive organ
	C78.89	Secondary malignant neoplasm of other digestive organs
	D0.02	Carcinoma in situ of stomach
	D37.1-D37.5	Neoplasm of uncertain behavior of digestive organs (code range)
	Z85.3	Personal history of malignant neoplasm of breast

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KEY WORDS:

FISH, HercepTest, HER-2 overexpression, HER-2 amplification, IHC, immunohistochemistry, PathVysion.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for HER-2 testing in invasive breast cancer using Fluorescence in situ hybridization (FISH) or immunohistochemistry IHC) assays.