

## Medical Policy



**Title: PET Scanning- Oncologic Applications (Hematologic)**

Related Policies:	<ul style="list-style-type: none"> <li>▪ <i>PET Scanning- Oncologic Applications (Breast and Gynecologic)</i></li> <li>▪ <i>PET Scanning- Oncologic Applications (Thyroid, Neuroendocrine, Head and Neck)</i></li> <li>▪ <i>PET Scanning- Oncologic Applications (Bone and Sarcoma)</i></li> <li>▪ <i>PET Scanning- Oncologic Applications (Lung)</i></li> <li>▪ <i>PET Scanning- Oncologic (Brain, Melanoma, Unknown Primary)</i></li> <li>▪ <i>PET Scanning- Oncologic Applications (Genitourinary)</i></li> <li>▪ <i>PET Scanning- Oncologic Applications (Gastrointestinal and Pancreatic)</i></li> <li>▪ <i>PET Scanning: Cardiac Applications</i></li> <li>▪ <i>PET Scanning: In Oncology to Detect Early Response during Treatment</i></li> <li>▪ <i>PET Scanning: Miscellaneous (Non-cardiac, Non-oncologic) Applications of Fluorine 18 Fluorodeoxyglucose</i></li> </ul>
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<b>Professional / Institutional</b>
Original Effective Date: October 1, 1997 / September 11, 2004
Latest Review Date: February 27, 2025
Current Effective Date: February 27, 2025

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With suspected or diagnosed Hodgkin or non-Hodgkin lymphoma and in need of staging or restaging information</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• <sup>18</sup>F-FDG-PET or <sup>18</sup>F-FDG-PET/CT</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional imaging techniques</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Test validity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• Who are asymptomatic after completing Hodgkin lymphoma treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• <sup>18</sup>F-FDG-PET or <sup>18</sup>F-FDG-PET/CT</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional imaging techniques</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Test validity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• Who are asymptomatic after completing non-Hodgkin lymphoma treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• <sup>18</sup>F-FDG-PET or <sup>18</sup>F-FDG-PET/CT</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional imaging techniques</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Test validity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With suspected or diagnosed multiple myeloma in need of staging or restaging information</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• <sup>18</sup>F-FDG-PET or <sup>18</sup>F-FDG-PET/CT</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional imaging techniques</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Test validity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• Who are asymptomatic after completing multiple myeloma treatment</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• <sup>18</sup>F-FDG-PET or <sup>18</sup>F-FDG-PET/CT</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional imaging techniques</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Test validity</li> </ul>

**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 improves the net health outcome in individuals with hematologic cancers.

**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**

A number of radiopharmaceuticals have been granted approval by the U.S. Food and Drug Administration, to be used with PET for various cancer-related indications, however none are specific to hematologic cancers. Fluorine-18 FDG is approved for use in suspected or existing diagnosis of cancer, all types.

**POLICY**

- All policy statements apply to both positron emission tomography (PET) scans and PET plus computed tomography (CT) scans (ie, 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. Hodgkin or non-Hodgkin Lymphoma**

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

**B. Multiple Myeloma**

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

**C. 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 ( $\geq 12$  months for lymphoma) after completion of treatment.

**B. Patient Selection**

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 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 (eg, CT, MRI) is inconclusive or not indicated, including situations when an individual has a contraindication to intravenous contrast agents, making initial CT scans unattainable.

Selection criteria for PET scanning may also be complex. 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.

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.

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## **RATIONALE**

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 24, 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to

these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

## **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 an individual 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 an individual 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 ( $\geq 12$  months for lymphoma) after completion of treatment.

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 hematologic cancers.
- Individuals diagnosed with hematologic cancers and need information on the extent of cancer (initial staging upon diagnosis confirmation or restaging following treatment).
- Individuals with hematologic cancers 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 ( $^{18}\text{F}$ ) 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**

### **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.<sup>1</sup> 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,<sup>2</sup> diffuse large B-cell lymphoma,<sup>3</sup> and suspected primary central nervous system lymphoma.<sup>4</sup>

## 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.<sup>5</sup>

The literature search, conducted through January 2016, identified 11 studies (N=139) for inclusion. Study quality was moderate, as assessed by the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Review (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.<sup>6</sup> 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.<sup>7</sup> 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 <sup>18</sup>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.<sup>8</sup> 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 (OS) 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.<sup>9</sup> The literature search identified 11 studies (N=1081) for inclusion. The pooled hazard ratio (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.<sup>10</sup>

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**

### **National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network (NCCN) guidelines for Hodgkin lymphoma (v. 3.2024)<sup>11</sup>, and non-Hodgkin lymphomas, including chronic lymphocytic leukemia/small

lymphocytic lymphoma (v.3.2024 ),<sup>12</sup> B-cell lymphomas (v.3.2024 ),<sup>13</sup> primary cutaneous lymphomas (v.3.2024 ),<sup>14</sup> and T-cell lymphomas (v.4.2024 ) 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."<sup>11</sup>

### **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.

## **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.<sup>15</sup>

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.<sup>16</sup> 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.<sup>17</sup> 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 by Rama et al (2022) compared the diagnostic accuracy of FDG-PET/CT and whole-body MRI for evaluation of multiple myeloma treatment response.<sup>18</sup> 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 area under the curve 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.<sup>19</sup> 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**

### **National Comprehensive Cancer Network**

Current NCCN guidelines for multiple myeloma (v.1.2025 ) recommend PET/CT as an imaging technique option for initial workup.<sup>20</sup> 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.

### **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.

#### **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 September 2024 did not identify any 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.**

<b>CPT/HCPCS</b>	
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
A9552	Fluorodeoxyglucose F-18 FDG, diagnostic, per study dose, up to 45 millicuries
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
G0235	PET imaging, any site not otherwise specified

<b>REVISIONS</b>	
Posted 01-28-2025 Effective 02-27-2025	Oncologic Applications Hematologic was originally part of the Positron Emission Tomography (PET) Scanning: Oncologic Applications medical policy. Oncologic Applications for Hematologic has been pulled out and placed into a separate medical policy, Positron Emission Tomography (PET) Scanning: Oncologic Applications (Hematologic). The medical policy language was unchanged.

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