Decision Memo for Positron Emission Tomography (FDG) for Solid Tumors (CAG-00181R4)

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Decision Summary

A. The Centers for Medicare & Medicaid Services (CMS) is ending the requirement for coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the "Act') for ^{18}F fluorodeoxyglucose positron emission tomography (FDG PET) for oncologic indications which are contained in section 220.6.17 of the Medicare National Coverage Determinations Manual. This removes the requirement for prospective data collection by the National Oncologic PET Registry (NOPR) for those cancers or cancer types that had been covered under CED (as listed in Appendix A).

B. CMS has determined that three FDG PET scans are covered under § 1862(a)(1)(A) when used to guide subsequent management of anti-tumor treatment strategy after completion of initial anticancer therapy. Coverage of any additional FDG PET scans (that is, beyond three) used to guide subsequent management of anti-tumor treatment strategy after completion of initial anti-tumor therapy will be determined by local Medicare Administrative Contractors.

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Decision Memo

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Subject: Decision Memorandum for Positron Emission Tomography (FDG) for Solid Tumors

Date: June 11, 2013

I. Decision

A. The Centers for Medicare & Medicaid Services (CMS) is ending the requirement for coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the "Act') for ^{18}F fluorodeoxyglucose positron emission tomography (FDG PET) for oncologic indications which are contained in section 220.6.17 of the Medicare National Coverage Determinations Manual. This removes the requirement for prospective data collection by the National Oncologic PET Registry (NOPR) for those cancers or cancer types that had been covered under CED (as listed in Appendix A).

B. CMS has determined that three FDG PET scans are covered under § 1862(a)(1)(A) when used to guide subsequent management of anti-tumor treatment strategy after completion of initial anticancer therapy. Coverage of any additional FDG PET scans (that is, beyond three) used to guide subsequent management of anti-tumor treatment strategy after completion of initial anti-tumor therapy will be determined by local Medicare Administrative Contractors.

II. Background

The scope of the first part of this reconsideration determination (described in paragraph IA above) is limited to those oncologic indications of FDG PET to guide subsequent anti-tumor treatment strategy, which had been covered only under CED. However, the scope of the second part of this reconsideration determination (paragraph IB above) includes any oncologic use(s) of FDG PET to guide subsequent antitumor treatment strategy, and specifically includes all types of solid tumors, not only those that had been covered under CED.

FDG PET is often performed using a device that combines FDG PET with other imaging modalities. Thus our evidence review includes reports derived from combination devices. Specifically, we include integrated FDG PET/computerized tomography (FDG PET/CT) and integrated FDG PET/magnetic resonance imaging (FDG PET/MRI) in the term FDG PET as used in this decision unless context indicates otherwise. However, we are not with this reconsideration determining any change in coverage either for CT or for MRI imaging.

Throughout this memorandum, we use the term FDG to refer to 2-deoxy-2-[^{18}F]-fluoro-D-glucose, also known as ^{18}F fluorodeoxyglucose. FDG is a radioactive tracer substance (radiopharmaceutical) that emits positrons as the radioisotope ^{18}F decays. We use the term PET more generally to refer to positron emission tomography or to a positron emission tomogram, depending on context. FDG PET refers to PET imaging utilizing FDG as the radioactive tracer. We use the abbreviation MBq to denote megabecquerel, a unit of radioactivity in the International System of Units (SI). We use the usual notation for denoting radioisotopes (e.g., ^{68}Ga for the gallium radioisotope with mass number 68, or ^{11}C for the carbon radioisotope with mass number 11). Atomic symbols are used infrequently for the elements they represent (e.g., Gd for gadolinium).

FDG PET is a minimally invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseased tissues such as cancers. As malignancies often have elevated rates of glucose metabolism, FDG PET imaging may indicate the probable presence of a malignancy based upon observed differences in glucose metabolic activity compared to adjacent tissue. Using co-registered ('integrated') PET/CT scanners (now in use in the overwhelming majority of PET centers (Hillner 2009 and Hillner 2012), FDG PET uses techniques to detect and count simultaneous gamma photons produced by ^{18}F decay, and also to assess the anatomic distribution of FDG.

Other diagnostic imaging technologies such as x-ray imaging, CT, and MRI primarily supply information about the anatomic features of suspected malignancies, such as their size, location, and relation to other organs or tissues. However, clinical imaging of glucose metabolism within tissues is unique to FDG PET technology. In many cases, while the anatomic information provided by CT or MRI is important in devising an initial or subsequent anti-tumor treatment strategy (ATS), the metabolic evidence provided by FDG PET imaging provides complementary information of value for ATS development.

For clarification, we use the phrase 'completion of initial anticancer therapy' to denote the conclusion of the first treatment regimen implemented for the elimination or control of a patient's cancer following its diagnosis. A treatment regimen could include multiple 'therapies' (such as chemotherapy, radiotherapy, and/or cancer surgery) in combination. Given this framework for anticancer therapy, the completion of initial anticancer therapy (that is, the conclusion or termination of all anticancer therapies in the initially intended (combination) treatment regimen) marks, in time, the starting point of subsequent ATS planning (and the completion of initial ATS planning). (Additionally, while we recognize that 'watchful waiting' represents a widespread clinical approach for patients with certain cancers, we do not intend that it is a 'therapy' to be included in an initial treatment regimen.)

III. History of Medicare Coverage

CMS has reviewed scientific literature and established coverage for many uses of FDG PET in oncology. See the CMS NCD Manual, Section 220.6, for currently covered indications at: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part4.pdf

Medicare coverage policies regarding FDG PET determine general and specific conditions of Medicare coverage for various indications. Some of these policies for oncologic indications specified CED, requiring prospective data collection used in initial treatment strategy and/or subsequent treatment strategy for oncologic indications.

A. Current Request

CMS was asked by the National Oncologic PET Registry (NOPR) to reconsider Section 220.6 of the NCD Manual to "end the remaining prospective data collection requirements under Coverage with Evidence Development (CED) for all oncology indications for FDG PET imaging." We have limited the scope of the first part of this

reconsideration decision to those uses that had up to now been covered only under CED. The need for a second part of this decision (see paragraph IB above) became apparent as we considered the consequences of the first part. The second part of this reconsideration, in contrast, is intended to apply to all oncologic indications of FDG PET imaging.

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. FDG PET is considered to be within the following benefit category: other diagnostic tests §1861(s)(3). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Medicare regulations at 42 CFR 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, except where other uses have been explicitly authorized by statute, Medicare does not cover diagnostic testing used for routine screening or surveillance.

IV. Timeline of Recent Activities

September 12, 2012	CMS accepts a formal request to reconsider Section 220.6 of the NCD Manual to end the prospective data collection requirements across all oncologic indications of FDG PET. As tracking sheet was posted to the web site and the initial 30-day public comment period commenced.
October 12, 2012	The initial 30-day public comment period ended. Eighty-two comments were received
March 13, 2013	CMS posts the proposed decision memorandum. The second 30-day public comment period begins. The comment period was extended for two days due to a technical problem.
April 14, 2012	The second public comment period ends. CMS received 202 comments.

V. FDA Status

The FDA described the safety and effectiveness findings of FDG in a Federal Register notice dated March 10, 2000 (Volume 65, Number 48) Pages 12999-13010:

" … The [FDA] Commissioner has concluded … that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer, as discussed in section III.A.1 and III.A.3 of this document."

VI. General Methodological Principles

When making national coverage determinations, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency generally uses to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited in public comments, as well as those found by a CMS literature review. The agency also conducted a review of applicable professional society and other group/organization statements, evidence-based practice guidelines and other relevant sources including recent texts of oncology. Citations are detailed below.

The Medicare regulations at 42 CFR 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of an FDG PET imaging test to inform subsequent anti-tumor treatment strategy (ATS) in beneficiaries with solid tumors who had completed initial anticancer treatment.

B. Discussion of Evidence Reviewed

1. Questions

a. *Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully improve health outcomes in beneficiaries who have completed an initial treatment regimen for any of the following types of solid tumors: brain, pancreas, prostate, soft tissue sarcoma, small cell (of lung), thyroid, testis, or for any other solid malignant tumor?*

We recognize that for diagnostic imaging, the following question is also pertinent if there is little evidence linking a test result directly to health outcomes.

b. *Is the evidence adequate to conclude that the results of an FDG PET scan will guide physician management of subsequent anti-tumor treatment strategy in beneficiaries who have completed an initial treatment regimen for any of the following types of solid tumors: brain, pancreas, prostate, soft tissue sarcoma, small cell (of lung), thyroid, testis, or for any other solid malignant tumor?*

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on this topic. However, CMS is aware of two external technology assessments relevant to this topic.

The first is a 2010 Special Report from the Blue Cross Blue Shield Technology Evaluation Center (BCBS/TEC) on the topic of PET for post-treatment surveillance of cancer. In that report 'surveillance', as it applies to patients after completion of initial anticancer therapy, means the use of FDG PET "in the absence of signs or symptoms of cancer recurrence or progression, for the purpose of detecting recurrence or progression or predicting outcome." (BCBSA 2010, p. 1) This special report was published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group. The BCBS/TEC report indicated that "(t)here is simply inadequate direct and indirect evidence supporting the efficacy of PET scanning for the purpose of surveillance. Reflecting this lack of evidence, current practice guidelines appear unanimously to recommend against the use of PET for surveillance. No strong support of the use of PET for surveillance was found in editorials, case reports, or other studies. … Clinical trials may be necessary to determine whether PET surveillance is effective in improving health outcomes." (BCBSA 2010)

The second external technology assessment is from the United Kingdom (UK), entitled "Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers" (Facey 2007). The authors reviewed the literature to late 2005 on FDG PET, and surveyed PET centres in the UK. The report concluded that "(t)he strongest evidence for the clinical effectiveness of FDG PET is in staging NSCLC (non-small cell lung cancer), restaging HL (Hodgkin lymphoma), staging/restaging colorectal cancer and detection of SPN (solitary pulmonary

nodule). Some of these may still require clinical audit to augment the evidence base. Other management decisions require further research to show the impact of FDG PET on patient management or added value in the diagnostic pathway." As noted above, this technology assessment reached conclusions on clinical effectiveness of indications for FDG PET on types of cancers already covered nationally by the Medicareprogram in the United States.

3. Internal technology assessment

The reviewed evidence was gathered from articles submitted by the requesters, cited in public comments during a public comments period (mid-December 2012 through mid-January 2013) and from a literature search of the PubMed database by CMS staff in December 2012 and January 2013.

Literature search methods

CMS staff used PubMED to search for relevant peer-reviewed articles published in the medical literature. The following search terms were used: "FDG PET", "cancer" or "soft tissue sarcoma", "subsequent" or "subsequent treatment strategy", and either "recurrence" or "response" for each tumor type listed above. The CMS internal search was limited to articles published in the last five years (i.e., published after the most recent prior reconsideration of this topic) about results of clinical trials involving adult human subjects; to reports of randomized and non-randomized controlled trials, cohort studies, and case series meeting certain criteria; and to articles published in English. Also, clinical trials were excluded from further review if:

- fewer than ten patients were studied;
- the type of cancer studied is currently nationally covered for FDG PET imaging without requiring data collection;
- the cited article did not indicate whether an initial treatment plan had been completed, or whether an FDG PET scan was performed after completion of the initial treatment plan; or
- the study was related to costs or cost-effectiveness of FDG PET imaging, or was based on a simulation or decision modeling approach rather than patients' actual outcomes.

CMS staff reviewed full-text versions of articles suggested by the requesters or cited in public comments. The usual CMS criteria for evidentiary value were used (please see Appendix B). In addition, any relevant article indexed by PubMED as 'Review' or 'Guideline' or 'Health-services research' was used only for background information and is listed in the Bibliography.

Summaries of articles about clinical trials are grouped below by:

1. trial design (as listed in decreasing order by evidentiary value (see Appendix B));
2. last name of first author in ascending alphabetical order; and
3. year of publication in reverse chronologic order.

Studies with the same first author in the same year of publication are distinguished by a one-letter suffix (e.g., 2011*A*, 2011*B*, etc.)

Prospective controlled trials

Garrett CR, Siu LL, El-Khoueiry A, et al. Phase I dose-escalation study to determine the safety, pharmacokinetics and pharmacodynamics of brivanib alaninate in combination with full-dose cetuximab in patients with advanced gastrointestinal malignancies who have failed prior therapy. Br J Cancer. 2011; 105(1):44-52.

This study of a new treatment agent for advanced gastrointestinal malignancies in patients who had failed prior therapy included a secondary objective of assessing the reproducibility of FDG PET measurements of SUV parameters in this multi-center trial. Eighty-five patients enrolled in the study included 61% males and 39% females, and their median age was 60 years. Most (59/61 who passed screening for treatment suitability) had colorectal cancer; two had esophageal cancer, and one had fibrolamellar hepatoma. Most frequent sites of metastases were liver (in 53 patients), lung (in 51) and lymph node (in 19). Results of the FDG PET analysis indicated that the percent difference of SUVmax as measured in the two baseline scans ranged from -34% to 52% (data not shown). The authors commented that metabolic response may represent a predictive marker of clinical outcomes.

Ruers TJ, Wiering B, van der Sijp JR, et al. Improved selection of patients for hepatic surgery of colorectal liver metastases with (18)F-FDG PET: a randomized study. J Nucl Med. 2009; 50(7): 1036-41.

In this randomized clinical trial, 150 patients with colorectal cancer metastases to the liver were randomized 1:1 to either the CT group or the CT and PET/CT imaging prior to surgery group. The mean age of patients was about 62.7, and 46 females and 104 males participated. The patients in each group were comparable at baseline, based on age, gender, stage of primary tumor, size and number of hepatic tumors, preoperative CEA, and other criteria. A laparotomy that did not allow for complete treatment of metastases, which revealed benign disease, or which resulted in less than six months' subsequent survival, was considered futile. The authors found that there were 34 (45%) futile laparotomies in the study arm with preoperative CT only, and 21 (28%) futile laparotomies in the study arm with preoperative FDG PET/CT and CT. The relative reduction in risk of futile laparotomies was 38% (4 -60%), with p=0.042. The authors concluded that adding FDG PET/CT to the presurgical evaluation workup prevented unnecessary surgery in (31-24)/75 or ~17% of patients (approximately one in six patients). However, during a followup period of up to 3.5 years, there was no significant difference found in overall survival between the control (CT only) and experimental (CT + PET) groups. The authors suggested, based on some research studies, that further studies of MRI for preoperative evaluation might further decrease futile laparotomies.

Benz MR, Herrmann K, Walter F, et al. FDG PET/CT for monitoring treatment responses to the epidermal growth factor receptor inhibitor erlotinib. J Nucl Med. 2011 (Nov); 52(11): 1684-9.

In their 2012 published article, Benz and colleagues prospectively studied whether early changes in tumor uptake of FDG, as measured by FDG PET/CT, can predict progression free and overall survival in non-small-cell lung cancer (NSCLC) treatment with erlotinib, a tyrosine kinase inhibitor that acts on the epidermal growth factor receptor (EGFR). 22 patients, age older than 18 years, with Stage IIIB or IV, who were scheduled to receive erlotinib, were recruited for this study. A baseline FDG PET/CT study was obtained a median of three days (range, 0 to 32 days) before start of erlotinib treatment ('ET'). This was followed by an 'early followup' FDG PET/CT study 14 +/- one day after initiation of ET. Eleven patients also underwent a third FDG PET/CT study 78 +/- 21 days after the start of ET (in the other eleven patients, ET therapy was discontinued before the third scan could be obtained). Study endpoints were progression-free survival (PFS) and overall survival (OS) of metabolic responders and non-responders. Metabolic responders were defined as complete (complete resolution of FDG uptake by tumor), partial (reduction of at least 30% in tumor FDG uptake), progressive disease (increase of a minimum of 30% in tumor FDG uptake or presentation of a new lesion), or stable metabolic disease (not complete or partial responses or progressive disease) on the basis of SUV calculated within the tumor volume (not, as the authors noted, as tumor SUVmax). Up to five lesions were assessed in any patient. The authors found that of the 22 patients, 16 were female, and six were male. 45% had a history of smoking. The study population included 14 Caucasians, six Asians, and two patients of other racial groups. The histologic types of the cancers included adenocarcinomas (77%), squamous cell carcinomas (14%), large cell carcinomas (4%) and unspecified cancers (4%). 19 of 22 patients (86%) had Stage IV disease at enrollment. 15 of 22 patients had prior therapy of som type, including two with resection as part of their treatments. Early response PET studies classified 6/22 (27%) patients as complete or partial responders, 7/22 (32%) patients as stable disease, and 9/22 (41%) patients as progressive disease. The median overall survival (OS) duration was 131 days (95% CI, 0-351 days). Patients classified as progressive disease on 'early' FDG PET/CT scans showed significantly (p=0.03) shorter OS than patients classified in other categories. The authors acknowledged some limitations of the study, including the high proportion of women, who tend, as never-smokers, to be more responsive to EGFR inhibitors such as erlotinib. Also, the study may have included patients whose EGFR mutations (which were not tested) might have affected response to treatment. Another possible interaction source may have affected response in patients on combination therapy, i.e., in the five (23%) of 22 patients treated with estrogen receptor or anti-inflammatory drugs, the effects of which might have affected FDG uptake. Additional research was suggested in larger patient populations.

Enslow MS, Zollinger LV, Morton KA, et al. Comparison of FDG and F-18 fluorothymidine PET in differentiating radiation necrosis from recurrent glioma. Clin Nucl Med. 2012 Sep; 37(9): 854-61.

Based on a prospective case series of patients with histologically proven primary malignant gliomas post radiation and/or chemotherapy, the authors investigated whether new enhancing lesions in the radiation field (as demonstrated on Gadolinium magnetic resonance imaging (Gd-MRI)) could be identified as recurrent tumor or as radiation necrosis by either FDG or ^{18}F fluorothymidine (FLT) PET studies. All scans were conducted according to study-specific protocols. Exclusion criteria included: pregnancy or lactation; signs of uncal herniation; prior reactions to administered radiopharmaceuticals; and requiring monitored anesthesia for PET scanning. PET images were interpreted by two experienced readers. Recurrent tumor was defined by definitive increase in size of the enhancing lesion on Gd-MRI as interpreted by a neuroradiologist, while radiation necrosis was defined by stability or regression of the enhancing lesion over time. The authors found that of 15 enrolled patients, nine were male and six were female, and their ages ranged from 22-75 years. Radiation therapy had been completed

four or more months prior to study entry. Ten patients had glioblastoma multiforme (GBM); three had grade III oligodendroglioma; one had grade II astrocytoma, and one had oligoastrocytoma. Based on longitudinal Gd-MRI, eleven patients had recurrent tumor, while four had radiation necrosis, including three patients with GBM, and one with grade II astrocytoma. The authors also found a statistically significant difference between FDG SUVmax for recurrent tumor (mean 8.2, range 5.3-12.1) and that for radiation necrosis (mean 5.5, range 4.3-6.5) (p = 0.019, Kruskal-Wallis one-way analysis of variance). A summary table (Table 2) described the performance characteristics of the different methods:

Adapted from Table 2 of Enslow 2012:

Parameter	FDG	FDG ratio	F-18 FLT	FLT Ki-max
Area under ROC curve	0.93	0.98	0.86	0.89
95% CI	0.75 – 1.00	0.91 – 1.00	0.56 – 1.00	– 1.00
Optimized cut-off for tumor	6.20	1.83	1.34	0.0165

The authors concluded that, although quantitative determinations of FDG uptake allow accurate differentiation of recurrent glioma from radiation necrosis, ^{18}F FLT had no striking advantage as a radiopharmaceutical for this indication over FDG PET.

Gayed I, Vu T, Iyer R, et al. The role of ^{18}F FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J Nucl Med. 2004 Jan; 45(1): 17-21.

This study compared the roles of FDG PET and CT in follow-up of gastrointestinal stromal tumors (GISTs) after treatment with imatinib mesylate. Forty-nine patients with GIST underwent FDG PET and CT within three weeks of starting imatinib therapy, and repeat scans two months after therapy. Fifty-four patients (23 women and 31 men) with a mean age of 56.4 years (range 30-82 years) were included in this study. Patients who had previously undergone chemotherapy or radiation therapy or had a second type of cancer were excluded. Five lesions outside the CT field were also excluded from analysis. True positive lesions were defined as those in which FDG PET and CT results were in agreement, or when alternate diagnostic tests were positive for the presence of malignancy, including evidence of progression on subsequent diagnostic imaging studies. False positive and false negatives were also defined by discordant findings of other diagnostic modalities or follow-up studies. Patients undergoing FDG PET scanning followed a standardized preparation protocol and dosing amount after blood glucose was checked. FDG PET scans covered the base of the skull through the mid-thighs. CT scans extended from the thoracic inlet through the ischial tuberosity. Criteria for response to therapy or disease progression included, for FDG PET, either a more than 25% increase or decrease in SUVmax, and for CT, a decrease of 5% or more in longest dimension or an increase of greater than 5% in longest dimension. Intermediate values of FDG PET SUV or CT longest dimensions were considered to show 'stable disease'.

The authors found that, in the 49 patients with repeated CT and FDG PET studies at two months, both types of scans showed responses to treatment in 28 (57%). Of these 28 patients, 17 experienced clinical improvement, while eleven remained asymptomatic. SUVmax decreased to background levels in 25/28 patients, and by at least 30% in the remaining three patients. In contrast, seven (14%) of forty-nine patients showed no response on either FDG PET or CT scans. Of these seven, six had no clinical change in symptoms, while one patient experienced deterioration. Discrepant results between FDG PET and CT scans were noted in 14 (29%) of 49 patients. Longer follow-up showed that FDG PET (on average, after 8.2 months) correctly predicted response to therapy earlier that CT in ten (71%) of 14 patients. The authors concluded that CT and FDG PET studies have comparable sensitivity and positive predictive value in staging recurrent malignant GISTs. FDG PET was found to be superior in predicting early response to therapy (i.e., at two months after initiation of imatinib treatment).

Hillner BE, Siegel BA, Hanna L, et al. Impact of FDG PET Used After Initial Treatment of Cancer: Comparison of the NOPR 2006 and 2009 Cohorts. J Nucl Med. 2012 May; 53(5): 831-7. (Hillner 2012)

NOTE: This was also submitted as a reference with NOPR's current request.
This prospective cohort study compared data on FDG PET studies performed for oncologic indications in two groups of Medicare beneficiaries: those enrolled from May 8, 2006 – April 3, 2009 ('2006 cohort'); and those enrolled from April 4, 2009 – November 30, 2011 ('2009 cohort'). For each patient in both cohorts, a before-FDG PET and after-FDG PET design examined physicians' intended management decisions for cancer patients. The 'after-FDG PET' data collection sought data from participating physicians about their impressions of the extent of disease in all patients (more extensive, unchanged, or less extensive than before PET results were known); and, for patients on chemotherapy, to record their assessment of the patient's prognosis (better, unchanged, or worse given the PET findings) and their intentions for patient management. The authors categorized decisions as 'treatment' (e.g., surgery, chemotherapy, radiation, or other active cancer treatment) or 'non-treatment' (e.g., observation, alternative imaging, or other non-invasive therapy, biopsy, or supportive care). For patients in the 2009 cohort receiving cancer chemotherapy, endpoints also included continuing, modifying, switching, or stopping chemotherapy. Statistics on the number of patients in whom intended therapeutic strategy changed after FDG PET (from treatment to non-treatment, or vice-versa) were aggregated and compared for each cohort, stratified by cancer type.

The authors found that 90% of participants were 65 years of age or older (younger participants were disabled beneficiaries). FDG PET studies were performed using integrated scanners in more than 90% of participants in both cohorts. Among patients undergoing FDG PET studies for chemotherapy monitoring, about 6% had less than one month of therapy; 32% had one to three months; 28% had three to six months; and about one-third had more than six months of treatment. About 70% of the time after PET findings, physicians changed patients' prognoses. This conclusion did not 'meaningfully' change from the 2006 to the 2009 cohort. A better prognosis than anticipated occurred in about 40%; prognosis was unchanged in 31%; and worse in 29%.

The table below shows the changes in intended management associated with FDG PET for some of the cancer types in this cohort, when used in restaging in beneficiaries over age 65.

Table (adapted from Table 3 of Hillner 2012):

Cancer Type	NOPR Cohort	Patients (n)	% Change in intended management	95% Conf. Int.
Pancreas	2006	2,876	40.2	38.4 – 42.0
	2009	4,238	40.0	38.6 – 41.5
Prostate	2006	4,856	37.8	36.5 – 39.2
	2009	5,465	41.4	40.0 – 42.7
Small cell, lung	2006	2,810	40.7	38.9 – 42.6
	2009	5,403	40.2	38.9 – 41.5
All other cancers	2006	5,280	34.3	33.0 – 35.6
	2009	15,466	33.4	32.7 – 34.2
Totals	**2006**	**27,860**	**35.8**	**35.3 – 36.4**
	2009	**48,831**	**35.9**	**35.4 – 36.3**

The authors also found that for the subset in each cohort of patients receiving cancer chemotherapy, PET results changed physicians' intentions to continue, switch, adjust, or stop chemotherapy ('ChemoRx') in about half of all patients, as shown in the following table.

Table (adapted from Table 4 of Hillner 2012):

Cancer Type	NOPR Cohort	Patients (n)	Switch ChemoRx (%)	Adjust ChemoRx (%)	Stop ChemoRx (%)
Pancreas	2006	1,783	26.8	15.2	13.1
	2009	2,198	25.0	6.9	13.5

Cancer Type	NOPR Cohort	Patients (n)	Switch ChemoRx (%)	Adjust ChemoRx (%)	Stop ChemoRx (%)
Prostate	2006	1,024	25.5	14.2	19.6
	2009	1,336	30.1	7.8	14.1
Small cell, lung	2006	1,346	28.9	15.4	20.5
	2009	2,083	24.1	4.8	19.0
All other cancers	2006	2,100	25.6	13.8	19.1
	2009	4,387	25.6	6.5	16.8
Total	**2006**	**10,234**	**26.7**	**14.6**	**18.6**
	2009	**15,611**	**25.9**	**6.3**	**16.3**

The authors concluded that, when used for subsequent ATS, an FDG PET scan was associated with about a 35% change in intended management of study participants. The observed intended management changes were minimally different between cancer types, cohorts, and age groups (i.e., when comparing younger (disabled) beneficiaries with those of 65 years of age or older).

The authors noted that when FDG PET scans were used for assessing response to chemotherapy (representing the indication for about 22% of FDG PET scans performed on study participants) there were some reasons to be cautious in using this study to assess FDG PET scans' utility. For example, although the authors mention that for treatment monitoring, a baseline image is often required for comparison, NOPR did not require that a preceding FDG PET scan be available; nor were the rates or timings of prior scans assessed in this study.

The authors further noted that, for participants who had already received six months or more of chemotherapy before FDG PET imaging, it was uncertain if these 'treatment monitoring' scans might have instead been classified instead as 're-staging' depending on how they may have been categorized by the referring physician.

The authors pointed out that the principal impact of FDG PET on management during chemotherapy occurred in patients whose FDG PET scans showed more extensive disease or a worse prognosis that was anticipated. In

these patients, physicians indicated they intended to continue chemotherapy without modification in only about 10% of patients for whom FDG PET indicated a worse-than-anticipated prognosis.

Separately, the authors suggested that, because the results based on the NOPR 2009 cohort data, including more than 70,000 PET studies, have shown little difference from those derived from data on the NOPR 2006 cohort, extension of data collection under NOPR may not provide much additional insight into how FDG PET affects intended clinical management in oncology. Instead, the authors suggested that further studies designed to compare and assess the roles of advanced imaging at several key decision points in 'real-world' clinical cancer care may be needed.

Hillner BE, Siegel BA, Shields AF, et al. Impact of dedicated brain PET on intended patient management in participants of the NOPR. Mol Imaging Biol. 2011; 13: 161-5. (Hillner 2011)

NOTE: This was also submitted as a reference with NOPR's current request.
The authors examined the demographic characteristics and changes in intended management after FDG PET scanning in patients in NOPR patients with brain tumors. The authors described their interest in assessing the role of FDG PET, both to determine tumor progression after therapy and to distinguish between radiation necrosis and tumor. Brain PET scans done between December 2006 and April 2009 were eligible for inclusion in this study. The authors found that of 274 brain PET scans done in participants with primary brain tumors, 61 were for the indication of restaging, and 213 were for detection / confirmation of suspected recurrences. Participants receiving brain PET scans in NOPR were found to be younger than NOPR cases overall (41.3% younger than 65 years vs. 10.5% overall). The authors also found that changes from treatment to non-treatment were more frequently seen in those with primary brain tumors than in the overall NOPR cohort (13.4% vs. 7.7% (OR 1.9, 95% CI 1.3-2.5)). The authors commented that, although PET scanning of primary brain tumors has limited sensitivity due to the background of high glucose avidity of normal gray matter, and accounts for only 0.67% of all NOPR cases, PET scans were informative about tumor grade and persistent or recurrent disease after therapy. The authors also suggested that referring physicians were selective in ordering PET scans infrequently to evaluate metastatic cancers to the brain.

Hillner BE, Siegel BA, Shields AF, et al. The impact of PET on expected management during cancer treatment: findings of NOPR. Cancer 2009 Jan 15; 115: 410-8. (Hillner 2009)

NOTE: This was also submitted as a reference with NOPR's current request.
This prospective cohort trial, based on NOPR data, reported on the impact of FDG PET on intended management of patients with cancer of any type except breast cancer. NOPR organization and study design had been previously described elsewhere. The endpoint in this analysis was the changes in referring physicians' decisions about intended therapy, before and after FDG PET results on their patients. Included in this study were those participants enrolled in NOPR from May 8, 2006 through December 31, 2007 with a PET scan for treatment monitoring. Excluded were those with FDG PET studies of cancer types already covered or non-covered by Medicare, or with oncologic indications other than treatment monitoring. The authors found that of the 10,247 participants in this study group, the mean patient age was 71.8 years, and 52% of these participants were female. Cancer types among these NOPR participants included ovary and uterine adnexa, pancreas, lung (all types), prostate, myeloma, bladder, stomach, colon, kidney and other urinary tract, lymphoma, and other. More than 90% of NOPR participants were scanned using an integrated PET/CT scanner. Most (72%) were studied at non-hospital based imaging centers. 83% had an Eastern Cooperative Oncology Group (ECOG) score of 0

(asymptomatic, fully active) or one (symptomatic, fully ambulatory). Types of therapy being monitored included chemotherapy in 81.7% of participants; radiation therapy in 6.2%; and combination therapy in 12.1%. The following table shows the impact of PET results on intended management: nearly half of participating physicians' post-PET plans changed therapy for their cancer patients.

Table (adapted from Table 3 of Hillner 2009):

Post-PET Plan	Participants (%)
No change in therapy	5321 (50.7%)
Switch to another therapy	2778 (26.5%)
Adjust dose or duration of therapy	1744 (16.6%)
Change to observation or supportive care plan	654 (6.2%)

The authors also found that the treatment plan was unchanged in only 21.4% of patients whose FDG PET scans indicated a worse prognosis. Finally, the authors noted that on the post-PET data collection form, physicians indicated that FDG PET results enabled them to avoid additional tests or procedures after 90.6% of scans.

The authors noted, among limitations of this study, that by design it collected data on 'intended' rather than 'actual' patient management decisions by participating physicians. A different design such as a prospective controlled clinical trial might allow a more nuanced examination of actual patient management changes after FDG PET scanning, as well as assess impact of FDG PET scanning on long-term outcomes.

Hillner BE, Siegel BA, Liu D, Shields AF, Gareen IF, Hanna L, Stine SH, Coleman RE. Impact of PET/CT and PET alone on expected management of patients with cancer: initial results from the NOPR. J Clin Oncol. 2008 May 1; 26(13): 2155-61. (Hillner 2008A)

NOTE: This was also submitted as a reference with NOPR's current request.
This article presented the findings of the first assessment of NOPR data to determine the impact of FDG PET results on intended management of Medicare beneficiaries with cancer. The design and procedures of NOPR have

been described previously. The authors found that 22,975 cases were eligible for study inclusion and included complete records for analysis. The mean patient age was 72.9 years; participants included nearly equal proportions of women and men (49.9% / 50.1% respectively); and about 10% of the cohort were patients younger than 65 years eligible for Medicare coverage on the basis of disability. The indication for FDG PET scanning in 24.4% of participants was restaging following treatment; in 23.5%, the indication was to detect/confirm suspected cancer recurrence. To examine the effect of FDG PET scans on intended management for subsequent antitumor treatment strategy, the table below shows the proportion of cases of cancers of all types with changes in intended management when FDG PET scans were performed for the indications of restaging and confirmation/detection of recurrence:

Table (adapted from Table 2 of Hillner 2008A):

Indication:	**Changes in Intended Management, All Cancer Types (Percentages of cases (95% C.I.))**
Restage	36.1 (34.9 – 37.4)
Confirm/Detect Recurrence	38.9 (37.6 – 40.2)

The authors commented that the NOPR-based studies were valuable in focusing on the effect of an advanced imaging technology on intended physician management decisions, in contrast with other types of clinical trials with patient survival as their most relevant outcome. They also comment that the values of their findings are strengthened by the substantial size of the data set examined, its national scope, and the completeness of data collection. Limitations noted by the authors include the absence of actual patient outcome data, and the unknown contribution of FDG PET or FDG PET/CT compared to those of other imaging modalities. Further research was suggested.

Hillner BE, Siegel BA, Shields AF, et al. Relationship between cancer type and impact of PET and PET/CT on intended management: findings of NOPR. J Nucl Med. 2008 Dec; 49(12):1928-35. (Hillner 2008B)

NOTE: This was also submitted as a reference with NOPR's current request.
This article presents the findings derived from the first two years' data collected by the NOPR. The impact of FDG PET on different oncologic indications by cancer type is presented for patients registered from May 8, 2006 through May 7, 2008. The study included consenting Medicare beneficiaries (and their referring physicians) with FDG PET scans for, among other indications, restaging and detection of recurrences of cancers that were not either nationally covered or nationally non-covered by CMS. Analyses of post-PET changes of intended therapy (treatment to non-treatment or vice versa) were performed for both restaging and detection of recurrences and were separately performed by cancer type. The authors found that the final analysis cohort for this article consisted of 40,863 scans on 34,536 participants. The mean patient age was 72.4 years, with nearly equal numbers of men and women (49.8% / 50.2% respectively). 16 cancer types had at least 500 cases each in the

registry, and the total of the number of cases for all 16 types represented about 90% of all registry cases.

For the indication of restaging, the following table shows, by cancer type, the % of cases with change in intended management:

Table (adapted from Table 6 of Hillner 2008B):

Cancer Type (number of scans)	Percentages of cases with changes in intended management
Ovary (1,971)	37.7
Prostate (1,477)	34.0
Small cell, lung (1,357	40.8
Bladder (1,239)	36.4
Uterus (1,064)	30.5
Pancreas (1,021)	38.3
Myeloma (1,009)	46.4
Kidney (979)	34.4

Cancer Type (number of scans)	Percentages of cases with changes in intended management
Stomach (916)	35.5
Connective tissue (450)	28.0
Skin, non-melanoma (363)	23.1
Cervix (353)	26.9
Liver and intrahepatic bile ducts (260)	41.9
Leukemia (229)	36.7
Gallbladder (215)	38.6
Thyroid (203)	34.5
All other (1,478)	33.2
Total (14,584)	**35.9**

For the indication of detection of recurrence, the following table shows, by cancer type, the % of cases with change in intended management:

Table (adapted from Table 7 of Hillner 2008B):

Cancer Type (number of scans)	Percentages of cases with changes in intended management
Ovary (2,160)	44.5
Prostate (1,790)	39.4
Uterus (1,059)	38.8
Kidney (1,003)	32.4
Bladder (878)	36.7
Pancreas (802)	39.3
Stomach (553)	29.3
Small cell, lung (544)	38.1
Myeloma (373)	50.9

Cancer Type (number of scans)	Percentages of cases with changes in intended management
Connective tissue (366)	34.7
Cervix (290)	35.9
Thyroid (253)	33.2
Primary brain (222)	40.5
Other female genital (206)	39.8
All other (1,415)	35.1
Total (11,914)	**38.5**

The authors concluded that based on physician records of intended subsequent antitumor treatment strategy, FDG PET results change intended management for a variety of common cancer types. The authors also calculated that, based on national incidence figures, the NOPR cohort included from 10 – 20% of patients with these types of cancers.

Kitajima K, Murakami K, Yamasaki E, et al. Performance of integrated FDG PET / contrast-enhanced CT in the diagnosis of recurrent pancreatic cancer: comparison with integrated FDG PET / non-contrast enhanced CT and enhanced CT. Mol Imaging Biol. 2010; 12: 452-9.

In this prospective study, the authors evaluated the accuracy of FDG PET/CT with intravenous contrast for detection of recurrent pancreatic cancer. Fifty patients who had undergone surgery for histopathologically proven pancreatic cancer with suspected recurrent and/or metastases were recruited to undergo FDG PET/CT (contrast-enhanced and non-enhanced) at one institution. Five patients were dropped from further analysis due to lack of follow-up information. A standard protocol was used in performing PT scans on all patients. Contrast-enhanced CT was retrospectively evaluated in consensus by two experienced radiologists who had no knowledge of either the other imaging results or of the clinical data. FDG PET/contrast-enhanced CT images were interpreted by two other experienced radiologists, also unaware of other imaging results or of clinical data. The reference standard for diagnosis was histopathologic examination after surgery or biopsy (n=21), or clinical follow-up of at least six months (range, 6 – 26 months) with a rising tumor marker (CA 19-9). The authors found that the mean patient age was 58 years, with a range of 45-81 years. The treatment included: surgery plus chemotherapy in 28/45 patients; surgery only in 14/45 patients; and surgery plus chemoradiotherapy in three of forty-five patients. Reasons for seeking the FDG PET/CT study included: an abnormal serum tumor marker (in 22/45 patients); an abnormal conventional imaging study (in seven); both in twelve patients; and an abnormal physical examination in four. Time between the last treatment and the study FDG PET/CT showed a mean of nine months and a range of four to twenty months. The authors found that in 24/45 patients, recurrence or distant metastasis were confirmed by pathologic examination. In 21/45 other patients, absence of recurrence was indicated by pathologic examination (n = 2), follow-up tumor marker and FDG PET/CT confirmation scans (n=9), and CA 19-9 levels with contrast-enhanced CT imaging (n=10). The following table (adapted from their Table 3, p. 457) compares FDG PET/CT (enhanced) and PET/CT (unenhanced) findings in patients with and without recurrence:

Table (adapted from Kitajima 2010, Table 3)

Imaging	TP	FN	TN	FP	Sensitivity	Specificity	PPV	NPV	Accuracy
CT	16	8	18	3	67%	86%	84%	69%	76%
PET/CT (non-enhanced)	20	4	19	2	91%	91%	91%	83%	87%
PET/CT (enhanced)	22	2	20	1	95%	95%	96%	96%	93%

The authors found no significant difference in accuracy between FDG PET with and without contrast-enhanced CT (McNemar test: $p = 0.083$). They concluded that FDG PET/CT (contrast-enhanced) was a valuable and potentially 'first-line' diagnostic tool for assessing patients with suspected recurrence of treated pancreatic cancer. The authors mentioned the limitations of the study, including the lack of histologic confirmation of all cases of recurrence as a reference standard, the relatively small number of patients studied, and the lack of a separate CT scan with which to compare diagnostic accuracy with FDG PET/CT.

Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the esophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007; 8(9):797-805.

In this study, the authors attempted to evaluate a PET-guided strategy to individualize therapy for patients with locally advanced adenocarcinoma of the esophagogastric junction (AEG). 119 patients were recruited into this prospective, single-center study. Patients were considered 'responders' if they showed a 35% or greater decrease in SUV by the FDG PET/CT study at the end of the treatment evaluation period (ie, after two weeks of platinum and fluorouracil induction therapy). Responders continued chemotherapy and then underwent surgery; non-responders proceeded to surgery. The primary endpoint was median overall survival of both responders and non-responders. The authors found that 110 patients could be evaluated for responder/non-responder status. 54/110 (49%, 95% CI of 39-59) were found to be responders. After a median follow-up of 2.3 years, median overall survival was not determined among responders, while non-responders had a median OS of 25.8 months (HR 2.13, 1.13-3.99, p = 0.15). Major histologic response was seen in 29 of 50 responders, but in none of the non-responders (p = 0.001)). The authors commented that use of a 35% decrease in SUV as the criterion for response was associated with a higher predictive value for histological response, and suggested that randomized clinical trials would be needed to determine the clinical relevance of this study.

Meirelles GS, Schoder H, Ravizzini GC, et al. Prognostic value of baseline [18F]-fluorodeoxyglucose positron emission tomography and 99mTc-MDP bone scan in progressing prostate cancer. Clin Cancer Res. 2010; 16:6093 -6099.

In this article, the authors prospectively investigated the value of SUVmax in FDG PET scans in contrast to bone scans with technetium-99m in progressing metastatic prostate cancer. Patients with histologically proven prostate adenocarcinoma and clinical evidence of disease progression as defined by a rising PSA and a detectable abnormality on a conventional imaging study, such as bone scan, CT, or MRI. Patients were considered castrate if testosterone levels were less than 50 nanograms/deciliter (ng/dL) in blood. Bone scan were performed at study initiation (30 days before to seven days after first treatment); FDG PET was performed in 43 patients before treatment initiation, and these 43 patients were further analyzed. Follow-up bone scans were performed three to six weeks after initiation of therapy. Images were interpreted by a radiologist and a nuclear medicine physician unaware of patients' specific findings (although they were aware of their progressive prostate cancer status). The authors found that in the 43 evaluable patients, the median time between bone scan and PET scan was 11.6 days with a maximum of 46 days. Bone scans indicated metastases in more patients (37/43, 86% of patients) than did FDG PET (31/43, 72% of patients) (p=0.01). In patients with negative bone scans, 1/6 had a metastatic lymph node lesion demonstrated on FDG PET. SUVmax on FDG PET scans did have some prognostic value for survival; in 22 patients whose metastases had an SUVmax ≤ 6.10, median survival was 32.6 months; in 21 other patients whose metastases had an SUVmax > 6.10, median survival was only 14.4 months (p = 0.002). The authors recognized some limitations of their study, for example the difficulty accurately sizing lesions in bone. They concluded that SUVmax is a prognostic indicator for prostate cancer metastatic to bone, even though FDG PET is able to detect osseous metastases in only 18-65% of patients based on previously published cases.

Prospective Case Series

Bannas P, Derlin T, Groth M, et al. Can 18F-FDG PET/CT be generally recommended in patients with differentiated thyroid carcinoma and elevated thyroglobulin levels but negative I-131 whole body scan? Ann Nucl Med 2012; 26: 77-85.

Based on a prospective case series of patients who had completed initial anticancer therapy with differentiated thyroid cancer, this article describes how the authors evaluated FDG PET/CT for recurrence of differentiated

thyroid carcinoma (DTC) with elevated thyroglobulin (Tg). After total thyroidectomy and radioiodine ablation, patients were referred for a whole body scan using 131I tracer. If that scan was negative, and the patient's Tg was > two ng/mL, the patient was a candidate for an FDG PET/CT study to detect possible DTC recurrence. Results were verified by histology, ultrasound, or clinical follow-up. FDG PET/CT images were interpreted by two nuclear medicine physicians and two radiologists. Results of FDG PET/CT images were correlated with histology, other diagnostic studies, and clinical follow-up. The authors found the performance characteristics of FDG PET/CT to be as shown in the table below.

Table (adapted from Bannas 2012, Table 4)

Performance indicator	All patients	Patients with Tg > 10 ng/mL
Sensitivity	68%	70%
Specificity	60%	100%
Negative predictive value	27%	14%
Positive predictive value	89%	100%
Accuracy	67%	71.4%

The authors concluded that FDG PET/CT enables detection and localization of recurrences of DTC. They also noted that post-PET/CT findings, treatment changed in 17 (57%) of 30 patients.

Benz M, Evilevitch V, Allen-Auerbach MS, et al. Treatment monitoring by 18F-FDG PET/CT in patients with sarcomas: interobserver variability of quantitative parameters in treatment-induced changes in histopathologically responding and non-responding tumors. J Nucl. Med. 2008 Jul; 49(7): 1038-46.

In this prospective study of patients with high-grade soft-tissue sarcomas undergoing neoadjuvant chemotherapy (a companion paper to the Evilevitch study 2008(below)), the authors measured various quantitative parameters (e.g., SUVmean) from before and after FDG PET scans and evaluated their relative variability. Although some of these parameters can be automatically assigned by software, high variability of FDG uptake within the tumor caused frequent failure of the automatic thresholding algorithm, necessitating manual corrections that may have increased variability of calculated parameters related to SUV (see below). Patients were eligible if they had either biopsy-proven osteosarcoma or soft tissue sarcoma, were considered surgical candidates, and were scheduled to undergo preoperative chemotherapy or chemoradiotherapy. Patients underwent pre- and post-therapy FDG PET/CT scans, following study-specific scanning and patient preparation protocols. FDG PET images were analyzed by two independent observers unaware of the clinical data and histopathologic response, using the same workstations and software to co-register baseline and follow-up FDG PET/CT studies. Tissue subsequently removed at surgery was evaluated for tumor necrosis, with histologic response based on a finding of 10% or fewer viable tumor cells in resected tissue. The following parameters were calculated based on FDG PET/CT scan data: maximum standardized uptake value (SUVmax), peak SUV (SUVpeak), mean SUV in all pixels with SUV > 50% of SUVmax (SUVauto), mean SUV based on baseline FDG PET/CT study (SUVmean), and tissue background ratio comparing tumor-region SUVs with those on the contralateral normal soft tissue (TBR).

The authors found that in these 33 patients, eight had osteosarcomas, and 25 had soft tissue sarcomas. The mean age of the 16 male and 17 female patients was 47.1 years, ranging from 19 to 86 years. Among these patients, 27 (82% of) patients presented with sarcoma in an extremity; 28 (85% of) patients had primary disease. Tumor size ranged from 3.4-20.3 cm (before presurgical therapy) to 2.3 to 25.8 cm afterwards. The average histologic response of tumors was 65%, ranging from 9 to 99.9%. Based on histopathology and the response criterion above, ten patients were classified as responders; 23 were non-responders. The authors concluded that SUVmax and SUVpeak showed low variability and separated histologic responders from non-responders. The authors commented that intratumoral heterogeneity was high in sarcomas and suggested that additional research studies would be valuable.

Evilevitch V, Weber WA, Tap WD, et al. Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. Clin Cancer Res. 2008 Jan; 14(3): 715-20.

In this multi-center study of patients with operable soft-tissue sarcomas, the authors used a before and after design to assess whether change in glucose metabolism after neoadjuvant chemotherapy as measured by positron emission tomography with FDG PET allows for a more accurate evaluation of histopathologic response than change in tumor size. Relative changes in tumor FDG uptake and size from the baseline to the follow-up scan were calculated, and their accuracy for assessment of histopathologic response was compared by receiver operating characteristic curve analysis. Histopathologic response was defined as ≥ 95% tumor necrosis.

The authors found that in histopathologic responders (n = 8; 19%), reduction in tumor FDG uptake was significantly greater than in non-responders ($P < 0.001$), whereas no significant differences were found for tumor size ($P = 0.24$). The area under the receiver operating characteristic curve for metabolic changes was 0.93, but only 0.60 for size changes ($P = 0.004$). Using a 60% decrease in tumor FDG uptake as a threshold resulted in a sensitivity of 100% and a specificity of 71% for assessment of histopathologic response, whereas Response Evaluation Criteria in Solid Tumors showed a sensitivity of 25% and a specificity of 100%. The authors concluded that quantitative FDG PET was significantly more accurate than size-based criteria at assessing histopathologic response to neoadjuvant therapy. However, the authors noted that the quantitation of response in patients with liposarcoma is limited due to the low metabolic level of such tumors.

Feigen M, Lee ST, Lawford C, et al. Establishing locoregional control of malignant pleural mesothelioma using high -dose radiotherapy and FDG PET/CT scan correlation. J Med Imaging Rad Oncol. 2011; 55: 320-22.

In this series of patients with malignant pleural mesothelioma, the authors used FDG PET/CT to assess response of disease to high-dose palliative radiotherapy. Eligible patients were those with histologically confirmed mesothelioma of any subtype, limited to one hemithorax and with otherwise normal physiology, and not dependent on prior pleurectomy/decortication or other therapy. Patients underwent FDG PET/CT studies prior to radiotherapy in order to plan the target volume for radiotherapy, with followup studies at least three months after completing radiotherapy by either external beam or intensity-modulated radiotherapy. Patient imaging was performed using study-specific preparation and scanning protocols. All FDG PET scans for short or long-term follow-up, performed a median of 17 months after completion of radiotherapy, were compared with pre-treatment scans and SUVmax and total glycolytic volumes (TGVs) were calculated by software. The authors found that of the 14 patients eligible for the study, there were twelve males and two females, with median age of 62 years, ranging from 37 to 72 years. All had prior exposure to asbestos. Median survival of all patients from the time of diagnosis was 28 months, range 10-79 months. In ten of 14 patients, TGV decreased a median of 61% from baseline to initial follow-up FDG PET/CT scan. The authors acknowledged that in some patients, inflammation within the treated volume (associated with radiation pneumonitis) and the ten millimeter resolution limit of FDG PET studies were confounding factors in assessing either tumor volume for radiation treatment or potential failure of locoregional control.

Giovanella L, Ceriani L, DePalma D, et al. Relationship between serum thyroglobulin and FDG PET/CT in ^{131}I-negative differentiated thyroid carcinomas. Head Neck. 2012; 34: 626-31.

In patients with histological proven differentiated thyroid carcinoma (DTC) treated with total thyroidectomy and subsequent ^{131}Iablation, the authors wished to determine the ability of FDG PET/CT to detect recurrent DTC in patients with elevated thyroglobulin (Tg) levels but who are negative for recurrence on ^{131}I imaging. Follow-up FDG PET/CT studies were performed an average of 2.2 months after ^{131}I ablation. Scans were performed after a study-specific patient preparation protocol. Serum Tg was sampled just before the FDG PET/CT study, and patients were screened for anti-Tg antibodies to detect possible assay interference. Studies for recurrence were interpreted by two experienced nuclear medicine physicians who were unaware of other clinical or imaging results. The gold standard for comparison was a combination of follow-up information, including Tg levels and cytologic or histologic results, or other imaging modalities including MRI, CT, and ultrasound. The authors found that data from 42 patients were available for analysis. Average patient age and exact numbers of male and female patients tested were not available from the information provided. The following table shows the authors' calculations of diagnostic performance indicators:

Table (adapted from Giovanella 2012, p. 629)

Performance Index	Percent (%)
Sensitivity	93
	84

Performance Index	Percent (%)
Specificity	
Negative predictive value	93
Positive predictive value	84
Accuracy	90

In the subset of patients with Tg levels of 4.6 ng/mL or greater, sensitivity increased from 93-96%). However, three of 27 patients with true positive FDG PET/CT scans had Tg levels less than 4.6 ng/mL. The authors concluded that use of a Tg cutoff level of 10 ng/mL might decrease sensitivity of FDG PET/CT studies in such patients.

Holdsworth CN, Badawi RD, Manola JB, et al. CT and PET: early prognostic indicators of response to imatinib mesylate in patients with GIST. Am J Roentgenol. 2007 Dec; 189 (6):W324-30.

In this retrospective re-analysis of patient data from a Phase II trial of imatinib mesylate therapy for patients with advanced GIST at two institutions, the authors reported results of a pilot study showing that FDG PET SUVmax results indicated response (as time to treatment failure (TTF)). Patients underwent FDG PET prior to imatinib treatment (baseline) and 21-40 days after treatment initiation. For each patient, SUVmax was calculated for the lesion with the most intense uptake at baseline and was subsequently calculated for the same lesion on follow-up scans. Percent change in SUVmax at one month was also calculated for each patient. Most patients also underwent CT scans before treatment and 21-40 days after treatment. Investigators used study-specific preparation and scanning protocols. The outcome measure, time-to-treatment failure, was defined as the time from the first dose of imatinib mesylate to the earliest occurrence of disease progression, death or discontinuation from the trial for any medical reason. Recursion methods were used to find the optimal SUVmax cutpoint for TTF. The authors found that participating patients included 40 men (with mean age 54 years, ranging from 25-80 years) and 23 women (mean age 56 years, ranging from 19-84 years). Twenty-seven patients were treated per prior study protocol with an initial imatinib dose of 400 mg per day; 36 patients received 600 mg per day. Using several PET-related criteria to separate tumor response groups, the authors showed the FDG PET related response metrics were significant predictors of actual TTF:

Table (Adapted from Table 1, Holdsworth 2007)

Metric	Threshold	TTF, months	Significance
PET SUVmax	> 3.4 vs. ≤ 3.4	2.9 vs. 26.3	$p < 0.0001$
40% or greater reduction in PET SUVmax	N/A	2.9 vs. 26.3	$p < 0.0001$
25% reduction in SUVmax	N/A	5.1 vs. 23.0	$p < 0.004$
Standard SUVmax	> 2.5 vs. < 2.5	5.7 vs. 24.5	$p < 0.04$

The authors concluded that current FDG PET-related response metrics for GIST therapy with imatinib mesylate should be re-analyzed and improved, given that prior criteria for tumor response might not be applicable to newer targeted therapies such as imatinib. They suggested additional studies would be appropriate.

Nahmias C and Wahl LM. Reproducibility of SUV measurements determined by FDG PET in malignant tumors. J. Nucl. Med. 2008 November; 49(11): 1804-8.

This clinical study attempted to estimate the reproducibility and confidence levels of metabolic activity in malignant tumors using standardized uptake values (SUVs), as determined by FDG PET on two occasions no more than five days apart. Twenty six patients were studied, including ten women and 16 men, with a mean age of 61 years (range 25-72 years). Nine patients had esophageal cancer; six had metastatic breast cancer; three had esophageal cancer; and the other eight had cancers in various other locations. None of the patients was undergoing chemotherapy at the time of the study. Before and during each of the two PET examinations, patients fasted on a standard protocol, received a standard dose of FDG, and were scanned on a single type of PET scanner from chin to pelvis with PET data acquired for the same time interval. A CT scan of the same area was performed with standard settings. For calculation of SUVmax and SUV_{mean}, ROIs were determined using PET images from the first study to define regions of interest and, if metastases were present, from the metabolically most active lesion. Resolution of reconstructed PET images was approximately 8 mm, and regions of interest (ROIs) varied between nine and 17 mm. The authors found that patient weights and plasma glucose concentrations between the studies were not significantly different from zero (in kg and mg/dL respectively). The mean FDG uptake period was 94 +/- 9 minutes; the mean difference between FDG uptake periods for the 26 subjects was 0 +/- 8 minutes (range, -26 to 18 minutes). SUV_{mean} for the first and second PET scans in the chosen regions of interest ranged from 1.49 to 17.48, and SUVmax ranged from 2.99 to 24.09. The Pearson correlation coefficient *r* between SUV_{mean} determined in the two scans was 0.99 (n = 26; p < 0.0001, 95% CI: 0.99-1.00). In addition the mean difference in SUVmax between the first and second PET scans was not significantly different from zero (mean difference -0.05; 95% CI: -2.32 to 2.23). The authors concluded that serial measurement of FDG PET SUVmax and SUV_{mean} can be performed reproducibly. The authors mentioned

that most commercial PET scanners are able to perform the SUVmax and SUV_{mean} calculations if the injected dose and the patient weight are entered.

Ozkan E, Soydal C, Araz M, et al. The additive clinical value of FDG PET/CT in defining the recurrence of disease in patients with differentiated thyroid cancer who have isolated increased antithyroglobulin antibody levels. Clin Nucl Med. 2012 Aug; 37: 755-8.

In this retrospective analysis of patients with differentiated thyroid carcinoma (DTC) who underwent FDG PET/CT examination, the authors investigated the clinical value of FDG PET/CT in detecting the recurrence of disease with negative ^{131}I whole-body scans, undetectable thyroglobulin (Tg) and increased anti-Tg levels. Patients with anti-Tg associated with lymphocytic thyroiditis were excluded from the study. Whole-body images were interpreted by consensus of two experienced nuclear medicine physicians. A combination of clinical follow-up and histologic results was used as the reference standard. The authors found that 27 women and four men, with average age of 50.2 years, qualified for the study. Average time from thyroidectomy to FDG PET/CT scan was 30 months. All these patients had undetectable serum Tg and increased anti-Tg levels. The authors calculated the performance characteristics of FDG PET/CT for recurrent DTC detection were as follows:

Table (adapted from Ozkan 2012, p. 757)

Performance Index	Percent (%)
Sensitivity	75
Specificity	76
Negative predictive value	86
Positive predictive value	75
Accuracy	80

The authors concluded that FDG PET/CT may be useful in patients with suspected DTC recurrence, whose Tg levels are undetectable due to anti-Tg antibodies.

Rubello D, Rampin L, Nanni C, et al. The role of FDG PET/CT in detecting metastatic deposits of recurrent medullary thyroid carcinoma: a prospective study. Eur J Surg Oncol. 2008; 34: 581-6.

Based on a series of patients with histologically confirmed, previously treated medullary thyroid carcinoma (MTC), the authors used FDG PET/CT and other imaging modalities to determine the optimal mode of detecting recurrent disease in this prospective study. Serum calcitonin and CEA levels were assessed at the time of referral to this study, along with high-resolution neck ultrasound (US), FDG PET/CT, ^{111}In pentetreotide scintigraphy, and whole body CT. Additional follow-up included periodic physical examination, calcitonin and CEA levels, and imaging as need for clinical management. FDG PET/CT was guided by study-specific patient preparation and scanning protocols. Interpretation of images was done visually by two experienced nuclear medicine physicians blinded to clinical information. SUV levels were used to highlight foci of greatest FDG accumulation. Final diagnoses were made by cytopathology of fine needle aspirates, or by histopathology. The authors found that of 19 patients referred to the study, eleven were female and eight were male, and that ages of patients ranged from 34 to 73 years with a mean age of 53.4 years. All had undergone total thyroidectomy and lymphadenectomy. Some had also been undergone chemotherapy or beam radiotherapy or radiopharmaceutical therapy. Time from first treatment to study entry ranged from 24 months to 13 years. FDG PET/CT detected metastases in 15/19 patients, with eight metastases in neck lymph nodes, five in head lymph nodes, and five in mediastinal lymph nodes, and two in both neck or mediastinal lymph nodes and in bone. In contrast, ^{111}In pentetreotide scanning detected eight patients with metastases (five with neck lymph node metastases, three with both neck and mediastinal metastases). CT detected metastases in eleven patients, and US detected neck metastases in six lymph nodes. In four of nineteen study patients, no imaging method detected metastases. No false positive findings of metastases were found in any patient based on FDG PET/CT, CT, or ^{111}In pentetreotide scanning, but US studies on three patients were false positive due to reactive enlargement of lymph nodes negative for malignancy by fine needle aspiration. The authors noted that calcitonin levels in the range 590 – 1350 pg/mL were more likely to reflect FDG PET/CT positive cases. It was also noted that FDG PET/CT findings of multiple metastases in the neck and mediastinum contributed to planning a subsequent re-excision in three patients. The authors concluded that FDG PET/CT is superior to other imaging methods for detecting and localizing recurrence of MTC. They acknowledged that the relative small size of the patient series (n = 19) was a limitation of their study.

Santra A, Kumar R, Sharma P, et al. F-18 FDG PET-CT in patients with recurrent glioma: comparison with contrast enhanced MRI. Eur J Radiol. 2012; 81: 508-13.

In this prospective series, the authors compared the efficacies of FDG PET-CT and contrast-enhanced MRI in detecting recurrent gliomas. 90 patients with histologically proven glioma suspected on clinical grounds of recurrent were recruited for the study between August 2006 and February 2008. Patients with other types of primary brain tumors or with metastases to brain were excluded. Studies were performed on an integrated PET-CT scanner in a single institution. All patients fasted for at least four hours preceding the FDG PET-CT scan and had glucose levels less than 140 mg/dL. 45-60 minutes after intravenous injection of a 370 MBq (10 mCi) dose, FDG PET-CT scans were performed. MRI images were acquired on a clinical MRI imaging unit, after IV administration of gadopentetate dimeglumine (Gd-DTPA) at a standard dose for contrast. Images were interpreted by experienced physicians, blinded to the clinical and structural findings. The comparison reference standard was a combination of biopsy (when available), repeat imaging, or clinical follow-up as available. The authors found that the patients' mean age was 36.8 years, ranging from 12 – 68 years. Sixty-six men and 24 women were participants. Tumor histologies included glioblastoma multiforme, astrocytoma, oligodendroglioma, or mixed gliomas. Surgery with radio- and/or chemotherapy had been the most frequent types of primary

therapy in these patients. After a follow-up period of at least six months, the table shows how many participants were positive for recurrent glioma by either PET-CT scan, MRI with contrast, or by clinical follow-up:

Table (adapted from Santra 2012, pp. 508-9)

Mode of recurrence detection:	Patients positive for recurrence:
Clinical follow-up, repeat imaging, or biopsy	59/90 (66%)
PET-CT	42/90 (47%)
MRI with contrast	80/90 (89%)

The authors concluded that overall, MRI with contrast had high sensitivity (95%) but poor specificity (23%) for detection of recurrent gliomas. FDG PET-CT in contrast had lower sensitivity (70%) but higher specificity (97%). The authors noted that FDG PET-CT was able to correctly delineate mixed lesions (of recurrent tumor and radiation necrosis) in eleven patients. The authors also noted that many primary brain gliomas are similar in glucose metabolism to adjacent gray matter, increasing the difficulty of distinguishing some gliomas from normal brain tissue. The authors suggested that the increased false-negative rate of FDG PET-CT make it less attractive as a primary imaging approach for detecting recurrences, and that it be used instead to characterize any abnormal lesion found on MRI. The authors commented that additional research might be of value. The authors also noted (as a study limitation) that only five of these 90 cases had confirmation of recurrence based on histologic evidence.

Seo JH, Lee SW, Ahn B-C, Lee J. Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: special emphasis on using FDG PET/CT. Clin Endocrinol 2010; 72: 558-63.

In this prospective series of patients with prior total or near-total thyroidectomy and high-dose radioiodine ablation, the authors investigated the use of FDG PET/CT in patients with elevated antibody to thyroglobulin (anti-Tg). The reference standard for recurrent differentiated thyroid cancer (DTC) was a combination of SUV of three or better; or follow-up imaging or histologic or cytologic confirmation; or clinical follow-up 6-12 months later. The authors found that in detecting recurrence of DTC among patients with anti-Tg, PET/CT showed sensitivity, specificity, and accuracy of 75.6%, 87%, and 85.6% respectively. They concluded that in patients with anti-Tg antibodies, FDG PET/CT was clinically useful, but suggested that additional studies were needed.

Sperti C, Pasquali C, Bissoli S, et al. Tumor relapse after pancreatic cancer resection is detected earlier by 18-FDG PET than by CT. J. Gastrointest Surg. 2010; 14: 131-40.

In this prospective study, the authors evaluated the impact of FDG PET in the diagnosis of recurrent pancreatic cancer. The study focused on 138 patients following resection of the pancreas for adenocarcinoma between January 1997 and July 2008. Of these, 66 patients were excluded as: lost to follow-up; due to death after surgery; or due to not having an FDG PET performed. Standardized follow-up on the remaining 72 included physical examination, laboratory studies including tumor markers, and imaging studies including CT and MRI on a standardized schedule. Of these 72 patients, pancreatic tumor relapse was detected by CT in 35 (49%) and by FDG PET in 61 (85%). FDG PET influenced treatment strategies in 32/72 patients (44.4%). Disease-free survival was similar in both groups. The authors concluded that FDG PET detected tumor relapse earlier, but that an earlier diagnosis of relapse did not affect survival due to the lack of effective therapy.

Tan H, Chen L, Guan Y, et al. Comparison of MRI, FDG, and ^{11}C methionine PET/CT for their potentials in differentiating brain tumor recurrence from brain tumor necrosis following radiotherapy. Clin Nucl Med 2011 Nov; 36(11): 978-81.

In this retrospective review of patients with primary and secondary (metastatic) brain tumors following radiotherapy, the authors compared the capacity of FDG PET to recognize recurrent tumor with radiation injury with those of several other imaging technologies, including ^{11}C methionine (MET) PET/CT and MRI. PET/CT scans were performed after a standardized patient preparation protocol. The reference standard was either pathologic verification or clinical follow-up. The authors found that among 55 subjects, 45 were male, and ten were female. Ages ranged from 17-79 years with a mean age of 57 years. Primary histologic diagnoses included: gliomas in 37 subjects; metastatic lesions in 15 subjects; and unusual primary brain tumors in three subjects (neuroblastoma, CNS lymphoma, and germinoma). All patients were suspected of recurrences or of radiation injury following radiotherapy. Each subject was followed up for at least eleven months. The following table illustrates how well the selected imaging studies performed.

Table (Adapted from Tan 2011, Table 1)

Diagnosis	n	MRI Sensitivity	FDG PET/CT Sensitivity	MET PET/CT Sensitivity
Recurrence	39	87.2%	76.9%	92.3%

The authors concluded that MET PET/CT offers an effective means to distinguish brain tumor recurrences from radiation injury. However, due to some false negatives with MET PET/CT, it should be combined with clinical assessment for optimal use.

Topkan E, Parlak C, Kotek A, et al. Predictive value of metabolic FDG PET response on outcomes in patients with locally advanced pancreatic carcinoma treated with definitive concurrent chemoradiotherapy. BioMedCentral Gastroenterol. 2011; 11: 123, 1-9.

In this prospective study of patients with unresectable, non-metastatic pancreatic cancer with histologic proof of malignancy, the authors evaluated the predictive utility of post-treatment FDG PET results. The extent of disease in enrolled patients was determined by CT, MRI, or MR-cholangiopancreaticography (MRCP), with restaging of patients for radiotherapy with FDG PET/CT within ten days of treatment. Imaging studies were guided by institution-specific protocols for patient preparation and scanning. Radiotherapy protocols observed maximum dosage limits for specific internal organs or structures (e.g., spinal cord). Patients received 5-fluorouracil (5-FU) during the RT course as a radiosensitizer. Treatment response and follow-up were based on FDG PET/CT at twelve weeks, in addition to a number of other laboratory and imaging tests. Predictive utility of FDG PET/CT on clinical outcomes was studied based on differences in SUVmax from pre- to post-treatment scans. Patients were grouped by SUVmax differences into two groups separated by the median SUVmax difference, and then compared to local/regional progression free survival (LRPFS), progression-free survival (PFS), and overall survival (OS). Statistical analysis of survival information and of the relation of SUVmax differences to known prognostic values (such as age, gender, and nodal involvement). The authors found that 44 patients were enrolled, and, after twelve were excluded due to distant metastases and referred for systemic therapy, 32 patients remained eligible for analysis. Median SUVmax difference was -63.7%. The authors found a statistically significant difference in all survival measures (OS (p = 0.009), PFS (p = 0.005), and LRPFS (p = 0.02)) for patients with an SUVmax reduction greater than 63.7%. Corresponding median survival times for the patient group with greater versus lesser SUVmax changes (compared to 63.7% decrease) are shown in the following table:

Table (adapted from Topkan 2011)

Survival Measure:	Median survival time, patients with greater SUVmax changes (months, with 95% CIs)	Median survival time, patients with lesser SUVmax changes (months, with 95% CIs)
PFS	8.4 (5.5 - 11.3)	3.8 (1.8 – 6.7)
LRPFS	12.3 (3.1 – 21.5)	6.9 (1.8 – 12.0)
OS	17.0 (14.5 – 19.4)	9.8 (7.2 – 12.4)

The authors noted that, in addition to its ability in pre-treatment radiotherapy planning, FDG PET/CT's ability to indicate improved survival by the difference in SUVmax from pre- to post-treatment images contributes its value in pancreatic cancer management. The authors acknowledged the small sample size of the study as a limitation, and suggested that larger studies would be useful.

Retrospective case series

Alousi AM, Saliba RM, Okoroji GJ, et al. Disease staging with positron emission tomography or gallium scanning and use of rituximab predict outcome for patients with diffuse large B-cell lymphoma treated with autologous stem cell transplantation. 2008. Brit J Haematol 142:786-792.

In this retrospective study, the authors evaluated the influence of rituximab on progression-free survival (PFS) in patients with diffuse large B-cell lymphoma (DLBCL), based on FDG PET scans and gallium scan ('PET/G') status before autologous stem cell transplant (ASCT). They included for review all patients with chemosensitive DLBCL who underwent ASCT in research protocols at one institution. The authors found that the median age of 174 patients reviewed was 47 years (range, 16-75 years) and included 101 men and 73 women. Except for 9/174 patients who had no scans, the patients had nearly equal numbers of FDG PET scans and gallium scans, because prior to December 2002, ^{67}Ga scans had been used at that institution. Based on either type of scan, 29/174 patients had positive scan results for lymphoma, while 136/174 had negative scan results. Most patients had undergone prior therapy of some type, and some had achieved complete remission. Outcomes after ASCT in these patients, as measured by PFS rate (the cumulative proportion surviving free of progression) at six years, was best (74%) among those with negative scan status before ASCT and whose therapy included rituximab; while PFS rate was worst (10%) among patients with positive scan status before ASCT and whose therapy did not include rituximab. The authors considered the inability of study size to enable a comparison of predictive value of gallium vs. FDG PET scans to be a limitation. The authors concluded that evidence of disease status by PET or gallium scan prior to ASCT was associated with progression free survival rate.

Amini A, Xiao L, Allen PK, et al. Celiac node failure patterns after definitive chemoradiation for esophageal cancer in the modern era. 2012. Int J Radiation Oncol Biol Phys 83:231-239.

In this study, the authors described a retrospective, single-center investigation to assess whether pre- and post-treatment FDG PET SUV changes predict local failure (metastases) to the celiac lymph nodes as a way to assess tumor response. The authors reviewed radiation treatment volumes for 131 patients who underwent definitive chemoradiation treatment (CRT) for esophageal cancer. Patients with celiac node involvement at baseline were excluded. The authors found that the median patient age was 71 years, ranging from 30 to 83 years. 113/131 study participants were males. Median followup time was 52.6 months, with a 95% CI of 46.1 – 56.7 months. In 60/131 patients in whom the radiation treatment volume did not include the celiac lymph nodes, six had celiac node failure. Of 71/131 patients whose celiac lymph nodes were within the radiation treatment volume, five patients had celiac node failure. The inclusion of the celiac lymph nodes in the radiation treatment volume was not associated in a statistically significant way with celiac lymph node failure. In multivariate analysis, a pre- to post-treatment change in PET SUV of 52% or more, in patients who had failure in the clinical target volume, were significantly associated with risk of celiac lymph node failure. Of those 60 patients whose radiation tumor volumes did not include the celiac lymph nodes, the six patients with celiac lymph node failure had a worse median overall survival time compared with the 54 who did not fail (median overall survival time: 16.5 vs. 31.5 months, p = 0.041). The authors noted that staging techniques improved greatly during the seven year period covered by this retrospective study.

Choi JW, Lee JH, Baek JH, et al. Diagnostic accuracy of ultrasound and FDG PET or PET/CT for patients with suspected recurrent papillary thyroid carcinoma. Ultrasound in Med. & Biol. 2010; 36(10): 1608-15.

In this retrospective consecutive case series of patients with papillary thyroid carcinoma who had undergone total thyroidectomy and radioiodine ablation, the authors compared the diagnostic accuracy of ultrasound to that of FDG PET for the diagnosis of recurrent disease. Eligibility for study selection included clinical suspicion of recurrent disease based on serum thyroglobulin levels or clinical examination. Ultrasound studies were done by physicians aware of the clinical diagnosis. FDG PET studies were guided by institutional protocols. Recurrence was considered proven based on results of fine needle aspirate, excisional biopsy; follow-up imaging studies of any type, including ^{131}I whole body scan; or a serologic test. The authors found that 76 patients were eligible for the study, including 18 men and 58 women. Their average age was 45.4 years, ranging from 17 to 77 years. Based on their definition of recurrence, 53/76 patients recurred. The following table compares the performance characteristics of each test for recurrent disease:

Table (adapted from Choi 2010, Table 3)

Performance Index	Ultrasound	FDG PET
Sensitivity	72%	57%
Specificity	70%	52%
Accuracy	71%	55%
Positive predictive value	84%	73%
Negative predictive value	52%	34%

The authors calculated that there were no statistically significant differences in sensitivity, specificity or accuracy. The authors also noted that either method of detecting recurrence led to treatment management changes in 30 - 40% of patients. In two of 76 cases, FDG PET was of value because distant metastases were detected. The authors concluded that neck ultrasound had higher accuracy than FDG PET in detecting local recurrences in patients with suspected recurrent papillary thyroid carcinoma.

Conry BG, Papathanasiou ND, Prakash V, et al. Comparison of ^{68}Ga-DOTATATE and FDG PET/CT in the detection of recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2010; 37: 49-57.

In this retrospective study, the authors compared the gallium-based PET radiopharmaceutical ^{68}Ga-DOTATATE (a somatostatin analogue) with FDG PET for detecting and assessing extent of recurrent medullary thyroid cancer (MTC). Verification of the lesions detected by either tracer was achieved by histopathologic analysis, further imaging studies, and clinical follow-up. The authors found that in 18 patients previously operated on for MTC and with either raised calcitonin levels or imaging evidence of recurrence, imaging for both ^{68}Ga-DOTATATE and FDG had been done within no more than four weeks, six patients were 60 years of age or older, and five of these six patients were men. Recurrent MTC was detected in 13 (72.2%) of 18 patients by ^{68}Ga-DOTATATE PET/CT and in 14 (77.8%) of 18 patients by FDG PET/CT. However, in ten patients the two radiotracers provided discordant images of the recurrent disease based on visual review of lesions and/or regions involved. The authors suggested that ^{68}Ga-DOTATATE PET/CT may be a useful complementary tool with FDG PET/CT for detection of MTC recurrence.

Dahele M, Ung YC, Ehrlich L, et al. FDG PET-CT for suspected recurrent papillary thyroid cancer: early experience at Sunnybrook Health Sciences Center. J Otolaryngol. – Head Neck Surg. 2008; 37: 712-7.

Based on a retrospectively studied series of patients with prior total or near-total thyroidectomy, some of whom had also received radioiodine ablation, these authors reported on their experience with FDG PET for detecting recurrent papillary thyroid cancer (PTC). The authors found that the 14 females and two males in the study had an average age of 47 years, ranging from 22 to 72 years. Median time from initial thyroid surgery was ten years (range: three – 17 years). Three (18%) of 17 FDG PET scans in these patients were reported as suspicious for recurrent PTC in the neck, and these were subsequently confirmed on histopathology. The authors commented that this preliminary report of one institution's experience might contribute to the use of FDG PET in patients with PTC.

Jacene HA, Leboulleux S, Baba S, et al. Assessment of interobserver reproducibility in quantitative FDG PET/CT measurements of tumor response to therapy. J. Nucl. Med. 2009 Nov; 50(11): 1760-9.

This retrospective clinical study compared the reproducibility of SUVs and CT size measurements, and changes in those measurements, in breast and lung cancers before and after therapy. A list of patients with both pre- and an early post-treatment FDG PET scans were retrospectively compiled from April 2003 to April 2005. Patients underwent FDG PET scans after a standardized fasting period and check that blood glucose was less than 200 mg/dL. Oral (not intravenous) contrast was administered for the CT portion of the study. After an approximately 60 minute uptake period, scanning was performed on the same type of integrated PET/CT scanner for all patients with standard scan parameters. Maximum SUVs and CT size measurements were determined for each selected tumor (based on the pre-treatment images) independently on pre- and post-treatment scans by eight different readers (four for PET, four for CT). Percentage changes between pre- and post-treatment scans, interobserver reproducibility by intraclass correlation coefficients (ICCs) and estimates of variance were calculated. PET images were reviewed on a single type of workstation, and PET, CT, and fused PET/CT images were reviewed on a single split screen. Readers were asked to identify the SUVmax on each tumor from both pre- and post-treatment scans using the SUV tools on the workstation. CT images were reviewed using CT image software from a single

manufacturer to measure the long and perpendicular axis of each tumor. Tumor volume was based on the product of these two measurements. Response assessments were based on criteria used in RECIST and WHO clinical trials. Results of measurements from at least three readers were required to include a case in the statistical analysis.

The authors found that 25 patients, six men and 19 women, had a mean age of 51 years. 16 had primary breast cancer, nine had primary lung cancer. Treatment modalities between the pre- and post-treatment PET/CT scans included chemotherapy (n = 21), hormonal therapy alone (n = 1) and chemotherapy with either hormonal, biologic, or radiotherapy (n = 3). 52 tumors (up to three per patient) were identified for review. The median tumor size was 22 mm (range 10-58 mm) by 15 mm (range 7-41 mm). The mean time between pre-treatment and post-treatment FDG PET/CT scans was 52 days (range: 8-175 days). Factors known to affect SUV such as serum glucose, body weight, injected dose activity, and FDG uptake time, were not significantly different among the patients. On average, SUVmax was significantly higher on the pre- than on the post-treatment scans (9.6 +/- 6.3 vs. 4.6 +/- 4.0, $p < 0.001$). The average 2-dimensional CT tumor size was also significantly higher on the pre - than on the post-treatment scans (541.8 +/- 607.8 sq. mm. pre- vs. 410.7 +/- 637.3 sq. mm. post-treatment, $p < 0.009$). The average percent decline in SUVmax was 45% +/- 35%, which exceeded the 1- and 2-dimensional declines in CT size (20% +/- 33%, $p < .001$ and 24% +/- 56%, $p = 0.003$). There was a very high degree of reproducibility for percentage decline in SUVmax among the four PET readers, with an estimated variance (ICC) or 0.94 (95% CI, .90 - .96; precision +/- 3%). The CV was also lower for SUVmax than for CT 1- and 2- dimensional measurements of tumor size, in both pre- and post-treatment studies. Reproducibility was found to be greater for larger tumors or those with higher SUVmax measurements. The authors concluded that the reproducibility in assessing FDG PET SUVmax values was greater than in assessing CT 1- or 2-dimensional extent, for pre- and post-treatment FDG PET/CT scans.

The authors commented that some readers may have had difficulty with measurement of tumor characteristics if multiple tumors were in close proximity, and that at least one reader measured a different tumor lesion than the other three. The authors concluded that percentage change in SUVmax is a highly reproducible measurement of tumor response pre- and post- cancer treatment, especially in comparison to estimates of percentage change in tumor volume based on 2-dimensional measurements of CT images. They also suggested that automated tools for image analysis might improve interobserver reproducibility.

Jadvar H, Quan V, Henderson RW and Conti PS. [F-18]-Fluorodeoxyglucose PET and PET/CT in diagnostic imaging evaluation of locally recurrent and metastatic bladder transitional cell carcinoma. Int J Clin Oncol. 2008 Feb; 13(1): 42-7.

In this retrospective cohort study of patients with treated urinary bladder cancer, the authors assessed the diagnostic utility of FDG PET or FDG PET/CT in the evaluation of recurrent and metastatic disease. Thirty-five patients with histologically confirmed transitional cell carcinoma of the bladder were referred to the authors' FDG PET imaging center during a six year period from 2000 – 2006. Prior treatment included cystectomy with urinary diversion in all patients, with subsequent chemotherapy in 13 patients, chemoradiation therapy in eleven patients, and no additional therapy in eleven patients. Diagnostic validation was by biopsy in one patient and by clinical and radiological follow-up for up to five years in the remaining patients. Diabetes mellitus was not present in any patient. Investigators followed a standard routine for patient preparation and FDG injection; all patients had plasma glucose levels below 120 mg/dL. The study included 25 men and ten women, with an age range of 39 -86 years. Both FDG PET and CT studies were true positive in 19 patients and true negative in twelve patients, while in four patients, FDG PET and CT results were discordant. The clinical management of 6/35 patients (17%) was changed due to FDG PET and CT combined results. The authors commented that "(w)hether such a change in short-term clinical management resulted in a long-term benefit in a cost-effective manner could not be addressed by our study." The authors also commented on the need for prospective studies in larger patient cohorts to clarify

the exact role of FDG PET in clinical decision-making and in affecting long-term outcomes.

Na SJ, Yoo IR, O JH, et al. Diagnostic accuracy of FDG PET/CT in DTC patients with elevated Tg and negative WBI: evaluation by Tg level. Ann Nucl Med. 2012; 26: 26-34.

The authors assessed the diagnostic accuracy of FDG PET, based on a retrospective review of FDG PET/CT images of patients with histologically proven, previously treated DTC with either elevated Tg levels or anti-Tg antibodies and with negative WBI scans. Studies were guided by institutional patient preparation and scanning protocols and interpreted by two experienced nuclear medicine physicians independently. FDG PET was considered positive based on visual interpretation, although SUVmax values were recorded. Recurrence was indicated by histopathology, persistent imaging abnormalities on US, CT, MRI, or abnormal follow-up Tg levels or anti-Tg levels. Performance characteristics were calculated at several different Tg levels. The authors found that 68 FDG PET images were available for review from 60 patients, 41 women and 19 men, with mean age 49 years, ranging from 26-75 years. All patients had undergone total thyroidectomy and high-dose radioiodine ^{131}I ablation. In 65 of 68 instances, Tg levels exceeded 2.0 ng/mL, ranging from 2.04 to 1015.65 ng/mL. Overall association of FDG PET results and evidence of recurrence or metastasis is shown in the following table.

Table (adapted from Na 2012, Table 3)

	Recurrence or metastasis by other tests		
FDG PET imaging	**Positive**	**Negative**	**Total**
Positive	43	2	45
Negative	19	4	23
Total	62	6	68

The authors also calculated the specificity of FDG PET based on Tg levels, and found generally that sensitivity increased with higher Tg levels, going from 29% at Tg levels of 2-5 ng/mL, to 86% at Tg levels of 20 ng/mL or more. They suggested that FDG PET was most helpful for detecting recurrent DTC at Tg levels of 5 ng/mL or more. They noted that future studies might examine the potentially complementary roles of ultrasound (US) and FDG PET for detecting recurrences. The authors also commented that the potential for elevated Tg levels due to other causes detracts from their use in detecting recurrence.

Ozkan E, Soydal C, Kucuk ON, et al. Impact of ^{18}F-FDG PET/CT for detecting recurrence of medullary thyroid carcinoma. Nucl. Med. Commun. 2011; 32: 1162-8.

In this retrospective study of 33 patients with elevated calcitonin levels, undergoing FDG PET/C for restaging of disease after total or near-total thyroidectomy, the authors studied the its value in detecting recurrent MTC. Scans were performed following a study-specific protocol, and images were interpreted by two experienced nuclear medicine physicians. True positive FDG PET/CT findings of recurrence were histologically confirmed by fine-needle aspiration or on re-operation. The authors found that all patients had elevated calcitonin levels. Among 33 patients, nine were men and 24 were women. The mean age of all patients was 50.3 years of age. The authors calculated sensitivity and specificity of FDG PET testing for recurrence as 93% and 68%, respectively. For the subgroup of patients with calcitonin levels of 150 pg/mL or greater, the sensitivity and specificity of FDG PET were 90% and 71%, respectively. The authors noted that recurrent disease of only a millimeter in size would probably not be detected by FDG PET, and suggested that additional studies would be valuable.

Park J-Y, Kim EN, Kim D-Y, et al. Role of PET or PET/CT in the post-therapy surveillance of uterine sarcoma. Gynecol Oncol. 2008; 109: 255-62.

This retrospective study of 36 patients with treated uterine sarcoma who underwent FDG PET or FDG PET/CT in post-therapy surveillance was conducted in order to evaluate the clinical accuracy and impact of these diagnostic studies. The authors studied medical records, histopathologic and diagnostic imaging studies and follow-up of 36 women with histologically proven uterine sarcoma and with surgical therapy with or without adjuvant therapy between August 1999 and November 2006 at one medical center. Studies were done following a standard protocol for patient preparation, with scanning from the skull base to the upper thighs. All FDG PET or PET/CT images were interpreted by a single experienced nuclear medicine physician who was aware of the patient's clinical history and prior imaging results. Sites of increased uptake that could not be interpreted as physiologic uptake (e.g., the brain and urinary bladder) or due to known benign processes were considered malignant; sites whose significance was unclear were considered equivocal. Histopathology or clinical follow-up information after at least six months was used as reference standards.

The median age of the 36 patients was 48 years of age, ranging from 30 – 61 years. Histologically, the uterine sarcomas included low and high grade endometrial stromal sarcomas, leiomyosarcomas, and malignant mixed müllerian tumors. Tumor staging included: 23/36 patients were FIGO stage I; 2/36 were FIGO stage II; 9/36 were FIGO stage III; 2/36 were FIGO stage IV. As part of post-therapy surveillance, thirty scans (8 PET, 22 PET/CT) were performed due to suspected disease recurrence; 18 scans (4 PET and 14 PET/CT) were performed in asymptomatic patients. Twenty-seven of 36 patients underwent one scan each; seven underwent two scans; and two other patients underwent three and four scans. Median time after initial therapy to FDG PET or PET/CT scan was eleven months (range, 1-60 months) and median follow-up time was twelve months (range, 6-58 months). The authors calculated that, for all patients:

Performance Index	Percent (%)
Sensitivity	91
Specificity	96
	93

Performance Index	Percent (%)
Negative predictive value	
Positive predictive value	95
Accuracy	94

Among asymptomatic patients, the authors calculated that:

Performance Index	Percent (%)
Sensitivity	87.5
Specificity	95.5
Accuracy	93.3
Positive predictive value	87.5
Negative predictive value	95.5

Among patients with suspected disease recurrence, the authors calculated that:

Performance Index	Percent (%)
Sensitivity	92.9
Specificity	100
Accuracy	94.4
Positive predictive value	100
Negative predictive value	80

The authors found that these results altered patient management in twelve of 36 (33%) patients; previously unplanned treatment was started in eight patients, and four patients avoided a planned treatment. FDG PET or FDG PET/CT also contributed to surgical planning by confirming isolated recurrences. The authors concluded that FDG PET or FDG PET/CT is a sensitive post-therapy surveillance modality with impact on patient management.

Rakheja R, Makis W, Skamene S, et al. Correlating metabolic activity on FDG PET/CT with histopathologic characteristics of osseous and soft-tissue sarcomas: a retrospective review of 136 patients. Am J Roentgenol. 2012; 198: 1409-16.

In a consecutive case series, identified retrospectively at one institution, the authors evaluated the relationship of SUVmax from FDG PET/CT images of recurrent soft-tissue or osseous sarcoma with histologic features from final pathology reports. During a specific four-year period, a list of patients was compiled from imaging databases, and then was used to search for corresponding pathology reports on tumor specimens. FDG PET/CT studies were guided by institution-specific protocols. FDG PET/CT images, and especially determinations of SUVmax, were reviewed by multiple physicians. Tumor histopathology reports use international standard definitions for histologic features, tumor grading, and classification. The issuing pathologists were unaware of the FDG PET/CT information. The authors found histopathology reports on resected or biopsied tumors from 136 patients imaged during the study time period. The 136 patients ranged in age from 15 to 90 years of age, with a median age of 50 years. Of the 136 sarcomas found in the study group, there were 122 soft-tissue sarcomas of various types. The authors used the Kruskal-Wallis non-parametric test and found that there was a statistically significant relationship ($p < 0.0001$) between histologic grade (of all 136 tumors) and median SUVmax:

Tumor Grade	Median SUVmax	Frequency
1	3.0	16
2	5.2	20
3	10.0	100

The authors also found a significant correlation between SUVmax and mitotic count, and between SUVmax and the presence of tumor necrosis. The authors suggested that biopsies should be guided to areas of highest SUVmax to sample the most aggressive areas within a tumor.

Razfar A, Branstetter IV BF, Christopoulos A, et al. Clinical usefulness of PET/CT in recurrent thyroid carcinoma. Arch Otolaryngol Head Neck Surg. 2010 Feb; 136(2): 120-5.

Based on a retrospective case series of patients with histologic evidence of differentiated thyroid carcinoma (DTC, limited to the histologic subtypes of papillary, follicular, or Hürthle cell) who had subsequently been treated with surgical resection and ^{131}I radioiodine ablation, the authors studied the performance characteristics of FDG PET-CT in identifying recurrent thyroid cancer and in contributing to the clinical management of this disease. FDG PET/CT studies were performed using a study-specific patient preparation and scanning protocol. In addition to FDG PET/CT, other imaging modalities included ultrasound (S), whole-body ^{131}I imaging (WBI), CT, or MRI. A positive finding was determined by FDG PET/CT evidence of malignant neoplasm, confirmed either by surgical pathology or by clinical progression. Clinical progression was defined as persistently elevated thyroglobulin (Tg) levels, a rise in Tg level, or progression of disease on serial imaging. Negative findings were clinically benign FDG PET/CT images in combination with negative surgical pathology findings, undetectable Tg levels, or absence of positive findings in serial images. Images were interpreted by one of two experienced head and neck radiologists. Visual interpretations, not SUV criteria, were used to define malignancy. The authors found that patients with treated DTC included 46 men and 76 women, and that their average age was 45 years, ranging from 5 to 85 years. Mean time to follow-up from initial FDG PET/CT was 37 months (range: 1-88 months). The authors calculated the performance characteristics of PET/CT for recurrent (residual) DTC on 124 follow-up FDG PET/CT scans as:

Performance Index	Percent (%)
Sensitivity	80.7
Specificity	88.9

Performance Index	Percent (%)
Positive predictive value	94.7
Negative predictive value	65.3

The authors also found that FDG PET/CT results affected clinical management, being decisive in 35/124 patients. Twenty-three of these 35 patients had negative WBI results, and an additional five had negative WBI and US results. Among eight patients with positive WBI results, FDG PET/CT identified distant metastases in five patients that had not been detected on WBI. Negative FDG PET/CT findings prevented unnecessary surgery in three patients with indeterminate or suspicious nodules on US. The authors concluded that FDG PET/CT for detection of recurrent DTC could provide clinical benefit with high diagnostic accuracy in detecting local, regional and distant metastases. However, they recommended that given the well-documented used of Tg levels to monitor for recurrence in treated DTC, FDG PET/CT be reserved for patients whose Tg levels are 10.0 ng/mL or higher, or for those whose Tg levels are rising. The authors acknowledged that a lack of prospective data collection was a limitation of the evidentiary value of their study, and suggested that additional prospective studies would be valuable.

Sharma P, Kumar R, Singh H, et al. Role of FDG PET-CT in detecting recurrence in patients with uterine sarcomas: comparison with conventional imaging. Nucl Med Comm. 2012; 33: 185-90.

In this retrospective study of twelve patients with histologically confirmed uterine sarcomas treated surgically with or without adjuvant therapy (chemotherapy, radiotherapy, or both), the authors' goal was to evaluate the role of FDG PET/CT either for recurrence or for post-therapy surveillance. Patients underwent a study-specific imaging protocol. The reference comparison standards for comparison were clinical or imaging follow-up with and histopathology (when available). Scans were examined by two experienced nuclear medicine physicians, who were unaware of any other imaging or clinical information. The performance characteristics of a diagnostic test were calculated with the 95% confidence interval. The authors found that the twelve patients' median age was 51.5 years, with an interquartile range of 47.5 – 57.3 years. Fifteen FDG PET/CT studies for suspected recurrence or routine surveillance were available on these twelve patients. The performance indices of FDG PET/CT for detecting recurrent disease (on a per-scan basis) were calculated and presented as a table:

Performance Index	PET-CT (95% CI)	Conventional Imaging
Sensitivity	86% (42-98%)	57% (19-89%)
Specificity	100% (69-100%)	88% (44-98%)

Performance Index	PET-CT (95% CI)	Conventional Imaging
Accuracy	93%	73%
Positive predictive value	100% (54-100%)	80% (29-97%)
Negative predictive value	89% (52-98%)	70% (35-93%)

In one patient, PET-CT was falsely negative for a lung metastasis, and in one study PET-CT was falsely negative for local recurrence. However, the authors concluded that there was no statistically significant advantage to PET-CT studies over conventional imaging for detecting recurrence or for routine surveillance. The authors also acknowledge that the sample size was small, perhaps a reflection of recruitment of a relatively uncommon type of tumor from a single medical center. They suggested that further research might be of value.

Skoura E, Rondogianni P, Alevizaki M, et al. Role of [^{18}F] FDG –PET/CT in the detection of occult recurrent medullary thyroid cancer. Nucl Med Commun. 2010; 31: 567-575.

In this retrospective case series of patients with histologically proven medullary thyroid carcinoma (MTC) and elevated calcitonin levels, the authors assessed the diagnostic accuracy of FDG PET/CT for detection of recurrent or persistent disease after thyroidectomy. All patients underwent a study-specific preparation protocol and PET-CT scan. PET-CT images were interpreted by a nuclear medicine physician and a radiologist. True positive findings on images were confirmed by either a) positive histopathology of biopsy; presence at the corresponding site of a detectable lesion by conventional imaging follow-up; or c) increase in lesion size or FDG uptake. False negative images were considered, in view of an elevated calcitonin, any study not showing a clear abnormality. The authors found that for the 32 patients, ten were men and 22 were women. Ages ranged from 21-73 years, with mean age of 52 years. Both hereditary and sporadic types of MTC were present in the study group. Conventional imaging procedures performed on patients in the study group included CT, MRI, ultrasound of the neck, and several types of nuclear medicine scans. True-positive recurrent lesions were mostly in the cervical lymph nodes. The authors calculated that the sensitivity of FDG PET/CT in detecting MTC lesions with either negative or equivocal conventional imaging was 47.4%, with higher sensitivity (about 80%) among patients with calcitonin elevated above 1000 pg/mL. The authors commented that FDG PET/CT was most sensitive in certain circumstances to detect recurrent or metastatic MTC. They suggested that additional research would be of value.

Treglia G, Castaldi P, Villani MF, et al. Comparison of ^{18}F-DOPA, FDG, and ^{68}Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2012; 39: 569-80.

The authors compared the diagnostic value of FDG PET/CT imaging with various radiotracers for detecting recurrence of medullary thyroid carcinoma (MTC) in patients from three medical centers with prior surgery for MTC and evidence of elevated serum calcitonin levels. Inclusion criteria included: availability of other relevant imaging studies; at least two measurements of carcinoembryonic antigen (CEA) per patient; and availability of either at least twelve months of available clinical follow-up, or of cytohistological diagnosis. The authors found that the study group included 18 patients (six men and twelve women), with a mean age of 53.1 years, ranging from 24 to 86 years. Patients had undergone total thyroidectomy with prophylactic central compartment neck dissection 12 – 192 months (median 90 months) before imaging. All imaging studies were conducted based on institutional protocols. PET/CT images were reviewed independently by two experienced nuclear medicine physicians who were blinded to the original clinical reports. Cytohistological diagnoses were available on eight of 18 study patients. All clinical information was used to determine the presence of recurrent disease; any negative FDG PET/CT results were considered false-negatives. In comparing the three radiotracers' performance, the authors noted that (adapted from Treglia, p. 573) :

Radiotracer	18F-DOPA	68Ga somatostatin analogue	FDG
Study patients with at least one focus of abnormal uptake	Thirteen of 18	Six of 18	Three of 18
'Sensitivity' (95% CI)	72% (49 – 88%)	33% (16 – 56%)	17% (5 – 40%)

The authors also noted that in eight of 18 patients, results of PET/CT scans led to a change in management. The authors acknowledged the small size of their study as a key limitation. The authors suggested that larger, prospective studies would be valuable to confirm their conclusion that FDG PET/CT was significantly less sensitive for recurrent MTC in patients with elevated calcitonin levels than were other imaging methods, especially ^{18}F-DOPA PET/CT.

Tripathi M, Sharma R, Varshney R, et al. Comparison of FDG and 11C methionine PET/CT for the evaluation of recurrent primary brain tumors. Clin Nucl Med. 2012; 37: 158-63.

Based on a series of patients with a history of treated primary brain tumors referred for evaluation of recurrence, these authors directly compared FDG and ^{11}C methionine PET/CT. Images were collected following a study-specific patient preparation protocol, and images were interpreted independently by two PET physicians. Image results were compared with either histopathology or with clinical follow-up and MRI, which served as reference standards as available. The authors found that the patients included 23 males and twelve females, ranging in age from 5 – 65 years with a mean of 34 years. The timing of PET images after primary tumor diagnosis was 20 months on average, ranging from six to 84 months. Interobserver agreement among interpreters was rated as good for MET (kappa 0.93); whereas for FDG, the authors considered it only fair (kappa 0.23). Findings on MET PET/CT were not significantly different from the reference standard, whereas FDG PET/CT results were

significantly different from MET PET/CT results. The authors found that MET PET/CT was more reliable than FDG PET/CT in detecting tumor recurrence, irrespective of tumor grade. The authors concluded that MET PET/CT is more useful in primary brain tumors when MRI is inconclusive. The authors noted that follow-up in this study was relatively short, i.e., for a period of about 18 months.

Yao M, Smith RB, Graham MM, et al. The role of RDG PET in management of neck metastasis from head-and-neck cancer after definitive radiation treatment. Int J Radiat Oncol Biol Phys. 2005; 63(4): 991-9.

In this retrospective single-center study, the authors measured the long-term outcomes of patients managed with post-treatment CT and FDG PET imaging results determining the need for neck dissection. The authors found that, of the 53 assessable patients (42 men and ten women, with median age of 55.5 years (range, 35-77 years)), mean time to FDG PET after completion of treatment was 15 weeks (range, 5-29 weeks). Based on an ROC curve analysis, the cutoff for post-treatment SUV was chosen as 2.9. A summary table below shows the relation of post-treatment FDG PET results (positive or negative, using 2.9 as the cutoff value for SUV, in 70 FDG PET scans following radiation treatment) and persistent/recurrent disease:

Table adapted from Table 2, Yao 2005:

	Persistent/Recurrent Disease:	
Post-RT FDG PET Results:	**Negative FDG PET Scans**	**Positive FDG PET Scans**
Negative	63	0
Positive	4	3

At a median followup of 26 months, no regional failure was identified. The authors concluded that for patients with no evidence of residual lymphadenopathy and a negative FDG PET results twelve weeks after definitive radiation, neck dissection can be safely withheld. If small residual lymphadenopathy is present but the FDG PET result is negative, withholding neck dissection was not associated with local failure. The authors suggested the need for larger prospective studies to determine if, in patients with large residual lymphadenopathy (greater than 2-3 cm in size) but a negative FDG PET result post-treatment, neck dissection can appropriately be withheld.

Case series or case reports:

Choi H, Charnsangavej C, Faria SC, et al. Correlation of CT and PET in patients with metastatic GIST treated at a single institution with imatinib mesylate: proposal of new CT response criteria. J Clin Oncol. 2007 May 1; 25(13): 1753-9.

The purpose of this study was both to determine whether CT changes in advanced gastrointestinal stromal tumors (GIST) from before to after imatinib treatment could be correlated with changes on FDG PET, and to find out if CT criteria (based on tumor size)could be used to evaluate tumor response. 44 patients had both CT and FDG PET within one week of each other before treatment and two months after treatment. Of these 44, four were excluded due to lack of measurable lesions. Among the remaining patients, there were 19 males and 21 females, ranging in age from 28 to 86 years. Lesions less than 1.5 cm in size at baseline were not included for analysis. The authors found that from before treatment to two months after treatment, 33/40 patients with good responses on FDG PET studies (that is, a decrease in SUVmax to below 2.5) showed an average decrease in tumor size of 26%, while those 7/40 with poor responses showed a size increase of 10%. In those with good responses by FDG PET, tumor density decreased by 15% or more in 27/33 (82%) of patients. In those with poor responses by FDG PET, 7/40 patients showed no tumor size or density decrease. The authors commented that with these criteria for 'good' and 'poor' response to treatment for GIST, FDG PET was useful to demonstrate treatment response to imatinib even in cases in which CT measurements did not show changes in tumor volume or density.

4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

The American College of Radiology provides guidelines for imaging for specific clinical situations, (for example, Lee 2010 regarding imaging for patients with uterine (endometrial) cancer with suspected recurrence after therapy). This guideline rates FDG PET/CT 'highly appropriate' in this situation but notes the relatively high radiation level involved.

However, a note in the Lee 2010 guideline explains that the guideline was developed by consensus (modified Delphi method). The guideline also notes that, for FDG PET/CT, "The role of positron emission tomography (PET) in endometrial cancer imaging is still under investigation."

A number of evidence based recommendations for use of FDG PET in therapeutic clinical trials have been proposed (for example, Scher 2004) but were not further reviewed for this coverage determination about FDG PET use in subsequent treatment strategy planning (following completion of initial therapy) in non-research settings.

6. Professional Society Position Statements

Several professional societies commented on the proposed decision determination and can be read in their entirety under the Public Comments section below.

7. Expert Opinion

CMS did not solicit any expert opinions on ending the prospective data collection requirements under CED for specific oncologic indications. Several public comments expressed the views of experienced oncologists, radiologists and nuclear medicine physicians on the use of FDG PET for subsequent treatment strategy planning.

8. Public Comments

Initial Comment Period: September 12, 2012 through October 12, 2012

CMS received 82 public comments during the first public comment period. Of those, 77 supported the request to end CED for all oncologic indications for FDG. Comments were received from medical and surgical oncologists, nuclear medicine physicians, general radiologists, other physicians, FDG PET facilities, industry associations and other sources. Any articles submitted with these public comments were not unique to those submitted by the requestor or identified by CMS during its literature review.

Second Comment Period: March 13, 2013 through April 14, 2013

CMS received 201 timely public comments during this period. Comments were received from beneficiaries, university and private cancer centers, nuclear medicine physicians, medical and surgical oncologists, professional societies, PET facilities, industry associations and others. CMS thanks those commenters that submitted references relevant to this review to assist in our decision making process. Twelve comments were not relevant to this topic.

Comment:

None of the commenters expressed opposition to ending the data collection requirements under CED for all oncologic indications for FDG PET.

Response:

CMS appreciates the support expressed in these comments.

Comment: CMS received 175 comments opposing the proposed one scan limitation of covered FDG PET scans used to guide subsequent physician management of anti-tumor treatment strategy after completion of initial anti-tumor treatment strategy. Some commenters recognized that we had also proposed that coverage of additional scans beyond one would be determined by the local Medicare Administrative Contractors (MACs.) Various commenters including the requestor noted that 3 scans was a typical number for patients undergoing second or third line anticancer treatment.

Response:

CMS appreciates these comments and will nationally cover at least three additional scans. Coverage of additional scans (that is, more than three) shall be determined by the local MACs.

Comment:

CMS received 23 comments in favor of covering FDG PET scans for the subsequent anti-tumor treatment strategy of prostate cancer. Commenters cited evidence that advanced hormone refractory prostate cancer demonstrates avidity for FDG, in contrast to the lack of FDG avidity in earlier prostate cancer. CMS also received seven comments from those requesting that CMS non-cover FDG PET for subsequent anti-tumor treatment strategy for prostate cancer.

Response:

CMS reviewed additional evidence and will nationally cover FDG PET for subsequent anti-tumor treatment strategy of prostate cancer. This is further discussed in the Analysis section below.

Comment:

Several commenters believed that certain language in the proposed decision memorandum was unclear with respect to the scope of the analysis and the proposed manualization of PET coverage.

Response:

CMS has revised this language such that the scope of this analysis includes all oncologic uses of FDG PET, not just those that are currently covered under CED.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A) of the Act. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment.

We are mindful of our past considerations of this topic, and in particular our April 2009 reconsideration, which included a review of CED derived evidence. In that decision we wrote in part "… the publication of results derived from NOPR and the advances in the current evidence base, which consistently note the physicians' use of FDG PET imaging results to guide management for several cancer indications, we believe that we have sufficient evidence to support broader FDG PET coverage for use in solid tumors in the context of initial treatment strategy..."

CMS' approach to this analysis is consistent with that expressed in 2009 (emphasis in bold by CMS):

"Ideally (from the standpoint of coverage decision-making), evidence about the clinical effect of any additional FDG PET scan for initial treatment planning would show benefits in healthcare outcomes compared to similar patients in whom any additional FDG PET scan for initial treatment planning was not performed. However, as noted in the Facey et al., 2007 evidence review (CMS note (2013): cited in bibliography as Facey 2007), such findings about improved healthcare outcomes are limited. … (P)ublished evidence from clinical studies about the benefit of any additional FDG PET scan … demonstrating changes in RT management or, less often, on studies demonstrating changes in treatment strategy (from intended cure to palliation) due to detection of distant metastases, undetected at the time of initial staging studies. In the future, we hope that additional clinical studies would focus on indicators of outcomes such as better local tumor control and longer patient survival. (Source: Section VIII, CMS reconsideration of FDG PET in initial ATS planning, Medicare National Coverage Database document CAG-00181R3 (2009). Emphasis in bold font added by CMS, 2013.)"

The Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of any additional FDG PET scan for treatment planning after completion of initial therapy, i.e. for the guidance of subsequent anti-tumor treatment strategy.

We considered the evidence in the efficacy framework of Fryback and Thornbury (1991) ('FT') where FT Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; FT Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; FT Level 4 concerns the effect on the patient management plan and FT Level 5 measures the effect of the diagnostic information on patient outcomes. We believe that evidence of improved health outcomes, such as treatment options offering prolonged survival, and diagnostic evidence supporting changes in therapeutic management, is more persuasive than evidence of test characteristics.

In evaluating diagnostic tests, Mol and colleagues (2003) reported: "Whether or not patients are better off from undergoing a diagnostic test will depend on how test information is used to guide subsequent decisions on starting, stopping, or modifying treatment. Consequently, the practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes." When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

While survival may be the most obvious outcome in cancer, we recognize that individual patients may follow better or worse paths even if both paths ultimately end in death. Cancer and its treatments may lead to significantly disabling symptoms such as pain, weakness, neuropathy, vomiting and infection to name only a few.

We also note that patients may not respond successfully to initial antitumor strategy for a number of reasons, e.g. ineffectiveness of the treatment, intolerability of the treatment, and that specific reasons may vary among patients. Thus, patients who are considered for subsequent anti-tumor treatment have already been unsuccessfully treated. This history may weigh heavily on the choices among available treatments.

As illustrated in the evidence section of this DM, many studies were considered during our review of this topic area. These studies included not only those of cancer types covered as CED under previous NCDs, but also other types of solid tumors. We used not only the studies of Hillner and colleagues in the National Oncologic Pet Registry (NOPR), but also evidentiary findings of published articles about clinical studies of FDG PET/CT as a diagnostic method, a number of which have been contributed by public commenters. Although we particularly looked for evidence at FT level 5 to more directly tie FDG PET to improvements in patient health outcomes, we also looked for evidence on the impact of FDG PET on the treating physician's management of patients.

NOPR Findings

In general, evidence derived from NOPR data indicate that FDG PET result changes physician's self-reported management, with reported means of approximately 35-40 percent. As discussed elsewhere, the NOPR methodology has a number of strengths: for example, the numbers of patients included in the NOPR-derived studies are larger by orders of magnitude than the numbers in other clinical studies, and reflect a large variety of healthcare settings in many areas of the U.S. However, methodological limitations include: the sources of NOPR's findings are self-reported, uncontrolled physician assessments of intended management; NOPR findings were generally based on pre- and post-imaging interpretation at the same imaging facility; there were admitted definitional problems for certain key outcomes (re-staging), and inconsistency with other studies (as recognized in NOPR publications, e.g., Hillner 2011).

Perhaps the primary shortcoming that has been recognized by NOPR's authors is that their findings are limited to FT Level 3: evidence that FDG PET/CT imaging results change the physician's intended patient management (not actual changes in management or outcomes). An early article about NOPR's design and its analysis plan concluded "(t)he NOPR will allow an accurate assessment of the impact of PET on intended patient management across a wide spectrum of cancer indications" (Lindsay 2007). CMS agrees with the comment (Hillner 2011) indicating that "(a) major limitation of the NOPR is the inability to determine whether the intended changes in management confer a benefit in long-term outcomes."

Nevertheless, NOPR-derived results have informed our consideration of the evidence base for covering FDG PET imaging for this oncologic indication. We are also mindful that anticancer treatment largely depends on advanced diagnostic imaging results that influence physician decision making. The practical decisions include for example, whether to pursue primarily curative or palliative strategies, or whether to administer treatments with risk of lethality. In the setting of anticancer treatment we believe that the choices made by treating physicians in many instances change the patient's experience of illness. Therefore we have largely accepted the persuasiveness of the NOPR report, except where we believe there is other evidence available to better support an alternative conclusion. This relationship of reported change in management to patient outcomes may not be apparent in other clinical contexts where the impact or the rationality of physician choice is more ambiguous.

Additional analyses are described below for specific tumor types that had been covered in prior NCDs under CED, with particular attention to evidence derived from non-NOPR data.

Primary brain malignancies

Clinical studies of FDG PET's role in detecting recurrence of primary brain tumors following initial treatment has been described in several articles, including: Enslow 2012; Santra 2012; Tan 2011; Tripathi 2012. However, these studies reflect at best FT Level 2 (as previously discussed).

The Enslow 2012 article compared FDG PET with gadolinium-MRI for differentiating radiation necrosis from recurrent glioma. However, the authors' description of the demographic characteristics of their small (n = 15) case series did not provide sufficient detail to know whether this study is characteristic of the senior Medicare patient population. We also note that a potential interference with FDG PET readings may arise from the high glucose metabolism in cerebral cortex (for example, Enslow 2012). However, a technique to minimize this effect has been suggested: confirmation of a suspected recurrent tumor in one cerebral hemisphere can best be identified by a ratio to contralateral FDG activity in unaffected white matter (Enslow 2012).

CMS did find evidence of FDG PET's contribution to changing patient management. The Enslow 2012 study found that FDG SUVmax could differentiate between recurrent disease and radiation fibrosis. Also, in the Hillner 2011 study, 274 FDG PET scans were performed in participants with primary brain tumors, both for restaging, and for detection / confirmation of suspected recurrences. A larger effect on intended treatment was found in those with primary brain tumors than those in the overall NOPR cohort.

For the above reasons, CMS concludes that the evidence supports the use of FDG PET as reasonable and necessary in the management of recurrent primary brain tumors, and thus is appropriate for Medicare coverage under § 1862(a)(1)(A).

Pancreatic cancers

Clinical studies of FDG PET's role in detecting recurrence of primary pancreatic tumors following initial treatment has been described in several articles, including: Hillner 2012; Kitajima 2010; Sperti 2010; Topkan 2011. Topkan 2011 also studied FDG PET's role in evaluating treatment response. Except for the Hillner 2012 article, these reflect studies of FDG PET/CT diagnostic performance (FT Level 2) in patients with pancreatic cancers.

The Kitajima 2010 article compared performance characteristics of FDG PET with contrast-enhanced CT to FDG PET with unenhanced CT for diagnosing recurrence pancreatic cancer. They found that, using a combination of histopathology findings and radiologic imaging follow-up as the combined gold standard, the sensitivity of FDG PET with contrast-enhanced CT was 83% for recurrence.

The authors of the Hillner 2012 article looked at the impact of FDG PET on intended management in more than 7,000 scans undergone by Medicare beneficiaries of pancreatic cancer, and found that in about 40% of cases physicians reported a likely change in post-PET intended management.

Sperti 2010 found that in 72 treated pancreatic cancer patients with 63 recurrences, FDG PET was positive in 61 patients when CT was non-diagnostic. These authors also found that treatment was changed by FDG PET results in 32 of 72 patients (44%).

For the above reasons, CMS concludes that the evidence supports the use of FDG PET as reasonable and necessary in the management of recurrent pancreatic tumors, and thus is appropriate for Medicare coverage under § 1862(a)(1)(A).

Prostate cancers

As reflected in the proposed decision memorandum (PDM), CMS found little evidence about effects of FDG PET on outcomes for patients whose initial therapy for prostate cancer had been completed. Current literature on PET tracers for recurrence or tumor response seemed to focus mainly on a different radiopharmaceutical, ^{11}C choline.

However, public comments about the PDM indicated that evidence of the value of FDG PET scans was in some cases provided in therapeutic studies and was also available in more recent articles. After review of these important components of the evidence base, CMS agrees that a significant benefit of FDG PET scans is their use to determine effect of treatment, especially at certain types of progressive prostate disease.

As examples of the importance of this, NOPR findings (e.g., Hillner 2012) indicate that in about 40% of instances, physicians would change their intended therapy for patients with prostate cancer. Despite the known concerns about lack of glucose avidity of prostate cancer cells, as mentioned in Hillner 2009other studies indicated that FDG PET CT could be valuable even for assessing activity of bone metastases of prostate cancers in a large majority of patients (Meirelles 2010).

Nevertheless, we are convinced that FDG PET/CT imaging's selective use in assessing progression of prostate cancer does provide valuable additional information for managing treatment decisions, and therefore we consider its use for subsequent treatment strategy planning to be reasonable and necessary. We note that in many of these studies, a rising PSA level was key to the clinical suspicion of progressive or recurrent prostate cancer.

We also agree with the NOPR public comments emphasizing that physicians were found to selectively employ FDG PET for subsequent anticancer treatment planning in appropriate patients. We expect that post-coverage analysis (PCA) review by CMS will confirm this NOPR observation.

Consequently, CMS proposes that use of FDG PET/CT when used to guide subsequent anti-tumor treatment strategy for patients with cancer of the prostate is reasonable and necessary under § 1862(a)(1)(A).

Soft tissue sarcomas

Studies of use of FDG PET/CT for treatment response (to imatinib chemotherapy) in GIST are available (e.g., Choi 2007). Other authors suggest that post-treatment PET imaging provides benefit by identifying distant metastases, in neither circumstance is evidence provided about improvement in beneficiaries' outcomes. Other studies show changes in intended treatment management for more than 28% of participants with soft tissue sarcomas in a NOPR-based study (Hillner 2008B).

Therefore, CMS finds that there is evidence that FDG PET/CT influences physician decision-making in beneficiaries with soft tissue sarcomas after completion of initial anticancer therapy. Under § 1862(a)(1)(A), CMS proposes that use of FDG PET in this context is reasonable and necessary and that its use be covered by the Medicare program.

Testicular cancers

Clinical studies (e.g., Huddart 2007) suggest that in patient with potential for recurrence after orchiectomy, FDG PET/CT imaging was associated with an unacceptably high rate of relapse (33 relapses (38%)) among (87) FDG PET negative nonseminomatous germ cell tumor patients). (Hillner 2012 does not include de-aggregated data about the effect of FDG PET/CT imaging on restaging or suspected recurrence.)

CMS found no evidence regarding the effect of FDG PET on patient outcomes. We note that testicular cancers are lumped with other solid tumors in NOPR-based studies. Nevertheless, we conclude that although additional studies might be valuable, the existing evidence base provides support for the use of FDG PET to guide therapy in beneficiaries with testicular cancer after completion of primary anticancer therapy. Therefore, CMS finds that Medicare coverage is appropriate for this indication under § 1862 (a)(1)(A).

Thyroid cancers

A number of clinical studies have examined the use of FDG PET/CT for detecting recurrence of various types of thyroid cancer, including: Bannas 2012, Choi 2010, Conry 2010, Dahele 208, Giovanella 2012, Na 2012, Ozkan 2011, Ozkan 2012, Razfar 2010, Rubello 2009, Seo 2010, Skoura 2010, and Treglia 2012. (Note: Hillner 2012 presents aggregated counts of all types of thyroid cancer in assessing the possible effects of FDG PET/CT findings on physicians' post-treatment management strategy.) The following table prepared by CMS briefly summarizes the key findings of these studies, and the FT Levels of evidence supported:

Study	Indication	FT Level
Bannas 2012	In a consecutive case series (n = 30), FDG PET showed89% positive predictive value in detecting recurrent DTC.	2
Choi 2010	In 76 patients with papillary thyroid cancer after treatment, FDG PET was less sensitive and specific for detecting recurrence than neck ultrasound; but differences were not statistically significant. Either method of detecting recurrence led to treatment changes in 30 - 40% of patients.	3
Conry 2010	In a series (n = 18) the diagnostic performances of FDG PET/CT and ^{68}Ga-DOTATATE in detecting recurrences of medullary thyroid cancer were compared. Sensitivities of the two methods were not statistically significant.	2
Dahele 2008	In 15 patients with treated papillary thyroid cancer, FDG PET was able to detect regional or distant recurrence in patients with low Tg levels	2

Study	Indication	FT Level
Giovanella 2012	FDG PET/Ct detected recurrent DTC after therapy with a sensitivity of 93% and a specificity of 84%	2
Na 2012	In this retrospective study of differentiated thyroid cancers, the authors found that sensitivity of FDG PET/CT increased with higher Tg levels, going from 29% at Tg levels of 2-5 ng/mL, to 86% at Tg levels of 20 ng/mL or more.	2
Ozkan 2011	In patients with medullary thyroid cancer after treatment, who had elevated calcitonin levels, FDG PET showed sensitivity of 93% and specificity of 68%.	2
Ozkan 2012	FDG PET/CT detected recurrent DTC in patients with anti-Tg levels, with a sensitivity of 74% and a specificity of 75%	2
Razfar 2010	FDG PET/CT was useful for detecting local, regional and distant recurrence of differentiated thyroid cancers, with sensitivity and specificity of 81% and 89%, respectively.	2
Rubello 2009	In 19 patients with recurrent MTC, FDG PET/CT was the most sensitive imaging modality (compared to results of ^{111}In pentetreotide, CT, and US), using cyto- or histopathology findings as the gold standard.	2
Seo 2010	Among patients with anti-Tg, FDG PET showed sensitivity of 76% and specificity of 87% in detecting recurrent differentiated thyroid cancer.	2

Study	Indication	FT Level
Skoura 2010	In patients with treated medullary thyroid cancer and elevated calcitonin levels (10 or more pg/mL), sensitivity of FDG PET/CT was nearly 100% in detecting recurrence if calcitonin was elevated above 1000 pg/mL.	2
Treglia 2012	FDG PET/CT was less sensitive (17%) than other methods, especially F-18 DOPA PET/CT (72%) in detecting recurrence of treated medullary thyroid cancer.	2

Several of the studies above used thyroglobulin (Tg) levels to detect recurrence of thyroid cancer, and noted that either radioactive iodine or FDG PET/CT are available to locate any recurrence(s). However, no studies directly examined the effect of FDG PET/CT imaging on improving outcomes for patients treated for any types of thyroid cancer.

Based on the above findings of diagnostic utility and changes in patient management, CMS finds that the evidence is sufficient to conclude that use of FDG PET imaging to guide subsequent anti-tumor strategy in beneficiaries who have completed initial anticancer therapy for thyroid cancer is reasonable and necessary in the context of § 1862(a)(1)(A).

All other solid malignant tumors

CMS recognizes the futility of attempting to conduct clinical trials covering all types and subtypes of solid malignant tumors. Therefore, we reviewed the findings about 'all other cancers' as tabulated above (Hillner 2012). We conclude that in the many beneficiaries with such tumors, FDG PET was associated with a 33-34% change in intended subsequent patient management.

Accordingly, CMS finds that available evidence supports use of FDG PET to influence physician management of beneficiaries with solid tumors other that those discussed above, and consequently proposes national Medicare coverage as reasonable and necessary in the context of § 1862(a)(1)(A).

In summary, based on evidence from NOPR and other sources that FDG PET imaging changes physician

management, CMS concludes that physicians are able to use the results of this diagnostic test in the treatment of patients with brain, pancreas, prostate, soft tissue sarcoma, small cell (of lung), thyroid, testis, and any other solid cancer. We further conclude that FDG PET is reasonable and necessary to guide anti-tumor strategy in beneficiaries with these various types of cancer after completion of initial anti-tumor therapy, and therefore is appropriate for coverage under § 1862(a)(1)(A). CMS therefore removes the requirement for CED for these tumor types, in response to the current request for reconsideration.

Concerns about FDG PET utilization

In our proposed decision, we discussed a concern that Medicare might inadvertently make payment for 'routine surveillance' with FDG PET (that is, FDG PET imaging of asymptomatic patients without clinical evidence of recurrence after completion of initial anticancer therapy, in whom no active anticancer decision making is occurring). Many public commenters agreed with us on this underlying principle, but questioned when unnecessary 'surveillance' began in the context of actual medical practice and patient care. Thus, in the preliminary decision memo we proposed permitting local Medicare Administrative Contractors to make the determination of medical necessity for additional scans beyond one used in subsequent anti-tumor treatment strategy.

However, based on public comments and additional NOPR data analysis (communicated to CMS by Dr. Hillner) we are now aware that many patients may expect to undergo more than one FDG PET scan during later phases of their medical treatment. CMS recognizes that a patient who has not been successfully treated with initial anti-tumor therapy might be a candidate for 'second line' or even further treatment, and there might be instances where additional FDG PET scans can be appropriately informative, depending on pertinent facts that can be found in the patient's medical documentation. Therefore, in this final decision memo we permit local Medicare Administrative Contractors to determine coverage for additional FDG PET scans beyond three used in subsequent anti-tumor treatment strategy.

This determination will both provide administrative flexibility to enhance patient access to needed medical care, and reduce potential overutilization of FDG PET scans that would not be found to be reasonable and necessary. Published data (Dinan 2010) examined the annual increase in FDG PET scans among Medicare beneficiaries with cancer of all types, and found utilization of FDG PET diagnostic imaging in patients with cancer rose each year from 35.9%-53.6% from 1999 through 2006. We realize that establishing a numerical criterion for nationally covered FDG PET scans subsequent to completion of initial therapy CMS has the potential to inform medical review activity by local Medicare administrative contractors.

Health disparities

A review of articles discussed above in this decision memorandum reveals no analysis of outcome by racial or ethnic categories. Any inference about relative benefits positron emission tomography in specific racial or ethnic groups would be speculative. CMS also notes the absence of evidence about benefits or harms related to other

population classifiers that have been associated historically with healthcare access or outcome disparities, such as gender, sexual orientation, religion, and age, and encourages additional studies in which such associations might be studied.

Results of cancer therapy continue to demonstrate racial/ethnic as well as socio-economic disparities. The authors of ACS 2012 stated that lack of health insurance and other barriers prevents many Americans from receiving optimal health care. This included, according to a US Census Bureau study in 2009, no health insurance coverage for one-third of Hispanics and one in ten children. Uninsured patients and those from ethnic minorities are more likely to be diagnosed with cancer at a later stage. At this point in the disease, treatment must be more extensive to be effective (ACS 2012).

African Americans are more likely to develop and die from cancer than any other racial or ethnic group. African American men have higher incidence and mortality rates than whites for each of the eight most frequent cancer sites (breast, colorectal, kidney, liver and intrahepatic bile duct, lung and bronchus, prostate, stomach, and uterine cervix), except for kidney cancer, for which the rates are the same (ACS 2012).

Persons with lower socioeconomic status (SES) have disproportionately higher death rates that those with higher SES. Lower SES is also associated with lower access to preventive services and to lower literacy rates. Behaviors that increase cancer risk, including tobacco use, lack of physical activity, and poor diet are more likely among those with lower SES. Progress in reducing cancer death rates has been slower in persons with lower SES (ACS 2012).

Genetic and cultural/familial behavioral factors may also drive cancer risk in selected minority groups. As examples: higher risk of breast and ovarian cancer among Ashkenazi Jews is believed to be due to increased frequency of mutations in *BRCA1* and *BRCA2*;and earlier childbearing among Hispanic women is thought to lower breast cancer risk (ACS 2012).

CMS recognizes that recent publications may reflect additional interest in examining disparities in PET use among geographic or sociodemographic population subgroups. A recent retrospective article examined disparities in FDG PET use by Medicare beneficiaries with cancer (Onega 2012). Using CMS files, Medicare claims for beneficiaries with any of five selected cancers (head and neck; lung; esophageal; colorectal; and lymphoma, based on icd-9-cm coding of the claim) were tabulated and examined in relation to a number of economic and demographic factors. Beneficiaries in Medicare advantage plans were excluded, as were beneficiaries less than 65 years old or more than 100 years old. The authors found that in the study population of cancer patients, the median age was 75 years, and 48% of study subjects were female. They found that PET use among beneficiaries with cancer increased from 2004 to 2008. In each of those years, PET use was higher among whites than among blacks. The authors concluded that the growth from 2004 to 2008 was not uniform across health care markets or patient populations.

CMS concludes that there is a need for additional evidence about racial and ethnic factors. In our view this

evidence gap should be considered by trial designers when proposing future clinical trial designs. All other factors being equal, CMS will prefer clinical study proposals in which data on racial and ethnic factors are specifically collected and analyzed.

Summary:

a. *Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully improve health outcomes in beneficiaries who have completed an initial treatment regimen for any of the following types of solid tumors: brain, pancreas, prostate, soft tissue sarcoma, small cell (of lung), thyroid, testis, or for any other solid malignant tumor?*

b. Is the evidence adequate to conclude that the results of an FDG PET scan will guide physician management of subsequent anti-tumor treatment strategy in beneficiaries who have completed an initial treatment regimen for any of the following types of solid tumors: brain, pancreas, prostate, soft tissue sarcoma, small cell (of lung), thyroid, testis, or for any other solid malignant tumor?

We have not found direct evidence that results of FDG PET imaging improve health outcomes, despite references provided by public commenters. Thus we determine that the answer to question a) is "no". However, the answer to question b) is, we believe, "yes".

IX. Conclusion

A. The Centers for Medicare & Medicaid Services (CMS) has determined to end the requirement for coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the "Act') for ^{18}F fluorodeoxyglucose positron emission tomography (FDG PET) for oncologic indications which are contained in section 220.6.17 of the Medicare National Coverage Determinations Manual. This removes the requirement for prospective data collection by the National Oncologic PET Registry (NOPR) for those cancers or cancer types that had been covered under CED (as listed in Appendix A).

B. CMS has determined that three FDG PET scans are covered under § 1862(a)(1)(A) when used to guide subsequent management of anti-tumor treatment strategy after completion of initial anticancer therapy. Coverage of any additional FDG PET scans (that is, beyond three) used to guide subsequent management of anti-tumor treatment strategy after completion of initial anti-tumor therapy will be determined by local Medicare Administrative Contractors.

See Appendix C for NCD manual language.

Appendix A: Summary of Coverage with Evidence Development (CED) Requirements for Oncologic Indications, as of September 2012

[Reference: CAG-00181R (2009), Appendix A.
Note: 'ATS' denotes anti-tumor treatment strategy]

Solid Tumor Type	Initial ATS	Subsequent ATS
Cervix uteri	1 or CED	Cover
Brain	Cover	CED
Pancreas	Cover	CED
Prostate	Non-cover	CED
Small cell lung	Cover	CED
Soft Tissue Sarcoma	Cover	CED
Testes	Cover	CED
Thyroid	Cover	2 or CED
All other solid tumors	Cover	CED
All other cancers not listed (see note below) in Appendix A, CAG-00181R (2009)	CED	CED

(1) Cervix: Nationally non-covered for diagnosis of cervical cancer. Covered for detection of pre-treatment metastases (i.e., staging) in newly diagnosed cervical cancer if prior conventional imaging is negative for extra-pelvic metastases. All other uses are CED.
(2) Thyroid: Covered for subsequent treatment strategy of recurrent or residual thyroid cancer of follicular cell origin previously treated by thyroidectomy and radioiodine ablation and have a serum thyroglobulin >10ng/ml and have a negative I-131 whole body scan. All other uses for subsequent treatment strategy are CED.

Note: Tumors listed in Appendix A, CAG-00181R (2009) for coverage, non-coverage or CED for either initial or subsequent ATS included the following:

Brain; cervix (uteri); colon and rectum; esophagus; head and neck (except thyroid and CNS); myeloma; pancreas; prostate; lymphoma; melanoma; ovary; pancreas; prostate; small-cell and non-small cell cancers of lung; soft tissue sarcoma; and testes.

APPENDIX B
General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of

evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.

Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).

Co-interventions or provision of care apart from the intervention under evaluation (performance bias).

Differential assessment of outcome (detection bias).

Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample

of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed an conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience

and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

220.6.17 - Positron Emission Tomography (FDG PET) for Oncologic Conditions - (Various Effective Dates) (Rev.)

General

FDG(2-[F18] fluoro-2-deoxy-D-glucose) PET is a minimally-invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseased tissues in conditions such as cancer, ischemic heart disease, and some neurologic disorders. FDG is an injected radionuclide (or radiopharmaceutical that emits sub-atomic particles, known as positrons, as it decays. FDG PET uses a positron camera (tomograph) to measure the decay of FDG. The rate of FDG decay provides biochemical information on glucose metabolism in the tissue being studied. As malignancies can cause abnormalities of metabolism and blood flow, FDG PET evaluation may indicate the probable presence or absence of a malignancy based upon observed differences in biologic activity compared to adjacent tissues.

The Centers for Medicare and Medicaid Services (CMS) was asked by the National Oncologic PET Registry (NOPR) to reconsider section 220.6 of the National Coverage Determinations (NCD) Manual to end the prospective data collection requirements under Coverage with Evidence Development (CED) across all oncologic indications of FDG PET imaging. The CMS received public input indicating that the current coverage framework of prospective data collection under CED be ended for all oncologic uses of FDG PET imaging.

1. Framework

Effective for claims with dates of service on and after June 11, 2013, CMS is adopting a coverage framework that ends the prospective data collection requirements by NOPR under CED for all oncologic uses of FDG PET imaging. CMS is making this change for all NCDs that address coverage of FDG PET for oncologic uses addressed in this decision. This decision does not change coverage for any use of PET imaging using radiopharmaceuticals NaF-18 (fluorine-18 labeled sodium fluoride), ammonia N-13, or rubidium-82 (Rb-82).

2. Initial Anti-tumor Treatment Strategy

CMS continues to believe that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate initial anti-tumor treatment strategy for beneficiaries with suspected cancer

and improve health outcomes and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the "Act").

Therefore, CMS continues to nationally cover one FDG PET study for beneficiaries who have cancers that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial anti-tumor treatment strategy:

- To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or
- To determine the optimal anatomic location for an invasive procedure; or
- To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor.

See the table at the end of this section for a synopsis of all nationally covered and non-covered oncologic uses of FDG PE imaging.

Initial Anti-Tumor Treatment Strategy Nationally Covered Indications Effective June 11, 2013

a. CMS continues to nationally cover FDG PET imaging for the initial anti-tumor treatment strategy for male and female breast cancer only when used in staging distant metastasis.

b. CMS continues to nationally cover FDG PET to determine initial anti-tumor treatment strategy for melanoma other than for the evaluation of regional lymph nodes.

c. CMS continues to nationally cover FDG PET imaging for the detection of pre-treatment metastasis (i.e., staging) in newly diagnosed cervical cancers.

Initial Anti-Tumor Treatment Strategy Nationally Non-Covered Indications Effective June 11, 2013

a. CMS continues to nationally non-cover initial anti-tumor treatment strategy in Medicare beneficiaries who have adenocarcinoma of the prostate. CMS continues to nationally non-cover FDG PET imaging for diagnosis of breast cancer and initial staging of axillary nodes.

b. CMS continues to nationally non-cover FDG PET imaging for initial anti-tumor treatment strategy for the evaluation of regional lymph nodes in melanoma.

c. CMS continues to nationally non-cover FDG PET imaging for the diagnosis of cervical cancer related to initial anti-tumor treatment strategy.

3. Subsequent Anti-Tumor Treatment Strategy

Subsequent Anti-Tumor Treatment Strategy Nationally Covered Indications Effective June 11, 2013

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

4. Synopsis of Coverage of PET FDG for Oncologic Conditions Effective June 11, 2013

Effective for claims with dates of service on and after June 11, 2013, the chart below summarizes national FDG PET coverage for oncologic conditions:

FDG PET for Solid Tumors and Myeloma Tumor Type	Initial Treatment Strategy (formerly "diagnosis" & "staging")	Subsequent Treatment Strategy (formerly "restaging" and "monitoring response to treatment")
Colorectal	Cover	Cover
Esophagus	Cover	Cover
Head and Neck (not thyroid or CNS)	Cover	Cover
Lymphoma	Cover	Cover

FDG PET for Solid Tumors and Myeloma Tumor Type	Initial Treatment Strategy (formerly "diagnosis" & "staging")	Subsequent Treatment Strategy (formerly "restaging" and "monitoring response to treatment")
Non-small cell lung	Cover	Cover
Ovary	Cover	Cover
Brain	Cover	Cover
Cervix	Cover with exceptions *	Cover
Small cell lung	Cover	Cover
Soft tissue sarcoma	Cover	Cover
Pancreas	Cover	Cover
Testes	Cover	Cover
Prostate	**Non-cover**	Cover
Thyroid	Cover	Cover

FDG PET for Solid Tumors and Myeloma Tumor Type	Initial Treatment Strategy (formerly "diagnosis" & "staging")	Subsequent Treatment Strategy (formerly "restaging" and "monitoring response to treatment")
Breast (male and female)	Cover with exceptions *	Cover
Melanoma	Cover with exceptions *	Cover
All other solid tumors	Cover	Cover
Myeloma	Cover	Cover
All other cancers not listed	Cover	Cover

*Cervix: Nationally non-covered for the initial diagnosis of cervical cancer related to initial anti-tumor treatment strategy. All other indications for initial anti-tumor treatment strategy for cervical cancer are nationally covered.

*Breast: Nationally non-covered for initial diagnosis and/or staging of axillary lymph nodes. Nationally covered for initial staging of metastatic disease. All other indications for initial anti-tumor treatment strategy for breast cancer are nationally covered.

*Melanoma: Nationally non-covered for initial staging of regional lymph nodes. All other indications for initial anti-tumor treatment strategy for melanoma are nationally covered.

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