

## Corporate Medical Policy

### Serum Tumor Markers for Malignancies AHS – G2124

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#### 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 used to help detect, diagnose, and manage some types of cancer (Hottinger & Hormigo, 2011).

**\*\*\*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 use of the serum tumor for the following indications:
  - A. Alpha fetoprotein (AFP) testing for:
    - a) Suspected germ cell tumor metastasis from an unknown primary site:
      1. Testicular mass
      2. Pelvic mass
      3. Mediastinal mass
      4. Peritoneal mass
      5. Retroperitoneal mass
      6. Intracranial mass
      7. Sacrococcygeal mass
    - b) For diagnosis, staging, surveillance, and/or monitoring therapy in the following:
      1. Hepatocellular carcinoma
      2. Thymoma
      3. Thyroid carcinoma
      4. Testicular germ cell tumor/carcinoma
      5. Ovarian germ cell tumor/carcinoma
      6. Saccrococcygeal teratoma

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- B. Alkaline Phosphatase (ALP)
  - a) Bone Cancers
- C. Beta human chorionic gonadotropin (beta-HCG) for:
  - a) Suspected germ cell tumor metastasis from an unknown primary site:
    - 1. Testicular mass
    - 2. Pelvic mass
    - 3. Mediastinal mass
    - 4. Peritoneal mass
    - 5. Retroperitoneal mass
    - 6. Intracranial mass
    - 7. Sacrococcygeal mass
  - b) For diagnosis, staging, surveillance, and/or monitoring therapy in the following:
    - 1. Thymoma
    - 2. Thyroid carcinoma
    - 3. Testicular germ cell tumor/carcinoma
    - 4. Ovarian germ cell tumor/carcinoma
    - 5. Saccrococcygeal teratoma
- D. Beta-2 microglobulin (B2M) for:
  - a) Multiple Myeloma initial diagnostic workup and follow-up/surveillance
  - b) Non-Hodgkin's Lymphoma workup
  - c) Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma workup
  - d) Castleman's Disease workup
  - e) Follicular Lymphoma
  - f) Mantle Cell Lymphoma
  - g) Diffuse B-Cell Lymphoma
  - h) AIDS related B-cell Lymphoma
  - i) Lymphoblastic Lymphoma
  - j) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
  - k) Systemic Light Chain Amyloidosis initial diagnostic workup
- E. Cancer Antigen 15-3 and 27.29 (CA 15-3 and 27-29) for:
  - a) Metastatic breast cancer monitoring during active therapy
- F. Cancer Antigen 19-9 (CA 19-9) for:
  - a) Pancreatic adenocarcinoma workup, post treatment and surveillance
  - b) Gallbladder cancer workup and surveillance
  - c) Hepatobiliary carcinoma workup and post biliary decompression
  - d) Intrahepatic and extrahepatic cholangiocarcinoma workup
  - e) Pancreatic or biliary tract primary workup
  - f) Small bowel adenocarcinoma workup
  - g) Epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer workup and monitoring
- G. Cancer Antigen 125 (CA-125) for:
  - a) Epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer workup and monitoring
  - b) BRCA mutation-positive individuals age 30 and older who have not elected risk-reducing salpingo-oophorectomy (RRSO)
  - c) Borderline epithelial tumors (low malignant potential) monitoring
  - d) Endometrial Cancer for workup and surveillance
  - e) Occult Primary - adenocarcinoma or carcinoma not otherwise specified workup
- H. Carcinoembryonic Antigen (CEA) for:
  - a) Colorectal carcinoma workup and surveillance every 3-6 months for 2 years, then every 6 months for a total of 5 years
  - b) Hepatobiliary Cancers including:

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- Intrahepatic Cholangiocarcinoma workup
  - Extrahepatic Cholangiocarcinoma workup
  - Gallbladder Cancer workup and surveillance
  - c) Medullary thyroid carcinoma workup and surveillance
  - d) Mucinous carcinoma of the ovary workup
  - e) Small Bowel adenocarcinoma workup
  - f) Rectal cancer workup
  - g) Epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer workup and monitoring
- I. Chromogranin A (CgA) for:
- a) Neuroendocrine tumors of:
    - gastrointestinal tract
    - lung
    - thymus (carcinoid tumors) evaluation
- J. Calcitonin (CALCA) expression for:
- a) Medullary thyroid carcinoma workup, surveillance and post-surgical evaluation
  - b) Adenocarcinoma or anaplastic/undifferentiated tumors of the head and neck workup
- K. Inhibin (INHA) expression for:
- a) Undiagnosed pelvic mass workup for clinical indication to assess for LCOC (Less Common Ovarian Cancers) and pregnancy
  - b) Granulosa cell tumors observation
- L. Lactate dehydrogenase (LDH) for:
- a) Acute Lymphoblastic Leukemia (ALL) workup and Pediatric Acute Lymphoblastic Leukemia (PED-ALL)
  - b) Acute Myeloid Leukemia (AML) workup
  - c) B-Cell lymphoma workup (including Castleman's disease)
  - d) Chronic Lymphocytic Leukemia workup
  - e) Hairy Cell Leukemia workup
  - f) Hodgkin's lymphoma workup
  - g) Ovarian cancer workup
  - h) Primary cutaneous B-cell Lymphoma workup
  - i) Non-Hodgkin's Lymphoma workup
  - j) Testicular germ cell tumors staging, prognosis before chemotherapy and/or additional surgery, monitoring response to treatment and detecting recurrence
  - k) Osteosarcoma and Ewing Sarcoma workup
  - l) Multiple Myeloma workup, follow-up/surveillance and staging
  - m) Myelodysplastic syndromes (initial evaluation)
  - n) Myeloproliferative neoplasms (initial evaluation)
  - o) Cutaneous melanoma
  - p) Kidney cancer
  - q) Small cell lung cancer
  - r) Systemic Light Chain Amyloidosis workup
  - s) Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma workup
- M. Troponin T
- a) Systemic Light Chain Amyloidosis diagnostic workup
- N. Tryptase
- a) Systemic Mastocytosis

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

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Reimbursement is not allowed for any of the tumor markers listed above for any cancer indication not otherwise listed and all other applications of serum tumor markers, including but not limited to:

1. A2-PAG (pregnancy associated alpha2 glycoprotein)
2. BCM (breast cancer mucin)
3. CA-50 (cancer antigen 50)
4. CA 72-4 (cancer antigen 72-4)
5. CA-242 (cancer antigen 242)
6. CA-195 (cancer antigen 195)
7. CA-549 (cancer antigen 549)
8. CAM 17-1 (antimucin monoclonal antibody)
9. CAM-26 (carcinoma associated mucin antigen)
10. CAM-29 (carcinoma associated mucin antigen)
11. CA-SCC (squamous cell carcinoma antigen)
12. CAR-3 (antigenic determinant recognized by monoclonal antibody AR-3)
13. Circulating extracellular domain of HER2 (human epidermal growth factor receptor 2)
14. DMSA (pentavalent technetium-99mm dimercaptosuccinic acid)
15. Du-PAN-2 (sialylated carbohydrate antigen)
16. Ki-67 antigen for esophageal or breast cancer
17. MCA (mucinous carcinoma associated antigen)
18. MSA (mammary serum antigen)
19. NSE (neuron specific enolase)
20. P-LAP (placental alkaline phosphatase)
21. PNA-ELLA (peanut lectin bonding assay)
22. P53 (monoclonal antibody)
23. SLEX (sialylated Lewis-X antigen)
24. SLX (sialylated SSEA-1 antigen)
25. SPAN-1 (sialylated carbonated antigen SPAN-1)
26. ST-439 (sialylated carbohydrate antigen ST-439)
27. TAG-12 (tumor associated glycoprotein 12)
28. TAG 72 (tumor associated glycoprotein 72)
29. TAG-72-3 (tumor associated glycoprotein 72-3)
30. TNF-alpha (TNF-a) (tumor necrosis factor alpha)
31. TATI (tumor associated trypsin inhibitor)
32. TPA (tissue polypeptide antigen)
33. TPS (tissue polypeptide specific antigen)

The following tests, including but not limited to, are **investigational** for all indications, as there is insufficient evidence to support the use of these tests.

1. AFP-L3 (Lens culinaris agglutinin reactive AFP)
2. Apifyny®
3. BeScreened™ (BeScreened™- CRC)
4. Carcinoembryonic antigen cell adhesion molecule 6 (CEACAM6) for predicting the risk of breast cancer.

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5. Carcinoembryonic antigen cellular adhesion molecule-7 (CEACAM-7) expression as a predictive marker for rectal cancer recurrence
6. CellSearch®
7. Cofilin (CFL1) as a prognostic and drug resistance marker in non-small cell lung cancer.
8. ColonSentry test for screening of colorectal cancer.
9. ColoPrint, CIMP, LINE-1 hypomethylation, and Immune cells for colon cancer.
10. Colorectal Cancer DSA (Almac Diagnostics, Craigavon, UK)
11. DCP (Des-Gamma-Carboxy Prothrombin)
12. HE4 immunoassay
13. HERmark®
14. Human epididymis protein (HE4)
15. Mucin 4 expression as a predictor of survival in colorectal cancer.
16. OncInsights (Intervention Insights, Grand Rapids, MI)
17. OVA1™
18. Ova Check™
19. OvaSure™
20. Overa (OVA1 Next Generation)
21. Panexia test
22. PreOvar test for the KRAS-variant to determine ovarian cancer risk.
23. REVEAL Lung Nodule Characterization
24. ROMA™
25. VeriStrat®
26. Xpresys Lung Test

The use of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) as serum tumor markers is considered **investigational**.

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 tumor (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

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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).

## **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  $< 10 \mu\text{g/L}$  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; 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).

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

b-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 (Goff, 2016; Harvey, 2019). 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).

## **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, Dong, LeBlanc, Daborowski, & Vachet, 2017). Elevated serum levels of B2M have been associated with cancers such as multiple myeloma or chronic leukocytic leukemia (Berrebi et al., 2009).

## **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

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(Tuttle, 2018; R.M. Tuttle, 2020). However, the ATA has noted this biomarker to have significant uncertainties (Haugen et al., 2016; Wells et al., 2015)

## **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).

## **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 damage or cigarette smoking may affect CEA levels as well (F.Uelnd, 2017; F.R. Ueland, Li, Andrew John, 2020). 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 (Chan, 2017; Strosberg, 2017). However, this biomarker is highly variable (Strosberg, 2017, 2019).

## **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, Bombardieri, Pitzalis, & Mauro, 2017). Increased LDH is found in several different cancers, such as B-cell lymphomas and osteosarcomas (NCCN, 2020t).

## **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, but this marker is noted to not be very specific and may be negative in patients with active tumors (Gershenson, 2017, 2020). 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).

## **Urokinase plasminogen activator**

Urokinase plasminogen activator (uPA) is a serine protease with an important role in cancer invasion and metastases (Stephens, Brunner, Janicke, & Schmitt, 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., 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

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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, 2019).

## 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, 2020, 2021).

## Clinical Validity and Utility

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, etc) and ability to improve clinical outcomes and decision-making is critical (Febbo et al., 2011).

Kim et al 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 and elevated CA 19-9 was found to be associated with high-risk or advanced adenoma, CRC, and advanced colorectal neoplasia (Kim et al., 2017).

Li et al performed a study assessing the association between CA 15-3 and CEA with breast cancer. 36 studies with 12933 subjects were included in the meta-analysis, and elevated levels of both markers were associated with poorer disease-free survival (DFS) and overall survival (OS) rates. The hazard ratio of CA 15-3 in OS rates was 2.03 and 1.79 for CEA. The hazard ratio for CA 15-3 in DFS rates was 1.56 and 1.77 for CEA (X. Li et al., 2018).

Liu et al 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 2 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 2 months but did not see their LDH decrease had an OS rate of 4 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).

A meta-analysis performed by Yang et al assessed the association of CgA with neuroendocrine tumors. 13 studies totaling 1260 patients (967 healthy controls) were included in the analysis, 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 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).

Isaakson et al 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



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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).

A study was performed by Feng et al that focused on the diagnostic and prognostic value of CEA, CA 19-9, AFP, and CA125 for early gastric cancer. 587 patients were evaluated, 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).

A study by Schraiber et al assessed AFP’s ability to predict recurrence of hepatocellular carcinoma (HCC) after liver transplant. 206 patients were analyzed, 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 (Schraiber Ldos et al., 2016).

Pre-treatment serum AFP-L3% predicts tumor progression, recurrence and poor clinical outcome (Saito et al., 2012; Song et al., 2002; Zhang et al., 2011), and it has superior prognostic accuracy as a tumor marker compared with AFP or DCP (des- $\gamma$ -carboxy prothrombin) (Beppu et al., 2010; Kobayashi et al., 2007). Nevertheless, conflicting data have emerged regarding the ability of pre-treatment serum AFP-L3% to predict disease-free survival (DFS) and overall survival (OS) in HCC. Yi et al performed a meta-analysis of AFP-L3’s accuracy for detection of HCC. 12 studies were evaluated, and the pooled sensitivity was found to be 0.483, the pooled specificity was found to be 0.929, the diagnostic odds ratio was found to be 12.33, and the area under the curve was found to be 0.7564 (Yi, Yu, & Bao, 2013).

Cheng et al. 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).”

Abdel-Aziz et al. performed a study comparing AFP-L3% to AFP as serum markers for HCC. 86 patients with chronic liver diseases were included along with 20 healthy controls. Serum concentrations of AFP, AFP-L3, and p53 protein were measured and correlations were determined. The authors found that AFP-L3% and p53 levels were significantly higher in HCC than non-HCC patients. “ROC curve analysis showed that the highest specificity and sensitivity of the studied parameters are gained at cutoffs of 15%, 120.5 ng/mL, and 0.14 ng/mL for AFP-L3, AFP, and p53; respectively. Combining AFP-L3 and p53 improved sensitivity to 95.4% with a specificity of 85%.” However, the authors concluded: “No significant correlation was found between AFP, AFP-L3%, and p53; however, the simultaneous determination of the three tumor markers yielded a better diagnostic accuracy and sensitivity in the detection of HCCs than each biomarker alone (Abdel-Aziz et al., 2016).”

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

Ryu et al. 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). 1182 consecutive patients underwent hepatic resection and surgical microwave

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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 5 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 5 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).”

Yamao et al. performed a study assessing the significance of high AFP-L3 with low AFP in HCC patients. 283 patients were divided into high AFP-L3 (>10%, n = 24) and low ( $\leq$ 10%, n = 249). Overall survival (OS) and 2-year recurrence rates were compared. The OS and recurrence rates were both found to be significantly worse than the low AFP-L3 group (Yamao et al., 2019).

Caviglia et al. conducted a study evaluating AFP, AFP-L3, and DCP as detection tools for HCC. 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).

Lucarelli et al. evaluated CA 15-3, CA125, and B2M as biomarkers for renal cell carcinoma (RCC). 332 patients undergoing nephrectomy for RCC were analyzed. 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).

J. Li et al. evaluated b-HCG as a marker for colorectal cancer (CRC). 50 patients out of 136 patients expressed b-HCG at the “invasive front”. The authors found that higher expression of b-HCG to be associated with worse prognosis than those with low b-HCG expression and that b-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 b-HCG expression level and tumor invasion in early-stage CRC patients (J. Li et al., 2018).

Seo et al. examined the prognostic value of B2M for diffuse large B-cell lymphoma. 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).

Farkkila et al. evaluated anti-Müllerian hormone (AMH) and inhibin B in the context of ovarian adult-type granulosa cell tumors (AGCTs). 560 samples were 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).

Tormey et al. evaluated measurement of serum calcitonin in patients presenting with thyroid nodules. 44 patients were evaluated, and 33 of them did not have a “detectable serum calcitonin”, noting that the 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 7 cases of medullary thyroid cancer (MTC) were diagnosed. The authors recommended not screening routinely for MTC (Tormey, Byrne, Hill, Sherlock, & Thompson, 2017).

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Chen et al. analyzed four serum tumor markers in patients with ovarian tumors. HE4, CA-125, CA19-9, and CEA were all studied. 386 healthy controls, 262 patients with benign ovarian tumors, and 196 patients with malignant ovarian tumors were evaluated. 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 (F. Chen, Shen, Wang, Cai, & Huang, 2018).

Feng et al. investigated the clinical significance of serum EGFR mutation as well as other markers in predicting tyrosine kinase inhibitor (TKI) efficacy in patients with lung adenocarcinoma. 90 patients were included, with 51 receiving an EGFR-TKI drug (oral gefitinib). The authors found serum CA19-9, CA24-2, and CEA levels to be significantly correlated with serum EGFR mutation. After receiving gefitinib, the progression-free survivals of patients with high serum level of CEA, CA19-9, or EGFR mutation was higher than those of other patients (L. X. Feng et al., 2019).

Bind et al. 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 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, Mishra, Kumar, Misra, & Singh, 2021)

Proteomic analyses have been performed in cancer patients to assess unusual levels of protein regulation. A study by Chen et al 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. 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).

### Practice Guidelines and Position Statements

#### National Academy of Clinical Biochemistry (NACB)

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 with ultrasound to inform detection and management, and AFP concentrations may provide prognostic information in untreated patients.

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Monitoring of disease should include measurement of AFP. However, other liver biomarkers such as Glypican-3 cannot be recommended at this time as further research is needed.

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 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 also 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. However, the NACB also did not make any recommendations on PSA screening for prostate cancer. PSA measuring is recommended to monitor disease status after treatment.

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. 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) (Allison et al., 2020; Gilligan et al., 2010; L. N. Harris et al., 2016; Kindler et al., 2018; Krop et al., 2017; Sepulveda et al., 2017; Stoffel et al., 2018; Van Poznak et al., 2015)**

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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 surveillance after “definitive therapy for NSGCT” 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).

In 2007, ASCO released an update of recommendations for the use of tumor markers in breast cancer (Harris et al., 2007).

CA 15-3 and CA 27.29 have insufficient data to recommend for screening, staging, monitoring, or diagnosis. These biomarkers, along with CEA, may be used in conjunction with other assessments for monitoring patients with metastatic disease during active therapy, but not alone. Increasing CA 15-3 or CA 27.39 may indicate treatment failure. CEA is not recommended for screening, diagnosis, staging, or routine surveillance after primary therapy (Harris et al., 2007).

ER, HER2 expression or amplification, PgR should be measured on “every primary invasive breast cancer and may be measured on metastatic lesions if the results would influence treatment planning”. HER2 should be used to identify good candidates for trastuzumab but should not be used to guide use of taxane chemotherapy in the adjuvant setting. HER2 should not be used to select endocrine therapy. Finally, measuring the extracellular domain of HER2 is not recommended (Harris et al., 2007).

Measurement of circulating tumor cells (CTCs) is not recommended. Insufficient data to recommend the use of flow cytometry-based markers, p53, cathepsin D, cyclin E, proteomic analysis, bone marrow micrometastases and immunohistochemically based markers of proliferation. uPA/PAI-1 measurement with ELISA may be used for prognosis determination. IHC for these biomarkers is not accurate (Harris et al., 2007).

In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen.

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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 on the basis of 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.

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

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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) (Detterbeck, Mazzone, Naidich, & Bach, 2013)**

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

### **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 1 combines CA-125, menopausal status and the ultrasound score).

The NICE guidelines did not recommend serum HE4 as a serum tumor marker for ovarian cancer.

### **National Comprehensive Cancer Network (NCCN, 2020t )**

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Serum Tumor Marker	Recommendation	Source
AFP	Hepatocellular workup (HCC). AFP for surveillance is optional	NCCN Hepatobiliary Cancers Version 5.2020 (NCCN, 2020q)
AFP	Intrahepatic cholangiocarcinoma workup	NCCN Hepatobiliary Cancers Version 4.2020 (NCCN, 2020q)
AFP	Women under 35 years with a pelvic mass	NCCN Ovarian Cancer Version 2.2020 (NCCN, 2021d)
AFP	Thymomas and thymic carcinoma initial workup  Both seminoma and nonseminoma, serum prognostic factor and contribute to diagnosis and staging	NCCN Thymomas and thymic carcinomas Version 1.2020 (NCCN, 2021ag)  NCCN Testicular Cancer Version 1.2021 (NCCN, 2020af)
Alkaline Phosphatase (ALP)	Should be assessed prior to treatment for bone cancers	NCCN Bone cancers Version 1.2020 (NCCN, 2020c)
Beta-HCG	Testicular cancer workup, beta hCG need to be assessed as it is a prognostic factor and contribute to diagnosis and staging. Assessed pre- and post-orchietomy	NCCN Testicular Cancer Version -1.2021 (NCCN, 2019q, 2020af)
Beta-HCG	Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer workup as clinically indicated	NCCN Ovarian Cancer Version 2.2020 (NCCN, 2019l, 2020x, 2021d)
Beta-HCG	Mediastinal mass/thymomas and thymic carcinoma workup	NCCN Thymomas and thymic carcinomas Version 1.2021 (NCCN, 2019r, 2020ag)
Beta-2 microglobulin (B2M)	Multiple myeloma workup and follow-up/surveillance and staging, solitary plasmacytoma (or solitary plasmacytoma with minimal marrow involvement), smoldering (asymptomatic) myeloma	NCCN Multiple Myeloma Version 4.2021 (NCCN, 2019j, 2021c)
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 4.2020 (NCCN, 2020b, 2021a)
Beta-2 microglobulin (B2M)	Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma essential workup, prognostic facto	NCCN Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma Version 1.2021 (NCCN, 2019s, 2020aj)
Beta-2 microglobulin (B2M)	Prognostic information ("useful under certain circumstances")	NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2021 (NCCN, 2019a, 2020f)



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Beta-2 microglobulin (B2M)	Initial diagnostic Workup	Systemic Light Chain Amyloidosis Version 1.2021 (NCCN, 2020ae)
BNP/NT-BNP	Initial diagnostic workup (may be considered)	Systemic Light Chain Amyloidosis Version 1.2021 (NCCN, 2019p, 2020ae)
Cancer Antigen 15-3 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 6.2020 (NCCN, 2020d, 2020e)
Cancer Antigen 19-9	Pancreatic adenocarcinoma pre-op workup, post treatment, and surveillance. Levels may be elevated up to 2 years before pancreatic CA diagnosis	NCCN Pancreatic Adenocarcinoma Version 1.2021 (NCCN, 2020y)
Cancer Antigen 19-9	Workup and surveillance for small bowel adenocarcinoma	NCCN Small Bowel Adenocarcinoma Version 2.2020 (NCCN, 2020ad)
Cancer Antigen 19-9	Gallbladder cancer workup 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	NCCN Hepatobiliary Cancers Version 5.2020 (NCCN, 2020q)
Cancer Antigen 19-9	Intrahepatic or extrahepatic cholangiocarcinoma workup. CA 19-9 is a baseline test and should not be done to confirm diagnosis	NCCN Hepatobiliary Cancers Version 5.2020 (NCCN, 2020q)
CA-125	Epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer workup, for “suspicious or palpable pelvic mass” or “symptoms without source of malignancy such as bloating or abdominal pain” as clinically indicated, prior to each chemotherapy, and monitoring. Borderline epithelial tumors (low malignant potential) monitoring- CA-125 every visit if initially elevated. Recommends CA-125 on workup if “clinically indicated” after clinical presentation	NCCN Ovarian Cancer Version 2.2020 (NCCN, 2019l, 2020x, 2021d)
CA-125	BRCA mutation-positive individuals – for those individuals who have not elected RRSO, serum CA-125 screening may be considered at the clinician’s discretion starting age 30-35 years	NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 2.2021 (NCCN, 2019f,2020n)
CA-125	Endometrial carcinoma CA-125 Consider CA-125 for suspected extrauterine disease, serous carcinoma, clear cell carcinoma, carcinosarcoma,	NCCN Uterine Neoplasms V 1.2021 (NCCN, 2020ai)

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	undifferentiated/dedifferentiated carcinoma; surveillance if initially elevated	
CA-125	Occult Primary - adenocarcinoma or carcinoma not otherwise specified workup for females	NCCN Occult Primary Version 1.2021 (NCCN, 2020w)
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. Not recommended beyond 5 years. Suspected or proven metastatic synchronous adenocarcinoma workup  Pedunculated or sessile polyp with invasive cancer but fragmented specimen/unknown margin or unfavorable histology	NCCN Colon Cancer Version 4.2020 (NCCN, 2019c, 2020h)
CEA	Workup for small bowel adenocarcinoma	NCCN Small Bowel Adenocarcinoma Version 2.2020 (NCCN, 2019o, 2020ad)
CEA	Pedunculated or sessile polyp with invasive cancer but fragmented specimen/unknown margin or unfavorable histology  Workup for: rectal cancer appropriate for resection, suspected or proven metastatic synchronous adenocarcinoma	Rectal Cancer Version 6.2020 (NCCN, 2019n, 2020ac)
CEA	Intrahepatic (such as isolated intrahepatic mass) and extrahepatic cholangiocarcinoma workup. CEA is a baseline test and should not be done to confirm diagnosis	NCCN Hepatobiliary Cancers Version 5.2020 (NCCN, 2019g, 2020q)
CEA	Gallbladder cancer workup and surveillance. CEA is a baseline test and should not be done to confirm diagnosis	NCCN Hepatobiliary Cancers Version 5.2020 (NCCN, 2019g, 2020q)
CEA	Thyroid carcinoma – medullary carcinomas workup and surveillance; surveillance every 6-12 mo.	NCCN Thyroid Carcinoma Version 2.2020 (NCCN, 2020ah)
CEA	Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer workup for suspicious or palpable pelvic mass or symptoms without source of malignancy such as bloating or abd pain as clinically indicated.	NCCN Ovarian Cancer Version 2.2020 (NCCN, 2019i, 2021d)
CgA	Neuroendocrine tumors of: gastrointestinal tract, lung, thymus (carcinoid tumors) evaluation. CgA is one of a set of tumor markers that may	NCCN Neuroendocrine Tumors. Version 2.2020 (NCCN, 2020v)

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	be used to establish neuroendocrine differentiation	
Calcitonin	Thyroid carcinoma - medullary carcinoma workup, post-surgical evaluation, and surveillance (surveillance every 6-12 mo.)	NCCN Thyroid carcinoma - medullary carcinoma Version 2.2020 (NCCN, 2019j, 2021c)
Hcg	May be evaluated during workup	NCCN Gestational Trophoblastic Neoplasia Version 3.2020
Hepatitis B Panel	Workup for chronic myeloid leukemia	NCCN Chronic Myeloid Leukemia Version 2.2021 (NCCN, 2019b, 2020g)
IGF	May be considered for evaluation of pituitary tumor (category 28)	NCCN Neuroendocrine Tumors Version 2.2020
IgM	Assessment of this immunoglobulin is essential for management of Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma	NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2020 (NCCN, 2019j, 2021c)
INHA	Undiagnosed pelvic mass workup to assess for LCOH (Less Common Ovarian Histopathologies) and pregnancy	NCCN Ovarian Cancer Version <del>3.2017</del> 2.2020 (NCCN, 2019l, 2020x, 2021d)
INHA	Inhibin levels can be followed if initially elevated for granulosa cell tumors	NCCN Ovarian Cancer Version 2.2020
LDH	Acute Lymphoblastic Leukemia (ALL) workup as part of a tumor lysis syndrome panel	NCCN Acute Lymphocytic Leukemia Version 2.2020
LDH	Acute myeloid leukemia workup	NCCN Acute Myeloid Leukemia. Version 2.2021
LDH	Primary cutaneous B-cell Lymphoma workup	NCCN Primary Cutaneous B-cell lymphomas. Version 2.2020
LDH	Chronic lymphocytic leukemia workup for histologic transformation (Richter's) and progression; workup for tumor lysis syndrome	NCCN Chronic lymphocytic leukemia/small lymphocytic Leukemia. Version 1.2020
LDH	Hairy cell leukemia workup	NCCN Hairy Cell Leukemia. Version 2.2020
LDH	Workup 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	NCCN B-cell Lymphomas. Version 1.2020

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LDH	Testicular cancer workup.; LDH, along with other tumor markers are critical in diagnosing GCTs, determining prognosis and assessing treatment outcomes	NCCN Testicular Cancer. Version 1.2021
LDH	Osteosarcoma and Ewing Sarcoma workup. Elevated levels at initial diagnosis and initial recurrence are considered adverse prognostic indicators	NCCN Bone cancers. Version 1.2020
LDH	Multiple Myeloma workup, follow-up/surveillance and staging	NCCN Multiple Myeloma. Version 4.2021
PD-L1	May be considered to assess response to PD-1 inhibitors. Other biomarkers such as CEA are of unknown utility.	NCCN Esophageal and Esophagogastric Junction Cancers Version 2.2020
PD-L1	May be considered to assess response to PD-1 inhibitors.	NCCN Gastric Cancer Version 2.2020
Soluble mesothelin-related peptide	Optional for initial evaluation of malignant pleural mesothelioma	NCCN Malignant Pleural Mesothelioma Version 1.2021 (NCCN, 2019h, 2020r)
Troponin T	Diagnostic workup	Systemic Light Chain Amyloidosis Version 1.202, NCCN, 2020ae)
Tryptase	Assessment of serum tryptase is critical for evaluating staging, prognosis, and diagnosis of systemic mastocytosis	NCCN Systemic Mastocytosis Version 1.2020 (NCCN, 2020)

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, 2021d).

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, 2020d).

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, 2019p, 2020ae).

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, 2020q)

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, 2019i). Small cell lung cancers (SCLCs) also stain positive for biomarkers of neuroendocrine differentiation but cannot be used to differentiate SCLCs from NSCLCs (NCCN, 2019i).

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NCCN recommends against using OVA1 or OvaSure as screening for ovarian cancer (NCCN, 2019k, 2021d).

## **International Mesothelioma Interest Group (Husain et al., 2018)**

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 (Halfdanarson et al., 2020; NANETS, 2017)**

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) (Haugen et al., 2016; Wells et al., 2015).**

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 (AASLD, 2018)**

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, 2018)**

EASL stated “Tumour 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).”

## **American College of Radiology (ACR, 2017)**

The ACR recommends against screening with AFP alone due to “inadequate sensitivity” and state that adding AFP to the ultrasound does not show a significant improvement in HCC detection. The ACR acknowledges a review that showed AFP  $\geq 20$  ng/mL to have a sensitivity of 0.41-0.65 and specificity of 0.80 to 0.94 (ACR, 2017).

## **Applicable State/Federal Regulations**

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.

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## 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: 81500, 81503, 81538, 81599, 82105, 82107, 82232, 82308, 82378, 82397, 82784, 83520, 83615, 83950, 83951, 84075, 84078, 84080, 84484, 84702, 84703, 84704, 84999, 85415, 86300, 86301, 86304, 86305, 86316, 86336, 0003U, 0067U, 0092U, 0163U*

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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# Serum Tumor Markers for Malignancies AHS – G2124

Zhang, X. F., Lai, E. C., Kang, X. Y., Qian, H. H., Zhou, Y. M., Shi, L. H., . . . Yin, Z. F. (2011). Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein as a marker of prognosis and a monitor of recurrence of hepatocellular carcinoma after curative liver resection. *Ann Surg Oncol*, 18(8), 2218-2223. doi:10.1245/s10434-011-1613-7

Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

Medical Director 4/2020

Specialty Matched Consultant Advisory Panel 8/2020

Medical Director 4/2021

## 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 Apifyn 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)



## Serum Tumor Markers for Malignancies AHS – G2124

- 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 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)

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