Interim Positron Emission Tomography Scanning in Oncology to Detect Early Response During Treatment

Policy # 00590
Original Effective Date: 01/02/2018
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Positron Emission Tomography (PET) Oncology Applications is addressed separately in medical policy 00105.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of interim fluorodeoxyglucose positron emission tomography (PET) scans to determine response to tyrosine kinase inhibitor treatment in patients with gastrointestinal stromal tumors to be **eligible for coverage.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of positron emission tomography (PET) scans to determine early response to treatment (positron emission tomography scans done during a planned course of chemotherapy and/or radiotherapy) in patients with gastrointestinal stromal tumors on palliative or adjuvant therapy, as well as all other cancers to be **investigational.***

Background/Overview

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 2 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, because tumor cells show increased metabolism of glucose.

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This evidence review focuses on the use of PET to determine early treatment response for cancer, ie, 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 2 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.

In 2009, Hillner et al 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.”

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
A number of PET scan platforms have been cleared by the U.S. 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 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.

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

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

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.

Centers for Medicare and Medicaid Services (CMS)
The national coverage determination on FDG-PET for oncologic conditions (220.6.17) makes the following coverage decisions:

> "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."

Rationale/Source

Most studies that evaluate PET during treatment have analyzed the association between PET findings and various intermediate end points, 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 end points 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. Therefore, direct evidence of the utility of PET-directed treatment is incomplete.

Evaluation of these types of treatment protocols would require direct evidence of utility from randomized controlled trials (RCTs). Thus, conclusions about efficacy could not follow directly from observational studies of PET. The following sections summarize published literature on the use of PET during treatment for several major cancers.

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity,

and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes).

POSITRON EMISSION TOMOGRAPHY

Clinical Context and Test Purpose

The purpose of fluorine 18 fluorodeoxyglucose PET (FDG-PET) scanning in patients with cancer who have initiated treatment is to determine early treatment response and guide decisions on maintaining or changing treatment.

The question addressed in this evidence review is: Does the use of FDG-PET to assess early treatment response improve the net health outcome in individuals with cancer?

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

Patients

The population of interest includes patients with cancer who have initiated treatment.

Interventions

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

Comparators

The comparator of interest is a computed tomography (CT) scan, performed to guide therapy.

Outcomes

The general outcomes of interest are quality of life, 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.

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

Setting
The setting is an outpatient imaging center equipped with a PET scanner.

Breast Cancer

Clinical Validity
Systematic Reviews
In 2017, Lindenberg et al published a systematic review on the use of imaging (FDG-PET and dynamic contrast-enhanced magnetic resonance imaging [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 8 or higher. Reviewers provided descriptions of the imaging methods (type of imaging, monitoring interval) and results (sensitivity, specificity, negative and positive predictive values) by breast cancer subtype: estrogen receptor (ER)–positive and 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%, positive predictive value estimates ranged from 0% to 100%, and negative predictive values ranged from 10% to 84%. Meta-analyses were not performed due to heterogeneity across studies. Studies differed by neoadjuvant chemotherapy regimen and definition of pathologic complete response (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.

Clinical 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.

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 by Schmitz et al (2017), 188 women with stages II or III breast cancer 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 may provide the best monitoring of treatment, though results were not

statistically significant. For triple-negative tumors, the 2 imaging techniques performed equally in predicting pCR.

Clinical Utility

Randomized Controlled Trials

Early results of the AVATAXHER (Addition of beVAcizumab to neoadjuvant doceTAXel and trastuzumab [HER]) trial were published in 2014. This randomized, open-label, multicenter phase 2 trial enrolled women (≥18 years) with early stage human epidermal growth factor receptor 2–positive breast cancer from 26 oncology centers in France. A total of 142 patients were enrolled between 2010 and 2012. Patients initially received 2 cycles of neoadjuvant docetaxel plus trastuzumab. Before the first and second cycles, change in standardized uptake value (SUV) measured by FDG-PET was used to predict pathologic complete PET responders continued to receive standard therapy. FDG-PET nonresponders were randomly assigned (2:1) to receive 4 cycles of docetaxel and trastuzumab plus bevacizumab or to continue on docetaxel plus trastuzumab alone (standard therapy). Investigators and patients were unblinded, but the pathologist in charge of central surgical sample and lymph node reviews was blinded. The primary end point was centrally assessed pathologic complete response according to the Chevallier classification.

Of the 142 patients, 69 were PET responders after 2 cycles of treatment 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. OS or PFS results were not available at reporting.

Nonrandomized Studies

Very little data are available on the use of FDG-PET or FDG-PET/CT to guide management decisions. A 2014 case series of breast cancer in 30 men reported on the use of interim FDG-PET/CT to alter management decisions in 6 (20%) subjects, but the investigators did not show any data on subsequent survival or other health outcomes. In a prospective study (2015) of all 38 biopsy-confirmed female patients diagnosed with locally advanced breast cancer receiving chemotherapy from April 2013 to May 2014 in India, 14 patients had FDG-PET/CT to assess response following initial chemotherapy. The authors reported that response assessment resulted in a change of treatment regimen in 14% of patients.

Section Summary: Breast Cancer

Evidence for the clinical validity of interim FDG-PET for monitoring disease in patients with breast cancer includes a systematic review and many observational studies. Results from the systematic review showed wide ranges in sensitivities, specificities, positive predictive values, and negative predictive values. The wide ranges may be due to small sample sizes, use of different definitions of the primary outcome (pCR), and differences in breast cancer subtype of the 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 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. The goal of using interim FDG-PET is to determine if the tumors would respond to the neoadjuvant therapy. Knowing whether tumors would respond to treatment would inform the decision to offer neoadjuvant therapy or proceed directly to surgery.

Clinical Validity
Systematic Reviews
In 2016, Cong et al 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 for inclusion in the meta-analysis. Four studies (n=192 patients) conducted PET during NCRT, and 11 studies (n=490 patients) conducted PET after NCRT. Study quality was assessed using QUADAS scores, which ranged from 9 to 12 (total points, 14) in the included studies. Only 5 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 6.3 (95% CI, 2.1 to 19.3), respectively. Subgroup analyses on studies that conducted PET after NCRT and included only patients with squamous cell carcinoma (4 studies, 129 patients), showed higher pooled 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
In 2017, van Rossum et al published a study evaluating the use of FDG-PET before and after induction chemotherapy to predict response to subsequent chemoradiotherapy in patients with adenocarcinoma. Patients who were to receive a 3-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 [TLG] after chemotherapy).

After a median follow-up duration 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.

In 2017, Hagen et al 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. The outcome of metabolic response, stable disease, or progression was assessed using Positron Emission Tomography Response Criteria in Solid Tumors (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 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
In 2017, Manoharan et al 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). 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 percent change in maximum SUV (SUVmax). Patients with 70% or more change in SUVmax had lower risks of death and recurrence than patients with less than 70% SUVmax.

Clinical Utility
No RCTs or observational studies were identified that evaluated outcomes of patients whose treatments were altered with interim FDG-PET.

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 and 3 studies published after the meta-analysis. Results were inconsistent among the studies. Results from the meta-analyses showed low pooled sensitivities and specificities, indicating FDG-PET may be a poor guide for 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 2 studies published after the meta-analysis, reported that FDG-PET could adequately predict responders to neoadjuvant therapy. No evidence was identified examining the clinical utility of FDG-PET for patients with esophageal cancer.

Gastrointestinal Stromal Tumors

Clinical Validity
A 2009 National Comprehensive Cancer Network (NCCN) task force report identified a small retrospective study of 20 patients with gastrointestinal stromal tumors (GIST) who were treated with imatinib and

underwent PET, CT, and PET/CT imaging. PET/CT was more accurate than either PET or CT alone for detecting tumor response at 1, 3, and 6 months after initiation of imatinib. Based on this study, the task force recommended PET for response assessment to targeted GIST therapy.

A 2012 systematic review of studies of FDG-PET for evaluating treatment response to imatinib and other drugs in GIST included the retrospective study identified by the NCCN. 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 tyrosine kinase inhibitor (imatinib, sunitinib, masitinib) therapy and survival outcomes, and 2 studies (n=44 patients) that did not show this association. 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 surgical approach or addition of second line treatment.

Clinical Utility
No RCTs or observational studies were identified that evaluated outcomes of patients whose treatments were altered with interim FDG-PET.

Section Summary: Gastrointestinal Stromal Tumors
There were no studies identified to provide support for long-term PET-guided treatment of patients with gastrointestinal tumors.

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 tyrosine kinase inhibitors (imatinib, sunitinib, masitinib), and could be a strong predictor of clinical outcome as early as 1 month after initiating treatment. While CT detects anatomic changes in the tumor, FDG-PET detects changes in 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 Validity
In 2017, Min et al 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 7 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.

In 2016, Castelli et al published a systematic review of the predictive value of FDG-PET/CT for patients with head and neck cancer who are 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 2017 Min systematic review. Study quality assessment was not mentioned in the review. Six of the 7 studies reported a correlation between PET measurements (SUVmax, TLG, MTV) and clinical outcomes (disease-free survival, OS). The optimal time to perform FDG-PET during treatment is unclear, though most of the studies used PET after 3 weeks of treatment. Meta-analyses were not conducted.

In 2016, dos Anjos et al published a systematic review of the effectiveness of FDG-PET/CT for patients with head and neck squamous cell carcinoma who are 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 absence of follow-up. Six of the 7 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.

Clinical Utility
No RCTs or observational studies were identified that evaluated outcomes of patients whose treatments were altered with interim FDG-PET.

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 studies 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 Validity
Systematic Reviews
In 2016, Adams and Kwee published a systematic review and meta-analysis calculating false-positive rates of FDG-PET during and at end of treatment, using biopsy as the reference standard in patients with

lymphoma and FDG-avid lesions. Overall methodologic study quality was moderate, as assessed by the QUADAS-2 tool. Table 2 shows the pooled false-positive rates.

Table 2. Pooled False-Positive Rates

Treatment	Condition	No. of Studies	Percentage	95% CI, %
Interim FDG-PET	Hodgkin lymphoma	0		
Interim FDG-PET	Non-Hodgkin lymphoma	4	83	72 to 90
End-of-treatment FDG-PET	Hodgkin lymphoma	3	23	5 to 65
End-of-treatment FDG-PET	Non-Hodgkin lymphoma	2	31	4 to 84

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.

Retrospective Studies
In 2017, Wong-Sefidan et al published a study evaluating the predictive value of FDG-PET/CT on survival in patients with follicular lymphoma. 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%. For PET-positive patients (n=155), the 5-year OS rate was 78%, and the PFS rate was 51%.

Clinical Utility
Systematic Reviews
A Cochrane systematic review of interim FDG-PET-adapted therapy following first-line treatment in Hodgkin lymphoma was published in 2015. 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). The quality of the evidence for the primary outcome of PFS was considered moderate. In all 3 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% confidence interval [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 3 trials. The studies included little to no data on response rates, treatment-related mortality, quality of life, 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 cancers and

cardiovascular disease 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 (previously described). Characteristics of the studies are summarized in Table 3 and briefly below.

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 VEBEP (vinblastine, etoposide, bleomycin, epirubicin, prednisone) were randomized to observation (PET-directed therapy) or 32 gray (Gy) RT (standard therapy). The study was powered to detect a 10% risk difference (RD) in event-free survival, defined as relapse, secondary malignancies, or death from any cause; the specific hypothesis (superiority vs noninferiority) was not reported.

In 2014, Raemaekers et al 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. The trial randomized patients who had previously untreated stage I or II Hodgkin lymphoma to PET-directed therapy or standard therapy. Standard therapy was additional ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine; 1 cycle for favorable and 2 cycles for unfavorable) plus 30-Gy radiation. PET images were scored according to the International Harmonisation 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 2 chemotherapy cycles) did not receive RT but received additional cycles of ABVD (2 cycles for favorable, 4 cycles for unfavorable). Patients with favorable or unfavorable prognostic factors were analyzed separately. The trial design was noninferiority, with margins for the hazard ratios of 3.2 and 2.1 for favorable and unfavorable, respectively.

The 2015 RAPID study 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 comprising ABVD and then PET scanning performed on full-ring PET or PET with CT cameras. 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 randomly assigned to receive 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.

The trial reported in 2016 by Johnson et al randomized 937 newly diagnosed advanced classic Hodgkin lymphoma patients (median age, 33 years; 55% men) who had an interim negative PET coupled with CT

scan after an initial 2 cycles of ABVD to receive continued ABVD for 4 cycles (ABVD group; standard therapy) or to omit bleomycin (AVD [doxorubicin, vinblastine, dacarbazine] group; PET-directed therapy). 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 omitting bleomycin for 3-year PFS with a 5 percentage point margin for the RD.

A phase 2 RCT published in 2017 by Casasnovas et al evaluated the use of interim FDG-PET in the treatment of 200 patients with diffuse large B-cell lymphoma. FDG-PET was conducted after cycles 2 (PET2) and 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 2 cycles of high-dose methotrexate, then 4 cycles of rituximab, ifosfamide, and etoposide, then 2 cycles of cytarabine. PET2-positive and PET4-negative patients (n=48) were treated with 2 cycles of high-dose methotrexate, then a high-dose therapy (carmustine, etoposide, cytarabine, and melphalan), followed by autologous cell transplantation.

Table 3. Summary of Key RCT Characteristics of PET-Guided Therapy in PET-Negative Patients

						Randomized Patients		
Author (Year)	**Study**	**Countries**	**Sites**	**Dates**	**Key Eligibility Criteria**	**PET-Directed Therapy, n**	**Standard Therapy, n**	**Primary Outcome**
Picardi et al (2007)		NR	NR	2000-2006	Untreated bulky HL	80	80	EFS
Raemaekers et al (2014)	EORTC/ LYSA/ FIL H10	Belgium, CH, Croatia, Italy, Denmark, France, SR, Netherlands	158	2006-2011	Untreated stage I/II HL	• 221 favorable prognoses[a] • 347 unfavorable prognoses[a]	• 233 favorable prognoses[a] • 346 unfavorable prognoses[a]	PFS
Radford et al (2015)	RAPID	UK	94	2003-2010	Untreated stage IA/IIA HL	211	209	PFS
Johnson et al (2016)		UK, Italy, Australia, NZ, Norway, Sweden, Denmark	138	2008-2012	Untreated stage IIA (with adverse features) or IIB-IV HL	465	470	PFS
Casasnovas et al (2017)		France		2007-2010	High-risk DLBCL	48 PET2+/ PET4-	52 PET2-/PET4-	PFS, OS

CH: Switzerland; DLBCL: diffuse large B-cell lymphoma; EFS: event-free survival; HL: Hodgkin lymphoma; NR: not reported; OS: overall survival; PET2/4: 2 or 4 cycles of positron emission tomography; PFS: progression-free survival; RCT: randomized controlled trial; SR: Slovak Republic; NZ: New Zealand.

[a] 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 5 RCTs for PET-directed therapy in PET-negative lymphoma patients are summarized in Table 4 and below.

In the Picardi 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 a 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.

The EORTC/LYSA/FIL H10 trial performed a prespecified interim analysis including 1124 randomized patients (favorable group, n=441; unfavorable group, n=683) with 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 RAPID 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, one 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 RD was -3.8 percentage points (95% CI, -8.8 to 1.3) and the CIs included the noninferiority margin.

In the Johnson trial, median follow-up was 41 months. There were 68 vs 74 events of disease progression, relapse, or death in the ABVD group vs the AVD group, respectively (HR with AVD=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 ABVD group and 84.4% (95% CI, 80.7% to 87.5%) in the AVD group (RD=1.6 percentage points; 95% CI, -3.2 to 5.3); CIs included the noninferiority margin. Three-year OS rates were similar in both 2 groups: 97.2% (95% CI, 95.1% to 98.4%) with ABVD and 97.6% (95% CI, 95.6% to 98.7%) with AVD. Grade 3 and 4 respiratory adverse events were more severe in the ABVD group than in the AVD 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 Casasnovas 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 4-year PFS or OS between the 2 treatment groups. The authors propose that the flawed criteria were used to determine PET-positive and -negative classifications. The International Harmonisation 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.

Table 4. Summary of Key RCT Trial Results of PET-Guided Therapy in PET-Negative Patients

Study (Year)	Primary Outcome	Results (95% CI)	Comments
Picardi et al (2007)	EFS	• EFS: 69 (86%) vs 77 (96%) • HR for ST, 3.32 (1.13 to 9.76)	
EORTC/LYSA/FIL H10 (2014)	PFS (favorable: n=188 vs n=193[a]; unfavorable: n=251 vs n=268[a])	Favorable: • PFS at 1 y: 94.9% vs 100% • 9 vs 1 events[a,b] • HR for ST, 9.36 (2.45 to 35.73) Unfavorable: • PFS at 1 y: 94.7% vs 97.3% • 16 vs 7 events[a,b] • HR for ST, 2.42 (1.35 to 4.36)	Recruitment stopped early after interim analysis suggested futility for noninferiority
RAPID (2015)	PFS (n=211 vs n=209)	• 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)	Unable to show noninferiority (RD margin, 7%)
Johnson et al (2016)	PFS (n=470 vs n=465)	• 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)	Unable to show noninferiority (RD margin, 5%)
Casasnovas et al (2017)	PFS and OS (n=48 vs n=52)	4-y PFS: • PET2+: 85% (71.1% to 92.6%) • PET2-: 75% (60.9% to 84.5%) 4-y OS: • PET2+: 90.4% (81% to 95.1%) • PET2-: 89.6% (85% to 92.2%)	

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.
[a] Results from interim analysis.
[b] Events of progression, relapse, or death.

Randomized Controlled Trials: 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. As previously described, the EORTC/LYSA/FIL H10 trial (2014) 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 ABVD chemotherapy cycles) received intensification of chemotherapy with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). 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 final results from the trial, published by André et al in 2017.

Both the RAPID trial (2015) and the Johnson trial (2016) included observation of patients with an interim positive PET after initial induction chemotherapy, although neither trial had a randomized comparison in the PET-positive group. In the RAPID trial, 145 patients with positive PET findings received a fourth cycle of ABVD 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 Johnson et al, 182 patients with a positive PET received accelerated BEACOPP (BEACOPP-14) or escalated BEACOPP. 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%).

The trial by Casasnovas et al (2017) described in the PET-negative section above also included patients who were PET-positive after induction chemotherapy. 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%).

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 showed 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 Validity
Eleven studies have been identified that evaluated a potential association between interim FDG-PET analyses during various treatments and OS or PFS in patients with non-small-cell lung cancer (NSCLC). The studies included patients with various stages of NSCLC, receiving various lung cancer treatments: chemotherapy (eg, gefitinib, carboplatin/paclitaxel, erlotinib, cisplatin/etoposide, docetaxel/cisplatin), chemoradiotherapy, chemotherapy with or without nitrogen patches, and low-dose fractionated radiotherapy with concurrent chemotherapy. Eight of the studies were small, with study populations less than 50. The remaining 3 studies had populations between 50 and 100. Most studies found correlations between early metabolic response detected by FDG-PET and survival, thereby proposing 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.

Clinical Utility
No RCTs or observational studies were identified that evaluated outcomes of patients whose treatments were altered with interim PET.

Section Summary: Non-Small-Cell Lung Cancer
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 may adequately detect responders and nonresponders, which may predict OS and PFS. However, early prediction of survival does not translate to patient benefit unless decisions based on those predictions result in improved patient outcomes by either extending OS or improving quality of life.

Ovarian Cancer

Clinical Validity
In 2017, Suppiah et al published a systematic review on 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 hazard ratios for the prediction of recurrence. Outcomes of the studies were metabolic parameters (SUVmax, MTV, and/or TLG). 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 TLG (n=304 patients) reported that it was a significant predictive factor for prognosis. Meta-analyses were not performed.

Clinical Utility
No RCTs or observational studies were identified that evaluated outcomes of patients whose treatments were altered based on interim PET measurements.

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 TLG 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 lead to improved patient outcomes. No case series or comparative trials of risk-adapted treatment for ovarian cancer were identified.

Other Malignant Solid Tumors

Clinical Validity
The 2007 and 2009 NCCN task force reports assessed other malignant solid tumors for interim PET. 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. The British National Health Service review (2007) also assessed other cancers for PET during treatment. For colorectal cancer, 1 study showed that PET after 1 month of chemotherapy predicted 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. The authors 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 reports, 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 1 or 2 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.

Clinical Utility
No RCTs or observational studies were identified that evaluated outcomes of patients whose treatments were altered with interim PET.

Section Summary: Other Cancers
Evidence for the use of interim PET during treatment of other cancers, such as bladder, colorectal, prostate, and thyroid consists of NCCN reports and mostly single-arm observational studies. Results were inconsistent for the use of interim PET for patients with colorectal cancer and renal cell carcinoma. While some studies 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 a systematic review, an RCT, and several observational studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, morbid events, and treatment-related morbidity. Results from the systematic review showed wide ranges in sensitivities, specificities, positive predictive values, and negative predictive values. 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 overall survival 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 and 3 studies published after the meta-analysis. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, 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 2 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 gastrointestinal stromal tumors receiving palliative or adjuvant therapy who receive interim FDG-PET as an adjunct to interim CT, the evidence includes a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, 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 gastrointestinal stromal tumors treated with tyrosine kinase inhibitors for 6 months or less who receive interim FDG-PET as an adjunct to interim CT, the evidence includes a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, morbid events, and treatment-related morbidity. The systematic review included 19 studies, 17 of which showed that FDG-PET detected an early response to tyrosine kinase inhibitor therapy, which was a strong predictor of clinical outcomes. FDG-PET detected treatment response as early as 1 week after initiation of treatment. While CT detects anatomic changes in the tumor, PET detects changes in 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 three systematic reviews. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, 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 overall survival. 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 maximum standardized uptake volume, 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, 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, 2 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 progression-free survival 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 non-small-cell lung cancer who receive interim FDG-PET as an adjunct to interim CT, the evidence includes many small observational studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, morbid events, and treatment-related morbidity. While most studies showed correlations between FDG-PET measurements and progression-free and overall survival, 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, morbid events, and treatment-related morbidity. The systematic review identified 9 studies that calculated hazard ratios 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. However, 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 National Comprehensive Cancer Network task force report and single-arm observational studies published after the task force report. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, 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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Interim Positron Emission Tomography Scanning in Oncology to Detect Early Response During Treatment”, 6.01.51, 9:2017.
2. Hillner BE, Siegel BA, Shields AF, et al. The impact of positron emission tomography (PET) on expected management during cancer treatment: findings of the National Oncologic PET Registry. Cancer. Jan 15 2009;115(2):410-418. PMID 19016303
3. Food and Drug Administration (FDA). PET Drugs - Current Good Manufacturing Practice (CGMP). 2009; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070306.pdf. Accessed August 4, 2017.
4. Food and Drug Administration (FDA). PET Drugs - Current Good Manufacturing Practice (CGMP) Small Entity Compliance Guide. 2011; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf. Accessed August 4, 2017.

5. Food and Drug Administration (FDA). Guidance: Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs. 2012; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf. Accessed August 4, 2017.
6. Lindenberg MA, Miquel-Cases A, Retel VP, et al. Imaging performance in guiding response to neoadjuvant therapy according to breast cancer subtypes: A systematic literature review. *Crit Rev Oncol Hematol.* Apr 2017;112:198-207. PMID 28325260
7. Boers-Sonderen MJ, de Geus-Oei LF, Desar IM, et al. Temsirolimus and pegylated liposomal doxorubicin (PLD) combination therapy in breast, endometrial, and ovarian cancer: phase Ib results and prediction of clinical outcome with FDG-PET/CT. *Target Oncol.* Dec 2014;9(4):339-347. PMID 24577626
8. Groheux D, Hindie E, Giacchetti S, et al. Early assessment with (18)F-fluorodeoxyglucose positron emission tomography/computed tomography can help predict the outcome of neoadjuvant chemotherapy in triple negative breast cancer. *Eur J Cancer.* Jul 2014;50(11):1864-1871. PMID 24841218
9. Humbert O, Cochet A, Riedinger JM, et al. HER2-positive breast cancer: (18)F-FDG PET for early prediction of response to trastuzumab plus taxane-based neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging.* Aug 2014;41(8):1525-1533. PMID 24647576
10. Andrade WP, Lima EN, Osorio CA, et al. Can FDG-PET/CT predict early response to neoadjuvant chemotherapy in breast cancer? *Eur J Surg Oncol.* Dec 2013;39(12):1358-1363. PMID 24120422
11. Mghanga FP, Lan X, Bakari KH, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography in monitoring the response of breast cancer to neoadjuvant chemotherapy: a meta-analysis. *Clin Breast Cancer.* Aug 2013;13(4):271-279. PMID 23714689
12. Humbert O, Riedinger JM, Charon-Barra C, et al. Identification of biomarkers including 18FDG-PET/CT for early prediction of response to neoadjuvant chemotherapy in triple-negative breast cancer. *Clin Cancer Res.* Dec 15 2015;21(24):5460-5468. PMID 26130460
13. Humbert O, Riedinger JM, Vrigneaud JM, et al. 18F-FDG PET-derived tumor blood flow changes after 1 cycle of neoadjuvant chemotherapy predicts outcome in triple-negative breast cancer. *J Nucl Med.* Nov 2016;57(11):1707-1712. PMID 27103025
14. Lee HW, Lee HM, Choi SE, et al. The prognostic impact of early change in 18F-FDG PET SUV after neoadjuvant chemotherapy in patients with locally advanced breast cancer. *J Nucl Med.* Aug 2016;57(8):1183-1188. PMID 27033896
15. Luo J, Zhou Z, Yang Z, et al. The value of 18F-FDG PET/CT imaging combined with pretherapeutic Ki67 for early prediction of pathologic response after neoadjuvant chemotherapy in locally advanced breast cancer. *Medicine (Baltimore).* Feb 2016;95(8):e2914. PMID 26937935
16. Pahk K, Kim S, Choe JG. Early prediction of pathological complete response in luminal B type neoadjuvant chemotherapy-treated breast cancer patients: comparison between interim 18F-FDG PET/CT and MRI. *Nucl Med Commun.* Sep 2015;36(9):887-891. PMID 25932536
17. Lin NU, Guo H, Yap JT, et al. Phase II study of lapatinib in combination with trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: clinical outcomes and predictive value of early [18F]fluorodeoxyglucose positron emission tomography imaging (TBCRC 003). *J Clin Oncol.* Aug 20 2015;33(24):2623-2631. PMID 26169615
18. Groheux D, Biard L, Giacchetti S, et al. 18F-FDG PET/CT for the early evaluation of response to neoadjuvant treatment in triple-negative breast cancer: influence of the chemotherapy regimen. *J Nucl Med.* Apr 2016;57(4):536-543. PMID 26697967
19. Groheux D, Majdoub M, Sanna A, et al. Early metabolic response to neoadjuvant treatment: FDG PET/CT criteria according to breast cancer subtype. *Radiology.* Nov 2015;277(2):358-371. PMID 25915099
20. van Ramshorst MS, Teixeira SC, Koolen BB, et al. Additional value of 18F-FDG PET/CT response evaluation in axillary nodes during neoadjuvant therapy for triple-negative and HER2-positive breast cancer. *Cancer Imaging.* May 25 2017;17(1):15. PMID 28545563
21. Schmitz AMT, Teixeira SC, Pengel KE, et al. Monitoring tumor response to neoadjuvant chemotherapy using MRI and 18F-FDG PET/CT in breast cancer subtypes. *PLoS One.* 2017;12(5):e0176782. PMID 28531188
22. Coudert B, Pierga JY, Mouret-Reynier MA, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. *Lancet Oncol.* Dec 2014;15(13):1493-1502. PMID 25456368
23. Groheux D, Hindie E, Marty M, et al. (1)(8)F-FDG-PET/CT in staging, restaging, and treatment response assessment of male breast cancer. *Eur J Radiol.* Oct 2014;83(10):1925-1933. PMID 24985086

24. Hulikal N, Gajjala SR, Kalawat TC, et al. Utility of [18F] fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in the initial staging and response assessment of locally advanced breast cancer patients receiving neoadjuvant chemotherapy. *Indian J Surg Oncol.* Dec 2015;6(4):330-336. PMID 27065657
25. Cong L, Wang S, Gao T, et al. The predictive value of 18F-FDG PET for pathological response of primary tumor in patients with esophageal cancer during or after neoadjuvant chemoradiotherapy: a meta-analysis. *Jpn J Clin Oncol.* Dec 2016;46(12):1118-1126. PMID 27702836
26. van Rossum PS, Fried DV, Zhang L, et al. The value of 18F-FDG PET before and after induction chemotherapy for the early prediction of a poor pathologic response to subsequent preoperative chemoradiotherapy in oesophageal adenocarcinoma. *Eur J Nucl Med Mol Imaging.* Jan 2017;44(1):71-80. PMID 27511188
27. Hagen PV, Heijl MV, Henegouwen MI, et al. Prediction of disease-free survival using relative change in FDG-uptake early during neoadjuvant chemoradiotherapy for potentially curable esophageal cancer: A prospective cohort study. *Dis Esophagus.* Feb 01 2017;30(2):1-7. PMID 27001344
28. Manoharan V, Lee S, Chong S, et al. Serial imaging using [18F]Fluorodeoxyglucose positron emission tomography and histopathologic assessment in predicting survival in a population of surgically resectable distal oesophageal and gastric adenocarcinoma following neoadjuvant therapy. *Ann Nucl Med.* May 2017;31(4):315-323. PMID 28299585
29. Podoloff DA, Advani RH, Allred C, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw.* May 2007;5 Suppl 1:S1-22; quiz S23-22. PMID 17509259
30. Treglia G, Mirk P, Stefanelli A, et al. 18F-Fluorodeoxyglucose positron emission tomography in evaluating treatment response to imatinib or other drugs in gastrointestinal stromal tumors: a systematic review. *Clin Imaging.* May-Jun 2012;36(3):167-175. PMID 22542374
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: Soft Tissue Sarcoma. Verizon 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed August 7, 2017.
32. Min M, Lin P, Liney G, et al. A review of the predictive role of functional imaging in patients with mucosal primary head and neck cancer treated with radiation therapy. *J Med Imaging Radiat Oncol.* Feb 2017;61(1):99-123. PMID 27469298
33. Castelli J, De Bari B, Depeursinge A, et al. Overview of the predictive value of quantitative 18 FDG PET in head and neck cancer treated with chemoradiotherapy. *Crit Rev Oncol Hematol.* Dec 2016;108:40-51. PMID 27931839
34. Dos Anjos RF, Dos Anjos DA, Vieira DL, et al. Effectiveness of FDG-PET/CT for evaluating early response to induction chemotherapy in head and neck squamous cell carcinoma: A systematic review. *Medicine (Baltimore).* Aug 2016;95(32):e4450. PMID 27512861
35. Adams HJA, Kwee TC. Proportion of false-positive lesions at interim and end-of-treatment FDG-PET in lymphoma as determined by histology: Systematic review and meta-analysis. *Eur J Radiol.* Nov 2016;85(11):1963-1970. PMID 27776647
36. Wong-Sefidan I, Byrtek M, Zhou X, et al. [18F] Positron emission tomography response after rituximab-containing induction therapy in follicular lymphoma is an independent predictor of survival after adjustment for FLIPI in academic and community-based practice. *Leuk Lymphoma.* Apr 2017;58(4):809-815. PMID 27562750
37. Sickinger MT, von Tresckow B, Kobe C, et al. Positron emission tomography-adapted therapy for first-line treatment in individuals with Hodgkin lymphoma. *Cochrane Database Syst Rev.* Jan 09 2015;1:CD010533. PMID 25572491
38. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med.* Apr 23 2015;372(17):1598-1607. PMID 25901426
39. Picardi M, De Renzo A, Pane F, et al. Randomized comparison of consolidation radiation versus observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans. *Leuk Lymphoma.* Sep 2007;48(9):1721-1727. PMID 17786707
40. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol.* Apr 20 2014;32(12):1188-1194. PMID 24637998
41. Deniz K, O'Mahony S, Ross G, et al. Breast cancer in women after treatment for Hodgkin's disease. *Lancet Oncol.* Apr 2003;4(4):207-214. PMID 12681264
42. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst.* Feb 6 2002;94(3):182-192. PMID 11830608
43. Galper SL, Yu JB, Mauch PM, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood.* Jan 13 2011;117(2):412-418. PMID 20858859
44. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst.* Feb 7 2007;99(3):206-214. PMID 17284715

45. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med.* Jun 23 2016;374(25):2419-2429. PMID 27332902
46. Casasnovas RO, Ysebaert L, Thieblemont C, et al. A FDG-PET driven consolidation strategy in diffuse large B-cell lymphoma: Final results of a randomized phase II study. *Blood.* Jul 12 2017. PMID 28701367
47. Raemaekers JM. Early FDG-PET adapted treatment improved the outcome of early FDG-PET positive patients with stages I/II Hodgkin lymphoma (HL): final results of the randomized Intergroup EORTC/LYSA/FIL H10 trial. Paper presented at: 13th International Conference on Malignant Lymphoma; 2015; Lugano, Switzerland.
48. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 Trial. *J Clin Oncol.* Jun 01 2017;35(16):1786-1794. PMID 28291393
49. Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. *Blood.* Feb 1 2007;109(3):905-909. PMID 17018856
50. Dann EJ, Blumenfeld Z, Bar-Shalom R, et al. A 10-year experience with treatment of high and standard risk Hodgkin disease: six cycles of tailored BEACOPP, with interim scintigraphy, are effective and female fertility is preserved. *Am J Hematol.* Jan 2012;87(1):32-36. PMID 21956220
51. Iltis A, Eder V, Blasco H, et al. Decisional early interim (18)F-fluoro-2-deoxy-D-glucose positron emission tomography after two cycles of chemotherapy in de novo Hodgkin lymphoma. *Acta Haematol.* 2015;133(2):172-178. PMID 25301496
52. Pardal E, Coronado M, Martin A, et al. Intensification treatment based on early FDG-PET in patients with high-risk diffuse large B-cell lymphoma: a phase II GELTAMO trial. *Br J Haematol.* Nov 2014;167(3):327-336. PMID 25066542
53. Kasamon YL, Wahl RL, Ziessman HA, et al. Phase II study of risk-adapted therapy of newly diagnosed, aggressive non-Hodgkin lymphoma based on midtreatment FDG-PET scanning. *Biol Blood Marrow Transplant.* Feb 2009;15(2):242-248. PMID 19167684
54. Kedmi M, Apel A, Davidson T, et al. High-risk, advanced-stage hodgkin lymphoma: the impact of combined escalated BEACOPP and ABVD treatment in patients who rapidly achieve metabolic complete remission on interim FDG-PET/CT scan. *Acta Haematol.* 2016;135(3):156-161. PMID 26588173
55. Press OW, Li H, Schoder H, et al. US Intergroup Trial of response-adapted therapy for stage iii to iv hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol.* Jun 10 2016;34(17):2020-2027. PMID 27069074
56. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet.* May 12 2012;379(9828):1791-1799. PMID 22480758
57. Zinzani PL, Broccoli A, Gioia DM, et al. Interim positron emission tomography response-adapted therapy in advanced-stage Hodgkin lymphoma: final results of the phase II part of the HD0801 Study. *J Clin Oncol.* Apr 20 2016;34(12):1376-1385. PMID 26884559
58. Han EJ, O JH, Yoon H, et al. FDG PET/CT response in diffuse large B-cell lymphoma: Reader variability and association with clinical outcome. *Medicine (Baltimore).* Sep 2016;95(39):e4983. PMID 27684851
59. Kanazu M, Maruyama K, Ando M, et al. Early pharmacodynamic assessment using (1)(8)F-fluorodeoxyglucose positron-emission tomography on molecular targeted therapy and cytotoxic chemotherapy for clinical outcome prediction. *Clin Lung Cancer.* May 2014;15(3):182-187. PMID 24518101
60. Stefano A, Russo G, Ippolito M, et al. Evaluation of erlotinib treatment response in non-small cell lung cancer using metabolic and anatomic criteria. *Q J Nucl Med Mol Imaging.* May 9 2016;60(3):264-273. PMID 24809275
61. Tiseo M, Ippolito M, Scarlattei M, et al. Predictive and prognostic value of early response assessment using 18FDG-PET in advanced non-small cell lung cancer patients treated with erlotinib. *Cancer Chemother Pharmacol.* Feb 2014;73(2):299-307. PMID 24258456
62. Tsuchida T, Morikawa M, Demura Y, et al. Imaging the early response to chemotherapy in advanced lung cancer with diffusion-weighted magnetic resonance imaging compared to fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography. *J Magn Reson Imaging.* Jul 2013;38(1):80-88. PMID 23239463
63. Usmanij EA, de Geus-Oei LF, Troost EG, et al. 18F-FDG PET early response evaluation of locally advanced non-small cell lung cancer treated with concomitant chemoradiotherapy. *J Nucl Med.* Sep 2013;54(9):1528-1534. PMID 23864719
64. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. *J Natl Compr Canc Netw.* Jun 2009;7 Suppl 2(suppl 1):S1-26. PMID 19555588

65. Grootjans W, Usmanij EA, Oyen WJ, et al. Performance of automatic image segmentation algorithms for calculating total lesion glycolysis for early response monitoring in non-small cell lung cancer patients during concomitant chemoradiotherapy. *Radiother Oncol.* Jun 2016;119(3):473-479. PMID 27178141
66. Han EJ, Yang YJ, Park JC, et al. Prognostic value of early response assessment using 18F-FDG PET/CT in chemotherapy-treated patients with non-small-cell lung cancer. *Nucl Med Commun.* Dec 2015;36(12):1187-1194. PMID 26375438
67. Nygard L, Vogelius IR, Fischer BM, et al. Early lesion-specific (18)F-FDG PET response to chemotherapy predicts time to lesion progression in locally advanced non-small cell lung cancer. *Radiother Oncol.* Mar 2016;118(3):460-464. PMID 26806265
68. Mattoli MV, Massaccesi M, Castelluccia A, et al. The predictive value of 18F-FDG PET-CT for assessing the clinical outcomes in locally advanced NSCLC patients after a new induction treatment: low-dose fractionated radiotherapy with concurrent chemotherapy. *Radiat Oncol.* Jan 05 2017;12(1):4. PMID 28057034
69. Crandall JP, Tahari AK, Juergens RA, et al. A comparison of FLT to FDG PET/CT in the early assessment of chemotherapy response in stages IB-IIIA resectable NSCLC. *EJNMMI Res.* Dec 2017;7(1):8. PMID 28102506
70. de Jong EE, van Elmpt W, Leijenaar RT, et al. [18F]FDG PET/CT-based response assessment of stage IV non-small cell lung cancer treated with paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches. *Eur J Nucl Med Mol Imaging.* Jan 2017;44(1):8-16. PMID 27600280
71. Suppiah S, Chang WL, Hassan HA, et al. Systematic review on the accuracy of positron emission tomography/computed tomography and positron emission tomography/magnetic resonance imaging in the management of ovarian cancer: Is functional information really needed? *World J Nucl Med.* Jul-Sep 2017;16(3):176-185. PMID 28670174
72. Facey K, Bradbury I, Laking G, et al. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. *Health Technol Assess.* Oct 2007;11(44):iii-iv, xi-267. PMID 17999839
73. Engelmann BE, Loft A, Kjaer A, et al. Positron emission tomography/computed tomography and biomarkers for early treatment response evaluation in metastatic colon cancer. *Oncologist.* Feb 2014;19(2):164-172. PMID 24451199
74. Hong YS, Kim HO, Kim KP, et al. 3'-Deoxy-3'-18F-fluorothymidine PET for the early prediction of response to leucovorin, 5-fluorouracil, and oxaliplatin therapy in patients with metastatic colorectal cancer. *J Nucl Med.* Aug 2013;54(8):1209-1216. PMID 23804324
75. Li C, Lan X, Yuan H, et al. (18)F-FDG PET predicts pathological response to preoperative chemoradiotherapy in patients with primary rectal cancer: a meta-analysis. *Ann Nucl Med.* Jun 2014;28(5):436-446. PMID 24623152
76. Memon S, Lynch AC, Akhurst T, et al. Systematic review of FDG-PET prediction of complete pathological response and survival in rectal cancer. *Ann Surg Oncol.* Oct 2014;21(11):3598-3607. PMID 24802909
77. Formiga MN, Fanelli MF, Dettino AL, et al. Is early response by (18)F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography a predictor of long-term outcome in patients with metastatic colorectal cancer? *J Gastrointest Oncol.* Jun 2016;7(3):365-372. PMID 27284468
78. Hendlisz A, Deleporte A, Delaunoit T, et al. The prognostic significance of metabolic response heterogeneity in metastatic colorectal cancer. *PLoS One.* Sep 2015;10(9):e0138341. PMID 26421426
79. Kim SJ, Chang S. Volumetric parameters changes of sequential 18F-FDG PET/CT for early prediction of recurrence and death in patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy. *Clin Nucl Med.* Dec 2015;40(12):930-935. PMID 26204222
80. Koo PJ, Kim SJ, Chang S, et al. Interim fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography to predict pathologic response to preoperative chemoradiotherapy and prognosis in patients with locally advanced rectal cancer. *Clin Colorectal Cancer.* Dec 2016;15(4):e213-e219. PMID 27316919
81. Nishimura G, Yabuki K, Hata M, et al. Imaging strategy for response evaluation to chemoradiotherapy of the nodal disease in patients with head and neck squamous cell carcinoma. *Int J Clin Oncol.* Aug 2016;21(4):658-667. PMID 26710795
82. Travaini LL, Zampino MG, Colandrea M, et al. PET/CT with fluorodeoxyglucose during neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Ecancermedicalscience.* Mar 2016;10:629. PMID 27110285
83. Woff E, Hendlisz A, Garcia C, et al. Monitoring metabolic response using FDG PET-CT during targeted therapy for metastatic colorectal cancer. *Eur J Nucl Med Mol Imaging.* Sep 2016;43(10):1792-1801. PMID 27072811
84. Skougaard K, Nielsen D, Jensen BV, et al. Early 18F-FDG-PET/CT as a predictive marker for treatment response and survival in patients with metastatic colorectal cancer treated with irinotecan and cetuximab. *Acta Oncol.* Sep - Oct 2016;55(9-10):1175-1182. PMID 27548393
85. Garcia Vicente AM, Soriano Castrejon A, Leon Martin A, et al. Early and delayed prediction of axillary lymph node neoadjuvant response by (18)F-FDG PET/CT in patients with locally advanced breast cancer. *Eur J Nucl Med Mol Imaging.* Jul 2014;41(7):1309-1318. PMID 24744045

86. Koolen BB, Valdes Olmos RA, Wesseling J, et al. Early assessment of axillary response with (1)(8)F-FDG PET/CT during neoadjuvant chemotherapy in stage II-III breast cancer: implications for surgical management of the axilla. *Ann Surg Oncol.* Jul 2013;20(7):2227-2235. PMID 23456316
87. Giannatempo P, Alessi A, Miceli R, et al. Interim fluorine-18 fluorodeoxyglucose positron emission tomography for early metabolic assessment of therapeutic response to chemotherapy for metastatic transitional cell carcinoma. *Clin Genitourin Cancer.* Dec 2014;12(6):433-439. PMID 24787972
88. Truong MT, Viswanathan C, Godoy MB, et al. Malignant pleural mesothelioma: role of CT, MRI, and PET/CT in staging evaluation and treatment considerations. *Semin Roentgenol.* Oct 2013;48(4):323-334. PMID 24034264
89. Francis RJ, Byrne MJ, van der Schaaf AA, et al. Early prediction of response to chemotherapy and survival in malignant pleural mesothelioma using a novel semiautomated 3-dimensional volume-based analysis of serial 18F-FDG PET scans. *J Nucl Med.* Sep 2007;48(9):1449-1458. PMID 17704250
90. Bhatnagar P, Subesinghe M, Patel C, et al. Functional imaging for radiation treatment planning, response assessment, and adaptive therapy in head and neck cancer. *Radiographics.* Nov-Dec 2013;33(7):1909-1929. PMID 24224586
91. Hoang JK, Das SK, Choudhury KR, et al. Using FDG-PET to measure early treatment response in head and neck squamous cell carcinoma: quantifying intrinsic variability in order to understand treatment-induced change. *AJNR Am J Neuroradiol.* Jul 2013;34(7):1428-1433. PMID 23391836
92. Lalami Y, Garcia C, Flamen P, et al. Phase II trial evaluating the efficacy of sorafenib (BAY 43-9006) and correlating early fluorodeoxyglucose positron emission tomography-CT response to outcome in patients with recurrent and/or metastatic head and neck cancer. *Head Neck.* Mar 2016;38(3):347-354. PMID 25332069
93. Wong KH, Panek R, Welsh L, et al. The predictive value of early assessment after 1 cycle of induction chemotherapy with 18F-FDG PET/CT and diffusion-weighted MRI for response to radical chemoradiotherapy in head and neck squamous cell carcinoma. *J Nucl Med.* Dec 2016;57(12):1843-1850. PMID 27417648
94. Wilson JM, Mukherjee S, Brunner TB, et al. Correlation of 18F-fluorodeoxyglucose positron emission tomography parameters with patterns of disease progression in locally advanced pancreatic cancer after definitive chemoradiotherapy. *Clin Oncol (R Coll Radiol).* Jun 2017;29(6):370-377. PMID 28190636
95. Eary JF, Conrad EU, O'Sullivan J, et al. Sarcoma mid-therapy [F-18]fluorodeoxyglucose positron emission tomography (FDG PET) and patient outcome. *J Bone Joint Surg Am.* Jan 15 2014;96(2):152-158. PMID 24430415
96. Hyun OJ, Luber BS, Leal JP, et al. Response to early treatment evaluated with 18F-FDG PET and PERCIST 1.0 predicts survival in patients with ewing sarcoma family of tumors treated with a monoclonal antibody to the insulinlike growth factor 1 receptor. *J Nucl Med.* May 2016;57(5):735-740. PMID 26795289
97. Farnebo J, Gryback P, Harmenberg U, et al. Volumetric FDG-PET predicts overall and progression- free survival after 14 days of targeted therapy in metastatic renal cell carcinoma. *BMC Cancer.* Jun 06 2014;14:408. PMID 24906441
98. Chen JL, Appelbaum DE, Kocherginsky M, et al. FDG-PET as a predictive biomarker for therapy with everolimus in metastatic renal cell cancer. *Cancer Med.* Aug 2013;2(4):545-552. PMID 24156027
99. Gilles R, de Geus-Oei LF, Mulders PF, et al. Immunotherapy response evaluation with (18)F-FDG-PET in patients with advanced stage renal cell carcinoma. *World J Urol.* Aug 2013;31(4):841-846. PMID 21739122
100. Horn KP, Yap JT, Agarwal N, et al. FDG and FLT-PET for Early measurement of response to 37.5 mg daily sunitinib therapy in metastatic renal cell carcinoma. *Cancer Imaging.* 2015;15:15. PMID 26335224
101. American College of Radiology (ACR) and the Society for Pediatric Radiology (SPR). ACR–SPR practice guideline for performing FDG-PET/CT in oncology, revised 2016. https://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/FDG_PET_CT.pdf. Accessed August 14, 2017.
102. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: bladder cancer. Version 5.2017. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed August 7, 2017.
103. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology:breast cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 7, 2017.
104. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: central nervous system cancers. Version 1.2016 http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed August 14, 2017.
105. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: cervical cancer. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed August 7, 2017.
106. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: colon cancer. Version 2.1017. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 7, 2017.

107. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed August 7, 2017.
108. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: head and neck cancers. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed August 7, 2017.
109. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers, v 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed August 14, 2017.
110. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, v 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed August 14, 2017.
111. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: melanoma. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed August 7, 2017.
112. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: malignant pleural mesothelioma. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed August 7, 2017.
113. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: multiple myeloma. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed August 7, 2017.
114. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: B-cells lymphomas. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed August 7, 2017.
115. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: T-cell lymphomas. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed August 7, 2017.
116. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: primary cutaneous B-cell lymphomas. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/pcbcl.pdf. Accessed August 7, 2017.
117. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: non-small cell lung cancer. Version 8.2017. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 7, 2017.
118. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: ovarian cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 7, 2017.
119. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: pancreatic adenocarcinoma version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed August 7, 2017.
120. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: prostate cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed August 7, 2017.
121. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: rectal cancer. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 17, 2017.
122. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: small cell lung cancer. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed August 7, 2017.
123. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: thyroid cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed August 7, 2017.
124. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: uterine neoplasms. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed August 7, 2017.
125. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol.* Feb 10 2007;25(5):571-578. PMID 17242397

Policy History

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Next Scheduled Review Date: 11/2018

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	78811, 78812, 78813, 78814, 78815, 78816
HCPCS	No codes
ICD-10 Diagnosis	C49.A0-C49.A9

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

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

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

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

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