Name of Policy: Biomarker Genes for Detection of Lymph Node Metastases in Breast Cancer

Policy #: 385
Category: Medicine

Latest Review Date: January 2013
Policy Grade: Effective 02/01/2013-
Active Policy but no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:
1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
Assessing the presence of tumor in axillary lymph nodes of patients with breast cancer is an important aspect in clinical staging of the disease. In addition, the presence of tumor is assessed in sentinel lymph nodes to help determine the extent of lymph node dissection that is needed. Patients with negative findings in the sentinel nodes have a low risk of having other nodes with positive findings and thus can often be spared the morbidity associated with a full axillary lymph node dissection (ALND). Currently, the presence of tumor is identified through traditional pathologic examination using frozen section or touch preparations at the time of surgery as well as the gold standard postoperative histologic examination of formalin-fixed tissue (permanent section) using hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC). If lymph nodes are found positive for metastases by intraoperative assay, ALND is done immediately. If positive findings are not detected until after histopathologic review of a permanent section, a second surgery for full ALND follows. When compared with final permanent histology results, intraoperative frozen section analysis of the sentinel lymph node has a reported sensitivity that varies from 58%–87%.

To improve the accuracy of current methods, newer techniques that yield reliable intraoperative results are being sought. One method identifies metastatic cells by detecting RNA transcribed from genes expressed at high levels in cells of breast origin but only at low levels in normal nodal tissue. Cytokeratin-19 and mammaglobin are two markers that have been studied. These genes are expressed at higher levels in breast tissue, but not in normal nodal tissue. These assays are being proposed as an alternative to the standard intraoperative use of frozen section for sentinel lymph nodes.

The only assay currently approved by the U.S. Food and Drug Administration (FDA) is the GeneSearch™ BLN Test Kit (Veridex, LLC). GeneSearch™ received premarket application approval from the FDA on July 16, 2007, for the “detection of greater than 0.2 mm metastases in nodal tissue removed from sentinel lymph node biopsies of breast cancer patients.” The product information notes that “Post-operative histological evaluation of permanent sections of the tissue specimen, in accordance with usual diagnostic practice and using the Veridex lymph node cutting scheme [alternating sections of <3 mm], is required.” The assay uses real-time polymerase chain reaction (RT-PCR) to qualitatively evaluate nodal sections for the presence of mammaglobin and cytokeratin 19 genes. The assay is automated and performed in a homogeneous, one-step, fully contained reaction; test results are available in about 35 to 40 minutes. The assay cutoff for positivity is designed to allow detection of metastases that are larger than 0.2 mm in size; however, the assay does not discriminate between micrometastases (i.e., between 0.2 mm and 2 mm) and macrometastases (i.e., larger than 2 mm).

On January 14, 2010, it was announced that Veridex had stopped selling the GeneSearch test in the U.S. and European markets due to “relatively low adoption.”
**Policy:**
**Evaluation of biomarker genes does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for detection of lymph node metastases in patients with breast cancer.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
**GeneSearch™**
The objective of a 2007 TEC Assessment was to evaluate the intraoperative use of the GeneSearch™ BLN assay in detecting early-stage breast cancer metastases in the sentinel lymph nodes compared to 1) postoperative histology or 2) other commonly used intraoperative evaluation methods, namely, intraoperative frozen section histology or imprint cytology.

Published studies provide evidence on the performance of the GeneSearch™ assay; additional information includes the manufacturer’s submissions to the FDA and other materials from the meeting of the Immunological Devices Panel meeting on November 16, 2006. One of the published studies reports on 416 subjects from 11 sites in the United States. Patients were diagnosed with breast cancer and were 18 years or older and were scheduled for sentinel lymph node biopsies. The GeneSearch™ assay was performed alongside other tests commonly used at each facility; the GeneSearch™ results were not used for clinical management. The assay was compared to a reference standard, postoperative histology (primary study outcome), and to other intraoperative techniques that were routinely conducted by the participating institution, namely, frozen section histology and imprint cytology. Among the 416 patients with postoperative histology results, 29.1% had positive lymph nodes for metastases, with a range across sites of 14.3% to 45.5%.

Compared to the reference standard, the sensitivity of the GeneSearch™ assay was 87.6% (95% CI: 80.4–92.9%); the specificity was 94.2% (95% CI: 90.9–96.6%); the positive predictive value was 86.2% (95% CI: 78.8–91.7%); and the negative predictive value was 94.9% (91.7–97.1%). The sensitivity was higher (97.9%; 95% CI: 92.5–99.7%) for patients with macrometastases than for those with micrometastases (56.5%; 95% CI: 34.5–76.8%). The authors assert that the false-positive rate may be lower than reported, because the results may be based on examination of parts of the lymph node that contain metastases, while the postoperative histology slides may come from a different slice of the node without metastases, i.e., differences may be due to sampling distinct parts of the lymph node. While the researchers provide suggestive evidence, further research is needed to confirm or deny this hypothesis.
The other published study included data from a beta trial to determine threshold levels of mammaglobin and cytokeratin 19 correlating with metastases larger than 0.2 mm.

The study presented to the FDA has a number of strengths, including the clear distinction between the training and test sets and double-reading of the permanent histology slides to increase the reliability of the reference standard. However, a number of weaknesses are present as well, such as lack of description regarding patient recruitment; substantial variation in assay performance across sites; lack of corroborating studies; inability of the assay to distinguish between micro- and macrometastases; and a learning curve for those performing the assay.

The key factor in assessing this assay is the tradeoff between avoiding a second surgery to remove axillary lymph nodes if the sentinel node is positive versus risking unnecessary ALND if the assay produces a false positive result. The reason sentinel lymph node biopsy is the standard of care in early breast cancer, in spite of the fact that trials on its impact are still incomplete, is the desire to avoid ALND when possible, given the potential for significant, long-term morbidity. While the researchers conducting the GeneSearch™ study suggest that many of the false-positive assay results detect real metastases in the additional sections of the node used for the assay, the evidence presented to support this argument is insufficient. Given that GeneSearch™ was not used for patient treatment decisions in this study, longer term follow-up of patients with false-positive test results to see if and when axillary metastases develop might be informative, although the utility of this approach may be compromised by the small number of patients involved.

As for avoiding a second surgery and undergoing an unnecessary ALND, patient preferences should play an important role in this decision. The FDA is requiring informed consent for participants in one of the postmarketing studies. Although the number of unnecessary ALNDs is substantially smaller than the number of second surgeries avoided, the “harms” from the former are more common and generally longer lasting than those associated with needing a second surgery. The sequelae of ALND can last for years or even a lifetime. The inconvenience of a second surgery, while difficult for patients coping with a serious diagnosis and substantial course of treatment, is likely to be short lived. For these women, the harms of ALND are unavoidable.

As for how the sensitivity and specificity of intraoperative use of GeneSearch™ during sentinel lymph node biopsy compare to those of alternative intraoperative tests (i.e., imprint cytology and frozen section histology), the test set data provided to the FDA are useful, as they provide a direct comparison of the tests in the same patients. Several concerns, however, are outlined below:

1. The comparison of GeneSearch™ to alternative, intraoperative tests was not planned; not all study sites performed such tests.
2. The sample size of 29 for the imprint cytology comparison is too small to be meaningful.
3. The alternative tests were not conducted with the rigorous double-reading, review by central laboratory pathologists, and reconciliation of discrepancies applied to the reference standard.
4. The statistical approach to evaluating the difference in the test characteristics between GeneSearch™ and frozen section histology is not well described.

The focus here is on which technique—the assay, frozen section histology, or imprint cytology—performs best at avoiding second surgeries versus undergoing unnecessary ALND. The data on imprint cytology are inadequate and will not be discussed further. Also, evidence is inadequate to determine whether the GeneSearch™ assay outperforms frozen section histology. However, a receiver operating characteristic (ROC) analysis conducted by the FDA suggests that the GeneSearch™ assay and frozen section histology operate at different points on the same or very similar ROC curves. If this is correct (the analysis is not sufficiently detailed to assess this), then the question is not whether one technique is better than the other overall, but what the optimal tradeoff (and therefore assay cutoff) is between false-positive and false-negative results. Given the longer term and potentially more serious sequelae from ALND than from a second surgery, increasing the sensitivity of the test while sacrificing some specificity, as the GeneSearch™ assay does, may not be optimal.

The GeneSearch™ assay also provides less information for staging than other intraoperative procedures, since it cannot distinguish between micro- and macrometastases. Nor can it indicate the location of the metastasis (inside or outside of the node). Postoperative histology is, therefore, required in all cases. It is less crucial when frozen section histology is performed, since pathologists can judge the size of the metastasis and its location from this test, although distortion is possible.

In summary, the data available are inadequate to assess the clinical utility and the impact on health outcomes of the GeneSearch™ assay compared to either postoperative histology alone or to alternative intraoperative tests such as imprint cytology and frozen section histology. In addition, the balance of benefits versus harms may require higher specificity to avoid unnecessary ALNDs and their sequelae, whereas the GeneSearch™ design emphasizes sensitivity. Patient preferences should also play a key role in this calculation.

Therefore, based on the above concerns regarding the single, published study for GeneSearch™, its use at this time is considered investigational.

Other Assays
Several published reports from European centers describe the use of similar tests. Berger and colleagues reported on sensitivity and specificity of cytokeratin-19, mammmoglobin, and DNA methyltransferase 3b (alone and in combination) in the evaluation of 290 axillary lymph nodes from 29 patients with breast cancer. Compared to standard histology, sensitivity of the individual markers varied, with mammmoglobin at 68% and cytokeratin-19 at 96%. Dell’Orto et al reported on results from qualitative and quantitative assays of mammaglobin1 mRNA in evaluating sentinel lymph nodes. In the validation sample, the quantitative assay had a sensitivity of 75% and specificity of 95% compared to standard histopathology.

At the present time, given the lack of FDA approval for these other assays, and the limited published information about these tests, their use is considered investigational.
GeneSearch™
Martin Martinez et al published the results of a prospective study validating the use of the GeneSearch™ assay at their institution to detect the presence of metastases larger than 0.2 mm. The study included 123 sentinel lymph nodes from 78 patients who underwent surgical lumpectomy and sentinel lymph node biopsy. Sentinel lymph nodes were analyzed by the GeneSearch™ assay and postoperative histology (H&E and IHC). The pathologist examining the postoperative H&E and IHC was blinded to the assay results. Thirteen cases were considered sentinel lymph node positive (metastasis larger than 0.2 mm) based on histology and 14 based on the assay. Of the 14 assay-positive cases, 2 were negative when assessed histologically. Conversely, 1 case that was negative by the assay, showed a micrometastatic focus (0.25 mm) with IHC. The assay results corroborated with the histologic results in 75 of 78 patients for an overall agreement of 96%, sensitivity of 92%, and specificity of 97%. Positive and negative predictive values of the assay were 86% and 98%, respectively. No patient management decisions were made based on the GeneSearch™ assay results.

Viale et al prospectively assessed the accuracy of the GeneSearch™ assay by evaluating a series of 293 consecutive sentinel lymph nodes from 293 patients. Assay results were compared to intraoperative histologic examination of the entire sentinel lymph node performed on serial frozen sections that were H&E stained (with IHC when deemed necessary). All of the interval tissue not examined histologically was subjected to the assay. Seventy-two (24.6%) of the sentinel lymph nodes were involved with histologically identifiable metastases. The assay was positive in 67 sentinel nodes; in 56 cases, the results correlated with positive histology, whereas, in 11 cases, the histologic examination of the sentinel lymph node did not show evidence of metastatic disease, even with the addition of IHC. Five of the 11 possible false positive cases were further analyzed with additional tumor mRNA markers, and 2 of 5 (40%) were confirmed to be positive (true positives). The assay correctly identified 98.1% of macrometastases and 25% of micrometastases. Overall concordance with histopathology was 90.8%, with sensitivity of 77.8%, specificity of 95%, positive predictive value of 83.6%, and negative predictive value of 92.9%.

Mansel et al prospectively examined 124 sentinel lymph nodes from 82 breast cancer patients, with 50% of each node analyzed by the GeneSearch™ assay and compared to H&E and IHC results. The assay correctly identified all 6 patients with sentinel lymph node macrometastatic disease and 2 of 3 with micrometastatic disease. Two of 4 sentinel nodes positive by the assay but negative by histology turned out to contain isolated tumor cells. Overall concordance with histology was 93.9%, with a sensitivity of 88.9%, specificity of 94.6%, positive predictive value of 66.7%, and negative predictive value of 98.6%. No patient management decisions were based on the assay results.

Other Assays
Visser et al compared a quantitative cytokeratin 19 (CK19) mRNA one-step nucleic acid amplification technique (OSNA-CK19) to histologic staining (H&E and IHC) in 346 axillary lymph nodes from 32 patients, using one-half of each node for each method. Sixty-one nodes were positive and 267 were negative by both methods. Three cases were positive by histology but negative by OSNA-CK19. Fifteen samples were negative by histology but positive by OSNA-CK19. Seven of the 15 cases were positive for other epithelial markers by RT-PCR.
and/or Western blot, suggesting that they were true positives. Overall concordance with histology was 94.8%, and 96.8% after exclusion of the 7 discordant cases. Sensitivity was 95.3% and specificity was 94.7% before and 97.1% after the discordant case investigation.

A recent editorial highlights the ongoing difficulties with using molecular techniques to detect metastases in sentinel lymph nodes that include 1) the uncertainty of the clinical significance of RT-PCR-positive but histologically and immunohistochemically negative sentinel lymph nodes; 2) the issue of possible false positives with a test as sensitive as RT-PCR; 3) the exact size of the metastasis cannot be determined because the tissue is digested in preparation for RT-PCR; and 4) the possibility that the assay is detecting small amounts of benign epithelial cells in the lymph node instead of metastatic carcinoma. What is still not clear is the clinical utility of using molecular methods to detect sentinel lymph node metastases in making patient management decisions.

2010 Update

GeneSearch™

Veys et al reported 18 months of experience with the GeneSearch™ assay at their institution. From November 2006 to January 2008, 253 consecutive patients with early stage breast cancer (tumor less than 2 cm and clinically negative axillary lymph nodes) were treated with breast-conserving surgery and sentinel lymph node biopsy. Of 435 nodes, 295 highly radioactive nodes (68%) from 253 patients were analyzed intraoperatively with the GeneSearch™ assay, and the results were compared to postoperative histology. The lymph nodes were submitted in their entirety, with alternating sections submitted for the GeneSearch™ assay and standard postoperative histology (which at their institution consisted of at least 1 H&E section and additional H&E sections plus immunohistochemistry if the initial H&E section was negative for tumor). Overall concordance for the GeneSearch™ assay with histopathology was 93%, with 87% sensitivity and 94% specificity. The sensitivity of the assay was dependent on the size of the metastasis with 89–100% of macrometastases detected by the assay versus 70–80% of micrometastases. Lymph node metastases were detected in 52 of the 253 patients by the assay versus 45 by standard histology. Thirteen percent of cases with metastases at least 0.2 mm in size detected by postoperative histology were negative by the assay. The percentage of patients with a positive assay but negative histology was 6% (n=13). These 13 patients underwent full axillary lymph node dissection based on the GeneSearch™ assay results, and 2 of the 13 were found to have nonsentinel lymph node metastases. No nonsentinel lymph node metastases were observed in the cases with histology-positive but assay-negative sentinel lymph nodes (n=5). Based on this, the authors did not consider assay-positive but histology-negative cases to be false positives.

Other Assays

Schem et al reported results comparing one-step nucleic acid amplification (OSNA) to routine histopathologic investigation in 343 non-sentinel axillary lymph nodes in 93 breast cancer patients. Lymph nodes were derived from completion axillary dissections performed because of a previously positive sentinel lymph node, or because the patient had a clinically positive lymph node. Lymph nodes were sampled with alternate slices allocated to the OSNA method or to histologic workup at five levels through the node. Of the 343 nodes, 211 were negative by both methods (which included two cases with isolated tumor cells) and 104 samples were positive.
with both methods. Discordant results were observed in 28 nodes, with 2 cases of OSNA negative/histology positive cases (both micrometastases) and 26 cases that were OSNA positive/histology negative. Discordant samples were subjected to further investigation including additional histologic workup, and Western Blot and quantitative RT-PCR on a different section of the lymph node. If these results gave the same result as the OSNA assay, they were not considered to be discordant cases. After discordant case investigation was performed, both of the OSNA negative/histology positive cases and 11 of the 26 OSNA positive/histology negative samples showed similar results to the OSNA assay. The authors no longer considered these to be discordant cases, and the concordance rate was 95.5% with a sensitivity of 100% and a specificity of 96.5% (before exclusion of these cases, concordance, sensitivity, and specificity were 91.8%, 98.1%, and 90.8%, respectively).

Several shortcomings were commented on in a letter to the editor, including that quantitative analysis of tumor is not possible using the authors’ methods because no calibration experiments were performed for the OSNA assay, that there is lack of information about the reproducibility of the test, and importantly, that the study suffers from a lack of gold standard to evaluate the sensitivity and specificity of the technique to detect tumor cells. The letter states that the current gold standard is histologic proof of tumor, and that if this had been accepted as the gold standard in the study, an intolerable rate of discordance would have been the result, with a false positive rate of 7.3% and a false negative rate of 1.2%. The letter also questioned the evidence to support the authors’ justification for discordant results to be the result of sampling bias.

2011 Update

GeneSearch™
Liu et al reported the results of a prospective clinical feasibility study of the GeneSearch BLN assay in 158 sentinel lymph nodes from 97 patients in China. Alternating slabs from the sentinel lymph nodes were prepared for intraoperative BLN assay testing. The results were compared to intraoperative imprint cytology and postoperative permanent section histopathology which consisted of examining alternating 1.5 to 3 mm slabs of the nodes by H&E. Overall, 31 of the 97 patients (32%) had sentinel lymph node metastases identified by histology, 20 of which were macrometastases (>2 mm) and 11 of which were micrometastases (0.2-2.0 mm). All of the patients with macrometastases were identified with the BLN assay, and 6 of 11 (54.5%) of the sentinel lymph nodes with micrometastases were detected by the assay. Overall, the BLN assay, compared with permanent section histopathology, had a sensitivity of 84%, specificity of 95.5%, positive predictive value of 90%, negative predictive value of 93%, and overall agreement of 92%. There were 5 cases of negative BLN assay/histology positive and 3 cases with positive BLN assay/histology negative. Eighty-six patients underwent complete axillary lymph node dissection after sentinel lymph node biopsy in the same surgery or in a second surgery. Non-sentinel lymph node metastases were detected in 16 (18.6%) patients, 14 of which were macrometastases and 2 of which were micrometastases. The BLN assay was positive in the sentinel lymph nodes of 66.7% of patients who were non-sentinel-lymph-node-positive and positive in 25.8% of patients without further axillary involvement.

Funakoso et al evaluated the clinical application of the GeneSearch assay in one Japanese institution in 117 patients with 204 sentinel lymph nodes. One-half of each node was examined with the GeneSearch assay and the other half by H&E and immunohistochemistry (IHC) for
pancytokeratin. H&E staining identified metastases in 31 of 204 sentinel lymph nodes (15.2%). A total of 173 sentinel lymph nodes without metastases detected by H&E staining were stained with IHC and an additional 6 sentinel lymph nodes were found to have metastases, all of which were isolated tumor cells. The sensitivity of the assay correlated with H&E and IHC 96% for macrometastases, 60% for micrometastases, and 56% for isolated tumor cells. Ten sentinel lymph nodes from 10 patients were positive with the BLN assay only, with no evidence of metastatic disease by H&E or IHC.

Veys et al retrospectively assessed the possible use of the BLN assay in estimating the size of nodal metastases and the risk of metastatic disease in non-sentinel lymph nodes, as the size of the metastasis in the sentinel lymph node may predict non-sentinel lymph node metastases. Between 2006 and 2008, 367 consecutive patients with clinically node-negative early stage (tumor size <2cm) breast cancer were treated with breast-conserving surgery and sentinel lymph node biopsy at one European institution. The BLN assay was performed intraoperatively and if the assay results were positive in the sentinel lymph node, a full axillary lymph node dissection was performed. If the tumor size was intraoperatively determined to be greater than 2 cm, a full lymph node dissection was also performed (n=58) despite sentinel lymph node negativity. Permanent section sentinel lymph node examination consisted of at least one H&E section from all 2 mm lymph node sections not used for the BLN assay. If no tumor was found on these H&E sections, additional sections were taken and alternatively stained with H&E and IHC until all nodal material was exhausted. Sentinel lymph node positivity was defined as metastasis larger than 0.2 mm. Pathologists examining the permanent section histology were blinded to the BLN assay results. Seventy-eight sentinel lymph nodes were positive (72 with the assay, 62 by histologic examination with 17 cases BLN positive/histology negative and 7 cases BLN negative/histology positive). BLN positivity was found in 19.6% (72/367) of patients versus 17% (62/367) assessed as positive by histologic evaluation. A total of 128 (35%) completion axillary lymph node dissections were performed, and residual metastases were found in 19 (14.8%). Eighteen of 19 of the axillary lymph node-positive cases were from patients with a sentinel lymph node positive with the BLN assay and 16 from patients with sentinel lymph node metastasis detected by histology. The sensitivity of the assay to determine sentinel lymph node status was 89%, with a specificity of 94.5% and a negative predictive value of 97.5%. For the 78 positive sentinel lymph nodes (either by assay, histology or both), the levels of mammoglobin and CK 19 expression were compared to the size of the metastases as measured by histology. The correlation observed between metastasis size and the level of expression of mammoglobin and CK 19 genes was reported as having a p value of 0.62 and 0.64, respectively. The authors suggest that most of the cases with discrepant results between the assay and histology were micrometastases or had borderline expression of both assay gene markers, suggesting sampling effect.

**National Cancer Institute Clinical Trials Database**
As of December 2010, no active Phase III trials using molecular methods for the intraoperative assessment of sentinel lymph nodes in patients with breast cancer were identified.

**2011 National Comprehensive Cancer Network (NCCN) Guidelines**
NCCN guidelines acknowledge the revised cancer staging manual by the American Joint Committee on Cancer (January 2003, sixth edition), which addresses the increasing use of novel
pathology diagnostic techniques, and the addition of identifiers to indicate the use of sentinel lymph node molecular pathology techniques in staging a patient. However, the NCCN makes no recommendations as how to incorporate molecular testing of a sentinel lymph node into clinical practice.

**Summary**
As highlighted in a 2008 editorial, the ongoing difficulties with using molecular techniques to detect metastases in sentinel lymph nodes include 1) the uncertainty of the clinical significance of RT-PCR-positive but histologically and immunohistochemically negative sentinel lymph nodes; 2) the issue of possible false positives with a test as sensitive as RT-PCR; 3) the exact size of the metastasis cannot be determined because the tissue is digested in preparation for RT-PCR; and 4) the possibility that the assay is detecting small amounts of benign epithelial cells in the lymph node instead of metastatic carcinoma. What is still not clear is the clinical utility of using molecular methods to detect sentinel lymph node metastases in making patient management decisions.

**Key Words:**
Biomarker Genes, Breast Cancer, Lymph Node Metastases, Cytokeratin-19, GeneSearch, Mammaglobin, Veridex

**Approved by Governing Bodies:**
Not applicable

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply  
AT&T contracts: No special consideration  
FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.  
Wal-Mart: Special benefit consideration may apply. Refer to member’s benefit plan.  
Pre-certification requirements: Not applicable

**Current Coding:**
CPT Codes:

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<th>Code</th>
<th>Description</th>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure (<strong>effective 1/1/13</strong>)</td>
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<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis (<strong>effective 1/1/13</strong>)</td>
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**Previous Coding:**

CPT Codes:

There are no specific CPT codes for this technology. Multiple codes describing genetic analysis would likely be used (e.g., codes from 83890-83914) (deleted 1/1/13)

**References:**


Policy History:
Medical Policy Group, September 2009 (3)
Medical Policy Administration Committee, September
Available for comment September 18-November 2, 2009
Medical Policy Group, January 2011: Key Points, References
Medical Policy Group, January 2013 (1) Update to Coding with addition of new codes 81479 and 81599 and deletion of code range 83890-83914; no change in policy statement
Medical Policy Group, February 2013 (1): Effective 02/01/2013 - Active Policy but no longer scheduled for regular literature reviews and updates.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.