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

Policy Number: 2.04.76  Last Review: 12/2016
Origination: 12/2015  Next Review: 12/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
The assessment of HER2 status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational.

Considerations
There is no specific CPT code for this testing. It would likely be reported using CPT code 84999 - Unlisted chemistry procedure.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Individuals: ▪ With breast cancer who are undergoing assessment of HER2 status</td>
<td>Interventions of interest are: ▪ Assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement</td>
<td>Comparators of interest are: ▪ Assessment of HER2 status using immunohistochemistry or fluorescence in situ hybridization</td>
<td>Relevant outcomes include: ▪ Overall survival ▪ Disease-specific survival ▪ Test accuracy ▪ Test validity</td>
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</table>

Novel assays that quantitatively measure total HER2 protein expression and homodimers have been developed in an effort to improve the accuracy and consistency of HER2 testing.
The evidence for assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement in patients who have breast cancer and are undergoing assessment of HER2 status includes validation studies and retrospective analysis of 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, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark® assay. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

The 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 (DFS) and overall survival (OS), 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 DFS and OS 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.(1)

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 relationship 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.(2) 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 [CISH]).

Normally, HER2 activates signaling pathways by dimerizing with ligand-bound EGFR-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; Monogram Biosciences, South San Francisco, CA) was developed to quantify total HER2 protein expression (H2T) and HER2 homodimers (H2D) in formalin-fixed, paraffin-embedded (FFPE) tissue samples.

Rationale
This evidence review was created in 2011, with the most recent MEDLINE literature search performed through November 12, 2015.

Validation of biomarker assessment to improve treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Analytic validity**: measures technical performance, ie, whether the test accurately and reproducibly detects the biomarker of interest.
- **Clinical validity**: measures the strength of the associations between the selected biomarkers and clinical status.
- **Clinical utility**: determines whether the use of specific biomarker assessments to guide treatment decisions improves patient outcomes such as survival or adverse event rate compared with standard treatment without genotyping.

Analytic Validity
The HERmark® assay uses a proprietary, proximity-based platform (proximity ligation assay) to measure total human epidermal growth factor receptor 2 (HER2) HER2 protein (H2T) expression and HER2 homodimers (H2D). Antibody binding to HER2 and other HER proteins releases fluorescent reporter tags (VeraTag™, Monogram Biosciences). Proximity of a bound HER2 antibody to a different bound HER antibody indicates an H2T; proximity of 2 bound HER2 antibodies indicates an H2D. Quantification of fluorescence permits quantification of H2T and H2D.

The HERmark® assay is currently commercially available only for quantification of H2T and H2D in breast cancer. The company plans to validate use of the HERmark® test to measure HER heterodimers. The company website indicates that assays currently are available for HER2:HER1 and HER2:HER3 heterodimers; these apparently are for use in drug development.(3)
HER2 protein quantification was normalized to tumor area and compared with receptor numbers in 12 human tumor cell lines (determined by fluorescence-activated cell sorting and standard immunohistochemistry [IHC]) and to IHC categories in 170 human breast tumors. In contrast to conventional IHC test categories, HER2 protein levels determined by the VeraTag™ assay represent a continuous measurement over a dynamic range greater than 2 log₁₀, and HER2 homodimer levels were consistent with crosslinking and immunoprecipitation results.

Huang et al (2010) compared results of the HERmark® assay with those of IHC and fluorescence in situ hybridization (FISH) centrally performed at the Mayo Clinic in 237 archived formalin-fixed, paraffin embedded (FFPE) breast cancers. IHC had already been performed at the time of initial diagnosis in all of the cases but was repeated for the purpose of this validation, and interpreted by 1 reviewer and scored as negative, equivocal, or positive according to the American Society of Clinical Oncologists/College of American Pathologists guidelines. Reflex FISH for HER2 gene amplification also had been performed at the time of initial diagnosis on all 94 of the IHC 2+ cases. Repeat FISH was performed at the same laboratory and an overall evaluation performed by 1 pathologist. Of the 84 cases in the immunohistochemically negative subgroup, 80 (95%), 2 (2%), and 2 (2%) were classified as negative, equivocal, and positive by HERmark®, respectively. Of the 101 cases in the immunohistochemically equivocal subgroup, 33 (32.7%), 31 (30.7%), and 37 (36.6%) were classified as negative, equivocal, and positive by HERmark®, respectively. Of the 52 cases in the immunohistochemically positive subgroup, 1 (2%), 3 (6%), and 48 (92%) were classified as negative, equivocal, and positive by HERmark®, respectively. Overall concordance was 67%, with a weighted κ of 63% (95% confidence interval [CI], 55% to 70%). When equivocal cases were excluded from the HERmark® and IHC results, positive and negative concordance between HERmark® and central IHC testing was 98%, and overall concordance was 98%, with a κ of 95% (95% CI, 89% to 100%).

Reflex FISH was performed on 94 breast cancers that had been determined as 2+ immunohistochemically at the time of initial diagnosis. Variable H2T and H2D levels were correlated with corresponding results for the HER2/centromeric probe for chromosome 17 (HER2/CEP17) ratio. Of 94 cases that were 2+ immunohistochemically, 62 (66%), 5 (5%), and 27 (29%) were determined at the same central laboratory as negative (<10.5), equivocal (10.5 ≤H2T ≤17.8), and positive (>17.8) by FISH, respectively. (Units of H2T measurement are relative fluorescence [defined as relative peak area □ illumination buffer volume] per mm² of invasive tumor [RF/mm²].) Of 62 FISH-negative cases, 24 (39%), 21 (34%), and 17 (27%) were determined as negative, equivocal, and positive by HERmark®, respectively. Of 5 FISH-equivocal cases, 1 (20%), 2 (40%), and 2 (40%) were determined as negative, equivocal, and positive by HERmark®, respectively. Of 27 FISH-positive cases, 3 (11%), 6 (22%), and 18 (67%) were determined as negative, equivocal, and positive by HERmark®, respectively.
Clinical Validity
Bates et al (2011) measured H2T in FFPE primary breast tumors from 98 women treated with trastuzumab-based therapy for metastatic breast cancer.(6) 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 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.

Joensuu et al (2011) reported results of measurement of H2T using HERmark® from formalin-fixed tumor tissue of 899 women (89%) 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.(7) In a chromogenic in situ hybridization (CISH) test, 197 patients (21.9%) had HER2-positive cancer and were randomly assigned to receive 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). 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 compared with those whose cancer has more moderate HER2 content.

Toi et al (2010) investigated the relationship 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.(8) Patients were originally selected for treatment with trastuzumab by 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). Median duration of trastuzumab treatment was 14.6 months. Overall 2-year survival was 60.8% (95% CI, 48.4% to 73.2%). 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 substantially lower risk of death than the middle 2 subgroups. Dividing the cohort into high HER2-expressing (≥ the median value of H2T) and low HER2-expressing (< 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 are 2 subpopulations of patients in this cohort that behave 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.

Lipton et al (2010) used the HERmark® assay to quantify HER2 expression and examined outcomes in 102 trastuzumab-treated metastatic breast cancer patients previously assessed as IHC 3+ by local but not central IHC, or FISH-positive, and then retested by central FISH.(9) Of 102 metastatic breast cancer patients previously scored as IHC 3+ or 2+/FISH-positive and treated with trastuzumab-containing regimens, 98 had both central FISH and H2T values. 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 (discordant H2T low). The concordant 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 concordant 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.

In a subsequent retrospective analysis of this cohort, Lipton et al (2013) examined progression-free survival (PFS) and OS in subgroups defined by expression of HER3 (H3T) and p95HER2 (p95), a truncated form of HER2 that does not bind trastuzumab and is a marker of trastuzumab resistance.(10) HER3 and p95 were quantified using VeraTag™ platforms. Results of H3T analysis were available from 89 patients; of these, 61 (69%) were H2T-high (>13.8). Within this group, median PFS was 12.1 months in patients with low H3T (≤3.5) and 5.0 months in patients with high H3T (>3.5; HR=2.7; p=0.002). Median PFS in patients with low H2T (<13.8) was 4.2 months. No significant difference in OS was observed among any groups. In exploratory analysis using regression tree analysis (recursive
partitioning), the first split of the tree was based on a H2T cutoff of 16.1, separating patients with low HER2 expression (H2T <16.1) from those with high HER2 expression (H2T ≥16.1). Patients were next segregated by intermediate HER2 expression (16.1 ≤H2T ≤68.3) versus very high HER2 expression (H2T >68.3). H2T cutoffs of 16.1 and 68.3 to define low, intermediate, and high groups were found to have greater discrimination. Median PFS (15.7 months) and OS (47.6 months) were longest in the subgroup characterized as H2T-intermediate (16.1 ≤H2T≤68.3), H3T-low (≤3.89), and p95 low (≤3.75), compared with other groups (median PFS range, 4.0-7.8 months; median OS range, 23-27 months). In the entire group of HER2-positive, trastuzumab-treated patients, low (normal) H2T (≤16.1) and very high H2T (>68.3) were correlated with shorter PFS and OS. A subsequent study that used VeraTag™ to quantify p95HER2 found significantly shorter PFS and OS among H2T-positive, hormone receptor-positive, trastuzumab-treated patients with high p95, using a different cutoff of 2.8.(11) This association was not found among hormone receptor-negative patients.

Han et al (2012) performed a similar retrospective analysis in 52 women with locally advanced or metastatic HER2-positive (3+ on IHC or gene amplification by FISH) breast cancer that had progressed after treatment with an anthracycline, a taxane, and trastuzumab.(12) Patients were treated with lapatinib and capecitabine until disease progression or intolerance. 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).

Duchnowska et al (2012) investigated the correlation between H2T in primary breast cancers and time-to-brain metastasis (TTBM) in HER2+ advanced breast cancer patients treated with trastuzumab.(13) The patient sample included 142 consecutive patients who were administered trastuzumab-based therapy for HER2+ metastatic breast cancer. 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) was 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+, 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). 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+ 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.

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 (DFI). (14) 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 DFI compared with low levels (range of HRs for BCSS, 0.62-0.66 [95% CIs, 0.45 to 0.92]; p values ≤0.014; range of HRs for DFI, 0.64-0.72 [95% CIs, 0.47 to 0.98]; p values ≤0.037). Cut points were determined using X-tile, a graphical method that has been used in breast cancer research. (15) However, among the subgroup of 224 patients who were HER2-positive by IHC/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. (16) 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.

**Section Summary: Clinical Validity**

Retrospective studies report an association between H2T levels and survival outcomes. However, for these analyses, different cut points were used and results varied (see Table 1).

<table>
<thead>
<tr>
<th>Table 1. Summary of Studies of HERmark® Clinical Validity</th>
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<tr>
<td><strong>Reference</strong></td>
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<td></td>
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<tr>
<td>Bates (2011)</td>
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<tr>
<td>Joensuu (2011)</td>
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<td>Toi (2010)</td>
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</tbody>
</table>
HER2-expressing group
- Patients with lower H2T values live longer than those with higher H2T values in the low HER2-expressing group

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>H2T Thresholds</th>
<th>Lipton (2010)</th>
<th>Better response to trastuzumab at higher levels of HER2 total expression observed</th>
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<tr>
<td>Lipton (2013)</td>
<td>&lt;16.1</td>
<td>&gt;68.3</td>
<td>Low H2T and high H2T correlated with shorter PFS and OS</td>
</tr>
<tr>
<td>Han (2012)</td>
<td>&lt;13.8</td>
<td>≥13.8</td>
<td>TTP was longer in patients with high H2T than in patients with low H2T</td>
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<tr>
<td>Duchnowska (2012)</td>
<td>&lt;58c</td>
<td>≥58c</td>
<td>Correlation between a continuous H2T level and TTBM was confirmed on multivariate analysis</td>
</tr>
<tr>
<td>Barros (2014)</td>
<td>Per specific heterodimer studied</td>
<td>Low heterodimer levels favored among unselected patients; no association observed among trastuzumab-treated or -naive HER2-positive patients</td>
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</table>

Clinical Utility
Data on the clinical utility of HERmark® are lacking. Clinical trials are needed to understand the relationship between quantitative HER2 expression and homodimer measurements with clinical outcomes in breast cancer patients stratified by the HERmark® assay receiving anti-HER2 therapy in the adjuvant and metastatic settings.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in October 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for assessment of HER2 status using quantitative total human epidermal growth factor receptor 2 (HER2) protein expression and HER2 homodimer measurement in patients who have breast cancer and are undergoing assessment of HER2 status includes validation studies and retrospective analysis.
of 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, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark® assay. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network Guidelines on the treatment of breast cancer (v.3.2015) do not address the use of HERmark®.(17)

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, 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 completed an assessment of HERmark® and determined that the test meets criteria for analytic and clinical validity, and clinical utility as a reasonable and necessary Medicare benefit.(18) Effective December 9, 2011, Palmetto GBA will reimburse HERmark® services for patients with breast cancer.

References:


**Billing Coding/Physician Documentation Information**

**84999**  Unlisted chemistry procedure

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

12/1/15  New policy; considered investigational.

12/1/16  No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating healthcare providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.