



TUMOR MARKERS

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Status: Current

Summary of Changes

Clarifications:

-

Deletions:

-

Additions:

- Pg 2, Section I, language added to reflect the addition of a second Appendix listing non-covered tumor markers. The list is not all-inclusive and any tumor marker not listed is still subject to the main policy criteria.
- Pg 9, Appendix II (Non-Covered Tumor Markers) added.

I. POLICY/CRITERIA

Serum tumor markers are considered medically necessary for a specific cancer type when proven to be clinically useful in the detection and management (as described in Section IV) of that specific cancer. The utilization of a specific tumor marker must be adopted into a clinical algorithm and endorsed by a professional cancer organization, i.e. NCCN, ASCO, NCI as part of routine care. Examples of this include the following:

1. Carcinoembryonic antigen (CEA) is considered medically necessary when used to detect asymptomatic recurrence of colorectal cancer after surgical and/or medical treatment for the diagnosis of colorectal cancer but is not considered medically necessary as a screening test for colorectal cancer.
2. Bladder tumor antigen (BTA) Stat test medically necessary in any of the following conditions:
 - A. Follow-up of treatment for bladder cancer; *or*
 - B. Monitoring for eradication of bladder cancer; *or*
 - C. Recurrences after eradication.

BTA Stat test is considered experimental and investigational for screening of bladder cancer and all other indications.

Refer to Appendix I below for a list of covered tumor markers and their associated cancers. For tumor markers not listed, please submit request for medical review and include documentation of clinical usefulness.



Refer to Appendix II for a list of non-covered tumor markers. This list is NOT all-inclusive and any tumor marker not listed is still subject to the main policy criteria listed above.

II. MEDICAL NECESSITY REVIEW

- All tests performed at non-participating laboratories will require prior authorization.

III. APPLICATION TO PRODUCTS

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

- ❖ **HMO/EPO:** *This policy applies to insured HMO/EPO plans.*
- ❖ **POS:** *This policy applies to insured POS plans.*
- ❖ **PPO:** *This policy applies to insured PPO plans. Consult individual plan documents as state mandated benefits may apply. If there is a conflict between this policy and a plan document, the provisions of the plan document will govern.*
- ❖ **ASO:** *For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern.*
- ❖ **INDIVIDUAL:** *For individual policies, consult the individual insurance policy. If there is a conflict between this medical policy and the individual insurance policy document, the provisions of the individual insurance policy will govern.*
- ❖ **MEDICARE:** *Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, this policy applies.*
- ❖ **MEDICAID:** *If there is a discrepancy between this policy and the Michigan Medicaid Provider Manual and the Michigan Medicaid Fee Schedule, the Michigan Medicaid Provider Manual and the Michigan Medicaid Fee Schedule at: http://www.michigan.gov/mdch/0,1607,7-132-2945_42542_42543_42546_42551-159815--00.html will govern.*
- ❖ **MICHILD:** *For MICHILD members, this policy will apply unless MICHILD certificate of coverage limits or extends coverage.*

IV. DESCRIPTION

Tumor markers are molecules or substances that are produced by the tumor itself or by the body in response to the presence of a cancerous or non-cancerous condition. These markers can be detected and measured in serum. Single measurements of serum tumor markers may be used to facilitate the diagnosis and prognosis in patients with symptoms suggestive of malignancy while serial monitoring of tumor markers may be used as a tool to monitor response to therapy, detect recurrence or predict development of cancer as a screening test. This policy addresses serum tumor markers in regards to the detection and the management of cancerous conditions.



V. CODING INFORMATION

ICD9 Diagnosis Codes:

*See Criteria*Covered Services

Estrogen receptor (ER) Progesterone receptor (PR)	84233	Receptor assay; estrogen
HER2	84234	Receptor assay; progesterone
	83950	Oncoprotein; HER-2/neu
	88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; manual
	88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; using computer-assisted technology
Oncotype Dx	84999	Unlisted chemistry procedure
	S3854	Gene expression profiling panel for use in the management of breast cancer treatment (<i>not billable for Medicaid or Medicare</i>)
Carcinoembryonic antigen (CEA)	82378	Carcinoembryonic antigen (CEA)
CA 15-3 and CA 27-29	86300	Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)
Cancer antigen 125 (CA 125)	86304	Immunoassay for tumor antigen, quantitative; CA 125
CA19-9	86301	Immunoassay for tumor antigen, quantitative; CA 19-9
Human Chorionic Gonadotropin (HCG)	84702	Gonadotropin, chorionic (hCG); quantitative
	84703	Gonadotropin, chorionic (hCG); qualitative
	84704	Gonadotropin, chorionic (hCG); free beta chain
Alpha Fetoprotein (AFP)	82105	Alpha-fetoprotein (AFP); serum
	82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)
K-ras(KRAS)	81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13 <i>See policy 91540 Genetics Counseling, Testing and Screening</i>
Placental alkaline phosphatase (PLAP)	84080	Phosphatase, alkaline; isoenzymes
	88342	Immunohistochemistry (including tissue immunoperoxidase), each antibody
Myeloperoxidase (MPO) immunostaining	83876	Myeloperoxidase (MPO)
	83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step



Bladder tumor antigen (BTA) Stat test; or nuclear matrix protein (NMP22) test; or fibrin/fibrinogen degradation products (Aura-Tek FDP) test,; or the UroVysion fluorescent in situ hybridization (FISH) test	88120 88121	method Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology
	86386	Nuclear Matrix Protein 22 (NMP22), qualitative
<u>Not Covered</u>		
cofilin (CFL1) as a prognostic and drug resistance marker in non-small cell lung cancer	83890 83891	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA) Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
	83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
	83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
	83912	Molecular diagnostics; interpretation and report
Autoantibody detection i.e. EarlyCDT-Lung test, as a screening test for the early detection of lung cancer	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
Mammostrat test for predicting recurrence of breast cancer	S3854	Gene expression profiling panel for use in the management of breast cancer treatment
PreOvar test for the KRAS-variant to determine ovarian cancer risk	83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
	83896	Molecular diagnostics; nucleic acid probe, each
	83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
	83907	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen
	83912	Molecular diagnostics; interpretation and report



Human epididymis protein 4 (HE4) for any indication, including assessment of ovarian adnexal mass or to monitor recurrence of ovarian cancer	86305	Human epididymis protein 4 (HE4)
Immunological techniques designed to detect epithelial cells circulating in the blood to quantify circulating tumor cells (i.e. The CellSearch™ System) for any cancer, including, but not limited to, metastatic breast, colorectal, or prostate cancers;	0279T	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
	0280T	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); interpretation and report
Fibrin/fibrinogen degradation products (FDP) testing, i.e., Onko-Sure™ blood test	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
Lectin-reactive alpha-fetoprotein (AFP-L3)	82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)
Septin 9 (SEPT9) DNA methylation assay for the early detection of colorectal cancer, i.e., Epi proColon or ColoVantage™	83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
	83896	Molecular diagnostics; nucleic acid probe, each
	83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
	83912	Molecular diagnostics; interpretation and report
Topoisomerase II alpha (TOP2A) gene amplification or deletion, i.e., TOP2A FISH pharmDx™ Assay	88365	In situ hybridization (eg, FISH), each probe
	88368	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; manual
Carcinoembryonic antigen cellular adhesion molecule-7 (CEACAM-7) expression as a predictive marker for rectal cancer recurrence	86849	Unlisted immunology procedure
	88299	Unlisted cytogenetic study
	88399	Unlisted surgical pathology procedure
	84999	Unlisted chemistry procedure
Mucin 4 expression as a predictor of survival in colorectal cancer		
ProOnc TumorSourceDx test to identify tissue or origin for metastatic tumors		



Serum amyloid A as a biomarker for endometrial endometrioid carcinoma to monitor disease recurrence and response to therapy

Caris Target Now Molecular Profiling Test

Biomarker translation test for early breast cancer detection, (i.e. BT Test™)

Guanylyl cyclase c (GCC or GUCY2C), i.e., Previstage™ GCC Colorectal Cancer Stage Test

Prostate PX
Topographic genotyping, such as PathFinderTG® for any indication including breast cancer and pancreatic cancer

VI. REFERENCES

1. Hayes Online Technology Assessment Service:
 - a. Serum Carcinoembryonic Antigen (CEA) Assay for Diagnosis of Ovarian Cancer
 - b. Total Sialic Acid and Lipid-Associated Sialic Acid as Tumor Markers
 - c. Somatostatin Receptor Scintigraphy (SRS) for Localization of Neuroendocrine Tumors and their Metastases
 - d. Ancillary Bladder Tumor-Associated Antigen (BTA) Testing for Bladder Cancer Screening and Detection
 - e. Cancer Antigen 27.29 (CA 27.29) for Diagnosis, Staging, and Treatment Monitoring of Breast Cancer
 - f. Selected Ancillary Urine Tests for Bladder Cancer Screening and Detection
 - g. Cancer Antigen 15-3 (CA 15-3) for Breast Cancer Prognosis
 - h. PathFinderTG® Test (RedPath Integrated Pathology) for the Diagnosis of Pancreatic Cancer
 - i. In Vitro Chemosensitivity Assays in Cancer Treatment
 - j. Cancer Antigen (CA) 19-9 for Pancreatic Cancer Screening
 - k. Ancillary UroVysion™ Fluorescence In Situ Hybridization (FISH) Testing for Bladder Cancer Screening and Detection



- l. Oncotype Dx™ (Genomic Health Inc.) Genetic Assay for Breast Cancer
 - m. Cancer Antigen (CA) 19-9 for Prognosis of Pancreatic Cancer Resectability
 - n. Ancillary Nuclear Matrix Protein 22 (NMP22) Testing for Bladder Cancer Screening and Detection
 - o. Prostate-Specific Antigen Testing for Prognosis and Monitoring of Patients with Prostate Cancer
 - p. Autoantibody Testing for the Early Diagnosis of Breast Cancer
 - q. Ancillary ImmunoCyt/uCyt+ Testing for Bladder Cancer Screening and Detection
 - r. Ancillary Urinary Cytokeratin (CK) Tests for Bladder Cancer Screening and Detection
 - s. CA 125 for Ovarian Cancer Screening in Average-Risk Women
 - t. Prostate Cancer Antigen 3 (PCA3) Genetic Assay for the Diagnosis and Management of Prostate Cancer
2. Aetna online medical policy bulletin: Tumor Markers -
http://www.aetna.com/cpb/medical/data/300_399/0352.html
 3. Cigna online medical policy bulletin: Tumor Markers for Diagnosis and Management of Cancer -
http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0172_coveragepositioncriteria_tumor_markers_for_diagnosis_mgmt_cancer.pdf
 4. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. *Journal of Clinical Oncology*, Vol 25, No 33 (November 20), 2007: pp. 5287-5312 © 2007 American Society of Clinical Oncology.
 5. ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer. *Journal of Clinical Oncology*, Vol 24, No 33(November 20), 2006: pp.5513-5527© 2006 American Society of Clinical Oncology.
 6. NCCN Clinical Practice Guidelines in Oncology™
 - a. Bladder Cancer version 1.2009:
http://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf
 - b. Breast Cancer version 1.2009:
http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf
http://www.nccn.org/professionals/physician_gls/PDF/breast-screening.pdf
 - c. Colon Cancer version 2.2009:
http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf
http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf
 - d. Gastric Cancer version 2.2009:
http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf
 - e. Kidney Cancer version 2.2009:
http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf



- f. Ovarian Cancer version 2.2009:
http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf
- g. Pancreatic Cancer version 2.2009:
http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf
- h. Prostate Cancer version 2.2009:
http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf
http://www.nccn.org/professionals/physician_gls/PDF/prostate_detection.pdf

**APPENDIX I**
Covered Markers

Marker	Application
Estrogen receptor (ER)	Invasive Breast Cancer including metastatic- help predict response to hormone therapy after surgery
Progesterone receptor (PR)	Invasive Breast Cancer including metastatic- help predict response to hormone therapy after surgery
HER2	Invasive Breast Cancer including metastatic and recurrent- help predict response to trastuzumab and other anti-HER2 treatments and some types of chemotherapy
Oncotype Dx	Invasive Breast cancer – stage I or II; and node negative; and ER/PR positive; and HER2 negative or HER2 positive BUT tumor <1cm
CA 15-3 and CA 27-29	Metastatic Breast Cancer and / or recurrent Breast cancer for treatment monitoring. to be used in conjunction with diagnostic imaging, history and physical exam.
Carcinoembryonic antigen (CEA)	<ol style="list-style-type: none"> 1. To detect asymptomatic recurrence of colorectal cancer after surgical and/or medical treatment for the diagnosis of colorectal cancer (not as a screening test for colorectal cancer); <i>or</i> 2. As a preoperative prognostic indicator in members with known colorectal carcinoma when it will assist in staging and surgical treatment planning; <i>or</i> 3. To monitor response to treatment for metastatic cancer.
Cancer antigen 125 (CA 125)	<ol style="list-style-type: none"> 1. Diagnosis of ovarian cancer in women with new symptoms (bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or urinary frequency and urgency) that have persisted for three or more weeks, where the clinician has performed a pelvic and rectal examination and suspects ovarian cancer; <i>or</i> 2. As a preoperative diagnostic aid in women with ovarian masses that are suspected to be malignant, such that arrangements can be made for intraoperative availability of a gynecological oncologist if the CA 125 is increased; <i>or</i> 3. In members with known ovarian cancer, as an aid in the monitoring of disease, response to treatment, detection of recurrent disease, or assessing value of performing second-look surgery; <i>or</i> 4. In members with adenocarcinoma of unknown primary, to rule out ovarian cancer. 5. As a screening test for ovarian cancer when there is a history of hereditary cancer syndrome (a pattern of clusters of ovarian cancer within two or more generations).



CA19-9	To monitor the clinical response to therapy or detect early recurrence of disease in members with known gastric cancer, pancreatic cancer, cholangiocarcinoma or adenocarcinoma of the ampulla of Vater.
Human Chorionic Gonadotropin (HCG)	To diagnose germ cell tumors in members with adenocarcinoma, or carcinoma not otherwise specified, involving mediastinal nodes, or to monitor treatment in members with known trophoblastic tumors (invasive hydatidiform moles and choriocarcinomas) and germinal cell tumors (teratocarcinoma and embryonal cell carcinoma) of the ovaries or testes, or to monitor for relapse after remission is achieved.
Alpha Fetoprotein (AFP)	To diagnose germ cell tumors in members with adenocarcinoma, or carcinoma not otherwise specified, involving mediastinal nodes; or the diagnosis and monitoring of hepatocellular carcinoma (e.g., before considering liver transplantation).
K-ras (KRAS)	Mutation analysis to predict non-response to cetuximab (Erbix) and panitumumab (Vectibix) in the treatment of metastatic colorectal cancer.
Placental alkaline phosphatase (PLAP)	To diagnose germ cell seminoma and non-seminoma germ cell tumors in unknown primary cancers
Myeloperoxidase (MPO) immunostaining	diagnosis of acute myeloid leukemia
Bladder tumor antigen (BTA) Stat test; or nuclear matrix protein (NMP22) test; or fibrin/fibrinogen degradation products (Aura-Tek FDP) test; or the UroVysion fluorescent in situ hybridization (FISH) test	Medically necessary in any of the following conditions: <ol style="list-style-type: none"> 1. Follow-up of treatment for bladder cancer; <i>or</i> 2. Monitoring for eradication of bladder cancer; <i>or</i> 3. Recurrences after eradication. Covered ICD9 codes: 188.0 – 188.9 Malignant neoplasm of bladder 233.7 Carcinoma in situ of bladder 239.4 Neoplasm of unspecified nature, bladder V10.51 Personal history of malignant neoplasm of bladder

APPENDIX II
Non-Covered Markers

Marker	Application
Carcinoembryonic antigen cellular adhesion molecule-7 (CEACAM-7) expression	Predictive marker for rectal cancer recurrence



Cofilin (CFL1)	Prognostic and drug resistance marker in non-small cell lung cancer
Autoantibody detection i.e. EarlyCDT-Lung test	Screening test for the early detection of lung cancer
Mammostrat test	Used for predicting recurrence of breast cancer
Mucin 4 expression	Used as a predictor of survival in colorectal cancer
PreOvar test for the KRAS-variant	To determine ovarian cancer risk
Human epididymis protein 4 (HE4) for any indication, including assessment of ovarian adnexal mass or to monitor recurrence of ovarian cancer	To monitor recurrence of ovarian cancer
ProOnc TumorSourceDx test to identify tissue or origin for metastatic tumors	To identify tissue or origin for metastatic tumors
Immunological techniques designed to detect epithelial cells circulating in the blood to quantify circulating tumor cells (i.e. The CellSearch™ System)	To detect epithelial cells circulating in the blood to quantify circulating tumor cells for any cancer, including, but not limited to, metastatic breast, colorectal, or prostate cancers
Serum amyloid A recurrence and response to therapy	Biomarker for endometrial endometrioid carcinoma to monitor disease
Caris Target Now Molecular Profiling Test	
Biomarker translation test (i.e. BT Test™)	Early breast cancer detection
Fibrin/fibrinogen degradation products (FDP) testing, i.e., Onko-Sure™ blood test	
Guanylyl cyclase c (GCC or GUCY2C), i.e., Previstage™ GCC Colorectal Cancer Stage Test	
Lectin-reactive alpha-fetoprotein (AFP-L3)	



Prostate PX®	
Septin 9 (SEPT9) DNA methylation assay, i.e., Epi proColon or ColoVantage™	Early detection of colorectal cancer
Topographic genotyping, such as PathFinderTG®	For any indication including breast cancer and pancreatic cancer
Topoisomerase II alpha (TOP2A) gene amplification or deletion, i.e., TOP2A FISH pharmDx™ Assay	

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