

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

Decision Memo

TO: Administrative File: CAG # 000181R1

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SUBJECT: Decision Memorandum for Positron Emission Tomography (FDG) for
Solid Tumors and Myeloma

DATE: April 3, 2009

I. Decision

CMS was asked to reconsider Section 220.6 of the National Coverage Determination (NCD) Manual to end the prospective data collection requirements across all oncologic indications of FDG PET except for monitoring response to treatment. Section 220.6 of the NCD Manual established the requirement for prospective data collection for FDG PET used in the diagnosis, staging, restaging and monitoring response to treatment for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers, as well as for cancer indications not previously specified in Section 220.6 in its entirety.

We received public input indicating that the coverage framework which required cancer-by-cancer consideration of diagnosis, staging, restaging and monitoring response to treatment should be replaced by a more omnibus framework. Thus, we broadened the scope of this review through an announcement on our website and solicited additional public comment on the use of FDG PET imaging for solid tumors so that we could transparently consider this possibility. Therefore, after receiving public comments as required by § 1862(l) of the Social Security Act (the ACT), we are revising Section 220.6 of the Medicare NCD Manual to reflect a new framework for most solid tumor oncologic indications and for myeloma. This decision replaces sections 220.6.2 (FDG PET for lung cancer); 220.6.3 (FDG PET for esophageal cancer); 220.6.4 (FDG PET for colorectal cancer); 220.6.5 (FDG PET for lymphoma); 220.6.6 (FDG PET for melanoma); 220.6.7 (FDG PET for head and neck cancers non-CNS/thyroid); 220.6.10 (FDG PET for breast cancer); 220.6.11 (FDG PET for thyroid cancer); 220.6.12 (FDG PET for soft tissue sarcoma); 220.6.14 (FDG PET for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers), and 220.6.15 (FDG PET for all other cancer indications) of the NCD Manual with a single section that outlines coverage of PET scans for oncologic conditions. Section 220.6, a general section on PET scanning, will be modified as required by this decision. Coverage determinations in Sections 220.6.1 (PET for perfusion of the heart); 220.6.8 (FDG PET for myocardial viability); 220.6.9 (FDG PET for refractory seizures); 220.6.13 (FDG PET for dementia and neurodegenerative diseases), and 220.6.16 (FDG PET for infection and inflammation) describe coverage of PET imaging for non-oncologic conditions and will not be modified.

1. Framework

CMS is adopting a coverage framework that replaces the four-part diagnosis, staging, restaging and monitoring response to treatment categories with a two-part framework that differentiates FDG PET imaging used to inform the initial antitumor treatment strategy from other uses related to guiding subsequent antitumor treatment strategies after the completion of initial treatment. We are making this change for all NCDs that address coverage of FDG PET for the specific oncologic conditions addressed in this decision.

2. Initial Antitumor Treatment Strategy

CMS has determined that the evidence is adequate to determine that the results of FDG PET imaging are useful in

determining the appropriate initial treatment strategy for beneficiaries with suspected solid tumors and myeloma and improve health outcomes and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore, CMS will cover only one FDG PET study for beneficiaries who have solid tumors 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 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.

As exceptions to the initial treatment strategy section above:

a. CMS has reviewed evidence on the use of FDG PET imaging to determine initial antitumor treatment in patients with adenocarcinoma of the prostate. CMS has determined that the available evidence does not demonstrate that FDG PET imaging improves physician decision making in the determination of initial anti-tumor treatment strategy in Medicare beneficiaries who have adenocarcinoma of the prostate, does not improve health outcomes and is thus not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore, FDG PET is nationally noncovered for this indication of this tumor type.

b. CMS received no new evidence demonstrating a change was warranted with respect to the use of FDG PET imaging to determine initial antitumor treatment in breast cancer; thus CMS is not making any change to the current coverage policy for FDG PET in breast cancer. We continue to cover FDG PET imaging for the initial treatment strategy for male and female breast cancer only when used in staging distant metastasis. FDG PET imaging for diagnosis and initial staging of axillary nodes will remain noncovered.

c. CMS received no new evidence demonstrating a change was warranted with respect to use of FDG PET imaging of regional lymph nodes in melanoma; thus we are not changing the current NCD for FDG PET in melanoma. CMS will continue noncoverage of FDG PET for the evaluation of regional lymph nodes in melanoma. Other uses to determine initial treatment strategy remain covered.

d. CMS received no new evidence demonstrating a change was warranted with respect to use of FDG PET imaging in the initial treatment strategy for cervical cancer. We continue to cover FDG PET imaging as an adjunct test for the detection of pre-treatment metastasis (i.e., staging) in newly diagnosed cervical cancers following conventional imaging that is negative for extra-pelvic metastasis. All other uses of FDG PET for the initial treatment strategy for beneficiaries diagnosed with cervical cancer will continue to only be covered as research under §1862(a)(1)(E) of the Act through Coverage with Evidence Development (CED) as outlined immediately below and in Section 3. Therefore, we will cover one initial FDG PET study for newly diagnosed cervical cancer when not used as an adjunct test for the detection of pre-treatment metastases following conventional imaging that is negative for extra-pelvic metastasis only when the beneficiary's treating physician determines that the FDG PET study is needed to inform the initial antitumor treatment strategy and the beneficiary is enrolled in, and the FDG PET provider is participating in, the following type of prospective clinical study:

- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The clinical studies for which we will provide coverage must answer one or more of the following questions: Prospectively, in Medicare beneficiaries with newly diagnosed cervical cancer who have not been found following conventional imaging to be negative for extra-pelvic metastases and whose treating physician determines that the FDG PET study is needed to inform the initial antitumor treatment strategy, does the addition of FDG PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

The study must adhere to the standards of scientific integrity and relevance to the Medicare population as described in part 3, items a through m, below

3. Subsequent Antitumor Treatment Strategy

CMS reviewed evidence on the use of FDG PET in the subsequent treatment strategy for patients with tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung and thyroid.

For tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid, CMS has determined that the available evidence is not adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent anti-tumor treatment strategy or improves health outcomes in Medicare beneficiaries and thus is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

However, CMS has determined that the available evidence is sufficient to determine that FDG PET imaging for subsequent anti-tumor treatment strategy for tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid may be covered as research under §1862(a)(1)(E) of the Act through Coverage with Evidence Development (CED).

Therefore, we will cover a subsequent FDG PET study for tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung and thyroid when the beneficiary's treating physician determines that the FDG PET study is needed to inform the subsequent antitumor treatment strategy and the beneficiary is enrolled in, and the FDG PET provider is participating in, the following type of prospective clinical study:

- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the FDG PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy and other Federal laws must be followed.

The clinical studies for which it will provide coverage must answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the FDG PET study is needed to inform the subsequent antitumor treatment strategy, does the addition of FDG PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
- g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.

- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

As exceptions to the subsequent treatment strategy section above:

a. CMS has reviewed evidence on the use of FDG PET imaging to determine subsequent treatment strategy in patients with ovarian cancer. CMS has determined that the available evidence is adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent treatment strategy in Medicare beneficiaries who have ovarian cancer, improves health outcomes and is thus reasonable and necessary under §1862(a)(1)(A) of the Act. Therefore, CMS has determined that FDG PET imaging is nationally covered for this indication for this tumor type.

b. CMS has reviewed evidence on the use of FDG PET imaging to determine subsequent treatment strategy in patients with cervical cancer. CMS has determined that the available evidence is adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent treatment strategy in Medicare beneficiaries who have cervical cancer, improves health outcomes and is thus reasonable and necessary under §1862(a)(1)(A) of the Act. Therefore, CMS has determined that FDG PET imaging is nationally covered for this indication for this tumor type.

4. Myeloma

CMS reviewed evidence on the use of FDG PET in the initial and subsequent treatment strategy for myeloma. CMS has determined that the available evidence is sufficient to determine that FDG PET imaging improves physician decision making for these uses in Medicare beneficiaries who have myeloma, improves health outcomes and is thus reasonable and necessary under §1862(a)(1)(A) of the Act. Therefore, CMS has determined that FDG PET imaging is nationally covered for this indication for this tumor type.

5. Further Exceptions

We specifically requested public comments with respect to treatment strategy of nine cancers that were covered in prior NCDs under 1862(a)(1)(A). For the nine tumor types listed below, we will continue to cover FDG PET for those specific indications currently covered under §1862(a)(1)(A) of the Act. We have not received public input suggesting coverage for these uses should be restricted. These include specific indications pertinent to:

- Breast
- Cervix
- Colorectal
- Esophagus
- Head and Neck (non-CNS/thyroid)

- Lymphoma
- Melanoma
- Non-small cell lung
- Thyroid

CMS has transitioned the prior framework—diagnosis, staging, restaging and monitoring response to treatment—into the initial treatment strategy and subsequent treatment strategy framework while maintaining current coverage. See Appendix A for a chart summarizing the effect of these changes.

II. Background

Throughout this memorandum, we use the term FDG to refer to 2-deoxy-2-[F-18] fluoro-D-glucose, also known as F-18 fluorodeoxyglucose. We use the term FDG PET 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. In the context of this document, the term FDG PET includes the use of combined or integrated positron emission tomography/computed tomography using FDG as the radioactive tracer (FDG PET/CT). We use the abbreviation TNM to denote the dimensions of malignant tumor spread within a given patient, as defined by the American Joint Committee on Cancer and as used by National Cancer Institute, other clinical standards organizations and healthcare providers.

FDG 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 radioactive tracer that gives off subatomic particles, known as positrons, as it decays. FDG PET uses a positron camera (tomograph) to measure the decay of radioisotopes such as 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.

Other forms of diagnostic imaging technologies such as x-ray imaging, computed tomography (CT), and magnetic resonance imaging (MRI) supply information about the anatomic structure of suspected malignancies, primarily their size and location. However, clinical imaging of glucose metabolism within cells is unique to FDG PET technology. In many cases, the anatomical information provided by CT or MRI is most important in devising a treatment strategy. However, the metabolic information provided by FDG PET imaging may provide complementary information that is helpful in determining treatment strategies.

III. History of Medicare Coverage

CMS previously reviewed scientific literature and established coverage for many uses of FDG PET. A summary of currently covered FDG PET indications is in the following table. For each indication, specific coverage limitations are listed in the CMS NCD Manual, Section 220.6.

Currently covered PET indications (FDG unless otherwise noted) are listed below.

Effective Date	Clinical Condition/Indication	Coverage
March 14, 1995	Myocardial perfusion	Rubidium-82 in coronary artery disease
January 1, 1998	Solitary pulmonary nodule	Characterization
January 1, 1998	Non small cell lung cancer	Initial staging
July 1, 1999	Colorectal cancer	Suggested recurrence with rising CEA
July 1, 1999	Lymphoma	Staging and restaging as alternative to gallium scan
July 1, 1999	Melanoma	Recurrence prior to surgery as alternative to gallium scan
July 1, 2001	Non small cell lung cancer	Diagnosis, staging and restaging
July 1, 2001	Esophageal cancer	Diagnosis, staging and restaging
July 1, 2001	Colorectal cancer	Diagnosis, staging and restaging
July 1, 2001	Lymphoma	Diagnosis, staging, and restaging
July 1, 2001	Melanoma	Diagnosis, staging and restaging. Non-covered for evaluating regional nodes.
July 1, 2001		Diagnosis, staging and restaging

Effective Date	Clinical Condition/Indication	Coverage
	Head and neck (excluding central nervous system and thyroid)	
July 1, 2001	Refractory seizures	Pre-surgical evaluation
July 1, 2001 to September 1, 2002	Myocardial viability	Only following inconclusive SPECT
October 1, 2002	Myocardial viability	Primary or initial diagnosis
October 1, 2002	Breast cancer	Staging, restaging, response to treatment
October 1, 2003	Myocardial perfusion	Ammonia N-13 in coronary artery disease
October 1, 2003	Thyroid cancer	Restaging of recurrent or residual disease
September 15, 2004	Alzheimer's disease and dementia	In CMS-approved clinical trial
January 28, 2005	Brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers	Coverage with evidence development
January 28, 2005	All other cancers and indications not previously specified	Coverage with evidence development

A. Current Request

Medicare coverage policy regarding PET resides in Section 220.6 of the National Coverage Determination (NCD) Manual. The section and its subparts determine the general and specific conditions of Medicare coverage for various indications, including coverage where there was prospective data collection for FDG PET used in the diagnosis, staging, restaging and monitoring response to treatment for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers, as well as for cancer indications not previously specified in Section 220.6 in its entirety.

The requestors asked CMS to reconsider Section 220.6 to end the prospective data collection requirements across all oncologic indications except for monitoring response to treatment.

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 authorized by statute, Medicare does not cover diagnostic testing used for routine screening or surveillance.

IV. Timeline of Recent Activities

- April 10, 2008 CMS accepts a formal request to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements across all oncologic indications of FDG PET except for monitoring response to treatment. A tracking sheet was posted on the web site and the initial 30-day public comment period commenced.
- May 10, 2008 The initial 30 day public comment period ended. Six hundred twenty-nine comments were received.
- June 10, 2008

CMS will convene the Medicare Evidence Development and Coverage Advisory Committee on August 20, 2008. The panel will review the scientific evidence of the impact of FDG PET as part of a cancer management strategy to improve patient-centered outcomes. The panel will also consider data generated pursuant to prior national coverage determination to cover FDG PET for specified cancers when additional data are prospectively collected.

August 20, 2008	CMS convened the Medicare Evidence Development and Coverage Advisory Committee.
September 16, 2008	CMS broadens the scope of the NCA for other solid tumors and an additional 30-day public comment commenced.
October 17, 2008	The additional 30-day public comment period ended. One hundred four comments were received.
January 6, 2009	CMS posts the proposed decision memorandum and opens a 30 day public comment period on the proposed decision

V. FDA Status

The FDA approved the following uses for FDG F-18 in a Federal Register notice dated March 10, 2000 (Volume 65, Number 48) Notices. 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 in patients with coronary artery disease CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function, as discussed in section III.A.1 and III.A.2 of this document. The Commissioner also 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. In addition, manufacturers of FDG F 18 injection and sodium fluoride F 18 injection may rely on prior agency determinations of the safety and effectiveness of these drugs for certain epilepsy-related and bone imaging indications, respectively, in submitting either 505(b)(2) applications or amended new drug applications ANDAs for these drugs and indications.”

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. CMS considered additional evidence submitted through the public comment period. CMS convened a Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting and commissioned an external technology assessment (TA) from the Agency for Healthcare Research and Quality (AHRQ). The agency also conducted its own independent search and review of applicable clinical studies, professional society and other group/organization statements, evidence-based practice guidelines and other relevant sources 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 conduct the anticancer management in patients who are known to have solid tumors or who are reasonably suspected to have a high likelihood of cancer based on clinical findings and preliminary diagnostic testing.

The evidence base for many uses of FDG PET has expanded greatly since the first reconsideration of this decision in 2005. The evidence reviewed spanned many but not all cancer types; hence, this review is organized based on how FDG PET may inform decisions regarding treatment strategy, both at the initial work-up stage and the subsequent work-up that might occur after a patient is initially treated. In many cases, prior NCDs have determined that FDG PET is nationally covered for specific indications. Given the scope of the reconsideration we did not generally review evidence for indications that we believe to have been well supported by prior evidence reviews. We expressly sought evidence and public comment on these indications. [January 6, 2009 Proposed Decision Memorandum, at 4. We received no additional evidence requesting a change in coverage for these indications.] We are, of course, open to reconsidering those coverage determinations if we become aware of evidence that they should be reconsidered. We did not consider here FDG PET for leukemia and myelodysplastic syndromes that are not classified as solid tumors.

Myeloma is a plasma cell neoplasm. Plasma cells are a type of white blood cell, and plasma cell neoplasms are not generally classified as a solid tumor. However, there are rare subtypes that may behave in a manner similar to solid tumors. Several public comments specifically addressed myeloma. As myeloma was among the common cancer types in the NOPR-generated evidence, we believe that it is in the public interest for us to consider the available evidence and make a specific determination regarding FDG PET for indications related to myeloma rather than to attempt to force fit myeloma into the definition of solid tumors. Evidence for the use of FDG PET for myeloma for both initial staging and for subsequent treatment planning is discussed below under question #4. We did not include hematological malignant conditions including leukemia or myelodysplastic syndromes in the scope of this reconsideration.

B. Discussion of Evidence Reviewed

1. Questions

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?

3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?

4. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended initial and subsequent treatment strategy in beneficiaries with myeloma?

We have, regarding subsequent treatment strategies, separately considered patients who have signs or symptoms of recurrence from those who do not have signs or symptoms of recurrence. We believe that a treating physician's approach may reasonably differ in these situations, possibly being more aggressive in a patient who is more acutely distressed and whose tumor has clearly not responded to the initial treatment strategy. Question 3 is posed in the context of a beneficiary who has a known diagnosis of a solid tumor and whose treating physician is still actively managing the treatment of the solid tumor. We are not considering the use of PET as a screening test rather than as a diagnostic test.

2. External Technology Assessment

CMS did request an external technology assessment (TA) on this issue from the Agency for Healthcare Research and Quality (AHRQ). This TA was completed prior to our expansion of the scope of this review. Nonetheless we believe that it is relevant to our broader consideration of this topic.

The TA on FDG PET, with or without computerized tomography (FDG PET/CT) scanning, was undertaken during 2008 by the University of Alberta Evidence-based Practice Center (UA-EPC) under contract from AHRQ. The UA-EPC reviewed and synthesized the evidence on the use of FDG PET in the assessment and treatment of nine types of cancer in the situations of diagnosis, staging, re-staging, and monitoring response to treatment.

In conducting this TA, the UA-EPC focused on the following questions:

Q1. How does the diagnostic test performance of FDG PET compare to conventional imaging modalities (for example, CT or magnetic resonance imaging (MRI)) or other diagnostic procedures (e.g., biopsy, serum tumor markers) in the following situations?:

- 1) Diagnosis
- 2) Staging
- 3) Restaging

4) Monitoring response to treatment

Q2. What is the magnitude of the impact of FDG PET on physician decision making regarding approaches to diagnosis and management in the following situations?

1) Diagnosis

2) Staging

3) Restaging

4) Monitoring response to treatment

Q3. What is the impact of FDG PET as part of a management strategy to improve patient-centered outcomes? What is the ability of FDG PET to improve patient-centered outcomes when used as a diagnostic test to identify patients suitable for a particular treatment?

Q4. What is the cost-effectiveness of FDG PET with respect to the following clinical situations?

1) Diagnosis

2) Staging

3) Restaging

4) Monitoring response to treatment

The UA-EPC noted that the TA did not focus on evidence concerning technical evaluation of imaging quality. Instead, the questions in this TA concentrated on studies evaluating FDG PET as related to Levels 2 – 6 of the Fryback and Thornbury model of technology assessment; that is, on diagnostic accuracy efficacy (Q1), diagnostic thinking efficacy (Q2), therapeutic efficacy, patient outcome efficacy (Q3), and societal efficacy (Q4).

In summary, the UA-EPC found that:

- The strongest evidence for diagnostic accuracy of FDG PET or FDG PET/CT was for staging locally advanced cervical cancer and detection and restaging of recurrent disease, detection of ovarian cancer recurrences following treatment, and diagnosis and initial staging of pancreatic cancer.
- Further research would be required to demonstrate the impact on patient management or value in the diagnostic or therapeutic process.
- For bladder, kidney, prostate, small cell lung cancer (SCLC), and testicular cancers, current evidence about the effect of FDG PET on treatment and outcome was inconclusive. The UA-EPC researchers suggested that more study would be needed.

CMS reviewers examined the methodology and results of the TA and agreed with the UA-EPC findings as to the presence and strength of effects, which were felt to be supported by the selected articles included. CMS reviewers also found that in general, the conclusions of this TA were consistent with findings of an internal evidence review separately conducted by CMS staff.

3. Internal technology assessment

The reviewed evidence was gathered from articles submitted by the requestor and a literature search of the PubMed database.

Literature search methods

CMS performed an extensive literature search on April 17, 2008 utilizing PubMed for search terms “FDG PET and cancer”. The search was limited to articles published in the last 5 years, humans, clinical trial, English, and age ≥ 65 . We have also reviewed additional evidence that has come to light since that time which has been provided by the requestors, other members of the public, or through our own surveillance of the relevant medical literature.

For clarity, we are sequentially addressing each question separately below.

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

Below is a summary of the methodologically stronger evidence that was used to answer this question. Please see the evidence tables (Appendix C) for all evidence reviewed and referenced.

Bastiaannet E, et al. 2006

This is a retrospective review of 257 subjects with melanoma. FDG PET was evaluated for its impact on treatment strategy. The investigators reviewed 257 medical records and treatment plans before and after FDG PET. Examples of treatment changes made include decreased surgical intensity or a change to palliative care, changing from surgery to no surgery, and changing from no-treatment to systematic drug treatment. See the table below for details. The authors conclude that the information provided by FDG PET is important for surgical planning.

Comparison of treatment intended before FDG PET and actual treatment given

Intended treatment		Treatment performed								
		Surgery	Systemic treatment	Radiotherapy	No treatment	Surgery and systemic treatment	Surgery and radiotherapy	Systemic treatment and radiotherapy	Not clear	Total Changed (%)
Surgery	172	155	9	1	6			1		17 (10)
Systemic treatment	13	2	9		1			1		4 (30.7)
Radiotherapy	6		1	3	1			1		3 (50)
No treatment	56	3	5	2	45			1		11 (19.6)
Surgery and systemic treatment	1					1				1(0)
Surgery and radiotherapy	3			1			2			1 (66.7)
Not clear	6			1	3				2	4 (66.7)

Pepe G, et al. 2005

This was a prospective case series of 75 subjects aged 33-82 with a diagnosis of a pulmonary lesion. Subjects were evaluated to see how FDG PET findings might alter treatment strategy. A questionnaire was sent to referring physicians before and after FDG PET results. Changes in patient management after FDG PET imaging occurred in 34 (45%) cases, with the most relevant variation occurring after FDG PET related to the surgical treatment strategy (see table below). Authors concluded that FDG PET was useful for altering treatment strategy, especially as relates to surgical strategy.

Results of treatment Strategy Changes pre- and post-FDG PET

	Pre-FDG PET	Post-FDG PET	% Change
Further Diagnostic work-up needed	44	27	-39%
Surgery	9	28	211%
Wait & See	5	3	-40%
Medical Therapy	17	17	No change

Castellucci P, et al. 2007

This prospective case series enrolled 50 consecutive female subjects, each of whom had a pelvic lesion suspicious for malignancy, had undergone transvaginal ultrasound and had elevated levels of CA-125. Subjects' ages were between 23 and 89 years, with a mean age of 64 years. Histopathologic findings at surgery were the comparison standard. The criterion for malignancy on FDG PET/CT was a maximum standardized uptake value (SUV_{max}) exceeding 3.0. Duplicate FDG PET/CT interpretations were performed by two experienced nuclear medicine physicians blinded to clinical and other diagnostic data. In FDG PET/CT scans of the 32 subjects with malignant lesions of the ovary, 28 had a SUV_{max} ranging from of 3.1 to 125.7 and were considered to have malignant disease. FDG PET/CT studies of the other 4 subjects showed an SUV_{max} less than 3.0, while histopathology identified two serous papillary adenocarcinomas with microinvasion and two borderline mucinous adenocarcinomas in these four subjects. In comparison to transvaginal ultrasound (TVUS), FDG PET/CT showed greater specificity, positive predictive value, and accuracy. In addition, this study also examined the performance of FDG PET/CT compared to CT alone for staging. For more advanced tumors (Stages III and IV), FDG PET/CT was better at staging than CT alone, correctly staging 15/18 subjects with Stage III and IV disease, as compared to correct CT staging of 9/18 subjects. However, FDG PET was falsely negative in 4/11 subjects with stage I disease. The authors concluded that FDG PET/CT was useful for initial treatment strategy and could change patient management.

Connell CA, et al. 2007

Based on a prospective case series of 76 subjects, this study examined the pre- and post-treatment impact of FDG PET

on patient management decisions in subjects with primary head and neck squamous cell cancer. Subjects' ages at diagnosis ranged from 21-83 years, with a median of 59 years. Thirty-five of 76 subjects underwent a staging FDG PET/CT scan, resulting in a change in TNM staging in 12/35 (34%). Two of these 12 had disease downstaged; 10/12 subjects had disease upstaged. These changes in stage had impacts on radiotherapy technique and dose planning. Seven subjects with negative neck node scans avoided futile neck dissections. One with persistent FDG-avid disease in the nasal cavity underwent earlier salvage surgery and two with suspected residual disease avoided systemic chemotherapy or biopsy. Finally, Kaplan-Meier survival analysis showed a significant difference in disease-free ($p = 0.046$) and overall ($p = 0.037$) survival based on FDG PET/CT assessment of a complete metabolic response, with a maximum clinical follow-up of as much as 45 months.

The authors concluded that FDG PET/CT imaging contributed to initial treatment strategy planning in patients with primary head and neck squamous cell cancer and suggested that the high FDG PET negative predictive value identified subjects in whom observation rather than surgical intervention would be appropriate and safe.

Hillner BE, et al. 2008A (Reference 7)

This prospective questionnaire-based case series of 22,976 subjects was undertaken in response to the 2005 NCD for FDG PET for cancer and resulted in the development and implementation of the National Oncologic PET Registry (NOPR), which was designed to meet coverage requirements and to assess how FDG PET affects care decisions. This study collected data from referring physicians on intended patient management before and after FDG PET. The cohort included data on 22,975 patient studies (83.7% FDG PET) from 1,178 centers. Prostatic, pancreatic and ovarian cancers represented in aggregate approximately 30% of cases. The post-FDG PET plan was three-fold more likely to lead to treatment than nontreatment (28.3% v 8.2%; odds ratio 3.4; 95% CI, 3.2 to 3.6). Overall, physicians changed their intended management in 36.5% (95% CI, 35.9 to 37.2) of cases after FDG PET. Authors conclude that physicians often change their intended management based on FDG PET scan results across the full spectrum of its potential uses.

Meyers BF, et al. 2007

This prospective multi-institutional trial of 189 subjects, a re-analysis of an American College of Surgeons Oncology Group trial, examined whether FDG PET scan for staging of esophageal carcinoma identifies metastatic disease and avoids esophagectomy in subjects who are surgical candidates after routine staging. Of the 262 subjects registered, 199 were considered eligible and of these, 189 subjects were evaluated. Ineligible subjects were those considered unresectable by routine staging procedures, those without cancer, those whose care violated FDG PET protocols or those with claustrophobia or other reasons. FDG PET indicated involvement of local lymph nodes in a greater proportion of study participants than did CT (58 (30.7%) with local lymph node involvement by FDG PET versus 23 (12.2%) by CT). Also, FDG PET detected involvement of distant organs in 33 subjects (17.5%) as opposed to none (0%) by CT. In 7/189 subjects, FDG PET findings of metastatic disease were not confirmed. The authors commented on the added burden of investigating the FDG PET false positives, including complications of procedures that resulted in serious outcomes for the participants such as unnecessary adrenalectomy or surgical site infection. However, FDG PET detection of metastases to distant lymph nodes or organs was a major reason for a decision to avoid surgery in 4.8% of surgical candidates.

The authors concluded that FDG PET after standard clinical staging for esophageal carcinoma identified previously undetected metastases in distant organs in 4.8% of subjects before resection. FDG PET evidence of metastases to distant lymph nodes or organs and of metastases to regional lymph nodes led to definitive nonsurgical or induction therapy in additional subjects.

Ng SH, et al. 2004

This prospective case series of 37 subjects was examined to assess the usefulness of FDG PET in subjects whose MRI findings during periodic (every 6 months during first two years after radio- or radio-chemotherapy) surveillance for nasopharyngeal carcinoma (NPC) were questionable for recurrence. The average age of the 37 subjects was 47.2 years, with 13 females and 24 males. Questionable MRI findings were those beyond expected morphologic findings after radio-therapy, either equivocal or suggesting residual or recurrent NPC. FDG PET was performed within two weeks of the MRI study and interpreted by three nuclear medicine physicians who were unaware of the MRI findings. Lesions were examined either by histopathology or by clinical follow-up of at least 6 months. Overall performance using either histopathology or clinical follow-up as the gold standard in these 37 subjects with questionable MRI findings for recurrence included:

Scan Type:	Sensitivity	Specificity	Accuracy	PPV	NPV
FDG PET	89.5%	55.6%	72.9%	68.0%	83.3%

In six subjects with false-positive FDG PET findings, inflammation was noted at the primary tumor site on histopathologic examination. In one patient, a false negative FDG PET finding at the primary site was attributed to intramucosal residual tumor by histopathology. FDG PET findings in regional lymph nodes were considered false-positives in three subjects, with inflammatory activity on histopathology in two subjects or regression on clinical follow

-up in one patient. One false-negative FDG PET finding was attributed to a small focus of metastatic involvement in a 0.5 cm diameter lymph node. Of eight subjects found positive by FDG PET for distant metastases, five were confirmed by histopathology or by progression in subsequent images, and three false positive FDG PET findings at distant sites were attributed to inflammation by either biopsy or resolution by imaging or clinical follow-up. Twenty-nine subjects were negative for distant metastases by FDG PET. However, in the discussion section, the authors comment that in one patient, small foci of lung metastases, visible on CT and enlarging in diameter on repeat CT two months later, were missed by FDG PET (although a larger perihilar focus was detected).

The authors concluded that significant additional information was provided by FDG PET findings for 18/37 participants with questionable MRI findings, including unexpected small metastases in lymph nodes in three, distant metastases in five, and exclusion of recurrence in 10 subjects.

Risum S, et al. 2007

This prospective case series of 97 subjects examined the use of combined FDG PET/CT in detecting malignancy in subjects with no cancer history but with a pelvic mass (and therefore suspected primary ovarian carcinoma). One hundred-one subjects referred for surgery from primary hospitals for suspected ovarian cancer were enrolled. Comparisons were based on 97 subjects for whom histopathologic studies were available (four subjects decided not to undergo surgery based on benign FDG PET/CT findings). The median patient age was 60 years. Risk for malignancy was estimated from ultrasound examination findings and elevated CA-125 antigen levels (median 784 U/mL, range 22-9665 U/mL). FDG PET/CT findings were compared with those of histopathologic studies of the pelvic masses for malignant and for borderline/benign lesions. Sensitivity and specificity for FDG PET/CT in diagnosing malignancy in a pelvic mass were, respectively, 100% (57/57) and 92.5% (37/40) ($p < 0.00005$). In several subjects, distant (inguinal and supraclavicular) lymph node or organ (spleen, lung) ovarian tumor metastases were detected by FDG PET/CT and confirmed by histopathology (and, in two subjects, metastases were found by FDG PET/CT from unsuspected primary malignancy elsewhere). Other subjects with FDG PET/CT evidence of abnormally increased metabolic activity that might have indicated metastatic disease were investigated in only one of sixteen. False positive FDG PET/CT results were noted in three subjects with benign pelvic masses (fibroma, leiomyoma and endometriosis by histopathology). The authors concluded that combined FDG PET/CT demonstrates high diagnostic value in identifying ovarian cancer. Authors suggest FDG PET/CT as the image modality of choice when ultrasound shows a pelvic tumor and additional information prior to surgery is needed.

Schmidt GP, et al. 2005

This prospective case series of 41 subjects examined the accuracy of staging MRI vs. FDG PET/CT. Test interpreters were blinded and solid tumors in various organs were evaluated—lung, liver, bone, soft tissue, CNS. The authors found that FDG PET/CT detects tumors as well as or better than MRI, was superior for lymph node staging and was helpful in guiding biopsy and avoiding unnecessary biopsy. For lymph node detection, FDG PET/CT was 98% sensitive and 83% specific. Authors conclude that by using FDG PET/CT, “fruitless diagnostics, which burden the patient and can occur in a multimodality approach, could be avoided.” However, the authors caution that MRI was superior to FDG PET for identifying distant metastases.

Suzuki, et al. 2007

This study of a prospective case series of 30 subjects with pelvic tumors addressed the value of FDG PET imaging for initial treatment strategy planning. Imaging findings before surgery were studied in subjects with biopsy-proven endometrial cancer, who underwent FDG PET, whole-body CT, and pelvic MRI within 2 weeks of surgery. The subjects' ages ranged from 27 to 73 years, with a mean of 55 years. Twenty-six of 30 subjects underwent retroperitoneal lymph node dissections; two had peritoneal dissemination of tumor. FDG PET was slightly more sensitive than CT/MRI for detection of extra-uterine metastases in other organs (5/6 (83%) vs. 4/6 (67%)), while both types of scans were equally specific for such lesions (both 24/24 (100%)). However, although FDG PET was less likely than CT/MRI to detect the rare, small (0.1 – 0.6 cm) pelvic lymph node metastases identified by histopathology in 5/26 subjects who underwent lymph node dissection, the difference was not statistically significant.

The authors conclude that negative FDG PET results should not be used to justify deferring surgical examination of regional lymph nodes.

Turkmen, et al. 2007

In this prospective study of the value of FDG PET in initial treatment strategy planning, pre-operative assessment of previously untreated non-small cell lung cancer (NSCLC) in 59 participants (47 men, 12 women) included FDG PET scans in addition to CT, with either thoracotomy for cure or lymph node biopsy for histopathologic staging. The median of the subjects' ages was 52 years, with ages of participants ranging from 44 – 83 years. For lymph node staging, FDG PET and CT performance characteristics were calculated separately for: a) patients with either no lymph nodes involved, or involvement limited to bronchopulmonary or hilar lymph nodes in the same lung; or b) patients limited to metastases of lymph nodes in the same side of the chest (including the mediastinum) but without lymph node involvement in the contralateral mediastinum or in the supraclavicular or scalene lymph nodes. These calculations are

shown in parts a) and b) of the following table:

Table: FDG PET and CT performance characteristics:

a) Local or no lymph node involvement

Scan Type:	Sensitivity	Specificity	Accuracy	PPV	NPV
CT	66%	43%	58%	68%	43%
FDG PET	79%	76%	78%	86%	76%

b) Ipsilateral intrathoracic lymph node involvement

Scan Type:	Sensitivity	Specificity	Accuracy	PPV	NPV
CT	43%	66%	54%	41%	66%
FDG PET	76%	79%	80%	67%	83%

The authors concluded that an FDG PET scan significantly improves diagnostic accuracy of lymph node involvement by tumor as compared with CT ($p < 0.01$). False positive studies on FDG PET images were mostly attributable to lymph node foci of granulomatous diseases of various types (e.g., pulmonary tuberculosis, silicosis), which the authors commented to be higher than expected among the study population.

The authors concluded that FDG PET was of value for initial treatment strategy planning in patients with NSCLC. However, in light of a false-negative rate exceeding 10% for mediastinal node involvement, with 20% of participants under-staged by FDG PET, the authors emphasized the importance of mediastinoscopy in FDG PET-negative patients for more accurate staging.

2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?

Connell CA, et al. 2007

Discussed above, this prospective case series of 35 subjects with head and neck cancer also addressed the impact of FDG PET on subsequent treatment strategy. FDG PET was performed in 32/35 subjects to assess response to therapy within a median of 3.2 months post-treatment (range 1.4 – 6.4 months). The FDG PET results were compared with ordinary radiologic assessments of treatment response done within 3 days of the FDG PET scan. Locoregional response of malignancy in 30 subjects changed due to FDG PET results in 13/30 (43%) of subjects. The authors concluded that the clinical impact was high for 11/30 subjects studied: 7 avoided unnecessary neck dissections, one with distant metastatic disease avoided futile salvage surgery, one with FDG non-avid residual disease avoided systemic chemotherapy, one with FDG non-avid disease in the tonsils avoided examination under anesthesia, and one with FDG-avid disease in the nasal cavity underwent salvage surgery.

Chung, et al. 2007

This prospective case series of 77 subjects was studied to evaluate the accuracy of integrated FDG PET/CT for detection of suspected recurrent ovarian carcinoma after treatment, using clinical or histopathologic findings as the reference standard. Seventy-seven women (median age, 51 years, range 21-80 years) with ovarian carcinoma treated with primary cytoreductive surgery followed by platinum-based combination chemotherapy were included. FDG PET/CT was performed for suspected recurrence. In all subjects, imaging findings were compared with results of histopathologic examination after surgical exploration or clinical follow-up to determine the diagnostic accuracy of FDG PET/CT in the evaluation of disease status. A high level of agreement was found between FDG PET/CT and histopathologic or clinical findings ($\kappa = 0.894$). The overall sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of FDG PET/CT were 93.3%, 96.9%, 94.8%, 97.7% and 91.2%, respectively. FDG PET/CT modified the diagnostic or treatment plan in 19 (24.7%) subjects by leading to the use of previously unplanned therapeutic procedures in 11 (57.9%) subjects and the avoidance of previously planned diagnostic procedures in eight (42.1%).

The authors concluded that FDG PET/CT is sensitive for detecting recurrent ovarian cancer and aids treatment planning.

Kim S, et al. 2004

This retrospective case series of 55 women compared the prognostic value of FDG PET with that of second-look laparotomy (SLL) to detect recurrences in subjects with advanced ovarian cancer following surgery and chemotherapy. Of the 55 enrolled subjects, 30 underwent SLL, while 25 had FDG PET without SLL. Subjects had a mean age of 49.2 years, ranging from 25-78 years. All had histopathologically proven ovarian cancer. Prognostic value was based on retrospective medical record review. Recurrence was identified in 37 of the 55 subjects; 17 in the FDG PET group and 20 in the SLL group. Recurrent disease was confirmed by histopathology or cytology in 16/37 subjects and by physical exam, MRI, ultrasound or CA-125 in 21/37 subjects. Diagnostic performance indices for recurrence identification by

FDG PET were as follows:

	Sensitivity	Specificity	Accuracy	PPV	NPV
FDG PET	82%	88%	84%	70%	84%

Progression-free intervals (PFI) were not significantly different between the two groups: an average PFI of 28.8 months in the FDG PET group and 30.6 months in the SLL group ($p = 0.29$). The average disease-free intervals were also not significantly different between the FDG PET group (40.5 months) and the SLL group (48.6 months) ($p = 0.12$), or the positive FDG PET group and the positive SLL group (23.7 months and 26.2 months, respectively). The authors concluded that FDG PET could be used to substitute for SLL in subjects with ovarian cancer.

Magne N et al. 2008

This review of primary clinical trials summarized findings of 14 published articles about the use of PET or PET/CT in post-therapy recurrence of cervical cancer. To determine the performance characteristics of PET or PET/CT in detecting relapse, sensitivity and specificity were assessed for a combined group of nearly 800 patients. The gold standard for evaluating recurrence was a combination of histopathologic findings and clinical followup. For 13 of 14 of the cited studies in which patient-level data were provided, weighted average sensitivity and specificity for PET or PET/CT to detect metastasis or relapse in the centropelvic area and in regional and distant lymph nodes were 92% and 84% respectively.

Mangili G et al. 2007

This article described the results of a retrospective study of PET/CT management of a series of 32 cases of ovarian cancer with suspected recurrence. Abdominal CT with contrast enhancement and PET/CT were performed in all 32 cases. Findings of recurrence and indications from medical records of changes in management were studied. 29/32 patients were positive at PET/CT for recurrence, in contrast to 20/32 patients positive by CT. Change in treatment modality was indicated in 14/32 patients (44%): six began chemotherapy; four avoided diagnostic surgery; three required further instrumental examination; and one underwent salvage surgery. The authors concluded that integrated PET/CT was more capable of detecting tumor recurrence than CT alone; and that patient management was affected in 44% of patients with suspected recurrence.

Mirallié E, et al. 2007

In this prospective multi-institutional study, the value of FDG PET was examined for subsequent treatment strategy planning in 45 patients with FDG PET findings indicating recurrences of differentiated thyroid cancer (DTC). The group included 31 males and 14 females. Subjects' ages ranged from 14-80 years, with a mean age of 55 years. All subjects had undergone total thyroidectomy and postoperative residual thyroid ablation with ^{131}I . All subjects had postoperative elevation of thyroglobulin levels, increased TSH, normal values of anti-thyroglobulin antibody, and negative whole-body ^{131}I scans. The study's findings are summarized in the following table.

FDG PET finding for recurrent DTC (# of patients)	Recurrence confirmed by histopathology	Recurrence confirmed on clinical follow-up with tissue confirmation	Recurrence not confirmed by any method
Positive (31)	24	0	7
Negative (14)	n/a	14	n/a

Histopathologic findings in those seven subjects with false-positive FDG PET results included: two patients with second primary tumors (one of lung, one of uterus); one patient with inflammation; and four patients with normal lymph nodes.

The study also assessed FDG PET performance characteristics for detecting recurrence. (In the absence of any true negative FDG PET studies for recurrence indicated in this article, specificity and negative predictive value were not assessed.)

	Sensitivity	Accuracy	PPV
FDG PET	63%	53%	77%

FDG findings also affected subsequent treatment strategy planning in 23 subjects:

FDG PET Finding	Outcome	Subjects:
Disseminated disease	Change from surgical to chemo- or radiation therapy	8
No abnormal focus	Change from surgical to chemo- or radiation therapy	14
		1

FDG PET Finding	Outcome	Subjects:
Focal increase of activity near a prosthesis	No further diagnostic effort (observation only)	

In a separate subgroup of 20 subjects, FDG PET findings localized recurrences in the neck, mediastinum and/or lung. In 17/20 subjects, FDG PET showed from one to five malignant foci in the lateral or central neck in each subject. In the other three subjects, FDG PET images showed: one lung focus in one; foci in both lung and neck in another; and foci in both lung and mediastinum in the third. Nineteen of these 20 subjects underwent resection. Histopathology confirmed lung metastasis in one patient; found no positive neck lymph nodes in three other patients; and detected from 1-6 lymph nodes positive for malignancy in the remaining 15. (One of the 20 subjects with FDG PET evidence of local recurrence did not undergo surgery.)

The authors concluded that, as a result of FDG PET findings, some subjects received curative secondary resection. In addition, surgery was avoided in eight subjects with disseminated disease.

Pepe G, et al. 2005

Discussed above, this prospective case series contained a subset (n = 20) of subjects in which they were monitoring treatments. The resulting management changes were mostly to surgery, which was either curative or palliative. The authors conclude that this study suggests a benefit for FDG PET scans for monitoring response to treatment and further studies are needed to confirm this result.

Yen TC, et al. 2004

This prospective case series of 55 subjects with recurrent cervical cancer examined the role of FDG PET in determining treatment options. FDG PET studies were used in addition to several clinical factors (including symptoms of recurrence, serological studies, and type of primary treatment) to determine whether salvage therapy or palliation would be appropriate. FDG PET results modified the treatment plan from radical surgery for cure to palliation in 27/55 subjects. In addition, the study examined the relative diagnostic performance of FDG PET and MRI/CT, with histopathologic examination or clinical outcome as the comparison standard. FDG PET sensitivity to detect metastatic lesions was significantly higher than that of MRI/CT (89.2% vs. 39.2%, p < .0001), but the sensitivities of the two methods were similar for detection of local lesions (90.0% vs. 80.0%, p = 0.472) (comparisons on a per-lesion basis). The authors concluded that FDG PET benefits decisions about subsequent therapy by selecting appropriate cases of recurrent cervical cancer for salvage therapy.

3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?

None of evidence reviewed evaluated the use of FDG PET for surveillance.

In their public comment, the requestors noted there were no well-accepted data showing a link between surveillance and improved health outcomes.

4. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended initial and subsequent treatment strategy in beneficiaries with myeloma?

Evidence for coverage of PET scans in cases of myeloma was provided by two cited clinical studies.

Nanni C et al. 2006

This study focused on a series of 28 newly diagnosed consecutive cases of multiple myeloma to evaluate the relative value of FDG PET to whole body X-ray (WBXR) or MRI, in terms of numbers and sites of lesions detected. The patients included 21 males and seven females, with a mean age of 55 years, and an age range of 35-74 years, referred for multiple myeloma to a single hospital between March 2003 and September 2004. WBXR included skull, spine, pelvis, ribs, femora and humeri. FDG PET scans were read by nuclear medicine physicians in a manner blinded to WBXR and MRI results. At the time of the scan, no patient had received therapy. In 16/28 patients, FDG PET detected more lesions than WBXR. In the other twelve patients, FDG PET and WBXR were equivalent for detecting lesions. Compared to MRI, FDG PET detected more lesions in 7/28 patients; the additional lesions were noted to be outside of the field of view of the MRI. In 14/28 patients, the MRI and FDG PET detected the same number of lesions, and in the remaining 7/28 patients, MRI detected more lesions than FDG PET, including an infiltrative pattern in three of those seven patients. The authors concluded that for initial evaluation of patients referred for multiple myeloma, although FDG PET is of greater sensitivity than WBXR for detecting multiple myeloma lesions, it may be employed with MRI in order to detect infiltrative myeloma lesions in the spine.

Hillner BE et al. 2008B (Reference 8)

This registry-based case series prospectively collected questionnaire data from physicians and patients related to 40,863 FDG PET scans performed for oncologic indications during a two year period (May 8, 2006 – May 7, 2008) at centers participating in the National Oncologic PET Registry. Among the many other cancer types, 1,784 scans were

performed for either initial staging of myeloma (402 scans) or for re-staging or evaluation of recurrence of myeloma (1,382 scans). The fraction of patients who had two or more scans was notably higher than average for myeloma (17.7%).

The authors noted that, compared with cancer of all other types, myeloma cases for which FDG PET scans were performed had the highest percentage of change in overall management 48.7% (46.3-51.0% CI) (on a per-scan basis). Changes were from treatment to non-treatment in 41.7% and from treatment to non-treatment in 7%. In comparison to other cancer types, FDG PET scans for myeloma had the highest odds ratio at 1.58 (1.43-1.73 CI) for change in management.

Using data from several tables in this article, it was possible to break out the effects of FDG PET scans used for initial staging (in 402/1,784 scans), which changed management 52.2% (47.4 – 57.1% CI) (percentage calculated on a per scan basis). For treatment planning subsequent to initial therapy, 50.9% of FDG PET scans done in myeloma cases with suspected recurrence were associated with a change in management, in contrast to other types of cancers in which FDG PET scans' effects ranged from 29.3-44.5%.

The authors concluded that FDG PET scans for myeloma differed quantitatively from other cancer types in the relative size of their effects on both initial and subsequent therapy planning, noting in their discussion that:

With the notable sole exception of multiple myeloma, there were no cancer types for which the impact of PET was consistently higher or lower than average across all indications studied.

4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was convened on this issue on August 20, 2008. Details are available at the following URL:

<https://www4.cms.hhs.gov/mcd/viewmccac.asp?where=index&mid=44>.

The Medical Evidence Development and Coverage Advisory Committee (MEDCAC) met to discuss the evidence, hear presentations and public comments, and make recommendations concerning the oncologic indications of FDG PET for nine cancers: brain, cervical, small cell lung, ovarian, pancreatic, testicular, prostate, bladder and kidney. After a presentation of the technology assessment by UA-EPC and several other presentations, the MEDCAC members voted using a numeric scale from 1 to 5, with 1 indicating no confidence and 5 indicating high confidence. The following indicates the average vote from MEDCAC members voting for each aspect. The results included:

The committee was asked to consider the following questions.

1. How confident are you that the evidence is adequate to conclude that FDG PET imaging improves physician decision making when used for the following indications for each in these nine cancers?

For Diagnosis: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in the diagnosis of ovary and pancreas neoplasms (3.0 and 2.75 respectively). MEDCAC members expressed decreased confidence in FDG PET effect on physician decision making in the diagnosis of bladder, cervix, prostate and testis neoplasms (all at 1.5).

For Staging: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in staging of cervix, ovary, and pancreas neoplasms (3.5, 3.5 and 3.25 respectively). MEDCAC members expressed relatively lower confidence in FDG PET effect on physician decision making in staging of bladder, prostate and testis neoplasms (all at 1.5).

For Restaging: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in restaging of cervix and ovary neoplasms (both at 3.5). MEDCAC members expressed relatively lower confidence in FDG PET effect on physician decision making in the restaging of bladder, testis and prostate neoplasms (1.5, 1.5 and 1.75 respectively).

For Monitoring: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in monitoring of cervix and ovary neoplasms (both at 3.5). MEDCAC members expressed relatively lower confidence in FDG PET effect on physician decision making in monitoring of testis and prostate neoplasms (1.5 and 1.75 respectively).

2. How confident are you that the evidence is adequate to conclude that FDG PET imaging improves patient oriented clinical outcomes when used for the following indications in each of these nine cancers?

For Diagnosis: MEDCAC members indicated relatively stronger confidence in FDG PET performance for diagnosis of ovary, pancreas and kidney neoplasms (3.25, 3.25 and 2.75 respectively). MEDCAC members expressed decreased confidence in FDG PET performance for diagnosis of cervix, testis and prostate neoplasms (1.5, 1.5 and 1.75 respectively).

For Staging: MEDCAC members indicated relatively stronger confidence in FDG PET performance for staging of cervix, ovary and pancreas neoplasms (3.75, 3.5 and 3.5 respectively). MEDCAC members expressed relatively lower confidence in FDG PET performance for staging of testis and brain neoplasms (1.5 and 1.67 respectively).

For Restaging: MEDCAC members indicated relatively stronger confidence in FDG PET performance for restaging of cervix and ovary neoplasms (both at 4.25). MEDCAC members expressed relatively lower confidence in FDG PET

performance for restaging of testis neoplasms (1.75).

For Monitoring: MEDCAC members indicated relatively stronger confidence in FDG PET performance for monitoring of cervix, ovary and kidney neoplasms (4.0, 3.75 and 3.5 respectively). MEDCAC members expressed relatively lower confidence in FDG PET performance for monitoring of testis neoplasms (1.75).

In addition, MEDCAC members also addressed three other issues:

1. In response to the question: How confident are you that these conclusions are generalizable to other cancers, the average of voting MEDCAC members' responses was 3, ranging from 1 to 5.
2. In response to the question: How confident are you that these conclusions are generalizable to non-research FDG PET facilities in the general community, the average of voting MEDCAC members' responses was 3.25, ranging from 3 to 4.
3. In response to the question: How confident are you that these conclusions are generalizable to the Medicare beneficiary population, the average of voting MEDCAC members' responses was 4, ranging from 4 to 5.

5. Evidence-based Guidelines

We did not locate nor were we provided any guidelines for the use of FDG PET imaging in cancer patients.

6. Professional Society Position Statements

During the third public comment period, the American Society of Clinical Oncology (ASCO) submitted that CMS must ensure uninterrupted access to FDG PET during the implementation of the new NCD. ASCO also recommended that the criteria for clinical studies specified in the proposed decision memorandum be excluded from the final policy.

7. Expert Opinion

In that prostate cancer is the most frequent indication for FDG PET imaging in NOPR, we solicited expert opinion from Howard Scher, MD, Chief, Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center on the usefulness of FDG PET in the management of prostate cancer. Included in this opinion were recommendations for use of FDG PET in prostate cancer for several clinical circumstances. These are:

- To identify systemic and/or local disease recurrence in a patient with a rising prostate-specific antigen (PSA) after surgery or radiation therapy as primary treatment;
- To identify and follow sites of tumor regrowth in patients who have failed hormonal therapy; and
- To provide an early readout of the effects of therapy on tumor growth.

Dr. Scher's opinion appears among others at the CMS webpage (alphabetically listed):

http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=218&rangebegin=09_16_2008&rangeend=10_17_2008#0916200810172008S

In addition, we asked the requestors to opine specifically on the topic of tumor FDG-avidity and whether or not that factor is helpful in predicting the usefulness of FDG PET for any particular indication. They made the following points:

- Glucose uptake depends upon degree of differentiation for all tumors. Some tumors e.g., well-differentiated hepatoma do not have uptake above background.
- All tumors [they] know about have some sufficiently aggressive forms that have high FDG uptake – as in the example of hormone-refractory prostate cancer.
- The presence or absence of FDG uptake in itself can be very clinically relevant. For example, presence or absence of FDG uptake is currently very important in the decision to pursue further treatment for iodine-refractory thyroid cancer, based upon data showing poor survival with FDG-avid forms of the disease and excellent survival for FDG-negative disease.
- Increased glycolytic metabolism is a fundamental property of cancer cells, and thus there is really not any cancer that is not FDG-avid. However, in general, low-grade tumors that grow more slowly tend to be less FDG avid than do their higher grade counterparts within a given tumor cell type. Examples where this has been demonstrated included low-grade sarcomas, lymphomas, and gliomas.
- Another general principle relates to those tumors that have large amounts of non-cellular stroma, such as mucinous carcinomas and desmoplastic tumors tend to be less FDG-avid; this is simply a function of partial volume averaging at the microscopic level. Commonly cited examples of tumors that are less FDG-avid than many other tumors are prostate cancer, thyroid cancer, hepatocellular carcinoma, and neuroendocrine tumors.

- Again, as a general rule, the less well differentiated all of these tumors are, the more likely they will be quite FDG-avid. In the case of prostate cancer, this typically corresponds with the onset of hormone-refractory disease. With thyroid cancer and neuroendocrine tumors, their FDG-avidity typically corresponds with their loss of endocrine-functional differentiation (so that they no longer accumulate I-131 or no longer express somatostatin receptors).
- There is apparently no current consensus standard that could be used to define FDG avidity via any *in vitro* or *in vivo* assay. A working definition of non-FDG-avid might be those cases where tumors that are large enough to be detected by FDG PET instrumentation do not have uptake above background, and are therefore not seen. A good example is Grade I hepatoma, which has SUVs ~ 2, as does normal liver.

8. Public Comments

Initial Comment Period: April 10, 2008 through May 10, 2008

CMS received 629 public comments during the first public comment period. All but one of the comments supported coverage of FDG PET for the requested indications. Eighty-five percent of the public comments were form letters expressing that support. 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 Period: September 16, 2008 through October 17, 2008

CMS received 104 public comments during the second comment period. Eighty percent of those comments were form letters from South Florida physicians expressing their support for coverage.

CMS received a comment by the requestors jointly signed by senior management of the National Oncologic FDG PET Registry (NOPR), the American College of Radiology (ACR), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Academy of Molecular Imaging (AMI) and the Society of Nuclear Medicine (SNM).

In summary, the requestors comment that they believe there is strong empirical evidence to support an omnibus cancer framework that would provide coverage of FDG PET across almost all oncologic indications for diagnosis, staging, and restaging, including detection of suspected recurrence. The requestors also comment that they do not believe there is sufficiently mature evidence from NOPR to recommend an end the CED requirement for the coverage of treatment monitoring at this time. The requestors proposed to continue using NOPR to collect data on the value of FDG PET for treatment monitoring.

CMS received five comments from imaging industry associations favoring coverage to include the requested indications. Among the industry association comments, US Oncology commented, in part, that CMS could integrate measures for FDG PET imaging efficiency into the Physician Quality Reporting Initiative (PQRI). The PQRI issue is beyond the scope of this national coverage analysis.

Three comments from health insurance plans criticized the available evidence and did not support coverage of the requested indications.

Additional comments of support for broader coverage came from medical and surgical oncologists, nuclear medicine physicians, general radiologists and other physicians. FDG PET facility staff, two foundations and those with unknown affiliations also submitted supportive comments.

Two comments addressed positron emission mammography (PEM). One comment addressed proton beam therapy. Neither of these topics is a component of this reconsideration request.

Third Comment Period: January 6, 2009 through February 5, 2009

During the third comment period, CMS received 91 timely comments on the proposed decision. Of the 91 comments received, 19 (approximately 21 percent) were submitted on one of two form letters. The comments fell into two broad categories: those expressing various rationales in favor of expanding coverage of FDG PET, and those opposed to expanding such. Commenters included physicians and their practice organizations – comprised largely of medical oncologists and radiation oncologists, insurers, specialty societies, industry and private individuals. Comments and CMS responses are summarized below.

Comment:

Many commenters expressed general support for the proposed decision along with the two part framework.

Response:

CMS appreciates general comments in favor of the proposed decision memorandum.

Comment:

CMS received a comment by the requestors jointly signed by senior management of the National Oncologic FDG PET Registry (NOPR), the American College of Radiology (ACR), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Academy of Molecular Imaging (AMI), the Society of Nuclear Medicine (SNM) and the American College of Nuclear Physicians (ACNP). The requestors strongly support the proposed two-part framework.

They also request CMS end the CED requirement for subsequent treatment strategy. If CED continues, the requestors encourage CMS to ensure uninterrupted access to PET during the implementation of the new NCD.

Response

CMS thanks these organizations for their comment. After review of evidence, CMS has determined that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate subsequent treatment strategy for beneficiaries with certain solid tumors. CMS reviewed the evidence on FDG PET for subsequent treatment strategy for ovarian and cervical cancer. CMS determined that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate subsequent treatment strategy for beneficiaries with these cancers.

We do not believe that the evidence supports a general removal at this time of the CED requirement from uses of FDG PET related to subsequent treatment. Anticancer therapy is risky and arduous. The treatments are often toxic and disfiguring. Thus the beneficiary may be harmed or killed if treatment is based on diagnostic modalities which have not been rigorously evaluated with respect to their impact on patient centered outcomes. As we noted in the proposed decision memorandum, cancer treatment guidelines provide more options and less direction for dealing with heterogenous clinical situations encountered in patients with recurrent solid malignancies, i.e. those patients in whom initial treatment has failed. There are many plausible causes of treatment failure. For example, the patient may have been unable to tolerate an ideal dose or duration of therapy, or may have opted for an alternative therapy for personal reasons, or the tumor may have atypical characteristics that are as yet unidentified, but that make it resistant to customary therapy. In this case we believe that the available evidence regarding the usefulness of FDG PET imaging to guide subsequent management is not broadly generalizable to the many cancers for which we have not determined exceptions. In light of the risks, we have determined that further evidence is required and that this should include adequate patient protections.

With the continuation of CED for certain FDG PET indications, CMS anticipates that the National Oncologic PET Registry (NOPR) may meet the standards and requirements listed in Section IX, below. CMS will consider proposals from other entities expressing interest in meeting these standards and requirements.

Comment

Along with other commenters, the requestors submit that CMS consider multiple myeloma as a solid tumor.

Response:

Myeloma (the most common plasma cell neoplasm) and other hematologic malignancies are not generally classified as solid tumors and thus fell outside the scope of a determination on solid tumors. Hematologic malignancies are disseminated rather than localized and their staging criteria differ from the TMN staging system used generally for solid tumors. As we noted in the proposed decision memorandum, we welcomed the submission of evidence that this position should be reconsidered.

We have reviewed additional evidence on the use of FDG PET to guide initial and subsequent treatment in myeloma. This is described elsewhere in this decision memorandum. We are also aware that a rare plasma cell malignancy (solitary plasmacytoma) may present as a single localized lesion. Thus we have decided to make a coverage determination regarding FDG PET in myeloma that is distinct from our coverage determination regarding solid tumors.

Comment:

Several commenters requested coverage for more than one PET scan for guiding initial treatment strategy, in particular for purposes of radiation planning and cases requiring prolonged evaluation.

Response:

The evidence we reviewed addressed the use of single scans. We believe that coverage as we have described of only one FDG PET scan to guide initial antitumor treatment is consistent with the current evidence base.

Comment:

Some insurers opposed the proposed framework that combines restaging and monitoring response to treatment into the single category deemed subsequent treatment strategy because of differing data sets for each indication. One commenter wrote that CMS should adopt a five-part framework that would help avoid inappropriate PET studies by more clearly defining scan indications.

Response

CMS believes that the evidence supports the two-part framework for coverage. We believe this simpler framework is consistent with the practice of medicine and is more easily understood by physicians and patients. As we discuss elsewhere in this memorandum, the uses of an FDG PET scan may overlap, i.e. a single scan may serve multiple purposes. We do not believe that the public would be served by making the framework more complex than is necessary for the efficient and correct administration of the Medicare benefit. Other insurers remain free to use other coverage frameworks and may continue to consider uses on a cancer-by-cancer basis if they wish.

Comment Some insurers also commented that coverage of FDG PET to guide subsequent treatment strategy for all solid tumors should continue as coverage with evidence development.

Response

We generally agree with the commenter on this point and, aside from specific exceptions, have retained the CED requirement for FDG PET to guide subsequent treatment strategy.

Comment

Several commenters asked us to re-evaluate the evidence on FDG PET in ovarian cancer in light of the MEDCAC scores for that cancer and additional evidence. They specifically asked that the CED requirement be removed for FDG PET scans used to guide subsequent antitumor treatment.

Response:

CMS re-evaluated the evidence regarding FDG PET for ovarian cancer. We agree with the commenters and have changed the decision to reflect this broader coverage of FDG PET.

Comment

A commenter suggested that CMS consider a project directed at pre-certification for FDG PET studies.

Response

A pre-certification project for FDG PET is outside the scope of this decision.

Comment:

An insurer organization expressed concern that blanket authorization of coverage for all PET oncologic indications, without review of medical appropriateness, will contribute to inappropriate use of PET.

Response:

The removal of some aspects of the CED requirement does not prevent our contractors from reviewing claims for oncologic uses of FDG PET.

Comment

An insurer organization also commented that CED data should be used to evaluate improved patient outcomes, and that NOPR should report separately for each cancer rather than aggregate reporting.

Response

We agree.

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 the expenses incurred for 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

In addition to section 1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—

...

(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]

...

Section 1142 of the Act describes the authority of the AHRQ. CMS has described this statute more fully in a Guidance Document available at https://www.cms.hhs.gov/ncpc_view_document.asp?id=8. See also section 310 Medicare NCD Manual.

Under the authority of section 1862(a)(1)(E) of the Act, CMS may pay for items and services furnished in connection with certain medical research. Coverage is conditioned on care being delivered in a setting with a pre-specified data collection process and additional protections in place such as are present in some research studies. Under section 1142 of the Act, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically. In addition, evaluations of the comparative effects, health and functional capacity; alternative services and procedures utilized in preventing, diagnosing, treating, and clinically managing diseases, disorders, and other health conditions may be conducted.

In rare instances, for some items or services, CMS may determine that the evidence is very preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A) of the Act, but, if the following criteria are met, coverage with study participation might be appropriate:

- a. The evidence includes assurance of basic safety;
- b. The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and

c. There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future NCD that would focus on whether the item or service should be covered by Medicare under 1862(a)(1)(A) of the Act. Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

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."

We considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. Most studies have focused on test characteristics and changes in physician diagnostic thinking and have not considered health outcomes, such as mortality or morbidity. We believe that health outcomes are more important than test characteristics.

As a diagnostic test, the FDG PET scan would not be expected to directly change health outcomes, i.e. there is no evidence that administration of FDG is therapeutic. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available management alternatives.

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.

Questions

- 1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?*
- 2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?*
- 3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?*
- 4. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended initial and subsequent treatment strategy in beneficiaries with myeloma?*

Analysis

Coverage Framework

We received public input indicating that the previous coverage framework which required cancer-by-cancer consideration of diagnosis, staging, restaging and monitoring response to treatment was challenging for a variety of reasons. They commented that it was burdensome to implement and was not consistent with the cancer treatment community's approach to cancer management. While that coverage framework was useful when introduced, we do not believe that it currently represents how physicians determine treatment for cancer patients. The treating physician's dilemma is to determine how to initially treat the tumor and then, based on response, develop a subsequent strategy. The core purpose of oncologic FDG PET imaging is to identify lesions that, based on their uptake of FDG, are more likely or less likely to represent active tumor tissue. This information would be used, for example, to determine the extent of tumor spread, particularly whether or not the patient is an appropriate candidate for a definitive cure. Accurate information on the extent of the cancer may prompt the treating physician to recommend palliative treatment that may be better tolerated by the patient.

As the technical capabilities of diagnostic imaging have improved over time, physicians' use of imaging has evolved.

When a patient is being evaluated for signs and symptoms that reasonably indicate the presence of a solid tumor, information on the extent and anatomic location of disease can inform the diagnosis itself. Some tumors consistently spread via hematogenous or lymphatic pathways or by local progression. Some tumors metastasize to characteristic distant anatomic locations, e.g. the liver, lungs or the spinal skeleton. This information informs both the diagnosis and the staging of the tumor. We do not believe that it is generally practical to try to apportion a single imaging study to its multiple subsidiary uses. We are unaware of any algorithm that would, for example, say that a single FDG PET study was 60 percent for diagnosis and 40 percent for staging.

This is consistent with the National Comprehensive Cancer Network (NCCN) guidelines which provide guidance to oncologists for the approach to initial and later treatment of solid malignant tumors. These guidelines (available at www.nccn.org) reflect the complex nature of cancer and explicitly call for individualization to the patient's situation and needs. We believe the guidelines offer a more directive approach for initial cancer treatment, recognizing a greater level of evidence for this. They provide more options and less direction for dealing with heterogeneous clinical situations encountered in patients with recurrent solid malignancies. CMS believes the revised coverage framework for oncologic uses of FDG PET reflects this fundamental dichotomy between the initial assessment and treatment planning of a solid tumor and subsequent assessment and treatment planning in the face of tumor recurrence.

Stakeholders have also noted that oncologic staging is a one-way-street, i.e. once assigned, tumor stage cannot be changed. Thus, the concept of restaging, while understandable in the context of determining ongoing tumor burden, has posed challenges. We have also been informed that restaging and monitoring response to therapy may be difficult to distinguish on a practical basis, i.e. the detection of residual tumor burden will provide information on the anatomic location of distal spread but at the same time indicate how well the patient has responded to the prior therapy.

Therefore, we are adopting a simpler framework for our coverage policies regarding the uses of FDG PET. This framework divides oncologic uses of FDG PET reconsidered herein into two distinct parts:

- Determination by the treating physician of the initial treatment strategy, and
- Assessment of the success of the initial treatment strategy to determine the need for and content of a subsequent treatment strategy.

The uses of FDG PET that were previously characterized as diagnosis and staging have been brought into the first part, as these clearly relate to the development of the initial treatment strategy. The uses of FDG PET that were previously characterized as restaging and monitoring response to treatment have been brought into the second part, as these clearly come after the initial treatment strategy. All current NCDs reconsidered in this final decision memorandum that address coverage of FDG PET imaging for oncologic conditions are transitioned into this new framework. Our further discussion below of FDG PET coverage should be read in the context of this new framework.

Separately, we know from clinical practice experience that patients are often confused by the terminology describing the anatomic location of a tumor and the histopathologic classification of a tumor. For example, cancerous tissue found in the lung may arise from a primary lung cancer, e.g. squamous carcinoma of the lung. Cancerous tissue found in the lung may also arise from metastases from other anatomic sites, e.g. the breast or the kidney. In essence, some cancers found in the lung are not lung cancer. Similar analogies can be made for other anatomic locations such as the liver, brain and bones, which are frequent sites of metastatic spread. Our point here is that the identification of a suspicious lesion in the lung does not always result in a diagnosis of lung cancer, even if the lesion is cancerous. In our prior NCD, we separately consider lung cancer and solitary pulmonary nodules. In light of this new framework, there is no longer a need to separately discuss the characterization of a solitary pulmonary nodule outside of the work-up for a possible lung cancer, and we are removing that distinction.

Summary of Evidence

As discussed in the 2005 NCA, we determined that FDG PET scans were no longer experimental, but at that time we believed the evidence was insufficient to reach a conclusion that FDG PET was broadly reasonable and necessary, though there was a sufficient inference of benefit drawn to support limited coverage if certain safeguards for patients were provided. This inference was based on both the pathophysiologic basis for FDG PET's usefulness in cancer, as well as the positive coverage in several cancers for which there is sufficient evidence to warrant coverage. As we also noted in 2005, we believed this to be a unique instance where general knowledge of a technology is well accepted. Now, however, in some instances, the specific applications are better determined. In the current reconsideration, we are reviewing the evidence of FDG PET in the context of our new coverage framework.

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

With 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. Specifically, we believe that FDG PET results are used by treating physicians to discriminate localized from widespread disease and to identify lesions that are appropriate for biopsy.

In general, the literature is consistent in finding FDG PET useful for initial treatment strategy in patients with both biopsy proven cancer and in patients with suspected tumor burden. Although most (except for NOPR) were case series and some were studies of fewer than 40 people (Suzuki, et al. 2007 , Ng SH, et al. 2004), there were appropriate comparators (histopathology) to FDG PET and the conclusions were consistent across most of the evidence presented in the evidence section and the appendix of studies.

We believe there is adequate evidence that FDG PET changes the physician-recommended treatment strategy, especially as related to surgical and possibly curative strategies. As presented in the evidence section, authors note that: When considering the overall patient population of our study, the most meaningful result was that...the majority would have been shifted to possible surgical treatment after FDG PET. This is important as a therapeutic option with curative intent administered as soon as possible, without awaiting evolution to malignancy in the case of indeterminate nodules, will certainly lead to the best achievable clinical outcome (Pepe 2005).

In addition, the TA (McEwan, et al. 2008) notes that there was evidence of the utility of FDG PET for diagnosing, staging, or detecting recurrences, all of which affect treatment strategy.

In our current NCD manual, coverages for three cancers, breast, melanoma and cervix do not easily fit this new framework. In breast cancer, we noncover FDG PET for the diagnosis of breast cancer and the staging of axillary lymph nodes. We cover FDG PET for staging of distant metastasis. We did not receive any evidence in response to our specific request for public comments that required a change in coverage, thus, we will maintain that coverage and make appropriate annotations in that regard in our revised NCD manual.

Similarly, for melanoma, we cover FDG PET for staging but we explicitly noncover FDG PET for evaluation of regional lymph nodes. We will maintain that coverage also. We also continue to cover FDG PET for the detection of pre-treatment metastases (i.e., staging) in newly diagnosed cervical cancer following conventional imaging that is negative for extra-pelvic metastasis as reasonable and necessary as an adjunct test. All other uses of FDG PET for the initial treatment strategy for beneficiaries diagnosed with cervical cancer will remain under CED.

Cervical cancer is diagnosed primarily via biopsy, as the cervix is readily accessible and is directly visualized with optical instruments without specialized imaging technologies. We have nationally covered FDG PET imaging as an adjunct test for the detection of pre-treatment metastases (i.e., staging) in newly diagnosed cervical cancer following conventional imaging that is negative. All other uses of FDG PET related to cervical cancer required CED. See Section 220.6.14 of the NCD Manual. Thus we did not propose to change coverage for FDG PET used to guide the initial treatment of cervical cancer. There was an error in the appended table, Appendix A, and it did not accurately reflect the limited scope of the reconsideration. A public commenter brought that to our attention after the proposed decision was posted.

We are making no change in coverage of FDG PET imaging related to guiding initial treatment strategy for cervical cancer. Thus, we are continuing to cover FDG PET imaging as an adjunct test for the detection of pre-treatment metastases (i.e., staging) in newly diagnosed cervical cancers following conventional imaging that is negative. Other uses of FDG PET related to the initial treatment of cervical cancer remain under CED. As described elsewhere in this decision, we have broadened coverage of FDG PET related to the subsequent treatment of cervical cancer and removed the CED requirement for that specific indication. In summary, Medicare coverage of FDG PET has not changed for uses related to initial treatment, and Medicare coverage of FDG PET for uses related to subsequent treatment strategy has been liberalized.

As part of this analysis, we did review new evidence on the use of FDG PET imaging for prostate cancer. We believe the evidence does not demonstrate that it is useful for the initial treatment strategy in that it does not alter patient management or improve health outcomes. Expert opinion generally agreed with this. Therefore, we are noncovering FDG PET in the initial management of prostate cancer

2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?

In this decision, we reviewed new evidence on the use of FDG PET imaging in the subsequent treatment strategy of solid tumors with the exception of breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid.

The need for additional evidence on the use of FDG PET to guide subsequent treatment strategy in this group is indicated by the internal technology assessment. The literature reviewed by CMS was promising, but had some limitations. In some studies (Connell CA, et al. 2007, Chung, et al. 2007, Magne N et al. 2008) histopathologic confirmation was not obtained in all samples, thus making it difficult to determine the true test performance of FDG PET for use in subsequent treatment strategy. In addition to a much smaller literature base from which to draw conclusions about the use of FDG PET to guide subsequent treatment strategy, the size of the studies was also small

(Pepe, et al 2005 n = 20; Connell CA, et al. 2007 n = 30). As noted previously, there continues to be some difficulty in distinguishing between inflammation (especially post-surgical) and malignancy when FDG PET is used alone and not in concert with other modalities (Votrubova J, et al. 2006).

Data from prospective clinical studies can inform the subsequent care provided to patients, and NOPR has contributed to this effort. We believe that there is a need for more prospective data to answer the question of use of FDG PET for guiding subsequent treatment strategy. The requestors have stated that continuation of NOPR in its present form would not provide information beyond what had already been derived from it. However, they do recommend that evidence development continue for the monitoring indication in the current framework. This is consistent with the external TA (McEwan, et al. 2008) conclusions that called for “additional studies ... to augment the evidence base...and reach firm conclusions.” (McEwan, et al 2008):

“Although FDG PET technology development appears to have reached maturity with the fusion of 18FDG PET and CT in an integrated system, imaging protocols will continue to be refined over the next few years. Further evaluations of the utility of this technology should be done with developments concentrating on enhancing patient throughput and establishing new and more focused clinical applications in various subpopulations of patients.

“...some of the most important roles of 18FDG PET and 18FDG PET/CT have not been sufficiently explored (e.g., estimating prognosis...changing treatment modalities). If the total clinical contributions of 18FDG PET and 18FDG PET/CT have to be evaluated to inform policy decisions, these information gaps need to be filled with new methodological approaches.”

Given the limitations of the medical literature reviewed for FDG PET for subsequent treatment strategy—it is much less robust than that for initial treatment strategy—and, given the findings of the external TA stated previously, CMS finds the use of FDG PET promising but not complete for guiding subsequent treatment strategy for the tumor types not previously covered, with notable exceptions as noted below for cervical cancer, ovarian cancer and myeloma.

Therefore, we have concluded that FDG PET for the determination of subsequent treatment strategy for tumor types other than breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, myeloma, non-small cell lung, ovary and thyroid is not reasonable and necessary under 1862(a)(1)(A). However, we do believe that FDG PET for the determination of subsequent therapy for tumor types other than breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, myeloma, non-small cell lung, ovary and thyroid is promising and support further research under §1862(a)(1)(E) and our CED policy.

Under the authority of §1862(a)(1)(E), coverage with evidence development/coverage with study participation (CED/CSP) will allow Medicare to cover certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CSP allows CMS to determine that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring and clinical expertise. Under section 1142, research may be conducted on the outcomes, effectiveness and appropriateness of health care services and procedures to identify the manner in which diseases, disorders and other health conditions can be prevented, diagnosed, treated and managed clinically.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under §1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

Ideally, this study would be designed to collect additional information at the time of the scan to assist in patient management. This study would examine valid, measurable outcomes when possible and avoid measuring intermediate outcomes. Changes in management that avoid unnecessary biopsy, invasive surgery or dangerous chemotherapeutic agents would be beneficial for patients. Outcomes that show significant changes in management with the use of FDG PET scans would improve the evidence in this arena.

We believe that a limited amount of additional evidence may conclusively address our concerns, as the outcomes of greatest interest are discrete events that are readily identified. These include

- surgical procedures, including biopsies,
- anticancer chemotherapy,
- radiotherapy,
- hospitalization and
- mortality.

We believe that prospective clinical studies are required to assure that any differences in outcomes are confidently attributable to the additional information provided by FDG PET rather than to bias or other factors. Furthermore,

enrolled subjects must adequately represent the Medicare beneficiary population. If these or other studies produce sufficient evidence for us to confidently conclude that such uses of FDG PET that are covered under §1862(a)(1)(E) can be covered under §1862(a)(1)(A), we anticipate reconsidering this NCD to make such changes as are appropriate. We therefore have determined that FDG PET to assess response to the initial antitumor treatment strategy and guide decisions on subsequent treatment strategies for tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, myeloma, non-small cell lung, ovary and thyroid is reasonable and necessary only under §1862(a)(1)(E) Coverage with Evidence Development, specifically Coverage with Study Participation (CSP).

We have consulted with AHRQ which has agreed that the study questions and requirements outlined above are consistent with section §1142 of the Social Security Act.

3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?

CMS notes that there is a paucity of evidence in the literature regarding the role of FDG PET for this use. In their public comment, requestors noted there was no well-accepted data showing that monitoring is linked to improved health outcomes. Hence, we believe that such uses should generally be covered only under CSP.

We remind the reader that Question 3 is posed in the context of a patient who has a known diagnosis of a solid tumor and in whom his treating physician is still actively managing the treatment of the solid tumor. We are not considering the use of FDG PET as a screening test rather than as a diagnostic test.

4. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended initial and subsequent treatment strategy in beneficiaries with myeloma?

Based on additional evidence considered since the publication of the proposed decision memorandum on this topic, such as Hillner 2008B and Nanni 2006, and in response to public comments as noted above, we find the evidence for coverage to be convincing, in guiding physician management of both the initial and subsequent treatment strategy for myeloma. We find evidence of the impact of FDG PET in both settings, for improved diagnostic sensitivity and for impact on initial and subsequent treatment strategy, to be sufficiently convincing to move FDG PET for myeloma from its current national coverage status under §1862(a)(1)(E) to national coverage under §1862(a)(1)(A). As discussed above, given that myeloma is not ideally classified as a solid tumor, despite the known occurrence of solitary plasmacytomas of bone and of soft tissue, we have adjusted Appendix A to reflect this decision to nationally cover FDG PET for myeloma, to avoid the potential difficulty of force-fitting it into the new framework applicable to solid cancers.

Indications not included in the scope of this reconsideration.

As we noted in the proposed decision memorandum, we proposed to continue to cover FDG PET for those specific indications that were already covered under §1862(a)(1)(A). We did not plan to review new evidence on these specific covered indications related to the nine tumor types described below since they were reviewed in prior NCDs and we had not received public input suggesting coverage for these uses should be restricted. Depending on the specific tumor, those covered indications may have been determined for initial or subsequent treatment or both. These tumors included:

- Breast
- Cervix
- Colorectal
- Esophagus
- Head and Neck (non-CNS/thyroid)
- Lymphoma
- Melanoma
- Non-small cell lung
- Thyroid

We remain receptive to considering evidence that would support reconsideration of our coverage policies for those uses.

We did receive evidence to support a liberalization of our coverage of FDG PET to guide subsequent treatment strategy for cervical cancer, and we have, therefore, removed the CED requirement for that specific indication.

CMS has transitioned the current framework—diagnosis, staging, restaging and monitoring response to treatment—into the initial treatment strategy and subsequent treatment strategy framework while maintaining prior coverage for the other eight cancers listed.

Health Disparities

A review of cited articles in this decision memorandum reveals no breakdown of FDG PET findings or of clinical outcome data by racial or ethnic categories. Any inference about relative benefits of FDG PET for initial or subsequent treatment strategy to any specific racial or ethnic groups would be, at best, speculative.

Additionally, we note the paucity of any national consensus guidelines on when FDG PET should be used in the management of solid tumors. Even the requestors have found instances where physicians were ordering FDG PET scans when there was little if any likelihood that the results would provide useful information. We believe that there is a pressing need for the oncology imaging community to create evidence-based guidelines for the use of FDG PET in 2009. CMS will look forward to reviewing these guidelines when they become public and, if necessary, re-opening the FDG PET decision in order to accommodate these evidence-based guidelines as necessary for the appropriate use of FDG PET in cancer management.

IX. Conclusion

CMS was asked to reconsider Section 220.6 of the National Coverage Determination (NCD) Manual to end the prospective data collection requirements across all oncologic indications of FDG PET except for monitoring response to treatment. Section 220.6 of the NCD Manual established the requirement for prospective data collection for FDG PET used in the diagnosis, staging, restaging and monitoring response to treatment for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers, as well as for cancer indications not previously specified in Section 220.6 in its entirety.

We received public input indicating that the coverage framework which required cancer-by-cancer consideration of diagnosis, staging, restaging and monitoring response to treatment should be replaced by a more omnibus framework. Thus, we broadened the scope of this review through an announcement on our website and solicited additional public comment on the use of FDG PET imaging for solid tumors so that we could transparently consider this possibility. Therefore, after receiving public comments as required by § 1862(l) of the Social Security Act (the ACT), we are revising Section 220.6 of the Medicare NCD Manual to reflect a new framework for most solid tumor oncologic indications and for myeloma. This decision replaces sections 220.6.2 (FDG PET for lung cancer); 220.6.3 (FDG PET for esophageal cancer); 220.6.4 (FDG PET for colorectal cancer); 220.6.5 (FDG PET for lymphoma); 220.6.6 (FDG PET for melanoma); 220.6.7 (FDG PET for head and neck cancers non-CNS/thyroid); 220.6.10 (FDG PET for breast cancer); 220.6.11 (FDG PET for thyroid cancer); 220.6.12 (FDG PET for soft tissue sarcoma); 220.6.14 (FDG PET for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers), and 220.6.15 (FDG PET for all other cancer indications) of the NCD Manual with a single section that outlines coverage of PET scans for oncologic conditions. Section 220.6, a general section on PET scanning, will be modified as required by this decision. Coverage determinations in Sections 220.6.1 (PET for perfusion of the heart); 220.6.8 (FDG PET for myocardial viability); 220.6.9 (FDG PET for refractory seizures); 220.6.13 (FDG PET for dementia and neurodegenerative diseases), and 220.6.16 (FDG PET for infection and inflammation) describe coverage of PET imaging for non-oncologic conditions and will not be modified.

1. Framework

CMS is adopting a coverage framework that replaces the four-part diagnosis, staging, restaging and monitoring response to treatment categories with a two-part framework that differentiates FDG PET imaging used to inform the initial antitumor treatment strategy from other uses related to guiding subsequent antitumor treatment strategies after the completion of initial treatment. We are making this change for all NCDs that address coverage of FDG PET for the specific oncologic conditions addressed in this decision.

2. Initial Antitumor Treatment Strategy

CMS has determined that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate initial treatment strategy for beneficiaries with suspected solid tumors and myeloma and improve health outcomes and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore, CMS will cover only one FDG PET study for beneficiaries who have solid tumors 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 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.

As exceptions to the initial treatment strategy section above:

a. CMS has reviewed evidence on the use of FDG PET imaging to determine initial antitumor treatment in patients with adenocarcinoma of the prostate. CMS has determined that the available evidence does not demonstrate that FDG PET imaging improves physician decision making in the determination of initial anti-tumor treatment strategy in Medicare beneficiaries who have adenocarcinoma of the prostate, does not improve health outcomes and is thus not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore, FDG PET is nationally noncovered for this indication of this tumor type.

b. CMS received no new evidence demonstrating a change was warranted with respect to the use of FDG PET imaging to determine initial antitumor treatment in breast cancer; thus CMS is not making any change to the current coverage policy for FDG PET in breast cancer. We continue to cover FDG PET imaging for the initial treatment strategy for male and female breast cancer only when used in staging distant metastasis. FDG PET imaging for diagnosis and initial staging of axillary nodes will remain noncovered.

c. CMS received no new evidence demonstrating a change was warranted with respect to use of FDG PET imaging of regional lymph nodes in melanoma; thus we are not changing the current NCD for FDG PET in melanoma. CMS will continue noncoverage of FDG PET for the evaluation of regional lymph nodes in melanoma. Other uses to determine initial treatment strategy remain covered.

d. CMS received no new evidence demonstrating a change was warranted with respect to use of FDG PET imaging in the initial treatment strategy for cervical cancer. We continue to cover FDG PET imaging as an adjunct test for the detection of pre-treatment metastasis (i.e., staging) in newly diagnosed cervical cancers following conventional imaging that is negative for extra-pelvic metastasis. All other uses of FDG PET for the initial treatment strategy for beneficiaries diagnosed with cervical cancer will continue to only be covered as research under §1862(a)(1)(E) of the Act through Coverage with Evidence Development (CED) as outlined immediately below and in Section 3. Therefore, we will cover one initial FDG PET study for newly diagnosed cervical cancer when not used as an adjunct test for the detection of pre-treatment metastases following conventional imaging that is negative for extra-pelvic metastasis only when the beneficiary's treating physician determines that the FDG PET study is needed to inform the initial antitumor treatment strategy and the beneficiary is enrolled in, and the FDG PET provider is participating in, the following type of prospective clinical study:

- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The clinical studies for which we will provide coverage must answer one or more of the following questions: Prospectively, in Medicare beneficiaries with newly diagnosed cervical cancer who have not been found following conventional imaging to be negative for extra-pelvic metastases and whose treating physician determines that the FDG PET study is needed to inform the initial antitumor treatment strategy, does the addition of FDG PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

The study must adhere to the standards of scientific integrity and relevance to the Medicare population as described in part 3, items a through m, below

3. Subsequent Antitumor Treatment Strategy

CMS reviewed evidence on the use of FDG PET in the subsequent treatment strategy for patients with tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung and thyroid.

For tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid, CMS has determined that the available evidence is not adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent anti-tumor treatment strategy or improves health outcomes in Medicare beneficiaries and thus is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

However, CMS has determined that the available evidence is sufficient to determine that FDG PET imaging for subsequent anti-tumor treatment strategy for tumor types other than breast, colorectal, esophagus, head and neck (non-

CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid may be covered as research under §1862(a)(1)(E) of the Act through Coverage with Evidence Development (CED).

Therefore, we will cover a subsequent FDG PET study for tumor types other than breast, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung and thyroid when the beneficiary's treating physician determines that the FDG PET study is needed to inform the subsequent antitumor treatment strategy and the beneficiary is enrolled in, and the FDG PET provider is participating in, the following type of prospective clinical study:

- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the FDG PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy and other Federal laws must be followed.

The clinical studies for which it will provide coverage must answer one or more of the following questions: Prospectively, in Medicare beneficiaries whose treating physician determines that the FDG PET study is needed to inform the subsequent antitumor treatment strategy, does the addition of FDG PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
- g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

- l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

As exceptions to the subsequent treatment strategy section above:

- a. CMS has reviewed evidence on the use of FDG PET imaging to determine subsequent treatment strategy in patients with ovarian cancer. CMS has determined that the available evidence is adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent treatment strategy in Medicare beneficiaries who have ovarian cancer, improves health outcomes and is thus reasonable and necessary under §1862(a)(1)(A) of the Act. Therefore, CMS has determined that FDG PET imaging is nationally covered for this indication for this tumor type.
- b. CMS has reviewed evidence on the use of FDG PET imaging to determine subsequent treatment strategy in patients with cervical cancer. CMS has determined that the available evidence is adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent treatment strategy in Medicare beneficiaries who have cervical cancer, improves health outcomes and is thus reasonable and necessary under §1862(a)(1)(A) of the Act. Therefore, CMS has determined that FDG PET imaging is nationally covered for this indication for this tumor type.

4. Myeloma

CMS reviewed evidence on the use of FDG PET in the initial and subsequent treatment strategy for myeloma. CMS has determined that the available evidence is sufficient to determine that FDG PET imaging improves physician decision making for these uses in Medicare beneficiaries who have myeloma, improves health outcomes and is thus reasonable and necessary under §1862(a)(1)(A) of the Act. Therefore, CMS has determined that FDG PET imaging is nationally covered for this indication for this tumor type.

5. Further Exceptions

We specifically requested public comments with respect to treatment strategy of nine cancers that were covered in prior NCDs under 1862(a)(1)(A). For the nine tumor types listed below, we will continue to cover FDG PET for those specific indications currently covered under §1862(a)(1)(A) of the Act. We have not received public input suggesting coverage for these uses should be restricted. These include specific indications pertinent to:

- Breast
- Cervix
- Colorectal
- Esophagus
- Head and Neck (non-CNS/thyroid)
- Lymphoma
- Melanoma
- Non-small cell lung
- Thyroid

CMS has transitioned the prior framework—diagnosis, staging, restaging and monitoring response to treatment—into the initial treatment strategy and subsequent treatment strategy framework while maintaining current coverage. See Appendix A for a chart summarizing the effect of these changes.

Appendix A: Effect of Coverage Changes on Oncologic Uses of FDG PET See NCD Manual for specific coverage language.

	Final Framework	
Solid Tumor Type	Initial Treatment Strategy*	Subsequent Treatment Strategy**
Colorectal	Cover	Cover
Esophagus	Cover	Cover
Head & Neck (not thyroid or CNS)	Cover	Cover
Lymphoma	Cover	Cover
Non-small cell lung	Cover	Cover
Ovary	Cover	Cover
Brain	Cover	CED
Cervix	1 or CED	Cover
Small cell lung	Cover	CED
Soft Tissue Sarcoma	Cover	CED
Pancreas	Cover	CED
Testes	Cover	CED
Breast (female and male)	2	Cover
Melanoma	3	Cover
Prostate	N/C	CED
Thyroid	Cover	4 or CED
All other solid tumors	Cover	CED
Myeloma	Cover	Cover
All other cancers not listed herein	CED	CED

* Formerly “diagnosis” and “staging”

** Formerly “restaging” and “monitoring response to treatment when a change in treatment is anticipated”

N/C = noncover

(1) Cervix: Covered for the detection of pre-treatment metastases (i.e., staging) in newly diagnosed cervical cancer subsequent to conventional imaging that is negative for extra-pelvic metastasis. All other uses are CED.

(2) Breast: Noncovered for diagnosis and/or initial staging of axillary lymph nodes. Covered for initial staging of metastatic disease.

(3) Melanoma: Noncovered for initial staging of regional lymph nodes. All other uses for initial staging are covered.

(4) 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.

APPENDIX B

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

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 systematic 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 and 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: Evidence Tables [PDF, 277KB] Studies of PET for Oncology Indications

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