**Serum Tumor Markers for Malignancies**

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| Policy Number: AHS – G2124 – Serum Tumor Markers for Malignancies | Original Effective Date: 05/15/2022<br>Current Effective Date: 09/15/2026 |

POLICY DESCRIPTION | RELATED POLICIES | INDICATIONS AND/OR LIMITATIONS OF COVERAGE | TABLE OF TERMINOLOGY | SCIENTIFIC BACKGROUND | GUIDELINES AND RECOMMENDATIONS | APPLICABLE STATE AND FEDERAL REGULATIONS | APPLICABLE CPT/HCPCS PROCEDURE CODES | EVIDENCE-BASED SCIENTIFIC REFERENCES | REVISION HISTORY

## I. Policy Description

Circulating tumor biomarkers are substances detected in the blood, urine, or other body fluids that are either produced by a tumor itself or in response to its presence. These biomarkers can be used to help detect, diagnose, stage, and manage some types of cancer, because their amounts are typically elevated in individuals harboring a tumor.[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]

## II. Related Policies

| Policy Number | Policy Title |
|---|---|
| N/A | Not Applicable |

## III. 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** for osteosarcoma |
| | Melanoma (uveal): **workup** for distant metastatic disease |

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| Serum Biomarker | Indication |
|---|---|
| | Systemic light chain amyloidosis: **initial diagnostic workup** to assess organ involvement for suspected SLCA |
| **Alpha fetoprotein (AFP)** | Hepatocellular carcinoma: **screening** for at risk individuals due to Child-Turcotte-Pugh A or B cirrhosis or hepatitis B infection; **workup** for confirmed HCC; **surveillance** (every 3-6 months for 2 years, then every 6 months) |
| | Intrahepatic cholangiocarcinoma: **workup** for isolated intrahepatic mass |
| | Occult primary: **additional workup** for adenocarcinoma or carcinoma not otherwise specified with a clinical presentation in the liver or mediastinum or for individuals <65 years of age with a retroperitoneal mass |
| | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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: **initial diagnostic workup** for a suspicious testicular mass; **post-diagnostic workup; post-orchiectomy; follow-up** for nonseminoma (no more than every 2 months); **follow-up** for pure seminoma (no more than every 3 months) |
| | Thymomas and thymic carcinomas: **initial evaluation** for individuals with a mediastinal mass |
| **Beta-2 microglobulin (B2M)** | B-cell lymphomas (classic follicular, diffuse large B-cell; HIV-related; lymphoblastic; mantle cell): **additional workup** for specified B-cell lymphomas |
| | Castleman Disease: **additional workup** with established diagnosis |
| | Chronic lymphocytic leukemia/small lymphocytic lymphoma: **additional workup** with established diagnosis; for **prognostic** and/or **therapy determination** |
| | Multiple myeloma: **initial diagnostic workup** |
| | Systemic light chain amyloidosis: **initial diagnostic workup** to assess organ involvement for suspected SLCA |
| | Waldenström macroglobulinemia/lymphoplasmacytic lymphoma: **additional workup** with established diagnosis |
| **BNP or NT-proBNP** | Multiple myeloma: **initial diagnostic workup** |
| | Systemic light chain amyloidosis: **initial diagnostic workup** to assess organ involvement for suspected SLCA |

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| Serum Biomarker | Indication |
|---|---|
| **Calcitonin (CALCA)** | Head and neck cancer - occult primary: **additional workup** for squamous cell carcinoma, adenocarcinoma, and anaplastic undifferentiated epithelial tumors of the neck |
| | Medullary carcinoma: **additional workup** with established diagnosis; **surveillance** (every 6-12 months) |
| | Multiple endocrine neoplasia, type 2: **at diagnosis** (clinical evaluation) to assess risk for medullary thyroid cancer |
| **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** |
| **Cancer antigen 19-9 (CA 19-9)** | Ampullary adenocarcinoma: **additional workup** with established diagnosis; **surveillance** for resected ampullary cancer (every 3-6 months for 2 years; every 6-12 months for up to 5 years as clinically indicated) |
| | Appendiceal adenocarcinoma: **workup** to establish baseline when imaging suggests appendiceal neoplasm or cancer or when there is a confirmed appendiceal neoplasm or cancer; **workup** for recurrence (3-6 months after CT imaging); **surveillance** (every 6-12 months for 2 years; annually up to 10 years) |
| | Extrahepatic cholangiocarcinoma: **workup** to establish baseline for individuals with abdominal pain, jaundice, abnormal liver function tests, or obstruction or abnormality on imaging |
| | Gallbladder cancer: **workup** to establish baseline for individuals with jaundice or a mass on imaging; **post-operative workup** of a suspicious mass; **surveillance** (as clinically indicated) post-resection |
| | Intrahepatic cholangiocarcinoma: **workup** to establish baseline for an isolated intrahepatic mass |
| | Occult primary - suspected metastatic malignancy: **initial workup** |
| | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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) |
| | Pancreatic adenocarcinoma: **workup** to establish baseline when there is either a clinical suspicion of pancreatic cancer with suspicious imaging or evidence of |

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| Serum Biomarker | Indication |
|---|---|
| | dilated pancreatic and/or bile duct (stricture) and when no metastatic disease is detected; **post-operative**, **post-adjuvant treatment surveillance** as appropriate |
| | Small bowel adenocarcinoma: **additional workup** with established diagnosis; **post-treatment surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years); **additional workup** for metastatic adenocarcinoma |
| **Cancer antigen 125 (CA-125)** | Appendiceal adenocarcinoma: **workup** to establish baseline when imaging suggests appendiceal neoplasm or cancer or when there is a confirmed appendiceal neoplasm or cancer; **workup** for recurrence (3-6 months after CT imaging); **surveillance** (every 6-12 months for 2 years; annually up to 10 years) |
| | Endometrial carcinoma: **additional workup**; **surveillance** (if initially elevated) |
| | Occult primary: **initial workup** for suspected metastatic malignancy, **additional workup** for adenocarcinoma or carcinoma not otherwise specified (in those with a uterus and/or ovaries present) with a clinical presentation in the peritoneal/ascites or inguinal nodes |
| | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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) |
| | Uterine neoplasms: **initial diagnostic workup** for known or suspected malignancy**, additional workup** for serous carcinoma, clear cell carcinoma, undifferentiated/dedifferentiated carcinoma, carcinosarcoma, suspected extrauterine disease**; surveillance** in endometrial carcinoma if initially elevated |
| **Carcinoembryonic antigen (CEA)** | Appendiceal adenocarcinoma: **workup** to establish baseline when imaging suggests appendiceal neoplasm or cancer or when there is a confirmed appendiceal neoplasm or cancer; **workup** for recurrence (3-6 months after CT imaging); **surveillance** (every 6-12 months for 2 years; annually up to 10 years) |
| | Breast cancer (invasive): **Monitoring** metastatic disease |
| | Colon cancer: **workup** to establish baseline for a pedunculated or sessile polyp with invasive cancer, colon cancer appropriate for resection, and suspected or proven metastatic adenocarcinoma; **surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years) |

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| Serum Biomarker | Indication |
|---|---|
| | Extrahepatic cholangiocarcinoma: **workup** to establish baseline for individuals with abdominal pain, jaundice, abnormal liver function tests, or obstruction or abnormality on imaging |
| | Gallbladder cancer: **workup** to establish baseline for individuals with jaundice or a mass on imaging; **post-operative workup** of a suspicious mass; **surveillance** (as clinically indicated) post-resection |
| | Intrahepatic cholangiocarcinoma: **workup** to establish baseline for an isolated intrahepatic mass |
| | Medullary carcinoma: **additional workup** with established diagnosis**; surveillance** (every 6-12 months) |
| | Multiple endocrine neoplasia, type 2: **at diagnosis** (clinical evaluation) to assess risk for medullary thyroid cancer |
| | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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) |
| | Rectal cancer: **workup** to establish baseline for diagnosed rectal cancer or for a pedunculated or sessile polyp with invasive cancer; **surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years) |
| | Small bowel adenocarcinoma: **additional workup** with established diagnosis; **post-treatment surveillance** (every 3-6 months for 2 years, then every 6 months for a total of 5 years); **additional workup** for metastatic adenocarcinoma |
| **Chorionic gonadotropin beta polypeptide (CGB3)** | Gestational trophoblastic neoplasia: **initial workup** for suspected GTN; **during and post treatment** (no more than weekly); **follow-up/surveillance** (no more than monthly for 12 months) |
| | Occult primary: **additional workup** for adenocarcinoma or carcinoma not otherwise specified with a clinical presentation in the mediastinum or for individuals <65 years of age with a retroperitoneal mass |
| | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-** |

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| Serum Biomarker | Indication |
|---|---|
| | **up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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: **initial diagnostic workup** for a suspicious testicular mass; **post-diagnostic workup; post-orchiectomy; follow-up** for nonseminoma (no more than every 2 months); **follow-up** for pure seminoma (no more than every 3 months) |
| | Thymomas and thymic carcinomas: **initial evaluation** for individuals with a mediastinal mass |
| **Human epididymis protein 4 (HE4)** | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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)** | Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer: **initial workup** for individuals with a suspicious mass found by palpation or imaging; **monitoring** prior to each cycle of chemotherapy; **monitoring/follow-up** for patients not receiving treatment (every 2-4 months for 2 years; every 3-6 months for 3 years; annually after year 5) |

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| Serum Biomarker | Indication |
|---|---|
| | Ovarian cancers (less common): **initial workup** for newly diagnosed ovarian cancer; **monitoring/follow-up** for recurrence<br>Less common ovarian cancers (additional **surveillance** recommendations):<br>– Malignant Germ cell tumors: **surveillance** (every 2 months in year 1, every 3 months in year 2, every 6 months in year 3; year 4 and beyond, annual testing up to year 10)<br>– 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: **additional workup** for established diagnosis |
| | Multiple myeloma: **initial diagnostic workup** for multiple myeloma and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS); **follow-up/surveillance** for solitary plasmacytoma (every 3-6 months), asymptomatic smoldering myeloma (every 3-6 months), symptomatic multiple myeloma |
| | Systemic light chain amyloidosis: **initial diagnostic workup** |
| **Troponin T** | Systemic light chain amyloidosis: **initial diagnostic workup** to assess organ involvement for suspected SLCA |
| **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**.

## IV. Table of Terminology

| Term | Definition |
|---|---|
| A2-PAG | Pregnancy associated alpha 2 glycoprotein |
| AACC | American Association for Clinical Chemistry |
| AASLD | American Association for the Study of Liver Diseases |

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| Term | Definition |
|---|---|
| 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 |
| 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 |

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| Term | Definition |
|---|---|
| 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 |
| 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 |

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| Term | Definition |
|---|---|
| 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 |
| 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 |
| 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 |

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| Term | Definition |
|---|---|
| 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 |
| TPS | Tissue polypeptide specific antigen |
| TTF-1 | Thyroid transcription factor-1 |
| TVUS | Transvaginal ultrasound |
| uPA | Urokinase plasminogen activator |
| uPAR | Urokinase plasminogen activator receptor |
| WM | Waldenström's Macroglobulinemia |
| WT1 | Wilms' tumor protein |

## V. 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:

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- **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.

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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

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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 individuals 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 > 40 mAU/mL and AFP > 10 ng/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]

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*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

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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

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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

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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

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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]

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*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]

## VI. 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

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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 ten 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 ten years following the conclusion of therapy.[15]

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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 six 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]

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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 three 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 individuals 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 tests and individuals with gestational trophoblastic disease (GTD). The article also notes that there is less consensus about using hCG in individuals with germ cell tumors of the ovary, as ovarian cancer monitoring is more commonly performed using the tumor marker CA-125.[92]

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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)."

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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 six to twelve months. Depending on these biomarker levels, further action may be warranted.[96]

## VII. 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.

## VIII. Applicable CPT/HCPCS Procedure Codes

| CPT | Code Description |
|---|---|
| 81500 | Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score<br>Proprietary test: Risk of Ovarian Malignancy Algorithm (ROMA)™<br>Lab/manufacturer: Fujirebio Diagnostics |

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| CPT | Code Description |
|---|---|
| 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<br>Proprietary test: OVA1™<br>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<br>Proprietary test: VeriStrat®<br>Lab/manufacturer: Biodesix, Inc |
| 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 |
| 83880 | Natriuretic peptide |
| 83950 | Oncoprotein; HER-2/neu |
| 83951 | Oncoprotein; des-gamma-carboxy-prothrombin (DCP) |
| 84075 | Phosphatase, alkaline |
| 84484 | Troponin, quantitative |
| 84702 | Gonadotropin, chorionic (hCG); quantitative |
| 84704 | Gonadotropin, chorionic (hCG); free beta chain |
| 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 |
| 0003U | Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score<br>Proprietary test: Overa™ (OVA1 Next Generation)<br>Lab/manufacturer: Aspira Labs, Inc, Vermillion, Inc |
| 0092U | Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, CPTsma, algorithm reported as risk score for likelihood of malignancy<br>Proprietary test: REVEAL Lung Nodule Characterization<br>Lab/Manufacturer: MagArray, Inc |
| 0163U | Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic |

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| CPT | Code Description |
|---|---|
| | data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas<br>Proprietary test: BeScreened™-CRC<br>Lab/Manufacturer: Beacon Biomedical Inc |
| 0404U | Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression<br>Proprietary test: Divitum®Tka<br>Lab/Manufacturer: Biovica Inc |
| 0558U | Oncology (colorectal), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted colorectal cancer protein marker (BF7 antigen), using serum, result reported as indicative of response/no response to therapy or disease progression/regression<br><br>Proprietary test: IGoCheckTM (Blood-Based Colorectal Cancer Test)<br>Lab/Manufacturer: Milagen, Inc |
| 0559U | Oncology (breast), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted breast cancer protein marker (BF9 antigen), serum, result reported as indicative of response/no response to therapy or disease progression/regression<br><br>Proprietary test: Haystack MRDTM Baseline<br>Lab/Manufacturer: Quest Diagnostics® |
| 0599U | Oncology (pancreatic cancer), multiplex immunoassay of ICAM1, TIMP1, CTSD, THBS1, and CA 19-9, serum, diagnostic algorithm reported as positive or negative |
| G0327 | Colorectal cancer screening; blood-based biomarker |

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

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## X. Review/Revision History

| Effective Date | Summary |
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| 09/15/2026 | Clinical Advisory Board Meeting, policy review and approval: 03/18/2026<br>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Based on guidance from the National Comprehensive Cancer Network's Biomarker's Compendium, the following coverage additions and removals were made:<br>Clinical recommendations for almost all indications for almost all biomarkers were adjusted to reflect current recommendations in NCCN guidelines (e.g., for ALP testing for bone neoplasms, added "for osteosarcoma")<br>For BNP/NT-proBNP, added SLCA indications for testing based on NCCN compendium updates<br>For calcitonin, CEA, and inhibin, removed "occult primary" recommendations, as the NCCN recommends these as an IHC marker for occult primary, not as a serum biomarker.<br>For CA-125, removed "peritoneal mesothelioma" and "Lynch syndrome", as the NCCN no longer includes it as a recommended biomarker in the compendium<br>Removed CPT code 83789, 84078, 84080, and 84703 |
| 11/15/2025 | Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Based on guidance from the National Comprehensive Cancer Network's Biomarker's Compendium, the following coverage additions and removals were made:<br>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."<br>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.<br>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. |

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| | 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.<br>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.).<br>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."<br>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.<br>Carcinoembryonic antigen (CEA): For Carcinoembryonic antigen (CEA), added Occult primary and indication for "workup for adenocarcinoma or carcinoma not otherwise specified."<br>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."<br>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 workup for adenocarcinoma or carcinoma not otherwise specified."<br>Lactate dehydrogenase (LDH): Removed the entire section on Lactate dehydrogenase (LDH) as LDH is a broad marker beyond serum tumor biomarker designation.<br>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.<br>Removed CPT code 83615 |
| 10/01/2025 | Off-cycle coding modification: Added CPT code 0599U |
| 07/01/2025 | Added CPT code 0558U, 0559U |
| 01/01/2025 | Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Based on guidance from the National Comprehensive Cancer Network's Biomarker's Compendium, the following coverage additions and removals were made:<br>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. |

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| | Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it.<br>Beta-2 microglobulin (B2M): For chronic lymphocytic leukemia/small lymphocytic lymphoma, added indications for prognostic and/or therapy determination.<br>Calcitonin (CALCA): For adenocarcinoma, and anaplastic/undifferentiated epithelial tumors added indication of workup. For occult primary (unknown primary cancer) added indication for workup.<br>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.<br>Cancer antigen 19-9 (CA 19-9): for occult primary cancers, added indications for assessing disease prognosis and monitoring/follow-up for response. For "Ovarian cancers (less common)", added indication for Carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it. For small bowel adenocarcinoma, added to other indications "at metastasis or recurrence."<br>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."<br>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.<br>Inhibin (INHA): For adrenocortical carcinoma added indication for workup. For "Ovarian cancers (less common)", added indication for carcinosarcoma (malignant mixed mullerian tumors) to include monitoring/follow-up; clear cell carcinoma of the ovary to include monitoring/follow-up; grade 1 endometrioid carcinoma: monitoring/follow-up; mucinous neoplasms of the ovary to include monitoring/follow-up; low-grade serous carcinoma to include monitoring/follow-up. Removed the "(less common)" designation from Ovarian cancer row that has "Borderline epithelial tumors" following it.<br>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 |

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| | 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. |
| 07/15/2024 | Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Reformatted coverage table in criterion 1 from listing by condition to listing by tumor marker for ease of reference. Minor edits to coverage language for clarity and consistency with the National Comprehensive Cancer Network's Biomarker's Compendium. Based on guidance from the National Comprehensive Cancer Network's Biomarker's Compendium, the following coverage additions and removals were made:<br>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.<br>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.<br>Beta-2 microglobulin (B2M): for Waldenström macroglobulinemia/lymphoplasmacytic lymphoma, removed indication for prognostication at the time of first-line treatment initiation.<br>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.<br>BNP or NT-proBNP: for multiple myeloma, added indication for initial diagnostic workup.<br>Calcitonin (CALCA): for medullary carcinoma, updated indication for initial diagnostic evaluation to additional workup and added indication for post-surgical evaluation.<br>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. |

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| | For intrahepatic cholangiocarcinoma, added indication for monitoring. For borderline ovarian epithelial tumors, updated frequency for monitoring/follow-up from every 3–6 months to every visit if initially elevated. For mucinous carcinoma of the ovary, removed specification for initial diagnostic evaluation; indication for additional workup (if not previously done) remains.<br>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.<br>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.<br>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.<br>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.<br>Serum free light chain: for multiple myeloma, updated frequency of surveillance from as needed to once per month. For Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma, removed indication for initial diagnostic evaluation.<br>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. |
| 10/01/2023 | Added CPT code 0404U |
| 01/01/2023 | Reviewed and Updated: Updated background, guidelines, and evidence based scientific references. Literature review necessitated the following |

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| | modification to coverage criteria:<br>Addition of note above criteria on frequency: "Note: Except for where otherwise specified in the coverage criteria below, quarterly measurement of designated serum tumor markers is permitted for followup, monitoring, and/or surveillance"<br>CC1 totally reformatted and reworded to meet current guidelines.<br>Addition of two new biomarkers in CC1:<br>c) B-type natriuretic peptide (BNP) or N-terminal fragment of B-type natriuretic peptide (NT-proBNP)<br>i) Systemic light chain amyloidosis: initial diagnostic evaluation<br>j) Free light chain (circulating serum kappa or lambda chains) for:<br>i) B-cell lymphoma – Castleman disease: initial diagnostic evaluation<br>ii) Multiple myeloma: initial diagnostic evaluation and/or surveillance as needed<br>iii) Systemic light chain amyloidosis: initial diagnostic evaluation<br>iv) Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma: initial diagnostic evaluation<br>CC4- OvaSure and Coloprint removed from list, as these tests are no longer on the market Added CPT code 83521, 83880 Removed CPT code 82397, 0067U, 83883 |
| 05/15/2022 | Initial Policy Implementation |

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