MITA
MEDICAL IMAGING
& TECHNOLOGY ALLIANCE
A DIVISION OF NEMA

1300 North 17th Street ▪ Suite 1752
Arlington, Virginia 22209
Tel: 703.841.3200
Fax: 703.841.3392
www.medicalimaging.org

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Louis Jacques, M.D.
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Formal Request for Reconsideration of the National Coverage Determination (NCD) of Positron Emission Tomography (CAG-00065N)

Dear Dr. Jacques:

On behalf of the undersigned organizations, this is a formal request that the Centers for Medicare & Medicaid (CMS) reopen and reconsider Section 220.6 of the Medicare National Coverage Determinations Manual, which addresses coverage limitations for PET scans. We respectfully request that CMS remove the current non-coverage language as it pertains to new PET radiopharmaceuticals that receive approval from the Food and Drug Administration (FDA).

This letter is submitted by the Medical Imaging Technology Alliance (MITA) jointly with the American College of Radiology (ACR), the Society of Nuclear Medicine (SNM), the Council on Radionuclides and Radiopharmaceuticals (CORAR) and the World Molecular Imaging Society (WMIS). Our groups collectively encompass clinicians, academicians, researchers and nuclear medicine providers who develop and utilize molecular imaging technologies, including integrated positron emission tomography/computed tomography (PET/CT). Our associations work together to serve patients through advanced imaging, and represent thousands of physicians, providers, innovators of imaging devices and radiopharmaceutical imaging agents, and manufacturers of radiopharmaceuticals (both commercial and academic radiopharmacies). We have worked closely with CMS over the past several years to provide clinically appropriate use of PET and PET/CT to Medicare beneficiaries. In July, 2011 the undersigned organizations participated in a PET Coverage Workshop to develop alternatives to the non-coverage policy for new FDA approved PET radiopharmaceuticals. Experts and stakeholders from the undersigned groups and from a wide variety of backgrounds -- including policymakers from CMS -- participated in the discussions and formulations of potential coverage options for new radiopharmaceuticals.

A publication summarizing the workshop and discussing issues arising from the NCD's legacy exclusionary policy has recently appeared.[1]

CMS Requirements for Coverage of Medical Services

To be covered under the Medicare program, an item or service must: 1) fall into a defined benefit category; 2) be "reasonable and necessary" for the diagnosis or treatment of illness or injury; and 3) not be specifically excluded from coverage on a basis other than medical necessity.[2] The second requirement – to determine whether an item or service is "reasonable and necessary" – flows from the general rule of § 1862(a)(1)(A) of the Social Security Act that payment may not be made under the Medicare program for those items or services that are determined to be not reasonable and necessary. CMS can, but is not required to, make formal determinations of coverage under § 1862(a)(1)(A) through the issuance of NCDs.

Since the beginning of the Medicare program in 1965, the agency generally does not issue a coverage decision for each particular item or service used in the healthcare for Medicare beneficiaries. The presumption, therefore, is that if a medically appropriate item or service meets a benefit category and is not specifically excluded from coverage, it is eligible to be covered in the absence of an NCD restricting coverage. Far more common than NCDs is the issuance of coverage decisions by CMS' local contractors.[3] A local coverage decision cannot conflict with an NCD, although it can supplement an NCD.[4] There is a well-established common principle that unnecessary services are unpayable, as formalized by an Administrator's Ruling.[5] Thus, association guidelines or other commonly available review standards can be applied by Medicare Administrative Contractors, Recovery Audit Contractors, and Zone Program Integrity Contractors, in lieu of a specific LCD.

Background on PET Scans

A PET scan is a nuclear medicine diagnostic test in which an FDA-approved radiopharmaceutical is used with approved devices to image and study diseased tissue in the human body.[6] The radioisotope may serve directly as the tracer (e.g., sodium fluoride

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[1] Hillman BJ et al. (2012) New pathways to Medicare coverage for innovative PET radiopharmaceuticals: report of a Medical Imaging & Technology Alliance (MITA) Workshop. J Am Coll Radiol 9:108-14; co-published in J Nucl Med J (2012) 53:336-42.

[2] *See* 68 Fed. Reg. 55634 at 55635 (Sept. 26, 2003) (describing the CMS process for issuance of a national coverage determination).

[3] Local versus National Medicare Coverage. (2007) J Oncol Pract 3:256

[4] 68 Fed. Reg. at 55636. An LCD may supplement an NCD by providing additional detail as to how the NCD will be implemented during claims processing. The process for creating LCDs is found in an internet-only policy manual: Program Integrity Manual, Chapter 13.

[5] Administrator's Ruling 95-1. https://www.cms.gov/Rulings/CMSR/list.asp Medicare contractors can rely on "acceptable standards of practice" which are reflected in "consensus of expert opinion" and "published medical literature" that is "well-recognized." Services failing these standards may be non-payable.

[6] National Institutes of Health, "PET scan," Medline Plus, *available at* http://www.nlm.nih.gov/medlineplus/ency/article/003827.htm (last accessed August 27, 2011).

F-18) or the radioisotope may be incorporated into a biologically active molecule. The radiopharmaceutical is injected as a bolus into the patient, and the active molecule carries the radioactive tracer to the tissue in the body that is the subject of the imaging study.[7] As the isotope decays, it emits a positron, which combines with a nearby electron to release two high-energy photons which are detected by the PET scanner.[8] A highly trained physician, board-certified in nuclear medicine and/or radiology, assesses the images for evidence of disease. CMS currently covers four tracers for clinical PET imaging, ammonia N-13, rubidium Rb-82, fluorodeoxyglucose F-18 (FDG), and sodium fluoride F-18. The most frequently used tracer is FDG, and is well-accepted in guidelines, CMS coverage policy, and clinical practice for the management of patients with cancer.[9] FDG-PET also facilitates the assessment and diagnosis of brain dysfunction in dementia.

A new generation of diagnostic radiopharmaceuticals that characterize other important physiologic processes is under review in clinical trials and at the FDA. These diagnostic radiopharmaceuticals are designed to have more accurate and specific mechanisms for diagnosing disease than FDG, because they will be capable of labeling only specific targets or pathophysiologic processes: for example, the characteristics of tumor cells for a specific cancer (rather than labeling all metabolically active organs, as occurs with FDG). Examples include new agents that evaluate myocardial perfusion and molecular processes inherent in cellular proliferation, programmed cell death (apoptosis), angiogenesis, and hypoxia. Other tracers under investigation assess the pathophysiology of Alzheimer's and Parkinson's diseases, reflected in changes in beta-amyloid and neuroreceptor density and function.

Medicare Coverage Policy on PET Scans

1. Overview of PET Coverage

Clinical use of PET scanning for cancer patient care began in the 1980s, when scanners were few and lesion detection was less reliable than it is today.[10] CMS first covered rubidium Rb-82 cardiac PET scans in 1995. In 1998, CMS covered FDG PET scans for staging lung cancer. In 1999, CMS provided additional coverage under specific circumstances for colorectal cancer, lymphoma, and melanoma. Medicare's coverage of PET scans at the time was forward-thinking and preceded coverage of PET scans by most private insurance. All of these indications are now standard-of-practice indications for nuclear imaging.

[7] *See, e.g.*, Michael E. Phelps, "PET: Physics, instrumentation, and scanners" pp. 8-10 (2006).
[8] Phelps, *id*.
[9] Shaikh S (2009) FDG-PET/CT provides added value in routine multiple imaging scans. Diagnostic Imaging (May 2009).
[10] Williams LE (2008) Anniversary paper: nuclear medicine: fifty years and counting. Med Phys 35:3020-9.

In July 2000, CMS received a consolidated request for coverage for some 22 distinct indications for PET scans with a generic tracer, FDG.[11] Because there was no specific FDA labeled indication and limited published literature for the majority of these indications, the agency took a conservative approach. Of the 22 indications requested, the December 2000 final decision memorandum covered only esophageal cancer, head and neck cancers (excluding thyroid and CNS), and refractory seizures. (Of the three indications, only refractory seizures had been specifically reviewed by the FDA.) The other 19 indications requested were non-covered, and any other uses of PET were non-covered.[12] CMS acknowledged that the field was rapidly advancing in both its technology and its clinical literature, and CMS encouraged ongoing submission of coverage requests.

In 2003, CMS issued a limited coverage policy for dementia when there was significant differential diagnostic challenge between a diagnosis of Alzheimer's disease and a diagnosis of frontotemporal dementia.[13] This coverage was supported by interdisciplinary stakeholders and guidance documents.

Through 2005, CMS undertook case-by-case review and expanded coverage for a range of biologically diverse cancers, usually providing coverage simultaneously for diagnosis, staging, and restaging. In cases where CMS initially provided limited coverage (e.g. for colorectal cancer or for lymphoma), later coverage was often revised to include diagnosis, staging, and restaging. These coverage policies reflected cumulative determinations that, across a broad range of common cancers, PET can be more accurate than CT or MRI scanning alone. In 2005, CMS coverage of most remaining and less-common cancers was linked to a requirement that providers collect clinical information about how the scans affected physicians' treatment decisions, creating a Coverage with Evidence Development (CED) study managed by the National Oncologic PET Registry (NOPR).[14]

In 2009, CMS reconsidered the evidence generated through NOPR, conducted a large-scale literature review, and convened an additional Medicare Evidence Development and Coverage Advisory Committee (MedCAC) meeting. Under the resulting revision of CED coverage, CMS removed the requirement that for a patient's initial treatment strategy scan, providers must report to the NOPR. As of today, under what is often called "NOPR 2" or "NOPR 2009,"[15] oncologists still report data to NOPR on each cancer patient with less-common cancers, when PET is ordered for management decisions regarding the treatment or restaging of cancer.[16]

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[11] https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=85&ver=6&NcaName=Positron+Emission+Tomography+(FDG)&bc=ACAAAAAAIAAA&

[12] Deferred for further review were breast cancer, dementia, and additional uses of cardiac imaging. ibid.

[13] *Id*. at § 220.6.13.

[14] http://www.cancerpetregistry.org/

[15] Hillner BE et al. (2012) Impact of FDG-PET Used after Initial Treatment of Cancer: Comparison of the National Oncologic PET Registry 2006 and 2009 Cohorts. (in press).

[16] CMS Press Release, "Medicare Expands Coverage of PET Scans as Cancer Diagnostic Tool" (Apr. 6, 2009), available at http://www.cms.gov/apps/media/press/release.asp?Counter=3436&intNumPerPage=10&checkDate=&chec

In summary, three PET tracers are covered in addition to FDG. Rubidium Rb-82 and ammonia N-13 are covered for perfusion imaging of the heart. Since February 26, 2010, CMS has covered sodium fluoride F-18 imaging to identify metastatic bone lesions in cancer within a CED registry.[17]

2. Origins of the National Non-coverage Policy

As part of the agency's response to the FDG-PET coverage request in July 2000, the December 15, 2000 NCD included the so-called "national non-coverage," language in direct reference to 19 indications that had been reviewed and non-covered. The Decision Memorandum states "The current request for broad coverage received on July 10, 2000 is now considered closed by virtue of this coverage decision. Our review of all evidence submitted and additional evidence gathered supports the conclusion that the request for broad coverage is denied."[18] The non-coverage statement led to a decade of indication-by-indication reviews for PET coverage.

In 2009, CMS consolidated and reformatted its coverage for PET. The introduction for Section 220.6. of the Medicare National Coverage Determinations Manual reiterated that:

> This manual … lists all Medicare-covered uses of PET scans. Except as set forth below in cancer indications listed as "Coverage with Evidence Development," a particular use of PET scans is not covered unless this manual specifically provides that such use is covered. Although this section … lists some non-covered uses of PET scans, it does not constitute an exhaustive list of all non-covered uses.

As discussed in more detail below, the non-coverage language applies to any new FDA approved radiopharmaceutical. In the near future, this policy position, now far removed from its original context, will present a substantial barrier to beneficiary access to appropriate and well-validated diagnostic healthcare as new, rigorously-reviewed, FDA-approved PET radiopharmaceuticals become available.

Coverage of New FDA Approved PET Radiopharmaceuticals

For nearly twenty years, Medicare has dealt with a family of four longstanding PET radiopharmaceuticals — rubidium Rb-82, ammonia N-13, fluorodeoxyglucose F-18, and sodium fluoride F-18 — which comprised the entire field of clinically and commercially available PET tracers. Each of these tracers followed a highly uncertain and multivariate path from use in animal models to early preclinical research, and then to tentative use. There was generally a lack of FDA-supervised phase II and phase III trials,

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[17] Medicare National Coverage Determinations Manual, § 220.6.19.

[18] : https://www.cms.gov/medicare-coverage-database/details/nca-details.aspx?NCAId=85&NcaName=Positron+Emission+Tomography+(FDG)&NCDId=211&ncdver=4&IsPopup=y&

clear metrics for reporting, nor a clear landmark to signify a satisfactory achievement of clinical evidentiary standards as to when clinical use should begin. Rather than review the developer/manufacturer's exhaustive dossier of data, as is familiar today, in 2000 the FDA simply issued a public notification of labeling for FDG in oncology ("to assist in evaluating malignancy") and ammonia N-13 (for myocardial blood flow), as it began to implement 1997 legislation to "establish appropriate procedures for the approval of PET drugs."[19,20] Because many of the potential clinical uses of these early tracers were for diseases common in the Medicare beneficiary population, such as cancer and heart failure, Medicare staff reviewed each possible indication for these four tracers on an individual basis. This led to rigorous, and sound yet forward-looking coverage decisions which made these tracers available for use to Medicare beneficiaries when clinical evidence showed they could be reasonable and necessary in medical care.

At the close of the 1990s, clinical use of PET scans was still new and viewed as experimental by most payers. CMS had yet approved only a very few single indications where PET scans could be used. The number and sophistication of scanners and software was limited, resolution was low, technical and clinical training and experience were limited, and the world literature for all tracers and all indications, including the earliest pilot studies, numbered at most a few hundred articles. This is the setting in which the exclusionary clause was written. Nearly fifteen years later, the medical landscape has changed markedly.

Today, the legacy non-coverage language results in several unintended consequences. First, it is incongruous that future FDA-approved radiopharmaceuticals are deemed <u>not</u> reasonable and necessary for medical care, regardless of their FDA-approved indication, clinical trial outcomes, publications, clinical utility, and without even *de minimis* review by CMS. Second, new radiopharmaceuticals now face a far more rigorous regulatory environment in numerous areas, including: Demonstration of Accuracy & Reliability, Demonstration of Clinical Usefulness, Image Interpretation / Radiologist Training and GMP Manufacturing. The improvements to PET radiopharmaceuticals in each of these areas resulting from the advanced level of current FDA oversight are briefly described below.

> **Demonstration of Accuracy & Reliability:** In June 2004, FDA published guidance on developing medical imaging radiopharmaceuticals. The FDA has stressed that new imaging agents (including PET radiopharmaceuticals) must adequately demonstrate accuracy and reliability through clinical trials. According to this guidance, "*To establish efficacy in clinical studies, we recommend that the accuracy and/or validity of the structural delineation, functional, physiological, or biochemical assessment and disease or pathology detection generally be demonstrated by comparing the performance of the medical imaging agent with that of a reference product or a truth standard in a relevant clinical setting*." The guidance provides adequate detail of FDA's expectations on how sponsors

[19] 65 Fed. Reg. 13002, March 10, 2000, implementing the 1997 FDA Modernization Act, § 121(c).

[20] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm181434.htm

can demonstrate accuracy and reliability through clinical trials of a new agent. This guidance has led to improvements in the strength of clinical data available to support that PET radiopharmaceuticals are accurate and reliable for imaging the desired targets.

Demonstration of Clinical Usefulness: In addition to being accurate and reliable, the FDA now requires PET radiopharmaceuticals to demonstrate clinical utility. Indeed, the FDA recognizes that in the absence of clinical usefulness, imaging agents can be harmful and should not be approved. As per FDA guidance: "*The use of medical imaging agents without defined benefits and without an understanding of how the imaging results can be used for patient management might cause harm to patients even if the agent has low toxicity. Such harm might include (1) conducting unnecessary diagnostic testing based on the results of the agent, (2) directing patients to invasive procedures or inappropriate or unnecessary therapy, and (3) creating unnecessary patient anxiety from abnormal test results*." Because the FDA now factors these potential risks into its approval decision, they have provided guidance on how to demonstrate or test clinical usefulness in defined populations and support a positive risk / benefit ratio. Indeed, recent FDA advisory meetings on new PET radiopharmaceuticals for amyloid imaging focused heavily on clinical usefulness, with the agency asking both in 2008 and in 2011 for the panel to confirm whether or not amyloid imaging PET radiopharmaceuticals had defined clinical utility in certain populations. This requirement of the FDA for demonstrating clinical usefulness creates confidence that new PET radiopharmaceuticals will not only be accurate and reliable, but also will have defined benefits for the patients in whom they are used as specified in the FDA-approved label.

Image Interpretation / Radiologist Training: In order for patients to benefit from PET radiopharmaceuticals, not only must the PET radiopharmaceuticals itself be safe, effective, reliable (and provide useful clinical information), but the radiologist reading the study must be able to interpret the image in an accurate and reliable method. Thus the FDA has recently focused on PET radiopharmaceuticals sponsors' development and implementation of radiologist training materials to ensure that sponsors provide not just a drug, but also a validated training program so that radiologists can interpret images accurately and reliably. This new focus on the human element of PET radiopharmaceuticals will bring improvements in standardization and quality of image interpretation, leading to benefits for patients in the form of more accurate, confident and reliable diagnostic information.

GMP Manufacturing: On December 9, 2009 the FDA published regulations documenting the GMP standards for PET radiopharmaceuticals manufacturing. These regulations (and accompanying FDA guidance) provide detailed requirements for PET radiopharmaceuticals production facilities.[21] Implementation of these regulations has led to a higher degree of uniformity /

[21] http://www.fda.gov/Drugs/Developmentapprovalprocess/manufacturing/ucm085783.htm

standardization of PET radiopharmaceuticals production across various sites, as well as higher levels of quality control on PET radiopharmaceuticals, thus promoting a greater degree of confidence that PET radiopharmaceuticals produced throughout the country will be safe and effective.

In summary, the application of the non-coverage language for new FDA approved PET radiopharmaceuticals creates an unnecessary delay in the adoption of new medical imaging advances. Based on our knowledge of radiopharmaceuticals currently in the FDA review process or under FDA-authorized rigorous investigational trials, these radiopharmaceuticals will be new innovations with unique clinical utility and will have no similar or alternative service. We also note that CMS has limited program resources to undertake new National Coverage Analyses each year. Within a few years, half or more of these NCAs could be devoted exclusively to new PET radiopharmaceuticals. This is unlikely to be a necessary or an efficient use of scarce agency resources.

Proposed Modification to Medicare Coverage Manual

We request that CMS undertake a limited revision of the PET NCD which maintains the integrity of the NCD for tracers reviewed within, but forecloses the inappropriate extension of non-coverage to new FDA-approved tracers that have not received even minimal actual review by the agency. We propose a revision as follows:

> This manual section 220.6 lists all Medicare-covered uses of PET scans **based on the tracers rubidium, ammonium, sodium fluoride, and fluorodexoyglucose**. Except as set forth below in cancer indications listed as "Coverage with Evidence Development", a particular use of PET scans **with these tracers** is not covered unless this manual specifically provides that such use is covered. Although this section 220.6 lists some non-covered uses of PET scans, it does not constitute an exhaustive list of all non-covered uses **of these tracers. Coverage of other FDA-approved PET radiopharmaceuticals is at the discretion of the local Medicare Administrative Contractors unless specifically addressed under a National Coverage Determination.**

Education Efforts

The undersigned organizations are committed to an ongoing dialogue with CMS to review new PET radiopharmaceuticals. As part of these efforts we plan to develop educational resources to help ensure appropriate utilization of PET/CT by referring physicians, as well as nuclear medicine physicians and radiologists. The groups will continue to support studies of potential additional benefits to patients that will serve as the basis for appropriateness criteria guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decisions.

Conclusion

We believe there is now consensus that the recent advances in imaging and CMS' past experience with PET coverage no longer support a clinical rationale for a pre-emptive national non-coverage policy for new PET radiopharmaceutical agents that undergo rigorous FDA review and approval.

We look forward to working closely with CMS and the local Medicare Administrative Contractor Medical Directors to establish appropriate local policies for the coverage as new PET agents are approved by the FDA. Please let us know if we can provide any additional information that CMS would find of use in revision to the Medicare Coverage Manual for PET scans.

Sincerely,

Gail M. Rodriguez, PhD
Executive Director, Medical Imaging & Technology Alliance

Harvey L. Neiman, MD, FACR
Chief Executive Officer, American College of Radiology

Michael J. Guastella
Executive Director, Council on Radionuclides and Radiopharmaceuticals

George Segall, MD
President, Society of Nuclear Medicine

Juri Gelovani, MD, PhD
President, World Molecular Imaging Society