Serum Tumor Markers for Malignancies AHS – G2124

Description of Procedure or Service

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).

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 (Sturgeon et al., 2008). Markers 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 (Hayes et al., 1996). 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 (Febbo et al., 2011).

Diagnostic – Tumor biomarkers that aid in the diagnosis or subclassification of a particular disease state. Detection of diagnostic biomarkers may result in different management of the disease, but the marker is used primarily to establish that a particular disease is present in the patient sample.

Prognostic – Tumor biomarkers that have an association with some clinical outcomes, such as overall survival or recurrence-free survival, independent of the treatment rendered.

Predictive - Tumor biomarkers predict the activity of a specific class or type of therapy, and are used to help make more specific treatment decisions.

Companion - Biomarkers may be diagnostic, prognostic, or predictive, but are used to identify a subgroup of patients for whom a therapy has shown benefit.

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 (Sturgeon et al., 2008).

***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
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

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. Sacrococcygeal teratoma
   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. Sacrococcygeal 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
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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. 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:
      • 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

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 LCOH (Less Common Ovarian Histopathologies) 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
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  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. Prostate-specific antigen (PSA) for:
   a) Prostate cancer screening, staging, monitoring response to therapy, and detecting disease recurrence

N. Thyroglobulin (TG) and/or Thyroglobulin antibodies for:
   a) Detection of tumor recurrence, post-surgical evaluation, surveillance and maintenance for differentiated thyroid carcinomas
   b) Adenocarcinoma or anaplastic/undifferentiated tumors of the head and neck

O. Troponin T
   a) Systemic Light Chain Amyloidosis diagnostic workup

P. Tryptase
   a) Systemic Mastocytosis

When Serum Tumor Markers for Malignancies is not covered

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-99m dimercaptosuccinic acid)
 15. Du-PAN-2 (sialylated carbohydrate antigen)
 16. EPCA-2 (early prostate cancer antigen)
 17. Ki-67 antigen for esophageal or breast cancer

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18. MCA (mucinous carcinoma associated antigen)
19. MSA (mammary serum antigen)
20. NSE (neuron specific enolase)
21. P-LAP (placental alkaline phosphatase)
22. PNA-ELLA (peanut lectin bonding assay)
23. P53 (monoclonal antibody)
24. SLEX (sialylated Lewis-X antigen)
25. SLX (sialylated SSEA-1 antigen)
26. SPAN-1 (sialylated carbonated antigen SPAN-1)
27. ST-439 (sialylated carbohydrate antigen ST-439)
28. TAG-12 (tumor associated glycoprotein 12)
29. TAG 72 (tumor associated glycoprotein 72)
30. TAG-72-3 (tumor associated glycoprotein 72-3)
31. TNF-alpha (TNF-a) (tumor necrosis factor alpha)
32. TATI (tumor associated trypsin inhibitor)
33. TPA (tissue polypeptide antigen)
34. 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. Apifiny®
3. AviseMCV
4. AvisePG
5. BeScreened™ (BeScreened™- CRC)
6. Carcinoembryonic antigen cell adhesion molecule 6 (CEACAM6) for predicting the risk of breast cancer.
7. Carcinoembryonic antigen cellular adhesion molecule-7 (CEACAM-7) expression as a predictive marker for rectal cancer recurrence
8. CellSearch®
10. ColonSentry test for screening of colorectal cancer.
11. ColoPrint, CIMP, LINE-1 hypomethylation, and Immune cells for colon cancer.
12. Colorectal Cancer DSA (Almac Diagnostics, Craigavon, UK)
13. ConfirmMDx™
14. DCIS Recurrence Score
15. DCP (Des-Gamma-Carboxy Prothrombin)
16. HE4 immunoassay
17. HERmark®
18. Human epididymis protein (HE4)
19. Mucin 4 expression as a predictor of survival in colorectal cancer.
20. OncInsights (Intervention Insights, Grand Rapids, MI)
21. OVA1™
22. Ova Check™
23. OvaSure™
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24. Overa (OVA1 Next Generation)
25. Panexia test
26. Post-Op Px™ (previously known as ProstatePX)
27. PreOvar test for the KRAS-variant to determine ovarian cancer risk.
28. Previstage GCC for colorectal cancer
29. ProOnc TumorSourceDx test (Prometheus Laboratories, San Diego, CA) to identify tissue or origin for metastatic tumor
30. Prostate Px+
31. Proveri prostate cancer assay (PPCA)
32. ResponseDx Colon
33. REVEAL Lung Nodule Characterization
34. ROMA™
35. UroCor cytology panels (DD23 and P53) for bladder cancer
36. VeriStrat®
37. 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**

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

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). 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 nonthrophoblastic 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 (Tuttle, 2018). 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)
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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 (Ueland, 2017). 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 is the primary marker used to evaluate neoplasms (Chan, 2017; Strosberg, 2017). However, this biomarker is highly variable (Strosberg, 2017).

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, 2019).

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). 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).

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, 2018).

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).
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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 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).

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
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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 >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).

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).

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 in 2008 and 2010 (Sturgeon et al., 2010; Sturgeon et al., 2008). They recommended “For testicular cancer, α-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase are recommended for diagnosis/case finding, staging, prognosis determination, recurrence detection, and therapy monitoring. α-Fetoprotein is also recommended for differential diagnosis of nonseminomatous and seminomatous germ cell tumors. Prostate-specific antigen (PSA) is not recommended for prostate cancer screening, but may be used for detecting disease recurrence and monitoring therapy. Free PSA measurement data are useful for distinguishing malignant from benign prostatic disease when total PSA is <10 μg/L. In colorectal cancer, carcinoembryonic antigen is recommended (with some caveats) for prognosis determination, postoperative surveillance, and therapy monitoring in advanced disease. Fecal occult blood testing may be used for screening asymptomatic adults 50 years or older. For breast cancer, estrogen and progesterone receptors are mandatory for predicting response to hormone therapy, human epidermal growth factor receptor-2 measurement is mandatory for predicting response to trastuzumab, and urokinase plasminogen activator/plasminogen activator inhibitor 1 may be used for determining prognosis in lymph node–negative patients. CA15-3/BR27–29 or carcinoembryonic antigen may be used for therapy monitoring in advanced disease. CA-125 is recommended (with transvaginal ultrasound) for early detection of ovarian cancer in women at high risk for this disease. CA-125 is also recommended for differential diagnosis of suspicious pelvic masses in postmenopausal women, as well as for detection of recurrence, monitoring of therapy, and determination of prognosis in women with ovarian cancer.”
NACB also recommended “Alpha-fetoprotein (AFP) may be used in conjunction with abdominal ultrasound for early detection of hepatocellular carcinoma (HCC) in patients with chronic hepatitis or cirrhosis associated with hepatitis B or C virus infection. AFP concentrations >200 microg/L in cirrhotic patients with typical hypervascular lesions >2 cm in size are consistent with HCC. After a diagnosis of HCC, posttreatment monitoring with AFP is recommended as an adjunct to imaging, especially in the absence of measurable disease. Although several urine markers have been proposed for bladder cancer, none at present can replace routine cystoscopy and cytology in the management of patients with this malignancy. Some may, however, be used as complementary adjuncts to direct more effective use of clinical procedures. Although carcinoembryonic antigen and CA 19-9 have been proposed for use gastric cancer and squamous cell carcinoma antigen for use in cervical cancer, none of these markers can currently be recommended for routine clinical use.”

American Society of Clinical Oncology
Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors (Gilligan et al., 2010)

<table>
<thead>
<tr>
<th>Marker Use</th>
<th>Setting</th>
<th>Recommendation</th>
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<td>1. Screening</td>
<td>Asymptomatic adults</td>
<td>Recommendation 1. The Panel recommends against use of STMs or any other blood tests to screen for GCTs.</td>
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<tr>
<td>2. Diagnosis</td>
<td></td>
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<tr>
<td>A. To determine need for orchiectomy</td>
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<td>Recommendation 2A. The Panel recommends drawing blood to measure serum AFP and hCG before orchiectomy for all patients suspected of having a testicular GCT to help establish the diagnosis and interpret postorchiectomy levels. However, the Panel recommends against use of STM assay results to guide decision making on need for an orchiectomy. Concentrations in the normal range do not rule out testicular neoplasm or the need for diagnostic orchiectomy.</td>
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<td>B. To evaluate CUP possibly derived from GCT</td>
<td></td>
<td>Recommendation 2B. The Panel recommends against using serum AFP and hCG assay results to guide treatment of patients with CUP and indeterminate histology, because evidence is lacking to support this use. Consider treatment with a chemotherapy regimen for disseminated GCT in patients presenting with undifferentiated midline carcinoma even if serum hCG and AFP concentrations are within normal ranges.</td>
</tr>
<tr>
<td>C. To evaluate patients presenting with metastasis and a primary tumor in testis, retroperitoneum, or anterior mediastinum</td>
<td></td>
<td>Recommendation 2C. In rare male patients presenting with testicular, retroperitoneal, or anterior mediastinal primary tumor and whose disease burden has resulted in an urgent need to start treatment, substantially elevated serum AFP and/or hCG may be considered sufficient for diagnosis of GCT. For such rare, medically unstable patients, treatment need not be delayed until after tissue diagnosis.</td>
</tr>
</tbody>
</table>

Part I: NSGCT
## Serum Tumor Markers for Malignancies AHS – G2124

<table>
<thead>
<tr>
<th>I-3. Monitoring during treatment (or observation)</th>
<th>A. For staging and prognosis before chemotherapy and/or additional surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommendation I-3A-1. Although evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes for these patients, the Panel recommends measuring serum AFP, hCG, and LDH for all patients with testicular NSGCT shortly after orchiectomy and before any subsequent treatment. The magnitude of postorchiectomy STM elevations is used to stratify risk and select treatment but must be interpreted appropriately. Serial STM measurements may be needed to determine whether STM levels are rising or falling and, if falling, whether the decline approximates the marker's biologic half-life.</td>
</tr>
<tr>
<td></td>
<td>Recommendation I-3A-2. Although direct evidence is lacking to demonstrate that decisions based on STM assay results improve survival or other health outcomes for these patients when compared with decisions made without assay results, the Panel recommends measuring serum AFP, hCG, and LDH before chemotherapy begins for those with mediastinal or retroperitoneal NSGCTs to stratify risk and select treatment.</td>
</tr>
<tr>
<td>B. To predict response to or benefit from treatment</td>
<td>Recommendation I-3B-1. The Panel recommends measuring AFP and hCG shortly before RPLND in patients with clinical stage I or II NSGCT; those with rising concentrations are beyond stages IA or IB and need systemic therapy similar to the regimens used for patients with stage III disease.</td>
</tr>
<tr>
<td></td>
<td>Recommendation I-3B-2. Although direct evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes when compared with decisions made without assay results, the Panel recommends measuring hCG, AFP, and LDH immediately prior to chemotherapy for stage II/III testicular NSGCT. The magnitude of marker elevations guides chemotherapy regimen choice and treatment duration.</td>
</tr>
<tr>
<td>C. To monitor response or progression during or soon after therapy</td>
<td>Recommendation I-3C. Although direct evidence is lacking to determine whether monitoring treatment response with STM assays during chemotherapy improves survival or other health outcomes of patients with NSGCT, the Panel recommends measuring serum AFP and hCG at the start of each chemotherapy cycle and again when chemotherapy concludes. However, the Panel sees no indication to delay the start of chemotherapy until after results of STM assays are known. Rising AFP and/or hCG levels during chemotherapy usually imply progressive disease and the need to change regimen.</td>
</tr>
</tbody>
</table>
Serum Tumor Markers for Malignancies AHS – G2124

<table>
<thead>
<tr>
<th>I-4. For surveillance</th>
<th>After presumably definitive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation I-4.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Although direct evidence is</td>
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<tr>
<td></td>
<td>unavailable to determine whether</td>
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<tr>
<td></td>
<td>monitoring STM concentrations</td>
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<td></td>
<td>during surveillance and following</td>
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<tr>
<td></td>
<td>definitive therapy for NSGCT</td>
</tr>
<tr>
<td></td>
<td>improves patients' survival</td>
</tr>
<tr>
<td></td>
<td>or other health outcomes, the Panel</td>
</tr>
<tr>
<td></td>
<td>recommends measuring AFP and hCG at</td>
</tr>
<tr>
<td></td>
<td>each visit during surveillance</td>
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<tr>
<td></td>
<td>after definitive therapy for NSGCT,</td>
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<tr>
<td></td>
<td>regardless of stage. Since evidence</td>
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<tr>
<td></td>
<td>also is lacking to directly compare</td>
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<tr>
<td></td>
<td>outcomes for different monitoring</td>
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<tr>
<td></td>
<td>intervals or durations, the Panel</td>
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<tr>
<td></td>
<td>recommends using intervals within</td>
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<td></td>
<td>the range used by the available</td>
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<tr>
<td></td>
<td>uncontrolled series: every 1 to 2</td>
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<tr>
<td></td>
<td>months in the first year, every 2 to</td>
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<td>4 months in the second year, every</td>
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<td>3 to 6 months in the third and</td>
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<td></td>
<td>fourth years, every 6 months in the</td>
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<tr>
<td></td>
<td>fifth year, and annually thereafter.</td>
</tr>
<tr>
<td></td>
<td>The Panel also recommends that</td>
</tr>
<tr>
<td></td>
<td>surveillance should continue for at</td>
</tr>
<tr>
<td></td>
<td>least 10 years after therapy is</td>
</tr>
<tr>
<td></td>
<td>completed.</td>
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<thead>
<tr>
<th>Part II. Seminoma</th>
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</table>

<table>
<thead>
<tr>
<th>II-3. Monitoring during treatment (or observation)</th>
<th>For staging and prognosis before RPLND, radiation, or chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation II-3A. Although direct evidence is</td>
<td></td>
</tr>
<tr>
<td>lacking to determine whether measuring STM</td>
<td></td>
</tr>
<tr>
<td>concentrations improves survival or other health</td>
<td></td>
</tr>
<tr>
<td>outcomes of these patients, the Panel recommends</td>
<td></td>
</tr>
<tr>
<td>measuring postorchietomy serum concentrations of</td>
<td></td>
</tr>
<tr>
<td>hCG and/or LDH for patients with testicular pure</td>
<td></td>
</tr>
<tr>
<td>seminoma and preorchietomy elevations. However,</td>
<td></td>
</tr>
<tr>
<td>the Panel recommends against using postorchietomy</td>
<td></td>
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<tr>
<td>serum concentrations of either hCG or LDH to stage</td>
<td></td>
</tr>
<tr>
<td>or predict prognosis of patients with involved</td>
<td></td>
</tr>
<tr>
<td>nodes and/or metastasis.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>II-3. Monitoring during treatment (or observation)</th>
<th>To predict response to or benefit from treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation II-3B. The panel recommends</td>
<td></td>
</tr>
<tr>
<td>against using tumor marker levels to guide</td>
<td></td>
</tr>
<tr>
<td>treatment decisions for seminoma. Evidence is</td>
<td></td>
</tr>
<tr>
<td>lacking that selecting therapy based on tumor</td>
<td></td>
</tr>
<tr>
<td>marker levels yields better outcomes.</td>
<td></td>
</tr>
</tbody>
</table>
Serum Tumor Markers for Malignancies AHS – G2124

| C. To monitor response or progression during or soon after therapy | Recommendation II-3C. The Panel recommends against using tumor markers to monitor response or progression of seminomas during treatment. However, serum hCG and AFP should be measured when seminoma treatment concludes. Rising concentrations usually indicate progressive disease and the need for salvage therapy (usually chemotherapy). |

| II-4. For surveillance | After presumably definitive therapy | Recommendation II-4. Conclusive evidence is lacking for clinical utility of STMs in post-treatment surveillance for stage I seminoma, and the Panel recommends against this use. However, while direct evidence is unavailable to determine whether monitoring STM concentrations improves survival or other health outcomes of patients who have completed therapy for advanced seminoma, rising levels may be the earliest sign of relapse, and the Panel recommends measuring STMs at each visit for these patients. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: 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. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed. |

ASCN 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer(Locker et al., 2006)

<table>
<thead>
<tr>
<th>Specific Markers</th>
<th>Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer</th>
</tr>
</thead>
</table>
| 1. CEA as a marker for colorectal cancer | 1a. Screening: CEA is not recommended as a screening test for colorectal cancer.  

1b. Staging/Treatment Planning: CEA may be ordered preoperatively in patients with colorectal carcinoma if it would assist in staging and surgical treatment planning. Although elevated preoperative CEA (> 5 mg/mL) may correlate with poorer prognosis, data are insufficient to support the use of CEA to determine whether to treat a patient with adjuvant therapy.  

1c. Postoperative: Postoperative serum CEA testing should be performed every 3 mo in patients with stage II or III disease for at least 3 yr after diagnosis, if the patient is a candidate for surgery or systemic therapy. An elevated CEA, if confirmed by retesting, warrants further evaluation for metastatic disease, but by itself does not justify systemic therapy for presumed metastatic disease. Because chemotherapy may falsely elevate |
<table>
<thead>
<tr>
<th>Serum Tumor Markers for Malignancies AHS – G2124</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA levels, waiting until chemotherapy is finished to initiate surveillance is advised.</td>
</tr>
<tr>
<td>1d. Monitoring Response to Therapy: CEA is the marker of choice for monitoring metastatic colorectal cancer during systemic therapy. CEA should be measured at the start of treatment for metastatic disease and every 1-3 mo during active treatment. Persistently rising values above baseline should prompt restaging but suggest progressive disease even in the absence of corroborating radiographs. Caution should be used when interpreting a rising CEA level during the first 4-6 wk of a new therapy, since spurious early rises may occur especially after oxaliplatin.2,3</td>
</tr>
<tr>
<td>2. CA 19-9 as a marker for colon cancer</td>
</tr>
<tr>
<td>2. Present data are insufficient to recommend CA 19-9 for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.</td>
</tr>
<tr>
<td>3. DNA ploidy or flow cytometric proliferation analysis as a marker for colon cancer</td>
</tr>
<tr>
<td>3. Neither flow cytometrically derived DNA ploidy (DNA index) nor DNA flow cytometric proliferation analysis (% S phase) should be used to determine prognosis of early-stage colorectal cancer.</td>
</tr>
<tr>
<td>4. p53 as a marker for colorectal cancer</td>
</tr>
<tr>
<td>4. Present data are insufficient to recommend the use of p53 expression or mutation for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.</td>
</tr>
<tr>
<td>5. ras as a marker for colorectal cancer</td>
</tr>
<tr>
<td>5. Present data are insufficient to recommend the use of the ras oncogene for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.</td>
</tr>
<tr>
<td>6. TS, DPD, and TP as markers in colorectal cancer (Note: This topic is new to the guideline.)</td>
</tr>
<tr>
<td>6a. Screening: TS, DPD, and TP are tissue markers that have been used to predict response to treatment of established carcinomas and thus are not useful for screening.</td>
</tr>
<tr>
<td>6b. Prognosis: None of the three markers—TS, DPD, or TP—are recommended for use to determine the prognosis of colorectal carcinoma.</td>
</tr>
<tr>
<td>6c. Predicting Response to Therapy: There is insufficient evidence to recommend use of TS, DPD, or TP as predictors of response to therapy.</td>
</tr>
<tr>
<td>6d. Monitoring Response to Therapy: There is insufficient evidence to recommend use of TS, DPD, or TP for monitoring response to therapy.</td>
</tr>
<tr>
<td>7. MSI/hMSH2 or hMLH1 as markers in colorectal cancer (Note: This topic is new to the guideline.)</td>
</tr>
<tr>
<td>7. MSI ascertained by PCR is not recommended at this time to determine the prognosis of operable colorectal cancer nor to predict the effectiveness of FU adjuvant chemotherapy.</td>
</tr>
<tr>
<td>8. 18q/DCC as markers for colorectal cancer (Note: This topic is new to the guideline.)</td>
</tr>
<tr>
<td>8. Assaying for LOH on the long arm of chromosome 18 (18q) or DCC protein determination by immunohistochemistry should not be used to determine the prognosis of operable colorectal cancer, nor to predict response to therapy.</td>
</tr>
<tr>
<td>9. CA 19-9 as a marker for pancreatic cancer</td>
</tr>
<tr>
<td>9a. Screening: CA 19-9 is not recommended for use as a screening test for pancreatic cancer.</td>
</tr>
</tbody>
</table>
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(Note: This topic is new to the guideline.)

<table>
<thead>
<tr>
<th>9b. Operability: The use of CA 19-9 testing alone is not recommended for use in determining operability or the results of operability in pancreatic cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>9c. Evidence of Recurrence: CA 19-9 determinations by themselves cannot provide definitive evidence of disease recurrence without seeking confirmation with imaging studies for clinical findings and/or biopsy.</td>
</tr>
<tr>
<td>9d. Monitoring Response to Therapy: Present data are insufficient to recommend the routine use of serum CA 19-9 rules alone for monitoring response to treatment. However, CA 19-9 can be measured at the start of treatment for locally advanced metastatic disease and every 1-3 mo during active treatment. If there is an elevation in serial CA 19-9 determinations, this may be an indication of progressive disease and confirmation with other studies should be sought.</td>
</tr>
</tbody>
</table>

American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer (Harris et al., 2007)

<table>
<thead>
<tr>
<th>Specific Marker</th>
<th>2007 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CA 15-3 and CA 27.29 as markers for breast cancer as screening, diagnostic, or staging tests</strong></td>
<td>Present data are insufficient to recommend CA 15-3 or CA 27.29 for screening, diagnosis, and staging. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
<tr>
<td><strong>CA 15-3 and CA 27.29 to detect recurrence after primary breast cancer therapy</strong></td>
<td>Present data do not support the use of CA 15-3 and CA 27.29 for monitoring patients for recurrence after primary breast cancer therapy. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
<tr>
<td><strong>CA 15-3 and CA 27.29 to contribute to decisions regarding therapy for metastatic breast cancer</strong></td>
<td>For monitoring patients with metastatic disease during active therapy, CA 27.29 or CA 15-3 can be used in conjunction with diagnostic imaging, history, and physical examination. Present data are insufficient to recommend use of CA 15-3 or CA 27.29 alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure. Caution should be used when interpreting a rising CA 27.29 or CA 15-3 level during the first 4-6 weeks of a new therapy, since spurious early rises may occur. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
<tr>
<td><strong>CEA for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy</strong></td>
<td>CEA is not recommended for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
<tr>
<td><strong>CEA to contribute to decisions regarding therapy for metastatic breast cancer</strong></td>
<td>For monitoring patients with metastatic disease during active therapy, CEA can be used in conjunction with diagnostic imaging, history, and physical examination. Present data are insufficient to recommend use of CEA alone for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CEA may be used to indicate</td>
</tr>
<tr>
<td>Serum Tumor Markers for Malignancies AHS – G2124</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>treatment failure. Caution should be used when interpreting a rising CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur. <strong>There is no change from the guideline published in 2000.</strong></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ERs and PgRs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ER and PgR should be measured on every primary invasive breast cancer and may be measured on metastatic lesions if the results would influence treatment planning. In both pre- and postmenopausal patients, steroid hormone receptor status should be used to identify patients most likely to benefit from endocrine forms of therapy in both the early breast cancer and metastatic disease settings. In patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PgR for therapy recommendations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DNA flow cytometry–based parameters</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Present data are insufficient to recommend use of DNA content, S phase, or other flow cytometry–based markers of proliferation to assign patients to prognostic groups. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Immunohistochemically based markers of proliferation (Note: This topic is new to the guideline)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Present data are insufficient to recommend measurement of Ki67, cyclin D, cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation to assign patients to prognostic groups.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HER2 evaluation in breast cancer</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 expression and/or amplification should be evaluated in every primary invasive breast cancer either at the time of diagnosis or at the time of recurrence, principally to guide selection of trastuzumab in the adjuvant and/or metastatic setting. Other utilities for HER2 evaluation are also discussed separately above.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HER2 to define prognosis for early-stage breast cancer patients in the absence of systemic therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 amplification, overexpression, and the presence of HER2 extracellular domain are generally associated with a poorer prognosis. However, the value of this information in clinical practice is questionable and the use of HER2 for determining prognosis is not recommended. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
</tbody>
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<thead>
<tr>
<th><strong>HER2 to select patients for antHER2–based therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>High levels of tissue HER2 expression or HER2 gene amplification should be used to identify patients for whom trastuzumab may be of benefit for treatment of breast cancer in the adjuvant or metastatic disease settings. <strong>There is no change from the guideline published in 2000.</strong></td>
</tr>
</tbody>
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<thead>
<tr>
<th><strong>The utility of HER2 for predicting response to specific chemotherapeutic agents</strong></th>
</tr>
</thead>
</table>
| Level II evidence (prospective therapeutic trials in which marker utility is a secondary study objective) suggests that overexpression of HER2 (3+ by protein or > 2.0 FISH ratio by gene amplification) identifies patients who have greater benefit from anthracycline-based adjuvant therapy. If a clinician is considering chemotherapy for a patient with HER2-positive breast cancer, it is recommended that an anthracycline be strongly considered, assuming there are no contraindications to anthracycline therapy. In the context of trastuzumab therapy, there is Level I evidence (single, high-powered, prospective,
**Serum Tumor Markers for Malignancies AHS – G2124**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2 to determine sensitivity to endocrine therapy</strong></td>
<td>HER2 should not be used to withhold endocrine therapy for a patient with hormone receptor–positive breast cancer, nor should it be used to select one specific type of endocrine therapy over another. <em>There is no change from the guideline published in 2000.</em></td>
</tr>
<tr>
<td><strong>Utility of circulating extracellular domain of HER-2</strong></td>
<td>Measuring circulating extracellular domain of HER2 is not currently recommended for any clinical setting. <em>There is no change from the guideline published in 2000.</em></td>
</tr>
<tr>
<td><strong>p53 as a marker for breast cancer</strong></td>
<td>Present data are insufficient to recommend use of <em>p53</em> measurements for management of patients with breast cancer. <em>There is no change from the guideline published in 2000.</em></td>
</tr>
<tr>
<td><strong>uPA and PAI-1 as a marker for breast cancer (Note: This topic is new to the guideline)</strong></td>
<td>uPA/PAI-1 measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer. IHC for these markers is not accurate, and the prognostic value of ELISA using smaller tissue specimens has not been validated. Low levels of both markers are associated with a sufficiently low risk of recurrence, especially in hormone receptor–positive women who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit. Furthermore, CMF-based adjuvant chemotherapy provides substantial benefit, compared with observation alone, in patients with high risk of recurrence as determined by high levels of uPA and PAI-1.</td>
</tr>
<tr>
<td><strong>Cathepsin D as a marker for breast cancer</strong></td>
<td>Present data are insufficient to recommend use of cathepsin D measurements for management of patients with breast cancer. <em>There is no change from the guideline published in 2000.</em></td>
</tr>
<tr>
<td><strong>Cyclin E fragments as markers for breast cancer (Note: This topic is new to the guideline)</strong></td>
<td>Present data are insufficient to recommend use of whole length or fragment measurements of cyclin E for management of patients with breast cancer.</td>
</tr>
<tr>
<td><strong>Proteomic analysis for breast cancer (Note: This topic is new to the guideline)</strong></td>
<td>Present data are insufficient to recommend use of proteomic patterns for management of patients with breast cancer.</td>
</tr>
<tr>
<td><strong>Multiparameter gene expression analysis for breast cancer (Note: This topic is new to the guideline)</strong></td>
<td>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. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy.</td>
</tr>
</tbody>
</table>
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In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay, the “Rotterdam Signature,” and the Breast Cancer Gene Expression Ratio are under investigation.

Bone marrow micrometastases as markers for breast cancer (Note: This topic is new to the guideline)

Present data are insufficient to recommend assessment of bone marrow micrometastases for management of patients with breast cancer.

Circulating tumor cell assays as markers for breast cancer (Note: This topic is new to the guideline)

The measurement of circulating tumor cells (CTCs) should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in patients with breast cancer. Similarly, the use of the recently FDA-cleared test for CTC (CellSearch Assay) in patients with metastatic breast cancer cannot be recommended until further validation confirms the clinical value of this test.

Use of Biomarkers to Guide Decisions on Systemic Therapy For Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline (Van Poznak et al., 2015)

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Recommendation</th>
<th>Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under what circumstances (i.e., for which patients) should metastases be biopsied or otherwise sampled to test for changes from the primary tumor with respect to endocrine receptor or HER2 status?</td>
<td>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. They should also be informed that if discordances are found, evidence is lacking to determine whether outcomes are better with treatment regimens based on receptor status in the metastases or the primary tumor. 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.</td>
<td>Type: Evidence-based for biomarker change from primary to metastasis, but no evidence to demonstrate that systemic therapy choices affect health outcomes when biomarker change occurs. Evidence quality: Insufficient Strength of recommendation: Moderate</td>
</tr>
<tr>
<td>For women with metastatic breast cancer and with known endocrine receptor and HER2 status, which additional tumor markers have demonstrated clinical</td>
<td>Decisions on initiating systemic therapy for metastatic breast cancer should be based on clinical evaluation, judgment, and patient preferences. There is no evidence at this time that initiating therapy solely on the basis of</td>
<td>Type: Evidence-based Evidence quality: Low</td>
</tr>
</tbody>
</table>
### Serum Tumor Markers for Malignancies AHS – G2124

<table>
<thead>
<tr>
<th>Tumor Biomarker</th>
<th>Clinical Utility</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>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. The recommendation for use is based on clinical experience and Panel informal consensus in the absence of studies designed to evaluate the clinical utility of the markers. As such, it is also reasonable for clinicians to not use these markers as adjunctive assessments.</td>
<td>Type: Informal consensus</td>
<td>Evidence quality: Insufficient</td>
</tr>
<tr>
<td>For each tumor biomarker shown to have clinical utility for guiding decisions on</td>
<td>Decisions for systemic therapy should be influenced by ER, PR, and HER2. To date, clinical utility has not been</td>
<td>Type: Informal consensus</td>
</tr>
<tr>
<td>utility to guide initiation of systemic therapy or direct selection of a new systemic therapy regimen?</td>
<td>biomarker results beyond that of ER, PR, and HER2 improves health outcomes.</td>
<td>Strength of recommendation: Moderate</td>
</tr>
<tr>
<td>Recommendations for tissue biomarkers: In patients who are already receiving systemic therapy for metastatic breast cancer, decisions on changing to a new drug or regimen or discontinuing treatment should be based on the patient’s goals for care and clinical evaluation and judgment of disease progression or response, given that there is no evidence at this time that changing therapy solely on the basis of biomarker results beyond ER, PR, and HER2 improves health outcomes, quality of life, or cost-effectiveness.</td>
<td>Type: Evidence-based</td>
<td>Evidence quality: Low</td>
</tr>
<tr>
<td>Strength of recommendation: Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendations for circulating tumor markers: In patients already receiving systemic therapy for metastatic breast cancer, decisions on changing to a new drug or regimen or discontinuing treatment should be based on clinical evaluation, judgment of disease progression or response, and the patient’s goals for care. There is no evidence at this time that changing therapy based solely on circulating biomarker results improves health outcomes, quality of life, or cost-effectiveness.</td>
<td>Type: Evidence-based</td>
<td>Evidence quality: Intermediate</td>
</tr>
<tr>
<td>Strength of recommendation: Moderate</td>
<td></td>
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</tr>
</tbody>
</table>

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**Serum Tumor Markers for Malignancies AHS – G2124**

| system therapy for metastatic disease in questions 2 or 3, what are the appropriate assays, timing, and frequency of measurement? | demonstrated for any additional biomarkers. | Strength of recommendation: Strong |

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update (Krop et al., 2017)

<table>
<thead>
<tr>
<th>2016 Recommendations</th>
<th>Focused Update Recommendations</th>
</tr>
</thead>
</table>

**Clinical Question 1:** For women with operable invasive breast cancer and with known ER/PgR and HER2 status, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

**Recommendation 1.7:** If a patient has ER/PgR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use the 70-gene assay (MammaPrint; Agendia, Irvine, CA) to guide decisions about adjuvant systemic chemotherapy (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

**Recommendation 1.1.1:** 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 per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

**Recommendation 1.1.2:** If a patient has ER/PgR-positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy as women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high risk cancer. (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

**Recommendation 1.2.1:** 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 per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node. (Type: Evidence based;
| Recommendation 1.2.2: If a patient has **ER/PgR-positive, HER2-negative, node-positive**, breast cancer, the MammaPrint assay should not be used in patients with 1-3 positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population. (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate). |
| Evidence quality: High; Strength of recommendation: Moderate). |

**Recommendation 1.8:** If a patient has HER2-positive breast cancer, the clinician should not use the 70-gene assay to guide decisions for adjuvant systemic therapy (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

**Recommendation 1.3:** If a patient has **HER2-positive** breast cancer, the clinician should not use the MammaPrint assay to guide decisions regarding adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER-2-targeted therapy. (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

**Recommendation 1.9:** If a patient has TN breast cancer, the clinician should not use the 70-gene assay to guide decisions about adjuvant systemic therapy (Type: Informal consensus; Evidence quality: Insufficient; Strength of recommendation: Strong).

**Recommendation 1.4:** If a patient has **ER/PgR negative and HER2-negative** breast cancer (triple negative), the clinician should not use the MammaPrint assay to guide decisions about adjuvant systemic chemotherapy (Type: Informal consensus; Evidence quality: Insufficient; Strength of recommendation: Strong).

### Unchanged 2016 Recommendations

**Recommendation 1.1** If a patient has **ER/PgR-positive, HER2-negative (node-negative)** breast cancer, the clinician may use the 21-gene recurrence score (RS; Oncotype DX; Genomic Health, Redwood City, CA) to guide decisions on adjuvant systemic chemotherapy. (Type: evidence based; Evidence quality: high. Strength of recommendation: strong)

**Recommendation 1.2** If a patient has **ER/PgR-positive, HER2-negative (nodepositive)** breast cancer, the clinician should not use the 21-gene RS to guide decisions on adjuvant systemic chemotherapy. (Type: evidence based. Evidence quality: intermediate; Strength of recommendation: moderate)

**Recommendation 1.3** If a patient has **HER2-positive breast cancer or TN breast cancer**, the clinician should not use the 21-gene RS (Oncotype DX) to guide decisions on adjuvant systemic therapy. (Type: informal consensus; Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.4** If a patient has **ER/PgR-positive, HER2-negative (node-negative)** breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Koln, Germany) to guide decisions on adjuvant systemic chemotherapy. (Type: evidence based; Evidence quality: intermediate. Strength of recommendation: moderate)

**Recommendation 1.5** If a patient has **ER/PgR-positive, HER2-negative (nodepositive)** breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy. (Type: evidence based. Evidence quality: intermediate; Strength of recommendation: moderate)

**Recommendation 1.6** If a patient has **ER/PgR-positive, HER2-negative (nodepositive)** breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy. (Type: evidence based. Evidence quality: intermediate; Strength of recommendation: moderate)
systemic chemotherapy. (Type: evidence based. Evidence quality: insufficient; Strength of recommendation: moderate)

**Recommendation 1.6** If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.10** If a patient has ER/PgR-positive, HER2-negative (nodenegative) breast cancer, the clinician may use the PAM50 risk of recurrence (ROR) score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA) in conjunction with other clinicopathologic variables to guide decisions on adjuvant systemic therapy. (Type: evidence based. Evidence quality: high. Strength of recommendation: strong)

**Recommendation 1.11** If a patient has ER/PgR-positive, HER2-negative (nodepositive) breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.12** If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.13** If a patient has TN breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.14** If a patient has ER/PgR-positive, HER2-negative (nodenegative) breast cancer, the clinician may use the Breast Cancer Index (bioTheranostics, San Diego, CA) to guide decisions on adjuvant systemic therapy. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)

**Recommendation 1.15** If a patient has ER/PgR-positive, HER2-negative (nodepositive) breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.16** If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.17** If a patient has ER/PgR-positive, HER2-negative (nodepositive or node- negative) breast cancer, the clinician should not use the five-protein assay (Mammostrat; Clarient, a GE Healthcare company, Aliso Viejo, CA) to guide decisions on adjuvant systemic therapy. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)

**Recommendation 1.18** If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the five-protein assay (Mammostrat) to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)

**Recommendation 1.19** If a patient has ER/PgR-positive, HER2-negative (nodepositive or node- negative) breast cancer, the clinician should not use the immunohistochemistry 4 (IHC4) assay to guide decisions on adjuvant systemic chemotherapy. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)
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<table>
<thead>
<tr>
<th>Recommendation 1.20</th>
<th>If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use IHC4 to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 1.21</td>
<td>If a patient has ER/PgR-positive, HER2-negative (nodenegative) breast cancer, the clinician may use urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) to guide decisions on adjuvant systemic therapy. (Type: evidence based. Evidence quality: high. Strength of recommendation: weak)</td>
</tr>
<tr>
<td>Recommendation 1.22</td>
<td>If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use uPA and PAI-1 to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak)</td>
</tr>
<tr>
<td>Recommendation 1.23</td>
<td>The clinician should not use circulating tumor cells (CTCs) to guide decisions on adjuvant systemic therapy. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: strong)</td>
</tr>
<tr>
<td>Recommendation 1.24</td>
<td>If a patient has ER/PgR-positive, HER2-negative (nodepositive or node-negative) breast cancer, the clinician should not use tumor-infiltrating lymphocytes (TILs) to guide decisions on adjuvant systemic therapy. (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong)</td>
</tr>
<tr>
<td>Recommendation 1.25</td>
<td>If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use TILs to guide decisions on adjuvant systemic therapy. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: strong)</td>
</tr>
<tr>
<td>Recommendation 1.26</td>
<td>Ki-67 labeling index by IHC should not be used to guide choice on adjuvant chemotherapy. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)</td>
</tr>
<tr>
<td>Recommendation 1.27</td>
<td>If a patient has ER/PgR-positive, HER2-negative (nodenegative) breast cancer and 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. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)</td>
</tr>
</tbody>
</table>

**Clinical Question 2:** For women with early-stage invasive breast cancer and with known ER/PgR and HER2 status, which additional biomarkers have demonstrated clinical utility to guide choice of specific drugs or regimens for adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Recommendation 2.1</th>
<th>The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 2.2</td>
<td>The clinician should not use p27 expression by IHC to guide adjuvant endocrine therapy selection. (Type: informal consensus. Evidence quality: low. Strength of recommendation: strong)</td>
</tr>
<tr>
<td>Recommendation 2.3</td>
<td>The clinician should not use Ki-67 labeling index by IHC to guide adjuvant endocrine therapy selection. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)</td>
</tr>
<tr>
<td>Recommendation 2.4</td>
<td>The clinician should not use microtubule-associated protein (MAP)-Tau mRNA expression or mRNA expression by IHC to guide adjuvant chemotherapy selection. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)</td>
</tr>
</tbody>
</table>
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**Recommendation 2.5** The clinician should not use HER1/epidermal growth factor receptor (EGFR) expression by IHC to guide adjuvant chemotherapy selection. (Type: evidence based. Evidence quality: low. Strength of recommendation: moderate)

**Recommendation 2.6** The clinician should not use TOP2A gene amplification or TOP2A protein expression by IHC to guide adjuvant chemotherapy selection. (Type: evidence based. Evidence quality: high. Strength of recommendation: moderate)

**Recommendation 2.7** The clinician should not use HER2 and TOP2A gene coamplification; CEP17 duplication; or TIMP-1, FOXP3, or p53 protein expression to guide adjuvant chemotherapy selection. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)

**Recommendation 2.8** If a patient has HER2-positive breast cancer, the clinician should not use PTEN to guide adjuvant therapy selection. (Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate)

**Recommendation 2.9** If a patient has HER2-positive breast cancer, the clinician should not use soluble HER2 levels to guide adjuvant therapy selection. (Type: evidence based. Evidence quality: low. Strength of recommendation: moderate)

American College of Chest Physicians (ACCP)

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

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

National Comprehensive Cancer Network (NCCN, 2019)

<table>
<thead>
<tr>
<th>Serum Tumor Marker</th>
<th>Recommendation</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>Hepatocellular workup (HCC). AFP for surveillance is optional</td>
<td>NCCN Hepatobiliary Cancers Version 1.2019</td>
</tr>
<tr>
<td>AFP</td>
<td>Intrahepatic cholangiocarcinoma workup</td>
<td>NCCN Hepatobiliary Cancers Version 1.2019</td>
</tr>
<tr>
<td>AFP</td>
<td>Women under 35 years with a pelvic mass</td>
<td>NCCN Ovarian Cancer Version 2.2018</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFP</strong></td>
<td>Thymomas and thymic carcinoma initial workup. Both seminoma and nonseminoma, serum prognostic factor and contribute to diagnosis and staging.</td>
<td>NCCN Thymomas and thymic carcinomas Version 2.2018, NCCN Testicular Cancer Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-HCG</strong></td>
<td>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-orchiectomy</td>
<td>NCCN Testicular Cancer Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-HCG</strong></td>
<td>Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer workup as clinically indicated</td>
<td>NCCN Ovarian Cancer Version 2.2018</td>
</tr>
<tr>
<td><strong>Beta-HCG</strong></td>
<td>Mediastinal mass/thymomas and thymic carcinoma workup</td>
<td>NCCN Thymomas and thymic carcinomas Version 2.2018</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Multiple myeloma workup and follow-up/surveillance and staging</td>
<td>NCCN Multiple Myeloma Version 2.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Solitary plasmacytoma and extraosseous plasmacytoma surveillance</td>
<td>NCCN Multiple Myeloma Version 2.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Smoldering (asymptomatic) myeloma</td>
<td>NCCN Multiple Myeloma Version 2.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Follicular lymphoma workup</td>
<td>NCCN B-cell Lymphomas Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Mantle cell lymphoma workup</td>
<td>NCCN B-cell Lymphomas Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Diffuse B-cell Lymphoma workup (useful in selected cases)</td>
<td>NCCN B-cell Lymphomas Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>AIDS-related B-cell lymphomas workup (useful in selected cases)</td>
<td>NCCN B-cell Lymphomas Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Lymphoblastic lymphoma workup (useful in selected cases)</td>
<td>NCCN B-cell Lymphomas Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Castleman’s disease workup</td>
<td>NCCN B-cell Lymphomas Version 1.2019</td>
</tr>
<tr>
<td><strong>Beta-2 microglobulin (B2M)</strong></td>
<td>Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma workup</td>
<td>NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2019</td>
</tr>
<tr>
<td><strong>Cancer Antigen 15-3 and 27.29</strong></td>
<td>Cancer Antigen 15-3 and 27.29 as part of findings for identification of disease progression</td>
<td>NCCN Breast Cancer Version 3.2018</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Cancer Antigen 19-9</th>
<th>Pancreatic adenocarcinoma pre-op workup, post treatment, and surveillance. Levels may be elevated up to 2 years before pancreatic CA diagnosis</th>
<th>NCCN Pancreatic Adenocarcinoma Version 1.2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Antigen 19-9</td>
<td>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</td>
<td>NCCN Pancreatic Adenocarcinoma Version 1.2019</td>
</tr>
<tr>
<td>Cancer Antigen 19-9</td>
<td>Intrahepatic or extrahepatic cholangiocarcinoma workup. CA 19-9 is a baseline test and should not be done to confirm diagnosis</td>
<td>NCCN Pancreatic Adenocarcinoma Version 1.2019</td>
</tr>
<tr>
<td>Cancer Antigen 19-9</td>
<td>Pancreatic or biliary tract primary suspected workup</td>
<td>NCCN Occult Primary Version 1.2019</td>
</tr>
<tr>
<td>CA-125</td>
<td>Epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer workup, prior to each chemotherapy, and monitoring</td>
<td>NCCN Ovarian Cancer Version 2.2018</td>
</tr>
<tr>
<td>CA-125</td>
<td>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</td>
<td>NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 1.2018</td>
</tr>
<tr>
<td>CA-125</td>
<td>Borderline epithelial tumors (low malignant potential) monitoring- CA-125 every visit if initially elevated</td>
<td>NCCN Ovarian Cancer Version 3.2017</td>
</tr>
<tr>
<td>CA-125</td>
<td>Endometrial carcinoma CA-125 optional; surveillance if initially elevated</td>
<td>NCCN Uterine Neoplasms V 1.2018</td>
</tr>
<tr>
<td>CA-125</td>
<td>Occult Primary - adenocarcinoma or carcinoma not otherwise specified workup for females</td>
<td>NCCN Occult Primary Version 1.2019</td>
</tr>
<tr>
<td>CEA</td>
<td>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.</td>
<td>NCCN Colon Cancer Version 4.2018</td>
</tr>
<tr>
<td>CEA</td>
<td>Suspected or proven metastatic synchronous adenocarcinoma workup</td>
<td>NCCN Colon Cancer Version 4.2018</td>
</tr>
<tr>
<td>CEA</td>
<td>Intrahepatic Cholangiocarcinoma workup. CEA is a baseline test and should not be done to confirm diagnosis</td>
<td>NCCN Hepatobiliary Cancers Version 1.2019</td>
</tr>
<tr>
<td>CEA</td>
<td>Extrahepatic Cholangiocarcinoma workup. CEA is a baseline test and should not be done to confirm diagnosis</td>
<td>NCCN Hepatobiliary Cancers Version 1.2019</td>
</tr>
<tr>
<td>CEA</td>
<td>Gallbladder cancer workup and surveillance. CEA is a baseline test and should not be done to confirm diagnosis</td>
<td>NCCN Hepatobiliary Cancers Version 1.2019</td>
</tr>
<tr>
<td>Marker</td>
<td>Description</td>
<td>Reference</td>
</tr>
<tr>
<td>--------</td>
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</tr>
<tr>
<td>CEA</td>
<td>Thyroid carcinoma – medullary carcinomas workup and surveillance; surveillance every 6-12 mo.</td>
<td>NCCN Thyroid Carcinoma Version 3.2018</td>
</tr>
<tr>
<td>CEA</td>
<td>Mucinous carcinoma of the ovary workup</td>
<td>NCCN Ovarian Cancer Version 2.2018</td>
</tr>
<tr>
<td>CgA</td>
<td>Neuroendocrine tumors of: gastrointestinal tract, lung, thymus (carcinoid tumors) evaluation. CgA is one of a set of tumor markers that may be used to establish neuroendocrine differentiation</td>
<td>NCCN Neuroendocrine Tumors. Version 4.2018</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thyroid carcinoma - medullary carcinoma workup, post-surgical evaluation, and surveillance (surveillance every 6-12 mo.)</td>
<td>NCCN Thyroid carcinoma - medullary carcinoma Version 3.2018</td>
</tr>
<tr>
<td>Hcg</td>
<td>May be evaluated during workup</td>
<td>NCCN Gestational Trophoblastic Neoplasia Version 1.2019</td>
</tr>
<tr>
<td>IGF</td>
<td>May be considered for evaluation of pituitary tumor (category 28)</td>
<td>NCCN Neuroendocrine Tumors Version 4.2018</td>
</tr>
<tr>
<td>IgM</td>
<td>Assessment of this immunoglobulin is essential for management of Waldenstrom’s Macroglobulinemia/Lymphoplasmacytic Lymphoma</td>
<td>NCCN Waldenstrom’s Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2019</td>
</tr>
<tr>
<td>INHA</td>
<td>Undiagnosed pelvic mass workup to assess for LCOH (Less Common Ovarian Histopathologies) and pregnancy</td>
<td>NCCN Ovarian Cancer Version 3.2017 2.2018</td>
</tr>
<tr>
<td>INHA</td>
<td>Inhibin levels can be followed if initially elevated for granulosa cell tumors</td>
<td>NCCN Ovarian Cancer Version 2.2018</td>
</tr>
<tr>
<td>LDH</td>
<td>Acute Lymphoblastic Leukemia (ALL) workup as part of a tumor lysis syndrome panel</td>
<td>NCCN Acute Lymphocytic Leukemia Version 2.2018</td>
</tr>
<tr>
<td>LDH</td>
<td>Acute myeloid leukemia workup</td>
<td>NCCN Acute Myeloid Leukemia. Version 3.2018</td>
</tr>
<tr>
<td>LDH</td>
<td>Primary cutaneous B-cell Lymphoma workup</td>
<td>NCCN Primary Cutaneous B-cell lymphomas. Version 2.2019</td>
</tr>
<tr>
<td>LDH</td>
<td>Chronic lymphocytic leukemia workup for histologic transformation (Richter’s) and progression; workup for tumor lysis syndrome</td>
<td>NCCN Chronic lymphocytic leukemia/small lymphocytic Leukemia. Version 2.2019</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Definition</th>
<th>Applicable NCCN Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>Testicular cancer workup.; LDH, along with other tumor markers are critical in diagnosing GCTs, determining prognosis and assessing treatment outcomes.</td>
<td>NCCN Testicular Cancer. Version 1.2019</td>
</tr>
<tr>
<td>LDH</td>
<td>Osteosarcoma and Ewing Sarcoma workup. Elevated levels at initial diagnosis and initial recurrence are considered adverse prognostic indicators.</td>
<td>NCCN Bone cancers. Version 1.2019</td>
</tr>
<tr>
<td>LDH</td>
<td>Multiple Myeloma workup, follow-up/surveillance and staging.</td>
<td>NCCN Multiple Myeloma. Version 2.2019</td>
</tr>
<tr>
<td>PD-L1</td>
<td>May be considered to assess response to PD-1 inhibitors. Other biomarkers such as CEA are of unknown utility.</td>
<td>NCCN Esophageal and Esophagogastric Junction Cancers Version 2.2018</td>
</tr>
<tr>
<td>PD-L1</td>
<td>May be considered to assess response to PD-1 inhibitors.</td>
<td>NCCN Gastric Cancer Version 2.2018</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate cancer workup, staging, surveillance, and detecting disease recurrence. PSA no more often than every 6 months unless clinically indicated.</td>
<td>NCCN Prostate Cancer. Version 4.2018</td>
</tr>
<tr>
<td>Thyroglobulin (TG) and/or thyroglobulin antibodies</td>
<td>Thyroid carcinoma – papillary carcinoma post thyroidectomy; consideration for initial postoperative RAI therapy after total thyroidectomy, surveillance and maintenance.</td>
<td>NCCN Thyroid carcinoma. Version 3.2018</td>
</tr>
<tr>
<td>Thymidine kinase</td>
<td>Prognostic information.</td>
<td>NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2019</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Assessment of serum tryptase is critical for evaluating staging, prognosis, and diagnosis of systemic mastocytosis.</td>
<td>NCCN Systemic Mastocytosis Version 2.2019</td>
</tr>
</tbody>
</table>

The NCCN guidelines on ovarian cancer (version 2.2017) also stated that “It has been suggested that specific biomarkers (serum HE4 and CA-125) along with an algorithm (Risk of Ovarian Malignancy Algorithm [ROMA]) may be useful for determining whether a pelvic mass is malignant or benign. The FDA has approved the use of HE4 and CA-125 for estimating the risk of ovarian cancer in women with a pelvic mass. Currently, the NCCN Panel does not recommend the use of these biomarkers for determining the status of an undiagnosed pelvic mass.”

Applicable State/Federal Regulations
Serum Tumor Markers for Malignancies AHS – G2124

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

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. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81500, 81503, 81538, 81551, 82232, 82308, 82378, 82397, 83520, 83615, 83950, 84075, 84078, 84080, 84152, 84153, 84154, 84432, 84484, 84702, 84703, 84704, 84999, 85415, 86300, 86301, 86304, 86305, 86316, 86800, 0003U, 0021U, 0045U, 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.

Scientific Background and Reference Sources


Serum Tumor Markers for Malignancies AHS – G2124


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Serum Tumor Markers for Malignancies AHS – G2124


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Serum Tumor Markers for Malignancies


Serum Tumor Markers for Malignancies


Serum Tumor Markers for Malignancies AHS – G2124

Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

Medical Director 4/2020

Policy Implementation/Update Information

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 1st 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 Apifiny 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 2nd 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 1st 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)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.