Tumor Markers for diagnosis and management of cancer

**PSA:** We have chosen to let doctors and patients make their own informed decisions, keeping in mind the American Cancer Society recommendation and others regarding counseling about PSA screening and digital rectal examination for asymptomatic men age 50 or older. Asymptomatic African American men may wish to begin at age 45. 4,5,6,7

**CA 15-3**: This controversial test is often used to monitor women for breast cancer. Experts disagree about whether this test gives valuable information to breast cancer patients. 1,2,11 Therefore, we have chosen to let doctors and patients make their own informed decisions about this test. (*also known as CA 27-29, Truquant BR RIA®)

For coverage for any screening test, please see subscriber certificate for details.

<table>
<thead>
<tr>
<th>When tests are covered</th>
<th>When tests are not covered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEA</strong></td>
<td></td>
</tr>
<tr>
<td>• Diagnosis and follow-up of metastatic <strong>breast cancer</strong>2 and for <strong>colon cancer</strong>4</td>
<td></td>
</tr>
<tr>
<td>• As an indicator of tumor size or grade for lung cancer for Medicare HMOB and Medicare PPO Blue members, only.18</td>
<td></td>
</tr>
<tr>
<td>Diagnosis, following, or prognosis of <strong>lung cancer</strong>, since it has not been shown to improve the health of lung cancer patients.8</td>
<td></td>
</tr>
<tr>
<td><strong>CA 19-9</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with an established diagnosis of <strong>pancreatic cancer or gastric cancer</strong>, when used to monitor the clinical response to therapy, in order to either discontinue ineffective therapy or to detect early recurrence of disease.12</td>
<td></td>
</tr>
<tr>
<td>**Colorectal,**13 **liver,**13 or <strong>breast</strong>1,11,12 cancer, since it has not been proven to improve the health outcome of these cancer patients.13</td>
<td></td>
</tr>
<tr>
<td><strong>CA-125</strong></td>
<td></td>
</tr>
<tr>
<td>• Patients with <strong>symptoms suggestive of ovarian cancer</strong>21 or those with <strong>known ovarian cancer</strong>, to aid in the monitoring of disease, response to treatment, and recurrence of disease (including assessing value of second-look surgery).</td>
<td></td>
</tr>
<tr>
<td>• Patients with <strong>pelvic mass with unknown diagnosis</strong>3,12,19</td>
<td></td>
</tr>
<tr>
<td>• Patients with <strong>other gynecologic malignancies, such as endometrial</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal, gastric, liver, or pancreatic cancer diagnosis</strong>, following, or prognosis, these have not been shown to improve the health outcome of cancer patients.13</td>
<td></td>
</tr>
<tr>
<td><strong>CA-125 in asymptomatic patients</strong> as a screening technique for <strong>ovarian cancer</strong>21</td>
<td></td>
</tr>
</tbody>
</table>
### Policy #167: Tumor Markers for diagnosis and management of cancer

**cancer**, in whom baseline levels of CA-125 have been shown to be elevated.  
- **Peritoneal primary cancer**, to aid in monitoring of disease.
- Patients with **adenocarcinoma of unknown primary** (abdominal or pelvic carcinomatosis).
- As an indicator of **tumor size or grade for lung cancer** for Blue Care 65 and Medicare PPO Blue members, only.

<table>
<thead>
<tr>
<th>Tumor Markers</th>
<th>Indications and Notes</th>
</tr>
</thead>
</table>
| **Prostatic acid phosphatase** | Rarely recommended for use; PSA is almost always a better test, but we do cover prostatic acid phosphatase.  
Not recommended for use, since PSA is superior. |
| **BTA-STAT®, BTA-TRAK®, NMP-22®, NMP22 Bladder CHEK® or Urovysion** | The use of these urinary bladder cancer tumor markers for the following:  
- As an adjunct in the diagnosis (in persons with hematuria) of bladder cancer, only in conjunction with current standard diagnostic procedures.  
- As an adjunct in the monitoring of bladder cancer, only in conjunction with current standard diagnostic procedures.  
**Note:** FDA approved indications.  
The use of these urinary bladder cancer tumor markers as screening for bladder cancer in asymptomatic persons is considered investigational. |
| **FISH** | The use of fluorescence in situ hybridization (FISH) as an adjunct in the diagnosis (in persons with hematuria suspected of having bladder cancer) and monitoring of bladder cancer only in conjunction with cystoscopy.  
The use of fluorescence in situ hybridization (FISH) is considered *investigational* for screening for bladder cancer in asymptomatic persons. |
| **Immunohistochemistry test, ImmunoCyt™** | The use of urinary bladder cancer tumor markers involving immunohistochemistry test ImmunoCyt as an adjunct in the monitoring of bladder cancer only in conjunction with current standard diagnostic procedures.  
**Note:** FDA approved indications.  
The use of this urinary bladder cancer tumor in the diagnosis of bladder cancer is considered investigational.  
The use of this urinary bladder cancer tumor marker as screening for bladder cancer in asymptomatic persons is considered investigational. |
| **Chromogranin A (CgA)** | Chromogranin A (CgA) when used to assist in the diagnosis and management of specific carcinoid tumors.  
The use of CgA is considered *investigational* when used in the diagnosing and management of tumors other than specific carcinoid tumors identified in footnote #24 |

---

**When services are not covered**

We do not cover the use of all other **bladder cancer tumor markers** including but not limited to the following because they are considered investigational in the diagnosis, monitoring, or screening for bladder cancer and do not meet our Medical Technology Assessment Guidelines, #350:

- BLCA-1 and BCLA-4;
- DD23 monoclonal antibody
- Hyaluronic acid and hyaluronidase;
- Lewis X antigen;
- Microsatellite markers (fibronectin, and protein, and mRNA human chorionic gonadotropin(HCG);
- Solubla Fas;
- Survivin;
- Telomerase;
- TATI (tumor associate trypsin inhibitor) soluable e-cadherin
- UBCT™ Rapid Test (urinary bladder cancer test for cytokeratins 8 and 18);
- Quanticyt

We do not cover the following tumor markers since they are considered investigational and therefore do not meet the BCBSMA Medical Technology Assessment Guidelines, #350:

<table>
<thead>
<tr>
<th>Tumor Markers</th>
<th>Use for Diagnosis, Prognosis, or Monitoring of Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 549, TPA, MCA, MSA, CAM26, CAM29, CA-SCC, TPS, CA 50, CA 195, CA-SCC, CAM17-1, CAR-3, DMSA, NSE, Du-PAN-2, TAG 12, TAG 72.3, TNF-alpha</td>
<td>Breast</td>
<td>use for diagnosis, prognosis, or monitoring of treatment of patients with breast cancer&lt;sup&gt;1,11,12, 22&lt;/sup&gt;</td>
</tr>
<tr>
<td>CA 242, CA 50, CA 72-4, TPA, CA-SCC, TPS, MCA, MSA, CA 195, CA 549, CAM17-1, CAM-26, CAM29, CAR-3, Du-PAN-2, DMSA, NSE, MCA, TAG 12, TAG 72.3, TNF-alpha</td>
<td>Colorectal, Gastric, Pancreatic</td>
<td>for diagnosis, following, or prognosis, of cancer patients&lt;sup&gt;13, 22&lt;/sup&gt;</td>
</tr>
<tr>
<td>CA 242, CA 50, CA 72-4, TPA,</td>
<td>Liver</td>
<td>for diagnosis, following, or prognosis, of cancer patients&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>LPA</td>
<td>Ovarian</td>
<td>for screening or diagnosis of ovarian cancer</td>
</tr>
<tr>
<td>TPA, NSE, CA-SCC, CYFRA 21-1</td>
<td>Lung</td>
<td>for diagnosis, following, or prognosis of lung cancer&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| TPS, CAM17-1, CA195, CAR-3, DU-PAN-2, TAG12, TAG72.3, TNF-alpha | Liver | tumor markers described by CPT procedure code 86316 (immunoassay for tumor antigen) are considered investigational. <sup>22</sup>  
Note: exception, when used to bill for Chromogranin A (CgA) when used to assist in the diagnosis and management of specific carcinoid tumors. <sup>24</sup> |
| AFP-L3 biomarkers | Liver | for screening, diagnosis, or monitoring of patients with suspected or known hepatocellular cancer<sup>23</sup> |
| Analysis of proteomic patterns in serum (including but not limited to tests such as OvaCheck®, MammoCheck®, and ProstaCheck®) | Ovarian, Prostate | for screening and detection of cancer, including but not limited to ovarian cancer, prostate, breast and colorectal cancer<sup>26</sup> |
| Multiplex assay that measures the concentration of six serum proteins | Ovarian | to screen for ovarian cancer<sup>27</sup> |
Individually considered

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual’s unique circumstances may be considered in light of current scientific literature. For example, CA-125 may be appropriate for patients who are BRCA-2 positive. For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed

Blue Cross Blue Shield of Massachusetts
Provider Appeals
PO Box 986065
Boston, MA 02298

Prior to performance of service

Blue Cross Blue Shield of Massachusetts
Case Creation/Medical Policy
One Enterprise Drive
Quincy, MA 02171
Tel: 1-800-327-6716
Fax: 1-888-282-0780

Managed care guidelines

- Referrals are not required.
- Authorizations are not required.

Indemnity and PPO guidelines

All authorization requirements are determined by the individual’s subscriber certificate, however:
- Authorizations are required for all inpatient services
- Authorizations are not required for most outpatient services as determined by the individual’s subscriber certificate
- Referrals to a specialist are not required.

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>82378</td>
<td>carcinoembryonic antigen (CEA)</td>
</tr>
<tr>
<td>84066</td>
<td>phosphatase, acid; prostatic</td>
</tr>
<tr>
<td>84152</td>
<td>prostate specific antigen (PSA); complexed (direct measurement)</td>
</tr>
<tr>
<td>84153</td>
<td>prostate specific antigen (PSA); total</td>
</tr>
<tr>
<td>84154</td>
<td>prostate specific antigen (PSA); free</td>
</tr>
<tr>
<td>86294</td>
<td>immunoassay for tumor antigen, qualitative or semiquantitative (eg, bladder tumor antigen)</td>
</tr>
<tr>
<td>86300</td>
<td>immunoassay for tumor antigen, quantitative; CA 15-3 (27.29)</td>
</tr>
<tr>
<td>86301</td>
<td>immunoassay for tumor antigen, quantitative; CA 19-9</td>
</tr>
<tr>
<td>86304</td>
<td>immunoassay for tumor antigen, quantitative; CA 125</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>88120</td>
<td>Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual</td>
</tr>
<tr>
<td>88121</td>
<td>Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology</td>
</tr>
<tr>
<td>88271</td>
<td>molecular cytogenetics; DNA probe, each (eg, FISH)</td>
</tr>
<tr>
<td>88274</td>
<td>molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells</td>
</tr>
<tr>
<td>88365</td>
<td>in situ hybridization (eg, FISH), each probe</td>
</tr>
<tr>
<td>88367</td>
<td>morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; using computer-assisted technology</td>
</tr>
<tr>
<td>88368</td>
<td>morphometric analysis, in situ hybridization (quantitative or semi-quantitative) each probe; manual</td>
</tr>
<tr>
<td>88369</td>
<td>in situ hybridization (eg, FISH), each probe</td>
</tr>
<tr>
<td>86304</td>
<td>immunoassay for tumor antigen; other antigen, quantitative (eg, CA 50, 72-4, 549), each</td>
</tr>
<tr>
<td>86316</td>
<td>immunoassay for tumor antigen; other antigen, quantitative (eg, CA 50, 72-4, 549), each</td>
</tr>
</tbody>
</table>

**Note:** See footnote 24 for covered diagnoses for Chromogranin A (CgA) when billed with CPT code 86316 for commercial products and for Medicare HMO Blue and Medicare PPO Blue. See footnote 27 for covered diagnoses for CA-125 when billed with CPT code 86304 for commercial products and for Medicare HMO and Medicare PPO Blue.

The procedure noted below will reject as non-covered, for commercial products and for Medicare HMO Blue and Medicare PPO Blue, leaving no patient balance, as this procedure does not meet our Medical Technology Assessment Guidelines.

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>82107</td>
<td>alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)</td>
</tr>
</tbody>
</table>

**Other information**

**Clinical trials for Cancer Mandate**

As required by law, we provide coverage for services and supplies received as part of a qualified clinical trial (for treatment of cancer) when the member is enrolled in that trial. This coverage is provided for services and supplies that are consistent with the study protocol and with the standard of care for someone with the patients’ diagnosis, and that would be covered if the patient did not participate in the trials. This coverage may also be provided for investigational drugs and devices that have been approved for use as part of the trial. Coverage for services and supplies that are received as part of a qualified clinical trial is provided to the same extent as it would have been provided if the patient did not participate in the trial.

However, no coverage is provided for:

- Investigational drugs and devices that have not been approved for use in the trial.
- Investigational drugs and devices that are paid for by the manufacturer, distributor or provider of the drug or device, whether or not the drug or device has been approved for use in the trial.
- Non-covered services under the member’s contract.
- Costs associated with managing the research for the trial.
- Items, services or costs that are reimbursed or otherwise furnished by the sponsor of the trial.
- Costs of services that are inconsistent with widely accepted and established national and regional standards of care.
- Costs of clinical trials that are not “qualified trials.”

**Policy update history**

Issued 10/88. Revised 9/95 to exclude coverage for certain breast cancer markers. Revised 1/96 to include coverage for CEA and ca-15-3 for breast cancer. Revised 5/96 to include information from CMS (Centers for...
Medicare & Medicaid Services) about 19-9 and prostatic acid phosphatase. Updated 11/96 to include information on CAM 17-1, CAM 26, CAM 29, CA 242, CA 50, CA 72-4, CA 195, CA 549, CA-SCC, CAR-3, DU-PAN-2, P-LAP, PNA/ELLA, SLEX, SLX, SPAN-1, ST-439, TAG12, TAG 72, TAG 72.3, TATI, TNF-α, a2-PAG, BCM, and exclusion of coverage for PSA for differential diagnosis or men with prostate symptoms. PSA reviewed 6/97; no changes in coverage were made. 9/97, ACS recommendations for PSA were adopted, and CA 15-3 was left to physician-patient discretion. Ca-125 covered for adenocarcinoma of unknown primary (abdominal or pelvic carcinomatosis). Updated 12/97 to further clarify that coverage for screening services is determined by subscriber certificates. Reviewed 6/98; included the Massachusetts Association of Practicing Urologists recommendation that PSA tests should be done in asymptomatic men only when life expectancy exceeds 10 years. Revised 10/98 to exclude LPA for ovarian cancer. Reviewed 6/99, no changes in coverage were made. Updated 10/99 to include individual consideration guidelines for CA-125 for patients who are BRCA-2 positive. Reviewed 6/00; no changes in coverage were made. Updated 6/01 to include coverage for BTA (bladder tumor antigen) and NMP22. Updated 10/01 to include coverage for CEA and CA 125 for lung cancer for BC 65 members only, effective 10/1/01. Updated 11/01 to include coverage for CA-125 for endometrial cancer, peritoneal primary cancer and for differential diagnosis of pelvic masses. Reviewed 6/02 (MPG urology), no changes in coverage were made. Reviewed 9/02 (MPG hematology/oncology), no changes in coverage were made. Updated 6/03 MPG Urology to delete the following statement from the policy as recommended by the Medical Policy Group and Dr. Jeffrey Steinberg: “The Massachusetts Association of Practicing Urologists recommends that PSA tests should be done in asymptomatic men only when life expectancy exceeds 10 years.” Reviewed 9/03 MPG hematology/oncology, no changes in coverage were made. Reviewed 10/03 MPG OB/GYN and infertility, no changes in coverage were made. Updated 2/04 to clarify coverage for CA-125 for patients with symptoms suggestive of ovarian cancer and to exclude coverage for asymptomatic patients as a screening technique for ovarian cancer. Reviewed 6/04 MPG urology, no changes in coverage were made. Reviewed 10/04 MPG Obstetrics and Gynecology, no changes in coverage were made. Updated 1/05 to include BCBSA national medical policy references. Updated body of policy to clarify investigational status for tumor makers previously noted in scientific background, and national policy: TPS, CAM17-1, CA195, CAR-3, DU-PAN-2, TAG12, TAG72.3, TNF-alpha based on National policy (see footnote #22). 5/05 updated to clarify coverage guidelines on CA-125 as noted in the 2005 BCBSA National policy. Updated 6/05 to include BCBSA national policy (2.03.02) rationale information, and two new references–footnote #22. Medicare PPO Blue product reference noted in medical policy when covered indications are limited to Medicare related products. Reviewed 6/05 MPG urology, no changes in coverage were made. Reviewed 9/05 MPG Hematology/Oncology, no changes in coverage were made. Reviewed 10/05 MPG Obstetrics/Gynecology, no changes in coverage were made. Updated 12/05 to clarify coverage statement on BTA or NMP-22, no change in coverage was made. Updated 12/05 to clarify coverage statement on FISH based upon the 2005 BCBSA National Policy, effective 2/2006. Reviewed 6/06 MPG-Urology, no changes in coverage were made. Reviewed 9/06 MPG Hematology/Oncology, no changes in coverage were made. Reviewed 10/06 MPG – Obstetrics and Gynecology, no changes in coverage were made. 6/07 Reviewed MPG Urology, no changes in coverage were made. 7/07 comparison review of BCBSA re: Urinary Tumor Markers for Bladder Cancer finalized; clarified coverage for ImmunoCyt™, an immunohistochemistry clinical lab, used as an adjunct test in the diagnosis of bladder cancer; footnote #17 edited to include recent BCBSA update and references. Comparison review of BCBSA national policy Alpha-Fetoprotein for Detection of Hepatocellular (Liver) Cancer completed; BCBSMA benchmarks the BCBSA policy which finds this biomarker- investigational, effective as published in Provider Focus– 9/07; footnote #23 edited to include BCBSA policy rationale and references. 8/07 Comparison review of BCBSA National policy Serum Tumor Markers for Breast and Gastrointestinal Malignancies, BCBSMA benchmarks the BCBSA policy; body of this policy updated to include tumor markers noted as investigational (described by narrative intent for CPT code 86316); footnote #21 edited to include BCBSA update and added references. Updated 9/07 MPG – Hematology/Oncology, to clarify text on AFP-L3 biomarkers. Reviewed 10/07 MPG – Obstetrics and Gynecology, no changes in coverage were made. 5/08 Comparison review of BCBSA National medical policy, Urinary Tumor Markers for Bladder Cancer: no change in BCBSA policy statement which BCBSMA benchmarks; footnote #17 edited to include references. Comparison review of BCBSA National medical policy, Alpha-Fetoprotein-L3 for Detection of Hepatocellular (Liver) Cancer, no change in BCBSA investigational policy statement which BCBSMA benchmarks; footnote #23 edited to include references.
Reviewed 6/08 MPG-Urology, no changes in coverage were made. 8/08 Comparison review of BCBSA National medical policy, *Urinary Tumor Markers for Bladder Cancer*; no change in BCBSA policy statement which BCBSMA benchmarks. Added coverage for tumor marker Chromogranin A (CgA) when used to assist in the diagnosis and management of carcinoid tumors, coverage restricted to those ICD-9-CM diagnoses listed in footnote #24, effective 12/2008 going forward (published in Provider Focus). Reviewed 10/08 MPG – Hematology/Oncology, no changes in coverage were made. Reviewed 10/08 MPG-obstetrics/gynecology, no changes in coverage were made. 12/08 added footnote #25 to clarify covered diagnosis of hematuria (ICD-9-CM 599.71, Gross hematuria) when billed with BTA stat ® or NMP-22 and based on the covered criteria as noted in this medical policy. 3/09 Clarified covered ICD-9-CM diagnoses codes for hematuria when billed with BTA stat ® or NMP-22 and based on the covered criteria as noted in this medical policy; see footnote #25. 5/09 updated to include non-covered information regarding testing to screen for ovarian cancer; analysis of proteomic patterns testing (including but not limited to tests such as OvaCheck®), and multiplex assay testing that measures the concentration of six serum proteins (including but limited to tests such as OvaSure™.) Related footnotes, 26 and 27 added. The information pertaining to proteomic patterns testing was previously noted in medical policy #366, *Cervical Cancer*. Reviewed 6/09 MPG-Urology, no changes in coverage were made. Updated 7/09 to clarify the covered and non-covered language for urinary bladder cancer tumor markers based on the BCBSA national medical policy, *Urinary Tumor Markers for Bladder Cancer*; footnote 17 edited to include updated rationale and added references, 21-27. Updated to clarify the non-covered language for analysis of proteomic patterns in serum based on the BCBSA national medical policy, Analysis of Proteomic Patterns in Serum to Identify Cancer, including proteomic blood tests for breast and prostate cancer; footnote 26 edited to include updated rationale and added references 1-5 and 12. 8/09 Updated after review of BCBSA policy issued 6/09 without change in coverage exclusion of evaluation of AFP-L3 biomarkers in screening, diagnosis, or monitoring of patients with suspected or known hepatocellular cancer; added rationale and references 10-13 under footnote 23. Reviewed 9/2009 MPG-Hematology and Oncology, no changes in coverage were made. Reviewed 10/2009 MPG-Obstetrics and Gynecology, no changes in coverage were made. Updated 1/2010 to remove Blue Medicare PFFS PlusRX. Reviewed 6/2010 MPG-Urology, no changes in coverage were made. Revised 7/10 based on a comparison review of the BCBSA policy, Analysis of Proteomic Patterns for Early Detection of Cancer, no change in the investigational policy statement which BCBSMA benchmarks. Reviewed 7/10 based on a comparison review of the BCBSA policy, Urinary Tumor Markers for Bladder Cancer, no changes were noted in the coverage and non-coverage of the BCBSA policy which BCBSMA benchmarks; coverage and non-coverage statements in the BCBSMA policy edited to add clarity. Footnote 17 updated including the addition of references 1, 4-5, 7-12, and 14-15, and other references re-numbered or removed. Reviewed 9/2010 MPG-Hematology and Oncology, no changes in coverage were made. Reviewed 10/2010 MPG-Obstetrics and Gynecology, no changes in coverage were made. Updated 3/2011 to add new CPT codes 88120 and 88121. Reviewed 7/2011 MPG – Hematology and Oncology, no changes in coverage were made. Reviewed 9/2011 MPG – Urology, Obstetrics and Gynecology, no changes in coverage were made. Updated 1/1/2012 with additional references based on BCBSA national policy reviewed 5/1/2011. Updated 2/2012 with additional references based on BCBSA policy reviewed 6/2011. Updated 3/2012 with additional references based on BCBSA national policy, reviewed 7/ 2011. Updated 6/2012 with additional references based on BCBSA national policy, reviewed 10/ 2011. 4/2014 Clarified coding information. Updated 6/2014 Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.

**Scientific background, Rationale and References**

1 Revised 9/95 to include the Technology Evaluation Center (TEC) 6/95 assessment of medical literature since 1985 on tumor markers for breast cancer. Low sensitivity precludes use in diagnosis. Sensitivities for stage I disease ranged from 0-29% for ca 15-3, 0-25% for CEA, 10-27% for MCA, 15-51% for TPA, 11-75% for MSA, 21% for ca 549. MSA is not superior to mammography for screening of asymptomatic women (Ward et al, 1992). There was insufficient evidence to support prognostic value of these markers. Markers were not specific, therefore could not be used in establishing a diagnosis in cancer of unknown primary. The most promising evidence focused on use for monitoring treatment response, but there is lack of validated criteria for interpreting changes in marker levels. There was no documentation of improved survival or other health outcomes as a result of measuring serum markers.

**Policy #167: Tumor Markers for diagnosis and management of cancer**

- 7 -
In 1996, ASCO (American Society of Clinical Oncologists) published practice guidelines for the use of tumor markers in breast and colorectal ca. The Society concluded that “The data are insufficient to recommend the routine use of DNA index, DNA flow cytometric proliferation analysis, CA 15-3, CEA, c-erbB-2, p53, or cathepsin-D.” They did suggest that CA 15-3 may be used to “suggest treatment failure” in the absence of readily measurable disease.

2 Revised 1/96 to allow coverage for CEA and CA 15-3 based in part on Ballesta et al., Tumor Biology, 16 (1):32-41, 1995: in 40-50% of breast cancer patients, a serial increase in CEA is the first sign of recurrence. As well, the absence of reduction during therapy signifies ineffective treatment. However, for the evaluation of recurrence, interpretation of the predictive value must be based on the prevalence of recurrence. For example, Streiber et al. (1989) calculated the predictive values of a rise in CA 15-3 levels based on varying probabilities of relapse. When prevalence of relapse is 68%, the predictive value was 78%, but dropped to only 4% when the probability of relapse was 2% (such as that seen with very early stage disease). Without specifying disease stage, it is difficult to interpret predictive values for these markers. A study by Loprinzi et al (1986), 6 patients had inappropriate treatment modifications when decisions were based on CEA alone. Tumor markers alone are insufficient to manage therapy, but in some circumstances, such as metastatic bone disease, marker levels may be detected more readily than radiologic changes.

Regarding the diagnosis of metastatic disease, sensitivities are reported as 46-89% for CA 15-3 (some variation depends on site of mets - bone vs. viscera), and similar ranges were reported for CEA. Specificities for all tumor markers evaluated ranged from a low of 22% (CA 15-3 for soft-tissue mets, Obrien et al 1992) to 99%.

In 1996, ASCO (American Society of Clinical Oncologists) published practice guidelines for the use of tumor markers in breast and colorectal ca. The Society concluded that “The data are insufficient to recommend the routine use of DNA index, DNA flow cytometric proliferation analysis, CA 15-3, CEA, c-erbB-2, p53, or cathepsin-D.” They did suggest that CA 15-3 may be used to “suggest treatment failure” in the absence of readily measurable disease.

3 Effective 1/95. Reviewed 2/96 to include the July 1995 ECRI (a non-profit technology assessment group) assessment of CA-125. The effectiveness of the assay depends on both the cut-off points and the indication. Combined data from 12 studies (1983-87) show elevated levels in 84% of epithelial ovarian ca, correlating with tumor size and stage of disease. CA-125’s sensitivity in patients with stage I disease is as low as 50%, but increases with stage of cancer. CA-125 is serum is not consistently reflective of this marker in tumor tissue itself. The low prevalence of ovarian ca and this poor sensitivity make this test unsuitable for screening. Whether repeated determination, perhaps combined with ultrasound, would improve the specificity is unknown. A definitive trial would require over 100,000 women over 6 years (Einhorn 1992, Andolf 1993). The NCI is planning an RCT for ovarian ca screening with 10 year follow-up as part of the PLCO (prostate, lung, colo-rectal, ovary) trial in the general population, which will feature transvaginal ultrasound, CA-125, and bimanual exams in women aged 60-74 years, in a number of patients sufficient to show a 35% decrease in specific mortality.

Regarding dx of pelvic masses: since ovarian cancer is so often fatal once advanced, a non-invasive test would have to be essentially perfect (sensitivity and NPV) to obviate the need for lap. Regarding prognosis, Mobus (1988) found negative correlation between CA-125 over 65 u/ml and 5-yr survival (p<0.005) in 202 ovarian cancer patients followed for a mean of over 6 years. This negative correlation appears most strongly with disease at later stages, and with larger tumors. In a report by Sevelda (1989), once tumor size is factored out, there may be little correlation with pre-op CA-125 and prognosis. However, post-op CA-125 > 65 u/ml was negatively correlated with survival, despite residual tumor size (Mobus).

Regarding follow-up, Jacobs and Bast’s literature summary (1989) found that in patients with elevated post-op CA-125, serial levels correlated to disease status in over 90% of patients. Van der Burg’s 1992 meta-analysis of 531 patients found that levels decreased in 87% of those whose clinical disease diminished, was stable in 67% of those with stable disease, and increased in 97% of those with progression. 89% of cases showed agreement.
between clinical course and serial levels. For the purpose of following disease status, ca-125 has a sensitivity of 91%, specificity of 96%, PPV of 97%, and NPV of 87%, with <3% false positives (allowing confidence for discontinuance of ineffective therapy) and 13% false negatives. This high false negative rate raises concerns about the need for vigilance in following patients whose levels are low.

Regarding second-look surgery: the false negative rate of ca-125 is too high to obviate the need for second look, regardless of whether or not second look surgery itself is valuable. A positive ca-125 is more reliable, and PPV and specificity are over 95% at the time of second look, with very few false positives. However, to the extent that secondary debulking at that time is useful, this opportunity would be missed. Therefore, it is unclear how either and high or low ca-125 might obviate the need for second look surgery.

N.B. It is known that ca-125 levels may peak 2-4 weeks after surgery in 60-80% of patients undergoing abdominal surgery for benign conditions, and levels may remain elevated for several months.

Conclusions Because morbidity and mortality from prostate cancer are significant, an effective and efficient strategy for early detection is desirable. However, without randomized trials to quantify the risks and benefits of screening, or proof that treating clinically localized cancer reduces disease-specific mortality rates, current data do not support the conclusion that early detection of prostate cancer unequivocally does more good than harm. This analysis of screening suggests that given a combination of favorable assumptions, early detection efforts that use digital rectal examination and PSA measurement might well be cost-effective, at least for men in their 50s and 60s, compared to other screening methods. The best combination of tests, and the most cost-effective frequency of their use, are unknown. None of the methods, alone or in combination, is an optimal screening tool.

Should widespread screening be encouraged until we can prove that it does not work, or be avoided until it is proven to work? Pending the results of crucial trials, given the availability of digital rectal examination and PSA measurement for the early detection of prostate cancer, decisions must be made by individual physicians and patients. This cost-effectiveness model suggests that one-time screening with DRE and PSA measurement may be defensible in younger men, given favorable but reasonable assumptions about existing data. Conversely, this model supports a reasonably strong case that early detection efforts for men aged 70 years and older are only marginally beneficial, even with very favorable assumptions. Even for men in their 50s, the maximum average health benefit averaged across all patients is no more than a few additional weeks of life expectancy. For those with clinically localized cancer, surgery offers a potential gain of approximately 3 years of life at age 55, and 1.5 years at age 65.

For some patients and physicians, the harms of screening and treatment will appear to outweigh even the maximum benefits presented, especially because risks are faced immediately, while potential benefits are often delayed for years. Others will discount the potential for complications and accept the associated hazards, even for a benefit of uncertain magnitude. Patients who place the highest premium on the chance of avoiding advanced prostate cancer should probably choose screening. Men who are averse to treatment-related risks or who prefer to pursue only therapy that has a proven benefit, should probably decline screening.

Primary care physicians should be aware of the uncertainties in the variables influencing early detection decisions, and the tradeoffs of potential benefits for known risks. This information should be discussed before they and their patients make a decision about screening. The lack of proof of net benefit from early detection with digital rectal examination and PSA measurement, and potential for serious harm warrant a higher level of informed consent than exists for simpler diagnostic tests. Patients must understand the long-term ramifications of screening, including the relatively high probability that further evaluation (including biopsy) will be required. They should also understand the often challenging decision about therapy that is associated with
considerable morbidity rates and uncertain benefit, should cancer be discovered. Screening should not be recommended for men who are unwilling to consider aggressive treatment or who are not candidates for such therapy.

Rectal examinations are also done for reasons other than prostate cancer screening. These conclusion about the limited usefulness of this examination for reducing prostate cancer morbidity and mortality does not preclude any benefit that may be derived from using this test for other indications. However, the value of the DRE for other purposes, particularly for colorectal cancer screening, is also poorly supported. Discovery of abnormalities of the prostate often triggers a cascade of additional evaluations, even if the physician and the patient were not specifically interested in prostate cancer screening. While “informed consent” is ethically responsible, it also poses significant logistical challenges. Strategies from simple handouts to videotapes, may improve the efficiency of the discussions about early detection of prostate cancer.

Some men have a higher lifetime risk for prostate cancer on the basis of race or family history. Such men should be informed by their physicians that they face a higher risk for developing clinically apparent prostate cancer, but whether screening reduces morbidity or mortality rates has not been proven in controlled studies. Men at higher risk for prostate cancer face the same risk from treatment as other men. Evidence does not justify the common but arbitrary policy of annual digital rectal examination and PSA measurement for men over 50. A specific screening interval cannot be supported with currently available data. Physicians must negotiate, on the basis of scant evidence, the need for follow-up testing with patients who decide to undergo initial screening.

5 Effective 1/95. Reviewed 2/96 to include the 3/94 TEC (Technology Evaluation Center) assessment of medical literature from 1980 to 3/94 on PSA for prostate cancer staging. Specifically, two uses were considered: PSA for selecting candidates for definitive therapy, and PSA for avoiding bone scan in untreated patients with no bony symptoms.

For determining candidates for definite tx: NPV of DRE ranges from 30-70%, thus resulting in understaging of patients undergoing radical prostatectomy. NPV of PSA was 36%-93%, however the false positive rate (which depends on exact cut-off of PSA used) implies some patients would be denied definitive therapy for disease which is actually localized (approximately 15-54% of patients staged by PSA as having extensive disease would fall in this category). Therefore, the positive predictive value is too low for selecting patients for definitive therapy. Several sophisticated analyses using logistic regressions (Kleer 1993, Partin 1993) suggest that PSA in combination with other tests improves prediction of pathologic stage at radical prostatectomy (compared with DRE or PSA alone). However, it is difficult to assess the impact of false positives in deciding to rule out radical prostatectomy.

For avoiding bone scan in previously untreated prostate ca with no signs of bony mets: + PSA is considered > 10ng/ml. Several studies (Oesterling, Pantelides, Chybowski) reported very high NPV (near 100%) for predicting a negative bone scan given a low PSA. Improved net health outcome in the form of safely avoiding the inconvenience and discomfort of an unnecessary bone scan (about 39% of patients evaluated would have fallen into this category) was clear. Less than 0.6% of patients being staged would have undetected bony mets as a result of not scanning, and likely fewer would be harmed by inappropriate treatment based on this lack of detection.

6 US Preventive Health Taskforce makes the following statement: “Routine screening for prostate cancer with digital rectal examinations, serum tumor markers (e.g. prostate-specific antigen), or transrectal ultrasound is not recommended.” page 119, Guide to Clinical Preventive Services, second edition, Williams and Wilkins, 1996.

Reviewed 2/96 to include the 11/91 TEC (Technology Evaluation Center) assessment of medical literature on PSA for screening. As many as 20% of patients with benign prostatic disease had elevated PSA levels, and 15-
20% of patients with histologic evidence of prostatic carcinoma had normal PSA values. Therefore, PSA to screen asymptomatic patients for prostate cancer is not likely to improve health outcome.

7 **American Cancer Society Recommendations:** The American Cancer Society recommends annual prostate cancer screening with prostate-specific antigen (PSA) and digital rectal examination for men who are 50 or older. Recent data has suggested that men at increased risk for developing prostate cancer should begin screening at an earlier age. Increased risk groups include African American men, and men with familial tendency (2 or more first degree relatives with prostate cancer).

8 Revised 2/96 based on the 2/96 TEC (Technology Evaluation Center) assessment of medical literature from 1985 through 12/95 on tumor markers for diagnosis, monitoring, and prognosis of both small cell and non-small cell lung cancer. Desirable health outcomes from effective tumor markers would include increased disease-free survival due to earlier diagnosis, or decreased use of ineffective chemo as a result of measuring markers to monitor disease. The majority of the 95 reports reviewed addressed CEA, TPA, NSE (neuron-specific enolase), SCC (Squamous cell carcinoma-associated antigen) and CYFRA 21-1 (fragment of cytokeratin 19). In summary, diagnosis of lung cancer is based on histopathology, and tumor markers offered no additional benefit. Sensitivities are quite poor, especially in early disease. While CYFRA 21-1 seems most sensitive, it is not specific for any particular cancer type. No evidence was shown that tumor marker measurements were useful clinical decision tools or that health outcome was improved by their use. While CEA was “grandfathered” into clearance, no other tumor marker has received FDA clearance for lung cancer. The International Society of Biological Markers (ISOBM) criteria for recurrence monitoring require a linear increase (log scale) in at least 3 consecutive samples in the absence of therapy. Progression should be manifest by a 25% or greater increase in levels, and response should be manifest by a 50% or more decrease in levels.

**Diagnosis:** Thirty studies on non-small cell (NSC), and 25 on small cell (SC) lung cancer were evaluated. CEA was most commonly reported, however sensitivities were poor (about 44% for NSC). CYFRA 21-1 sensitivities ranged from 22% for early NSC to 84% for Stage IV disease, averaging an overall sensitivity of 57% for NSC and 36% for SC. NSE was less than 50% sensitive for NSC, and over 50% sensitive for SC. Gail et al. (1986 and 1988) used logistic regressions and recursive partitional methods to evaluate the capability of multiple markers to distinguish patients with cancer from those with benign lung disease. Banked serum was evaluated for 10 markers, including CEA. Not even a combination of markers was found to distinguish cancer from benign disease (sensitivity of 30% for local disease, and 52% for advanced disease).

**Monitoring:** Van der Gaast et al. (1994) published the only study evaluating tumor marker changes in the context of clinical response according to WHO criteria, without prior knowledge of marker levels. Definitions included: complete response = normal levels x 1 month; partial response = 65% or greater decrease in levels x 1 month; stable disease = less than 65% decrease or less than 40% increase; progressive disease = 40% or greater increase in levels, or an increase from normal into the above normal range. Reference values were based upon 95% specificity as determined in 546 patients without malignant disease. NSC patients were prospectively followed. In 23 patients with squamous cell, CYFRA 21-1 showed a 65% concordance between marker level changes and WHO criteria. However, marker level changes preceded clinical changes by only 1-2 months, a lead time which is unlikely to foster improvement in health outcome. There was no evidence to suggest that tumor marker measurements improved quality of life or survival. More information is required not only about the adequacy of the markers themselves, but of the ability of clinicians and patients to modify existing treatment plans based on the information provided by marker levels.

**Prognosis:** Of numerous studies, there was not consensus regarding an independent association with clinical outcomes. The studies of CEA and TPA as prognosticators beyond known extent of disease (Buccheri and Ferrigno 1992, Gronowitz 1990), were inconsistent with the results of van der Gaast (1994), who found no additional survival information beyond that obtainable by extent of disease (TPA, NSE, thymidine kinase, LDH, for small cell lung cancer only).

Effective 5/1/96. Revised 5/1/96 to include CMS (Centers for Medicare and Medicaid Services) regulations. Medicare policy is developed separately from BCBSMA. While BCBSMA policy is based upon scientific evidence, Medicare policy incorporates scientific evidence with local expert opinion, and governmental regulations from CMS (Centers for Medicare & Medicaid Services) and the US Congress. While BCBSMA and Medicare policies may differ, our Blue Care 65 and Medicare PPO Blue patients must be offered the same services as Medicare offers. In many instances, BCBSMA policies offer more benefits than does Medicare.

Revised 11/96 based on the 10/96 TEC (Technology Evaluation Center) assessment of medical literature through 9/96 on tumor markers encoded by the MUC 1 gene, including CA-15-3, 27.29 (Truquant BR RIA), and CA 549 specifically to assess their use in monitoring for disease recurrence. A CA 27.29 kit recently approved marketing clearance by the FDA, for use in monitoring previously treated stage 2 and 3 disease for recurrence.

Fourteen studies used these tests (referred generically as CA 15-3) for monitoring for recurrence, and reported on the resultant lead time gain: Muss (1996) abstract), Jager (1995), Molina (1995), O’Hanlon (1995), Nekulova (1994), Vizcarra (1994), Repetto (1993), Soletormos (1993), Geraghty (1992), O’Brien (1992), Dnistrian (1991), O’Dwyer (1990), Colomer (1989), and Bieglmayer (1988). 12 studies defined a positive test as any single increase above the state reference value; one defined positive as 2x the coefficient of variation, and one study as a 25% increase from previous levels. Poor study design makes currently available evidence difficult to interpret. While most studies were prospective, specific criteria for timing of evaluation and testing were lacking, and no study reported impact on survival.

Sensitivity of CA 15-3 is poor with low tumor burdens. For disease recurrence, sensitivities ranged from 50-60%. Detection of relapse in metastatic disease may be advanced by about 3-5 months (in 30-71% of patients who relapsed, marker preceded clinical dx by 2-9.5 months), yet firm estimates in lead time are hampered by the very small number of patients with elevations in marker levels which preceded clinical diagnosis of recurrence. Even so, whether an advance detection of 3-5 months would lead to improved survival or quality of life has not been evaluated. The test has very limited sensitivity for detecting low tumor burden, when treatments are most likely to be beneficial. False positives may result in unnecessary evaluations and anxiety.

In 1996, ASCO (American Society of Clinical Oncologists) published practice guidelines for the use of tumor markers in breast and colorectal ca. The Society concluded that “The data are insufficient to recommend the routine use of DNA index, DNA flow cytometric proliferation analysis, CA 15-3, CEA, c-erbB-2, p53, or cathepsin-D.” They did suggest that CA 15-3 may be used to “suggest treatment failure” in the absence of readily measurable disease.

The markers evaluated, the most promising were CEA and CA 242 for colorectal ca. One study reported that a combined use of these markers increased recurrence detection to 88%, median lead time of 5 months. However, the increased sensitivity is associated with a higher false positive rate, which may result in unnecessary anxiety and testing. Whether or not health outcomes would be improved is uncertain.

The American Society of Clinical Oncology (ASCO) published guidelines in 1996 about the use of serum tumor markers in breast and colorectal ca. The Society concludes that “The data are insufficient to recommend the routine use of lipid-associated sialic acid (LASA), CA 19-9, DNA index, DNA flow cytometric proliferation analysis, p53 tumor suppressor gene, and ras oncogene”.

Updated 11/96 based on the 10/31 National BCBSA policy on tumor markers. This assessment was based upon a literature review from 1992 to 8/96, in addition to the full assessments mentioned above. Prior to April 1996, covered by Blue Care 65, only. Effective April 1996, covered by all plans.
Revised 11/96 based on the 10/96 TEC (Technology Evaluation Center) assessment of medical literature from 1985 through 9/96 on serum tumor markers for diagnosis, monitoring, and prognosis of GI cancers. CA 19-9, CA 242, CA 50, CA 72-4, CA-125, and tissue polypeptide antigen (TPA) were evaluated for use in diagnosis and management of colorectal, gastric, pancreatic, and liver cancers. None of these markers has received FDA approval for this purpose. Evidence was insufficient to permit conclusions about the effects of these markers upon health outcomes such as survival or quality of life. While an elevated level may increase suspicion of cancer, false positives are fairly common (10-15%). Sensitivity is generally low for early stage disease. A negative test offers little reassurance to a patients with clinical signs and symptoms of disease. None of these markers are specific for a given tumor type or site. Since many of these cancers are diagnosed at advanced stages, and carry poor survival rates, it is unclear that earlier diagnosis would result in improved health outcomes.

See comments from Rebar RW in Oct 1,1998, Journal Watch, vol 18, no.19, p.150 regarding studies by Xu et al. in JAMA 1998 Aug 26;280:719-23; Roberts JA, JAMA 1998 Aug 26; 280:739. While small numbers of patients with ovarian cancer did have elevated plasma levels of LPA, women with non-ovarian malignancies also had elevated levels, as did some control patients. One editorialist noted that the sensitivity (95%) and specificity (89%) were encouraging, the test cannot yet be accepted as a screening test or diagnostic marker for ovarian ca. Since apparently 25% of women with benign conditions have elevated levels, the test’s value is limited, and a large longitudinal study is necessary to determine the value of this test.

Based on recommendations from MSCO (Massachusetts Society of Clinical Oncology), to BCBSMA Medical Policy Group, September 1999.

Based on BCBSA national policy 2.04.07, Urinary Tumor Markers for Bladder Cancer, issued 5/2010.

Rationale
This policy was originally created in 1997 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period April 2009 through March 2010. Following is a summary of the key literature to date:

The discussion below focuses on the fundamental attributes of any diagnostic test: technical performance; diagnostic performance (sensitivity, specificity, positive and negative predictive values) compared to a gold standard; and data demonstrating how the results of the test can be used to benefit patient outcomes.

1. Technical performance
All of the FDA-approved tests for urinary tumor markers involve the use of standard laboratory procedures.

2. Diagnostic performance
Studies have evaluated the diagnostic performance of individual markers compared to urine cytology, the standard urine-based test for bladder tumor diagnosis and surveillance. Cystoscopy and biopsy are generally used as the gold standard comparison. Of particular interest are the relative performance of individual markers and the performance of individual markers compared to combinations of markers.

The U.K. Health Technology Assessment Program published a systematic review in 2010 of studies on the diagnostic performance of the urine biomarkers Fluorescence in Situ Hybridization (FISH, e.g., UroVysion test), ImmunoCyt, and NMP22. (1) The review combined studies that evaluated the tests for initial diagnosis of bladder cancer and those evaluating tests to identify bladder cancer recurrence. Studies used cystoscopy with biopsy as the reference standard. Results of pooled patient-level analyses are:

<table>
<thead>
<tr>
<th></th>
<th>FISH</th>
<th>ImmunoCyt</th>
<th>NMP22</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. studies</td>
<td>12</td>
<td>8</td>
<td>28</td>
</tr>
</tbody>
</table>
The BTA stat® test was evaluated in a prospective multicenter study conducted by the FinnBladder Group at 18 medical institutions in Finland and compared to cytology. (2) Consecutive patients (n=501; men = 397; mean age, 69 years, range 28–92) with a history of transitional cell carcinoma who were under follow-up, were recruited. The primary tumor classification for the recruited patients was Ta (n=215), 48%; T1 (n=171), 38%; T2-3 (n=7), 1.6%; carcinoma in situ (CIS; n=15), 3.4%; and classification unknown (n=37), 8.3%. A majority of patients (n=327, 67%) had no prior history of intravesical instillation treatments; 97 patients (20%) had past (at least 3 months from the last) instillation (Group B); 66 patients (14%) had present instillations. Patients with missing instillation information (n=9) and patients with urine infection (n=6) were excluded. Freshly voided urine samples were obtained from all participants before cystoscopy and split for culture, cytology, and BTA testing. Cytology specimens were not available for central review in all patients; only patients with available cytology (n=445) were included in the analysis comparing BTA and cytology. The overall sensitivity and specificity were calculated based on cystoscopy findings, including those for which further examination was performed. The key results were as follows:

- 133 patients had recurrence of bladder cancer at cystoscopy; BTA detected 71 (53.4%)
- In the remaining 368 patients, 96 (26.1%) had a positive BTA test result
- An additional 9 (16.4%) recurrences were detected at further examinations
- The overall sensitivities were 56.0% and 19.2%, and specificities were 85.7% and 98.3% for BTA and cytology, respectively
- Urine infection, past bacillus Calmette-Guerin (BCG) instillations, and present instillations of any type caused false positive test results.

Limitations of this study include lack of both cytology and BTA test results on approximately 10% of patients and lack of follow-up on all patients with negative cystoscopic and positive BTA test and/or cytology findings.

Sarosdy and colleagues compared FISH to the BTA test and voided cytology. (3) In a multicenter trial, each of the 3 tests was performed on urine samples from 176 patients with known transitional cell carcinoma to determine sensitivities. The authors reported finding overall sensitivities of 71%, 50%, and 26% for FISH, BTA test, and cytology, respectively.

A cross-sectional study from Germany, published by Horstmann and colleagues in 2009, compared the performance of UroVysion, ImmunoCyt and NMP22 used to detect bladder cancer recurrence in a sample of 221 patients diagnosed with non-muscle-invasive transitional cell carcinoma. (4) Patients subsequently underwent cystoscopy as part of regular follow-up (n=49) or transurethral reception of the bladder (TURB) for suspicion of recurrent disease (n=172). Findings from cystoscopy or TURB were considered the gold standard diagnosis. The investigators evaluated the diagnostic performance of individual markers, urinary cytology, and all possible combinations of markers. When combinations of markers were used, the test was considered positive if at least one marker was positive. The main findings are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>84</td>
<td>62</td>
</tr>
</tbody>
</table>

---

**Policy #167: Tumor Markers for diagnosis and management of cancer**

- 14 -
Cytology was the most sensitive single marker (84%) but was less specific than ImmunoCyt (62% and 72%, respectively). The authors commented that the performance of cytology was better than in previous similar studies and the performance of other single markers were similar to previous studies. All combinations of two tests increased the sensitivity. Sensitivities varied from 94%, with a combination of cytology and NMP22, to 87% for the combination of cytology and UroVysion. Combining two tests generally lowered the specificity. In monitoring patients for bladder cancer recurrence, sensitivity is the more important test characteristic. Still, the combination with the best tradeoff of sensitivity and specificity was cytology and ImmunoCyt, which had a sensitivity of 93% and a specificity of 56%. Combining three tests increased the sensitivity even further. Two combinations attained a sensitivity of 98%, NMP22 and ImmunoCyt combined with either cytology or UroVysion. Specificity of these combinations was low, 31%-32%. The best tradeoff with 3 markers was the combination of cytology, ImmunoCyt, and UroVysion, which had a sensitivity of 93% and a specificity of 49%. Combining all 4 tests did not substantially improve the diagnostic performance.

Sullivan and colleagues also recently published a cross-sectional study that compared urinary tumor markers. (5) A single voided sample was obtained from 100 patients with a history of bladder cancer. Immediately after urine collection, patients underwent cystoscopy to identify cancer recurrence. Cystoscopy with biopsy was the gold standard; only biopsy-proven cases were considered positive. The urine sample was divided and used to evaluate cytology, ImmunoCyt and UroVysion; each type of analysis was conducted blindly in a different laboratory. Of the 100 samples, 2 were considered inadequate for cytology, 2 were inadequate for ImmunoCyt analysis, and 12 had cell counts too low for UroVysion analysis. Thus, sample size was 98 for cytology and ImmunoCyt and 88 for UroVysion. Sensitivities were 21% for cytology, 76% for ImmunoCyt, and 13% for UroVysion. Specificities were 97% for cytology, 63% for ImmunoCyt, and 90% for UroVysion. Diagnostic performance of the combination of cytology and ImmunoCyt, but not cytology and UroVysion, was reported. In the analysis of 2 tests, sensitivity was calculated with either test positive and specificity with both tests negative. For the combination of cytology and ImmunoCyt, the sensitivity was 75% and specificity was 63%. The specificity of this combination of tests was similar to that found by Horstmann and colleagues, described above, 56%. The combined sensitivity was lower than in the Horstmann study (93%), likely due to the higher sensitivity of urinary cytology found by Horstmann et al. The Sullivan study was limited by a small sample size.
size. Moreover, the study was supported by DiagnoCure, the manufacturer of ImmunoCyt; the Horstmann study did not receive industry funding.

3. Impact on patient care
Because of the potential consequences of missing a diagnosis of recurrent bladder cancer, it is unlikely that the schedule of cystoscopies will be altered unless the sensitivity of a urinary marker/markers approaches 100%. However, some authors have suggested that consideration be given to lengthening the intervals of cystoscopy in patients with low levels of an accurate marker and low-grade bladder cancer. In addition, while urinary tumor markers might not alter the schedule of cystoscopies, if their results suggest a high likelihood of tumor recurrence, the resulting cystoscopy might be performed more thoroughly, or investigation of the upper urinary tract might be instigated. (6) Other authors comment that tests could be performed in a stepwise approach, with a positive test triggering a cystoscopy and a negative test leading to an additional tumor marker test. (4)

No studies were identified that prospectively evaluated patients who were managed with and without the use of urinary tumor marker tests.

Other Markers
Studies have been published with other potential tumor markers in bladder cancer. These potential new markers include the following: telomerase, soluble Fas, tumor-associated trypsin inhibitor (TATI), soluble e-cadherin, bladder cancer specific biomarkers BLCA-1 and BLCA-4, cytokeratins 8 18 19 and 20, survivin, microsatellite markers, hyaluronic acid/hyaluronidase (HYAL1), DD23 monoclonal antibody, fibronectin, and protein and mRNA human chorionic gonadotropin (HCG). There are no FDA-approved tests using any of the above markers. A 2009 review article on potential new tumor markers comments that bladder cancer tumor markers is a rapidly evolving field in which new markers are constantly identified. (7) The review concludes, “1) there exists a dizzying number of markers identified using newer expertise, and 2) much more work will need to be done to delineate which markers may be clinically applicable and which will be discarded.”

Published studies that evaluate these markers have generally included small numbers of patients and were preliminary investigations (e.g., 8-10). Recently, a larger prospective study was published by Eissa and colleagues in Egypt evaluating HYAL1 and survivin. (11) This study included a total of 278 patients who underwent urine analysis and cystoscopy; 166 were found to have bladder cancer, and 112 had benign bladder lesions. One hundred healthy volunteers served as controls and did not undergo cystoscopy. The authors aimed to determine the ability of the two urinary tumor markers to identify malignant cases. Using qualitative RT-PCR analysis, HYAL1 was identified in 153 (92%) malignant samples and 12 (11%) of benign samples, and survivin in 126 (76%) of malignant samples and 12 (11%) of benign samples. HYAL1 and survivin were not identified in any of the control samples. Using the best cutoffs for discriminating the malignant and non-malignant groups, the sensitivity of HYAL1 was 92.2% at 94.3% specificity. This was higher than a comparable analysis of survivin which had a 75.9% sensitivity and 94.3% specificity. Using semi-quantitative RT-PCR analysis, the sensitivity of HYAL1 was 91% and of survivin was 95.9%; specificity in both cases was 100%. The sensitivity and specificity of the two markers would need to be confirmed in additional studies.

Urinary Markers to Screen Asymptomatic Individuals for Bladder Cancer
In 2004, the U.S. Preventive Services Task Force updated their recommendation on screening for bladder cancer in asymptomatic adults. (12) They found fair evidence that available screening tests can detect bladder cancer; however, they concluded that the potential benefit would be small, at best, for the following reasons: “there is fair evidence that many of the cancers detected by screening, have a low tendency to progress to invasive disease; there is a relatively low overall prevalence of asymptomatic bladder cancer that would eventually lead to important clinical consequences; and there is limited evidence that early treatment of bladder cancer detected through screening improves long-term health outcomes.” Moreover, the Task Force concluded that the potential harms of screening are at least small because, since screening tests have a low positive predictive value, there would be many false-positive findings which would lead to unnecessary invasive procedures. In their recommendation statement, they commented that smoking increases the risk of bladder cancer, and that current smokers should be counseled on quitting smoking. Working in certain occupations
such as the dye or rubber industries may also increase the risk of bladder cancer; they did not review evidence on targeted screening of individuals who may be at risk due to occupational exposure.

A modeling study published in 2006 reported that screening the general population for bladder cancer using tumor markers would not be beneficial but that screening an asymptomatic high-risk population would yield a benefit similar to other cancer screening programs (e.g., prostate, colon, and breast cancer). (13) In 2009, Lotan and colleagues published a prospective study in which 1502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure were screened. (14) Approximately 60% of the sample was recruited from a Veterans Administration hospital and 1175 (78%) of the study population was male. Participants were all at least 50 years old (mean age was 62.5 years). A total of 1298 individuals had a 10-year or greater smoking history, and 513 had a greater than 15-year occupational exposure. Approximately 73% of participants had undergone urinalysis within 3 years of screening. Individuals with a history of urological malignancy or gross malignancy and those with current urinary problems that might increase the false positive rate were excluded. The study used the NMP22 BladderChek test and was supported by Matritech, the test manufacturer. Individuals with positive BladderChek tests underwent additional testing, beginning with urinalysis. Those found to have infection on urinalysis were treated and their urine was re-tested; others who tested positive received cystoscopy and cytology. Individuals with a negative BladderChek test did not have to undergo additional testing. However, all participants were contacted after 12 months to determine whether they had been diagnosed with bladder cancer or were experiencing gross hematuria. Eighty-five (5.7%) of the 1502 participants had a positive BladderChek test. Of these, 69 (81%) underwent cystoscopy; 14 refused, and 2 patients with urethral strictures were unable to be examined. Two of the 85 patients were found to have bladder cancer (non-invasive), yielding a positive predictive value of 2.4%. There was also one case of atypia. Follow-up at a mean of 12 months was obtained for 1309 of 1502 (87%) screened individuals. No additional cancers were diagnosed in the group that had had positive BladderChek tests. Two participants with negative BladderChek screen had been diagnosed with bladder cancer; both tumors were less than 1 cm. Since no follow-up tests were done on participants who initially tested negative, it cannot be known whether these were false negative findings or new cancers. The authors report that there was a lower cancer prevalence in this population than expected, which could be due in part to the large proportion that had previously undergone urinalysis. Study limitations include lack of follow-up testing on approximately 20% of participants who tested positive, and lack of early cystoscopy and incomplete one-year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (e.g., sensitivity) cannot be calculated.

Summary
Numerous well-designed studies have evaluated the diagnostic performance of the FDA-approved urinary tumor markers. Overall, studies have found reasonable sensitivities and specificities, and a recent study found that one or two of these urinary tumor markers can enhance the sensitivity of urinary cytology. Studies describing other, non-FDA approved markers generally involve limited numbers of patients, and they have not been compared to urinary cytology or the commercially available tests. Based on the available evidence, the FDA-approved urinary markers are considered medically necessary for their approved indications when used in conjunction with standard diagnostic procedures, and other markers are considered investigational.

The existing evidence does not support the use of urinary tumor markers to screen for bladder cancer due to the low prevalence of asymptomatic disease in the general population and the lack of evidence that early treatment of screen-detected bladder cancer improves health outcomes. A recent prospective study also found a low yield when the BladderChek test was used in an industry-sponsored trial to screen high-risk asymptomatic individuals. Thus, urinary tumor markers to screen asymptomatic individuals is considered investigational.

Technology Assessments, Guidelines, and Position Statements
The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, published in 2010, do not recommend use of any of the FDA-approved urinary tumor marker tests for diagnosis of bladder tumors or for monitoring bladder cancer patients. (15) The guideline states, “In selected patients, and when used in
combination with cystoscopy, their measurement may provide additional information, but there is no evidence that this improves outcome.” The tests are also not recommended for bladder cancer screening.

National Comprehensive Cancer Network (NCCN) 2009 Practice Guidelines in Oncology Bladder Cancer (16) include the following statements regarding urothelial tumor markers: “…Urine molecular tests for urothelial tumor markers are now available. Most of these tests have a better sensitivity for detecting bladder cancer than urine cytology, but specificity is lower. However, it remains unclear whether these tests offer additional information which is useful for detection and management of non-muscle invasive bladder tumors. Therefore, The NCCN Bladder Cancer panel members consider this a category 2B recommendation.”

National Cancer Institute (NCI) Bladder and Other Urothelial Cancers Physician Data Query (PDQ®) (17) provides comprehensive, peer-reviewed information about general population screening for bladder and other urothelial cancers. The summary, updated in 2008, includes the following statements regarding screening for bladder and other urothelial cancers: “…There is inadequate evidence to determine whether screening for bladder and other urothelial cancers has an impact on mortality. Based on fair evidence, screening for bladder and other urothelial cancers would result in unnecessary diagnostic procedures with attendant morbidity. “

The American Urological Association’s 2007 guideline on management of bladder cancer (18) includes the following statement regarding urine-based markers for bladder cancer: “Despite their present and future potential, the critical evaluation and comparison of urine-based markers is beyond the scope of the current guideline involving the management of nonmuscle invasive bladder cancer.”

The U.S. Preventive Services Task Force recommends against routine screening for bladder cancer in adults (D recommendation). (12) The recommendation was last updated in 2004.

The Canadian Task Force on Preventive Health Care’s current screening for bladder cancer recommendations (19) regarding bladder cancer screening for the general population concludes: “…Routine screening is not recommended for asymptomatic persons.”

Medicare National Coverage
No Medicare national coverage determination.

References:

18 Based on the 1997 local Medicare policy on immunoassay for tumor antigen. See also www.medicarenhic.com

Medicare policy is developed separately from BCBSMA policy. While BCBSMA policy is based upon scientific evidence, Medicare policy incorporates scientific evidence with local expert opinion, and governmental guidelines from CMS (Centers for Medicare & Medicaid Services) and the US Congress. While BCBSMA and Medicare policies may differ, our Blue Care 65 and Medicare PPO Blue patients must be offered the same services as Medicare offers. In many instances, BCBSMA policies offer more benefits than does Medicare policy.

20 Based upon Blue Cross Blue Shield national policy 2.04.27, reviewed 10/2011. Measurements of CA-125 are medically necessary in endometrial cancer when CA-125 baseline levels have been shown to be elevated.

2003-5 Update
Updated reviews of the peer-reviewed literature on MEDLINE found no clinical trials to support the use of CA-125 screening for ovarian cancer in asymptomatic, low- to average-risk women. In addition, a December 2002 Committee Opinion of the American College of Obstetricians and Gynecologists notes currently available screening tests, including CA-125, do not appear to be beneficial for screening low-risk, asymptomatic women for ovarian cancer. (5) Therefore, the policy statement is unchanged.
References:

21 Based upon the Blue Cross Blue Shield Association National policy 2.04.27, Serum Tumor Markers for Breast and Gastrointestinal Malignancies (original issue date 1/2003.)

1/2003- The National policy notes that there were no clinical trials to support the use of CA-125 screening for ovarian cancer in asymptomatic, low-to average-risk women. Currently, the American Cancer Society and the U.S Preventive Services Task Force do not recommend ovarian cancer screening for average risk women. Additionally, a December 2002 Committee Opinion Report of the American College of Obstetrician and Gynecologists notes that CA-125 do not appear to be beneficial for screening low-risk, asymptomatic women for ovarian cancer.

Based on Blue Cross Blue Shield Association National Policy 2.03.02. Tumor markers described by CPT procedure code 86316 (immunoassay for tumor antigen) are considered investigational, including but not limited to (TPS, CAM17-1, CA195, CAR-3, DU-PAN-2, TAG12, TAG72.3, TNF-alpha, CA 242, CA 50, CA 72-4, TPA, CA-SCC, TPS, MCA, MSA, CA 549, CAM-26, CAM29, DMSA, NSE, MCA. Lipid associated sialic acid-LASA))

2005, 2006, and 2007 Updates Literature searches for the periods of 2004 through October 2005 and October 2005 through May 2007 did not identify additional studies that would prompt reconsideration of the policy statement. Specifically, the searches did not identify any controlled studies in which the clinical use of serum tumor markers improved health outcomes in patients with breast, pancreatic, gastric, or colon cancer. CA 19-9 continues to be of interest as a prognostic factor or as a monitoring tool in patients with pancreatic cancer, but no studies were identified that focused on how measurements of CA 19-9 could be used to direct management and improve patient outcomes. Preliminary studies of novel tumor markers have been published, including RCAS1, ICAM-1, and matrix metalloproteinases. (21-24) The National Cancer Institute and the European Organisation for Research and Treatment of Cancer (NCI-EORTC) have developed reporting recommendations for tumor marker prognostic studies. (24) This document points out that despite years of research the number of markers that have emerged as clinically useful is pitifully small. Updated ASCO guidelines on breast cancer follow-up and management (5) and on tumor markers in colorectal cancer (6), and recent reviews on serum tumor markers in breast cancer (25, 26) also did not cite any studies that would prompt changes to the policy statement. As of May 2007, an update to ASCO’s 2000 guideline on breast cancer tumor markers was in progress.
POLICY RATIONALE
This policy is based on the following: one 1995 and two 1996 TEC Assessments that addressed tumor markers in breast and gastrointestinal malignancy (1-3), a review of studies published since the TEC Assessments, and practice guidelines published by the American Society of Clinical Oncology (ASCO). (4-6) The following discussion does not address the use of CA-125, since this tumor marker is considered among the standard laboratory tests for patients with ovarian cancer.

Two key determinants of the clinical use of tumor markers are how their results will be used to affect patient management and whether the subsequent intervention will ultimately result in improved patient outcome. The application most extensively studied in breast and gastrointestinal malignancies is the use of tumor markers to monitor for recurrence. The outcomes most frequently reported are the interval between the diagnosis of metastases based on serial monitoring of tumor markers and the time at which the metastases become clinically apparent. However, these intervals may be related to both lead and length time bias and thus may have no impact on the final patient outcome of overall survival. Lead time bias refers to the fact that earlier diagnosis may not be related to improved overall survival, if there is no effective treatment. Length time bias refers to the fact that increased monitoring may detect primarily indolent, slow-growing metastases that are associated with prolonged survival regardless of treatment.

Two randomized studies of intensive surveillance of breast cancer follow-up illustrate this point. (7, 8) Both studies randomized breast cancer patients with no evidence of disease after primary treatment to receive usual care or intensive follow-up care, consisting of regularly scheduled chest x-ray and bone scan to provide early detection of the metastases in the most common sites, i.e., lungs and bone. While 1 study reported an earlier detection of metastases in the intensively monitored group (7), the other did not. (8) However, no difference was noted in 5-year overall survival. The lack of an improved outcome is in part related to the relatively ineffective curative treatment options for metastatic breast cancer. In this setting, quality of life issues related to the timing of treatment of metastatic disease may be relevant. These issues are similar to those associated with serial monitoring for recurrence of pancreatic or gastric cancer in which treatment options for recurrent disease are primarily palliative in nature.

The issues associated with serial monitoring of colorectal cancer are slightly different, since it has been shown that surgical resection of isolated liver or lung metastases may result in long-term survival in 20%–30% of patients. Therefore, early diagnosis may lead to a greater incidence of detection of surgically resectable lesions. In addition, serial monitoring of serum levels of carcinoembryonic antigen (CEA) is an established practice for colorectal cancer, and thus the sensitivities and specificities of mucinous glycoprotein tumor markers must be compared to CEA, considered the gold standard. The ASCO guidelines suggest that, if resection of liver metastases would be clinically indicated, it is recommended that postoperative serum CEA testing be performed every 2–3 months in patients with stage II or III disease for 2 or more years after diagnosis. (4) The ASCO guidelines published in 2000 did not make any explicit recommendations regarding the use of serum tumor markers related to the mucinous glycoproteins.

With this background in mind, the following discussion summarizes the TEC Assessments and the practice guidelines of ASCO regarding tumor markers for breast and gastrointestinal malignancies.

Breast Cancer
A 1995 TEC Assessment addressed the use of serum tumor markers in the diagnosis and monitoring of breast cancer (1), which specifically examined the role of tumor markers as a prognostic factor in breast cancer, while a 1996 TEC Assessment focused on their use to detect recurrence. (3) These assessments provided the following observations and conclusions:

Diagnosis and Monitoring
The evidence did not support a role for the use of serum tumor markers in the diagnosis of primary breast cancer, particularly for early stage disease, since sensitivities are low. Since none of the serum tumor markers is specific for breast cancer, they have limited utility in the differential diagnosis of metastatic disease of
unknown primary. Finally, no evidence supported the use of the level of serum tumor markers as independent predictors of prognosis.

In terms of monitoring response to therapy of metastatic disease, the serial measurement of serum tumor markers correlated well with clinical response criteria. However, of concern was the lack of valid criteria for interpreting changes in marker levels. Criteria have been suggested, but these have not been universally accepted.

Detection of Recurrence
The overall quality of the available studies was poor, and no studies addressed the impact of measurement of tumor markers on survival rates.

In most studies the reported lead times (i.e., difference in time of diagnosis between metastases identified with tumor marker compared to the clinical diagnosis) was 3–4 months. Whether this amount of lead time is adequate to improve therapy results is uncertain.

One of the rationales of early identification of metastatic disease is that chemotherapy may be most effective in the setting of minimal tumor burden. However, since the level of serum tumor markers is related to tumor burden, the sensitivity of serum tumor markers falls when tumor burden is low. In addition, the false positive rate may be high; 1 study reported a specificity of only 60% for detection of recurrence. A high false positive rate may be associated with unnecessary additional diagnostic testing and patient anxiety.

No studies published since the 1995 TEC Assessment have addressed the above limitations. In particular, no studies have specifically examined any relationship between serial monitoring of serum tumor markers for breast cancer and the overall survival of patients, primarily related to earlier treatment of metastatic disease. Also, no studies have specifically examined the quality-of-life issues related to the timing of treatment. (8) While some studies have suggested that serum tumor markers function as prognostic factors, no trials have specifically used the results of tumor marker studies to guide treatment of the patients. (9-12) The use of tumor markers, specifically CA 15-3 or CA 27.29, may have the most value in following up response to therapy of bone metastases, which are difficult to monitor radiologically. However, no studies have validated criteria for interpreting changes in marker levels or how these criteria may be used in the management of patients.

In 2001, the American Society of Clinical Oncology (ASCO) published breast cancer surveillance guidelines that stated that the routine use of CA 15-3 or CA 27.29 tumor marker for breast cancer surveillance is not recommended. (4)

Gastrointestinal Cancer (i.e., colon, gastric, and pancreatic)
A 1996 TEC Assessment addressed the use of serum mucinous glycoprotein tumor markers (i.e., CA 19-9, CA 242, CA 50, and CA 72-4) for both diagnosis and monitoring of gastric, pancreatic, and colorectal cancer. (2) These tumor markers were compared to the performance of CEA. The assessment reported the following observations and conclusions.

None of the tumor markers are specific for a particular tumor site, thus the markers are of limited value in determining the site of origin. CA 19-9, CA 50, and CA 242 have higher sensitivities than CEA in the diagnosis of pancreatic cancer, although these markers are also elevated in other cancer sites.

For gastric and colorectal cancer, no other marker appeared to provide prognostic information beyond that supplied by CEA. Prognostic information may be of value in determining appropriate treatment strategies, for example, selecting poorer prognostic patients for more aggressive therapy; however, the use of serum tumor marker levels in clinical decision making for treatment planning has not been appropriately assessed. No evidence was available to determine the use of serum tumor markers in the clinical management of gastric or pancreatic cancer.
For colorectal cancer, the most promising marker for the detection of recurrence or response appeared to be the combination of CEA and CA 242. In 1 study, the combined use of the markers was reported to increase the detection rate of recurrence to 88%, with a median lead time of 5 months. The trade-off for the increased sensitivity is a higher false-positive rate, which would result in unnecessary anxiety and additional testing. Whether the use of multiple serum markers improves health outcomes requires further study.

In addition, ASCO has published guidelines regarding the use of tumor markers in colon cancer. (4) The guideline stated that data were insufficient to recommend CA 19-9 or lipid-associated sialic acid (LASA) for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer. The guidelines also point out that CA 19-9 and CEA in combination did not improve the performance of CEA tests used alone as an indicator of asymptomatic recurrence. In terms of monitoring response to treatment, the guidelines state that CA19-9 does not add significant information to that provided by CEA, which is currently regarded as the marker of choice for colorectal cancer.

A literature review of studies published since the above TEC Assessment did not identify any study that would alter its conclusions. Specifically, no studies examined the health outcomes of patients whose disease recurrence had been identified by mucinous glycoproteins compared to CEA. The literature review further focused on the role of CA 19-9 in patients with pancreatic cancer. Although the ASCO guidelines state that CA 19-9 has become an established marker for pancreatic cancer, there is no further discussion, and the references cited are all from the 1980s and were considered as part of the 1996 TEC Assessment. The use of CA 19-9 as a prognostic factor continues to be of interest in pancreatic cancer, and as an intermediate outcome used to monitor treatment response. (13-20) However, there have been no prospective studies examining how this prognostic information may be used in patient management, either in selecting the type of therapy, duration of therapy, or initiation of salvage therapy.

Other Malignancies
The TEC Assessments did not address other serum tumor markers such as TPA (tumor polypeptide antigen), NSE (neuron specific enolase), or the other markers listed in the policy statement above. However, even less data are available on these markers for other malignancies (e.g., lung cancer) than those reported in the TEC Assessments, particularly in terms of primary health outcomes.

References:
1. 1995 TEC Assessments; Tab 19: Serum tumor markers for the diagnosis and monitoring of breast cancer.
2. 1996 TEC Assessments; Tab 23: Serum tumor markers for the diagnosis and monitoring of gastrointestinal cancer.
3. 1996 TEC Assessments; Tab 24: Serum tumor markers (CA 15-3, CA 27.29 and CA 549) for the monitoring of breast cancer recurrence.


Rationale
Taketa reported results on AFP-L3 (as a % of AFP) in a group of 424 patients with acute and chronic liver disease including cirrhosis and hepatocellular carcinoma. Using a cutoff level of 15% (15% or more was abnormal) they found sensitivity of 55% and specificity of 95% for hepatocellular carcinoma. Thirty-eight percent of tumors less than 20 mm in diameter were positive for AFP-L3. AFP-L3 exceeded the cutoff level of 15% an average of 4.0 months before detection by imaging techniques.

Oka and colleagues reported on a prospective study of AFP-L3 (lens culinaris agglutinin-reactive fraction of alpha-fetoprotein) in 388 patients with newly diagnosed hepatocellular cancer (HCC) at 9 Japanese hospitals. The cutoff level for an abnormal value was reduced from >15% to >10% during the study. Patients with abnormal levels were found to have more aggressive cancers. Tada reported that AFP-L3 percentage of >10% was associated with pathologic features of HCC that indicated aggressive tumor such as capsule infiltration and portal vein invasion.

In summary, while a number of studies show a relationship between this biomarker and hepatocellular cancer (both presence and severity), no studies have shown how prospective use of this marker in clinical care will improve patient outcomes. Thus, use of this assay is considered investigational.

Of note, neither the US Preventive Services Task Force (USPSTF) nor the National Comprehensive Cancer Network clinical guidelines discuss the use of this test in screening or clinical care for patients with known or suspected hepatocellular cancer.

2008 Update A literature search was conducted for the period December 2006 through March 2008. None of the studies identified lead to a change in the policy statement. In a prospective cohort of 332 HCV patients observed for 2 years at 7 North American institutions, Sterling et al compared AFP-L3% with or without AFP to AFP. The authors used cutoff points of 10% for AFP-L3 and 20 ng/ml for AFP. Overall sensitivity of AFP-L3 was 44.1%, increasing with AFP from 31% for AFP values less than 20 ng/ml to 60% for AFP values
greater than 200 ng/ml; sensitivity for AFP was 52.9%. Overall specificity of AFP-L3 was 91.6%, varying with AFP from 86.6% to 100%; specificity for AFP was 71.1%. Using area under the ROC curves, there was no statistical difference (p=0.586) between AFP-L3 (r=0.75) and AFP (r=0.72). Investigators were blinded to AFP-L3% results, which were therefore not guiding treatment decisions. A retrospective analysis of 272 patients referred to a single center for HCC, chronic liver disease or liver masses evaluated the performance characteristics of AFP-L3%. (9) The objective was to determine the added benefit of the AFP-L3% test over AFP alone. Because all patients in the cohort with AFP of 200ng/ml or greater had HCC and the AFP-L3% is often not reported if AFP is less than 10 ng/ml, the relevant group was the subset of patients with AFP 10ng/ml or greater but less than 200ng/ml. In this group, the areas under the ROC curve for distinguishing between HCC and chronic liver disease were nearly significant (p=0.074), with areas of 0.76 and 0.59 for AFP-L3% and AFP, respectively. The sensitivity and specificity (using the 10% cutoff point for AFP-L3%) were 71% and 63%, respectively. In this cohort, both AFP of 200 or greater and AFP-L3% of 10% or more were predictive of poor survival, but once the AFP level was taken into account, there was no prognostic value of the AFP-L3%. These equivocal findings are insufficient to change the policy statement at this time. This is investigational because the impact of this testing on health outcomes is uncertain.

2009 Update  A MEDLINE search was conducted for the period March 2008 through March 2009. All of the studies identified for this update compared AFP, AFP-L3% and des-Γ-carboxyprothrombin (DCP), an abnormal prothrombin produced by malignant hepatocytes. The prognostic use of AFP-L3% as a predictor of post-treatment survival or recurrence of HCC was addressed in 3 studies from Japan that addressed different aspects of prognosis; AFP-L3% values did not affect treatment decisions in any of them. Kitai and colleagues incorporated biomarker information into the Japan Integrated Staging (JIS) tool, where, within strata of the existing JIS staging system, patients with elevated values of 2 or 3 biomarkers had poorer survival compared to those with no biomarker elevations. (10) The 2 other studies used either pretreatment biomarker levels, (11) or pre- and post-treatment biomarker levels (12) as prognostic indicators for survival and recurrence of HCC treated with ablation or hepatectomy. The Owaga study (12) noted a statistically significant prognostic effect in a subset (n=19) of the study population of 124 patients; in a multivariate model, only AFP-L3% elevated (>15%) before and reduced after treatment (radiofrequency ablation) compared to AFP-L3% elevated both before and after treatment showed statistically significant improvement in both survival and recurrence. Neither post-treatment improvements in AFP (from >200ng/ml to <200ng/ml) nor DCP (from >100mAU/ml to <100mAU/ml) levels showed statistical improvements despite comprising slightly larger subsets of the main population. In the Toyoda cohorts (11), multivariate analyses showed that pretreatment levels of none of the 3 studied tumor markers significantly affected survival when hepatectomy was the treatment (n=345), but that elevated pretreatment AFP-L3% (15% or greater) and DCP (100mAU/ml or greater) levels were prognostic indicators of survival among patients treated with locoregional thermal ablation (n=456). Elevated pretreatment DCP was the only biomarker to statistically predict tumor recurrence.

A fourth study was the only one to address test characteristics and their utility for surveillance in high risk patients. (13) In this study from the US, 240 patients with either HBV or HCV with (n=144) or without (n=96) HCC attending a liver center were identified. Stored samples were tested for AFP, AFP-L3%, and DCP. Receiver-operator curves identified optimal cutoffs for the 3 biomarkers (25ng/ml, 10%, and 84mAU/l respectively). HCC was diagnosed using the American Association for the Study of Liver Diseases Practice Guidelines. The sensitivity, specificity and positive predictive value for each marker was as follows: 69%, 87% and 70% for AFP; 56%, 90%, and 56% for AFP-L3%; and 87%, 85%, and 87% for DCP. Combining tests yielded no additional improvements in predictive power. The biomarkers were not used for surveillance, nor were they used to guide treatment decisions; rather this was a retrospective assessment of their potential to guide surveillance activities.

The roll of AFP-L3% in improving health outcomes of patients with known or suspected HCC has yet to be determined, particularly in comparison or conjunction with DCP. Adding biomarker data may be helpful when staging HCC, as shown by Katai (10), although the contribution made by each biomarker was not demonstrated in this study. The policy statement remains unchanged.
References:

Coverage language determined by Associate Medical Director, effective December 2008

Other endocrine disorders
259.2 Carcinoid syndrome

Malignant carcinoid tumors of the small intestine
209.00 Malignant carcinoid tumor of the small intestine, unspecified portion
209.01 Malignant carcinoid tumor of the duodenum
209.02 Malignant carcinoid tumor of the jejunum
209.03 Malignant carcinoid tumor of the ileum

Malignant carcinoid tumors of the appendix, large intestine, and rectum
209.10 Malignant carcinoid tumor of the large intestine, unspecified portion
209.11 Malignant carcinoid tumor of the appendix
209.12 Malignant carcinoid tumor of the cecum
209.13 Malignant carcinoid tumor of the ascending colon
Policy #167: Tumor Markers for diagnosis and management of cancer

- Malignant carcinoid tumors of other and unspecified sites
  - 209.20 Malignant carcinoid tumor of unknown primary site
  - 209.21 Malignant carcinoid tumor of the bronchus and lung
  - 209.22 Malignant carcinoid tumor of the thymus
  - 209.23 Malignant carcinoid tumor of the stomach
  - 209.25 Malignant carcinoid tumor of the foregut, NOS
  - 209.26 Malignant carcinoid tumor of the midgut, NOS
  - 209.27 Malignant carcinoid tumor of the hindgut, NOS

- Benign carcinoid tumors of the small intestine
  - 209.40 Benign carcinoid tumor of the small intestine, unspecified portion
  - 209.41 Benign carcinoid tumor of the duodenum
  - 209.42 Benign carcinoid tumor of the jejunum
  - 209.43 Benign carcinoid tumor of the ileum
  - 209.50 Benign carcinoid tumor of the large intestine, unspecified portion
  - 209.51 Benign carcinoid tumor of the appendix
  - 209.52 Benign carcinoid tumor of the cecum
  - 209.53 Benign carcinoid tumor of the ascending colon
  - 209.54 Benign carcinoid tumor of the transverse colon
  - 209.55 Benign carcinoid tumor of the descending colon
  - 209.56 Benign carcinoid tumor of the sigmoid colon
  - 209.57 Benign carcinoid tumor of the rectum
  - 209.61 Benign carcinoid tumor of the bronchus and lung
  - 209.63 Benign carcinoid tumor of the stomach
  - 209.65 Benign carcinoid tumor of the foregut, NOS
  - 209.66 Benign carcinoid tumor of the midgut, NOS
  - 209.67 Benign carcinoid tumor of the hindgut, NOS
  - 209.69 Benign carcinoid tumor of other sites

- Family history of malignant neoplasm
  - V16.0 Gastrointestinal tract
  - V16.1 Trachea, bronchus, and lung
  - V16.9 Unspecified malignant neoplasm

- Personal history of malignant neoplasm
  - V10.00 Gastrointestinal tract, unspecified
  - V10.05 Large intestine
  - V10.06 Rectum, rectosigmoid junction, and anus
  - V10.11 Bronchus and lung

- ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>209.00</td>
<td>Malignant carcinoid tumor of the small intestine, unspecified portion</td>
</tr>
<tr>
<td>209.01</td>
<td>Malignant carcinoid tumor of the duodenum</td>
</tr>
<tr>
<td>209.02</td>
<td>Malignant carcinoid tumor of the jejunum</td>
</tr>
<tr>
<td>ICD-10-CM diagnosis codes:</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>C7A.019</td>
<td>Malignant carcinoid tumor of the small intestine, unspecified portion</td>
</tr>
<tr>
<td>C7A.010</td>
<td>Malignant carcinoid tumor of the duodenum</td>
</tr>
<tr>
<td>C7A.011</td>
<td>Malignant carcinoid tumor of the jejunum</td>
</tr>
<tr>
<td>C7A.012</td>
<td>Malignant carcinoid tumor of the ileum</td>
</tr>
<tr>
<td>C7A.019</td>
<td>Malignant carcinoid tumor of the large intestine, unspecified portion</td>
</tr>
<tr>
<td>C7A.010</td>
<td>Malignant carcinoid tumor of the duodenum</td>
</tr>
<tr>
<td>C7A.011</td>
<td>Malignant carcinoid tumor of the jejunum</td>
</tr>
<tr>
<td>C7A.012</td>
<td>Malignant carcinoid tumor of the ileum</td>
</tr>
</tbody>
</table>

ICD-10 Diagnosis Codes
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C7A.029</td>
<td>Malignant carcinoid tumor of the large intestine, unspecified portion</td>
</tr>
<tr>
<td>C7A.020</td>
<td>Malignant carcinoid tumor of the appendix</td>
</tr>
<tr>
<td>C7A.021</td>
<td>Malignant carcinoid tumor of the cecum</td>
</tr>
<tr>
<td>C7A.022</td>
<td>Malignant carcinoid tumor of the ascending colon</td>
</tr>
<tr>
<td>C7A.023</td>
<td>Malignant carcinoid tumor of the transverse colon</td>
</tr>
<tr>
<td>C7A.024</td>
<td>Malignant carcinoid tumor of the descending colon</td>
</tr>
<tr>
<td>C7A.025</td>
<td>Malignant carcinoid tumor of the sigmoid colon</td>
</tr>
<tr>
<td>C7A.026</td>
<td>Malignant carcinoid tumor of the rectum</td>
</tr>
<tr>
<td>C7A.00</td>
<td>Malignant carcinoid tumor of unspecified site</td>
</tr>
<tr>
<td>C7A.090</td>
<td>Malignant carcinoid tumor of the bronchus and lung</td>
</tr>
<tr>
<td>C7A.091</td>
<td>Malignant carcinoid tumor of the thymus</td>
</tr>
<tr>
<td>C7A.092</td>
<td>Malignant carcinoid tumor of the stomach</td>
</tr>
<tr>
<td>C7A.094</td>
<td>Malignant carcinoid tumor of the foregut NOS</td>
</tr>
<tr>
<td>C7A.095</td>
<td>Malignant carcinoid tumor of the midgut NOS</td>
</tr>
<tr>
<td>C7A.096</td>
<td>Malignant carcinoid tumor of the hindgut NOS</td>
</tr>
<tr>
<td>D3A.019</td>
<td>Benign carcinoid tumor of the small intestine, unspecified portion</td>
</tr>
<tr>
<td>D3A.010</td>
<td>Benign carcinoid tumor of the duodenum</td>
</tr>
<tr>
<td>D3A.011</td>
<td>Benign carcinoid tumor of the jejunum</td>
</tr>
<tr>
<td>D3A.012</td>
<td>Benign carcinoid tumor of the ileum</td>
</tr>
<tr>
<td>D3A.029</td>
<td>Benign carcinoid tumor of the large intestine, unspecified portion</td>
</tr>
<tr>
<td>D3A.020</td>
<td>Benign carcinoid tumor of the appendix</td>
</tr>
<tr>
<td>D3A.021</td>
<td>Benign carcinoid tumor of the cecum</td>
</tr>
<tr>
<td>D3A.022</td>
<td>Benign carcinoid tumor of the ascending colon</td>
</tr>
<tr>
<td>D3A.023</td>
<td>Benign carcinoid tumor of the transverse colon</td>
</tr>
<tr>
<td>D3A.024</td>
<td>Benign carcinoid tumor of the descending colon</td>
</tr>
<tr>
<td>D3A.025</td>
<td>Benign carcinoid tumor of the sigmoid colon</td>
</tr>
<tr>
<td>D3A.026</td>
<td>Benign carcinoid tumor of the rectum</td>
</tr>
<tr>
<td>D3A.090</td>
<td>Benign carcinoid tumor of the bronchus and lung</td>
</tr>
<tr>
<td>D3A.092</td>
<td>Benign carcinoid tumor of the stomach</td>
</tr>
<tr>
<td>D3A.094</td>
<td>Benign carcinoid tumor of the foregut NOS</td>
</tr>
<tr>
<td>D3A.095</td>
<td>Benign carcinoid tumor of the midgut NOS</td>
</tr>
<tr>
<td>D3A.096</td>
<td>Benign carcinoid tumor of the hindgut NOS</td>
</tr>
<tr>
<td>D3A.098</td>
<td>Benign carcinoid tumors of other sites</td>
</tr>
<tr>
<td>E34.0</td>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td>Z85.00</td>
<td>Personal history of malignant neoplasm of unspecified digestive organ</td>
</tr>
<tr>
<td>Z85.038</td>
<td>Personal history of other malignant neoplasm of large intestine</td>
</tr>
<tr>
<td>Z85.048</td>
<td>Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus</td>
</tr>
<tr>
<td>Z85.118</td>
<td>Personal history of other malignant neoplasm of bronchus and lung</td>
</tr>
<tr>
<td>Z80.0</td>
<td>Family history of malignant neoplasm of digestive organs</td>
</tr>
<tr>
<td>Z80.1</td>
<td>Family history of malignant neoplasm of trachea, bronchus and lung</td>
</tr>
<tr>
<td>Z80.9</td>
<td>Family history of malignant neoplasm, unspecified</td>
</tr>
</tbody>
</table>

25 Blue Cross Blue Shield of Massachusetts’ covered ICD-9-CM diagnoses codes for *BTA stat* ® or NMP-22 based on the covered criteria as noted in this medical policy.

**Hematuria**

599.70, hematuria, unspecified
599.71, gross hematuria
599.72, microscopic hematuria
ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>599.70</td>
<td>Hematuria, unspecified</td>
</tr>
<tr>
<td>599.71</td>
<td>Gross hematuria</td>
</tr>
<tr>
<td>599.72</td>
<td>Microscopic hematuria</td>
</tr>
</tbody>
</table>

ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>R31.9</td>
<td>Hematuria, unspecified</td>
</tr>
<tr>
<td>R31.0</td>
<td>Gross hematuria</td>
</tr>
<tr>
<td>R31.1</td>
<td>Benign essential microscopic hematuria</td>
</tr>
<tr>
<td>R31.2</td>
<td>Other microscopic hematuria</td>
</tr>
</tbody>
</table>

26 Based on the BCBSA national medical policy 2.04.34, Analysis of Proteomic Patterns in Serum to Identify Cancer, reviewed 7/2011.

27 Blue Cross Blue Shield of Massachusetts’ covered ICD-9-CM diagnoses codes for CA-125 (86304) based on the covered criteria as noted in this medical policy.

158.8: Malignant neoplasm of specified parts of peritoneum
158.9: Malignant neoplasm of peritoneum, unspecified
159.8: Malignant neoplasm of other sites of digestive system and intra-abdominal organs
171.5: Malignant neoplasm of connective and other soft tissue of abdomen
182.0: Malignant neoplasm of corpus uteri, except isthmus
183.0: Malignant neoplasm of ovary
183.2: Malignant neoplasm of fallopian tube
183.3: Malignant neoplasm of broad ligament of uterus
183.4: Malignant neoplasm of parametrium of uterus
183.5: Malignant neoplasm of round ligament of uterus
183.8: Malignant neoplasm of other specified sites of uterine adnexa
183.9: Malignant neoplasm of uterine adnexa, unspecified site
195.2: Malignant neoplasm of abdomen
195.3: Malignant neoplasm of pelvis
196.2: Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
196.6: Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
196.9: Secondary and unspecified malignant neoplasm of lymph nodes, site unspecified
197.6: Secondary malignant neoplasm of retroperitoneum and peritoneum
198.6: Secondary malignant neoplasm of ovary
198.82: Secondary malignant neoplasm of genital organs
233.2: Carcinoma in situ of other and unspecified parts of uterus
233.30: Carcinoma in situ, unspecified female genital organ
233.31: Carcinoma in situ, vagina
233.32: Carcinoma in situ, vulva
233.39: Carcinoma in situ, other female genital organ
235.4: Neoplasm of uncertain behavior of retroperitoneum and peritoneum
236.0: Neoplasm of uncertain behavior of uterus
236.2: Neoplasm of uncertain behavior of ovary
Rationale
The potential role for proteomics for cancer screening and detection has undergone considerable discussion (1-5); however, data in the peer-reviewed literature are inadequate to permit scientific conclusions regarding ovarian, prostate, or other malignancies.

Ovarian Cancer
Petricoin and colleagues reported on the technical feasibility of proteomic screening in a test series of serum from 50 patients with and 50 patients without ovarian cancer. (6) The spectra of proteins were analyzed by an iterative searching algorithm that identified a cluster pattern that segregated the patients with cancer from those without. This discovered pattern was then used to classify an independent set of 116 masked serum samples; 50 were from women with ovarian cancer and 66 were from unaffected women or those with nonmalignant conditions. Patients without cancer were considered at high risk, due either to familial breast or cancer syndrome or positivity of BRCA 1 or BRCA 2 mutations. All 50 with ovarian cancer were correctly identified, including the 18 with Stage I cancer. Of the 66 benign cases, 63 were identified as not being positive for cancer, yielding a sensitivity of 100% and a positive predictive value of 94%. The authors noted that while a positive predictive value of 94% may be acceptable for high-risk patients, in the larger population of average-risk patients, the positive predictive value must be close to 100% to avoid a high number of false-positive results, which, in turn, would generate additional workup. One of the key outcomes of an ovarian cancer screening test is the ability to identify Stage I ovarian cancer that is potentially curable with surgery. The described study only included 18 patients with Stage I ovarian cancer. The authors stated that an important future goal is the confirmation of the diagnostic performance of proteomic screening for the prospective detection of Stage I ovarian cancer in trials of both high- and low-risk women.

It should also be noted that the technology used in the Petricoin study (6) is not the same as that proposed for the OvaCheck® test. According to the National Cancer Institute, “The two techniques use different mass spectrometry instrumentation and detection methods, as well as different sample handling and processing methods. Therefore the class of molecules analyzed by these two approaches, and thus the molecules that constitute the diagnostic patterns would be expected to be entirely different.” (7) Other comments and correspondence in the literature (8) also question the statistical analysis used by Petricoin and other technical issues. (9) The results of the Petricoin study have not been reproduced elsewhere. (5)

Prostate Cancer
Ornstein and colleagues reported the results of serum proteomic profiling in 154 men with serum PSA ranging from 2.5 to 15.0 ng/mL. (10) A total of 63 samples (30 malignant, 33 benign) were used as the training set to identify a proteomic pattern that could distinguish benign from malignant disease. The results of the training set were then applied to the remaining 91 samples (i.e., the “testing” set) in a blinded fashion. In this testing set of 63 negative biopsies and 28 positive biopsies, there was 100% sensitivity and 67% specificity. These data imply that if the results of proteomic profiling were used to deselect patients for biopsy; 42 of 63 (67%) patients without prostate cancer could have avoided biopsy. The authors noted that using a training set of only 63 samples may be inadequate, and that “before this new technology can be applied in clinical practice, much larger and diverse training and testing sets will be needed.”
McLerran and colleagues selected serum samples from biorepositories from patients with 1) prostate cancer with a Gleason score of 7 or higher; 2) prostate cancer with a Gleason score of less than 7; or 3) negative prostate biopsies with a PSA of 10 mcg/L or less and no history of cancer of any kind, a normal digital rectal examination, and no inflammatory disease. They also selected two control groups: one with a history of inflammatory disease but no cancer and one with no history of prostate cancer but a history of another type of cancer. (11) Four hundred specimens were analyzed by mass spectrometry after random selection from the 5 groups of patients, with 125 from the group with high Gleason grade, 125 with low Gleason grade, 125 from the biopsy-negative group, and 50 from each of the control groups. The investigators sought to derive a decision algorithm for classification of prostate cancer from the mass spectrometry data, but found that they were unable to separate the patients with prostate cancer from biopsy-negative controls. They also were not able to separate patients with high and low Gleason scores. The conclusion was made that in the validation process, this protein-expression profiling approach did not perform well enough to advance to the prospective study stage.

Miscellaneous Cancers
A number of preliminary proteomic studies are available for many cancers including lung, colorectal, gastric, pancreatic, liver, cervical, endometrial, bladder, lymphoma/leukemia, melanoma, and astrocytomas. (1, 12-16).

Professional Societies
The Society of Gynecologic Oncologists released the following statement in February 2004, which remains unchanged to date (17):
“The Society of Gynecologic Oncologists (SGO) recognizes the importance of accurate early detection biomarkers for ovarian cancer. For this reason SGO reviewed the literature regarding OvaCheck, a serum based diagnostic test for ovarian cancer. In the opinion of SGO, more research is needed to validate the test’s effectiveness before offering it to the public.

SGO is committed to actively following and contributing to this vitally important research. As physicians who care only for women with gynecologic cancer, our hope is that these cancers can either be prevented or detected early. Because no test now exists to routinely detect ovarian cancer in its earliest and most curable stage, we will await the results of further clinical validation of OvaCheck with great interest.”

National Cancer Institute (NCI) PDQ®/Clinical Trials
As of May 2009, there are 8 ongoing phase III trials for a variety of malignancies, which are secondarily analyzing proteomic profiles in serum as predictors of survival, risk of disease progression, and response to treatment: non-small cell lung cancer (NCT00300729 and NCT00738881), melanoma (NCT00389571), ovarian cancer (NCT00426257), breast cancer (NCT00516425), prostate cancer (NCT00567580), hepatoblastoma (NCT00652132), and colon cancer (NCT00647530).

National Comprehensive Cancer Network (NCCN) Guidelines
2009 NCCN guidelines for the common cancers addressed in this policy do not comment on the use of proteomics.

References:


This document is designed for informational purposes only and is not an authorization, or an explanation of benefits, or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

©2014 Blue Cross and Blue Shield of Massachusetts, Inc. All rights reserved. Blue Cross and Blue Shield of Massachusetts, Inc. is an Independent Licensee of the Blue Cross and Blue Shield Association.