

Reimbursement Policy

Policy Number: RPLAB037

Policy Title: Serum Tumor Markers for Malignancies

Approval Date: May 15, 2026

Effective Date: Sept. 4, 2026

Policy Disclaimer

If a conflict arises between a Reimbursement 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 reimbursement policy 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's 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 Oklahoma may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSOK has full and final discretionary authority for their interpretation and application to the extent provided under any applicable Plan documents.

Providers are responsible for submitting 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 ICD-10-PCS, National Drug Codes, Diagnosis Related Group guidelines, Centers for Medicare & 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 and procedures billed. Claim submissions are subject to claim review, including but not limited to, any terms of benefit coverage, provider contract language, medical policies, and reimbursement policies, as well as coding software logic. Upon request, the provider is urged to submit any additional documentation.

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 Biomarkers	Indication
Alkaline phosphatase (ALP)	<u>Bone neoplasms:</u> <ul style="list-style-type: none">• Workup for osteosarcoma
	<u>Melanoma (uveal):</u> <ul style="list-style-type: none">• Workup for distant metastatic disease
	<u>Systemic light chain amyloidosis:</u> <ul style="list-style-type: none">• Initial diagnostic workup to assess organ involvement for suspected SLCA
Alpha fetoprotein (AFP)	<u>Hepatocellular carcinoma:</u> <ul style="list-style-type: none">• Screening for at risk individuals due to Child-Turcotte-Pugh A or B cirrhosis or hepatitis B infection;• Workup for confirmed HCC;• Surveillance (every 3-6 months for 2 years, then every 6 months)
	<u>Intrahepatic cholangiocarcinoma:</u> <ul style="list-style-type: none">• Workup for isolated intrahepatic mass
	<u>Occult primary:</u> <ul style="list-style-type: none">• Additional workup for adenocarcinoma or carcinoma not otherwise specified with a clinical presentation in the liver or mediastinum, or for individuals <65 years of age with a retroperitoneal mass
	<u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> <ul style="list-style-type: none">• Initial workup for individuals with a suspicious mass found by palpation or imaging;• Monitoring prior to each cycle of chemotherapy;

	<ul style="list-style-type: none"> Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) <p><u>Ovarian cancers (less common):</u></p> <ul style="list-style-type: none"> Initial workup for newly diagnosed ovarian cancer Monitoring/follow-up for recurrence <p><u>Less common ovarian cancers (additional surveillance recommendations):</u></p> <ul style="list-style-type: none"> <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> Surveillance (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10) <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) <p><u>Testicular cancer:</u></p> <ul style="list-style-type: none"> Initial diagnostic workup for a suspicious testicular mass; Post-diagnostic workup; Post orchiectomy Follow-up for non-seminoma (no more than every 2 months) Follow-up for pure seminoma (no more than every 3 months) <p><u>Thymomas and thymic carcinomas:</u></p> <ul style="list-style-type: none"> Initial evaluation for individuals with a mediastinal mass
<p>Beta-2 microglobulin (B2M)</p>	<p><u>B-cell lymphomas (classic follicular, diffuse large B-cell; HIV-related; lymphoblastic; mantle cell):</u></p> <ul style="list-style-type: none"> Additional workup for specified B-cell lymphomas <p><u>Castleman Disease:</u></p> <ul style="list-style-type: none"> Additional workup with established diagnosis <p><u>Chronic lymphocytic leukemia/small lymphocytic lymphoma:</u></p> <ul style="list-style-type: none"> Additional workup with established diagnosis For prognostic and/or therapy determination <p><u>Multiple myeloma:</u></p> <ul style="list-style-type: none"> Initial diagnostic workup; <p><u>Systemic light chain amyloidosis:</u></p> <ul style="list-style-type: none"> Initial diagnostic workup to assess organ involvement for suspected SLCA

	<p>Waldenström macroglobulinemia / lymphoplasmacytic lymphoma:</p> <ul style="list-style-type: none"> • Additional workup with established diagnosis
BNP or NT-proBNP	<p>Multiple myeloma:</p> <ul style="list-style-type: none"> • Initial diagnostic workup
	<p>Systemic light chain amyloidosis:</p> <ul style="list-style-type: none"> • Initial diagnostic workup to assess organ involvement for suspected SLCA
Calcitonin (CALCA)	<p>Head and neck cancer – occult primary:</p> <ul style="list-style-type: none"> • Additional workup for squamous cell carcinoma, adenocarcinoma, and anaplastic undifferentiated epithelial tumors of the neck
	<p>Medullary carcinoma:</p> <ul style="list-style-type: none"> • Additional workup with established diagnosis; • Surveillance (every 6-12 months)
	<p>Multiple endocrine neoplasia, type 2:</p> <ul style="list-style-type: none"> • At diagnosis (clinical evaluation) to assess risk for medullary thyroid cancer
Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29)	<p>Breast cancer (invasive):</p> <ul style="list-style-type: none"> • Monitoring metastatic disease
	<p>Occult primary: suspected metastatic malignancy:</p> <ul style="list-style-type: none"> • Initial workup
Cancer antigen 19-9 (CA 19-9)	<p>Ampullary adenocarcinoma:</p> <ul style="list-style-type: none"> • Additional workup with established diagnosis; • Surveillance for resected ampullary cancer (every 3-6 months for 2 years, every 6-12 months for up to 5 years as clinically indicated)
	<p>Appendiceal adenocarcinoma:</p> <ul style="list-style-type: none"> • Workup to establish baseline when imaging suggests appendiceal neoplasm or cancer or when there is a confirmed appendiceal neoplasm or cancer; • Workup for recurrence (3-6 months after CT imaging); • Surveillance (every 6-12 months for 2 years; annually up to 10 years)
	<p>Extrahepatic cholangiocarcinoma:</p> <ul style="list-style-type: none"> • Workup to establish baseline for individuals with abdominal pain, jaundice, abnormal liver function tests, or obstruction or abnormality on imaging
	<p>Gallbladder cancer:</p> <ul style="list-style-type: none"> • Workup to establish baseline; for individuals with jaundice or a mass on imaging; • Post-operative workup of a suspicious mass;

	<ul style="list-style-type: none"> • Surveillance (as clinically indicated), post-resection
	<p><u>Intrahepatic cholangiocarcinoma:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline for an isolated intrahepatic mass
	<p><u>Occult primary- suspected metastatic malignancy:</u></p> <ul style="list-style-type: none"> • Initial workup
	<p><u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u></p> <ul style="list-style-type: none"> • Initial workup for individuals with a suspicious mass found by palpation or imaging; • Monitoring prior to each cycle of chemotherapy; • Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5)
	<p><u>Ovarian cancers (less common):</u></p> <ul style="list-style-type: none"> • Initial workup for newly diagnosed ovarian cancer; • Monitoring/follow-up for recurrence
	<p><u>Less common ovarian cancers (additional surveillance recommendations):</u></p> <ul style="list-style-type: none"> • <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> ○ Surveillance (every 2 months in year 1; every 3 months in year 2; every 6 months in year 3; year 4 and beyond, annual testing up to year 10) • <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> ○ Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
	<p><u>Pancreatic adenocarcinoma:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline when there is either a clinical suspicion of pancreatic cancer with suspicious imaging or evidence of dilated pancreatic and/or bile duct (stricture) and when no metastatic disease is detected; • Post-operative, post-adjuvant treatment surveillance as appropriate
	<p><u>Small bowel adenocarcinoma:</u></p> <ul style="list-style-type: none"> • Additional workup with established diagnosis; • Post-treatment surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years) • Additional workup for metastatic adenocarcinoma
Cancer antigen 125 (CA-125)	<p><u>Appendiceal adenocarcinoma:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline when imaging suggests appendiceal neoplasm or cancer or when

	<p>there is a confirmed appendiceal neoplasm or cancer;</p> <ul style="list-style-type: none"> • Workup for recurrence (3-6 months after CT imaging); • Surveillance (every 6-12 months for 2 years; annually up to year 10)
	<p><u>Endometrial carcinoma:</u></p> <ul style="list-style-type: none"> • Additional workup; • Surveillance (if initially elevated)
	<p><u>Occult primary:</u></p> <ul style="list-style-type: none"> • Initial workup for suspected metastatic malignancy; • Additional workup for adenocarcinoma or carcinoma not otherwise specified (in those with a uterus and/or ovaries present) with a clinical presentation in the peritoneal/ascites or inguinal nodes
	<p><u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u></p> <ul style="list-style-type: none"> • Initial workup for individuals with a suspicious mass found by palpation or imaging; • Monitoring prior to each cycle of chemotherapy; • Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5)
	<p><u>Ovarian cancers (less common):</u></p> <ul style="list-style-type: none"> • Initial workup for newly diagnosed ovarian cancer; • Monitoring/follow-up for recurrence
	<p><u>Less common ovarian cancers (additional surveillance recommendations):</u></p> <ul style="list-style-type: none"> • <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> ○ Surveillance (every 2 months in year 1; every 3 months in year 2; every 6 months in year 3; year 4 and beyond, annual testing up to year 10) • <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> • Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)

	<p><u>Uterine neoplasms:</u></p> <ul style="list-style-type: none"> • Initial diagnostic workup for known or suspected malignancy; • Additional workup for serous, clear cell carcinoma, undifferentiated/dedifferentiated carcinoma, carcinosarcoma, suspected extrauterine disease; • Surveillance in endometrial carcinoma if initially evaluated
<p>Carcinoembryonic antigen (CEA)</p>	<p><u>Appendiceal adenocarcinoma:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline when imaging suggests appendiceal neoplasm or cancer or when there is a confirmed appendiceal neoplasm or cancer • Workup for recurrence (3-6 months after CT imaging); • Surveillance (every 6-12 months for 2 years; annually up to year 10)
	<p><u>Breast cancer (invasive):</u></p> <ul style="list-style-type: none"> • Monitoring metastatic disease
	<p><u>Colon cancer:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline for a pedunculated or sessile polyp with invasive cancer, colon cancer appropriate for resection, and suspected or proven metastatic adenocarcinoma; • Surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	<p><u>Extrahepatic cholangiocarcinoma:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline for individuals with abdominal pain, jaundice, abnormal liver function test, or obstruction or abnormality on imaging;
	<p><u>Gallbladder cancer:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline for individuals with jaundice or a mass on imaging; • Post-operative workup of a suspicious mass; • Surveillance (as clinically indicated) post-resection
	<p><u>Intrahepatic cholangiocarcinoma:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline for an isolated intrahepatic mass
	<p><u>Medullary carcinoma:</u></p> <ul style="list-style-type: none"> • Additional workup with established diagnosis; • Surveillance (every 6-12 months)
	<p><u>Multiple endocrine neoplasia, type 2:</u></p> <ul style="list-style-type: none"> • At diagnosis (clinical evaluation) to assess risk for medullary thyroid cancer

	<p><u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u></p> <ul style="list-style-type: none"> • Initial workup for individuals with a suspicious mass found by palpation or imaging; • Monitoring prior to each cycle of chemotherapy; • Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5)
	<p><u>Ovarian cancers (less common):</u></p> <ul style="list-style-type: none"> • Initial workup for newly diagnosed ovarian cancer; • Monitoring/follow-up for recurrence
	<p><u>Less common ovarian cancers (additional surveillance recommendations):</u></p> <ul style="list-style-type: none"> • <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> ○ Surveillance (every 2 months in year 1; every 3 months in year 2; every 6 months in year 3; year 4 and beyond, annual testing up to year 10)) • <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> ○ Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
	<p><u>Rectal cancer:</u></p> <ul style="list-style-type: none"> • Workup to establish baseline for diagnosed rectal cancer or for pedunculated or sessile polyp with invasive cancer; • Surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	<p><u>Small bowel adenocarcinoma:</u></p> <ul style="list-style-type: none"> • Additional workup with established diagnosis; • Post-treatment surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years) • Additional workup for metastatic adenocarcinoma
<p>Chorionic gonadotropin beta polypeptide (CGB3)</p>	<p><u>Gestational trophoblastic neoplasia:</u></p> <ul style="list-style-type: none"> • Initial workup for suspected GTN; • During and post treatment (no more than weekly); • Follow-up/surveillance (no more than monthly for 12 months)
	<p><u>Occult primary:</u></p> <ul style="list-style-type: none"> • Additional workup for adenocarcinoma or carcinoma not otherwise specified with a clinical presentation in the mediastinum or for individuals < 65 years of age with a retroperitoneal mass

	<p><u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u></p> <ul style="list-style-type: none"> • Initial workup for individuals with a suspicious mass found on palpation or imaging; • Monitoring prior to each cycle of chemotherapy; • Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) <p><u>Less common ovarian cancers:</u></p> <ul style="list-style-type: none"> • Initial workup for newly diagnosed ovarian cancer; • Monitoring/follow-up for recurrence <p><u>Less common ovarian cancers (additional surveillance recommendations:</u></p> <ul style="list-style-type: none"> • <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> ○ Surveillance (every 2 months in year 1; every 3 months in year 2; every 6 months in year 3; year 4 and beyond, annual testing up to year 10) • <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> ○ Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) <p><u>Testicular cancer:</u></p> <ul style="list-style-type: none"> • Initial diagnostic workup for a suspicious testicular mass; • Post-diagnostic workup; • Post-orchietomy; • Follow-up for non-seminoma (no more than every 2 months) • Follow-up for pure seminoma (no more than every 3 months) <p><u>Thymomas and thymic carcinomas:</u></p> <ul style="list-style-type: none"> • Initial evaluation for individuals with a mediastinal mass
<p>Human epididymis protein 4 (HE4)</p>	<p><u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u></p> <ul style="list-style-type: none"> • Initial workup for individuals with a suspicious mass found on palpation or imaging; • Monitoring prior to each cycle of chemotherapy; • Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) <p><u>Ovarian cancers (less common):</u></p> <ul style="list-style-type: none"> • Initial workup for newly diagnosed ovarian cancer;

	<ul style="list-style-type: none"> Monitoring/follow-up for recurrence <p><u>Less common ovarian cancers (additional surveillance recommendations):</u></p> <ul style="list-style-type: none"> <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> Surveillance (every 2 months in year 1; every 3 months in year 2; every 6 months in year 3; year 4 and beyond, annual testing up to year 10) <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
Inhibin (INHA)	<p><u>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u></p> <ul style="list-style-type: none"> Initial workup for individuals with a suspicious mass found on palpation or imaging; Monitoring prior to each cycle of chemotherapy; Monitoring/follow-up for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) <p><u>Ovarian cancers (less common):</u></p> <ul style="list-style-type: none"> Initial workup for newly diagnosed ovarian cancer; Monitoring/follow-up for recurrence <p><u>Less common ovarian cancers (additional surveillance recommendations):</u></p> <ul style="list-style-type: none"> <u>Malignant germ cell tumors:</u> <ul style="list-style-type: none"> Surveillance (every 2 months in year 1; every 3 months in year 2; every 6 months in year 3; year 4 and beyond, annual testing up to year 10) <u>Malignant sex cord stromal tumors:</u> <ul style="list-style-type: none"> Surveillance if clinically indicated. If done, frequency based on stage (e.g., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
Serum free light chains	<p><u>Castleman disease:</u></p> <ul style="list-style-type: none"> Additional workup for established diagnosis <p><u>Multiple myeloma:</u></p> <ul style="list-style-type: none"> Initial diagnostic workup for multiple myeloma and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS);

	<ul style="list-style-type: none"> Follow-up/surveillance for solitary plasmacytoma (every 3-6 months), asymptomatic smoldering myeloma (every 3-6 months), symptomatic multiple myeloma
	<u>Systemic light chain amyloidosis:</u> <ul style="list-style-type: none"> Initial diagnostic workup
Troponin T	<u>Systemic light chain amyloidosis:</u> <ul style="list-style-type: none"> Initial diagnostic workup to assess organ involvement for suspected SLCA
Tryptase	<u>Systemic mastocytosis:</u> <ul style="list-style-type: none"> 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.

Code	Description
81500	ONCO (OVAR) TWO PROTEINS
81503	ONCO (OVAR) FIVE PROTEINS
81538	ONCOLOGY LUNG
82105	ALPHA-FETOPROTEIN SERUM
82107	ALPHA-FETOPROTEIN L3
82232	ASSAY OF BETA-2 PROTEIN
82308	ASSAY OF CALCITONIN
82378	CARCINOEMBRYONIC ANTIGEN
83520	IMMUNOASSAY QUANT NOS NONAB
83521	IG LIGHT CHAINS FREE EACH
83880	ASSAY OF NATRIURETIC PEPTIDE
83950	ONCOPROTEIN HER-2/NEU
83951	ONCOPROTEIN DCP
84075	ASSAY ALKALINE PHOSPHATASE
84484	ASSAY OF TROPONIN QUANT
84702	CHORIONIC GONADOTROPIN TEST
84704	HCG FREE BETACHAIN TEST

86300	IMMUNOASSAY TUMOR CA 15-3
86301	IMMUNOASSAY TUMOR CA 15-3
86304	IMMUNOASSAY TUMOR CA 125
86305	HUMAN EPIDIDYMIS PROTEIN 4
86316	IMMUNOASSAY TUMOR OTHER
86336	INHIBIN A
0003U	ONC OVAR 5 PRTN SER ALG SCOR
0092U	ONC LNG 3 PRTN BMRK PLSM ALG
0163U	ONC CLRCT SCR 3 PRTN ALG
0404U	ONC BRST SEMIQ MEAS THYM KN
0558U	ONC CLRCT ELISA BF7 AG SERUM
0559U	ONC BRS QUAN ELISA BF9AG SRM
0599U	ONC PNCRTC CA MULT IA SERUM
G0327	Colon ca scrn;bld-bsd biomrk

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Centers for Medicare & Medicaid Services. (2026). Healthcare Common Procedure Coding System (HCPCS) Level II.

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- NCCN. Biomarkers Compendium. <https://www.nccn.org/compendia-templates/compendia/biomarkers-compendium>
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- ASPIRA. OvaWatch. <https://aspirawh.com/ovawatch/>
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Policy History

Approval Date	Description
05/15/2026	09/04/2026; Document updated with literature review. The following changes were made: Revisions made to indications in numerous biomarkers to reflect current recommendations in NCCN Biomarker’s Compendium (e.g., for ALP testing for bone neoplasms, added “for osteosarcoma”). For BNP/NT-proBNP, added SLCA indications for testing. For calcitonin, CEA, and inhibin, removed “occult primary” recommendations, as the NCCN recommends these as an IHC marker for occult primary, not as a serum biomarker. For CA-125, removed “peritoneal mesothelioma” and “Lynch syndrome”, as the NCCN no longer includes it as a recommended biomarker. Removed codes 81599, 83789, 84078, 84080, 84703, 84999. References revised.
07/25/2025	11/07/2025; Document updated with literature review. The following changes were made to Reimbursement Information: Changed “serum tumor markers” to “biomarkers” in initial note and in #1 to broaden definition as some serum-related markers are more accurately describes as biomarkers rather than serum tumor markers. Changed title in table to “Serum Biomarkers.” Alkaline phosphatase: Removed “during treatment” and “surveillance” from Bone neoplasms indication; Added: Melanoma (uveal): Workup. Alpha fetoprotein: Removed “Post-diagnostic” from Workup under Testicular cancer – non-seminoma; Beta-2 microglobulin: removed “Castleman disease) from B-cell lymphoma title and added a new row which identifies the indication for Castleman disease as “workup” with B2M measurement; Beta human chorionic gonadotropin (beta HCG) was renamed to Chorionic gonadotropin beta polypeptide (CGB3); Changed the words “testes presenting with” to “mediastinum or” under “Occult primary” designation. BNP or NT-proBNP: For BNP or NT-proBNP, removed “systemic light chain amyloidosis” and indication for “initial diagnostic workup” from BNP or NT-proBNP section (this was moved to a separate section with Troponin T.). Cancer antigen 19-9: removed “Monitoring” from Occult primary indication; In “Ovarian cancers (less common)”:

	<p>Added "monitoring/follow up" as indications to "Carcinosarcoma, Clear cell carcinoma of the ovary, Grade 1 endometrial carcinoma, low-grade serous carcinoma," and "mucinous neoplasms of the ovary." Cancer antigen 125 (CA-125): For cancer antigen 125 (CA-125), added "initial evaluation/workup" to indications for Occult primary. Added "additional workup/surveillance" indications to uterine neoplasms. Carcinoembryonic antigen (CEA): For Carcinoembryonic antigen (CEA), added "Occult primary (unknown primary cancer)" and indication for "workup for adenocarcinoma or carcinoma not otherwise specified." Human epididymis protein 4 (HE4): For Human epididymis protein 4, added new section to the table. Added "Ovarian cancer/fallopian tube cancer/primary peritoneal cancer" with indications for "initial workup during primary chemotherapy; monitoring/follow-up for complete response (as clinically indicated)." Added "Ovarian cancers (less common) and indications for various cancers under this designation for "monitoring/follow-up." Added "Ovarian cancers" and additional indications for "borderline epithelial tumors." Added Inhibin (INHA) for Occult primary (unknown primary cancer); Ovarian cancer/fallopian tube cancer/primary peritoneal cancer; Ovarian cancers. Removed entire section on Lactate dehydrogenase (LDH) as LDH is a broad marker beyond serum tumor biomarker designation; Serum free light chains: Added "Castleman disease" with indication of workup; and added "follow-up" to Multiple myeloma. Added codes 0558U, 0559U effective 7/1/2025; added 0599U effective 10/1/2025; removed code 83615. References revised.</p>
10/30/2024	<p>01/15/2025; Document updated with literature review. The following changes were made to Reimbursement Information: Alpha fetoprotein: For "Ovarian cancers (less common)", added indication for Carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it. Beta-2 microglobulin (B2M): For chronic lymphocytic leukemia/small lymphocytic lymphoma, added indications for prognostic and/or therapy determination. Calcitonin (CALCA): For adenocarcinoma, and anaplastic/undifferentiated epithelial tumors added indication of workup. For occult</p>

primary (unknown primary cancer) added indication for workup. Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29): for occult primary cancers (cancers of unknown primary origin) added indications for assessing disease prognosis; and monitoring/follow-up for response. Cancer antigen 19-9 (CA 19-9): for occult primary cancers, added indications for assessing disease prognosis and monitoring/follow-up for response. For "Ovarian cancers (less common)", added indication for Carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it. For small bowel adenocarcinoma, added to other indications "at metastasis or recurrence." Cancer antigen 125 (CA-125): For "Ovarian cancers (less common)", added indication for Carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it. For uterine neoplasms added indication for "initial workup." Carcinoembryonic antigen (CEA): For gallbladder cancer added indication "of adjuvant treatment (as clinically indicated)" For "Ovarian cancers (less common)", added indication for Carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it. Inhibin (INHA): For adrenocortical carcinoma added indication for workup. For "Ovarian cancers (less common)", added indication for carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the

	<p>ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the “(less common)” designation from Ovarian cancer row that has “Borderline epithelial tumors” following it. Lactate dehydrogenase (LDH): For “Ovarian cancers (less common)”, added indication for carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the “(less common)” designation from Ovarian cancer row that has “Borderline epithelial tumors” following it. For systemic mastocytosis, added indications for initial diagnostic workup. References revised; some added, others updated.</p>
<p>04/15/2024</p>	<p>04/15/2024: Document updated with literature review. Reimbursement Information revised to place serum tumor markers and appropriate indications into a table format by marker. The following additions and removals were made: Alkaline Phosphatase (ALP): for bone neoplasms, added indications for measurement during treatment and surveillance. For uveal melanoma, removed indication for initial diagnostic evaluation for metastatic or recurrent disease.</p> <p>Alpha fetoprotein (AFP): for borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated. For occult primary cancers, updated specification from initial diagnostic evaluation to additional workup. For sacrococcygeal teratomas, removed indications for initial diagnostic evaluation and surveillance. For testicular cancer (nonseminoma), removed indication for initial diagnostic evaluation.</p> <p>Beta-2 microglobulin (B2M): for Waldenström macroglobulinemia/lymphoplasmacytic lymphoma, removed indication for prognostication at the time of first-line treatment initiation.</p> <p>Beta human chorionic gonadotropin (beta-HCG): for gestational trophoblastic neoplasia, added indications for initial workup; during and post treatment (no more than weekly); follow-up/surveillance (no more than monthly for 12 months). For occult primary cancers, updated specification from initial diagnostic evaluation to additional workup. For borderline ovarian epithelial tumors, updated frequency for</p>

monitoring/follow-up from every 3–6 months to every visit if initially elevated. For sacrococcygeal teratomas, removed indication for initial diagnostic evaluation. For testicular cancer (nonseminoma), removed indication for initial diagnostic evaluation.

BNP or NT-proBNP: for multiple myeloma, added indication for initial diagnostic workup.

Calcitonin (CALCA): for medullary carcinoma, replaced indication for initial diagnostic evaluation to additional workup and added indication for post-surgical evaluation.

Cancer Antigen 19-9 (CA 19-9): Added ampullary adenocarcinoma and indications for its 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. Added appendiceal adenocarcinoma and indications for workup to establish baseline with note that “abnormal measurements should be trended.” For extrahepatic cholangiocarcinoma, added indication for monitoring. For gallbladder cancer, added indication for monitoring. For hepatocellular carcinoma, removed indication for initial diagnostic evaluation. For intrahepatic cholangiocarcinoma, added indication for monitoring. For borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated. For mucinous carcinoma of the ovary, removed specification for initial diagnostic evaluation; indication for additional workup (if not previously done) remains.

Cancer Antigen 125 (CA-125): for appendiceal adenocarcinoma, added indication for workup to establish baseline. Added Lynch syndrome and indications for surveillance/prevention strategies. For borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated.

Carcinoembryonic Antigen (CEA): for appendiceal adenocarcinoma, added indications for workup to establish baseline; monitoring; post-treatment surveillance. For colon cancer, extrahepatic cholangiocarcinoma, gallbladder cancer, intrahepatic cholangiocarcinoma, and medullary carcinoma, added indication for monitoring. For borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated. For mucinous carcinoma of the ovary, removed specification for initial diagnostic evaluation; indication for additional workup (if not previously done) remains.

	<p>Inhibin (INHA): for borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated. For undiagnosed pelvic masses, removed indication for initial diagnostic evaluation.</p> <p>Lactate dehydrogenase (LDH): for acute lymphoblastic leukemia (ALL), pediatric acute lymphoblastic leukemia (PED-ALL), Hodgkin lymphoma, myelodysplastic syndrome, and acute myeloid leukemia (AML), removed indication for initial diagnostic evaluation. For chronic lymphocytic leukemia/small lymphocytic lymphoma, added indication for measurement at transformation or histologic progression (if applicable). For myeloproliferative neoplasms, removed indications for initial diagnostic evaluation and/or monitoring while on and after therapy. For borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated. For small cell lung cancer, removed indication to measure for prognosis. For testicular cancer (nonseminoma), removed indication for initial diagnostic evaluation.</p> <p>Serum free light chain: for multiple myeloma, updated frequency of surveillance from as needed to once per month. For Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma, removed indication for initial diagnostic evaluation.</p> <p>Tryptase: for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes, removed indication for initial diagnostic evaluation. For systemic mastocytosis, removed indications for monitoring response to therapy and/or risk classification. References revised; some added; others removed. Added code 83521.</p>
03/01/2024	03/01/2024: Added code 0404U. No other changes made.
11/01/2023	11/01/2023: Document updated with literature review. The following changes were made to Reimbursement Information: Reorganized #1 such that the focus is the cancer and then the appropriate biomarkers. In #1, removed CEA and inhibin for occult primary adenocarcinoma or carcinoma not otherwise specified; calcitonin expression testing for cervical cancer; CEA for NSCLC; calcitonin expression testing for occult primary adenocarcinoma or anaplastic/undifferentiated tumors of the head and neck, or otherwise unspecified; CEA for peritoneal mesothelioma; CEA for pleural mesothelioma; and inhibin expression testing for uterine sarcoma. Removed “The use of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI 1) as serum tumor markers is

	not reimbursable. Remainder of reimbursement information revised for clarity. References revised.
11/1/2022	11/01/2022: New policy