January 11, 2013

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Centers for Medicare & Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

By Online Submission

RE: World Molecular Imaging Society (WMIS) Comment on Proposed Decision Memorandum for Positron Emission Tomography (CAG-00065R2)

Dear Dr. Jacques:

The World Molecular Imaging Society (WMIS) appreciates the effort by the Centers for Medicare & Medicaid Services (CMS) over the past year to revise the national coverage policy for Positron Emission Tomography (PET) imaging. WMIS strongly supports the Proposed Decision Memorandum proposal to permit local contractors to determine coverage for new oncologic PET radiopharmaceuticals approved by the U.S. Food and Drug Administration (FDA).

However, WMIS remains concerned that the scope of the proposed decision is unnecessarily limited to oncology. We believe that there is no clinical basis that justifies the proposed requirement that every future FDA-approved cardiac and neurological PET radiopharmaceutical must seek a case-by-case National Coverage Determination (NCD) for an exemption from the non-coverage language of NCD 220.6. As is the case for oncology, we believe a more flexible coverage policy is also clinically appropriate for cardiology and neurology.

Background on WMIS

WMIS is an international scientific and educational organization dedicated to the understanding of biology and medicine through multimodal *in vivo* imaging and the utilization of quantitative molecular imaging in patient care. The foremost and authoritative society in molecular imaging, WMIS was formed in 2011, as a result of the merger of two of the premier molecular imaging societies—the Academy of Molecular Imaging (AMI) and the Society for Molecular-Genetic Imaging. Between 2006 and 2011, AMI was the sponsor of the original NOPR, and since 2011, WMIS has continued to sponsor the current iterations of the registry, NOPR 2009 and NOPR (NaF-PET). WMIS is also a cosignatory to the March 30, 2012 NCD reconsideration request.

WMIS Supports Ending the National Non-Coverage Policy for New Imaging Agents

WMIS strongly supports the proposal to permit local Medicare Administrative Contractors (MACs) to determine coverage for oncologic PET that uses new radiopharmaceuticals for their labeled indications as approved by the FDA. As we articulated in our previous comments, for more than a decade, significant data have been accumulated to demonstrate both the clinical accuracy of FDG-PET and its impact on patient management. To date, each change in PET coverage has required a lengthy NCD reopening and review. Based on the past reviews of FDG-PET, and now NaF-PET, it is appropriate that FDA-approved imaging agents, in the future, should not face a *de facto* national non-coverage policy following their approval.

In the United States and internationally, the molecular imaging clinical community and the radiopharmaceutical industry are undertaking clinical trials on numerous new oncologic imaging agents that hold great promise for the treatment and management of patients with cancer. In the next few years, we expect that several other PET radiopharmaceuticals for oncologic imaging will obtain FDA approval. These include agents for assessing tumor proliferation rates, hypoxia, angiogenesis, amino acid transport, and estrogen, androgen and somatostatin receptor status, as well as several radiolabeled monoclonal antibodies directed against receptors and other cellular antigens. These agents all hold promise for improved cancer care by individualizing therapy. Moreover, they likely will enable more cost-effective application of expensive therapies to those patients in whom the likelihood of therapeutic benefit can be established by imaging biomarkers before (or soon after) the start of treatment. For instance, Ga-68 DOTATOC or DOTATATE have been used worldwide for imaging somatostatin receptor expression in neuroendocrine tumors. These PET methods are more accurate and, at the same time, less expensive than currently covered conventional planar scintigraphy and SPECT with In-111 pentetreotide.

Most recently, in September 2012, the Mayo Clinic received FDA approval for Choline C-11 Injection to help detect sites of recurrent prostate cancer. C-11 Choline is a radioactive tracer involved chiefly in a metabolic pathway leading to the synthesis of cell membrane lipids. Since cancer cells take up more choline than do normal cells, the images can be used to help determine areas of probable cancer in patients with biochemical recurrence of their disease when bone scintigraphy, computed tomography or magnetic resonance imaging is non-informative. The review that preceded FDA approval was rigorous and exhaustive, and is publicly available.[1]

CMS Should Expand the Final Decision to Include Cardiology Tracers

The FDA's standards for new radiopharmaceuticals in oncology do not differ from its standards for approval of tracers in other diseases. Therefore, WMIS is highly concerned that the Proposed Decision only lifts the national non-coverage policy in the field of oncology (with the possibility of an extension to include cardiology).

The Proposed Decision memorandum requests public comments on lifting the national non-coverage policy for cardiac PET imaging agents. For several decades, members of WMIS have generated an extensive body of clinical research, and by now have over a decade of clinical

practice, with cardiac PET. Chronic cardiac disease is associated with one of the highest morbidities among Medicare recipients, and several new cardiac PET imaging agents that may be highly relevant to the Medicare population are currently advancing through clinical trials.

WMIS believes that new PET tracers for myocardial perfusion imaging, such as F-18 flurpiridaz, should be open to coverage review by MACs following their FDA approval for the same indications for which Rb-82 and N-13 ammonia are currently covered. Requiring each one of the new FDA-approved agents for myocardial imaging to proceed through a lengthy and administratively burdensome NCD reconsideration process would be unnecessarily duplicative and would delay the availability of safe, FDA-approved tracers to Medicare beneficiaries. This would be unfortunate, because the longer half-life of F-18 flurpiridaz means that this agent should be readily distributable as unit doses (like FDG) and thus be more widely available to Medicare beneficiaries than either Rb-82 or N-13 ammonia.

In addition to perfusion radiotracers, new PET molecular imaging agents are being evaluated in humans with various forms of cardiovascular disease. For example, PET with F-18 galacto-RGD to target $\alpha_v\beta_3$ integrin is undergoing human evaluation to detect vascular inflammation in atherosclerosis and angiogenesis in left ventricular remodeling that occurs following myocardial infarction. Successful detection of these processes has the potential for more targeted and earlier intervention of patients with atherosclerosis and its complications. Abnormalities in myocardial fatty acid metabolism are central to the pathogenesis to various forms of heart failure, particularly those secondary to cardiometabolic disease such as obesity and diabetes mellitus. To this end, several F-18 radiolabeled fatty acid imaging agents are undergoing early phase clinical trials. The availability of these imaging agents has the potential to provide both new prognostic markers in heart failure patients and an imaging surrogate for new therapies entering the clinic designed to modulate myocardial metabolism in these patients.

WMIS requests that the Final Decision memorandum include cardiology along with oncology as categories where MACs may determine whether (or not) the use of PET scans with such new FDA-approved radiopharmaceuticals is reasonable and necessary.

CMS Should Not Foreclose Local Coverage for Future Imaging Agents for Neurology

WMIS strongly recommends that the most appropriate framework for the next generation of PET tracers in oncology, cardiology, and neurology (including dementia and Alzheimer's disease), is the elimination of tracer-by-tracer and indication-by-indication national coverage reviews. Coverage should be reviewed through the local contractor process and, when appropriate, through a national coverage analysis.

In the Proposed Decision memorandum, CMS has summarily foreclosed the possibility of coverage of neurological PET tracers except on a case-by-case basis through the NCA process. While this is the approach already taken for beta-amyloid imaging, it seems unnecessarily restrictive to repeat the same process over and over for all future FDA-approved neurological PET tracers, and for review of each indication for each of the widening spectrum of tracers. If CMS is not prepared to delegate neurological PET imaging (other than beta-amyloid imaging) to the MACs at this time, we believe CMS should open a review of the national non-coverage

policy for neurology following the completion of the current national coverage analysis Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease.

Although fewer PET radiopharmaceuticals are currently under clinical development for neurologic applications (other than for amyloid imaging), a notable exception is in tracers for evaluation of patients with movement disorders due to Parkinsonian syndromes. These agents will allow for earlier and more accurate diagnosis, prognosis, and treatment selection. The majority of these PET agents assess specific targets present in neurons in the brain that use the neurotransmitter dopamine, and can quantify the loss of this neuronal population due to neurodegeneration. These PET tracers are clearly superior for detecting the loss of dopaminergic neurons compared to the SPECT agent, I-123 ioflupane, which is FDA-approved for distinguishing Parkinsonsian syndromes from essential tremor and other non-degenerative causes of movement disorders. The overall cost of performing studies with PET tracers for the brain dopaminergic systems would likely be similar to — or less than — the cost of I-123 ioflupane SPECT.

Moreover, in the Proposed Decision, CMS has affirmatively retained the express option to supersede or preclude local coverage decisions on specific uses of neurological PET where CMS believes centralized control is warranted. Indeed, CMS has already exercised this option in the review of beta-amyloid PET. Given the ample regulatory authorities and safeguards that exist, there appears no compelling reason for CMS to preclude preemptively any possibility of local coverage for FDA-approved neurological PET tracers by leaving in place the categorical exclusion for one or another specific group of Medicare's beneficiaries.

There is a genuine and growing concern in the medical community that the United States is falling behind Europe and the rest of the world in terms of clinical molecular imaging. The continuation of blanket national non-coverage policies for new FDA-approved PET imaging agents discourages continued domestic research and investment in molecular imaging, the adverse impact of which is borne by the patients and Medicare beneficiaries who stand to benefit from such technological advances.

WMIS Plans to Work with Medicare Administrative Contractors

Over the past decade, WMIS has had extensive experience working with MAC medical directors on PET coverage, coding and payment issues. The years of indication-by-indication review of FDG-PET — and the subsequent multiple phases of Coverage with Evidence Development (CED) for FDG-PET — raised numerous coverage implementation issues for local MACs and Medicare Advantage plans. At the same time, PET imaging has undergone near-annual coding and reimbursement methodology policy changes, each of which has in turn created new implementation issues for MACs.

As CMS introduces this new and more efficient coverage framework for new PET radiopharmaceuticals, WMIS stands ready to work closely with CMS, local medical directors, and other stakeholders in advance of the FDA approval of any new imaging agent, in order to provide technical assistance and help mitigate any coverage implementation issues that may arise at the local level.

Conclusion

WMIS strongly supports the proposal in the Proposed Decision to permit local contractors to determine coverage for new oncologic PET FDA-approved radiopharmaceuticals, and respectfully requests that the Final Decision memorandum provide local contractors with the same latitude for cardiac and neurologic PET imaging agents as well.

WMIS appreciates the opportunity to comment on the Proposed Decision, and looks forward to continuing to work collaboratively with CMS to make innovative imaging technology available to the providers and Medicare beneficiaries who will benefit most from its use. We are of course pleased to provide CMS with any additional information that it may find useful in reaching its Final Decision.

Sincerely,

Zaver Bhujwalla, Ph.D.
President, WMIS

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[1] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203155Orig1s000TOC.cfm