

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 New Mexico may use reasonable discretion interpreting and applying this policy to services being delivered in a particular case. BCBSNM 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: August 1, 2025

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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 tumor markers is permitted for follow-up, monitoring, and/or surveillance.

- 1) Measurement of the following serum tumor markers **may be reimbursable** for the following indications:

Serum Tumor Marker	Indication
Alkaline phosphatase (ALP)	<u>Bone neoplasms:</u> • Workup; • During treatment; • Surveillance
	<u>Systemic light chain amyloidosis:</u> • Initial diagnostic workup
Alpha fetoprotein (AFP)	<u>Hepatocellular carcinoma:</u> • Screening; • Workup for confirmed HCC; • Surveillance (every 3-6 months for 2 years, then every 6 months)
	<u>Intrahepatic cholangiocarcinoma:</u> • Workup for isolated intrahepatic mass
	<u>Occult primary:</u> • Additional workup for localized adenocarcinoma or carcinoma not otherwise specified; liver, mediastinum, or retroperitoneal mass
	<u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> • Initial workup; • During primary chemotherapy; • Monitoring/follow-up for complete response (as clinically indicated)
	<u>Ovarian cancers (less common):</u> • <u>Carcinosarcoma (malignant mixed mullerian tumors):</u> ◦ Monitoring/follow-up • <u>Clear cell carcinoma of the ovary:</u> ◦ Monitoring/follow-up • <u>Grade 1 endometrioid carcinoma:</u>

Serum Tumor Marker	Indication
	○ Monitoring/follow-up • <u>Mucinous neoplasms of the ovary:</u> ○ Monitoring/follow-up • <u>Low-grade serous carcinoma:</u> ○ Monitoring/follow-up
	<u>Ovarian cancers:</u> • <u>Borderline epithelial tumors:</u> ○ Monitoring/follow-up (every visit if initially elevated) • <u>Malignant germ cell tumors:</u> ○ 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) • <u>Malignant sex cord stromal tumors:</u> ○ 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)
	<u>Testicular cancer – non-seminoma:</u> • Post-diagnostic workup; • Risk classification; • Surveillance (no more than every 2 months)
	<u>Testicular cancer - pure seminoma:</u> • Initial diagnostic workup; • Post-diagnostic workup; • Risk classification; • Post-treatment surveillance (no more than every 2 months)
	<u>Thymomas and thymic carcinomas:</u> • Initial evaluation, if appropriate
Beta-2 microglobulin (B2M)	<u>B-cell lymphomas (Castleman disease; diffuse large B-cell; follicular [grade 1-2]; HIV-related; lymphoblastic; mantle cell):</u> • Workup
	<u>Chronic lymphocytic leukemia/small lymphocytic lymphoma:</u> • Workup • For prognostic and/or therapy determination
	<u>Multiple myeloma:</u> • Initial diagnostic workup; • Follow-up/surveillance (as needed) for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement
	<u>Systemic light chain amyloidosis:</u> • Initial diagnostic workup

Serum Tumor Marker	Indication
	<u>Waldenström macroglobulinemia / lymphoplasmacytic lymphoma:</u> • Workup
Beta human chorionic gonadotropin (beta-HCG)	<u>Gestational trophoblastic neoplasia:</u> • Initial workup; • During and post treatment (no more than weekly); • Follow-up/surveillance (no more than monthly for 12 months)
	<u>Occult primary:</u> • Additional workup for localized adenocarcinoma or carcinoma not otherwise specified; • Individuals < 65 years of age with testes presenting with retroperitoneal mass
	<u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> • Initial workup; • During primary chemotherapy; • Monitoring/follow-up for complete response (as clinically indicated)
	<u>Ovarian cancers:</u> • <u>Borderline epithelial tumors:</u> ◦ Monitoring/follow-up (every visit if initially elevated) • <u>Malignant germ cell tumors:</u> ◦ 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) • <u>Malignant sex cord stromal tumors:</u> ◦ 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)
	<u>Testicular cancer – non-seminoma:</u> • Post-diagnostic workup; • Risk classification; • Surveillance (no more than every 2 months)
	<u>Testicular cancer - pure seminoma:</u> • Initial diagnostic workup; • Post-diagnostic workup; risk classification; • Post-treatment surveillance (no more than every 2 months)
BNP or NT-proBNP	<u>Thymomas and thymic carcinomas:</u> • Initial evaluation, if appropriate
	<u>Multiple myeloma:</u> • Initial diagnostic workup

Serum Tumor Marker	Indication
	<u>Systemic light chain amyloidosis:</u> Initial diagnostic workup
Calcitonin (CALCA)	<u>Adenocarcinoma and anaplastic/undifferentiated epithelial tumors:</u> Workup
	<u>Medullary carcinoma:</u> - Additional workup; - Post-surgical evaluation; - Monitoring; - Surveillance (2-3 months postoperative, then every 6-12 months)
	<u>Multiple endocrine neoplasia, type 2:</u> At diagnosis (clinical evaluation) for medullary thyroid cancer
	<u>Occult primary (unknown primary cancer):</u> Workup
Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29)	<u>Breast cancer (invasive):</u> Monitoring metastatic disease
	<u>Occult primary: suspected metastatic malignancy:</u> - Initial workup - Assessing disease prognosis - Monitoring/follow-up for response
Cancer antigen 19-9 (CA 19-9)	<u>Ampullary adenocarcinoma:</u> - 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
	<u>Appendiceal adenocarcinoma:</u> Workup to establish baseline. Abnormal measurements should be trended
	<u>Extrahepatic cholangiocarcinoma:</u> - Workup to establish baseline; - Monitoring
	<u>Gallbladder cancer:</u> - Workup to establish baseline; - Monitoring; - Surveillance (as clinically indicated), post-resection
	<u>Intrahepatic cholangiocarcinoma:</u> - Workup to establish baseline; - Monitoring
	<u>Occult primary:</u> - Workup to establish baseline; - Monitoring
	<u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u>

Serum Tumor Marker	Indication
	- Initial workup; - During primary chemotherapy; - Monitoring/follow-up for complete response (as clinically indicated)
	<u>Ovarian cancers (less common):</u> <u>Carcinosarcoma (malignant mixed mullerian tumors):</u> - Workup <u>Clear cell carcinoma of the ovary:</u> - Workup <u>Grade 1 endometrioid carcinoma:</u> - Workup <u>Low-grade serous carcinoma:</u> - Workup <u>Mucinous neoplasms of the ovary:</u> - Workup
	<u>Ovarian cancers:</u> <u>Borderline epithelial tumors:</u> - Monitoring/follow-up (every visit if initially elevated) <u>Malignant germ cell tumors:</u> - 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) <u>Malignant sex cord stromal tumors:</u> - 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) <u>Mucinous carcinoma of the ovary:</u> - Additional workup (if not previously done)
	<u>Pancreatic adenocarcinoma:</u> - 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)
	<u>Small bowel adenocarcinoma:</u> - 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)	<u>Appendiceal adenocarcinoma:</u> Workup to establish baseline
	<u>Endometrial carcinoma:</u>

Serum Tumor Marker	Indication
	• Additional workup; • Surveillance (if initially elevated)
	<u>Lynch syndrome:</u> • Surveillance
	<u>Occult primary:</u> • Additional workup for adenocarcinoma or carcinoma not otherwise specified, in those with a uterus and/or ovaries present
	<u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> • Initial workup; • During primary chemotherapy; • Monitoring/follow-up for complete response (as clinically indicated)
	<u>Ovarian cancers (less common):</u> • <u>Carcinosarcoma (malignant mixed mullerian tumors):</u> ◦ Monitoring/follow-up • <u>Clear cell carcinoma of the ovary:</u> ◦ Monitoring/follow-up • <u>Mucinous neoplasm of the ovary:</u> ◦ Monitoring/follow-up • <u>Grade 1 endometrioid carcinoma:</u> ◦ Monitoring/follow-up • <u>Low-grade serous carcinoma:</u> ◦ Monitoring/follow-up
	<u>Ovarian cancers:</u> • <u>Borderline epithelial tumors:</u> ◦ Monitoring/follow-up (every visit if initially elevated) • <u>Malignant germ cell tumors:</u> ◦ 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) • <u>Malignant sex cord stromal tumors:</u> • 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)
	<u>Peritoneal mesothelioma:</u> • Initial evaluation
	<u>Uterine neoplasms:</u> • Initial workup
Carcinoembryonic antigen (CEA)	Appendiceal adenocarcinoma: • Workup to establish baseline;

Serum Tumor Marker	Indication
	- Monitoring; - Post-treatment surveillance
	<u>Breast cancer (invasive):</u> Monitoring metastatic disease
	<u>Colon cancer:</u> - Workup to establish baseline; - Monitoring; - Surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	<u>Extrahepatic cholangiocarcinoma:</u> - Workup to establish baseline; - Monitoring
	<u>Gallbladder cancer:</u> - Workup to establish baseline; - Monitoring; - Surveillance - Monitoring of adjuvant treatment (as clinically indicated) - Post-resection
	<u>Intrahepatic cholangiocarcinoma:</u> - Workup to establish baseline; - Monitoring
	<u>Medullary carcinoma:</u> - Diagnosis and additional workup; - Monitoring; - Post-surgical surveillance (2-3 months postoperative, then every 6-12 months)
	<u>Multiple endocrine neoplasia, type 2:</u> At diagnosis (clinical evaluation) for medullary thyroid cancer
	<u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> - Initial workup; - During primary chemotherapy; - Monitoring/follow-up for complete response (as clinically indicated)
	<u>Ovarian cancers (less common):</u> <u>Carcinosarcoma (malignant mixed mullerian tumors):</u> - Monitoring/follow-up <u>Clear cell carcinoma of the ovary:</u> - Monitoring/follow-up <u>Grade 1 endometrioid carcinoma:</u> - Monitoring/follow-up <u>Low-grade serous carcinoma:</u>

Serum Tumor Marker	Indication
	○ Monitoring/follow-up • <u>Mucinous neoplasms of the ovary:</u> ○ Monitoring/follow-up
	<u>Ovarian cancers:</u> • <u>Borderline epithelial tumors:</u> ○ Monitoring/follow-up (every visit if initially elevated) ○ Post-adjuvant treatment • <u>Malignant germ cell tumors:</u> ○ 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) • <u>Malignant sex cord stromal tumors:</u> ○ 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) • <u>Mucinous carcinoma of the ovary:</u> ○ Additional workup (if not previously done)
	<u>Rectal cancer:</u> • Workup to establish baseline; • Monitoring; surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	<u>Small bowel adenocarcinoma:</u> • Workup to establish baseline; • Post-treatment surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
Inhibin (INHA)	<u>Adrenocortical carcinoma:</u> • Workup
	<u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> • Initial workup; • During primary chemotherapy; • Monitoring/follow-up for complete response (as clinically indicated)
	<u>Ovarian cancers (less common):</u> • <u>Carcinosarcoma (malignant mixed mullerian tumors):</u> ○ Monitoring/follow-up • <u>Clear cell carcinoma of the ovary:</u> ○ Monitoring/follow-up • <u>Grade 1 endometrioid carcinoma:</u> ○ Monitoring/follow-up • <u>Low-grade serous carcinoma:</u> ○ Monitoring/follow-up

Serum Tumor Marker	Indication
	• <u>Mucinous neoplasms of the ovary:</u> ◦ Monitoring/follow-up <u>Ovarian cancers :</u> • <u>Borderline epithelial tumors:</u> ◦ Monitoring/follow-up (every visit if initially elevated) • <u>Malignant Germ cell tumors:</u> ◦ 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) • <u>Malignant sex cord stromal tumors:</u> ◦ 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)	<u>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):</u> • Workup <u>Bone neoplasms:</u> • Workup <u>Chronic lymphocytic leukemia/small lymphocytic lymphoma:</u> • Workup, and at transformation or histologic progression (if applicable) <u>Hairy cell leukemia:</u> • Workup <u>Kidney cancer:</u> • Initial workup <u>Melanoma (cutaneous and uveal):</u> • Workup for metastatic or recurrent disease <u>Multiple myeloma:</u> • Initial workup; • Surveillance (as needed) post primary treatment for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement <u>Ovarian cancer/fallopian tube cancer/primary peritoneal cancer:</u> • Initial workup; • During primary chemotherapy, monitoring/follow-up for complete response (as clinically indicated)

Serum Tumor Marker	Indication
	<u>Ovarian cancers (less common):</u> • <u>Carcinosarcoma (malignant mixed mullerian tumors):</u> ○ Monitoring/follow-up • <u>Clear cell carcinoma of the ovary:</u> ○ Monitoring/follow-up • <u>Grade 1 endometrioid carcinoma:</u> ○ Monitoring/follow-up • <u>Low-grade serous carcinoma:</u> ○ Monitoring/follow-up • <u>Mucinous neoplasms of the ovary:</u> ○ Monitoring/follow-up
	<u>Ovarian cancers:</u> • <u>Borderline epithelial tumors:</u> ○ Monitoring/follow-up (every visit if initially elevated) • <u>Malignant germ cell tumors:</u> ○ 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) • <u>Malignant sex cord stromal tumors:</u> ○ 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)
	<u>Primary cutaneous lymphomas (mycosis fungoides/Sezary syndrome; primary cutaneous CD30+ T-cell lymphoproliferative disorders):</u> • Workup
	<u>Systemic light chain amyloidosis:</u> • Initial diagnostic workup
	<u>Systemic mastocytosis:</u> • Initial diagnostic workup
	<u>T-cell lymphomas (adult T-cell; breast implant-associated ALCL; extranodal NK/T-cell; hepatosplenic; peripheral; T-cell prolymphocytic leukemia):</u> • Workup; • Staging (breast implant-associated ALCL only)
	<u>Testicular cancer – non-seminoma:</u> • Post-diagnostic workup; • Risk classification; • Surveillance (no more than every 2 months)
	<u>Testicular cancer – pure seminoma:</u> • Initial diagnostic workup; • Post-diagnostic workup;

Serum Tumor Marker	Indication
	- Risk classification; - Post-treatment surveillance (no more than every 2 months)
	<u>Waldenström macroglobulinemia / lymphoplasmacytic lymphoma:</u> Workup
Serum free light chain	<u>Multiple myeloma:</u> - Initial diagnostic workup; - Surveillance (up to once per month)
	<u>Systemic light chain amyloidosis:</u> Initial diagnostic workup
Troponin T	<u>Systemic light chain amyloidosis:</u> Initial diagnostic workup
Tryptase	<u>Systemic mastocytosis:</u> 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, 83615, 83789, 83880, 83950, 83951, 84075, 84078, 84080, 84484, 84702, 84703, 84704, 84999, 86300, 86301, 86304, 86305, 86316, 86336, 0003U, 0092U, 0163U, 0404U, 0599U, G0327

References:

- AAAAI. (2024). *Systemic Mastocytosis*. <https://www.aaaai.org/conditions-treatments/related-conditions/systemic-mastocytosis>
- ACS. (2018a). *What Is Multiple Myeloma?* <https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html>

- ACS. (2018b). *What Is Waldenstrom Macroglobulinemia?*
<https://www.cancer.org/cancer/waldenstrom-macroglobulinemia/about/what-is-wm.html>
- ADLM. (2024). *Serum Free Light Chains: Optimal Testing Recommendations*.
<https://www.myadlm.org/advocacy-and-outreach/optimal-testing-guide-to-lab-test-utilization/g-s/serum-free-light-chains>
- Akar, H., Seldin, D. C., Magnani, B., O'Hara, C., Berk, J. L., Schoonmaker, C., Cabral, H., Dember, L. M., Sanchowala, V., Connors, L. H., Falk, R. H., & Skinner, M. (2005). Quantitative serum free light chain assay in the diagnostic evaluation of AL amyloidosis. *Amyloid*, 12(4), 210-215.
<https://doi.org/10.1080/13506120500352339>
- ASPIRA. (2024a). *OVA1 Products*. <https://aspirawh.com/ova-products/>
- ASPIRA. (2024b). *OvaWatch*. <https://aspirawh.com/ovawatch/>
- ATA. (2017). *Revised ATA Management Guidelines for MTC*.
<https://www.thyroid.org/wp-content/uploads/2017/03/revised-ata-management-guidelines-for-MTC.pdf>
- Berrebi, A., Shvidel, L., Arditti, F. D., Bassous, L., Haran, M., & Shtalrid, M. (2009). The Significance of Elevated Beta 2-Microglobulin (b2-m) in B-CLL: Evidence of in Vitro b2-m Secretion Following Activation of B-CLL Cells. *Blood*, 114(22), 4380.
<http://www.bloodjournal.org/content/114/22/4380.abstract>
- BeScreened. (2024). BeScreened. <https://bescreened.com/>
- Bhole, M. V., Sadler, R., & Ramasamy, K. (2014). Serum-free light-chain assay: clinical utility and limitations. *Ann Clin Biochem*, 51(Pt 5), 528-542.
<https://doi.org/10.1177/0004563213518758>
- Bind, M. K., Mishra, R. R., Kumar, V., Misra, V., & Singh, P. A. (2021). Serum CA 19-9 and CA 125 as a diagnostic marker in carcinoma of gallbladder. *Indian J Pathol Microbiol*, 64(1), 65-68. <https://pubmed.ncbi.nlm.nih.gov/33433411/>
- Bowlus, C. L., Arrive, L., Bergquist, A., Deneau, M., Forman, L., Ilyas, S. I., Lunsford, K. E., Martinez, M., Sapisochin, G., Shroff, R., Tabibian, J. H., & Assis, D. N. (2023). AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology*, 77(2), 659-702.
<https://doi.org/10.1002/hep.32771>
- Cautha, S., Gupta, S., Hanif, A., Moirangthem, V., & Jain, K. (2022). Lymphoplasmacytic Lymphoma with Only Lambda Light Chain Monoclonal Paraprotein Expression. *Eur J Case Rep Intern Med*, 9(2), 003106.
https://doi.org/10.12890/2022_003106
- Caviglia, G. P., Abate, M. L., Petrini, E., Gaia, S., Rizzetto, M., & Smedile, A. (2016). Highly sensitive alpha-fetoprotein, Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein and des-gamma-carboxyprothrombin for hepatocellular carcinoma detection. *Hepatol Res*, 46(3), E130-135.
<https://doi.org/10.1111/hepr.12544>
- Chappuis, P. O., Dieterich, B., Sciretta, V., Lohse, C., Bonnefoi, H., Remadi, S., & Sappino, A. P. (2001). Functional evaluation of plasmin formation in primary breast cancer. *J Clin Oncol*, 19(10), 2731-2738.
<https://doi.org/10.1200/jco.2001.19.10.2731>
- Chaulin, A. M. (2022). Biology of Cardiac Troponins: Emphasis on Metabolism. *Biology (Basel)*, 11(3). <https://doi.org/10.3390/biology11030429>

- Chen, F., Shen, J., Wang, J., Cai, P., & Huang, Y. (2018). Clinical analysis of four serum tumor markers in 458 patients with ovarian tumors: diagnostic value of the combined use of HE4, CA125, CA19-9, and CEA in ovarian tumors. *Cancer Manag Res*, 10, 1313-1318. <https://doi.org/10.2147/cmar.S155693>
- Chen, Y., Xie, Y., Xu, L., Zhan, S., Xiao, Y., Gao, Y., Wu, B., & Ge, W. (2017). Protein content and functional characteristics of serum-purified exosomes from patients with colorectal cancer revealed by quantitative proteomics. *Int J Cancer*, 140(4), 900-913. <https://doi.org/10.1002/ijc.30496>
- Cheng, J., Wang, W., Zhang, Y., Liu, X., Li, M., Wu, Z., Liu, Z., Lv, Y., & Wang, B. (2014). Prognostic role of pre-treatment serum AFP-L3% in hepatocellular carcinoma: systematic review and meta-analysis. *PLoS One*, 9(1), e87011. <https://doi.org/10.1371/journal.pone.0087011>
- Di Castelnuovo, A., Veronesi, G., Costanzo, S., Zeller, T., Schnabel, R. B., de Curtis, A., Salomaa, V., Borchini, R., Ferrario, M., Giampaoli, S., Kee, F., Soderberg, S., Niiranen, T., Kuulasmaa, K., de Gaetano, G., Donati, M. B., Blankenberg, S., Iacoviello, L., & BiomarCa, R. E. I. (2019). NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) and the Risk of Stroke. *Stroke*, 50(3), 610-617. <https://doi.org/10.1161/STROKEAHA.118.023218>
- Dispenzieri, A. (2024). *Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis*. <https://www.uptodate.com/contents/clinical-presentation-laboratory-manifestations-and-diagnosis-of-immunoglobulin-light-chain-al-amyloidosis>
- Dorigo, O., & Berek, J. S. (2011). Personalizing CA125 levels for ovarian cancer screening. *Cancer Prev Res (Phila)*, 4(9), 1356-1359. <https://doi.org/10.1158/1940-6207.Capr-11-0378>
- Duffy, M. J. (2001). Carcinoembryonic Antigen as a Marker for Colorectal Cancer: Is It Clinically Useful? *Clinical Chemistry*, 47(4), 624. <https://doi.org/10.1093/clinchem/47.4.624>
- Farkkila, A., Koskela, S., Bryk, S., Alfthan, H., Butzow, R., Leminen, A., Puistola, U., Tapanainen, J. S., Heikinheimo, M., Anttonen, M., & Unkila-Kallio, L. (2015). The clinical utility of serum anti-Mullerian hormone in the follow-up of ovarian adult-type granulosa cell tumors--A comparative study with inhibin B. *Int J Cancer*, 137(7), 1661-1671. <https://doi.org/10.1002/ijc.29532>
- Febbo, P. G., Ladanyi, M., Aldape, K. D., De Marzo, A. M., Hammond, M. E., Hayes, D. F., Iafrate, A. J., Kelley, R. K., Marcucci, G., Ogino, S., Pao, W., Sgroi, D. C., & Birkeland, M. L. (2011). NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. *J Natl Compr Canc Netw*, 9 Suppl 5, S1-32; quiz S33. <https://doi.org/10.6004/jnccn.2011.0137>
- Feng, F., Tian, Y., Xu, G., Liu, Z., Liu, S., Zheng, G., Guo, M., Lian, X., Fan, D., & Zhang, H. (2017). Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. *BMC Cancer*, 17(1), 737. <https://doi.org/10.1186/s12885-017-3738-y>
- Foekens, J. A., Peters, H. A., Look, M. P., Portengen, H., Schmitt, M., Kramer, M. D., Brunner, N., Janicke, F., Meijer-van Gelder, M. E., Henzen-Logmans, S. C., van Putten, W. L., & Klijn, J. G. (2000). The urokinase system of plasminogen activation and prognosis in 2780 breast cancer patients. *Cancer Res*, 60(3), 636-643. <https://pubmed.ncbi.nlm.nih.gov/10676647/>

- Foukakis, T., & Bergh, J. (2022). Prognostic and predictive factors in early, nonmetastatic breast cancer - UpToDate. In D. Hayes (Ed.), *UpToDate*. <https://www.uptodate.com/contents/prognostic-and-predictive-factors-in-early-non-metastatic-breast-cancer>
- Gershenson, D. (2022). *Sex cord-stromal tumors of the ovary: Epidemiology, clinical features, and diagnosis in adults*. <https://www.uptodate.com/contents/sex-cord-stromal-tumors-of-the-ovary-epidemiology-clinical-features-and-diagnosis-in-adults>
- Gilligan, T. D., Seidenfeld, J., Basch, E. M., Einhorn, L. H., Fancher, T., Smith, D. C., Stephenson, A. J., Vaughn, D. J., Cosby, R., & Hayes, D. F. (2010). American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol*, 28(20), 3388-3404. <https://doi.org/10.1200/jco.2009.26.4481>
- Halfdanarson, T. R., Strosberg, J. R., Tang, L., Bellizzi, A. M., Bergsland, E. K., O'Dorisio, T. M., Halperin, D. M., Fishbein, L., Eads, J., Hope, T. A., Singh, S., Salem, R., Metz, D. C., Naraev, B. G., Reidy-Lagunes, D. L., Howe, J. R., Pommier, R. F., Menda, Y., & Chan, J. A. (2020). The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. *Pancreas*, 49(7), 863-881. <https://doi.org/10.1097/mpa.0000000000001597>
- Harris, L. N., Ismaila, N., McShane, L. M., Andre, F., Collyar, D. E., Gonzalez-Angulo, A. M., Hammond, E. H., Kuderer, N. M., Liu, M. C., Mennel, R. G., Van Poznak, C., Bast, R. C., & Hayes, D. F. (2016). Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*, 34(10), 1134-1150. <https://doi.org/10.1200/jco.2015.65.2289>
- Harvey, R. A. (2023). *Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease*. <https://www.uptodate.com/contents/human-chorionic-gonadotropin-testing-in-pregnancy-and-gestational-trophoblastic-disease-and-causes-of-low-persistent-levels>
- Haugen, B. R., Alexander, E. K., Bible, K. C., Doherty, G. M., Mandel, S. J., Nikiforov, Y. E., Pacini, F., Randolph, G. W., Sawka, A. M., Schlumberger, M., Schuff, K. G., Sherman, S. I., Sosa, J. A., Steward, D. L., Tuttle, R. M., & Wartofsky, L. (2016). 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*, 26(1), 1-133. <https://doi.org/10.1089/thy.2015.0020>
- Hotakainen, K., Ljungberg, B., Paju, A., Rasmuson, T., Alfthan, H., & Stenman, U. H. (2002). The free beta-subunit of human chorionic gonadotropin as a prognostic factor in renal cell carcinoma. *Br J Cancer*, 86(2), 185-189. <https://doi.org/10.1038/sj.bjc.6600050>
- Hottinger, A., & Hormigo, A. (2011). Serum Biomarkers. In *Encyclopedia of Cancer* (pp. 3390-3394). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-16483-5_5269
- Husain, A. N., Colby, T. V., Ordonez, N. G., Allen, T. C., Attanoos, R. L., Beasley, M. B., Butnor, K. J., Chirieac, L. R., Churg, A. M., Dacic, S., Galateau-Salle, F., Gibbs, A., Gown, A. M., Krausz, T., Litzky, L. A., Marchevsky, A., Nicholson, A. G., Roggli, V. L., Sharma, A. K., . . . Wick, M. R. (2018). Guidelines for Pathologic Diagnosis of

- Malignant Mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. *Arch Pathol Lab Med*, 142(1), 89-108. <https://doi.org/10.5858/arpa.2017-0124-ra>
- Isaksson, S., Jönsson, P., Monsef, N., Brunnström, H., Bendahl, P. O., Jönsson, M., Staaf, J., & Planck, M. (2017). CA 19-9 and CA 125 as potential predictors of disease recurrence in resectable lung adenocarcinoma. *PLoS One*, 12(10), e0186284. <https://doi.org/10.1371/journal.pone.0186284>
- Katou, H., Kanno, T., Hoshino, M., Hagihara, Y., Tanaka, H., Kawai, T., Hasegawa, K., Naiki, H., & Goto, Y. (2002). The role of disulfide bond in the amyloidogenic state of beta(2)-microglobulin studied by heteronuclear NMR. *Protein Sci*, 11(9), 2218-2229. <https://doi.org/10.1110/ps.0213202>
- Katzmann, J. A., Clark, R. J., Abraham, R. S., Bryant, S., Lymp, J. F., Bradwell, A. R., & Kyle, R. A. (2002). Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. *Clin Chem*, 48(9), 1437-1444. <https://www.ncbi.nlm.nih.gov/pubmed/12194920>
- Kim, N. H., Lee, M. Y., Park, J. H., Park, D. I., Sohn, C. I., Choi, K., & Jung, Y. S. (2017). Serum CEA and CA 19-9 Levels are Associated with the Presence and Severity of Colorectal Neoplasia. *Yonsei Med J*, 58(5), 918-924. <https://doi.org/10.3349/ymj.2017.58.5.918>
- Kindler, H. L., Ismaila, N., Armato, S. G., Bueno, R., Hesdorffer, M., Jahan, T., Jones, C. M., Miettinen, M., Pass, H., Rimner, A., Rusch, V., Sterman, D., Thomas, A., & Hassan, R. (2018). Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*, 36(13), 1343-1373. <https://doi.org/10.1200/JCO.2017.76.6394>
- Kumar, S., Dispenzieri, A., Katzmann, J. A., Larson, D. R., Colby, C. L., Lacy, M. Q., Hayman, S. R., Buadi, F. K., Leung, N., Zeldenrust, S. R., Ramirez-Alvarado, M., Clark, R. J., Kyle, R. A., Rajkumar, S. V., & Gertz, M. A. (2010). Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features. *Blood*, 116(24), 5126-5129. <https://doi.org/10.1182/blood-2010-06-290668>
- Kyrtsonis MC, K. E., Bartzis V, Pessah I, Nikolaou E, Karalis V, Maltezas D, Panayiotidis P, Harding S. (2012). Monoclonal Immunoglobulin. In *Multiple Myeloma - A Quick Reflection on the Fast Progress*. <https://doi.org/10.5772/55855>
- Leru, P. M. (2022). Evaluation and Classification of Mast Cell Disorders: A Difficult to Manage Pathology in Clinical Practice. *Cureus*, 14(2), e22177. <https://doi.org/10.7759/cureus.22177>
- Li, A. J. (2024). *Serum biomarkers for evaluation of an adnexal mass for epithelial carcinoma of the ovary, fallopian tube, or peritoneum*. <https://www.uptodate.com/contents/serum-biomarkers-for-evaluation-of-an-adnexal-mass-for-epithelial-carcinoma-of-the-ovary-fallopian-tube-or-peritoneum>
- Li, J., Yin, M., Song, W., Cui, F., Wang, W., Wang, S., & Zhu, H. (2018). B Subunit of Human Chorionic Gonadotropin Promotes Tumor Invasion and Predicts Poor Prognosis of Early-Stage Colorectal Cancer. *Cell Physiol Biochem*, 45(1), 237-249. <https://doi.org/10.1159/000486770>
- Liu, R., Cao, J., Gao, X., Zhang, J., Wang, L., Wang, B., Guo, L., Hu, X., & Wang, Z. (2016). Overall survival of cancer patients with serum lactate dehydrogenase

- greater than 1000 IU/L. *Tumour Biol*, 37(10), 14083-14088.
<https://doi.org/10.1007/s13277-016-5228-2>
- Lucarelli, G., Ditunno, P., Bettocchi, C., Vavallo, A., Rutigliano, M., Galleggiante, V., Larocca, A. M., Castellano, G., Gesualdo, L., Grandaliano, G., Selvaggi, F. P., & Battaglia, M. (2014). Diagnostic and prognostic role of preoperative circulating CA 15-3, CA 125, and beta-2 microglobulin in renal cell carcinoma. *Dis Markers*, 2014, 689795. <https://doi.org/10.1155/2014/689795>
- MagArray. (2024). REVEAL. <https://magarray.com/reveal/#>
- Magnani, J. L. (2004). The discovery, biology, and drug development of sialyl Lea and sialyl Lex. *Archives of Biochemistry and Biophysics*, 426(2), 122-131.
<https://doi.org/10.1016/j.abb.2004.04.008>
- Malmstrom, P., Bendahl, P. O., Boiesen, P., Brunner, N., Idvall, I., & Ferno, M. (2001). S-phase fraction and urokinase plasminogen activator are better markers for distant recurrences than Nottingham Prognostic Index and histologic grade in a prospective study of premenopausal lymph node-negative breast cancer. *J Clin Oncol*, 19(7), 2010-2019. <https://doi.org/10.1200/jco.2001.19.7.2010>
- Marcillac, I., Troalen, F., Bidart, J.-M., Ghillani, P., Ribrag, V., Escudier, B., Malassagne, B., Droz, J.-P., Lhommé, C., Rougier, P., Duvillard, P., Prade, M., Lugagne, P.-M., Richard, F., Poynard, T., Bohuon, C., Wands, J., & Bellet, D. (1992). Free Human Chorionic Gonadotropin β Subunit in Gonadal and Nongonadal Neoplasms. *Cancer Research*, 52(14), 3901.
<http://cancerres.aacrjournals.org/content/52/14/3901.abstract>
- Marcinko, T. M., Dong, J., LeBlanc, R., Daborowski, K. V., & Vachet, R. W. (2017). Small molecule-mediated inhibition of β -2-microglobulin-based amyloid fibril formation. *J Biol Chem*, 292(25), 10630-10638.
<https://doi.org/10.1074/jbc.M116.774083>
- Merlini, G., Wechalekar, A. D., & Palladini, G. (2013). Systemic light chain amyloidosis: an update for treating physicians. *Blood*, 121(26), 5124-5130.
<https://doi.org/10.1182/blood-2013-01-453001>
- Moreau AS, L. X., Manning R, Coiteux V, Darre S, Hatjiharisi E, Hunter Z, Jia X, Ngo H, O'Sullivan G, Santos D, Treon S, Facon T, Anderson K, Ghobrial I. (2006). Serum Free Light Chain in Waldenstrom Macroglobulinemia.
<https://doi.org/10.1182/blood.V108.11.2420.2420>
- NANETS. (2017). The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. <https://doi.org/10.1097%2FMPA.0000000000000850>
- NCCN. (2023). *Biomarkers Compendium*. <https://www.nccn.org/compendia-templates/compendia/biomarkers-compendium>
- NCCN. (2024a). *NCCN Clinical Practice Guidelines in Oncology*.
https://www.nccn.org/professionals/physician_gls/default.aspx
- NCCN. (2024b). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Multiple Myeloma Version 3.2024*.
https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf#Page=9
- NCCN. (2024c). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Systemic Light Chain Amyloidosis Version 2.2024*.
https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf
- NCCN. (2024d). *Ovarian Cancer*.
https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

- NCI. (2023). *Tumor Markers*. <https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet>
- Oyaert, M., Boone, E., De Ceuninck, L., Moreau, E., Van Dorpe, J., Vanpoucke, H., & Deeren, D. (2014). Clonal multicentric Castleman's disease with increased free Kappa light chains in a patient with systemic lupus erythematosus. *Ann Hematol*, 93(7), 1255-1257. <https://doi.org/10.1007/s00277-013-1962-3>
- Park, S. J., Jang, J. Y., Jeong, S. W., Cho, Y. K., Lee, S. H., Kim, S. G., Cha, S. W., Kim, Y. S., Cho, Y. D., Kim, H. S., Kim, B. S., Park, S., & Bang, H. I. (2017). Usefulness of AFP, AFP-L3, and PIVKA-II, and their combinations in diagnosing hepatocellular carcinoma. *Medicine (Baltimore)*, 96(11), e5811. <https://doi.org/10.1097/md.00000000000005811>
- Payne, V., & Kam, P. C. (2004). Mast cell tryptase: a review of its physiology and clinical significance. *Anaesthesia*, 59(7), 695-703. <https://doi.org/10.1111/j.1365-2044.2004.03757.x>
- Pejler, G., Ronnberg, E., Waern, I., & Wernersson, S. (2010). Mast cell proteases: multifaceted regulators of inflammatory disease. *Blood*, 115(24), 4981-4990. <https://doi.org/10.1182/blood-2010-01-257287>
- Perfetto, F., Bergesio, F., Emdin, M., & Cappelli, F. (2014). Troponins in cardiac amyloidosis: multipurpose markers. *Nat Rev Cardiol*, 11(3), 179. <https://doi.org/10.1038/nrcardio.2013.129-c1>
- Pinzani, P., D'Argenio, V., Del Re, M., Pellegrini, C., Cucchiara, F., Salvianti, F., & Galbiati, S. (2021). Updates on liquid biopsy: current trends and future perspectives for clinical application in solid tumors. *Clin Chem Lab Med*, 59(7), 1181-1200. <https://doi.org/10.1515/cclm-2020-1685>
- Popat, S., Baas, P., Faivre-Finn, C., Girard, N., Nicholson, A. G., Nowak, A. K., Opitz, I., Scherpereel, A., & Reck, M. (2022). Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up^{#x2606}. *Annals of Oncology*, 33(2), 129-142. <https://doi.org/10.1016/j.annonc.2021.11.005>
- Pucino, V., Bombardieri, M., Pitzalis, C., & Mauro, C. (2017). Lactate at the crossroads of metabolism, inflammation, and autoimmunity. *European Journal of Immunology*, 47(1), 14-21. <https://doi.org/10.1002/eji.201646477>
- Qin, J., Yang, Q., Ye, H., Wang, K., Zhang, M., Zhu, J., Wang, X., Dai, L., Wang, P., & Zhang, J. (2020). Using Serological Proteome Analysis to Identify and Evaluate Anti-GRP78 Autoantibody as Biomarker in the Detection of Gastric Cancer. *J Oncol*, 2020, 9430737. <https://doi.org/10.1155/2020/9430737>
- Raby, B. (2023). *Personalized medicine*. <https://www.uptodate.com/contents/personalized-medicine>
- Ryu, T., Takami, Y., Wada, Y., Tateishi, M., Matsushima, H., Mikagi, K., & Saitsu, H. (2017). Double- and Triple-Positive Tumor Markers Predict Early Recurrence and Poor Survival in Patients with Hepatocellular Carcinoma within the Milan Criteria and Child-Pugh Class A. *J Gastrointest Surg*, 21(6), 957-966. <https://doi.org/10.1007/s11605-017-3394-1>
- Santos Schraiber, L. d., de Mattos, A. A., Zanotelli, M. L., Cantisani, G. P., Brandao, A. B., Marroni, C. A., Kiss, G., Ernani, L., & Santos Marcon, P. d. (2016). Alpha-fetoprotein Level Predicts Recurrence After Transplantation in Hepatocellular Carcinoma. *Medicine (Baltimore)*, 95(3), e2478. <https://doi.org/10.1097/md.00000000000002478>

- Schefer, H., Mattmann, S., & Joss, R. A. (1998). Hereditary persistence of α -fetoprotein Case report and review of the literature. *Annals of Oncology*, 9(6), 667-672. <https://doi.org/10.1023/A:1008243311122>
- Seo, S., Hong, J. Y., Yoon, S., Yoo, C., Park, J. H., Lee, J. B., Park, C. S., Huh, J., Lee, Y., Kim, K. W., Ryu, J. S., Kim, S. J., Kim, W. S., Yoon, D. H., & Suh, C. (2016). Prognostic significance of serum beta-2 microglobulin in patients with diffuse large B-cell lymphoma in the rituximab era. *Oncotarget*, 7(47), 76934-76943. <https://doi.org/10.18632/oncotarget.12734>
- Sharma, S., Jackson, P. G., & Makan, J. (2004). Cardiac troponins. *J Clin Pathol*, 57(10), 1025-1026. <https://doi.org/10.1136/jcp.2003.015420>
- Sharma, U., Pal, D., & Prasad, R. (2014). Alkaline phosphatase: an overview. *Indian J Clin Biochem*, 29(3), 269-278. <https://doi.org/10.1007/s12291-013-0408-y>
- Singal, A. G., Llovet, J. M., Yarchoan, M., Mehta, N., Heimbach, J. K., Dawson, L. A., Jou, J. H., Kulik, L. M., Agopian, V. G., Marrero, J. A., Mendiratta-Lala, M., Brown, D. B., Rilling, W. S., Goyal, L., Wei, A. C., & Taddei, T. H. (2023). AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. <https://doi.org/10.1097/HEP.0000000000000466>
- Stankowski-Drengler, T., Gertz, M. A., Katzmann, J. A., Lacy, M. Q., Kumar, S., Leung, N., Hayman, S. R., Buadi, F., Kyle, R. A., Rajkumar, S. V., & Dispenzieri, A. (2010). Serum immunoglobulin free light chain measurements and heavy chain isotype usage provide insight into disease biology in patients with POEMS syndrome. *Am J Hematol*, 85(6), 431-434. <https://doi.org/10.1002/ajh.21707>
- Stephens, R. W., Brunner, N., Janicke, F., & Schmitt, M. (1998). The urokinase plasminogen activator system as a target for prognostic studies in breast cancer. *Breast Cancer Res Treat*, 52(1-3), 99-111. https://doi.org/10.1007/978-1-4615-5195-9_15
- Stoffel, E. M., McKernin, S. E., Brand, R., Canto, M., Goggins, M., Moravek, C., Nagarajan, A., Petersen, G. M., Simeone, D. M., Yurgelun, M., & Khorana, A. A. (2018). Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion. *Journal of Clinical Oncology*, 37(2), 153-164. <https://doi.org/10.1200/JCO.18.01489>
- Strosberg, J. (2024). *Diagnosis of carcinoid syndrome and tumor localization*. <https://www.uptodate.com/contents/diagnosis-of-the-carcinoid-syndrome-and-tumor-localization>
- Sturgeon, C. M., Duffy, M. J., Hofmann, B. R., Lamerz, R., Fritsche, H. A., Gaarenstroom, K., Bonfrer, J., Ecke, T. H., Grossman, H. B., Hayes, P., Hoffmann, R. T., Lerner, S. P., Lohe, F., Louhimo, J., Sawczuk, I., Taketa, K., & Diamandis, E. P. (2010). National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. *Clin Chem*, 56(6), e1-48. <https://doi.org/10.1373/clinchem.2009.133124>
- Sturgeon, C. M., Duffy, M. J., Stenman, U. H., Lilja, H., Brunner, N., Chan, D. W., Babaian, R., Bast, R. C., Jr., Dowell, B., Esteva, F. J., Haglund, C., Harbeck, N., Hayes, D. F., Holten-Andersen, M., Klee, G. G., Lamerz, R., Looijenga, L. H., Molina, R., Nielsen, H. J., . . . Diamandis, E. P. (2008). National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clin Chem*, 54(12), e11-79. <https://doi.org/10.1373/clinchem.2008.105601>

- Sturgeon, C. M., Hoffman, B. R., Chan, D. W., Ch, ng, S.-L., Hammond, E., Hayes, D. F., Liotta, L. A., Petricoin, E. F., Schmitt, M., Semmes, O. J., Söletormos, G., van der Merwe, E., & Diamandis, E. P. (2008). National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Quality Requirements. *Clinical Chemistry*, 54(8), e1. <https://doi.org/10.1373/clinchem.2007.094144>
- Szulc, P., Bauer, D. C., Dempster, D. W., Luckey, M., & Cauley, J. A. (2013). Osteoporosis. 1. <https://doi.org/10.1016/B978-0-12-415853-5.00067-4>
- Thio, Q., Karhade, A. V., Notman, E., Raskin, K. A., Lozano-Calderon, S. A., Ferrone, M. L., Bramer, J. A. M., & Schwab, J. H. (2020). Serum alkaline phosphatase is a prognostic marker in bone metastatic disease of the extremity. *J Orthop*, 22, 346-351. <https://doi.org/10.1016/j.jor.2020.08.008>
- Tian, T., Gao, J., Li, N., Li, Y., Lu, M., Li, Z., Lu, Z., Li, J., & Shen, L. (2016). Circulating Chromogranin A as A Marker for Monitoring Clinical Response in Advanced Gastroenteropancreatic Neuroendocrine Tumors. *PLoS One*, 11(5), e0154679. <https://doi.org/10.1371/journal.pone.0154679>
- Tormey, W. P., Byrne, B., Hill, A. D., Sherlock, M., & Thompson, C. J. (2017). Should serum calcitonin be routinely measured in patients presenting with thyroid nodule? *Minerva Endocrinol*, 42(4), 306-310. <https://doi.org/10.23736/s0391-1977.17.02566-4>
- Tosi, P., Tomassetti, S., Merli, A., & Polli, V. (2013). Serum free light-chain assay for the detection and monitoring of multiple myeloma and related conditions. *Ther Adv Hematol*, 4(1), 37-41. <https://doi.org/10.1177/2040620712466863>
- Tuttle, R. M. (2022). *Medullary thyroid cancer: Clinical manifestations, diagnosis, and staging*. <https://www.uptodate.com/contents/medullary-thyroid-cancer-clinical-manifestations-diagnosis-and-staging>
- Van Poznak, C., Somerfield, M. R., Bast, R. C., Cristofanilli, M., Goetz, M. P., Gonzalez-Angulo, A. M., Hicks, D. G., Hill, E. G., Liu, M. C., Lucas, W., Mayer, I. A., Mennel, R. G., Symmans, W. F., Hayes, D. F., & Harris, L. N. (2015). Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*, 33(24), 2695-2704. <https://doi.org/10.1200/jco.2015.61.1459>
- Venner, C. P. (2019). AL amyloidosis cardiac staging updated using BNP. *Blood*, 133(3), 184-185. <https://doi.org/10.1182/blood-2018-10-882159>
- Walentowicz, P., Krintus, M., Sadlecki, P., Grabiec, M., Mankowska-Cyl, A., Sokup, A., & Walentowicz-Sadlecka, M. (2014). Serum inhibin A and inhibin B levels in epithelial ovarian cancer patients. *PLoS One*, 9(3), e90575. <https://doi.org/10.1371/journal.pone.0090575>
- Weber, M., & Hamm, C. (2006). Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart*, 92(6), 843-849. <https://doi.org/10.1136/hrt.2005.071233>
- Wells, S. A., Jr., Asa, S. L., Dralle, H., Elisei, R., Evans, D. B., Gagel, R. F., Lee, N., Machens, A., Moley, J. F., Pacini, F., Raue, F., Frank-Raue, K., Robinson, B., Rosenthal, M. S., Santoro, M., Schlumberger, M., Shah, M., & Waguespack, S. G. (2015). Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*, 25(6), 567-610. <https://doi.org/10.1089/thy.2014.0335>

- Wu, D., Lim, M. S., & Jaffe, E. S. (2018). Pathology of Castleman Disease. *Hematol Oncol Clin North Am*, 32(1), 37-52. <https://doi.org/10.1016/j.hoc.2017.09.004>
- Wu, M., Liu, H., Liu, Z., Liu, C., Zhang, A., & Li, N. (2018). Analysis of serum alpha-fetoprotein (AFP) and AFP-L3 levels by protein microarray. *J Int Med Res*, 46(10), 4297-4305. <https://doi.org/10.1177/0300060518789304>
- Yang, X., Yang, Y., Li, Z., Cheng, C., Yang, T., Wang, C., Liu, L., & Liu, S. (2015). Diagnostic value of circulating chromogranin a for neuroendocrine tumors: a systematic review and meta-analysis. *PLoS One*, 10(4), e0124884. <https://doi.org/10.1371/journal.pone.0124884>

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Approval Date	Effective Date; Summary of Changes
08/01/2025	10/01/2025; Added code 0599U effective 10/01/2025.
10/30/2024	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 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 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.
04/15/2024	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. 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. Beta-2 microglobulin (B2M): for Waldenström macroglobulinemia/lymphoplasmacytic lymphoma, removed indication for prognostication at the time of first-line treatment initiation. 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 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
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	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. 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. 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. 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.
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	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.
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