DESCRIPTION

Serum tumor markers are molecules or substances shed by a tumor into the circulation where they can be detected and quantitated. Noncirculating tumor markers include those that can be detected histochemically or cytogenetically on a tissue sample. Examples of the latter include the HER2 oncoprotein, detected by immunohistochemistry on a subset of breast cancers, and the Philadelphia chromosome, which is a cytogenetic marker for chronic myelogenous leukemia.

Serum tumor markers have been investigated in many malignancies, including most prominently myeloma (i.e., beta-2 microglobulin), germ cell tumors (i.e., alpha feto-protein, human chorionic gonadotropin), and prostate cancer (i.e., PSA). The HER2 oncoprotein extracellular domain has been studied as a serum tumor marker in breast and other malignancies. Carcinoembryonic antigen (CEA) has also been widely investigated in gastrointestinal malignancies. This policy focuses on specific tumor markers for breast and gastrointestinal malignancies.
For breast cancer, the most extensively investigated serum tumor markers besides HER2 are those associated with the MUC-1 gene. For gastrointestinal cancer, including gastric, pancreatic, and colorectal cancer, the most extensively studied tumor markers, other than CEA, are those related to mucinous glycoproteins. The MUC-1 gene encodes a cell-associated mucin-like antigen, and different antibodies may be used to detect different epitopes. CA 15-3 and CA 27.29 are 2 related monoclonal antibodies that detect epitopes encoded by the MUC-1 gene. While much of the literature has focused on the use of CA 15-3, it has been largely replaced by CA 27.29, which is reportedly more sensitive. The mucinous glycoproteins of the gastrointestinal tract include CA 19-9, and CA 72-4, depending on which antibody is used.

Since serum tumor markers can also be detected in normal or benign lesions, significantly elevated circulating levels may occur with malignancy by one or more of the following mechanisms: 1) overexpression of the antigen by malignant cells; 2) a large tumor burden; and/or 3) slower clearance of the marker. For example, since most tumor markers are cleared by the liver, liver abnormalities (whether benign, malignant, or inflammatory) may elevate tumor marker concentrations due to impaired clearance. Because most tumor markers are not unique to malignancy, cut-off points must be established for normal versus abnormal marker levels. In contrast, serial monitoring of serum tumor markers in a setting of established malignancy may not require such cut-off points. Various clinical applications of serum tumor markers can be broadly divided into 2 categories, those involving a single measurement and those involving serial measurements.

**Single Measurement of Serum Tumor Markers**

- **Diagnosis**
  Diagnosis of a suspected malignancy or unknown primary requires a tumor marker that is relatively specific for a given tumor. Since most tumor markers, including those discussed above, are expressed both in normal, benign conditions and malignancies, serum tumor markers are rarely used for diagnosis. Exceptions include human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP), whose elevated levels are both consistently seen with germ cell tumors. In addition, markedly elevated prostate-specific antigen (PSA) is highly suggestive of a prostatic malignancy.

- **Prognosis**
  A key determinant of initial therapy for epithelial tumors is their surgical resectability, generally excluded by the presence of distant metastases. Elevated tumor markers may relate to tumor burden. Thus they may suggest presence of, and prompt a more vigorous search for, metastatic disease not detected by routine clinical examination prior to surgery. For example, markedly elevated levels of PSA are highly suggestive of metastatic prostate cancer.

- **Choosing a Treatment Regimen**
  Certain cancer therapies specifically target a tumor marker protein. In addition, patients whose tumors express a given marker may be more likely to benefit from certain chemotherapy regimens. Thus, for example, breast cancer patients with HER2-positive tumors are often treated with regimens that combine trastuzumab (which targets the HER2 molecule) plus an anthracycline-based chemotherapy regimen (which has a greater impact on outcomes than other regimens in HER2-positive women).
Serial Monitoring of Serum Tumor Markers

- Monitoring response to therapy
  Response to systemic therapy, whether hormonal or cytotoxic, may be reflected by decreasing levels of serum tumor markers. In this setting, the value of a single tumor marker measurement, and whether it represents positive or negative response relative to an arbitrarily defined cut-off, is not as important as the trend analysis observed in serial monitoring. Interpreting trends in sequential tumor marker assays depends on understanding their normal biologic variation, as well as the analytic variability.

- Monitoring for Recurrence
  Patients who are no longer receiving therapy may be monitored for suspected recurrence by increasing tumor marker concentrations detected in serial monitoring. Serial monitoring of PSA in patients with a history of prostate cancer and CA-125 in patients with ovarian cancer are common examples. Limitations on interpreting results are similar to those described above for monitoring therapy response. In patients with a history of breast or gastrointestinal malignancy, serial monitoring for recurrence using serum tumor markers related to the MUC-1 gene (breast) or mucinous glycoproteins (gastrointestinal) has been the application most widely studied.

POLICY

A. Tumor marker CA 27.29 may be used:
   1. To monitor an already elevated titer or antigen in patients with metastatic disease.
   2. In surveillance of patients with elevated initial studies after the removal of an initial primary tumor.

B. Tumor marker CA 27.29 testing frequency:
   1. Treatment – baseline and every six weeks to assess response.
   2. Surveillance – every three months for post treatment follow-up

C. Tumor markers CA -15-3 and CA 27.29 are considered experimental / investigational as a technique to diagnose, determine prognosis, select therapy, assess response to therapy or monitor for reoccurrence of gastrointestinal malignancies. Gastrointestinal malignancies include gastric, pancreatic, and colorectal cancer.

RATIONALE

This policy is based on the following: one 1995 and two 1996 TEC Assessments that addressed tumor markers in breast and gastrointestinal malignancy, (1-3) a review of studies published since the TEC Assessments, and practice guidelines published by the American Society of Clinical Oncology (ASCO). (4,5) The following discussion does not address the use of CA-125, since this tumor marker is considered among the standard laboratory tests for patients with ovarian cancer.
Two key determinants of the clinical use of tumor markers are how their results will be used to affect patient management and whether the subsequent intervention will ultimately result in improved patient outcome. The application most extensively studied in breast and gastrointestinal malignancies is the use of tumor markers to monitor for recurrence. The outcomes most frequently reported are the interval between the diagnosis of metastases based on serial monitoring of tumor markers and the time at which the metastases become clinically apparent. However, these intervals may be related to both lead and length time bias and thus may have no impact on the final patient outcome of overall survival. Lead time bias refers to the fact that earlier diagnosis may not be related to improved overall survival, if there is no effective treatment. Length time bias refers to the fact that increased monitoring may primarily detect indolent, slow-growing metastases that are associated with prolonged survival regardless of treatment.

Two randomized studies of intensive surveillance of breast cancer follow-up illustrate this point. (6,7) Both studies randomized breast cancer patients with no evidence of disease after primary treatment to receive usual care or intensive follow-up care, consisting of regularly scheduled chest x-ray and bone scan to provide early detection of the metastases in the most common sites, i.e., lungs and bone. While one study reported an earlier detection of metastases in the intensively monitored group, (6) the other did not. (7) However, no difference was noted in 5-year overall survival. The lack of an improved outcome is in part related to the relatively ineffective curative treatment options for metastatic breast cancer. In this setting, quality-of-life issues related to the timing of treatment of metastatic disease may be relevant. These issues are similar to those associated with serial monitoring for recurrence of pancreatic or gastric cancer in which treatment options for recurrent disease are primarily palliative in nature.

The issues associated with serial monitoring of colorectal cancer are slightly different, since it has been shown that surgical resection of isolated liver or lung metastases may result in long-term survival in 20–30% of patients. Therefore, early diagnosis may lead to a greater incidence of detection of surgically resectable lesions. In addition, serial monitoring of serum levels of carcinoembryonic antigen (CEA) is an established practice for colorectal cancer, and thus the sensitivities and specificities of mucinous glycoprotein tumor markers must be compared to CEA, considered the gold standard. The ASCO guidelines suggest that, if resection of liver metastases would be clinically indicated, it is recommended that postoperative serum CEA testing be performed every 2–3 months in patients with stage II or III disease for 2 or more years after diagnosis. (4)

With this background in mind, the following discussion summarizes the TEC Assessments and the practice guidelines of ASCO regarding tumor markers for breast and gastrointestinal malignancies.

**Breast Cancer**
A 1995 TEC Assessment addressed the use of serum tumor markers in the diagnosis and monitoring of breast cancer, (1) which specifically examined the role of tumor markers as a prognostic factor in breast cancer, while a 1996 TEC Assessment focused on their use to detect recurrence. (3) These assessments provided the following observations and conclusions:
Diagnosis and Monitoring
• The evidence did not support a role for the use of serum tumor markers in the diagnosis of primary breast cancer, particularly for early stage disease, since sensitivities are low. Since none of the serum tumor markers is specific for breast cancer, they have limited utility in the differential diagnosis of metastatic disease of unknown primary. Finally, no evidence supported the use of the level of serum tumor markers as independent predictors of prognosis.
• In terms of monitoring response to therapy of metastatic disease, the serial measurement of serum tumor markers correlated well with clinical response criteria. However, of concern was the lack of valid criteria for interpreting changes in marker levels. Criteria have been suggested, but these have not been universally accepted.

Detection of Recurrence
• The overall quality of the available studies was poor, and no studies addressed the impact of measurement of tumor markers on survival rates.
• In most studies the reported lead times (i.e., difference in time of diagnosis between metastases identified with tumor marker compared to the clinical diagnosis) was 3–4 months. Whether this amount of lead time is adequate to improve therapy results is uncertain.
• One of the rationales of early identification of metastatic disease is that chemotherapy may be most effective in the setting of minimal tumor burden. However, since the level of serum tumor markers is related to tumor burden, the sensitivity of serum tumor markers falls when tumor burden is low. In addition, the false positive rate may be high; one study reported a specificity of only 60% for detection of recurrence. A high false positive rate may be associated with unnecessary additional diagnostic testing and patient anxiety.

No studies published since the 1995 TEC Assessment have addressed the above limitations. In particular, no studies have specifically examined any relationship between serial monitoring of serum tumor markers for breast cancer and the overall survival of patients, primarily related to earlier treatment of metastatic disease. Also, no studies have specifically examined the quality-of-life issues related to the timing of treatment. (7) While some studies have suggested that serum tumor markers function as prognostic factors, no trials have specifically used the results of tumor marker studies to guide treatment of the patients. (8-11) The use of tumor markers, specifically CA 15-3 or CA 27.29, may have the most value in following up response to therapy of bone metastases, which are difficult to monitor radiologically. However, no studies have validated criteria for interpreting changes in marker levels or how these criteria may be used in the management of patients.

A 2010 review article summarized the uses and limitations of CA 15-3 as a biomarker for breast cancer. (12) The article states that its main use is for monitoring therapy in patients with metastatic disease, but that it should not be used alone in this setting, but in conjunction with imaging and history and physical examination. The article suggests that the test may be most valuable for treatment monitoring in patients who have disease that cannot be evaluated using existing radiologic procedures (e.g. bone metastases, ascites, pleural effusions) and that the main limitation is that serum levels are rarely increased in early or localized disease. Finally, although serial measurements of CA 15-3 in the postoperative surveillance of asymptomatic women who have undergone surgery for invasive breast cancer may provide a median lead time
of 5-6 months in recurrent/metastatic cancer, it is unclear whether systemic therapy based on this lead time improves patient outcomes for survival and quality of life.

In 2007, the American Society of Clinical Oncology (ASCO) published recommendations for the use of tumor markers in breast cancer, which were unchanged from the previously published guidelines. (5) In summary, CA 15-3 and CA 27.29 are not recommended as prognostic markers for routine clinical use because there are no trials available demonstrating a clear benefit with their use. Details of the guideline recommendations for the use of CA 15-3 and CA 27.29 are as follows: Present data are insufficient to recommend their use for screening, diagnosis, staging, or monitoring patients for recurrence after primary breast cancer therapy. For monitoring patients with metastatic disease during active therapy, CA 15-3 or CA 27.29 can be used in conjunction with diagnostic imaging, history, and physical examination. Present data are insufficient to recommend use of CA 15-3 or CA 27.29 alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure. Caution should be used when interpreting a rising CA 15-3 or CA 27.29 during the first 4-6 weeks of a new therapy, since spurious early rises may occur.

**Gastrointestinal Cancer (i.e., colon, gastric, and pancreatic)**

A 1996 TEC Assessment addressed the use of serum mucinous glycoprotein tumor markers for both diagnosis and monitoring of gastric, pancreatic, and colorectal cancer. (2) These tumor markers were compared to the performance of CEA. The assessment reported the following observations and conclusions regarding the markers addressed in this policy.

- None of the tumor markers are specific for a particular tumor site, thus the markers are of limited value in determining the site of origin. CA 19-9 has a higher sensitivity than CEA in the diagnosis of pancreatic cancer, although this marker is also elevated in other cancer sites.
- For gastric and colorectal cancer, no other marker appeared to provide prognostic information beyond that supplied by CEA. Prognostic information may be of value in determining appropriate treatment strategies, for example, selecting poorer prognostic patients for more aggressive therapy; however, the use of serum tumor marker levels in clinical decision making for treatment planning has not been appropriately assessed.
- No evidence was available to determine the use of serum tumor markers in the clinical management of gastric or pancreatic cancer.

ASCO has published guidelines regarding the use of tumor markers in gastrointestinal cancer. (4) The most recent guidelines state that present data are insufficient to recommend CA 19-9 for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer. For pancreatic cancer, CA 19-9 is not recommended for use as a screening test or to determine operability. For evidence of recurrence, the guidelines state that CA 19-9 determinations by themselves cannot provide definitive evidence of disease recurrence without confirmation with imaging studies and/or biopsy. The guidelines state that present data are insufficient to recommend the routine use of serum CA 19-9 alone for monitoring response to therapy; however, CA 19-9 can be measured at the start of treatment for locally advanced or metastatic disease and every 1-3 months during active treatment. If there is an elevation in serial CA 19-9 determinations, this may be an indicator of progressive disease and confirmation with other studies should be sought.
The use of CA 19-9 as a prognostic factor continues to be of interest in pancreatic cancer and as an intermediate outcome used to monitor treatment response. (13-17) However, there have been no prospective studies that have shown how this prognostic information may be used in patient management, either in selecting the type of therapy, duration of therapy, or initiation of salvage therapy.

A 2010 review article on tumor markers in pancreatic cancer summarizes the literature on the use of CA 19-9 in the diagnosis, prognosis, postoperative surveillance, and monitoring therapy in advanced disease. (18) The article discusses how inadequate sensitivity and specificity limit the use of CA 19-9 in the early diagnosis of pancreatic cancer. For postoperative surveillance, the article highlights how, while studies have shown that serial determinations of CA 19-9 postoperatively can detect recurrent/metastatic disease several months before finding clinical or radiologic evidence of disease, the clinical value of this lead time is unclear (i.e. whether it impacts on patient survival outcomes or quality of life).

Berger and colleagues reported outcomes from a Phase III trial that performed a prospective analysis of CA 19-9 levels in patients with pancreatic cancer treated with adjuvant chemoradiation. (19) The trial was randomized and compared the use of either continuous infusion fluorouracil (5-FU) or gemcitabine before and after adjuvant chemoradiotherapy with 5-FU in patients with resected pancreatic adenocarcinoma. A secondary endpoint was prospective evaluation of the ability of postresectional CA 19-9 to predict survival. A total of 538 patients were accrued to the study, and of these, 385 who were eligible had analyzable CA 19-9. CA 19-9 expression was analyzed as a dichotomized variable (<180 U/mL vs. ≥180 U/mL) or (<90 U/mL vs. 90 U/mL). When CA 19-9 was analyzed as a dichotomized variable, there was a significant survival difference favoring patients with a CA 19-9 level lower than 180 (HR, 3.53; p<0.0001), which corresponded to a 72% reduction in the risk of death for patients with a CA 19-9 lower than 180. This was also true for patients with a level equal to or less than 90 (hazard ratio [HR], 3.4; p<0.0001). The authors concluded that the study confirms the prognostic importance of post resectional CA 19-9 levels after surgery in patients with pancreatic cancer.

Hess and colleagues reported the results of a randomized trial of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. (20) During the study, CA 19-9 serum concentration was measured at baseline and every 3 weeks thereafter, to test the hypothesis that an early decrease in baseline serum CA 19-9 (on day 42, after 2 cycles of chemotherapy) by at least 50% is associated with lengthened survival and that a decrease of at least 50% from the baseline concentration to the lowest value measured at any time during treatment is of prognostic significance, enabling its use as a surrogate endpoint for survival. 247 of 319 randomized patients were assessable for baseline serum CA 19-9, and of these, 175 were assessable for tumor marker response to treatment. The median overall survival for the patients with a baseline CA 19-9 concentration equal to or above the median value was 5.8 months (95% confidence interval [CI], 5.1-7.0), which was significantly shorter than that for patients with baseline concentrations below the median value (10.3 months [95% CI 8.6-12.8], p<0.0001). An early decrease in CA 19-9 concentration of at least 50% after 2 cycles of chemotherapy was not associated with a longer overall survival compared with patients who did not have a decrease of at least 50% (median 10.1 months [9.2-12.7] vs. 8.6 months [6.9-11.2], p=0.53; HR for death 1.11 [0.81-1.52]). The authors concluded that pretreatment serum CA 19-9 concentration is an independent prognostic factor for survival, but a decrease in concentration during chemotherapy is not significantly associated with lengthened survival compared with
those who did not have a corresponding decrease and that the data suggest that CA 19-9 response during chemotherapy is not a valid surrogate endpoint for survival in clinical trials.

**Summary**

Controlled studies showing the clinical utility of the serum tumor markers addressed in this policy and improved health outcomes in patients with breast, pancreatic, gastric, or colon cancer are lacking. CA 19-9 continues to be of interest as a prognostic factor or as a monitoring tool in patients with pancreatic cancer, but no studies have shown how measurements of CA 19-9 can be used to direct management and improve patient outcomes.

**Practice Guidelines and Position Statement**

**National Comprehensive Cancer Network (NCCN) Guidelines**

2011 NCCN guidelines for breast cancer (v2.2011) state that the Panel notes no evidence to support the use of “tumor markers” for post-surveillance and follow-up in breast cancer.

2011 NCCN guidelines for pancreatic adenocarcinoma (v2.2011) recommend measurement of serum CA 19-9 level following surgery prior to administration of adjuvant therapy (pretreatment baseline assessment following surgery) to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. As a category 2B recommendation, the guidelines recommend CA 19-9 determinations and follow-up computed tomography (CT) scans every 3 to 6 months for 2 years after surgical resection because data are not available to show that earlier treatment of recurrences, following detection by increased tumor marker levels or CT scan, leads to better patient outcomes.

2011 NCCN guidelines for colon cancer (v3.2011) do not address the use of the tumor biomarkers discussed in this policy.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

**CPT/HCPCS**

86300 Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)

**DIAGNOSES**

174.0 Malignant neoplasm of female breast, nipple and areola
174.1 Malignant neoplasm of female breast, central portion
174.2 Malignant neoplasm of female breast, upper-inner quadrant
174.3 Malignant neoplasm of female breast, lower-inner quadrant
174.4 Malignant neoplasm of female breast, upper-outter quadrant
174.5 Malignant neoplasm of female breast, lower-outter quadrant
174.6 Malignant neoplasm of female breast, axillary tail
174.8 Malignant neoplasm of female breast, other specified sites of female breast
174.9 Malignant neoplasm of female breast, unspecified
175.0 Malignant neoplasm of male breast
175.9 Malignant neoplasm of male breast, other and unspecified sites of male breast
V10.3 Personal history of malignant neoplasm, breast

ICD-10 Diagnosis (Effective October 1, 2014)
C50.011 Malignant neoplasm of nipple and areola, right female breast
C50.012 Malignant neoplasm of nipple and areola, left female breast
C50.021 Malignant neoplasm of nipple and areola, right male breast
C50.022 Malignant neoplasm of nipple and areola, left male breast
C50.111 Malignant neoplasm of central portion of right female breast
C50.112 Malignant neoplasm of central portion of left female breast
C50.121 Malignant neoplasm of central portion of right male breast
C50.122 Malignant neoplasm of central portion of left male breast
C50.211 Malignant neoplasm of upper-inner quadrant of right female breast
C50.212 Malignant neoplasm of upper-inner quadrant of left female breast
C50.221 Malignant neoplasm of upper-inner quadrant of right male breast
C50.222 Malignant neoplasm of upper-inner quadrant of left male breast
C50.311 Malignant neoplasm of lower-inner quadrant of right female breast
C50.312 Malignant neoplasm of lower-inner quadrant of left female breast
C50.321 Malignant neoplasm of lower-inner quadrant of right male breast
C50.322 Malignant neoplasm of lower-inner quadrant of left male breast
C50.411 Malignant neoplasm of upper-outer quadrant of right female breast
C50.412 Malignant neoplasm of upper-outer quadrant of left female breast
C50.421 Malignant neoplasm of upper-outer quadrant of right male breast
C50.422 Malignant neoplasm of upper-outer quadrant of left male breast
C50.511 Malignant neoplasm of lower-outer quadrant of right female breast
C50.512 Malignant neoplasm of lower-outer quadrant of left female breast
C50.521 Malignant neoplasm of lower-outer quadrant of right male breast
C50.522 Malignant neoplasm of lower-outer quadrant of left male breast
C50.611 Malignant neoplasm of axillary tail of right female breast
C50.612 Malignant neoplasm of axillary tail of left female breast
C50.621 Malignant neoplasm of axillary tail of right male breast
C50.622 Malignant neoplasm of axillary tail of left male breast
C50.811 Malignant neoplasm of overlapping sites of right female breast
C50.812 Malignant neoplasm of overlapping sites of left female breast
C50.821 Malignant neoplasm of overlapping sites of right male breast
C50.822 Malignant neoplasm of overlapping sites of left male breast
C50.911 Malignant neoplasm of unspecified site of right female breast
C50.912 Malignant neoplasm of unspecified site of left female breast
C50.921 Malignant neoplasm of unspecified site of right male breast
C50.922 Malignant neoplasm of unspecified site of left male breast
Z85.3 Personal history of malignant neoplasm of breast
REVISIONS

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<td>07-13-2003</td>
<td>Deleted old policy and added new policy.</td>
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<tr>
<td>03-27-2014</td>
<td>Title changed from: &quot;Tumor Markers CA-15-3 and CA-27.29&quot; to &quot;Serum Tumor Markers for Breast and Gastrointestinal Malignancies&quot;</td>
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<td>Added Medical Policy and Coding Disclaimers</td>
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<td>- Removed &quot;Tumor marker CA 27.29 will not be used: for screening patients who have not been proven to have breast cancer.&quot;</td>
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<td>- Removed &quot;Tumor marker CA 27.29 is a superior test to CA-15-3 and therefore CA-15-3 should be used.&quot;</td>
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<td>- Inserted &quot;Tumor markers CA-15-3 &amp; CA 27.29 are considered experimental/investigational as a technique to diagnose, determine prognosis, select therapy, assess response to therapy or monitor for reoccurrence of gastrointestinal malignancies. Gastrointestinal malignancies include gastric, pancreatic, and colorectal cancer.&quot;</td>
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REFERENCES

1. 1995 TEC Assessments; Tab 19: Serum tumor markers for the diagnosis and monitoring of breast cancer.
2. 1996 TEC Assessments; Tab 23: Serum tumor markers for the diagnosis and monitoring of gastrointestinal cancer.
3. 1996 TEC Assessments; Tab 24: Serum tumor markers (CA 15-3, CA 27.29 and CA 549) for the monitoring of breast cancer recurrence.

Other References
1. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee, February 2003; February 2014.