



Name of Policy:

Serum Tumor Markers for Breast and Gastrointestinal Malignancies

Policy #: 195
Category: Medical

Latest Review Date: October 2013
Policy Grade: A

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:

Serum tumor markers are molecules or substances that are shed by a tumor into the circulation where they can be detected and quantitated. Non-circulating tumor markers include those that can be detected histologically on a tissue sample, or even cytogenetically. 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 a wide variety of malignancies, including most prominently myeloma (i.e., beta-2 microglobulin), germ cell tumors (i.e., alpha fetoprotein, human chorionic gonadotropin), and prostate cancer (i.e., PSA). Carcinoembryonic antigen (CEA) has also been widely investigated in gastrointestinal malignancies.

For breast cancer, the most extensively investigated tumor markers 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 two related monoclonal antibodies that detect antigens encoded by the MUC-1 gene. While much of the literature has focused on the use of CA 15-3, this tumor marker has been largely replaced by CA 27.29, which is considered 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, significant circulating levels are associated with malignancy due to one or more of the following mechanisms: 1) overexpression of the antigen by individual malignant cells; 2) a large tumor burden; and/or 3) the clearance rate of the marker. For example, since the liver clears most tumor markers, liver abnormalities (whether benign, malignant, or inflammatory) may be associated with elevated tumor markers due to impaired clearance. Because most tumor markers are not unique to malignancy, cut-off points for what are considered normal or abnormal levels of tissue marker must be established. Alternatively, 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 two categories, those involving a single measurement of the serum tumor marker 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 PSA is highly suggestive of a prostatic malignancy.

Prognosis

A key determinant of initial therapy of epithelial tumors is to determine their surgical resectability; the presence of distant metastases generally excludes surgical resectability.

Therefore, the presence of elevated tumor markers (whose levels are related to tumor burden) may suggest metastatic disease not otherwise detected by routine clinical exam and prompt a more vigorous search for metastatic disease 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

Decreasing levels of serum tumor markers, whether hormonal or cytotoxic, may reflect response to systemic therapy. In this setting, the value of an individual tumor marker and whether it represents positive or negative relative to an arbitrarily defined cut-off is not as important as the trend analysis observed in serial monitoring. Interpretation of trends in tumor markers will depend on an understanding of the normal biologic variation of tumor markers as well as the analytic variation.

Monitoring for recurrence

Patients who are no longer receiving therapy may be monitored for recurrence as evidenced by increasing tumor markers detected in serial monitoring. For example, serial monitoring of PSA in patients with a history of prostate cancer and CA-125 in patients with ovarian cancer are common examples. The limitations of interpretation are similar to those described for monitoring therapy response, described above. 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.

For serum tumor markers for bladder cancer refer to policy #433 Urinary Tumor Markers for Bladder Cancer

Policy:

Breast Cancer

Measurement of serum tumor marker CA 15-3 (27.29) for monitoring patients with known breast cancer meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Measurement of serum tumor marker CA 15-3 (27.29) when used as a diagnostic or screening test for breast cancer does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Gastrointestinal Cancer

Measurement of serum tumor marker CA 19-9 for monitoring patients with known pancreatic or biliary cancer (i.e., gallbladder, intrahepatic biliary and extrahepatic biliary) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Measurement of serum tumor marker CA 19-9 does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** as a technique to screen, diagnose, determine prognosis, assess response to therapy, or monitor for recurrence of gastrointestinal malignancies, **except as indicated above**. Gastrointestinal malignancies include cancers associated with the esophagus, stomach, small intestine, appendix, colon, rectum, anus, liver, biliary tract and pancreas.

Measurements of serum tumor marker CA 72-4 does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** as a technique to screen, diagnose, determine prognosis, assess response to therapy, or monitor for recurrence of gastrointestinal malignancies. Gastrointestinal malignancies include cancers associated with the esophagus, stomach, small intestine, appendix, colon, rectum, anus, liver, biliary tract and pancreas.

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:

This policy is based on the following: one 1995 and two 1996 TEC Assessments that addressed tumor markers in breast and gastrointestinal malignancy, a review of studies published since the TEC Assessments, and practice guidelines published by the American Society of Clinical Oncology (ASCO). 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 of the 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 detect primarily 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. 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, the other did not. However, no difference was noted in five-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% to 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 two to three months in patients with Stage II or III disease for two or more years after diagnosis. The ASCO guidelines do not make any explicit recommendations regarding the use of serum tumor markers related to the mucinous glycoproteins.

With the above 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, 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. These assessments provided the following observations and conclusions:

Diagnosis and Monitoring

- The evidence did not support a role for the use of tumor markers in the diagnosis of primary breast cancer, particularly for early stage disease, since sensitivities are low. Since none of the 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 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 three to four 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. While some studies have suggested that serum tumor markers function as prognostic factors, there are no trials that have specifically used the results of tumor marker studies to guide treatment of the patients. 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.

Cancer antigen (CA) 27.29 is a monoclonal antibody to a glycoprotein (MUC1) that is present on the apical surface of normal epithelial cells. CA 27.29 is highly associated with breast cancer, although levels are elevated in several other malignancies. CA 27.29 also can be found in patients with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts. However, CA 27.29 levels higher than 100 units per mL are rare in benign conditions.

Disagreement exists about the ability of CA 27.29 to detect asymptomatic recurrence after curative treatment. One trial in patients at high risk for recurrence of breast cancer (Stage II or III) found that CA 27.29 was highly specific and sensitive in detecting preclinical metastasis. The average time from initial elevation of CA 27.29 to onset of symptoms was five months. Because CA 27.29 testing may lead to prompt imaging of probable sites of metastasis, it may be possible to decrease morbidity through earlier institution of therapy.

In 2001, the American Society of Clinical Oncology (ASCO) published breast cancer surveillance guidelines that stated that the routine use of CA 15-3 or CA 27.29 tumor marker for breast cancer surveillance is not recommended.

In 2006, ASCO updated breast cancer follow-up and management guidelines in the adjuvant setting. In this update, the panel stated, “The use of CBCs, chemistry panels, bone scans, chest radiographs, liver ultrasounds, computed tomography scans, PET scanning, magnetic resonance imaging, or tumor markers (CEA, CA, 15-3, and CA27.29) is not recommended for routine breast cancer follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination.”

In 2007, ASCO published recommendations for the use of tumor markers in breast cancer, which were unchanged from the previously published guidelines. 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 four to six weeks of a new therapy, since spurious early rises may occur.

A 2010 review article summarized the uses and limitations of CA 15-3 as a biomarker for breast cancer. 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 five to six 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.

Although of little use for early diagnosis, CA15-3 may be the first independent circulating prognostic marker described for breast cancer. Preoperative CA 15-3 concentrations may be combined with established prognostic factors for use in deciding which lymph node-negative breast cancer patients should receive adjuvant chemotherapy.

Gastrointestinal Cancer (i.e., esophagus, stomach, small intestine, appendix, colon, rectum, anus, liver, biliary tract and pancreas)

A 1996 TEC Assessment addressed the use of serum mucinous glycoprotein tumor markers for both diagnosis and monitoring of gastric, pancreatic, and colorectal cancer. 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.

In addition, ASCO has published guidelines regarding the use of tumor markers in colon cancer. The guideline stated that data were insufficient to recommend CA 19-9 or lipid-associated sialic acid (LASA) for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer. The guidelines also point out that CA 19-9 and CEA in combination did not improve the performance of CEA tests used alone as an indicator of asymptomatic recurrence. In terms of monitoring response to treatment, the guidelines state that CA19-9 does not add significant information to that provided by CEA, which is currently regarded as the marker of choice for colorectal cancer.

A literature review of studies published since the above TEC Assessment did not identify any study that would alter its conclusions. Specifically, no studies examined the health outcomes of patients whose disease recurrence had been identified by mucinous glycoproteins compared to CEA. The literature review further focused on the role of CA 19-9 in patients with pancreatic cancer. Although the ASCO guidelines state that CA 19-9 has become an established marker for pancreatic cancer, there is no further discussion, and the references cited are all from 1980s and were considered as part of the 1996 TEC Assessment. The use of CA 19-9 continues to be of interest in CA 19-9 as a prognostic factor in pancreatic cancer, and as an intermediate outcome used to monitor treatment response. However, there have been no prospective studies that have examined how this prognostic information may be used in the management of the patient, either in selecting the type of therapy, duration of therapy, or initiation of salvage therapy.

In November 2006 an Update of the ASCO Recommendations on the Use of Tumor Markers in Gastrointestinal Cancer was published. The following recommendations were made regarding the use of CA 19-9 as a marker for pancreatic and colon cancer. For colon cancer, the Update Committee identified no literature supporting the role of CA19-9 in colorectal cancer management. The test for this antigen is less sensitive than the CEA test for all stages of

colorectal cancer. Additionally, CA 19-9 and CEA in combination do not improve the performance of the CEA test alone or add significant information to that provided by CEA, which is currently regarded as the marker of choice for patients with colorectal cancer.

For pancreatic cancer, CA 19-9 is a tumor-associated antigen, which was originally defined by a monoclonal antibody. Reports are mixed regarding this antigen and pre and postoperative determinations, as well as CA 19-9 measurements to monitor patients receiving chemotherapy or radiotherapy. The specificity and sensitivity of CA 19-9 is inadequate for reliable diagnosis in pancreatic cancer if used alone. However, CA 19-9 monitoring in conjunction with other studies has been shown to be useful for locally advanced or metastatic pancreatic cancer.

A review of the literature indicated that high levels of CA 19-9 are increased in biliary disease due to the enhanced production of CA 19-9 from the biliary epithelial cells. Extreme increases in CA 19-9 levels can lead to a misdiagnosis of pancreatic or biliary malignancy. CA 19-9 should never be considered the gold standard for diagnosis. The value of CA19-9 is in evaluating response to treatment.

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. 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. 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 et al 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. 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 post-resectional 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 et al reported the results of a randomized trial of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. During the study, CA 19-9 serum concentration was measured at baseline and every three weeks thereafter, to test the hypothesis that an early decrease in baseline serum CA 19-9 (on day 42, after two 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 two 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 three to six months for two 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

Key Words:

Serum tumor markers, CA 19-9, CA 72-4, CA 15-3, CA 27.29, pancreatic cancer, biliary cancer, breast cancer

Approved by Governing Bodies:

FDA approved

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP contracts: FEP does not consider investigational if FDA approved and may be reviewed for medical necessity. Special benefit consideration may apply. Refer to member's benefit plan.

Pre-certification/Pre-determination requirements: Not applicable

Current Coding:

CPT codes:

86300	Immunoassay for tumor antigen, quantitative ³ ; CA 15-3 (27.29)
86301	Immunoassay for tumor antigen, quantitative, CA 19-9
86316	Immunoassay for tumor antigen, other antigen quantitative (e.g. CA 50, 72-4, CA 549), each

References:

1. 1995 TEC Assessment; Tab 19: Serum tumor markers for the diagnosis and monitoring of breast cancer.
2. 1996 TEC Assessment; Tab 23: Serum tumor markers for the diagnosis and monitoring of gastrointestinal cancer.
3. 1996 TEC Assessment; Tab 24: Serum tumor markers (CA 15-3, CA 27.29, and CA 549) for the monitoring of breast cancer recurrence.
4. Bast RC, Ravdin P, Hayes DF et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19(6):1865-78.
5. Berger AC, Garcia Jr M, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: A prospective validation by RTOG 9704. J Clin Oncol 2008; 26:5918-22.
6. Ebeling FG, Stieber P, Untch M et al. Serum CEA and CA 15-3 as prognostic factors in primary breast cancer. Br J Cancer 2002; 86(8): 1217-22.
7. Duffy MJ. Serum tumor markers in breast cancer: are they of clinical value? Clinical Chemistry 2006; 52:345-51.
8. Gion M, Boracchi P, Dittadi R et al. Prognostic role of serum CA 15.3 in 362 node-negative breast cancers. An old player for a new game. Eur J Cancer 2002;38(9):1181-8.

9. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; 25:5287-5312.
10. Hess V, Glimelius B, Grawe P, et al. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomized controlled trial. *Lancet Oncol* 2008; 9(2):132-8.
11. John AR, Haghighi KS, Tanriere P, et al. Is a raised CA 19-9 level diagnostic for a cholangiocarcinoma in patients with no history of sclerosing cholangitis? *Dig. Surg.* 2006;23(5-6):319-24.
12. Katz A, Hanlon A, Lanciano R et al. Prognostic value of CA 19-9 levels in patients with carcinoma of the pancreas treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 1998; 41(2): 393-6.
13. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 2006;24(31):5091-7.
14. Kokko R, Holli K, Hakama M. CA 15-3 in the follow-up of localized breast cancer; a prospective study. *Eur J Cancer* 2002;38(9):1189-93.
15. Kurebayashi J, Yamamoto Y, Tanaka K et al. Significance of serum carcinoembryonic antigen and CA 15-3 in monitoring advanced breast cancer patients treated with systemic therapy: a large-scale retrospective study. *Breast Cancer* 2003; 10(1): 38-44.
16. Locker GY, Hamilton S, Harris J, et al. 2006 Update of ASCO recommendations for the use of tumor markers in gastrointestinal cancer. *Journal of Oncology Practice* 2006, Vol. 2, Issue 6.
17. Micke O, Bruns F, Kurowski R, et al. Predictive value of carbohydrate antigen 19-9 in pancreatic cancer treated with radiochemotherapy. *Int J Radiat Oncol Biol Phys* 2003; 57(1): 90-7.
18. Ohara K, Tatsuzaki H, Molotkova NG et al. Utility of serum CA 19-9 monitoring in preoperative radiotherapy for pancreatic cancer. *Hepatogastroenterology* 2001; 48(39): 859-63.
19. Perkins GL, Slater ED, et al. Serum tumor markers. *American Family Physician* 2003; 68(6).
20. Rocha Lima CM, Savarese D, Bruckner H et al. Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. *J Clin Oncol* 2002; 20(5): 1182-91.
21. Rosselli Del Turco, M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. *JAMA* 1994; 271(20): 1593-7.
22. Shukla VK, Gurubachan, Sharma D, et al. Diagnostic value of serum CA-242, CA 19-9, CA15-3 and CA 125 in patients with carcinoma of the gallbladder. *Trop Gastroenterol* 2006;27(4):160-5.
23. The GIVIO Investigators. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. *JAMA* 1994; 271(20): 1587-92.
24. Ziske C, Schlie C, Gorschluter M et al. Prognostic value of CA 19-9 levels in patients with inoperable adenocarcinoma of the pancreas treated with gemcitabine. *Br J Cancer* 2003; 89(8): 1413-7.

Policy History:

Medical Policy Group, August 2004 (2)

Medical Policy Administration Committee, August 2004

Available for comment October 5-November 18, 2004

Medical Policy Group, March 2005 (2)

Medical Policy Administration Committee, April 2005

Available for comment April 13-May 27, 2005

Medical Policy Group, July 2005 (2)

Medical Policy Administration Committee, July 2005

Available for comment July 28-September 10, 2005

Medical Policy Group, December 2006 (1)

Medical Policy Administration Committee, December 2006

Available for comment January 30-March 8, 2007

Medical Policy Group, March 2007 (2)

Medical Policy Administration Committee, March 2007

Medical Policy Group, November 2008 (2)

Medical Policy Administration Committee, April 2009

Available for comment April 1-May 15, 2009

Medical Policy Group, June 2010 (3)

Medical Policy Administration Committee July 2010

Available for comment July 2-August 16, 2010

Medical Policy Group, June 2011 (1): Updated Description, narrowed number of serum markers under Policy; policy statement unchanged, updated Key Points and References; completely removed all aspects of bladder cancer tumor markers and placed on policy 433

Medical Policy Administration Committee, August 2011

Medical Policy Group, October 2013 (1): Policy updated with literature review; clarification to policy criteria and reformatting of policy section, no change to coverage criteria; removed ICD-9 diagnosis codes; addition of pancreatic, biliary and breast cancer to Key Words

Medical Policy Administration Committee, December 2013

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.