Medical Policy

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Current Policy Effective Date: 7/1/12

Title: Positron Emission Tomography (PET) for Oncologic Conditions

Description / Background

Positron emission tomography (PET) 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 fluorodeoxyglucose (FDG), which has a metabolism related to glucose metabolism. FDG 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.

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.

This policy only addresses the use of radiotracers detected with the use of dedicated PET scanners.

Medical Policy Statement

The safety and effectiveness of PET scanning for selected oncologic applications have been established. It is a useful diagnostic option for patients meeting patient selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

1) Diagnosis:
   PET is appropriate 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. Therefore, the use of PET in the diagnosis of lymphoma, colorectal cancers or melanoma should be rare.

2) Staging and/or Restaging:
   a) PET is appropriate in clinical situations in which the stage of the cancer remains in doubt after completion of a standard diagnostic workup, including conventional imaging (computed tomography, magnetic resonance imaging or ultrasound).
   b) PET would also be considered reasonable and necessary if it 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.
   c) When clinical management of the patient would differ depending on the stage of the cancer identified, PET done for restaging after the completion of treatment for detecting residual disease, detecting suspected recurrence or to determine the extent of a known recurrence is appropriate.

PET scans are considered *appropriate* for the following oncologic conditions:

<u>Anal Cancer</u>

- **Inclusions:**
  - For the diagnosis, staging, restaging and monitoring of anal cancer.
- **Exclusions:**
  - Conditions not listed above.

<u>Brain Cancer</u>

- **Inclusions:**
  - For diagnosis and staging, where lesions metastatic from the brain are identified but no primary is found
  - For restaging, to distinguish recurrent tumor from radiation necrosis.
- Exclusions:
  - Conditions not listed above.

Breast Cancer

- **Inclusions:**
  - For staging and restaging of breast cancer for detecting locoregional or distant recurrence or metastasis (except axillary lymph nodes) when suspicion of disease is high and other imaging is inconclusive.
- **Exclusions:**
  - For the differential diagnosis in patients with suspicious breast lesions or an indeterminate/low suspicion finding on mammography
  - Staging axillary lymph nodes.

Cancers of Unknown Primary

- **Inclusions:**
  Patients with an unknown primary who meet **ALL** of the following criteria:
  - In patients with a single site of disease outside the cervical lymph nodes
  - Patient is considering local or regional treatment for a single site of metastatic disease;
  - Patient has received a negative workup for a occult primary tumor
  - The PET scan will be used to rule out or detect additional sites of disease that would eliminate the rationale for local or regional treatment.
- **Exclusions:**
  For patients with an unknown primary, including, but not limited to the following:
  - As part of the initial workup of an unknown primary
  - As part of the workup of patients with multiple sites of disease

Cervical Cancer

- **Inclusions:**
  - For the initial staging of patients with locally advanced cervical cancer.
- **Exclusions:**
  - For the evaluation of known or suspected cervical cancer in all other situations.

Colorectal Cancer

- **Inclusions:**
  - Staging and restaging to detect and assess resectability of hepatic or extrahepatic metastases of colorectal cancer, and
  - To evaluate a rising and persistently elevated carcinoembryonic antigen (CEA) level when standard imaging, including CT scan, is negative.
- **Exclusions:**
  - When used as a technique to assess the presence of scarring versus local bowel recurrence in patients with previously resected colorectal cancer.

Differentiated Thyroid Cancer

- **Inclusions:**
  - Initial staging of thyroid cancer. For staging of thyroid cancer of follicular cell origin previously treated by thyroidectomy and radioiodine ablation with an elevated or rising serum thyroglobulin (Tg) greater than 10 ng/ml and negative I-131 whole body scintigraphy.
  - Restaging of patients with differentiated thyroid cancer when thyroglobulin (Tg) levels are elevated and whole-body I-131 imaging is negative. In those patients with thyroid antibodies present, the Tg levels may not be elevated.
- **Exclusions:**
  - In the evaluation of known or suspected differentiated thyroid cancer in all other situations.

Esophageal Cancer

- **Inclusions:**
  - Staging and restaging of esophageal cancer, and
  - Determining response to preoperative induction therapy.
- **Exclusions:**
  - Detection of primary esophageal cancer.

Gastric (Stomach) Cancer

- **Inclusions:**
  - Diagnosis,* staging and restaging of gastric carcinoma if other imaging is inconclusive. *Note: A diagnostic tissue sample is usually obtainable without PET localization. Therefore, PET for diagnosis of gastric cancer is rarely considered medically necessary.
- **Exclusions:**
  - PET is not indicated in T1 gastric cancers due to the risk of false positives.

Head and Neck Cancer

- **Inclusions:**
  - Identifying an unknown primary suspected to be head and neck cancer In patients with known head and neck cancer, as a technique of staging the cervical lymph nodes and assessing resectability of the tumor
  - For restaging to detect residual or recurrent disease in patients being followed up after treatment for head and neck cancer
- **Exclusions:**
  - Conditions not listed above.

Lung Cancer

- **Inclusions:**
  - Patients with a solitary pulmonary nodule as a technique to distinguish between benign and malignant disease when prior CT scan and chest x-ray findings are inconclusive or discordant,
  - To determine resectability for patients with a presumed solitary metastatic lesion from lung cancer.
  - As a staging or restaging technique in those with known non-small cell lung cancer
  - As a staging or restaging technique of small cell lung cancer (although PET/CT is superior to PET alone)
- **Exclusions:**
  - Conditions not listed above.

Lymphoma, Including Hodgkin's Disease

- **Inclusions:**
  - PET scanning as a technique for staging lymphoma either during initial staging or for restaging at follow-up.
- **Exclusions:**
  - Conditions not listed above.

Melanoma

- **Inclusions:**
  Assessing extranodal spread of malignant melanoma at initial staging or at restaging during follow-up treatment.
- **Exclusions:**
  When used as a technique to detect regional lymph node metastases in patients with clinically localized melanoma who are candidates to undergo sentinel node biopsy.

Neuroendocrine Tumors

- **Inclusions:**
  For the diagnosis, staging, restaging and monitoring of neuroendocrine tumors
- **Exclusions:**
  - Conditions not listed above.

Ovarian Cancer

- **Inclusions:**
  - Initial staging of ovarian cancer
  - For the evaluation of patients with signs and/or symptoms of suspected ovarian cancer recurrence (restaging) when standard imaging, including CT scan, is inconclusive.
- **Exclusions:**
  For the evaluation of known or suspected ovarian cancer in all other situations, including, but not limited to the following:
  - Patients with an adnexal mass or other symptoms suggestive of ovarian cancer for whom the need for full exploratory laparotomy must be considered
  - Patients with likely ovarian cancer diagnosed by conventional methods who require initial staging in preparation for exploratory laparotomy
  - Patients with a history of treated ovarian cancer who are being monitored for recurrence or progression
  - Patients with ovarian cancer who are being monitored for response to treatment.

Pancreatic Cancer

- **Inclusions:**
  For the initial diagnosis and staging of pancreatic cancer when other imaging and biopsy are inconclusive.
- **Exclusions:**
  Evaluating other aspects of pancreatic cancer

Prostate Cancer

- **Inclusions:**
  N/A
- **Exclusions:**
  For the diagnosis and management of known or suspected prostate cancer.

Soft Tissue Sarcoma

- **Inclusions:**
  - For initial staging prior to resection of an apparently solitary metastasis
  - When the grade of a unresectable tumor remains in doubt after biopsy
  - When a solitary metastasis amenable to resection needs further assessment
  - Differentiation of suspected tumor from radiation or surgical fibrosis
  - Determination of response to therapy

  - Gastrointestinal stromal tumor (GIST) for initial staging and re-staging when there is documented recurrence
- **Exclusions:**
  - Distinguishing between benign lesions and malignant soft tissue sarcoma
  - Distinguishing between low grade and high grade soft tissue sarcoma
  - Detecting locoregional recurrence
  - Detecting distant metastasis

Testicular Cancer

- **Inclusions:**
  For the evaluation of residual mass following chemotherapy of stage IIB and III seminomas. (The PET scan should be completed not sooner than 6 weeks following chemotherapy.)
- **Exclusions:**
  Except as noted above for seminoma; the evaluation of testicular cancer, including but not limited to the following applications:
  - Distinguishing between viable tumor and necrosis/fibrosis after treatment of testicular cancer
  - Detection of recurrent disease after treatment of testicular cancer

Cancer Surveillance

- **Inclusions:**
  N/A
- **Exclusions:**
  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:
Other oncologic applications of PET scanning are considered experimental and investigational.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

78608	78609	78811	78812	78813

Regulatory Status:

PET scanners are generally approved by the FDA via the 510(k)-approval process. Regulation of PET centers and PET radiopharmaceuticals is also addressed by the FDA. FDA approval for the different types of radiopharmaceuticals used in PET scanning may be limited not only to a particular indication but also to the particular area where the compound is produced.

Rationale

This policy is based on multiple evaluations of positron emission tomography (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. (1) 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; 2). Three 1999 TEC Assessments (3-5) and one 2000 TEC Assessment (6) 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. (6, 7) One 2001 TEC Assessment, a 2002 decision analysis, and a 2005 systematic review focused on esophageal cancer. (8-10) Pancreatic cancer was evaluated in a 1999 TEC Assessment and the 2004 AHRQ systematic review. (11, 12) 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 (13). 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 (14-18). In the Assessments, PET scanning was considered an adjunct to other imaging methods (i.e., computed tomography [CT], magnetic resonance imaging [MRI], ultrasonography) 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:

Lung Cancer (1, 2)

- PET 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).
- 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 TEC Assessment (1) 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.
- Six studies of patients with small cell lung cancer (SCLC) reported evidence suggesting that for non-brain metastases PET added to conventional staging is more sensitive in detecting disease than conventional staging alone (2). PET 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. 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.

Melanoma (3)

- 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. PET 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

Lymphoma, including Hodgkin's disease (4)

- 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%. PET 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.

Colorectal Cancer (5)

- 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.

Head and Neck Cancer (6)

- 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.

Unknown Primary (7)

- The 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.

Esophageal Cancer (8-10)

- 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.
- Regarding staging, 9 studies addressed staging of locoregional lymph nodes. Given concerns about study quality and inconsistent results, the available evidence on locoregional lymph nodes was considered inadequate to support conclusions about this application of PET scanning. While the studies on detection of distant disease suggest better diagnostic

performance for PET over CT, the available body of evidence is small. Only 1 study clearly avoided verification bias, only 1 clearly interpreted PET blind to the reference standard, and none clearly interpreted the reference standard blind to PET. A 2002 decision analysis (8) found that PET used along with endoscopic ultrasound achieved a higher number of quality-adjusted life-years (QALYs) than 5 other diagnostic strategies; however, it did not address the potential impact of study quality concerns on estimates of the relative diagnostic accuracy of different imaging modalities. Thus, the findings of the decision analysis are in question.

- Regarding evaluation of treatment response, the 2001 TEC Assessment (9) identified only 1 small study of 14 patients. While PET found evidence of response not shown on CT, these data are insufficient to permit conclusions regarding the value of PET in evaluating response to treatment. A 2005 systematic review and meta-analysis (10) compared CT, endoscopic ultrasound, and FDG PET for assessing response to neoadjuvant therapy. It found 7 PET studies, 4 of which provided diagnostic accuracy data. While the report suggested that PET has better diagnostic accuracy than CT, findings were based on 4 small studies, none of which made direct comparisons between PET and CT. The authors also did not address the influence of study quality characteristics on diagnostic accuracy. Furthermore, whether neoadjuvant therapy is beneficial for esophageal cancer is still under investigation, so this report does not demonstrate that use of PET in assessing response to neoadjuvant therapy improves health outcomes.

Pancreatic Cancer (11-13)

- Both the 2004 AHRQ systematic review and the 1999 TEC Assessment focused on two 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 negative predictive value would be required. The key statistic underlying the negative predictive value 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 negative predictive value 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 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.

Ovarian Cancer (12)

- 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 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 has not been demonstrated in an adequately powered prospective study. There was insufficient evidence to permit scientific conclusions regarding this application.

Testicular Cancer (12)

- 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 two 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.
- Studies were lacking on the use of PET to detect recurrence in patients treated for testicular cancer.

Soft Tissue Sarcoma (13)

- 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.

Breast Cancer (14-18)

- The 2001 TEC Assessment (14) 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 (15) 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 (16) 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 cost-effectiveness analysis from 2005 (17) addressed use of PET for staging axillary lymph nodes. The authors stated that a meta-analysis of PET studies was performed. The analysis found cost savings and a gain in life expectancy for a strategy using PET compared to one without PET. Some patients could avoid axillary lymph node resection, however the model in this analysis failed to compare PET with the most prominent alternative strategy for staging axillary lymph nodes, sentinel lymph node biopsy. The preferred method of meta-analysis for diagnostic accuracy data is the summary receiver-operating characteristic (ROC) curve, but these authors used a simple unweighted pooling technique that fails to account for the dependence between sensitivity and specificity. This cost-effectiveness analysis does not demonstrate that staging axillary lymph nodes with PET improves health outcomes.
- A systematic review published in 2007 (18) 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.

Gastric Cancer

A study by Yamada et al. in 2006 performed a study clarify FDG uptake in gastric carcinomas especially focusing on histological subtypes, the depth of tumor invasion, and glucose transporter-1 (GLUT-1) expression which is considered to be one of the major factors for higher FDG uptake in human malignant tumors. FDG-PET was performed on 35 preoperative patients with gastric carcinoma. Forty macroscopically distinguishable lesions on a surgical specimen were histologically classified into two subtypes: Cohesive type (papillary adenocarcinoma, tubular adenocarcinoma, and solid type poorly differentiated adenocarcinoma) or noncohesive type (signet-ring cell carcinoma and non-solid type poorly differentiated carcinoma).

GLUT-1 expression was immunohistochemically determined. Histological parameters (GLUT-1 expression, histological subtypes, the depth of invasion, lymphatic permeation, venous invasion and tumor size) were evaluated, and factors for FDG uptake (detectability and the degree) and GLUT-1 overexpression were determined by multiple regression analysis.

Nineteen of 40 gastric carcinomas showed detectable FDG uptake (48%), multiple regression analysis revealed that both the depth of invasion and histological subtypes are independent factors that influence the detectable FDG uptake in gastric carcinoma (R2 = 0.66). GLUT-1 expression was seen from an early cancer stage and the cohesive type was an independent factor influencing the overexpression of GLUT-1 (R2 = 0.66). GLUT-1 expression was the most influential factor for the degree of FDG uptake in gastric carcinoma (R2 = 0.68). ***Conclusions:*** This study provided important information on the clinical application of FDG-PET in gastric carcinoma that early or non-cohesive gastric carcinoma may show lower FDG uptake and therefore limit the usefulness of FDG-PET for the detection of gastric carcinoma. However, the FDG uptake associated with GLUT- 1 expression may serve as a prognostic factor of gastric carcinoma representing tumor metabolism.

Other Malignancies

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

2009–2010 Update
The policy was updated with a literature search using the MEDLINE database through October 2009. In reviewing the literature, emphasis was placed on condition-specific systematic reviews as well as reviews of PET use in various oncologic applications.

The National Comprehensive Cancer Network (NCCN) has published 2 reviews on the use of PET scanning in various oncologic applications. (19, 20) The first review (19) discussed use of PET scanning in breast cancer, colon cancer, lymphoma, and non-small cell lung cancer (NSCLC). Based on data from studies summarized in this article along with data from other reviews, the policy statements are updated. For breast cancer, PET scanning may be considered medically necessary in staging and restaging disease (detecting locoregional or distant metastasis or recurrence) when the suspicion of disease is high and other imaging is inconclusive. For colon cancer, the terms staging and restaging are added (to be more explicit) to the medically necessary policy statement and use in evaluating a rising and elevated CEA level is another indication that may be considered medically necessary. For non-small cell lung cancer, restaging and evaluation of a suspected solitary metastatic lesion (to determine resectability) are both added as indications that may be considered medically necessary.

The second review by NCCN (20) dealt with brain cancer, gastric and esophageal cancers, genitourinary cancer (including prostate cancer), gynecologic cancer (including cervical, uterine and ovarian cancer), myeloma, pancreatic and hepatobiliary cancers, sarcoma, small cell lung cancer (SCLC), and thyroid cancer.

An AHRQ technology assessment was also recently published. (21) For this report, comprehensive searches were conducted in four relevant electronic databases for the time period from 2003 to March 2008. Studies selected were published in English and had more than 12 adult participants with primary cancer of the following nine types: bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small cell lung, and testicular. Included in this report were 109 articles. The strongest evidence for the diagnostic accuracy of 18FDG-PET or 18FDG-PET/CT was noted for staging of locally advanced cervical cancer and the detection and restaging of recurrent disease, the detection of ovarian cancer recurrences following treatment, and the diagnosing and initial staging of pancreatic cancer. These and other indications require further research to show the impact of18FDG-PET or 18FDG-PET/CT on patient management or added value in the diagnostic and therapeutic process. These authors concluded that for some type of cancers (e.g., cervical, ovarian, and pancreatic cancer), there is some evidence of the utility of 18FDG-PET or 18FDG-PET/CT for diagnosing, staging, or detecting recurrences, but they may still require more studies to augment the evidence base. Further studies are needed to reach firm conclusions about the clinical effectiveness of 18FDG-PET and 18FDG-PET/CT in terms of the impact on diagnosis and treatment options, patient-centered outcomes, and economic costs. It is still unclear how 18FDG-PET and 18FDG-PET/CT affects patient treatment and ultimately their outcome. For other types of cancer examined in the review (e.g., bladder, kidney, prostate, SCLC, and testicular) the answers are still inconclusive and require more careful study.

Based on data from studies summarized in the NCCN review and the technology assessment performed for AHRQ, additional policy statements are updated. For pancreatic cancer, PET scanning may be considered medically necessary for initial diagnosis and staging when other imaging and biopsy are inconclusive. PET scanning may also be considered medically necessary in restaging differentiated thyroid cancer when thyroglobulin levels are elevated and whole-body I-131 imaging is negative. For esophageal cancer, PET scanning may be considered medically

necessary in the staging of esophageal cancer and in determining response to preoperative induction therapy. For ovarian cancer, PET scanning may be considered medically necessary in patients with suspected recurrent disease when standard imaging such as CT is inconclusive. For cervical cancer, PET scanning may be considered medically necessary in the initial staging of those with locally advanced disease. Finally, PET scanning is considered investigational in the diagnosis and management of prostate cancer.

In addition, PET scanning may be considered medically necessary for evaluating residual mass in patients post-chemotherapy for seminoma (testicular cancer). This indication for evaluating residual mass following chemotherapy in patients with seminoma is based on the findings that with a negative scan no treatment is given but a positive scan is followed by biopsy and treatment or at times by treatment (radiation therapy). (22, 23)

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 (20) 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 the 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. (24)

Related Policies

- PET/CT Fusion
- PET scans for Cardiac Applications
- PET scans for Miscellaneous Applications

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 4/1/12, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/13/11	12/21/11	Joint policy established. Information was pulled from previous consolidated policy "PET Scans." Added additional covered indications for PET scanning: certain gastric cancers, small cell lung cancer, anal cancer and neuroendocrine cancers
7/1/12	4/10/12	5/18/12	Added additional recommendations to policy based on input from American Imaging Management (AIM)

Next Review Date: 2nd Qtr, 2013

Previous Joint BCBSM/BCN Consolidated Medical Policy History (Positron Emission Tomography)Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/13/02	11/13/02	11/13/02	Joint policy established
3/1/07	12/28/06	9/18/09	Routine maintenance; new diagnoses added
11/1/08	8/19/08	10/30/08	Maintenance, combined PET for brain-non-oncologic and initial diagnosis of breast cancer with this policy; added PET for myocardial indications
5/1/09	2/10/09	2/10/09	Maintenance, initial diagnosis of breast cancer added as investigational to PET scan policy
9/1/09	6/16/09	6/16/09	Redefined criteria for PET myocardial perfusion
7/1/11	4/19/11	5/3/11	Additional references added. Clarified indications for PET for oncologic conditions.

Pre-Consolidation	Comments

Medical Policy HistoryOriginal Policy Date		
BCN	10/12/98	Revised: 5/8/01, 1/4/02
BCBSM	10/30/00	Revised: 12/4/00

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: POSITRON EMISSION TOMOGRAPHY (PET) FOR ONCOLOGIC CONDITIONS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered; criteria apply.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Covered; criteria apply.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.