Medical Policy

BlueCross BlueShield Kansas
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Title: Positron Emission Tomography (PET) Scanning: Oncologic Applications

Related Policies:	▪ *PET Scanning: Cardiac Applications* ▪ *PET Scanning: In Oncology to Detect Early Response during Treatment* ▪ *PET Scanning: Miscellaneous (Non-cardiac, Non-oncologic) Applications of Fluorine 18 Fluorodeoxyglucose*

Professional / Institutional
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The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

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If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected or diagnosed muscle-invasive bladder cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing muscle-	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
invasive bladder cancer treatment			
Individuals: • With suspected or diagnosed bone sarcoma and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing bone sarcoma treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed brain tumor and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET • 18F-FET-PET • 11C-methionine PET	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected brain tumor or who are asymptomatic after completing brain tumor treatment	Interventions of interest are: • 18F-FDG-PET • 18F-FET-PET • 11C-methionine PET	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed breast cancer and inconclusive results from other imaging techniques	Interventions of interest are: • Adjunctive 18F-FDG-PET or 18F-FDG-PET/CT for staging or restaging	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed breast cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing breast cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed cervical cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected cervical cancer or who are asymptomatic	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
after completing cervical cancer treatment			
Individuals: • With diagnosed colorectal cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected colorectal cancer or who are asymptomatic after completing colorectal cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed endometrial cancer in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing endometrial cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed esophageal cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected esophageal cancer or who are asymptomatic after completing esophageal cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed gastric cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
completing gastric cancer treatment			
Individuals: • With suspected or diagnosed head and neck cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing head and neck cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected non-small-cell lung cancer and inconclusive results from other imaging techniques	Interventions of interest are: • Adjunct 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed non-small-cell lung cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected non-small-cell lung cancer or who are asymptomatic after completing non-small-cell lung treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed small-cell lung cancer diagnosis and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected small-cell lung cancer or who are asymptomatic after completing small-cell lung treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed Hodgkin lymphoma and in	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
need of staging or restaging information			
Individuals: • Who are asymptomatic after completing Hodgkin lymphoma treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed non-Hodgkin lymphoma and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing non-Hodgkin lymphoma treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed stage I or II melanoma and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed advanced melanoma (stage III or IV) and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing melanoma treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed multiple myeloma in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing multiple myeloma treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected or diagnosed neuroendocrine tumors and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing neuroendocrine tumor treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed neuroendocrine tumors and in need of staging or restaging information	Interventions of interest are: • 68Ga-PET, 68Ga-PET/CT, ^{64}Cu-PET, or ^{64}Cu-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing neuroendocrine tumor treatment	Interventions of interest are: • 68Ga-PET, 68Ga-PET/CT, ^{64}Cu-PET, or ^{64}Cu-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed ovarian cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected ovarian cancer or who are asymptomatic after completing ovarian cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected pancreatic cancer and with inconclusive results from other imaging techniques	Interventions of interest are: • Adjunctive 18F-FDG-PET or 18F-FDG-PET/CT for staging or restaging	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed pancreatic cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic after completing pancreatic cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed node negative penile cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed node positive penile cancer and in need of staging or restaging information	Interventions of interest are: • ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing penile cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected or diagnosed prostate cancer and in need of staging or restaging information	Interventions of interest are: • ^{11}C-choline-PET, ^{11}C-choline-PET/CT, ^{18}F-fluciclovine-PET, or ^{18}F-fluciclovine-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing prostate cancer treatment	Interventions of interest are: • 11C-choline-PET, ^{11}C-choline-PET/CT, ^{18}F-fluciclovine-PET, or ^{18}F-fluciclovine-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected prostate cancer	Interventions of interest are: • 68Ga-PSMA PET, 68Ga-PSMA PET/CT, piflufolastat-F18 PET, piflufolastat-F18 PET/CT, flotufolastat-F18 PET, and flotufolastat-F18 PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
Individuals: • With or diagnosed prostate cancer and in need of staging or restaging information	Interventions of interest are: • 68Ga-PSMA PET, 68Ga-PSMA PET/CT, piflufolastat-F18 PET, piflufolastat-F18 PET/CT, flotufolastat-F18 PET, flotufolastat-F18 PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • Who are asymptomatic after completing prostate cancer treatment	Interventions of interest are: • 68Ga-PSMA PET, 68Ga-PSMA PET/CT, piflufolastat-F18 PET, piflufolastat-F18 PET/CT, flotufolastat-F18 PET, flotufolastat-F18 PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed renal cell carcinoma and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed soft tissue sarcoma and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed soft tissue sarcoma and in need of rapid reading of response to imatinib treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected soft tissue sarcoma or who are asymptomatic after completing soft tissue sarcoma treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With diagnosed testicular cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected testicular cancer or who are asymptomatic	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

Populations	Interventions	Comparators	Outcomes
after completing testicular cancer treatment			
Individuals: • With diagnosed thyroid cancer and in need of staging or restaging information	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With suspected thyroid cancer or who are asymptomatic after completing thyroid cancer treatment	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity
Individuals: • With cancer of unknown primary and single-site metastatic disease	Interventions of interest are: • 18F-FDG-PET or 18F-FDG-PET/CT	Comparators of interest are: • Conventional imaging techniques	Relevant outcomes include: • Test validity

DESCRIPTION

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, comprising multiple stationary detectors that encircle the area of interest.

The utility of PET scanning for the diagnosis, staging and restaging, and surveillance of malignancies varies by type of cancer. In general, PET scanning can distinguish benign from malignant masses in certain circumstances and improve 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 medically necessary when specific criteria are met for specific cancers, as outlined in the policy statements. For follow-up, after initial diagnosis and staging have been performed, there are a few situations in which PET can improve detection of recurrence, and lead to changes in management that improve the net health outcome.

OBJECTIVE

The objective of this evidence review is to examine whether the use of positron emission tomography for the diagnosis, staging and restaging, and/or surveillance of various carcinomas improves the net health outcome in individuals with cancer.

BACKGROUND

A variety of tracers are used for positron emission tomography (PET) scanning, including oxygen 15, nitrogen 13, carbon 11 choline, fluorine 18, gallium 68, fluciclovine 18, and copper 64. 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 correlates with glucose metabolism. Fluorodeoxyglucose has been considered useful in cancer imaging because tumor cells show increased metabolism of glucose. The most common malignancies studied have been melanoma, lymphoma, lung, colorectal, and pancreatic cancer.

This evidence review focuses on the use of radiotracers detected with dedicated PET scanners. Radiotracers, such as FDG, may be detected using single-photon emission computerized tomography cameras, a technique that may be referred to as FDG-single-photon emission computerized tomography imaging. The use of single-photon emission computerized tomography cameras for PET radiotracers presents unique issues of diagnostic performance and is not considered herein.

REGULATORY STATUS

The following radiopharmaceuticals have been granted approval by the FDA, to be used with PET for cancer-related indications (see Table 1).[1,]

Table 1. Radiopharmaceuticals Approved for Use With PET for Oncologic Applications

Radiopharmaceutical	Manufacturer	Name	Carcinoma-Related Indication With PET
Carbon-11 choline (C-11)	Various		Suspected prostate cancer recurrence based on elevated blood PSA after therapy and noninformative bone scintigraphy, CT, or MRI
Copper-64 dotatate	Curium	Detectnet™	Localization of somatostatin receptor-positive NETs in adult individuals
Fluorine-18 fluorodeoxyglucose (FDG)	Various		Suspected or existing diagnosis of cancer, all types
Fluorine-18 fluoroestradiol	Zionexa USA	Cerianna™	Detection of ER-positive lesions as an adjunct to biopsy in individuals with recurrent or metastatic breast cancer

Radiopharmaceutical	Manufacturer	Name	Carcinoma-Related Indication With PET
Fluorine-18 fluciclovine	Blue Earth Diagnostics	Axumin™	Suspected prostate cancer recurrence based on elevated blood PSA levels after treatment
Gallium-68 dotatoc	UIHC - P E T Imaging Center		Localization of somatostatin receptor-positive NETs in adult and pediatric individuals
Gallium-68 dotatate	Advanced Accelerator Applications	NETSPOT™	Localization of somatostatin receptor-positive NETs in adult and pediatric individuals
Gallium-68 PSMA-11§	University of California, Los Angeles and the University of California, San Francisco		PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level
Piflufolastat fluorine-18	Progenics Pharmaceuticals, Inc	Pylarify®	PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level
Flotufolastat fluorine-18	Blue Earth Diagnostics	Posluma®	PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level

§ FDA-approval given to the University of California, Los Angeles and the University of California, San Francisco.
CT: computerized tomography; ER: estrogen receptor; MRI: magnetic resonance imaging; NET: neuroendocrine

tumors; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen.

Two kits used for the preparation of Gallium-68 PSMA-11 have received FDA approval: the Illuccix® (Telix Pharmaceuticals) kit, approved in December 2021; and the Locametz® (Advanced Accelerator Applications/Novartis) kit, approved in March 2022.[2,] The preparation kits are for use in individuals with PSMA-positive prostate cancer with suspected metastasis who are candidates for initial definitive therapy, or with suspected recurrence based on elevated serum PSA level. In addition, Locametz is approved for selection of patients with metastatic prostate cancer, for whom lutetium Lu-177 vipivotide tetraxetan (Pluvicto™; Novartis) PSMA-directed therapy is indicated.

POLICY

- All policy statements apply to both positron emission tomography (PET) scans and PET plus computed tomography (CT) scans, i.e., PET scans with or without PET/CT fusion.
- For the clinical situations indicated that may be considered medically necessary, this assumes that the results of the PET scan will influence treatment decisions. If the results will not influence treatment decisions, these situations would be considered not medically necessary.

A. **Bladder Cancer**
   1. PET scanning may be considered **medically necessary** in the staging or restaging of muscle-invasive bladder cancer when CT or magnetic resonance imaging are not indicated or remained inconclusive on distant metastasis.
   2. PET scanning is considered **experimental / investigational** for bladder tumors that have not invaded the muscle (stage < cT2).

B. **Bone Sarcoma**
   1. PET scanning may be considered **medically necessary** in the staging or restaging of Ewing sarcoma and osteosarcoma.
   2. PET scanning is considered **experimental / investigational** in the staging of chondrosarcoma.

C. **Brain Cancer**
   1. PET scanning may be considered **medically necessary** in the staging or restaging of brain cancer.

D. **Breast Cancer**
   1. PET scanning may be considered **medically necessary** in the staging and restaging of breast cancer for the following application:
      a. Detecting locoregional or distant recurrence or metastasis (except axillary lymph nodes) when suspicion of disease is high and other imaging is inconclusive.
   2. PET scanning is considered **experimental / investigational** in the evaluation of breast cancer for all other applications, including but not limited to the following:
      a. Differential diagnosis in individuals with suspicious breast lesions or an indeterminate or low suspicion finding on mammography.
      b. Staging axillary lymph nodes.
      c. Predicting pathologic response to neoadjuvant therapy for locally advanced disease.

E. **Cervical Cancer**
   1. PET scanning may be considered **medically necessary** in the initial staging of individuals with locally advanced cervical cancer.
   2. PET scanning may be considered **medically necessary** in the evaluation of known or suspected recurrence.

F. **Colorectal Cancer**
1. PET scanning may be considered **medically necessary** as a technique for
   a. Staging or restaging to detect and assess resectability of hepatic or extrahepatic metastases of colorectal cancer, **AND**
   b. To evaluate a rising and persistently elevated carcinoembryonic antigen levels when standard imaging, including CT scan, is negative.
2. PET scanning is considered **experimental / investigational** as
   a. A technique to assess the presence of scarring versus local bowel recurrence in individuals with previously resected colorectal cancer.
   b. A technique contributing to radiotherapy treatment planning.

G. **Endometrial Cancer**
1. PET scanning is considered **medically necessary** in the
   a. Detection of lymph node metastases, **AND**
   b. Assessment of endometrial cancer recurrence.

H. **Esophageal Cancer**
1. PET scanning may be considered **medically necessary** in the
   a. Staging of esophageal cancer, **AND**
   b. Determining response to preoperative induction therapy.
2. PET scanning is considered **experimental / investigational** in other aspects of the evaluation of esophageal cancer, including but not limited to the following applications:
   a. Detection of primary esophageal cancer.

I. **Gastric Cancer**
1. PET scanning may be considered **medically necessary** in the
   a. Initial diagnosis and staging of gastric cancer, **AND**
   b. Evaluation for recurrent gastric cancer after surgical resection, when other imaging modalities are inconclusive.

J. **Head and Neck Cancer**
1. PET scanning may be considered **medically necessary** in the evaluation of head and neck cancer in the
   a. Initial diagnosis of suspected cancer,
   b. Initial staging of disease, and restaging of residual or recurrent disease during follow-up; **AND**
   c. Evaluation of response to treatment.

K. **Lung Cancer**
1. PET scanning may be considered **medically necessary** for any of the following applications:
   a. Individuals with a solitary pulmonary nodule as a single scan technique (not dual-time) to distinguish between benign and malignant disease when prior CT scan and chest x-ray findings are inconclusive or discordant,
   b. As staging or restaging technique in those with known non-small-cell lung cancer, **AND**
   c. To determine resectability for individuals with a presumed solitary metastatic lesion from lung cancer.
2. PET scanning may be considered **medically necessary** in staging of small-cell lung cancer if limited stage is suspected based on standard imaging.
3. PET scanning is considered **experimental / investigational** in staging of small-cell lung cancer if extensive stage is established and in all other aspects of managing small-cell lung cancer.

L. **Lymphoma, Including Hodgkin Disease**
1. PET scanning may be considered **medically necessary** as a technique for staging lymphoma either during initial staging or for restaging at follow-up.

M. **Melanoma**
1. PET scanning may be considered **medically necessary** as a technique for assessing extranodal spread of malignant melanoma at initial staging or at restaging during follow-up treatment for advanced disease (stage III or IV).
2. PET scanning is considered **experimental / investigational** in managing stage 0, I, or II melanoma.
3. PET scanning is considered **experimental / investigational** as a technique to detect regional lymph node metastases in individuals with clinically localized melanoma who are candidates to undergo sentinel node biopsy.

N. **Multiple Myeloma**
1. PET scanning is considered **medically necessary** in the staging or restaging of multiple myeloma, particularly if the skeletal survey is negative.

O. **Neuroendocrine Tumors**
1. PET scanning with gallium 68 and copper 64 may be considered **medically necessary** as a technique for staging neuroendocrine tumors either during initial staging or for restaging at follow-up.
2. PET scanning with all other radiotracers is considered **experimental / investigational** in all aspects of managing neuroendocrine tumors.

P. **Ovarian Cancer**
1. PET scanning may be considered **medically necessary** in the evaluation of individuals with signs and/or symptoms of suspected ovarian cancer recurrence (restaging) when standard imaging, including CT scan, is inconclusive.
2. PET scanning is considered **experimental / investigational** in the initial evaluation of known or suspected ovarian cancer in all situations.

Q. **Pancreatic Cancer**
1. PET scanning may be considered **medically necessary** in the initial diagnosis and staging of pancreatic cancer when other imaging and biopsy are inconclusive.
2. PET scanning is considered **experimental / investigational** as a technique to evaluate other aspects of pancreatic cancer.

R. **Penile Cancer**
1. PET scanning may be considered **medically necessary** for staging and restaging in individuals with suspected inguinal lymph node positive disease.
2. PET scanning is considered **experimental / investigational** in all other aspects of managing penile cancer.

S. **Prostate Cancer**
1. PET scanning with carbon 11 choline and fluorine 18 fluciclovine may be considered **medically necessary** for evaluating suspected or biochemically recurrent prostate cancer after primary treatment to detect small volume disease in soft tissues.
2. PET scanning with gallium 68-prostate-specific membrane antigen, flotufolastat fluorine-18 and piflufolastat fluorine-18 may be considered **medically necessary** for any of the following applications:
    a. Individuals with diagnosed prostate cancer in need of staging information and:
        i. NCCN unfavorable intermediate-, high-, or very-high-risk prostate cancer (see Policy Guidelines); **OR**
        ii. NCCN unfavorable intermediate-, high-, or very-high-risk prostate cancer with equivocal results or oligometastatic disease on initial conventional imaging (see Policy Guidelines).
    b. Individuals with suspected recurrence of prostate cancer based on serum PSA level who have received:
        i. Radical prostatectomy with PSA level persistence or rise from undetectable level (see Policy Guidelines); **OR**
        ii. Definitive radiotherapy with PSA rise above nadir (see Policy Guidelines).
    c. Individuals with treated prostate cancer (including active surveillance/observation) in need of imaging as part of a workup for progression (see Policy Guidelines).
    d. Individuals with metastatic prostate cancer for whom lutetium Lu-177 vipivotide tetraxetan PSMA-directed therapy is indicated.
3. Use of gallium 68-prostate-specific membrane antigen, flotufolastat fluorine-18 and piflufolastat fluorine-18 in known or suspected prostate cancer is considered **experimental / investigational** for all other indications, including diagnosis, primary staging of very-low, low- or favorable intermediate-risk prostate cancer, and evaluation of response to therapy.
4. PET scanning for all other indications in known or suspected prostate cancer is considered **experimental / investigational**.

T. **Renal Cell Carcinoma**
1. PET scanning is considered **experimental / investigational** in all aspects of managing renal cancer.

U. **Soft Tissue Sarcoma**
1. PET scanning is considered **medically necessary** for evaluating response to imatinib and other treatments for gastrointestinal stromal tumors
2. PET scanning is considered **experimental / investigational** in evaluation of soft tissue sarcoma, including but not limited to the following applications:
   a. Distinguishing between benign lesions and malignant soft tissue sarcoma
   b. Distinguishing between low-grade and high-grade soft tissue sarcoma
   c. Detecting locoregional recurrence
   d. Detecting distant metastasis

V. **Testicular Cancer**
1. PET scanning may be considered **medically necessary** in evaluation of residual mass following chemotherapy of stage IIB and III seminomas. (The scan should be completed no sooner than 6 weeks after chemotherapy.)
2. Except as noted above for seminoma, PET scanning is considered **experimental / investigational** in evaluation of testicular cancer, including but not limited to the following applications:
   a. Initial staging of testicular cancer
   b. Distinguishing between viable tumor and necrosis/fibrosis after treatment of testicular cancer, and
   c. Detection of recurrent disease after treatment of testicular cancer

W. **Thyroid Cancer**
1. PET scanning may be considered **medically necessary** in the restaging of individuals with differentiated thyroid cancer when thyroglobulin levels are elevated and whole-body iodine-131 imaging is negative.
2. PET scanning is considered **experimental / investigational** in the evaluation of known or suspected differentiated or poorly differentiated thyroid cancer in all other situations.

X. **Cancer of Unknown Primary**
1. PET scanning may be considered **medically necessary** in individuals with a cancer of unknown primary who meet **ALL** of the following criteria:
   a. In individuals with a single site of disease outside the cervical lymph nodes; **AND**
   b. Individuals is considering local or regional treatment for a single site of metastatic disease; **AND**
   c. After a negative workup for an occult primary tumor; **AND**
   d. PET scan will be used to rule out or detect additional sites of disease that would eliminate the rationale for local or regional treatment.
2. PET scanning is considered **experimental / investigational** for other indications in individuals with a cancer of unknown primary, including, but not limited to the following:
   a. As part of the initial workup of an unknown primary, and
   b. As part of the workup of individuals with multiple sites of disease

Y. **Cancer Surveillance**

1. PET scanning is considered **experimental / investigational** when used as a surveillance tool for individuals 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 individuals without objective signs or symptoms suggestive of cancer recurrence (see Policy Guidelines section).

POLICY GUIDELINES

A. For this policy, PET scanning is discussed for the following 4 applications in oncology.

1. Diagnosis
   Diagnosis refers to use of PET as part of the testing used in establishing whether a patient has cancer.
2. Staging
   Staging 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 the cancer is localized. This may also be referred to as initial staging.
3. Restaging
   Restaging refers to imaging after treatment in 2 situations.
   a. Restaging is part of the evaluation of a patient in whom a disease recurrence is suspected based on signs and/or symptoms.
   b. Restaging also includes determining the extent of malignancy after completion of a full course of treatment.
4. Surveillance
   Surveillance refers to the 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 for lymphoma) after completion of treatment.

B. **Selection Criteria**

1. As with any imaging technique, the medical necessity of positron emission tomography (PET) scanning depends in part on what imaging techniques are used before or after the PET scanning. Due to its expense, PET scanning is typically considered after other techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography, provide inconclusive or discordant results. In individuals 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, (e.g., CT, MRI) is inconclusive or not indicated.
2. Selection criteria for PET scanning may also be complex. For example, it may be difficult to determine from claims data whether a PET scan in an individual 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 an individual with colorectal cancer is being performed to detect hepatic disease or evaluate local recurrence. Due to the complicated hierarchy of imaging options in individuals with malignancy and complex selection criteria, a possible implementation strategy for this policy is its use for retrospective review, possibly focusing on cases with multiple imaging tests, including PET scans.

3. 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 individuals at various intervals. This is not the same as the use of PET for detecting recurrent disease in symptomatic individuals; these applications of PET are considered within tumor-specific categories in the policy statements.

C. **Prostate-Specific Membrane Antigen Positron Emission Tomography**

1. Appropriate selection of patients for prostate-specific membrane antigen (PSMA) PET imaging may be guided according to National Comprehensive Cancer Network (NCCN) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) criteria (see policy section ^{68}Ga-PSMA PET, ^{68}Ga-PSMA PET/CT, Piflufolastat-F^{18} PET, and Piflufolastat-F^{18} PET/CT Guidelines). NCCN and SNMMI recommendations for use of PSMA PET in individuals with newly diagnosed prostate cancer in need of staging are based on the following NCCN risk criteria:

Risk Group	**Clinical/Pathological Features**
Very Low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g
Low	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL

Intermediate	Has all of the following:
	• No high-risk group features
	• No very-high-risk group features
	• Has one or more intermediate risk factor:
	  ○ cT2b–cT2c
	  ○ Grade Group 2 or 3
	• PSA 10–20 ng/mL

Favorable Intermediate	Intermediate risk criteria, AND all of the following: • 1 intermediate risk factor • Grade Group 1 or 2 • <50% biopsy cores positive (e.g., <6 of 12 cores)
Unfavorable Intermediate	Intermediate risk criteria AND one or more of the following: • 2 or 3 intermediate risk factors • Grade Group 3 • ≥50% biopsy cores positive (e.g., ≥6 of 12 cores)
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL

Risk Group	Clinical/Pathological Features
Very High	Has at least one of the following: • cT3b– cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5

2. Individuals who meet unfavorable intermediate-, high- and very-high risk criteria are suitable candidates for PSMA PET bone and/or soft tissue imaging, either following equivocal results on initial conventional imaging (e.g., MRI) or as alternative to conventional imaging.
3. PSMA PET imaging is not recommended for staging newly diagnosed individuals in very low, low, or favorable intermediate NCCN risk groups, or for individuals with suspected prostate cancer based on elevated PSA, increasing PSA on serial measurements, and/or clinical signs (e.g., abnormal digital rectal exam).
4. Use of PSMA PET imaging is appropriate for individuals who have undergone radical prostatectomy or radiation therapy for prostate cancer with subsequent suspected persistence or recurrence. Specific considerations for use of PSMA PET are:
    a. Following radical prostatectomy AND:
        i. Failure of PSA to fall to undetectable levels; OR
        ii. Previously undetectable PSA with a subsequent detectable PSA that increases on ≥2 measurements
    b. Following definitive radiation therapy AND:
        i. A PSA rise ≥2 ng/mL above the nadir; OR
        ii. A positive digital rectal exam.
5. PSMA PET may also be considered when PSA has been confirmed to be increasing after radiation therapy even if the increase above nadir is not yet 2 ng/mL, particularly in candidates with a favorable prognosis for salvage local therapy.
6. PSMA PET use is appropriate in individuals who have previously been treated for prostate cancer (including those under active surveillance/observation) who require imaging as part of a workup for progression. NCCN guidelines include recommended workup protocols, which vary according to prior treatment and cancer stage. The guidelines recommend use of PSMA PET bone and soft tissue imaging when conventional imaging results are equivocal, but also state that PSMA PET imaging is more accurate than conventional imaging at detecting micrometastatic disease, and as such, the guidelines note that conventional imaging is not a necessary prerequisite to PSMA PET imaging.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 26, 2024.

The review has been informed by multiple evaluations of positron emission tomography (PET), including TEC Assessments, other systematic reviews, meta-analyses, and decision analyses.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

POSITRON EMISSION TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY PLUS COMPUTED TOMOGRAPHY

Clinical Context and Test Purpose

For this evidence review, PET and PET plus computed tomography (CT) scanning is discussed for the following 4 applications in oncology: diagnosis, staging, restaging, and surveillance. Diagnosis refers to the use of PET as part of the testing used in establishing whether a patient has cancer. Staging refers to the use of PET to determine the stage (extent) of cancer at the time of diagnosis before any treatment is given. Imaging during staging is generally to determine whether the cancer is localized. This also may be referred to as initial staging. Restaging refers to imaging after treatment in 2 situations. First, restaging is part of the evaluation of a patient in whom disease recurrence is suspected based on signs and/or symptoms. Second, restaging also includes determining the extent of malignancy after completion of a full course of treatment. Surveillance refers to the use of imaging in asymptomatic individuals (individuals without objective signs or symptoms of recurrent disease). Surveillance is completed 6 months or more (≥12 months for lymphoma) after completion of treatment.

The question addressed in this evidence review is: Does the use of PET or PET/CT improve the net health outcome in individuals with suspected, diagnosed, or treated cancer compared with conventional imaging techniques?

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are:

- Individuals who are suspected of having cancer.
- Individuals diagnosed with cancer and need information on the extent of cancer (initial staging upon diagnosis confirmation or restaging following treatment).
- Individuals with cancer who have completed a round of treatment and may be at risk of recurrence.

Interventions
The test being considered is PET or PET/CT. A PET scan is a nuclear medicine 3-dimensional imaging technique. Radioactive tracers are ingested or injected, and radioactive emissions are detected by an imaging device, allowing observations on blood flow, oxygen use, and metabolic processes around the lesions. When CT is added to PET, the images are superimposed, providing additional anatomic information. The most common radioactive tracer used for oncologic applications is fluorine 18 (^{18}F) fluorodeoxyglucose (FDG). Radiation exposure from PET and PET/CT is considered moderate to high.

Comparators
The comparators of interest are conventional imaging techniques such as ultrasound, magnetic resonance imaging (MRI), and x-rays.

Outcomes
The general outcomes of interest are related to the clinical validity of PET and PET/CT in (1) diagnosing suspected cancers, (2) providing staging or restaging information, and (3) detecting recurrence following cancer treatment. Clinical validity is most often measured by sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV). For the clinical utility of PET and PET/CT to be demonstrated, the tests would need to inform treatment decisions that would improve survival and quality of life.

Clinical validity can be measured as soon as results from PET or PET/CT can be compared with results from conventional imaging techniques. Outcomes for clinical utility are long-term, which, depending on the type of cancer, can range from months or a few years for more aggressive cancers to many years for less aggressive cancers.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of PET and PET/CT, studies should report sensitivity, specificity, PPV, and NPV. Additionally, studies reporting false-positive rates and false-negative rates are informative.
- To assess the clinical utility of PET and PET/CT, studies should demonstrate how results of these imaging techniques impacted treatment decisions and overall management of the patient.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy or more effective therapy, avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Most of the evidence on the use of PET scanning in oncology focuses on clinical validity (sensitivity, specificity), and consists mostly of systematic reviews and meta-analyses. There are few rigorous studies assessing the impact of PET on clinical utility. A few studies that have reported on changes in staging and/or treatment that result from the PET scan do not evaluate whether these changes resulted in improvements in the net health outcome. Due to the lack of direct evidence for clinical utility, evidence for clinical validity is presented first, followed by clinical guidelines, which help to outline the indications for which clinical utility is supported.

REVIEW OF EVIDENCE

BLADDER CANCER

Systematic Reviews
A systematic review and meta-analysis (10 studies, N=433) by Zhang et al (2015) evaluated the diagnostic accuracy of FDG-PET and FDG-PET with CT (FDG-PET/CT) in individuals with urinary bladder cancer.[3,] The 10 studies were assessed for quality using the 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Median QUADAS score was 9 (range, 7-10). Nine of the 10 studies used FDG-PET/CT and 1 used FDG-PET. Nine studies were retrospective and 1 prospective. Meta-analyses showed relatively high sensitivity (82%; 95% confidence interval [CI], 75% to 88%) and specificity (92%; 95% CI, 87% to 95%) in the diagnosis of bladder cancer, with the reference test of pathology results. The meta-analysis funnel plots showed some asymmetry, indicating a potential for publication bias.

Guidelines

American College of Radiology
In 2018, the American College of Radiology (ACR) issued an Appropriateness Criteria for pretreatment staging of muscle-invasive bladder cancer.[4,] The ACR stated that FDG-PET/CT "may be appropriate" for the pretreatment staging of muscle-invasive bladder cancer. However, the ACR cited CT, MRI, and chest radiographs as the most appropriate imaging techniques for pretreatment staging.

In 2021, the ACR issued an Appropriateness Criteria for post-treatment surveillance of bladder cancer. For muscle-invasive bladder cancer, FDG-PET/CT may be appropriate for surveillance; however, the ACR states that chest radiograph, CT, and MRI are usually appropriate procedures.[5,]

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines for bladder cancer (2.2024) state that FDG-PET/CT may be useful in assessing the presence of regional or distant metastases, though it is not the preferred imaging modality.[6,] Recommendations for FDG-PET/CT in muscle-invasive bladder cancer include (all category 2B):

- For chest imaging:
  - Staging: "may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with ≥cT3 disease"
  - Follow-up with or without cystectomy: "may be performed if not previously done or if metastasis is suspected in selected patients"
  - Follow-up of cT4b and metastatic disease: "may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected"
- For abdominal and pelvic imaging:
  - Staging: "may be useful in selected patients with ≥cT2 disease and may change management in patients with ≥cT3 disease"
  - Follow-up: "may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected; this could also be used to guide biopsy in certain patients"
- Evaluation of suspected bone metastases
  - "Symptomatic, or high-risk patients, or those with laboratory indicators of bone metastasis may be imaged with MRI, FDG-PET/CT (category 2B), or bone scan. FDG-PET/CT (category 2B) may also be considered in cases when additional sites of extraosseous metastatic disease are suspected or previously documented."

However, the guidelines note that "PET/CT should not be used to delineate the anatomy of the upper urinary tract" or in patients with nonmuscle invasive bladder cancer.

Section Summary: Bladder Cancer
Evidence for the use of FDG-PET and FDG-PET/CT for the diagnosis and for the staging and restaging of muscle-invasive bladder cancer consists of a systematic review and meta-analysis of several studies. Pooled analyses have shown that PET/CT is effective in the staging of muscle-invasive bladder cancer. The evidence supports the use of FDG-PET/CT for the diagnosis and staging and restaging of muscle-invasive bladder cancer.

The evidence does not support the use of FDG-PET/CT for nonmuscle invasive bladder cancer.

BONE SARCOMA

Systematic Reviews
A meta-analysis (12 studies, N=375) by Zhang et al (2020) evaluated FDG-PET and FDG-PET/CT in the diagnosis and staging of chondrosarcoma, a common type of bone sarcoma.[7,] Six studies used PET/CT, 5 studies used PET, and 1 study utilized both. For differentiating between chondrosarcoma and benign lesions, the pooled sensitivity and specificity of FDG-PET were 84% (95% CI, 46% to 97%) and 82% (95% CI, 55% to 94%), respectively. The sensitivity and specificity for FDG-PET/CT were also found to be high at 94% (95% CI, 86% to 97%) and 89% (95% CI, 82% to 93%), respectively. There was substantial heterogeneity for sensitivity (I^2, 86.90%; 95% CI, 76.8% to 97.0%) and specificity (I^2, 70.32%; 95% CI, 42.57 to 98.07%)

among studies. Most included studies were retrospective (75%) and included small sample sizes (n=7 to 95), potentially introducing bias and variability.

A systematic review and meta-analysis (35 studies, N=2171) by Liu et al (2015) evaluated FDG-PET and FDG-PET/CT in the diagnosis, staging, and recurrence assessment of bone sarcoma.[8,] Most selected studies used PET/CT (n=29). Meta-analyses showed high sensitivity (96%; 95% CI, 93% to 98%) and specificity (79%; 95% CI, 63% to 90%) of FDG-PET and FDG-PET/CT to differentiate primary bone sarcomas from benign lesions. For pooled results for detecting recurrence, sensitivity was 92% (95% CI, 85% to 97%) and specificity was 93% (95% CI, 88% to 96%). For pooled results for detecting distant metastases, sensitivity was 90% (95% CI, 86% to 93%) and specificity was 85% (95% CI, 81% to 87%). Subgroup analysis by specific metastatic site revealed that PET alone was less effective in detecting lung metastases than other metastatic sites (sensitivity, 71%; 95% CI, 52% to 86%; specificity, 92%; 95% CI, 87% to 96%).

A systematic review (13 studies, N=342) and meta-analysis (5 studies, n=279) by Treglia et al (2012) examined the diagnostic accuracy of FDG-PET and FDG-PET/CT in Ewing sarcoma.[9,] The meta-analysis showed high estimates of sensitivity and specificity for FDG-PET and FDG-PET/CT (pooled sensitivity, 96%; pooled specificity, 92%).

GUIDELINES

American College of Radiology

In 2020, the ACR issued an Appropriateness Criteria for primary bone tumors.[10,] For suspected primary bone tumors with evidence of lesions on radiographs and indeterminate or aggressive appearance for malignancy, FDG-PET/CT of the whole body may be appropriate; MRI of area of interest with or without contrast was deemed usually appropriate. Use of FDG-PET/CT was considered usually not appropriate for other diagnostic and staging imaging procedures addressed in the guidance.

National Comprehensive Cancer Network

Current NCCN guidelines for bone cancer (v.2.2024) state that PET/CT may be considered for[11,]:

- Diagnostic workup of individuals with suspected primary bone cancer, including chordoma, Ewing sarcoma, or osteosarcoma,
- Restaging in individuals with Ewing sarcoma or osteosarcoma, and
- Surveillance of individuals with Ewing sarcoma or osteosarcoma (category 2B).

Section Summary: Bone Sarcoma

Evidence for the use of FDG-PET and FDG-PET/CT for the diagnosis and for the staging and restaging of bone sarcoma consists of systematic reviews and meta-analyses. Pooled analyses have shown that PET is effective in the staging of bone sarcoma, including chondrosarcoma. Use of PET has also shown high sensitivities and specificities in detecting metastases in bone and lymph nodes but low sensitivity in detecting lung metastases. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging of bone sarcoma.
The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of bone sarcoma.

BRAIN TUMORS

FDG-PET AND ^{18}F-FET PET

Systematic Reviews

A systematic review and meta-analysis by Dunet et al (2016) included studies published through January 2015 in which individuals with suspected primary or recurrent brain tumors underwent both fluorine 18 fluoro-ethyl-tyrosine PET (^{18}F-FET-PET) and FDG-PET.[12,] Four studies (N =109) met the inclusion criteria. All 4 studies included in the meta-analysis had scores greater than 10 in the 15-point QUADAS tool. The ^{18}F-FET PET (pooled sensitivity, 94%; 95% CI, 79% to 98%; pooled specificity, 88%; 95% CI, 37% to 99%) performed better than FDG-PET (pooled sensitivity, 38%; 95% CI, 27% to 50%; pooled specificity, 86%; 95% CI, 31% to 99%) in the diagnosis of brain tumors. Target to background ratios of both FDG and FET were similar in detecting low- and high-grade gliomas.

A systematic review and meta-analysis by Dunet et al (2012) included studies published through January 2011 and assessed the use of ^{18}F-FET PET in detecting primary brain tumors.[13,] Thirteen studies (N=462) were included in the systematic review and 5 (n=224) were included in the meta-analysis. All 5 studies in the meta-analysis had scores above 10 on the 14-point QUADAS scale. The pooled sensitivity for ^{18}F-FET PET in detecting primary brain tumors was 82% (95% CI, 74% to 88%) and pooled specificity was 76% (95% CI, 44% to 92%). Other imaging modalities for diagnosing brain tumors were not included in this analysis, so no conclusions could be made about comparative effectiveness.

FDG-PET AND ^{11}C-METHIONINE PET

Systematic Reviews

A meta-analysis by Zhao et al (2014) compared the diagnostic performance of FDG-PET with carbon 11 (^{11}C) methionine PET in the detection of suspected primary brain tumors and suspected recurrence of brain tumors following treatment.[14,] The literature search included studies published through February 2013. A total of 24 studies provided data on the use of FDG-PET and 11 studies reported on the use of ^{11}C-methionine PET. The pooled sensitivity and specificity of FDG-PET in detecting primary or recurrent brain tumors were 71% (95% CI, 63% to 78%) and 77% (95% CI, 67% to 85%), respectively. Diagnostic performance was better with ^{11}C-methionine PET, with a pooled sensitivity and specificity of 91% (95% CI, 85% to 94%) and 86% (95% CI, 78% to 92%), respectively.

In another meta-analysis, Deng et al (2013) assessed the ability of ^{11}C-methionine PET and MRI to detect glioma recurrence.[15,] The literature search included articles through March 2012. All selected studies were retrospective cohorts, 11 using ^{11}C-methionine PET (n=244) and 7 using MRI (n=214). Meta-analyses found that the dynamic susceptibility contrast-enhanced MRI (pooled sensitivity, 88%; 95% CI, 82% to 93%; pooled specificity, 85%; 95% CI, 75% to 92%) performed similarly to ^{11}C-methionine PET (pooled sensitivity, 87%; 95% CI, 81% to 92%; pooled specificity, 81%; 95% CI, 72% to 89%) in glioma recurrence detection, with ^{11}C-methionine being slightly less specific.

Guidelines

Current NCCN guidelines for brain cancer (v.1. 2022) include these statements:[16,]

- PET can assess metabolism within the tumor and normal tissue by using radio-labeled tracers, which may be useful in differentiating tumor from radiation necrosis, may correlate with tumor grade, or provide an optimal area for biopsy.
- Limitations include the accuracy of interpretations and availability of equipment and isotopes.
- Close follow-up imaging, MR perfusion, MR spectroscopy, PET/CT imaging, and repeat surgery may be necessary if clinically indicated. Educate patients on the uncertainty of imaging as a whole, and the potential need for corollary testing to interpret scans.

Section Summary: Brain Tumors

Evidence for the use of PET to diagnose and stage brain cancer consists of several systematic reviews and meta-analyses. The diagnostic capabilities of PET vary by radiotracer used. There was a direct comparison of radiotracers, with ^{18}F-FET-PET showing better diagnostic accuracy than FDG-PET. An indirect comparison between FDG-PET and ^{11}C-methionine PET showed that ^{11}C-methionine PET performed better, and another indirect comparison of ^{11}C-methionine PET and MRI showed a comparable diagnostic capability between methods. The evidence supports the use of FDG-PET, ^{18}F-FET-PET, and ^{11}C-methionine PET for the diagnosis and staging and restaging of brain tumors.

The evidence does not support the use of FDG-PET, ^{18}F-FET-PET, and ^{11}C-methionine PET for surveillance of brain tumors.

BREAST CANCER

BREAST CANCER DIAGNOSIS

Systematic Reviews

Liang et al (2017) conducted a meta-analysis on the use of PET/CT to assess axillary lymph node metastasis.[17,] Results from the meta-analyses of 14 studies using MRI and 10 studies using PET/CT showed that MRI had a higher sensitivity in diagnosing axillary lymph node status.

In a meta-analysis of 8 studies (N=873) on FDG-PET performed in women with newly discovered suspicious breast lesions, Caldarella et al (2014) reported pooled sensitivity and specificity of 85% (95% CI, 83% to 88%) and 79% (95% CI, 74% to 83%), respectively, on a per lesion basis.[18,] As previously noted, a false-negative rate of 15% (100% - sensitivity) may be considered unacceptable given the relative ease of breast biopsy.

A systematic review by Sloka et al (2007) on PET for staging axillary lymph nodes identified 20 studies.[19,] Three of these 20 studies were rated high quality, indicating broad generalizability to a variety of individuals and no significant flaws in research methods. The remaining studies were less generalizable due to flaws in the methodology. Reviewers observed that there was great variability in estimates of sensitivity and specificity from the selected studies and that it was difficult to draw conclusions from the evidence.

A TEC Assessment (2001) focused on multiple applications of PET scanning in breast cancer, including characterizing breast lesions, staging axillary lymph nodes, detecting recurrence, and evaluating response to treatment.[20,]A TEC Assessment (2003) reexamined all indications except for characterizing breast lesions.[21,]The bulk of the data on FDG-PET for breast cancer focuses on its ability to characterize breast lesions further such that individuals could avoid biopsy of a mammographically indeterminate or suspicious lesion. The key statistic in this analysis is the false-negative rate, because individuals with a false-negative result on a PET scan may inappropriately forgo 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 individuals may undergo biopsy regardless of the results of a PET scan.

Breast Cancer Staging

A meta-analysis by Han et al (2021) evaluated the impact of FDG- PET, PET/CT, and PET/MRI on staging and management during the initial staging of breast cancer.[22,] A total of 29 studies (N=4276) were identified. The pooled results for all 3 imaging studies demonstrated that they led to a change in staging in 25% (95% CI, 21% to 30%) of individuals and a change in management in 18% (95% CI, 14% to 23%) of individuals.

A meta-analysis by Hong et al (2013) reported a sensitivity and a specificity of FDG-PET/CT in diagnosing distant metastases in breast cancer individuals of 96% (95% CI, 90% to 98%) and 95% (95% CI, 92% to 97%), respectively, based on 8 studies (N=748).[23,] In a meta-analysis of 6 comparative studies (n=664 individuals), the sensitivity and specificity were 97% (95% CI, 84% to 99%) and 95% (95% CI, 93% to 97%) with FDG-PET/CT compared with 56% (95% CI, 38% to 74%) and 91% (95% CI, 78% to 97%) with conventional imaging, all respectively.

Rong et al (2013) conducted a meta-analysis of 7 studies (N =668 individuals) and reported that the sensitivity and specificity of FDG-PET/CT were greater than bone scintigraphy for detecting bone metastasis in breast cancer individuals.[24,] The sensitivity and specificity of FDG-PET/CT were 93% (95% CI, 82% to 98%) and 99% (95% CI, 95% to 100%) compared with 81% (95% CI, 58% to 93%) and 96% (95% CI, 76% to 100%) for bone scintigraphy, all respectively.

A meta-analysis by Isasi et al (2005) focused on PET for detecting recurrence and metastases.[25,] The analysis concluded that PET is a valuable tool; however, they did not compare PET performance with that of other diagnostic modalities, so it is unclear whether the use of PET resulted in different management decisions and health outcomes.

The TEC Assessment (2003) described above in the Breast Cancer Diagnosis section concluded that the use of FDG-PET for staging axillary lymph nodes did not meet TEC criteria.[21,]

Breast Cancer Restaging

A systematic review by Xiao et al (2016) evaluated the diagnostic efficacy of FDG-PET and FDG-PET/CT in detecting breast cancer recurrence.[26,] The literature search, conducted through January 2016, identified 26 studies (N=1752) for inclusion in the analysis; 12 studies used PET and 14 studies used PET/CT. Fourteen studies had QUADAS scores greater than 10. Reasons for suspected recurrence in the 1752 individuals were: elevated tumor markers (57%), suspicion from conventional imaging modalities (34%), and suggestive clinical symptoms or physical

examination results (9%). Pooled sensitivity and specificity are presented in Table 2. Subgroup analyses showed that PET/CT was more specific than PET alone in diagnosing recurrent breast cancer (p=.035).

A systematic review by Liu et al (2016) compared FDG-PET or FDG-PET/CT with MRI in assessing pathologic complete response to neoadjuvant chemotherapy in individuals with breast cancer.[27,] The literature search, conducted through August 2015, identified 6 studies (N=382) for inclusion. Quality assessment of the studies was deemed satisfactory using the QUADAS-2 scale. Meta-analysis results are presented in Table 2.

In another meta-analysis comparing FDG-PET with MRI and evaluating pathologic complete response to neoadjuvant chemotherapy in individuals with breast cancer, Sheikhbahaei et al (2016) selected 10 studies for analysis.[28,] The inclusion criteria differed slightly from Liu et al (2016). Liu et al (2016) required that both FDG-PET and MRI be performed before and during (or after) neoadjuvant chemotherapy, while Sheikhbahaei et al (2016) did not require the scanning before neoadjuvant chemotherapy. Pooled sensitivities and specificities are listed in Table 2. Subgroup analysis was performed, by the time of scanning (during neoadjuvant chemotherapy and after neoadjuvant chemotherapy was completed).

Other reviews, including Li et al (2018), have also compared MRI with PET or PET/CT in evaluating response to neoadjuvant chemotherapy.[29,] Meta-analytic results are similar to previous studies and are presented in Table 2.

Table 2. Pooled Diagnostic Performance of FDG-PET and MRI in Detection of Residual Disease After Neoadjuvant Chemotherapy for Breast Cancer

Type of Imaging	No. of Studies (N)	Sensitivity (95% CI), %	Specificity (95% CI), %
Li et al (2018)[29,]			
MRI	13 (575)	88 (78 to 94)	69 (51 to 83)
FDG-PET or FDG-PET/CT	13 (618)	77 (58 to 90)	78 (63 to 88)
Xiao et al (2016)[26,]			
FDG-PET or FDG-PET/CT	26 (1752)	90 (88 to 90)	81 (78 to 84)
Liu et al (2016)[27,]			
MRI	6 (382)	65 (45 to 80)	88 (75 to 95)
FDG-PET or FDG-PET/CT	6 (382)	86 (76 to 93)	72 (49 to 87)
Sheikhbahaei et al (2016)[28,]			
All studies			
MRI	10 (492)	88 (76 to 95)	55 (41 to 68)
FDG-PET or FDG-PET/CT	10 (535)	71 (52 to 85)	77 (58 to 89)
FDG-PET/CT	7 (385)	82 (62 to 92)	79 (52 to 93)

Type of Imaging	No. of Studies (N)	Sensitivity (95% CI), %	Specificity (95% CI), %
FDG-PET	3 (150)	43 (26 to 63)	73 (44 to 91)
During neoadjuvant chemotherapy			
MRI	3 (256)	89 (66 to 97)	42 (20 to 68)
FDG-PET/CT	3 (256)	91 (86 to 95)	69 (25 to 93)
After neoadjuvant chemotherapy completion			
MRI	7 (236)	88 (71 to 96)	63 (51 to 74)
FDG-PET or FDG-PET/CT	7 (279)	57 (40 to 71)	80 (65 to 90)
FDG-PET/CT	4 (129)	71 (42 to 89)	88 (73 to 95)

CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; MRI: magnetic resonance imaging; PET: positron emission tomography.

Two 2012 meta-analyses pooled studies on the use of FDG-PET to predict pathologic response to neoadjuvant therapy before surgery for locally advanced breast cancer.[30,31,] Both reviews reported similar pooled point estimates for sensitivity and specificity. Both concluded that PET had reasonably high sensitivity and relatively low specificity. Neither 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.

GUIDELINES

American College of Radiology

In 2017, the ACR issued an Appropriateness Criteria for the initial workup and surveillance for local recurrence and distant metastases in asymptomatic women with stage I breast cancer.[32,] The ACR noted that FDG-PET/CT is usually not appropriate during initial workup or surveillance of these individuals to rule out metastases.

National Comprehensive Cancer Network

Current NCCN guidelines on breast cancer (v.4.2022) include a category 2B recommendation for FDG-PET/CT as an optional test in the workup of breast cancer.[33,]The use of FDG-PET/CT is "most helpful in situations where standard staging studies are equivocal or suspicious. FDG-PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies."

The NCCN recommends against FDG-PET/CT for lower stage breast cancer (I, II, or operable III) due to high false-negative rates in detecting low-grade lesions or lesions less than 1 cm, low sensitivity in detecting axillary node metastasis, the low prior probability of detectable metastases in these individuals, and high false-positive rates.

The NCCN guidelines do not recommend routine use of PET in asymptomatic individuals for surveillance and follow-up after breast cancer treatment. When monitoring the metastatic disease, the guidelines note that PET is "challenging because of the absence of a reproducible, validated, and widely accepted set of standards for disease activity assessment."

Section Summary: Breast Cancer
Evidence for the use of PET or PET/CT in individuals with breast cancer consists of TEC Assessments, systematic reviews, and meta-analyses. There is no evidence that PET is useful in diagnosing breast cancer. The false-negative rates of PET in individuals with breast cancer are estimated to be between 5.5% and 8.5%, which can be considered unacceptable, given that breast biopsy can provide more definitive results. Use of PET/CT might be useful in detecting metastases when results from other imaging techniques are inconclusive. The evidence supports the use of FDG-PET and FDG-PET/CT for staging and restaging only if standard staging methods are inconclusive.

The evidence does not support the use of FDG-PET and FDG-PET/CT for diagnosis, staging, and restaging when standard staging methods are conclusive.

The evidence does not support the use of FDG-PET or FDG-PET/CT for surveillance of breast cancer.

CERVICAL CANCER

Systematic Reviews
In a systematic review of 20 studies, Chu et al (2014) reported a pooled sensitivity and specificity for FDG-PET or FDG-PET/CT of 87% (95% CI, 80% to 92%) and 97% (95% CI, 96% to 98%), respectively, for distant metastasis in recurrent cervical cancer.[34,] For local-regional recurrence, pooled sensitivity and specificity were 82% (95% CI, 72% to 90%) and 98% (95% CI, 96% to 99%), respectively.

In a meta-analysis of 9 cervical cancer recurrence studies, Rong et al (2013) reported sensitivity and a specificity for PET/CT of 94.8% (95% CI, 91.2% to 96.9%) and 86.9% (95% CI, 82.2% to 90.5%), respectively.[24,] Reviewers 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.

An Agency for Healthcare Research and Quality (AHRQ) review (2008) identified several studies using FDG-PET or FDG-PET/CT to stage advanced cervical cancer and to detect and stage recurrent disease.[35,] The report concluded that most studies supported enhanced diagnostic accuracy, which would improve the selection of appropriate treatment for individuals. For recurrent disease, PET identified additional sites of metastasis, which would alter treatment decisions in some cases. For example, in a study by Yen et al (2004) of 55 individuals whose recurrences were initially considered curable with radical surgical treatment, 27 instead underwent palliative therapy based on PET results.[36,] An NCCN report conducted by Podoloff et al (2009) also identified several studies supporting the use of PET for initial staging and identifying and staging recurrent disease.[37,]

Guidelines
Current NCCN guidelines on cervical cancer (v.1.2022) state that PET/CT may be considered under the following conditions:[38,]

- Part of the initial non-fertility and fertility-sparing workup for individuals with stage I cervical cancer.
- Part of the initial staging workup for detection of stage II, III, or IV metastatic disease.
- Follow-up/surveillance for stage I (only nonfertility sparing) through stage IV at 3 to 6 months after completion of therapy or if there is suspected recurrence or metastases.
- To assess response or determine future therapy in individuals with Stage IVB or cervical cancer recurrence.
- PET/CT should cover neck, chest, abdomen, pelvis, and groin.

Section Summary: Cervical Cancer
Evidence for the use of PET in individuals with cervical cancer consists of systematic reviews and meta-analyses. Pooled results have shown that PET can be used for staging or restaging and detecting recurrent disease. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of cervical cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of cervical cancer.

COLORECTAL CANCER

COLORECTAL CANCER DIAGNOSIS

Systematic Reviews
Mahmud et al (2017) conducted a systematic review comparing the use of FDG-PET and FDG-PET/CT with conventional imaging techniques in the staging, treatment response, and follow-up of individuals with rectal cancer.[39,] The literature review, conducted through April 2016, identified 17 studies (N=791) for the qualitative review, with 8 of those studies (n=428) included in the meta-analysis. The QUADAS-2 tool was used to assess study quality. A limitation of many of the studies was that there was either no blinding or unclear blinding used for assessing the index test or the reference standard. For the detection of a primary tumor, pooled sensitivity and specificity were 99% (95% CI, 97% to 100%) and 67% (95% CI, 50% to 82%), respectively. For the detection of inguinal lymph nodes, the pooled sensitivity and specificity were 93% (95% CI, 76% to 99%) and 76% (95% CI, 61% to 87%), respectively.

A systematic review by Jones et al (2015) compared the role of FDG-PET and FDG-PET/CT with conventional imaging in the detection of primary nodal disease.[40,] Twelve studies met inclusion criteria (N=494). A meta-analysis for detecting primary disease in situ showed that PET and PET/CT had a higher sensitivity (99%; 95% CI, 96% to 100%) than CT alone (60%; 95% CI, 46% to 75%).

Two clinical applications of PET scanning were considered in a TEC Assessment (1999): (1) to detect hepatic or extrahepatic metastases and to assess their resectability in individuals with colorectal cancer (CRC), 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.[41,]

The body of evidence indicated that PET scanning added useful information to conventional imaging in detecting hepatic and extrahepatic metastases. In particular, PET detected additional metastases leading to more identification of nonresectable disease, allowing individuals to avoid surgery. The strongest evidence came from a study that directly assessed the additional value of PET. In a group of 37 individuals thought to have a solitary liver metastasis by conventional imaging, PET correctly upstaged 4 individuals and falsely overstaged 1. This and another study found that when PET results were discordant with conventional imaging results, PET was correct in 88% and 97% of individuals, respectively. When PET affected management decisions, it was more often used to recommend against surgery.

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

COLORECTAL CANCER STAGING

Systematic Reviews

Results from a meta-analysis of 10 studies by Albertsson et al (2018) found that PET/CT influenced treatment plans for anal cancer, though the impact on survival and quality of life could not be determined.[42,]

A meta-analysis by Ye et al (2015) assessed the use of FDG-PET/CT in preoperative TNM staging of CRC.[43,] The literature search, conducted through July 2014, identified 28 studies for inclusion. Of the 28 studies, 12 assessed tumor detection rates; 4 evaluated T staging, 20 N staging, and 5 M staging; while 8 examined stage change. Using the QUADAS tool, all studies met 9 or more of the 14 criteria. Pooled diagnostic estimates are listed in Table 3.

Three systematic reviews published in 2014 included overlapping studies that assessed the predictive value of FDG-PET/CT in individuals with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy.[44,45,46,] Various PET parameters were investigated (standardized uptake value, response index [percentage of the standardized uptake value decrease from baseline to post neoadjuvant treatment]), and cutoff values varied. Pooled sensitivities ranged from 74% to 82%, and pooled specificities ranged from 64% to 85%. The value of FDG-PET/CT in this setting has yet to be established.

Two systematic reviews were conducted to evaluate the use of PET/CT for radiotherapy planning in individuals with rectal cancer. Gwynne et al (2012) compared different imaging techniques for radiotherapy treatment planning and concluded that additional studies would be needed to validate the use of PET in this setting.[47,]

Table 3. Pooled Diagnostic Performance of FDG-PET, FDG-PET/CT, and CT Alone in the Staging of Colorectal Cancer

Type of Imaging	No. of Studies	Diagnostic Threshold	Sensitivity (95% CI), %	Specificity (95% CI), %
T staging				
FDG-PET or FDG-PET/CT	4	Yes	73 (65 to 81)	99 (98 to 99)
N staging				
FDG-PET or FDG-PET/CT	20	Yes	62 (59 to 66)	70 (67 to 73)
FDG-PET/CT alone	12	Yes	70 (66 to 74)	63 (59 to 67)
FDG-PET alone	8	No	36 (29 to 44)	93 (89 to 96)
CT alone	7	No	79 (75 to 80)	46 (41 to 51)
M staging				
FDG-PET or FDG--PET/CT	5	No	91 (80 to 96)	95 (91 to 98)
CT alone	5	No	91 (87 to 94)	16 (8 to 27)

Adapted from Ye et al (2015).[43,]
CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; M staging: distant metastases; N staging: regional lymph nodes; PET: positron emission tomography; T staging: primary tumor.

COLORECTAL CANCER RESTAGING

Systematic Reviews

A systematic review by Rymer et al (2016) evaluated the use of FDG-PET/CT in the assessment of the response of locally advanced rectal cancer to neoadjuvant chemoradiotherapy.[48,] The literature search, conducted through April 2014, identified 10 studies (N=538) for inclusion. Selected studies were high quality, complying with an average 12.7 items on the 14-item QUADAS checklist. Tumors confirmed to have regressed following chemoradiotherapy (responders) had a higher response index with a mean difference of 12% (95% CI, 7% to 18%) and a lower standardized uptake value of -2.5 (95% CI, -3.0 to -1.9) compared with nonresponders.

A meta-analysis by Yu et al (2015) evaluated the diagnostic value of FDG-PET/CT for detecting local recurrent CRC.[49,] The literature search, conducted through October 2014, identified 26 studies (N=1794) for inclusion. Study quality was assessed using QUADAS. Pooled sensitivity and specificity were 95% (95% CI, 93% to 97%) and 93% (95% CI, 92% to 95%), respectively.

Maffione et al (2015) conducted a systematic review of FDG-PET for predicting response to neoadjuvant therapy in individuals with rectal cancer.[50,] The literature search was conducted through January 2014, with 29 studies meeting inclusion criteria for the meta-analysis. The studies had QUADAS scores ranging from 8 to 14 (median, 12). The pooled sensitivity and specificity for FDG-PET assessment of response to chemoradiotherapy in locally advanced rectal cancer were 73% (95% CI, 71% to 76%) and 77% (95% CI, 75% to 79%), respectively.

In a systematic review, Lu et al (2013), evaluated 510 individuals from 11 studies on FDG-PET for CRC tumor recurrence detection in individuals with elevated carcinoembryonic antigen.[51,] The literature search ran through April 2012. Estimates for FDG-PET and PET/CT pooled sensitivity 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.

COLORECTAL CANCER SURVEILLANCE

Randomized Controlled Trials

Sobhani et al (2018) conducted an open-label RCT to determine whether adding 6 monthly FDG-PET/CT scans to usual surveillance (i.e., 3 monthly physicals and tumor marker assays; 6 monthly liver ultrasounds and chest radiographs; 6 monthly CT scans) of individuals with CRC following surgery and/or chemotherapy improves health outcomes.[52,] A total of 239 individuals in remission were enrolled, with 120 in the intervention arm and 119 in the control arm. After 3 years of follow-up, the failure rate in the intervention group was 29% (31 unresectable recurrences, 4 deaths) and 24% in the control group (27 unresectable recurrences, 1 death), which was not a statistically significant difference.

GUIDELINES

American College of Radiology

In 2017, the ACR issued Appropriateness Criteria for the pretreatment staging of CRC.[53,] In the evaluation of distant metastases, the criteria stated that "routine use of PET/CT is likely not indicated; however, it may provide guidance in cases of advanced, bilobar liver disease to exclude extrahepatic metastases prior to surgical intent to cure."

National Comprehensive Cancer Network

Current NCCN guidelines for colon cancer (v.1.2022) "strongly discourages the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up" for metastatic disease 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."[54,] For initial workup of nonmetastatic individuals, the guidelines state that PET/CT is not routinely indicated, and "PET/CT does not supplant a contrast-enhanced diagnostic CT or MR scan and should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or MR scan or in individuals with strong contraindications to IV [intravenous] contrast." PET/CT can be considered in select individuals "considered for image-guided liver-directed therapies," "for assessment of response and liver recurrence after image-guided liver-directed therapies, or serial carcinoembryonic antigen elevation during follow-up." Otherwise, use of PET/CT is not recommended for surveillance. The NCCN has noted that PET/CT should not be used to assess response to chemotherapy. The NCCN was divided on the appropriateness of PET/CT when carcinoembryonic antigen level is rising; PET/CT might be considered when imaging study results (e.g., a good quality CT scan) are normal.

Current NCCN guidelines for rectal cancer (v.1.2022) state that PET/CT is "not routinely indicated" and "should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MR scan or in patients with strong contraindications to IV contrast."[55,] For certain individuals

with potential surgically-curable M1 disease or who are being considered for image-guided liver-directed therapies, a PET/CT may be considered. Use of PET/CT is not recommended for restaging or for surveillance with the exception of surveillance in individuals who are considered for image-guided liver-directed therapies for hepatic metastases. Use of PET/CT can be considered if serial carcinoembryonic antigen elevation occurs during follow-up.

Section Summary: Colorectal Cancer
Evidence for the detection of primary nodal disease, staging, restaging, and detecting recurrence of CRC consists of several meta-analyses and a RCT. A meta-analysis evaluating the diagnostic accuracy of PET or PET/CT found a high sensitivity but low specificity. Several pooled analyses evaluating staging or restaging using PET or PET/CT resulted in sensitivities and specificities ranging from 16% to 99%. The evidence for the use of PET or PET/CT did not show a benefit over the use of contrast CT in individuals with CRC. The RCT found no differences in outcomes when FDG-PET/CT was added to usual surveillance compared to usual surveillance only. The evidence does not support the use of FDG-PET and PET/CT for the diagnosis, staging and restaging, or surveillance of CRC.

ENDOMETRIAL CANCER

Systematic Review
Bollineni et al (2016) published a systematic review and meta-analysis on the diagnostic value of FDG-PET for endometrial cancer.[56,] The literature search, conducted through August 2015, identified 21 studies for inclusion in the meta-analysis: 13 on detection of lymph node metastases (n=861) and 8 on detection of endometrial cancer recurrence (n=378). Pooled sensitivity and specificity for FDG-PET for detecting lymph node metastases were 72% (95% CI, 63% to 80%) and 94% (95% CI, 93% to 96%), respectively. Pooled sensitivity and specificity for FDG-PET for detecting endometrial cancer recurrence following primary surgical treatment were 95% (95% CI, 91% to 98%) and 91% (95% CI, 86% to 94%), respectively.

Guidelines

American College of Radiology
In 2020, the ACR issued Appropriateness Criteria for the pretreatment evaluation and follow-up of endometrial cancer.[57,] Skull base to mid-thigh PET/CT may be appropriate for pretreatment evaluation for lymph node and distant metastases, is usually appropriate for initial staging for high-grade tumors, and is usually appropriate for evaluation of clinically suspected recurrence of endometrial cancer.

National Comprehensive Cancer Network
Current NCCN guidelines for endometrial cancer (v.1.2022) state that neck/chest/abdomen/pelvis/groin PET/CT can be considered in the initial workup, in both non-fertility- and fertility-sparing management, if metastases are suspected in select individuals (based on clinical symptoms, physical findings, or abnormal laboratory findings).[58,]Whole-body PET/CT may also be considered for individuals with suspected recurrence or metastases as clinically indicated. Following treatment, PET/CT can be considered in select individuals for surveillance, if findings on MRI or CT imaging require clarification or if metastasis is suspected.

Section Summary: Endometrial Cancer
The evidence includes a systematic review and meta-analysis. Pooled estimates from the meta-analysis showed high sensitivities and specificities for FDG-PET/CT in detecting lymph node metastases and endometrial cancer recurrence following treatment. The evidence supports the use of FDG-PET and PET/CT for the diagnosis, staging and restaging, or surveillance of endometrial cancer.

Esophageal Cancer
For initial diagnosis, PET is generally not considered for detecting primary esophageal tumors, and evidence is lacking in its ability to differentiate between esophageal cancer and benign conditions.

Systematic Reviews
Kroese et al (2018) conducted a systematic review of the use of FDG-PET and FDG-PET/CT for detecting interval metastases following neoadjuvant therapy in individuals with esophageal cancer.[59,] The literature search identified 14 studies for inclusion. The QUADAS tool was used to assess quality, with most studies rated moderate. The pooled proportion of individuals with true distant metastases as detected by FDG-PET and FDG-PET/CT was 8% (95% CI, 5% to 13%). The pooled proportion of individuals with false-positive distant findings was 5% (95% CI, 3% to 9%).

Cong et al (2016) published a meta-analysis evaluating the predictive value of FDG-PET and FDG-PET/CT for tumor response during or after neoadjuvant chemoradiotherapy in individuals with esophageal cancer.[60,] The literature search, conducted through January 2016, identified 4 studies (n=192 individuals) in which PET or PET/CT was performed during neoadjuvant chemoradiotherapy and 11 studies (n=490) in which PET or PET/CT was performed after neoadjuvant chemoradiotherapy. All studies scored between 9 and 12 using the QUADAS tool. Pooled sensitivity and specificity for PET and PET/CT performed during neoadjuvant chemoradiotherapy were 85% (95% CI, 76% to 91%) and 59% (95% CI, 48% to 69%), respectively. Pooled sensitivity and specificity for PET and PET/CT performed after neoadjuvant chemoradiotherapy were 67% (95% CI, 60% to 73%) and 69% (95% CI, 63% to 74%), respectively.

Goense et al (2015) published a systematic review evaluating FDG-PET and FDG-PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent.[61,] The literature search, conducted through December 2014, identified 8 studies (N=486) for inclusion. The quality of the studies was considered reasonable using the QUADAS tool, with a low-risk of bias for most studies, and high-risk of bias in a few studies for patient selection. Pooled estimates of sensitivity and specificity of FDG-PET and FDG-PET/CT combined were 96% (95% CI, 93% to 97%) and 78% (95% CI, 66% to 86%), respectively. Subgroup analysis by technique (PET alone and PET/CT) was not possible for sensitivity due to heterogeneity. Specificity subgroup analysis showed no statistical difference between PET alone and PET/CT in detecting recurrent esophageal cancer.

In a meta-analysis of 245 individuals with esophageal cancer from 6 studies, Shi et al (2013) reported that, for detection of regional nodal metastases, FDG-PET/CT had a sensitivity of 55% (95% CI, 34% to 74%) and specificity of 76% (95% CI, 66% to 83%), respectively.[62,]

An NCCN report conducted by Podoloff et al (2009) found studies showing that PET is more sensitive than other diagnostic imaging in detecting stage IV disease with distant lymph node involvement.[37,] A meta-analysis described in the report found a 67% pooled sensitivity, 97% specificity, and small added value after conventional staging in detecting distant metastasis. Another use of PET in esophageal cancer is in determining whether to continue chemotherapy for potentially curative resection. The NCCN report by Podoloff et al (2009) described several studies in which response to chemotherapy, defined as a decline in standardized uptake values, correlated with long-term survival.[37,]Individuals who do not respond to chemotherapy might 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 RCTs showing improved net health outcome.

GUIDELINES

American College of Radiology

In 2022, the ACR issued Appropriateness Criteria for staging and follow-up of esophageal cancer.[63,] Skull base to mid-thigh PET/CT is considered usually appropriate for pretreatment clinical staging, imaging during treatment, and for post-treatment imaging in individuals with or without suspected or known recurrence.

National Comprehensive Cancer Network

Current NCCN guidelines for esophageal cancer (v.3.2022) indicate that PET/CT can be considered under the following conditions:[64,]

- Part of the initial workup if there is no evidence of M1 disease.
- To assess response to preoperative or definitive chemoradiation.
- For staging purposes, prior to surgery to obtain nodal distribution information

The guidelines note that PET/CT for these indications is preferable to PET alone.

Section Summary: Esophageal Cancer

Evidence for PET or PET/CT to detect metastases, predict tumor response to treatment, or to detect recurrence in individuals with esophageal cancer consists of meta-analyses. The meta-analyses have shown high sensitivity and specificity estimates for these indications. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of esophageal cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of esophageal cancer.

GASTRIC CANCER

Systematic Reviews

A systematic review by Li et al (2016) evaluated FDG-PET and FDG-PET/CT for detecting recurrent gastric cancer.[65,] The literature search, conducted through February 2015, identified 14 studies (N=828) for analysis. The analysis combined both imaging techniques; 3 studies used PET alone and 11 studies used PET/CT. Pooled sensitivity and specificity were 85% (95% CI, 75% to 92%) and 78% (95% CI, 72% to 84%), respectively.

In a meta-analysis, Zou and Zhou (2013) evaluated studies published through May 2013 and calculated the sensitivity and specificity of FDG-PET/CT for detecting recurrence of gastric cancer after surgical resection.[66,] Eight studies (N=500) were eligible for the meta-analysis. The studies fulfilled 12 of the 14 QUADAS criteria for methodologic quality. Pooled sensitivity was 86% (95% CI, 71% to 94%) and pooled specificity was 88% (95% CI, 75% to 94%).

A systematic review by Wu et al (2012) pooled 9 studies (N=562 patient) published through July 2011 that used FDG-PET alone for evaluating recurrent gastric cancer.[67,] Each selected study fulfilled at least 9 of the 14 criteria in the QUADAS tool for methodologic quality. Pooled sensitivity and specificity were 78% (95% CI, 68% to 86%) and 82% (95% CI, 76% to 87%), respectively. Reviewers concluded that PET/CT might be more effective than either PET alone or CT alone, but it was unclear what sources reviewers used for their estimates for PET/CT and CT alone.

Guidelines

Current NCCN guidelines for gastric cancer (v.2.2022) indicate that FDG-PET/CT (but not PET alone) can be used as part of an initial workup if there is no evidence of metastatic disease and if use is clinically indicated.[68,] The guidelines note that the accuracy of FDG-PET/CT is lower than for CT alone due to low tracer accumulation in diffuse and mucinous tumor types but specificity for detecting local lymph node involvement is higher. Use of FDG-PET/CT adds value to the diagnostic workup with higher accuracy in staging (identifying tumor and pertinent nodal groups). The NCCN guidelines also indicate that FDG-PET/CT can be used to evaluate response to treatment, in cases of renal insufficiency or allergy to CT contrast. For surveillance in individuals with stage II or III disease, FDG-PET/CT can be considered as clinically indicated, but CT scan with oral and intravenous contrast is preferred.

Section Summary: Gastric Cancer

Evidence for the use of PET to diagnose recurrent gastric cancer consists of meta-analyses. One meta-analysis evaluated FDG-PET alone, 1 evaluated FDG-PET/CT, and another combined the 2 techniques into a single estimate. Sensitivity estimates ranged from 78% to 85% and specificity estimates ranged from 78% to 88%. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of gastric cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of gastric cancer.

HEAD AND NECK CANCER

Systematic Reviews

A meta-analysis by Chen et al (2016) compared MRI, CT, and FDG-PET/CT in the detection of local and metastatic nasopharyngeal carcinomas.[69,] A literature search, conducted through April 2015, identified 23 studies (N=2413) for inclusion. Table 4 summarizes the results of the meta-analysis.

Table 4. Pooled Diagnostic Performance of FDG-PET/CT, MRI, and CT Alone in the Detection of Nasopharyngeal Carcinomas

Type of Imaging	No. of Studies (N)	Sensitivity (95% CI), %	Specificity (95% CI), %
T staging			
MRI	8 (984)	95 (93 to 97)	76 (71 to 80)
CT alone	4 (404)	84 (79 to 88)	80 (71 to 88)
N staging			
MRI	10 (750)	82 (79 to 84)	71 (65 to 78)
CT alone	4 (340)	92 (85 to 95)	93 (76 to 99)
FDG-PET/CT	10 (629)	88 (85 to 90)	95 (93 to 97)
M staging			
MRI	2 (261)	53 (35 to 70)	99 (96 to 100)
CT alone	2 (98)	80 (44 to 97)	93 (86 to 97)
FDG-PET/CT	7 (1009)	82 (74 to 88)	98 (96 to 99)

Adapted from Chen et al (2016).[69,]
CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; MRI: magnetic resonance imaging; M staging: distant metastases; MRI: magnetic resonance imaging; N staging: regional lymph nodes; PET: positron emission tomography; T staging: primary tumor.

A meta-analysis by Wei et al (2016) compared diagnostic capabilities of FDG-PET/CT, MRI, and single-photon emission CT in individuals with residual or recurrent nasopharyngeal carcinoma.[70,] The literature search, conducted through December 2014, identified 17 studies for inclusion. All studies scored at least 9 of 14 in the QUADAS tool. Pooled sensitivity and specificity for F-FDG-PET/CT (n=12 studies) were 90% (95% CI, 85% to 94%) and 93% (95% CI, 90% to 95%), respectively. Pooled sensitivity and specificity for single-photon emission CT (n=8 studies) were 85% (95% CI, 77% to 92%) and 91% (95% CI, 85% to 95%), respectively. Pooled sensitivity and specificity for MRI (n=9 studies) were 77% (95% CI, 70% to 83%) and 76% (95% CI, 73% to 79%), respectively.

Two meta-analyses evaluated FDG-PET or FDG-PET/CT in the detection of residual or recurrent head and neck cancer at various times following treatment.[71,72,] Results from these analyses are summarized in Table 5.

Table 5. Pooled Diagnostic Performance of FDG-PET or FDG-PET/CT in the Detection of Head and Neck Cancer

Indication	No. of Studies(N)	Sensitivity (95% CI), %	Specificity (95% CI), %
Cheung et al (2016)[71,]			
Residual/recurrent at primary site	18 (805)	86 (80 to 91)	82 (79 to 85)

Indication	No. of Studies(N)	Sensitivity (95% CI), %	Specificity (95% CI), %
Residual/recurrent at neck nodes	15 (726)	72 (63 to 80)	88 (85 to 91)
Recurrent at distant metastases	3 (184)	85 (65 to 96)	95 (90 to 98)
Local residual/recurrent, <12 wk since therapy	NR	85 (75 to 92)	80 (76 to 83)
Local residual/recurrent, ≥12 wk since therapy	NR	87 (78 to 94)	88 (83 to 93)
Nodal residual/recurrent, <12 wk since therapy	NR	67 (56 to 78)	86 (83 to 89)
Nodal residual/recurrent, ≥12 wk since therapy	NR	83 (61 to 95)	96 (90 to 99)
Sheikhbahaei et al (2015)[72,]			
Local recurrence, ≥4 mo since therapy	10 (992)	91 (86 to 95)	89 (83 to 94)
Regional recurrence, ≥4 mo since therapy	8 (885)	88 (80 to 93)	95 (92 to 97)
Distant metastases/second primary, ≥4 mo since therapy	9 (958)	93 (86 to 96)	97 (95 to 98)
Overall diagnostic performance, 4-12 mo since therapy	11 (1003)	95 (91 to 97)	78 (70 to 84)
Overall diagnostic performance, ≥12 mo since therapy	7 (923)	92 (85 to 96)	91 (78 to 96)

CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; NR: not reported; PET: positron emission tomography.

A systematic review by Sheikhbahaei et al (2015) calculated the predictive value of intratherapy or posttherapy FDG-PET or FDG-PET/CT for overall survival (OS) and event-free survival.[73,] The literature search, conducted through November 2014, identified 9 studies (n=600) for inclusion in OS calculations and 8 studies (n=479) for inclusion in event-free survival calculations. Individuals with a positive scan had significantly worse OS than individuals with negative scans (hazard ratio [HR], 3.5; 95% CI, 2.3 to 5.4). The pooled HR for event-free survival was 4.7 (95% CI, 2.6 to 8.6). Relative risks at 2 years and at 3 to 5 years for death and recurrence or progression were calculated, based on the timing of FDG-PET or FDG-PET/CT (see Table 6).

Table 6. Pooled Diagnostic Performance of FDG-PET or FDG-PET/CT in the Detection of Head and Neck Cancer

Outcome	No. of Studies	2 Year RR (95% CI)	No. of Studies	3 to 5 Year RR (95% CI)
Death				
Final FDG-PET or FDG-PET/CT	6	8.3 (3.8 to 18.0)	6	2.2 (1.6 to 3.2)
FDG-PET or FDG-PET/CT, <12 wk posttreatment	8	3.0 (1.9 to 4.6)	4	2.0 (1.3 to 3.2)

Outcome	No. of Studies	2 Year RR (95% CI)	No. of Studies	3 to 5 Year RR (95% CI)
FDG-PET or FDG-PET/CT, ≥12 wk posttreatment	3	8.5 (4.0 to 18.3)	6	2.8 (1.9 to 4.0)
Recurrence or progression				
Final FDG-PET or FDG-PET/CT	6	5.2 (3.3 to 8.3)	5	2.6 (1.7 to 4.1)
FDG-PET or FDG-PET/CT, <12 wk posttreatment	9	3.2 (2.0 to 5.2)	6	4.3 (2.1 to 8.7)
FDG-PET or FDG-PET/CT, ≥12 wk posttreatment	2	3.2 (2.0 to 5.2)	2	2.2 (1.5 to 3.1)

Adapted from Sheikhbahaei et al (2015).[73,]
CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; PET: positron emission tomography; RR: relative risk.

Four meta-analyses in 2013, 2014, and 2018 reported good sensitivities and specificities with FDG-PET/CT for diagnosing head and neck squamous cell cancers (better than CT and MRI), detecting head and neck cancer metastases (better than bone scintigraphy), and detecting recurrence.[74,75,76,77,]

Additional meta-analyses by Li et al (2017) and Lin et al (2017) have reported that higher values of standard uptake value, metabolic tumor volume, and total lesion glycolysis from FDG-PET/CT might predict a poorer prognosis for individuals with nasopharyngeal cancer.[78,79,]

Among the 3 studies identified in the TEC Assessment (2000) that used other diagnostic modalities to identify a primary tumor in individuals with positive cervical lymph nodes, PET found more primary tumors than the other modalities in 2 studies and identified similar proportions in the third.[80,] When data from these 3 studies were pooled, PET was found to identify a tumor in 38% of cases and other modalities in 21% of cases.

When PET was used to stage cervical lymph nodes initially, the addition of PET to other imaging modalities increased the proportion of individuals correctly staged, as confirmed histologically. When compared directly with other imaging modalities, pooled data from several studies has suggested that PET has a better diagnostic performance than 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 with CT.

A 2022 systematic review and meta-analysis by Zhu et al assessed the diagnostic accuracy of PET/CT and MRI for surveillance of treated head and neck squamous cell cancer.[81,] The meta-analysis included 3 studies that included 176 individuals who underwent imaging 3 to 6 months post-treatment for assessment of potential recurrence or residual disease. For a positive imaging test, the reference standard was histological confirmation, and for a negative imaging test the reference standard was histological confirmation or clinical follow up for at least 6 months. Sensitivity of PET/CT was 68% (95% CI, 49% to 84%) and specificity was 89% (95% CI, 84% to 93%); corresponding values for MRI were 72% (95% CI, 54% to 88%) and 85% (95% CI, 79%

to 89%). The review concluded that evidence was insufficient to recommend either imaging modality over the other for surveillance of recurrent or residual head and neck cancer.

Guidelines
Current NCCN guidelines on head and neck cancer (v.2.2022) indicate that PET/CT can be appropriate for disease evaluation, for detection of metastases or recurrence, and for evaluation of response to treatment (at a minimum of 12 weeks posttreatment to reduce false-positive rate).[82,] For surveillance of locoregionally advanced disease, an initial 3-month PET/CT scan may be useful, but if the scan is negative, then further routine imaging is not supported in an asymptomatic patient.

Section Summary: Head and Neck Cancer
Evidence for the use of FDG-PET/CT in the management of individuals with head and neck cancer consists of systematic reviews and meta-analyses. In individuals with head and neck cancers, PET or PET/CT is better able to detect local and metastatic disease than other imaging techniques. Evidence has also shown that FDG-PET/CT may be useful in predicting response to therapy. Two meta-analyses calculated the ability of FDG-PET or PET/CT to detect the residual or recurrent disease during various stages of treatment and another meta-analysis calculated the ability of positive PET or PET/CT results to predict overall survival and event-free survival. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of head and neck cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of head and neck cancer.

Lung Cancer
Use of PET scanning may have a clinical role in individuals with solitary pulmonary nodules for whom a diagnosis is uncertain after CT scan or chest radiograph. Younger individuals who have no smoking history have a relatively low-risk for lung cancer and, in this setting, the NPV 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 individuals would choose to avoid the harms of an invasive sampling procedure (i.e., biopsy). A meta-analysis by Barger et al (2012) 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.[83,]

Non-Small-Cell Lung Cancer
In individuals with known non-small-cell lung cancer (NSCLC), the clinical value of PET scanning relates to improved staging information regarding the involvement of mediastinal lymph nodes, which generally excludes individuals from surgical excision. A TEC Assessment (1997) discussed a decision analysis that suggested the use of CT plus PET scanning in staging mediastinal lymph nodes resulted in fewer surgeries and an average gain in life expectancy of 2.96 days.[84,] This suggests that the reduction in surgeries was not harmful to individuals.

Systematic Reviews
Brea et al (2018) conducted a systematic review comparing MRI, CT, FDG-PET, and FDG-PET/CT in differentiating metastatic and nonmetastatic lymph nodes.[85,] A meta-analysis was not conducted. Reviewers reported that most studies showed MRI had higher sensitivities,

specificities, and diagnostic accuracy than CT and PET in determining the malignancy of lymph nodes in individuals with NSCLC.

A systematic review by Ruilong et al (2017) evaluated the diagnostic value of FDG-PET/CT for detecting solitary pulmonary nodules.[86,] The literature search, conducted to May 2015, identified 12 studies (N=1297 individuals) for inclusion in the analysis. The pooled sensitivity and specificity of FDG-PET/CT to detect malignant pulmonary nodules are presented in Table 7.

He et al (2014) compared PET, PET/CT, and conventional imaging techniques for detecting recurrent lung cancer.[87,] Table 7 summarizes the diagnostic performances of the different imaging techniques.

Other meta-analyses have reported good sensitivities and specificities in the detection of lung cancer metastases (Table 7). Seol et al (2021) investigated the diagnostic performance of FDG-PET or PET/CT for detection of occult lymph node metastases in individuals with NSCLC.[88,] The literature search, conducted through March 2020, identified 14 studies (N=3535). The pooled sensitivity and specificity analyses had a high level of heterogeneity (I^2: 81.5 and 93.7, respectively). Li et al (2017) conducted a meta-analysis of studies that compared FDG-PET/CT with gadolinium-enhanced MRI in the detection of brain metastases in individuals with NSCLC.[89,] The literature search identified 5 studies (N=941) for inclusion. Study quality was assessed using criteria recommended by the Cochrane Methods Working Group, with scores ranging from 9 to 11 on the 12-point scale. A meta-analysis by Li et al (2013) calculated the sensitivity and specificity of PET/CT in the detection of distant metastases in individuals with lung cancer and with NSCLC (see Table 7).[90,]

Table 7. Pooled Diagnostic Performance of Various Imaging Techniques in Individuals With Lung Cancer

Type of Imaging	Detection Measured	Sensitivity (95% CI), %	Specificity (95% CI), %	DOR (95% CI)
Ruilong et al (2017)[86,]	Solitary pulmonary nodules			
FDG-PET/CT		82 (76 to 87)	81 (66 to 90)	18 (8 to 38)
Li et al (2017)[89,]	Brain metastases			
FDG-PET/CT		21 (13 to 32)	100 (99 to 100)	235 (31 to 1799)
Gadolinium MRI		77 (60 to 89)	99 (97 to 100)	657 (112 to 3841)
He et al (2014)[87,]	Recurrent NSCLC			
FDG-PET		94 (91 to 97)	84 (73 to 89)	65 (19 to 219)
FDG-PET/CT		90 (84 to 95)	90 (87 to 93)	79 (19 to 335)
CIT		78 (71 to 84)	80 (75 to 84)	13 (4 to 40)
Li et al (2013)[90,]	Distant metastases			

Type of Imaging	Detection Measured	Sensitivity (95% CI), %	Specificity (95% CI), %	DOR (95% CI)
FDG-PET/CT		87 (55 to 98)	96 (93 to 98)	196 (22 to 1741)
Seol et al (2021)[88,]	Occult lymph node metastases			
FDG-PET or FDG-PET/CT		79 (70 to 86)	65 (57 to 72)	7 (5 to 10)

CI: confidence interval; CIT: conventional imaging technique; CT: computed tomography; DOR: diagnostic odds ratio; FDG: fluorine 18 fluorodeoxyglucose; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; PET: positron emission tomography.

GUIDELINES

American College of Chest Physicians

In 2013 the American College of Chest Physicians issued guidelines for the diagnosis and management of NSCLC.[91,] The guidelines stated that RCTs support the use of PET or PET/CT scanning as a component of lung cancer treatment and recommended PET or PET/CT for staging, detection of metastases, and avoidance of noncurative surgical resections.

American College of Radiology

In 2019, the ACR issued Appropriateness Criteria for noninvasive clinical staging of primary lung cancer.[92,] Skull base to mid-thigh PET/CT is recommended in initial clinical staging to evaluate for extrathoracic metastases in individuals with NSCLC.

National Comprehensive Cancer Network

Current NCCN guidelines for NSCLC (v.3.2022) indicate that PET/CT can be used in the staging of the disease, detection of metastases, treatment planning, restaging after adjuvant treatment, and detection of disease recurrence.[93,] The guidelines note that PET is "best performed before a diagnostic biopsy site is chosen in cases of high clinical suspicion for aggressive, advanced-stage tumors." However, PET is not recommended for detection of brain metastasis from lung cancers. While PET/CT is not routinely recommended for surveillance after completion of definitive therapy, it may be considered to differentiate between true malignancies and benign conditions (e.g., atelectasis, consolidation, and radiation fibrosis), which may have been detected by CT imaging. If PET/CT detects recurrent disease, biopsy confirmation is necessary prior to initiating additional treatment because FDG remains avid in areas treated with radiation therapy up to 2 years.

Section Summary: Non-Small Cell Lung Cancer

Evidence for PET or PET/CT in individuals with NSCLC consists of meta-analyses. The meta-analyses have shown that use of PET or PET/CT in individuals with lung cancer can aid in the diagnosis, staging, as well as detecting metastases and recurrence. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of NSCLC.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of NSCLC.

Small-Cell Lung Cancer

Approximately 15% of all lung cancers are small-cell lung cancer (SCLC). individuals with SCLC are typically defined as having either limited stage or extensive-stage disease. Most individuals diagnosed with SCLC have an extensive-stage disease, which is characterized by distant metastases, malignant pericardial or pleural effusions, and/or contralateral hilar lymph node involvement. Limited stage SCLC includes the ipsilateral hemithorax and regional or mediastinal lymph nodes and can be encompassed in a safe radiotherapy field.

Systematic Reviews

A systematic review by Lu et al (2014) included 12 studies (N=369) of FDG-PET/CT for staging SCLC.[94,] Although estimated pooled sensitivity and pooled specificity were 98% (95% CI, 94% to 99%) and 98% (95% CI, 95% to 100%), respectively, included studies were small (median sample size=22); of primarily fair to moderate quality; and heterogeneous in design (e.g., retrospective, prospective), PET parameter assessed, indication for PET, and reference standard used. It is not possible from the limited, poor-quality evidence in this systematic review to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

A systematic review by Ruben and Ball (2012) on staging SCLC found PET to be more effective than conventional staging methods; however, a limitation of this review is that the reviewers did not conduct a quality assessment of individual studies.[95,]

GUIDELINES

American College of Radiology

In 2019, the ACR issued Appropriateness Criteria for noninvasive clinical staging of primary lung cancer.[92,] Use of PET or PET/CT is recommended for initial clinical staging in individuals with clinical stage I or II limited stage SCLC being considered for curative treatment.

National Comprehensive Cancer Network

Current NCCN guidelines for SCLC (v.2.2022) indicate PET/CT can be used in the staging of the disease if limited stage is suspected or if needed to clarify stage. If extensive-stage is established, brain imaging, MRI (preferred), or CT with contrast is recommended. Use of PET/CT "is not recommended for routine follow-up."[96,]

Section Summary: Small Cell Lung Cancer

Evidence for PET or PET/CT for individuals with SCLC consists of systematic reviews and meta-analyses. These reviews have shown potential benefits in using PET for staging, though the quality of the studies was low. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging of SCLC. Guidelines support the use of PET/CT if a limited stage is suspected or to clarify staging. If extensive-stage is established, other imaging techniques (MRI or CT with contrast) are preferred.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of SCLC.

LYMPHOMA, INCLUDING HODGKIN DISEASE

Systematic Reviews
Of the 14 studies reviewed in a TEC Assessment (1999), 3 compared PET with anatomic imaging in initial staging and restaging of individuals with Hodgkin disease and non-Hodgkin lymphoma.[97,] Two of these studies included data from both diseased and nondiseased sites for PET and CT. Both studies found PET had better overall diagnostic accuracy than CT. The third study addressed the detection of diseased sites only and found PET to have a sensitivity similar to that 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% of cases; PET was correct among discordances in 40% to 75% of cases. Use of PET has been reported to affect patient management decisions in 8% to 20% of individuals 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 selecting effective and appropriate treatment for the correct stage of the disease.

Lymphoma Diagnosis
Meta-analyses have reported good sensitivities and specificities with PET/CT in the detection of newly diagnosed Hodgkin lymphoma (2014), diffuse large B-cell lymphoma (2014), and suspected primary central nervous system lymphoma.[98,99,100,]

Lymphoma Restaging
A systematic review and meta-analysis by Adams and Kwee (2016) evaluated the proportion of false-positive lesions at interim and end-of-treatment as detected by FDG-PET in individuals with lymphoma.[101,] The literature search, conducted through January 2016, identified 11 studies (N=139) for inclusion. Study quality was moderate, as assessed by the QUADAS-2 tool. The weighted summary proportion of false-positive results among all biopsied lesions both during and after completion of treatment was 56% (95% CI, 33% to 77%). Subgroup analyses found the FDG-PET false-positive proportions for: interim non-Hodgkin lymphoma (83%; 95% CI, 72% to 90%), end-of-treatment non-Hodgkin lymphoma (31%; 95% CI, 4% to 84%), and end-of-treatment Hodgkin lymphoma (23%; 95% CI, 5% to 65%). No studies calculating the false-positive rate for interim Hodgkin lymphoma were identified.

A systematic review by Adams et al (2015) focused on the outcomes of individuals with Hodgkin lymphoma who had negative residual mass after FDG-PET scanning.[102,] When a persistent mass is non-FDG-avid, the patient is considered to be in complete remission, though the significance of having a residual mass is unclear. The literature search, conducted through December 2014, identified 5 studies (N=727) for inclusion. Follow-up of individuals in the studies ranged from 1 to 13 years. The pooled relapse proportion was 6.8% (95% CI, 2.6% to 12.5%).

LYMPHOMA MANAGEMENT

Systematic Reviews
Another systematic review by Adams and Kwee (2017) evaluated the prognostic value of FDG-PET in individuals with refractory or relapsed Hodgkin lymphoma considering autologous cell transplantation.[103,] The literature search, conducted through May 2016, identified 11 studies (N=664) for inclusion. In general, the overall quality of selected studies was poor, based on Quality in Prognosis Studies (QUIPS). Pooled sensitivity and specificity of pretransplant ^{18}F-FDG-PET in predicting treatment failure were 54% (95% CI, 44% to 63%) and 73% (95% CI, 67% to

79%), respectively. Pooled sensitivity and specificity of pretransplant FDG-PET in predicting death after treatment was 55% (95% CI, 39% to 70%) and 69% (95% CI, 61% to 76%), respectively.

A meta-analysis by Adams and Kwee (2016) evaluated the prognostic value of FDG-PET in individuals with aggressive non-Hodgkin lymphoma considering autologous cell transplantation.[104,] The literature search, conducted through July 2015, identified 11 studies (N=745) for inclusion. The overall quality of the selected studies was moderate, based on QUIPS criteria. Individuals with positive pretransplant FDG-PET results had progression-free survival (PFS) rates ranging from 0% to 52%. Individuals with negative pretransplant FDG-PET results had PFS rates ranging from 55% to 85%. Overall survival was 17% to 77% in individuals with positive FDG-PET results and 78% to 100% in individuals with negative FDG-PET results. Based on 5 studies, pooled sensitivity and specificity of pretransplant FDG-PET for predicting treatment failure (defined as progressive, residual, or relapsed disease) were 67% (95% CI, 58% to 75%) and 71% (95% CI, 64% to 77%), respectively.

A systematic review by Zhu et al (2015) evaluated the prognostic value of FDG-PET in individuals with diffuse B-cell lymphoma treated with rituximab-based immune chemotherapy.[105,] The literature search identified 11 studies (N=1081) for inclusion. The pooled HR comparing PFS of individuals with positive interim FDG-PET results and negative interim FDG-PET results was 3.0 (95% CI, 2.3 to 3.9). Individuals with a negative interim FDG-PET result had a higher complete remission rate than individuals with a positive interim FDG-PET result (relative risk, 5.5; 95% CI, 2.6 to 11.8).

Randomized Controlled Trials

Borchmann et al (2017) reported on an open-label phase 3 RCT by the German Hodgkin Study Group, which randomized individuals newly diagnosed with advanced Hodgkin lymphoma to different levels of eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) based on PET results.[106,] After 2 cycles of eBEACOPP, PET-positive individuals were randomized to 6 more cycles of eBEACOPP (n=217) or eBEACOPP plus rituximab (n=217). Individuals that were PET-negative were randomized to 6 more cycles of eBEACOPP (n=504) or 4 more cycles of eBEACOPP (n=501). Five-year PFS rates for the PET-positive 6-cycle eBEACOPP and 6-cycle eBEACOPP plus rituximab arms were 90% (95% CI, 85% to 94%) and 88% (95% CI, 83% to 93%), respectively. Five-year PFS rates for the PET-negative 6-cycle and 4-cycle arms were 91% (95% CI, 88% to 94%) and 92% (95% CI, 89% to 95%), respectively. Results showed that PET-negative individuals can receive fewer cycles of treatment without a negative impact on PFS and that PET-positive individuals do not need an intensified treatment (addition of rituximab) to improve PFS.

Guidelines

Current NCCN guidelines for Hodgkin lymphoma (v.2.2022)[107,] and non-Hodgkin lymphomas, including chronic lymphocytic leukemia/small lymphocytic lymphoma [v.3.2022],[108,] B-cell lymphomas [v.5.2022],[109,] primary cutaneous lymphomas [v.2.2022],[110,] and T-cell lymphomas [v.2.2022])[111,] indicate that PET/CT (in some cases PET only) may be used in the diagnostic workup, staging, restaging, and evaluating treatment response. The guidelines recommend using the internationally recognized Deauville 5-point PET scale for initial staging and assessment of treatment response. The following PET/CT results are assigned the corresponding scores: 1=no uptake; 2=uptake ≤ mediastinum; 3=uptake > mediastinum but ≤ liver; 4=uptake moderately

higher than liver; and 5=uptake markedly higher than liver and/or new lesions. The Deauville PET scores can be used to determine the course of treatment. The guidelines note that if PET/CT detects 3 or more skeletal lesions, the marrow may be assumed to be involved and marrow biopsies are no longer indicated. The Hodgkin lymphoma guidelines also note "Surveillance PET should not be done routinely due to risks for false-positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed."[107,]

Section Summary: Lymphoma, Including Hodgkin Disease
Evidence for the use of FDG-PET/CT in the management of individuals with lymphoma consists of systematic reviews, meta-analyses, and an RCT. In individuals with lymphoma, PET can provide information for staging or restaging. Evidence has also shown that FDG-PET/CT can be useful in predicting response to therapy in individuals with lymphoma. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of Hodgkin lymphoma and non-Hodgkin lymphoma.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of Hodgkin lymphoma and non-Hodgkin lymphoma.

Melanoma
Surgical resection for melanoma is limited to those with local disease. Individuals with widespread disease are not candidates for resection. Frequently, there is a microscopic spread of cancer cells to the proximal lymph nodes. Therefore, individuals 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*. Use of PET scanning has been investigated both as a technique to detect the widespread disease as part of an initial staging procedure and to evaluate the status of local lymph nodes to determine the necessity of sentinel node biopsy.

To consider PET as a useful alternative to sentinel node biopsy, it must have high sensitivity and specificity when 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, a TEC Assessment (1999) concluded that PET is not as beneficial as sentinel node biopsy for assessing regional lymph nodes.[112,]

"The intent of using PET to detect extranodal metastases is to aid in selecting treatment appropriate to the patient's extent of disease…. It may be inferred from [the evidence] that PET was usually correct when discordant with other modalities. PET affects management in approximately 18% of patients."

Systematic Reviews
In a meta-analysis of 9 studies (N=623), Rodriquez Rivera et al (2014) reported pooled sensitivity and specificity of FDG-PET for detecting systemic metastases in individuals with stage III cutaneous melanoma of 89% (95% CI, 65% to 98%) and 89% (95% CI, 77% to 95%), respectively.[113,]

Guidelines

Current NCCN guidelines for cutaneous melanoma (v.3.2022) indicate that PET/CT can be used at baseline in stage IV disease to evaluate for distant metastases.[114,] For stage III disease, cross-sectional imaging, including PET/CT can be consider at baseline (category 2B) or to assess specific signs and symptoms. Use of PET/CT is not recommended for stage I or II diseases. Also, PET/CT is listed as an option for surveillance screening for recurrence every 3 to 12 months (category 2B) at the physician's discretion. Because most recurrences occur within the first 3 years, routine screening for asymptomatic recurrence is not recommended beyond 3 to 5 years. The guidelines note that the safety of PET/CT is of concern due to cumulative radiation exposure.

Section Summary: Melanoma

Evidence for the use of FDG-PET/CT in the management of individuals with melanoma consists of a TEC Assessment and a meta-analysis. In individuals with melanoma, PET can provide information for staging or restaging in individuals with more advanced disease (stage III or higher). The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of stage III or IV melanoma.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis or staging and restaging of stage I or II melanoma.

The evidence supports the use of FDG-PET and FDG-PET/CT for surveillance of melanoma.

MULTIPLE MYELOMA

Systematic Reviews

Lu et al (2012) included 14 studies (N=395) of FDG-PET or FDG-PET/CT and reported pooled estimates of sensitivity and specificity of 96% (95% CI, 80% to 100%) and 78% (95% CI, 40% to 95%), respectively, in the detection of extramedullary lesions in individuals with multiple myeloma.[115,]

Van Lammeren-Venema et al (2012) included 18 studies (N=798) in a systematic review that compared FDG-PET with whole-body x-ray in staging and response assessment of individuals with multiple myeloma.[116,] Using the QUADAS tool to assess quality, the studies received a mean percentage of the maximum score of 61%. Reviewers reported that, in general, FDG-PET is more sensitive than whole body x-ray in detecting myeloma bone lesions.

Han et al (2021) conducted a meta-analysis to evaluate the prognostic value of FDG-PET/CT in newly diagnosed multiple myeloma individuals.[117,] Eleven articles (N=1542) were included in the quantitative analysis. The prognostic performance of 3 PET findings were evaluated, extramedullary disease, >3 focal bone lesions, and high FDG uptake as measured by the maximum standardized uptake value (SUVmax) in the study. All 3 PET findings were significant predictors for a shorter PFS and OS. For detection of extramedullary disease, the pooled HR for PFS and OS were 2.12 (95% CI, 1.52 to 2.96) and 2.37 (95% CI, 1.77 to 3.16), respectively, with significant heterogeneity observed with PFS and publication bias with OS. For >3 focal lesions, the pooled HR for PFS and OS were 2.38 (95% CI, 1.84 to 3.07) and 3.29 (95% CI, 2.38 to 4.56), respectively. For high FDG uptake, the pooled HR for PFS and OS were 2.02 (95% CI, 1.51 to 2.68) and 2.28 (95% CI, 1.67 to 3.13), respectively.

A systematic review and meta-analysis conducted Rama et al (2022) compared the diagnostic accuracy of FDG-PET/CT and whole-body MRI for evaluation of multiple myeloma treatment response.[118,] The review included 12 studies (N=373), 6 of which provided direct comparison of FDG-PET/CT and whole-body MRI. The remaining 6 studies assessed only whole-body MRI (4 studies) or FDG-PET/CT (2 studies). Risk of bias was assessed using the QUADAS-2 tool, and was generally low across the studies. A funnel plot analysis did not reveal evidence of publication bias for either FDG-PET/CT (p=.31) or whole-body MRI (p=.43). Based on pooled analysis, the sensitivity of FDG-PET/CT was 64% (95% CI, 45% to 79%; I^2=48%) and specificity was 82% (95% CI, 75% to 88%; I^2=0%). MRI was more sensitive (87%; 95% CI, 75% to 93%) and less specific (57%; 95% CI, 37% to 76%; p=.01 vs. FDG-PET/CT specificity). Sensitivity and specificity of FDG-PET/CT (66% and 81%) and whole-body MRI (90% and 56%) were similar when limited to the 6 studies directly comparing the 2 imaging modalities, as were corresponding AUC values (0.83 and 0.84). The clinical significance of these findings is unclear, and NCCN guidelines do not recommend either FDG-PET/CT or whole-body MRI for routine assessment of treatment response in multiple myeloma.

Comparative Studies

Mesguich et al (2020) prospectively compared FDG-PET/CT to whole body MRI, as a reference standard, for the initial staging of multiple myeloma.[119,] The number of focal bone lesions detected and the diagnostic performance of FDG-PET/CT to diagnose diffuse bone marrow infiltration were assessed. Thirty individuals were included in the study. The mean number of focal bone lesions detected in the body was 16.7 and 23.9 for FDG-PET/CT and whole body MRI, respectively. The number of focal bone lesions detected was higher with MRI in the skull and spine; no significant differences were noted in number of bone lesions detected in the pelvis, sternum-ribs, upper limbs, and lower limbs. Both imaging modalities were interpreted as positive in 28 out of 30 individuals (100% agreement). For the diagnosis of diffuse bone marrow infiltration with FDG-PET/CT, the sensitivity, specificity and accuracy were 0.75, 0.79, and 0.77, respectively. Overall, whole body MRI detected more focal bone lesions, but there was no difference in the detection of bone disease on a per-patient basis.

Guidelines

Current NCCN guidelines for multiple myeloma (v.5.2022) recommend PET/CT as an imaging technique option for initial workup.[120,] The NCCN recommends using PET/CT for follow-up and surveillance as needed, ideally if utilized for initial workup. Use of PET/CT is considered first choice during initial work up of solitary extraosseous plasmacytoma. Use of PET/CT may also be considered to detect disease progression.

Section Summary: Multiple Myeloma

Evidence for the use of PET or PET/CT in the management of individuals with multiple myeloma consists of systematic reviews and a prospective, comparative study. The sensitivity of FDG-PET was greater than whole body x-ray in a meta-analysis and was similar to whole-body MRI, with MRI having a higher sensitivity for detecting skull and spine bone lesions, in a prospective evaluation. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging.

The evidence does not support the use of FDG-PET and FDG-PET/CT for routine surveillance of multiple myeloma.

NEUROENDOCRINE TUMORS

SYSTEMATIC REVIEWS

^{68}Ga-PET and ^{68}Ga-PET/CT

Barrio et al (2017) conducted a systematic review and meta-analysis on the impact of gallium 68 (^{68}Ga) PET/CT on management decisions in individuals with neuroendocrine tumors.[121,] Reviewers selected 14 studies (N=1561). Change in management occurred in 44% of the individuals following ^{68}Ga-PET/CT. Clinical outcomes were not reported.

Deppen et al (2016) conducted a systematic review assessing the use of ^{68}Ga-PET/CT for the diagnosis and staging of gastroenteropancreatic neuroendocrine tumors.[122,] Seventeen studies (N=971) were included in the analysis. Comparators differed among the studies: octreotide and conventional imaging (3 studies), other radiopharmaceuticals without direct imaging comparators (5 studies), and conventional imaging (9 studies). Meta-analysis of the 9 studies that compared ^{68}Ga-PET/CT scanning with conventional imaging resulted in a sensitivity of 91% (95% CI, 81% to 96%) and a specificity of 91% (95% CI, 78% to 96%).

Two meta-analyses from Treglia et al (2012) addressed the use of PET in individuals with neuroendocrine tumors.[123,124,] One report included individuals with thoracic and gastroenteropancreatic neuroendocrine tumors who had imaging with PET using ^{68}Ga-PET and ^{68}Ga-PET/CT.[123,] Sixteen studies (N=567) were included in the analysis. The studies were considered medium to high quality, based on an assessment using the QUADAS tool. Meta-analysis showed a sensitivity and specificity of 93% (95% CI, 91% to 95%) and 91% (95% CI, 82% to 97%), respectively, with histology and/or clinical or imaging follow-up as the reference standard in diagnostic accuracy.

^{18}F-DOPA PET and ^{18}F-DOPA PET/CT

The other meta-analysis included studies of individuals with paragangliomas scanned by PET with fluorine 18-dihydroxyphenylalanine (^{18}F-DOPA) PET and ^{18}F-DOPA PET/CT.[124,] Eleven studies (N=275) were analyzed. The QUADAS tool was used to assess quality: 2 studies had a B rating, 4 a C rating, and 5 a D rating. Reference standards varied across studies, with 2 using MRI, 3 using histology on all individuals, and the remaining using histology only when feasible. Meta-analysis showed a sensitivity and specificity of 91% (95% CI, 87% to 94%) and 79% (95% CI, 76% to 81%), respectively.

PROSPECTIVE STUDIES

^{64}Cu-PET and ^{64}Cu-PET/CT

Delpassand et al (2020) conducted a phase 3, reader-masked, controlled trial to evaluate the sensitivity and specificity of copper 64 (^{64}Cu) PET/CT for detecting neuroendocrine tumors.[125,]Individuals with known or suspected disease, along with healthy volunteers, were recruited and results of imaging with ^{64}Cu PET/CT was compared against a standard of truth, based on an alternative, established imaging modality. Three readers evaluated the sensitivity

and specificity of ^{64}Cu PET/CT compared with a standard truth in 63 evaluable individuals with known or suspected neuroendocrine tumors. The overall sensitivity and specificity based on the standard of truth was 100% and 96.8%, respectively. This translated to a PPV of 96.7%, a NPV of 100%, and an accuracy of 98.4%.

Johnbeck et al (2017) conducted a head-to-head trial comparing the diagnostic performance of ^{64}Cu PET/CT to ^{68}Ga-PET/CT in individuals with neuroendocrine tumors. Individuals (N=59) were prospectively enrolled and underwent both ^{64}Cu PET/CT and ^{68}Ga-PET/CT within 1 week.[126,] Clinical follow-up was over 2 years, which allowed verification of discordant lesions (only found by 1 tracer) as either true- or false-positive findings. Overall, 701 PET-positive lesions were found by both tracers (concordant lesions), whereas an additional 68 discordant lesions were found. Forty-two of the discordant lesions were found by ^{64}Cu PET/CT, of which 33 were eventually confirmed to be true-positives. In contrast, ^{68}Ga-PET/CT found 26 discordant lesions, of which 7 were confirmed as true-positives. The probability that a true-positive discordant lesion was detected by ^{64}Cu PET/CT was 83% (95% CI, 67% to 93%; p<.001 compared to ^{68}Ga-PET/CT).

GUIDELINES

National Comprehensive Cancer Network

Current NCCN guidelines for neuroendocrine tumors (v.1.2022) have recommended somatostatin receptor-based imaging with PET/CT or PET/MRI, using somatostatin receptor PET tracers,^{68}Ga-dotatate, ^{68}Ga-dotatoc, or ^{64}Cu-dotatate,to assess receptor status and presence of distant disease.[58,] Somatostatin receptor imaging can assist in determining if a patient would benefit from receiving a somatostatin receptor-directed therapy. Use of FDG-PET may be considered to identify high-grade active disease in selected individuals when high-grade neuroendocrine tumors or poorly differentiated carcinomas are documented or suspected or when disease is growing rapidly. For certain types of neuroendocrine tumors (e.g., well-differentiated, grade 3), somatostatin receptor-based imaging with PET/CT or PET/MRI or FDG-PET/CT scans for surveillance are recommended as clinically indicated. Use of ^{18}F-DOPA PET/CT is not discussed in the guidelines.

Section Summary: Neuroendocrine Tumors

Evidence for the use of PET or PET/CT in the management of individuals with neuroendocrine tumors consists of meta-analyses and prospective, comparative studies. Meta-analyses of studies using ^{68}Ga-PET/CT as the radiotracer for diagnosis and staging of neuroendocrine tumors report relatively high sensitivities and specificities compared with conventional imaging techniques. A study comparing the diagnostic performance between ^{64}Cu PET/CT and ^{68}Ga-PET/CT reported an increase in detection of lesions with ^{64}Cu PET/CT. Current guidelines recommend using somatostatin receptor PET tracers, ^{68}Ga-dotatate, ^{68}Ga-dotatoc, or ^{64}Cu-dotatate, to assess receptor status and presence of distant disease.

The evidence does not support the use of FDG-PET/CT for the diagnosis, staging, and restaging of neuroendocrine tumors.

The evidence does not support the use of FDG-PET/CT for surveillance of neuroendocrine tumors.

The evidence supports the use of ^{68}Ga or ^{64}Cu PET/CT for the diagnosis, staging, and restaging of neuroendocrine tumors.

The evidence does not support the use of ^{68}Ga or ^{64}Cu PET/CT for surveillance of neuroendocrine tumors.

Ovarian Cancer
For primary evaluation (i.e., suspected ovarian cancer), the ability to rule out malignancy with a high NPV would change management by avoiding unnecessary exploratory surgery. However, available studies have suggested that PET scanning has a poorer NPV than other options, including transvaginal ultrasound, Doppler studies, or MRI. Adding PET scan to ultrasound or MRI did not improve results.

PPV is of greatest importance in evaluating individuals with known ovarian cancer, either to detect disease recurrence or progression or to monitor response to treatment.

Systematic Reviews
A meta-analysis by Xu et al (2017) evaluated the diagnostic value of PET and PET/CT for recurrent or metastatic ovarian cancer.[127,] The literature search, conducted through August 2014, identified 64 studies for inclusion: 15 studies (n=657) using PET and 49 studies (n=3065) using PET/CT. The pooled sensitivity and specificity for PET were 89% (95% CI, 86% to 92%) and 90% (95% CI, 84% to 93%), respectively. The pooled sensitivity and specificity for PET/CT were 92% (95% CI, 90% to 93%) and 91% (95% CI, 89% to 93%), respectively. Subgroup analyses were conducted by study region (Asia, Europe, and America). For PET/CT, sensitivities in the Asia and Europe studies were significantly higher compared with the sensitivity in the America studies.

A meta-analysis by Limei et al (2013), included 28 studies (N=1651) published through December 2012; it evaluated the diagnostic value of PET/CT in suspected recurrent ovarian cancer.[128,] Using the Oxford Evidence rating system for quality, 7 studies were considered high quality and 21 were low-quality. Reviewers found PET/CT was useful for detecting ovarian cancer recurrence, with pooled sensitivity and specificity of 89% and 75% for the high-quality studies and 89% and 93% for the low-quality studies, respectively.

An AHRQ systematic review conducted by Matchar et al (2004) suggested that PET might have value for detecting recurrence when cancer antigen 125 is elevated and conventional imaging does not clearly show recurrence, this had not been demonstrated in an adequately powered prospective study.[129,] An AHRQ systematic review conducted by Ospina et al (2008) found that evidence supported the use of PET/CT for detecting recurrent ovarian cancer.[35,] Evidence for initial diagnosis and staging of ovarian cancer was inconclusive.

GUIDELINES

American College of Radiology
In 2018, the ACR published Appropriateness Criteria on staging and follow-up of ovarian cancer stating that PET/CT and MRI may be appropriate when lesions are indeterminate with contrast-enhanced CT.[130,]

National Comprehensive Cancer Network
Current NCCN guidelines for ovarian cancer (v.3.2022) indicate that PET/CT can be appropriate "for indeterminate lesions if results will alter management."[131,] Use of PET/CT may be considered for monitoring individuals with stage I through IV ovarian cancer receiving adjuvant chemotherapy or after initial treatment (e.g., surgery followed by chemotherapy) if clinically indicated. PET/CT also can be considered if clinically indicated after complete remission, for follow-up and for monitoring for recurrence if cancer antigen 125 is rising or clinical relapse is suspected.

Section Summary: Ovarian Cancer
Evidence for PET and PET/CT for the initial diagnosis of ovarian cancer consists of an AHRQ systematic review (2014), which reported that the evidence is inconclusive. Evidence on the use of PET and PET/CT for the detection of ovarian cancer recurrence includes 2 meta-analyses and an AHRQ systematic review (2008). Pooled sensitivities and specificities support the use of PET and PET/CT for the detection of recurrent ovarian cancer. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of ovarian cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of ovarian cancer.

PANCREATIC CANCER

Systematic Reviews
A Cochrane review by Best et al (2017) compared the diagnostic accuracy of several imaging techniques (CT, MRI, PET, and endoscopic ultrasound) in detecting cancerous and precancerous lesions in the pancreas.[132,] The literature review, conducted through July 2016, identified 54 studies total, 10 using PET. Assessment of the selected studies found none to have high methodologic quality. A meta-analysis of 3 studies reported a sensitivity and specificity in diagnosing pancreatic cancer of 92% (95% CI, 80% to 97%) and 65% (95% CI, 39% to 84%), respectively. The PPV and NPV (calculated by BCBSA) were 89% and 71%, respectively. Reviewers could not adequately compare the various techniques due to the imprecision of estimates, poor quality of studies, and heterogeneity in categorizing lesions.

Wang et al (2017) conducted a meta-analysis comparing CT alone, PET alone, and PET/CT in the preoperative assessment of individuals with pancreatic cancer.[133,] The literature review identified 13 studies (N=1343). The Newcastle-Ottawa Scale was used to assess study quality, with scores ranging from 6 to 8 on the 9-point scale. Use of PET alone was not superior to CT alone (pooled odds ratio [OR], 1.0; 95% CI, 0.6 to 1.6) in detecting distant metastases. However, PET/CT was superior to CT alone (pooled OR=1.7; 95% CI, 1.3 to 2.1) in detecting distant metastases. Neither PET nor PET/CT was superior to CT alone in detecting lymph node invasion (pooled OR, 1.0; 95% CI, 0.6 to 1.5).

In a meta-analysis of 9 studies (N=526), Rijkers et al (2014) reported pooled sensitivity and specificity of FDG-PET/CT for confirming suspected pancreatic cancer of 90% (95% CI, 87% to 93%) and 76% (95% CI, 66% to 84%), respectively.[134,] Two reviews on pancreatic carcinoma,

conducted by Ospina et al (2008) and Podoloff et al (2009) have suggested that PET/CT can be useful for staging certain individuals when the standard staging protocol is inconclusive.[35,37,]

An AHRQ systematic review by Matchar et al (2004) and a TEC Assessment (1999) focused on 2 clinical applications of PET scanning in individuals 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 individuals with known pancreatic cancer.[129,]

In terms of distinguishing between benign and malignant disease, the criterion standard is a percutaneous or open biopsy. If PET were to be used to allow individuals with scans suggesting benign masses to avoid a biopsy, a very high NPV would be required. The key statistic underlying the NPV is the false-negative rate. Individuals with false-negative results are incorrectly considered to have a benign disease and thus are not promptly treated for pancreatic cancer. Based on the TEC literature review, the NPV ranged between 75% and 92%, depending on an underlying prevalence of disease ranging from 50% to 75%. The TEC Assessment concluded that this level of diagnostic performance would not be adequate to recommend against biopsy. The Matchar AHRQ report found that sometimes PET was more accurate than other modalities, but a meta-analysis showed that it is unclear whether PET's diagnostic performance would surpass decision thresholds for biopsy or laparotomy.[129,] In both the TEC and AHRQ reviews, data were inadequate to permit conclusions on the role of PET scanning as a technique to stage known pancreatic cancer.

Observational Studies
Ghaneh et al (2018) conducted the largest study to date, measuring the incremental diagnostic value of PET/CT when added to a standard diagnostic workup with multidetector CT.[135,] The study was a prospective nonrandomized study of 550 individuals. Sensitivity and specificity were 88.5% and 70.6%, respectively, which was a significant improvement from CT alone. Use of PET/CT also correctly changed staging in 56 individuals, influenced management in 250 individuals, and stopped resection in 58 individuals scheduled for surgery.

GUIDELINES

American College of Radiology
In 2017, the ACR published Appropriateness Criteria on staging of pancreatic ductal adenocarcinoma, which note that PET/CT may be appropriate as a supplemental imaging evaluation to detect additional distant metastases.[136,]

National Comprehensive Cancer Network
Current NCCN guidelines for pancreatic cancer (v.1.2022) state "the role of PET/CT (without iodinated intravenous contrast) remains unclear…[PET/CT] may be considered after formal pancreatic CT protocol in high-risk patients to detect extrapancreatic metastasis.[131,] It is not a substitute for high-quality, contrast-enhanced CT."

Section Summary: Pancreatic Cancer
Evidence for PET and PET/CT for the initial diagnosis of pancreatic cancer consists of a TEC Assessment, a Cochrane review, a meta-analysis, and a large observational study published subsequent to the reviews. The TEC Assessment reported that the NPVs in several studies were

inadequate to influence the decision for a biopsy. Other reviews also noted limitations such as imprecise estimates and poor quality of studies. Studies published subsequent to the reviews also reported low NPVs. The large observational study, which assessed the incremental diagnostic value of PET/CT when added to standard workup with CT, showed significant improvements in sensitivity and specificity compared with CT alone.

The evidence supports the use of FDG-PET and FDG-PET/CT for suspected pancreatic cancer when results from other imaging techniques are inconclusive.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis, staging and restaging, or surveillance of pancreatic cancer.

PENILE CANCER

Systematic Reviews

Lee et al (2022) conducted a systematic review and meta-analysis of 5 prospective and 7 retrospective cohort studies (12 studies; N=479) published through August 2021 on the diagnostic accuracy of FDG-PET/CT for lymph node staging in penile cancer.[137,] Histopathological analysis was the reference standard in all included studies; direct comparison of FDG-PET/CT with other imaging modalities was not reported. Most studies had low or unclear risk of bias across QUADAS-2 domains, and Deek's test for publication bias was not significant (p=.45). FDG-PET/CT was associated with a pooled sensitivity of 87% (95% CI, 79% to 92%) and a pooled specificity of 88% (95% CI, 79% to 93%). Heterogeneity was present for both sensitivity (I^2=68%) and specificity (I^2=85%) and meta-regression analysis could not account for the heterogeneity. The analysis found a positive likelihood ratio of 7.2 (95% CI 3.9 to 13.1) and a negative likelihood ratio of 0.15 (95% CI 0.10 to 0.24). The pooled diagnostic odds ratio was 47 (95% CI, 19 to 116) and the AUC was 0.93 (95% CI, 0.90 to 0.95). Subgroup analysis of diagnostic accuracy stratified according to inguinal or pelvic lymph nodes found similar sensitivities (84% and 89%) and specificities (79% and 83%) with no difference between groups in AUC (area difference -0.044; p=.34). Although the review showed that FDG-PET/CT had good diagnostic capability, this study is limited by the heterogeneity among the studies and the lack of comparison with other imaging modalities.

Comparative Studies

Jakobsen et al (2021) retrospectively evaluated the diagnostic accuracy of FDG-PET/CT compared to contrast-enhanced CT in the assessment of inguinal lymph node status, distant metastases and synchronous cancer at 2 medical centers.[138,]ndividuals diagnosed with invasive penile squamous cell carcinoma who received a preoperative FDG-PET/CT were included. A radiologist, blinded to FDG-PET/CT results, analyzed and interpreted the CT part of the scan for suspicious findings. There were 171 individuals evaluated for distant metastases and synchronous incident cancers. Additionally, there were 286 groins in 143 individuals evaluated for lymph node metastases. For detection of lymph node metastases, 6 of the 171 groins read as negative by FDG-PET/CT were false positives (false negative rate of 11.5% per groin). For the diagnostic accuracy for inguinal lymph node status, with histopathology or complete clinical follow-up as reference, FDG PET/CT sensitivity and specificity was 85.4% and 57.8% per patient, respectively. For CT, sensitivity and specificity was 47.5% and 95.8% per patient, respectively.

Guidelines

Current NCCN guidelines for penile cancer (v.2.2022) state that PET/CT may be considered for cross-sectional imaging of the chest/abdomen/pelvis for staging or treatment response assessment in individuals with suspected inguinal lymph node positive disease. PET/CT can also be used to evaluate enlarged pelvic lymph nodes if percutaneous lymph node biopsy is not technically feasible.[139,]

Section Summary: Penile Cancer

Evidence for the use of PET or PET/CT in the management of individuals with penile cancer consists of a systematic review and a retrospective comparative study. In individuals with suspected inguinal lymph node positive disease, PET/CT may offer increased sensitivity compared to CT alone for staging. Current NCCN guidelines note that PET/CT can be considered for staging or treatment response assessment in individuals with node positive disease.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, restaging, or surveillance of node negative penile cancer.

The evidence does support the use of FDG-PET and FDG-PET/CT for the staging and treatment response assessment of node positive penile cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis or surveillance of node positive penile cancer.

PROSTATE CANCER

^{11}C-CHOLINE PET, ^{11}C-CHOLINE PET/CT, ^{18}F-FLUCICLOVINE PET

Prostate Cancer Diagnosis

Liu et al (2016) and Ouyang et al (2016) conducted meta-analyses comparing the diagnostic accuracy of 4 radiotracers (FDG, carbon 11 choline [^{11}C-choline], fluorine 18 fluorocholine [^{18}F-FCH], and carbon 11 acetate [^{11}C-acetate]) in detecting prostate cancer.[140,141,] The literature search for the Liu review, conducted through July 2015, identified 56 studies (N=3586) for inclusion. Using the QUADAS-2 system to evaluate study quality, reviewers determined that the studies were reliable, with scores of 6 to 9 out of 10. Pooled estimates for the 4 types of radiotracers are summarized below (see Table 8). The literature search for the Ouyang et al (2016) review included studies using elastography and was conducted through April 2015. Study quality was not addressed.

Biscontini et al (2021) conducted a meta-analyses to evaluate the diagnostic accuracy of ^{18}F-fluciclovine for the diagnosis of primary cancer, pre-operative lymph node staging, detection of recurrent disease, and for bone metastasis assessment.[142,] Fifteen studies (N=697) were evaluated: 6 studies for diagnosis, 3 for staging, 6 for recurrence of disease, and 1 for evaluation of bone metastasis. Pooled estimates for diagnosis are included in Table 8.

Table 8. Pooled Diagnostic Performance of Different Radiotracers in Detecting Prostate Cancer

Imaging Technique	No. of Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
Liu et al (2016)[140,]				
^{11}C-choline PET/CT	31	81 (77 to 88)	82 (73 to 88)	0.89 (0.86 to 0.91)
^{18}F-FCH-PET/CT	15	76 (49 to 91)	93 (84 to 97)	0.94 (0.92 to 0.96)
^{11}C-acetate PET/CT	5	79 (70 to 86)	59 (43 to 73)	0.78 (0.74 to 0.81)
FDG-PET/CT	5	67 (55 to 77)	72 (50 to 87)	0.73 (0.69 to 0.77)
Ouyang et al (2016)[141,]				
Elastography[a]	26	76 (68 to 83)	78 (72 to 83)	0.84 (NR)
^{11}C-choline PET/CT	31	78 (72 to 84)	79 (71 to 82)	0.85 (NR)
^{18}F-FCH-PET/CT	15	73 (54 to 87)	59 (41 to 75)	0.91 (NR)
^{11}C-acetate PET/CT	5	79 (68 to 86)	59 (41 to 75)	0.77 (NR)
FDG-PET/CT	5	76 (68 to 83)	78 (72 to 83)	0.84 (NR)
Biscontini et al (2021)[142,]				
^{18}F-fluciclovine	6	83 (80 to 86)	77 (74 to 80)	0.92 (NR)

11C-acetate: carbon 11 acetate; 11C-choline: carbon 11 choline; 18F-FCH: fluorine 18 fluorocholine; AUC: area under the curve; CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; NR: not reported; PET: positron emission tomography.
[a] Includes transrectal real-time elastosonography and shear-wave elastography.

PROSTATE CANCER STAGING AND RESTAGING

Systematic Reviews

The meta-analysis by Biscontini et al (2021), described previously, assessed the accuracy of ^{18}F-fluciclovine.[142,] For pre-operative lymph node staging (3 studies), the pooled sensitivity and specificity was 57% (95% CI, 39% to 73%) and 99% (95% CI, 94% to 100%), respectively. For the detection of recurrent disease (6 studies), the pooled sensitivity and specificity was 68% (95% CI, 63% to 73%) and 68% (95% CI, 60% to 75%), respectively.

A meta-analysis by Fanti et al (2016) assessed the accuracy of ^{11}C-choline PET/CT in the restaging of individuals with prostate cancer with biochemical recurrence after initial treatment with curative intent.[143,] The literature search, conducted through December 2014, identified 12 studies (N =1270) for inclusion in the analysis. Pooled sensitivity and specificity were 89% (95% CI, 83% to 93%) and 89% (95% CI, 73% to 96%), respectively.

In a meta-analysis by von Eyben and Kairemo (2014), the pooled sensitivity and specificity of ^{11}C-choline PET/CT for detecting prostate cancer recurrence in 609 individuals were 62% (95% CI, 51% to 66%) and 92% (95% CI, 89% to 94%), respectively.[144,] In an evaluation of 280 individuals from head-to-head studies comparing choline PET/CT with bone scans, PET/CT identified metastases significantly more often than did bone scanning (127 [45%] vs 46 [16%], respectively; OR, 2.8; 95% CI, 1.9 to 4.1; p<.001). Reviewers also reported that ^{11}C-choline PET/CT changed treatment in 381 (41%) of 938 individuals. Complete prostate-specific antigen (PSA) response occurred in 101 (25%) of 404 individuals.

A systematic review by Umbehr et al (2013) investigated the use of ^{11}C-choline and ^{18}F-FCH-PET and ^{18}F-FCH-PET/CT in staging and restaging of prostate cancer. The literature search, conducted through July 2012, identified 10 studies (N=637) to be included in the initial prostate cancer staging analysis; pooled sensitivity was 84% (95% CI, 68% to 93%) and specificity was 79% (95% CI, 53% to 93%).[145,] Twelve studies (N=1055) were included in the restaging analysis; pooled sensitivity and specificity were 85% (95% CI, 79% to 89%) and 88% (95% CI, 73% to 95%), respectively.

Mohsen et al (2013) conducted a systematic review of 23 studies on ^{11}C-acetate PET imaging for the detection of primary or recurrent prostate cancer.[146,] For detection of recurrence, 14 studies were included in a meta-analysis. The pooled sensitivity was 68% (95% CI, 63% to 73%) and pooled specificity was 93% (95% CI, 83% to 98%). Study quality was considered poor, and low sensitivities and specificities appear to limit the validity of ^{11}C-acetate imaging in prostate cancer. Currently, ^{11}C-acetate is not approved by the U.S. Food and Drug Administration.

Other systematic reviews, including those by Sandgren et al (2017) and Albisinni et al (2018), have also reported that ^{11}C-choline PET/CT exhibits high sensitivity and specificity estimates in the staging and restaging of prostate cancer.[147,148,]

Prostate Cancer Management

Jani et al (2021) conducted a single-center, open-label, phase 2/3 randomized controlled trial that evaluated the benefit of ^{18}F-fluciclovine-PET/CT in individuals who had undergone radical prostatectomy and were experiencing biochemical recurrence to guide final radiotherapy treatment decisions.[149,]ndividuals were randomly assigned in a 1:1 ratio to radiotherapy directed by conventional imaging only, or to radiotherapy directed by conventional imaging plus ^{18}F-fluciclovine-PET/CT. All 81 individuals in the conventional imaging group received radiotherapy (56 to prostate bed alone and 25 to prostate bed and pelvic nodes). In the ^{18}F-fluciclovine-PET/CT group, 76 (95%) of the 80 individuals received radiotherapy (41 to the prostate bed alone and 35 to the prostate bed and pelvic nodes). Median follow-up for the whole cohort was 3.52 years. Median survival was not reached in both groups. Three-year event-free survival was 63% (95% CI, 49.2 to 74) in the conventional imaging group compared with 75.5% (95% CI, 62.5 to 84.6 in the ^{18}F-fluciclovine-PET/CT group (difference, 12.5 percentage points [95% CI, 4.3 to 20.8]; p=.0028).

Dreyfuss et al (2021) conducted a single-center retrospective evaluation of individuals with biochemical recurrence after primary treatment for prostate cancer who received imaging with ^{18}F-fluciclovine-PET/CT.[150,] A total of 328 individuals were included resulting in 336 ^{18}F-fluciclovine PET/CT scans, which were classified as positive (65%), negative (25%), or equivocal

(10%) based on radiology reports. Sensitivity and specificity were 93% (95% CI, 86% to 96%) and 63% (95% CI, 45% to 77%), respectively, using biopsy and other imaging as the reference standard. Management recommendations after imaging was only available for 241 scans (72%). Of the evaluable scans, 73% had management changes with ^{18}F-fluciclovine-PET/CT data with 58% of those recommendations involving treatment modality decisions.

Andriole et al (2018) presented results from the LOCATE trial.[151,] The study population consisted of 213 men who had undergone curative-intent treatment of histologically confirmed prostate cancer and were suspected to have recurrence based on rising PSA levels. Fluciclovine-avid lesions were detected in 122 (57%) individuals. Compared with management plans specified by the treating physicians prior to the PET scans, 126 (59%) individuals had a change in management. The most frequent change in management was from salvage or noncurative systemic therapy to watchful waiting (n=32) and from noncurative systemic therapy to salvage therapy (n=30).

Akin-Akintayo et al (2017) evaluated the role of fluciclovine PET/CT in the management of post-prostatectomy individuals with PSA failure being considered for salvage radiotherapy.[152,] Forty-two individuals who were initially planning radiotherapy due to post-prostatectomy PSA failure underwent fluciclovine PET/CT. Based on the PET/CT results, 17 (40.5%) individuals changed a decision relating to the radiotherapy: 2 individuals received hormonal therapy rather than radiotherapy when fluciclovine showed extrapelvic disease; 11 individuals increased the radiotherapy field from prostate bed only to prostate plus pelvis, and 4 individuals reduced the radiotherapy fields from prostate plus pelvis to prostate bed only.

In a meta-analysis of 14 studies (N=1667) of radiolabeled choline PET/CT for restaging prostate cancer, Treglia et al (2014) reported a maximum pooled sensitivity of 77% (95% CI, 71% to 82%) in individuals with a PSA velocity of greater than 2 ng/mL per year.[153,] Pooled sensitivity was lower for individuals with a PSA velocity of less than 2 ng/mL per year or with a PSA level doubling time of 6 months or less. In meta-analysis of 11 studies (N=609) of radiolabeled choline PET/CT for staging or restaging prostate cancer, von Eyben et al (2014) reported a pooled sensitivity and specificity of 59% (95% CI, 51% to 66%) and 92% (95% CI, 89% to 94%), respectively.[144,] Pooled PPV and NPV were 70% and 85%, respectively.

GUIDELINES

American College of Radiology

In 2018, the ACR published an Appropriateness Criteria on the posttreatment follow-up of individuals with prostate cancer stating that PET and PET/CT using ^{11}C-choline or ^{18}F-fluciclovine radiotracers is usually appropriate for individuals with a clinical concern for residual or recurrent disease following radical prostatectomy, nonsurgical treatments, or systemic therapy.[154,]

American Urological Association et al

Practice guidelines from the American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (2021) recommend CT or MRI for cross-sectional imaging, along with bone scintigraphy, as the standard imaging approach for the post-treatment biochemical recurrence after exhaustion of local treatment.[155,] Novel PET tracers (^{11}C-choline, ^{18}F-fluciclovine, prostate-specific membrane antigen [PSMA]-targeting radiotracers) "appear to show

greater sensitivity than conventional imaging for the detection of prostate cancer recurrence and metastases at low PSA values (<2.0 ng/mL)." However, the guideline notes that it is unclear what clinical benefits and impact on OS is achieved with earlier detection of recurrent disease, and that "to date there is only evidence that it may delay initiation of systemic therapy. There is no evidence yet that metastasis directed therapy confers a survival benefit."

National Comprehensive Cancer Network
Current NCCN guidelines for prostate cancer (4.2024) indicate that ^{11}C-choline or ^{18}F-fluciclovine PET/CT or PET/MRI may be used for detection of biochemically recurrent small-volume disease in soft tissues and in bone.[156,]^{18}F-sodium fluoride PET/CT or PET/MRI may be considered for further bone assessment. Use of FDG-PET should not be used routinely for initial assessment due to limited evidence of clinical utility.

Society of Nuclear Medicine and Molecular Imaging
The Society of Nuclear Medicine and Molecular Imaging (SNMMI) published appropriate use criteria (2020) on evaluation of men with biochemical recurrence of prostate cancer after definitive primary therapy with radical prostatectomy or radiotherapy.[157,] For those with negative or equivocal results on initial standard imaging, ^{11}C-choline or ^{18}F-fluciclovine PET/CT are considered appropriate to use.

Subsection Summary: ^{11}C-Choline PET, ^{11}C-Choline PET/CT, ^{18}F-Fluciclovine PET, and ^{18}F-Fluciclovine PET/CT for Prostate Cancer
Evidence for the use of ^{11}C-choline PET, ^{11}C-choline PET/CT, ^{18}F-fluciclovine PET, and ^{18}F-fluciclovine PET/CT for diagnosis, staging, and restaging of prostate cancer, consists of meta-analyses, which have shown that the use of ^{11}C-choline and ^{18}F-fluciclovine radiotracers result in similar sensitivities and specificities. Prospective studies in men with biochemical recurrence after primary treatment have reported that a majority of management decisions were changed based on ^{18}F-fluciclovine PET/CT. One of those studies evaluated the impact on clinical outcomes and reported an increase in 3-year event-free survival rates. Further study is needed to compare PET and PET/CT with other imaging techniques, such as MRI and radionuclide bone scan. The evidence supports the use of ^{11}C-choline PET and PET/CT and ^{18}F-fluciclovine PET and PET/CT for the diagnosis, staging, and restaging of prostate cancer.

The evidence does not support the use of ^{11}C-choline PET and PET/CT and ^{18}F-fluciclovine PET and PET/CT for surveillance of prostate cancer.

^{68}Ga-PSMA PET, ^{68}Ga-PSMA PET/CT, Piflufolastat-F^{18} PET, Piflufolastat-F^{18} PET/CT, Flotufolastat-F^{18} PET, and Flotufolastat-F^{18} PET/CT
FDA-approved PSMA-targeting radiotracers for PET include ^{68}Ga PSMA, piflufolastat-F^{18}, and flotufolastat-F^{18}. The Albisinni et al (2018) review, discussed in the ^{11}C-choline PET/CT section, and a systematic review by Eissa et al (2018) noted that an advantage of using PSMA-targeting radiotracers compared with ^{11}C-choline and ^{18}F-fluciclovine is the potential to detect local and distant recurrences in individuals with lower PSA levels.[148,158,]

Prostate Cancer Diagnosis
Kawada et al (2022) conducted a systematic review on the diagnostic accuracy of PSMA PET for detection of clinically significant prostate cancer.[159,] Five studies reporting data from 497

individuals with suspected prostate cancer due to elevated PSA were included in the review; 2 studies included only biopsy-naïve individuals (N=333) while in the remaining 3 studies participants had a prior negative biopsy. The median pre-imaging PSA was 8.0 ng/mL (range, 5.6 to 18 ng/mL). The prevalence of clinically significant prostate cancer, variably defined among the studies but generally requiring an International Society of Urologic pathology grade group ≥2, was 59% (range, 32% to 75%). ^{68}GA was the imaging agent in 4 of the studies. Three of the studies (N=228) assessed PSMA PET, MRI, and PSMA PET/MRI and reported diagnostic measures for all 3 imaging modalities. In all studies, systemic and targeted biopsy was the reference standard. Risk of bias, assessed using the QUADAS-2 tool, was judged to be low in one study and moderate in the other studies.

Measures of diagnostic accuracy are reported in Table 9. Results were similar for PSMA PET and MRI, alone and in combination, with overlapping CIs, and were consistent when limited to 2 studies of biopsy-naïve individuals.

Table 9. Diagnostic Performance of Imaging Modalities in Detecting Clinically Significant Prostate Cancer

Imaging Technique for Targeted Biopsy	No. of Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	DOR (95% CI)	AUC
Kawada et al 2022[159,]							
All studies PSMA PET	5	89 (85 to 93)	56 (29 to 80)	69 (58 to 79)	78 (50 to 93)	10.50 (2.59 to 42.57)	0.88
Studies comparing imaging techniques PSMA PET	3	90 (85 to 93)	39 (14 to 71)	68 (62 to 73)	72 (29 to 94)	5.16 (1.07 to 24.79)	0.88
MRI	3	84 (78 to 88)	53 (46 to 60)	70 (46 to 87)	76 (55 to 89)	6.40 (4.00 to 10.32)	0.81
PSMA PET/MRI	3	91 (77 to 97)	64 (40 to 82)	75 (56 to 87)	85 (62 to 95)	19.04 (9.54 to 38.02)	0.87

AUC: area under the curve; DOR: diagnostic odds ratio; MRI: magnetic resonance imaging; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; PSMA: prostate-specific membrane antigen.

Prostate Cancer Staging

Stabile et al (2022)[160,] and Wang et al (2021)[161,] conducted systematic reviews on the use of PSMA PET for prostate cancer staging.

The Stabile review included 27 studies (N=2832) assessing the diagnostic accuracy of PSMA PET/CT for prostate cancer staging in newly diagnosed individuals. Specifically, studies were included that reported on the predictive ability of PSMA PET for lymph node invasion. The mean

PSA at baseline, reported in 14 studies, was 12.2 ng/mL. Among the studies, 9 included high-risk individuals, 1 included intermediate-risk individuals, 15 included individuals with mixed risk levels, and 2 did not report risk. ^{68}GA was the imaging agent used in 22 of the studies. The reference standard was pelvic lymph node dissection in all of the included studies. Risk of bias was assessed using QUADAS-2 criteria; nearly all the studies had limitations resulting in unclear or high risk of bias ratings for 1 or more QUADAS-2 domain. Funnel plots and Egger's test found potential publication bias for sensitivity (p=.002) and negative predictive value (p=.02), but not for specificity (p=.1) or positive predictive value (p=.1).

Measures of diagnostic accuracy are reported in Table 10. Among the studies, the median prevalence of lymph node invasion was 26% (interquartile range [IQR], 20% to 34%; range 5% to 58%). Higher prevalence was associated with a significant decrease in negative predictive value (p=.04). Study authors stated that the clinical implication of these findings suggested that for individuals with a nomogram-calculated borderline risk of lymph node invasion and negative PSMA PET/CT, avoidance of pelvic lymph node dissection might be considered, while in individuals with higher-risk prostate cancer, avoidance of pelvic lymph node dissection should not be considered due to the decreased NPV in this risk group.

Wang et al (2021)[161,] conducted a systematic review of 9 studies (N=640) comparing the diagnostic accuracy of ^{68}GA PSMA PET/CT with multiparametric MRI for lymph node staging prior to prostatectomy in individuals with intermediate or high-risk prostate cancer. The reference standard was pelvic lymph node dissection. The median prevalence of pelvic lymph node metastases was 25% (range, 4% to 58%). The median PSA ranged widely among 6 studies from 7.4 to 37.3 ng/mL and was not reported in the other 3 studies. Eight studies were retrospective, and the other was prospective; QUADAS-2 assessment of study quality found the majority of studies had low or unclear risk of bias for most domains. No publication bias was found for either ^{68}GA PSMA PET/CT (p=.15) or multiparametric MRI (p=.87). Study results are summarized in Table 10. Sources of heterogeneity based on meta-regression analysis included pelvic lymph node metastases prevalence, PSA level, risk group, and reference standard for ^{68}GA PSMA PET/CT and number of patients and PSA level for multiparametric MRI.

Table 10. Diagnostic Performance of Imaging Modalities for Prostate Cancer Staging

	No. of Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	DOR (95% CI)	AUC (95% CI)
Stabile et al (2022)[160,]							
PSMA PET Overall	27	58 (50 to 66)	95 (93 to 97)	79 (72 to 85)	87 (84 to 89)	14.76 (to 19.00)	0.84 (0.87 to 0.81)
High-risk	9	54 (37 to 70)	95 (91 to 98)	77 (67 to 86)	83 (79 to 87)	18.97 (10.65 to 33.78)	-
Intermediate-risk	1	93 (76 to 100)	96 (86 to 100)	93 (76 to 100)	96 (86 to 100)	364 (21.12 to 6273)	-

	No. of Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	DOR (95% CI)	AUC (95% CI)
Mixed-risk	15	58 (49 to 67)	94 (92 to 96)	77 (68 to 85)	88 (84 to 91)	13.58 (9.98 to 18.47)	-
p value for between risk group difference	-	.008	.9	.3	.04		
Wang et al (2021)[161,]							
PSMA PET	9	71 (48 to 86); I^2=75%	92 (88 to 95); I^2=54%	-	-	-	0.92 (0.89 to 0.94)
Multiparametric MRI	9	40 (16 to 71); I^2=5%	92 (80 to 97); I^2=91%	-	-	-	0.82 (0.79 to 0.86)

AUC: area under the curve; DOR: diagnostic odds ratio; MRI: magnetic resonance imaging; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; PSMA: prostate-specific membrane antigen.

Prostate Cancer Management

Systematic Reviews

Systematic reviews conducted by Mazrani et al (2022)[162,] and Pozdnyakov et al (2022)[163,] assessed the effect of PSMA PET imaging for detection of biochemical prostate cancer recurrence, change in management, and patient outcomes following PSMA PET. Study characteristics of the reviews are summarized in Table 11. In both reviews, ^{68}GA was the imaging agent used in the majority of studies (80% [16/20] and 88% [30/34], respectively). Only 6 studies overlapped between the 2 reviews, potentially due to Mazrani et al limiting their inclusion criteria to prospective studies and differences in study search dates. Of note, the Fendler 2019 study (N=635) discussed below in the Prospective Studies section was included in both reviews, accounting for 30% of the total population in Mazrani and 17% of the total population in Pozdnyakov. Mazrani assessed the quality of the included studies using the QUADAS-2 tool. For most studies, risk of bias was determined to be high or unclear for the patient selection domain (17/20 studies) and for the reference standard domain (17/20 studies). Study quality was assessed by Pozdnyakov using National Heart, Lung, and Blood Institute (NHLBI) criteria for observational and cohort studies. Studies were scored on a scale of 0 to 14, with higher scores reflecting a lower risk of bias. Scores for individual studies ranged from 1 to 11; the median score for the change in management studies was 8, and median score for clinical outcome studies was 9. A funnel plot analysis conducted by Pozdnyakov suggested the presence of publication bias (Egger's test p=.008).

Table 11. Characteristics of Systematic Reviews of PSMA PET Imaging for Prostate Cancer Management

Study	Dates	No. of Included Studies	Reference Standard	Participants	N (Range)	Study Design(s)
Mazrani et al 2022[162],	Through July 1, 2021	20	Conventional imaging or histopathology	Individuals with biochemical prostate cancer recurrence • Mean PSA NR; range 0.2 to 14.9 ng/mL • Initial prostate cancer treatment NR	2110 (30-635)	Prospective
Pozdnyakov et al 2022[163],	Through October 1, 2020	34 for change in management 27 for clinical outcomes	NR	Individuals with biochemical prostate cancer recurrence • Median PSA 7.6 ng/mL at time of diagnosis and 1.3 ng/mL at time of PET imaging • 63% had a Gleason score <7 • Initial treatment: 56% radical prostatectomy, 24% radiotherapy plus radical prostatectomy, 18% radiotherapy only • Androgen-deprivation therapy prior to PET imaging: 18%	3680 for change in management 2674 for clinical outcomes	Prospective or retrospective

NR: not reported; PET: positron emission tomography; PSA: prostrate-specific antigen.

Study results are summarized in Table 12. The reviews found similar proportions of individuals with positive PSMA imaging and with a change in management based on PSMA PET imaging results. Meta-regression analysis conducted by Pozdnyakov[163,] found increasing age (p=.0003), Gleason score ≥8 (p=.016), prior treatment with androgen-deprivation therapy (p<.001), initial

treatment with radical prostatectomy (p=.003), and a higher PSA at initial diagnosis and the time of PET (p=.003 for both) all associated with PSMA positive imaging. Regarding change in management, PSMA positivity was the only variable with a significant association (p=.001).

Twenty-seven studies (n=2674) included in Pozdnyakov review[163,] reported clinical outcomes following PSMA PET imaging. In this subset of studies, individuals received treatment after PSMA PET with metastasis-directed radiotherapy (61%), standard salvage radiotherapy (26%), or surgical mastectomy (8.3%). Twenty percent also received adjunctive androgen-deprivation therapy. The median duration of follow-up was 16 months across the studies, but varied according to outcome from 11 months for complete biochemical response (9 studies), 20 months for biochemical recurrence-free survival (9 studies), and 24 months for overall survival (12 studies). Heterogeneity was 75% or higher for all outcomes. Additional analyses limited to data from individuals who underwent metastasis-directed treatment found similar results for biochemical recurrence-free survival (63.7%, 95% CI, 53.3% to 74.1%) and overall survival (96.9%, 95% CI, 95.1% to 98.8%); data on complete biochemical response were too limited in this population to pool.

Table 12. Results of Systematic Reviews of PSMA PET Imaging for Prostate Cancer Management

Study	Positive PSMA Imaging	Change in Management	Complete Biochemical Response	Biochemical Recurrence-Free Survival[a]	Overall Survival
Mazrani et al 2022[162,]					
Total N	2210	330	Not reported	Not reported	Not reported
Proportion (n/N)	66.6% (1406/2110)	42.7% (141/330)	-	-	-
95% CI	-	-	-	-	-
I^2(p)	-	-	-	-	-
Podzdynakov et al 2022[163,]					
Total N	3680	Not reported	558	1057	1684
Proportion (n/N)	68.2%	56.4%	23.3%	60.2%	98.3%
95% CI	-	48.0% to 63.9%	14.6% to 32.0%	49.1% to 71.4%	97.2% to 99.4%
I^2(p)	-	96%	86%	94%	75%

[a] PSA <0.2 ng/ml or <nadir

Prospective Studies

Prospective studies not included in one of the systematic reviews are summarized below. The exception is the Fendler 2019 study, which although included in both the Mazrani and Pozdnyakov reviews, is described separately as it is one of the largest studies published to date

and was one of the studies upon which FDA approval of the Locametz ^{68}GA preparation kit was based (see Prostate Cancer Treatment, below).

Jani et al (2023) published results from the SPOTLIGHT trial, which was a prospective, open-label, multicenter, phase 3 study to assess the diagnostic performance and safety of flotufolastat-F18.[33,] Men (N=389) with elevated PSA levels suspicious for recurrent prostate cancer were administered an intravenous bolus of flotufolastat-F^{18} 50-70 minutes before PET/CT. Three separate, blinded readers each provided their local interpretation of the images. Among the patients with an evaluable scan, the total flotufolastat-F^{18} detection rate was 83%. Verified detection rates ranged from 51% (95% CI, 46.1 to 56.6) to 54% (95% CI, 48.8 to 59.3) among the 366 patients for whom a standard of truth (histopathology [n=69]/confirmatory imaging only [n=297]) was available which surpassed the prespecified statistical threshold. The total region-level PPV fell short of the prespecified threshold, ranging from 46% (95% CI 42.0 to 50.3) to 60% (95% CI 55.1 to 65.5).

Surasi et al (2023) conducted a prospective, open-label, multicenter, phase 3 study (LIGHTHOUSE) to evaluate the diagnostic performance and safety of flotufolastat-F18 in patients with newly diagnosed prostate cancer. [34,] Men (N=356) with biopsy-proven adenocarcinoma of the prostate and unfavorable intermediate- to very-high-risk disease classification were administered an intravenous bolus of flotufolastat-F^{18} 50-70 minutes before PET/CT. Three separate, blinded readers each provided their local interpretation of the images. For readers 1, 2, and 3, the sensitivity for pelvic lymph node detection was 30% (95% CI, 19.6 to 42.1), 27% (95% CI, 17.2 to 39.1), and 23% (95% CI, 13.7 to 34.4), respectively, not reaching the predetermined threshold. Specificity exceeded the criteria for all readers with 93% (95% CI, 88. to 95.9), 94% (95% CI, 89.8 to 96.6), and 97% (95% CI, 93.7 to 98.7), respectively.

Hofman et al (2020) published results from the multicenter, randomized proPSMA trial (N=300) that evaluated the diagnostic utility of ^{68}Ga-PSMA PET/CT as a replacement for conventional imaging in newly diagnosed individuals with prostate cancer and high-risk features.[164,] Individuals were randomly assigned 1:1 to receive ^{68}Ga-PSMA PET/CT or conventional imaging prior to radical prostatectomy or radiotherapy with curative intent. The primary outcome was accuracy for identifying either pelvic nodal or distant-metastatic disease. A reference standard was assessable for 98% of individuals, with 30% of the cohort positive for nodal or distant metastases. ^{68}Ga-PSMA PET/CT had an improved sensitivity (85% vs. 38%) and specificity (98% vs. 91%) compared to conventional imaging. This translated to a greater AUC for accuracy with ^{68}Ga-PSMA PET/CT (92% vs. 65% with conventional imaging; absolute difference, 27%; 95% CI, 23 to 31, p<.0001). A change in intended management was reported more frequently with ^{68}Ga-PSMA PET/CT compared to conventional imaging (28% vs. 15%, p=.008).

Pienta et al (2021) published results from the prospective Phase 2/3, multi-center Study of 18-F-DCFPyL PET/CT imaging in individuals with prostate cancer: Examination of diagnostic accuracy (OSPREY) trial[165,]. Two different cohorts were evaluated: individuals with high-risk prostate cancer undergoing radical prostatectomy with pelvic lymphadenectomy (cohort A) and individuals with suspected recurrent/metastatic prostate cancer on conventional imaging (cohort B). Both cohorts received conventional imaging at baseline and piflufolastat-F^{18} PET/CT 4 to 6 weeks later. In cohort A, 268 individuals with high-risk prostate cancer were evaluable to determine the

diagnostic performance of piflufolastat-F^{18} PET/CT in detecting pelvic nodal metastases. The median specificity was 97.9% (95% CI, 94.5% to 99.4%) and median sensitivity was 40.3% (95% CI, 28.1% to 52.5%). The sensitivity end point was not met, as the lower bounds of the 95% CI did not reach the pre-specified success threshold of 40%. In cohort B, 93 individuals were analyzed to assess the diagnostic performance for detecting sites of prostate cancer metastases or locoregional occurrence. Median sensitivity was 95.8% (95% CI, 87.8% to 99.0%) and median PPV was 81.9% (95% CI, 73.7% to 90.2%). Specificity was not reported.

Morris et al (2021) published results from the CONDOR trial, which was a prospective, multicenter, phase 3 study.[166,] The performance of piflufolastat-F^{18} PET/CT in individuals with biochemical recurrence and uninformative conventional imaging (including ^{18}F-fluciclovine or ^{11}C-choline PET, CT, MRI, and/or whole-body bone scintigraphy) was evaluated. The primary endpoint was correct localization rate, a measure of PPV plus anatomic lesion colocalization based on histopathology, imaging findings, or therapy response. It was further defined as the percentage of individuals with a 1:1 correspondence between at least 1 lesion identified on piflufolastat-F^{18} PET/CT by central readers and the composite standard of truth. The FDA considered correct localization rate to functionally represent a patient-level PPV.[167,] It also stated that due to high disease prevalence in individuals with biochemically recurrent prostate cancer, true negative regions are difficult to identify and would require long-term follow-up. Thus, specificity is not considered a practical endpoint in this patient population. However, "PPV can also provide some information related to false positive patients and is much more readily estimated."

The CONDOR trial included 208 individuals (median PSA of 0.8 ng/mL) who received piflufolastat-F^{18} PET/CT.[166,] The correct localization rate across the 3 readers ranged from 84.8% to 87.0% (lower bound of 95% CI, 77.8 to 80.4), meeting the pre-specified success threshold of 20% for the lower bound of the 95% CI in the primary analysis, which excluded individuals with a negative PET result or if there was no reference standard data available for a PET-positive region. The detection rate rose with increasing PSA levels ranging from 36.2% (<0.5 ng/mL) to 96.7% (≥5 ng/mL). A change in intended management was reported in 63.9% (131/205) of evaluable individuals.

Hope et al (2021) included 764 individuals with intermediate or high-risk prostate cancer undergoing ^{68}GA PSMA PET imaging, 277 of whom had subsequent radical prostatectomy and pelvic lymph node dissection.[168,] The median PSA was 11.4 mg/ml, and 78% of the study population was high-risk, based on D'Amico risk classification. Compared with a histopathological reference standard, sensitivity of ^{68}GA PSMA PET in this population was 40% (95% CI, 34% to 46%), specificity 95% (95% CI, 92% to 97%), PPV 75% (95% CI, 70% to 80%), and NPV 81% (95% CI, 76% to 85%).

Fendler et al (2019) conducted a prospective single-arm clinical trial to evaluate the accuracy of ^{68}Ga-PSMA PET/CT in individuals with biochemically recurrent prostate cancer after prostatectomy, radiation therapy, or both.[169,] The primary endpoint was PPV on a per-patient and per-region basis of ^{68}Ga-PSMA PET for detection of tumor location. A total of 635 individuals were enrolled. On a per-patient basis, PPV was 84% (95% CI, 75% to 90%) by histopathologic validation (primary endpoint, n=87) and 92% (95% CI, 88% to 95%) by the composite reference standard (n=217). Detection rates significantly increased with increasing PSA levels.

Prostate Cancer Treatment
Individuals with previously treated metastatic castration-resistant prostate cancer (mCRPC) who are potential candidates for treatment with ^{177}Lu-vipivotide tetraxetan (Pluvicto) should undergo PSMA PET imaging to appropriately select those individuals with PSMA-positive lesions. The Locametz ^{68}GA preparation kit received FDA approval as a theranostic agent in conjunction with Pluvicto, although Pluvicto labeling indicates that other PSMA PET imaging agents may also be used for identification of PSMA-positive individuals. FDA approval of Locametz was based on the Hope et al (2021)[168,] and Fendler et al (2019)[169,] studies, described above.

Guidelines

National Comprehensive Cancer Network
NCCN guidelines for initial workup of suspected prostate cancer (v.1.2024) recommend multiparametric MRI prior to biopsy in certain individuals and include no recommendations on the use of PSMA PET or PET/CT.[170,]

NCCN prostate cancer treatment guidelines (v.4.2024)[156,] indicate that flotufolastat-F^{18}, piflufolastat-F^{18} or ^{68}Ga-PSMA PET/CT or PET/MRI imaging may be appropriate following equivocal standard imaging or as an alternative to standard imaging for initial staging of individuals who are symptomatic and/or with a life expectancy >5 years with unfavorable intermediate-, high-, or very high-risk disease, for the detection of biochemically recurrent disease following initial definitive therapy, and as part of a workup for progression in individuals with N1 cancer on androgen deprivation therapy or localized cancer on observation. The guidelines include the following specific imaging recommendations:

- Bone imaging can be achieved by conventional technetium-99m-MDP bone scan.
    - Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 prostate-specific membrane antigen (PSMA)-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging.
- oft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CTor abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging.
- Alternatively, Ga-68 PSMA-11, F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
    - Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front- line imaging tool for these patients.

Imaging (including PSMA PET) is not recommended for individuals with asymptomatic very low, low, or favorable intermediate risk disease and life expectancy of ≤5 years.

Society of Nuclear Medicine and Molecular Imaging
The SNMMI has published appropriate use criteria (2022) for PSMA PET imaging.[171,] Panel recommendations for PSMA PET imaging are as follows, based on clinical scenarios and appropriate use scores (scale 1-9):

- Appropriate use scenarios (score 7-9)
    - Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer (score: 8)
    - Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging (score: 8)
    - PSA persistence or PSA rise from undetectable level after radical prostatectomy (score: 9)
    - PSA rise above nadir after definitive radiotherapy (score: 9)
    - nmCRPC (M0) on conventional imaging (score: 7)
- Potentially appropriate use scenarios (score 4-6)
    - Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging (score 4)
    - PSA rise after focal therapy of the primary tumor (score 5)
    - Posttreatment PSA rise in the mCRPC setting (score 6)
    - Evaluation of response to therapy (score 5)
- Rarely appropriate use scenarios (score 1-3)
    - Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) evaluated for targeted biopsy and detection of intraprostatic tumor (score 3)
    - Patients with very-low, low-, and favorable intermediate-risk prostate cancer (score: 2)

American Society of Clinical Oncology
The American Society of Clinical Oncology (2021) recommends against the use of "PET, CT, and radionuclide bone scans, or newer imaging scans in the staging of early prostate cancer at low risk for metastasis."[172,] The recommendations note that current evidence does not support the use of PSMA PET imaging modalities for staging newly diagnosed prostate cancer with low risk of distant metastasis based on clinicopathologic features (grade 1 disease, T1c/T2a disease, prostate-specific antigen (PSA) <10 ng/ml, Gleason score ≤6).

American Urological Association et al
The American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO; 2022)[173,] joint guideline on risk assessment, staging and risk-based management of clinically localized prostate cancer includes the following statements:

- Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer. (Expert Opinion)
- Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
    - To evaluate for the presence of bone metastasis, conventional bone scan should be obtained as the initial staging study. As robust evidence to support an imaging

evaluation in unfavorable intermediate-risk disease remains lacking, the Panel offers that clinicians may consider obtaining staging imaging for patients within this risk classification.

- In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion)

The guideline notes "while data to date supporting a clinical benefit to novel imaging modalities for patients with negative conventional imaging remain quite limited, the Panel did conclude that clinicians may offer molecular imaging in patients at high risk for metastatic disease based on the demonstrated enhanced staging accuracy."

The guideline states that the systematic review used to provide evidence for the AUA/ASTRO guideline conducted literature searches through September 2021. Although the systematic review has not yet been published, the literature search end date was prior to the November 2021 publication of the Hope et al[168,] prospective study (described above), which informed the updated NCCN treatment guideline. It is unclear how inclusion of the Hope et al results would impact the AUA/ASTRO guideline recommendations.

Subsection Summary: ^{68}Ga-PSMA PET, ^{68}Ga-PSMA PET/CT, Piflufolastat-F^{18} PET, and Piflufolastat-F^{18} PET/CT, Flotufolastat-F^{18} PET, and Flotufolastat-F^{18} PET/CT for Prostate Cancer

Evidence for the use of ^{68}Ga-PSMA PET, ^{68}Ga-PSMA PET/CT, piflufolastat-F^{18} PET, piflufolastat-F^{18} PET/CT, flotufolastat-F^{18} PET, and flotufolastat-F^{18} PET/CT consists of systematic reviews and prospective, multicenter trials.

A systematic review of studies conducted in individuals with suspected prostate cancer found similar sensitivity and specificity for PSMA PET and MRI for detection of clinically significant prostate cancer, but only 3 studies of 228 individuals were included in the analysis. The evidence does not support the use of PSMA PET for initial diagnosis of prostate cancer.

Systematic reviews have found PSMA PET to have similar diagnostic accuracy across risk groups in newly diagnosed individuals, and to be similar to MRI for staging intermediate/high-risk prostate cancer. Systematic reviews of studies conducted in individuals with biochemical recurrence, found high proportions with positive PSMA PET imaging often leading to change in management. Individual prospective trials have generally found that PSMA-targeted radiotracers provide a high specificity for detecting pelvic lymph node or distant metastases in newly diagnosed individuals with high-risk disease and a clinically relevant PPV in individuals with biochemical recurrence. NCCN guidelines and SNMMI recommend the use of PSMA PET in specific clinical circumstances. The evidence supports the use of ^{68}Ga-PET, ^{68}Ga-PET/CT, piflufolastat-F^{18} PET, piflufolastat-F^{18} PET/CT, flotufolastat-F^{18} PET, and flotufolastat-F^{18} PET/CT for staging, restaging, and surveillance of prostate cancer in selected individuals.

RENAL CELL CARCINOMA

Systematic Reviews

A systematic review by Ma et al (2017) evaluated the use of FDG-PET or FDG-PET/CT for restaging renal cell carcinoma (RCC).[174,] The literature search, conducted through July 2016, identified 15 studies, mostly retrospective, for inclusion into a meta-analysis. Pooled estimates for sensitivity and specificity were 86% (95% CI, 88% to 93%) and 88% (95% CI, 84% to 91%), respectively. Reviewers concluded that PET showed potential for identifying metastatic or recurrent lesions in individuals with RCC but that more prospective studies would be needed.

Guidelines
Current NCCN guidelines for kidney cancer (v.1.2025) state that "The value of PET in RCC remains to be determined. Currently, PET or PET/CT alone is not a tool that is standardly used to diagnose kidney cancer or follow for evidence of relapse after nephrectomy."[175,]

Section Summary: Renal Cell Carcinoma
The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis, staging and restaging, or surveillance of RCC.

SOFT TISSUE SARCOMA

Systematic Reviews
A systematic review by Treglia et al (2012) evaluated PET for assessing response to imatinib and other treatments for gastrointestinal stromal tumors.[176,] Reviewers included 19 studies. They concluded there was sufficient evidence that PET/CT can be used to monitor response to imatinib treatment, and that the information can be used to adapt treatment strategies. However, the review had the following limitations: it lacked appraisal of the methodologic quality of individual studies and lacked comparison of decision making and outcomes between PET-guided and non-PET-guided management.

An AHRQ systematic review by Ioannidis et al (2002) on the use of PET for soft tissue sarcoma evaluated 5 indications: 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.[177,] Reviewers found that PET had low diagnostic accuracy in distinguishing low-grade tumors from benign lesions; however, PET performed better at differentiating high- or intermediate-grade tumors from low-grade tumors. It is unclear whether this would impact management decisions and health outcomes. Evidence was 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 evaluation of treatment response.

Guidelines
Current NCCN guidelines for soft tissue sarcoma (v.2.2022) state that PET/CT may be useful in staging, prognostication, grading, and determining response to neoadjuvant therapy.[178,]PET/CT can be considered as a tool to help differentiate between well-differentiated and de-differentiated liposarcoma.

Section Summary: Soft Tissue Sarcoma
Evidence for the use of PET or PET/CT in individuals with soft tissue sarcoma consists of 2 systematic reviews. Results of the ARHQ review showed that PET or PET/CT had low diagnostic

accuracy. Another systematic review reported evidence supporting the use of PET/CT in monitoring response to imatinib treatment.

The evidence does not support the use of FDG-PET and FDG--PET/CT for the diagnosis and staging and restaging of soft tissue sarcoma.

The evidence supports the use of FDG-PET and FDG-PET/CT for rapid reading of response to imatinib therapy.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of soft tissue sarcoma.

TESTICULAR CANCER

Systematic Reviews

An AHRQ technology assessment conducted by Ospina et al (2008) and studies evaluating residual masses in individuals after chemotherapy for seminoma has supported the use of PET. [35,179,]

The AHRQ systematic review conducted by Matchar et al (2004) found 1 prospective study and 4 retrospective studies that generally showed higher sensitivity and specificity for PET compared with CT.[129,] However, these studies were small in size and failed to report separate results for individuals with and without seminoma. Studies also failed to report separate results by clinical stage of the disease.

In addition, studies on PET's ability to discriminate viable tumor and necrosis or 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 the use of PET leads to different patient management decisions and health outcomes compared with other imaging modalities.

Guidelines

Current NCCN guidelines for testicular cancer (v.2.2022) support the use of PET/CT to evaluate residual masses that are greater than 3 cm following primary treatment with chemotherapy (at ≥6 weeks posttreatment).[180,] If a PET/CT scan is negative, surveillance is recommended. If a PET/CT scan is positive, resection or biopsy of the residual mass is recommended. If the PET/CT scan results are indeterminate, then a repeat PET/CT is recommended in 6 to 8 weeks. Use of PET is not recommended for nonseminoma individuals.

Section Summary: Testicular Cancer

Evidence for the use of PET or PET/CT in individuals with testicular cancer consists of an AHRQ systematic review of small studies. Results showed that PET or PET/CT can be useful in evaluating residual masses following chemotherapy for seminoma. There is no evidence supporting the use of PET or PET/CT in nonseminoma individuals. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of testicular cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of testicular cancer.

THYROID CANCER

SYSTEMATIC REVIEWS

Differentiated

Schutz et al (2018) conducted a systematic review and meta-analysis of 29 prospective studies (22 differentiated, 7 medullary) investigating the staging, restaging, and recurrence of thyroid cancer.[181,] Meta-analyses showed higher sensitivity and specificity with PET compared with conventional imaging.

Haslerud et al (2016) conducted a systematic review of studies using FDG-PET to detect recurrent differentiated thyroid cancer in individuals who had undergone ablative therapy.[182,] The literature search, conducted through December 2014, identified 34 studies (N=2639) for inclusion: 17 using FDG-PET/CT, 11 using FDG-PET, and 6 using both methods. Study quality was assessed using the QUADAS tool. Pooled sensitivity and specificity for FDG-PET/CT were 80% (95% CI, 74% to 86%) and 76% (95% CI, 63% to 85%), respectively. Pooled sensitivity and specificity for FDG-PET alone were 77% (95% CI, 63% to 86%) and 76% (95% CI, 60% to 87%), respectively. Combining all 34 studies in the meta-analysis resulted in a pooled sensitivity and specificity of 79% (95% CI, 74% to 84%) and 79% (95% CI, 71% to 85%), respectively.

The NCCN report conducted by Podoloff et al (2009) showed that PET can localize recurrent disease when other imaging tests are negative.[37,] Additionally, PET was found to be prognostic in this setting, showing that more metabolically active lesions on PET were strongly correlated with reduced survival.[183,]

Medullary

A meta-analysis of studies on detecting recurrent or metastatic medullary thyroid carcinoma was conducted by Cheng et al (2012).[184,] The literature search, conducted through December 2010, identified 15 studies to be included in the meta-analysis: 8 used FDG-PET and 7 used FDG-PET/CT. The pooled sensitivity for FDG-PET alone in detecting recurrent or metastatic medullary thyroid cancer was 68% (95% CI, 64% to 72%). The pooled sensitivity for FDG-PET/CT was 69% (95% CI, 64% to 74%).

Guidelines

Current NCCN guidelines for thyroid carcinomas (v.2.2022) support use of FDG-PET/CT during disease monitoring for thyroid carcinomas when iodine-131 imaging is negative and stimulated thyroglobulin is greater than 2 to 5 ng/mL.[185,] For medullary thyroid cancer, Ga-68-dotatate PET/CT may be considered as part of the diagnostic workup, and recommend Ga-68-dotatate PET/CT or FDG-PET in certain cases for disease monitoring. Additionally, FDG-PET/CT may be considered as part of the diagnostic workup and as part of disease monitoring 3 to 6 months after initial therapy for anaplastic carcinoma.

Section Summary: Thyroid Cancer
Evidence for the use of PET and PET/CT to diagnose recurrently differentiated and medullary thyroid cancer consists of systematic reviews and meta-analyses. Pooled sensitivity and specificity for FDG-PET and FDG-PET/CT in detecting recurrent differentiated thyroid cancer were comparable, ranging from 76% to 80%. Pooled sensitivity for both PET and PET/CT in detecting recurrent medullary thyroid cancer were also comparable (68% to 69%). The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of thyroid cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of thyroid cancer.

Cancer of Unknown Primary
Burglin et al (2017) conducted a systematic review and meta-analysis on the use of PET/CT for the detection of the primary tumor in individuals with extra cervical metastases.[186,] The literature search identified 20 studies (N=1942) published between 2005 and 2016 for inclusion. The QUADAS tool was used to assess the risk of bias. In regard to patient selection and reference standard, the risk of bias was low; however, the risk of bias was high or unclear for most studies in regard to flow and timing of the index test. The pooled detection rate was 41% (95% CI, 39% to 43%), with large heterogeneity among the studies.

A larger (N=2795) systematic review conducted by Woo et al (2021) included 38 cohort studies (29 of which were retrospective) published through February 2021 assessing the effect of FDG-PET or FDG-PET/CT on patient management.[187,] Study quality was assessed using the QUADAS-2 tool; no studies were judged low risk of bias for all QUADAS-2 domains. A funnel plot analysis did not reveal publication bias (Egger's test p=.98). In pooled analysis, 35% (95% CI 31% to 40%) of individuals undergoing FDG-PET or FDG-PET/CT imaging had a change in management, although the proportions among the individual studies ranged widely from 0% to 73%, and heterogeneity was high when pooled (I^2=82%). The reason for change in management was detection of the primary cancer site in 22% (95% CI, 19% to 28%) of individuals undergoing imaging, and detection of metastatic site(s) in 14% (95% CI 10% to 19%).

No evidence was identified that evaluated the use of FDG-PET for surveillance of individuals with cancer of unknown primary.

Guidelines
Current NCCN guidelines for occult primary cancers (v.1.2023) state the PET has been useful in the diagnosis, staging, and restaging of many malignancies, so it may be warranted in some situations for cancers of unknown primary.[188,] However, the exact role of PET/CT remains undetermined. The guideline does not recommend PET/CT for the initial evaluation of cancers of unknown primary individuals, but notes that it can be useful in certain cases, especially when considering local or regional therapy.

Section Summary: Cancer of Unknown Primary
The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging of cancer of unknown primary.

Other Oncologic Applications
There are inadequate scientific data to permit conclusions on the role of PET scanning in other malignancies.

SUMMARY OF EVIDENCE

Bladder Cancer
For individuals who have suspected or diagnosed bladder cancer in need of staging or restaging information who receive ^{18}F coupled with FDG PET or FDG-PET/CT, the evidence includes a systematic review and meta-analysis. Relevant outcome is test validity. Pooled analyses showed relatively high sensitivity and specificity for muscle-invasive bladder cancer. Clinical guidelines include PET and PET/CT as considerations in staging muscle-invasive bladder cancer, though CT, magnetic resonance imaging, and chest radiographs are also appropriate techniques for staging purposes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing bladder cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Bone Sarcoma
For individuals who have suspected or diagnosed bone sarcoma and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes systematic reviews and meta-analyses. Relevant outcome is test validity. Pooled analyses have shown that PET or PET/CT can effectively diagnose and stage bone sarcoma, including chondrosarcoma. Use of PET or PET/CT has high sensitivities and specificities in detecting metastases in bone and lymph nodes; however, the tests have low sensitivity in detecting lung metastases. Clinical guidelines include PET and CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing bone sarcoma treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Brain Tumors
For individuals who have diagnosed brain tumors and in need of staging or restaging information or who have suspected brain tumor who receive FDG-PET, ^{18}F FET-PET, or ^{11}C methionine PET, the evidence includes several systematic reviews and meta-analyses. Relevant outcome is test validity. Pooled analyses have shown that PET or PET/CT can be effective in distinguishing brain tumors from normal tissue. Indirect comparisons between the radiotracers ^{11}C-methionine and FDG have shown that ^{11}C-methionine may have better diagnostic performance. Clinical guidelines include PET to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing brain cancer treatment who receive FDG-PET, ^{18}F FET-PET, or ^{11}C-methionine PET, the evidence includes systematic reviews and meta-analyses. Relevant outcome is test validity. Pooled analyses did not support the use of PET for surveillance of brain cancer following treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Breast Cancer
For individuals who have diagnosed breast cancer and inconclusive results from other imaging techniques who receive adjunctive FDG-PET or FDG-PET/CT for staging or restaging, the evidence includes meta-analyses. Relevant outcome is test validity. While studies included in the meta-analyses reported variability in estimates of sensitivity and specificity, FDG-PET or FDG-PET/CT may be helpful in situations in which standard staging results are equivocal or suspicious, particularly in individuals with locally advanced or metastatic disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or diagnosed breast cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a TEC Assessment, several systematic reviews, and meta-analyses. Relevant outcome is test validity. There is no evidence supporting the use of PET in diagnosing breast cancer. The false-negative rates (5.5% to 8.5%) using PET in individuals with breast cancer can be considered unacceptable, given that breast biopsy can provide more definitive results. Use of PET/CT may be considered for the detection of metastases only when results from other imaging techniques are inconclusive. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing breast cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cervical Cancer
For individuals who have diagnosed cervical cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes an AHRQ report and meta-analyses. Relevant outcome is test validity. Pooled results have shown that PET can be used for staging or restaging and for detecting recurrent disease. Clinical guidelines include PET and CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected cervical cancer or who are asymptomatic after completing cervical cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Colorectal Cancer
For individuals who have diagnosed CRC and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes several meta-analyses. Relevant outcome is test validity. A meta-analysis evaluating the diagnostic accuracy of PET or PET/CT found a high

sensitivity but low specificity. Several pooled analyses evaluating staging or restaging using PET or PET/CT resulted in wide ranges of sensitivities and specificities, from 16% to 99%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected CRC or who are asymptomatic after completing CRC treatment who receive FDG-PET or FDG-PET/CT, the evidence includes a RCT. Relevant outcome is test validity. The RCT found no differences in outcomes when FDG-PET/CT was added to usual surveillance compared to usual surveillance only. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Endometrial Cancer
For individuals who have diagnosed endometrial cancer in need of staging or restaging information or who are asymptomatic after completing endometrial cancer treatment who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review and meta-analysis. Relevant outcome is test validity. Pooled estimates from the meta-analysis showed high sensitivities and specificities for FDG-PET/CT in detecting lymph node metastases and endometrial cancer recurrence following treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Esophageal Cancer
For individuals who have diagnosed esophageal cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes several meta-analyses. Relevant outcome is test validity. Pooled estimates have shown high sensitivities and specificities compared to other diagnostic imaging techniques. Clinical guidelines include PET and CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected esophageal cancer or who are asymptomatic after completing esophageal cancer treatment who receive FDG-PET or FDG-PET/CT, the evidence includes meta-analyses. Relevant outcome is test validity. Pooled analyses have shown adequate sensitivities but low specificities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Gastric Cancer
For individuals who have suspected or diagnosed gastric cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes several meta-analyses. Relevant outcome is test validity. Pooled analyses, with sensitivities and specificities ranging from 78% to 88%, have shown that PET or PET/CT can inform staging or restaging of individuals with gastric cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing gastric cancer treatment who receive FDG-PET or FDG-PET/CT, the evidence includes meta-analyses. Relevant outcome is test validity. Pooled analyses have shown low sensitivities and specificities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Head and Neck Cancer
For individuals who have suspected or diagnosed head and neck cancer in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes several systematic reviews and meta-analyses. Relevant outcome is test validity. In individuals with head and neck cancers, PET and PET/CT are better able to detect local and metastatic disease compared with other imaging techniques. Evidence has also shown that FDG-PET/CT may be useful in predicting response to therapy. Two meta-analyses calculated the ability of FDG-PET or PET/CT to detect the residual or recurrent disease during various stages of treatment and another meta-analysis calculated the ability of positive PET or PET/CT results to predict OS and event-free survival. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing head and neck cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Non-Small-Cell Lung Cancer
For individuals who have suspected NSCLC and inconclusive results from other imaging techniques or who have diagnosed NSCLC and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes several meta-analyses. Relevant outcome is test validity. Pooled analyses have shown that PET and PET/CT have better diagnostic performance than conventional imaging techniques. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected NSCLC or who are asymptomatic after completing NSCLC treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Small-Cell Lung Cancer
For individuals with diagnosed SCLC and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes systematic reviews and meta-analyses. Relevant outcome is test validity. While the quality of the studies was considered low, PET and PET/CT can be considered for staging or restaging in individuals with SCLC if a limited stage is suspected. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected SCLC or who are asymptomatic after completing SCLC treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Hodgkin and Non-Hodgkin Lymphoma
For individuals who have suspected or diagnosed Hodgkin and non-Hodgkin lymphoma in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a TEC Assessment, several meta-analyses, and a RCT. Relevant outcome is test validity. Both PET and PET/CT have been found to provide useful information in the management of Hodgkin and non-Hodgkin lymphoma. The Deauville 5-point scale was developed based on PET results and can be used for staging and treatment response for individuals with lymphoma. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing Hodgkin lymphoma treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing non-Hodgkin lymphoma treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Melanoma
For individuals who have suspected or diagnosed stage I or II melanoma and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a TEC Assessment. Relevant outcome is test validity. Evidence has shown PET and PET/CT are not as beneficial as the reference standard (sentinel node biopsy) for assessing regional lymph nodes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have diagnosed advanced melanoma (stage III or IV) and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a TEC Assessment and a meta-analysis. Relevant outcome is test validity. Evidence has shown PET and PET/CT can detect systemic metastases in individuals with advanced melanoma. Clinical guidelines include PET/CT for staging or restaging stage III or IV disease and for surveillance. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing melanoma treatment who receive FDG-PET or FDG-PET/CT, the evidence includes retrospective and observational studies. Relevant outcome is test validity. At the discretion of the physician, imaging surveillance can be considered every 3 to 12 months. Because recurrences usually occur within 3 years, screening asymptomatic individuals beyond 3 to 5 years is not recommended. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Multiple Myeloma
For individuals who have suspected or diagnosed multiple myeloma in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes systematic reviews and a prospective, comparative study. Relevant outcome is test validity. The meta-

analysis reported high sensitivity in detecting extramedullary lesions in individuals with multiple myeloma. The sensitivity of FDG-PET was greater than whole body x-ray in a meta-analysis and was similar to whole-body MRI, with MRI having a higher sensitivity for detecting skull and spine bone lesions, in a prospective evaluation. Clinical guidelines include PET/CT on the list of imaging techniques that may be useful for initial workup, as well as follow-up and surveillance as indicated. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing multiple myeloma treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Neuroendocrine Tumors

For individuals who have suspected or diagnosed neuroendocrine tumors and in need of staging or restaging information or who are asymptomatic after completing neuroendocrine tumor treatment who receive FDG-PET or FDG-PET/CT, the evidence includes 2 meta-analyses. Relevant outcome is test validity. The evidence did not compare PET or PET/CT with other modalities and, therefore, did not provide comparative effectiveness information. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or diagnosed neuroendocrine tumors and in need of staging or restaging information who receive ^{68}Ga or ^{64}Cu PET or PET/CT , the evidence includes several systematic reviews with meta-analyses and prospective, comparative studies. Relevant outcome is test validity. The meta-analyses showed relatively high sensitivities and specificities using ^{68}Ga-PET/CT as the radiotracer compared with other imaging techniques in the diagnosis and staging of neuroendocrine tumors. A study comparing the diagnostic performance between ^{64}Cu PET/CT and ^{68}Ga-PET/CT reported an increase in detection of lesions with ^{64}Cu PET/CT. Current guidelines recommend using somatostatin receptor PET tracers, ^{68}Ga-dotatate, ^{68}Ga-dotatoc, or ^{64}Cu-dotatate, to assess receptor status and presence of distant disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing neuroendocrine tumor treatment who receive^{68}Ga or ^{64}Cu PET or PET/CT , there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ovarian Cancer

For individuals who have diagnosed ovarian cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes an AHRQ systematic review and several meta-analyses. Relevant outcome is test validity. Pooled sensitivities and specificities have supported the use of PET and PET/CT for the detection of recurrent ovarian cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected ovarian cancer or who are asymptomatic after completing ovarian cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Pancreatic Cancer
For individuals who have suspected or diagnosed pancreatic cancer and with inconclusive results from other imaging techniques who receive adjunctive FDG-PET or FDG-PET/CT for staging or restaging, the evidence includes a TEC Assessment, systematic reviews, and a large observational study. Relevant outcome is test validity. The evidence has shown that PET and PET/CT do not have a high enough negative predictive value to surpass current standard decision thresholds. The large observational study, which assessed the incremental diagnostic value of PET/CT when added to standard workup with CT, showed significant improvements in sensitivity and specificity compared with CT alone. Clinical guidelines state that PET or PET/CT should only be considered if the results from standard staging methods are inconclusive. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or diagnosed pancreatic cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes an AHRQ systematic review, a TEC Assessment, and a meta-analysis published after the review and assessment. Relevant outcome is test validity. The evidence has shown that PET and PET/CT do not have a high enough NPV to surpass current standard decision thresholds. Therefore, PET or PET/CT should only be considered if the results from standard staging methods are inconclusive. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing pancreatic cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Penile Cancer
For individuals who have suspected or diagnosed node negative penile cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review. Relevant outcome is test validity. The evidence has shown that PET had a low sensitivity, and no comparisons were made with other modalities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or diagnosed node positive penile cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review and a retrospective comparative study. Relevant outcome is test validity. In individuals with suspected inguinal lymph node positive disease, PET/CT may offer increased sensitivity compared to CT alone for staging. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing penile cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is

insufficient to determine that the technology results in an improvement in the net health outcome.

Prostate Cancer

For individuals who have suspected or diagnosed prostate cancer and in need of staging or restaging information who receive ^{11}C-choline PET, ^{11}C-choline PET/CT, ^{18}F-fluciclovine PET, or ^{18}F-fluciclovine PET/CT, the evidence includes several meta-analyses. Relevant outcome is test validity. Meta-analyses have reported that use of ^{11}C-choline and ^{18}F-fluciclovine radiotracers result in similar sensitivities and specificities. Prospective studies in men with biochemical recurrence after primary treatment have reported that a majority of management decisions were changed based on ^{18}F-fluciclovine PET/CT results among men with suspected recurrence. One of those studies evaluated the impact on clinical outcomes and reported an increase in 3-year event-free survival rates. Further study is needed to compare PET and PET/CT with other imaging techniques, such as MRI and radionuclide bone scan. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing prostate cancer treatment who receive ^{11}C-choline PET, ^{11}C-choline PET/CT, ^{18}F-fluciclovine PET, or^{18}F-fluciclovine PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected prostate cancer who receive ^{68}Ga-prostate-specific membrane antigen (PSMA) PET, ^{68}Ga-PSMA PET/CT, piflufolastat-F^{18} PET, and piflufolastat-F^{18} PET/CT, the evidence includes a systematic review. Relevant outcome is test validity. The systematic review found similar diagnostic accuracy for PSMA PET and MRI for detection of clinically significant prostate cancer, but evidence was too limited to draw conclusions as only 3 studies of 228 individuals were included in the analysis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have diagnosed prostate cancer and in need of staging or restaging information who receive ^{68}Ga-prostate-specific membrane antigen (PSMA) PET, ^{68}Ga-PSMA PET/CT, piflufolastat-F^{18} PET, and piflufolastat-F^{18} PET/CT, the evidence includes systematic reviews and prospective, multicenter trials. Relevant outcome is test validity. Systematic reviews have found and PSMA PET to have similar diagnostic accuracy across prostate cancer risk groups in newly diagnosed individuals, and to be similar to MRI for staging intermediate/high-risk prostate cancer. Systematic reviews of studies conducted in individuals with biochemical recurrence found high proportions with positive PSMA PET imaging, often leading to change in management. Individual prospective trials have generally found that PSMA PET provides a high specificity for detecting pelvic lymph node or distant metastases in newly diagnosed individuals with high-risk disease and a clinically relevant PPV in individuals with biochemical recurrence. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing prostate cancer treatment who receive ^{68}Ga-PSMA PET, ^{68}Ga-PSMA PET/CT, piflufolastat-F^{18} PET, and piflufolastat-F^{18} PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Renal Cell Carcinoma
For individuals who are diagnosed with renal cell carcinoma and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review and meta-analysis. Relevant outcome is test validity. The review concluded that PET has the potential to detect metastatic or recurrent lesions in individuals with renal cell cancer but that additional prospective studies are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Soft Tissue Sarcoma
For individuals who have diagnosed soft tissue sarcoma and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes an AHRQ review and a systematic review using PET for assessing response to imatinib. Relevant outcome is test validity. The review reported that PET had low diagnostic accuracy and there was a lack of studies comparing PET with alternative diagnostic modalities. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diagnosed soft tissue sarcoma and in need of rapid reading of response to imatinib treatment who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review. Relevant outcome is test validity. The review concluded that PET/CT can be used to monitor treatment response to imatinib, which can lead to individually adapted treatment strategies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected soft tissue sarcoma or who are asymptomatic after completing soft tissue sarcoma treatment who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review. Relevant outcome is test validity. The review concluded that there was insufficient evidence on the use of PET for the detection of locoregional recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Testicular Cancer
For individuals with diagnosed testicular cancer in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes an AHRQ systematic review and assessment. Relevant outcome is test validity. Results have shown that PET or PET/CT can evaluate residual masses following chemotherapy for seminoma. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. There is no evidence supporting the use of PET or PET/CT in nonseminoma individuals. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected testicular cancer or who are asymptomatic after completing testicular cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Thyroid Cancer
For individuals with diagnosed thyroid cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes systematic reviews and meta-analyses. Relevant outcome is test validity. Pooled analyses have shown that PET or PET/CT can effectively detect recurrent differentiated thyroid cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected thyroid cancer or who are asymptomatic after completing thyroid cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. Relevant outcome is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cancer of Unknown Primary and Single-Site Metastatic Disease
For individuals with cancer of unknown primary and single-site metastatic disease who receive FDG-PET or FDG-PET/CT, the evidence includes a TEC Assessment. Relevant outcome is test validity. Studies reviewed in the assessment showed that PET identified previously undetected metastases confirmed by biopsy. Additionally, PET can contribute to the management of individuals with cancer of unknown primary. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies And Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Clinical input was sought to help determine whether the use of PET imaging using either of the FDA-approved prostate-specific membrane antigen (PSMA) agents for individuals with known or suspected prostate cancer would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input on the use of PSMA PET was received from 2 society-level respondents.

For individuals with suspected or diagnosed prostate cancer who are in need of staging information and receive Ga-68 PSMA-11 PET/CT or F-18 Piflufolastat-PSMA PET/CT, clinical input provides consistent support that the use of FDA-approved PSMA PET agents provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Respondents noted such use is consistent with NCCN guidelines and SNMMI appropriate use criteria, and the high utility of PSMA PET in these clinical scenarios. In addition, respondents stated that in the ProPSMA trial (PMID 32209449), prostate cancer staging with PSMA PET was more accurate than conventional imaging, with fewer equivocal imaging results, lower radiation exposure to the patient, and greater treatment impact.

For individuals with suspected recurrence of prostate cancer based on elevated serum PSA level who receive Ga-68 PSMA-11 PET/CT or F-18 Piflufolastat-PSMA PET/CT, clinical input provides consistent support that the use of FDA-approved PSMA PET agents provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Respondents noted such use is consistent with SNMMI appropriate use criteria and that the high sensitivity of PSMA PET in localizing recurrent disease has been shown to significantly affect clinical management.

For individuals with prostate cancer and in need of workup for progression who receive Ga-68 PSMA-11 PET/CT or F-18 Piflufolastat-PSMA PET/CT, clinical input provides consistent support that the use of FDA-approved PSMA PET agents provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Respondents provided examples of the effective use of PSMA PET imaging in accurate diagnosis of progression and noted that use of PSMA PET imaging in this clinical context is consistent with NCCN and SNMMI guidelines.

Respondents believe there is compelling evidence supporting the use of PSMA PET imaging modalities in changing disease management for the benefit of patients, while recognizing that no single imaging method should be used for all potential clinical situations (diagnosis, staging and restaging, and surveillance) because use is dependent on a strictly defined clinical context based on FDA labeling.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Current National Comprehensive Cancer Network, American College of Radiology, and other relevant U.S.-based guidelines are summarized in each section of the Rationale.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in July 2024 identified a large number of ongoing and unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
78608	Brain imaging, positron emission tomography (PET); metabolic evaluation
78609	Brain imaging, positron emission tomography (PET); perfusion evaluation
78811	Positron emission tomography (PET) imaging; limited area (e.g. Chest, head/neck)
78812	Positron emission tomography (PET) imaging; skull base to mid-thigh
78813	Positron emission tomography (PET) imaging; whole body
78814	Tumor imaging, positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization; limited area (e.g. chest, head/neck)
78815	Tumor imaging, positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization; skull base to mid-thigh
78816	Tumor imaging, positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization; whole body
A9515	Choline C-11, diagnostic, per study dose up to 20 millicuries
A9526	Nitrogen N-13 ammonia, diagnostic, per study dose, up to 40 millicuries
A9552	Fluorodeoxyglucose F-18 FDG, diagnostic, per study dose, up to 45 millicuries
A9580	Sodium fluoride F-18, diagnostic, per study dose, up to 30 millicuries
A9587	Gallium ga-68, dotatate, diagnostic, 0.1 millicurie
A9588	Fluciclovine f-18, diagnostic, 1 millicurie
A9591	Fluoroestradiol f 18, diagnostic, 1 millicurie
A9592	Copper cu-64, dotatate, diagnostic, 1 millicurie
A9593	Gallium ga-68 psma-11, diagnostic, (ucsf), 1 millicurie
A9594	Gallium ga-68 psma-11, diagnostic, (ucla), 1 millicurie
A9595	Piflufolastat f-18, diagnostic, 1 millicurie
A9596	Gallium ga-68 gozetotide, diagnostic, (illuccix), 1 millicurie
A9597	Positron emission tomography radiopharmaceutical, diagnostic, for tumor identification, not otherwise classified
A9598	Positron emission tomography radiopharmaceutical, diagnostic, for non-tumor identification, not otherwise classified
A9608	Flotufolastat f 18, diagnostic, 1 millicurie
A9800	Gallium Ga-68 gozetotide, diagnostic, (Locametz), 1 mCi

G0219	PET imaging whole body; melanoma for noncovered indications
G0235	PET imaging, any site, not otherwise specified
G0252	PET imaging, full and partial-ring PET scanners only, for initial diagnosis of breast cancer and/or surgical planning for breast cancer (e.g., initial staging of axillary lymph nodes)

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10-30-2013	Oncologic Applications was originally part of the Positron Emission Tomography (PET) medical policy. Oncologic Applications has been pulled out and placed into a separate medical policy, Positron Emission Tomography (PET): Oncologic Applications. The medical policy language was unchanged.
	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis codes *(Effective October 1,2014)*
	Updated Reference section.
10-28-2014	In Coding section: ▪ Removed ICD-9 Diagnosis code 793.1 (expired 09/30/2011) ▪ Added ICD-9 Diagnosis code 793.19
10-22-2015	Description section updated
	In Policy section: ▪ Revised to current policy language by location of cancer from the following policy language by diagnosing, staging, re-staging: "I. PET scan with or without PET/CT fusion is considered medically necessary for the following tumors when results are expected to influence treatment decisions and standard imaging (e.g., CT, MRI or ultrasound) is inconclusive or not indicated: A. Diagnosing or Staging 1. Bone—Ewing sarcoma and osteosarcoma; 2. Brain; 3. Breast (except initial staging of axillary lymph nodes); 4. Cervix; 5. Colorectal; 6. Esophageal; 7. Gastric Cancer; 8.Gastrointestinal Stromal Tumors; 9. Kidney Cancer; 10. Head and Neck; 11. Lung: •Non-Small Cell (NSCLC), •Small Cell (SCLC), •Evaluation of Solitary Pulmonary Nodule; 12. Lymphoma: •Hodgkin's, •Non-Hodgkin's; 13. Melanoma (except initial evaluation of regional lymph nodes); 14. Musculoskeletal (including soft tissue sarcoma); 15. Myeloma; 16. Neuroblastoma; 17. Neuroendocrine Tumor, poorly differentiated; 18. Pancreas; 19. Thyroid; 20. Cancer of Unknown Primary; 21. Paraneoplastic Syndromes; B. Re-Staging 1. Brain; 2. Breast; 3. Cervix; 4. Colorectal; 5. Esophageal; 6. Gastric Cancer; 7. Gastrointestinal Stromal Tumors; 8. Head and Neck; 9. Kidney Cancer; 10 Lung – Non-Small Cell (NSCLC); 11. Lymphoma: •Hodgkin's, •Non-Hodgkin's; 12. Melanoma; 13. Myeloma; 14.Musculoskeletal (including Soft Tissue Sarcoma); 15. Neuroblastoma; 16. Neuroendocrine Tumor, poorly differentiated; 17. Ovarian 18. Testicular; 19. Thyroid C. Other oncologic indications may be considered medically necessary on a case by case basis when results are expected to influence treatment decisions. D. Experimental / experimental / investigational oncologic application include, but not limited to: 1. Initial therapy for ovarian cancer or testicular cancer; or

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	2. Subsequent therapy for small cell lung cancer (SCLC) or pancreatic cancer; or 3. Diagnosis and management of prostate cancer; or 4. To determine early response to treatments (PET scans done during a course of chemotherapy of reduction therapy). E. Surveillance Intermittent surveillance scanning for Ewing Sarcoma is considered medically necessary." ▪ Policy Guidelines Updated
	Rationale section updated
	In Coding section: ▪ Added CPT and HCPCS Codes: 78608, 78609, G0252 ▪ Updated Coding notations
	References updated
10-22-2015	Published 10-22-2015. Effective 10-22-2015.
	▪ Correction to 10-22-2015 Revision section above. ▪ In Coding section changed "G0525" to "G0252" to read, "Added CPT and HCPCS Codes: 78608, 78609, G0252"
10-01-2015	Published 11-10-2015. Effective 10-01-2015 with ICD-10 coding implementation.
	In Coding Section: ▪ Removed ICD-10 Codes: C34.10, C47.10, C47.20, C49.10, C49.20, C50.911, C50.912, C50.921, C50.922, C74.91, C74.92, C84.70 ▪ Added ICD-10 Codes: C16.5, C16.6, C47.9, C4A.0, C4A.11, C4A.12, C4A.21, C4A.22, C4A.31, C4A.39, C4A.4, C4A.51, C4A.52, C4A.59, C4A.61, C4A.62, C4A.71, C4A.72, C4A.8, C7A.010, C7A.011, C7A.012, C7A.019, C7A.020, C7A.021, C7A.022, C7A.023, C7A.024, C7A.025, C7A.026, C7A.029, C7A.090, C7A.091, C7A.092, C7A.093, C7A.094, C7A.095, C7A.096, C7A.098, C7A.1, C7A.8, C80.0, C80.1, C81.01, C81.02, C81.03, C81.04, C81.05, C81.06, C81.07, C81.08, C81.09, C81.11, C81.12, C81.13, C81.14, C81.15, C81.16, C81.17, C81.18, C81.19, C81.21, C81.22, C81.23, C81.24, C81.25, C81.26, C81.27, C81.28, C81.29, C81.31, C81.32, C81.33, C81.34, C81.35, C81.36, C81.37, C81.38, C81.39, C81.41, C81.42, C81.43, C81.44, C81.45, C81.46, C81.47, C81.48, C81.49, C81.71, C81.72, C81.73, C81.74, C81.75, C81.76, C81.77, C81.78, C81.79, C81.91, C81.92, C81.93, C81.94, C81.95, C81.96, C81.97, C81.98, C81.99, C82.01, C82.02, C82.03, C82.04, C82.05, C82.06, C82.07, C82.08, C82.09, C82.11, C82.12, C82.13, C82.14, C82.15, C82.16, C82.17, C82.18, C82.19, C82.22, C82.23, C82.24, C82.25, C82.26, C82.28, C82.29, C82.31, C82.32, C82.33, C82.34, C82.35, C82.36, C82.37, C82.38, C82.39, C82.41, C82.42, C82.43, C82.44, C82.45, C82.46, C82.47, C82.48, C82.49, C82.51, C82.52, C82.53, C82.54, C82.55, C82.56, C82.57, C82.58, C82.59, C82.61, C82.62, C82.63, C82.64, C82.65, C82.66, C82.67, C82.68, C82.69, C82.81, C82.85, C82.89, C82.90, C82.91, C82.95, C82.99, C84.01, C84.02, C84.03, C84.04, C84.05, C84.06, C84.07, C84.08, C84.09, C84.11, C84.12, C84.13, C84.14, C84.15, C84.16, C84.17, C84.18, C84.19, C84.41, C84.42, C84.43, C84.44, C84.45, C84.46, C84.47, C84.48, C84.49, C84.90, C84.91, C84.93, C84.95, C84.96, C84.97, C84.98, C84.99, C84.A1, C84.A3, C84.A5, C84.A6, C84.A7, C84.A8, C84.A9, C84.Z1, C84.Z2, C84.Z3, C84.Z4, C84.Z5, C84.Z6, C84.Z7, C84.Z8, C84.Z9, C85.11, C85.13, C85.14, C85.16, C85.17, C85.18, C85.19, C85.81, C85.82, C85.83, C85.84, C85.85, C85.86, C85.87, C85.88, C85.89, C85.91, C85.92, C85.93, C85.94, C85.95, C85.96, C85.97, C85.98, C85.99, C86.0, C86.1, C86.2, C86.3, C86.4, C88.2, C88.3, C88.4, C88.8, C88.9, C90.00, C90.01, C90.02, C90.20, C90.21, C90.22, C90.30, C90.31, C90.32, C91.40, C91.41, C91.42, C96.0, C96.2, C96.4, C96.9, C96.A, C96.Z, D00.1, D01.0, D01.1, D01.2, D01.3, D01.7, D02.21, D02.22, D06.0, D06.1, D06.7, D07.39,

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	D09.3, D09.8, D12.0, D12.1, D12.2, D12.3, D12.4, D12.5, D12.7, D12.8, D12.9, D13.0, D14.31, D14.32, D35.01, D35.02, D37.1, D37.2, D37.3, D37.4, D37.5, D37.8, D37.9, D38.1, D3A.010, D3A.011, D3A.012, D3A.019, D3A.020, D3A.021, D3A.022, D3A.023, D3A.024, D3A.025, D3A.026, D3A.029, D3A.090, D3A.091, D3A.092, D3A.093, D3A.094, D3A.095, D3A.096, D3A.098, D3A.8, D43.0, D43.1, D43.4, D44.6, D44.7, D47.Z9, D48.1, D48.2, D49.0, D49.1, D49.6, J98.4, K63.5, R22.0, R22.1, R59.0, R59.1, R59.9, R76.0, R76.8, R76.9, R90.0, Z85.01, Z85.038, Z85.048, Z85.118, Z85.12, Z85.20, Z85.21, Z85.22, Z85.238, Z85.29, Z85.43, Z85.71, Z85.72, Z85.79, Z85.810, Z85.818, Z85.819, Z85.820, Z85.850
10-01-2016	In Coding section: ▪ ICD-10 Codes Added Effective 10-01-2016: C49.A1, C49.A2, C49.A3, C49.A4, C49.A5, C49.A9 ▪ ICD-10 Codes Revised Effective 10-01-2016: C7A.094, C7A.095, C7A.096, C81.11, C81.12, C81.13, C81.14, C81.15, C81.16, C81.17, C81.18, C81.19, C81.21, C81.22, C81.23, C81.24, C81.25, C81.26, C81.27, C81.28, C81.29, C81.31, C81.32, C81.33, C81.34, C81.35, C81.36, C81.37, C81.38, C81.39, C81.41, C81.42, C81.43, C81.44, C81.45, C81.46, C81.47, C81.48, C81.49, C81.71, C81.72, C81.73, C81.74, C81.75, C81.76, C81.77, C81.78, C81.79, D3A.094, D3A.095, D3A.096
10-01-2017	In Coding section: ▪ Added HCPCS Codes: A9515, A9587, A9588, A9598 ▪ Added ICD Codes: C96.20, C96.21, C96.22, C96.29 ▪ Removed ICD Code: C96.2 ▪ Updated Coding notations.
10-01-2018	In Coding section: ▪ Added ICD-10 Codes: C43.111, C43.112, C43.121, C43.122, C4A.111, C4A.112, C4A.121, C4A.122, D03.111, D03.112, D03.121, D03.122 ▪ Removed ICD-10 Codes: C43.11, C43.12, C4A.11, C4A.12, D03.11, D03.12
02-18-2019	Policy published 01-18-2019. Policy effective 02-18-2019.
	Description section updated
	In Policy section: ▪ Added Bladder Cancer indication to read "A. Bladder Cancer 1. PET scanning may be considered medically necessary in the staging or restaging of muscle-invasive bladder cancer when CT or magnetic resonance imaging are not indicated or remained inconclusive on distant metastasis. 2. PET scanning is considered experimental / investigational for bladder tumors that have not invaded the muscle (stage <cT2). ▪ In Item B added "or restaging" to read "PET scanning may be considered medically necessary in the staging or restaging of Ewing sarcoma and osteosarcoma." ▪ Added Brain Cancer indication to read "C. Brain Cancer 1. PET scanning may be considered medically necessary in the staging or restaging of brain cancer." ▪ In Item G added "Endometrial Cancer PET scanning is considered medically necessary in the: 1. Detection of lymph node metastases, and 2. Assessment of endometrial cancer recurrence." ▪ In Item J 1 a added "Initial" to read "Initial diagnosis of suspected cancer" ▪ In Item J added 1 c "Evaluation of response to treatment" ▪ In Item K added "2. PET scanning may be considered medically necessary in staging of small-cell lung cancer if limited stage is suspected based on standard imaging."

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	▪ In Item K 3 added "if extensive stage is established and in all other aspects of managing small cell lung cancer" to read "PET scanning is considered experimental / investigational in staging of small-cell lung cancer if extensive stage is established and in all other aspects of managing small-cell lung cancer." ▪ In Item M 1 added "for advanced disease (stage III or IV)" to read "PET scanning may be considered medically necessary as a technique for assessing extranodal spread of malignant melanoma at initial staging or at restaging during follow-up treatment for advanced disease (stage III or IV)." ▪ In Item M added "2. PET scanning is considered experimental / investigational in managing stage 0, I, or II melanoma" ▪ In Item N (Multiple Myeloma) removed "PET scanning is considered experimental / investigational in all aspects of managing multiple myeloma" and added "1. PET scanning is considered medically necessary in the staging or restaging of multiple myeloma, particularly if the skeletal survey is negative." This item was previously listed in an E/I section, so is not new to the policy, but the policy position is changed. ▪ In Item O (Neuroendocrine Tumors) added "1. PET scanning is considered experimental / investigational in all aspects of managing neuroendocrine tumors." This item was previously listed in an E/I section, so is not new to the policy but the policy position is changed. ▪ In Item O 2 (Neuroendocrine Tumors) added "with all other radiotracers" to read "PET scanning with all other radiotracers is considered experimental / investigational in all aspects of managing neuroendocrine tumors." ▪ In Item R added "Penile Cancer PET scanning is considered experimental / investigational in all aspects of managing penile cancer." This item was previously listed in an E/I section, so is not new to the policy. ▪ Added Item S "Prostate Cancer "1. PET scanning with 11 choline and fluorine 18 fluciclovine may be medically necessary for evaluating suspected or biochemically recurrent prostate cancer after primary treatment to detect small volume disease in soft tissues. 2. PET scanning with gallium 68 is considered experimental / investigational in all aspects of managing prostate cancer. 3. PET scanning for all other indications in known or suspected prostate cancer is considered experimental / investigational. This item was previously listed in an E/I section, so is not new to the policy but the policy position is changed. Added Item T "Renal Cell Carcinoma PET scanning is considered experimental / investigational in all aspects of managing renal cancer." ▪ In Item U (Soft Tissue Sarcoma) removed "Evaluating response to imatinib and other treatments for gastrointestinal stromal tumors" and added "1. PET scanning is considered medically necessary for evaluating response to imatinib and other treatments for gastrointestinal stromal tumors" ▪ In Item X added "Cancer of" to "Unknown Primary" to read "Cancer of Unknown Primary" ▪ Removed "Other Oncologic Applications 1. Other oncologic applications of PET scanning, including but not limited to the following, are considered experimental / investigational: a. Diagnosis and management of known or suspected prostate cancer b. Diagnosis of brain tumors

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	c. Staging of multiple myeloma d. Evaluation of neuroendocrine tumors e. Staging inguinal lymph nodes in patients with squamous cell carcinoma of the penis. Policy Guidelines updated
	Rationale section updated
	In Coding section: ▪ Added CPT Code: A4641 ▪ Added ICD Codes: C00.0, C00.1, C00.3, C00.4, C00.6, C00.8, C00.9, C01, C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C03.0, C03.1, C43.111, C43.112, C43.121, C43.122, C48.0, C4A.111, C4A.112, C4A.121, C4A.122, C54.1, C60.1, C60.2, C60.8, C61, C67.0, C67.1, C67.2, C67.3, C67.4, C67.5, C67.6, C67.7, C67.8, C67.9, C70.0, C70.1,C78.2, C78.6, C82.21, C82.82, C82.83, C82.84, C82.86, C82.87, C82.88, C84.92, C84.94, C84.A2, C84.A4, C88.0, D03.111, D03.112, D03.121, D03.122, R91.1, ▪ Removed ICD Codes: C34.91, C34.92, C62.91, C62.92, C80.1, C81.91, C81.92, C81.93, C81.94, C81.95, C81.96, C81.97, C81.98, C81.99, C82.90, C82.91, C82.92, C82.93, C82.94, C82.95, C82.96, C82.97, C82.98, C82.99, C84.90, C91.40, C91.41, C91.42, D3A.8, J98.4, K63.5, R22.0, R22.1, R59.0, R59.1, R59.9, Z85.01, Z85.038, Z85.048, Z85.118, Z85.12, Z85.20, Z85.21, Z85.22, Z85.238, Z85.29, Z85.43, Z85.71, Z85.72, Z85.79, Z85.810, Z85.818, Z85.819, Z85.820, Z85.850 ▪ Updated Coding notations
	References updated
06-12-2020	Description section updated
	In Policy Section: ▪ In Item B revised "Bone Cancer" to "Bone Sarcoma"
	Rationale section updated
	References updated
05-23-2021	Description section updated
	Rationale section updated
	In Coding section added HCPCS codes A9592 and A9597
	References updated
	Added Appendix
07-01-2021	In Coding section: ▪ Added codes A9593 and A9594 (effective 7/1/21)
10-01-2021	In Coding section Effective 10-01-2021 In ICD-10 codes Added C56.3, C79.63, C84.7A
02-14-2022	Updated Description Section
	Updated Policy Section ▪ Added in O1 "and copper 64" ▪ Added R1 PET scanning may be considered medically necessary for staging and restaging in patients with suspected inguinal lymph node positive disease. ▪ Added R2 changed "all aspects" to "all other aspects" ▪ Added S2 "prostate -specific membrane antigen and piflufolastat fluorine-18"
	Updated Rationale section
	Updated References section
07-01-2022	Updated Coding Section ▪ Added: A9596
11-27-2022	Updated Description Section
	Updated Policy Section

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Section S Prostate Cancer

- Section S1 Added: "carbon" to "PET scanning with carbon 11 choline"
- Section S2 Changed: experimental and investigational statement to medically necessary criteria. Reads:

  2. PET scanning with gallium 68-prostate-specific membrane antigen and piflufolastat fluorine-18 may be considered medically necessary for any of the following applications:
     a. Individuals with diagnosed prostate cancer in need of staging information and:
        i. NCCN unfavorable intermediate-, high-, or very-high-risk prostate cancer (see Policy Guidelines); OR
        ii. NCCN unfavorable intermediate-, high-, or very-high-risk prostate cancer with equivocal results or oligometastatic disease on initial conventional imaging (see Policy Guidelines).
     b. Individuals with suspected recurrence of prostate cancer based on serum PSA level who have received:
        i. Radical prostatectomy with PSA level persistence or rise from undetectable level (see Policy Guidelines); OR
        ii. Definitive radiotherapy with PSA rise above nadir (see Policy Guidelines).
     c. Individuals with treated prostate cancer (including active surveillance/observation) in need of imaging as part of a workup for progression (see Policy Guidelines).
     d. Individuals with metastatic prostate cancer for whom lutetium Lu-177 vipivotide tetraxetan PSMA-directed therapy is indicated.
- Added Section S3: "Use of gallium 68-prostate-specific membrane antigen and piflufolastat fluorine-18 in known or suspected prostate cancer is considered experimental / investigational for all other indications, including diagnosis, primary staging of very-low, low- or favorable intermediate-risk prostate cancer, and evaluation of response to therapy."

Updated Policy Guidelines

- Added Section C:

C. Prostate-Specific Membrane Antigen Positron Emission Tomography

1. Appropriate selection of patients for prostate-specific membrane antigen (PSMA) PET imaging may be guided according to National Comprehensive Cancer Network (NCCN) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) criteria (see policy section ^{68}Ga-PSMA PET, ^{68}Ga-PSMA PET/CT, Piflufolastat-F^{18} PET, and Piflufolastat-F^{18} PET/CT Guidelines). NCCN and SNMMI recommendations for use of PSMA PET in individuals with newly diagnosed prostate cancer in need of staging are based on the following NCCN risk criteria:

Risk Group	Clinical/Pathological Features
Very Low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g
Low	Has all of the following but does not qualify for very low risk:

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	• cT1–cT2a • Grade Group 1 • PSA <10 ng/mL

Intermediate	Has all of the following:
	• No high-risk group features
	• No very-high-risk group features
	• Has one or more intermediate risk factor:
	  ○ cT2b–cT2c
	  ○ Grade Group 2 or 3
	• PSA 10–20 ng/mL

Favorable Intermediate	Intermediate risk criteria, AND all of the following: • 1 intermediate risk factor • Grade Group 1 or 2 • <50% biopsy cores positive (e.g., <6 of 12 cores)
Unfavorable Intermediate	Intermediate risk criteria AND one or more of the following: • 2 or 3 intermediate risk factors • Grade Group 3 • ≥50% biopsy cores positive (e.g., ≥6 of 12 cores)
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL
Very High	Has at least one of the following: • cT3b– cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5

2. Individuals who meet unfavorable intermediate-, high- and very-high risk criteria are suitable candidates for PSMA PET bone and/or soft tissue imaging, either following equivocal results on initial conventional imaging (e.g., MRI) or as alternative to conventional imaging.
3. PSMA PET imaging is not recommended for staging newly diagnosed individuals in very low, low, or favorable intermediate NCCN risk groups, or for individuals with suspected prostate cancer based on elevated PSA, increasing PSA on serial measurements, and/or clinical signs (e.g., abnormal digital rectal exam).
4. Use of PSMA PET imaging is appropriate for individuals who have undergone radical prostatectomy or radiation therapy for prostate cancer with subsequent suspected persistence or recurrence. Specific considerations for use of PSMA PET are:
    c. Following radical prostatectomy AND:
        i. Failure of PSA to fall to undetectable levels; OR
        ii. Previously undetectable PSA with a subsequent detectable PSA that increases on ≥2 measurements
    d. Following definitive radiation therapy AND:
        i. A PSA rise ≥2 ng/mL above the nadir; OR

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	ii. A positive digital rectal exam. 5. PSMA PET may also be considered when PSA has been confirmed to be increasing after radiation therapy even if the increase above nadir is not yet 2 ng/mL, particularly in candidates with a favorable prognosis for salvage local therapy. 6. PSMA PET use is appropriate in individuals who have previously been treated for prostate cancer (including those under active surveillance/observation) who require imaging as part of a workup for progression. NCCN guidelines include recommended workup protocols, which vary according to prior treatment and cancer stage. The guidelines recommend use of PSMA PET bone and soft tissue imaging when conventional imaging results are equivocal, but also state that PSMA PET imaging is more accurate than conventional imaging at detecting micrometastatic disease, and as such, the guidelines note that conventional imaging is not a necessary prerequisite to PSMA PET imaging.
	Update Rationale Section
	Updated Coding Section ▪ Added: A9591, A9595, and A9800 ▪ Removed: A4641 ▪ Changed ICD-10 Diagnoses Box: form ICD-10 codes to statement "An appropriate ICD-10 diagnosis code should be used when reporting negative Positron Emission Tomography (PET) Scanning: Oncologic Applications" ▪ Removed ICD-10 codes: C00.0, C00.1, C00.3, C00.4, C00.6, C00.8, C00.9, C01, C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C03.0, C03.1, C04.0, C04.1, C04.8, C05.0, C05.1, C05.2, C05.8, C06.0, C06.1, C06.2, C06.89, C09.0, C09.1, C09.8, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C11.0, C11.1, C11.2, C11.3, C11.8, C12, C13.0, C13.1, C13.2, C13.8, C14.2, C14.8, C15.3, C15.4, C15.5, C15.8, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C19, C20, C21.1, C21.2, C21.8, C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8, C26.1, C26.9, C30.0, 30.1, C31.0, C31.1, C31.2, C31.3, C31.8, C32.0, C32.1, C32.2, C32.3, C32.8, C33, C34.01, C34.02, C34.11, C34.12, C34.2, C34.31, C34.32, C34.81, C34.82, C40.01, C40.02, C40.11, C40.12, C40.21, C40.22, C40.31, C40.32, C40.81, C40.82, C40.91, C40.92, C41.0, C41.1, C41.2, C41.3, C41.4, C43.0, C43.111, C43.112, C43.121, C43.122, C43.21, C43.22, C43.31, C43.39, C43.4, C43.51, C43.52, C43.59, C43.61, C43.62, C43.71, C43.72, C43.8, C47.0, C47.11, C47.12, C47.21, C47.22, C47.3, C47.4, C47.5, C47.8, C47.9, C48.0, C49.0, C49.11, C49.12, C49.21, C49.22, C49.3, C49.4, C49.5, C49.8, C49A1, C49A2, C49A3, C49A4, C49A5, C49A9, C4A.0, C4A.111, C4A.112, C4A.121, C4A.122, C4A.21, C4A.22, C4A.31, C4A.39, C4A.4, C4A.51, C4A.52, C4A.59, C4A.61, C4A.62, C4A.71, C4A.72, C4A.8, C50.011, C50.012, C50.021, C50.022, C50.111, C50.112, C50.121, C50.122, C50.211, C50.212, C50.221, C50.222, C50.311, C50.312, C50.321, C50.322, C50.411, C50.412, C50.421, C50.422, C50.511, C50.512, C50.521, C50.522, C50.611, 50.612, C50.621, C50.622, C50.811, C50.812, C50.821, C50.822, C51.8, C53.0, C53.1, C53.8, C54.1, C56.1, C56.2, C56.3, C57.4, C57.8, C60.0, C60.1, C60.2, C60.8, C61, C62.01, C62.02, C62.11, C62.12, C64.1, C64.2, C65.1, C65.2, C67.0, C67.1, C67.2, 67.3, C67.4, C67.5, C67.6, C67.7, C67.8, C67.9, C70.0, C70.1, C71.0, C71.1, C71.2, C71.3, C71.4, 71.5, C71.6, C71.7, C71.8, C71.9, C72.0, C72.1, C72.21, C72.22, C72.31, 72.32, C72.41, C72.42, C72.59, C72.9, C73, C74.01, C74.02, C74.11, C74.12, C75.1, C75.2, C75.3, C75.4, C75.5, C76.0, C78.01, C78.02, C78.2, C78.5, C78.6, 78.7, C78.89, C79.31, C79.49, C79.61, C79.62, C79.3, C79.81, C79.82, C7A.010, C7A.011, C7A.012, C7A.019, C7A.020, C7A.021, C7A.022, C7A.023, C7A.024, C7A.025, C7A.026, C7A.029, C7A.090, C7A.091, C7A.092, C7A.093, C7A.094, C7A.095, C7A.096, C7A.098, C7A.1, C7A.8, C80.0, C81.01, C81.02, C81.03, C81.04, C81.05, C81.06, C81.07, C81.08, C81.09, C81.11, C81.12, C81.13, C81.14, C81.15, C81.16, C81.17, C81.18, C81.19, C81.21, C81.22, C81.23, C81.24, C81.25, C81.26, C81.27, C81.28, C81.29, C81.31, C81.32, C81.33, C81.34, C81.35, C81.36, C81.37, C81.38, C81.39,C81.41, C81.42, C81.43, C81.44, C81.45, C81.46, C81.47, C81.48, C81.49, C81.71, C81.72, C81.73, C81.74, C81.75, C81.76, C81.77, C81.78, C81.79, C82.01, C82.02, C82.03, C82.04, C82.05, C82.06, C82.07, C82.08,C82.09, C82.11, C82.12, C82.13, C82.14, C82.15, C82.16, C82.17, C82.18, C82.19, C82.21, C82.22, C82.23, C82.24, C82.25, C82.26, C82.28, C82.29, C82.31, C82.32, C82.33, C82.34, C82.35, C82.36, C82.37, C82.38, C82.39, C82.41, C82.42, C82.43, C82.44, C82.45, C82.46, C82.47, C82.48, C82.49, C82.51, C82.52, C82.53, C82.54, C82.55, C82.56, C82.57, C82.58, C82.59, C82.61, C82.62, C82.63, C82.64, C82.65, C82.66, C82.67, C82.68, C82.69, C82.81, C82.82, C82.83, C82.84, C82.85, C82.86, C82.87, C82.88, C82.89, C83.01, C83.02, C83.03, C83.04, C83.05, C83.06, C83.07, C83.08, C83.09, C83.11, C83.12, C83.13, C83.14, C83.15, C83.16, C83.17, C83.18, C83.19,

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	C83.31, C83.32, C83.33, C83.34, C83.35, C83.36, C83.37, C83.38, C83.39, C83.51, C83.52, C83.53, C83.54, C83.55, C83.56, C83.57, C83.58, C83.59, C83.71, C83.72, C83.73, C83.74, C83.75, C83.76, C83.77, C83.78, C83.79, C83.81, C83.82, C83.83, C83.84, C83.85, C83.86, C83.87, C83.88, C83.89, C83.91, C83.92, C83.93, C83.94, C83.95, C83.96, C83.97, C83.98, C83.99, C84.01, C84.02, C84.03, C84.04, C84.05, C84.06, C84.07 C84.08 C84.09 C84.11 C84.12 C84.13 C84.14, C84.15, C84.16, C84.17, C84.18, C84.19, C84.41, C84.42, C84.43, C84.44, C84.45, C84.46, C84.47, C84.48, C84.49, C84.61, C84.62, C84.63, C84.64, C84.65, C84.66, C84.67, C84.68, C84.69, C84.71, C84.72, C84.73, C84.74, C84.75, C84.76, C84.77, C84.78, C84.79, C84.7A, C84.91, C84.92, C84.93, C84.94, C84.95, C84.96, C84.97, C84.98, C84.99, C84.A1, C84.A2, C84.A3, C84.A4, C84.A5, C84.A6, C84.A7, C84.A8, C84.A9, C84.Z1, C84.Z2, C84.Z3, C84.Z4, C84.Z5, C84.Z6, C84.Z7, C84.Z8, C84.Z9, C85.11, C85.13, C85.14, C85.16, C85.17, C85.18, C85.19, C85.21, C85.22, C85.23, C85.24, C85.25, C85.26, C85.27, C85.28, C85.29, C85.81, C85.82, C85.83, C85.84, C85.85, C85.86, C85.87, C85.88, C85.89, C85.91, C85.92, C85.93, C85.94, C85.95, C85.96, C85.97, C85.98, C85.99, C86.0, C86.1, C86.2, C86.3, C86.4, C86.5, C86.6, C88.0, C88.2, C88.3, C88.4, C88.8, C88.9, C90.00, C90.01, C90.02, C90.20, C90.21, C90.22, C90.30,C90.31, C90.32, C96.0, C96.20, C96.21, C96.22, C96.29, C96.4, C96.9, C96.A, C96.Z, D00.1, D01.0, D01.1, D01.2, D01.3, D01.7, D02.21, D02.22, D03.0, D03.111, D03.112, D03.121, D03.122, D03.21, D03.22, D03.39, D03.4, D03.51, D03.52, D03.59, D03.61, D03.62, D03.71, D03.72, D03.8, D06.0, D06.1, D06.7, D07.39, D09.3, D09.8, D12.0, D12.1, D12.2, D12.3, D12.4, D12.5, D12.7, D12.8, D12.9, D13.0, D14.31, D14.32, D35.01, D35.02, D37.1, D37.2, D37.3, D37.4, D37.5, D37.8, D37.9, D38.1, D3A.010, D3A.011, D3A.012, D3A.019, D3A.020, D3A.021, D3A.022, D3A.023, D3A.024, D3A.025, D3A.026, D3A.029, D3A.090, D3A.091, D3A.092, D3A.093, D3A.094, D3A.095, D3A.096, D3A.098, D43.0, D43.1, D43.4, D44.6, D44.7, D47.Z9, D48.1, D48.2,D49.0, D49.1, D49.6, R76.0, R76.8, R76.9, R90.0, R91.1 ▪ Removed Coding Bullets o A PET scan involves 3 separate activities: o (1) manufacture of the radiopharmaceutical, which may be on site or at a regional center with delivery to the institution performing PET; o (2) actual performance of the PET scanner; and o (3) interpretation of the results. o o Two 2 new modifiers were added in July 2009. The modifiers are: o PI - Positron emission tomography (PET) or PET/computed tomography (CT) to inform the initial treatment strategy of tumors that are biopsy proven or strongly suspected of being cancerous based on other diagnostic testing, 1 per cancer diagnosis o PS - Positron emission tomography (PET) or PET/computed tomography (CT) to inform the subsequent treatment strategy of cancerous tumors when the beneficiary's treating physician determines that the PET study is needed to inform subsequent anti-tumor strategy
	Updated References Section
	Removed Appendix
01-05-2024	Medical policy reviewed with no updates made.
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box
11-20-2024	Updated Description Section
	Updated Policy Section ▪ Added to Section S Prostate Cancer: ▪ Added: "flotufolastat fluorine-18" to S2 and S3
	Updated Policy Guidelines ▪ Added to Selection Criteria: "Selection criteria for PET scanning may also be complex. For example, it may be difficult to determine from claims data whether a PET scan in an individual 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 an individual with colorectal cancer is being performed to detect

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	hepatic disease or evaluate local recurrence. Due to the complicated hierarchy of imaging options in individuals with malignancy and complex selection criteria, a possible implementation strategy for this policy is its use for retrospective review, possibly focusing on cases with multiple imaging tests, including PET scans." Update Rationale Section Updated Coding Section ▪ Added: A9608 Updated References Section

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