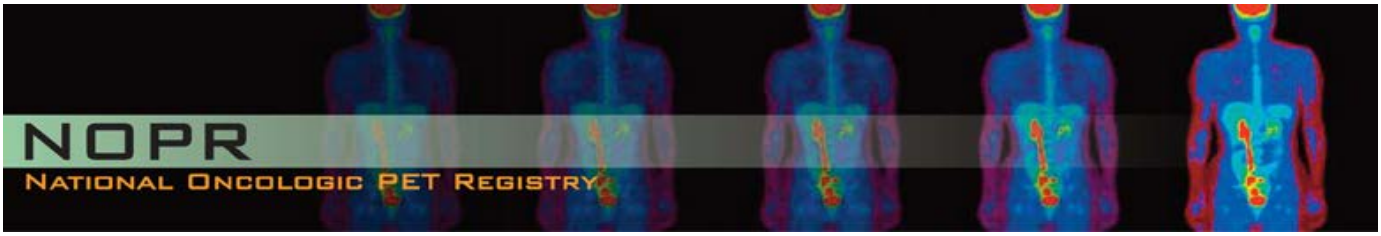


February 5, 2015

Tamara Syrek Jensen, Esq.
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

*Via Electronic Delivery*

**RE: National Oncologic PET Registry (NOPR) Working Group Updated Request for Reconsideration of NCA for Positron Emission Tomography (NaF-18) To Identify Bone Metastasis of Cancer (CAG-00065R)**

Dear Director Syrek Jensen:

As the co-chairs of the National Oncologic PET Registry (NOPR) Working Group, we write to provide additional new data in support of our initial May 15, 2014 request for a formal reconsideration of the Centers for Medicare & Medicaid Services (CMS) National Coverage Analysis (NCA) on Positron Emission Tomography (NaF-18) (CAG-00065R).[1] The NOPR is sponsored by the World Molecular Imaging Society (WMIS) (formerly the Academy of Molecular Imaging (AMI)) and managed by the American College of Radiology (ACR).

For the convenience of CMS, this letter supplements our May 15, 2014 reconsideration letter with the presentation of new data, and we respectfully renew our underlying request: that CMS end the prospective data collection requirements under Coverage with Evidence Development (CED) for all oncologic indications for $^{18}$F-sodium fluoride (NaF) PET imaging, and revise the National Coverage Determination (NCD) for PET Scans, Manual Section 220.6.19, to provide Medicare coverage of NaF PET for bone metastasis for all oncologic indications.[2]

We continue to believe that both CMS and Medicare beneficiaries have benefited from the NOPR's experience in implementing, improving, and operating a large-scale CED study for NaF PET over the last four years. As discussed more fully below, we strongly believe that the purpose of CED for NaF PET for bone metastasis has been fulfilled, as the NOPR has now demonstrated through its published

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[1] National Coverage Analysis (NCA) for Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (CAG-00065R), *available at* http://www.cms.gov/medicare-coverage-database/details/nca-details.aspx?NCAId=233.
[2] National Coverage Determination (NCD) for Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (220.6.19), *available at* http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=336.

research of the CED evidence that NaF PET is both reasonable and necessary in this regard. In light of the extensive NOPR data collection on NaF PET since 2011, including newly published data in the *Journal of Nuclear Medicine*, we are convinced that there remains no clinical need to continue CED data collection for NaF PET for bone metastasis. Attached are the three manuscripts published in the *Journal of Nuclear Medicine* that summarize our results. The first two manuscripts—one on our findings in patients with prostate cancer[3] and another on our findings in patients with other cancer types (principally breast and lung)[4]—were attached to our May 2014 letter. The third manuscript, published in February 2015, assesses the impact of NaF PET on treatment monitoring of systemic cancer therapy for bone metastasis.[5] The results reported in these three peer-reviewed publications, and discussed in greater detail below, further confirm our view.

In sum, we urge CMS to formally reconsider the existing NCD in light of the published evidence, which we believe supports our conclusion that the remaining CED restrictions pertaining to NaF PET for bone metastasis should be ended.

## I. Background and Accomplishments of NOPR and CED

The NOPR was launched as a clinical study in 2006, in response to a CMS proposal to expand coverage for $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) to a variety of oncologic indications not previously eligible for Medicare reimbursement.[6,7] From the beginning, the WMIS and the ACR—the organizations developing the NOPR—worked closely with CMS staff on design and implementation of all aspects of the NOPR.

The initial purpose of the NOPR was to enable Medicare beneficiaries with less common cancer types to have equal access to FDG PET, in order to both inform clinical management decisions and provide prospective data collection within the NOPR.[8] The primary scientific objective of the NOPR was to assess the impact of FDG PET on the referring physician's intended patient management by collecting questionnaire data before PET and again after the PET results were available for decision making.

In April 2009, CMS expanded coverage of FDG PET for initial evaluation of patients with nearly all types of cancer, and for subsequent treatment strategy evaluations of an expanded number of cancer

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[3] Hillner BE, Siegel BA, Hanna L, et al. Impact of $^{18}$F-fluoride PET in patients with known prostate cancer: initial results from the National Oncologic PET Registry. J Nucl Med 2014;55:1-8. *See also* Segall, GM, PET/CT with sodium $^{18}$F-fluoride for management of patients with prostate cancer, J Nucl Med 2014;55:531-533.

[4] Hillner BE, Siegel BA, Hanna L, et al. Impact of $^{18}$F-fluoride PET on intended management of patients with cancers other than prostate cancer: results from the National Oncologic PET Registry. J Nucl Med 2014;55:1054-1061.

[5] Hillner BE, Siegel BA, Hanna L, et al. $^{18}$F-fluoride PET used for treatment monitoring of systemic cancer therapy: results from the National Oncologic PET Registry. J Nucl Med 2015;56:222-228.

[6] Centers for Medicare & Medicaid Services, *Coverage with evidence development Medicare coverage—general information, available at* https://www.cms.gov/CoverageGenInfo/03_CED.asp.

[7] Centers for Medicare & Medicaid Services, CMS Transmittal AB-01-54, *Expanded coverage of positron emission tomography (PET) scans and related claims processing changes, available at* http://www.cms.gov/transmittals/downloads/AB0154.pdf.

[8] Tunis S, Whicher D. The National Oncologic PET Registry: lessons learned for coverage with evidence development. J Am Coll Radiol. 2009;6:360–365. *See also* Hillner BE, Liu D, Coleman RE, et al. The National Oncologic PET Registry (NOPR): design and analysis plan. J Nucl Med 2007;48:1901–1908.

types. In June 2013, CMS approved the reconsideration request from NOPR to end the CED prospective data collection requirements for FDG PET and to provide coverage for essentially all oncologic indications for all cancers.[9]

In 2011, the NOPR expanded by developing a new, second registry for the use of the radiopharmaceutical $^{18}$F sodium fluoride (NaF) in PET for identification of osseous metastasis. It is this second follow-on registry for which the data collected form the basis for this reconsideration request. The NOPR NaF PET registry built on the experience, infrastructure, and staffing of the FDG PET registry. Accrual to NOPR NaF PET began on February 8, 2011. Through December 31, 2014, the NaF PET registry has collected data from 35,468 scans performed on 27,713 patients at 1,000 different PET facilities nationwide. The monthly average number of completed scans was 564 in 2011, 720 in 2012, 843 in 2013, and 909 in 2014. Overall, consent for research use of the data was obtained from all three participants in each case (the patient, the referring physician and the interpreting physician) in 85.8% of the scans.

Consistent with CMS policy, the NOPR NaF registry undertook prospective data collection of the impact of NaF PET in patients with suspected or known osseous metastasis in any cancer type, using a questionnaire-based approach to assess referring physician–intended management. Structured information on NaF PET scan results is also collected from interpreting physicians. Preliminary analysis of the initial data revealed that over 60% of pre-PET plans proposed "other imaging" if neither NaF PET nor conventional bone scintigraphy (BS) were available. To better understand this decision strategy, the data collection protocol was revised to ask what the alternative "other imaging" method would have been. If prior BS was available to the interpreting physician, the revised form also requested the date of that study. These protocol revisions were implemented on January 27, 2012, and this date was used as the starting point of the research dataset analyses in our three published papers.

## II. CED Data Collection for NaF PET

Table 1 below summarizes the profile of the NOPR cohort by imaging indication and cancer type for all scans accrued over 47 months. Approximately 69% of scans were done for prostate cancer, 14% for breast cancer, and 6% for lung cancer. The remaining 11% were distributed across all other cancers. Approximately 5% of the scans were done for diagnosis of suspected primary or metastatic osseous cancer (in patients without known cancer), about one-fifth for initial staging of newly diagnosed cancer, about one-half for suspected first development of osseous metastasis as a site of known cancer recurrence or progression, 14% for suspected progression of known osseous metastasis, and 17% for treatment monitoring.

[9] Decision Memo for Positron Emission Tomography (FDG) for Solid Tumors (CAG-00181R4) (June 11, 2013), *available at* http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=263.

**Table 1: Profile by Indication and Cancer Type***

| Indication | Prostate[(a)] | Breast[(a)] | Lung[(a)] | Others[(a)] | Total by Indication[(b)] |
|---|---|---|---|---|---|
| Diagnosis of suspected osseous metastatic disease in patients without proven cancer[†] | 960 (4.0) | 214 (4.4) | 117 (5.3) | 560 (14.4) | 1,851 (5.3) |
| Initial staging of newly diagnosed cancer | 5,536 (23.2) | 501 (10.2) | 435 (19.7) | 619 (15.9) | 7,091 (20.3) |
| Suspected new osseous metastasis as a site of recurrence or progression | 10,824 (45.3) | 2,285 (46.7) | 1,036 (46.9) | 1,751 (45.0) | 15,896 (45.6) |
| Suspected progression of known osseous metastasis | 3,239 (13.6) | 769 (15.7) | 254 (11.5) | 469 (12.0) | 4,731 (13.6) |
| Monitoring treatment response during systemic therapy | 3,329 (13.9) | 1,128 (23.0) | 368 (16.7) | 494 (12.7) | 5,319 (15.2) |
| Total by cancer type | 23,888 (68.5) | 4,897 (14.0) | 2,210 (6.3) | 3,893 (11.2) | 34,888 (100.0) |

* Based on data for scans enrolled from February 8, 2011 through December 31, 2014 (all ages)

[(a)] Count (Column %); [(b)] Count (Overall %)

## III. Clinical Evidence in Support of NaF PET Coverage for Oncologic Indications

$^{18}$F-NaF is an FDA-approved radiopharmaceutical that allows physicians to use PET to detect metastasis to bone from many common cancers (including prostate, breast, and lung), thus facilitating the development of treatment programs for affected individuals. In March 2000, the FDA reaffirmed through a published Federal Register notice its previous conclusion that $^{18}$F-NaF was deemed to be safe and effective.[10] In August 2011, in guidance issued on the preparation of New Drug Applications and Abbreviated New Drug Applications for several PET radiopharmaceuticals, the FDA again reaffirmed this conclusion.[11]

The joint AMI-ACNP-ACR-ASTRO-SNM comment letter submitted in support of the original reconsideration request for NaF PET provided a detailed summary of the clinical evidence supporting the use of NaF PET.[12] As has been previously detailed in the literature, NaF PET has many advantageous technical features over conventional planar bone scintigraphy (BS) performed with $^{99m}$Tc-diphosphonate agents, including: superior pharmacokinetics with a shorter time from injection to imaging, higher bone

[10] 65 Fed. Reg. 12,999 (Mar. 10, 2000).
[11] U.S. Food and Drug Administration, *Guidance: PET Drug Applications — Content and Format for NDAs and ANDAs*, at 3-4 (Aug. 2011), *available at* http://www.fda.gov/downloads/Drugs/Guidances/ucm078738.pdf.
[12] Comment Letter of AMI-ACNP-ACR-ASTRO-SNM on CAG-00065R (July 2, 2009), *available at* http://www.cms.gov/medicare-coverage-database/staticpages/public-comment.aspx?commentID=19910&ReportType=nca.

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uptake, faster blood clearance, lower radiation dose, and superior image quality.[13,14] However, at the time CMS issued its NaF PET Decision Memorandum in February 2010, CMS believed that the existing evidence was not yet sufficient to determine whether the results of NaF PET imaging to identify bone metastases improved health outcomes of beneficiaries.[15]

**a. NaF PET Literature (pre-Decision Memorandum)**

The literature review in the February 2010 Decision Memorandum commented upon nine published reports involving NaF PET. Only six of these included comparisons to conventional bone scintigraphy with $^{99m}$Tc-diphosphonate agents. The sample sizes of these reports were quite small, ranging from n=34 to n=103. One was exclusively limited to prostate cancer (n=44).

**b. NaF PET Literature (post-Decision Memorandum)**

Since the approval of CED coverage for NaF PET in 2010, there have been several new additions to the NaF PET literature. Tateishi et al. reported a meta-analysis of published data from 1993-2008 involving 350 patients.[16] Although the reported sensitivities and specificities were high (> 0.96), the sample sizes in each report were small and there were probable publication biases and heterogeneity in metastatic burden.

The largest series identified was from Damle et al. that prospectively assessed the results of NaF PET in high-risk patients with breast (n=72), prostate (n=49) and lung (n=30) cancer studied for a mix of initial staging and restaging.[17] This series did not include any specific symptoms like bone pain to define risk. All patients had NaF PET, conventional BS and FDG-PET within two weeks. Given the small sample sizes by cancer type, it is not surprising that, although NaF PET had higher sensitivity and specificity than conventional BS, the confidence intervals overlapped.

Iagaru et al. reported another single-center, prospective series comparing conventional BS, FDG PET, and NaF PET in 52 patients with miscellaneous cancer types (including 19 sarcomas).[18] They asserted that NaF PET was slightly more sensitive and superior in evaluation of the extent of disease over conventional BS.

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[14] Jadvar H. Molecular imaging of prostate cancer with PET. J Nucl Med 2013;54:1685-1688.
[15] Decision Memo for Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (CAG-00065R) (Feb. 26, 2010), *available at* http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=233.
[16] Tateishi U, Morita S, Taguri M, et al. A meta-analysis of $^{18}$F-fluoride positron emission tomography for assessment of metastatic bone tumor. Ann Nucl Med. 2010;24:523–531.
[17] Damle NA, Bal C, Bandopadhyaya GP, et al. The role of $^{18}$F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and $^{99m}$Tc-MDP bone scan. Jpn J Radiol. 2013;31:262–269.
[18] Iagaru A, Mittra E, Dick DW, Gambhir SS. Prospective evaluation of $^{99m}$Tc MDP scintigraphy, $^{18}$F NaF PET/CT, and $^{18}$F FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol 2012;14:252-259.

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PET/CT to conventional BS and FDG PET/CT that used data from 1,170 patients in publications thorough September 1, 2013.[19] On a per patient basis, the pooled sensitivity, specificity, and area under the receiver operating characteristic curve of NaF-PET/CT were 92% (95% CI, 89%-95%), 93% (95% CI, 91%-95%), and 0.985 respectively. When compared with conventional BS, NaF PET/CT showed both higher sensitivity (96% vs. 88%, P = 0.002) and specificity (91% vs. 80%, P = 0.001). When compared with FDG PET/CT, NaF PET/CT showed higher sensitivity (94% vs. 73%, P = 0.003), but no significant difference in specificity (88% vs. 98%, P = 0.06). They concluded that NaF-PET has excellent diagnostic capacity for the detection of bone metastases and shows advantages when compared to either conventional BS or FDG PET/CT.

**c. NOPR-based NaF PET Reports**

Our recent analyses of the NOPR NaF PET data fill the gap in the literature identified by CMS in February 2010: that the existing evidence was not yet sufficient to determine whether the results of NaF PET imaging to identify bone metastases improved health outcomes of beneficiaries.

Our research provides, for the first time, a large-scale evidence-based analysis of the advantages of NaF PET as an alternative to conventional BS.[20,21,22] Selected tabular results from our papers are included in the Appendices. The following is a list of notable findings.

- Our report on prostate cancer patients used data from January 27, 2012 through December 31, 2012. Our report including all other cancers and expanding the prostate cancer comparison cohort used data from January 27, 2012 through December 31, 2013. Our report on monitoring the response to systemic therapies used data from January 27, 2012 through June 30, 2014.

- Symptoms, signs and other findings prompting NaF PET were quite different for patients with prostate versus other cancers. For prostate cancer patients, elevated or rising PSA was the dominant indication, and 59% of patients had no specific symptoms or other indications. For non-prostate cancer patients, only 30% to 46% of patients had no symptoms or evidence of suspected metastases. Bone pain was the dominant and only sign in 36-46%% of patients depending on indication. Evidence of metastasis using other imaging was noted in about 10% of patients. (Appendix 1)

- When referring physicians were asked for a pre-PET plan assuming both NaF PET and conventional BS to be unavailable, the vast majority stated that they would utilize alternative advanced imaging (FDG PET, MRI or CT scanning). (Appendix 2)

- Within each imaging indication, there were minimal differences between non-prostate and prostate cancer patients in the distribution of abnormal findings. Scan findings were interpreted as

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[19] Shen CT, Qiu ZL, Han TT, Luo QY. Performance of $^{18}$f-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. Clin Nucl Med. 2015;40:103-10.
[20] Hillner BE, et al., *supra* note 3.
[21] Hillner BE, et al., *supra* note 4.
[22] Hillner BE, et al., *supra* note 5.

definitely positive for osseous metastasis in 13-24% of studies done for initial staging, 25-28% done for suspected first osseous metastasis, and 63-76% done for progression of osseous metastasis, respectively (Appendices 3 and 4).

- Referring physicians indicated that the NaF PET findings reduced the need for additional diagnostic tests in 78% to 90% of cases, depending upon cancer type and indication for the scan.

- The impact of NaF PET on intended management (classified as either treatment or non-treatment) before and after PET differed substantially between scans done for suspected first osseous metastasis (the most frequent indication) compared to either initial staging or suspected progression of osseous metastasis (Appendix 4).

  The impact of NaF PET done for suspected first osseous metastasis was lowest in breast cancer patients (24%), followed by all other cancers (31%), lung (36%) and prostate (43%). This is principally explained by the much greater frequency of non-treatment plans after NaF PET in non-prostate cancer patients (58% to 68%) than in prostate cancer patients (39%).

  In contrast, in initial staging or suspected progression of osseous metastasis, the plans for non-prostate cancer patients were slightly more likely to be switched after NaF PET from non-treatment to treatment than were the plans for prostate cancer patients. The overall impact on intended management was greatest in suspected progression of known osseous metastasis (52% to 60%) and initial staging (42% to 54%).

  Finally, in comparing management plans before and after NaF PET in patients receiving systemic therapy for metastatic cancer, four treatment-related options—continue, modify, switch or stop all therapy—were considered. Overall, we found a 40% change in treatment plan after NaF PET.

- New to the NaF PET registry was detailed categorization of the NaF PET findings from the interpreting physician. These data allowed a broad assessment of whether the differences in post-PET action by cancer types were appropriate in light of the scan findings. The scan results were categorized as: normal, benign findings only and equivocal (combined into one category for data analysis); probable metastatic disease; and definite metastatic disease. For the most common indication—suspected first osseous metastasis—benign findings were found in 53% of prostate, 54% of lung, 62% of breast, and 64% of other cancer patients. Treatment plans in these patients predominantly reflected actions to non-osseous sites (e.g., 21% to 25% chemotherapy in lung and other cancers versus 6% to 7% in prostate and breast cancers) and the availability of hormonal therapy in prostate (24%) and breast cancer (8%).

  When NaF PET findings were categorized as definite metastasis, about one-quarter of breast and lung cancer patients had post-PET plans for biopsy or other imaging, rather than proceeding directly to treatment. This likely reflects physician assessment of a lower post-PET probability of "true" osseous metastasis for these cancer types, compared with prostate cancer. This is fully consistent with current practice guidelines.

- In the prostate cancer-only cohort, approximately one third of men scanned for suspected first osseous metastasis or suspected progression of osseous metastasis had previously undergone

conventional BS. However, about 70% of these conventional BS studies were conducted more than one year earlier. When the interval between BS and NaF PET was less than 90 days, 35% of NaF PET scans showed evidence of more extensive osseous metastasis than did BS. For suspected first osseous metastasis or suspected progression of osseous metastasis NaF PET scans with an interval from BS less than 180 days, 40% and 76% of NaF PET scans, respectively, showed more extensive disease.

- In instances where NaF PET was used for monitoring systemic therapies (hormonal or chemotherapies in prostate and breast vs. chemotherapy only in other cancers) in patients age > 65 years, the pre-PET plans were to continue therapy in 67.3%, switch to another therapy in 24.8%, modify dose or therapy schedule in 7.0% and stop systemic therapy and switch to supportive care in 0.8%. Prior to imaging, suspected progressive disease was much higher in prostate (34%) than in other cancer types (14% to 19%).

  The overall post-NaF PET change in intended management was 40% (42% prostate, 39% breast and 35% all other cancers). After NaF PET, continuing current therapy was planned in 59%, switching therapy in 33%, modifying dose or schedule in 5% and stopping all therapy in 3%. Additionally, the referring physician judged the post-PET prognosis to be better then the pre-PET prognosis in 28% of instances, unchanged in 40% and worse in 32%.

  After NaF PET, continuing current therapy was planned in 81% of patients with a better or unchanged prognosis in contrast to those with a worse prognosis where 76% had plans to switch therapy in 76%. Among the 57% of patients with prior NaF PET scans for comparison, the plan when the new scan showed either no metastases, a reduction (improvement) in metastatic disease, or no change in metastatic disease was to continue current therapy in 82% of cases. However, when there was worsening or new osseous metastatic disease, the post-NaF PET plan was to switch therapies in 59%.

- Our unpublished data regarding use of NaF-PET for diagnosis of suspected bone metastasis in patients without proven cancer show the following. As noted in Table 1, 1,851 scans (5.3% of total scans) were performed for this indication, and consent for use of the data for research was obtained for 1,557 scans (84.1%).

  In keeping with the use of NaF-PET for all other indications, the most common primary tumor suspected was prostate cancer (53.1%). Clinical conditions that prompted NaF-PET differed between prostate cancer and other cancers: skeletal pain in 42.5% (28.1% in suspected prostate cancer vs. 58.9% for all other suspected cancer types), elevated tumor markers in 29.5% (47.0% prostate vs. 9.6%% other) and findings on prior imaging studies in 28.8% (15.5% prostate cancer vs. 44.0% other). These differences observed by suspected cancer type almost certainly indicate that most of the patients suspected to have prostate cancer were identified on the basis of abnormal PSA levels. More than one of these features occurred in 19.1% and 17.1% had none of the signs, symptoms or testing results offered as choices on the pre-PET form.

  Based on the PET assessment forms completed by the interpreting radiologists/nuclear medicine physicians, over one-third of scans (37.5%) showed probable or definite evidence of osseous metastatic disease, an additional 8.4% were considered equivocal for metastasis, and the rest were

normal or showed only benign findings (with little difference as a function of suspected cancer type). Referring physicians reported that they thought osseous metastatic disease was probably or definitely present in 39.1% of patients. Bone lesion biopsy after the scan was reported in only 5.3%; of these, 32.9% were positive, 19.5% were negative and 47.6% were still pending at the time the post-PET form was completed. However, a pathologic diagnosis of cancer was confirmed from any site in 58.3% of patients after the scan; this occurred less frequently in cases where the suspected cancer type was denoted as cancer of unknown primary origin (15.7%) than for other suspected cancers (65.9%). Referring physicians reported that NaF-PET allowed them to avoid ordering additional noninvasive tests in 71.1% of cases and invasive procedures in 65.6%.

- Excessive multiple scanning remains a potential concern. Table 2 is an assessment of all patients scanned for any "subsequent treatment strategy" indication—including those done for suspected first osseous metastasis, suspected progression of osseous metastasis or treatment monitoring. We considered all patients initially scanned from the opening of the registry (February 8, 2011) through June 30, 2014 with a minimal follow-up of six months (through December 31, 2014). Table 2 shows that about 80% of patients had a single scan, with minimal differences across cancer types. About 7% of patients had three or more scans.

**Table 2: Scans for Subsequent Treatment Strategy Indications (including all enrolled cases)**

| Scan Number for Subsequent Treatment Strategy Indications | Prostate | Breast | Lung | Others |
|---|---|---|---|---|
| 1, n (%) | 10,490 (79.1) | 2,418 (80.0) | 1,038 (83.2) | 1,740 (84.0) |
| 2, n (%) | 1,823 (13.7) | 354 (11.7) | 127 (10.2) | 191 (9.2) |
| 3, n (%) | 575 (4.3) | 125 (4.1) | 38 (3.0) | 81 (3.9) |
| 4, n (%) | 213 (1.6) | 54 (1.8) | 13 (1.0) | 22 (1.1) |
| ≥5, n (%) | 167 (1.3) | 72 (2.4) | 32 (2.6) | 38 (1.8) |
| Interval between scans 1 and 2, mean (sd) in mo. | 10.3 (7.0) | 8.5 (7.0) | 5.9 (5.5) | 7.4 (6.9) |
| Interval between scans 1 and 3, mean (sd) in mo. | 13.2 (6.6) | 10.3 (5.0) | 8.3 (5.1) | 8.8 (5.4) |

## IV. NOPR Data and Reconsideration of Coverage with Evidence Development

A key goal of CMS in establishing CED for NaF PET was determining whether NaF PET is associated with appropriate changes in the goals of managing osseous metastatic disease and in the associated quality of life.[23] Although these goals are clear, it was recognized from the inception of the NaF PET registry (the design of which was approved by CMS) that NOPR would not be able to obtain definitive evidence of those outcomes given the limitations of a questionnaire-based registry. However, at

[23] Decision Memo for CAG-00065R, *supra* note 15.

a November 2012 Medical Imaging and Technology Alliance meeting on types of evidence needed for coverage of PET, then-director of the CMS Coverage and Analysis Group Dr. Louis Jacques noted that CMS remained willing to consider intermediate endpoints for diagnostic test results (such as change in intended management) under circumstances where the different management strategies are well defined (e.g., for loco-regional versus systemic disease of cancer).[24]

Indeed, NOPR's NaF PET and FDG PET registries share the same limitations: the lack of confirmation of actual initiation or cessation of treatments or changes in the use of relevant diagnostic studies, the uncertain effect of patient acceptance and patient preferences on post-scan management intentions, and the lack of a comparator cohort. However, in subsequent work with FDG PET registry data we have been able to address, at least in part, the concordance of planned and actual actions by inference from participant's Medicare claims. We found in our data linkage between NOPR identifiers and participant's Medicare claims, that claims confirmations of NOPR intended management were reasonably good for initial staging but less so among patients scanned for restaging or suspected recurrent disease.[25] Notwithstanding these acknowledged limitations, CMS removed the CED requirements for FDG PET on the basis of NOPR data, and we believe that a similar decision is justified for NaF PET on the basis of NOPR data.

The NOPR has been successful in meeting the goal for which it was established —providing clear, extensive data on the previously little-researched question of whether there is a clinical benefit of NaF PET for physician decision making in identifying bone metastasis. NOPR has now produced evidence that the impact of NaF PET in these circumstances is measurable, significant and greater than the investigative team had anticipated. These new research findings do suggest that the patterns of use of NaF PET in prostate cancer (when compared to other cancers) differ slightly. However, the relative impact on subsequent care predominantly reflects differences in the underlying pathology of bone metastases (osteoblastic versus osteolytic), availability and effectiveness of hormonal therapy, and the need for chemotherapy. In conjunction with the other published literature cited above (documenting the greater sensitivity and specificity of NaF PET by comparison with conventional BS), it is our opinion that it is unlikely that significant new useful information will be obtained if coverage for NaF PET continues to be available under CED, without adding substantial new data collection requirements and response burdens to referring physicians and providers.

In short, although there remain important open questions concerning PET—such as how PET should be most effectively sequenced with other imaging resources in patient care pathways and the frequency of its use—we believe such research would require a very different vehicle than the NOPR, and thus that there is little benefit to such research in continuing to maintain the existing CED requirements for NaF PET.

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[24] Hillman BJ, Frank RA, Abraham BC. The Medical Imaging and Technology Alliance Conference on Research Endpoints Appropriate for Medicare Coverage of New PET Radiopharmaceuticals. J Am Coll Radiol. 2013; 10:689–694.

[25] *See, e.g.*, Hillner BE, Tosteson TD, Tosteson AN, et al. Intended versus inferred management after PET for cancer restaging: analysis of Medicare claims linked to a coverage with evidence development registry. Med Care. 2013; 51:361–367; Hillner BE, Tosteson TD, Tosteson AN, et al. Intended versus inferred care after PET performed for initial staging in the National Oncologic PET Registry. J Nucl Med. 2013; 54:2024–2031.

## V. Non-Oncologic Bone Imaging Uses of NaF PET

In addition to the data published on NaF PET in identifying bone metastasis of cancer, we strongly believe that the evidence indicates that NaF PET is equal or superior to the current covered technology of conventional BS for non-oncologic bone imaging purposes. Use of NaF PET for a variety of indications related to benign skeletal diseases falls within the FDA-approved indication for this radiopharmaceutical, namely: "Sodium Fluoride F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity."[26] NaF PET is especially advantageous for imaging those portions of the body that are difficult to image well by conventional bone scintigraphy (including single-photon emission computed tomography [SPECT] or SPECT/CT), such as the skull base, facial bones and cervical spine, or where better resolution than can be achieved by SPECT is necessary, e.g., in investigation of unexplained foot pain.

NaF PET has been used as a diagnostic tool for investigating a variety of diverse clinical problems that are relevant in the Medicare population. Examples include suspected osteomyelitis in patients who cannot undergo MRI, assessing mandibular osteonecrosis associated with bisphosphonate therapy and assessing mandibular (or other) bone graft viability, and evaluation of failed joint arthroplasties or spinal fusions, and evaluation of suspected facetogenic pain in the cervical and lumbar spine prior to planned local therapies. Prospective randomized trials are unlikely to ever be conducted for these problems. The studies in the published literature have the usual limitations and largely consist of single-site, non-comparative series with small sample sizes from across the U.S. and Europe. Several recent review articles have summarized the uses of NaF PET for benign bone diseases.[27]

As a policy matter, we also believe it would be advantageous to migrate away from older tracers and imaging methods, such as $^{99m}$Tc-diphosphonates and planar scintigraphy, just as previous advances in FDG PET led to the markedly decreased clinical reliance on scintigraphy with $^{67}$Ga. The recent history of repeated worldwide shortages of $^{99}$Mo, the parent radionuclide for production of $^{99m}$Tc via the $^{99}$Mo/$^{99m}$Tc generator, further supports the migration to NaF as an alternative method for radionuclide bone imaging.

We encourage CMS to cover NaF PET for bone imaging across a spectrum of non-cancer/benign bone diseases, and favor authorizing *local contractor discretion* for the use of NaF PET across the broad universe of benign indications.

## V. Conclusion and Reconsideration Request

On behalf of the NOPR, we appreciate the assistance and support that CMS has provided to the NOPR over the past decade, and particularly over the past four years with respect to NaF PET. We

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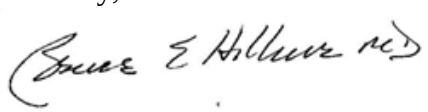
[26] U.S. Food and Drug Administration, *Fluorine 18 ($^{18}$F) as Fluoride Ion in Saline Solution — Package Insert Information, available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM257994.pdf.

[27] Strobel K, Vali R. $^{18}$F NaF PET/CT versus conventional bone scanning in the assessment of benign bone disease. *PET Clin* 2012:7; 249-261; Fischer DR. Musculoskeletal imaging using fluoride PET *Semin Nucl Med* 2013: 43: 427-433; Wieder HA, Pomykala KL, Benz MR, Buck AK, Herrmann K. PET tracers in musculoskeletal disease beyond FDG. *Semin Musculoskelet Radiol* 2014;18: 123-132; Even-Sapir E. $^{18}$F-fluoride PET/computed tomography imaging, PET Clin 2014;9:277-285; Jadvar H, Desai B, Conti PS. Sodium $^{18}$F-fluoride PET/CT of bone, joint and other disorders. Semin Nucl Med 2015;45:58-65.

believe that the evidence-based conclusions from our analysis of the extensive NOPR NaF data set strongly support this reconsideration request: to end the CED data collection requirement in the context of NaF PET, and to authorize national coverage of NaF PET for bone metastasis for all oncologic indications.

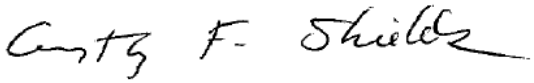
We look forward to continuing to work closely with CMS to provide any additional information that would be valuable in supporting our conclusion: that the CED data collection on NaF PET has demonstrated that NaF PET imaging is reasonable and necessary, and thus can be ended without detriment to either the Medicare program or to its beneficiaries.

Sincerely,



Bruce E. Hillner, M.D., *Chair*

Barry A. Siegel, M.D., *Co-chair*



Anthony F. Shields, M.D., *Co-chair*

## Appendix 1: Profile of Patients Undergoing NaF PET

| | IS | | | | FOM | | | | POM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Profile** | **Breast** | **NSCLC** | **Other** | **Prostate** | **Breast** | **NSCLC** | **Other** | **Prostate** | **Breast** | **Other** | **Prostate** |
| Scans by indication, n | 181 | 166 | 223 | 2,301 | 781 | 380 | 653 | 4,686 | 199 | 236 | 1,297 |
| Symptoms, signs or test results, % | | | | | | | | | | | |
| None | 45.9 | 30.1 | 38.1 | 58.9 | 10.0 | 18.9 | 19.9 | 16.2 | 8.5 | 12.7 | 10.7 |
| Pain only | 36.5 | 45.8 | 37.7 | 5.0 | 57.0 | 56.6 | 49.3 | 14.6 | 47.2 | 52.5 | 25.9 |
| Elevated or rising tumor marker* | 1.7 | 3.6 | 1.8 | 27.2 | 7.2 | 2.1 | 3.8 | 49.5 | 10.6 | 3.8 | 36.5 |
| Evidence from other imaging | 10.5 | 11.4 | 9.4 | 4.5 | 9.6 | 10.3 | 10.1 | 6.2 | 6.5 | 11.9 | 5.9 |
| Others | 5.5 | 9.0 | 13.0 | 4.4 | 16.3 | 12.1 | 16.8 | 13.6 | 27.1 | 19.1 | 20.9 |
| Pre- NaF PET summary stage, % | | | | | | | | | | | |
| Local/no evidence of disease | 39.8 | 12.0 | 22.0 | 57.8 | 28.2 | 19.5 | 21.7 | 24.8 | 4.5 | 6.4 | 5.2 |
| Regional (direct extension or nodal) | 14.9 | 12.7 | 9.0 | 5.0 | 1.9 | 7.6 | 3.4 | 5.0 | 0.5 | 1.3 | 0.8 |
| Single metastasis | 5.0 | 13.3 | 5.8 | 3.3 | 11.1 | 12.6 | 10.6 | 11.2 | 13.6 | 12.7 | 15.2 |
| Multiple metastases | 10.5 | 29.5 | 24.2 | 4.6 | 19.6 | 30.0 | 30.5 | 21.1 | 74.9 | 68.2 | 67.3 |
| Unknown | 29.8 | 32.5 | 39.0 | 29.5 | 39.2 | 30.3 | 33.8 | 37.8 | 6.5 | 11.4 | 11.5 |

From: Hillner BE, Siegel BA, Hanna L, et al. Impact of $^{18}$F-fluoride PET on intended management of patients with cancers other than prostate cancer: results from the National Oncologic PET Registry. J Nucl Med 2014;55:1054-1061.

IS: Initial staging; FOM: Suspected first osseous metastasis; POM Suspected progression of osseous metastasis

NSCLC: non-small cell lung cancer

* Abnormal tumor markers include an elevated alkaline phosphatase

## Appendix 2: Pre-PET Plans of Patients Undergoing NaF PET (Stratified by Indication)

| Profile | IS | | | | FOM | | | | POM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cancer Type | Breast | NSCLC | Other | Prostate | Breast | NSCLC | Other | Prostate | Breast | Other | Prostate |
| Scans by indication, n | 181 | 166 | 223 | 2,301 | 781 | 380 | 653 | 4,686 | 199 | 236 | 1,297 |
| Pre-PET plan (%) | | | | | | | | | | | |
| Image | 50.3 | 52.4 | 66.4 | 52.6 | 73.2 | 77.4 | 70.8 | 57.1 | 66.3 | 72.0 | 59.5 |
| Body CT | 9.4 | 11.4 | 16.1 | 23.6 | 16.9 | 18.2 | 16.5 | 22.6 | 17.6 | 19.9 | 21.4 |
| Body MRI | 9.9 | 10.2 | 11.7 | 12.0 | 13.6 | 15.0 | 11.9 | 16.8 | 15.6 | 20.8 | 18.3 |
| FDG PET | 25.4 | 27.1 | 32.7 | 14.0 | 26.4 | 29.2 | 29.9 | 13.0 | 25.1 | 24.6 | 15.8 |
| Plain Films | 3.3 | 2.4 | 3.1 | 1.4 | 12.8 | 9.2 | 8.6 | 2.9 | 3.5 | 3.0 | 1.3 |
| Other imaging | 2.2 | 1.2 | 2.7 | 1.7 | 3.6 | 5.8 | 3.8 | 1.9 | 4.5 | 3.8 | 2.7 |
| Treatment (overall) | 39.8 | 38.0 | 24.7 | 39.6 | 11.0 | 10.8 | 15.6 | 25.6 | 21.6 | 17.8 | 29.6 |
| Radiotherapy | 26.0 | 22.3 | 9.9 | 33.1 | 6.8 | 5.3 | 7.7 | 12.2 | 10.1 | 5.9 | 8.6 |
| Hormonal | 23.2 | 1.2 | 0.4 | 20.2 | 4.1 | 0.3 | 1.4 | 16.6 | 8.0 | 0.4 | 18.4 |
| Surgery | 27.6 | 11.4 | 7.6 | 12.6 | 1.4 | 1.1 | 2.0 | 1.8 | 0.5 | 0.0 | 0.3 |
| Chemotherapy | 25.4 | 33.7 | 20.6 | 5.1 | 6.1 | 8.7 | 11.3 | 8.5 | 14.6 | 14.4 | 13.5 |
| Bisphosphonates | 1.7 | 1.2 | 3.6 | 3.3 | 2.8 | 2.1 | 2.8 | 7.1 | 4.5 | 5.9 | 11.5 |
| Biopsy | 3.9 | 3.6 | 4.0 | 1.5 | 4.4 | 3.7 | 4.6 | 3.4 | 4.0 | 2.5 | 1.9 |
| Watch/No additional therapy | 6.1 | 6.0 | 4.9 | 6.2 | 11.4 | 8.2 | 9.0 | 13.8 | 8.0 | 7.6 | 8.9 |

From: Hillner BE, Siegel BA, Hanna L, et al. Impact of $^{18}$F-fluoride PET on intended management of patients with cancers other than prostate cancer: results from the National Oncologic PET Registry. J Nucl Med 2014;55:1054-1061.

*Referring physicians could select more than one treatment modality. Percentages do not sum to 100.

IS: initial staging, FOM: Suspected first osseous metastasis, POM: Suspected progression of osseous metastasis.

NSCLC: non-small cell lung cancer

## Appendix 3: Findings of NaF PET by Indication and Cancer Type

| Indication | IS | | | | FOM | | | | POM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cancer Type | Breast | NSCLC | Other | Prostate | Breast | NSCLC | Other | Prostate | Breast | Other | Prostate |
| Scans by indication, n | 181 | 166 | 223 | 2,301 | 781 | 380 | 653 | 4,686 | 199 | 236 | 1,297 |
| **NaF PET Findings (%)** | | | | | | | | | | | |
| Benign | 72.4 | 59.6 | 70.9 | 71.9 | 62.1 | 54.2 | 57.1 | 53.3 | 14.6 | 18.2 | 15.0 |
| Equivocal | 4.4 | 7.8 | 4.9 | 8.7 | 7.2 | 8.9 | 7.4 | 7.8 | 3.0 | 4.2 | 2.9 |
| Probable | 4.4 | 9.0 | 7.6 | 6.6 | 6.3 | 10.3 | 9.2 | 10.8 | 6.5 | 14.8 | 6.6 |
| Definite | 18.8 | 23.5 | 16.6 | 12.8 | 24.5 | 26.6 | 26.3 | 28.1 | 75.9 | 62.7 | 75.6 |
| Unifocal | 1.1 | 5.4 | 3.6 | 1.7 | 2.7 | 3.7 | 5.4 | 3.5 | 4.5 | 8.5 | 4.0 |
| Multifocal | 9.4 | 16.3 | 9.4 | 8.3 | 15.4 | 19.7 | 16.2 | 18.8 | 42.7 | 44.9 | 44.7 |
| Diffuse | 8.3 | 1.8 | 3.6 | 2.9 | 6.4 | 3.2 | 4.7 | 5.9 | 28.6 | 9.3 | 26.8 |

From: Hillner BE, Siegel BA, Hanna L, et al. Impact of $^{18}$F-fluoride PET on intended management of patients with cancers other than prostate cancer: results from the National Oncologic PET Registry. J Nucl Med 2014;55:1054-1061.

IS: initial staging, FOM: Suspected first osseous metastasis, POM: Suspected progression of osseous metastasis. NSCLC: non-small cell lung cancer

## Appendix 4: Change in Intended Management by Indication and Cancer Type

| Indication | Breast | NSCLC§ | Others | Prostate‡ | p-value‡ |
|---|---|---|---|---|---|
| **Initial Staging** | | | | | |
| **Participants**, n | 181 | 166 | 223 | 2301 | |
| Change in intended management, % | 42.5 | 54.2 | 52.0 | 46.4 | 0.059 |
| 95% CI† | 35.3 - 49.7 | 46.6 - 61.8 | 45.5 - 58.6 | 44.4 - 48.5 | |
| Imaging adjusted frequency of change, % | 11.0 | 13.9 | 11.2 | 10.3 | 0.52 |
| 95% CI† | 6.5 - 15.6 | 8.6 - 19.1 | 7.1 - 15.4 | 9.0 - 11.5 | |
| **Suspected first osseous metastasis** | | | | | |
| **Participants**, n | 781 | 380 | 653 | 4686 | |
| Change in intended management, % | 24.3*** | 36.0** | 31.1*** | 43.6 | <0.0001 |
| 95% CI† | 21.3 - 27.3 | 31.2 - 40.9 | 27.5 - 34.6 | 42.2 - 45.0 | |
| Imaging adjusted frequency of change, % | 7.7*** | 8.7** | 8.0*** | 15.0 | <0.0001 |
| 95% CI† | 5.8 - 9.5 | 5.8 - 11.5 | 5.9 - 10.0 | 13.9 – 16.0 | |
| **Suspected progression of osseous metastasis** | | | | | |
| **Participants**, n | 199 | -- | 236 | 1297 | |
| Change in intended management, % | 60.3 | -- | 52.1 | 53.0 | 0.14 |
| 95% CI† | 53.5 - 67.1 | -- | 45.7 - 58.5 | 50.2 - 55.7 | |
| Imaging adjusted frequency of change, % | 11.6 | -- | 9.3 | 10.9 | 0.72 |
| 95% CI† | 7.1 - 16.0 | -- | 5.6 - 13.0 | 9.2 - 12.6 | |

From: Hillner BE, Siegel BA, Hanna L, et al. Impact of $^{18}$F-fluoride PET on intended management of patients with cancers other than prostate cancer: results from the National Oncologic PET Registry. J Nucl Med 2014;55:1054-1061.

STATISTICAL NOTES:

†: 95% confidence intervals (CI) were computed using the normal approximation for the binomial proportion.

§: For "Suspected progression of osseous metastasis (POM)" stratum, NSCLC participants were grouped into other cancer type.

‡: For each comparison, a logistic regression was performed to test the difference of rates across specified cancer types on the change (or the imaging adjusted) in intended management, respectively. Prostate cancer group was used as the reference level in the regression. P-value was calculated using the global Wald test.

If global Wald test from the logistic regression was significant ($p<0.05$), individual tests were performed to find out which cancer types were different from prostate cancer (reference) in terms of the change rates. Multiple comparisons were corrected for within this analysis, such that the cutoff value for the significance level was 0.0167 (0.05/3).

* One asterisk (*) was marked if p-value of the individual test was smaller than 0.0167.

** Two asterisks (**) were marked if p-value was smaller than 0.01.

*** Three asterisks (***) were marked if p-value was smaller than 0.001.

## Appendix 5: NaF-PET for Treatment Monitoring by Cancer Type

**Pre-PET therapeutic plan**

| | Continue current treatment | Modify dose or schedule | Switch to another treatment | Stop treatment and switch to supportive care | Overall Change, % |
|---|---|---|---|---|---|
| **Scans, (%)** | 1,911 (67.3) | 200 (7.0) | 705 (24.8) | 23 (0.8) | |
| | | | | | |
| **Post-PET plans (rows)** | | | | | |
| **All cancers** | | | | | 40.3 |
| Continue current therapy | 1,286 (67.3) | 106 (53.0) | 258 (36.6) | 11 (47.8) | |
| Modify dose or schedule | 82 (4.3) | 22 (11.0) | 43 (6.1) | 2 (8.7) | |
| Switch to another therapy | 497 (26.0) | 64 (32.0) | 382 (54.2 | 5 (21.7) | |
| Stop therapy and switch to supportive care | 46 (2.4) | 8 (4.0) | 22 (3.1) | 5 (21.7) | |
| **Prostate** | | | | | 41.8* |
| Continue current therapy | 790 (65.2) | 76 (52.4) | 203 (35.6) | 5 (38.5) | |
| Modify dose or schedule | 46 (3.8) | 16 (11.0) | 35 (6.1) | 1 (7.7) | |
| Switch to another therapy | 351 (29.0) | 46 (31.7) | 320 (56.0) | 4 (30.8) | |
| Stop therapy and switch to supportive care | 24 (2.0) | 7 (4.8) | 13 (2.3) | 3 (23.1) | |
| **Breast** | | | | | 39.3† |
| Continue current therapy | 2,534 (69.3) | 16 (61.5) | 38 (46.9) | 4 (100.0) | |
| Modify dose or schedule | 17 (4.7) | 1 (3.8) | 5 (6.2) | 0 (0) | |
| Switch to another therapy | 91 (24.9) | 9 (34.6) | 35 (43.2) | 0 (0) | |
| Stop therapy and switch to supportive care | 4 (1.1) | 0 | 3 (3.7) | 0 (0) | |
| **Other cancers ∫** | | | | | 34.5 |
| Continue current therapy | 243 (72.5) | 14 (48.3) | 17 (32.1) | 2 (33.3) | |
| Modify dose or schedule | 19 (5.7) | 5 (17.2) | 3 (5.7) | 1 (16.7) | |
| Switch to another therapy | 55 (16.4) | 9 (31.0) | 27 (50.9) | 1 (16.7) | |
| Stop therapy and switch to supportive care | 18 (5.4) | 1 (3.4) | 6 (11.3) | 2 (33.3) | |

From: Hillner BE, Siegel BA, Hanna L, et al. $^{18}$F-fluoride PET used for treatment monitoring of systemic cancer therapy: results from the National Oncologic PET Registry. J Nucl Med 2015;56:222-228.

Agreement shown in shaded cells.

∫ Other cancers include lung cancer

* Difference between prostate cancer and other cancers, p<0.01.
† Difference between breast cancer and other cancer patients, p=0.20.

* Difference between prostate and other cancer patients, p=0.018.

## Appendix 6: Change in NaF-PET scan and estimated prognosis on post-PET plans

**Post-PET plans**

| | N* | | Continue current treatment | Modify dose or schedule | Switch to another treatment | Stop treatment/ switch to supportive care |
|---|---|---|---|---|---|---|
| **All scans** | 2,839 | | 1,661(58.5) | 149 (5.2) | 948 (33.4) | 81 (2.9) |
| | | | | | | |
| **Comparison made to prior NaF-PET** | 1,630 | | | | | |
| No change, normal | 290 (17.8) | | 218 (75.2) | 10 (3.4) | 50 (17.2) | 12 (4.1) |
| Resolution of previously seen metastatic disease | 30 (1.8) | | 24 (80.0) | 1 (3.3) | 1 (3.3) | 4 (13.3) |
| Decrease in metastases | 275 (16.9) | | 238 (86.5) | 10 (3.6) | 22 (8.0) | 5 (1.8) |
| No change in metastases | 443 (27.2) | | 345 (77.9) | 23 (5.2) | 64 (14.4) | 11 (2.5) |
| Progression of metastases | 506 (31.0) | | 166 (32.8) | 30 (5.9) | 300 (59.3) | 10 (2.0) |
| New metastases | 86 (5.3) | | 30 (34.9) | 5 (5.8) | 50 (58.1) | 1 (1.2) |
| | | | | | | |
| **Prognosis in light of PET (all scans)** | | | | | | |
| Better | 796 (28.0) | | 643 (80.8) | 37 (4.6) | 74 (9.3) | 42 (5.3) |
| No change | 1,128(39.7) | | 892 (79.1) | 42 (3.7) | 177 (15.7) | 17 (1.5) |
| Worse | 915 (32.2) | | 126 (13.8) | 70 (7.7) | 697 (76.2) | 22 (2.4) |

From: Hillner BE, Siegel BA, Hanna L, et al. $^{18}$F-fluoride PET used for treatment monitoring of systemic cancer therapy: results from the National Oncologic PET Registry. J Nucl Med 2015;56:222-228.

* The relative percentage of the column