



July 2, 2009

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Centers for Medicare & Medicaid Services  
7500 Security Blvd., Mail Stop C1-09-06  
Baltimore, MD 21244

**Re: Joint Comments on Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (CAG-00065R1)**

Dear Acting Director Jensen:

We are writing in response to the Centers for Medicare & Medicaid Services' (CMS) request for comments on the reconsideration of Section 220.6 of the National Coverage Determination (NCD) on Positron Emission Tomography (PET), opened for the purpose of reviewing evidence on the use of NaF-18 to identify bone metastasis of cancer. For the reasons stated below, we strongly support Medicare coverage of oncologic NaF-18 PET and/or PET/CT, (hereinafter "NaF-18 PET") and encourage CMS to act favorably in this regard.

This letter is submitted jointly on behalf of the Academy of Molecular Imaging (AMI), the American College of Nuclear Physicians (ACNP), the American College of Radiology (ACR), the American Society for Radiation Oncology (ASTRO), and the Society of Nuclear Medicine (SNM). These organizations are composed of clinicians, academicians, researchers and nuclear medicine providers utilizing molecular imaging technologies, including integrated positron emission tomography/computed tomography (PET/CT). We represent tens of thousands of physicians, providers, and patients with regard to this technology, and have worked closely with CMS over the past several years to increase beneficiary access to PET/CT through the development of the National Oncologic PET Registry (NOPR).

**I. Overview**

We strongly believe that the evidence indicates that NaF-18 PET is equal or superior to the current covered technology in identifying bone metastasis of cancer, and encourage CMS to cover NaF-18 PET for this purpose without restriction. NaF-18 is an FDA-approved USP radiotracer that allows physicians to use PET to detect metastasis to the bone of many common cancers (including breast, lung, and prostate), thus facilitating the development of treatment programs for affected individuals. While NaF-18 held a previous New Drug Application (NDA), that NDA was withdrawn solely for market reasons. No safety issues have been reported with

NaF-18, and the Food and Drug Administration (FDA) conducted a formal review of PET drugs in 2000 that specifically deemed NaF-18 to be safe and effective.<sup>1</sup> The National Cancer Institute has recently conducted an extensive literature review (attached) that evaluates the clinical value of NaF-18 for bone imaging,<sup>2</sup> and the AMI has recently embarked upon a randomized, multi-center trial investigating the use of NaF-18 PET for detection of bone metastasis, further illustrating the value that the clinical and imaging community believe that NaF-18 PET holds for this purpose.

In addition, the recent shortage of Technetium-99m (Tc-99m), lends urgency to this reconsideration. Tc-99m is the radionuclide used in approximately 80 percent of nuclear medicine scans worldwide, and the Tc-99m bone imaging agents are the only radiopharmaceuticals approved by CMS for bone scintigraphy. This shortage has therefore led to a significant reduction in the availability of bone scintigraphy. As a result, many Medicare beneficiaries with cancer who need bone imaging now face the prospect of lengthy delays or alternative diagnostic procedures that may involve greater radiation dosage, less accuracy, or higher cost. Fortunately, the radiotracer NaF-18 is unaffected by this severe shortage. The availability of NaF-18 PET bone imaging as a CMS-approved alternative to conventional bone scintigraphy performed with Tc-99m agents (e.g., <sup>99m</sup>Tc-MDP) will thus enable beneficiaries who require bone imaging in such circumstances to obtain these essential tests.

We believe that the evidence supports coverage of oncologic NaF-18 PET without restriction. However, should CMS decide that further evidence on the clinical value of oncologic NaF-18 PET is necessary, we would encourage CMS to cover NaF-18 PET through a CED program via the National Oncologic PET Registry (NOPR). Utilizing CED would enable CMS to acquire more robust evidence on the value of oncologic NaF-18 PET, while simultaneously ensuring that cancer beneficiaries receive the imaging they require. We estimate that the number of oncologic NaF-18 PET bone scans that would be performed under CED would be relatively limited, perhaps totaling half the number of oncology scans that were registered through the original NOPR process. In short, should CMS disagree that the existing evidence supports full coverage, we believe that NaF-18 PET is an excellent candidate for CED, and urge CMS to use this opportunity to acquire additional evidence regarding its clinical value to Medicare beneficiaries.

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<sup>1</sup> See Food and Drug Administration, *Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications*, 65 Fed. Reg. 12,999 (2000), available at <http://www.fda.gov/ohrms/dockets/98fr/031000a.txt>. (“FDA reviewed its records and, under Sec. 314.161, determined that sodium fluoride F 18 injection was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will list sodium fluoride F 18 injection in the *Orange Book’s* ‘Discontinued Drug Product List’ section, which delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. Because sodium fluoride F 18 injection was not withdrawn from sale for reasons of safety or effectiveness, it is still a listed drug, and FDA can approve ANDAs that refer to it.”)

<sup>2</sup> Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, National Institutes of Health, *Review of Published Literature on the Use of Sodium Fluoride F 18 (<sup>18</sup>F-NaF) Positron Emission Tomography (PET) in the Evaluation of Altered Osteogenic Activity* (Mar. 2009).

## II. Clinical Support

The clinical evidence supporting the use of NaF-18 PET is presented in the appended March 2009 *Review of Published Literature on the Use of Sodium Fluoride F18 (<sup>18</sup>F-NaF) Positron Emission Tomography (PET) in the Evaluation of Altered Osteogenic Activity*, prepared by the Cancer Imaging Program at the National Cancer Institute. Results from 41 clinical trials published since 1992 are summarized in the *Review*, including 10 well-controlled studies of <sup>18</sup>F-fluoride PET to identify bone metastases in adults.

These studies show that <sup>18</sup>F-fluoride PET is more sensitive and selective than <sup>99m</sup>Tc-MDP bone scintigraphy for diagnosis and detection of bone metastases [8–12, 45]. Use of CT in conjunction with <sup>18</sup>F-fluoride PET improves sensitivity and specificity, and enhances the ability to distinguish benign from malignant lesions [12]. Several of these studies included subjects with multiple types of cancer; some study cohorts were specific to lung, breast and prostate cancer. The results of the 10 well-controlled studies are briefly summarized below. Citations are numbered according to the appended report.

***Beheshti, M., et al. Detection of bone metastases in patients with prostate cancer by <sup>18</sup>F fluorocholine and <sup>18</sup>F fluoride PET-CT: a comparative study. Eur J Nucl Med Mol Imag. 35:1766–1774, 2008 [6].*** The aim of this prospective trial was to compare the potential value of <sup>18</sup>F-fluorocholine (FCH) PET-computerized tomography (CT) and <sup>18</sup>F-fluoride PET-CT for the detection of bone metastases in 38 subjects with prostate cancer. 321 lesions (151 malignant, 155 benign and 15 equivocal) were evaluated in the study. <sup>18</sup>F-FCH PET-CT showed 106 sites with increased tracer uptake (100 malignant, 6 benign), while <sup>18</sup>F-fluoride PET-CT detected 200 bone lesions (116 malignant, 84 benign). The sensitivity, specificity and accuracy, respectively, for detection of bone metastases were 74%, 99% and 85% for <sup>18</sup>F-FCH PET-CT, and 81%, 93% and 86% for <sup>18</sup>F-fluoride PET-CT.

***Petren-Mallmin, M., et al. Skeletal metastases from breast cancer: uptake of <sup>18</sup>F-fluoride measured with positron emission tomography in correlation with CT. Skeletal Radiol. 27(2):72–76, 1998 [7].*** Uptake of <sup>18</sup>F-fluoride in skeletal metastases was characterized in five breast cancer patients, and compared to CT. All patients had multiple skeletal metastases. Focally increased uptake of <sup>18</sup>F-fluoride was seen in both 7 osteolytic and osteoblastic bone lesions as defined by CT; however, lesions less than 3 mm on CT were not detected by <sup>18</sup>F-fluoride PET. Overall, the areas of abnormal high accumulation of <sup>18</sup>F correlated well with the pathological appearance on CT.

***Schirrmeister, H., et al. Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. J Clin Oncol. 17(8):2381–2389, 1999 [8].*** This was a prospective trial to evaluate the sensitivity and specificity of <sup>18</sup>F-fluoride PET to detect bone metastases compared to conventional bone scans in 34 patients with breast cancer. <sup>18</sup>F-fluoride PET outperformed <sup>99m</sup>Tc-MDP bone scintigraphy by both patient-based and lesion-based analyses. <sup>18</sup>F-fluoride PET detected 64 bone metastases in 17 patients, whereas bone scan only identified 29 metastases in 11 patients. All lesions detected by bone scan were also identified by <sup>18</sup>F-fluoride PET. The full extent of metastatic bone disease was correctly characterized by <sup>18</sup>F-fluoride PET in all patients, but in only 6 patients (35.3%) with <sup>99m</sup>Tc-MDP. <sup>18</sup>F-fluoride PET resulted in restaging of disease in three patients and subsequent change in the disease management of four patients (11.7%).

**Hetzl, M., et al. F-18 NaF PET for detection of bone metastases in lung cancer: accuracy, cost-effectiveness, and impact on patient management. J Bone Miner Res. 18(12): 2206–2214, 2003** [9]. This was a prospective study to evaluate the use of  $^{18}\text{F}$ -fluoride PET, SPECT and  $^{99\text{m}}\text{Tc}$ -MDP planar bone scan for detection of bone metastases in 103 patients with lung cancer. Bone metastases were present in 33 patients.  $^{18}\text{F}$ -fluoride PET correctly identified bone metastases in 31 of these patients compared with 20 by planar  $^{99\text{m}}\text{Tc}$ -MDP scan and 29 by SPECT. In addition, two patients with negative  $^{18}\text{F}$ -fluoride PET scan but positive MRI were later confirmed to have no bone metastases by clinical follow-up or autopsy. Compared with  $^{18}\text{F}$ -fluoride PET, the extent of bone metastases was underestimated in 23 (69.7%) patients with  $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy and in 16 (48.5%) of 33 patients with SPECT.

**Schirrmeister, H., et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and ( $^{18}\text{F}$ )-labeled NaF PET in newly diagnosed lung cancer. J Nucl Med. 42(12):1800–1804, 2001** [10]. This was a prospective study designed to compare the sensitivities and specificities of  $^{18}\text{F}$ -fluoride PET and  $^{99\text{m}}\text{Tc}$ -MDP bone scan with and without and SPECT to detect bone metastases in 53 subjects with newly diagnosed lung cancer. Of the 53 patients, 12 (23%) had metastatic bone disease as determined by a whole spine survey of MRI, which served as a standard reference method.  $^{18}\text{F}$ -fluoride correctly detected bone metastases in 11 patients, correctly diagnosed 41 subjects as not having bone metastases, and interpreted one patient with a single rib metastases as equivocal. The combination of planar scan and SPECT, however, missed bone metastases in one patient and underestimated the extent of bone involvement in seven of 12 patients (58%) as compared with  $^{18}\text{F}$ -fluoride PET. All metastases that were detected by  $^{99\text{m}}\text{Tc}$ -MDP planar scan and SPECT were identified by  $^{18}\text{F}$ -fluoride PET. For the patient whose bone metastases were missed by both planar scan and SPECT, the clinical management was changed as a result of  $^{18}\text{F}$ -fluoride PET findings.

**Schirrmeister, H., et al. Anatomical distribution and sclerotic activity of bone metastases from thyroid cancer assessed with F-18 sodium fluoride positron emission tomography. Thyroid. 11(7):677–683, 2001** [11]. This was a prospective study to evaluate the anatomical distribution and metabolic behavior of bone metastases in 35 subjects with thyroid cancer. The study identified 18 patients with 41 metastases (nine single, nine multiple).  $^{18}\text{F}$ -fluoride PET identified 21 previously unknown metastases. The sensitivity of the combination of bone scan and whole-body iodine scan was as high as that obtained with  $^{18}\text{F}$ -fluoride PET and MRI, which were used as the primary reference methods.

**Even-Sapir, E., et al. Assessment of malignant skeletal disease: Initial experience with  $^{18}\text{F}$ -fluoride PET/CT and comparison between  $^{18}\text{F}$ -fluoride PET and  $^{18}\text{F}$ -fluoride PET-CT. J Nucl Med. 45(2):272–278, 2004** [12]. This was a prospective study to evaluate the diagnostic accuracy of  $^{18}\text{F}$ -fluoride PET and  $^{18}\text{F}$ -fluoride PET-CT in assessing malignant osseous involvement in 44 patients with various types of cancer. In a patient-based analysis, the sensitivities of PET and PET-CT were 88% and 100%, respectively ( $p < 0.05$ ), and the specificities were 56% and 88%, respectively (difference not statistically significantly). In 12 patients referred for  $^{18}\text{F}$ -fluoride assessment due to bone pain despite negative findings with  $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy,  $^{18}\text{F}$ -fluoride PET/CT suggested malignant bone involvement in all four patients with proven skeletal metastases, a potential benign cause in four of seven patients who had no evidence of metastatic disease, and a soft-tissue tumor mass invading a sacral foramen in one patient.

**Hoegerle, S., et al. Combined FDG and [F-18]Fluoride whole-body PET: a feasible two-in-one approach to cancer imaging? *Radiology*. 209(1):253–258, 1998 [13]** . This was a prospective trial conducted to determine the feasibility of conducting combined  $^{18}\text{F}$ -FDG and  $^{18}\text{F}$ -fluoride PET for cancer imaging in 30 patients with various types of cancer, and to evaluate the utility of this approach compared to  $^{18}\text{F}$ -FDG alone in another 30 patients. 73 lesions were diagnosed (41 soft-tissue and 32 skeletal) in the combined group. The interobserver agreement for the differentiation between soft-tissue and skeletal lesions was 1.00. Interobserver agreement for the localization of all lesions was 0.95 (95% CI=0.81 to 1.00) in the combined group, compared to 0.74 in the group having  $^{18}\text{F}$ -FDG alone (p=0.007).

**Hoh, C.K., et al. Whole body skeletal imaging with [ $^{18}\text{F}$ ]fluoride ion and PET. *J Comput Assist Tomogr*. 17(1):34–41, 1993 [14]** . This was a prospective trial to evaluate the sensitivity and specificity of  $^{18}\text{F}$ -fluoride PET to detect areas of altered osteogenic activity in 19 patients with various malignant and benign skeletal conditions and 19 normal volunteers. In the 19 normal volunteers, no unexpected sites of uptake of  $^{18}\text{F}$ -fluoride were evident. In subjects with malignant or benign skeletal lesions, a total of 101 bone lesions (94 malignant and seven benign) were analyzed. Both malignant and benign skeletal lesions were correctly identified in 18 patients.

**Schirrmeyer, H., et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus  $^{18}\text{F}$  PET. *J Nucl Med*. 40(10):1623–1629, 1999 [8]**. This was prospective study to evaluate the accuracy of planar  $^{99\text{m}}\text{Tc}$ -MDP bone scanning vs. tomographic bone imaging with  $^{18}\text{F}$ -NaF PET for detection of osteolytic and osteoblastic bone metastases in 44 patients with various cancers. Fifteen of the 44 patients had bone metastases by the reference methods. All 15 were identified by  $^{18}\text{F}$ -fluoride PET and 13 were identified by  $^{99\text{m}}\text{Tc}$ -MDP bone scanning.  $^{18}\text{F}$ -fluoride PET detected two-fold more lesions, both benign and malignant, than planar  $^{99\text{m}}\text{Tc}$ -MDP scan.  $^{18}\text{F}$ -fluoride PET was equally sensitive in detecting osteoblastic metastases and osteolytic metastases with a 100% detection rate, whereas planar  $^{99\text{m}}\text{Tc}$ -MDP scan detected 49.3% of osteoblastic and 44.8% of osteolytic lesions.

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In addition, two other studies of NaF- $^{18}\text{F}$  PET (published since the March 2009 NCI report) are summarized below; also summarized below is a 2006 NaF- $^{18}\text{F}$  PET study that was not included in the NCI report.

**Krüger S., et al. Detection of bone metastases in patients with lung cancer:  $^{99\text{m}}\text{Tc}$ -MDP planar bone scintigraphy,  $^{18}\text{F}$ -fluoride PET or  $^{18}\text{F}$ -FDG PET/CT. *Eur J Nucl Med Mol Imaging*. 2009 Jun 6. [Epub ahead of print].** The study compared the diagnostic accuracy of  $^{18}\text{F}$ -FDG PET/CT(n=126) versus standard planar  $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy(n=58) and  $^{18}\text{F}$ -fluoride PET(n=68) for the detection of bone metastases in patients with non-small cell lung cancer. Bone metastases were diagnosed in 34 patients (27%). In 13 of 18 patients metastases were concordantly diagnosed with  $^{18}\text{F}$ -FDG PET/CT and  $^{18}\text{F}$  PET.  $^{18}\text{F}$ -FDG PET/CT showed more metastases compared to  $^{18}\text{F}$  PET (53 vs 40). However,  $^{18}\text{F}$  PET identified four patients with metastases compared to negative findings on  $^{18}\text{F}$ -FDG PET/CT. Of 16 patients, 11 had concordant findings of metastases on  $^{18}\text{F}$ -FDG PET/CT and bone scintigraphy. In three patients bone scintigraphy was false-negative and in two patients metastases were diagnosed as

equivocal.  $^{18}\text{F}$ -FDG PET/CT may obviate additional bone scintigraphy or  $^{18}\text{F}$ -fluoride PET in the staging of NSCLC.

*Iagaru A., et al. Novel strategy for a cocktail  $^{18}\text{F}$ -fluoride and  $^{18}\text{F}$ -FDG PET/CT scan for evaluation of malignancy: results of the pilot-phase study. J Nucl Med 2009 Apr;50(4):501-5.*

This was a prospective pilot study of 14 patients with various malignancies who underwent separate  $^{18}\text{F}$  and  $^{18}\text{F}$ -FDG PET/CT, as well as combined  $^{18}\text{F}$  and  $^{18}\text{F}$ -FDG PET/CT scans. Interpretation of the combined scans compared favorably (no lesions missed) with both scans performed separately. Seven patients had osseous metastases. Skeletal disease was more extensive with  $^{18}\text{F}$  PET/CT in six patients, and osseous metastases in one patient was only detected with  $^{18}\text{F}$  PET/CT. Both  $^{18}\text{F}$  PET/CT and combined  $^{18}\text{F}$  and  $^{18}\text{F}$ -FDG PET/CT showed more extensive skeletal disease than  $^{18}\text{F}$ -FDG PET/CT alone.

*Even-Sapir E., et al. The detection of bone metastases in patients with high-risk prostate cancer:  $^{99\text{m}}\text{Tc}$ -MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT,  $^{18}\text{F}$ -fluoride PET, and  $^{18}\text{F}$ -fluoride PET/CT. J Nucl Med. 2006 Feb;47(2):287-97.*

This prospective study of 44 patients compared the detection of bone metastases by  $^{99\text{m}}\text{Tc}$ -MDP planar bone scintigraphy, SPECT,  $^{18}\text{F}$ -Fluoride PET, and  $^{18}\text{F}$ -Fluoride PET/CT in patients with high-risk prostate cancer. In patient-based analysis, 23 patients had skeletal metastatic spread (52%) and 21 did not. Categorizing equivocal and malignant interpretation as suggestive for malignancy, the sensitivity, specificity, positive predictive value, and negative predictive value of planar bone scintigraphy were 70%, 57%, 64%, and 55%, respectively, of multi-FOV SPECT were 92%, 82%, 86%, and 90%, of  $^{18}\text{F}$ -Fluoride PET were 100%, 62%, 74%, and 100%, and of  $^{18}\text{F}$ -Fluoride PET/CT were 100% for all parameters. Of the 156  $^{18}\text{F}$ -Fluoride lesions, 81 lesions (52%), including 34 metastases, were overlooked with normal appearance on planar bone scintigraphy. SPECT identified 62% of the lesions overlooked by planar bone scintigraphy. The authors concluded that  $^{18}\text{F}$ -Fluoride PET/CT is a highly sensitive and specific modality for detection of bone metastases in patients with high-risk prostate cancer. It is more specific than  $^{18}\text{F}$ -Fluoride PET alone and more sensitive and specific than planar and SPECT bone scintigraphy. Detection of bone metastases is improved by SPECT compared with planar bone scintigraphy and by  $^{18}\text{F}$ -Fluoride PET compared with SPECT. This added value of  $^{18}\text{F}$ -Fluoride PET/CT may beneficially impact the clinical management of patients with high-risk prostate cancer.

### **III. Conclusion and Request for Expedited Review**

On the basis of the evidence presented above, we strongly encourage CMS to amend NCD CAG-00065R and adopt a manual policy providing coverage for NaF-18 PET in identifying bone metastasis of cancer without restriction. This will afford Medicare cancer patients the widest possible access to bone imaging.

However, should CMS decide that further evidence on the clinical value of oncologic NaF-18 is necessary, we would recommend that CMS cover NaF-18 PET through the CED program via the National Oncologic PET Registry (NOPR). In the absence of unrestricted coverage, we believe that CED coverage of NaF-18 PET is an efficient path forward, as CED will not only provide CMS and the medical community with the information necessary to analyze the value of oncologic NaF-18 PET, but will simultaneously provide Medicare beneficiaries nationwide with access to much-needed imaging technology.

Regardless of the precise parameters of any eventual coverage decision, the PET imaging community acknowledges that while many providers have significant experience with FDG-PET imaging techniques, fewer providers have routinely offered bone imaging with NaF-18 PET for cancer patients. We can assure CMS that we recognize the importance of ensuring that PET imaging centers and physicians quickly gain the imaging, interpreting and reporting skills necessary to maximize the benefit for these cancer patients. We are collectively committed to the development of training materials aimed at educating providers on all relevant technical and clinical challenges, and will be diligent in disseminating such information widely through webcasts, in-service trainings, self-guided training programs, FAQs, sample protocols, and other means. These resources will be publicly accessible via imaging organizations' websites and other communications.

Finally, in light of the aforementioned severity and expected long-term duration of the Tc-99m shortage, we urge CMS to act quickly and expeditiously in reaching a determination on NaF-18 PET so as to ensure minimal disruption in the availability of bone imaging to beneficiaries. If CED is mandated by CMS, we believe that the NOPR is prepared to develop the necessary processes and data collection forms expeditiously, so that such coverage could be rapidly instituted.

We appreciate the opportunity to provide comments to CMS concerning NaF-18 PET, and look forward to working with CMS to provide any additional information that you would find valuable in your decision making process.

Sincerely,



Timothy McCarthy, PhD  
President, AMI



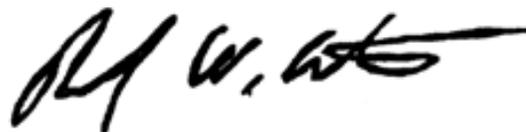
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Encl.: National Cancer Inst., *Review of Published Literature on the Use of Sodium Fluoride F 18*