MEDICAL POLICY

SUBJECT: SERUM TUMOR MARKERS FOR DIAGNOSIS AND MANAGEMENT OF CANCER	**EFFECTIVE DATE: 10/18/01** **REVISED DATE: 07/18/02, 08/21/03, 11/18/04, 09/15/05, 11/30/05, 07/20/06, 07/19/07, 09/18/08, 09/17/09** **ARCHIVED DATE: 09/16/10** **EDITED DATE: 09/15/11, 09/20/12, 09/19/13, 09/18/14, 09/17/15, 9/15/16, 09/21/2017, 09/20/18**
POLICY NUMBER: 2.02.10 **CATEGORY: Laboratory Test**	**PAGE: 1 OF: 9**

- ***If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.***
- ***If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.***
- ***If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.***

POLICY STATEMENT:

I. Based on our criteria and review of the peer-reviewed literature, the following serum tumor markers have been medically proven to be effective and therefore considered **medically appropriate** for the indications listed when measurement may be used to influence the management of patients, and when these management changes will result in an improvement in patient outcomes:
   A. CEA (carcinoembryonic antigen) for diagnosis, and follow-up of metastatic colorectal cancer, including preoperative staging, or for monitoring patients with metastatic breast cancer during active therapy;
   B. CA 19-9 (carbohydrate antigen 19-9) for patients with an established diagnosis of pancreatic cancer or gastric cancer, when used to monitor the clinical *response to therapy* in order to either discontinue ineffective therapy or to detect early *recurrence* of disease;
   C. CA-125 (carbohydrate antigen 125):
      1. For patients with symptoms suggestive of or in those with known ovarian cancer; or
      2. For patients with other gynecologic malignancies that may have CA-125 elevations (such as endometrial cancer) to establish a baseline, or in whom baseline levels of CA-125 have been shown to be elevated, to monitor progression of disease; or
      3. For patients with significant risk factors for ovarian cancer (e.g., strong family history or known BRCA mutation) who have been counseled by their physician regarding the risks and benefits of screening; or
      4. For the surveillance of primary peritoneal carcinoma following treatment;
   D. CA 15-3 (carbohydrate antigen 15-3) or CA 27.29 (a monoclonal antibody used to detect CA 15-3 and often used interchangeably with CA 15-3) can be used for monitoring patients with metastatic breast cancer during active therapy;
   E. HCG (human chorionic gonadotropin): Serial measurements of HCG to monitor treatment in patients with known trophoblastic tumors and germinal cell tumors of the ovaries and testes, or to monitor for relapse after remission is achieved;
   F. AFP (alpha-fetoprotein): Serial measurements of AFP for the diagnosis and monitoring of hepatocellular carcinoma and testicular cancer; and
   G. CgA (chromogranin A) in the work-up of neuroendocrine tumors.

II. Based on our criteria and review of the peer reviewed literature, the following serum tumor markers have not been medically proven to be effective and are considered **not medically necessary**:
   A. CEA for *screening*, *diagnosis*, *staging*, *surveillance*, or *monitoring* of breast or lung cancer after primary therapy;
   B. CEA for *screening* asymptomatic patients for colorectal cancer**;**
   C. CA 19-9 for *screening* asymptomatic patients, *diagnosis*, *staging*, *surveillance*, or *monitoring treatment* of colorectal, liver, or breast cancer;
   D. CA 19-9 for *screening* asymptomatic patients, *diagnosis*, *staging*, *determining operability* or *the results of operability* of pancreatic cancer;
   E. CA-125:
      1. For *screening* asymptomatic patients without significant risk factors for ovarian cancer;

2. For *screening, diagnosis, staging, surveillance,* or *monitoring treatment* of colorectal, gastric, liver, or pancreatic cancer; and

F. CA 15-3 or CA 27.29 for *screening, diagnosis, staging* for breast cancer or for *monitoring* patients for recurrence after primary breast cancer therapy.

III. Based on our criteria and review of the peer reviewed literature, all other serum tumor markers have not been medically proven to be effective and are considered **investigational** in the diagnosis and management of cancer, including but not limited to:

A. CA (cancer antigen) 50, CA 72.4, CA 195, CA 242, CA 549, CA-SCC (squamous cell carcinoma);
B. CAM (monoclonal atimucin antibody) 17-1,CAM-26, CAM-29;
C. CAR-3 (antigenic determinant recognized by monoclonal antibody AR3);
D. Du-PAN-2 (sialylated carbohydrate antigen Du-PAN-2);
E. EPCA-2 (Early prostate cancer antigen);
F. Ki-67 antigen (marker of proliferation) for esophageal or breast cancer;
G. MCA (mucin-like cancer antigen);
H. Mcm2, Mcm5 (minichromosome maintenance proteins);
I. MSA (mammary serum antigen);
J. NSE;
K. Serum protein panel (leptin, prolactin, osteopontin and insulin-like growth factor-II) for ovarian cancer;
L. TAG (tumor-associated glycoprotein) 12, TAG 72.3;
M. TNF-alpha (tumor necrosis factor alpha); and
N. TPA (tissue polypeptide antigen), TPS.

Refer to Corporate Medical Policy #2.01.27 regarding Genetic Assay of Tumor Tissue to Determine Prognosis of Breast Cancer (Oncotype DX).

Refer to Corporate Medical Policy # 2.02.06 regarding Genetic Testing for Hereditary BRCA Mutations

Refer to Corporate Medical Policy #2.02.07 regarding Genetic Testing for Germline Mutations of the RET Proto Oncogene in Medullary Carcinoma of the Thyroid.

Refer to Corporate Medical Policy #2.02.11 regarding Genetic Testing for Inherited Susceptibility to Colorectal Cancer.

Refer to archived Corporate Medical Policy #2.02.12 regarding Urinary Tumor Markers for Bladder Cancer.

Refer to Corporate Medical Policy #2.02.31 regarding FISH (fluorescence in situ hybridization) Testing for HER-2/neu Amplification in Breast Cancer.

Refer to Corporate Medical Policy #2.02.43 regarding Proteomic-based Testing for the Evaluation of Ovarian (Adnexal) Masses.

Refer to Corporate Medical Policy #2.02.44 regarding Genetic Testing for Susceptibility to Hereditary Cancers.

Refer to Corporate Medical Policy #10.01.05 regarding Prostate Cancer Screening.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental or Investigational Services.

This policy does not address detection of circulating tumor cells (CTC) for the monitoring of patients with cancer.

POLICY GUIDELINES:

According to ASCO 2007 guidelines for use of tumor markers in breast cancer:

I. CEA can be used in conjunction with diagnostic imaging, history, and physical examination for monitoring patients with metastatic breast cancer during active therapy. Present data are insufficient to recommend use of CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CEA may be used to indicate treatment failure. Caution should be used when interpreting a rising CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.

II. CA 15-3 or CA 27.29 can be used in conjunction with diagnostic imaging, history, and physical examination for monitoring patients with metastatic breast cancer during active therapy. 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 level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.

According to the ASCO 2010 guidelines for uses of serum tumor markers in adult males with germ cell tumors:

I. AFP, hCG and LDH is recommended before and after orchiectomy and before chemotherapy for those with extra-gonadal non-seminomas.
II. AFP and hCG is recommended shortly before retroperitoneal lymph node dissection and at the start of each chemotherapy cycle for non-seminoma, and periodically to monitor for relapse.
III. hCG and LDH post-orchiectomy for patients with seminoma and pre-orchiectomy elevations.
IV. AFP and hCG is recommended to monitor for relapse in patients treated for advanced seminoma but not to guide or to guide or monitor treatment for seminoma or to detect relapse in those treated for stage I.
V. Serum tumor markers should not be used to screen for GCTs , decide whether orchiectomy is indicated, or to select treatment for patients with cancer of unknown primary.

DESCRIPTION:

Serum tumor markers are molecules or substances that are shed by a tumor into the circulation where they can be detected and quantitated. They have been investigated in a wide variety of malignancies. Non-circulating tumor markers include those that can be detected histologically on a tissue sample or cytogenetically. 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. 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.

I. Single measurement of serum tumor markers:
   A. *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 are expressed both in normal, benign conditions and by malignancies, serum tumor markers are rarely used for diagnosis. Exceptions include human chorionic gonadotropin (HCG) and alpha feto protein (AFP), whose elevated levels are both seen with germ cell tumors. In addition, markedly elevated PSA is highly suggestive of a prostatic malignancy.

   B. *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.

II. Serial Monitoring of Serum Tumor Markers:

A. *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 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.

B. *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 CA-125 in patients with ovarian cancer. 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.

While research into the genetic basis of cancer has been an intense research focus, genetic mutations do not reflect the complicated interactions between individual cells, tissue, and organs. Proteins are the functional units of cells and represent the end product of the interactions among the underlying genes. Therefore, recently, research interest has been increasing in the pattern of proteins associated with malignancies. This field may be referred to as proteomics (to distinguish it from genomics), defined as the study of all protein forms expressed within an organism as a function of time, age, state, and external factors. Within cancer research, one research application has been the identification of a pattern of proteins detected in a given fluid, such as serum, that are associated with an underlying cancer. Essentially, the identification of patterns of proteins in the serum could function as serum tumor marker, similar in concept to the more familiar prostate specific antigen (PSA) or CA-125, which are used in the detection and monitoring of prostate and ovarian cancer, respectively. This type of proteomic profiling has also been referred to as a "protein fingerprint." There are potential applications of proteomics in a variety of malignancies, but the two most commonly mentioned are ovarian and prostate cancer.

RATIONALE:

CA-125. The use of CA-125 to monitor ovarian cancer *recurrence* in patients with known ovarian cancer is considered standard practice. Other gynecologic malignancies, particularly endometrial cancer, may also be associated with CA-125 in individual cases. If so, levels of CA-125 may be similarly monitored for cancer recurrence. Although measurement of CA-125 has been of interest as a *screening* technique for ovarian cancer in asymptomatic patients, published clinical trials have not provided evidence to support its efficacy in this role. The high false positive rate and subsequent low positive predictive value indicate that many patients will unnecessarily undergo invasive procedures (laparoscopy or laparotomy) to rule out malignancy. In addition, there is inadequate evidence that screening reduces the morbidity and mortality of ovarian cancer.

The American Cancer Society and the U.S. Preventive Services Task Force (USPSTF) recommend against ovarian cancer *screening* for average risk women. USPSTF found fair evidence that screening with serum CA-125 level or transvaginal ultrasound can detect ovarian cancer at an earlier stage than can be detected in the absence of screening. However, they found fair evidence that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer. Because of the low prevalence of ovarian cancer and the invasive nature of diagnostic testing after a positive screening test, there is fair evidence that screening could likely lead to important harms. The USPSTF concluded that the potential harms outweigh the potential benefits.

A prospective study assessed the effectiveness of annual ovarian cancer *screening* using transvaginal ultrasound and serum CA-125 in detecting pre-symptomatic ovarian cancer in a cohort of 1,110 women who were at increased genetic risk. Of 13 epithelial ovarian malignancies developed in the cohort, ten tumors were detected at screening. 29 women underwent diagnostic surgery but were found not to have ovarian cancer. Authors concluded that annual surveillance by

transvaginal ultrasound and serum CA-125 measurement in women at increased familial risk of ovarian cancer is ineffective in detecting tumors at a sufficiently early stage to influence prognosis.

The use of CA-125 for the surveillance of *primary peritoneal adenocarcinoma* (PPA) after treatment is due to PPA's similarity to epithelial ovarian carcinoma. PPA is uncommon. It behaves and is treated like ovarian cancer, and symptoms and staging are similar to ovarian cancer.

CA 19-9. Prospective clinical trials concluded that CA19-9 is of predictive value for prognosis, response and detecting recurrence of pancreatic cancer in patients undergoing combined radiochemotherapy and serves as an early indicator of response to chemotherapy in advanced *pancreatic cancer*.

The American Society of Clinical Oncology (ASCO) 2006 Recommendations for the use of Tumor Markers in Gastrointestinal Cancer do not recommend the use of CA 19-9 testing alone for use in *determining operability or the results of operability* in *pancreatic cancer*. ASCO states that some investigators have found that elevation of CA 19-9 above certain levels have correlated with unresectable disease, or disease that recurs early in the postoperative period. However, such preoperative determinations alone have yet to be widely used as a means of establishing inoperability. ASCO also states that elevating levels of CA 19-9 postoperatively may predict asymptomatic recurrent disease, which may be helpful in the management of patients following attempted definitive surgery in patients who are receiving adjuvant therapy with either or both chemotherapy and radiation therapy, or who are being observed after surgery without adjuvant therapy. However, CA 19-9 determinations *by themselves* cannot provide definitive evidence of disease recurrence without seeking *confirmation by imaging studies and/or biopsy*.

Data are insufficient to recommend CA 19-9 for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with *colorectal cancer*; or for screening for *pancreatic* cancer.

CEA. The American Society of Clinical Oncology (ASCO) 2006 Recommendations for the use of Tumor Markers in Gastrointestinal Cancer do not recommend the use of CEA as a *screening* test for colorectal cancer. The specificity of CEA for identifying occult colorectal cancers is high but the sensitivity is very low. This is in accordance with the 2003 recommendation for CEA by the European group on Tumor Markers (EGTM).

Clinical evidence supports the utility of *preoperative* CEA levels as prognostic factors for *colorectal cancer*. A study of 2,230 patients demonstrated that preoperative CEA was an important independent prognostic variable in predicting outcome. A study of 1,146 rectal patients using a multivariate analysis confirmed that preoperative CEA level was a highly significant prognostic covariate even after stage and grade were included in the model.

The American Society of Clinical Oncology (ASCO) 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer do not recommend the use of CEA for screening, diagnosis, staging, or routine surveillance of *breast cancer* patients after primary therapy. The recommendations indicate that CEA can be used in conjunction with diagnostic imaging, history, and physical examination for monitoring patients with metastatic breast cancer during active therapy. Present data are insufficient to recommend use of CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CEA may be used to indicate treatment failure. Caution should be used when interpreting a rising CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.

CA 15-3 (CA 27.29). The American Society of Clinical Oncology (ASCO) 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer do not recommend the use of CA 15-3 or CA 27.29 for screening, diagnosis, staging, or routine surveillance after primary therapy, for *breast cancer*. The recommendations indicate that CA 15-3 (27.29) can be used in conjunction with diagnostic imaging, history, and physical examination for monitoring patients with metastatic breast cancer during active therapy. 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 CEA may be used to indicate treatment failure. Caution should be used when interpreting a rising CA 15-3 or CA 27.29 level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.

The OvaCheck™ test is based on proteomic patterns in serum, which are further analyzed by mass spectrometry to profile a population of proteins based on size and electrical charge. The analysis contains thousands of data points,-which undergo further sophisticated computer analysis using artificial intelligence-based algorithms that are proposed to identify a pattern consistent with ovarian cancer. There is inadequate evidence that this test will be effective for *screening* women with *undetected ovarian cancer*. Given the low prevalence of ovarian cancer, there is also concern that this test is not sufficiently specific for use in screening.

The National Cancer institute states that even an ovarian cancer test with a specificity of 99% means that 1% of those who did not have cancer would test positive, which is "far too high a rate for commercial use" (NCI 2004). For a rare disease such as ovarian cancer, which has an approximate prevalence of 1 in 2,500 in the general population, a 99% specificity and 100% sensitivity translates into 25 women falsely identified for every one true cancer found. The American College of Obstetrics and Gynecology (2004) and the Society for Gynecologic Oncologists (2004) has stated that "more research is needed to validate the test's effectiveness before recommending it to the public."

Proteomics has also been proposed as a technique to further evaluate cancer risk of *prostate* specific antigen (PSA) values falling in the in the non-specific diagnostic "gray" zone between 2.5 and 10.0 ng/ml. Therefore, it is proposed that identification of patterns of proteins in serum could function as a serum tumor marker for ovarian and prostate cancer. Preliminary results of small studies regarding prostate cancer indicate that before this new technology can be applied in clinical practice, large and diverse training and testing sets are needed.

HCG. Human chorionic gonadotropin (HCG) is normally produced in increasing quantities by the placenta during pregnancy. Accepted guidelines provide that HCG levels can be used to screen for choriocarcinoma in women who are at high risk for the disease, and to monitor the treatment of trophoblastic disease. Literature states that elevated HCG levels may also indicate the presence of cancers of the testis, ovary, liver, stomach, pancreas and lung.

Accepted guidelines provide that AFP and HCG measurements are valuable for determining prognosis and monitoring therapy in patients with non-seminomatous germ cell cancer. The value of AFP and HCG as markers is enhanced by a low frequency of false-positive results and by the chemoresponsiveness of testicular cancer.

AFP. Alpha-fetoprotein (AFP) is normally produced by a developing fetus. AFP levels begin to decrease soon after birth and are usually undetectable in the blood of healthy adults, except during pregnancy. According to accepted guidelines, an elevated level of AFP strongly suggests the presence of either primary liver cancer, or germ cell cancer of the ovary or testicle. As AFP is an established test for the diagnosis and monitoring of hepatoma, it is used as a screening tool to rule out the presence of a liver neoplasm before liver transplantation. This is especially pertinent in cases (e.g. cirrhosis) where there is an increased risk of developing a primary liver tumor.

CgA. Chromogranin A is produced by neuroendocrine tumors, which include carcinoid tumors, neuroblastoma, and small cell lung cancer. The blood level of CgA is often elevated in people with carcinoid tumors or other neuroendocrine tumors. The National Comprehensive Cancer Network (NCCN) 2007 Clinical Practice Guidelines in Oncology, Neuroendocrine Tumors, recommends the use of CgA in the additional work-up of gastrinoma (usually intraduodenal or head of pancreas), and in the clinical diagnosis and additional work-up of pancreatic polypeptidoma, somatostatinoma, and non-functioning pancreatic tumors. There have been preliminary studies done in the use of CgA for prostate cancer.

Other Tumor Markers. Data is insufficient to substantiate the effectiveness of the tumor markers listed as investigational in this policy in the diagnosis and management of cancer.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT:	82105	Alpha-fetoprotein (AFP); serum
	82378	Carcinoembryonic antigen (CEA)
	84702	Gonadotropin, chorionic (hCG); quantitative
	86300	Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)
	86301	Immunoassay for tumor antigen, quantitative; CA 19-9
	86304	Immunoassay for tumor antigen, quantitative; CA-125
	86316 **(E/I)**	Immunoassay for tumor antigen; other antigen, quantitative (eg, CA-50, 72-4, 549) each **E/I designation does not apply to CgA in the work up of neuroendrocrine tumors.**

ICD10:	C17.0-C17.9	Malignant neoplasm of small intestine (code range)
	C18.0-C18.9	Malignant neoplasm of colon (code range)
	C19	Malignant neoplasm of rectosigmoid junction
	C20	Malignant neoplasm of rectum
	C21.0-C21.8	Malignant neoplasm of anus and anal canal (code range)
	C56.1-C56.9	Malignant neoplasm of ovary (code range)
	C57.00-C57.4	Malignant neoplasm of other and unspecified female genital organs (code range)
	Z80.41	Family history of malignant neoplasm of ovary
	Z85.3	Personal history of malignant neoplasm of breast

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*key article

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KEY WORDS:

AFP, CA-125, CA 15-3, CA 19-9, CEA, HCG, Proteomic

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There are currently National Coverage Determinations (NCDs) for the following serum tumor markers for diagnosis and management of cancer. Please refer to the following NCD websites for Medicare Members:

https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=121&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&

https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=118&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&

https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=130&ncdver=2&bc=AgAAgAAAAAAAAA%3d%3d&

https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=134&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&

https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=142&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&