If a conflict arises between a Clinical Payment and Coding Policy and any plan document under which a member is entitled to Covered Services, the plan document will govern. If a conflict arises between a CPCP and any provider contract pursuant to which a provider participates in and/or provides Covered Services to eligible member(s) and/or plans, the provider contract will govern. "Plan documents" include, but are not limited to, Certificates of Health Care Benefits, benefit booklets, Summary Plan Descriptions, and other coverage documents. Blue Cross and Blue Shield of Illinois may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSIL has full and final discretionary authority for their interpretation and application to the extent provided under any applicable plan documents.

Providers are responsible for submission of accurate documentation of services performed. Providers are expected to submit claims for services rendered using valid code combinations from Health Insurance Portability and Accountability Act approved code sets. Claims should be coded appropriately according to industry standard coding guidelines including, but not limited to: Uniform Billing Editor, American Medical Association, Current Procedural Terminology, CPT® Assistant, Healthcare Common Procedure Coding System, ICD-10 CM and PCS, National Drug Codes, Diagnosis Related Group guidelines, Centers for Medicare and Medicaid Services National Correct Coding Initiative Policy Manual, CCI table edits and other CMS guidelines.

Claims are subject to the code edit protocols for services/procedures billed. Claim submissions are subject to claim review including but not limited to, any terms of benefit coverage, provider contract language, medical policies, clinical payment and coding policies as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

Serum Tumor Markers for Malignancies

Policy Number: CPCPLAB037

Version 1.0

Approval Date: September 5, 2025

Plan Effective Date: January 1, 2026

Description

The Plan has implemented certain lab management reimbursement criteria. Not all requirements apply to each product. Providers are urged to review Plan documents for eligible coverage for services rendered.

Reimbursement Information

NOTE: Except for where otherwise specified in the table below, quarterly measurement of designated serum biomarkers is permitted for follow-up, monitoring, and/or surveillance.

1) Measurement of the following serum biomarkers **may be reimbursable** for the following indications:

Serum Biomarker	Indication
Alkaline phosphatase (ALP)	Bone neoplasms: • Workup
	Melanoma (uveal): • Workup
	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
	Occult primary: • Additional workup for localized adenocarcinoma or carcinoma not otherwise specified; liver, mediastinum, or retroperitoneal mass
	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):
	• Carcinosarcoma (malignant mixed mullerian tumors):
	  ○ Monitoring;
	  ○ Follow-up
	• Clear cell carcinoma of the ovary:
	  ○ Monitoring;
	  ○ Follow -up

Serum Biomarker	Indication

	• Mucinous neoplasms of the ovary:
	  ○ Monitoring
	  ○ Follow-up
	• Low-grade serous carcinoma:
	  ○ Monitoring
	  ○ Follow-up
	Ovarian cancers:
	• 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)

	Testicular cancer – non-seminoma: • Workup; • Risk classification; • Surveillance (no more than every 2 months)
	Testicular cancer - pure seminoma: • Initial diagnostic workup; • Post-diagnostic workup; • Risk classification; • Post-treatment surveillance (no more than every 2 months)
	Thymomas and thymic carcinomas: • Initial evaluation, if appropriate
Beta-2 microglobulin (B2M)	B-cell lymphomas (diffuse large B-cell; follicular [grade 1-2]; HIV-related; lymphoblastic; mantle cell): • Workup
	Castleman Disease: • Workup
	Chronic lymphocytic leukemia/small lymphocytic lymphoma: • Workup • For prognostic and/or therapy determination
	Multiple myeloma: • Initial diagnostic workup; • Follow-up/surveillance (as needed) for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement
	Systemic light chain amyloidosis:

Serum Biomarker	Indication
	• Initial diagnostic workup
	Waldenström macroglobulinemia / lymphoplasmacytic lymphoma: • Workup
BNP or NT-proBNP	Multiple myeloma: • Initial diagnostic workup
Calcitonin (CALCA)	Adenocarcinoma, and anaplastic/undifferentiated epithelial tumors: • Workup
	Medullary carcinoma: • Additional workup; • Post-surgical evaluation; • Monitoring; • Surveillance (2-3 months postoperative, then every 6-12 months)
	Multiple endocrine neoplasia, type 2: • At diagnosis (clinical evaluation) for medullary thyroid cancer
	Occult primary (unknown primary cancer): • Workup
Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29)	Breast cancer (invasive): • Monitoring metastatic disease
	Occult primary- suspected metastatic malignancy: • Initial workup; • Assessing disease prognosis; • Monitoring/follow-up for response
Cancer antigen 19-9 (CA 19-9)	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
	Appendiceal adenocarcinoma: • Workup to establish baseline. Abnormal measurements should be trended.
	Extrahepatic cholangiocarcinoma: • Workup to establish baseline; • Monitoring
	Gallbladder cancer: • Workup to establish baseline; • Monitoring; • Surveillance (as clinically indicated), post-resection
	Intrahepatic cholangiocarcinoma: • Workup to establish baseline; • Monitoring

Serum Biomarker	Indication
	Occult primary: • Workup to establish baseline
	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):
	• Carcinosarcoma (malignant mixed mullerian tumors):
	  ○ Workup
	  ○ Monitoring/follow-up
	• Clear cell carcinoma of the ovary:
	  ○ Workup
	  ○ Monitoring/follow-up
	• Grade 1 endometrioid carcinoma:
	  ○ Workup
	  ○ Monitoring/follow-up
	• Low-grade serous carcinoma:
	  ○ Workup
	  ○ Monitoring/follow-up
	• Mucinous neoplasms of the ovary:
	  ○ Workup
	  ○ Monitoring/follow-up
	Ovarian cancers:
	• 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)
	• Mucinous carcinoma of the ovary:
	  ○ Additional workup (if not previously done)

	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)

Serum Biomarker	Indication
	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
Cancer antigen 125 (CA-125)	Appendiceal adenocarcinoma: • Workup to establish baseline
	Endometrial carcinoma: • Additional workup; • Surveillance (if initially elevated)
	Lynch syndrome: • Surveillance
	Occult primary: • Initial evaluation/workup; • Additional workup for adenocarcinoma or carcinoma not otherwise specified, in those with a uterus and/or ovaries present
	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):
	• Carcinosarcoma (malignant mixed mullerian tumors):
	  ○ Monitoring/follow-up
	• Clear cell carcinoma of the ovary:
	  ○ Monitoring/follow-up
	• Mucinous neoplasm of the ovary:
	  ○ Monitoring/follow-up
	• Grade 1 endometrioid carcinoma:
	  ○ Monitoring/follow-up
	• Low-grade serous carcinoma:
	  ○ Monitoring/follow-up
	Ovarian cancers:
	• 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 6 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

Serum Biomarker	Indication
	early-stage, low-risk disease; 4-6 months if high-risk disease)
	Peritoneal mesothelioma: • Initial evaluation
	Uterine neoplasms • Initial workup; • Additional workup; • Surveillance
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
	Occult primary (unknown primary cancer): • Workup for adenocarcinoma or carcinoma not otherwise specified
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: • Initial workup; • During primary chemotherapy;

Serum Biomarker	Indication
	• Monitoring/follow-up for complete response (as clinically indicated)

	Ovarian cancers (less common):
	• 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:
	• 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)
	Mucinous carcinoma of the ovary:
	• Additional workup (if not previously done)

	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)
	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)
Chorionic gonadotropin beta polypeptide (CGB3)	Gestational trophoblastic neoplasia: • Initial workup; • During and post treatment (no more than weekly); • Follow-up/surveillance (no more than monthly for 12 months)
	Occult primary: • Additional workup for localized adenocarcinoma or

Serum Biomarker	Indication
	carcinoma not otherwise specified; individuals < 65 years of age with mediastinum or retroperitoneal mass
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: • Initial workup; • During primary chemotherapy; • Monitoring/follow-up for complete response (as clinically indicated)

	Ovarian cancers:
	• 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)

	Testicular cancer – non-seminoma: • Workup; • Risk classification; • Surveillance (no more than every 2 months)
	Testicular cancer – pure seminoma: • Workup; • Post-diagnostic workup; • Risk classification; • Post-treatment surveillance (no more than every 2 months)
	Thymomas and thymic carcinomas: • Initial evaluation, if appropriate
Human epididymis protein 4 (HE4)	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):
	• Carcinosarcoma (malignant mixed mullerian tumors:
	  ○ Monitoring/follow-up
	• Clear cell carcinoma of the ovary:
	  ○ Monitoring/follow-up

Serum Biomarker	Indication

	• Grade 1 endometrioid carcinoma:
	  ○ Monitoring/follow-up
	• Low-grade serous carcinoma:
	  ○ Monitoring/follow-up
	• Mucinous neoplasms of the ovary:
	  ○ Monitoring/follow-up
	Ovarian cancers:
	• 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)

Inhibin (INHA)	Occult primary (unknown primary cancer): • Additional workup for adenocarcinoma or carcinoma not otherwise specified
	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):
	• 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:
	• Borderline epithelial tumors:
	  ○ Monitoring/follow-up (every visit if initially elevated)
	• Malignant germ cell tumors:

Serum Biomarker	Indication
	○ 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)
Serum free light chains	Castleman disease: • Workup
	Multiple myeloma: • Initial diagnostic workup; • Follow-up • 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

2) For all other cancer indications not discussed above, use of the above biomarkers (alone or in a panel of serum tumor markers) **are not reimbursable.**

3) All other serum tumor markers not addressed above (alone or in a panel of serum tumor markers) **are not reimbursable.**

4) For the screening and detection of cancer, analysis of proteomic patterns in serum **are not reimbursable**.

Procedure Codes

The following is not an all-encompassing code list. The inclusion of a code does not guarantee it is a covered service or eligible for reimbursement.

Codes
81500, 81503, 81538, 81599, 82105, 82107, 82232, 82308, 82378, 83520, 83521, 83789, 83880, 83950, 83951, 84075, 84078, 84080, 84484, 84702, 84703, 84704, 84999, 86300, 86301, 86304, 86305, 86316, 86336, 0003U, 0092U, 0163U, 0404U, 0558U, 0559U, 0599U, G0327

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Policy Update History

Approval Date	Effective Date; Summary of Changes
09/05/2025	01/01/2026: New policy