ConnectiCare

Reimbursement Policy:

Serum Tumor Markers for Malignancies - Lab Benefit Program (LBM)

POLICY NUMBER	EFFECTIVE DATE:	APPROVED BY
AHS-G2124	3/01/2023	RPC (Reimbursement Policy Committee)

Policy Description:

Circulating tumor biomarkers are substances detected in the blood, urine, or other body fluids that are either produced by a tumor itself or in response to its presence. These biomarkers can be used to help detect, diagnose, stage, and manage some types of cancer, because their amounts are typically elevated in individuals harboring a tumor.[1,2] There are currently dozens of tumor markers in common use; this laboratory policy addresses tumor markers which may be measured in an individual's serum.

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

The following management of serum tumor markers is built from recommendations from the National Comprehensive Cancer Network (NCCN) Biomarkers Compendium®, which contains information "designed to support decision making around the use of biomarker testing in patients with cancer. The NCCN Biomarkers Compendium® is updated in conjunction with the NCCN Guidelines on a continual basis."[3]

Indications and/or Limitations of Coverage:

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

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

1) Measurement of the following serum biomarkers **MEETS COVERAGE CRITERIA** for the following indications:

Serum Biomarker	Indication
Alkaline phosphatase (ALP)	Bone neoplasms: **workup**
	Melanoma (uveal): **workup**
	Systemic light chain amyloidosis: **initial diagnostic workup**
Alpha fetoprotein (AFP)	Hepatocellular carcinoma: **screening**; **workup** for confirmed HCC; **surveillance** (every 3-6 months for 2 years, then every 6 months)
	Intrahepatic cholangiocarcinoma: **workup** for isolated intrahepatic mass
	Occult primary: **additional workup** for localized adenocarcinoma or carcinoma not otherwise specified; liver, mediastinum, or retroperitoneal mass
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)
	Ovarian cancers (less common): – Carcinosarcoma (malignant mixed mullerian tumors): **monitoring/follow-up** – Clear cell carcinoma of the ovary: **monitoring/follow-up** – Grade 1 endometrioid carcinoma: **monitoring/follow-up** – Mucinous neoplasms of the ovary: **monitoring/follow-up** – Low-grade serous carcinoma: **monitoring/follow-up** Ovarian cancers: – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated) – Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
	Testicular cancer – nonseminoma: **workup**; **risk classification**; **surveillance** (no more than every 2 months)
	Testicular cancer - pure seminoma: **initial diagnostic workup**; **post-diagnostic workup**; **risk classification**; **post-treatment surveillance** (no more than every 2 months)
	Thymomas and thymic carcinomas: **initial evaluation**, if appropriate

Serum Biomarker	Indication
Beta-2 microglobulin (B2M)	B-cell lymphomas (diffuse large B-cell; follicular [grade 1-2]; HIV-related; lymphoblastic; mantle cell): **workup**
	Castleman Disease: workup
	Chronic lymphocytic leukemia/small lymphocytic lymphoma: **workup**; for **prognostic** and/or **therapy determination**
	Multiple myeloma: **initial diagnostic workup**; **follow-up/surveillance** (as needed) for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement
	Systemic light chain amyloidosis: **initial diagnostic workup**
	Waldenström macroglobulinemia / lymphoplasmacytic lymphoma: **workup**
BNP or NT-proBNP	Multiple myeloma: **initial diagnostic workup**
Calcitonin (CALCA)	Adenocarcinoma, and anaplastic/undifferentiated epithelial tumors: **workup**
	Medullary carcinoma: **additional workup**; **post-surgical evaluation**; **monitoring**; **surveillance** (2-3 months postoperative, then every 6-12 months)
	Multiple endocrine neoplasia, type 2: **at diagnosis** (clinical evaluation) for medullary thyroid cancer
	Occult primary (unknown primary cancer): **workup**
Cancer antigen 15-3 and 27.29 (CA 15-3 and 27.29)	Breast cancer (invasive): **monitoring** metastatic disease
	Occult primary: suspected metastatic malignancy: **initial workup**; assessing disease **prognosis**; **monitoring/follow-up** for response
Cancer antigen 19-9 (CA 19-9)	Ampullary adenocarcinoma: **workup**; **surveillance** (every 3-6 months for 2 years, then every 6-12 months for up to 5 years as clinically indicated) for resected ampullary cancer, stage I-III
	Appendiceal adenocarcinoma: **workup** to establish baseline. Abnormal measurements should be trended
	Extrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring**
	Gallbladder cancer: **workup** to establish baseline; **monitoring**; **surveillance** (as clinically indicated), post-resection
	Intrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring**
	Occult primary: workup to establish baseline;

Serum Biomarker	Indication
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)
	Ovarian cancers (less common): – Carcinosarcoma (malignant mixed mullerian tumors): **workup/monitoring/follow up** – Clear cell carcinoma of the ovary: **workup/monitoring/follow up** – Grade 1 endometrioid carcinoma: **workup/monitoring/follow up** – Low-grade serous carcinoma: **workup/monitoring/follow up** – Mucinous neoplasms of the ovary: **workup/monitoring/follow up** Ovarian cancers – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated) – Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) – Mucinous carcinoma of the ovary: **additional workup** (if not previously done)
	Pancreatic adenocarcinoma: **workup** to establish baseline; **monitoring**; **post-operative**, **post-adjuvant treatment surveillance** (every 3-6 months for 2 years, then every 6-12 months as clinically indicated)
	Small bowel adenocarcinoma: **workup** to establish baseline; **post-treatment surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years); **at metastasis or recurrence**
Cancer antigen 125 (CA-125)	Appendiceal adenocarcinoma: **workup** to establish baseline
	Endometrial carcinoma: **additional workup**; **surveillance** (if initially elevated)
	Lynch syndrome: **surveillance**
	Occult primary: initial evaluation/workup, **additional workup** for adenocarcinoma or carcinoma not otherwise specified, in those with a uterus and/or ovaries present
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)

Serum Biomarker	Indication
	Ovarian cancers (less common): – Carcinosarcoma (malignant mixed mullerian tumors): **monitoring/follow-up** – Clear cell carcinoma of the ovary: **monitoring/follow-up** – Mucious neoplasms of the ovary: **monitoring/follow-up** – Grade 1 endometrioid carcinoma: **monitoring/follow-up** – Low-grade serous carcinoma: **monitoring/follow-up** Ovarian cancers: – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated) – Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 6 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
	Peritoneal mesothelioma: **initial evaluation**
	Uterine neoplasms: **initial workup, additional workup, surveillance**
Carcinoembryonic antigen (CEA)	Appendiceal adenocarcinoma: **workup** to establish baseline; **monitoring**; **post-treatment surveillance**
	Breast cancer (invasive): **Monitoring** metastatic disease
	Colon cancer: **workup** to establish baseline; **monitoring**; **surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	Extrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring**
	Gallbladder cancer: **workup** to establish baseline; **monitoring**; **surveillance; monitoring of adjuvant treatment** (as clinically indicated), **post-resection**
	Intrahepatic cholangiocarcinoma: **workup** to establish baseline; **monitoring**
	Medullary carcinoma: **diagnosis and additional workup**; **monitoring**; **post-surgical surveillance** (2-3 months postoperative, then every 6-12 months)
	Multiple endocrine neoplasia, type 2: **at diagnosis** (clinical evaluation) for medullary thyroid cancer
	Occult primary (unknown primary cancer): **workup** for adenocarcinoma or carcinoma not otherwise specified
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial**

Serum Biomarker	Indication
	workup; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)
	Ovarian cancers (less common): – Carcinosarcoma (malignant mixed mullerian tumors: **monitoring/follow-up** – Clear cell carcinoma of the ovary: **monitoring/follow-up** – Grade 1 endometrioid carcinoma: **monitoring/follow-up** – Low-grade serous carcinoma: **monitoring/follow-up** – Mucinous neoplasms of the ovary: **monitoring/follow-up** Ovarian cancers: – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated); **post-adjuvant treatment** – Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease) – Mucinous carcinoma of the ovary: **additional workup** (if not previously done)
	Rectal cancer: **workup** to establish baseline; **monitoring**; **surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
	Small bowel adenocarcinoma: **workup** to establish baseline; **post-treatment surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
Chorionic gonadotropin beta polypeptide (CGB3)	Gestational trophoblastic neoplasia: **initial workup**; **during and post treatment** (no more than weekly); **follow-up/surveillance** (no more than monthly for 12 months)
	Occult primary: **additional workup** for localized adenocarcinoma or carcinoma not otherwise specified; individuals < 65 years of age with mediastinum or retroperitoneal mass
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)
	Ovarian cancers: – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated)

Serum Biomarker	Indication
	– Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
	Testicular cancer – nonseminoma: **workup; risk classification; surveillance** (no more than every 2 months)
	Testicular cancer – pure seminoma: **workup; post-diagnostic workup; risk classification; post-treatment surveillance** (no more than every 2 months)
	Thymomas and thymic carcinomas: **initial evaluation**, if appropriate
Human epididymis protein 4 (HE4)	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)
	Ovarian cancers (less common): – Carcinosarcoma (malignant mixed mullerian tumors: **monitoring/follow-up** – Clear cell carcinoma of the ovary: **monitoring/follow-up** – Grade 1 endometrioid carcinoma: **monitoring/follow-up** – Low-grade serous carcinoma: **monitoring/follow-up** – Mucinous neoplasms of the ovary: **monitoring/follow-up** Ovarian cancers : – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated); **post-adjuvant treatment** – Malignant germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
Inhibin (INHA)	Occult primary (unknown primary cancer): **additional workup** for adenocarcinoma or carcinoma not otherwise specified
	Ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup**; **during primary chemotherapy**; **monitoring/follow-up for complete response** (as clinically indicated)

Serum Biomarker	Indication
	Ovarian cancers (less common): – Carcinosarcoma (malignant mixed mullerian tumors: **monitoring/follow-up** – Clear cell carcinoma of the ovary: **monitoring/follow-up** – Grade 1 endometrioid carcinoma: **monitoring/follow-up** – Low-grade serous carcinoma: **monitoring/follow-up** – Mucinous neoplasms of the ovary: **monitoring/follow-up** Ovarian cancers: – Borderline epithelial tumors: **monitoring/follow-up** (every visit if initially elevated) – Malignant Germ cell tumors: **surveillance** (no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5) – Malignant sex cord stromal tumors: **surveillance** if clinically indicated. If done, frequency based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
Serum free light chains	Castleman disease: workup Multiple myeloma: **initial diagnostic workup**; **follow-up; surveillance** (up to once per month) Systemic light chain amyloidosis: **initial diagnostic workup**
Troponin T	Systemic light chain amyloidosis: **initial diagnostic workup**
Tryptase	Systemic mastocytosis: **initial diagnosis**

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

2) For all other cancer indications not discussed above, use of the above biomarkers (alone or in a panel of serum tumor markers) **DOES NOT MEET COVERAGE CRITERIA.**

3) All other serum tumor markers not addressed above (alone or in a panel of serum tumor markers) **DO NOT MEET COVERAGE CRITERIA.**

4) For the screening and detection of cancer, analysis of proteomic patterns in serum **DOES NOT MEET COVERAGE CRITERIA**.

Definitions:

Term	Definition
A2-PAG	Pregnancy associated alpha 2 glycoprotein
AACC	American Association for Clinical Chemistry
AASLD	American Association for the Study of Liver Diseases
ACCP	American College of Chest Physicians
ACR	American College of Radiology
ADLM	Association for Diagnostics & Laboratory Medicine
AFP	Alpha fetoprotein
AGA	American Gastroenterological Association
AGCT	Adult-type granulosa cell tumor
AIDS	Acquired immune deficiency syndrome
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
AMH	Anti-müllerian hormone
AML	Acute myeloid leukemia
ASCO	American Society of Clinical Oncology
ATA	American Thyroid Association
AUC	Area under curve
B7-H4	V-set domain-containing T-cell activation inhibitor 1
B2M	Beta-2 microglobulin
BCM	Breast cancer mucin
beta-HCG	Beta-human chorionic gonadotropin
BG8	Blood group 8
BNP	Brain natriuretic peptide
BRCA	Breast cancer gene
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CA	Cancer antigen
CA-9	Carbonic anhydrase 9

Term	Definition
CALCA	Calcitonin
CAM 17-1	Antimucin monoclonal antibody
CAM-26	Carcinoma associated mucin antigen
CAM-29	Carcinoma associated mucin antigen
CAR-3	Antigenic determinant recognized by monoclonal antibody AR-3
CA-SCC	Squamous cell carcinoma antigen
CEA	Carcinoembryonic antigen
CEACAM6	Carcinoembryonic antigen cell adhesion molecule 6
CEACAM-7	Carcinoembryonic antigen cellular adhesion molecule-7
CEP17	Chromosome 17 centromere
CFL1	Cofilin
CgA	Chromogranin A
CGB3	Chorionic gonadotropin beta polypeptide expression
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CRC	Colorectal cancer
CSS	Cancer specific survival
CTC	Circulating tumor cell
CUP	Cancers of unknown primary
CYP2D6	Cytochrome P450 2D6
DCIS	Ductal carcinoma in situ
DCP	Des-γ-carboxy prothrombin
DcR3	Decoy receptor 3
DFS	Disease-free survival
DMSA	Pentavalent technetium-99mm dimercaptosuccinic
Du-PAN-2	Sialylated carbohydrate antigen
EASL	European Association for the Study of the Liver
ECM	Extracellular matrix protein
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EPCAM	Epithelial cell adhesion molecule

Term	Definition
ER	Estrogen receptor
FDA	Food and Drug Administration
FLC	Free-light chain
FOXP3	Forkhead box P3
GC	Gastric cancer
GCTs	Germ cell tumors
GRP78	78-kDa glucose-regulated protein
HCC	Hepatocellular carcinoma
hCGβ	Free β-subunit of human chorionic gonadotropin
HE4	Human epididymis protein 4
HEC1	Highly expressed in cancer protein
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HYAL1	Hyaluronoglucosaminidase
IGF	Insulin-like growth factors
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
INHA	Inhibin
Ki-67	Antigen KI-67
KRAS	Kirsten rat sarcoma viral oncogene homolog
LCA	Lens culinaris agglutinin
LCOC	Less common ovarian cancers
LCOH	Less common ovarian histopathologies
LDH	Lactate dehydrogenase
LDT	Laboratory-developed test
LINE-1	Long interspersed nuclear elements 1
MALDI	Matrix-assisted laser desorption/ionization
MAP	Microtubule-associated protein
MCA	Mucinous carcinoma associated antigen

Term	Definition
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
MINDACT	Microarray in node-negative disease may avoid chemotherapy
MMP-1	Matrix metalloproteinase-1
mRNA	Messenger ribonucleic acid
MSA	Mammary serum antigen
MTC	Medullary thyroid carcinoma
NACB	National Academy of Clinical Biochemistry
NANETS	North American Neuroendocrine Tumor Society
NCCN	National Comprehensive Cancer Network
NET	Neuroendocrine tumor cells
NICE	National Institute for Health and Clinical Excellence
NMP22	Nuclear matrix protein 22
non-HCC	Non-hepatocellular carcinoma
NSE	Neuron specific enolase
NSGCT	Nonseminomatous germ cell tumor
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
OS	Overall survival
P53	Tumor protein P53
PAGE	Polyacrylamide gel electrophoresis
PAI-1	Plasminogen activator inhibitor type 1
PAM50-ROR	Prediction analysis of microarray 50-risk of recurrence
PcSt	Pancreastatin
PD-L1	Programmed Death-ligand 1
PED-ALL	Pediatric acute lymphoblastic leukemia
PgR	Plant growth regulator
PIVKA-II	Protein induced by vitamin K absence/antagonist-II
P-LAP	Placental alkaline phosphatase
PNA-ELLA	Peanut lectin bonding assay
PR	Progesterone receptor
PSA	Prostate specific antigen

Term	Definition
PTEN	Phosphatase and tensin homolog
RCC	Renal cell carcinoma
RMI I	Risk of malignancy index I
ROC	Receiver operating characteristic
ROMA	Risk of ovarian malignancy algorithm
ROR	Risk of recurrence
RRSO	Risk-reducing salpingo-oopherectomy
SCC	Squamous cell carcinoma
SCLCs	Small cell lung cancers
SLEX	Sialylated lewis-x antigen
SLX	Sialylated SSEA-1 antigen
SMRP	Mesothelin-related peptide expression
SPAN-1	Sialylated carbonated antigen span-1
ST-439	Sialylated carbohydrate antigen st-439
STMs	Serum tumor markers
TAG	Tumor associated glycoprotein
TATI	Tumor associated trypsin inhibitor
TG	Thyroglobulin
TILs	Tumor-infiltrating lymphocytes
TIMP-1	Tissue inhibitor of metalloproteinase-1
TKI	Tyrosine kinase inhibitor
TN	Triple-negative
TNF-a	Tumor necrosis factor alpha
TnI	Troponin I
TnT	Troponin T
TOP2A	Deoxyribonucleic acid topoisomerase II alpha
TPA	Tissue polypeptide antigen

Scientific Background:

Actionable molecular assays for tumor biomarkers may guide treatment decisions for common malignancies.[4] Circulating tumor biomarkers are proteins detected in blood, urine, or other body fluids that serve as surrogate indicators to increase or decrease the clinician's suspicion of future clinically important events. These can be used to determine risk, screen for early cancers, establish diagnosis, estimate prognosis, predict that a specific

therapy will work, and/or monitor for disease recurrence or progression.[5] The National Comprehensive Cancer Network (NCCN) task force guidelines recommend that tumor markers be classified by indication as diagnostic, prognostic, predictive, and companion tests. An individual marker may serve more than one purpose and thus can fall into more than one category of biomarker. Biomarkers may also have different categorization across different stages of disease or different types of tumors.[4] Some of these categories are listed below:

- **Diagnostic** – Tumor biomarkers that aid in the diagnosis or subclassification of a particular disease state. Detection of diagnostic biomarkers may result in different management of the disease, but the marker is used primarily to establish that a particular disease is present in the patient sample. An example of a diagnostic biomarker is the Philadelphia chromosome in chronic myelogenous leukemia.
- **Prognostic** – Some tumor biomarkers have an association with certain clinical outcomes, such as overall survival or recurrence-free survival, independent of the treatment rendered. An example is a mutant p53 gene, whose presence may indicate a more aggressive type of cancer.
- **Predictive** – Tumor biomarkers can predict the activity of a specific class or type of therapy and are used to help make more specific treatment decisions. An example is human epidermal growth factor 2 (HER2), which is assessed in breast cancer patients. Patients who are negative for this biomarker do not respond as well to trastuzumab.
- **Companion** – Biomarkers may be diagnostic, prognostic, or predictive, but are used to identify a subgroup of patients for whom a therapy has shown benefit. This category of biomarker is similar to the predictive category, but these biomarkers do not usually have independent prognostic or predictive strength.[4]

Proprietary Testing

There are laboratory developed tests that utilize serum tumor markers intended to aid in the management of individuals with cancer or those at increased risk of developing cancer. The clinical validity and utility of these tests is still emerging. Examples of commercialized tests in current use include the following:

BeScreened™–CRC is a colorectal cancer (CRC) screening test. BeScreened™–CRC tests three blood-based proteins that are thought to play a role in the immunological activities of colorectal cancer. The test results are reported as either “negative” or “positive” for the likely presence of CRC. The test is reported to have 94% accuracy in determining the “likely presence or absence of colorectal cancer.” The test developer reports “BeScreened™-CRC is not a test for colorectal cancer diagnosis; it is a screening test that aides in the detection of colorectal cancer and is not intended to replace a colonoscopy.”[6]

The Ova1Plus® by Aspira Health is a combination of two tests designed to assess the risk of ovarian malignancy in women presenting with pelvic masses who are scheduled for surgery. It combines two FDA cleared blood tests— Ova1® and Overa® -- to enhance the accuracy of cancer risk assessment. The Ova1® test measures the levels of five biomarkers in the blood: cancer antigen 125, transferrin, Apolipoprotein A-1, Beta-2 Microglobulin (B2M), and Prealbumin. These values are integrated using proprietary software to produce a numerical score between 0.0 and 10.0 which is then interpreted based on the patient’s menopausal status. The Overa® test also measures five protein biomarkers: cancer antigen 125, transferrin, apolioprotein A-1, follicle-stimulating hormone, and human epididymis protein 4. In the complete Ova1Plus® process, the Ova1® test is performed first, and then the Overa® test is automatically conducted if the result falls into an intermediate-risk category. This reflex testing strategy aims to improve tests sensitivity and reduce false-positive results.[7]

For individuals with an adnexal mass who are not planned for surgery, OvaWatch℠ may be considered for ovarian cancer risk refinement when initial assessment of the mass was indeterminate or benign. This test considers seven tumor biomarkers, an individual’s age, and menopausal status, to produce a single risk assessment score with a reported negative predictive value of 99%.[8]

Clinical Utility and Validity

Most biomarkers are not specific for tumors or organs and their levels may rise in other diseases. The diagnostic value of a tumor marker will depend on the prevalence of the disease and on the specificity and sensitivity of the marker.[1] The analytic and clinical validity as well as the clinical utility of each biomarker should be taken into account before it is used for screening and or management of malignancies.[5] Establishing a biomarker's ability to associate with a given outcome of interest (diagnostic, prognostic, et al.) and ability to improve clinical outcomes and decision making is critical.[4]

With respect to biomarker acquisition, growing evidence continues to support the utility of liquid biopsy. Compared to the "gold standard" tissue biopsy, serum can be obtained in a relatively non-invasive manner, without the need for surgery and the associated risks and recovery time. Further, serum is generally always available; tumor tissue, conversely, may not always be accessible or present in a clinically useful quantity.[9]

Alkaline phosphatase (ALP)

Alkaline phosphatase is an enzyme that is highly concentrated in the liver, kidneys, placenta, and bone.[10] While the physiological functions of the various isozymes of ALP are incompletely understood, there is a stronger consensus that the bone isoenzyme contributes to skeletal mineralization.[11] Serum ALP has thus been identified as a useful marker for diseases of the bone and liver, and is often measured during the workup and management of disorders that include bone neoplasms, systemic light chain amyloidosis to confirm liver involvement, as well as other cancerous and non-cancerous conditions.[10,12,13]

Alpha-fetoprotein (AFP)

Alpha-fetoprotein is a commonly assessed biomarker in cancer patients. AFP is a protein that is normally produced by the fetal yolk sac, and its concentration stabilizes at approximately < 10 µg/L shortly after birth.[14] Many tissues produce this protein if they become malignant, and AFP is elevated in a variety of cancers, such as hepatocellular carcinomas (HCC). False positives may occur due to liver damage or a rare hereditary syndrome.[15]

Alpha-fetoprotein can be fractionated into three different isoforms based on reactivity with Lens culinaris agglutinin (LCA), and the three types are as follows: L1 (no reactivity), L2 (low reactivity), and L3 (high reactivity). AFP-L3 is theorized to associate with HCC because the dedifferentiation of HCC tissues correlates with the production of the enzyme that produces AFP-L3. This means that AFP-L3 may be closely related to cancer-specific events and are at least more specific to certain malignant cancers.[16] The AASLD update on HCC stated that while AFP-L3 is technically FDA-approved for risk stratification, it is not yet used for HCC surveillance in the United States. Specifically, "AFP-L3% and DCP have insufficient sensitivity to detect early-stage HCC when used alone." In the past years, a diagnostic model was proposed to incorporate three biomarkers (one being AFP-L3%). This GALAD model (AFP, AFP-L3%, and DCP levels) was evaluated in a phase III study. The model was found to have a sensitivity and specificity of 65% and 82% for HCC, respectively. More phase III and phase IV studies are needed to validate the model's clinical utility.[17]

A study by Santos Schraiber, et al. (2016) assessed the ability to predict recurrence of HCC after liver transplant using AFP. The authors analyzed 206 patients and the recurrence frequency was found to be 15.5%. However, the authors' multivariate analysis found that the only risk factor for recurrence was an AFP level of >200 ng/mL, which was associated with a 3.32 times higher increase in the probably of HCC recurrence. The authors noted that recurrence was also associated with lower survival rate.[18]

Cheng, et al. (2014) conducted a meta-analysis of fifteen studies (4465 patients) to evaluate the association of high pre-treatment serum AFP-L3 percentage (%) with overall survival (OS) and disease-free survival (DFS) in

HCC patients. The authors found that high pre-treatment serum AFP-L3% implied poor OS (Hazard Ratio [HR]: 1.65), and DFS (HR: 1.80) of individuals with HCC. The authors found an association between pre-treatment serum AFP-L3% and OS and DFS in low AFP concentration HCC patients (HR: 1.96 and 2.53 respectively). The authors concluded that "high pre-treatment serum AFP-L3% levels indicated a poor prognosis for patients with HCC."[19]

Park, et al. (2017) compared the diagnostic values of AFP, AFP-L3, and protein induced by vitamin K absence/antagonist-II (PIVKA-II) individually and in combination to find the best biomarker or biomarker panel. A total of 79 patients with newly diagnosed HCC and 77 control patients with liver cirrhosis were enrolled. When the three biomarkers were analyzed individually, AFP showed the largest area under the receiver-operating characteristic curve (AUC) (0.751). For combinations of the biomarkers, the AUC was highest (0.765) for PIVKA-II>40mAU/mL and AFP>10ng/mL. Adding AFP-L3>10% led to worse sensitivity and lower AUC. The authors concluded that "the diagnostic value of AFP was improved by combining it with PIVKA-II, but adding AFP-L3 did not contribute to the ability to distinguish between HCC and non-HCC liver cirrhosis" and that "AFP showed the best diagnostic performance as a single biomarker for HCC."[20]

Ryu, et al. (2017) investigated the prognostic implications of the expression patterns of three tumor markers, AFP, AFP-L3, and des-γ-carboxy prothrombin (DCP). The study included 1182 consecutive patients that underwent hepatic resection and surgical microwave ablation for HCC. This study analyzed 475 patients within the Milan criteria and Child-Pugh class A. Cumulative OS and DFS rates were analyzed relative to the number of positive tumor markers. OS and DFS at five years postoperatively were 85.3 and 44.2% in triple-negative patients, 79.4 and 48.0% in single-positive patients, 56.2 and 32.9% in double-positive patients, and 61.7 and 35.7% in triple-positive patients. The authors concluded that "both double- and triple-positive tumor markers are associated with early recurrence and poor survival in HCC patients within the Milan criteria and Child-Pugh class A."[21]

Caviglia, et al. (2016) conducted a study evaluating AFP, AFP-L3, and DCP as detection tools for HCC. A total of 98 patients were enrolled (44 without HCC, 54 with), and the FDA-approved automated immunoassay system uTASWako was used to measure these biomarkers. AFP-L3 demonstrated an AUC of 0.867, a sensitivity of 0.849, a specificity of 0.886, a negative predictive value of 0.830, and a positive predictive value of 0.900. The combination of all three biomarkers had an accuracy of 87.6%. The overall accuracy of uTASWako was 84.5%. The authors concluded that the uTASWako had a "high analytical performance" and that the biomarker combination was superior to any of the individual markers alone.[22]

Beta-2 microglobulin (B2M)

Beta-2 microglobulin is the light chain component of the MHC-1 molecule and is present in most cells of the body.[23] This protein may aggregate and eventually form insoluble amyloid fibrils, which cause numerous conditions such as bone and joint damage.[24,25] Elevated serum levels of B2M have been associated with cancers such as multiple myeloma or chronic leukocytic leukemia.[23]

Seo, et al. (2016) examined the prognostic value of B2M for diffuse large B-cell lymphoma. A total of 833 patients at a ≥2.5 mg/L cutoff were analyzed, and both five-year survival and overall survival rates were found to be significantly worse in patients with elevated B2M (290 patients or 34.8%). The elevated B2M cohort was calculated to have a 41% five-year survival rate and a 49.2% overall survival rate, compared to 76.1% five-year survival and 83.8% overall survival for the remaining 543 patients.[26]

BNP/NT-proBNP

Brain natriuretic peptide (also known as B-type natriuretic peptide) is thought to play important roles in the regulation of blood pressure, blood volume, and sodium balance.[27,28] BNP is synthesized as a prehormone

(proBNP) within cardiomyocytes that is cleaved into the biologically active 32 amino acid BNP and the inactive 76 amino acid N-terminal fragment (NT-proBNP).[27]

Interest in BNP as a potential marker for cardiac function has existed for decades, lending credence to the utility of BNP to aid in the management of disorders that may affect the heart. These include systemic light chain amyloidosis and multiple myeloma, where serum concentrations of BNP or NT-proBNP may inform the degree of heart involvement.[12,29,30]

Calcitonin

Serum calcitonin is the primary tumor marker for medullary thyroid carcinoma (MTC). MTC is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland, and production of calcitonin is a signifying characteristic of this tumor. The concentration of calcitonin tends to correlate with tumor mass.[31] However, the American Thyroid Association (ATA) has noted that there is a lack of agreement on the utility of routine calcitonin measurement as a screening test for individuals with thyroid nodules.[32,33]

Tormey, et al. (2017) evaluated measurement of serum calcitonin in patients presenting with thyroid nodules. A total of 44 patients were evaluated and 33 of the patients were reported to not have "detectable serum calcitonin," noting that three patients had an initially elevated serum concentration that became undetectable. The authors also note that out of the 2070 patients in their sample, only seven cases of MTC were diagnosed. The authors recommended not screening routinely for MTC.[34]

Cancer antigens (CA)

Cancer antigens refer to any substance produced by the body in response to a tumor. Various cancer antigens have been proposed as biomarkers for numerous types of cancer, such as CA 19-9, CA-125, and CA 15-3. CA 19-9 (also called carbohydrate antigen) refers to a specific antibody that binds a sialyl compound produced by cancer tissue (Sialyl Lewis A). CA 19-9 is elevated in several different types of cancer, such as adenocarcinomas or colorectal cancer.[35] CA-125 is a glycoprotein produced in fetal tissue as well as mesothelial cells in adults.[36] Its function is thought to assist with cell adhesion, metastasis, and immunosuppression.[37]

Kim, et al. (2017) performed a study assessing the association of serum CA 19-9 and carcinoembryonic antigen (CEA) with colorectal neoplasia. A total of 124509 measurements of serum CEA level and 115833 measurements of serum CA 19-9 were taken. All subjects were asymptomatic and underwent a colonoscopy. Elevated serum levels of CEA were found to be associated with any adenoma. Elevated CA 19-9 was found to be associated with high-risk or advanced adenoma, CRC, and advanced colorectal neoplasia.[38]

A study was performed by Feng, et al. (2017) that focused on the diagnostic and prognostic value of CEA, CA 19-9, AFP, and CA-125 for early gastric cancer. The authors evaluated 587 patients and the positive rate for all markers combined was 10.4%. CEA's positive rate was 4.3%, CA 19-9's was 4.8%, AFP's was 1.5%, and CA-125's was 1.9%. The authors noted that elevated CEA was correlated with lymph node metastasis and concluded that CEA was an independent risk factor for poor prognosis of early gastric cancer.[39]

Lucarelli, et al. (2014) evaluated CA 15-3, CA-125, and B2M as biomarkers for renal cell carcinoma (RCC). A total of 332 patients undergoing nephrectomy for RCC were analyzed. The authors found that 35.2% (117/332) of patients had abnormal levels of CA 15-3, 9.6% (32/332) had abnormal levels of CA-125, and 30.4% (101/332) had abnormal B2M. Cancer specific survival (CSS) rates significantly decreased for high levels of any of the three biomarkers, and at a multivariate analysis high levels of CA 15-3 were found to be an independent adverse prognostic risk factor for CSS.[40]

Chen, et al. (2018) analyzed four serum tumor markers in patients with ovarian tumors. Human epididymis protein four (HE4), CA-125, CA19-9, and CEA were all studied. The authors evaluated 386 healthy controls, 262 patients with benign ovarian tumors, and 196 patients with malignant ovarian tumors. The authors found that the serum marker levels were significantly higher in patients with malignant tumors than the two other groups. HE4 was found to have a high specificity (96.56%) in malignant tumors. HE4, CA-125, CA19-9, and CEA had sensitivities of 63.78%, 62.75%, 35.71%, and 38.78%, respectively. HE4 and CA-125 combined were found to have the highest diagnostic sensitivity at 80.10%, as well as a specificity of 69.08%. Although adding markers to the HE4/CA-125 combination increased diagnostic sensitivity (to 88.52%), this difference was not considered significant.[41]

Isaksson, et al. (2017) performed a study of tumor markers' association with resectable lung adenocarcinomas. The study evaluated blood samples from 107 patients with stages I-III lung adenocarcinoma and examined the following markers: CEA, CA 19-9, CA-125, HE4, and neuron-specific enolase (NSE). When the authors calculated the disease-free survival rate, CA 19-9 and CA-125 were found to be significantly associated with recurrent disease with a combined hazard ratio of 2.8. The authors stated that "high pre-operative serum CA 19-9 and/or CA 125 might indicate an increased incidence of recurrent disease in resectable lung adenocarcinomas."[36]

Bind, et al. (2021) evaluated the diagnostic performance of CA19-9 and CA-125 for gallbladder cancers. A total of 118 patients were included; 91 benign cases and 27 malignant. The mean value of CA19-9 was found to be 12.86 U/mL in benign cases and 625.35 U/mL in malignant cases. For CA-125, the mean value for benign cases was found to be 17.98 U/mL and for malignant cases, 239.63 U/mL. The authors examined a theoretical diagnostic cut-off value of 252.31 U/mL for CA19-9 and 92.19 U/mL for CA-125. At this cutoff, sensitivity and specificity for CA19-9 were 100% and 98.9% respectively, and for CA-125, 100% and 94.5%. The authors concluded that "…both serum CA 19-9 and serum CA 125 may act as a good adjunct for diagnosis of cases of carcinoma gallbladder along with imaging studies. However, changes in CA19-9 are more significant than CA 125."[42]

Carcinoembryonic antigen (CEA)

Carcinoembryonic antigen is a protein normally produced by fetal tissue, and as with AFP, stabilizes soon after birth. CEA is often elevated in malignancies such as breast or pancreatic cancer, although other conditions such as liver damage or cigarette smoking may affect CEA levels as well.[43] The gene encoding CEA encompasses certain genes encoding for cell adhesion, as well as MHC antigens.[44]

Chorionic gonadotropin beta polypeptide expression (CGB3)

Chorionic gonadotropin beta polypeptide 3 (CGB3) is one of several genes that encode the beta subunit of human chorionic gonadotropin. Beta-human chorionic gonadotropin is the beta subunit of the normal hCG hormone produced during pregnancy. Some malignancies express the gene for the beta subunit of hCG, thereby producing this protein independent of pregnancy, particularly in germ cell tumors and trophoblastic disease.[45] The beta subunit is responsible for providing the biological and immunological specificity to each hormone.[46] This biomarker is typically associated with aggressive disease in nontrophoblastic tumors. This biomarker may be elevated in ovarian cancers, testicular cancers, and more.[47]

Li, et al. (2018) evaluated beta-hCG as a marker for CRC. In total, 50 patients out of 136 patients expressed beta-hCG at the "invasive front." The authors found higher expression of beta-hCG to be associated with worse prognosis than those with low beta-hCG expression and reported that beta-hCG "promoted the migration and invasion of CRC in vitro and in vivo but had no effect on the proliferation of tumor cells." A correlation was also found between beta-HCG expression level and tumor invasion in early-stage CRC patients.[48]

Chromogranin A (CgA)

Chromogranins are proteins contained in neurosecretory vesicles of NET cells and are typically elevated in neuroendocrine neoplasms. CgA is the most sensitive of the three chromogranins, and as such as the primary marker used to evaluate neoplasms. However, this biomarker is highly variable.[49]

A meta-analysis performed by Yang, et al. (2015) assessed the association of CgA with neuroendocrine tumors. The analyses included 13 studies totaling 1260 patients (967 healthy controls), and the pooled sensitivity was found to be 0.73. The pooled specificity was found to be 0.95. However, the study stressed that further research needs to be undertaken.[50] Another study by Tian, et al. (2016) found that although median CgA levels were significantly higher than healthy controls (93.8 ng/mL compared to 37.1 ng/mL), only a weak correlation was found between changes in serum CgA levels and clinical regimen. The CgA cutoff value for this study was 46.2 ng/mL, which led to a sensitivity of 78.8% and specificity of 73.8%.[51]

Inhibins

The primary function of inhibins is to inhibit hormones such as follicle stimulating hormone. However, since this protein is restricted to ovarian granulosa cells in individuals with ovaries, unusual levels of inhibins may signal tumors in this region.[52] This marker exists as two different isoforms: inhibin A and B. Either form can be measured, although an active tumor may over-secrete one or both forms.[53] Inhibin B is generally considered to be more accurate than inhibin A, with sensitivities ranging from 0.88 to 1.00 whereas inhibin A's sensitivity ranges from 0.67-0.77. However, inhibin B has limitations of its own such as fluctuations with the menstrual cycle.[54]

Farkkila, et al. (2015) evaluated anti-Müllerian hormone (AMH) and inhibin B in the context of ovarian adult-type granulosa cell tumors (AGCTs). The study included 560 samples taken from 123 patients, and both markers were significantly elevated in AGCTs. The area under the curve for inhibin B was 0.94, but measurement of both markers was noted to be a better method than measuring either marker individually.[54]

Serum free light chains

Light chains are proteins produced by plasma cells that, along with heavy chains, collectively make up an immunoglobulin macromolecule. There are a total of five heavy chain protein classes (IgG, IgE, IgA, IgD, and IgM), and two light chain protein classes (kappa and lambda). Healthy plasma cells produce polyclonal immunoglobulins that are capable of binding to antigens and inducing an immune response; unhealthy plasma cells produce monoclonal immunoglobulins that do not effectively engage antigens.[55] In the case of certain plasma cell disorders, an abundance of monoclonal immunoglobulin or free light chains (kappa and/or lambda) may accumulate in the serum and serve as useful diagnostic markers.

For example, multiple myeloma is an uncontrolled growth of plasma cells.[56] In most cases, the cancerous clonal cells secrete an intact monoclonal immunoglobulin, where the gold standard for diagnosis is serum protein electrophoresis and immunofixation.[57] Less commonly, however, myeloma clones will secrete only light chains; in these instances, a serum free light chain assay can be employed to quantify the ratio of kappa and lambda chains in the serum. It has been demonstrated that in healthy individuals, the kappa/lambda ratio in the serum is approximately 0.58.[58] In the case of plasma cell neoplasms, free light chains are overproduced, and the kidneys are unable to completely clear them, resulting in accumulation in the serum and a change in the kappa/lambda ratio. This ratio is often used to aid in the diagnosis, prognosis, and monitoring of plasma cell disorders.[57]

Waldenström's Macroglobulinemia (WM) is a type of cancer that is similar to multiple myeloma and non-Hodgkin lymphoma. WM cells are called "lymphoplasmacytoid" because they have features of both plasma cells and

lymphocytes.[59] WM cells are distinguished by the production of immunoglobulin M (IgM) serum monoclonal protein, also referred to as a "macroglobulin."[60] While serum IgM level is useful for diagnostic purposes, it does not correlate with prognosis. The addition of a serum free light chain assay to the care of patients with suspected Waldenström's Macroglobulinemia has been postulated to improve overall care, as it may help differentiate patients with another, potentially benign disorder called monoclonal gammopathy of undetermined significance (MGUS), as well as influence prognosis.[61]

Castleman disease represents a group of B-cell lymphoproliferative disorders characterized by distinct pathogenesis and clinical outcomes.[62,63] Patients with suspected Castleman disease have been reported to present with abnormal levels or kappa or lambda light chains, making the serum free light chain assay a potentially useful tool in the management of this disease.[62,63] Utilization of a serum free light chain assay has been reported to be clinically useful in the workup of Castleman disease, though an important caveat is that changes in the absolute values of both kappa and lambda free light chain in the serum can occur with preservation of a ratio within the normal reference range;[64] hence, both the free light chain ratio as well as the absolute values of each light chain protein should be considered.

Immunoglobulin light chain amyloidosis is a disorder that results from the accumulation of amyloid fibrils due to the production of fragments of monoclonal light chains.[65,66] As amyloid fibrils continue to accumulate, they begin to interfere with the biological function of various organs, eventually resulting in organ damage and potentially organ failure. Due to the involvement of light chains in the pathogenesis of amyloidosis, serum free light chain measurement may hold diagnostic and prognostic value and be a viable response marker following therapy.[66-69]

Importantly, Bhole, et al. (2014) highlighted key challenges with serum free light chain assays that include but are not limited to over or under-estimation of the monoclonal protein, and performance differences between available tests. Therefore, despite the demonstrated utility of these assays, clinicians should be aware of their limitations.

Troponin

Troponins are proteins that reside in muscle cells and function as part of the protein complex responsible for generating muscular contraction and relaxation.[70] Two forms of troponin (troponin I [TnI] and troponin T [TnT]) have particular utility as biomarkers of cardiac dysfunction or damage due to their relative abundance in cardiac cells.[71] Accordingly, TnI and TnT have been studied as potentially useful markers for the management of various disorders that affect the heart, including systemic light chain amyloidosis. Persistently elevated cardiac troponin levels are frequently observed in individuals with amyloidosis and can serve as an indicator of cardiac amyloid infiltration.[72]

Tryptase

Tryptases are tetrameric enzymes and one of the major types of protease found in mast cells, which play an integral role in the allergic and inflammatory responses.[73,74] Normal allergic responses involve the release of these proteases in addition to other active mediators including histamine, serotonin, lysosomal enzymes, and proteoglycans,[75] which can be measured in an individual's tissue or serum. These mediators can thus serve as useful markers for disorders involving mast cell production and activation, such as systemic mastocytosis, where serum tryptase is an accepted diagnostic criterion.[76]

Urokinase plasminogen activator (uPA)

Urokinase plasminogen activator is a serine protease with an important role in cancer invasion and metastasis.[77] When bound to its receptor (uPAR), uPA converts plasminogen into plasmin and mediates degradation of the

extracellular matrix during tumor cell invasion. High levels have been associated with shorter survival in individuals with breast cancer.[77-80] American Society of Clinical Oncology guidelines include recommendations for the appropriate clinical situations in which measurement of uPA may be helpful.[81,82]

Proteomics

Proteomics is a qualitative and quantitative assessment of the protein constituents in a biological sample. This is typically performed with modification of polyacrylamide gel electrophoresis (PAGE) or matrix-assisted laser desorption/ionization (MALDI). However, this method is still under investigation.[83]

Proteomic analyses have been performed in cancer patients to assess unusual levels of protein regulation. A study by Chen, et al. (2017) evaluated the proteomes of patients with CRC and healthy controls. The investigators found thirty-six proteins that were upregulated in cancer patients as well as twenty-two proteins that were downregulated compared to healthy controls. The proteins that were upregulated tended to be involved in processes that regulated the "pretumorigenic microenvironment for metastasis" and the downregulated proteins tended to be ones that controlled tumor growth and cell survival.[84]

Qin, et al. (2020) performed a "serological proteome analysis" to explore the association between an identified protein marker and gastric cancer (GC). Proteomic analysis was used to identify the protein marker of interest, an autoantibody called "anti-GRP78" (along with its corresponding antigen, the 78-kDa glucose-regulated protein [GRP78]). Two cohorts were included, a test group of 266 patients (133 GC patients, 133 controls) and a validation group of 600 patients (300 GC, 300 control). The authors found that the level of anti-GRP78 was higher in both cohorts. The receiver operating characteristic (ROC) curve analysis found similar values for both groups to identify GC patients among control patients. The AUC ranged from 0.676 to 0.773 in the test group and 0.645 to 0.707 in the validation group. The authors noted this marker's potential diagnostic use.[85]

Guidelines and Recommendations:

National Comprehensive Cancer Network (NCCN)

The NCCN provides a Biomarkers Compendium to "support decision-making around the use of biomarker testing in patients with cancer,"[3] which serves as a primary source of guidance for coverage criteria in this policy. The Biomarkers Compendium may be accessed through nccn.org.

In the most recently published clinical practice guidelines for ovarian cancer, NCCN states they recommend "that all patients with suspected ovarian malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery."[86] "A number of specific biomarkers and algorithms using multiple biomarker test results have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass. Biomarker tests developed and evaluated in prospective trials comparing preoperative serum levels to postoperative final diagnosis include serum HE4 and CA-125, either alone or combined using the Risk of Ovarian Malignancy Algorithm [ROMA] algorithm; the MIA (brand name OVA1) based on serum levels of five markers: transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125; and the second-generation MIA (MIA2G, branded name OVERA) based on CA-125, transferrin, apolipoprotein A1, follicle-stimulating hormone [FSH], and HE4. The FDA has approved the use of ROMA, Ova1, or Overa for estimating the risk for ovarian cancer in those with an adnexal mass for which surgery is planned, and have not yet been referred to an oncologist. Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and Ova1 may be useful for deciding which patients to refer to a gynecologic oncologist, other professional organizations have been non-committal. Not all studies have found that multi-biomarker assays improve all metrics (i.e., sensitivity, specificity,

positive predictive value, negative predictive value) for prediction of malignancy compared with other methods (e.g., imaging, single-biomarker tests, symptom index/clinical assessment). Currently, the NCCN Panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass."[86]

American Society of Clinical Oncology (ASCO)

Clinical Practice Guideline on Uses of Serum Tumor Markers (STMs) in Adult Males with Germ Cell Tumors (GCTs) were released in 2010.[15] ASCO recommends against any STMs to screen for GCTs. While ASCO recommends assessment of serum AFP and hCG before orchiectomy to establish a diagnosis and baseline levels, it recommends against its use to decide whether to perform an orchiectomy. The society also recommends against using these biomarkers to "guide treatment of patients with CUP and indeterminate histology." However, substantially elevated serum AFP and/or hCG may be considered sufficient for a diagnosis in unusual cases such as patients presenting with a retroperitoneal or anterior mediastinal primary tumor. Their recommendations also include measuring serum AFP, hCG, and LDH for "all patients with testicular nonseminomatous germ cell tumors (NSGCTs) shortly after orchiectomy and before any subsequent treatment," "before chemotherapy begins for those with mediastinal or retroperitoneal NSGCTs to stratify risk and select treatment", and "immediately prior to chemotherapy for stage II/III testicular NSGC."[15]

The society recommends measuring AFP and hCG before retroperitoneal lymph node dissection in patients with stage I or II NSGCT and recommends measuring serum AFP and hCG at the start of each chemotherapy cycle and when chemotherapy concludes. These biomarkers are also recommended to be measured during surveillance after "definitive therapy for NGSCT" and this surveillance should continue for 10 years after therapy concludes.[15]

Measuring "postorchiectomy serum concentrations of hCG and/or LDH for patients with testicular pure seminoma and preorchiectomy elevations" was also discussed, but ASCO recommends against using these concentrations for staging or prognosis. No markers are recommended to guide treatment decisions, monitor response, or progression for seminomas. However, serum hCG and AFP should be measured both when treatment concludes as well as during post-treatment surveillance. ASCO recommends these intervals: every two to four months in the first year, every three to four months in the second year, every four to six months in the third and fourth years, and annually thereafter. Surveillance should last for at least 10 years following the conclusion of therapy.[15]

Guidelines were released on the use of biomarkers to inform treatment decisions regarding systemic therapy for women with metastatic breast cancer. "Patients with accessible, newly diagnosed metastases from primary breast cancer should be offered biopsy for confirmation of disease process and testing of ER, PR, and HER2 status. With discordance of results between primary and metastatic tissues, the panel consensus is to preferentially use the ER, PR, and HER2 status from the metastasis to direct therapy if supported by the clinical scenario and the patient's goals for care." Decisions on changing to a new drug or regimen, initiating, or discontinuing treatment should be based on the patient's goals for care and clinical evaluation and judgment of disease progression or response. There is no evidence at this time that changing therapy solely based on tissue or circulating biomarker results beyond ER, PR, and HER2 improves health outcomes, quality of life, or cost-effectiveness. To date, clinical utility has not been demonstrated for any additional biomarkers. "CEA, CA 15-3, and CA 27.29 may be used as adjunctive assessments to contribute to decisions regarding therapy for metastatic breast cancer. Data are insufficient to recommend use of CEA, CA 15-3, and CA 27.29 alone for monitoring response to treatment."[87]

A provisional clinical opinion on evaluating susceptibility to pancreatic cancer was released by ASCO, stating that "there are currently no proven biomarkers using noninvasively obtained biospecimens (eg, blood, urine, stool) for early detection of pancreatic cancer in asymptomatic individuals." ASCO states that further validation

of biomarkers is needed.[88]

Finally, a guideline on treatment of malignant pleural mesothelioma was published, stating that calretinin, keratins five and six, and nuclear WT-1 are expected to be positive while CEA, EPCAM, Claudin four, and TTF-1 should be negative. Non-tissue based biomarkers are currently not recommended due to their unvalidated statistical accuracy.[89]

Association for Diagnostics & Laboratory Medicine (ADLM); formerly the National Academy of Clinical Biochemistry (NACB) and AACC Academy

Practice guidelines on the use of tumor markers for liver, bladder, cervical, and gastric cancers were released by ADLM.[90] The association recommends use of AFP measurements when managing hepatocellular carcinoma (HCC). For screening, ADLM recommends AFP be measured at 6-month intervals in patients at high risk of HCC, noting that concentrations above 20 µg/L should "prompt further investigation even if an ultrasound is negative." Sustained increases of serum AFP may be used in combination with ultrasound to inform detection and management and AFP concentrations may provide prognostic information in untreated patients. Monitoring of disease should include measurement of AFP. However, other liver biomarkers such as Glypican-3 cannot be recommended at this time without further research.[90]

The association did not recommend any biomarkers for the management of bladder cancer (such as NMP22, UroVysion, etc.), stating that further research is required to assess their utility. ADLM did not recommend any biomarkers for screening, monitoring, prognosis, or diagnosis of cervical cancer. While pretreatment measurements of squamous cell carcinoma antigen (SCC) were acknowledged to provide information, their routine use could not be recommended. ADLM did not recommend any biomarkers for screening, diagnosis, or prognosis of gastric cancer. Routine measurement of CEA or CA 19-9 was also not recommended.[90]

Guidelines on use of tumor markers for testicular, prostate, colorectal, breast, and ovarian cancers were also released by ADLM.[91] For testicular cancer, ADLM stated that pretreatment determination of AFP, lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG) was mandatory if testicular cancer was suspected or if risk stratification and staging was done. These three biomarkers were also recommended for monitoring. ADLM notes that measurement of the free β-subunit of human chorionic gonadotropin (hCGβ) component is essential when measuring hCG. For prostate cancer, PSA assessment is required during all stages of the disease, with ADLM recommending against age-specific intervals. PSA measuring is recommended to monitor disease status after treatment. However, ADLM did not make any recommendations on PSA screening for prostate cancer.[91]

For colorectal cancer (CRC), carcinoembryonic antigen (CEA) measurement is recommended every 3 months in stage II or III if "patient is a candidate for surgery or systemic therapy of metastatic disease." Pre-operative CEA measurements may be used in conjunction with other factors to plan surgery. Regular CEA measurements should be done in patients with advanced CRC that are undergoing systemic therapy. However, CEA is not recommended for screening in healthy individuals. Routine measurement of other biomarkers such as CA 19-9, TIMP-1, or CA 242 is not recommended for prognosis or predicting response to treatment. ADLM recommends individuals older than 50 be screened for CRC. Fecal DNA is also recommended for CRC screening, as joint guidelines from other societies such as the American Cancer Society have recommended its use. Finally, ADLM supports guidelines such as the NCCN and AGA regarding genetic testing for CRC.[91]

According to ADLM, estrogen receptor (ER) and progesterone receptor (PR) measurements should be done in all patients diagnosed with breast cancer. HER-2 should be measured in all patients with invasive breast cancer, while urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1) may be used to identify "lymph node–negative breast cancer patients who do not need or are unlikely to benefit from adjuvant chemotherapy." CA 15-3, CEA, and BR 27.29 should not routinely be used for early detection in asymptomatic

patients with diagnosed breast cancer. *BRCA1* and *BRCA2* mutation testing may be used to identify women at high risk of developing breast or ovarian cancer, while OncoType DX may be used to predict recurrence in "lymph node–negative, ER-positive patients receiving adjuvant tamoxifen." ADLM does recommend that microarray-based gene signatures should be routinely used for predicting patient outcome.[91]

For ovarian cancer, CA-125 screening is not recommended for asymptomatic women but is recommended (with transvaginal ultrasound) for early detection of ovarian cancer in women with hereditary syndromes. CA-125 is also recommended for distinguishing benign from malignant masses and may be used to monitor chemotherapeutic response. Measurement of CA-125 during follow-up visits is recommended if the patient's initial values were increased. CA-125 measurement is also recommended during primary therapy. Other biomarkers such as inhibin and hCG cannot be recommended at this time.[91]

In the uses of Human Chorionic Gonadotropin (hCG) measurement as a tumor marker, ADLM recommends this marker in the workup and monitoring of patients with suspected or known germ cell tumors of the testes and patients with gestational trophoblastic disease (GTD). The article also notes that there is less consensus about using hCG in patients with germ cell tumors of the ovary, as ovarian cancer monitoring is more commonly performed using the tumor marker CA-125.[92]

Addressing serum free light chains, ADLM recommends ordering serum free light chain testing (with serum protein electrophoresis and immunofixation) when screening for patients suspected of having a malignant monoclonal process: multiple myeloma (MM), Waldenstrom macroglobulinemia, B-cell lymphoproliferative process, AL amyloidosis, or monoclonal gammopathy of renal significance (MGRS). When it comes to prognosis, the ADLM recommends using serum light chains as a baseline measurement to assess the risk of all plasma cell disorders. For monitoring, the ADLM recommends using serum light chains to determine complete stringent remission; to follow patients with oligosecretory multiple myeloma and an abnormal serum free light chain ratio; and to follow AL amyloidosis with an abnormal serum free light chain ratio.[93]

North American Neuroendocrine Tumor Society (NANETS)

NANETS provides information about select tumor markers that pertain to advanced unresectable or metastatic gastroenteropancreatic (GEP)- Neuroendocrine neoplasms:

- "Significantly elevated serum CgA levels at baseline may be prognostic; however, the optimal threshold for prognostication and relevance within specific tumor grades or sites of origin is unclear. Change in CgA levels following treatment may be associated with response, but there is substantial variability within current studies, and high-quality prospective data are lacking. Neither serum CgA levels at baseline or following therapy are treatment informing and should not be ordered/used for the purpose of guiding treatment routinely (quality of evidence: low)."
- "Significantly elevated pancreastatin at baseline may be prognostic; however, there is insufficient evidence to support the value of pancreastatin as a treatment-informing biomarker. It should not be monitored routinely outside the context of a research setting (quality of evidence: low)."
- "Chromogranin A is often significantly elevated in patients with proton pump inhibitors (PPIs) or with coexisting medical conditions including atropic gastritis and renal insufficiency. Multiples studies have show that higher CgA levels corelate with shorter survival and more advanced disease, but the value of CgA when added to imaging studies is likely low. Preoperatively elevated CgA seems to predict higher recurrence risk after resection, but there are inadequate data to suggest routinely incorporating CgA measurements in surveillance strategies after resection."

Additionally, “use of nonspecific tumor markers such as CgA, pancreastatin (PcST), and other is not recommended for routine use in patients with PNETs.” The results of tumor marker analyses “rarely, if ever” influence treatment.[94]

American Association for the Study of Liver Diseases (AASLD)

The American Association for the Study of Liver Diseases provided updated guidance on the prevention, diagnosis, and treatment of hepatocellular carcinoma in May 2023. This guideline states that several promising biomarkers are being investigated for potential utility in HCC surveillance, but most have not been sufficiently validated for this purpose, with the exception of AFP-L3% and DCP. Hence, “AASLD does not recommend routine use of CT- or MRI-based imaging and tumor biomarkers, outside of AFP, for HCC surveillance in at-risk patients with cirrhosis or chronic HBV (Level 5, Weak Recommendation).” While AFP may be used for screening purposes, AASLD does not yet support its diagnostic use, stating that “the diagnosis of HCC should be based on noninvasive imaging criteria or pathology. Biomarkers, such as AFP, are not sufficiently accurate to make a diagnosis of HCC.”[17] Finally, AASLD advises use of the BCLC (Barcelona Liver Clinic Cancer) system for disease staging, which incorporates AFP levels.

The association also published updated guidance on primary sclerosing cholangitis and cholangiocarcinoma in February 2023. This guideline acknowledges that CA 19-9 is the most common serum marker associated with cholangiocarcinoma (CCA), but is limited by variable sensitivity and specificity, particularly because it may be elevated in many benign and other malignant conditions.[95]

American Thyroid Association (ATA)

The American Thyroid Association cannot recommend for or against routine measurement of serum calcitonin in patients with thyroid nodules. Furthermore, ATA cautions that unusual levels of calcitonin may occur with a variety of other conditions apart from medullary thyroid carcinoma, and notes that calcitonin levels are often elevated in young children and males compared to females.[32,33]

Regarding management of patients following thyroidectomy for persistent or recurrent medullary thyroid carcinomas, measurement of serum calcitonin does play an important role. Along with a physical exam, serum calcitonin levels, CEA, TFTs, and TSH should be measured every 6 to 12 months. Depending on these biomarker levels, further action may be warranted.[96]

Applicable State and Federal Regulations:

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

Food and Drug Administration (FDA)

There are numerous FDA-approved tests for the assessment of serum tumor markers. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid Services (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). LDTs are not approved or cleared by the

U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Applicable CPT/HCPCS Procedure Codes:

CPT	Code Description
81479	Unlisted molecular pathology procedure
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score Proprietary test: Risk of Ovarian Malignancy Algorithm (ROMA)™ Lab/manufacturer: Fujirebio Diagnostics
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score Proprietary test: OVA1™ Lab/manufacturer: Vermillion, Inc
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival Proprietary test: VeriStrat® Lab/manufacturer: Biodesix, Inc
81599	Unlisted multianalyte assay with algorithmic analysis
82105	Alpha-fetoprotein (AFP); serum
82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)
82232	Beta-2 microglobulin
82308	Calcitonin
82378	Carcinoembryonic antigen (CEA)
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83521	Immunoglobulin light chains (ie, kappa, lambda), free, each
83789	Mass spectrometry and tandem mass spectrometry (eg, MS, MS/MS, MALDI, MS-TOF, QTOF), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
83880	Natriuretic peptide
83950	Oncoprotein; HER-2/neu
83951	Oncoprotein; des-gamma-carboxy-prothrombin (DCP)
84075	Phosphatase, alkaline
84078	Phosphatase, alkaline; heat stable (total not included)
84080	Phosphatase, alkaline; isoenzymes
84484	Troponin, quantitative

CPT	Code Description
84702	Gonadotropin, chorionic (hCG); quantitative
84703	Gonadotropin, chorionic (hCG); qualitative
84704	Gonadotropin, chorionic (hCG); free beta chain
84999	Unlisted chemistry procedure
86300	Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)
86301	Immunoassay for tumor antigen, quantitative; CA 19-9
86304	Immunoassay for tumor antigen, quantitative; CA 125
86305	Human epididymis protein 4 (HE4)
86316	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each
86336	Inhibin A
G0327	Colorectal cancer screening; blood-based biomarker

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

Evidence-based Scientific References:

1. Hottinger A, Hormigo A. Serum Biomarkers. *Encyclopedia of Cancer*. Springer Berlin Heidelberg; 2011. http://link.springer.com/referenceworkentry/10.1007/978-3-642-16483-5_5269
2. NCI. Tumor Markers. https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet
3. NCCN. Biomarkers Compendium. https://www.nccn.org/compendia-templates/compendia/biomarkers-compendium
4. Febbo PG, Ladanyi M, Aldape KD, et al. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. *Journal of the National Comprehensive Cancer Network : JNCCN*. Nov 2011;9 Suppl 5:S1-32; quiz S33. doi:10.6004/jnccn.2011.0137
5. Sturgeon CM, Hoffman BR, Chan DW, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Clinical Practice: Quality Requirements. *Clinical Chemistry*. 2008;54(8):e1. doi:10.1373/clinchem.2007.094144
6. BeScreened. BeScreened. https://bescreened.com/
7. Aspira Health. Ova1Plus®. https://aspirawh.com/ova1plus/
8. ASPIRA. OvaWatch. https://aspirawh.com/ovawatch/
9. Pinzani P, D'Argenio V, Del Re M, et al. Updates on liquid biopsy: current trends and future perspectives for clinical application in solid tumors. *Clin Chem Lab Med*. Jun 25 2021;59(7):1181-1200. doi:10.1515/cclm-2020-1685
10. Sharma U, Pal D, Prasad R. Alkaline phosphatase: an overview. *Indian J Clin Biochem*. Jul 2014;29(3):269-78. doi:10.1007/s12291-013-0408-y
11. Szulc P, Bauer DC, Dempster DW, Luckey M, Cauley JA. Osteoporosis. 2013;1doi:10.1016/B978-0-12-415853-5.00067-4
12. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Systemic Light Chain Amyloidosis Version Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf
13. Thio Q, Karhade AV, Notman E, et al. Serum alkaline phosphatase is a prognostic marker in bone metastatic disease of the extremity. *J Orthop*. Nov-Dec 2020;22:346-351. doi:10.1016/j.jor.2020.08.008
14. Schefer H, Mattmann S, Joss RA. Hereditary persistence of α-fetoproteinCase report and review of the literature. *Annals of Oncology*. 1998;9(6):667-672. doi:10.1023/A:1008243311122

15. Gilligan TD, Seidenfeld J, Basch EM, et al. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 10 2010;28(20):3388-404. doi:10.1200/jco.2009.26.4481
16. Wu M, Liu H, Liu Z, Liu C, Zhang A, Li N. Analysis of serum alpha-fetoprotein (AFP) and AFP-L3 levels by protein microarray. *The Journal of international medical research*. Oct 2018;46(10):4297-4305. doi:10.1177/0300060518789304
17. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. May 22 2023;doi:10.1097/HEP.0000000000000466
18. Santos Schraiber Ld, de Mattos AA, Zanotelli ML, et al. Alpha-fetoprotein Level Predicts Recurrence After Transplantation in Hepatocellular Carcinoma. *Medicine*. Jan 2016;95(3):e2478. doi:10.1097/md.0000000000002478
19. Cheng J, Wang W, Zhang Y, et al. Prognostic role of pre-treatment serum AFP-L3% in hepatocellular carcinoma: systematic review and meta-analysis. *PloS one*. 2014;9(1):e87011. doi:10.1371/journal.pone.0087011
20. Park SJ, Jang JY, Jeong SW, et al. Usefulness of AFP, AFP-L3, and PIVKA-II, and their combinations in diagnosing hepatocellular carcinoma. *Medicine*. Mar 2017;96(11):e5811. doi:10.1097/md.0000000000005811
21. Ryu T, Takami Y, Wada Y, et al. 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. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. Jun 2017;21(6):957-966. doi:10.1007/s11605-017-3394-1
22. Caviglia GP, Abate ML, Petrini E, Gaia S, Rizzetto M, Smedile A. Highly sensitive alpha-fetoprotein, Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein and des-gamma-carboxyprothrombin for hepatocellular carcinoma detection. *Hepatology research : the official journal of the Japan Society of Hepatology*. Mar 2016;46(3):E130-5. doi:10.1111/hepr.12544
23. Berrebi A, Shvidel L, Arditti FD, Bassous L, Haran M, Shtalrid M. 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*. 2009;114(22):4380.
24. Katou H, Kanno T, Hoshino M, et al. The role of disulfide bond in the amyloidogenic state of beta(2)-microglobulin studied by heteronuclear NMR. *Protein science : a publication of the Protein Society*. Sep 2002;11(9):2218-29. doi:10.1110/ps.0213202
25. Marcinko TM, Dong J, LeBlanc R, Daborowski KV, Vachet RW. Small molecule-mediated inhibition of β-2-microglobulin-based amyloid fibril formation. *The Journal of biological chemistry*. Jun 23 2017;292(25):10630-10638. doi:10.1074/jbc.M116.774083
26. Seo S, Hong JY, Yoon S, et al. Prognostic significance of serum beta-2 microglobulin in patients with diffuse large B-cell lymphoma in the rituximab era. *Oncotarget*. Nov 22 2016;7(47):76934-76943. doi:10.18632/oncotarget.12734
27. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart*. Jun 2006;92(6):843-9. doi:10.1136/hrt.2005.071233
28. Di Castelnuovo A, Veronesi G, Costanzo S, et al. NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) and the Risk of Stroke. *Stroke*. Mar 2019;50(3):610-617. doi:10.1161/STROKEAHA.118.023218
29. Venner CP. AL amyloidosis cardiac staging updated using BNP. *Blood*. Jan 17 2019;133(3):184-185. doi:10.1182/blood-2018-10-882159
30. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Multiple Myeloma Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
31. Tuttle RM. Medullary thyroid cancer: Clinical manifestations, diagnosis, and staging. Updated July 29, 2024. https://www.uptodate.com/contents/medullary-thyroid-cancer-clinical-manifestations-diagnosis-and-staging

32. Wells SA, Jr., Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid : official journal of the American Thyroid Association*. Jun 2015;25(6):567-610. doi:10.1089/thy.2014.0335
33. Haugen BR, Alexander EK, Bible KC, et al. 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 : official journal of the American Thyroid Association*. Jan 2016;26(1):1-133. doi:10.1089/thy.2015.0020
34. Tormey WP, Byrne B, Hill AD, Sherlock M, Thompson CJ. Should serum calcitonin be routinely measured in patients presenting with thyroid nodule? *Minerva endocrinologica*. Dec 2017;42(4):306-310. doi:10.23736/s0391-1977.17.02566-4
35. Magnani JL. The discovery, biology, and drug development of sialyl Lea and sialyl Lex. *Archives of Biochemistry and Biophysics*. 2004/06/15/ 2004;426(2):122-131. doi:10.1016/j.abb.2004.04.008
36. Isaksson S, Jönsson P, Monsef N, et al. CA 19-9 and CA 125 as potential predictors of disease recurrence in resectable lung adenocarcinoma. *PloS one*. 2017;12(10):e0186284. doi:10.1371/journal.pone.0186284
37. Dorigo O, Berek JS. Personalizing CA125 levels for ovarian cancer screening. *Cancer prevention research (Philadelphia, Pa)*. Sep 2011;4(9):1356-9. doi:10.1158/1940-6207.Capr-11-0378
38. Kim NH, Lee MY, Park JH, et al. Serum CEA and CA 19-9 Levels are Associated with the Presence and Severity of Colorectal Neoplasia. *Yonsei medical journal*. Sep 1 2017;58(5):918-924. doi:10.3349/ymj.2017.58.5.918
39. Feng F, Tian Y, Xu G, et al. Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. *BMC cancer*. Nov 9 2017;17(1):737. doi:10.1186/s12885-017-3738-y
40. Lucarelli G, Ditonno P, Bettocchi C, et al. Diagnostic and prognostic role of preoperative circulating CA 15-3, CA 125, and beta-2 microglobulin in renal cell carcinoma. *Disease markers*. 2014;2014:689795. doi:10.1155/2014/689795
41. Chen F, Shen J, Wang J, Cai P, Huang Y. 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*. 2018;10:1313-1318. doi:10.2147/cmar.S155693
42. Bind MK, Mishra RR, Kumar V, Misra V, Singh PA. Serum CA 19-9 and CA 125 as a diagnostic marker in carcinoma of gallbladder. *Indian J Pathol Microbiol*. Jan-Mar 2021;64(1):65-68.
43. Li AJ. Serum biomarkers for evaluation of an adnexal mass for epithelial carcinoma of the ovary, fallopian tube, or peritoneum. Updated October 31, 2024. https://www.uptodate.com/contents/serum-biomarkers-for-evaluation-of-an-adnexal-mass-for-epithelial-carcinoma-of-the-ovary-fallopian-tube-or-peritoneum
44. Duffy MJ. Carcinoembryonic Antigen as a Marker for Colorectal Cancer: Is It Clinically Useful? *Clinical Chemistry*. 2001;47(4):624. doi:10.1093/clinchem/47.4.624
45. Harvey RA. Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease. Updated June 23, 2023. https://www.uptodate.com/contents/human-chorionic-gonadotropin-biochemistry-and-measurement-in-pregnancy-and-disease
46. Marcillac I, Troalen F, Bidart J-M, et al. Free Human Chorionic Gonadotropin β Subunit in Gonadal and Nongonadal Neoplasms. *Cancer Research*. 1992;52(14):3901.
47. Hotakainen K, Ljungberg B, Paju A, Rasmuson T, Alfthan H, Stenman UH. The free beta-subunit of human chorionic gonadotropin as a prognostic factor in renal cell carcinoma. *British journal of cancer*. Jan 21 2002;86(2):185-9. doi:10.1038/sj.bjc.6600050
48. Li J, Yin M, Song W, et al. B Subunit of Human Chorionic Gonadotropin Promotes Tumor Invasion and Predicts Poor Prognosis of Early-Stage Colorectal Cancer. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology*. 2018;45(1):237-249. doi:10.1159/000486770
49. Strosberg J. Diagnosis of carcinoid syndrome and tumor localization. Updated March 19, 2025. https://www.uptodate.com/contents/diagnosis-of-the-carcinoid-syndrome-and-tumor-localization
50. Yang X, Yang Y, Li Z, et al. Diagnostic value of circulating chromogranin a for neuroendocrine tumors: a systematic review and meta-analysis. *PloS one*. 2015;10(4):e0124884. doi:10.1371/journal.pone.0124884

51. Tian T, Gao J, Li N, et al. Circulating Chromogranin A as A Marker for Monitoring Clinical Response in Advanced Gastroenteropancreatic Neuroendocrine Tumors. *PloS one*. 2016;11(5):e0154679. doi:10.1371/journal.pone.0154679
52. Walentowicz P, Krintus M, Sadlecki P, et al. Serum inhibin A and inhibin B levels in epithelial ovarian cancer patients. *PloS one*. 2014;9(3):e90575. doi:10.1371/journal.pone.0090575
53. Gershenson D. Sex cord-stromal tumors of the ovary: Epidemiology, clinical features, and diagnosis in adults. Updated July 8, 2024. https://www.uptodate.com/contents/sex-cord-stromal-tumors-of-the-ovary-epidemiology-clinical-features-and-diagnosis-in-adults
54. Farkkila A, Koskela S, Bryk S, et al. 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. *International journal of cancer*. Oct 1 2015;137(7):1661-71. doi:10.1002/ijc.29532
55. Kyrtsonis MC KE, Bartzis V, Pessah I, Nikolaou E, Karalis V, Maltezas D, Panayiotidis P, Harding S. Monoclonal Immunoglobulin. *Multiple Myeloma - A Quick Reflection on the Fast Progress*. 2012.
56. ACS. What Is Multiple Myeloma? https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html
57. Tosi P, Tomassetti S, Merli A, Polli V. Serum free light-chain assay for the detection and monitoring of multiple myeloma and related conditions. *Ther Adv Hematol*. Feb 2013;4(1):37-41. doi:10.1177/2040620712466863
58. Katzmann JA, Clark RJ, Abraham RS, et al. 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*. Sep 2002;48(9):1437-44.
59. ACS. What Is Waldenstrom Macroglobulinemia? https://www.cancer.org/cancer/waldenstrom-macroglobulinemia/about/what-is-wm.html
60. Cautha S, Gupta S, Hanif A, Moirangthem V, Jain K. Lymphoplasmacytic Lymphoma with Only Lambda Light Chain Monoclonal Paraprotein Expression. *Eur J Case Rep Intern Med*. 2022;9(2):003106. doi:10.12890/2022_003106
61. Moreau AS LX, 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. Serum Free Light Chain in Waldenstrom Macroglobulinemia. 2006;doi:10.1182/blood.V108.11.2420.2420
62. Wu D, Lim MS, Jaffe ES. Pathology of Castleman Disease. *Hematol Oncol Clin North Am*. Feb 2018;32(1):37-52. doi:10.1016/j.hoc.2017.09.004
63. Oyaert M, Boone E, De Ceuninck L, et al. Clonal multicentric Castleman's disease with increased free Kappa light chains in a patient with systemic lupus erythematosus. *Ann Hematol*. Jul 2014;93(7):1255-7. doi:10.1007/s00277-013-1962-3
64. Stankowski-Drengler T, Gertz MA, Katzmann JA, et al. Serum immunoglobulin free light chain measurements and heavy chain isotype usage provide insight into disease biology in patients with POEMS syndrome. *Am J Hematol*. Jun 2010;85(6):431-4. doi:10.1002/ajh.21707
65. Merlini G, Wechalekar AD, Palladini G. Systemic light chain amyloidosis: an update for treating physicians. *Blood*. Jun 27 2013;121(26):5124-30. doi:10.1182/blood-2013-01-453001
66. Dispenzieri A. Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis. Updated February 19, 2025. https://www.uptodate.com/contents/clinical-presentation-laboratory-manifestations-and-diagnosis-of-immunoglobulin-light-chain-al-amyloidosis
67. Kumar S, Dispenzieri A, Katzmann JA, et al. Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features. *Blood*. Dec 9 2010;116(24):5126-9. doi:10.1182/blood-2010-06-290668
68. Bhole MV, Sadler R, Ramasamy K. Serum-free light-chain assay: clinical utility and limitations. *Ann Clin Biochem*. Sep 2014;51(Pt 5):528-42. doi:10.1177/0004563213518758
69. Akar H, Seldin DC, Magnani B, et al. Quantitative serum free light chain assay in the diagnostic evaluation of AL amyloidosis. *Amyloid*. Dec 2005;12(4):210-5. doi:10.1080/13506120500352339
70. Chaulin AM. Biology of Cardiac Troponins: Emphasis on Metabolism. *Biology (Basel)*. Mar 11 2022;11(3)doi:10.3390/biology11030429

71. Sharma S, Jackson PG, Makan J. Cardiac troponins. *J Clin Pathol*. Oct 2004;57(10):1025-6. doi:10.1136/jcp.2003.015420
72. Perfetto F, Bergesio F, Emdin M, Cappelli F. Troponins in cardiac amyloidosis: multipurpose markers. *Nat Rev Cardiol*. Mar 2014;11(3):179. doi:10.1038/nrcardio.2013.129-c1
73. Pejler G, Ronnberg E, Waern I, Wernersson S. Mast cell proteases: multifaceted regulators of inflammatory disease. *Blood*. Jun 17 2010;115(24):4981-90. doi:10.1182/blood-2010-01-257287
74. Payne V, Kam PC. Mast cell tryptase: a review of its physiology and clinical significance. *Anaesthesia*. Jul 2004;59(7):695-703. doi:10.1111/j.1365-2044.2004.03757.x
75. Leru PM. Evaluation and Classification of Mast Cell Disorders: A Difficult to Manage Pathology in Clinical Practice. *Cureus*. Feb 2022;14(2):e22177. doi:10.7759/cureus.22177
76. AAAAI. Systemic Mastocytosis. https://www.aaaai.org/conditions-treatments/related-conditions/systemic-mastocytosis
77. Stephens RW, Brunner N, Janicke F, Schmitt M. The urokinase plasminogen activator system as a target for prognostic studies in breast cancer. *Breast cancer research and treatment*. 1998;52(1-3):99-111. doi:10.1007/978-1-4615-5195-9_15
78. Malmstrom P, Bendahl PO, Boiesen P, Brunner N, Idvall I, Ferno M. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 01 2001;19(7):2010-9. doi:10.1200/jco.2001.19.7.2010
79. Foekens JA, Peters HA, Look MP, et al. The urokinase system of plasminogen activation and prognosis in 2780 breast cancer patients. *Cancer Res*. Feb 01 2000;60(3):636-43.
80. Chappuis PO, Dieterich B, Sciretta V, et al. Functional evaluation of plasmin formation in primary breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. May 15 2001;19(10):2731-8. doi:10.1200/jco.2001.19.10.2731
81. Foukakis T, Bergh J. Prognostic and predictive factors in early, nonmetastatic breast cancer - UpToDate. Updated March 17, 2025. https://www.uptodate.com/contents/prognostic-and-predictive-factors-in-early-non-metastatic-breast-cancer
82. Harris LN, Ismaila N, McShane LM, et al. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 01 2016;34(10):1134-50. doi:10.1200/jco.2015.65.2289
83. Raby B. Personalized medicine. Updated September 6, 2023. https://www.uptodate.com/contents/personalized-medicine
84. Chen Y, Xie Y, Xu L, et al. Protein content and functional characteristics of serum-purified exosomes from patients with colorectal cancer revealed by quantitative proteomics. *International journal of cancer*. 2017/02/15 2017;140(4):900-913. doi:10.1002/ijc.30496
85. Qin J, Yang Q, Ye H, et al. Using Serological Proteome Analysis to Identify and Evaluate Anti-GRP78 Autoantibody as Biomarker in the Detection of Gastric Cancer. *J Oncol*. 2020;2020:9430737. doi:10.1155/2020/9430737
86. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ovarian Cancer Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
87. Van Poznak C, Somerfield MR, Bast RC, et al. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 20 2015;33(24):2695-704. doi:10.1200/jco.2015.61.1459
88. Stoffel EM, McKernin SE, Brand R, et al. Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion. *Journal of Clinical Oncology*. 2019/01/10 2018;37(2):153-164. doi:10.1200/JCO.18.01489
89. Kindler HL, Ismaila N, Armato SG, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*. 2018/05/01 2018;36(13):1343-1373. doi:10.1200/JCO.2017.76.6394

90. Sturgeon CM, Duffy MJ, Hofmann BR, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. *Clin Chem*. Jun 2010;56(6):e1-48. doi:10.1373/clinchem.2009.133124
91. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clin Chem*. Dec 2008;54(12):e11-79. doi:10.1373/clinchem.2008.105601
92. ADLM. Human Chorionic Gonadotropin (hCG). https://myadlm.org/cln/articles/2021/april/using-human-chorionic-gonadotropin-as-a-tumor-marker
93. ADLM. 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
94. NANETS. NANETS 2024 Compendium. 2025. https://nanets.net/images/NANETS_2024_Symposium_Guidelines_Compendium.pdf
95. Bowlus CL, Arrive L, Bergquist A, et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology*. Feb 1 2023;77(2):659-702. doi:10.1002/hep.32771
96. ATA. Revised ATA Management Guidelines for MTC. https://www.thyroid.org/wp-content/uploads/2017/03/revised-ata-management-guidelines-for-MTC.pdf

Revision History

Company(ies)	DATE	REVISION
ConnectiCare	8/2025	• Removed codes: 83615, 0003U, 0092U, 0163U and 0404U • Based on guidance from the National Comprehensive Cancer Network's Biomarker's Compendium, the following coverage additions and removals were made **effective 11/13/2025**: Adjusted terminology from 'serum tumor markers' in Note and CC1 to broaden definition as some serum-related markers are more accurately described as biomarkers rather than serum tumor markers. Changed title in table from "Serum Tumor Markers" to "Serum Biomarkers." **Alkaline phosphatase:** For ALP, removed "during treatment, surveillance" from indications for ALP testing for bone neoplasms. Added "Melanoma (uveal)" as an indication for workup for ALP. Removed the words "post-diagnostic" from "Testicular cancer – nonseminoma" to clarify that workup can occur before or after diagnosis. **Beta-2 microglobulin:** For Beta-2 microglobulin, removed "Castleman disease" from B-cell lymphoma title and created a new row which identifies the indication for Castleman disease as "workup" with B2M measurement.

Company(ies)	DATE	REVISION
		Chorionic gonadotropin beta polypeptide expression (CGB3): Changed the title of "Beta-human chorionic gonadotropin (beta-HCG)" 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 (CA 19-9):** For cancer antigen 19-9 (CA 19-9), removed "assessing disease prognosis; monitoring/follow-up for response" from Occult primary indications. In "Ovarian cancers (less common)" merged ovarian cancer sections. 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 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, malignant germ cell tumors, malignant sex cord stromal tumors." **Inhibin (INHA):** For Inhibin (INHA), removed "adrenocortical carcinoma" and indication for "workup" from Inhibin (INHA) section. Added "Occult primary (unknown primary cancer)" with indications for "additional

Company(ies)	DATE	REVISION
		workup for adenocarcinoma or carcinoma not otherwise specified." **Lactate dehydrogenase (LDH):** Removed the entire section on Lactate dehydrogenase (LDH) as LDH is a broad marker beyond serum tumor biomarker designation. **Serum free light chains:** Under Serum free light chains added "Castleman disease:" with indications for "workup" and added "follow-up" to Multiple myeloma as an indication. • Updated the background, guidelines and recommendations, and evidence-based scientific references.
ConnectiCare	8/2025	• Transferred policy content to individual company-branded template. No changes to policy title or policy number.
EmblemHealth ConnectiCare	11/2024	• Updates in Coverage Criteria table with **effective date 3/15/2025:** ○ 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

Company(ies)	DATE	REVISION
		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

Company(ies)	DATE	REVISION
		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.
EmblemHealth ConnectiCare	2/2024	• Updated coverage table in Criterion 1 from listing by condition to listing by tumor marker for ease of reference • Updates in Coverage Criteria table with **effective date 6/15/2024:** ○ 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 *saccrococcygeal teratomas*, removed indications for initial diagnostic evaluation and surveillance. For *testicular cancer (nonseminoma)*, removed indication for initial diagnostic evaluation.

Company(ies)	DATE	REVISION
		○ 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 *saccrococcygeal 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*, updated indication for initial diagnostic evaluation to additional workup and added indication for post-surgical evaluation. ○ Cancer Antigen 19-9 (CA 19-9): for *ampullary adenocarcinoma*, added indications for 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*. For *appendiceal adenocarcinoma*, added indication 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

Company(ies)	DATE	REVISION
		○ Cancer Antigen 125 (CA-125): for *appendiceal adenocarcinoma*, added indication for workup to establish baseline. For *Lynch syndrome*, added indication for surveillance. 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*,

Company(ies)	DATE	REVISION
		removed indication for initial diagnostic evaluation. ○ 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. ○ Addition of CPT code 0404U to Applicable CPT/HCPCS Procedure Codes table
EmblemHealth ConnectiCare	11/2023	• Added CPT code 0404U to Applicable CPT/HCPCS Procedure Codes table **effective 10/1/2023**
EmblemHealth ConnectiCare	8/2023	• Reorganization of Coverage Criteria 1; ○ Focus placed on cancer diagnoses as opposed to biomarkers ○ Clinical indications for several biomarkers adjusted to reflect current recommendations • Former Coverage Criterion 3 & 4 edited for clarity and consistency. • Updates with **effective date 1/13/2024**: ○ Removed Carcinoembryonic Antigen (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 due to a lack of consensus that serum measurement of these markers is beneficial for disease managementarcinoembryonic Antigen (CEA) ○ Removal of Coverage Criteria 2: of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) for individuals with estrogen receptor (ER)- or progesterone receptor (PgR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (node-negative) breast

Company(ies)	DATE	REVISION
		cancer ○ Removal of CPT code 85415
EmblemHealth ConnectiCare	11/2022	• Reformatted and reorganized policy, transferred content to new template with new Reimbursement Policy Number