Decision Memo for Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers (CAG-00181N)

Decision Summary

CMS has determined that there is sufficient evidence to conclude that an FDG PET scan 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 is reasonable and necessary as an adjunct test, and CMS intends to issue a national coverage determination (NCD) for this indication.

For all other indications in this decision memorandum, CMS has determined that the evidence is sufficient to conclude that an FDG PET scan is reasonable and necessary only when the provider is participating in and patients are enrolled in one of the following types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (42 CFR 405.201) or;
- 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.

All other previous positive national coverage determinations will remain in effect. (See Appendix A.)

All other previous national non-coverage determinations based on evidence of lack of benefit will remain in effect. (See Appendix A.)

For all other indications for which CMS currently has a noncoverage determination (see Appendix A), CMS has determined that an FDG PET scan is be reasonable and necessary only when the provider is participating in and patients are enrolled in one of the prospective clinical studies described above.

As an Agency, CMS recognizes the complex nature of the prospective clinical studies discussed in this decision memorandum. The broad range of public comments received exemplifies the multifaceted interests to be considered when implementing such a program. It is CMS' understanding that there are clinical studies currently being developed which will fully implement this coverage decision. However, no clinical study will be fully operational by the effective date of this decision. Therefore, while this coverage decision is effective, it will not be fully implemented until a clinical study is ready to enroll providers and patients. CMS will continue working with the oncology imaging communities to develop the systems necessary to implement this NCD.

Back to Top

Decision Memo

To: Administrative File: CAG 00181N
Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers

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Subject: Decision Memorandum: Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers

Date: January 28, 2005

I. Decision

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II. Background

FDG PET is a minimally-invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseases such as cancer, ischemic heart disease, and some neurological disorders. 2-[F-18] Fluoro-D-Glucose (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 of the tissue being studied. As malignancies can cause abnormalities of metabolism and blood flow, FDG PET evaluation can indicate the probable presence or absence of malignancy based upon observed differences in biologic activity of adjacent tissues.

Diagnostic imaging technologies such as x-ray films, computed tomography (CT), and magnetic resonance imaging (MRI) supply information about the anatomic structure of suspected malignancies, primarily their size and location. FDG PET's utility in cancer imaging is its ability to differentiate some abnormalities based on metabolic or molecular function. Detecting alteration in glucose metabolism within cells is unique to PET technology.

An FDG PET scan can be interpreted based on qualitative and/or semi-quantitative evaluation. Qualitative FDG PET involves making assessments by visually interpreting the scan results. Metabolically active areas of the body "light up" on an FDG PET scan more so than less active areas. Metabolically active areas may include areas of cancer, inflammation, and benign cellular activity. Semi-quantitative evaluation uses the glucose metabolic rate of a tumor and, through computer software, determines a numeric value representing the metabolic activity for that tumor. Tumor-to-background ratio is a semi-quantitative method that compares a tumor's glucose uptake to the glucose uptake of surrounding or background tissue. This ratio is reported as standardized uptake value (SUV) and takes into account such factors as patient weight and injected FDG dosage, as well as the time lapsed from injection to metabolic imaging. FDG PET has been proposed as one possible test for determining the diagnosis, initial staging, restaging, and monitoring response to therapy for many cancers.

On February 24, 2003, CMS began an NCD process for FDG PET for brain, cervical, ovarian, pancreatic, small cell lung, and testicular cancers. This is a continuation of numerous NCDs in the past on many disparate types of cancer. Unfortunately, there is a paucity of published, methodologically robust, peer-reviewed clinical research data to support most of these requests. In some instances in the past, we have determined that enough evidence existed to warrant some limited coverage for some of these cancers. However, most of the recent NCD requests lacked sufficient evidence to determine a benefit and therefore remained noncovered. In addition, there is a high likelihood that opening NCDs for additional cancers, based on our conversations with the National Cancer Institute's Biomedical Imaging Program, would lead to the same outcome.

III. History of Medicare Coverage

CMS previously reviewed scientific literature and established coverage for many uses of FDG PET. A summary of each prior PET NCD follows. For each indication, there are specific coverage limitations listed in the CMS NCD Manual, Section 220.6.[1] A synopsis of the CMS NCD Manual Section 220.6 appears as Appendix B.

In addition to these positive coverage determinations, there have been certain noncoverage determinations, some based upon evidence of lack of benefit and some based upon lack of evidence. Those are summarized in Appendix A.

For services performed on or after March 14, 1995, CMS covered PET using Rubidium 82 (not FDG) as the tracer for noninvasive imaging of myocardial perfusion in patients with known or suspected coronary artery disease.

Beginning January 1, 1998, FDG PET was covered when used for the initial staging of suspected metastatic non-small cell lung cancer (NSCLC) and for the characterization of suspected solitary pulmonary nodule (SPN).

On July 1, 1999, FDG PET coverage was expanded to include 3 additional oncology indications. These were: 1) location of recurrent colorectal tumors when rising CEA suggests recurrence; 2) staging and restaging of lymphoma only when used as an alternative to gallium scan; and 3) evaluating recurrence of melanoma prior to surgery only when used as an alternative to gallium scan.

On July 10, 2000, CMS received a request for broad coverage of FDG PET for 22 oncologic, cardiac, and neurologic conditions.[2] Included in the request was coverage of FDG PET for brain, cervical, ovarian, pancreatic, small cell lung, and testicular cancers—the same cancers comprising this current request. CMS commissioned a technology assessment (TA) from the Agency for Healthcare Research and Quality (AHRQ) and referred the issue to the Medicare Coverage Advisory Committee (MCAC) for consideration. In a decision memorandum of December 15, 2000, based on available evidence, CMS announced its intent to expand coverage of FDG PET to include the indications listed below in Table 1. At that time, CMS did not find sufficient evidence to support coverage of FDG PET for the other indications included in the request, of which brain, cervical, ovarian, pancreatic, small cell lung, and testicular were a part. As a result, the December 15, 2000 decision memorandum announced a national non-coverage determination for these six cancers.

Table 1: Expanded coverage announced in decision memorandum of December 15, 2000

Effective Date	Clinical Condition	Coverage
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.

Effective Date	Clinical Condition	Coverage
July 1, 2001	Head and neck (excluding central nervous system and thyroid)	Diagnosis, staging, and restaging
July 1, 2001	Refractory seizures	Pre-surgical evaluation
July 1, 2001 to September 1, 2002	Myocardial Viability	Following inconclusive SPECT

On December 15, 2000, CMS accepted a request for FDG PET for diagnosis of early dementia in certain geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. CMS commissioned a TA from AHRQ and presented the issue to the MCAC Diagnostic Imaging Panel for consideration. The MCAC Executive Committee then met and ratified the Panel's recommendations. In a decision memorandum of April 16, 2003, based on available evidence, CMS announced it would maintain noncoverage of FDG PET for the requested indications. On October 7, 2003 CMS accepted a request for reconsideration for a narrow use of FDG-PET in the diagnosis of Alzheimer's Disease (AD). Effective on September 15, 2004, CMS expanded coverage specifically for patients with early dementia for whom the differential diagnosis between frontotemporal dementia and AD remained uncertain after a comprehensive clinical evaluation. In addition, coverage was expanded for use of FDG-PET in the diagnosis and treatment of other patient groups with early dementia or those with mild cognitive impairment (MCI) in the context of protocol-driven, controlled clinical investigations that evaluate the effect of FDG-PET use on clinical outcomes and meet other stipulated criteria.

On October 18, 2001, CMS accepted a request for FDG PET for diagnosing, staging, restaging, and monitoring therapy for soft tissue sarcoma. CMS commissioned a TA from AHRQ to evaluate the available literature. CMS determined that the evidence was not adequate to conclude that FDG PET was reasonable and necessary for the requested indications. As a result, a decision memorandum of April 16, 2003 announced CMS would maintain noncoverage of FDG PET for soft tissue sarcoma.

Beginning in July 2001, CMS allowed only specific types of PET systems to be covered according to their design characteristics. These characteristics included so-called full-ring, partial-ring, and coincidence systems.[3].

For services performed on or after October 1, 2002, FDG PET coverage was expanded to include two additional applications. For breast cancer, FDG PET was covered for certain women as an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with locoregional recurrence or metastasis, and as an adjunct to standard imaging modalities for monitoring tumor response to treatment for women with locally advanced and metastatic breast cancer when a change in therapy is anticipated. For myocardial viability, FDG PET was covered for initial diagnosis or following inconclusive SPECT prior to a revascularization procedure.

For services performed on or after October 1, 2003, FDG PET coverage was expanded to include two additional applications involving two different radiopharmaceuticals. FDG PET was covered for restaging of recurrent or residual follicular cell thyroid cancer under certain conditions. PET using ammonia N-13 as the tracer was covered for noninvasive imaging of myocardial perfusion.

IV. Timeline of Recent Activities

February 24, 2003	CMS accepted five formal NCA requests. Requests included brain, cervical, pancreatic, small cell lung, and testicular cancers.
March 24, 2003	CMS accepted a formal NCA request for ovarian cancer.
March 24, 2003	CMS asked AHRQ to commission a TA of FDG PET for six cancer indications.

February 12, 2004	TA received.
February 27, 2004	Staff from CMS, the National Cancer Institute's Cancer Imaging Program, and AHRQ discussed FDG PET imaging for the specific oncologic indications in this decision memorandum.
October 14, 2004	CMS announced expanding this NCA to also address a potentially different process for determining when a PET scan is reasonably and necessary for all cancers that are currently noncovered. We welcomed public comment suggesting how CMS might do this.
November 1, 2004	CMS requested public comment on the proposed coverage determination pursuant to Section 731 of the Medicare Modernization Act.
November 1, 2004 through December 1, 2004	CMS receives public comments on proposed decision memorandum. Public comments can be viewed at: https://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=92

V. Food and Drug Administration (FDA) Status

The FDA approval letter for new drug application NDA 20-306, dated June 2, 2000 included the following language:

"This new drug application provides for the use of Fluorodeoxyglucose F-18 injection for the following indications:

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.... We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter..."[4]

The FDA has cleared PET devices, along with various software packages used to perform PET for general diagnostic use, through the 510(k) clearance process.

VI. General Methodological Principles of Study Design

When making national coverage determinations under §1862(a)(1)(A) of the Social Security Act, 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 for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. 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 net health outcomes for patients. A detailed account of the general methodological principles of study design agency staff utilizes to assess the relevant literature on the therapeutic or diagnostic item or service for specific conditions can be found in Appendix C. In general, features of diagnostic 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.[5]

VII. Evidence

A. Introduction.

Consistent findings across studies of net health outcomes associated with an intervention or diagnostic test as well as the magnitude of its risks and benefits are key to the coverage determination process. For this decision memorandum, CMS commissioned an external TA from AHRQ to review the published clinical evidence on use of FDG PET in the following six cancers: brain, cervical, ovarian, pancreatic, small cell lung, pancreatic, and testicular. CMS staff reviewed the commissioned TA, evaluated the individual clinical studies included in that document, and searched for any additional relevant articles subsequently published for all six cancers to determine if use of FDG PET improved net health outcomes when compared with conventional imaging modalities such as CT or MRI. In addition to our review of the clinical and scientific literature, we sought information from professional societies and searched for evidence based practice guidelines, other technology assessments, consensus statements, and position papers.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but include beneficial or adverse clinical effects, such as change in management due to test findings or, preferably, improved health outcomes for Medicare beneficiaries. Accuracy refers to the ability of the test to distinguish patients who have or do not have the target disorder when compared to a reference standard. Measures used to determine accuracy include sensitivity (probability of a positive test result in patients with the disease) and specificity (probability of a negative test in patients who do not have the disease).

In evaluating diagnostic tests based on a reference standard (such as histology or prolonged clinical follow up), higher sensitivity and specificity values for a test like FDG PET when compared to another diagnostic modality would be an outcome of interest. In the absence of direct evidence to show that the diagnostic test under review improves health outcome, evidence of improved sensitivity or specificity could still prove useful as an intermediate outcome and data point estimate in the construction of a decision or evidence model (indirect evidence).

We will evaluate additional evidence and data submitted in response to this proposed decision.

B. Discussion of Evidence Reviewed

1. Assessment questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: “Is the evidence sufficient to conclude that the application of the technology under study will improve net health outcomes for Medicare patients?” The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. Assessment questions are listed in Appendix D.

2. External systematic reviews/technology assessments

Systematic reviews are based on a comprehensive and unbiased search of published studies to answer a clearly defined and specific set of clinical questions such as those related to the effectiveness of FDG PET in oncology applications. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and the sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included.[6]

As mentioned above, CMS commissioned a TA from the AHRQ to assess the value of FDG PET for listed oncology applications.[7]

AHRQ TA Report on Positron Emission Testing for Six Cancers (Brain, Cervical, Small Cell Lung, Ovarian, Pancreatic, and Testicular)[8]

Search strategy

An OVID search of the MEDLINE® database was conducted on April 18, 2003. Filters and limitations were used, and inclusion and exclusion criteria developed to identify articles to be reviewed. The search used applicable MeSH headings and textwords and resulted in 1058 citations for download and screening. Review of the abstracts resulted in accepting 226 citations that met the criteria for full-text article retrieval.[9] Articles providing information regarding technical feasibility only were excluded from further review. The number of articles providing information beyond the level of technical feasibility and addressing the analytic questions posed by CMS was as follows: brain (13), cervical (13), ovarian (10), pancreatic (24), SCLC (6), and testicular (11).

Results and appraisal

For complete results and appraisal of the AHRQ TA for each cancer, see Appendix E.

Brain: The TA authors noted that, although the use of FDG PET “may be a valuable modality” in distinguishing tumor from radiation necrosis, this assessment is “tempered by the results of three studies in which PET had comparable operating characteristics to the more accessible radionuclide studies (SPET/SPECT).”

The TA notes that it is unclear to what degree to which FDG PET performance for patients with truly indeterminate biopsy results will resemble the reviewed studies.

Cervical: The TA authors found with respect to FDG PET compared to conventional imaging in detecting pre-treatment metastasis that “there is fair to good evidence that PET is more sensitive than CT or MRI for detection of retroperitoneal nodal metastasis in patients with newly diagnosed cervical cancer.”

Data suggest that PET is more sensitive than conventional imaging and has the potential to improve the early diagnosis of recurrent cervical cancer. These data are limited by small sample sizes. In addition, it is unclear whether improved early diagnosis of extra-pelvic recurrent cervical cancer leads to improved patient outcomes except in the setting of patients who have not previously received radiation.

Ovarian: The TA authors were unable to identify studies providing evidence for the utility of FDG PET in the initial staging of ovarian cancer. The authors concluded that FDG PET as an adjunct to conventional imaging “is not expected to be useful in the routine surveillance of patients with a history of ovarian cancer”. The TA authors noted that for patients with rising CA-125 titer and negative conventional imaging there is “fair evidence to support the use of FDG PET for the detection of recurrent ovarian cancer”.

Pancreatic: All studies reviewed assessed FDG PET only as an adjunct to other imaging and diagnostic modalities. No studies assessed FDG PET as a stand-alone method of diagnosing, staging, or monitoring for residual disease in pancreatic malignancy.

The TA notes that when FDG PET is used as an adjunct to conventional imaging in diagnosing metastatic disease, studies generally demonstrate a trend toward greater sensitivity of FDG PET compared to use of conventional imaging alone. However, the lack of complete comparisons between FDG PET and other conventional imaging techniques, and the lack of information on the quality of the comparators makes it difficult to assess the strength of this finding. The TA finds that specificity of FDG PET for the detection of metastasis is somewhat lower than the comparators.

With respect to FDG PET providing useful data in subpopulations with likely metastatic disease, the TA authors found it was difficult to identify subgroups that might achieve a substantially greater benefit from FDG PET data.

Diabetes and abnormal glucose metabolism, both of which are increased in the population with pancreatic malignancy and chronic pancreatic disease, can affect FDG PET results (usually with false negatives), but are treated inconsistently from study to study.

Small Cell Lung Cancer (SCLC): The TA authors commented that inadequate information was present to comment on the comparative performance of FDG PET relative to conventional imaging in staging SCLC; that no conclusion could be made in evaluating FDG PET performance compared to conventional imaging in restaging SCLC post treatment; and that, with regard to occult SCLC in paraneoplastic syndrome, the one study cited suggests a role for FDG PET, but “one that remains to be confirmed using larger sample size as well as a comparator test."

Testicular: TA authors concluded that the literature suggests a possible role for FDG PET in staging testicular cancer, but that studies had significant limitations and that further research was needed to confirm this finding.

In distinguishing between tumor versus necrosis, the TA authors note that in four studies FDG PET shows low sensitivity. This is largely due to the inability of FDG PET to distinguish between teratoma and necrosis/fibrosis. The TA authors commented that the specificity of FDG PET is consistently higher than that of CT in this context, but with significant study limitations.

In detecting recurrence in patients with rising tumor markers and negative CT, the authors note that one study addressed this question. FDG PET was found to have a sensitivity of 71% and a specificity of 83% for the diagnosis of recurrent germ cell tumor in patients with rising tumor markets but normal CT, but the study had significant limitations.

The TA can be found at http://63.241.27.78/mcd/viewtrackingsheet.asp?id=85.

3. Internal technology assessments

Search strategy

CMS conducted an OVID search of the MEDLINE® database on January 20, 2004 for the period January 1, 2003 through January 20, 2004. CMS used the same filters, limitations, and inclusion and exclusion criteria as those in the AHRQ literature search. This systematic review was conducted to help assure the most current review of published studies. Analysis of the abstracts resulted in 37 citations that met the criteria for full-text article retrieval. Articles providing information on technical feasibility were excluded from further review.

This systematic review of citations for brain cancer resulted in a single citation that met the criteria for full-text article review.

Two articles provided information for use of FDG PET in cervical cancer beyond the level of technical feasibility but focused on the evaluation of a specific technique, dual-phase or delayed FDG PET, and were thus not included in this review.

For ovarian cancer, analysis of the abstracts resulted in a single citation that met the criteria for full-text article retrieval.

For pancreatic cancer, analysis of the abstracts resulted in 33 citations that met the criteria for full-text article retrieval. Articles providing information on technical feasibility were excluded from further review. Eleven additional articles were found pertaining to FDG PET use related to pancreatic cancer.

There were no additional articles found pertaining to SCLC or testicular cancer beyond the level of technical feasibility.

CMS conducted an additional OVID search of the MEDLINE® database on October 1, 2004 for the period February 1, 2004 through September 15, 2004. CMS again used the same filters, limitations, and inclusion and exclusion criteria as those in the AHRQ literature search conducted on April 18, 2003. This review was conducted in order to help assure that our analysis included the most current review of published, peer-reviewed literature. Analysis of the abstracts from this search yielded 11 citations beyond the level of technical feasibility that met criteria for full-text review. One article was identified for brain cancer, six for cervical, two for ovarian, two for small cell lung, and none for either pancreatic or testicular cancers. None of the articles contributed uniquely to the findings of the AHRQ TA.

Review

CMS has carefully reviewed evidence for each of the six cancers. In general, the evidentiary base suffers from insufficient information about patient characteristics, the comparative imaging studies used, and the lack of standardized criteria for evaluating FDG PET results. Finally, no guidelines were located from any specialty society supporting routine use of FDG PET for patients with any of the six cancers.

Brain: The requested indications for appraisal of FDG PET compared with conventional imaging were: guided lesion biopsy of recurrent low-grade brain tumors in patients with an indeterminate MRI; distinguishing high-grade from low-grade tumors; distinguishing tumor from radiation necrosis in recurrent brain lesions; and as an adjunct to biopsy in the initial grading when the initial biopsy result was indeterminate grade II/III glioma.

There were twelve articles providing information beyond the level of technical feasibility, and the quality of these studies was inadequate to issue a positive coverage decision. There were several limitations to the data:

- test characteristics varied widely and sample sizes were small, thereby making it difficult to determine the clinical utility of an FDG PET scan and to determine when an FDG PET scan was reasonable and necessary
- FDG PET has similar operating characteristics to readily available imaging technology, potentially offering no increased benefit from an FDG PET scan
- there is uncertainty in generalizing FDG PET results from patients with definitive grade biopsies (the only literature provided) to settings with indeterminate grade

Cervical: The requested indications for appraisal of FDG PET compared with conventional imaging were: detection of pre-treatment metastases in newly diagnosed cervical cancer and residual or recurrent cervical cancer following treatment.

There were thirteen articles providing information beyond the level of technical feasibility.

Eight studies addressed the detection of pre-treatment metastases in newly diagnosed cervical cancer compared with conventional imaging. There was no literature that directly evaluated the impact of substituting or adding FDG PET to conventional imaging on patient health outcomes. Studies only provided estimates of FDG PET specificity and sensitivity. Although there remains concern about small sample sizes and other potential sources of bias, estimates were acceptable to use in extrapolating the potential impact of FDG PET on changing management when used as an adjunct to pre-treatment staging.

The body of evidence reviewed suggested improved sensitivity for FDG PET compared to conventional imaging in detecting nodal metastases generally, and para-aortic nodal metastases specifically, in patients with newly diagnosed cervical cancer. However, trial design features that could have introduced selection and observer bias and large confidence intervals preclude a conclusion that FDG PET should substitute for conventional imaging modalities currently in use for extended pre-treatment staging.

In summary, our analysis of the evidence and simulations undertaken using sensitivity and specificity estimates from the literature suggest that the addition of FDG PET subsequent to a negative CT or MRI that is negative for extra-pelvic metastasis can improve clinical decision-making.

Six articles assessed the diagnostic capabilities of FDG PET in detecting residual or recurrent disease. CMS found that no routine imaging modality has been established for post-treatment follow-up in cervical cancer and that uncertainty exists about the ability of early detection of residual or recurrent lesions in asymptomatic patients to affect clinical outcomes. In addition, the quality of these studies on post-treatment surveillance raised questions not only about the effects on clinical management or health outcomes but also about the sensitivity and specificity values reported for FDG PET.

Limitations included:

- lack of blinding for the pathologists or reference standard readers
- clinical applicability of FDG PET for monitoring and restaging (although treatment options varied depending on the primary treatment received, the studies reviewed did not present results by clinically relevant subgroups).
- low specificity values increasing the risk of a false positive result, a substantial concern in this group of patients who have already undergone anticancer therapies and, if thought to have recurrence, might lead to unnecessary and potentially harmful subsequent interventions

Ovarian: The requested indications for appraisal of FDG PET as an adjunct to conventional imaging were: initial staging, routine surveillance for recurrence, monitoring the response to chemotherapy, or for enhancing the accuracy of CA 125 testing.

There were eleven articles providing information beyond the level of technical feasibility. Specific limitations were that studies using FDG PET to detect recurrence in subjects with elevated CA 125 levels and negative conventional imaging were conducted in populations where the data from CA 125 levels alone were sufficient to produce perfect diagnostic accuracy. Hence, FDG PET could not improve the diagnostic results. These populations are unlikely to be representative of the true performance of either CA 125 or FDG PET. Additionally, when using FDG PET as an adjunct to conventional imaging in monitoring response to chemotherapy, we were unable to identify evidence that demonstrated improved outcomes with the addition of FDG PET to the standard workup.

Pancreatic: The requested indications for appraisal of FDG PET compared with conventional imaging were: detecting malignancy, metastasis, residual or recurrent disease, and defining the subpopulation(s) of patients for which adjunctive FDG PET is superior. There were twenty-four articles providing information beyond the level of technical feasibility. There were several limitations to the studies:

- details about both patients' conditions and the tests they received were sparse making it difficult to determine when an FDG PET scan was reasonable and necessary
- no consistency in study protocols which would permit a determination as to the clinical utility of FDG PET for this malignancy

Finally, a problem unique to pancreatic cancer was its association with diabetes and a general failure to follow recommended procedures for control of blood glucose to assist in obtaining accurate FDG PET results.

The quality of the studies was such that we were unable to determine a benefit to the addition of FDG PET to patient management.

Small Cell Lung Cancer (SCLC): The requested indications for appraisal of FDG PET compared with conventional imaging were: initial staging, restaging, and diagnosing occult disease in paraneoplastic syndrome.

There were six articles providing information beyond the level of technical feasibility and the quality of these studies was inadequate to issue a positive coverage decision. Limitations included:

- absence of comparator tests
- small sample sizes
- conflicting results pertaining to test accuracy
- retrospective nature

The literature available is not robust enough to determine a benefit of FDG PET in the management of SCLC.

Testicular: The requested indications for appraisal of FDG PET compared with conventional imaging were: initial staging, evaluating recurrence or residual disease, and determining recurrence in patients with rising serum tumor markers and a normal CT.

There were eleven articles providing information beyond the level of technical feasibility. Studies had several limitations including:

- mixed patient populations (both by cancer type and stage)
- a lack of blinding
- studies with conflicting results
- FDG PET was not compared to the same conventional imaging modalities in all studies, if compared at all
- FDG PET false positive rate depends on the time interval post chemotherapy[10] and there is no standard for this time interval

Given the significant limitations with all studies, some authors question the utility of FDG PET for initial staging of testicular cancer. However, even with the limitations of the studies and some authors' reservations regarding the technology, several studies provide consistent evidence that the sensitivity and specificity of FDG PET is higher than CT for the initial staging of patients with germ cell tumors.

There are several difficulties with using FDG PET for distinguishing recurrence and residual disease from benign masses. FDG PET was not useful in detecting tumor of less than 0.5cm or teratoma of any size secondary to a low proliferation rate and glucose metabolism. Furthermore, FDG PET cannot reliably distinguish between teratoma and necrosis. Since FDG PET cannot reliably distinguish between teratoma, cancer and necrosis, regardless of a positive FDG PET, you will still resect the testicular mass (or at least perform a retroperitoneal lymph node dissection post chemotherapy if serum tumor markers are not elevated) because the standard of care is to leave no mass (or suspected recurrence) unexamined for fear of malignant transformation or "growing teratoma syndrome."

Though many studies showed FDG PET with a high specificity for detecting residual tumor, the converse, that sensitivity is low, is also true. Given this relationship, a negative FDG PET scan does not provide complete assurance that the patient does not have a mass requiring resection, especially in patients with NSGCT. To improve sensitivity of FDG PET, some authors advocate avoiding its use in patients with high probability of having residual teratoma (i.e. patients with teratomatous elements in the primary tumor).

Notwithstanding the reportedly high specificity of FDG PET for detecting residual tumor, authors note that false positive results secondary to FDG PET accumulating in tissue macrophages are a common problem, especially post chemotherapy or if the patient has an infection. Additionally, false negative results are common post chemotherapy because the chemotherapy drug leads to a transient suppression of metabolic activity in germ cell tumors regardless of their final response to therapy. Though some authors conclude that they cannot recommend the routine use of FDG PET scans in the evaluation of residual postchemotherapy masses in seminoma, one potential safeguard against the false negative results is to perform PET scans at least 2 weeks or more after chemotherapy.

As stated above, because of these limitations and the inability of FDG PET to distinguish between teratoma, necrosis and tumor, we urge caution in using FDG PET in the management of residual tumor.

For detailed results by article, see AHRQ TA evidence tables, Appendix G.

4. Professional Society Position Statements

An on-line search of national cancer and surgical society websites found no position statements or clinical practice guidelines that mention FDG PET as part of the management of patients with brain, cervical, SCLC, or ovarian cancer.

The National Comprehensive Cancer Network's (NCCN) "2003 Practice Guideline for Pancreatic Adenocarcinoma,"[11] does not mention FDG PET among the imaging tests useful in the diagnosis and staging of pancreatic malignancy. The current guideline for diagnosis and treatment of pancreatic ductal adenocarcinoma, issued by the American Gastroenterological Association[12] makes no reference to the use of FDG PET. The National Cancer Institute in its February 2001,[13] "Report of the Pancreatic Cancer Progress Review Group," does not mention FDG PET for use in pancreatic cancer.

FDG PET for staging patients with SCLC is not recommended outside of a clinical trial setting.[14]

5. Public Comments

On February 24, 2003, when the formal NCD request for was initially accepted for FDG PET for brain, cervical, pancreatic, small cell lung, and testicular cancers, CMS announced a 30-day public comment period which ended on March 6, 2003. On March 24, 2003, CMS expanded this NCD request to include ovarian cancer. As a result, a new 30-day public comment began for the ovarian cancer indication which ended on April 23, 2003. CMS received no comments or letters of support regarding FDG PET for any of the six cancers during either of these 30-day public comment periods.

In response to the publication of the draft decision memorandum on November 1, 2004, CMS received comments from 92 individuals and groups during the 30-day period ending December 1, 2004. Those commenting included national professional organizations, university medical centers, individual practicing physicians, patient advocacy groups, cancer survivors, PET facility managers, and other individuals. A summary of the comments, which informed the final analysis of the evidence and coverage decision, follows.

In general, the majority of commenters commended CMS for the decision to expand coverage of FDG PET for non-covered oncology indications when the studies are performed in various types of prospective clinical studies, as stated in the draft decision memorandum. A recurrent theme in these comments was that expanded coverage allows for collection of data which permits additional evaluation of FDG PET's effect on patient management and health outcomes.

Several commenters posed questions regarding how the prospective clinical studies will be implemented and maintained as well as how clinical information in these studies will be communicated to radiologists, oncologists, and other clinicians. CMS agrees that this is a complex issue. Information regarding clinical study operations will be communicated via industry and professional society websites as well as by program memoranda, transmittals, and manual instructions issued and distributed via the internet by CMS.

In a decision memorandum of February 27, 2002 (and for services performed on or after October 1, 2002) FDG PET for breast cancer was covered for certain women as an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with locoregional recurrence or metastasis, and as an adjunct to standard imaging modalities for monitoring tumor response to treatment for women with locally advanced and metastatic breast cancer when a change in therapy is anticipated. FDG PET for diagnosis of breast cancer and initial staging of axillary lymph nodes was nationally noncovered due to evidence of lack of benefit.[15] [16] A number of commenters expressed concern that the draft decision memorandum posted on November 1, 2004 did not expand coverage of FDG PET to include the use of FDG PET in the diagnosis of breast cancer for beneficiaries enrolled in approved data collection systems. This DM reviews evidence for FDG PET indications that have not been reviewed in previous NCDs. In this DM, our change in coverage for previously reviewed cancers was only for those cancers in which we determined noncoverage was based upon a lack of evidence. This DM was not intended to include those cancers where we found evidence of benefit and provided coverage or evidence of lack of benefit and provided noncoverage. The proper venue to address expanding coverage of FDG PET for breast cancer is to review evidence via the NCD reconsideration process, as explained in a Federal Register Notice of September 26, 2003[17]. CMS staff is available to work with the medical and scientific community to facilitate this process.

A few commenters believed CMS should re-evaluate the evidence in the internal and external technology assessments and consider covering FDG PET for testicular cancer when performed under prospective clinical studies rather than nationally non-covering FDG PET for these cancers as in the proposed DM. We have reviewed those comments and the evidence and will modify our proposed decision for testicular cancer to allow coverage in an approved study.

Several commenters wrote that CMS should cover FDG PET for all oncology indications, without qualification, although they did not provide documentation in support of their request.

One university school of medicine requested a broader expansion of benefits for FDG PET for cervical cancer than was outlined in the proposed DM. The proposed DM would expand coverage of FDG PET to include detection of pre-treatment metastases (i.e., staging) in newly diagnosed cervical cancer subsequent to negative conventional imaging. The commenter requested unrestricted coverage of FDG PET for both staging and restaging of cervical cancer. A journal article and list of citations accompanied their comments. Following review of those comments and the evidence, along with a discussion with the commenter, we clarified the covered use of FDG PET for staging as an adjunct to standard imaging.

An alliance of nationally recognized cancer institutions wrote to express their concerns regarding the potential for reduced access to care as a result of the proposed policy. The commenter stated that the clinical study program should be built on a consensus model. CMS agrees that the clinical study program be created with multidisciplinary input and has involved national radiology, radiation oncology, molecular imaging organizations, and others in the clinical study's design. CMS also agrees that providers and beneficiaries should have ready access to the clinical study nationwide. The commenter also believed FDG-PET coverage should not be based on primary cancer diagnosis, as outlined in the proposed DM. They believed coverage should be based on specific diagnostic questions to be answered by multiple specialists at the time of referral for testing. CMS believes the evidence in the internal and external technology assessments supports our decision to base coverage on the primary cancer diagnosis.

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 under title XVIII of the Social Security Act § 1869(f)(1)(B). 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." § 1862(a)(1)(A).

The adequacy of evidence for FDG PET's diagnostic accuracy and clinical utility in cancer (and subsequent CMS coverage decisions) may be categorized in three ways:

- Coverage based on evidence of benefit (positive evidence),
- Non-coverage based on evidence of harm or no benefit (negative evidence), and
- Non-coverage based on lack of evidence sufficient to establish either benefit or harm.

This section presents the agency's evaluation of the evidence available and coverage determinations reached for each request. It summarizes our analysis and conclusions for the cancers reviewed and the category, as defined above, in which they fit.

For cervical cancer, CMS considers the evidence adequate to conclude that use of FDG PET as an adjunct to MRI or CT improves net health outcomes in 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 and is therefore reasonable and necessary for this indication. We will therefore issue a positive coverage determination for this indication.

In our review of the other cancer indications, we found sufficient evidence to determine that PET scans are no longer experimental. However, the evidence was insufficient to reach a conclusion that FDG PET is reasonable and necessary in all instances. A sufficient inference of benefit can, however, be drawn to support limited coverage if certain safeguards for patients are provided. This inference is based on both the pathophysiological basis for FDG PET's usefulness in cancer, described in the Background Section, as well as the positive coverage in several cancers for which there is evidence of sufficient quality to warrant coverage. We believe that patient protection can be provided by requiring, as part of a clinical study, data collection on patients receiving FDG PET scans for indications for which there is not sufficient evidence to reach a firm conclusion that the scan is reasonable and necessary. This is consistent with the general application of diagnostic tests. Diagnostic tests provide results that are used to influence patient management (42 CFR 410.32), but the conclusions are reevaluated as additional data are obtained from other tests or results from therapeutic interventions. The additional data may alter the interpretation of the original test result. Likewise, the information collected through this data collection may require the physician to reevaluate the original PET scan results, alter the management plan, and potentially improve health outcomes. The effective and accurate use of the PET scan for these cancer indications can only be ensured by this data collection.

In addition, patient care provided under clinical protocols is typically associated with a higher quality of care. Protocols include patient selection criteria, guidelines for test administration, and recommended treatments. These benefits offer safeguards for patients to ensure appropriate evaluation and use of FDG PET scan results.

Finally, it is important to have a means of assessing the quality of patient care over time to ensure that positive outcomes are maintained or improved. Data from prospective clinical studies can be an invaluable aid in ongoing assessment of the quality of care provided to patients.

We believe this to be a unique instance where general knowledge of a technology is well accepted while specific applications are not necessarily well proven. This lends itself to this type of coverage. We do not expect to apply this principle except in rare instances.

CMS considers acceptable any one of the following types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (42 CFR 405.201); or
- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management.

The clinical study must ensure that:

1. Specific hypotheses are identified prospectively;
2. Hospitals and providers are qualified to provide the FDG PET scan and interpret the results;
3. Participating hospitals and providers report data on all enrolled patients undergoing FDG PET scans for cancer therapeutic or diagnostic indications;
4. The data to be collected includes:
    - Baseline patient characteristics
    - Scan type and characteristics
    - Scan results
    - Results of all other imaging studies
    - Facility and provider characteristics
    - Information on cancer type, grade, and stage
    - Long-term patient outcomes and disease management changes
    - Anti-cancer treatment received
    - All applicable patient confidentiality, privacy, and other Federal laws are complied with, including the Standards for Privacy of Individually Identifiable Health Information (Privacy Rule).

Further refinement of the clinical study design is expected to occur based on further discussion with clinicians, methodology experts, and stakeholders.

When requested, CMS will review evidence to reconsider the classification of FDG PET for individual cancers. We are particularly interested in seeing evidence that would permit us to make a coverage or non-coverage decision, i.e., to move an FDG PET indication from coverage under a clinical trial or study to coverage or non-coverage based on definitive evidence of benefit, no benefit, or harm. If adequate new evidence is available, the decision may be changed to either “coverage based on evidence of benefit” or “non-coverage based on evidence of harm or no benefit.”

We strongly encourage oncology imaging communities to develop evidence-based clinical practice guidelines for the use of PET and other cancer imaging modalities in diagnosing, staging, restaging, and monitoring of cancer patients.

In response to the comments asking for greater clarity in how CMS will choose studies to cover, the CMS Council on Technology and Innovation will now begin to develop a draft guidance document on this policy approach in order to make the process more systematic, predictable and transparent. We will shortly announce an open door forum and separately convene an expert panel. Comments on this policy can be submitted through the CTI website at http://www.cms.hhs.gov/providers/cti. An initial draft guidance will be issued in March, at which time additional public feedback will be solicited.

IX. Conclusions

CMS has determined that there is sufficient evidence to conclude that an FDG PET scan 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 is reasonable and necessary as an adjunct test, and CMS intends to issue a national coverage determination (NCD) for this indication.

For all other indications in this decision memorandum, CMS has determined that the evidence is sufficient to conclude that an FDG PET scan is reasonable and necessary only when the provider is participating in and patients are enrolled in one of the following types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (42 CFR 405.201); or
- 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.

All other previous positive national coverage determinations will remain in effect. (See Appendix A.)

All other previous national non-coverage determinations based on evidence of lack of benefit will remain in effect. (See Appendix A.)

For all other indications for which CMS currently has a noncoverage determination (see Appendix A), CMS has proposed that an FDG PET scan would be reasonable and necessary only when the provider is participating in and patients are enrolled in one of the prospective clinical studies described above.

As an Agency, CMS recognizes the complex nature of the prospective clinical studies discussed in this decision memorandum. The broad range of public comments received exemplifies the multifaceted interests to be considered when implementing such a program. It is CMS' understanding that there are clinical studies currently being developed which will fully implement this coverage decision. However, no clinical study will be fully operational by the effective date of this decision. Therefore, while this coverage decision is effective, it will not be fully implemented until a clinical study is ready to enroll providers and patients. CMS will continue working with the oncology imaging communities to develop the systems necessary to implement this NCD.

APPENDIX A: PET Oncology Coverage Indications

APPENDIX B: Synopsis of CMS NCD Manual

APPENDIX C: General Methodological Principles of Study Design

APPENDIX D: Assessment Questions by Cancer

APPENDIX E: Results and Appraisal of AHRQ TA by Cancer

APPENDIX F: AHRQ TA Evidence Tables by Cancer

APPENDIX G: References

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[1] http://www.cms.hhs.gov/manuals/103_cov_determ/ncd103c1_Part4.pdf

[2] The decision memorandum and technology assessment addressing the July 10, 2000 request can be found at http://63.241.27.78/mcd/viewtrackingsheet.asp?id=85.

[3] http://www.cms.hhs.gov/manuals/103_cov_determ/ncd103c1_Part4.pdf

[4] Letter from Patricia Love, FDA, to Downstate Clinical PET Center. June 2, 2000. This letter is available on the FDA web site through a link at http://www.fda.gov/cder/approval/index.htm.

[5] Deeks J. Systematic reviews of evaluations of diagnostic and screening tests. In Egger M et al, editors. *Systematic reviews in healthcare.* BMJ. 2001.

[6] Hulley et al. *Designing Clinical Research.* 2001.

[7] The TA report can be found at http://63.241.27.78/mcd/viewtechassess.asp?id=92-

[8] Technology Assessment submitted to AHRQ by the Duke Center for Clinical Health Policy Research and Evidence Practice Center, David B. Matchar, MD, Shalini L. Kulasingam, PhD, Laura Havrilesky, MD, et al., December 2003.

[9] See the TA for a complete description of the inclusion and exclusion criteria and search strategy.

[10] because FDG accumulates in inflammatory tissue post chemotherapy

[11] NCCN Practice Guidelines in Oncology v.1.2003. Pancreatic Adenocarcinoma.

[12] AGA guideline: Epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. May 1999.

[13] National Cancer Institute. Pancreatic Cancer: An Agenda for Action. February 2001.

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[15] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=71

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Appendices [PDF, 5MB]

Back to Top