

## Corporate Medical Policy

### Serum Tumor Markers for Malignancies AHS – G2124

**File Name:** serum\_tumor\_markers\_for\_malignancies  
**Origination:** 1/2019  
**Last Review:** 7/2023

#### Description of Procedure or Service

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Tumor biomarkers are proteins detected in the blood, urine, or other body fluids that are either produced by the tumor itself or in response to its presence. These biomarkers are used to help detect, diagnose, stage and manage some types of cancer. (Hottinger & Hormigo, 2011).

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

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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**BCBSNC will provide coverage for serum tumor markers for malignancies when it is determined the medical criteria and guidelines below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

#### When Serum Tumor Markers for Malignancies is covered

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1. Reimbursement is allowed for the measurement of the following serum tumor markers for these indications:
  - a. Acute lymphoblastic leukemia (ALL) and pediatric acute lymphoblastic leukemia (PED-ALL)
    - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
  - b. Acute myeloid leukemia (AML)
    - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
  - c. B-cell lymphoma
    - i. **Beta-2 microglobulin (B2M)**: initial diagnostic evaluation
    - ii. **Serum light chains** (Castleman disease only): initial diagnostic evaluation
    - iii. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
  - d. Bone neoplasms (metastatic and primary)
    - i. **Alkaline Phosphatase (ALP)**: initial diagnostic evaluation
    - ii. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
  - e. Breast cancer (metastatic)
    - i. **Cancer Antigen 15-3 and 27.29 (CA 15-3 and 27.29)**: monitoring
    - ii. **Carcinoembryonic Antigen (CEA)**: monitoring
  - f. Breast implant-associated anaplastic large cell lymphoma (ALCL)
    - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation and staging
  - g. Chronic lymphocytic leukemia/small lymphocytic lymphoma

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- i. **Beta-2 microglobulin (B2M)**: initial diagnostic evaluation
  - ii. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- h. Colon cancer
  - i. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation and post-treatment surveillance every 3-6 months for 2 years, then every 6 months for a total of 5 years
- i. Endometrial cancer
  - i. **Cancer Antigen 125 (CA-125)**: additional diagnostic evaluation and/or surveillance
- j. Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer:
  - i. initial diagnostic evaluation, during primary chemotherapy, and/or monitoring for complete response:
    - a. **Alpha fetoprotein (AFP)**
    - b. **Beta human chorionic gonadotropin (beta-hCG)**
    - c. **Cancer Antigen 19-9 (CA 19-9)**
    - d. **Cancer Antigen 125 (CA-125)**
    - e. **Carcinoembryonic Antigen (CEA)**
    - f. **Inhibin (INHA) expression**
    - g. **Lactate dehydrogenase (LDH)**
- k. Extrahepatic cholangiocarcinoma
  - i. **Cancer Antigen 19-9 (CA 19-9)**: initial diagnostic evaluation
  - ii. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation
- l. Gallbladder cancer
  - i. **Cancer Antigen 19-9 (CA 19-9)**: initial or postoperative diagnostic evaluation and/or surveillance
  - ii. **Carcinoembryonic Antigen (CEA)**: initial or postoperative diagnostic evaluation and/or surveillance
- m. Hairy cell leukemia
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- n. Hepatocellular carcinoma
  - i. **Alpha fetoprotein (AFP)**: initial diagnostic evaluation and screening and/or surveillance (every 3-6 months for 2 years, then every 6 months up to 5 years)
  - ii. **Cancer Antigen 19-9 (CA 19-9)**: initial diagnostic evaluation
- o. Hodgkin lymphoma
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- p. Intrahepatic cholangiocarcinoma
  - i. **Alpha fetoprotein (AFP)**: initial diagnostic evaluation
  - ii. **Cancer Antigen 19-9 (CA 19-9)**: initial diagnostic evaluation
  - iii. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation
- q. Kidney cancer
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- r. Less common ovarian cancers
  - i. Mucinous Carcinoma of the Ovary: initial diagnostic and (if necessary) additional evaluations
    - a. **Cancer Antigen 19-9 (CA 19-9)**
    - b. **Carcinoembryonic Antigen (CEA)**
  - ii. Ovarian low malignant potential tumors (borderline ovarian epithelial tumors): monitoring/follow-up every 3–6 months for up to 5 years, then annually
    - a. **Alpha fetoprotein (AFP)**
    - b. **Beta human chorionic gonadotropin (beta-hCG)**
    - c. **Cancer Antigen 19-9 (CA 19-9)**
    - d. **Cancer Antigen 125 (CA-125)**
    - e. **Carcinoembryonic Antigen (CEA)**
    - f. **Inhibin (INHA) expression**
    - g. **Lactate dehydrogenase (LDH)**
  - iii. Malignant germ cell tumors: surveillance no more than every 2 months for the first 2 years, every 4 months in years 3-5, and then annually after year 5
    - a. **Alpha fetoprotein (AFP)**

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- b. **Beta human chorionic gonadotropin (beta-hCG)**
- c. **Cancer Antigen 19-9 (CA 19-9)**
- d. **Cancer Antigen 125 (CA-125)**
- e. **Carcinoembryonic Antigen (CEA)**
- f. **Inhibin (INHA) expression**
- g. **Lactate dehydrogenase (LDH)**
- iv. Malignant sex cord stromal tumors: surveillance based on stage (i.e., 6-12 months if early-stage, low-risk disease; 4-6 months if high-risk disease)
  - a. **Alpha fetoprotein (AFP)**
  - b. **Beta human chorionic gonadotropin (beta-hCG)**
  - c. **Cancer Antigen 19-9 (CA 19-9)**
  - d. **Cancer Antigen 125 (CA-125)**
  - e. **Carcinoembryonic Antigen (CEA)**
  - f. **Inhibin (INHA) expression**
  - g. **Lactate dehydrogenase (LDH)**
- s. Medullary carcinoma
  - i. **Calcitonin (CALCA) expression**: initial diagnostic evaluation, monitoring, and/or surveillance 2-3 months postoperative, then every 6-12 months
  - ii. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation and surveillance 2-3 months postoperative, then every 6-12 months
- t. Melanoma (cutaneous)
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation for metastatic or recurrent disease
- u. Melanoma (uveal)
  - i. **Alkaline phosphatase (ALP)**: initial diagnostic evaluation for metastatic or recurrent disease
  - ii. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation for metastatic or recurrent disease
- v. Multiple myeloma
  - i. **Beta-2 microglobulin (B2M)**: initial diagnostic evaluation, staging, and/or follow-up/surveillance as needed
  - ii. **Serum free light chain**: initial diagnostic evaluation and/or surveillance as needed
  - iii. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation, staging, and/or follow-up/surveillance as needed
- w. Myelodysplastic syndromes
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- x. Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes
  - i. **Tryptase**: initial diagnostic evaluation
- y. Myeloproliferative neoplasms
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation and/or monitoring while on and after therapy
- z. Neuroendocrine and adrenal tumors - multiple endocrine neoplasia, type 2
  - i. **Calcitonin (CALCA) expression**: initial diagnostic evaluation
  - ii. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation
- aa. Occult primary mass of the liver, mediastinum, or retroperitoneum
  - i. **Alpha fetoprotein (AFP)**: initial diagnostic evaluation
- bb. Occult primary mass of the mediastinum or retroperitoneum
  - i. **Alpha fetoprotein (AFP)**: additional diagnostic evaluation
  - ii. **Beta human chorionic gonadotropin (beta-hCG)**: initial diagnostic evaluation
- cc. Occult primary adenocarcinoma or carcinoma not otherwise specified
  - i. **Cancer Antigen 125 (CA-125)**: additional diagnostic evaluation (in those with a uterus and/or ovaries present)
- dd. Pancreatic adenocarcinoma
  - i. **Cancer Antigen 19-9 (CA 19-9)**: initial diagnostic evaluation, risk classification, monitoring, and/or surveillance (every 3-6 months for 2 years, then every 6-12 months as clinically indicated)

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- ee. Pediatric aggressive mature B-cell lymphomas
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- ff. Peritoneal mesothelioma (malignant)
  - i. **Cancer Antigen 125 (CA-125)**: initial diagnostic evaluation
- gg. Primary cutaneous lymphomas
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- hh. Rectal cancer
  - i. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation, monitoring, and/or surveillance every 3-6 months for 2 years, then every 6 months for a total of 5 years
- ii. Richter's syndrome
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- jj. Sacrococcygeal teratoma
  - i. **Alpha fetoprotein (AFP)**: initial diagnostic evaluation and surveillance for up to 3 years
  - ii. **Beta human chorionic gonadotropin (beta-hCG)**: initial diagnostic evaluation
- kk. Small bowel adenocarcinoma
  - i. **Cancer Antigen 19-9 (CA 19-9)**: initial diagnostic evaluation and/or surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
  - ii. **Carcinoembryonic Antigen (CEA)**: initial diagnostic evaluation and/or surveillance (every 3-6 months for 2 years, then every 6 months for a total of 5 years)
- ll. Small cell lung cancer
  - i. **Lactate dehydrogenase (LDH)**: prognosis
- mm. Systemic light chain amyloidosis
  - i. **Alkaline Phosphatase (ALP)**: initial diagnostic evaluation
  - ii. **B-type natriuretic peptide (BNP) or N-terminal fragment of B-type natriuretic peptide (NT-proBNP)**: initial diagnostic evaluation and staging
  - iii. **Beta-2 microglobulin (B2M)**: initial diagnostic evaluation
  - iv. **Serum free light chain**: initial diagnostic evaluation
  - v. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
  - vi. **Troponin T**: initial diagnostic evaluation and staging
- nn. Systemic mastocytosis
  - i. **Tryptase**: initial diagnostic evaluation, monitoring response to therapy, and/or risk classification
- oo. T-cell lymphomas
  - i. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation
- pp. Testicular cancer (nonseminoma and pure seminoma):
  - i. Initial and post diagnostic evaluation, staging, risk classification, post-treatment follow-up, and surveillance:
    - a. **Alpha fetoprotein (AFP)**
    - b. **Beta human chorionic gonadotropin (beta-hCG)**
    - c. **Lactate dehydrogenase (LDH)**
- qq. Thymomas and thymic carcinomas
  - i. **Alpha fetoprotein (AFP)**: initial diagnostic evaluation
  - ii. **Beta human chorionic gonadotropin (beta-hCG)**: initial diagnostic evaluation
- rr. Undiagnosed pelvic mass
  - i. **Inhibin (INHA) expression**: initial diagnostic evaluation for clinical indication to assess for LCOC (Less Common Ovarian Cancers) and pregnancy
- ss. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
  - i. **Beta-2 microglobulin (B2M)**: initial diagnostic evaluation and prognostication at the time of first-line treatment initiation
  - ii. **Serum free light chain**: initial diagnostic evaluation
  - iii. **Lactate dehydrogenase (LDH)**: initial diagnostic evaluation

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

## **When Serum Tumor Markers for Malignancies is not covered**

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Reimbursement is not allowed for all other cancer indications not discussed above (use of the above biomarkers alone or in a panel of serum tumor markers).

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Analysis of proteomic patterns in serum for screening and detection of cancer is **investigational**.

## **Policy Guidelines**

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### **Scientific Background**

Actionable molecular assays for tumor biomarkers may guide treatment decisions for common malignancies (Febbo et al., 2011). Tumor biomarkers are proteins detected in blood, urine or 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 (Catharine M. Sturgeon et al., 2008). The 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 (Febbo et al., 2011). Some of these categories are listed below:

- **Diagnostic biomarkers** – 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** – Tumor biomarkers that have an association with some clinical outcomes, such as overall survival or recurrence-free survival, independent of the treatment rendered. An example is the p53 gene, whose presence may indicate a more aggressive type of cancer.
- **Predictive** - Tumor biomarkers 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 (Febbo et al., 2011).

### ***Proprietary Testing***

There are laboratory developed tests for serum tumor markers, but the clinical validity of these test have not been clearly proven yet.

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The IMMray® PanCan-d test measures nine serum biomarkers, including immunoregulatory and tumor biomarkers. The test uses IMMray microarray technology that prints single chain fragment antibodies onto a slide. The slide is preloaded with a microarray of antibodies. The slide can then be screened to measure the serum response to each biomarker. In a blind validation study, the test was reported to have a 99% specificity and 89% sensitivity rate when identifying stages I and II PDAC (n=56) versus high-risk individual controls. The accuracy increased to 92% sensitivity and 99% specificity across stage I-IV PDAC (n=157) (Immunovia, 2023).

BeScreened™-CRC is a colorectal cancer screening test. BeScreened™-CRC tests three blood-based proteins that are connected to 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.” “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” (BeScreened, 2023).

REVEAL Lung Nodule Characterization is a blood test that specifically aids in “characterizing indeterminate pulmonary nodules (4-30mm) in current smokers aged 25 years and older.” The test results are based on three clinical factors and three blood proteins associated with lung cancer. “REVEAL Lung Nodule Characterization is a risk assessment tool, that is to be used only in conjunction with standard clinical assessments. The test is not intended as a screening or stand-alone diagnostic assay” (MagArray, 2023).

OVA1® and OVERA® are blood tests for ovarian cancer. OVA1® has FDA-clearance for testing ovarian cancer risk in women planning to have surgery for a pelvic mas. OVA1® is a first-generation multivariate index assay that measures five ovarian cancer-associated markers. “A negative OVA1 (MIA) result is accompanied by a 98% likelihood that the woman being tested is in fact disease-free.” OVERA® has been FDA-cleared for people with a pelvic mass who are planned for surgery. OVERA® is a second-generation multivariate index assay that measures different markers and uses a more refined algorithm than OVA1® (ASPIRE, 2023).

## *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 (Hottinger & Hormigo, 2011). The analytic and clinical validity as well as the clinical utility of each biomarker should be taken into account before its use for screening and or management of malignancies (Catharine M. Sturgeon et al., 2008). 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 (Febbo et al., 2011).

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 (Pinzani et al., 2021).

## *Alpha-fetoprotein (AFP)*

AFP 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 (Schefer, Mattmann, & Joss, 1998). Many tissues produce this protein if they become malignant, and AFP is elevated in a variety of cancers, such as hepatocellular carcinomas and gastric cancers (Gilligan et al., 2010;

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Michaelson, 2017). False positives may occur due to liver damage or a rare hereditary syndrome (Gilligan et al., 2010).

AFP 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), 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 more malignant cancers (Wu et al., 2018).

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

Cheng et al. (2014) conducted a meta-analysis of fifteen studies (4465 patients) to evaluate the association between high pre-treatment serum AFP-L3% and 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 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" (Cheng et al., 2014).

Park et al. (2017) compared the diagnostic values of AFP, AFP-L3, and 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" (Park et al., 2017).

Ryu et al. (2017) investigated the prognostic implications of the expression patterns of three tumor markers, alpha-fetoprotein (AFP), the Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and des- $\gamma$ -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 overall survival (OS) and disease-free survival (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. OS in triple-negative or single-positive patients was 85.3%, and that in all double- or triple-positive patients was 58.0%; DFS at five years postoperatively in these two groups was 45.9 and 34.0%, respectively. 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" (Ryu et al., 2017).

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 uTASWako was used to measure these biomarkers. AFP-L3 had an area under the curve 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 them alone (Caviglia et al., 2016).

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## *Beta-human chorionic gonadotropin (beta-HCG)*

Beta-human chorionic gonadotropin (beta-hCG) 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 outside of pregnancy (Harvey, 2023). The beta subunit is responsible for providing the biological and immunological specificity to each hormone (Marcillac et al., 1992) This biomarker is typically associated with aggressive disease in nontrophoblastic tumors. This biomarker may be seen in ovarian cancers, testicular cancers, and more (Hotakainen et al., 2002).

Li et al. (2018) evaluated beta-hCG as a marker for colorectal cancer (CRC). In total, 50 patients out of 136 patients expressed beta-hCG at the “invasive front.” The authors found that higher expression of beta-hCG to be associated with worse prognosis than those with low beta-hCG expression and 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 (Li et al., 2018).

## *Beta-2 microglobulin (B2M)*

B2M is the light chain component of the MHC-1 molecule and is present in most cells of the body (Berrebi et al., 2009). This protein may aggregate and eventually form insoluble amyloid fibrils, which cause numerous conditions such as bone and joint damage (Katou et al., 2002; Marcinko et al., 2017). Elevated serum levels of B2M have been associated with cancers such as multiple myeloma or chronic leukocytic leukemia (Berrebi et al., 2009).

Seo et al. (2016) examined the prognostic value of B2M for diffuse large B-cell lymphoma. A total of 833 patients at a  $\geq 2.5$  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 (Seo et al., 2016).

## *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 (Tuttle, 2023). However, the ATA has noted this biomarker to have significant uncertainties (Haugen et al., 2016; Wells et al., 2015).

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 did not have a “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 medullary thyroid cancer (MTC) were diagnosed. The authors recommended not screening routinely for MTC (Tormey et al., 2017).

## *Cancer antigens (CA)*

Cancer antigens (CA) refer to any substance produced by the body in response to a tumor. Various cancer antigens have been proposed as biomarkers for numerous types of cancer, such as CA 19-9, CA 125, and CA 15-3. CA 19-9 (also called carbohydrate antigen) refers to a specific antibody that binds a sialyl compound produced by cancer tissue (Sialyl Lewis A). CA 19-9 is elevated in several different types of cancer, such as adenocarcinomas or colorectal cancer (Magnani, 2004). CA 125 is a glycoprotein produced in fetal tissue as well as mesothelial cells in adults (Isaksson et al., 2017). Its function is thought to assist with cell adhesion, metastasis, and immunosuppression (Dorigo & Berek, 2011).



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Kim et al. (2017) performed a study assessing the association of serum CA 19-9 and 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 (Kim et al., 2017).

A study was performed by Feng et al. (2017) that focused on the diagnostic and prognostic value of CEA, CA 19-9, AFP, and CA125 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 CA125'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 (Feng et al., 2017).

Lucarelli et al. (2014) evaluated CA 15-3, CA125, 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 CA125, 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 found high levels of CA 15-3 to be an independent adverse prognostic risk factor for CSS (Lucarelli et al., 2014).

Chen et al. (2018) analyzed four serum tumor markers in patients with ovarian tumors. 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, CA125, CA19-9, and CEA had sensitivities of 63.78%, 62.75%, 35.71%, and 38.78%, respectively. HE4 and CA125 combined was found to have the highest diagnostic sensitivity at 80.10%, as well as a specificity of 69.08%. Although adding markers to the HE4-CA125 combination increased diagnostic sensitivity (to 88.52%), this difference was not considered significant (Chen et al., 2018).

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, human epididymis protein 4 (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" (Isaksson et al., 2017).

Bind et al. (2021) evaluated the diagnostic ability of CA19-9 and CA 125 for gallbladder cancers. A total of 118 patients were included, 91 benign cases and 27 malignant. The mean value of CA19-9 was found to be 12.86 U/mL in benign cases and 625.35 U/mL in malignant cases. For CA 125, the mean value for benign cases was found to be 17.98 U/mL, and for malignant cases, 239.63 U/mL. The authors examined a theoretical diagnostic cut-off value of 252.31 U/mL for CA19-9 and 92.19 U/mL for CA 125. At this cutoff, sensitivity and specificity for CA19-9 was 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" (Bind et al., 2021).

### *Carcinoembryonic antigen (CEA)*

CEA 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

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damage or cigarette smoking may affect CEA levels as well (Ueland, 2023). The gene encoding CEA encompasses certain genes encoding for cell adhesion, as well as MHC antigens (Duffy, 2001).

### *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 (Strosberg, 2023).

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 (Yang et al., 2015). Another study by Tian et al. (2016) found that although median CgA levels were significantly higher than healthy controls (93.8 ng/mL compared to 37.1 ng/mL), only a weak correlation was found between changes in serum CgA levels and clinical regimen. The CgA cutoff value for this study was 46.2 ng/mL, which led to a sensitivity of 78.8% and specificity of 73.8% (Tian et al., 2016).

### *Lactate Dehydrogenase (LDH)*

LDH is an enzyme that catalyzes the interconversion between lactate and pyruvate. LDH is often found to be upregulated in tumors, and a key feature of cancer sites is the accumulation of lactate or lactic acid. This is thought to be caused by increased glycolysis and this increase in lactate causes an elevated concentration of LDH (Pucino et al., 2017). Increased LDH is found in several different cancers, such as B-cell lymphomas and osteosarcomas (NCCN, 2023t).

Liu et al. (2016) performed a study evaluating the OS rates of an extremely high concentration of LDH (>1000 IU/L, considered by the study to be four times the upper normal limit). A total of 311 patients with >1000 U/L were examined, and the OS rate of this cohort was 1.7 months with 163 perishing within two months. However, 51 patients' LDH decreased to normal following chemotherapy, and the OS rate of this group was 22.6 months. The cohort who survived at two months but did not see their LDH decrease had an OS rate of four months. There was no positive association found between OS and type of cancer, although there were different OS rates for patients at different stages of lymphoma (Liu et al., 2016).

### *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 women, unusual levels of inhibins may signal tumors in this region (Walentowicz et al., 2014). 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 (Gershenson, 2023). 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 (Farkkila et al., 2015).

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 (Farkkila et al., 2015).

### *Urokinase plasminogen activator*

Urokinase plasminogen activator (uPA) is a serine protease with an important role in cancer invasion and metastases (Stephens et al., 1998). 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 women with breast cancer (Chappuis et al., 2001; Foekens et al.,

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2000; Malmstrom et al., 2001; Stephens et al., 1998). ASCO guidelines include the option for using uPA and PAI-1 to guide decisions on adjuvant systemic therapy for patients with node-negative, hormone-positive/HER2-negative disease, but not for patients with HER2-positive or triple-negative disease (L. N. Harris et al., 2016; Theodoros & Bergh, 2023).

### *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 5 heavy chain protein classes (IgG, IgE, IgA, IgD, and IgM), and 2 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 (Kyrtsonis MC, 2012). 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.

Multiple myeloma is an uncontrolled growth of plasma cells (ACS, 2018a). In most cases, the cancerous clonal cells secrete an intact monoclonal immunoglobulin, and the gold standard for diagnosis is serum protein electrophoresis and immunofixation (Tosi et al., 2013). 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 (Katzmann et al., 2002). 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 (Tosi et al., 2013).

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 (ACS, 2018b). WM cells are distinguished by the production of immunoglobulin M (IgM) serum monoclonal protein, also referred to as a "macroglobulin" (Cautha et al., 2022). 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 shown to improve overall care, as it may help differentiate patients with another, potentially benign disorder called monoclonal gammopathy of undetermined significance (MGUS), as well as influence prognosis (Moreau AS, 2006).

Castleman disease represents a group of B-cell lymphoproliferative disorders characterized by distinct pathogenesis and clinical outcomes (Oyaert et al., 2014; D. Wu et al., 2018). Patients with suspected Castleman disease have been reported to present with abnormal levels of kappa or lambda light chains, making the serum free light chain assay a potentially useful tool in the management of this disease (Oyaert et al., 2014; D. Wu et al., 2018). Utilization of a serum free light chain assay has been shown 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 (Stankowski-Drengler et al., 2010); 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 (Dispenzieri, 2023; Merlini et al., 2013). 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 (Akar et al., 2005; Bhole et al., 2014; Kumar et al., 2010).

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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.

### *Proteomics*

Proteomics is a qualitative and quantitative assessment of the protein constituents in a given 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 (Raby, 2023).

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. Chen et al found 36 proteins that were upregulated in cancer patients as well as 22 proteins that were downregulated compared to healthy controls. The proteins that were upregulated tended to be processes that regulated the “pretumorigenic microenvironment for metastasis” and the downregulated proteins tended to be ones that controlled tumor growth and cell survival (Chen et al., 2017).

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 levels 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 area under curve (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 use as a diagnostic marker (Qin et al., 2020).

### **Guidelines and Recommendations**

#### **National Academy of Clinical Biochemistry (NACB) now known as the American Association for Clinical Chemistry (AACC) Academy**

The National Academy of Clinical Biochemistry published practice Guidelines for the use of major tumor markers for Liver, Bladder, Cervical, and Gastric Cancers (Sturgeon et al., 2010).

The NACB recommends use of AFP measurements when managing hepatocellular carcinoma (HCC). For screening, the NACB recommends AFP be measured at 6-month intervals in patients at high risk of HCC, noting 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 (Sturgeon et al., 2010).

The NACB 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. The NACB did not recommend any biomarkers for screening, monitoring, prognosis, or diagnosis of cervical cancer. Pretreatment measurements of squamous cell carcinoma antigen (SCC) were acknowledged to provide information, but their routine use could not be recommended. The NACB 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 (Sturgeon et al., 2010).

The NACB also published guidelines on use of major tumor markers for Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers (C. M. Sturgeon et al., 2008). For testicular cancer, the NACB stated that

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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. NACB notes that measurement of the hCG $\beta$  component is essential when measuring hCG. For prostate cancer, PSA assessment is required during all stages of the disease. NACB recommends against age-specific intervals for PSA. PSA measuring is recommended to monitor disease status after treatment. However, the NACB also did not make any recommendations on PSA screening for prostate cancer (C. M. Sturgeon et al., 2008).

For colorectal cancer (CRC), carcinoembryonic antigen (CEA) measurement is recommended every 3 months in stage II or III CRC if “patient is a candidate for surgery or systemic therapy of metastatic disease”. Pre-operative CEA measurements may be used in conjunction with other factors to plan surgery. Regular CEA measurements should be done in patients with advanced CRC that are undergoing systemic therapy. However, CEA is not recommended for screening in healthy individuals. Routine measurement of other biomarkers such as CA 19-9, TIMP-1, or CA 242 is not recommended, for prognosis or predicting response to treatment. The NACB recommends individuals older than 50 to 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, the NACB supports guidelines such as the NCCN and AGA regarding genetic testing for CRC (C. M. Sturgeon et al., 2008).

For breast cancer, the NACB states estrogen receptor (ER) and progesterone receptor (PR) measurement should be done in all patients with breast cancer. HER-2 should be measured in all patients with invasive breast cancer. 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 be routinely 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. OncoType DX may be used to predict recurrence in “lymph node–negative, ER-positive patients receiving adjuvant tamoxifen”. However, microarray-based gene signatures should be routinely used for predicting patient outcome (C. M. Sturgeon et al., 2008).

For ovarian cancer, CA125 is not recommended for screening asymptomatic women, but is recommended (with transvaginal ultrasound) for early detection of ovarian cancer in women with hereditary syndromes. CA125 is also recommended as distinguishing benign from malignant masses and may be used to monitor response to chemotherapeutic response. Measurement of CA125 during follow-up visits is recommended if initial values were increased. CA125 measurement is also recommended during primary therapy. Other biomarkers such as inhibin and hCG cannot be recommended at this time (C. M. Sturgeon et al., 2008).

### **American Society of Clinical Oncology (ASCO)**

The ASCO released Clinical Practice Guideline on Uses of Serum Tumor Markers (STMs) in Adult Males With Germ Cell Tumors (GCTs) in 2010 (Gilligan et al., 2010). ASCO recommends against any STMs to screen for GCTs. ASCO recommends assessment of serum AFP and hCG before orchiectomy to establish a diagnosis and baseline levels but 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” (Gilligan et al., 2010).

ASCO recommends measuring AFP and hCG before retroperitoneal lymph node dissection in patients with stage I or II NSGCT. ASCO 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

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surveillance after “definitive therapy for NGSCT” and that surveillance should continue for 10 years after therapy concludes (Gilligan et al., 2010).

ASCO recommends measuring “postorchiectomy serum concentrations of hCG and/or LDH for patients with testicular pure seminoma and preorchiectomy elevations” but 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 when treatment concludes and during post-treatment surveillance. ASCO recommends these intervals: every 2 to 4 months in the first year, every 3 to 4 months in the second year, every 4 to 6 months in the third and fourth years, and annually thereafter. Surveillance should last for at least 10 years after therapy concludes (Gilligan et al., 2010).

ASCO also published joint guidelines with the **American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology** regarding biomarkers for colorectal cancer. In it, they do not mention any serum tumor markers for testing (Sepulveda et al., 2017).

The ASCO also released guidelines on use of biomarkers to inform treatment decisions on 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” (Van Poznak et al., 2015).

ASCO released a focused update for women with early-stage invasive breast cancer, which is as follows (Krop et al., 2017).

- If a patient has **ER/PgR-positive, HER2-negative, node-negative** breast cancer, the MammaPrint assay may be used in those with **high clinical risk, but not low clinical risk** per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy.
- If a patient has **ER/PgR-positive, HER2-negative, node-positive** breast cancer, the MammaPrint assay may be used in patients with 1-3 positive nodes and at **high clinical risk**, but not for patients at **low clinical risk**.
- If a patient has **HER2-positive** breast cancer or **ER/PgR negative and HER2-negative** breast cancer (triple negative) the clinician should not use the MammaPrint assay.

The following recommendations were unchanged from the 2016 version:

- If a patient has ER/PgR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use tumor-infiltrating lymphocytes (TILs), the five-protein assay (Mammostrat), and the immunohistochemistry 4 (IHC4) assay, to guide decisions on adjuvant systemic therapy.
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the Breast Cancer Index, the PAM50-ROR, the 12-gene risk score, or the 21-gene RS, (EndoPredict), to guide decisions on adjuvant systemic therapy.

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- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use urokinase plasminogen activator (uPA), plasminogen activator inhibitor type 1 (PAI-1), the Breast Cancer Index, the PAM50 risk of recurrence (ROR) score, the 12-gene risk score (EndoPredict), and the 21-gene recurrence score (Oncotype DX) to guide decisions on adjuvant systemic therapy. If the patient has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, or IHC4) to guide decisions on extended endocrine therapy.
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use uPA, IHC4, the 12-gene risk score (EndoPredict), PAI-1, the 21-gene RS (Oncotype DX), the five-protein assay (Mammostrat), the Breast Cancer Index or TILs to guide decisions on adjuvant systemic therapy. The clinician should not use circulating tumor cells (CTCs) to guide decisions on adjuvant systemic therapy.
- The clinician should not use CYP2D6 polymorphisms, p27 expression, Ki-67 labeling index, microtubule-associated protein (MAP)-Tau mRNA expression or mRNA expression, HER1/epidermal growth factor receptor (EGFR) expression, TOP2A gene amplification or TOP2A protein expression, HER2 and TOP2A gene coamplification; CEP17 duplication; or TIMP-1, FOXP3, or p53 protein expression (all by IHC) to guide adjuvant endocrine therapy selection. If a patient has HER2-positive breast cancer, the clinician should not use PTEN or soluble HER2 levels to guide adjuvant therapy selection.
- If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy.
- If a patient has TN breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy.

ASCO released a provisional clinical opinion on evaluating susceptibility to pancreatic cancer, 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 (Stoffel et al., 2018).

ASCO also released a guideline on treatment of malignant pleural mesothelioma, stating that calretinin, keratins 5 and 6, and nuclear WT-1 are expected to be positive while CEA, EPCAM, Claudin 4, and TTF-1 should be negative. Non-tissue based biomarkers are currently not recommended due to their unvalidated statistical accuracy (Kindler et al., 2018).

ASCO remarks that “If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use urokinase plasminogen activator and plasminogen activator inhibitor type 1 to guide decisions on adjuvant systemic therapy”. The guidelines also recommend against using IHC4 to guide decisions on adjuvant systemic therapy (Lyndsay N. Harris et al., 2016).

ASCO released an update on ER / PgR testing for breast cancer. In it, they continue to recommend ER testing for predicting success of endocrine therapy. They remark that similar principles apply to PgR testing, which provides prognostic information for ER+ cancer. ASCO also recommends testing ER for patients with ductal carcinoma in situ (DCIS) to determine benefit of endocrine therapies (Allison et al., 2020).

### **American College of Chest Physicians (ACCP)**

In 2013, the ACCP published evidence-based clinical practice guidelines for diagnosis and management of lung cancer. The guidelines did not mention proteomic markers as a potential diagnostic or screening tool. (Detterbeck et al, 2013).

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## National Institute for Health and Clinical Excellence (NICE, 2011, 2018)

The National Institute for Health and Clinical Excellence (NICE) issued guidelines in 2011 on the recognition and initial management of ovarian cancer. It stated that the routine use of CA-125 is recommended; the data on other serum markers is not substantial enough to recommend their use. It included the following recommendations:

1. Measure serum CA-125 in primary care in women with symptoms that suggest ovarian cancer.
2. If serum CA-125 is 35 IU/mL or greater, arrange an ultrasound scan of the abdomen and pelvis.
3. If the ultrasound suggests ovarian cancer, refer the woman urgently for further investigation.
4. For any woman who has normal serum CA-125 (less than 35 IU/mL), or CA-125 of 35 IU/mL or greater but a normal ultrasound: 1) assess her carefully for other clinical causes of her symptoms and investigate if appropriate; 2) if no other clinical cause is apparent, advise.
5. Calculate a risk of malignancy index I (RMI I) score (after performing an ultrasound). (The RMI I combines CA-125, menopausal status and the ultrasound score).

The NICE guidelines also suggested to measure AFP, beta-HCG and serum CA125 in women under 40 with suspected ovarian cancer (NICE, 2011).

NICE also recommends using a serum free-light chain assay to “confirm the presence of a paraprotein indicating possible myeloma or monoclonal gammopathy of undetermined significance (MGUS).” Serum immunofixation is recommended if serum protein electrophoresis is abnormal. Finally, serum free light-chain ratio is recommended for prognosis (NICE, 2018).

## National Comprehensive Cancer Network (NCCN)

| Serum Tumor Marker | Recommendation  | Source   |
|--------------------|---|--|
| AFP                | Hepatocellular workup (HCC). AFP for surveillance and screening is optional   | NCCN Hepatobiliary Cancers Version 1.2023 (NCCN, 2023k)          |
| AFP                | Resectable HCC. Surveillance imaging and AFP should continue for at least 5 years and thereafter screening is dependent on HCC risk factors.  |  |
| AFP                | Consider for intrahepatic cholangiocarcinoma workup   | NCCN Hepatobiliary Cancers Version 1.2023 (NCCN, 2023k)          |
| AFP                | Individuals younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors and to rule out pregnancy.<br><br>Patients achieving a complete clinical response after chemotherapy for germ cell tumors should be observed clinically every 2 to 4 months with AFP and beta-HCG levels (if initially elevated) for 2 years. | NCCN Ovarian Cancer Version 1.2023 (NCCN, 2023x)                 |
| AFP                | Thymomas and thymic carcinoma initial evaluation to rule out germ cell tumors.  | NCCN Thymomas and thymic carcinomas Version 1.2023 (NCCN, 2023x) |



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|----------------------------|--|--|
|                            |  |  |
| AFP                        | Both seminoma and nonseminoma, serum prognostic factor and contribute to diagnosis and staging. Also indicated for “suspicious testicular mass” workup   | NCCN Testicular Cancer Version 1.2023 (NCCN, 2023ah)   |
| AFP                        | Workup for occult primary mass of the liver, mediastinum, or retroperitoneum   | NCCN Occult Primary Version 3.2023 (NCCN, 2023w)   |
| Alkaline Phosphatase (ALP) | Should be assessed prior to treatment for bone cancers   | NCCN Bone cancers Version 3.2023 (NCCN, 2023b)   |
| Alkaline Phosphatase (ALP) | Part of the initial diagnostic workup for systemic light chain amyloidosis   | NCCN Systemic Light Chain Amyloidosis Version 2.2023 (NCCN, 2023ae)                            |
| Beta-HCG                   | Testicular cancer workup for a “suspicious mass”, beta hCG needs to be assessed as it is a prognostic factor and contributes to diagnosis and staging. Assessed pre- and post-orchietomy   | NCCN Testicular Cancer Version 2.2023 (NCCN, 2023ah)   |
| Beta-HCG                   | May be clinically indicated in the workup and management of epithelial ovarian, fallopian tube, primary peritoneal, and less common ovarian cancers.   | NCCN Ovarian Cancer Version 1.2023 (NCCN, 2023x)   |
| Beta-HCG                   | Thymomas and thymic carcinoma initial evaluation   | NCCN Thymomas and Thymic Carcinomas Version 1.2023 (NCCN, 2023ai)                              |
| Beta-HCG                   | Workup for occult primary mass of the mediastinum or retroperineum   | NCCN Occult Primary Version 3.2023(NCCN, 2023w)  |
| Beta-2 microglobulin (B2M) | Multiple myeloma initial workup and follow-up/surveillance   | NCCN Multiple Myeloma Version 3.2023 (NCCN, 2023p)   |
| Beta-2 microglobulin (B2M) | Workup for: follicular lymphoma (grades 1-2), mantle cell lymphoma, diffuse B-cell Lymphoma (useful in selected cases), AIDS-related B-cell lymphoma (useful in selected cases), lymphoblastic lymphoma workup (useful in selected cases), Castleman’s disease | NCCN B-cell Lymphomas Version 2.2023 (NCCN, 2023a)   |
| Beta-2 microglobulin (B2M) | Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma essential workup, prognostic factor  | NCCN Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma Version 1.2023 (NCCN, 2023al) |
| Beta-2 microglobulin (B2M) | Workup and prognostic information (“useful under certain circumstances”)   | NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2023 (NCCN, 2023e)      |
| Beta-2 microglobulin (B2M) | Initial diagnostic Workup  | Systemic Light Chain Amyloidosis Version 2.2023 (NCCN, 2023ae)                                 |

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|                                     |  |   |
|-------------------------------------|--|---|
| BNP/NT-<br>BNP                      | Initial diagnostic workup (may be considered)  | Systemic Light Chain Amyloidosis<br>Version 2.2023 (NCCN, 2023c)  |
| Cancer<br>Antigen 15-3<br>and 27.29 | Cancer Antigen 15-3 and 27.29 as part of findings for identification of disease progression. An isolated increase in tumor marker should not be used as the only indicator of disease progression as these two biomarkers may also increase if metastatic disease is responding to treatment   | NCCN Breast Cancer Version 3.2023<br>(NCCN, 2023c)  |
| Cancer<br>Antigen 19-9              | Pancreatic adenocarcinoma pre-op workup, post treatment, and surveillance, differential diagnosis, screening, staging, determining resectability, et al. Levels may be elevated up to 2 years before pancreatic CA diagnosis   | NCCN Pancreatic Adenocarcinoma<br>Version 2.2022 (NCCN, 2023y)  |
| Cancer<br>Antigen 19-9              | Workup and surveillance for small bowel adenocarcinoma   | NCCN Small Bowel Adenocarcinoma<br>Version 1.2023 (NCCN, 2023ac)  |
| Cancer<br>Antigen 19-9              | Gallbladder cancer workup (on findings such as jaundice or a mass found on imaging) and surveillance. CA 19-9 is a baseline test and should not be done to confirm diagnosis. Consider baseline CA 19-9 after biliary decompression.<br><br>Intrahepatic (such as isolated intrahepatic mass) and extrahepatic cholangiocarcinoma workup. CA 19-9 is a baseline test and should not be done to confirm diagnosis | NCCN Hepatobiliary Cancers Version<br>1.2022 (NCCN, 2023k)  |
| Cancer<br>Antigen 19-9              | May be clinically indicated in the workup and management of epithelial ovarian, fallopian tube, primary peritoneal, and less common ovarian cancers  | NCCN Ovarian Cancer Version 1.2023<br>(NCCN, 2023x)   |
| CA-125                              | May be clinically indicated in the workup and management of epithelial ovarian, fallopian tube, primary peritoneal, and less common ovarian cancers  | NCCN Ovarian Cancer Version<br>1.2023(NCCN, 2023x)  |
| CA-125                              | <i>BRCA</i> mutation-positive individuals – for those individuals who have not elected RRSO or TVUS serum CA-125 screening may be considered at the clinician’s discretion starting age 30-35 years  | NCCN Genetic/Familial High-Risk<br>Assessment: Breast and Ovarian, and<br>Pancreatic Version 3.2023 (NCCN, 2023h) |
| CA-125                              | Endometrial carcinoma: consider CA-125 for suspected extrauterine disease, serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated/dedifferentiated   | NCCN Uterine Neoplasms Version 1.2023<br>(NCCN, 2023ak)   |

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|        |  |  |
|--------|--|--|
|        | carcinoma; surveillance if initially elevated  |  |
| CA-125 | Occult Primary - localized adenocarcinoma or carcinoma not otherwise specified workup for individuals assigned female sex at birth   | NCCN Occult Primary Version 3.2023 (NCCN, 2023w)                               |
| CA-125 | Lynch Syndrome: surveillance/prevention strategies. CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound   | Genetic/Familial High-Risk Assessment: Colorectal Version 2.2022 (NCCN, 2022b) |
| CA-125 | CA-125 may be considered in the initial evaluation of peritoneal mesothelioma  | NCCN Malignant Peritoneal Version 1.2023 (NCCN, 2023n)                         |
| CEA    | Colon cancer appropriate for resection (non-metastatic) workup and surveillance every 3-6 months for 2 years, then every 6 months for a total of 5 years for stages II-III cancer. Not recommended beyond 5 years.<br><br>Suspected or proven metastatic synchronous adenocarcinoma workup<br><br>Pedunculated or sessile polyp with invasive cancer but fragmented specimen/unknown margin or unfavorable histology | NCCN Colon Cancer Version 3.2023 (NCCN, 2023f)                                 |
| CEA    | Workup and surveillance for small bowel adenocarcinoma   | NCCN Small Bowel Adenocarcinoma Version 1.2023 (NCCN, 2023ac)                  |
| CEA    | Pedunculated or sessile polyp with invasive cancer but fragmented specimen/unknown margin or unfavorable histology<br><br>Workup, monitoring, and/or surveillance for rectal cancer  | Rectal Cancer Version 4.2022 (NCCN, 2023ab)                                    |
| CEA    | Intrahepatic (such as isolated intrahepatic mass) and extrahepatic cholangiocarcinoma workup and monitoring. CEA is a baseline test and should not be done to confirm diagnosis  | NCCN Hepatobiliary Cancers Version 1.2022 (NCCN, 2023k)                        |
| CEA    | Gallbladder cancer initial workup (on findings such as jaundice or a mass found on imaging) and surveillance. CEA is a baseline test and should not be done to confirm diagnosis   | NCCN Hepatobiliary Cancers Version 1.2022 (NCCN, 2023k)                        |
| CEA    | Thyroid carcinoma – medullary carcinoma diagnostic procedure,  | NCCN Thyroid Carcinoma Version 3.2022 (NCCN, 2023aj)                           |

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|                                    | additional workup, and surveillance; surveillance every 6-12 mo.   |  |
| CEA                                | May be clinically indicated in the workup and management of epithelial ovarian, fallopian tube, primary peritoneal, and less common ovarian cancers  | NCCN Ovarian Cancer Version 1.2023 (NCCN, 2023x)   |
| CEA                                | Initial diagnostic evaluation for malignant pleural or peritoneal mesothelioma   | NCCN Malignant Peritoneal Mesothelioma Version 1.2023 (NCCN, 2023n) and Pleural Mesothelioma Version 1.2023 (NCCN, 2023o)  |
| CEA                                | Monitoring of metastatic breast cancer and definition of disease progression. An isolated increase in tumor marker should rarely be used as the only indicator of disease progression.   | NCCN Breast Cancer Version 3.2023 (NCCN, 2023c)  |
| CEA                                | Neuroendocrine and Adrenal tumors- Multiple Endocrine Neoplasia, Type 2: initial diagnostic evaluation and/or surveillance   | NCCN Neuroendocrine and Adrenal Tumors. Version 2.2022 (NCCN, 2023u)   |
| CEA                                | Initial workup for non-small cell lung cancer  | NCCN Non-Small Cell Lung Cancer Version 2.2023 (NCCN, 2023v)   |
| CEA                                | Commonly used immunohistochemistry marker for unknown primary cancers. Positive marker for hepatocellular carcinoma. Useful for mesothelioma, thyroid carcinoma (medullary carcinoma).   | NCCN Occult Primary Version 3.2023 (NCCN, 2023w)   |
| Calcitonin (CALCA)                 | Thyroid carcinoma - medullary carcinoma based evaluation, post-surgical evaluation, and surveillance (surveillance every 6-12 mo.)   | NCCN Thyroid carcinoma Version 3.2022 (NCCN, 2023aj)   |
| Calcitonin (CALCA)                 | Cervical cancer-workup   | NCCN Cervical Cancer Version 1.2023 (NCCN, 2023d)  |
| Calcitonin (CALCA)                 | Multiple endocrine neoplasia, type 2 – clinical evaluation   | NCCN Neuroendocrine and Adrenal Tumors Version 2.2022 (NCCN, 2023u).   |
| Calcitonin (CALCA)                 | Workup for occult primary adenocarcinoma or anaplastic/undifferentiated tumors of the head and neck, or otherwise unspecified  | NCCN Head and Neck Cancers Version 1.2023 (NCCN, 2023)   |
| Serum Free-light chain (FLC) assay | Plasma cell disorders, such as myelomas, immunoglobulin light chain amyloidosis, B-cell lymphoma, Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma, and solitary plasmocytoma—included in initial diagnostic workup; surveillance (as needed) for multiple myeloma | NCCN Multiple Myeloma Version 3.2023 (NCCN, 2023p), B-Cell Lymphomas Version 2.2023 (NCCN, 2023a), Systemic Light Chain Amyloidosis Version 2.2023 (NCCN, 2023ae), Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma Version 1.2023 (NCCN, 2023al) |
| Inhibin (INHA)                     | May be clinically indicated in the workup and management of an   | NCCN Ovarian Cancer Version 1.2023 (NCCN, 2023x)   |

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|                | undiagnosed pelvic mass, epithelial ovarian, fallopian tube, primary peritoneal, and less common ovarian cancers  |   |
| Inhibin (INHA) | Commonly used immunohistochemistry marker for unknown primary cancers. Positive marker for adrenocortical carcinoma.  | NCCN Occult Primary Version 3.2023 (NCCN, 2023w)  |
| Inhibin (INHA) | Uterine Sarcoma-additional confirmatory tests   | NCCN Uterine Neoplasms Version 1.2023 (NCCN, 2023ak)  |
| LDH            | May be clinically indicated in the workup and management of epithelial ovarian, fallopian tube, primary peritoneal, and less common ovarian cancers   | NCCN Ovarian Cancer Version 1.2023 (NCCN, 2023x)  |
| LDH            | Acute Lymphoblastic Leukemia (ALL) workup as part of a tumor lysis syndrome panel; useful for workup under certain circumstances; essential for Richter’s transformation  | NCCN Acute Lymphocytic Leukemia Version 1.2022 (NCCN, 2022a)  |
| LDH            | Pediatric Acute Lymphoblastic Leukemia (ALL) workup as part of a tumor lysis syndrome panel   | NCCN Pediatric Acute Lymphoblastic Leukemia Version 2.2023 (NCCN, 2023z)                            |
| LDH            | Chronic lymphocytic leukemia workup for histologic transformation (Richter’s) and progression; workup for tumor lysis syndrome. Listed as “useful under certain circumstances”  | NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Version 2.2023 (NCCN, 2023e)          |
| LDH            | Hairy cell leukemia workup  | NCCN Hairy Cell Leukemia. Version 1.2023 (NCCN, 2023i)  |
| LDH            | Prognostic factor, 1.5 times the upper limit of normal amount; included in the initial workup for kidney cancer   | NCCN Kidney Cancer. Version 4.2022  |
| LDH            | Prognostic factor, metastatic disease. Utilized also for stage IV metastatic workup to predict outcomes.  | NCCN Cutaneous Melanoma. Version 2.2023 (NCCN, 2023g)   |
| LDH            | Workup and/or surveillance may be indicated for: Follicular lymphoma, Extranodal marginal zone B-cell lymphoma, Gastric and non-gastric MALT, Nodal marginal zone lymphoma, Splenic marginal zone lymphoma, Mantle cell lymphoma, Diffuse large B-cell lymphoma, Burkitt lymphoma, AIDS-related B-cell lymphomas, Post-transplant lymphoproliferative disorders, Castleman’s disease, lymphoblastic lymphoma. Workup for Hodgkin Lymphoma | NCCN B-cell Lymphomas. Version 2.2022, (NCCN, 2023a). Hodgkin Lymphoma Version 2.2023 (NCCN, 2023l) |
| LDH            | Testicular cancer workup (for suspicious testicular mass”); LDH,  | NCCN Testicular Cancer. Version 12.2023(NCCN, 2023ah)   |

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|            | along with other tumor markers are critical in diagnosing GCTs, determining prognosis and assessing treatment outcomes  |  |
| LDH        | Osteosarcoma and Ewing Sarcoma workup and/or surveillance. Elevated levels at initial diagnosis and initial recurrence are considered adverse prognostic indicators. ALP measurement may have clinical relevance and should be done before treatment. | NCCN Bone Cancer Version 2.2023 (NCCN, 2023b)  |
| LDH        | Multiple Myeloma initial workup, follow-up/surveillance and staging   | NCCN Multiple Myeloma. Version 3.2023 (NCCN, 2023p)  |
| LDH        | Initial Workup for Systemic Light Chain Amyloidosis   | NCCN Systemic Light Chain Amyloidosis Version 2.2023 (NCCN, 2023ae)  |
| LDH        | Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma essential workup  | NCCN Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma Version 1.2023 (NCCN, 2023al)                           |
| LDH        | Initial evaluation for myelodysplastic syndromes or in the workup of suspected myeloproliferative neoplasms; initial evaluation for cytopenia and myelodysplasia  | NCCN Myelodysplastic Syndromes Version 3.2023 (NCCN, 2023q)<br>Myeloproliferative Neoplasms Version 3.2022 (NCCN, 2023s) |
| LDH        | Prognostic factor, “one of the most important”  | NCCN Small Cell Lung Cancer Version 3.2023 (NCCN, 2023ad)  |
| LDH        | Workup for primary cutaneous lymphomas  | NCCN Primary Cutaneous Lymphoma Version 1.2023 (NCCN, 2023aa)  |
| LDH        | T-cell lymphomas – workup, prognosis (except Breast Implant-Associated ALCL). May be used in staging breast implant-associated ALCL   | NCCN T-Cell Lymphomas Version 1.2023 (NCCN, 2023ag)  |
| Troponin T | Diagnostic workup and staging for systemic light chain amyloidosis  | Systemic Light Chain Amyloidosis Version 2.2023, NCCN, 2023ae)   |
| Tryptase   | Serum total tryptase is a WHO diagnostic criterion for systemic mastocytosis. Serum tryptase may also be useful in risk classification and monitoring response to therapy   | NCCN Systemic Mastocytosis Version 2.2022 (NCCN, 2023af)   |
| Tryptase   | Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes - Initial evaluation  | NCCN Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes Version 2.2022 (NCCN, 2023r)          |

The NCCN guidelines on ovarian cancer (version 2.2020) also stated that certain biomarker panels such as OVA1, ROMA (Risk of Ovarian Malignancy Algorithm) and OVERA have been approved by the FDA for “estimating risk of ovarian cancer in women with an adnexal mass for which surgery is planned, and have not yet been referred to an oncologist”. However, “currently, the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed adnexal/pelvic mass.” The NCCN further notes that CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 (DcR3), and spondin-2 “do not increase early enough to be useful in detecting early-stage ovarian cancer” (NCCN, 2023x).

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Monitoring of disease relapse with any tumor markers is not recommended for breast cancer. Ki-67 is not recommended for any assessment of breast cancer. Testing for immunohistochemical markers such as ER/PR and HER2 is recommended for assessment of breast cancer (NCCN, 2023c).

Cardiac biomarkers such as troponin I or T and BNP (or NT-proBNP) may be considered important predictors of outcome of systemic light chain amyloidosis (NCCN, 2023ae).

The 2020 NCCN Guidelines on Hepatocellular Carcinoma states, “serum biomarkers such as AFP may incrementally improve the performance of imaging-based screening and surveillance, but their cost effectiveness has not been established; their use as supplementary surveillance tests is optional.” (NCCN, 2023k)

For Merkel Cell Carcinoma, the NCCN stated a neuroendocrine marker such as chromogranin, CD56, neurofilament protein, neuron-specific enolase, or synaptophysin may be used (NCCN, 2022l). Small cell lung cancers (SCLCs) also stain positive for biomarkers of neuroendocrine differentiation but cannot be used to differentiate SCLCs from NSCLCs (NCCN, 2023m).

NCCN recommends against using OVA1 or OvaSure as screening for ovarian cancer (NCCN, 2023t, 2023x).

## **International Mesothelioma Interest Group**

The Interest Group considers the following biomarkers to be “very useful”: Calretinin Cytokeratin 5/6, WT1, Podoplanin (D2-40) (for epitheloid mesothelioma), Claudin 4, MOC31, B72.3, CEA, BER-EP4, BG8 (Lewis<sup>Y</sup>), TTF-1, and Napsin A (for lung adenocarcinoma) (Husain et al., 2018).

## **North American Neuroendocrine Tumor Society**

NANETS notes that although most of its expert panel’s members measure CgA and/or pancreastatin, a majority of them believed that “these tumor markers assist in patient management only occasionally or rarely”. No consensus was reached on whether these tumor markers should be routinely measured (NANETS, 2017).

In 2020, NANETS published a guideline focusing on the “Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors”. In it, they remark that “Use of nonspecific tumor markers such as CgA, pancreastatin (PcSt), and others is not recommended for routine use in patients with pNETs”, stating that these marker analyses “rarely, if ever” influence treatment (Halfdanarson et al., 2020)

## **American Thyroid Association (ATA)**

The ATA cannot recommend for or against routine measurement of serum calcitonin in patients with thyroid nodules. Furthermore, the ATA cautions that unusual levels of calcitonin may occur with a variety of other conditions apart from MTC, and notes that calcitonin levels are often elevated in young children and males compared to females (Haugen et al., 2016; Wells et al., 2015).

## **American Association for the Study of Liver Diseases**

The AASLD states that ultrasound surveillance for hepatocellular carcinoma may be done with or without AFP, every 6 months. However, other biomarkers apart from AFP need more research and validation (AASLD, 2018).

## **European Association for the Study of the Liver**

EASL stated “Tumor biomarkers for accurate early detection are still lacking. The data available show that the biomarkers tested (i.e. AFP, AFP-L3 and DCP) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC (evidence low) (EASL, 2018).”

# Serum Tumor Markers for Malignancies AHS – G2124

## American College of Radiology

The ACR recommends against screening serum markers for the diagnosis of hepatic fibrosis and cirrhosis disease and disease progression, stating that “although a variety of serum markers exist for this purpose, they are inaccurate for intermediate stages of fibrosis, and imaging by conventional ultrasound (US), CT, and MRI is frequently performed to assess for cirrhosis and its complications in this patient population,” (ACR, 2019).

## Applicable State/Federal Regulations

### 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 (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81479, 81500, 81503, 81538, 81599, 82105, 82107, 82232, 82308, 82378, 83520, 83521, 83615, 83789, 83880, 83950, 83951, 84075, 84078, 84080, 84484, 84702, 84703, 84704, 84999, 86300, 86301, 86304, 86305, 86316, 86336, G0327, 0003U, 0092U, 0163U, 0404U*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Yang, X., Yang, Y., Li, Z., Cheng, C., Yang, T., Wang, C., Liu, L., & Liu, S. (2015). Diagnostic value of circulating chromogranin for neuroendocrine tumors: a systematic review and meta-analysis. *PLoS One*, 10(4), e0124884. <https://doi.org/10.1371/journal.pone.0124884>

Medical Director review 4/2021

Medical Director review 8/2022

Medical Director review 7/2023

## Policy Implementation/Update Information

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- 1/1/2019 New policy developed. BCBSNC will provide coverage for serum tumor markers for malignancies when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
- 5/14/19 Reviewed by Avalon 1<sup>st</sup> Quarter 2019 CAB. Updated Policy Guidelines and added State/Federal Regulations section. Updated NCCN Table. Added the following CPT & PLA codes to the “Billing/Coding section: 84432, 84702, 84703, 84704, 84999, 86152, 86153, 86300, 86301, 86304, 86316, 86336, 86800, 0003U, 1121U, 0045U, 0067U. Added the following indications to When Covered criteria: Castleman’s disease workup, AML workup, Hairy Cell Leukemia workup, Tryptase, and Systemic Mastocytosis. Added Apify and Overa (OVA1 Next Generation) to When Not covered section. Medical Director review 5/2019. (lpr)
- 10/1/19 Specialty Matched Consultant Advisory Panel review 8/21/2019. Reviewed by Avalon 2<sup>nd</sup> Quarter 2019 CAB. Under “When Covered” section: K.d. added ovarian cancer workup. Under “When Not Covered” section: added investigational statement “The use of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) as serum tumor markers is considered investigational; added AFP-L3 (Lens culinaris agglutinin reactive AFP) as investigational; added REVEAL Lung Nodule Characterization as investigational. Under Billing/Coding section: deleted coding table. Added CPT codes 81500, 81538, 81551, 82107, 83950, 85415, 86305, PLA code 0092U; Deleted CPT codes 81525, 81539. Medical Director review 8/2019. (lpr)
- 10/1/2019 Policy Statement revised to read: BCBSNC will provide coverage for serum tumor markers for malignancies when it is determined the medical criteria and guidelines below are met. Wording changed in the When Covered section. “Medically Necessary” changed to “Reimbursement is allowed...” Wording revised in the Not Covered section. “Investigational” changed to read “Reimbursement is not allowed...”. Notification given 10/1/2019 for effective date 12/2/2019. (an)
- 5/12/20 Reviewed by Avalon 1<sup>st</sup> Quarter 2020 CAB. Medical Director review 4/2020. Added CPT codes 84075, 84078, 84080, 84484, 0163U and deleted CPT codes 86152, 86153 in Billing/Coding section. Added several indications to Reimbursement allowed section. References updated. (lpr)
- 9/8/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No changes to policy statement. (lpr)
- 5/4/21 Reviewed by Avalon 1<sup>st</sup> Quarter 2021 CAB. Medical Director review 4/2021. Under “When Covered” section F. (g) (Cancer Antigen 19-9) and H.(g) (Carcinoembryonic Antigen CEA), added covered indication: epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer workup and monitoring; Under section K. (a) removed word “histopathologies” for clarity. Also under “When Covered” section, removed language in



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sections M. (PSA) and moved to AHS-G2008 Prostate Cancer Screening; and N. (Thyroglobulin TG) and moved to AHS-G2045 Thyroid Disease Testing. Under “When Not Covered” section, deleted the following tests since they have been removed from the market: EPCA-2, Advise MCV, Advise PG, ConfirmMDx, DCIS Recurrence Score, Postop Px(Prostate PX), Previstage GCC, ProOnc Tumor Source Dx test, Prostate Px and Proveri Prostate cancer assay, Response Dx colon, UroCor cytology panels. Under Billing/Coding section: removed CPT codes 81551, 84152, 84153, 84154, 84432, 86800, 0021U, 0045U. Updated Policy Guidelines and references. (lpr)

- 9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. No change to policy statement. (lpr)
- 9/13/22 Reviewed by Avalon 2<sup>nd</sup> Quarter 2022 CAB. Medical Director review 8/2022. Updated When Covered section: added medically necessary coverage criteria for full adoption of AHS policy. Updated policy guidelines and references. Under Billing/Coding section, removed CPT 82397, 0067U and added CPT 83521, 83880, G0327, 81479. (lpr)
- 8/15/23 Reviewed by Avalon Q2 2023 CAB. Medical Director review 7/2023. Updated description section, policy guidelines and references. Re-organized “When Covered” section for focus on the cancer and then all appropriate biomarkers. Clarified “When Covered” section. Deleted CPT code 85415 from Billing/Coding section. (lpr)
- 9/29/23 Added PLA code 0404U to Billing/Coding section for 10/1/23 code update. (lpr)

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