

Reimbursement Policy

Serum Tumor Markers for Malignancies

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I. Policy Description

Circulating tumor biomarkers are substances detected in the blood, urine, or other body fluids that are either produced by a tumor itself or in response to its presence. These biomarkers can be used to help detect, diagnose, stage, and manage some types of cancer, because their amounts are typically elevated in individuals harboring a tumor (Hottinger & Hormigo, 2011; NCI, 2023). There are currently dozens of tumor markers in common use; this laboratory policy addresses tumor markers which may be measured in an individual’s serum.

Terms such as male and female are used when necessary to refer to sex assigned at birth.

The following management of serum tumor markers is built from recommendations from the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium®, which contains information “designed to support decision making around the use of biomarker testing in patients with cancer. The NCCN Biomarkers Compendium® is updated in conjunction with the NCCN Guidelines on a continual basis” (NCCN, 2023).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

Note: Except for where otherwise specified in the coverage criteria below, quarterly measurement of designated serum tumor markers is permitted for follow-up, monitoring, and/or surveillance

- 1) Measurement of the following serum tumor markers **MEETS COVERAGE CRITERIA** for the following indications:

Serum Tumor Marker	Indication
Alkaline phosphatase (ALP)	Bone neoplasms: workup; during treatment; surveillance
	Systemic light chain amyloidosis: initial diagnostic workup
Alpha fetoprotein (AFP)	Hepatocellular carcinoma: screening; workup for confirmed HCC; surveillance (every 3-6 months for 2 years, then every 6 months)
	Intrahepatic cholangiocarcinoma: workup for isolated intrahepatic mass

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Serum Tumor Marker	Indication
	<p>Occult primary: additional workup for localized adenocarcinoma or carcinoma not otherwise specified; liver, mediastinum, or retroperitoneal mass</p> <hr/> <p>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)</p> <hr/> <p>Ovarian cancers (less common):</p> <ul style="list-style-type: none"> – Carcinosarcoma (malignant mixed mullerian tumors): monitoring/follow-up – Clear cell carcinoma of the ovary: monitoring/follow-up – Grade 1 endometrioid carcinoma: monitoring/follow-up – Mucinous neoplasms of the ovary: monitoring/follow-up – Low-grade serous carcinoma: monitoring/follow-up <hr/> <p>Ovarian cancers:</p> <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated) – Malignant germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) <hr/> <p>Testicular cancer – nonseminoma: post-diagnostic workup; risk classification; surveillance (no more than every 2 months)</p> <hr/> <p>Testicular cancer - pure seminoma: initial diagnostic workup; post-diagnostic workup; risk classification; post-treatment surveillance (no more than every 2 months)</p> <hr/> <p>Thymomas and thymic carcinomas: initial evaluation, if appropriate</p>
<p>Beta-2 microglobulin (B2M)</p>	<p>B-cell lymphomas (Castleman disease; diffuse large B-cell; follicular [grade 1-2]; HIV-related; lymphoblastic; mantle cell): workup</p> <hr/> <p>Chronic lymphocytic leukemia/small lymphocytic lymphoma: workup; for prognostic and/or therapy determination</p> <hr/> <p>Multiple myeloma: initial diagnostic workup; follow-up/surveillance (as needed) for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement</p> <hr/> <p>Systemic light chain amyloidosis: initial diagnostic workup</p>

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Serum Tumor Marker	Indication
	Waldenström macroglobulinemia / lymphoplasmacytic lymphoma: workup
Beta human chorionic gonadotropin (beta-HCG)	<p>Gestational trophoblastic neoplasia: initial workup; during and post treatment (no more than weekly); follow-up/surveillance (no more than monthly for 12 months)</p> <hr/> <p>Occult primary: additional workup for localized adenocarcinoma or carcinoma not otherwise specified; individuals < 65 years of age with testes presenting with retroperitoneal mass</p> <hr/> <p>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)</p> <hr/> <p>Ovarian cancers:</p> <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated) – Malignant germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) <hr/> <p>Testicular cancer – nonseminoma: post-diagnostic workup; risk classification; surveillance (no more than every 2 months)</p> <hr/> <p>Testicular cancer - pure seminoma: initial diagnostic workup; post-diagnostic workup; risk classification; post-treatment surveillance (no more than every 2 months)</p> <hr/> <p>Thymomas and thymic carcinomas: initial evaluation, if appropriate</p>
BNP or NT-proBNP	<p>Multiple myeloma: initial diagnostic workup</p> <hr/> <p>Systemic light chain amyloidosis: initial diagnostic workup</p>
Calcitonin (CALCA)	<p>Adenocarcinoma, and anaplastic/undifferentiated epithelial tumors: workup</p> <hr/> <p>Medullary carcinoma: additional workup; post-surgical evaluation; monitoring; surveillance (2-3 months postoperative, then every 6-12 months)</p> <hr/> <p>Multiple endocrine neoplasia, type 2: at diagnosis (clinical evaluation) for medullary thyroid cancer</p> <hr/> <p>Occult primary (unknown primary cancer): workup</p>

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Serum Tumor Marker	Indication
Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29)	<p>Breast cancer (invasive): monitoring metastatic disease</p> <hr/> <p>Occult primary: suspected metastatic malignancy: initial workup; assessing disease prognosis; monitoring/follow-up for response</p>
Cancer antigen 19-9 (CA 19-9)	<p>Ampullary adenocarcinoma: workup; surveillance (every 3-6 months for 2 years, then every 6-12 months for up to 5 years as clinically indicated) for resected ampullary cancer, stage I-III</p> <hr/> <p>Appendiceal adenocarcinoma: workup to establish baseline. Abnormal measurements should be trended</p> <hr/> <p>Extrahepatic cholangiocarcinoma: workup to establish baseline; monitoring</p> <hr/> <p>Gallbladder cancer: workup to establish baseline; monitoring; surveillance (as clinically indicated), post-resection</p> <hr/> <p>Intrahepatic cholangiocarcinoma: workup to establish baseline; monitoring</p> <hr/> <p>Occult primary: workup to establish baseline; assessing disease prognosis; monitoring/follow-up for response</p> <hr/> <p>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)</p> <hr/> <p>Ovarian cancers (less common):</p> <ul style="list-style-type: none"> – Carcinosarcoma (malignant mixed mullerian tumors): workup – Clear cell carcinoma of the ovary: workup – Grade 1 endometrioid carcinoma: workup – Low-grade serous carcinoma: workup – Mucinous neoplasms of the ovary: workup <hr/> <p>Ovarian cancers</p> <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated) – Malignant germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)

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Serum Tumor Marker	Indication
	<ul style="list-style-type: none"> – Mucinous carcinoma of the ovary: additional workup (if not previously done) <hr/> <p>Pancreatic adenocarcinoma: workup to establish baseline; monitoring; post-operative, post-adjuvant treatment surveillance (every 3-6 months for 2 years, then every 6-12 months as clinically indicated)</p> <hr/> <p>Small bowel adenocarcinoma: workup to establish baseline; post-treatment surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years); at metastasis or recurrence</p>
<p>Cancer antigen 125 (CA-125)</p>	<p>Appendiceal adenocarcinoma: workup to establish baseline</p> <hr/> <p>Endometrial carcinoma: additional workup; surveillance (if initially elevated)</p> <hr/> <p>Lynch syndrome: surveillance</p> <hr/> <p>Occult primary: additional workup for adenocarcinoma or carcinoma not otherwise specified, in those with a uterus and/or ovaries present</p> <hr/> <p>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)</p> <hr/> <p>Ovarian cancers (less common):</p> <ul style="list-style-type: none"> – Carcinosarcoma (malignant mixed mullerian tumors): monitoring/follow-up – Clear cell carcinoma of the ovary: monitoring/follow-up – Mucinous neoplasms of the ovary: monitoring/follow-up – Grade 1 endometrioid carcinoma: monitoring/follow-up – Low-grade serous carcinoma: monitoring/follow-up <hr/> <p>Ovarian cancers:</p> <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated) – Malignant germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) <hr/> <p>Peritoneal mesothelioma: initial evaluation</p> <hr/> <p>Uterine neoplasms: initial workup</p>

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Serum Tumor Marker	Indication
Carcinoembryonic antigen (CEA)	Appendiceal adenocarcinoma: workup to establish baseline; monitoring; post-treatment surveillance
	Breast cancer (invasive): Monitoring metastatic disease
	Colon cancer: workup to establish baseline; monitoring; surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	Extrahepatic cholangiocarcinoma: workup to establish baseline; monitoring
	Gallbladder cancer: workup to establish baseline; monitoring; surveillance; monitoring of adjuvant treatment (as clinically indicated), post-resection
	Intrahepatic cholangiocarcinoma: workup to establish baseline; monitoring
	Medullary carcinoma: diagnosis and additional workup; monitoring; post-surgical surveillance (2-3 months postoperative, then every 6-12 months)
	Multiple endocrine neoplasia, type 2: at diagnosis (clinical evaluation) for medullary thyroid cancer
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)
	Ovarian cancers (less common): <ul style="list-style-type: none"> – Carcinosarcoma (malignant mixed mullerian tumors): monitoring/follow-up – Clear cell carcinoma of the ovary: monitoring/follow-up – Grade 1 endometrioid carcinoma: monitoring/follow-up – Low-grade serous carcinoma: monitoring/follow-up – Mucinous neoplasms of the ovary: monitoring/follow-up
	Ovarian cancers : <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated); post-adjuvant treatment – Malignant germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)

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Serum Tumor Marker	Indication
	<ul style="list-style-type: none"> – Mucinous carcinoma of the ovary: additional workup (if not previously done) <hr/> <p>Rectal cancer: workup to establish baseline; monitoring; surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)</p> <hr/> <p>Small bowel adenocarcinoma: workup to establish baseline; post-treatment surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)</p>
Inhibin (INHA)	<p>Adrenocortical carcinoma: workup</p> <hr/> <p>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)</p> <hr/> <p>Ovarian cancers (less common):</p> <ul style="list-style-type: none"> – Carcinosarcoma (malignant mixed mullerian tumors): monitoring/follow-up – Clear cell carcinoma of the ovary: monitoring/follow-up – Grade 1 endometrioid carcinoma: monitoring/follow-up – Low-grade serous carcinoma: monitoring/follow-up – Mucinous neoplasms of the ovary: monitoring/follow-up <hr/> <p>Ovarian cancers:</p> <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated) – Malignant Germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
Lactate dehydrogenase (LDH)	<p>B-cell lymphomas (Burkitt; Castleman disease; diffuse large B-cell; extranodal marginal zone lymphoma of nongastric sites [noncutaneous] and of the stomach; follicular [grade 1-2]; HIV-related; lymphoblastic; mantle cell; nodal marginal zone; pediatric aggressive mature; post-transplant lymphoproliferative disorders; primary cutaneous; splenic marginal zone): workup</p> <hr/> <p>Bone neoplasms: workup</p> <hr/> <p>Chronic lymphocytic leukemia/small lymphocytic lymphoma: workup, and at transformation or histologic progression (if applicable)</p>

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Serum Tumor Marker	Indication
	Hairy cell leukemia: workup
	Kidney cancer: initial workup
	Melanoma (cutaneous and uveal): workup for metastatic or recurrent disease
	Multiple myeloma: initial workup; surveillance (as needed) post primary treatment for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: initial workup; during primary chemotherapy, monitoring/follow-up for complete response (as clinically indicated)
	Ovarian cancers (less common): <ul style="list-style-type: none"> – Carcinosarcoma (malignant mixed mullerian tumors): monitoring/follow-up – Clear cell carcinoma of the ovary: monitoring/follow-up – Grade 1 endometrioid carcinoma: monitoring/follow-up – Low-grade serous carcinoma: monitoring/follow-up – Mucinous neoplasms of the ovary: monitoring/follow-up
	Ovarian cancers: <ul style="list-style-type: none"> – Borderline epithelial tumors: monitoring/follow-up (every visit if initially elevated) – Malignant germ cell tumors: surveillance (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: surveillance if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
	Primary cutaneous lymphomas (mycosis fungoides/Sezary syndrome; primary cutaneous CD30+ T-cell lymphoproliferative disorders): workup
	Systemic light chain amyloidosis: initial diagnostic workup
	Systemic mastocytosis: initial diagnostic workup
	T-cell lymphomas (adult T-cell; breast implant-associated ALCL; extranodal NK/T-cell; hepatosplenic; peripheral; T-cell prolymphocytic leukemia): workup; staging (breast implant-associated ALCL only)
	Testicular cancer – nonseminoma: post-diagnostic workup; risk classification; surveillance (no more than every 2 months)

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Serum Tumor Marker	Indication
	Testicular cancer – pure seminoma: initial diagnostic workup; post-diagnostic workup; risk classification; post-treatment surveillance (no more than every 2 months)
	Waldenström macroglobulinemia / lymphoplasmacytic lymphoma: workup
Serum free light chain	Multiple myeloma: initial diagnostic workup; surveillance (up to once per month)
	Systemic light chain amyloidosis: initial diagnostic workup
Troponin T	Systemic light chain amyloidosis: initial diagnostic workup
Tryptase	Systemic mastocytosis: initial diagnosis

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 2) For all other cancer indications not discussed above, use of the above biomarkers (alone or in a panel of serum tumor markers) **DOES NOT MEET COVERAGE CRITERIA.**
- 3) All other serum tumor markers not addressed above (alone or in a panel of serum tumor markers) **DO NOT MEET COVERAGE CRITERIA.**
- 4) For the screening and detection of cancer, analysis of proteomic patterns in serum **DOES NOT MEET COVERAGE CRITERIA.**

III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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There are numerous FDA-approved tests for the assessment of serum tumor markers. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid Services (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

IV. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
82105	Alpha-fetoprotein (AFP); serum
82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)
82232	Beta-2 microglobulin
82308	Calcitonin
82378	Carcinoembryonic antigen (CEA)
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83521	Immunoglobulin light chains (ie, kappa, lambda), free, each
83615	Lactate dehydrogenase (LD), (LDH);
83789	Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
83880	Natriuretic peptide
83950	Oncoprotein; HER-2/neu
83951	Oncoprotein; des-gamma-carboxy-prothrombin (DCP)
84075	Phosphatase, alkaline
84078	Phosphatase, alkaline; heat stable (total not included)
84080	Phosphatase, alkaline; isoenzymes
84484	Troponin, quantitative
84702	Gonadotropin, chorionic (hCG); quantitative
84703	Gonadotropin, chorionic (hCG); qualitative
84704	Gonadotropin, chorionic (hCG); free beta chain
84999	Unlisted chemistry procedure
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
86305	Human epididymis protein 4 (HE4)

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CPT	Code Description
86316	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549),
86336	Inhibin A
0404U	Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression Proprietary test: Divitum®Tka Lab/Manufacturer: Biovica Inc

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Evidence-based Scientific References

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