Policy Statement

The assessment of human epidermal growth factor receptor 2 (HER2) status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational.

Policy Guidelines

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

There is no specific CPT code for this testing. It would likely be reported using the following CPT code:

- **84999**: Unlisted chemistry procedure

Palmetto GBA’s MolDX® program instructs that for Medicare this test should be reported with the following unlisted code

- **81479**: Unlisted molecular pathology procedure

Description

Novel assays that quantitatively measure total human epidermal growth factor receptor 2 (HER2) protein expression and homodimers have been developed to improve the accuracy and consistency of HER2 testing.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. HERmark® Breast Cancer Assay (Monogram Biosciences) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background

Human Epidermal Growth Factor Receptor 2

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (EGFR/HER1, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4) plays a major role in the pathogenesis of many solid tumors. In approximately 25% to 30% of breast cancers, overexpression of HER2 has been linked to shorter disease-free and overall survival, lack of responsiveness to tamoxifen antiestrogen therapy, and altered responsiveness to a variety of cytotoxic chemotherapy regimens.

Trastuzumab, a monoclonal antibody directed at the extracellular domain of HER2, has offered significant shorter disease-free and overall survival advantages in the metastatic and adjuvant settings in HER2-overexpressing patients, although not all patients respond. Fewer than 50% of patients with metastatic HER2-positive breast cancer show initial benefit from trastuzumab treatment, and many of those eventually develop resistance.

Current methodologies for the selection of HER2-positive patients include immunohistochemistry (IHC) to detect HER2 protein overexpression and fluorescence in situ hybridization (FISH) to detect HER2 gene amplification. However, controversy still exists regarding the accuracy, reliability, and interobserver variability of these assay methods. IHC provides a semiquantitative measure of protein levels (scored as 0, 1+, 2+, 3+) and the interpretation may be subjective. FISH is a quantitative measurement of gene amplification, in which the HER2 gene copy number is counted. However, FISH, which is considered to be more quantitative analytically, is not always representative of protein expression, and multiple studies have failed to demonstrate a relation between HER2 gene copy number and response to trastuzumab. Whereas patients who overexpress HER2 protein (IHC) or show evidence of HER2 gene amplification (FISH) have been shown to experience better outcomes on trastuzumab than those scored negative by those assays, differences in the degree of expression or amplification by these methods have generally not been shown to discriminate between groups with different outcomes. IHC and FISH testing may be affected by interlaboratory variability, and neither test provides quantitative data that reflect the activation state of signaling pathways in tumors, which may limit their utility in patient selection. Most laboratories in North America and Europe use IHC to determine HER2 protein status, with equivocal category results (2+) confirmed by FISH (or more recently by chromogenic in situ hybridization).

Typically, HER2 activates signaling pathways by dimerizing with ligand-bound epidermal growth factor receptor family members such as HER1 and HER3. A HER2 ligand has not been identified, but overexpressed HER2 is constitutively active. When HER2 is pathologically overexpressed, the receptor may homodimerize and activate signaling cascades in the absence of the normal regulatory control imposed by the requirement for ligand binding of its heterodimerization partners.

A novel assay (HERmark® Breast Cancer Assay) was developed to quantify total HER2 protein expression and HER2 homodimers in formalin-fixed, paraffin-embedded tissue samples.
Literature Review

See Appendix Table 1 for genetic testing categories.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose.

Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

Clinical Context and Test Purpose

The purpose of assessment of human epidermal growth factor receptor 2 (HER2) status using quantitative total HER2 protein expression and HER2 homodimer measurement in patients who have breast cancer is to inform a decision whether to modify treatment strategies to include HER2-targeted therapy or not.

The question addressed in this evidence review is: Does an assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement in patients who have breast cancer result in an improved health outcome compared with assessment of HER2 status using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH)?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with breast cancer who are undergoing assessment of HER2 status.

Interventions
The relevant intervention is assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement.

Comparators
The relevant comparators of interest currently used to make decisions about assessment of HER2 status are: IHC and ISH.

Outcomes
The general outcomes of interest are overall survival, disease-free survival, test accuracy, and test validity.

The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to inappropriate clinical management with HER2-targeted therapy. False-negative test results can lead to absence or delayed HER2-targeted therapy.

Timing
The timeframe for outcome measures varies from immediately following testing diagnosis to long-term health outcomes subsequent to management changes.

Setting
Patients requiring treatment for breast cancer are managed by an oncologist and are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the
explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Study Selection Criteria**
Below are selection criteria for studies to assess whether a test is clinically valid.
1. The study population represents the population of interest. Eligibility and selection are described.
2. The test is compared with a credible reference standard.
3. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
4. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
Retrospective studies, discussed below, have reported on the association between H2T levels and survival outcomes (see Tables 1).

**Table 1. Summary of Studies of HERmark Clinical Validity**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cutoffs Used</th>
<th>Result</th>
<th>Favored Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipton et al (2010)⁵</td>
<td>≤13.8 &gt;68.5</td>
<td>Better response to trastuzumab at higher levels of HER2 total expression observed</td>
<td>●</td>
</tr>
<tr>
<td>Toi et al (2010)⁶</td>
<td>≤median H2T&lt;sup&gt;b&lt;/sup&gt; ≥median H2T&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Patients with higher H2T values (&gt;75% percentile) lived longer than those with lower H2T values in the high HER2-expressing group &lt;br&gt; • Patients with lower H2T values lived longer than those with higher H2T values in the low HER2-expressing group</td>
<td>● ●</td>
</tr>
<tr>
<td>Bates et al (2011)⁷</td>
<td>≤13.8 &gt;68.5</td>
<td>Group with intermediate H2T levels experienced longest TTP and OS</td>
<td>●</td>
</tr>
<tr>
<td>Joensuu et al (2011)⁸</td>
<td>NA ≥125.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Patients with HER2-positive breast cancer with very high tumor HER2 content may benefit less from a adjuvant trastuzumab than those whose cancer has more moderate HER2 content</td>
<td>● ●</td>
</tr>
<tr>
<td>Duchnowska et al (2012)⁹</td>
<td>&lt;58&lt;sup&gt;c&lt;/sup&gt; ≥58&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Correlation between continuous H2T level and TTBM confirmed on multivariate analysis</td>
<td>● ●</td>
</tr>
<tr>
<td>Han et al (2012)¹⁰</td>
<td>≤13.8 ≥13.8</td>
<td>TTP longer in patients with high H2T than in patients with low H2T</td>
<td>● ●</td>
</tr>
<tr>
<td>Lipton et al (2013)¹¹</td>
<td>≤16.1 &gt;68.3</td>
<td>Low H2T and high H2T correlated with shorter PFS and OS</td>
<td>●</td>
</tr>
<tr>
<td>Barros et al (2014)¹²</td>
<td>Per specific heterodimer studied</td>
<td>Low heterodimer levels favored among unselected patients; no association among trastuzumab-treated or -naive HER2-positive patients</td>
<td>●</td>
</tr>
<tr>
<td>Montemurro et al (2014)¹⁴</td>
<td>≤median H2T ≥median H2T</td>
<td>Increasing log (H2T) was associated with a longer persistence on protocol</td>
<td>● ●</td>
</tr>
<tr>
<td>Yardley et al (2015)¹³</td>
<td>≤13.8 ≥13.8</td>
<td>High H2T associated with significantly shorter OS vs low H2T</td>
<td>●</td>
</tr>
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<tr>
<td>Scaltriti et al (2015)</td>
<td>&lt;median H2T, ≥median H2T</td>
<td>Increasing H2T associated with improved pathologic complete response</td>
<td>●</td>
</tr>
<tr>
<td>Duchnowska et al (2017)</td>
<td>&lt;13.8 ≤median H2T, ≥median H2T</td>
<td>Patients with moderately overexpressed HER2 levels and high p95HER2 expression may have better outcomes while receiving lapatinib following progression on trastuzumab</td>
<td>●</td>
</tr>
<tr>
<td>Chumsri et al (2018)</td>
<td>&lt;10.5 &gt;17.8</td>
<td>High H2T levels correlated with longer progression free survival</td>
<td>●</td>
</tr>
</tbody>
</table>

HER2: human epidermal growth factor receptor 2; H2T: HER2 protein; Int: intermediate; NA: not applicable; NR: not reported; OS: overall survival; PFS: progression-free survival; TTBM: time to brain metastasis; TTP: time to progression.

a Cutoff for very high H2T (≥22-fold the median H2T of cancers HER2-negative by chromogenic in situ hybridization [5.7])
b Absolute values not reported.
c Median H2T level. H2T value of 50 was a better discriminator (smaller p value in Cox models).

Bates et al (2011) measured H2T in HER2 overexpressing and/or amplified primary breast tumors from 98 women treated with trastuzumab-based therapy for metastatic breast cancer. Cut points for defining levels of H2T were not prespecified. Instead, using subpopulation treatment effect pattern plots, the population was divided into H2T low (H2T <13.8), H2T high (H2T ≥68.5), and H2T intermediate (13.8 ≤H2T<68.5) subgroups. Kaplan-Meier analyses were used to compare groups for time-to-progression (TTP) and overall survival (OS). Cox multivariate analyses were used to identify correlates of clinical outcome. Bootstrapping analyses were used to test the robustness of results. TTP improved with increasing H2T until, at the highest levels of H2T, an abrupt decrease in the TTP was observed. Kaplan-Meier analyses demonstrated that patients with H2T low tumors (median TTP, 4.2 months; hazard ratio [HR], 3.7; p<0.001) or H2T high tumors (median TTP, 4.6 months; HR=2.7; p=0.008) had significantly shorter TTP than patients whose tumors were H2T intermediate (median TTP, 12 months). OS analyses yielded similar results. The authors concluded that patients with high levels of H2T may represent a subgroup with de novo resistance to trastuzumab but that these results were preliminary and required confirmation in larger controlled clinical cohorts. Subgroup analysis of patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Joensuu et al (2011) reported results of measurement of H2T using HERmark from FFPE tumor tissue of 899 (89%) women who participated in the FinHer trial (ISRCTN76560285) to determine if very high tumor H2T content influences outcome in early breast cancer treated with adjuvant trastuzumab plus chemotherapy. HER2 status was determined prior to entry to the study by IHC; CISH was used to confirm HER2 status for cases with IHC +2 or +3. Using chromogenic in situ hybridization (CISH) test, 197 (21.9%) patients had HER2-positive cancer and were randomized to trastuzumab or control. Tumor H2T levels varied greatly, by 1808-fold. High H2T levels strongly correlated with a positive HER2 status by CISH (p<0.001). Cut points for defining levels of H2T were not prespecified. Patients with very high H2T (defined by ≥22-fold the median of HER2-negative cancers [5.7; range, 0.4-118.4]; 13% of CISH-positive cancers) did not benefit from adjuvant trastuzumab (HR for distant recurrence, 1.23; 95% CI, 0.33 to 4.62; p=0.75), whereas the remaining patients with HER2-positive disease by CISH (87%) did benefit (HR for distant recurrence, 0.52; 95% CI, 0.28 to 1.00; p=0.050). The authors concluded that patients with HER2-positive breast cancer with very high tumor HER2 content may benefit less from adjuvant trastuzumab than those whose cancer has more moderate HER2 content. Subgroup analysis of patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Toi et al (2010) investigated the relation between H2T or H2D and OS in 72 patients drawn from 6 oncology clinics in Japan who had metastatic breast cancer and had been treated with at least 1 chemotherapy regimen before receiving trastuzumab. Patients were originally selected for treatment with trastuzumab using IHC (88%) or FISH (12%). HERmark assay results were correlated with OS using univariate Kaplan-Meier, hazard function plots, and multivariate Cox regression analyses. Clinical outcome data were drawn from medical chart review.
Measurements of H2T and H2D were tested for association with OS, defined as the time from start of trastuzumab treatment to cancer-associated death or end of follow-up (median, 18.2 months). The median duration of trastuzumab treatment was 14.6 months. The 2-year OS rate was 60.8% (95% CI, 48.4% to 73.2%). Cut points for defining levels of H2T were not prespecified. In univariate analyses, patients were classified into 4 subgroups defined by the 25th, 50th, and 75th percentiles for each of the 3 variables, H2T, H2D, and their ratio, H2D/H2T. Hazard function plots were estimated in the 4 H2T subgroups, and subgroups with the 25% highest and lowest H2T values had a substantially lower risk of death than the middle 2 subgroups. Dividing the cohort into high HER2-expressing (greater than or equal to the median value of H2T) and low HER2-expressing (less than the median value of H2T) subgroups and using Cox regression with the continuous H2T value in each of subgroup, patients with higher HER2 values had longer survival than those with lower H2T values in the high HER2-expressing group (HR=0.06; 95% CI, 0.01 to 0.51; p=0.010). In contrast, in the low HER2-expressing group, the opposite trend (those with lower H2T values were favored) was observed (HR=16.0; 95% CI, 1.64 to 155.9; p=0.017). The authors concluded that there were 2 subpopulations in this cohort that behaved differently with respect to HER2 expression and OS and that the quantitative amount of HER2 expression measured by HERmark may be a useful new marker to identify a more relevant target population for trastuzumab treatment in patients with metastatic breast cancer. Statistical analysis of patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Lipton et al (2010) used the HERmark assay in patients with HER2 overexpressing and/or amplified metastatic breast cancer who were treated with trastuzumab. Of 102 patients, FISH testing was repeated in 99 patients. Per NCCN guidelines, further tests are not recommended in patients with IHC +1 or +3 scores; all patients found to be FISH negative on retesting were previously scored as IHC +3Cut points for defining levels of H2T were not prespecified. Sixty-six (87%) of 76 central FISH-positive patients had high H2T levels (concordant positive), and 19 (86%) of 22 central FISH-negative patients were H2T low (concordant negative). Three (14%) of 22 central FISH-negative patients were H2T high (discordant H2T high), and 10 (13%) of 76 central FISH-positive patients were H2T low (ISH/H2T discordant H2T low). The discordant positive group had a significantly longer TTP (median, 11.3 months) compared with the concordant negative group (median, 4.5 months; HR=0.42; p<0.001), and also compared with the discordant H2T low group (median, 3.7 months; HR=0.43; p<0.01). The discordant H2T low group behaved similarly compared with discordant negatives (HR=1; p=0.99). In analyses restricted to central FISH-positive patients only (n=77), Cox proportional hazards multivariate regression identified H2T as an independent predictor of TTP (HR=0.29; p<0.001) and OS (HR=0.19, p<0.001). The authors concluded that a subset of patients with HER2 gene amplification by FISH express low levels of HER2 protein and have reduced response to trastuzumab-containing therapy, similar to FISH-negative.

Han et al (2012) performed a retrospective analysis in 52 women with HER2 overexpressing and/or amplified locally advanced or metastatic breast cancer that had progressed after treatment with an anthracycline, a taxane, and trastuzumab. Patients were treated with lapatinib and capecitabine until disease progression or intolerance. Cut points for defining levels of H2T were not prespecified. Among all patients, median TTP was longer in patients with high H2T (>13.8; 5.0 months) than in patients with low H2T (<13.8; 1.8 months; p=0.047). However, a cutoff of 14.95 had greater discrimination (lower chi-square p value). Results were similar using this cutoff; median TTP in patients with high H2T (>14.95) was 5.2 months and in those with low H2T (<14.95), 1.8 months (p=0.018). No significant association was found between H2T levels and OS using either cut point. Among subgroups defined by H3T levels, median TTP was significantly longer (5.6 months) in patients with both high H2T (>14.95) and high H3T (>0.605) than in other groups (2.2 months; p=0.002). Subgroup analysis of patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Duchnowska et al (2012) investigated the correlation between H2T in primary breast cancers and time-to-brain metastasis (TBM) in HER2-positive advanced breast cancer patients treated with trastuzumab. The patient sample included 142 consecutive patients who were
administered trastuzumab-based therapy. HER2 status was initially determined by IHC; subsequently, HER2/neu gene copy number was quantified as the HER2/CEP17 ratio by central laboratory FISH. HER2 protein was quantified as H2T by the HERmark assay in FFPE tumor samples. HER2 variables were correlated with clinical features, and TTBM was measured from the initiation of trastuzumab-containing therapy. A higher H2T level (continuous variable) correlated with shorter TTBM, whereas HER2 amplification by FISH and a continuous HER2/CEP17 ratio were not predictive (p = 0.013, 0.28, and 0.25, respectively). In the subset of patients that was centrally determined by FISH to be HER2-positive, an above-the-median H2T level (>58) was significantly associated with a shorter TTBM (HR = 2.4; p = 0.005), whereas this was not true for the median HER2/CEP17 ratio by FISH (p = 0.4). The correlation between a continuous H2T level and TTBM was confirmed on multivariate analysis (HR = 3.3, p = 0.024). The authors concluded that their data revealed a strong relationship between quantitative HER2 protein expression level and risk for brain relapse in HER2-positive advanced breast cancer patients and that quantitative assessment of HER2 protein expression may inform and facilitate refinements in therapeutic treatment strategies for selected subpopulations of patients in this group. Subgroup analysis in patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Barros et al. (2014) used proximity ligation assays to characterize specific HER2 heterodimers and their association with breast cancer-specific survival (BCSS) and disease-free interval. Tumor samples were from patients who had primary operable, invasive breast cancer at a single center in England. Among 1858 unselected patients, high levels of all 3 HER2 heterodimers (HER2/HER1 (EGFR), HER2/HER3, HER2/HER4) showed statistically worse BCSS and disease-free interval compared with low levels (range of HRs for BCSS, 0.62-0.66 [95% CI, 0.45 to 0.92]; p ≤ 0.014; range of HRs for disease-free interval, 0.64-0.72 [95% CI, 0.47 to 0.98]; p ≤ 0.037). Cut points were determined using X-tile, a graphical method that has been used in breast cancer research. However, among the subgroup of 224 patients who were HER2-positive by IHC and FISH, associations between HER2 heterodimers and patient outcomes were not statistically significant, regardless of trastuzumab therapy. In a follow-up study, Green et al. (2014) showed that HER2/HER3 heterodimers were significantly associated with shorter BCSS among unselected estrogen receptor-positive patients, but not among estrogen receptor-negative patients. Among the subset of HER2-positive patients, there was no association between HER2/HER3 heterodimers and BCSS in estrogen receptor-positive or -negative patients who had or had not received trastuzumab.

Montemuro et al. (2014) measured H2T in patients with HER2-amplified metastatic breast cancer. Of the original cohort (N = 19), H2T was measured in 16 patients. HER2 status was determined by testing with IHC and FISH; cut points for defining levels of H2T were not prespecified. Focusing on analysis of H2T, authors noted that increasing log (H2T) was correlated with a corresponding increase in persistence in protocol (HR = 0.73 per 2-fold increase; p = 0.046). The study was limited by the small sample size. Subgroup analysis in patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Yardley et al. (2015) in their retrospective multicenter study examined the correlation of results obtained by various HER2 methods with OS of breast cancer patients. Testing for HER2 status was completed both at individual institutions (IHC, FISH) and centrally (IHC); patients with positive, negative, and equivocal HER2 status were included. Of the original cohort (N=232), H2T was reported for 194 patients. The authors used a predefined, published HERmark clinical cutoff (13.8 RF/mm²) to define H2T levels as H2Tlow and H2Thigh in OS analysis. Kaplan-Meier analysis was performed in cases that had HER2 testing results and available survival data (177 cases with local IHC, 188 cases with central IHC, 65 cases with local FISH, 190 cases with local HER2 status, 190 cases with HERmark). OS analysis revealed a significant correlation between shorter OS and HER2 positivity by local IHC (HR = 2.6, p = 0.016), central IHC (HR = 3.2, p = 0.015), and HERmark (HR = 5.1, p < 0.001) in this cohort of patients. The OS curve of discordant low (HER2 positive but H2Tlow, 10% of all cases) was aligned with discordant negative (HER2 negative and H2Tlow, HR = 1.9, p = 0.444), but showed a significantly longer OS than discordant positive (HER2 positive and H2Thigh, HR = 0.31, p = 0.024). Conversely, the OS curve of
discordant high (HER2 negative but H2T high, 9% of all cases) was aligned with concordant positive (HR=0.41, p=0.105), but showed a significantly shorter OS than concordant negative (HR=41, p<0.001). Most patients with HER2 positive tumors (78%) were not given HER2-targeted therapy, limiting conclusions relating to treatment response in patients with discordant test results; further limitations include the small population of the study.

Scaltriti et al (2015) examined H2T in patients with HER2 overexpressing and/or amplified invasive breast cancer. Drawing from the cohort (N =455) identified in the NeoALTTO phase III study, H2T was reported for 324 patients. Cut points for defining levels of H2T were prespecified. Focusing on analysis of H2T, improved pathologic complete response is associated with high H2T. Use of Cox models to predict progression-free survival demonstrated that log2(H2T) correlated with longer progression free survival (HR 0.66, p = 0.01). Further modeling suggests that patients with high H2T benefited most from combination treatment with lapatinib and trastuzumab, compared to trastuzumab alone. Subgroup analysis in patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Duchnowska et al (2017) examined H2T in patients with HER2 positive advanced breast cancer who demonstrated progression on trastuzumab; these patients were subsequently treated with lapatinib plus capecitabine. Testing for HER2 status was not described. Of the 189 patients in the original cohort, H2T was successfully measured for 182 patients. Cut points for defining levels of H2T were not uniformly prespecified. For patients with overexpression of H2T, overall survival was inversely correlated with H2T (HR: 1.9; p=0.009); the authors state that a U-shaped parabolic function could describe the relationship between H2T and overall survival (p = 0.004). Population selection and duration of follow up was not reported. Subgroup analysis in patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

Chumsri et al (2017) examined H2T in patients with HER2-positive metastatic breast cancer. Of the 91 patients in the original cohort, consisting of patients from three separate trials, H2T was reported for all patients. Cut points for defining levels of H2T were prespecified. While prior testing had established that all patients in this population were HER2-positive by IHC or ISH testing, 10% of patients had equivocal H2T results and 18% had negative H2T results. This was attributed in several cases to use of different tissue samples for H2T testing compared to IHC/ISH testing, and to tumor heterogeneity. Increasing H2T was correlated with longer overall survival of patients (HR: 0.33; p = 0.002). Subgroup analysis in patients with equivocal or discordant HER2 tests by IHC or ISH was not performed.

**Section Summary: Clinically Valid**
Retrospective studies have reported an association between H2T levels and survival outcomes. However, these studies are limited by variability in cutoff points used to define patient groups. Analysis of H2T testing in patients with equivocal or discordant HER2 test results by IHC or ISH was performed in one retrospective study; however, the majority of patients did not receive HER2-specific therapy, limiting findings. Further studies are needed to assess the ability of the test to reclassify patients.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. Data on the clinical utility of HERmark are lacking.
Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to
demonstrate test performance, no inferences can be made about clinical utility.

Summary of Evidence
For individuals who have breast cancer and are undergoing assessment of HER2 status who
receive quantitative total HER2 protein expression and HER2 homodimer measurement,
the evidence includes validation studies and retrospective analysis of the association between
levels and survival outcomes. Relevant outcomes are overall survival, disease-specific survival,
test accuracy, and test validity. Retrospective analysis using HERmark have shown that the assay
may predict a worse response to trastuzumab in certain populations. However, findings have
been inconsistent, and no clear association with clinical outcomes has been shown.
Additionally, cut points for defining patient groups varied across studies. Clinical utility of the
HERmark assay has not been demonstrated. The evidence is insufficient to determine the effects
of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
National Comprehensive Cancer Network guidelines on the treatment of breast cancer
(v.3.2018) do not address the use of HERmark.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage
determination, coverage decisions are left to the discretion of local Medicare carriers.
Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular
diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada,
Hawaii). Palmetto GBA’s decisions apply for all molecular diagnostic tests for Medicare.
Palmetto GBA has assessed HERmark and determined that the test meets criteria for analytic
and clinical validity and clinical utility as a reasonable and necessary Medicare
benefit. Effective December 9, 2011, Palmetto GBA will reimburse HERmark services for patients
with breast cancer.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in October 2018 did not identify any ongoing or unpublished trials
that would likely influence this review.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.76

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<tr>
<th>Category</th>
<th>Addressed</th>
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</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
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<tr>
<td>1a. Diagnostic</td>
<td></td>
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<tr>
<td>1b. Prognostic</td>
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<tr>
<td>1c. Therapeutic</td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
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<tr>
<td>2a. Diagnostic</td>
<td></td>
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<tr>
<td>2b. Prognostic</td>
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<tr>
<td>2c. Therapeutic</td>
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<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
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<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
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<tr>
<td>5. Reproductive testing</td>
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<tr>
<td>5a. Carrier testing: preconception</td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
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<tr>
<td>5c. In utero testing: aneuploidy</td>
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</tr>
</tbody>
</table>
5d. In utero testing: familial variants
5e. In utero testing: other
5f. Preimplantation testing with in vitro fertilization

References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<td>84999</td>
<td>Unlisted chemistry procedure</td>
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<tr>
<td>HCPCS</td>
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<tr>
<td>ICD-10 Procedure</td>
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</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.