Positron Emission Tomography (PET) Oncology Applications

Policy # 00105
Original Effective Date: 01/28/2002
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cardiac applications of positron emission tomography (PET) scanning are considered in medical policy 00103.

Note: Miscellaneous applications of positron emission tomography (PET) scanning are considered in medical policy 00104.

Note: This policy only addresses the use of radiotracers detected with the use of dedicated PET scanners. Radiotracers such as fluorodeoxyglucose (FDG) may be detected using single photon emission computed tomography (SPECT) cameras, a hybrid PET/SPECT procedure that may be referred to as FDG-SPECT or molecular coincidence.

For this policy, PET scanning is discussed for the following four applications in oncology:

**Diagnosis.** Diagnosis refers to use of PET as part of the testing used in establishing whether or not a patient has cancer.

**Staging.** This refers to use of PET to determine the stage (extent) of the cancer at the time of diagnosis, before any treatment is given. Imaging at this time is generally to determine whether or not the cancer is localized. This may also be referred to as initial staging.

**Restaging.** This refers to imaging following treatment in two situations. Restaging is part of the evaluation of a patient in whom a disease recurrence is suspected based on signs and/or symptoms. Restaging also includes determining the extent of malignancy following completion of a full course of treatment.

**Surveillance.** This refers to use of imaging in asymptomatic patients (patients without objective signs or symptoms of recurrent disease). This imaging is completed 6 months or more (12 months or more for lymphoma) following completion of treatment.

Coverage Eligibility
The following apply to the listed oncologic applications of PET scanning:

**Eligible for Coverage**
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

**Investigational**
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.
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Based on review of available data, the Company considers the use of PET scans for oncology applications to be either eligible for coverage or investigational* as indicated below:

**Bone Cancer**

**Eligible for Coverage**

**Staging** When used in the staging of Ewing sarcoma and osteosarcoma may be eligible for coverage.

**Investigational**

**Staging** When used in the staging of chondrosarcoma is considered investigational.*

**Brain Cancer**

**Eligible for Coverage**

**Diagnosis** When utilized to differentiate scar tissue or tumor necrosis from active disease following radiation or chemotherapy the use of PET scanning may be eligible for coverage.

**Investigational**

**Diagnosis** When used for diagnosis (other than described above) PET scanning is considered investigational.*

**Staging** When used for staging of brain cancer PET scanning is considered investigational.*

**Restaging** When used for restaging of brain cancer PET scanning is considered investigational.*

**Starting**

**Eligible for coverage**

When used in the staging of breast cancer may be eligible for coverage for the following application:

- Detecting locoregional or distant recurrence or metastasis (except axillary lymph nodes).

**Restaging** When used in restaging breast cancer may be eligible for coverage for the following application:

- Detecting locoregional or distant recurrence or metastasis (except axillary lymph nodes).

**Investigational**

All other applications of PET scans in the evaluation of breast cancer are considered investigational* including, but not limited to, the following:

- Differential diagnosis in patients with suspicious lesions or an indeterminate/low suspicion on mammography;
- Staging axillary lymph nodes.
- Predicting pathologic response to neoadjuvant therapy for locally advanced disease.
Cervical Cancer

**Eligible for Coverage**

- *Staging*: When used in the staging of cervical cancer PET scans may be eligible for coverage.
- *Restaging*: When used in the restaging of cervical cancer PET scans may be eligible for coverage.

PET scanning in the evaluation of known or suspected recurrence of cervical cancer may be eligible for coverage.

Colorectal Cancer

**Eligible for Coverage**

- *Diagnosis*: When PET results may assist in the following situations PET scanning may be eligible for coverage:
  - Avoiding an invasive diagnostic procedure, or
  - Determining the optimal anatomical location to perform an invasive diagnostic procedure.

- *Staging*: When PET results may assist in the following situations PET scanning may be eligible for coverage:
  - To detect and assess resectability of hepatic or extrahepatic metastases of colorectal cancer; or
  - Cancer stage remains in doubt after completion of a standard diagnostic workup; or
  - PET could potentially replace one or more conventional imaging studies, when it is expected that conventional study information is insufficient for the clinical management of the patient, or
  - Clinical management would differ depending on the cancer stage.

- *Restaging*: When PET results may assist in the following situations PET scanning may be eligible for coverage:
  - To detect and assess resectability of hepatic or extrahepatic metastases of colorectal cancer; or
  - Detecting residual disease (after completion of treatment), or
  - Detecting suspected recurrence (example: rising carcinoembryonic antigen [CEA] levels; clinical signs/symptoms suspicious for recurrence); or
  - Determination of the extent of known recurrence.

**Investigational**

- *Differentiation*: When used as a technique to assess the presence of scarring versus local bowel recurrence in patients with previously resected colorectal cancer PET scanning is considered investigational.*
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**Esophageal Cancer**

**Eligible for Coverage**

*Diagnosis* When PET results may assist in the following situations PET scanning may be eligible for coverage:
- To avoid an invasive diagnostic procedure; or
- To determine the optimal anatomical location to perform an invasive diagnostic procedure.

*Staging* When PET results may assist in the following situations PET scanning may be eligible for coverage:
- Staging of esophageal cancer; or
- Staging of esophageal cancer when the stage of the cancer remains in doubt after completion of a standard diagnostic workup.

*Restaging* When PET results may assist in the following situations PET scanning may be eligible for coverage:
- Restaging after the completion of treatment; or
- Detection of residual disease, suspected recurrence, or to determine the extent of a known recurrence.

**Investigational**

*Diagnosis* When used in the evaluation and detection of primary esophageal cancer PET scanning is considered investigational.*

**Head and Neck Cancers (excluding CNS and Thyroid)**

**Eligible for Coverage**

*Diagnosis* When PET results may assist in the following situation PET scanning may be eligible for coverage:
- In the evaluation of head and neck cancer in the diagnosis of suspected cancer.

*Staging* When PET results may assist in the following situation PET scanning may be eligible for coverage:
- In the evaluation of head and neck cancer in the initial staging of disease.

*Restaging* When PET results may assist in the following situation PET scanning may be eligible for coverage:
- In the evaluation of head and neck cancer in the restaging of residual or recurrent disease during follow-up.

**Investigational**

When used for applications not discussed above, PET scanning for the evaluation of head and neck cancer is considered investigational*.

**Lung Cancer/Solitary Pulmonary Nodule**

**Eligible for Coverage**

*Diagnosis* When PET results may assist in the following situations PET scanning may be eligible for coverage:
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- Solitary Pulmonary Nodule - In patients with a solitary pulmonary nodule to distinguish between benign and malignant disease when prior CT and chest x-ray findings are inconclusive or discordant; or
- Lung Cancer - To determine resectability for patients with a presumed solitary metastatic lesion from lung cancer; or
- Lung Cancer - To distinguish between benign and malignant disease when prior CT scan and chest x-ray findings are inconclusive or discordant.

Staging  When PET results may assist in the following situations PET scanning may be eligible for coverage:
- In clinical situations in which the stage of cancer remains in doubt after completion of a standard diagnostic workup; or
- As staging technique in those with known non-small cell lung cancer (NSCLC).

Restaging  When PET results may assist in the following situations PET scanning may be eligible for coverage:
- As a restaging technique in those with known non-small cell lung cancer (NSCLC); or
- For restaging after the completion of treatment; or
- For the purpose of detecting residual disease; or
- For detecting suspected recurrence; or
- To determine the extent of a known recurrence.

Investigational

Staging  When used as a technique in the staging of small cell lung cancer PET scanning is investigational.*

Lymphoma, including Hodgkin's Disease

Eligible for Coverage

Diagnosis  Only in clinical situations in which the PET results may assist in avoiding an invasive diagnostic procedure, or in which the PET results may assist in determining the optimal anatomical location to perform an invasive diagnostic procedure. In general, for most solid tumors, a tissue diagnosis is made prior to the performance of PET scanning. Positron emission tomography scans following a tissue diagnosis are performed for the purpose of staging, not diagnosis. Therefore, the use of PET in the diagnosis of lymphoma should be rare.

Staging  When PET results may assist in the following situations PET scanning may be eligible for coverage:
- For staging lymphoma during initial staging; or
- In clinical situations in which the stage of the cancer remains in doubt after completion of a standard diagnostic workup.

Restaging  When PET results may assist in the following situations PET scanning may be eligible for coverage:
- For restaging at follow-up; or
- For the purpose of detecting residual disease; or
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- For detecting suspected recurrence; or
- To determine the extent of a known recurrence; or
- For restaging after the completion of treatment.

**Investigational**

When used for applications not discussed above, PET scanning for the evaluation of lymphoma is considered investigational.

**Melanoma**

**Eligible for Coverage**

**Diagnosis** When PET results may assist in the following situations PET scanning may be eligible for coverage:

- Only in clinical situations in which the PET results may assist in avoiding an invasive diagnostic procedure, or in which the PET results may assist in determining the optimal anatomical location to perform an invasive diagnostic procedure. In general, for most solid tumors, a tissue diagnosis is made prior to the performance of PET scanning. Positron emission tomography scans following a tissue diagnosis are performed for the purpose of staging, not diagnosis. Therefore, the use of PET in the diagnosis of melanoma should be rare; or
- As a technique for assessing extranodal spread of malignant melanoma at initial staging.

**Restaging** When PET results may assist in the following situations PET scanning may be eligible for coverage:

- For assessing extranodal spread of malignant melanoma at initial staging or at restaging during follow-up treatment; or
- For the purpose of detecting residual disease; or
- For detecting suspected recurrence; or
- To determine the extent of a known recurrence.

**Investigational**

When used for applications not discussed above PET scanning for the evaluation of melanoma is considered investigational.

When used as a technique in the evaluation of regional nodes PET scanning is considered investigational.

**Multiple Myeloma**

**Eligible for Coverage**

**Staging**

- To assess extent of disease at time of diagnosis

**Restaging**

- Restaging after completion of treatment
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- Detection of residual disease, suspected recurrence, or to determine the extent of a known recurrence.

**Ovarian Cancer**

**Eligible for Coverage**

**Diagnosis**
When PET results may assist in the following situations PET scanning may be eligible for coverage:
- Avoiding an invasive diagnostic procedure, or
- Determining the optimal anatomical location to perform an invasive diagnostic procedure.

**Staging**
When PET results may assist in the following situations PET scanning may be eligible for coverage:
- For staging ovarian cancer during initial staging; or
- In clinical situations in which the stage of the cancer remains in doubt after completion of a standard diagnostic workup.

**Restaging**
When PET results may assist in the following situations PET scanning may be eligible for coverage:
- For restaging at follow-up; or
- For the purpose of detecting residual disease; or
- For detecting suspected recurrence; or
- To determine the extent of a known recurrence; or
- For restaging after the completion of treatment.

**Pancreatic Cancer**

**Eligible for Coverage**

**Diagnosis**
When used as a technique in the initial diagnosis of pancreatic cancer when other imaging and biopsy are inconclusive PET scanning may be eligible for coverage.

**Staging**
When used as a technique for staging of pancreatic cancer when other imaging and biopsy are inconclusive PET scanning may be eligible for coverage.

**Investigational**
When used as a technique to evaluate other aspects of pancreatic cancer PET scanning is considered investigational.*

**Prostate Cancer**

**Investigational**

**Diagnosis**
When used in diagnosis and management of known or suspected prostate cancer PET scanning is considered investigational*.
Soft Tissue Sarcoma

Investigational
PET scanning is considered investigational* in evaluation of soft tissue sarcoma, including but not limited to the following applications:
- Distinguishing between benign lesions and malignant soft tissue sarcoma; or
- Distinguishing between low grade and high grade soft tissue sarcoma; or
- Detecting locoregional recurrence; or
- Detecting distant metastasis.
- Evaluating response to imatinib and other treatments for gastrointestinal stromal tumors.

Testicular Cancer

Eligible for Coverage
Restaging When used as a technique in evaluation of residual mass following chemotherapy of stage IIB and III seminomas PET scanning may be eligible for coverage.

Note: The PET scan should be completed not sooner than 6 weeks following chemotherapy.

Investigational
Except as noted above for seminoma, PET scanning is investigational* in evaluation of testicular cancer, including but not limited to the following applications:
- Initial staging of testicular cancer; or
- Distinguishing between viable tumor and necrosis/fibrosis after treatment of testicular cancer; or
- Detection of recurrent disease after treatment of testicular cancer.

Thyroid Cancer, Differentiated

Eligible for Coverage
Diagnosis When used as a technique in the diagnosis of patients with differentiated thyroid cancer when thyroglobulin (Tg) levels are elevated and whole-body I-131 imaging is negative PET scanning may be eligible for coverage.

Restaging When used as a technique for restaging patients with differentiated thyroid cancer when thyroglobulin (Tg) levels are elevated and whole-body I-131 imaging is negative PET scanning may be eligible for coverage.

Investigational
When used as a technique in the evaluation of known or suspected differentiated thyroid cancer in all other situations PET scanning is considered investigational.*

Unknown Primary

Eligible for Coverage
Diagnosis When used in patients with an unknown primary who meet all of the following criteria PET scanning may be eligible for coverage:
- Single site of disease outside the cervical lymph nodes; and
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- Patient is considering local or regional treatment for a single site of metastatic disease; and
- Negative workup for an occult primary tumor; and
- PET scan will be used to rule out or detect additional sites of disease that would eliminate the rationale for local or regional treatment.

**Investigational Diagnosis**

PET scanning is considered investigational* in evaluation of unknown primary, including but not limited to the following applications:

- As part of the initial workup of an unknown primary; or
- As part of the workup of patients with multiple sites of disease.

**Cancer Surveillance**

PET scanning is considered investigational* when used as a surveillance tool for patients with cancer or with a history of cancer. A scan is considered surveillance if performed more than 6 months after completion of cancer therapy (12 months for lymphoma) in patients without objective signs or symptoms suggestive of cancer recurrence.

**Other Oncologic Applications**

PET scanning for other oncologic applications is considered investigational*.

- Evaluation of neuroendocrine tumors
- Staging inguinal lymph nodes in patients with squamous cell carcinoma of the penis

**Background/Overview**

Positron emission tomography scans are based on the use of positron-emitting radionuclide tracers coupled to organic molecules, such as glucose, ammonia, or water. The radionuclide tracers simultaneously emit 2 high-energy photons in opposite directions that can be simultaneously detected (referred to as coincidence detection) by a PET scanner, consisting of multiple stationary detectors that encircle the area of interest.

A variety of tracers are used for PET scanning, including oxygen-15, nitrogen-13, carbon-11, and fluorine-18. Because of their short half-life, some tracers must be made locally using an onsite cyclotron. The radiotracer most commonly used in oncology imaging has been fluorine-18 coupled with FDG, which has a metabolism related to glucose metabolism. Fluorodeoxyglucose has been considered useful in cancer imaging, since tumor cells show increased metabolism of glucose. The most common malignancies studied have been melanoma, lymphoma, lung, colorectal, and pancreatic cancer.

As with any imaging technique, the medical necessity of PET scanning depends in part on what imaging techniques are used either before or after the PET scanning. Due to its expense, PET scanning is typically considered after other techniques, such as CT, magnetic resonance imaging (MRI), or ultrasonography, provide inconclusive or discordant results. In patients with melanoma or lymphoma, PET scanning may be considered an initial imaging technique. If so, the medical necessity of subsequent imaging during the same diagnostic evaluation is unclear. Thus, PET should be considered for the medically necessary indications above only when standard imaging, such as CT or MRI, is inconclusive or not indicated.
Patient selection criteria for PET scanning also may be complex. For example, it may be difficult to determine from claims data whether a PET scan in a patient with malignant melanoma is being done primarily to evaluate extranodal disease or regional lymph nodes. Similarly, it may be difficult to determine whether a PET scan in a patient with colorectal cancer is being performed to detect hepatic disease or evaluate local recurrence. Due to the complicated hierarchy of imaging options in patients with malignancy and complex patient selection criteria, one possible implementation strategy for this policy is its use for retrospective review, possibly focusing on cases with multiple imaging tests, including PET scans.

Use of PET scanning for surveillance as described in the policy statement and policy rationale refers to the use of PET to detect disease in asymptomatic patients at various intervals. This is not the same as the use of PET for detecting recurrent disease in symptomatic patients; these applications of PET are considered within tumor-specific categories in the policy statements.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

In 1997, the U.S. FDA Modernization Act (FDAMA) attempted to resolve the controversy regarding PET scans first by establishing FDA authority over the safety and effectiveness of locally manufactured radiotracers and second, by developing streamlined regulations for good manufacturing practices with which each PET facility must comply.

The FDA issued a notice in the Federal Register on March 10, 2000, summarizing the regulatory history of PET radiotracers and highlighting its decisions on safety and effectiveness for certain uses of certain PET radiotracers. The FDA conducted a literature review and Advisory Committee meetings to discuss the following uses:

- $^{18}$F-FDG for evaluation of glucose metabolism in oncology
- $^{18}$F-FDG for evaluation of myocardial hibernation
- $^{13}$N-ammonia for evaluation of myocardial blood flow
- $^{15}$O-water for assessment of cerebral perfusion

However, only the first three of these were subsequently approved by the FDA. In September 2012, FDA approved choline C-11 for PET imaging in patients with suspected prostate cancer recurrence (ie, elevated serum prostate-specific antigen after initial therapy) in whom bone scintigraphy, CT, or MRI is noninformative. Potential sites of prostate cancer recurrence identified on choline C-11 PET scanning require subsequent histologic confirmation.

A draft guidance document for Current Good Manufacturing Practice (CGMP) requirements for the production of PET drug products was issued on April 1, 2002. The final CGMP regulation was issued on December 9, 2009, and took effect on December 12, 2011.

The following FDA web page includes various PET-related documents:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm
Centers for Medicare and Medicaid Services (CMS)
Medicare has issued a detailed medical policy regarding oncologic applications of PET scans, which requires documentation on what tests come before and after the PET scan.

Rationale/Source
This policy is based on multiple evaluations of PET, including TEC Assessments, other systematic reviews, meta-analyses, decision analyses, and cost-effectiveness analyses.

From the perspective of evidence-based medicine, overall, the literature on use of PET scanning in oncology is quite limited. There are few rigorous studies that assess the impact of PET on clinical outcomes. The majority of the studies that report on outcomes describe changes in staging and/or treatment that result from the PET scan; however, the studies do not evaluate whether or not these changes result in an improvement in the net health outcome.

A 1997 TEC Assessment considered the use of PET scanning in the evaluation of solitary pulmonary nodules and staging of known lung cancer. A 2006 evidence report by TEC for the Agency for Healthcare Research and Quality (AHRQ) addressed use of PET for staging small cell lung cancer (SCLC). Three 1999 TEC Assessments and one 2000 TEC Assessment considered the use of PET scanning in the evaluation of melanoma, lymphoma, colorectal, and head and neck cancer. TEC Assessments from 2000 and 2002 addressed unknown primaries. One 2001 TEC Assessment, a 2002 decision analysis, and a 2005 systematic review focused on esophageal cancer. Pancreatic cancer was evaluated in a 1999 TEC Assessment and the 2004 AHRQ systematic review. The 2004 AHRQ systematic review also focused on ovarian cancer, as well as testicular cancer. Soft tissue sarcoma was the subject of a 2002 AHRQ systematic review. Breast cancer was the focus of 2 TEC Assessments from 2001 and 2003, a systematic review from 2005, a systematic review from 2007, and a cost-effectiveness analysis from 2005. Several uses of PET were reviewed in National Comprehensive Cancer Network (NCCN) Task Force documents released in 2007 and 2009. Another AHRQ systematic review evaluating use of PET for 9 cancers was published in 2008. Systematic reviews and meta-analyses published in 2011 and 2012 address 10 indications for 9 malignancies. In the Assessments, PET scanning was considered an adjunct to other imaging methods (i.e., CT, MRI, and US) often used when previous imaging studies are inconclusive or provide discordant results. In this setting, the clinical value of PET scans is the rate of discordance among imaging techniques and the percentage of time that PET scanning results in the correct diagnosis, as confirmed by tissue biopsy. The Assessments and literature reviews offered the following observations and conclusions:

Bone Cancer
A systematic review and meta-analysis of studies examining the diagnostic accuracy of PET in Ewing sarcoma showed very high estimates of sensitivity and specificity (pooled sensitivity 96%, pooled specificity 92%). Another study of PET in pediatric sarcoma (Ewing sarcoma and osteosarcoma) patients in which PET was used in addition to conventional imaging showed that PET was superior to conventional imaging in detecting lymph node and bone involvement. The most thorough assessment of cancer involvement used both PET and conventional tests and produced important changes in therapy decisions.
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There are very few studies examining the utility of PET in chondrosarcoma.

Brain Tumors
A systematic review and meta-analysis addressed use of fluorine-18 fluoro-ethyl-tyrosine (FET) in detecting primary brain tumors. While it used a sophisticated meta-analytic method, it did not compare use of 18F-FET PET with another imaging modality for diagnosis of brain tumors, so no conclusions can be reached about comparative effectiveness. A 2013 meta-analysis found limited use for 18F-FDG-PET in differentiating brain tumors. Diagnostic performance was better with 11C-methionine PET. However, another meta-analysis found dynamic susceptibility contrast-enhanced MRI performed better than 11C-methionine PET in glioma recurrence detection.

Breast Cancer
The 2001 TEC Assessment focused on multiple applications of PET scanning in breast cancer, including characterization of breast lesions, staging axillary lymph nodes, detection of recurrence, and evaluating response to treatment. The 2003 TEC Assessment re-examined all of the above indications except for its role in characterizing breast lesions.

- The bulk of the data regarding PET scanning for breast cancer focuses on its use as a technique to further characterize breast lesions such that patients could avoid biopsy of a mammographically indeterminate or suspicious lesion. The key statistic in this analysis is the false-negative rate, since patients with a false-negative result on a PET scan may inappropriately forego a biopsy and subsequent treatment. The false-negative rate will vary with the underlying prevalence of the disease, but may range from 5.5% to 8.5%. Given the relative ease of breast biopsy, this false-negative rate may be considered unacceptable, and thus patients may undergo biopsy regardless of the results of a PET scan.
- A 2005 systematic review and meta-analysis focused on use of PET for detecting recurrence and metastases. The report concluded that PET is a valuable tool; however, it did not compare PET performance with that of other diagnostic modalities, so it is unclear if PET results in different management decisions and health outcomes.
- A systematic review published in 2007 on use of PET for staging axillary lymph nodes identified 20 studies. Of these, 3 studies were rated with the highest quality grade, corresponding to broad generalizability to a variety of patients and no significant flaws in research methods. The remaining studies were more flawed and/or were more narrowly generalizable. The review observed that there was great variability in estimates of sensitivity and specificity from the selected studies and that it is difficult to draw conclusions from the evidence.

A 2013 meta-analysis by Hong et al reported sensitivity and specificity of PET/CT in diagnosing distant metastases in breast cancer patients of 0.96 (95% confidence interval [CI], 0.90 to 0.98) and 0.95 (95% CI, 0.92 to 0.97), respectively, when 8 studies totaling 748 patients were included. When the meta-analysis included 6 comparative studies totaling 664 patients, sensitivity and specificity were 0.97 (95% CI, 0.84 to 0.99) and 0.95 (95% CI, 0.93 to 0.97), compared with 0.56 (95% CI, 0.38 to 0.74) and 0.91 (95% CI, 0.78 to 0.97) with conventional imaging.
Rong et al (2013) meta-analyzed 7 studies totaling 668 patients and reported that PET/computed tomography (CT) sensitivity and specificity were greater compared with bone scintigraphy for detecting bone metastasis in breast cancer patients. PET/CT sensitivity and specificity were 0.93 (95% CI, 0.82 to 0.98) and 0.99 (95% CI, 0.95 to 1.00), respectively, compared with 0.81 (95% CI, 0.58 to 0.93) and 0.96 (95% CI, 0.76 to 1.00), respectively, for bone scintigraphy.

In a meta-analysis of 8 studies (total N=873) of FDG-PET in women with suspicious breast lesions, Caldarella et al (2014) reported pooled sensitivity and specificity of 0.85 (95% CI, 0.83 to 0.88) and 0.79 (95% CI, 0.74 to 0.83), respectively, on a per-lesion basis. As previously noted, a false-negative rate of 15% (1 – sensitivity) may be considered unacceptable given the relative ease of breast biopsy.

A 2007 National Comprehensive Cancer Network (NCCN) review of PET concluded that PET is optional and may be useful for staging and restaging regional or distant metastasis when suspicion is high and other imaging is inconclusive. Current NCCN guidelines include an optional category 2B recommendation for FDG-PET/CT in the work-up of clinical stage IIIA breast cancer. NCCN recommends against FDG-PET/CT for lower stage breast cancer due to high false-negative rates in detecting low-grade lesions or lesions less than 1 cm; low sensitivity in detecting axillary node metastasis; low prior probability of detectable metastases in these patients; and high false-positive rates. PET or PET/CT is considered most helpful when “standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.” Additionally, NCCN guidelines do not recommend routine use of PET scans in asymptomatic patients for surveillance and follow-up after breast cancer treatment.

Two 2012 meta-analyses pooled studies on use of FDG PET to predict pathologic response to neoadjuvant therapy before surgery for locally advanced breast cancer. These articles reported similar pooled point estimates of both sensitivity and specificity. They both concluded that PET has reasonably high sensitivity and relatively low specificity. Neither article described how PET should be used to influence patient management decisions and therefore whether health outcomes would be changed relative to decisions not based on PET results. Thus, it is unclear whether PET improves outcomes for predicting pathologic response to neoadjuvant therapy for locally advanced breast cancer.

Cervical Cancer
An AHRQ review published in 2008 identified several studies in which PET or PET/CT was used in the staging of advanced cervical cancer and for detection and staging of recurrent disease. The report concluded that the majority of studies supported enhanced diagnostic accuracy, which would improve the selection of appropriate treatment for patients. For recurrent disease, PET identifies additional sites of metastasis which would alter treatment decisions in some cases. For example in a study by Yen et al of 55 patients whose recurrences were initially considered curable with radical surgical treatment, 27 instead underwent palliative therapy based on PET results. An NCCN Task Force Report on PET also identifies several studies that support use of PET for initial staging and identification and staging of recurrent disease. In a 2013 meta-analysis of 9 cervical cancer recurrence studies, Meads et al reported sensitivity and specificity of PET/CT of 94.8 (95% CI, 91.2 to 96.9) and 86.9 (95% CI, 82.2 to 90.5), respectively. The authors found the quality of studies on recurrence was average with some limitations. For example, studies included mostly symptomatic women and did not differentiate between PET for diagnosis or surveillance. In
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a meta-analysis of 20 studies, Chu et al (2014) reported pooled sensitivity and specificity for FDG-PET or FDG-PET/CT of 0.87 (95% CI, 0.80 to 0.92) and 0.97 (95% CI, 0.96 to 0.98), respectively, for distant metastasis in recurrent cervical cancer. For local regional recurrence, pooled sensitivity and specificity were 0.82 (95% CI, 0.72 to 0.90) and 0.98 (95% CI, 0.96 to 0.99), respectively.

Current NCCN guidelines state that PET/CT “may aid in treatment planning but is not accepted for formal staging purposes.” A single PET/CT at 3 to 6 months after therapy for locally advanced cervical cancer is recommended to detect persistent or recurrent disease. PET/CT is not recommended for surveillance.

Colorectal Cancer

Two clinical applications of PET scanning were considered: 1) To detect hepatic or extrahepatic metastases and to assess their resectability in patients with colorectal cancer, either as part of initial staging or after primary resection, and 2) to evaluate the presence of postoperative scar versus recurrent disease as a technique to determine the necessity of tissue biopsy.

- The body of evidence indicates that PET scanning adds useful information to conventional imaging in detecting hepatic and extrahepatic metastases. In particular, PET can detect additional metastases leading to more identification of non-resectable disease, allowing patients to avoid surgery. The strongest evidence comes from a study that directly assessed the additional value of PET. In a group of 37 patients thought to have solitary liver metastases by conventional imaging, PET correctly upstaged 4 patients and falsely overstaged 1 patient. This study and another further found that, when PET is discordant with conventional imaging, PET is correct in 88% and 97% of patients. When PET affects management decisions, it is more often used to recommend against surgery.

- When used to distinguish between local recurrence and scar, the comparison is between performing histological sampling in all patients with a suspected local recurrence and avoiding sampling in patients whose PET scans suggest the presence of postoperative scar. The key concern is whether the negative predictive value for PET is sufficiently high to influence decision making, specifically to avoid tissue biopsy when the PET scan is negative. The available studies suggest a probability of false negative results of 8%, making it unlikely that patients and physicians would be willing to forgo histologic sampling and delay potentially curative repeat resection.

- A systematic review of different imaging techniques for radiotherapy treatment planning of rectal cancer concluded that additional studies are needed to validate use of PET in this setting. Three systematic reviews published in 2014 included overlapping studies that assessed the predictive value of FDG-PET/CT in patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy. Various PET parameters were investigated (standardized uptake value [SUV], response index [percentage of SUV decrease from baseline to post-neoadjuvant treatment]), and cutoff values varied. Pooled sensitivities ranged from 0.74 to 0.82, and pooled specificities ranged from 0.64 to 0.85. The value of FDG-PET/CT in this setting has yet to be clarified.

In a 2013 meta-analysis, Lu et al evaluated 510 patients from 11 studies on PET for colorectal cancer tumor recurrence detection in patients with carcinoembryonic antigen (CEA) elevation. FDG-PET and PET/CT
pooled sensitivity estimates were 90.3% (95% CI, 85.5% to 94.0%) and 94.1% (95% CI, 89.4% to 97.1%), respectively, and specificities were 80.0% (95% CI, 67.0% to 89.6%) and 77.2% (95% CI, 66.4% to 85.9%), respectively.

Current NCCN guidelines for colon cancer “strongly discourage the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up and recommend consideration of a preoperative PET/CT scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease.” NCCN panel opinion was divided on appropriateness of PET/CT when CEA level is rising; PET/CT may be considered when imaging study results (eg, a good quality CT scan) are normal.

Current NCCN guidelines for rectal cancer state that PET/CT is “not routinely indicated” and “should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan.”

**Esophageal Cancer**

Regarding diagnosis, PET is generally not considered a test for detecting primary esophageal tumors, and evidence is lacking on its use to differentiate between esophageal cancer and benign conditions.

A 2009 NCCN Task Force report found studies showing that PET is more sensitive than other diagnostic imaging in detecting stage IV disease with distant lymph node involvement. A meta-analysis described in the report found a 0.67 pooled sensitivity, 0.97 specificity, and small added value after conventional staging in detecting distant metastasis. In a 2013 meta-analysis of 245 patients with esophageal cancer from 6 studies, Shi et al reported that for detection of regional nodal metastases, FDG PET/CT had a sensitivity of 0.55 (95% CI, 0.34 to 0.74) and specificity of 0.76 (95% CI, 0.66 to 0.83). Current NCCN guidelines for esophageal cancer indicate that PET/CT may be considered in the initial workup of esophageal cancer if there is no evidence of M1 disease and to assess response to preoperative or definitive chemoradiation.

Another use of PET in esophageal cancer is in determining whether to continue chemotherapy for potential curative resection. The NCCN Task Force report described several studies in which response to chemotherapy, defined as a decline in standardized uptake values, correlated with long-term survival. Patients who do not respond to chemotherapy may benefit from this test by being spared futile and toxic chemotherapy. However, the treatment strategy of PET-directed chemotherapy does not appear to have been validated with randomized controlled trials (RCTs) showing improved net health outcome. Current NCCN guidelines for esophageal cancer state that PET/CT may be considered to assess treatment response 5 to 6 weeks after preoperative therapy.

**Gastric Cancer**

A systematic review and meta-analysis pooled 9 studies of PET for evaluating recurrent gastric cancer. The meta-analysis used methods that do not adequately account for dependence of sensitivity and specificity, nor did the authors adequately handle covariates that might explain between-study heterogeneity. The authors concluded that PET combined with CT may be more effective than either modality alone, but the data presented do not support this conclusion. In a 2013 meta-analysis, the sensitivity of PET/CT for detecting recurrence of gastric cancer after surgical resection was 0.86 (95% CI, 0.71 to 0.94), and specificity was 0.88 (95% CI, 0.75 to 0.94).
Current NCCN guidelines for gastric cancer indicate that PET/CT (but not PET alone) may be used as part of an initial workup if there is no evidence of metastatic disease. The guidelines note that the sensitivity of PET/CT is lower than CT, but specificity is higher, and PET/CT adds value to the diagnostic workup. NCCN guidelines also indicate that PET/CT may be used to evaluate response to treatment.

**Head and Neck Cancer**
Among the 3 studies that used other diagnostic modalities to attempt to identify a primary tumor in patients with positive cervical lymph nodes, PET found more primary tumors than other modalities in 2 studies and identified similar proportions in 1 study. When data from these 3 studies are pooled, PET was found to identify tumor in 38% of cases and other modalities found tumor in 21% of cases.

- When PET is used to initially stage the cervical lymph nodes (i.e., the status of the cervical nodes is unknown), the addition of PET to other imaging modalities increased the proportion of patients who were correctly staged, as confirmed histologically. When compared head to head with other imaging modalities, the pooled data from a variety of studies suggested that PET had a better diagnostic performance compared to CT and MRI.
- Of 8 studies focusing on the use of PET to detect residual or recurrent disease, 5 found PET to be more specific and sensitive, 2 reported mixed or equivalent results, and 1 reported worse results compared to CT.

Meta-analyses in 2013 and 2014 reported good sensitivities and specificities with PET/CT for diagnosing head and neck squamous cell cancers (better than CT and MRI) and for detecting head and neck cancer metastases (better than bone scintigraphy) and recurrence. Current NCCN guidelines for head and neck cancer indicate that PET/CT may be appropriate for stage III-IV disease evaluation, for detection of metastases or recurrence, and for evaluation of response to treatment.

**Lung Cancer**
Positron emission tomography scanning may have a clinical role in patients with solitary pulmonary lung nodules in whom the diagnosis is uncertain after prior CT scan and chest x-ray. Patients who are relatively young and have no smoking history are at a relatively low risk for lung cancer, and in this setting the negative predictive value of a PET scan is relatively high. If presented with a negative PET scan and information about the very low probability of undetected malignancy, it is quite likely that some patients would choose to avoid the harms of an invasive sampling procedure (i.e., biopsy). A meta-analysis on evaluating pulmonary nodules using dual-time PET (a second scan added after a delay) found that its additive value relative to a single PET scan is questionable.

In patients with known non-small cell lung cancer, the clinical value of PET scanning relates to improved staging information regarding the involvement of mediastinal lymph nodes, which generally excludes patients from surgical excision. The 1997 TEC Assessment cited a decision-analysis study that suggested that the use of CT plus PET scanning in staging the mediastinal lymph nodes resulted in fewer surgeries and an average gain in life expectancy of 2.96 days. The gain in life expectancy suggests that avoidance of surgery was not harmful to the patients in that potentially beneficial surgery was not withheld on the basis of false positive imaging results.
A 2009 NCCN report on the use of PET scanning supported an indication for patients who are suspected to have solitary metastases who may be candidates for surgical resection. In such patients, the test may detect additional metastases, which would rule out or change the extent of planned surgery.

Six studies of patients with SCLC reported evidence suggesting that for non-brain metastases PET added to conventional staging is more sensitive in detecting disease than conventional staging alone. Positron emission tomography may correctly upstage and downstage disease, and studies reported very high occurrence of patient management changes that were attributed to PET. However, the quality of these studies is consistently poor, and insufficient detail in reporting was the norm, especially with respect to the reference standard. A systematic review of staging SCLC found PET to be more effective than conventional staging methods; however, this review was heavily flawed by not conducting a quality assessment of individual studies, so its conclusions may not be sound. A 2014 meta-analysis included 12 studies (total N=369) of FDG-PET/CT for staging SCLC. Although estimated pooled sensitivity and pooled specificity were 0.98 (95% CI, 0.94 to 0.99) and 0.98 (95% CI, 0.95 to 1.00), included studies were small (median sample size, 22 patients); of primarily fair to moderate quality; and heterogeneous in design (retrospective, prospective), PET parameter assessed, indication for PET, and reference standard used. It is not possible from the limited and poor quality evidence that is available to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

Meta-analyses in 2013 have reported good sensitivities and specificities in lung cancer detection with PET/CT.

The American College of Chest Physicians issued guidelines for the diagnosis and management of lung cancer in 2013. The guidelines state that RCTs support the use of PET or PET/CT scanning as a component of lung cancer treatment and recommend PET or PET/CT for staging, detection of metastases, and avoidance of noncurative surgical resections.

Current NCCN guidelines for NSCLC indicate that PET may be used in the staging of disease, detection of metastases, treatment planning, and detection of disease recurrence. However, PET is not recommended for detection of brain metastasis from lung cancers. Current NCCN guidelines for SCLC indicate PET may be used in the staging of disease and treatment planning but "is not recommended for routine follow-up."

Lymphoma, including Hodgkin’s disease

Of the 14 available studies, 3 compared PET with anatomic imaging in initial staging and restaging of patients with Hodgkin’s disease (HD) and non-Hodgkin's lymphoma. Two of these studies included data from both diseased and nondiseased sites for PET and CT. Both studies found PET to have better overall diagnostic accuracy than CT. The third study addressed detection of diseased sites only and found PET to have the same sensitivity as use of CT or MRI. Among the 6 studies that reported on concordance between PET and other imaging modalities, PET was discordant with other modalities in 11% to 50%, PET was correct among discordances in 40% to 75%. Positron emission tomography has been reported to affect patient management decisions in 8%–20% of patients in 5 studies mainly by correctly upstaging disease, but also by correctly downstaging disease. Thus when PET is added to conventional imaging, it can provide useful information for selective effective treatment that is appropriate to the correct stage of disease.
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Meta-analyses in 2013 reported good sensitivities and specificities with PET/CT in the detection of newly diagnosed Hodgkin lymphoma and diffuse large B-cell lymphoma.

Current NCCN guidelines for Hodgkin lymphoma and non-Hodgkin lymphomas indicate that PET/CT may be used in staging, restaging, and evaluating treatment response.

Melanoma
Surgical resection for melanoma is limited to those with local disease. Patients with widespread disease are not candidates for resection. Frequently, there is microscopic spread to the proximal lymph nodes. Therefore, patients with a high risk of nodal spread, as assessed by the thickness of the primary melanoma, may be candidates for lymph node sampling, termed sentinel node biopsy. Positron emission tomography scanning has been investigated both as a technique to detect widespread disease as part of an initial staging procedure, and also to evaluate the status of the local lymph nodes to determine the necessity of sentinel node biopsy.

To consider PET a useful alternative to sentinel node biopsy, it must have high sensitivity and specificity when either sentinel node biopsy or lymph node dissection serves as the reference standard. In the only study of this kind, PET had a sensitivity of only 17%, suggesting that PET rarely detects small metastases that can be discovered by sentinel node biopsy. Thus the TEC Assessment concluded that PET is not as beneficial as sentinel node biopsy in assessing regional lymph nodes.

- The intent of using PET to detect extranodal metastases is to aid in selecting treatment appropriate to the patient's extent of disease. For example, surgical resection is typically not appropriate for widespread disease. A prospective blinded study of 100 patients found that PET was much more sensitive and specific than conventional imaging. Another prospective study of 76 patients found that, compared to CT, PET had much higher sensitivity and equivalent specificity. A third comparative study of 35 patients found that PET was much more sensitive than CT. It may be inferred from these studies that PET was usually correct when discordant with other modalities. Positron emission tomography affects management in approximately 18% of patients.

In meta-analysis of 9 studies (total N=623), Rodriguez Rivera et al reported pooled sensitivity and specificity of FDG-PET for detecting systemic metastases in patients with stage III cutaneous melanoma of 0.89 (95% CI, 0.65 to 0.98) and 0.89 (95% CI, 0.77 to 0.95), respectively.

Current NCCN guidelines for melanoma indicate that PET/CT may be used for staging and restaging for more advanced disease, such as stage III, in the presence of specific signs and symptoms. PET/CT is not recommended for stage I or II disease. PET/CT also is listed as an option for surveillance screening for recurrent or metastatic disease.

Multiple Myeloma
Two systematic reviews, one of which also conducted a meta-analysis, addressed PET for staging of multiple myeloma. Neither report compared the diagnostic performance of PET with other imaging modalities, so they do not support conclusions about comparative effectiveness.
Neuroendocrine Tumors

Two meta-analyses from the same investigators addressed use of PET in patients with neuroendocrine tumors (NETs). One report included patients with thoracic and gastroenteropancreatic NETs who had imaging with PET using gallium 68-somatostatin receptor radiotracers. The other report included studies of paragangliomas scanned by PET with fluorine-18-dihydroxyphenylalanine. Neither study compared PET with other imaging modalities, precluding conclusions about comparative diagnostic performance.

Ovarian Cancer

For primary evaluation, i.e., in patients with suspected ovarian cancer, the ability to rule out malignancy with a high negative predictive value would change management by avoiding unnecessary exploratory surgery. However, available studies suggest that PET scanning has poorer negative predictive value compared to other options, including transvaginal ultrasound (TVUS), Doppler studies, or MRI. Adding PET scanning to TVUS or MRI did not improve results.

Positive predictive value (PPV) is of greatest importance in evaluating patients with known ovarian cancer, either to detect disease recurrence or progression or monitor response to treatment. While the 2004 AHRQ systematic review suggested that PET may have value for detecting recurrence when CA125 is elevated and conventional imaging does not clearly show recurrence, this had not been demonstrated in an adequately powered prospective study. A 2008 AHRQ systematic review found that the evidence supported the use of PET/CT in detecting recurrent ovarian cancer. The evidence for initial diagnosis and staging of ovarian cancer was still inconclusive.

A 2013 meta-analysis found PET/CT was useful for detecting ovarian cancer recurrence. American College of Radiology Appropriateness Criteria, also issued in 2013, indicated that PET/CT is appropriate for detecting and restaging ovarian cancer recurrence. Current NCCN guidelines for ovarian cancer indicate that PET/CT may be appropriate “for indeterminate lesions if results will alter management.”76 PET/CT also may be appropriate if clinically indicated after complete remission, for follow-up and to monitor for recurrence.

Pancreatic Cancer

Both the 2004 AHRQ systematic review and the 1999 TEC Assessment focused on 2 clinical applications of PET scanning in patients with known or suspected pancreatic cancer: the use of PET to distinguish between benign or malignant pancreatic masses, and the use of PET as a staging technique in patients with known pancreatic cancer.

- In terms of distinguishing between benign and malignant disease, the gold standard is percutaneous or open biopsy. If PET were to be used to allow patients with scans suggesting benign masses to avoid biopsy, a very high NPV would be required. The key statistic underlying the NPV is the false-negative rate. Patients with false-negative results are incorrectly assumed to have benign disease and are thus not promptly treated for pancreatic cancer. Based on the literature review, the NPV ranged between 75% and 92%, depending on an underlying prevalence of disease ranging from 50–75%. The Assessment concluded that this level of diagnostic performance would not be adequate to recommend against biopsy. The 2004 AHRQ report found that PET was
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sometimes found to be more accurate than other modalities, but the meta-analysis stated that it is unclear whether PET’s diagnostic performance surpasses decision thresholds for biopsy or laparotomy.

- In both the TEC Assessment and AHRQ systematic review, there were inadequate data to permit conclusions regarding the role of PET scanning as a technique to stage known pancreatic cancer.

In meta-analysis of 9 studies (total N=526), Rijkers et al (2014) reported pooled sensitivity and specificity of FDG-PET/CT for confirming suspected pancreatic cancer of 0.90 (95% CI, 0.87 to 0.93) and 0.76 (95% CI, 0.66 to 0.84), respectively. A 2008 AHRQ review and past NCCN guidelines for pancreatic carcinoma suggested that PET/CT may be useful for staging in certain patients when the standard staging protocol is inconclusive. Current NCCN guidelines state that “the role of PET/CT remains unclear [PET/CT] may be considered after formal pancreatic CT protocol in high-risk patients to detect extra pancreatic metastasis.”

Penile Cancer
A systematic review and meta-analysis of PET focused on staging inguinal lymph nodes among patients with penile squamous cell carcinoma. No comparisons were made with other imaging modalities. The report found that PET had low sensitivity, and the authors concluded that PET is not suited for routine clinical use in this setting.

Prostate Cancer
Both an NCCN Task Force Report and an AHRQ systematic review do not find sufficient evidence to support use of PET for any indication in patients with prostate cancer. Reports show significant overlap between benign prostatic hyperplasia, malignant tumor, local recurrence, and postoperative scarring. PET may have limited sensitivity in detecting distant metastatic disease. The AHRQ report identified only 4 studies of PET for the indications of restaging and recurrence, none of which addressed the effect of PET on management decisions.

In a 2013 meta-analysis by Umbehr et al of 10 studies (total N=637) of initial prostate cancer evaluation, pooled sensitivity was 0.84 (95% CI, 0.68 to 0.93), and specificity was 0.79 (95% CI, 0.53 to 0.93).79 In meta-analysis of 12 studies (total N=1055) of patients with biochemical failure after local treatment, pooled sensitivity was 0.85 (95% CI, 0.79 to 0.89), and specificity was 0.88 (95% CI, 0.73 to 0.95).

In a 2014 meta-analysis by von Eyben and Kairemo, pooled sensitivity and specificity of choline PET/CT for detecting prostate cancer recurrence in 609 patients was 0.62 (95% CI, 0.51 to 0.66) and 0.92 (95% CI, 0.89 to 0.94), respectively. In an evaluation of 280 patients from head-to-head studies comparing choline PET/CT with bone scans, PET/CT identified metastasis significantly more often than did bone scanning (127 [45%] vs 46 [16%], respectively; odds ratio, 2.8; 95% CI, 1.9 to 4.1; p<0.001). The authors also reported that choline PET/CT changed treatment in 381 (41%) of 938 patients. Complete prostate-specific antigen (PSA) response occurred in 101 (25%) of 404 patients.

Mohsen et al (2013) conducted a meta-analysis of 23 studies on C-11-acetate PET imaging for primary or recurrent prostate cancer. Pooled sensitivity for primary tumor evaluation was 0.75 (95% CI, 0.70 to 0.80), and pooled specificity was 0.76 (95% CI, 0.72 to 0.79). For detection of recurrence, pooled sensitivity was
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0.64 (95% CI, 0.59 to 0.69), and pooled specificity was 0.93 (95% CI, 0.83 to 0.98). Although study quality was considered poor, low sensitivities and specificities appeared to limit the utility of C-11-acetate imaging in prostate cancer. C-11-acetate is not currently FDA-approved.

Current NCCN guidelines for prostate cancer indicate that C-11-choline PET may be considered for biochemical failure after primary treatment, ie, radiotherapy or radical prostatectomy, although further study is needed to determine the best use of this imaging modality in men with prostate cancer. FDG or fluoride PET should not be used routinely, for initial assessment or in other settings, due to limited evidence of clinical utility.

The European Association of Urology guidelines for prostate cancer indicate that C-11-choline PET/CT has limited value unless PSA levels exceed 1.0 ng/mL. In meta-analysis of 14 studies (total N=1667) of radiolabelled choline PET/CT for restaging prostate cancer, Treglia et al (2014) reported a maximum pooled sensitivity of 0.77 (95% CI, 0.71 to 0.82) in patients with PSA rate of increase greater than 2 ng/mL per year. Pooled sensitivity was lower for patients with PSA rate of increase less than 2 ng/mL per year or with PSA doubling time of 6 months or less. In meta-analysis of 11 studies (total N=609) of radiolabelled choline PET/CT for staging or restaging prostate cancer, Von Eyben et al (2014) reported pooled sensitivity and specificity of 0.59 (95% CI, 0.51 to 0.66) and 0.92 (95% CI, 0.89 to 0.94), respectively. Pooled PPV and NPV were 0.70 and 0.85, respectively.

Recent meta-analyses do not report strong evidence for the use of PET or PET/CT in the initial staging or management of prostate cancer or in the evaluation of possible recurrence related to biochemical failure. Studies evaluated contained large heterogeneity including the use of different radiotracers and PET with and without CT. Pooled sensitivities and specificities for the use of PET in initial prostate cancer treatment are generally low with wide ranges reported. While pooled sensitivities and specificities reported may be higher for PET for the detection of prostate cancer recurrence, further studies are needed for comparison of PET and PET/CT with other imaging techniques, such as MRI and radionuclide bone scan.

Soft Tissue Sarcoma

A 2002 AHRQ systematic review on use of PET for soft tissue sarcoma evaluated 5 applications: distinguishing between benign lesions and malignant soft tissue sarcoma, distinguishing between low grade and high grade soft tissue sarcoma, detecting locoregional recurrence, detecting distant metastases, and evaluating response to therapy.

- The review found that PET has low diagnostic accuracy in distinguishing low-grade tumors from benign lesions. PET performs better at differentiating high- or intermediate-grade tumors from low-grade tumors; however, it is unclear whether this will have an impact on management decisions and health outcomes. Evidence is insufficient on the comparative diagnostic performance of PET and alternative diagnostic modalities in the diagnosis of soft tissue sarcoma, detection of locoregional recurrence, detection of distant metastasis, and evaluating response to therapy.
Testicular Cancer
The 2004 AHRQ systematic review found 1 prospective study and 4 retrospective studies that generally showed higher sensitivity and specificity for PET over CT. However these studies were small in size and failed to report separate results for patients with seminoma versus those with non-seminoma. Studies also failed to report separate results by clinical stage of disease. Thus, it is unclear whether this evidence translates to changes in patient management and improved health outcomes.

- Studies on distinguishing between viable tumor and necrosis/fibrosis after treatment of testicular cancer were flawed in 2 main ways. First, most studies did not compare the diagnostic accuracy of PET with other imaging modalities. Second, studies that did compare PET and CT did not state a clear threshold for a positive CT test, making study results difficult to interpret. Therefore, it is uncertain whether use of PET leads to different patient management decisions and health outcomes than other imaging modalities.

A 2008 AHRQ technology assessment published in 2008 and studies evaluating residual masses in patients after chemotherapy for seminoma support the use of PET. Current NCCN guidelines support the use of PET for this indication. PET is not recommended for nonseminoma patients.

Thyroid Cancer, Differentiated
The 2009 NCCN Task Force Report on PET reviewed studies which showed that PET can localize recurrent disease when other imaging tests are negative. Additionally, PET is prognostic in this setting: More metabolically active lesions on PET are strongly correlated with reduced survival. Current NCCN guidelines for thyroid carcinoma continue to support the use of FDG-PET/CT in thyroid cancer evaluations, such as when iodine-131 imaging is negative and stimulated thyroglobulin is greater than 2-5 ng/mL.

Thyroid Cancer, Poorly Differentiated
A meta-analysis of studies on detecting recurrent or metastatic medullary thyroid carcinoma did not compare PET with other imaging modalities and did not clearly perform quality assessment of individual studies or incorporate study quality concerns into conclusions. Current NCCN guidelines for thyroid carcinoma do not include PET or PET/CT in the management of medullary thyroid cancer.

Unknown Primary
The 2002 TEC Assessment concluded that the TEC criteria were met for the limited indication of the workup and management of patients with unknown primaries and a single site of metastatic disease. Specifically, local or regional therapy may be offered to these patients. In this setting, PET scanning may be used to verify the absence of disseminated disease.

- Regarding this application, the TEC Assessment identified 4 reports, including a total of 47 patients referred for imaging with a single known metastatic site from an unknown primary. In 13 (28%) of these patients, PET scanning identified previously undetected metastases that were confirmed by biopsy. Therefore, the use of PET can contribute to optimal decision making regarding the appropriateness of local or regional therapy.
Cancer Surveillance
The clinical utility for PET scanning in surveillance, i.e., in performing follow-up PET scans in asymptomatic patients to detect early disease recurrence, is not well-studied. (For this policy, a scan is considered a surveillance scan if performed more than 6 months following therapy, but 12 months for lymphoma.) The most recent NCCN publication indicates, “The use of PET as a surveillance tool should only be used in clinical trials.” In addition, the NCCN guidelines for various malignancies often note that PET scans are not recommended in asymptomatic patients. For example the NCCN breast cancer guidelines comment that PET scans (as well as many other modalities) provide no advantage in survival or ability to palliate recurrent disease and are not recommended.

Other Malignancies
There are inadequate scientific data to permit conclusions regarding the role of PET scanning in other malignancies.

Summary
The utility of PET scanning for the diagnosis and staging of malignancies varies by specific type of cancer. In general, PET scanning can be useful for distinguishing benign from malignant masses in certain circumstances and for increasing the accuracy of staging by detecting additional disease not detected by other imaging modalities. Therefore, PET scanning for diagnosis and staging of malignancies can be considered eligible for coverage when specific criteria are met for specific cancers, as outlined in the coverage statement. For follow-up after the initial diagnosis and staging has been performed, there are a few situations in which PET can improve detection of recurrence, which may lead to changes in management that improve net health outcome. For routine tumor surveillance, clinical utility is uncertain, and this use of PET scanning is considered investigational.

References
8. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). FDG Positron Emission Tomography to Manage Patients with an Occult Primary Carcinoma and Metastasis outside the Cervical Lymph Nodes. TEC Assessments 2002; Volume 17, Tab 14.
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10/18/2001 Medical Policy Committee review
11/12/2001 Managed Care Advisory Council approval
06/24/2002 Format revision. No substance change to policy
10/05/2004 Medical Director review
12/14/2004 Medical Policy Committee review. Format revision. Coverage eligibility criteria for Unknown Primary and Thyroid Cancer added.
01/31/2005 Managed Care Advisory Council approval
07/19/2005 Omission corrected: Melanoma, Staging and Restaging for the purpose of detecting disease was corrected to reflect policy intent: for the purpose of detecting residual disease.
10/10/2005 Medical Director review
10/27/2005 Quality Care Advisory Council approval
12/20/2005 Medical Policy Committee review. Coverage eligibility coverage changes: The terms Staging and Restaging have been substituted for “differentiation” for Colorectal Cancer indications. Use of PET in the restaging of colorectal cancer was added; “To detect recurrence of colorectal cancer in patients with rising CEA levels and/or in patients who present with signs and symptoms of recurrence”.
Appendix 1 Table 1 removed from the policy.
02/23/2006 Quality Care Advisory Council approval
08/09/2006 Medical Policy Committee approval. PET for follicular and papillary thyroid cancer is now eligible for coverage to detect recurrent thyroid cancer or metastasis when Tg and 131 scans are non-diagnostic.
12/06/2006 Medical Director review
12/20/2006 Medical Policy Committee approval. Coverage eligibility updated:
Breast Cancer changed from:
- Diagnosis
  - o in clinical situations in which the PET results may assist in avoiding an invasive diagnostic procedure, or in which the PET results may assist in determining the optimal anatomical location to perform an invasive diagnostic procedure. In general, for most solid tumors, a tissue diagnosis is made prior to the performance of PET scanning. PET scans following a tissue diagnosis are performed for the purpose of staging, not diagnosis.
- Staging and/or Restaging
  - o in clinical situations in which the stage of the cancer remains in doubt after completion of standard diagnostic workup or for restaging after the completion of treatment; or

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- for the purpose of detecting residual disease; or
- for detecting suspected recurrence; or
- to determine the extent of a known recurrence.

Changed To:

- Staging (before any treatment)
  - As an adjunct to standard imaging modalities in the staging of breast cancer with distant metastases, excluding staging of axillary lymph nodes.
  - Restaging (after treatment has been completed)
  - As an adjunct to standard imaging in the restaging of loco-regional recurrence or metastases

- Treatment Response Monitoring
  - For women with locally advanced and metastatic breast cancer, when a change in therapy is anticipated.

Colorectal Cancer changed from:

- Diagnosis
  - as a technique to detect and assess resectability of hepatic or extrahepatic metastases of colorectal cancer.

- Restaging
  - to assess the presence of scarring versus local bowel recurrence in patients with previously resected colorectal cancer.
  - to detect recurrence of colorectal cancer in patients with rising CEA levels and/or in patients who present with signs and symptoms of recurrence.

Changed To:

- Diagnosis-when PET results may assist in
  - Avoiding an invasive diagnostic procedure, or
  - Determining the optimal anatomical location to perform an invasive diagnostic procedure
  - The diagnosis has not been confirmed by tissue biopsy

- Staging
  - The cancer stage remains in doubt after completion of a standard diagnostic workup.
  - PET could potentially replace one or more conventional imaging studies, when it is expected that conventional study information is insufficient for the clinical management of the patient, or
  - Clinical management would differ depending on the cancer stage

- Restaging for the purpose of
  - Detecting residual disease (after completion of treatment), or
  - Detecting suspected recurrence (ex: rising CEA levels; clinical signs/symptoms suspicious for recurrence)
  - Determination of the extent of known recurrence
  - Potentially replacing one or more conventional imaging studies, when it is expected that information from these studies will be insufficient for clinical management of the patient.

06/13/2007 Medical Director review
06/20/2007 Medical Policy Committee approval. No change to coverage eligibility. Decided not to differentiate between small cell and non small cell lung cancer.
08/06/2008 Medical Director review
08/20/2008 Medical Policy Committee approval. No change to coverage eligibility.
08/06/2009 Medical Policy Committee approval
08/26/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.
01/01/2010 Coding revision
08/05/2010 Medical Policy Committee review
08/18/2010 Medical Policy Implementation Committee approval. Coverage eligibility extensively updated.
12/08/2011 Medical Policy Committee review

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12/21/2011 Medical Policy Implementation Committee approval. Revised the ovarian cancer coverage so that diagnosis, staging and restaging is covered for certain situations.

12/06/2012 Medical Policy Implementation Committee approval. Added that bone cancer in the staging of Ewing Sarcoma and osteosarcoma may be eligible for coverage, but is investigational in the staging of chondrosarcoma. Reworded the eligible for coverage statements for breast cancer. Added that PET scanning may be eligible for coverage in the evaluation of known or suspected recurrence of cervical cancer. Reworded coverage for head and neck cancer to be more liberal. Prostate cancer given a separate section as investigational. All other oncologic applications are remain investigational, but examples of some investigational applications were removed.

06/06/2013 Medical Policy Committee review
06/25/2013 Medical Policy Implementation Committee approval. Added coverage for staging and restaging of multiple myeloma.

05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Deleted “when suspicion of disease is high and other imaging is inconclusive” from the Eligible for Coverage statements for breast cancer staging and restaging.

06/25/2015 Medical Policy Committee approval

06/30/2016 Medical Policy Committee approval
07/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis codes and HCPCS code changes

Next Scheduled Review Date: 07/2017

Coding

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

**Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts in accordance with nationally accepted standards of medical practice; or
   1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

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Positron Emission Tomography (PET) Oncology Applications

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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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