APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services (CMS) National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs) or other published documents). The terms of a member’s particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member’s benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any. All links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change prior to the annual review date. Lines of business (LOB) are subject to change without notice; current LOBs can be found at www.wellcare.com. All guidelines can be found at this site as well but selecting the Provider tab, then “Tools” and “Clinical Guidelines”.

BACKGROUND

The amplification and over-expression of the HER-2/neu gene, also known as the c-erbB-2 gene, has been detected in 20% to 30% of breast cancers. Alterations of this gene or an increase in gene products in breast cancer specimens are associated with shorter survival rates and a higher likelihood of disease recurrence and death. The accurate identification of patients with the gene alteration would allow them to be targeted for more aggressive therapy. Such alterations have also been associated with higher or lower response rates to specific anticancer therapies, potentially allowing physicians to select treatments for individual patients, which have the greatest likelihood of success for that individual. In particular, one therapy (trastuzumab) specifically targets HER-2/neu gene products and is only appropriate for members with alterations in this gene.
Various methods have been used to detect the HER-2/neu gene and its products in archival tissue specimens, including: gene expression analysis by Western blot testing or immunohistochemistry; measurement of messenger RNA (mRNA) levels by Northern blot analysis; and the direct measurement of gene amplification by Southern blot testing. At present, the two most commonly used methods for evaluating HER-2/neu status in a clinical setting are immunohistochemistry (IHC), which measures the over-expression of HER-2/neu gene products, and fluorescence in situ hybridization (FISH), which detects amplification of the gene itself. Chromogenic in situ hybridization (CISH) is a much newer technology and is still being tested, but is believed to have great potential, since it combines the advantages of the other two methods (from Hayes, 2004).

Algorithm for HER2 Testing

Positive for HER2 is either IHC HER2 3+ (defined as uniform intense membrane staining of > 30% of invasive tumor cells) or FISH amplified (ratio of HER2 to CEP17 of > 2.2 or average HER2 gene copy number > six signals/nucleus for those test systems without an internal control probe).

Equivocal for HER2 is defined as either IHC 2+ or FISH ratio of 1.8-2.2 or average HER2 gene copy number four to six signals/nucleus for test systems without an internal control probe.

Negative for HER2 is defined as either IHC 0-1+ or FISH ratio of <1.8 or average HER2 gene copy number of < four signals/nucleus for test systems without an internal control probe.

Trastuzumab (Herceptin®)

Trastuzumab (Herceptin®, Genentech Inc.) is a humanized monoclonal antibody that binds selectively to the human epidermal growth factor receptor 2 (HER2), which is expressed in large quantities on the surface of cancer cells in some types of breast tumors. Binding of trastuzumab to HER2 can slow the growth of the cancer cells and prevent spread of the tumor. Initially investigated for use in patients with metastatic breast cancer, trastuzumab is now also being studied as a neoadjuvant or adjuvant treatment for patients with early (localized) breast cancer. (1Hayes Directory, 2007). Herceptin® is manufactured by Genentech Inc. and contains the active substance trastuzumab. It is a humanized monoclonal antibody that binds selectively to the antigen human epidermal growth factor 2 (HER2), which is found in large amounts on the surface of some cancer cells and therefore stops growth of such cells. (2Hayes Directory, 2007).

Herceptin is prescribed for the treatment of patients with early breast cancer who have completed chemotherapy and for the treatment of patients with metastatic breast cancer (i.e., breast cancer that has spread beyond the original tumor) who have tumors that produce large amounts of HER2. It is used either alone, in conditions where other treatments proved unsuccessful, or in combination with the chemotherapy agents paclitaxel or docetaxel as first treatment for metastatic breast cancer. (2Hayes Directory, 2007).

American Society of Clinical Oncology

The ASCO (2013) updated their original statement and recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to evidence of protein overexpression (IHC) or gene amplification (by ISH based on counting at least 20 cells within the area). If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity.
Exclusions

The following tests are considered experimental and investigational in nature:

- Chromogenic in situ hybridization (CISH)
- HERmark™ Breast Cancer Assay (Monogram Biosciences)

Coverage

The testing of breast cancers for HER-2/neu gene amplification or for over-expression of the protein produced by HER-2/neu is considered medically necessary in conjunction with standard histopathological and clinical indicators of disease prognosis in order to:

- Stratify members into low- and high-risk categories for recurrence and disease-related death; OR,
- Identify members who might benefit from treatment with trastuzumab (Herceptin®); OR,
- To predict response to different chemotherapy regimens.

The following tests are considered medically necessary for the determination of HER-2/neu status in primary invasive breast cancer with negative axillary lymph nodes, positive axillary lymph nodes, or distant metastases, when test results will be used for determining prognosis and/or treatment planning:

1. Immunohistochemistry (IHC) testing IF:
   - Performed by trained personnel; AND,
   - The test has been calibrated against fluorescence in situ hybridization (FISH) or some other known standard; AND,
   - If equivocal cases are referred for FISH testing (see background section for more detail on equivocal results)

2. Fluorescence in situ hybridization (FISH) IF:
   - Performed by trained personnel according to manufacturer’s standards; AND,
   - Used only after an IHC test has been performed and the IHC results are equivocal

NOTE: Equivocal FISH samples should be confirmed through additional cell counts or by repeating the FISH test. If additional FISH analysis proves equivocal, confirmatory IHC testing is recommended.

CODING

NOTE: This CCG applies to Medicaid only; for Medicare, refer to Palmetto LCD (see reference section).

Covered CPT® Codes

- 83950 Oncoprotein; HER-2/neu
- 88360 Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen each antibody; stain procedure manual
- 88361 Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each single antibody stain procedure; using computer-assisted technology
- 88365 In situ hybridization (eg FISH), each probe stain procedure

Non-Covered CPT® Codes – (The following tests are considered experimental and investigational in nature).

- 84999 CISH -Chromogenic in situ hybridization
- 84999 HERmark™ Breast Cancer Assay (Monogram Biosciences)

HCPCS Codes – No applicable codes.

ICD-10-PCS Procedure Codes – No applicable codes.

Covered ICD-10-CM Diagnosis Codes

- C50.011 - C50.929 Malignant neoplasm of nipple and areola breast
Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member's benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

REFERENCES


MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/2/2013</td>
<td>Approved by MPC. Applies to Medicaid only; for Medicare, see Palmetto LCD.</td>
</tr>
<tr>
<td>4/5/2012</td>
<td>Approved by MPC. Added two Hayes references regarding Trastuzumab (Herceptin) and ratings for metastatic and early stage breast cancer.</td>
</tr>
<tr>
<td>12/1/2011</td>
<td>New template design approved by MPC.</td>
</tr>
<tr>
<td>8/2/2011</td>
<td>Approved by MPC. No changes.</td>
</tr>
</tbody>
</table>