Proposed Decision Memo for Positron Emission Tomography (FDG) for Cervical Cancer (CAG-00181R2)

Decision Summary

CMS was asked to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements for FDG PET for initial staging of cervical cancer. CMS proposes that the evidence is adequate to determine that the results of FDG PET imaging for cervical cancer staging of beneficiaries diagnosed with cervical cancer are used by the treating physician to make meaningful changes in therapeutic management and improve health outcomes, and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

Therefore, CMS proposes to cover only one FDG PET for staging in beneficiaries who have biopsy proven cervical cancer 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.

The requestor also noted that "CMS may find it appropriate to exclude coverage for diagnosis of cervical cancer since this disorder is initially diagnosed by biopsy. CMS agrees and proposes that there is no credible evidence that the results of FDG PET imaging are useful to make the initial diagnosis of cervical cancer, and therefore do not improve health outcomes, and thus are not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore CMS proposes to noncover FDG PET for this indication.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Social Security Act.

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Proposed Decision Memo

TO: Administrative File: CAG #00181R2 FDG PET to Guide Initial Management of Cervical Cancer

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SUBJECT: Proposed Coverage Decision Memorandum for FDG PET to Guide Initial Management of Cervical Cancer (CAG-00181R2)

DATE: August 13, 2009

I. Proposed Decision

CMS was asked to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements for FDG PET for initial staging of cervical cancer. CMS proposes that the evidence is adequate to determine that the results of FDG PET imaging for cervical cancer staging of beneficiaries diagnosed with cervical cancer are used by the treating physician to make meaningful changes in therapeutic management and improve health outcomes, and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

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- 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
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The requestor also noted that "CMS may find it appropriate to exclude coverage for diagnosis of cervical cancer since this disorder is initially diagnosed by biopsy. CMS agrees and proposes that there is no credible evidence that the results of FDG PET imaging are useful to make the initial diagnosis of cervical cancer, and therefore do not improve health outcomes, and thus are not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore CMS proposes to noncover FDG PET for this indication.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Social Security Act.

II. Background

FDG PET

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 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). MRI denotes magnetic resonance imaging, and CT (used separately) indicates computed tomography without PET. 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 substance (radionuclide) that gives off sub-atomic 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 the initial treatment.

Cervical Cancer

There are approximately 11,000 new cases of cervical cancer and almost 4000 deaths annually in the US. Widespread screening of cervical cytology (Papanicolaou screening) has significantly reduced the frequency and burden of this disease. Treatment recommendations for cervical cancer depend on the stage of the cancer, which in turn depends on its anatomic spread and other factors.

The cervix is easily accessible for examination, and the diagnosis itself is readily made by biopsy without the need for complex medical imaging. There are several methods to determine the extent of disease, and these may include surgical exploration, endoscopic procedures or complex medical imaging.

Interested readers can obtain more information on cervical cancer from the NCI website at http://www.cancer.gov/cancertopics/types/cervical/.

III. History of Medicare Coverage

CMS previously reviewed scientific literature and established coverage for many uses of FDG PET. A summary of currently covered oncologic 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 FDG PET oncologic indications are listed below.

Effective Date	Clinical Condition/Indication	Coverage
January 28, 2005	Brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers	Coverage with evidence development (CED) for all FDG PET indications except limited cervical staging conditions
January 28, 2005	All other cancers and indications not previously specified	Coverage with evidence development
April 3, 2009	Solid Tumors and Myeloma	Coverage for most uses related to initial management, coverage with evidence development for most uses related to subsequent management. Noncoverage for uses related to initial management of prostate cancer.

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. We recently reconsidered that NCD and published an April 3, 2009 final decision memorandum on many but not all oncologic uses of FDG PET. Those reconsidered indications were also transitioned to a new, simplified framework. Indications that were formerly categorized as diagnosis and/or staging are now categorized as guiding initial antitumor treatment strategy. Indications that were formerly categorized as restaging and/or monitoring response to treatment are now categorized as guiding subsequent i.e. after initial definitive anti-tumor treatment, antitumor treatment strategy.

Our Current NCD for Cervical Cancer Provides:

A. Staging for Invasive Cervical Cancer as an Adjunct to Conventional Imaging

The CMS has determined that there is sufficient evidence to conclude that an FDG PET scan is reasonable and necessary for the detection of metastases during the pre-treatment management phase (i.e., staging) in patients with newly diagnosed and locally advanced cervical cancer with no extra-pelvic metastasis on conventional imaging tests, such as computed tomography (CT) or magnetic resonance imaging (MRI). Use of FDG PET as an adjunct may more accurately assist in the non-invasive detection of para-aortic, pelvic nodal involvement and other metastases in the pre-treatment phase of disease. The following conditions must be met:

A pathologic diagnosis of cervical cancer must have already been made before the FDG PET scan is performed,
The results of other imaging procedures used (e.g., MRI or CT) must be reported, and,
The available conventional imaging tests are negative for extra-pelvic metastasis.

NOTE: Other staging utilizing FDG PET (e.g., as a substitute for conventional structural imaging; when a previous MRI or CT is positive or inconclusive for para-aortic metastasis and negative for supra-clavicular nodal metastasis) are only covered as "coverage with evidence development".

Medicare shall notify providers and beneficiaries where these services can be accessed, as they become available, via the following:

Federal Register Notice
CMS coverage Web site at: www.cms.gov/coverage
B. Brain, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers, and other indications of Cervical Cancer not mentioned in Section A above

"Coverage with evidence development" applies to all FDG PET indications for brain, ovarian, pancreatic, small cell lung, testicular cancers, and other indications of cervical cancer not mentioned in Section A above.

The requestors asked CMS to reconsider Section 220.6 to end the prospective data collection requirements for FDG PET used for initial staging of cervical cancer in beneficiaries who have already been diagnosed with cervical cancer by biopsy. The requestors also note that FDG PET is not clinically appropriate for the diagnosis of cervical cancer and request that FDG PET be noncovered for that use.

B. Benefit Category

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

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

IV. Timeline of Recent Activities

May 8, 2009	CMS posts a tracking sheet on the website and opens a 30 day public comment period.

V. Food and Drug Administration (FDA) Status

Consistent with a Federal Register notice dated March 10, 2000 (Volume 65, Number 48) Notices, Pages 12999-13010, the FDA has concluded that FDG F18, when produced under the conditions specified in an approved application, can be found to be safe and effective in the following conditions:
"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 NCDs, 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 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 Medicare beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary under § 1862(a)(1)(A) of the Act.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information 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 public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We recently conducted an exhaustive review of the evidence for a clinical benefit of many oncologic uses of FDG PET (Medicare National Coverage Determinations Manual, §220.6.) A complete discussion of that review can be found at https://www4.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=218.

Below is a summary of the evidence we considered during our current review. CMS considered additional evidence submitted through the public comment period. As part of our earlier review 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). We believe that portions of that earlier review are relevant to the current reconsideration and we note them below. 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 cervical cancer or who are reasonably suspected to have a high likelihood of cancer based on clinical findings and preliminary diagnostic testing.

B. Discussion of evidence reviewed

1. Questions & Outcomes of Interest

1. Is the evidence adequate to conclude that the results of an FDG PET scan for the indication of initial tumor staging will meaningfully alter the recommended treatment strategy for beneficiaries who have a diagnosis of cervical cancer?

2. Is the evidence adequate to conclude that the results of an FDG PET scan for the indication of tumor diagnosis will meaningfully alter the recommended treatment strategy for beneficiaries who are suspected to have cervical cancer but who do not have a tissue diagnosis of cervical cancer?

As a diagnostic test, FDG PET would not be expected to directly change health outcomes, i.e. there is no evidence that the administration of FDG is therapeutic in and of itself. 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 treatment options.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but also include beneficial or adverse clinical effects, such as changes in management due to test findings or preferably, improved health outcomes for Medicare beneficiaries. Ideally, we would see evidence that the systematic incorporation of FDG PET results into a treatment algorithm leads treating physicians to prescribe different and better treatment than they would otherwise have prescribed, and that those patients whose treatment is changed by test results achieve improved outcomes.

2. External technology assessments

As part of our review leading up to the April 3, 2009 NCD on FDG PET for Solid Tumors, CMS had requested an external technology assessment (TA) from the Agency for Healthcare Research and Quality (AHRQ). That TA reviewed FDG PET, with or without computerized tomography (FDG PET/CT)) scanning, and 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.

We believe that the evidence reviewed in that TA is relevant to our current reconsideration of FDG PET for the staging of cervical cancer. For the convenience of the reader we provide a brief description below. The full document is available at the following link: https://www4.cms.hhs.gov/mcd/viewtechassess.asp?where=index&tid=54.

In that TA, the authors commented that:

The strongest evidence for the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT has been produced for staging of locally advanced cervical cancer … Anatomical imaging techniques such as CT and MRI can be fairly inaccurate in detecting retroperitoneal nodal metastasis and therefore, it is important to explore whether functional imaging methods such as ^{18}FDG-PET can help to improve the accuracy of pretreatment staging and have a positive impact on patient survival.

In assessing the overall effect of FDG PET for use in staging of cervical cancer, the authors commented:

When ^{18}FDG-PET and ^{18}FDG-PET/CT were evaluated for staging purposes, we found that the values in the positive and negative LRs [likelihood ratios] were similar for both techniques. Significant results were reported for the positive LR, indicating that both techniques seem to be useful to detect the stage of the disease. The results for the negative LR were not statistically significant and therefore, it appears that a negative result both in 18FDG-PET and ^{18}FDG-PET/CT is not useful to identify the stage of cervical cancer. The 62 findings were consistent across the different reference standards and study designs (i.e., retrospective v. prospective).

The TA authors also examined studies of the effect of FDG PET on clinical decision making and commented that:

[B]oth ^{18}FDGPET and ^{18}FDG-PET/CT assisted in guiding the management strategy by allowing for more precise restaging. Notably, the use of ^{18}FDG-PET and ^{18}FDG-PET/CT most often altered the management course from curative to palliative care, thus avoiding unnecessary treatment. Further, two prospective studies found improved survival among patients who had 18FDG-PET as part of their management strategy.

3. Internal technology assessment

Literature Search

CMS performed a literature search utilizing PubMed for randomized controlled trials (RCTs), systematic reviews, and series studies evaluating the technology used for the diagnosis and staging of cervical cancer. The literature search was limited to humans, and to articles in English published in the last five years (prior to April 2009).

Chao A et al. 2008

This report summarized a study of a case series of 47 patients with cervical cancer with suspected metastases by MRI to para-aortic, inguinal, or supraclavicular lymph nodes. A PET or PET/CT scan had positive clinical impact in 21/47 patients (45%), including disclosure of additional curable sites; down-staging, offering metabolic biopsy, or changing treatment plan to palliation. Prognosis varied for patients based on site of most distant metastases. Two year survival in patient with para-aortic lymph node metastases was 50.6% but was 24.7% in patients with supraclavicular lymph node metastases. The authors concluded that PET or PET/CT added benefit to primary treatment planning for cervical cancer patients with MRI-suspected distant lymph node metastases.

Choi 2006

In this article the authors reviewed their experience with PET/CT diagnostic performance in comparison to MRI in 22 untreated patients with histopathologically confirmed invasive cervical carcinoma. Patients in this prospective study had no evidence of distant metastases and no contraindications to surgery. Pre-operative imaging included both MRI and PET/CT scans. Patients underwent subsequent lymphadenectomies. Compared with histopathological findings, MRI and PET/CT scans were compared for diagnostic performance, based on lymph node groups detected in all patients:

Imaging	Sensitivity	Specificity	Accuracy
MRI	10/33 (30%)	112/121 (93%)	112/154 (73%)
PET/CT	19/33 (58%)	112/121 (93%)	131/154 (85%)

The difference in sensitivity between MRI and PET/CT was statistically significant ($p = 0.026$), but the differences in specificity and accuracy were not.

The authors conclude that PET/CT was more sensitive that MRI in detecting lymph node metastases in patients with cervical cancer.

Grigsby PW et al. 2001

This retrospective study of 101 consecutive patients compared the use of CT and FDG PET for lymph node staging in 101 patients with histologically confirmed carcinoma of the cervix. Patients ranged in age from 26 to 88 years, with a mean age of 53 years. CT and FDG PET findings in pelvic and para-aortic lymph nodes were as follows:

Imaging Method	Pelvic Lymph Nodes with enlargement (CT) or abnormal uptake (FDG PET)	Para-aortic Lymph Nodes with enlargement (CT) or abnormal uptake (FDG PET)
CT	20/101 (20%)	7/101 (7%)
FDG PET	67/101 (67%)	21/101 (21%)

In patients who were had no evidence by CT of pelvic or para-aortic lymph node involvement, there were significant differences in 2-year progression-free survival in patients with evidence of FDG accumulation in para-aortic lymph nodes (64% vs. 18%, (CT-/FDG PET- vs. CT-/FDG PET+, $p = 0.001$). FDG PET status of the para-aortic lymph nodes was the most significant independent prognostic factor for progression-free survival. 8/101 patients also showed FDG PET involvement (later histologically confirmed) of supraclavicular nodes, and all 8 patients also had pelvic and para-aortic involvement by FDG PET. The authors concluded that routine diagnostic evaluation of patients with carcinoma of the cervix should include PET imaging, and suggested that FDG PET findings would affect treatment planning.

Hillner BE, et al. 2008
In this prospective questionnaire-based case series of a total 22,976 subjects with various types of malignancies, conducted by the National Oncologic FDG PET Registry (NOPR), cancer of the cervix accounted for 984 scans, including both initial and subsequent treatment planning. 341 scans were performed during initial assessment of patients with cervical cancer, and of these, changes in treatment plan were noted in 36.1% (from either treatment to non-treatment or vice versa). Authors concluded that physicians often changed their intended management in cases of cervical cancer, based on FDG PET/CT scan performed during initial assessment and treatment planning.

Magne 2008
This article described a summary of published clinical articles about the use of FDG PET/CT in cervical cancer. The authors reviewed the literature up to May 2008. They concluded that, based on the articles reviewed, FDG PET/CT is valuable in the initial assessment of invasive cervical cancer, even when CT findings alone were negative. These articles also suggested that substantial changes in treatment planning occur for a number of patients. However, the authors noted that published studies suggest a limited role for FDG PET/CT in staging of early stage (FIGO Stage IA or IB) due to FDG PET/CT's known insensitivity for detecting lesions of less than one centimeter in diameter. Because of this, the authors also noted that no studies supported the use of FDG PET/CT for lymph node assessment as a replacement for lymphadenectomy.

Selman 2008
This publication describes a literature search and meta-analysis of the accuracy of several diagnostic methods for assessing lymph node status in the preoperative staging of cervical cancer. The literature search eventually focused on 72 published articles, including 8 studies about positron emission tomography involving a total of 445 patients.
A table of their results follows ("LR" denotes likelihood ratio):

Method	Sensitivity	Specificity	Pooled positive LR	Pooled negative LR
Sentinel node biopsy	91%	100%	40.8	0.18
PET	75%	98%	15.3	0.27
MRI	56%	93%	6.4	0.50
CT	58%	92%	4.3	0.58

The authors concluded that sentinel biopsy was the most accurate method for determining lymph node status, but that sentinel biopsy and FDG PET were significantly better methods for determining lymph node status than were MRI or computed tomography. They also noted that the relatively small numbers of studies of FDG PET limited the precision of their conclusions of its diagnostic performance.

Tran BN et al., 2003

This article describes findings in this case series of 186 patients with a histologically confirmed new diagnosis of cervical cancer evaluated prior to therapy. (The article noted that the 101 patients on whose findings the Grigsby PW et al., 2001 article (above) was based are included in this study, including 8 patients with supraclavicular lymph node involvement.) Based on whole-body FDG PET scans, 14 patients had abnormal FDG uptake in the left supraclavicular lymph nodes without palpable disease on clinical examination. These 14 patients ranged in age from 25 to 72 years, with a mean age of 52 years. These 14 patients also had abnormal FDG uptake in pelvic and para-aortic lymph nodes. Sonographically guided fine-needle aspiration of supraclavicular lymph nodes identified tumor by cytology in all 14 of these patients, suggesting an overall FDG PET specificity of 100%. Median overall survival in these 14 patients was 7.5 months. The authors concluded that whole-body FDG PET is an appropriate method for evaluating the supraclavicular lymph nodes in patients with invasive cervical cancer but without palpable lymphadenopathy.

4. MEDCAC

CMS did not convene the MEDCAC for this reconsideration on cervical cancer. However, during an August 20, 2008 MEDCAC meeting pursuant to the April 3, 2009 NCD, the panel opined on FDG PET imaging for the diagnosis and treatment of cervical cancer in the context of a broader discussion of FDG PET for many cancer indications.

The 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. Additional materials of that meeting are available at the following URL: https://www4.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=44.

The committee was asked to consider the following questions pertinent to our current consideration of FDG PET and cervical cancer. The following indicate the average vote of MEDCAC members voting for each question.

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 cervical cancers?

For Diagnosis, MEDCAC members expressed little confidence in FDG PET effect on physician decision making in the diagnosis of cervix neoplasms (average of 1.5 on a scale of 0 to 5).

However, for Staging, MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in staging of cervix neoplasms (average of 3.5 on a scale of 0 to 5).

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 little confidence in FDG PET performance for diagnosis of cervix neoplasms (1.5 on a scale of 0 to 5).

However, for staging, MEDCAC members indicated relatively stronger confidence in FDG PET performance for staging of cervix (an average of 3.75 on a scale of 0 to 5).

In addition, MEDCAC members also addressed several other issues, 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. 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 identified the following evidence based guidelines that address the initial management of cervical cancer.

The National Comprehensive Cancer Network (NCCN) Practice Guidelines (NCCN 2009) address the uses of FDG PET/CT in the initial assessment of patients with cervical cancer. This includes the suggestion that FDG PET/CT be used in staging during initial workup of cervical cancer, although this is optional if the tumor appears to be Stage IB1 or lower (Stage IB1: Cervical cancer, confined to uterus, clinically visible lesion 4.0 cm or less in greatest dimension).

6. Professional Society Position Statements

We expect to receive professional society position statements on this proposed decision.

7. Expert Opinion

We expect to receive expert opinion on this proposed decision.

8. Public Comments

CMS received a total of twenty-four comments during the first comment period including those from professional societies, surgical oncologists, nuclear medicine physicians, professors of medicine at various university hospitals and health insurance companies among others. The comments criticized the current coverage policy and expressed overwhelming support for amending the current national coverage determination to provide coverage of FDG PET for the initial staging of cervical cancer.

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 Social Security Act.

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."

As a diagnostic test, FDG PET would not be expected to directly change health outcomes, i.e. there is no evidence that administration of FDG is, in and of itself, 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.

Based on the legal framework set forth above, this section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions posed above.

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. Many studies have focused on test characteristics but others have considered health outcomes, such as symptom improvement in patients who receive CPAP treatment based on sleep test results. We believe that evidence of improved health outcomes is more persuasive than evidence of test characteristics.

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

Questions

1. Is the evidence adequate to conclude that the results of an FDG PET scan for the indication of initial tumor staging will meaningfully alter the recommended treatment strategy for beneficiaries who have a diagnosis of cervical cancer?

2. Is the evidence adequate to conclude that the results of an FDG PET scan for the indication of tumor diagnosis will meaningfully alter the recommended treatment strategy for beneficiaries who are suspected to have cervical cancer but who do not have a tissue diagnosis of cervical cancer?

Staging

Based upon our review of the evidence we believe that the results of FDG PET imaging provide clinically meaningful information about the initial stage of the tumor and that this information is used by the treating physician to determine the appropriate initial antitumor strategy. We believe that this conclusion is supported by the TA, the August 20, 2008 MEDCAC vote and by our own internal assessment of the technology.

As the requestors have written, the appropriate treatment strategy for cervical cancer is meaningfully changed if the patient is found to have distant metastases, in particular to the supraclavicular lymph nodes (Grigsby 2001, Tran 2003). The findings in several of the articles we have reviewed agree with the consensus of the MEDCAC: that, compared with other non-invasive methods, FDG PET is more sensitive in determining lymph node involvement in initial assessment of cervical cancer (Choi 2006; Selman 2008). In addition, publications support the beneficial effect on initial treatment planning of cervical cancer (Chao 2008, Hillner 2008), with the majority of the effect being avoidance of futile surgery.

In summary, we propose that the evidence is sufficient to determine that FDG PET for the initial staging of cervical cancer leads to improved physician management of this condition and improves health outcomes in Medicare beneficiaries who have been diagnosed with cervical cancer and is thus reasonable and necessary under Section 1862(a)(1)(A) of the Social Security Act.

The effect of this decision, if finalized as we have proposed, would be to provide national Medicare coverage of FDG PET for the initial staging of cervical cancer and remove the coverage with evidence development (CED) requirement for coverage of those uses of FDG PET for cervical cancer initial staging which heretofore have been only reasonable and necessary under Section 1862(a)(1)(E) of the Act. This decision would not restrict those uses that are already covered under Section 1862(a)(1)(A) of the Social Security Act, i.e. the detection of metastases during the pre-treatment management phase (i.e., staging) in patients with newly diagnosed and locally advanced cervical cancer with no extra-pelvic metastasis on conventional imaging tests, such as computed tomography (CT) or magnetic resonance imaging (MRI). We would for administrative efficiency amend those provisions of the NCD manual so as to clearly describe the national coverage of FDG PET for the initial staging of cervical cancer.

Diagnosis

As the requestor has noted, there is "essentially no clinical evidence that PET has a role in the diagnosis of cervical cancer." The MEDCAC expressed little confidence that FDG PET imaging improves physician decision making when used for the diagnosis of cervical cancer.

The appropriate method for the diagnosis of cervical cancer is biopsy, given that the cervix is easily visualized and readily accessible for direct biopsy. We note that the American College of Obstetricians & Gynecologists (ACOG) includes the following information for patients on its website. (Accessed 6/8/2009 at http://www.acog.org/publications/patient_education/bp163.cfm)

Diagnosis

Most dysplastic changes and early cancers are found in women who have regular Pap tests. Most advanced cancers of the cervix are found in women who have not had routine Pap tests. That is why it is important to have routine Pap tests.

If you have an abnormal Pap test result or symptoms of cervical cancer, you may need further testing. Further testing methods, such as colposcopy and biopsy, can help show if abnormal cells are dysplastic or cancer. These tests also help your doctor decide if you need treatment. You may be referred to another doctor or a special clinic for these tests:

- Colposcopy. This test lets your doctor look at the end of the cervix through a microscope. It can help your doctor find problems that cannot be seen with the eye alone.
- Biopsy. In this procedure, a small sample of tissue is removed. The sample is sent to a lab to be studied.
- Cone biopsy. In this procedure, a cone-shaped wedge of the cervix is removed. The sample is sent to a lab to be studied.
- Loop electrosurgical excision procedure (LEEP). In this procedure, a thin wire loop that carries an electric current is used to remove abnormal areas of the cervix. This electric energy also is used to close off the blood vessels on the surface of the cervix.

We are unable to find credible evidence that FDG PET imaging is required to make the diagnosis of cervical cancer, and we believe that it is neither reasonable nor necessary for this purpose under Section 1862(a)(1)(A) of the Social Security Act.

We believe that the evidence is also inadequate to provide coverage of FDG PET for the diagnosis of cervical cancer under Coverage with Evidence Development (CED). Despite adequate time and infrastructure to develop evidence to support this use of FDG PET, there remains no evidence of meaningful benefit and we have no credible reason to believe that continued data collection under CED will provide sufficient evidence.

The effect of this decision, if finalized as we have proposed, would be to nationally noncover FDG PET for cervical cancer diagnosis..

X. Proposed Conclusion

CMS was asked to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements for FDG PET for initial staging of cervical cancer. CMS proposes that the evidence is adequate to determine that the results of FDG PET imaging for cervical cancer staging of beneficiaries diagnosed with cervical cancer are used by the treating physician to make meaningful changes in therapeutic management and improve health outcomes, and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

Therefore, CMS proposes to cover only one FDG PET for staging in beneficiaries who have biopsy proven cervical cancer 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.

The requestor also noted that "CMS may find it appropriate to exclude coverage for diagnosis of cervical cancer since this disorder is initially diagnosed by biopsy. CMS agrees and proposes that there is no credible evidence that the results of FDG PET imaging are useful to make the initial diagnosis of cervical cancer, and therefore do not improve health outcomes, and thus are not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore CMS proposes to noncover FDG PET for this indication.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Social Security Act.

APPENDIX A

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 systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

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

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed 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.

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