Title: Positron Emission Tomography (PET) Scanning: In Oncology to Detect Early Response During Treatment

See also:
- PET Scanning: Cardiac Applications
- PET Scanning: Miscellaneous (Non-cardiac, Non-oncologic) Applications of Fluorine 18 Fluorodeoxyglucose
- PET Scanning: Oncologic Applications

Professional
Original Effective Date: October 1, 1997
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Original Effective Date: October 1, 1997
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<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals: With breast cancer</td>
<td>Interim positron emission tomography as an adjunct to interim computed tomography</td>
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<td>Individuals: • With esophageal cancer</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
<td>Comparators of interest are: • Interim computed tomography</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Morbid events • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With gastrointestinal stromal tumors receiving palliative or adjuvant therapy</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
<td>Comparators of interest are: • Interim computed tomography</td>
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<td>Individuals: • With gastrointestinal stromal tumors treated with tyrosine kinase inhibitors for &lt;6 months</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
<td>Comparators of interest are: • Interim computed tomography</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Morbid events • Treatment-related morbidity</td>
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<td>Individuals: • With head and neck cancer</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
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<td>Individuals: • With lymphoma</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
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<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Morbid events • Treatment-related morbidity</td>
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<td>Individuals: • With non-small-cell lung cancer</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
<td>Comparators of interest are: • Interim computed tomography</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Morbid events • Treatment-related morbidity</td>
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<td>Individuals: • With ovarian cancer</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
<td>Comparators of interest are: • Interim computed tomography</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Morbid events • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With other malignant solid tumors (eg, bladder, colorectal, prostate, thyroid) during treatment</td>
<td>Interventions of interest are: • Interim positron emission tomography as an adjunct to interim computed tomography</td>
<td>Comparators of interest are: • Interim computed tomography</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Morbid events • Treatment-related morbidity</td>
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DESCRIPTION
Positron emission tomography (PET) scanning has many established roles in oncology. One potential use of PET scanning is to assess treatment response early in the course of therapy with the intent of potentially altering the regimen based on PET scan results. While several types of PET scanning are used for interim detection of cancer, this policy refers to fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) unless otherwise noted.

Objective
The objective of this evidence review is to evaluate the technical reliability, clinical validity, and clinical utility of positron emission tomography in assessing early response to treatment in individuals with various types of cancer.

Background

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

A variety of tracers are used for PET scanning, including oxygen 15, nitrogen 13, carbon 11, and fluorine 18. The radiotracer most commonly used in oncology imaging has been fluorine 18, coupled with deoxyglucose to form fluorodeoxyglucose (FDG), which has a metabolism related to glucose metabolism. FDG has been considered potentially useful in cancer imaging, since tumor cells show increased metabolism of glucose.

This evidence review focuses on the use of PET to determine early treatment response for cancer, i.e., assessment of therapy response during cancer treatment. The purpose of the PET scan at this particular interval is to determine whether the treatment should be maintained or changed. Such a treatment strategy has been called “risk-adapted” or “response-adapted” treatment. This evidence review addresses detecting early response during short-term therapy, (eg, during cycle(s) of chemotherapeutic agents and/or a course of radiotherapy) and not response during use of long-term agents, (eg, tamoxifen).

The technique of using PET for early treatment response assessment involves comparing PET images before treatment and at some interval after the initial course of treatment. Many intervals have been used in various studies, and there appears to be no standard interval. Comparison of the pre- and mid-treatment PET images can either be performed qualitatively or quantitatively. If a quantitative technique is used, the most common quantity measure is the standardized uptake value calculated for a specific region of the
image. Various methods are used to compare standardized uptake values between two images, and a specific cutoff value is selected to determine whether the patient is responding to therapy. A change in standardized uptake value between 40% and 60% often has been used in studies of early treatment response. Other metabolic parameters measured are total lesion glycolysis and metabolic tumor volume.

Hillner et al (2009) published results of a survey of physicians who had registered patients in the National Oncologic PET Registry, assessing the impact of PET on clinical management decisions for their patients with cancer. PET scans were most frequently ordered for patients with ovarian cancer (14%), followed by pancreatic cancer (8%), non-small-cell lung cancer (7%), and small-cell lung cancer (7%). Physicians considered the patients’ prognoses as better (42%), unchanged (31%), or worse (26%) compared with the prognosis assessment before receiving information from PET. Physicians reported changing the management plan (switching therapy, adjusting the dose or duration of therapy, or switching to observation or supportive care) in 41% of their patients whose prognosis assessment was better based on PET results, in 35% of patients whose prognosis did not change based on PET results, and in 79% of patients whose prognosis was worse based on PET results.

Use of interim PET to guide therapy decisions is to be distinguished from uses of PET in the initial diagnosis and staging of cancer and other uses after treatment, such as routine surveillance, detection of progression, or recurrence. This use also differs from what has been called “response assessment” or “treatment response” in some reports, which refers to imaging done after completion of therapy for prognosis and future treatment planning. Some differentiate between PET during and after treatment by referring to PET during cancer treatment as “interim treatment response” or “interim staging” and PET at the conclusion of treatment as “restaging.”

**Regulatory Status**

A number of PET scan platforms have been cleared by the U.S. Food and Drug Administration (FDA) through the 510(k) process since the Penn-PET scanner was approved in 1989. These systems are intended to aid in detecting, localizing, diagnosing, staging, and restaging of lesions, tumors, disease, and organ function for the evaluation of diseases and disorders such as, but not limited to, cardiovascular disease, neurologic disorders, and cancer. The images produced by the system can aid in radiotherapy treatment planning and interventional radiology procedures.

PET radiopharmaceuticals have been evaluated and approved as drugs by the FDA for use as diagnostic imaging agents. These radiopharmaceuticals are approved for specific conditions. In December 2009, FDA issued guidance for Current Good Manufacturing Practice for PET drug manufacturers and, in August 2011, issued similar Current Good Manufacturing Practice guidance for small businesses compounding radiopharmaceuticals. An additional final guidance document issued in December 2012 required all PET drug manufacturers and compounders to operate under an approved...
new drug application or abbreviated new drug application, or investigational new drug application, by December 12, 2015.4

Table 1 lists some of the radiopharmaceuticals granted FDA approval for use with PET for oncologic-related indications.

**Table 1. Radiopharmaceuticals Approved for Use With PET for Carcinoma-Related Indications**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Date Approved</th>
<th>NDA No.</th>
<th>Carcinoma-Related Indication With PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon 11 choline</td>
<td>NA</td>
<td>Various</td>
<td>2012</td>
<td>203155</td>
<td>Suspected prostate cancer recurrence based on elevated blood PSA after therapy and noninformative bone scintigraphy, CT, or MRI</td>
</tr>
<tr>
<td>Fluorine 18 fluorodeoxyglucose</td>
<td>NA</td>
<td>Various</td>
<td>2000</td>
<td>20306</td>
<td>Suspected or existing diagnosis of cancer, all types</td>
</tr>
<tr>
<td>Fluorine 18 fluciclovine</td>
<td>Axumin™</td>
<td>Blue Earth Diagnostics</td>
<td>2016</td>
<td>208054</td>
<td>Suspected prostate cancer recurrence based on elevated blood PSA levels after treatment</td>
</tr>
<tr>
<td>Gallium 68 dotatate</td>
<td>NETSPOT™</td>
<td>Advanced Accelerator Applications</td>
<td>2016</td>
<td>208547</td>
<td>Localization of somatostatin receptor positive NETs in adult and pediatric patients</td>
</tr>
</tbody>
</table>

CT: computed tomography; MRI: magnetic resonance imaging; NA: not applicable; NDA: new drug application; NETs: neuroendocrine tumors; PET: positron emission tomography; PSA: prostate-specific antigen.

**POLICY**

A. The use of interim fluorine 18 fluorodeoxyglucose positron emission tomography scans to determine response to tyrosine kinase inhibitor treatment in patients with gastrointestinal stromal tumors is considered **medically necessary**.

B. The use of positron emission tomography scans to determine early response to treatment (positron emission tomography scans done during a planned course of chemotherapy and/or radiation) in patients with gastrointestinal stromal tumors on palliative or adjuvant therapy, as well as all other cancers, is considered **experimental / investigational**.

**RATIONALE**

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through July 8, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—excluding benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or
worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This evidence review discusses only studies that explicitly stated positron emission tomography (PET) was used to guide therapeutic decisions in cancer patients. Most studies that evaluate PET during treatment have analyzed the association between PET findings and various intermediate endpoints, such as pathologic or clinical response at the end of treatment, PET findings at the end of treatment, or long-term results. Although associations between PET and all these endpoints have consistently been found for a number of cancers, whether such associations lead directly to improved patient outcomes depends on the specific context of the treatment decisions being made in response to PET findings and available alternatives.

**Breast Cancer**

**Clinical Context and Test Purpose**

The purpose of interim PET as an adjunct to interim computed tomography (CT) in patients with breast cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with breast cancer?

The following PICOs were used to select literature to inform this review.

**Patients**

The population of interest are patients with breast cancer.

**Interventions**

The intervention of interest is interim PET scan, performed to guide therapy.

**Comparators**

The following test is currently being used to make decisions about managing breast cancer who have initiated treatment to determine therapeutic response and guide decision making: interim CT.
Outcomes
The general outcomes of interest are QOL, overall survival (OS), and progression-free survival (PFS).

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of radiotherapy (RT).

Table 2. Outcomes of Interest for Individuals with Breast Cancer

<table>
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<tr>
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<tr>
<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
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Systematic Reviews
The purpose of the systematic review and meta-analysis by Li et al (2018) relates to the current lack of consensus on the best tool to evaluate pathologic response to neoadjuvant chemotherapy (NAC) in breast cancer patients. Selection criteria included patients who had undergone both magnetic resonance imaging (MRI) and PET/CT after preoperative NAC. The postoperative pathologic result (pathologic complete response [pCR] vs non-pCR) served as the criterion standard for inclusion, and each study required a minimum of ten patients and associated raw data. The evaluation parameter for MRI was tumor size or maximum diameter, while the parameter for PET/CT was the maximum standardized uptake value (SUVmax) or peak SUV served. The literature search included the Cochrane, PubMed, EMBASE, Web of Science, and CBM databases from inception to February 2017. Thirteen studies involving 575 patients who underwent MRI and 618 who underwent PET/CT were analyzed. The pooled sensitivity and specificity of MRI were 88% (95% confidence interval [CI] 78% to 94%) and 69% (95% CI, 51% to 83%) and the corresponding PET/CT values were 77% (95% CI, 78% to 94%) and 69% (95% CI, 63% to 88%), respectively. The area under the summary receiver operating characteristic curve for MRI and PET/CT were 0.88 and 0.84, respectively. Reviewers concluded that MRI had a higher sensitivity and PET/CT has a higher specificity but based on the area under the summary receiver operating characteristic curve and anatomic discriminative resolution, MRI was deemed more suitable for predicting breast cancer pathologic response after NAC. Subgroup analysis to address the different definitions of pCR and histology subtypes and various receptor statuses was not conducted due to the limited number of patients, possibly suggesting heterogeneity. Other study limitations included inconsistencies in definitions and criteria and exclusion of non-English studies.

Lindenberg et al (2017) published a systematic review on the use of imaging (fluorine 18 fluorodeoxyglucose PET [FDG-PET] and dynamic contrast-enhanced MRI) to monitor response to neoadjuvant therapy in patients with breast cancer. The literature search, conducted through March 2015, identified 15 observational studies for inclusion. Studies were assessed for quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, and all included studies had scores of eight or higher. Reviewers provided descriptions of the imaging methods (type of imaging, monitoring interval) and results (sensitivity, specificity, negative [NPV] and positive predictive values [PPV]) by breast cancer subtype: estrogen receptor (ER)-positive and
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human epidermal growth factor receptor 2 (HER2)-negative, triple-negative, HER2-positive, ER-positive and HER2-positive, and ER-negative and HER2-positive. Sensitivity estimates ranged from 18% to 89%, specificity estimates ranged from 52% to 100%, PPV estimates ranged from 0% to 100%, and NPV ranged from 10% to 84%. Meta-analyses were not performed due to heterogeneity across studies. Studies differed by neoadjuvant chemotherapy regimen and definition of pCR. While reviewers intended to determine the best performing imaging technique by breast cancer subtype, selected articles showed that there is a lack of evidence with adequate statistical power to draw conclusions by each subtype.

To compare the utility of PET/CT with MRI of the breast in the assessment of pCR to NAC, Chen et al (2017) conducted meta-analysis using head-to-head comparative studies. Analysis of 11 studies with a total of 527 patients calculated a pooled sensitivity of 87% (95% CI, 71% to 95%) and a specificity of 85% (95% CI, 70% to 93%) for PET/CT. The pooled sensitivity was 79% (95% CI, 68% to 87%) and the specificity was 82% (95% CI, 72% to 89%) for MRI. Reviewers concluded that diagnostic performance of MRI was similar to that for PET/CT when assessing breast cancer response to NAC, however, they found PET/CT more sensitive than conventional contrast-enhanced MRI (88% [95% CI, 71% to 95%] vs 74% [95% CI, 60% to 85%]; p=0.018) and more specific when scanned within 3 cycles of NAC (94% [95% CI, 78% to 98%] vs 83% [95% CI, 81% to 87%]; p=0.015). Limitations of the studies assessed included small sample sizes, potential publication bias, and the decision to exclude factors such as the definition of pCR and breast cancer phenotypes, which are known to affect estimate accuracy.

**Randomized Controlled Trials**

Early results of the Addition of beVacizumab to neoadjuvant doceTAXel and trastuzumab (HER) trial were reported by Coudert et al (2014). This randomized, open-label, multicenter phase 2 trial enrolled women (318 years) with early-stage HER2-positive breast cancer from 26 oncology centers in France. A total of 142 patients were enrolled between 2010 and 2012. Patients initially received two cycles of neoadjuvant chemotherapy (standard regimen). Before the first and second cycles, the change in SUV measured by FDG-PET was used to predict pathologic complete response. PET responders continued to receive standard therapy. FDG-PET nonresponders were randomized (2:1) to four cycles of one chemotherapy regimen or to continue on the standard regimen. Investigators and patients were unblinded but the pathologist in charge of central surgical sample and lymph node reviews was blinded. The primary endpoint was centrally assessed pathologic complete response according to the Chevallier classification.

Of the 142 patients, 69 were PET responders after 2 cycles and 73 were nonresponders. Pathologic complete responses were noted in 37 (54%) of the FDG-PET responders. In the randomized participants (PET nonresponders), 27 (37%) of 73 achieved pCR, as did 21 (43.8%; 95% CI, 29.5% to 58.8%) of those in PET-directed therapy group, and 6 (24.0%; 95% CI, 9.4% to 45.1%) of those in standard therapy group. Incidences of grade 3 or 4 adverse events were similar in both groups, with the most common grade being neutropenia and febrile neutropenia. Fifteen serious adverse events were reported in 11 (15%) of 73 patients. No deaths occurred during the trial. The OS or PFS results were not available at reporting.

**Nonrandomized Studies**

Several clinical studies of breast cancer in the neoadjuvant setting have demonstrated associations between early or interim PET and recurrence, response, or survival outcomes.
Kitajima et al (2018) compared the response classifications Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), version 1.0, with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, to evaluate the pathologic therapeutic response to NAC in 32 breast cancer patients who underwent both MRI and FDG-PET. Based on RECIST 1.1 using MRI measurements, treatment efficacy was graded as complete response in 5 (15.6%) patients, partial response in 25 (78.1%), stable disease in 2 (6.3%), and progressive disease in 0. Based on PERCIST 1.0 with FDG-PET/CT findings, treatment efficacy was graded as complete metabolic response in 28 (87.5%) patients, partial metabolic response in 2 (6.3%), stable metabolic disease in 1 (3.1%), and progressive metabolic disease in 1 (3.1%). Concordance between RECIST 1.1 and PERCIST 1.0 classifications was found in 7 (21.9%) cases, while discordance was found in 25 (78.1%)(k=0.103, p<0.001). This study found the two classifications to be complementary in predicting pathologic response to NAC. Study limitations include the retrospective design, small sample size collected at a single-center, and inability to analyze OS due to a small number of deaths in the cohort (n=3).

In a multicenter study of 59 breast cancer patients, Kitajima et al (2018) found that, based on PERCIST response, FDG-PET/CT underestimated the residual tumor volume following NAC and had both a relatively low specificity for pCR and PPV, and that a combination of other imaging modalities would still be needed to predict pCR of primary tumors. Other limitations included retrospective design, small sample size, heterogeneous chemotherapy regimen across centers, and an inability to assess OS.

Retrospectively, Yoon et al (2018) investigated the prognostic value of tumor heterogeneity using analysis of texture parameters with FDG-PET and diffusion-weighted imaging in 83 patients who had locally advanced breast cancer and had completed NAC. Among the 83 patients, 46 were pathologic responders and 37 were nonresponders. Authors concluded the results suggested that texture-based analysis of tumor heterogeneity on FDG-PET/CT and diffusion-weighted imaging could be used to predict NAC response and disease recurrence in this population, and in particular, higher metabolic heterogeneity on PET was a significant predictor of unfavorable response to chemotherapy and worse disease prognosis (p=0.009).

Quantitative indexes of PET findings used to identify response vs nonresponse on PET or PET plus CT may depend on the type of chemotherapy and tumor phenotype. For example, van Ramshorst et al (2017) found that for patients with triple-negative tumors (n=45) receiving neoadjuvant systemic therapy, FDG-PET/CT of the breast can predict pCR, while patients with HER2-positive tumors (n=60) may need both FDG-PET/CT of the breast and axilla for a more accurate pCR.

In a larger study, Schmitz et al (2017) assessed 188 women with stages II or III breast cancer who underwent MRI and FDG-PET/CT before and after neoadjuvant chemotherapy. Analyses were stratified by tumor type: HER2-positive, ER-positive and HER2-negative, and triple-negative. The primary outcome was pCR defined as no or only small numbers of scattered invasive tumor cells. Results showed that for HER2-positive tumors, MRI was a significantly better predictor of pCR than FDG-PET/CT. For ER-positive and HER2-negative tumors, combining MRI and FDG-PET/CT might provide the best monitoring of treatment, though results were not statistically significant. For triple-negative tumors, the two imaging techniques performed equally in predicting pCR.
Riedl et al (2017) compared the efficacy of FDG-PET/CT with contrast-enhanced CT for the primary outcomes of PFS and disease-free survival in 65 patients undergoing systemic therapy for stage IV breast cancer. Treatment response was evaluated using RECIST for contrast-enhanced CT and using PERCIST for PET. Results suggested that PET/CT was superior to contrast-enhanced CT in predicting PFS and disease-free survival. For example, responses using RECIST and PERCIST both correlated with PFS, but PERCIST showed significantly higher predictive accuracy (concordance index for PFS: 0.70 vs 0.60), and at 1 year, responders vs nonresponder rates using RECIST were 59% vs 27%, compared with 63% vs 0% using PERCIST, respectively. At 4 years, disease-free survival for responders and nonresponder rates using RECIST were 50% and 38%, respectively (p=0.2, concordance index: 0.55) compared with 58% and 18% using PERCIST (p<0.001, concordance index: 0.65). Use of multiple therapy protocols, the inclusion of various breast cancer subtypes, small sample size, and a retrospective design limit conclusions drawn from this study.

Very little data are available on the use of FDG-PET or FDG-PET/CT to guide management decisions.

**Section Summary: Breast Cancer**

Evidence for the clinical validity of interim FDG-PET for monitoring disease in patients with breast cancer includes several systematic reviews, numerous observational studies, and an RCT. Results from the systematic reviews showed wide ranges in sensitivities, specificities, PPV, and NPV. The wide ranges may be due to small sample sizes, use of different definitions of the primary outcome (pCR), and differences in breast cancer subtypes in the sample populations. Data from observational studies have suggested a need for considering breast cancer subtype and the type of treatment in creating criteria for assessing early prediction of response with PET. Evidence for the clinical utility of interim FDG-PET or PET/CT to evaluate early response in breast cancer is limited and consists of early results of an RCT that included patients identified as nonresponders by interim PET randomized to more intensive chemotherapy or standard care. The results showed higher response rates in the more intensive group but clinical outcomes such as PFS or OS were not available. As yet, the evidence does not permit conclusions on whether PET improves health outcomes because data are not available showing that response-adaptive therapy leads to improved outcomes.

**Esophageal Cancer**

The current treatment strategy for patients with esophageal cancer depends on the cancer stage. Patients who do not have lymph node involvement and have no evidence of metastases usually undergo surgery alone. Patients with locally advanced disease are often offered neoadjuvant treatment (chemotherapy and/or chemoradiotherapy) followed by esophagectomy.

**Clinical Context and Test Purpose**

The purpose of interim PET as an adjunct to interim CT in patients with esophageal cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies. Specifically, the goal of using interim FDG-PET is to determine whether the tumors would respond to the neoadjuvant therapy, which in turn would inform a decision to offer neoadjuvant therapy or proceed directly to surgery.
The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with esophageal cancer?

The following PICOs were used to select literature to inform this review.

**Patients**
The population of interest are patients with esophageal cancer.

**Interventions**
The intervention of interest is interim PET scan, performed to guide therapy.

**Comparators**
The following test is currently being used to make decisions about managing those with esophageal cancer: interim CT.

**Outcomes**
The general outcomes of interest are QOL, OS, and PFS.

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

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**Systematic Reviews**
Cong et al (2016) published a meta-analysis on the predictive value of FDG-PET for the pathologic response during and after neoadjuvant chemoradiotherapy (NCRT) in patients with esophageal cancer. The literature review, conducted through January 2016, identified 15 publications. Four studies (n=192 patients) conducted PET during NCRT, and 11 studies (n=490 patients) conducted a PET after NCRT. Study quality was assessed using QUADAS scores, which ranged from 9 to 12 (total points, 14) in the included studies. Only five studies described blinding of the pathology reviewers to FDG-PET data and other test results. The pooled sensitivity, specificity, and diagnostic odds ratio for the studies conducting PET during NCRT were: 85% (95% CI, 76% to 91%), 59% (95% CI, 48% to 69%), and 6.8 (95% CI, 2.3 to 20.7), respectively. The pooled sensitivity, specificity, and diagnostic odds ratio for the studies conducting PET after NCRT were: 67% (95% CI, 60% to 73%), 69% (95% CI, 63% to 74%), and 6.0 (95% CI, 2.1 to 19.3), respectively. Subgroup analyses of studies that conducted PET after NCRT and included only patients with squamous cell carcinoma (4 studies, 129 patients), showed higher pooled a sensitivity, specificity, and diagnostic odds ratio: 90% (95% CI, 80% to 96%), 69% (95% CI, 56% to 80%), and 17.3 (95% CI, 3.1 to 95.4), respectively. Reviewers concluded that FDG-PET should not be used routinely to guide treatment strategies in patients...
with esophageal cancer based on the low pooled estimates; however, PET may be considered for the subset of patients with squamous cell carcinoma.

Nonrandomized Studies
Van Rossum et al (2017) published a study evaluating the use of FDG-PET before and after induction chemotherapy to predict response to subsequent chemoradiotherapy in patients with adenocarcinoma.31 Patients who were to receive a three-step treatment strategy of induction chemotherapy, followed by chemoradiotherapy and then surgery (n=70), underwent FDG-PET before and after the induction chemotherapy phase of the treatment. PET identified 27 patients with poor pathologic responses to the induction chemotherapy (defined as <26% reduction in total lesion glycolysis after chemotherapy). After a median follow-up of 48 months (range, 15-99 months), PFS was significantly lower among patients identified by PET as poor responders compared with patients identified by PET as good responders.

Hagen et al (2017) published a study evaluating the predictive value of FDG-PET before and 2 weeks after chemoradiotherapy in 106 patients with esophageal cancer who then underwent potentially curative surgery.32 The outcome of metabolic response, stable disease, or progression was assessed using PERCIST. Patients were followed until disease recurrence or death. Minimum follow-up of surviving patients was 60 months. Five-year disease-free survival rates for patients determined by FDG-PET as having a metabolic response, stable disease, or progression were 66%, 53%, and 67%, respectively. These rates did not differ statistically. The authors concluded that FDG-PET should not be used as a prognostic tool for these patients.

Retrospective Studies
A retrospective study by Odawara et al (2018) compared classification using RECIST and PERCIST in the assessment of response to NAC for 62 patients who had esophageal cancer.33 Patients underwent FDG-PET/CT, contrast-enhanced CT scanning, esophageal fiberscopy, endoscopic ultrasonography, or esophagography before and after NAC. Patients were divided into responders and nonresponders by the pathologic response, and concordance between RECIST and PERCIST for response classification was seen in 28 (45.2%) patients. The authors concluded that PERSIST might be better suited to evaluate neoadjuvant therapeutic response to esophageal cancer. Study limitations included the retrospective design, small sample size, and single-institution sample, as well as the lack of correlation between PERCIST criteria and prognosis.

Manoharan et al (2017) published a study evaluating the use of FDG-PET before and after neoadjuvant therapy in patients with resectable distal esophageal cancer (n=21) and gastric adenocarcinoma (n=14).34 Maximum and percent change of both SUV and metabolic tumor volume (MTV) were measured and correlated with tumor regression and survival to assess predictive value. The best PET-based biomarker for predicting pathologic response and survival was the percent change in SUVmax. Patients with 70% or more change in SUVmax had lower risks of death and recurrence than patients with less than 70% SUVmax.

Section Summary: Esophageal Cancer
Evidence for the clinical validity of FDG-PET as an adjunct to CT to determine early treatment response for patients with esophageal cancer consists of a meta-analysis, three nonrandomized studies, and two retrospective studies. Results were inconsistent across studies. Results from the meta-analyses showed low pooled sensitivities and specificities, indicating FDG-PET may be a poor guide to inform treatment strategies in patients with esophageal cancer. One of the
nonrandomized trials published after the meta-analysis supported this conclusion. However, a subgroup analysis in the meta-analysis that included only studies of patients with squamous cell carcinoma, and two studies published after the meta-analysis, reported that FDG-PET could adequately predict responders to neoadjuvant therapy. No evidence was identified examining the clinical validity of FDG-PET for patients with esophageal cancer.

**Gastrointestinal Stromal Tumors**

**Palliative or Adjuvant Therapy**

**Clinical Context and Test Purpose**
The purpose of interim PET as an adjunct to interim CT in patients with GIST who are receiving palliative or adjuvant therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with GIST who are receiving palliative or adjuvant therapy?

The following PICOs were used to select literature to inform this review.

**Patients**
The population of interest are patients with GIST who are receiving palliative or adjuvant therapy.

**Interventions**
The intervention of interest is interim PET scan, performed to guide therapy.

**Comparators**
The following test is currently being used to make decisions about managing those with GIST: interim CT.

**Outcomes**
The general outcomes of interest are QOL, OS, and PFS.

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

**Table 4. Outcomes of Interest for Individuals with Gastrointestinal Stromal Tumors**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Outcomes of interest include patient response and disease progression</td>
<td>≥1 month</td>
</tr>
<tr>
<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

**Systematic Reviews**
A systematic review by Treglia et al (2012) assessed studies of FDG-PET for evaluating treatment response to imatinib and other drugs to treat GIST.35 Reviewers identified 2 studies (n=44
patients) relative to this patient population that did not show an association between PET and long-term (>6 months) response to tyrosine kinase inhibitors (TKIs). None of the reviewed studies assessed the impact of PET-directed treatment changes on net health outcome.

**Section Summary: Palliative or Adjuvant Therapy**

There were no studies identified to provide support for long-term PET-guided palliative or adjuvant treatment of patients with GIST.

**With Tyrosine Kinase Inhibitors**

**Clinical Context and Test Purpose**

The purpose of interim PET as an adjunct to interim CT in patients with GIST treated with TKIs for less than six months is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with GIST treated with TKIs?

The following PICOs were used to select literature to inform this review.

**Patients**

The population of interest includes patients with GIST treated with TKIs for less than six months.

**Interventions**

The intervention of interest is interim PET scan, performed to guide therapy.

**Comparators**

The following test is currently being used to make decisions about managing those with GIST: interim CT.

**Outcomes**

The general outcomes of interest are QOL, OS, and PFS.

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

**Table 5. Outcomes of Interest for Individuals with Tyrosine Kinase Inhibitors**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Outcomes of interest include patient response and disease progression</td>
<td>≥1 month</td>
</tr>
<tr>
<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

**Systematic Reviews**

The systematic review by Treglia et al (2012) assessed studies of FDG-PET for evaluating treatment response to imatinib and other drugs in GIST. Reviewers concluded that "FDG PET allows an early assessment of treatment response and is a strong predictor of clinical outcome."
This conclusion was based on 19 studies (n=192 patients) that showed associations between PET as early as 1 week after initiation of TKI (imatinib, sunitinib, masitinib) therapy and survival outcomes. None of the reviewed studies assessed the impact of PET-directed treatment changes on net health outcome. A chain of evidence was identified; in patients with borderline resectable GIST involvement, rapid assessment of treatment response can guide clinical decision making regarding the surgical approach or addition of second-line treatment.36,37,

Retrospective Studies
A National Comprehensive Cancer Network (NCCN; 2009) task force report (included in the Treglia et al [2012] review) identified a small retrospective study of 20 patients with GIST who were treated with the TKI imatinib and underwent PET, CT, and PET/CT imaging.36, PET/CT was more accurate than either PET or CT alone for detecting tumor response at one, three, and six months after initiation of imatinib. Based on this study, the task force recommended PET for response assessment to targeted GIST therapy.

Section Summary: With TKIs
Evidence for the clinical validity of the use of interim FDG-PET as an adjunct to CT to evaluate treatment response in patients with GIST consists of a systematic review of 19 studies. Seventeen of the studies found that interim FDG-PET adequately measured tumor response to TKIs (imatinib, sunitinib, masitinib), and could be a strong predictor of clinical outcome as early as one month after initiating treatment. While CT detects anatomic changes in the tumor, FDG-PET detects changes in the metabolic activity of the tumor. Because metabolic changes precede anatomic changes by several weeks or even months, FDG-PET can detect treatment response earlier, compared with CT’s size-based criteria. PET is therefore preferred if a rapid read-out of response to targeted therapy is needed to guide treatment decisions.

Head and Neck Cancer
Clinical Context and Test Purpose
The purpose of interim PET as an adjunct to interim CT in patients with head and neck cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with head and neck cancer?

The following PICOs were used to select literature to inform this review.

Patients
The population of interest are patients with head and neck cancer.

Interventions
The intervention of interest is interim PET scan, performed to guide therapy.

Comparators
The following test is currently being used to make decisions about managing those with head and neck cancer: interim CT.

Outcomes
The general outcomes of interest are QOL, OS, and PFS.
Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

Table 6. Outcomes of Interest for Individuals with Head and Neck Cancer

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Outcomes of interest include patient response and disease progression</td>
<td>≥1 month</td>
</tr>
<tr>
<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

Systematic Reviews

The diagnostic value of FGD-PET/CT used to evaluate treatment response in head and neck squamous cell carcinoma was analyzed in a systematic review and meta-analysis by Helsen et al (2018). A search of the MEDLINE and Web of Knowledge databases identified 20 studies (total n=1293 patients). The pooled sensitivity, specificity, and diagnostic odds ratio were 85% (95% CI, 76% to 91%), 93% (95% CI, 89% to 96%), and 76 (95% CI, 35 to 165), respectively. PPV and NPV were 58% and 98% at a prevalence of 10%, and significant heterogeneity was shown between trials (p<0.001). FDG-PET/CT within six months of chemoradiotherapy was a reliable detector of residual/recurrent nodal disease in head and neck squamous cell carcinoma patients. This analysis suggested that the timing of FDG-PET/CT after therapy completion is important particularly after 11 weeks.

Min et al (2017) published a systematic review of the predictive value of functional imaging (MRI, CT, PET) in patients with mucosal primary head and neck cancer treated with RT. The literature search, conducted through March 2015, identified 99 studies for inclusion, 7 of which used interim PET/CT and 9 which used different radiotracers with PET (fluorine 18 misonidazole, fluorine 18 thymidine, fluoroazomycin arabinoside, and methionine carbon 11). Study quality assessment was not mentioned in the review. Five of the seven studies using PET/CT confirmed the predictive value of PET for disease-free survival and OS. The non-FDG-PET studies had small sample sizes and inconsistent results. One study showed that fluorine 18 thymidine may have better predictive value than FDG.

Castelli et al (2016) published a systematic review of the predictive value of FDG-PET/CT for patients with head and neck cancer who were treated with chemoradiotherapy. The literature search, conducted through March 2016, identified 45 studies for inclusion. Most studies evaluated the predictive value of FDG-PET for diagnosing head and neck cancer. Seven of the studies (n=374 patients) investigated interim FDG-PET in patients receiving RT with or without chemotherapy. Five of the 7 studies overlapped with those identified in the Min et al (2017) review. Study quality assessment was not mentioned in the review. Six of the seven studies reported a correlation between PET measurements (SUVmax, total lesion glycolysis, MTV) and clinical outcomes (disease-free survival, OS). The optimal time to perform FDG-PET during treatment is unclear, though most studies used PET after three weeks of treatment. Meta-analyses were not conducted.
Dos Anjos et al (2016) published a systematic review of the effectiveness of FDG-PET/CT for patients with head and neck squamous cell carcinoma receiving induction chemotherapy. The literature search, conducted through May 2016, identified 7 articles for inclusion (n=207 patients). Based on an Agency for Healthcare Research and Quality checklist for assessing the quality of observational studies, the articles were considered to have a moderate risk of bias. Methodologic limitations included incomplete explanations of confounding variables and the absence of follow-up. Six of the seven articles reported that FDG-PET/CT provided an adequate early response prediction of survival. Meta-analysis could not be conducted due to the heterogeneity in response criteria, SUVmax thresholds, and outcomes.

Section Summary: Head and Neck Cancer
Evidence for the clinical validity of interim FDG-PET as an adjunct to CT in predicting disease-free survival and OS in patients with head and neck cancer consists of several systematic reviews. Most showed that FDG-PET used during RT, with or without chemotherapy, can adequately predict disease-free survival and OS. Meta-analyses could not be performed in any of the systematic reviews due to the heterogeneity in the methods used across the studies to determine response. Most studies used SUVmax, however, thresholds varied across the studies. No studies were identified that could provide evidence for the clinical utility of interim FDG-PET for patients with head and neck cancer.

Lymphoma
Clinical Context and Test Purpose
The purpose of interim PET as an adjunct to interim CT in patients with lymphoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with lymphoma?

The following PICOs were used to select literature to inform this review.

Patients
The population of interest are patients with lymphoma.

Interventions
The intervention of interest is interim PET scan, performed to guide therapy.

Comparators
The following test is currently being used to make decisions about managing those with lymphoma: interim CT.

Outcomes
The general outcomes of interest are QOL, OS, and PFS. Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.
Table 7. Outcomes of Interest for Individuals with Lymphoma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Outcomes of interest include patient response and disease progression</td>
<td>≥1 month</td>
</tr>
<tr>
<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

**Systematic Reviews**

Adams and Kwee (2016) published a systematic review and meta-analysis calculating false-positive rates of FDG-PET during and at the end of treatment, using biopsy as the reference standard in patients with lymphoma and FDG-avid lesions.42 Overall methodologic study quality was moderate, as assessed by the QUADAS-2 tool. Table 8 summarizes the pooled false-positive rates.

Table 8. Pooled False-Positive Rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Condition</th>
<th>No. of Studies</th>
<th>False-Positive Rate</th>
<th>95% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim FDG-PET</td>
<td>Hodgkin lymphoma</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Interim FDG-PET</td>
<td>Non-Hodgkin lymphoma</td>
<td>4</td>
<td>83</td>
<td>72 to 90</td>
</tr>
<tr>
<td>End-of-treatment FDG-PET</td>
<td>Hodgkin lymphoma</td>
<td>3</td>
<td>23</td>
<td>5 to 65</td>
</tr>
<tr>
<td>End-of-treatment FDG-PET</td>
<td>Non-Hodgkin lymphoma</td>
<td>2</td>
<td>31</td>
<td>4 to 84</td>
</tr>
</tbody>
</table>

CI: confidence interval; FDG-PET: fluorine 18 fluorodeoxyglucose positron emission tomography.

Reviewers questioned the use of FDG-PET for assessing lymphoma treatment due to these high false-positive rates. FDG-PET exposes patients to potentially harmful levels of radiation and may provide misinformation leading to incorrect treatment changes and/or unnecessary biopsies.

A Cochrane systematic review by Sickinger et al (2015) evaluating interim FDG-PET-adapted therapy following first-line treatment in Hodgkin lymphoma.43 The search strategy included RCTs comparing PET-adapted therapy to nonadapted therapy in patients with previously untreated Hodgkin lymphoma of all stages and ages published in Cochrane Central Register of Controlled Trials, MEDLINE, or presented at conference proceedings from 1990 to 2014. Reviewers found 2 publications and 1 abstract for a total of 3 eligible trials (total n=1480 participants).44,45,46 The quality of the evidence for the primary outcome of PFS was considered moderate. In all three trials, PET-adapted therapy included no RT after PET-negative results following initial chemotherapy. The pooled estimate of PFS was shorter in participants with PET-adapted therapy (without RT) than in those receiving standard treatment with RT (hazard ratio [HR], 2.38; 95% CI, 1.62 to 3.50; p<0.001). The authors were unable to draw conclusions about OS due to the small number of deaths reported in the three trials. The studies included little to no data on response rates, treatment-related mortality, QOL, or short- and long-term adverse events.

**Randomized Controlled Trials**

**Interim PET-Negative**

Patients with PET-negative results following induction chemotherapy tend to have a good prognosis. The goal of PET-directed therapy is to achieve similar efficacy concerning PFS while avoiding unnecessary exposure to radiation, which can have toxic side effects, including late secondary cancers47,48 and cardiovascular disease49,50, or to reduce the side effects of additional chemotherapy by decreasing the number of cycles or chemotherapeutic agents.

Five RCTs have compared PET-directed therapy with standard therapy in patients who had lymphoma and had negative interim PET findings after an initial course of chemotherapy. Three
studies were evaluated in the Cochrane review (2015; previously described). Characteristics of the studies are summarized in Table 9 and briefly below.

A phase 2 RCT by Casasnovas et al (2017) evaluated the use of interim FDG-PET in the treatment of 200 patients with diffuse large B-cell lymphoma.51 FDG-PET was conducted after cycles 2 (PET2) and cycles 4 (PET4) of induction therapy. Patients who were PET4-positive (n=100) were advised to proceed with a salvage regimen followed by autologous cell transplantation; the final treatment decision was made by the patients and their clinicians. Patients who were PET4-negative (n=100) were given different therapies depending on whether the PET2 was negative or positive. PET2- and PET4-patients (n=52) were treated with 8 cycles of various chemotherapy regimens. PET2-positive and PET4-negative patients (n=48) were treated with 3 cycles of different chemotherapy regimens, followed by autologous cell transplantation.

Wong-Sefidan et al (2017) published a study evaluating the predictive value of FDG-PET/CT on survival in patients with follicular lymphoma.52 Among 1289 patients in the National LymphoCare Study, 447 underwent FDG-PET/CT following rituximab induction therapy. After a median follow-up of 7.6 years, the 5-year OS rate for PET-negative patients (n=292) was 88%, and the PFS rate was 65%.

The trial reported by Johnson et al (2016) randomized 937 newly diagnosed advanced classic Hodgkin lymphoma patients (median age, 33 years; 55% men) who had a negative interim PET coupled with CT scan after an initial 2 cycles of standard chemotherapy to continued standard chemotherapy for 4 cycles or to a different combination of chemotherapy agents (PET-directed therapy).53 A Deauville score of 1, 2, or 3 was regarded as indicating negative PET findings, and a score of 4 or 5 as indicating positive PET findings. The trial evaluated the noninferiority of the chemotherapy regimen in the PET-directed therapy for three-year PFS with a 5% point margin for the risk difference.

The RAPID study, reported by Radford et al (2015) recruited 602 patients (53.3% male; median age, 34 years) with newly diagnosed stage IA or stage IIA Hodgkin lymphoma, of whom 571 patients received 3 cycles of chemotherapy and then PET scanning performed on full-ring PET or PET with CT cameras.44 A Deauville score of 1 or 2 indicated negative findings and a score of 3, 4, or 5 indicated positive findings. A total of 420 patients with negative PET findings were randomized to involved-field RT (standard therapy) or no further treatment (PET-directed therapy). This trial assessed the noninferiority of no further treatment, designed to exclude a difference in the 3-year PFS rate of 7 or more percentage points from the assumed 95% PFS rate in the RT group.

Raemaekers et al (2014) published a preplanned interim futility analysis of the European Organization for Research and Treatment of Cancer/Lymphoma Study Association/Fondazione Italiana Linfomi (EORTC/LYSA/FIL) Intergroup H10 trial.46 The trial randomized patients who had previously untreated stage I or II Hodgkin lymphoma to PET-directed therapy or standard therapy. Standard therapy was chemotherapy plus 30-gray radiation. PET images were scored according to the International Harmonization Project criteria, with a negative PET corresponding to scores 1 (no uptake) and 2 (uptake ≤ mediastinum) on the 5-point Deauville scale. Patients in the PET-directed therapy arm who had a negative early PET scan (after two chemotherapy cycles) did not receive RT but received additional chemotherapy cycles. Patients with favorable or
unfavorable prognostic factors were analyzed separately. The trial design was noninferiority, with margins for the HRs of 3.2 and 2.1 for favorable and unfavorable, respectively.

Picardi et al (2007) reported on a trial of PET-directed therapy vs standard therapy in 160 patients (median age, 31 years; 55% men) with newly diagnosed bulky Hodgkin lymphoma. PET scans were performed using a dedicated tomography scanner (Advanced NXi, General Electrics). Negative PET was defined as no evidence of uptake, and positive PET was defined as increased uptake in a focus within an abnormal area. Patients having negative PET scans following induction chemotherapy with 6 cycles of chemotherapy were randomized to observation (PET-directed therapy) or 32-gray RT (standard therapy). The study was powered to detect a 10% risk difference in event-free survival, defined as relapse, secondary malignancies, or death from any cause; the specific hypothesis (superiority vs noninferiority) was not reported.

Table 9. Summary of Key RCT Characteristics of PET-Guided Therapy in PET-Negative Patients

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casasnovas et al (2017)51,</td>
<td>France</td>
<td></td>
<td>2007-2010</td>
<td>High-risk DBCL</td>
<td>48 PET2+/PET4-</td>
</tr>
<tr>
<td>Johnson et al (2016)53,</td>
<td>5 European countries plus Australia, NZ</td>
<td>138</td>
<td>2008-2012</td>
<td>Untreated stage IIA (with adverse features) or IIB-IV HL</td>
<td>465</td>
</tr>
</tbody>
</table>

DLBCL: diffuse large B-cell lymphoma; ESR: erythrocyte sedimentation rate; HL: Hodgkin lymphoma; NR: not reported; PET2/4: 2 or 4 cycles of positron emission tomography; RCT: randomized controlled trial; NZ: New Zealand.

Favorable prognosis: age <50 y with ≤3 involved nodal areas, absence of mediastinal bulk (mediastinum-to-thorax ratio <0.35), and ESR <50 mm without B symptoms or ESR <30 mm with B symptoms; Unfavorable prognosis: age ≥50 y, >4 involved nodal areas, presence of mediastinal bulk (mediastinum-to-thorax ratio ≥0.35), or ESR ≥50 mm without B symptoms or ESR ≥30 mm with B symptoms.

The results of these five RCTs for PET-directed therapy in PET-negative lymphoma patients are summarized in Table 10 and below.

In the Casasnovas et al (2017) trial, median follow-up was 45 months (range, 1-63 months). Of the 100 patients who were PET4-negative, 55 progressed or relapsed and 39 died. There was no significant difference in four-year PFS or OS between the two treatment groups. The trialists proposed that the flawed criteria were used to determine PET-positive and -negative classifications. The International Harmonization Project criteria were used because these criteria were accepted at the time of the trial launch. The International Harmonization Project criteria are
now known to generate high false-positive results. The authors suggested that SUVmax may guide treatment decisions more effectively.

In the Johnson et al (2016) trial, median follow-up was 41 months. There were 68 vs 74 events of disease progression, relapse, or death in the standard chemotherapy group vs the PET-directed therapy group, respectively (HR with PET-directed therapy, 1.13; 95% CI, 0.81 to 1.57; p=0.48). Three-year PFS rate was 85.7% (95% CI, 82.1% to 88.6%) in the standard chemotherapy group and 84.4% (95% CI, 80.7% to 87.5%) in the PET-directed therapy group (risk difference, 1.6 percentage points; 95% CI, -3.2 to 5.3); CIs included the noninferiority margin. Three-year OS rates were similar in both groups: 97.2% (95% CI, 95.1% to 98.4%) with standard chemotherapy and 97.6% (95% CI, 95.6% to 98.7%) with PET-directed therapy. Grade 3 and 4 respiratory adverse events were more severe in the standard chemotherapy group than in the PET-directed therapy group, and the difference in change in the diffusing capacity of the lung for carbon monoxide from baseline to the completion of therapy was -7.4% (95% CI, -5.1% to -9.7%; p<0.001).

In the RAPID (2015) trial, with a median of 60 months of follow-up, 8 instances of disease progression occurred in the RT group (standard therapy), and 8 patients had died (3 with disease progression, 1 of whom died from Hodgkin lymphoma); 20 instances of disease progression occurred in the group with no further therapy (PET-directed therapy), and 4 patients had died (2 with disease progression and none from Hodgkin lymphoma). The 3-year PFS rate was 95% (95% CI, 91.5% to 97.7%) in the RT group and 90.8% (95% CI, 86.9% to 94.8%) in the group that received no further therapy; the absolute risk difference was -3.8 percentage points (95% CI, -8.8 to 1.3) and the CIs included the noninferiority margin.

The EORTC/LYSA/FIL H10 (2014) trial, performed a prespecified interim analysis including 1124 randomized patients (favorable group, n=441; unfavorable group, n=683) with a median follow-up of 1.1 years. Progression or death was more common among patients in PET-guided therapy arms than in standard therapy arms of both groups (5% vs 0.5%, respectively, in the favorable group; 6% vs 3%, respectively, in the unfavorable group). Estimated HRs for progression or death were 9.4 (80% CI, 2.5 to 35.7) in the favorable group and 2.4 (80% CI, 1.4 to 4.4) in the unfavorable group. Based on these findings, futility was declared, and accrual to the early PET-negative experimental arm was discontinued.

In the Picardi et al (2007) trial, all 80 patients were included in the analysis with a median of 40 months of follow-up. Events were more common in the PET-directed arm. Eleven (14%) events vs 3 (4%) events were reported, corresponding to an event-free survival rate of 86% in the PET-directed arm vs 96% in the standard arm (HR for standard therapy, 3.32; 95% CI, 1.13 to 9.76; p=0.03). Twenty percent of patients in PET-directed vs 22% in standard therapy experienced hematologic toxicity of at least World Health Organization grade 2. The nonhematologic toxicity (including pneumonitis, cardiovascular abnormality, and peripheral neuropathy) of at least World Health Organization grade 2 was 5% in both groups. No deaths were reported.
Table 10. Summary of Key RCT Trial Results of PET-Guided Therapy in PET-Negative Patients

<table>
<thead>
<tr>
<th>Study or Trial</th>
<th>Primary Outcome</th>
<th>Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casasnovas et al (2017)²⁵</td>
<td>PFS and OS</td>
<td>4-y PFS: 4-y OS: • PET2+: 85% (71.1% to 92.6%) • PET2-: 75% (60.9% to 84.5%) • PET2+: 90.4% (81% to 95.1%) • PET2-: 89.6% (85% to 92.2%)</td>
</tr>
<tr>
<td>Johnson et al (2016)²³</td>
<td>PFS</td>
<td>• 3-y PFS: 84.4% (80.7% to 87.5%) vs 85.7% (82.1% to 88.6%) • HR for ST, 1.13 (0.81 to 1.57) • RD for ST, 1.6 (-3.2 to 5.3)</td>
</tr>
<tr>
<td>Radford et al (2015)⁴⁴; RAPID</td>
<td>PFS</td>
<td>• 3-Y PFS: 90.8% (86.9% to 94.8%) vs 94.6% (91.5% to 97.7%) • HR for PET-directed, 0.51 (0.15 to 1.68) • RD for PET-directed, -3.8 (-8.8 to 1.3)</td>
</tr>
<tr>
<td>Raemaekers et al (2014)⁶⁶; EORTC/LYSA/FIL H10</td>
<td>PFS (favorable: n=188 vs n=193; unfavorable: n=251 vs n=268)</td>
<td>Favorable: • PFS at 1 y: 94.9% vs 100% • 9 vs 1 events⁶⁶;⁶⁷ • HR for ST, 9.36 (2.45 to 35.73) Unfavorable: • PFS at 1 y: 94.7% vs 97.3% • 16 vs 7 events⁶⁶;⁶⁷ • HR for ST, 2.42 (1.35 to 4.36)</td>
</tr>
<tr>
<td>Picardi et al (2007)⁵⁵</td>
<td>EFS</td>
<td>EFS: 69 (86%) vs 77 (96%) • HR for ST, 3.32 (1.13 to 9.76)</td>
</tr>
</tbody>
</table>

CI: confidence interval; EFS: event-free survival; HR: hazard ratio; OS: overall survival; PET: positron emission tomography; PET2: 2 cycles of positron emission tomography; PFS: progression-free survival; RCT: randomized controlled trial; RD: risk difference; ST: standard therapy.

² Results from interim analysis.
³ Events of progression, relapse, or death.

Interim PET-Positive

The goal of PET-directed therapy for PET-positive patients is to intensify therapy for those at highest risk of treatment failure to improve PFS or OS. The trial by Casasnovas et al (2017) described in the PET-negative section above also included patients who were PET-positive after induction chemotherapy.²⁵ For patients who were PET-positive after induction therapy, guidance was given to proceed with a salvage regimen followed by autologous cell transplantation, though the final treatment decision was left to the patient’s clinician. The 4-year PFS rate was lower in patients who were PET-positive (72.9%; 95% CI, 63.1% to 80.6%) than in patients who were PET-negative following induction therapy (79.8%; 95% CI, 79.4% to 86.4%). The 4-year OS rate was also lower in PET-positive patients (80%; 95% CI, 69.0% to 87.5%) than in PET-negative patients (88.9%; 95% CI, 82.1% to 94.4%).

Wong-Seefidan et al (2017) evaluated the predictive value of FDG-PET/CT on survival in patients with follicular lymphoma.²² Among 1289 patients in the National LymphoCare Study, 447 underwent FDG-PET/CT following rituximab induction therapy. After a median follow-up of 7.6 years, the 5-year OS rate for PET-positive patients (n=155) was 78% and the PFS rate was 51%.

Both the RAPID (2015) trial⁴⁴ and the Johnson et al (2016) trial,⁵³ included observation of patients with a positive interim PET after initial induction chemotherapy, although neither trial had a randomized comparison in the PET-positive group. In the RAPID (2015) trial, 145 patients with positive PET findings received a fourth cycle of chemotherapy and involved-field RT. After a median of 62 months of follow-up, there were 18 events of progression, relapse, or death for a PFS rate in the PET-positive patients of 87.6% (precision not given). In the Johnson et al (2016)
trial, 182 patients with a positive PET received accelerated or escalated chemotherapy regimens. There were 55 events of disease progression, relapse, or death in the PET-positive group. The 3-year PFS rate was 67.5% (95% CI, 59.7% to 74.2%) and the OS rate was 87.8% (95% CI, 81.5% to 92.1%).

As previously described, the EORTC/LYSA/FIL H10 (2014) trial, randomized 1925 patients who had previously untreated stage I or II Hodgkin lymphoma to PET-directed therapy or standard therapy; patients in the PET-directed therapy arm who had a positive early PET scan (after 2 chemotherapy cycles) received intensified chemotherapy. Available results were presented at the 13th International Conference on Malignant Lymphoma in June 2015. These preliminary results indicated improvement in 5-year PFS rates in the PET-directed arm (91%) vs standard arm (77%; HR=0.42; 95% CI, 0.23 to 0.74; p=0.002) and were confirmed in the final results from the trial, published by André et al (2017).

Other Clinical Studies
Some single-arm early-phase trials, observational studies, and secondary analyses of RCT data that have assessed outcomes of patients with Hodgkin lymphoma and diffuse large B-cell lymphoma who received treatment changes based on interim PET/CT scans suggest that some chemotherapeutic regimens can be intensified or switched to less-toxic regimens without harm.

Conclusions of single-arm and retrospective studies may be limited by selection and lead-time bias and lack concurrent comparators. Given the potential for biases, comparative trials would be necessary to determine the efficacy of such a strategy.

Section Summary: Lymphoma
Evidence for the validity of using interim FDG-PET as an adjunct to CT consists of a systematic review, which has shown high false-positive rates for patients with Hodgkin or non-Hodgkin lymphoma. Evidence for the utility of interim FDG-PET for guided treatment in patients with lymphoma consists of a Cochrane review and several RCTs. The Cochrane review reported lower PFS in patients receiving PET-guided therapy compared with patients receiving standard care. Two retrospective studies published after the review evaluated interim FDG-PET in patients with follicular lymphoma and T-lymphoblastic leukemia/lymphoma; the studies showed that PET may have potential in predicting survival in these specific lymphomas. In the RCTs comparing PET-guided therapy with standard therapy, results did not show noninferiority.

Non-Small-Cell Lung Cancer
Clinical Context and Test Purpose
The purpose of interim PET as an adjunct to interim CT in patients with NSCLC is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with NSCLC?

The following PICOs were used to select literature to inform this review.

Patients
The population of interest are patients with NSCLC.
**Interventions**
The intervention of interest is interim PET scan, performed to guide therapy.

**Comparators**
The following test is currently being used to make decisions about managing those with NSCLC: interim CT.

**Outcomes**
The general outcomes of interest are QOL, OS, and PFS.

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Outcomes of interest include patient response and disease progression</td>
<td>≥1 month</td>
</tr>
<tr>
<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

**Nonrandomized Studies**
Thirteen studies identified have evaluated a potential association between interim FDG-PET analyses during various treatments and OS or PFS in patients with NSCLC. The studies included patients with various stages of NSCLC, receiving various lung cancer treatments: chemotherapy, chemoradiotherapy, chemotherapy with or without nitrogen patches, and low-dose fractionated radiotherapy with concurrent other studies had populations between 50 and 100. Most studies found correlations between early metabolic response detected by FDG-PET and survival, thereby suggesting that FDG-PET might be used to personalize treatment for patients with NSCLC. Generalizability of these results is limited due to the heterogeneity across studies, which included patients at various stages of the disease, undergoing various treatment regimens, and receiving FDG-PET during different cycles of treatment.

**Section Summary: NSCLC**
Evidence for the clinical validity of interim FDG-PET as an adjunct to CT, following various treatments for NSCLC, consists of many small observational studies. The studies were heterogeneous, with different patient populations, different therapies, and different timings of PET assessments. Most studies concluded that FDG-PET might adequately detect responders and nonresponders, which may predict OS and PFS. However, early prediction of survival does not translate into patient benefit unless decisions based on those predictions result in improved patient outcomes by either extending OS or improving QOL.
**Ovarian Cancer**

**Clinical Context and Test Purpose**
The purpose of interim PET as an adjunct to interim CT in patients with ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with ovarian cancer?

The following PICOs were used to select literature to inform this review.

**Patients**
The population of interest are patients with ovarian cancer.

**Interventions**
The intervention of interest is interim PET scan, performed to guide therapy.

**Comparators**
The following test is currently being used to make decisions about managing those with ovarian cancer: interim CT.

**Outcomes**
The general outcomes of interest are QOL, OS, and PFS.

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

**Table 12. Outcomes of Interest for Individuals with Ovarian Cancer**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
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<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

**Systematic Reviews**
Suppiah et al (2017) published a systematic review of the accuracy of PET/CT and PET/MRI in managing patients with ovarian cancer. The literature search, conducted through December 2016, identified 9 articles that addressed the use of PET/CT for treatment response and provided HRs for the prediction of recurrence. Outcomes of the studies were metabolic parameters (SUVmax, MTV, and/or total lesion glycolysis). Six of the 7 studies that measured SUVmax (n=750 patients) reported that it was not a significant indicator of survival. Two of the 3 studies that measured MTV (n=129 patients) reported that it was not a significant indicator of survival. All 4 studies that measured total lesion glycolysis (n=304 patients) reported that it was a significant predictive factor for prognosis. Meta-analyses were not performed.
Section Summary: Ovarian Cancer
Evidence for the use of PET as an adjunct to CT for assessing treatment response in patients with ovarian cancer consists of a systematic review of nonrandomized studies. Although total lesion glycolysis as measured by interim PET appeared to be associated with response and may be better than other methods of prognosis, these studies did not demonstrate whether such improved prediction leads to improved patient outcomes. No case series or comparative trials of risk-adapted treatment for ovarian cancer were identified.

Other Malignant Solid Tumors
Clinical Context and Test Purpose
The purpose of interim PET as an adjunct to interim CT in patients with other malignant solid tumors (eg, bladder, colorectal, prostate, thyroid) during treatment is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of interim PET as an adjunct to interim CT improve the net health outcome in individuals with other malignant solid tumors?

The following PICOs were used to select literature to inform this review.

Patients
The population of interest are patients with other malignant solid tumors (eg, bladder, colorectal, prostate, thyroid) during treatment.

Interventions
The intervention of interest is interim PET scan, performed to guide therapy.

Comparators
The following test is currently being used to make decisions about managing those with other malignant solid tumors: interim CT.

Outcomes
The general outcomes of interest are QOL, OS, and PFS.

Both false-positive test results and false-negative results can lead to incorrect treatment recommendations, such as continuing treatment that is ineffective, stopping treatment that is effective, and/or delaying initiation of more appropriate therapy.

The timing is during cycles of chemotherapeutic agents and/or a course of RT.

Table 13. Outcomes of Interest for Individuals with Other Malignant Solid Tumors

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
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</tr>
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<tr>
<td>Change in disease status</td>
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<td>Morbid events</td>
<td>Outcomes of interest include adverse events such as neutropenia and febrile neutropenia</td>
<td>≥1 month</td>
</tr>
</tbody>
</table>

Systematic Reviews
Singh et al (2018) published a systematic review and meta-analysis of PET imaging in patients with neuroendocrine tumors.76 Twenty-two studies (range of participants, n=15–728), published
between 2007 and 2017, were included in the analysis. Sensitivity of PET or PET/CT for detecting primary and/or metastatic lesions ranged from 78.3% to 100% in the staging and restaging setting, and specificity ranged from 83% to 100%. Change in management occurred in 45% (95% CI 36%--55%) of patients, the majority of which involved surgical planning and patient selection for peptide receptor radionuclide therapy. The analysis was limited by many included studies being small and lacking a control arm, a high degree of heterogeneity, and most studies consisting of a mixed population of patients with neuroendocrine tumors.

Beckers et al (2018) conducted a PRISMA-based systematic review to assess the value of FDG-PET, FDG-PET/CT, CT, and MRI in predicting response to chemotherapy in colorectal liver metastases. PubMed and EMBASE databases were searched up to October 2016 to select studies assessing the accuracy of PET, PET-CT, CT, and MRI in predicting RECIST or metabolic response to chemotherapy and/or survival in patients with colorectal liver metastases; 16 studies met inclusion criteria. Results included six studies on FDG-PET(CT), six studies on CT, and nine studies on MRI. FDG-PET/CT findings were ambiguous. Meta-analysis could not be conducted due to the heterogeneity of populations, scan protocols, types of chemotherapy, and the use of targeted therapy. The quality of this review was reduced by the lack of histopathology reference standards.

The 2007 and 2009 NCCN task force reports assessed the use of interim PET for other malignant solid tumors. The 2007 report cited a small study of patients with colorectal cancer that showed an association between PET and tumor response to 5-fluorouracil after 1 month of therapy. For colorectal cancer, one study showed that PET after one month of chemotherapy predicted the outcome but predictive accuracy was low. For head and neck cancer, esophageal cancer, and melanoma, only studies that evaluated PET after treatment were identified. In total, the British National Health Service review found 22 studies of PET during treatment. Reviewers concluded that many studies were small and evaluated different treatments using a diversity of response targets and monitoring methods. There was little evidence of change in patient management, even anecdotally, and no published evidence of successful applications to drug development.

The 2009 NCCN report reviewed cancers not discussed in the 2007 report. For most cancers (eg, bladder, prostate, thyroid), evidence for interim PET was not cited. Although the task force included a recommendation for PET to assess response to liver-directed therapies in patients with localized hepatocellular carcinoma, the recommendation was based on studies of PET after transcatheter chemo-embolization and/or radiofrequency ablation (ie, not interim PET).

Since the NCCN and the National Health Service report, other studies have been reported in patients with colon cancer demonstrating associations between early or interim PET and recurrence or survival outcomes. Evidence in rectal or colorectal cancer was mixed, and studies of early (during or after one or two neoadjuvant chemotherapy cycles) PET to predict axillary lymph node response reported conflicting results. Studies have also reported on associations between early or interim PET during treatment and recurrence or survival outcomes in bladder cancer, malignant pleural mesothelioma, squamous cell carcinomas of the head and neck, pancreatic cancer, and bone or soft tissue sarcoma.
Conversely, evidence for advanced renal cell carcinoma was mixed. Method of measurement of quantitative parameters and cutpoint thresholds for PET-positivity varied across studies within the same cancer. No study demonstrated the impact of PET-directed treatment on net health outcome.

**Section Summary: Other Malignant Solid Tumors**
Evidence for the use of interim PET during treatment of other cancers, such as bladder, colorectal, prostate, and thyroid consists of a systematic review, NCCN reports, and mostly single-arm observational studies. Results have been inconsistent with the use of interim PET for patients with colorectal cancer and renal cell carcinoma. While some studies have reported on associations between interim PET and recurrence or survival, the lack of comparative trials of risk-adapted treatment was identified.

**Summary of Evidence**

**Breast Cancer**
For individuals with breast cancer who receive interim FDG-PET as an adjunct to interim CT, the evidence consists of several systematic reviews, an RCT, and many observational studies. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. Results from the systematic review have shown wide ranges in sensitivities, specificities, PPVs, and NPVs. The wide ranges might be due to small sample sizes, the use of various definitions of the outcome measure (pathologic complete response), and differences in breast cancer subtype populations. One RCT was identified in which therapy decisions were guided by FDG-PET results. Nonresponders, determined by PET measures, were given more intensive chemotherapy. Clinical outcomes such as progression-free survival and OS are not yet available for this RCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Esophageal Cancer**
For individuals with esophageal cancer who receive interim FDG-PET as an adjunct to interim CT, the evidence includes a meta-analysis, three nonrandomized studies, and two retrospective studies. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. Results on clinical validity were inconsistent across the studies. The meta-analysis reported low pooled sensitivities and specificities, while a subgroup analysis including only patients with squamous cell carcinoma and two studies published after the meta-analysis reported an adequate potential in predicting responders to neoadjuvant therapy. No evidence was identified that examined the clinical utility of PET for patients with esophageal cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Gastrointestinal Stromal Tumors**
For individuals with GIST receiving palliative or adjuvant therapy who receive interim FDG-PET as an adjunct to interim CT, the evidence includes a systematic review. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. The systematic review included 19 studies, 2 of which reviewed FDG-PET scans more than 6 months after the start of treatment. CT is currently recommended for standard long-term follow-up and surveillance of gastrointestinal stromal tumors. FDG-PET is equivalent to CT in the detection of treatment response when follow-up is long-term. No studies were identified.
that tested outcomes following PET-guided treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with GIST treated with TKIs for six months or less who receive interim FDG-PET as an adjunct to interim CT, the evidence includes a systematic review. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. The systematic review included 19 studies, 17 of which showed that FDG-PET detected an early response to TKI therapy, which was a strong predictor of clinical outcomes. FDG-PET detected treatment response as early as one week after initiation of treatment. While CT detects anatomic changes in the tumor, PET detects changes in the metabolic activity of the tumor. Because metabolic changes precede anatomic changes by several weeks or sometimes months, PET can detect treatment response earlier than CT. PET is therefore preferred if a rapid read-out of response to targeted therapy is needed to guide treatment decisions (eg, change in targeted therapy or surgery). While no studies were identified that tested outcomes following PET-guided treatment, it is possible to construct a chain of evidence demonstrating improved patient outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Head and Neck Cancer**

For individuals with head and neck cancer who receive interim FDG-PET as an adjunct to CT, the evidence includes several systematic reviews and a retrospective study. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. There was an overlap of studies among the systematic reviews. Most studies included in the reviews showed that FDG-PET used during radiotherapy, with or without chemotherapy, can adequately predict disease-free and OS. Meta-analyses to determine response could not be performed in any of the systematic reviews due to the heterogeneity in the methods across the studies. Most studies used SUVmax, however, threshold values to determine response varied across studies. No studies were identified that provided evidence for the clinical utility of PET. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Lymphoma**

For individuals with lymphoma who receive interim FDG-PET as an adjunct to interim CT, the evidence includes systematic reviews with meta-analyses and RCTs. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. The systematic review evaluating the validity of interim FDG-PET showed high false-positive rates for both Hodgkin and non-Hodgkin lymphomas. After the systematic review, two studies were published; one focused on patients with follicular lymphoma and the other on patients with T-lymphoblastic leukemia/lymphoma. These studies showed a potential for FDG-PET to predict survival rates for these specific lymphomas. Evidence for the clinical utility of interim PET for guiding treatment in patients with lymphoma consists of a Cochrane review and several RCTs. The review reported lower PFS rates in patients who received PET-guided therapy. The RCTs that compared PET-guided therapy with standard therapy did not demonstrate noninferiority. The evidence is insufficient to determine the effects of the technology on health outcomes.
Non-Small-Cell Lung Cancer
For individuals with NSCLC who receive interim FDG-PET as an adjunct to interim CT, the evidence includes numerous small observational studies. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. While most studies showed correlations between FDG-PET measurements and PFS and OS, the generalizability of the results is limited. The studies were small, with most population sizes fewer than 50 patients. The studies were also heterogeneous, including patients at different stages of the disease, undergoing different treatment regimens, and receiving PET at different times during treatment cycles. No studies were identified that evaluated outcomes after PET-guided therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ovarian Cancer
For individuals with ovarian cancer who receive interim FDG-PET as an adjunct to interim CT, the evidence includes a systematic review. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. The systematic review identified nine studies that calculated HRs for various FDG-PET parameters (eg, maximum standardized uptake value, metabolic tumor volume, tumor lesion glycolysis). The only parameter consistently showing prognostic value was tumor lesion glycolysis. Additionally, no studies were identified that evaluated outcomes after PET-guided therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Other Cancers
For individuals with other malignant solid tumors (eg, bladder, colorectal, prostate, thyroid) who receive FDG-PET as an adjunct to interim CT, the evidence includes a systematic review, NCCN task force report, and single-arm observational studies published after the task force report. The relevant outcomes are OS, disease-specific survival, change in disease status, QOL, morbid events, and treatment-related morbidity. Results have been inconsistent on the use of interim FDG-PET among the various cancers. While some have reported associations between interim FDG-PET and recurrence or survival, there is a lack of comparative trials evaluating outcomes in patients whose treatments were altered based on PET measurements. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

In response to requests, input was received from 1 physician specialty society and 5 academic medical centers while this policy was under review in 2011. In general, there was an agreement with the conclusions of this policy from those providing input. Most disagreement related to the use of positron emission tomography scans during a planned course of treatment for patients with Hodgkin lymphoma. Some reviewers felt current data were sufficient to show benefit; others commented that additional studies needed to evaluate this issue.
Practice Guidelines and Position Statements
American College of Radiology and Society for Pediatric Radiology
The American College of Radiology and the Society for Pediatric Radiology (2016; revised 2019) updated their joint practice guidelines for performing fluorine 18 fluorodeoxyglucose positron emission tomography (FDG-PET) coupled with computed tomography (CT) in oncology.109, The guidelines stated that FDG-PET/CT imaging in oncology patients "should only be performed when there is reasonable expectation that the results will have an impact on patient care." Examples of indications for imaging included "Monitoring response to therapy to include determining whether residual abnormalities identified with another imaging modality represent persistent viable tumor or post-treatment changes (inflammation, fibrosis, or necrosis)" and "Guiding specific clinical strategies, such as radiation therapy planning or directed biopsy." Further clarification was not provided.

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network recommendations for interim PET scanning during treatment to assess early response in a variety of cancers are summarized in Table 14.

Table 14. Recommendations for Interim PET Scanning

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Version</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder cancer110,</td>
<td>4.2019</td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
<tr>
<td>Breast cancer111,</td>
<td>2.2019</td>
<td>&quot;Studies of functional imaging [for monitoring metastatic disease], such as radionuclide bone scans and PET imaging, are particularly challenging when used to assess response... PET imaging is challenging because of the absence of a reproducible, validated, and widely accepted set of standards for disease activity assessment.&quot;</td>
</tr>
<tr>
<td>CNS cancers112,</td>
<td>1.2019</td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
<tr>
<td>Cervical cancer113,</td>
<td>4.2019</td>
<td>&quot;For patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB2 or patients who required postoperative adjuvant radiation or chemoradiation due to high-risk factors, a whole-body PET/CT may be performed at 3-6 months after completion of treatment.&quot; &quot;Patients with stage II-IV, whole-body PET/CT is preferred or chest/abdomen/pelvic CT with contrast within 3-6 months of completion of therapy.&quot;</td>
</tr>
<tr>
<td>Colon cancer114,</td>
<td>2.2019</td>
<td>&quot;PET/CT should not be used to monitor progress of therapy. PET/CT scans should not be used to assess response to chemotherapy because a PET/CT scan can become transiently negative after chemotherapy. False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection.&quot;</td>
</tr>
<tr>
<td>Esophageal and EGJ cancers115,</td>
<td>2.2019</td>
<td>In the clinical setting of patients with squamous cell carcinoma or adenocarcinomas following preoperative chemoradiation or definitive chemoradiation, the response to treatment assessment using PET/CT or PET is preferred.</td>
</tr>
<tr>
<td>Soft tissue sarcoma37,</td>
<td>2.2019</td>
<td>&quot;PET/CT may be useful in determining response to neoadjuvant chemotherapy for lesions that are larger than 3 cm, firm, deep (not superficial)&quot; &quot;PET may give an indication of imatinib activity after 2-4 weeks of [primary or preoperative] therapy when rapid readout of activity is necessary.&quot;</td>
</tr>
<tr>
<td>Head and neck cancers116,</td>
<td>2.2019</td>
<td>After either radiation therapy or chemoradiation, post-treatment evaluation with imaging (ie, CT and/or MRI with contrast, FDG-PET/CT) guides the use of neck dissection. If PET/CT is used for follow-up, the first scan should be performed at a minimum of 12 weeks after treatment to reduce the false-positive rate.</td>
</tr>
<tr>
<td>Hepatobiliary cancers117,</td>
<td>2.2019</td>
<td>&quot;In PET/CT it is not recommended for detection of HCC because of limited sensitivity. When an HCC is detected by CT or MRI and has increased metabolic activity on PET/CT, higher intralesional standardized uptake value is a marker of biologic aggressiveness and might predict less optimal response to locoregional therapies.&quot;</td>
</tr>
<tr>
<td>Guideline</td>
<td>Version</td>
<td>Recommendation</td>
</tr>
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<td>-----------------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hodgkin lymphoma118,</td>
<td>2.2019</td>
<td>“PET scans are increasingly being used to assess treatment response during therapy. Interim PET scans may be useful to identify a subgroup of patients with early-stage disease that can be treated with chemotherapy alone. The NCCN Guidelines emphasize that the value of interim PET scans remains unclear for many clinical scenarios and all measures of response should be considered in the context of management decisions. It is important that the Deauville score be incorporated into the nuclear medicine PET scan report, since subsequent management is often dependent upon that score. Suggested treatment regimens for stage I-II unfavorable or stage III-IV disease: “A (B) VD (2cycles) followed by AVD (4cycles), if PET scan is negative after 2 cycles of ABVD. Patients with positive PET scan after 2 cycles of ABVD need individualized treatment.”</td>
</tr>
<tr>
<td>Melanoma119,</td>
<td>2.2019</td>
<td>“Recent studies in patients with stage III or IV melanoma... indicated that additional information provided by PET/CT may impact treatment decisions in up to 30% of patients, with the greatest impact seen in surgical management.”</td>
</tr>
<tr>
<td>MPM120,</td>
<td>2.2019</td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
<tr>
<td>Multiple myelomas 121,</td>
<td></td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma: B-cell122,</td>
<td>4.2019</td>
<td>“Further prospective studies are warranted to determine whether interim PET scans have a role in guiding post-induction therapeutic interventions.” “A negative PET scan after 2 to 4 cycles of induction therapy has been associated with significantly higher EFS and OS rates in several studies. However, interim PET scans can produce false-positive results and many patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan.”</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma: T-cell123,</td>
<td>2.2019</td>
<td>“The guidelines recommend interim restaging with PET/CT or CT scan for all patients.”</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma: PCBCL124,</td>
<td>2.2019</td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
<tr>
<td>NSCLC125,</td>
<td>5.2019</td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
<tr>
<td>Ovarian cancer126,</td>
<td>1.2019</td>
<td>Primary chemotherapy regimens include monitoring with chest/abdominal/pelvic CT or MRI with contrast, PET/CT (skull base to mid-thigh), or PET as indicated.</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma127,</td>
<td>3.2019</td>
<td>“PET/CT scan may be considered after formal pancreatic CT protocol of high-risk patients to detect extrapancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT. See Principles of Diagnosis, Imaging, and Staging (PANC-A).”</td>
</tr>
<tr>
<td>Prostate cancer128,</td>
<td>2.2019</td>
<td>“F-18 FDG-PET/CT should not be used routinely since data are limited in patients with prostate cancer.”</td>
</tr>
<tr>
<td>Rectal cancer129,</td>
<td>2.2019</td>
<td>“Chest/abdominal/pelvic ST with contrast or chest CT and abdominal/pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used. See Principles of Imaging (REC-A).”</td>
</tr>
<tr>
<td>SCLC130,</td>
<td>1.2019</td>
<td>“Patients most likely to benefit from surgery are those with SCLC that is clinical stage I-IIA (T1-2,N0, M0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and PET/CT imaging).”</td>
</tr>
<tr>
<td>Thyroid carcinoma131,</td>
<td>1.2019</td>
<td>Post-treatment 131 I imaging may indicate the location of metastases when the serum Tg level is increased, but a tumor [or metastases] cannot be found by physical examination or other localizing techniques such as diagnostic 131 I imaging, neck ultrasonography, CT, MRI, or PET.</td>
</tr>
<tr>
<td>Uterine neoplasms132,</td>
<td>3.2019</td>
<td>Interim PET for assessing response to ongoing treatment is not addressed.</td>
</tr>
</tbody>
</table>


“This statement is a footnote to epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer treatment recommendations and is uncited.
U.S. Preventive Services Task Force Recommendations
Not applicable.

"Three FDG PET scans are nationally covered when used to guide subsequent management of anti-tumor treatment strategy after completion of initial anti-cancer therapy. Coverage of more than three FDG PET scans to guide subsequent management of anti-tumor treatment strategy after completion of initial anti-cancer therapy shall be determined by the local Medicare Administrative Contractors."

Ongoing and Unpublished Clinical Trials
Currently, ongoing and unpublished trials that might influence this review are listed in Table 15.

Table 15. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01356680</td>
<td>HD17 for Intermediate Stages - Treatment Optimization Trial in the First-Line Treatment of Intermediate Stage Hodgkin Lymphoma</td>
<td>1100</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT00822120</td>
<td>A Phase II Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging</td>
<td>371</td>
<td>Apr 2020</td>
</tr>
<tr>
<td>NCT00736320</td>
<td>HD16 for Early Stages - Treatment Optimization Trial in the First-line Treatment of Early Stage Hodgkin Lymphoma; Treatment Stratification by Means of FDG-PET</td>
<td>1150</td>
<td>May 2021</td>
</tr>
<tr>
<td>NCT01118026</td>
<td>Phase II Trial of Response-Adapted Therapy Based on Positron Emission Tomography (PET) for Bulky Stage I and Stage II Classical Hodgkin Lymphoma (HL)</td>
<td>101</td>
<td>Aug 2020</td>
</tr>
<tr>
<td>NCT00515554</td>
<td>HD18 for Advanced Stages in Hodkins Lymphoma</td>
<td>1500</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT00943423</td>
<td>A Randomised Phase III Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodkin’s Disease</td>
<td>602</td>
<td>Dec 2030</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01478542</td>
<td>Improvement of Outcome and Reduction of Toxicity in Elderly Patients With CD20+ Aggressive B-Cell Lymphoma by an Optimised Schedule of the Monoclonal Antibody Rituximab, Substitution of Conventional by Liposomal Vincristine, and FDG-PET Based Reduction of Therapy in Combination with Vitamin D Substitution</td>
<td>1152</td>
<td>Jan 2025</td>
</tr>
<tr>
<td>NCT01285765</td>
<td>Randomized Phase III Study Evaluating the Non-inferiority of a Treatment Adapted to the Early Response Evaluated With 18F-FDG PET Compared to a Standard Treatment, for Patients Aged From 18 to 80 Years With Low Risk (aa IPI = 0) Diffuse Large B-cells Non-Hodgkin’s Lymphoma CD 20+</td>
<td>650</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02063685</td>
<td>A Multicenter, Phase III, Randomized Study to Evaluate the Efficacy of Response-adapted Strategy to Define Maintenance After Standard Chemoimmunotherapy in Patients With Advanced-stage Follicular Lymphoma</td>
<td>810</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02507518</td>
<td>Role of 18FDG PET in the Evaluation of Early Response to Maintenance Treatment With Bevacizumab or Pemetrexed in Advanced Non-small-cell Lung Cancer</td>
<td>80</td>
<td>Mar 2019</td>
</tr>
<tr>
<td>Stomach or gastroesophageal junction cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02485834</td>
<td>Impact of Early FDG-PET Directed Intervention on Preoperative Therapy for Locally Advanced Gastric Cancer: A Random Assignment Phase II Study</td>
<td>5</td>
<td>Aug 2018 (terminated)</td>
</tr>
</tbody>
</table>
### NCT No. | Trial Name                                                                                                                                                                                                                                                                                                                                 | Planned Enrollment | Completion Date |
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01718873</td>
<td>Randomized Phase 3 Study on the Optimization of Bevacizumab With mFOLFOX/mOXXEL in the Treatment of Patients With Metastatic Colorectal Cancer</td>
<td>230</td>
<td>Jun 2018 (unknown)</td>
</tr>
<tr>
<td><strong>Esophageal cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02469922</td>
<td>Prospective Study Assessing Predictive Value of $^{18}$FDG Positron Emission Tomography During Radiochemotherapy for Locally Advanced Epidermoid Carcinoma of the Head and Neck</td>
<td>123</td>
<td>Nov 2020</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hodgkin Lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01132807</td>
<td>Phase II Trial of Response-Adapted Chemotherapy Based on PositronEmission Tomography for Non-Bulky Stage I and II Hodgkin Lymphoma</td>
<td>164</td>
<td>Jan 2018 ()</td>
</tr>
<tr>
<td><strong>Breast Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01142778</td>
<td>An Open-Label, Randomized, Multicenter, Phase II, Non Comparative, Exploratory Study on Neoadjuvant Treatment With Trastuzumab Plus Docetaxel Plus Bevacizumab According to Positron Emission Tomography (PET) Value Modification in Patients With Early Stage HER2 Positive Breast Cancer</td>
<td>152</td>
<td>Dec 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

### CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

### CPT/HCPCS

- 78811 Positron emission tomography (PET) imaging; limited are (eg, chest, head/neck)
- 78812 Positron emission tomography (PET) imaging; skull base to mid-thigh
- 78813 Positron emission tomography (PET) imaging; whole body
- 78814 Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (eg., chest, head/neck)
- 78815 Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
- 78816 Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body
- G0235 PET imaging, any site, not otherwise specified

- There is a HCPCS modifier:
  - Modifier PS: PET or PET/ 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 antitumor strategy.
DIAGNOSES
C49.A1 Gastrointestinal stromal tumor of esophagus
C49.A2 Gastrointestinal stromal tumor of stomach
C49.A3 Gastrointestinal stromal tumor of small intestine
C49.A4 Gastrointestinal stromal tumor of large intestine
C49.A5 Gastrointestinal stromal tumor of rectum
C49.A9 Gastrointestinal stromal tumor of other sites

REVISIONS
10-16-2013 PET Scanning in Oncology to Detect Early Response during Treatment was originally part of the Positron Emission Tomography (PET) medical policy. This portion was pulled out and placed into a separate medical policy, Positron Emission Tomography (PET) Scanning: In Oncology to Detect Early Response during Treatment.

10-22-2015 Description section updated
Rationale section updated
In Coding section:
- Added HCPCS Code: G0235
- Coding notations updated
References updated

In Description section updated
In Policy section:
- Added medically necessary indication of "The use of interim florine 18 fluorodeoxyglucose positron emission tomography scans to determine response to tyrosine kinase inhibitor treatment in patients with gastrointestinal stromal tumors is considered medically necessary."
- Added to Item B "gastrointestinal stromal tumors on palliative or adjuvant therapy, as well as all other" to read "The use of positron emission tomography scans to determine early response to treatment (positron emission tomography scans done during a planned course of chemotherapy and/or radiation) in patients with gastrointestinal stromal tumors on palliative or adjuvant therapy, as well as all other cancers is considered experimental / investigational."
Rationale section updated
In Coding section:
- Removed "Experimental / Investigational on all diagnoses related to this medical policy." statement.
- Updated Coding notations.
References updated

06-12-2020 Description section updated
Rationale section updated
References updated

REFERENCES


101. Wong KH, Panek R, Welsh L, et al. The predictive value of early assessment after 1 cycle of induction chemotherapy with \textsuperscript{18}F-FDG PET/CT and diffusion-weighted MRI for response to radical


**Other References**

1. Blue Cross and Blue Shield of Kansas, Medical Advisory Committee meeting, April 24, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC–02-03).
2. Blue Cross and Blue Shield of Kansas, Oncology Liaison Committee meeting, February 18, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC–02-03).
3. Blue Cross and Blue Shield of Kansas, Radiology Liaison Committee meeting, February 11, 2003 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report MAC–02-03).
4. MCMC, Medical Care Ombudsman Program (MCOP), August 11, 2006, MCOP ID 1071-0720.
6. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee, February 2009.