March 25, 2008

Steve Phurrough, M.D., M.P.A.
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Centers for Medicare & Medicaid Services
7500 Security Blvd., Mail Stop C1-09-06
Baltimore, MD 21244

Re: Formal Request for Reconsideration of National Coverage Determination (NCD) CAG-00181N, Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers

Dear Dr. Phurrough:

Since May of 2006, the National Oncologic PET Registry (NOPR) Working Group has operated the NOPR with guidance from the Centers for Medicare & Medicaid Services (CMS), in conjunction with the American College of Radiology (ACR) and the Academy of Molecular Imaging (AMI), and with the endorsement of ACR, the Society of Nuclear Medicine (SNM), and the American Society of Clinical Oncology (ASCO). As the chair and co-chairs of the NOPR Working Group, we want to express our appreciation for the leadership and ongoing support that that CMS has devoted to making "Coverage with Evidence Development" (CED) a success -- both specifically as it applies to PET, and generally for providing a blueprint applicable to other future collaborative efforts.

Based on the data collected by the NOPR over the past eighteen months, we formally request that CMS reconsider NCD CAG-00181N, Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers to end the data collection requirements, and provide coverage of PET across all oncologic indications for diagnosis, staging, and restaging/suspected recurrence purposes.

Summary

We have worked closely with CMS and other key stakeholders to implement one of the first NCDs to employ the innovative CED policy. This particular NCD has provided coverage of positron emission tomography/computed tomography (PET/CT) and PET (hereinafter collectively referred to as PET) with F-18 fluorodeoxyglucose (FDG) for selected indications and cancers, on the condition that coverage would be accompanied by an evidence development mechanism (the NOPR) that would enable CMS to develop an evidence-based coverage policy.

In its first year of operation, complete data were obtained for 34,358 PET studies performed under the conditions of the NOPR. After removal of those cases for which the patient or referring physician did not give consent for research use of the data, those cases apparently done for covered indications, and those cases done for treatment monitoring

(this latter subset will be analyzed separately), there were 22,975 remaining cases that formed the analysis cohort. The study results for this cohort, described below, were first made public by presentation at the annual scientific meeting of the Radiological Society of North America in Chicago, IL on November 24, 2007. These initial results (and a more detailed data analysis for this cohort) have been published recently in the *Journal of Clinical Oncology*, accompanied by an editorial (both attached as Appendix A).[1] Peer-reviewed analysis of the NOPR data reveals that PET is associated with a 36.5% change in physicians' pre-PET treatment or no-treatment decision, and these changes spanned the full spectrum of potential oncologic uses of PET (diagnosis, initial staging, restaging, and detection of suspected recurrence).

On the basis of the NOPR data, there is strong empirical evidence to justify a decision to end the CED requirements as a condition of coverage of PET, and to support a Medicare coverage policy for PET across all cancer types for the diagnosis, staging, and restaging/suspected recurrence indications. Attached as Appendix B is a draft revision of the relevant portion of the Medicare National Coverage Determinations Manual (Sections 220.6 et seq.), which both reflects the substance of this request and provides additional guidance for practitioners regarding the circumstances under which PET would be covered.

At this time we do not believe that there is sufficiently mature NOPR evidence to recommend that CMS end the data collection requirements for the coverage of PET for treatment monitoring, but we are now analyzing the data for this cohort from the first 19 months of NOPR operation. While this analysis continues, we propose to maintain operation of the NOPR to collect PET data related to this indication.

I. Background and history of PET coverage

Between 1998 and 2005, CMS approved coverage of PET performed on Medicare beneficiaries on a cancer-by-cancer and indication-by-indication basis for nine malignancies. In 2005, after a lengthy period of collaboration (between the academic research community, professional societies, the imaging industry, and CMS), extensive project design, and regulatory review by multiple federal agencies, the NOPR was established in response to the CMS proposal to expand coverage for PET with FDG to include cancers and indications that were otherwise ineligible for Medicare coverage.[2] Medicare coverage for these cancers can now be obtained on the condition that the patient's referring physician and the provider submit data to a clinical registry to assess the impact of PET on cancer patient intended management, pursuant to Medicare's CED

[1] Hillner BE, Siegel BA, Liu D, et al. Impact of positron emission tomography/computed tomography and positron emission tomography alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. J Clin Oncol 2008, published ahead of print on March 24, 2008 as 10.1200/JCO.2007.14.5631 (http://jco.ascopubs.org/cgi/content/abstract/JCO.2007.14.5631v1); Larson SM. Practice-based evidence of the beneficial impact of positron emission tomography in clinical oncology. J Clin Oncol 2008, published ahead of print on March 24, 2008 as 10.1200/JCO.2007.15.6935 (http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2007.15.6935).

[2] Except breast cancer diagnosis and axillary staging, and melanoma regional nodal staging.

policy. During 2005 and 2006, CMS and the NOPR Working Group developed the NOPR to both meet this CED coverage requirement and provide a mechanism for assessing how PET affects clinical care decisions.

II. Operation of the NOPR

The NOPR is a prospective nationally representative data registry that collects information from all Medicare-eligible PET facilities, from the physician requesting the PET, and from the interpreting physician's PET report. Data submission to the registry (and from the registry to CMS) is required by CMS as a condition for Medicare coverage. All data are entered by participating PET facilities via a secure web-based interface and are stored at the ACR in Reston, Virginia.[3] The NOPR's operations and human subject protection protocols have been previously reported in detail.[4] The NOPR is sponsored by AMI and managed by the ACR through the American College of Radiology Imaging Network (ACRIN). The NOPR received input from, and is endorsed by, ACR, ASCO, and SNM. Data analysis is provided by the Center for Statistical Sciences at Brown University. The NOPR began accepting facility registrations in late November 2005, and patient registration began on May 8, 2006.

The NOPR collected questionnaire data from the referring physicians on their intended patient management before and after PET. After one year of data collection,[5] there were 34,358 eligible and complete cases in the NOPR, collected from 1,178 centers in all 50 states. Of these, 4,170 were nonconsenting cases, and 1,170 were indications that were either already nationally covered or explicitly not covered. Of the remaining 28,478 cases, 5,503 were performed for treatment monitoring (and will be analyzed separately). Thus, the analysis cohort consisted of data from 22,975 PET or PET/CT studies, with the latter accounting for 84% of the total. The number of scans done for diagnosis of suspected cancer (or unknown primary cancer), initial staging of known cancer, restaging and suspected cancer recurrence were approximately equal (24% for diagnosis, 28.1% for initial staging, 24.4% for restaging following completion of therapy, and 23.5% for suspected recurrence). Prostatic, pancreatic and ovarian cancers represented about 30% of the cohort (Table 1).[6]

Table 1. The ten most common cancer types in the NOPR

Prostate	2,692 (12%)

[3] The NOPR homepage and web application, including all forms, are located at http://www.cancerPETregistry.org/.

[4] *See* Hillner BE, Siegel BA, Liu D, et al: The National Oncologic PET Registry (NOPR): Design and Analysis Plan. *J Nucl Med* 48:1901-1908, 2007; Lindsay MJ, Siegel BA, Tunis SR, et al: The National Oncologic PET Registry: Expanded Medicare Coverage for PET Under Coverage with Evidence Development. *Am J Roentgenol* 188:1109-13, 2007.

[5] May 8, 2006 to May 7, 2007.

[6] We believe our findings are representative of Medicare patients for whom PET would be ordered if it were covered by CMS for the expanded indications. Patient eligibility was determined solely by a request for PET that was presumably motivated because the referring physician needed the information to guide patient management.

Ovary and uterine adnexa	2,096 (9%)
Pancreas	2,068 (9%)
Bladder	1,615 (7%)
Kidney and other urinary tract	1,600 (7%)
Unknown Primary	1,579 (7%)
Stomach	1,412 (6%)
Lung, small cell	1,403 (6%)
Uterine	1,198 (5%)
Liver and intrahepatic bile ducts	819 (4%)

III. Analysis of the NOPR data: Clinical benefits of PET coverage

The main finding is that PET is associated with a 36.5% change in the treatment or no-treatment decision (Table 2). Within this 36.5%, the PET findings prompted a change from a non-treatment to a treatment plan 28% of the time, three-fold more likely than the converse change from treatment to non-treatment (8%). The specific cancer-imaging indication (diagnosis, staging, etc) had minimal impact. PET was associated with delineation of greater cancer burden or more sites of disease more often than with downstaging. In addition, the 36.5% figure only considers full changes between non-treatment and treatment, which underestimates the clinical impact of PET imaging. PET was actually associated with a management change in almost three-quarters of patients when the addition or deletion to specific modes of therapy are included, and as well as alterations in the type of non-treatment care recommended.

Table 2. Changes in intended management (%).

Pre-PET Plan	**Post-PET Plan**	**Diagnosis n=5,616**	**Staging n=6,464**	**Restaging n=5,607**	**Recurrence n=5,388**	**All n=22,975**
Treat	Treat	16	46	16	20	26
Non-Treat	Non-Treat	53	14	48	41	38
Non-Treat	**Treat**	**23**	**32**	**29**	**29**	**28**
Treat	**Non-Treat**	**8**	**8**	**7**	**10**	**8**
TOTAL	**CHANGE**	**31**	**40**	**36**	**39**	**36**

If PET had been unavailable, the data reveal that the most common plan would have been other imaging (41%) (Table 3). In these patients, the post-PET strategies changed to watching in 37% of patients and to treatment in 48% of patients. In a smaller

group of patients, patients with a pre-PET plan of biopsy (15% of all patients), the post-PET plan had a high impact on care, avoiding a biopsy in about 75% of cases. If the pre-PET strategy was to initiate treatment (34% of all patients), the post-PET strategy involved a major change in type of treatment in about 9%.[7]

Table 3. Changes in intended management plan stratified by pre-PET plan (%).

	Pre-PET Plan			
	Image n=9,518	**Biopsy n=3,552**	**Watch n=2,199**	**Treatment n=7,706**
Post-PET Plan				
Image	6	6	5	4
Biopsy	9	24	9	7
Watch	37	34	62	16
Same Rx	NA	NA	NA	42
New or Major Change in Rx	48	36	24	9
Minor change Rx	NA	NA	NA	24

There were also associated changes in management when the goal of treatment - either curative or palliative - is considered. In 5.6% of all cases, representing 16.7% of cases whose pre-PET plan was treatment, there was a change in the therapeutic goal itself. On the post-PET form, referring physicians indicated that the results of PET enabled them to avoid additional tests or procedures in 76.9% of cases (range 71.5% - 82.0% by indication).

We investigated the impact of including or excluding cases where the pre-PET plan was imaging. Inclusion of such cases could overestimate the impact of PET, since using CT or other imaging, the same management changes (post-imaging) which were observed post-PET might have occurred. However, even when these cases (40% of the total cohort) were excluded, PET was associated with a major change in management in 33% of the remaining cases. As a worst-case estimate, even if one assumed no benefit at all from PET for cases with a pre-PET imaging plan, PET still would be associated with a major change in nearly 20% of patients.

In summary, over one-third of patients undergoing PET for one of the cancer types covered under Medicare's CED policy had a major change in intended

[7] A major change was defined as a switch in type of treatment (e.g., from surgery to chemotherapy) where the original mode of treatment was not included in the post-PET plan even if the treatment goal were constant. A minor change was defined as the addition or deletion of treatments, but where one type of treatment remained constant across the pre- and post-PET plan.

management, including type of treatment. The relative impact of PET on intended management was observed across the full spectrum of indications of its potential uses in cancer patients. The change in intended management in our cohort of previously non-covered cancers is similar to that reported in single-institution studies evaluating patients with covered cancers. The clinical impact of PET appears to be even greater than the impact of body CT when it was introduced thirty years ago.[8]

IV. Formal request for reconsideration

Coverage with Evidence Development offers an innovative approach for the coverage of evolving diagnostic and treatment methods. The primary purpose of CED is to equip CMS with the data necessary to reach well-informed payment determinations. Indeed, in the absence of CED and NOPR, CMS acknowledges that it would have "continued adding coverage for specific clinical use of FDG PET in cancer as each of these potential uses was shown through well-designed clinical trials to influence patient management and alter patient outcomes."[9]

Based on the above analysis of the 22,975 PET studies contained in the NOPR, we believe that there is strong empirical evidence to justify a decision to end the evidence collection requirements as a condition of coverage of PET. Furthermore, we believe that this evidence also justifies a decision to authorize coverage for PET across cancer types for diagnosis, staging, and restaging/suspected recurrence purposes. However, we do not believe that there is sufficiently mature NOPR evidence to recommend that CMS end the CED requirements for the coverage of PET for treatment monitoring at this time. We propose to continue using the NOPR to collect data on the value of PET for this purpose, and we will continue to analyze additional data over a longer period.

We formally request that CMS reconsider NCD CAG-00181N to end the data collection requirements, and thereby authorize the coverage of PET across all oncologic indications for diagnosis, staging, and restaging/suspected recurrence purposes. Attached as Appendix B is a draft revision of the relevant portion of the Medicare National Coverage Determinations Manual (Sections 220.6 et seq.), which both reflects the substance of this request and provides additional guidance for practitioners regarding the circumstances under which PET would be covered.

We look forward to working closely with CMS throughout the reconsideration process, and to providing any additional information that CMS may require.

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[8] *See* Wittenberg J, Fineberg HV: Evaluating efficacy. *Am. J. Roentgenol*. 134:1277-1279, 1980; Wittenberg J, Fineberg HV, Ferrucci JT, Jr., et al: Clinical efficacy of computed body tomography, II. *Am. J. Roentgenol*. 134:1111-1120, 1980; Wittenberg J, Fineberg HV, Black EB, et al: Clinical efficacy of computed body tomography. *Am. J. Roentgenol*. 131:5-14, 1978.

[9] Centers for Medicare & Medicaid Services, *Decision memo for positron emission tomography (FDG) for brain, cervical, ovarian, pancreatic, small cell lung, and testicular cancers*. Baltimore, MD: Centers for Medicare & Medicaid Services, issued January 28, 2005.

Sincerely,

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