



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Tumor Markers for Diagnosis and Management of Cancer

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers EACH of the following tumor markers as medically necessary for the specific condition(s) noted:

Tumor Marker	Condition(s)
AFP (alpha-fetoprotein)	<ul style="list-style-type: none"> Hepatocellular cancer
AFP in combination with b-HCG (beta-human chorionic gonadotropin)	<ul style="list-style-type: none"> Germ cell testicular cancer Germ cell ovarian cancer Undiagnosed pelvic mass

B ₂ M (beta ₂ -microglobulin)	<ul style="list-style-type: none"> Multiple myeloma
Bladder-tumor associated antigen (BTA)	<ul style="list-style-type: none"> Bladder cancer
Calcitonin	<ul style="list-style-type: none"> Thyroid medullary carcinoma
CA (cancer antigen) 15-3, CA 27.29, BR 27.29 or Truquant RIA	<ul style="list-style-type: none"> Metastatic breast cancer
CA 19.9	<ul style="list-style-type: none"> Pancreatic cancer
CA 125	<ul style="list-style-type: none"> Epithelial ovarian cancer Endometrial cancer Undiagnosed pelvic mass
CEA (carcinoembryonic antigen)	<ul style="list-style-type: none"> Colorectal cancer Medullary thyroid cancer Breast cancer
CgA (chromogranin A)	<ul style="list-style-type: none"> Neuroendocrine tumors (e.g., carcinoid tumors, neuroblastoma, and small cell lung cancer)
C-kit (CD-117 [cluster of differentiation-117])	<ul style="list-style-type: none"> Gastrointestinal stromal tumors
ER/PR (estrogen receptors and progesterone receptors)	<ul style="list-style-type: none"> Breast cancer
HCG (human chorionic gonadotropin)	<ul style="list-style-type: none"> Trophoblastic testicular cancer Trophoblastic ovarian cancer
HER2 (human epidermal growth factor receptor 2) when performed by immunohistochemical (IHC) and/or fluorescent in situ hybridization (FISH)	<ul style="list-style-type: none"> Breast cancer
ImmunoCyte™/yCyte+™	<ul style="list-style-type: none"> Bladder cancer
KRAS (Kirsten rat sarcoma)	<ul style="list-style-type: none"> Metastatic colorectal cancer
MPO (myeloperoxidase)	<ul style="list-style-type: none"> Acute myeloid leukemia
Nuclear-Matrix Protein (NMP22)	<ul style="list-style-type: none"> Bladder cancer
NSE (neuron-specific enolase)	<ul style="list-style-type: none"> Small cell lung cancer
PSA (prostate-specific antigen)	<ul style="list-style-type: none"> Prostate cancer (For Screening - Refer to the Prostate-Specific Antigen (PSA) Screening for Prostate Cancer Coverage Policy)
Thyroglobulin	<ul style="list-style-type: none"> Differentiated thyroid cancer
UroVysion™	<ul style="list-style-type: none"> Bladder cancer

CIGNA does not cover any of the tumor markers listed above for ANY unlisted indication because it is considered experimental, investigational, unproven.

CIGNA covers the following paraneoplastic (onconeural) antibodies as medically necessary for the evaluation of neurological symptoms when the diagnosis remains uncertain following conventional work-up and an occult neoplasm is suspected:

- anti-Hu (ANNA-1 [antineuronal nuclear autoantibodies-1])
- anti-Yo (PCA-1 [Purkinje cell antibody-1])
- anti-CV2 (CRMP5 [collapsing mediator response protein5])
- anti-Ri (ANNA-2)
- anti-MA2 (Ta)
- anti-amphiphysin

CIGNA does not cover ANY of the following tumor markers for the screening, staging, diagnosis, monitoring and/or surveillance of cancer because EACH is considered experimental, investigational or unproven (this list may not be all-inclusive):

- CA 50 (cancer antigen 50)
- CA 72-4 (cancer antigen 72-4)
- CA 195 (cancer antigen 195)
- CA 242 (cancer antigen 242)

- CA 549 (cancer antigen 549)
- CAM 17.1 (monoclonal antimucin antibody 17.1)
- Cathepsin-D (Ab-1 monoclonal antibody)
- CYFRA21-1 (cytokeratin fragment 19)
- DCP (des-gamma-carboxy-prothrombin)
- DNA Ploidy (deoxyribonucleic acid ploidy)
- DU-PAN-2 (sialylated carbohydrate antigen)
- 5-HIAA (5-hydroxyindoleacetic acid)
- GCC (guanylyl cyclase C)
- HER2 gene amplification testing of breast cancer tissue (e.g., SPoT-Light[®] HER2 CISH[™])
- hMAM (human mammoglobin)
- LASA-P (lipid-associated sialic acid in plasma)
- LPA (lysophosphatidic acid)
- MCA (mucin-like cancer antigen)
- MCAM (melanoma cell adhesion molecule)
- microarray analysis for measuring the degree of similarity in undifferentiated tumor types (e.g., Pathwork[®] Tissue of Origin)
- microRNA testing for ANY of the following indications:
 - differentiating squamous cell non-small cell lung cancer (e.g., ProOnc SquamousDx[™])
 - aiding in the diagnosis of mesothelioma (e.g., ProOnc MesotheliomaDx[™])
 - identifying the tissue of origin of a metastatic tumor (e.g., ProOnc TumorSourceDx[™])
- multigene expression testing for EITHER of the following:
 - colon cancer recurrence (e.g., Oncotype DX[®] Colon Cancer Assay)
 - determining the molecular signature of a glioblastoma multiforme (GBM) tumor (e.g., DecisionDx-GBM)
- multiprotein panel testing for detection of ovarian cancer in a pelvic mass (e.g., OVA1[™])
- OPN (osteopontin)
- P53 (monoclonal antibody)
- P-LAP (placental alkaline phosphatase)
- PSMA (prostate-specific membrane antigen)
- S 100
- SCC-Ag (squamous cell carcinoma antigen)
- SLEX (sialyl Lewis x-antigen)
- SLX (sialyl X)
- TA-90
- TATI (tumor-associated trypsin inhibitor)
- TNF-a (tumor necrosis factor alpha)
- TPA (tissue polypeptide antigen)

General Background

Tumor markers are substances produced by cells in the body in response to cancer or certain benign conditions. The markers may be found in the blood, plasma, other bodily fluids (e.g., urine, saliva, sputum, cerebrospinal fluid, or effusions) and/or tissue. Although an abnormal marker level may suggest cancer, their presence does not confirm a diagnosis of cancer. Tumor markers are typically combined with other diagnostic studies (e.g., laboratory test, biopsy, radiological imaging) to confirm the presence of cancer. These markers may not be elevated in the presence of some cancers, especially in early stages of the disease, may not be specific to a particular type of cancer, and/or may be elevated by more than one type of cancer (National Cancer Institute [NCI], 2006; Nordenson, 2002).

In some types of cancers, tumor marker levels may reflect the extent or stage of the disease and can be useful in determining the most effective treatment and how well the disease will respond to the treatment. Typically, the primary use of tumor markers is to monitor a cancer's response to treatment with periodic measurements following therapy. Following therapy, a decrease in the marker level may indicate a response to therapy as

opposed to consistently elevated or rising marker levels which may be indicative of a lack of response to treatment or recurrence of the disease (American Cancer Society [ACS], 2009; NCI, 2006). The evidence in the published peer-reviewed literature and professional societies support tumor makers for the diagnosis and management of some cancers, while other tumor markers are still evolving and their clinical utility has not been proven.

U.S. Food and Drug Administration (FDA)

Devices with reagents that are used to “qualitatively or quantitatively measure, by immunochemical techniques, tumor-associated antigens in serum, plasma, urine, or other body fluids” and intended as an aid in monitoring patients for disease progress or response to therapy or for the detection of recurrent or residual disease” are approved by the FDA 510(k) process (FDA, 2009). Examples of these devices include the ARCHITECT® CA 125 II™ Assay (Fujirebio Diagnostics, Inc., Malvern, PA) and the IMMULITE® 2000 Calcitonin (Diagnostic Products Corporation, Los Angeles, CA) (FDA, 2004; FDA, 2002).

Urine-based tumor markers used for the management of bladder cancer also require FDA approval under the 510(k) process or the premarket approval process to aide in the diagnosis and monitoring of bladder cancer. The tests are not stand alone tests and are to be used in conjunction with cystoscopy, the gold standard for detecting bladder cancer. Examples of these urine-based tests include: BTA stat® Test (Bard Diagnostic, Redmond, WA); ImmunoCyte™ (Diagno-Cure Inc., Saite-Foy, Quebec, Canada); NMP22® BladderChek® Test (Matriech, Newton, MA); and the UroVysion™ Bladder Cancer Kit (UroVysion Kit, Vysis, Inc. [a wholly-owned subsidiary of Abbott Laboratories] Downers Grove, IL) (FDA, 2005; FDA, 2000).

Specific Tumor Markers (Refer to Appendix A for specific tumor markers by cancer type)

Evidence in the published peer-reviewed literature and/or professional societies and organizations, support the following tumor makers as established markers for the screening, staging, diagnosing, treatment planning, and/or follow-up of the indicated carcinomas. By using the information that these markers provide, patient-specific treatment protocols may be developed, implemented, and/or monitored for improved outcomes.

- AFP (alpha-fetaprotein) is recommended for the management of primary liver cancer or hepatocellular carcinoma (HCC) (also called hepatoma).
- AFP in combination with b-HCG (beta- human chorionic gonadotropin) is indicated for the diagnostic work-up, treatment monitoring and/or follow-up of individuals with suspected testicular germ cell carcinoma, germ cell ovarian cancer or an undiagnosed pelvic mass.
- β_2 M (beta₂-microglobulin) is included in the initial diagnostic work-up for multiple myeloma and is useful in the staging of the disease.
- Calcitonin may be used to help diagnose early thyroid medullary carcinoma and is recommended to assist in determining the extent of surgical intervention and follow-up of residual disease.
- CA (cancer antigen) 15-3 also referred to as CA 27.29, BR 27.29 or Truquant RIA, is an established marker used for the monitoring and follow-up of breast cancer.
- CA 19.9 (carbohydrate antigen 19.9) is the standard tumor marker for pancreatic cancer. It is also expressed in other malignancies (e.g., colorectal, lung, liver, gallbladder and gastric) but its usefulness in other cancers has not been proven.
- CA-125 is the standard tumor marker used for treatment monitoring and follow-up of epithelial ovarian cancer, endometrial cancer, and undiagnosed suspicious pelvic masses. CA-125 levels may also be elevated in cancers of the pancreas, liver, colon, breast, lung, and digestive tract, but its clinical utility in these cancers has not been established.
- CEA (carcinoembryonic antigen) is used for the management of colorectal cancer (CRC), medullary thyroid cancer and breast cancer. CEA has a low sensitivity and specificity; therefore, it not recommended as a screening tool.
- CgA (chromogranin A) is used primarily in the diagnosis and monitoring of patients with carcinoid tumors, islet cell tumors, pheochromocytoma, neuroblastoma, and other neuroendocrine tumors.
- C-kit, KIT, or CD-117 (cluster of differentiation-117) is a gene found in all cells of the body and leads to the formation of a protein called KIT. Most gastrointestinal stromal tumors (GIST) contain c-kit, making the test a useful diagnostic tool for this cancer. According to NCCN (2010), 95% of GISTs are positive for c-kit. C-kit is used to determine a patient’s eligibility for treatment with Gleevec® (imatinib mesylate), a protein-tyrosine kinase inhibitor. Gleevec inhibits c-kit inducing apoptosis. Gleevec is also indicated for the treatment of other cancers (e.g., chronic myeloid leukemia) by a proposed mechanism of inhibiting the BCR-ABL gene.

- ER/PR (estrogen receptors/progesterone receptors) receptors are recommended as part of the general work-up and treatment planning in breast cancer patients. These receptors are used to predict response to therapy and the likelihood of recurrence.
- HCG (human chorionic gonadotropin) or beta-HCG (β -HCG) may be elevated in patients with trophoblastic testicular cancer or trophoblastic ovarian cancer. HCG can be used to assist in the diagnosis of the cancer and monitoring the effectiveness of treatment.
- HER2 (human epidermal growth factor receptor 2), HER-2/neu, erbB-2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2) or EGFR2 (epidermal growth factor receptor), is a protein used to assist in the personal stratification of breast cancer patients to anti-HER-2-based therapies. The measurement of HER-2 is recommended in primary breast tumors at the time of diagnosis or at the time of recurrence. According to the National Comprehensive Cancer Network[®] (2010) and the National Academy of Clinical Biochemistry (2008), immunohistochemical (IHC) or fluorescent in situ hybridization (FISH) are the two established platforms used to evaluate HER2 levels in breast cancer patients. IHC measures the levels of the HER2 proteins on the surface of the tumor cells using monoclonal or polyclonal antibodies. The antibodies bind to the HER2 protein making it visible under a microscope. Fluorescent in situ hybridization (FISH) is a technique that uses fluorescent pieces of DNA that bind to the HER2 gene causing the gene to light up and be visualized under a microscope. Fish counts the HER2 gene copies and quantifies them in a ratio with chromosome 17 (CEP17). Typically, IHC is the first test used. If the results are unequivocal, or intermediate, FISH may be conducted. If FISH is unequivocal, the test should be repeated or additional cells counted (NACB, 2008). Detailed testing guidelines for IHC and FISH have been published by the American Society of Clinical Oncology (2007) and NCCN (2010). It has been reported that IHC has a false negative/false positive rate as high as 20% depending on the quality of the test utilized. FDA approval is not required for IHC- and FISH-based assays. Some tests are developed and performed in Clinical Laboratory Improvement Amendments (CLIA) laboratories.
- KRAS (Kirsten rat sarcoma) testing is recommended in patients with metastatic colorectal carcinoma from either a primary tumor or metastatic tumor tissue and in the work-up of patients with stage IV rectal cancer. KRAS has also been proposed for use in the management of non-small cell lung cancer and potentially other cancers, but its clinical utility has not been established (Okudela, 2010; Mao, 2009).
- MPO (myeloperoxidase) is a protein that is considered the hallmark enzyme of the myeloid lineage. The expression of the myeloid gene is specific for myeloid precursors and their leukemic counterparts. A positive stain analysis for MPO is diagnostic of acute myeloid leukemia (also called acute myelogenous leukemia, acute nonlymphocytic leukemia, or ANLL).
- NSE (neuron-specific enolase) is used to help determine the extent of the disease, the patient's prognosis, and the patient's response to treatment in the presence of small cell lung cancer (SCLC). This marker is not used as a screening test for cancer and should not be used alone to distinguish SCLC from non-small cell lung cancers.
- PSA (prostate-specific antigen) is an established marker used in the management of prostate cancer including risk stratification and predicting prognosis. PSA is commonly used as an adjunct to digital rectal exam. (For information on screening refer to the CIGNA Coverage Policy Prostate-Specific Antigen (PSA) Screening for Prostate Cancer).
- Thyroglobulin is most often measured in differentiated thyroid cancers (i.e., papillary, follicular, and Hurthle cell). Postoperative elevation of the thyroglobulin level above 10 nanograms per milliliter is suggestive of cancer recurrence.

Bladder Cancer Urine-Based Tumor Markers

Numerous urine-based tumor markers have been proposed for use as an adjunct in the diagnosis and management of bladder cancer. Standard testing includes the non-invasive urine cytology and the gold standard invasive cystoscopy which are typically used for diagnosing and monitoring bladder carcinoma. Following diagnosis and treatment for bladder cancer, urine-based tumor markers may be performed on a routine bases (e.g., every three to six months) to monitor for recurrence. It has been proposed that the use of these bladder markers, especially in combination (e.g., BTA with NMP22 or urine cytology with ImmunoCyte) may enhance specificity and sensitivity producing more reliable outcomes, and are therefore, indicated for the monitoring and/or surveillance of treatment response in patients with bladder cancer. These markers have not been established as a screening tool for bladder cancer.

- Bladder Tumor Associated Antigen (BTA) test, BTA stat[®] Test and the BTA TRAK[®] Assay tests are proposed for use in the early detection and monitoring for recurrence of bladder cancer. The BTA stat Test

is FDA approved for point-of-care and prescribed in-home use and may be used for the management of bladder cancer patients in conjunction with cystoscopy. These tests are proposed for use in the early detection and monitoring for recurrence of bladder cancer (FDA, 1998).

- ImmunoCyt™/yCyt+™ is an immunocytofluorescence assay FDA approved “for use in conjunction with cytology to increase overall sensitivity for the detection of tumor cells exfoliated in the urine in patients previously diagnosed with bladder cancer”. The intent is that the test be used in conjunction with urine cytology and cystoscopy (FDA, 2000).
- Nuclear matrix protein (NMP) 22, NMP22 Test Kit, is FDA approved as an aid in the diagnosis of individuals “with symptoms or risk factors for transitional cell cancer (TCC) of the bladder in conjunction with and not in lieu of current standard diagnostic procedures” and for the management of TCC of the bladder after surgical intervention to identify occult or rapidly recurring disease. The NMP22 BladderChek Test is FDA-approved for point-of-care professionals, as well as prescribed in-home use (FDA, 2002). NMP22 has not gained wide acceptance because of the high rate of false-positive tests and controversy over the optimal cut point for a positive test.
- UroVysion™ Bladder Cancer Kit (UroVysion Kit) is FDA approved for use in conjunction with standard diagnostic procedures “as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer” (FDA, 2005).

Other Bladder Cancer Markers: Several additional urine-based tumor markers are being investigated for use in diagnosing and managing bladder cancer, but their clinical utility has not been established. These include: UBC™ (IDL Biotech, Bromma, Sweden); BLCA-1 and BLCA-2; cytokeratins 8, 18 and 19; fibronectin; hyaluronic acid/ hyaluronidase; Lewis X antigen, microsatellite analysis; quanticyte; soluble fas; survivin (protein and mRNA), and telomerase (e.g., TRAP, hTert, hTR) (Hayes, Oct 2008; Shariat, et al., 2008).

Hyaluronic acid (HA)/hyaluronidase (HAase) testing has been proposed as a diagnostic tool for the screening and detection of bladder cancer. Studies have been primarily in the form of case series with small patient populations using various study protocol, HA assays, and criteria for outcomes (Simpson and Lokeshwar, 2008; Eissa, et al., 2005; Posey, et al., 2003). Lokeshwar et al. (2002) reported 91.0% sensitivity, 70% specificity, 87% accuracy, 92% positive predictive value (PPV), and 67% negative predictive value (NPV) in 70 bladder cancer patients. There were 14 false positives. The evidence in the peer-reviewed scientific literature does not support the accuracy and clinical utility of HA testing, nor have the data shown meaningful improvements in health outcomes.

Professional Societies/Organizations: NCCN (2010) does not recommend the use of bladder cancer tumor markers (e.g., NMP-22, BTA, M344) in the management of bladder cancer and states that “they are not used to guide treatment decisions outside of the experimental protocol setting”.

In their discussion of tumor marker studies, the ACS (2010) recognizes that NMP22, BTA stat test, ImmunoCyt test and UroVysion may be used to test for cancer but that most physicians felt that cystoscopy is the best way to diagnose bladder cancer. According to ACS, 50% of patients with bladder cancer have an abnormal NMP22, but the test seems better suited to check for bladder cancer recurrence.

The United States Preventive Services Task Force (USPSTF) (2004) published a recommendation on screening for bladder cancer in adults and noted that “screening tests have a low positive predictive value and yield many false-positive results, leading to unnecessary invasive procedures”. As a result, the USPSTF concluded that the potential harms of screening for bladder cancer outweigh any potential benefits.

Paraneoplastic Antibodies

While the supporting published evidence is limited, certain paraneoplastic/onconeural antibodies (i.e., anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-MA1 and anti amphiphysin), are established markers used to aid in the diagnosis of paraneoplastic syndromes and occult neoplasms (i.e., cancers of unknown origin). Paraneoplastic neurological syndromes/disorders (PNS/PND), a rare group of disorders (e.g., limbic encephalitis, progressive cerebellar degeneration), are associated with malignancies but not directly related to the physical effects of the tumor or its metastasis. PNS occurs as a result of damage to the nervous system in the presence of cancer and is thought to arise from an autoimmune response against neuronal antigens (onconeural antibodies) expressed by malignant tumors. It presents in less than 1% of patients with cancer and may be evident prior to the

diagnosis of cancer. PNS is most often associated with small cell lung cancer, but can also be present in other cancers (e.g., thymoma and neuroblastoma), and nonmalignant disorders (National Institute of Neurological Disorders and Stroke, 2009; Dalmau and Rosenfeld, 2008; Rugo, 2007; Spiro, et al., 2007; Bataller and Dalmau, 2005; Graus, et al., 2004).

Patients with paraneoplastic antibodies typically present with neurological symptoms (e.g., abnormal balance, coordination, motor skills). If initial diagnostic studies (e.g., laboratory, radiography, cerebral spinal fluid analysis, and/or electromyography) are negative, testing for paraneoplastic antibodies may be warranted. If the test is positive for a paraneoplastic antibody, it may help to focus the search for the neoplasm and establish the diagnosis of cancer. Continued testing (e.g., computed tomography, ultrasound) and early diagnosis for an underlying neoplasm would allow for early treatment of the cancer and could also improve the symptoms of PNS. The diagnosis of PNS is typically made when the neurological syndrome, the associated cancer and the paraneoplastic antibodies are identified. In 90% of patients with paraneoplastic antibodies, the underlying tumor is diagnosed within the first year of PNS symptoms (NCCN, 2009; Dalmau and Rosenfeld, 2008; Spiro et al., 2007; Bataller and Dalmau, 2005).

The specificity of paraneoplastic antibodies reported to be greater than 90% for paraneoplastic neurologic syndromes or some types of cancer makes them useful diagnostic tools. However, not all paraneoplastic antibodies have the same sensitivity and specificity. Hu antibodies, most often associated with subacute sensory neuropathy (SSN) and small cell lung cancer, have an estimated specificity of 99% and a sensitivity of 82% (Dalmau and Rosenfeld, 2008; Honnorat and Antoine, 2007; Vedeler, et al., 2006).

According to an international panel of neurologists, paraneoplastic antibodies are generally categorized as well-characterized or partial characterized. Well-characterized, antibodies are reactive with molecularly defined onconeural antigens, prove the paraneoplastic etiology of the neurological syndrome, and are strongly associated with cancer. The well-characterized paraneoplastic antibodies include: anti-Hu (antineuronal nuclear autoantibodies-1 [ANNA-1]), anti-Yo (PCA-1 [Purkinje cell antibody-1]), anti-CV2 (CRMP5 [collapsing mediator response protein]), anti-Ri (ANNA-2), anti-MA2 (Ta), and anti-amphiphysin. Partially-characterized antibodies are antibodies with an unidentified target antigen and have only been found in a few patients. The partially-characterized antibodies (i.e., antibodies with an unidentified target antigen) include anti-Tr (PCA-Tr), ANNA-3, PCA-2, anti-recoverin, anti-Zic4, anti-mGluR1. The detection of partially-characterized antibodies is considered of limited diagnostic value. Antibodies that can be detected in paraneoplastic and nonparaneoplastic form and can occur with and without cancer include: anti-VGCC (voltage-gated calcium channel), anti-AchR (acetylcholine receptor), anti-nAChR (nicotine acetylcholine receptor), and anti-VGKC (voltage-gated potassium channels) (Monstad, et al., 2009; De Graaf and Smitt, 2008; deBeukelaar and Smitt, 2006; Vedeler, et al., 2006; Battler and Dalmau, 2005; Karim, et al., 2005; Vincent, 2005; Graus, et al., 2004).

Professional Societies/Organizations: In their guidelines for small cell lung cancer the National Comprehensive Cancer Network® (NCCN) (2010) notes that “many neurologic and endocrine paraneoplastic syndromes are associated with SCLC [small cell lung cancer]”. In the thymic malignancies guidelines under the principles of radiation therapy, NCCN (2010) states that “prior RT [radiation therapy], any cardiac, pulmonary and/or neurological toxicities related to the paraneoplastic syndrome, surgery or the induction chemotherapy need to be documented as baseline”. In the NCCN 2009 task force report on the management of neuropathy in cancer, NCCN stated that a number of paraneoplastic antibodies have been characterized including anti-CV2/CRMP5 and anti-Hu. NCCN noted that laboratory studies such as the paraneoplastic panel (anti-Hu, anti-Yo, anti Mag) may aid in the diagnosis of PNS.

The National Cancer Institute (2010) states that SCLC is the cancer most often associated with paraneoplastic syndromes (e.g., syndrome of antidiuretic hormone secretion, paraneoplastic cerebellar degeneration and Lambert-Eaton myasthenic syndrome). NCI (2010) also notes that PNS may be present in thymoma/thymic cancers.

In their guideline for the initial evaluation of patients with lung cancer, the American College of Chest Physicians (ACCP) (Spiro, et al., 2007) stated that the initial evaluation of the patient should include identification of those patients with PNS and recommended “that patients with lung cancer and a paraneoplastic syndrome not be precluded from potentially curative therapy on the basis of these symptoms alone”.

The European Federation of Neurological Societies (Vedeler, et al., 2006) published guidelines for the management of PNS and stated that “patients with paraneoplastic neurological syndrome (PNS) most often present with neurological symptoms before an underlying tumor is detected. Onconeural antibodies should be sought in sera from patients with suspected PNS. The antibodies are important for diagnosis and tumor search”.

Other Markers

Numerous proteins, receptors, and antigens are currently being investigated to determine their accuracy in cancer detection, measurement of tumor treatment response, and determination of recurrence. The role of these markers in the management of various carcinomas has not yet been established. Research through well-designed, randomized controlled trials is indicated to aid in determining the clinical utility of these additional tumor markers.

CA 50 (Cancer Antigen 50): This antigen has yet to be proven effective in the diagnosis, prognosis, management or surveillance of pancreatic cancer (NACB, 2006).

CA 72-4 (Cancer Antigen 72-4): CA 72-4 is being studied for possible prognostic use and post-operative surveillance of patients who have been diagnosed with gastric and colorectal cancer. It detects the presence of AG-72, a mucin-like complex molecule found on the surface of cancer cells. Studies have provided conflicting results and its use is not recommended (NACB, 2010; ACS, 2009; Lee, et al., 2006; Nordenson, 2002).

CA 195 (Cancer Antigen 195): In studies conducted to date, this antigen has yet to be proven effective in the diagnosis, prognosis, management or surveillance of pancreatic cancer (NACB, 2006).

CA 242 (Cancer Antigen 242): Ca 242 has been proposed as a surveillance marker for colorectal cancer. This marker is less sensitive than CEA but may complement CEA. Some preliminary studies have suggested that preoperative concentration of CA 242 may be prognostic of colorectal cancer. However, routine use of CA 242 is not recommended in patients with CRC (NACB, 2009).

CA 549 (Cancer Antigen 549): CA 549 has been proposed as a marker for breast cancer, has been studied in pleural fluids, and used in conjunction with CEA. Its clinical value has not been established (Lee et al., 2006).

CAM 17.1 (Monoclonal Mucin-Based Antibody): CAM 17.1 is an antigen and a mucin-based marker. The diagnostic sensitivity of CAM has not been proven to be as effective as CA 19-9 in studies that have been conducted to date for the treatment of pancreatic cancer (NACB, 2006).

Cathepsin D (Ab-1 Monoclonal Antibody): This is an Ab-1 monoclonal antibody that is currently being studied as a possible marker for use in determining breast cancer prognosis. The results obtained from the studies have been conflicting and this marker is not in clinical use (NACB, 2009; ASCO, 2007).

CYFRA 21-1 (Cytokeratin-19 fragments): This tumor marker has been found in the presence of urological, gastrointestinal, and gynecological cancers. Although some study results are promising for the use of this marker in detecting squamous cell tumors, additional research is needed to determine if its specificity can be useful in the diagnosis and treatment of patients with lung cancer (Lokeshwar, 2005).

DCP (Des-Gamma-Carboxy Prothrombin): DCP, also known as protein induced by vitamin K absence-II (PIVKA-II), is a serum marker under investigation for the detection of hepatobiliary carcinoma. DCP has been proposed as a prognostic factor for recurrence and survival after hepatic resection. Studies are comparing DCP to AFP to determine if DCP is more accurate than AFP or if DCP could be used in conjunction with AFP. The rate of detectable serum DCP is low in patients with small hepatocellular cancers and sensitivity has been reported at 50% (Hakamade, et al., 2008; Wang, et al., 2005). According to the National Comprehensive Cancer Network (2010) and the NACB (2010) DCP is not an established marker for hepatobiliary cancers.

DNA Ploidy (Deoxyribonucleic Acid Ploidy): A DNA ploidy test can measure DNA in tumor cells, and researchers have proposed its use in detecting breast cancer. Studies to date have failed to show its effectiveness in the diagnosis or surveillance of breast cancer. ASCO does not recommend the use of this tumor marker as a prognostic indicator or as a monitor of treatment response in women with breast cancer (ACSO, 2007; Harris, et al., 2007).

DU-PAN-2: Is a sialylated carbohydrate antigen expressed in the presence of pancreatic cancer but its sensitivity and specificity have not been proven to be as good as CA 19.9 (Chung and Podolsky, 2006; Cwik, et al., 2006).

5-Hydroxyindoleacetic Acid (5-HIAA): 5-HIAA is proposed for use in the diagnosis of carcinoid tumors especially of the small intestine and is being investigated as a prognostic factor. However, poor correlation exists between 5-HIAA levels and the clinical severity of carcinoid syndrome. 5-HIAA is measured in the urine and can also be measured within plasma, but its levels may fluctuate; and its use as a long-term follow-up marker has not been proven (AHRQ, 2006; NACB, 2006)

GCC (Guanylyl Cyclase C): GCC or GUCY2C is a heat-stable enterotoxin receptor that may be useful as a marker to identify patients with colorectal cancer or early pre-malignant changes in the upper gastrointestinal tract. GCC is normally expressed in the intestinal tract on the luminal side of the intestinal epithelial cells, and it persists after neoplastic changes occur (Schulz, et al., 2006). An example of a GCC test is the Previstage™ GCC Colorectal Cancer Staging Test (DiagnoCure Oncology Laboratories, Quebec QC, CAN).

HER2 Gene Amplification Testing of Breast Cancer Tissue (e.g., SPoT-Light® HER2 CISH™): Spot-Light HER2 CISH (Invitrogen Corp, Carlsbad, CA) received FDA premarket approval to “quantitatively determine HER2 gene amplification in formalin-fixed, paraffin-embedded (FFPE) breast carcinoma tissue sections using Chromogenic In Situ Hybridization (CISH) and brightfield microscopy”. The test “is indicated as an aid in the assessment of patients for whom Herceptin® (trastuzumab) treatment is being considered. The assay results are intended for use as an adjunct to the clinicopathological information currently being used as part of the management of breast cancer patients. Interpretation of test results must be made within the context of the patient's clinical history by a qualified pathologist”. The test is proposed to detect hybridization of labeled nucleic acid probes using conventional peroxidase-diaminobenzidine (DAB) reactions, allowing the pathologist to see tissue morphology and gene aberrations simultaneously (FDA, 2008). CISH is an evolving technology that is also purposed to incorporate advantages of both IHC and FISH. There is insufficient evidence in the published peer-reviewed scientific literature to support the accuracy, clinical utility, and impact on meaningful health outcomes of Spot-Light HER2 CISH.

Madrid and Lo (2004) conducted a study to assess the accuracy of the Spot-Light CISH assay (n=160) compared to results of previously reported IHC analysis in women with breast cancer. The specimens were divided into the four IHC scores, 0–1+ (negative), 2+ (equivocal), and 3+ (positive) (n=40 samples per group), and compared to the CISH low and high risk scores. The concordance between CISH and IHC 0–1+ and 3+ tumors was 100% each, 45% on IHC 2+ tumors, 72.50% on all positive IHC tumors, and overall concordance was 86.25%. All IHC negatives were CISH non-amplified and all IHC 3+ were CISH amplified. The authors acknowledged that the clinical utility of the low- and high-amplified CISH results has not been established.

hMAM or MG (Human Mammoglobin): hMAM is a gene which encodes similar to epithelial secretory proteins which are part of the uteroglobin family. Its expression has been linked to epithelial breast tumor cells. There is minimal information in the literature that demonstrates the clinical utility of hMAM expression or patient net health outcomes from its clinical application (Nunez-Villar, 2003).

LASA-P (Lipid Associated Sialic Acid in Plasma): LASA-P has been studied as a possible marker for ovarian cancer as well as several other cancers. This marker has not been proven to be valuable in the detection of cancer. LASA-P is not specific for any particular cancer or even for cancer in general, as it can also be elevated in some noncancerous conditions. It may be occasionally used along with other markers to follow response to treatment, but CA 125 is the standard marker (ACS, 2009).

LPA (Lysophosphatidic Acid): LPA is a “multifunctional signaling molecule in fibroblasts and other cells” and has been found in patients with ascitic fluid due to ovarian cancer cell proliferation (Hussain, 2010). According to NCI, studies have included small patient populations and “comprise highly-selected known ovarian cancer cases and healthy controls of the type evaluated in early biomarker development phases I and II. Results have not been consistently replicated in multiple studies; presently, none are considered ready for widespread clinical application” (NCI, 2010)

MCA (mucin-like carcinoma antigen): MCA is a glycoprotein oncofetal antigen related to tumor burden, milk production and fetal development that has been proposed as a tumor marker for breast cancer. The low specificity of MCA limits its clinical application (Sarandakou, et al., 2007; Nicolini, et al., 2006).

MCAM (Melanoma Cell Adhesion Molecule): This molecule is an integral membrane glycoprotein with Ca^{2+} independent cell adhesive properties, which can result in dynamic actin-cytoskeleton rearrangements. This activity can lead to cell detachment and migration which are key functions in metastases and invasion of cancers. The presence of this glycoprotein has been noted in the presence of several cancers, and promising findings have been noted in its relation to melanoma. Its use is currently under investigation to determine its ability to be utilized as a melanoma tumor marker (NACB, 2006).

Microarray Analysis for Measuring the Degree Of Similarity in Undifferentiated Tumor Types (e.g., Pathwork[®] Tissue Of Origin): The Pathwork[®] Tissue of Origin (Pathwork Diagnostics, Inc., Redwood City, CA) is a 510(k) FDA-approved microarray analysis intended to “measure the degree of similarity between the RNA expression patterns in a patient’s formalin-fixed, paraffin-embedded (FFPE) tumor and the RNA expression patterns in a database of fifteen tumor types (poorly differentiated, undifferentiated and metastatic cases) that were diagnosed according to then current clinical and pathological practice. This test should be evaluated by a qualified physician in the context of the patient’s clinical history and other diagnostic test results”. The test is “not intended to establish the origin of tumors (e.g. cancer of unknown primary) that cannot be diagnosed according to current clinical and pathological practice” nor is it intended to “subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathological practice, nor to predict disease course or survival or treatment efficacy, nor to distinguish primary from metastatic tumor”. Pathwork uses the Pathchip technology (Affymetrix, Inc., Santa Clara, CA) which is a custom-designed microarray that uses oligonucleotide features to analyze the tissue samples (FDA, 2010).

An algorithm using a list of markers, a set of reference genes, and a set of coefficients were combined to produce 15 Similarity Scores (ranging from 0–100), one for each of the possible tissues on the test panel. The higher the score, the more likely the tissue corresponds to the molecular marker (i.e., reference tissue). The 15 tumor types that the study analyzes include: bladder, breast, colorectal, gastric, hepatocellular, kidney, melanoma, non-Hodgkins lymphoma, non-small cell lung, ovarian, pancreatic, prostate, sarcoma, testicular germ cell tumor, and thyroid (FDA, 2010). The proposed utility of the test is that the ability to identify the tissue of origin would increase the chances of the patient receiving more targeted, less toxic therapy; enhance optimal management; and reduce the amount of time and expense diagnosing the primary tumor (Monzon, et al., 2010).

For FFPE testing, overall accuracy (n=162 total samples) tested by three laboratories was 82.1%. Agreement/non-agreement was reported by tissue type and agreement ranged from 79.3% (bladder) to 96.5% (breast). Overall agreement to available diagnosis was 88.5% and non-agreement was 11.5%. Agreement for metastatic tumors was 91.1%, and non-agreement was 8.9%. Agreement for poorly and undifferentiated primary tumors was 86.9% and non-agreement was 11.5% (FDA, 2010). There is insufficient evidence in the published peer-reviewed literature to support the clinical utility of Pathwork and its impact on meaningful health outcomes.

Using the Pathwork Tissue of Origin test, Monzon, et al (2010) retrospectively measured gene expression of fresh-frozen specimens from 21 patients with carcinoma of unknown primary (CUP). The specimens were obtained from tissue bank archives and taken from over a dozen biopsy sites. The study aims were to “evaluate the test’s ability to issue a clear positive call in classic CUP specimens, to check the consistency of the test results against a short-list of diagnostic possibilities based on clinicopathology, and to estimate the potential added clinical value of positive and negative results in guiding management”. Pathwork reported a positive single tissue in 16 (76%) specimens and identified 16 primary sites (i.e., five colorectal, four breast, three ovary, two lung and two pancreas). Five cases were indeterminate (24%). The Pathwork results were consistent with 10 (62%) clinicopathologic suggestions. On average, the test ruled out 11 tissue types per case. The small patient population and retrospective design preclude the ability to draw any conclusions from this study.

Monzon et al. (2009) conducted a blinded multicenter validation study (n=547) of the Pathwork test using a 1550 gene expression profile. The study included 351 frozen specimens obtained from a tissue bank and 271 electronic files of microarray data from the International Genomics Consortium. The specimens were histologically verified and included metastatic tumors and poorly differentiated or undifferentiated primary tumors. Overall agreement was 87.8%, positive percent agreement (sensitivity) was 87.8% and the negative

percent agreement (specificity) was 99.4%. Overall rate of non-agreement was 7.1% and the rate of indeterminate calls was 5.1% (n=28). Highest rate of agreement was for breast cancer (94.1%) (n=68) and the lowest was 72% for gastric and pancreatic cancers (n=25 each). Performance for the test was significantly better for primary tumors (90.7% agreement) (n=289) than for metastatic tumors (84.5% agreement) (n=258) (p=0.04). There were no significant differences in the rates of agreement between the three laboratories. Author noted limitations of the study included: the “inability to independently verify the reference diagnosis used to assess the accuracy of the test” (i.e., diagnoses were taken from the surgical pathology report at the time the tissue was banked); due to blinding, the pathologist was unable to consult with the treating physician, and the test is designed to be interpreted with clinical information; and there is a possibility that an uncertain primary cancer could originate from a site that is not included in the Pathwork test.

The 2010 National Institute for Health and Clinical Excellence (NICE) guidance document on the diagnosis and management of carcinomas of unknown primary (CUP) recommends against the use of gene-expression-based profiling (e.g., Pathwork Tissue of Origin) to identify primary tumors in patients with provision CUP. There is limited evidence that gene-expression profiling changes the management of the patient, there is no evidence of improvement of outcomes.

In their clinical practice guidelines on CUP, NCCN (2010) states that “gene signature profiling for tissue of origin is not recommended for standard management at this time”. The data is insufficient to determine if testing would improve prognosis.

MicroRNA Testing: MicroRNA testing has been proposed for aiding in the differentiation or diagnosis of various types of cancers. Studies supporting the accuracy, clinical utility and impact on meaningful health outcomes of microRNA testing for these indications are lacking.

ProOnc Squamous^{Dx™} is proposed to differentiate squamous from non-squamous non-small cell lung cancer (NSCLC) based on miRNA hsa-miR-205 expression levels which may be over expressed in squamous cancers. The hypothesis is that once the cell type is identified, treatment can be targeted to the specific cancer type (Prometheus, 2010). In a validation study, using quantitative real-time polymerase chain reaction (qRT-PCR), Lebanony et al. (2009) reported that the sensitivity of identifying squamous cell carcinoma with has-miR-205 expression was 96% (23 of 24 samples) with 79% classified as squamous with high confidence. The specificity of the test for classifying samples as nonsquamous was 90% (44 of 49 samples).

ProOnc Mesothelioma^{Dx™} is proposed to aid in the diagnosis of mesothelioma based on the expression level of three microRNAs, hsa-miR-193-3p, hsa-miR-200c, hsa-miR-192. The test is purported to differentiate mesothelioma from other lung and pleura carcinomas (Prometheus, 2010).

ProOnc TumorSource^{Dx™} is described as using 48 miRNAs to identify the tissue of origin of a metastatic tumor, also called unknown primary cancer, occult primary malignancy, or occult primary tumor, from fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tissue. The test is proposed to identify 25 classes of tissue origin including breast, colon, lung, prostate, ovarian and kidney. Using a dual algorithm approach of decision tree and K Nearest Neighbor analyses, concordant results were reported as having occurred with 66% of samples with 80%–84% overall sensitivity of tissue-of origin/histological type and 87%-90% sensitivity of single predicted origin (Prometheus, 2010).

Multigene Expression Testing: Multigene expression testing has been proposed as a platform for genetic profiling for predicting colon cancer recurrence and for determining the molecular signature of a glioblastoma multiform (GBM) tumor.

The 12-gene Oncotype DX[®] Colon Cancer Assay (Genomic Health, Redwood City, CA) reverse transcriptase polymerase chain reaction (RT-PCR) assay is a proposed method of predicting the risk of stage II colon cancer recurrence and aiding in the decision regarding adjuvant chemotherapy. This is done through the reporting of an individualized Recurrent Score (RS) that ranges from 0-100. The RS is based on the quantitative expression of seven cancer genes (i.e., Ki-67, MYBL2, C-MYC, FAP, INHBA, BGN and GADD45B) and five reference genes (i.e., ATP5E, PGK1, GPX1, UBB, VDAC2). The test is only applicable to newly diagnosed adenocarcinoma or mucinous stage II colon cancer patients who have undergone surgical resection. It has been suggested that patients with a high RS (i.e. ≥ 41) are the best candidates for adjuvant therapy. The assay is performed on

paraffin-embedded primary colon tumor tissue by Genomic[®] Health's clinical laboratory improvement amendments (CLIA)-certified, College of American Pathologists (CAP)-certified laboratory (Genomic Health, 2010; Webber, et al., 2010). Studies supporting the accuracy, clinical utility and impact on meaningful health outcomes of Oncotype DX Colon Cancer Assay are lacking (Marshall, 2010; Midgley, et al., 2010; Rasul and Kerr, 2010; Webber, et al., 2010). The role of this testing in patient management has not yet been established.

In their colon cancer guidelines, NCCN (2010) states that there is "insufficient evidence to recommend the use of multi-gene assay panels to determine adjuvant therapy".

The DecisionDx-GBM (Castle Biosciences Inc., Phoenix AZ) is a multigene expression assay proposed to allow stratification of a tumor's response to first-line therapy (i.e., radiation and temozolomide) in a newly-diagnosed patient with a grade IV GBM. The assay uses reverse transcriptase polymerase chain reaction (RT-PCR) to determine the expression of a 12-gene panel (i.e., AQP1, CHI3L1, EMP3, GPNMB, IGFBP2, LGALS3, OLIG2, PDPN, RTN1 and three control genes, EEF1A1, GUSB, RPS27). Validation studies (n=169) reported that DecisionDX-GBM was significantly predictive of progression-free (p=0.0003) and overall survival (p=0.003). It is proposed that a patient with a DecisionDX score within the first quintile has a likelihood of survival for up to two years. The hypothesis is that if the patient is not predicted to survive for two or more years the treatment plan would be altered and not include first-line therapy. The test is performed by Castle, a CLIA-certified laboratory (Castle Biosciences Inc., 2009; Colman et al., 2009). There is insufficient evidence in the published peer-reviewed literature to support the accuracy and clinical utility of DecisionDx, and its impact on meaningful health outcomes.

Multiprotein Panel Testing for the Detection of Ovarian Cancer in a Pelvic Mass (e.g., OVA1™): OVA1 (Vermillion, Inc., Fremont, CA) is an FDA 510(k)-approved in vitro diagnostic multivariate index (IVDMIA) test performed on serum and includes five immunoassay biomarkers: transthyretin (TT or prealbumin), apolipoprotein A-1 (Apo A-1), beta2-microglobulin (beta2M), transferrin (Tfr) and cancer antigen 125 (CA 125 II). Using an algorithm, a numerical score of 0–10 is produced from the results of all five markers to help determine if a pelvic mass is benign or malignant. This information is proposed to aid the physician in determining what type of surgery should be done and by which specialist. The test is intended for use in women age 18 years and older who have an ovarian adnexal mass for which surgery is planned, but prior clinical and radiological evaluation does not indicate a malignancy. The test should not be used alone, is not recommended for screening or diagnosing ovarian cancer, and should not be used in an individual with a diagnosis of malignancy within the past five years. (FDA, 2009; Quest Diagnostics, 2009). There is insufficient evidence in the published, peer-reviewed literature to establish the clinical utility of OVA1.

In a study submitted to the FDA in which patients (n=269) were treated by non-gynecologic oncologists, results of OVA1 were compared to pathology reports from biopsied tissue. Overall, pre-surgical assessment (i.e., single assessment) revealed a sensitivity of 61.0%–81.2%, specificity of 76.9%–87.4%, positive predictive value of 49.9%–70.1%, and a negative predictive value of 83.7%–92.8%. With dual assessments (i.e., pre-surgical and OVA1 assessment), the values included: sensitivity of 83.0%–96.1%, specificity of 35.0%–48.6%, positive predictive value of 29.8%–43.7%, and negative predictive value of 85.9%–96.8%. Sensitivity was as high as 96% in postmenopausal women. The prevalence of malignancy among patients with adnexal mass assessed by non-gynecologic oncologists was 26.8% (FDA, 2009).

Kozak et al. (2005) tested samples collected preoperatively from 31 healthy individual and 43 patients with ovarian tumors stages I-IV. Samples were tested with purified protein preparations of transthyretin (TTR), hemoglobin (Hb), transferrin (TF) and apolipoprotein AI (ApoAI). Using search criteria, TTR, beta-Hb, and ApoAI, were identified as potential candidate proteins for markers 13.9, 15.9, and 28 kDa peaks, respectively. Using Western blotting, TTR, Hb and TF expression were further confirmed. Elisa experiments confirmed differential expression of TTR, Hb, ApoAI and TF. With the exception of Hb, statistical analysis of Elisa data showed a statistically significant difference between normal tissue samples and the early stage tumor samples. Results showed that when combined with CA125, sensitivity and specificity were improved for all histological groups. Based on the stage of the tumor, the percentage of sensitivity and specificity varied from 64% (n=11) with CA 125 alone to 100% (n=3) when TTR, Hb, ApoAI, TF were combined with CA125. Together TTR, Hb, ApoAI, TF and CA125 improved ovarian tumor detection by 8% compared to CA125 alone and improved sensitivity of detecting mucinous tumors (n=11) by 31% over CA125 alone.

In their practice guidelines for ovarian, fallopian tube, and primary peritoneal cancers, NCCN (2010) notes that the Society of Gynecologic Oncologists and the FDA do not recommend OVA1 as a screening tool to detect ovarian cancer, but agree that all patients should undergo surgery by an experienced gynecologic oncologist.

The Society of Gynecologic Oncologists' statement regarding OVA1 (2009) included "this test has not been approved for use as an ovarian cancer screening tool, nor has it been proven to result in early detection or reduce the risk of death from this disease".

OPN (Osteopontin): OPN is a secreted adhesive glycoprotein, originally isolated from bone extracellular matrix and proposed as a potential marker for metastatic uveal melanoma. An early pilot study (n=27) reported statistically significant differences in the levels of OPN in patients with metastases compared to patient without metastases (Reiniger, et. al., 2007). There is insufficient evidence to support the use of OPN as a marker for uveal melanoma.

P53 (Monoclonal Antibody): P53 has been proposed for use in prognosis and prediction of recurrence and disease-free survival of breast, prostate, colorectal, gastric and bladder cancer. Although researchers have used immunohistochemical assays in an attempt to determine if the detection of P53 could be a useful marker, their findings have been inconclusive (ASCO, 2006; AHRQ, 2006; Pister, et al., 2005). Regarding bladder cancer NCCN (2010) states that P53 is still considered experimental.

PLAP (Placental Alkaline Phosphatase): PLAP was first identified in patients with lung cancer and later in other cancers. PLAP has been proposed as a marker for testicular cancer and "is detected in most seminomas and embryonal carcinomas, in 50% of yolk sac tumors and choriocarcinomas, but only rarely in teratomas". PLAP levels may be increased up to 10-fold in smokers. This and the paucity of commercial assays limit its clinical application and serum assays for PLAP are not routinely included in the diagnostic work up of testicular cancer patients (NACB, 2009).

PSMA (Prostate-Specific Membrane Antigen): PSMA has been proposed as a marker for the monitoring of prostate cancer, but has not been proven to be better than PSA (ACS, 2009).

S-100: S-100 is a protein that can be found in most melanoma cells. Tissue samples may be tested for this marker to help in diagnosing melanoma metastasis (ACS, 2009). Additional research of this protein is needed to determine its accuracy in being used as a tumor marker.

SCC-Ag (Squamous Cell Carcinoma Antigen): SCC-Ag has been proposed as a possible serum tumor marker to be used for the detection of various types of squamous cell tumors, including non-small cell lung cancer, cervical cancer, and esophageal cancer. This marker may also be referred to as tumor-associated antigen (TA-4) because SCC-Ag is thought to be a part of this larger molecule. Studies conducted to date on this antigen have not proven its efficacy on patient morbidity and mortality. Sensitivity and specificity have not been analyzed to identify which patient population would benefit from the use of this marker in determining prognosis, treatment planning and/or follow-up (Hayes, Jul 2005).

SLEX (Sialyl Lewis X Antigen): SLEX is proposed to be expressed in liver disease, and hepatocellular carcinomas. The expression of SLEX by cancer of an epithelial origin correlates with metastases and poor prognosis (Varki, et al., 2008; Malagolini et al., 2007; Bachner, 2005). There is a lack of evidence to support the use of SLEX as a tumor marker in the management of carcinomas.

SLX (Sialyl X): SLX is a carbohydrate antigen adhesion molecule on the cell surface of adenocarcinomas. It has been reported to be elevated in many types of carcinoma including advanced non-small lung cancer or in the presence of metastasis. In gastric and colon cancer, elevated levels of SLX have been associated with lymph node and distant metastasis, but its clinical utility has not been established (Mizuguchi, et al., 2007).

TA-90 (Tumor Antigen 90): TA-90 is a protein that is found on the outer surface of melanoma cells and has been proposed for the detection of metastasis of melanoma cells. TA-90 has also been proposed for use in colon and breast cancers but its value is undetermined and it is not widely used at this time (ACS, 2009).

TATI (Tumor-Associated Trypsin Inhibitor): Elevated levels of this inhibitor have been found in patients with various cancers including gynecological and pancreatic. Because of TATI's low sensitivity it is not recommended for monitoring disease (NACB, 2009).

TNF-a (tumor necrosis factor alpha): TNF plays a significant role in inflammation and immune response and is found in the serum of cancer patients, rheumatoid arthritis, infections and acquired immunodeficiency syndrome (AIDS) (Tisdale 2008; Elghetany and Banki, 2006). The clinical utility of this marker in the management of cancer patients has not been established.

TPA (Tissue Polypeptide Antigen): This protein marker has been found in high levels in patients with lung, liver, bladder, and many other cancers. TPA is not an established tumor marker because it is not specific to one particular cancer and is also elevated in noncancerous conditions (NACB, 2010; NACB, 2009).

Summary

Recommendations and guidelines by professional societies and organizations and evidence in the published peer-reviewed scientific literature support the use of defined tumor makers for the screening, diagnosis, treatment planning, treatment-monitoring and/or follow-up of specific cancers. However, numerous proposed other tumor markers have not been proven to be of clinical value and are still being investigated to determine their utility in the management of individuals with cancer.

Appendix A Tumor Markers by Cancer Type Covered as Medically Necessary

Cancer Type	Tumor Marker(s)
Acute myeloid leukemia	MPO
Bladder	BTA, ImmunoCyte, NMP22, UroVysion
Breast	CA 15-3 (for metastatic breast cancer), CEA, ER/PR, HER2
Colorectal	CEA
Colorectal, Metastatic	KRAS
Endometrial	CA-125
Gallbladder	None Indicated
Gastrointestinal stromal tumors	C-kit, CD-117
Gastric	None Indicated
Hepatocellular	AFP
Lung, Non-Small Cell	NSE
Multiple Myeloma	B ₂ M
Neuroendocrine (e.g., carcinoid tumors, neuroblastoma, and small cell lung cancer)	CgA
Ovarian, Epithelial	CA-125
Ovarian, Germ Cell	AFP with b-HCG
Ovarian, Trophoblastic	HCG
Pancreatic	CA 19.9
Pelvic Mass, Undiagnosed	AFP with b-HCG, CA-125
Prostate	PSA*
Gastric	None Indicated
Testicular, Germ Cell	AFP with b-HCG
Testicular Trophoblastic	HCG
Thyroid, Medullary	Calcitonin, CEA
Thyroid, Differentiated	Thyroglobulin

*Refer to CIGNA Coverage Policy Prostate-Specific Antigen (PSA) Screening for Prostate Cancer

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT^{®*} Codes	Description
82105	Alpha-fetoprotein; serum
82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)
82232	Beta-2 microglobulin
82308	Calcitonin
82378	Carcinoembryonic antigen (CEA)
83520 [†]	Immunoassay, analyte, quantitative; not otherwise specified
83876	Myeloperoxidase (MPO)
83950	Oncoprotein, HER-2/neu
84152	Prostate specific antigen (PSA); complexed (direct measurement)
84153	Prostate specific antigen (PSA); total
84154	Prostate specific antigen (PSA); free
84181	Protein; Western Blot, with interpretation and report, blood or other body fluid
84182	Protein; Western Blot, with interpretation and report, blood or other body fluid, immunological probe for band identification, each
84233	Receptor assay; estrogen.
84234	Receptor assay; progesterone
84432	Thyroglobulin
84702	Gonadotropin, chorionic (hCG); quantitative
84703	Gonadotropin, chorionic (hCG); qualitative
84704	Gonadotropin, chorionic (hCG); free beta chain
86294	Immunoassay for tumor antigen, qualitative or semiquantitative (eg, bladder tumor antigen)
86300	Immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)
86301	Immunoassay for tumor antigen, quantitative; CA 19-9
86304	Immunoassay for tumor antigen, quantitative; CA 125
86316 ^{††}	Immunoassay for tumor antigen, other antigen, quantitative (eg, CA 50, 72-4, 549), each
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; manual
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody; using computer-assisted technology
88367	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; using computer-assisted technology
88368	Morphometric analysis, in situ hybridization, (quantitative or semi-quantitative) each probe; manual

[†]**Note:** Covered as medically necessary when used to report the anti-Hu (ANNA-1 [antineuronal nuclear autoantibodies-1]) test.

^{††}**Note:** Covered as medically necessary when used to report the Chromogranin A (CgA) and Neuron-specific enolase (NSE) tests.

HCPCS Codes	Description
G0103	Prostate cancer screening; prostate specific antigen test (PSA)
S3713	Kras mutation analysis testing

ICD-9-CM Diagnosis Codes	Description
153.0-153.9	Malignant neoplasm of colon
154.1	Malignant neoplasm of rectum
155.0	Malignant neoplasm of liver, primary
157.0-157.9	Malignant neoplasm of pancreas
162.2-162.9	Malignant neoplasm of trachea, bronchus and lung; bronchus and lung
174.0-174.9	Malignant neoplasm of female breast
182.0	Malignant neoplasm of body of uterus
183.0	Malignant neoplasm of ovary and other uterine adnexa; ovary
186.0	Malignant neoplasm of testis; undescended testis
186.9	Malignant neoplasm of testis; other and unspecified testis
188.0-188.9	Malignant neoplasm of bladder
203.00- 203.02	Multiple myeloma
205.00- 205.02	Acute myeloid leukemia
209.00- 209.79	Neuroendocrine tumors
789.30- 789.39	Abdominal or pelvic mass, swelling or lump
V10.00	Personal history of malignant neoplasm; gastrointestinal tract, unspecified
V10.05	Personal history of malignant neoplasm of gastrointestinal tract; large intestine
V10.07	Personal history of malignant neoplasm; liver
V10.1	Personal history of malignant neoplasm; bronchus and lung
V10.3	Personal history of malignant neoplasm; breast
V10.42	Personal history of malignant neoplasm; other parts of uterus
V10.43	Personal history of malignant neoplasm; ovary
V10.46	Personal history of malignant neoplasm; prostate
V10.47	Personal history of malignant neoplasm; testis
V10.51	Personal history of malignant neoplasm; bladder
V10.62	Personal history of malignant neoplasm; myeloid leukemia
V10.87	Personal history of malignant neoplasm; thyroid
V10.91	Personal history of malignant neuroendocrine tumor

Experimental/Investigational/Unproven/Not Covered for the screening, staging, diagnosis, monitoring and/or surveillance of cancer:

CPT* Codes	Description
82387	Cathepsin-D
83497	Hydroxyindolacetic acid, 5-(HIAA)
83520	Immunoassay, analyte, quantitative; not otherwise specified (Hu)
83951	Oncoprotein; des-gama-carboxy-prothrombin (DCP)
84275	Sialic acid
84999 ^{†††}	Unlisted chemistry procedure
88358	Morphometric analysis; tumor (eg, DNA ploidy)
88384	Array-based evaluation of multiple molecular probes; 11 through 50 probes
88385	Array-based evaluation of multiple molecular probes; 51 through 250 probes
88386	Array-based evaluation of multiple molecular probes; 251 through 500 probes
	Multiple/Varied

††† **Note:** Not covered when used to report any tumor marker indicated in this Coverage Policy as experimental, investigational/unproven.

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	10/15/2007	0172	Tumor Markers for Diagnosis and Management of Cancer

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.