Decision Memo for Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (CAG-00065R2)

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Decision Summary

A. The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to determine that use of a NaF-18 positron emission tomography (PET) scan to identify bone metastasis of cancer is not reasonable and necessary to diagnose or treat an illness or injury or to improve the functioning of a malformed body member and, therefore, is not covered under § 1862(a)(1)(A) of the Social Security Act.

B. CMS shall continue the requirement for coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act for NaF-18 PET to identify bone metastasis of cancer contained in section 220.6.19B of the Medicare National Coverage Determinations Manual for 24 months from the final date of this decision. This extension is to allow confirmatory analyses to be performed and resulting evidence to be published to definitely answer the following question:

Does the addition of NaF-18 PET imaging lead to:

- A change in patient management to more appropriate palliative care; or
- A change in patient management to more appropriate curative care; or
- Improved quality of life; or
- Improved survival?

All other uses and clinical indications for NaF-18 PET are nationally non-covered.

CMS will reconsider the NCD at such time when the evidence has been published in a peer-reviewed journal.

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Decision Memo

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SUBJECT: Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer

DATE: December 15, 2015

I. Decision

A. The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to determine that use of a NaF-18 positron emission tomography (PET) scan to identify bone metastasis of cancer is not reasonable and necessary to diagnose or treat an illness or injury or to improve the functioning of a malformed body member and, therefore, is not covered under § 1862(a)(1)(A) of the Social Security Act.

B. CMS shall continue the requirement for coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act for NaF-18 PET to identify bone metastasis of cancer contained in section 220.6.19B of the Medicare National Coverage Determinations Manual for 24 months from the final date of this decision. This extension is to allow confirmatory analyses to be performed and resulting evidence to be published to definitely answer the following question:

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II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology.

AHRQ – Agency for Healthcare Research and Quality
BM - bone (or bony) metastasis
BS - either bone scan or bone scintigraphy
CT – computed tomography
FDG F-18 – fluorodeoxyglucose fluoride 18
MBq - megabecquerel, a unit of radioactivity
mCi - millicuries, an alternative unit of radioactivity (1 mCi = 37 MBq)
MRI – magnetic resonance imaging
NaF-18 - tracer fluorine-18 labeled sodium fluoride, also known as F-18 sodium fluoride
NaF-18 PET refers to sodium fluoride PET imaging utilizing NaF-18 as the radioactive tracer
PET - positron emission tomography or to a positron emission tomogram
PET/CT - positron emission tomography – computerized tomography PET

Detection and assessment of the extent of cancer metastases to bone are important diagnostic issues. Of all malignant neoplasms in bone, metastatic tumors (from other primary sites) are the most frequent. Of cancer metastases to bone, an estimated 80% are due to primary malignancies in specific organs, including breast, lung, prostate, thyroid or kidney; but may be due to a variety of other primary cancers. More than two-thirds of bone metastases involve the axial skeleton, that is, the cranium, ribs, spine, and sacrum. Although many bone metastases are clinically silent, pain due to bone destruction or weakening is a well-described complication (Rosai 2004). There are three general classifications of bone metastases: osteoblastic (e.g., as commonly seen with prostate cancer), osteolytic (e.g., as commonly seen with breast cancer) and a combination. Several imaging tests can detect bone metastases including conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy (BS) with technetium 99, and PET with FDG F-18 or NaF-18. Bone scans and regular x-rays are common conventional tests. PET scans can give useful information, but they aren't very detailed (compared to the finely detailed images from CT and MRI) (American Cancer Society). Hillman et al. (2015) noted that "NaF PET shares the same limitations as conventional BS—it is an indicator of reactive bone formation in response to various insults and is not tumor specific, and it is subject to the flare phenomenon associated with systemic therapy." For similar reasons, appropriate choice of imaging for bone metastasis may be influenced by classification of metastases and cancer type.

The clinical value of detecting and assessing the extent of bone metastases is suggested by a number of professional guidelines for oncology. For example, the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer, recommended staging workup includes bone scan for those patients with symptoms or with favorable 5-year survival findings. For other cancers, finding metastases on bone scan or on other imaging studies changes therapy recommendations (NCCN 2009). Imaging to detect bone metastases is also recommended when a patient, following completion of initial treatment, is symptomatic with bone pain suspicious for metastases from a known primary tumor.

In making national coverage determinations on diagnostic tests, CMS considers evidence on technical performance (analytic validity), the ability of the test to accurately and reliably identify the disorder of interest as reflected in the test sensitivity, specificity, positive predictive value and negative predictive value (clinical validity), and importantly evidence that demonstrates that use of the test changes patient management resulting in improved health outcomes (clinical utility). This general framework was outlined in the 2000 decision memo on positron emission tomography (FDG) where we assessed "the direct empirical studies that have been performed to evaluate the test performance and clinical utility of PET." Since then, CMS has accrued considerable experience in analyzing evidence to determine Medicare coverage of diagnostic tests. Improved health outcomes are fundamental to an evidence-based framework and are also important to high quality care and value.

In 2010, we determined that NaF-18 to identify bone metastasis of cancer is reasonable and necessary under §1862(a)(1)(E) through Coverage with Evidence Development (CED). We noted that the clinical studies in which Medicare will provide coverage must answer one or more of the following questions: prospectively in Medicare beneficiaries, does the addition of NaF-18 PET imaging lead to:

- A change in patient management to more appropriate palliative care; or
- A change in patient management to more appropriate curative care; or
- Improved quality of life; or
- Improved survival?

III. History of Medicare Coverage

CMS has reviewed the scientific literature and established coverage for use of NaF-18 PET to identify bone metastasis of cancer. See the CMS NCD Manual, Section 220.19, for currently covered indications at: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part4.pdf.

Current Medicare coverage policy regarding NaF-18 PET requires prospective data collection used in initial anti-tumor treatment strategy and/or subsequent anti-tumor treatment strategy for NaF-18 PET in identifying bone metastases under §1862(a)(1)(E).

A. Current Request

CMS was asked by the National Oncologic PET Registry (NOPR) to reconsider Section 220.6.19 of the NCD Manual to end the CED data collection requirements in the context of NaF-18 PET, and to authorize national coverage of NaF-18 PET for bone metastasis of all oncologic indications. Since our CED decision was on NaF-18 PET to identify bone metastasis of cancer (CAG-00065R), this reconsideration is limited to NaF-18 PET to identify bone metastasis of cancer. All other uses of NaF-18 PET are outside the scope of this NCD.

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. NaF-18 PET is considered to be within the following benefit category: other diagnostic tests §1861(s)(3). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Medicare regulations at 42 CFR 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, except where other uses have been explicitly authorized by statute, Medicare does not cover diagnostic testing used for routine screening or surveillance.

IV. Timeline of Recent Activities

Date	Action
March 16, 2015	CMS accepts a formal request to reconsider Section 220.6.19 of the NCD Manual to end the prospective data collection requirements for use of NaF-18 PET in identifying bone metastasis of cancer. As tracking sheet was posted to the coverage web site, and the initial 30-day public comment period commenced.
April 15, 2015	The initial 30-day public comment period ended. Sixty-one comments are received.
September 16, 2015	CMS posts the proposed decision memorandum. The second 30-day public comment period begins. CMS receives 221 comments.
December 15, 2015	CMS posts the final decision memorandum.

V. FDA Status

Sodium Fluoride F18 injection for diagnostic PET imaging of bone to define areas of altered osteogenic activity

was approved by the FDA on January 26, 2011.

VI. General Methodological Principles

When making national coverage determinations, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency generally uses to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited by the requestor, in public comments, as well as those found by a CMS literature review. The agency also conducted a review of applicable evidence-based practice guidelines and other relevant sources including recent texts of oncology. Citations are detailed below.

With respect to diagnostic tests, the Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of a NaF-18 PET imaging test for cancer metastasis to bone in whom bone metastases are strongly suspected based on clinical symptoms or the results of other diagnostic studies. In past decisions on PET imaging, CMS had differentiated initial and subsequent treatment. We have not used this distinction for NaF-

18 PET for bone metastasis of cancer since it applies more directly to early diagnostic evaluation than to advanced metastatic disease. The analysis and CED questions also combine into general use.

B. Discussion of evidence reviewed

1. Questions & Outcomes of Interest

1. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully alter treatment for beneficiaries who have cancer?

2. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully improve patient centered health outcomes for beneficiaries who have cancer?

As a diagnostic test, NaF-18 PET would not be expected to directly change health outcomes, i.e., there is no evidence that the administration of NaF-18 is therapeutic for cancer in and of itself. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available treatment options.

As with other diagnostic tests, CMS considers evidence on technical performance (analytic validity), the ability of the test to accurately and reliably identify the disorder of interest as reflected in the test sensitivity, specificity, positive predictive value and negative predictive value (clinical validity), and importantly evidence that demonstrates that use of the test changes patient management resulting in improved health outcomes (clinical utility). In general, test parameters measured at one point in time do not provide evidence on improvements in health outcomes over time.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but also include beneficial or adverse clinical effects, such as changes in management due to test findings or preferably, improved health outcomes for Medicare beneficiaries. Ideally, we would see evidence that the systematic incorporation of NaF-18 PET results into treatment decisions leads physicians to prescribe different treatment than they would otherwise have prescribed, and that those patients whose treatment is changed by test results achieve improved outcomes.

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on this topic.

3. Internal technology assessment

The reviewed evidence was gathered from articles submitted by the requesters, cited in public comments during a public comments period and from a literature search of the PubMed database by CMS staff.

Literature search methods

CMS staff used PubMED to search for relevant peer-reviewed articles published in the medical literature. The following search terms were used: 18F-fluoride PET, 18F-fluoride PET/CT, 18F-NaF PET, 18F-NaF PET/CT, NaF-18 PET, bone metastasis, skeletal metastasis, metastatic bone tumor, and osseous metastasis.

The CMS internal search was limited to articles published since the original NaF-18 final decision memorandum was posed on February 26, 2010. CMS reviewed results of clinical trials involving adult human subjects; to reports of randomized and non-randomized controlled trials, cohort studies, meta-analyses and case series meeting certain criteria; and to articles published in English. Also, clinical trials were excluded from further review if:

- fewer than ten patients were studied;
- the cited article did not indicate whether an initial treatment plan had been completed, or whether an NaF-18 PET scan was performed after completion of the initial treatment plan; or
- the study was related to costs or cost-effectiveness of NaF-18 PET imaging, or was based on a simulation or decision modeling approach rather than patients' actual outcomes.

CMS staff reviewed full-text versions of articles suggested by the requesters or cited in public comments. The usual CMS methodology for evidentiary value were used (please see Appendix A). In addition, any relevant article indexed by PubMED as 'Review' or 'Guideline' or 'Health-services research' was used only for background information and is listed in the Bibliography.

Summaries of articles about meta-analyses or clinical trials are grouped below by:

1. trial design (as listed in decreasing order by evidentiary value (see Appendix A)); and
2. last name of first author in ascending alphabetical order.

Studies with the same first author in the same year of publication are distinguished by a one-letter suffix (e.g., 2011*A*, 2011*B*, etc.)

Bibliographies of the retrieved papers were searched for other relevant citations.

Article summaries below are listed alphabetically within study design categories in order of decreasing validity (See Appendix A).

Meta-Analyses:

Shen C-T, Qiu Z-L, Han T-T, and Luo Q-Y. Performance of NaF PET or PET/CT for the detection of bone metastases – a meta-analysis. Clin Nucl Med 2015; 40: 103-10.

To update a 2010 meta-analysis of the diagnostic performance of NaF-18 PET/CT, which had been based on a literature search for clinical studies published before 2009, the authors performed an updated literature search for relevant clinical studies. The current literature search included relevant articles through August 31, 2013, which met specific stated criteria. Articles were extracted to obtain true and false negatives and positives, and a random-effects model was used to derive the weighted mean pooled sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR) and diagnostic odds ratio (DOR, defined as the ratio of PLR to NLR). On performing the updated literature search, the authors found 20 articles representing 1170 patients. These 20 articles, published between 1999 and 2013, included 15 prospective articles, and reflected results of NaF-18 PET/CT to detect bone metastases from various oncologic conditions. The authors commented that absent histopathologic verification of the metastatic lesion, a multi-mode reference standard was used in many studies (i.e., clinical followup, other diagnostic imaging techniques (MRI, etc.)). The authors also indicated that due to limited data on different types of cancer, a subgroup analysis of results by cancer type was not performed. The weighted pooled estimates for the various imaging modalities are shown in the following table.

	Sensitivity	**Specificity**	**DOR**	**Studies/Patients**
	0.96	0.91	341	11/613

	Sensitivity	Specificity	DOR	Studies/Patients
NaF-18 PET/CT				
Tc-MDP BS	0.88	0.80	20	11/613
FDG PET/CT	0.73	0.98	112	4/351

The authors concluded that based on findings from the current meta-analysis, NaF-18 PET/CT showed better diagnostic accuracy in detecting bone metastases compared with Tc-MDP BS or FDG PET/CT. They reported that compared with Tc-MDP BS, NaF-18 PET/CT showed better sensitivity and better specificity. In comparison with FDG PET/CT, NaF-18 PET/CT showed higher sensitivity but no significant difference in specificity.

Tateishi U, Morita S, Taguri M, et al. A meta-analysis of Fluoride(18) (F-18) PET for assessment of metastatic bone tumor. Ann Nucl Med (2010); 24: 523-31.

The authors performed meta-analysis of multiple articles of the diagnostic performance of fluoride (18) PET or PET/CT ('F(18) PET'), compared with bone scintigraphy (BS) or SPECT, to evaluate patients with metastatic bone tumor. They noted that previous studies have limited external validity because single studies are inconclusive due to small sample size, and that comparisons of different methods, as well as comparisons of different combinations of methods for determining the diagnostic performance of F(18) PET in evaluating bone metastases in cancer patients is also an issue. Following a literature search for articles, the authors excluded articles with verification bias, including patients with hematologic malignancies. Studies using F-18 PET to evaluate status after treatment, including recurrence, were excluded. Studies lacking standard reference methods to establish diagnosis, and those in which patients with concomitant disease were excluded. Sensitivities and specificities were combined across studies using a weighted mean value, using an inverse of variance of sensitivity and specificity as a weight. The authors found eleven articles, representing 425 patients, meeting their criteria. Of these eleven articles, five (45%) stated that they were prospective. The eleven articles varied by diagnostic modality employed, histology of the primary tumor, and methods employed as reference diagnostic standards (such as MRI or clinical followup). Although the analysis included effective dose and cost-effectiveness estimates, these are not further included in this summary. The authors concluded that compared with the diagnostic performance of BS or SPECT, that of F(18) PET was excellent in detecting the metastatic bone tumor. They suggested that F(18) PET can substitute for BS until the usual supply of technetium preparations is restored.

<u>Prospective Case Series observing effect of NaF PET on Anticipated Patient Management:</u>

Hillner BE, Siegel BA, Hanna L, Duan F, Quinn B, Shields AF. NaF PET use for treatment monitoring of systemic cancer therapy: results from the National Oncology PET Registry. J Nucl Med 2015; 56: 222-8. ('Hillner 2015').

In this article, the authors reported on whether NaF-18 PET scan results influenced providers to plan to modify systemic cancer therapy in patients with cancer with osseous metastases. Patients younger than 65 years were not eligible for participation in this study. The study protocol followed a pre-NaF-18 PET / post-NaF-18 PET design. Referring physicians were asked, once before and again after the availability of NaF-a8 PET scan results, which of four categories of treatment the physician would select absent results of any other testing (PET, CT, MRI, or biopsy):

1. Continue and complete currently ongoing therapy;
2. Modify dose or schedule of currently ongoing therapy;
3. Switch to a different therapy or add an additional mode of therapy; or
4. Stop therapy and switch to supportive care.

Before and after NaF-18 PET results became available after the referring physician was asked to record his or her impression of the patient's therapy response or prognosis. Cases were accrued from January 27, 2012 through June 30, 2014.

The authors found that the final dataset included 2,839 scans done in 2,217 patients. Median age was 75 years. The pre-PET plans for all patients are shown in the following table.

Pre-NaF-18 PET Plan	Percent of all patients
Continue therapy	67.3%
Switch to another therapy	24.8%
Modify dose or schedule of therapy	7.0%
Stop systemic therapy and switch to supportive care	0.8%

After NaF-18 PET, the frequency of a change in therapeutic plan was 40.3% overall.

Physicians were also surveyed, pre- and post-NaF-18 PET, about their impressions of the progression and prognosis of the patient's disease. 36% of scans showed progression (worsening of previously seen metastatic disease or development of new osseous metastatic disease). For those patients with progression, physicians planned to switch to another therapy. When the prognosis was judged worse by the physicians, current therapy was planned to continue 13.8% of the time, and a therapy switch was planned in 76.2% of the time. Physicians' estimates of prognosis were based on their impressions rather than on defined parameters of the NaF-18 PET scan findings.

The authors concluded that for all patients combined, there was a 40% change in treatment plans after NaF-18 PET. In patients with evidence of progressive disease, physicians planned to switch to a new active cancer directed therapy rather than to supportive care.

Hillner BE, Siegel BA, Hanna L, Duan F, Shields AF, Quinn B, and Coleman RE. Impact of 18F-fluoride PET on intended management of patients with cancers other than prostate cancer: results from the National Oncologic PET Registry. J Nucl Med 2014; 55:1054-61. ('Hillner 2014B').

Using a before-and-after design to survey referring and interpreting providers, the authors asked if NaF-18 PET scan information would have changed intended management in those 65 years in age or older with pathologically confirmed cancers other than prostate ('nonprostate'). In particular, the impact of a NaF-18 PET scan on eligible study patients was linked to any pre-PET to post-PET change in intended management, grouped into either treatment (e.g., radiotherapy) or non-treatment (e.g., observation only) groups. The authors found that, from the NOPR facilities submitting information to the NaF-18 PET registry from January 31, 2011 through December 31, 2013, the 2,819 scans met all eligibility criteria and formed the analysis dataset. The nonprostate cancer types represented in the analysis dataset were breast (44%), lung (~20%), and bladder, kidney, colorectal cancers and lymphoma and myeloma (each type about 3-5%). Of the 2,819 scans, 570 were ordered for initial staging (IS), 1,814 for evaluation of a suspected first osseous metastasis (FOM), and 435 were for evaluation of a suspected progression of osseous metastasis (POM). The frequency of change from treatment to non-treatment or vice versa varied by indication as shown in the following table.

Indication	IS	FOM	POM
Change in intended management from treatment to non-treatment or vice-versa	49.6%	29.2%	55.9%

Referring physicians reported that NaF-18 PET may allow them to avoid additional diagnostic tests in about three-quarters of patients, and to avoid invasive procedures in about one-half. The authors concluded that in this survey of impact on intended management using data from the national NaF-18 PET registry, results of NaF-18 PET scans have a substantial impact across the common testing implications (IS, FOM and POM) for those of

Medicare beneficiary age with pathologically confirmed nonprostate cancer.

Hillner BE, Siegel BA, Hanna L, Duan F, Shields AF, and Coleman RE. Impact of 18F-fluoride PET in patients with known prostatic cancer: initial results from the National Oncologic PET Registry. J Nucl Med 2014; 55:574-561. ('Hillner 2014A').

The authors asked, using a before-and-after study design of referring and interpreting providers, if Na-F18 PET information would have changed intended management in men 65 years in age or older with pathologically confirmed prostate cancer. In particular, the impact of a NaF18-PET scan on eligible study patients was linked to any pre-PET to post-PET change in intended management, categorized into groups assessed as treatment (e.g., radiotherapy) or non-treatment (observation only). The authors found that, from the more than 600 facilities submitting information to the NaF-18 PET registry from January 31, 2011 through December 31, 2012, the analysis dataset included 3,531 NaF-18 scans performed on 3,396 patients and met all eligibility criteria. Of these 3,531 NaF-18 PET scans, 1,024 were ordered for initial staging (IS), 1,997 for evaluation of a suspected first osseous metastasis (FOM), and 510 were for evaluation of a suspected progression of osseous metastasis (POM). The frequency of change from treatment to non-treatment or vice versa varied by indication is shown in the following table.

Indication	IS	FOM	POM
Change in intended management from treatment to non-treatment or vice-versa	46.7%	44.1%	52.0%

Referring physicians reported that NaF-18 PET allowed them to avoid additional diagnostic tests in about three-quarters of patients, and to avoid invasive procedures in about one-half. The authors concluded that in this survey of impact of NaF-18 PET on intended management conducted among eligible patients from the national NaF-18 PET registry, NaF-18 PET has a substantial impact across the common testing implications (IS, FOM and POM) in prostate cancer.

<u>Prospective Clinical Case Series Comparing NaF-18 PET to other diagnostic imaging methods:</u>

Bortot DC, Amorim BS, Oks DC, et al. NaF PET/CT is highly effective for excluding bone metastases even in patients with equivocal bone scintigraphy. Eur J Nucl Med Mol Imaging 2012; 39:1730-6.

In this prospective study, the authors assessed patients with various types of tumors, whose BS results were

inconclusive (BS was considered inconclusive when a patient had one or a few areas of uptake that could not be differentiated as a metastatic or benign lesion, such as joint damage, trauma, or benign tumor). The authors found that 42 patients were eligible for the study. 16 were men, 26 were women, and mean patient age was 60 years. The following primary malignancies were included: breast (20 patients); prostate (nine); lung (three); and one each of colon, esophagus, rectum, ovary, liver, stomach and melanoma. Two of the primary tumors were from an unknown primary. The final diagnosis of bone metastasis was defined by followup studies and was established at least 15 months after the NaF-18 PET/CT scan. NaF-18 PET/CT correctly excluded bone metastases in 23 patients identified as metastasis-free. Of 19 patients classified by NaF PET/CT as having metastatic bone involvement, three were eventually classified as free of bone metastases. The analytic performance indices of NaF-18 PET/CT were computed as:

	Sensitivity	Specificity	Accuracy
NaF-18 PET/CT	100%	88%	93%

The authors commented that patients undergoing NaF-18 PET/CT spent less time in the imaging department than those undergoing BS. They concluded that NaF-18 PET/CT has a high sensitivity rate for bone metastases and a high negative predictive value for excluding bone metastases even in patients with inconclusive BS findings.

Chakraborty D, Bhattacharya A, Mete UK, Mittal BR. Comparison of NaF PET/CT and Tc-MDP bone scan for the detection of skeletal metastases in urinary bladder carcinoma. Clin Nucl Med 2013; 38:616-21.

This prospective study compared NaF-18 PET/CT with Tc-MDP planar scintigraphy (BS) and SPECT/CT to detect skeletal metastases in cases of carcinoma of the urinary bladder. 48 consecutive patients with newly diagnosed carcinoma of the urinary bladder, irrespective of histologic type and with high likelihood of bone metastases (muscle invasion; history of bone pain; increased alkaline phosphatase; lytic lesions on X-ray, etc.) were included. Patients who refused written consent, were pregnant, or were severely debilitated were excluded. BS and NaF-18 PET were performed on each patient within 48 hours. The authors found that of 48 eligible patients, 44 were men. The median patient age was 60 years, ranging from 35-80 years. All 48 had muscle-invasive disease. 12 patients had bone pain, and 25 had increased alkaline phosphatase. Imaging and clinical follow-up information was used to confirm the diagnosis of metastasis in patients in whom histopathologic confirmation was not feasible. Bony metastases were identified in 17 of 48 (44%) of patients and in these 17 patients management was changed to systemic therapy with chemotherapy and bisphosphonate therapy. The kappa statistic for agreement between SPECT/CT and NaF-18 PET was termed 'excellent' at 0.74; in contrast, the kappa value for statistical agreement between BS and FDG PET/CT was 0.42. Sensitivity of either planar or SPECT bone scintigraphy was less than the sensitivity of NaF-18 PET. The authors concluded that for detecting bony metastases in patients with confirmed urinary bladder cancer, findings of NaF-18 PET have a superior sensitivity and should be considered for clinical use.

Iagaru A, Mittra E, Dick DW, Sanjiv SG. Prospective evaluation of technetium MDP scintigraphy, NaF PET/CT and FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol 2012; 14: 252-9.

In this prospective study, the authors compared the performances of technetium (Tc) MDP scintigraphy (BS), NaF -18 PET/CT and FDG PET/CT to detect skeletal metastases in patients with histologically confirmed malignant neoplasms. Accrual of patients referred for assessment of suspected bone metastases continued from September 2007 through December 2010. The authors found that there were 52 eligible patients, each of whom underwent BS, NaF-18 PET/CT and FDG PET/CT within a one month time period. Various types of malignancies, including 19 sarcomas, 18 prostate cancers, six breast cancers, two colon cancers, and one lymphoma, one malignant paraganglioma, one gastrointestinal stromal tumor (GIST), and one of each of the following cancer types: bladder, renal, salivary gland, and lung. The following table shows the performance of each of the three techniques in detecting each type of malignant neoplasm.

Performance Indicator	Bone Scan (Tc MDP)	NaF-18 PET/CT	FDG PET/CT
Sensitivity (%)	87.5	95.8	66.7
Specificity (%)	92.9	92.9	96.4
Positive Predictive Value (%)	91.3	92.0	94.1
Negative Predictive Value (%)	89.7	96.3	77.1
Accuracy (%)	90.4	94.2	82.7

The authors commented that NaF-18 PET/CT (for bony metastases) and FDG PET/CT (for soft tissue metastases) might optimize detection of metastases. They concluded that NaF-18 PET/CT had greater accuracy in detection, and that further studies with larger numbers of participants may clarify which imaging method is to be preferred for detecting bone metastases.

Jadvar H, Bhushan D, Ji L, et al. Prospective evaluation of NaF and FDG PET/CT in detection of occult metastatic disease in biochemical relapses of prostate cancer. Clin Nucl Med. 2012 July; 37(7): 637-43.

In this prospective study, the authors examined the ability of NaF-18 PET/CT and FDG PET/CT to detect occult metastatic disease in men with prostate cancer, with PSA relapse after definitive therapy (i.e., radical

prostatectomy or external beam radiation therapy). The reference standard was a combination of imaging results and clinical followup. Patients with a personal history of some other type of cancer, and with a number of other clinical conditions were excluded. Biochemical relapse was defined using published American Urological Association (AUA) and ASTRO criteria for change in PSA. The authors found that the 37 men participating in the study had a median age of 71.1 years (range: 53.5 – 86.9 years) and biopsy-proven prostate cancer. The median time interval between primary therapy and PSA relapse was 5.7 years (range: 0.07 – 22.3 years). Although not stated to be within the scope of the study, given available follow-up data, the authors found that significant therapeutic management change was noted in five (45%) of the eleven patients in the positive PET/CT group, and in nine (35%) of the 26 patients in the negative PET/CT group. They noted that changes in management in the PET/CT negative group were at times associated with rapidly rising PSA levels (or other conditions) even absent suspicious imaging results or clinical findings. The authors concluded that NaF-18 PET/CT might be diagnostically informative in detecting and localizing occult metastases in men with known prostate cancer and with PSA relapse.

Retrospective Case Series comparing NaF PET to other diagnostic imaging methods:

Krueger S, Buck AK, Mottaghy FM, et al. Detection of bone metastases in patients with lung cancer: Tc-MDP planar bone scintigraphy (BS), NaF Pet, or FDG PET/CT. Eur J Nucl Med Mol Imaging 2009; 36: 1809-12.

In this retrospective study, the authors compared the diagnostic accuracy of FDG PET/CT versus either BS or NaF -18 PET in the detection of bone metastases of non-small cell lung cancer (NSCLC). Histologic findings determined the final diagnoses in all patients. A history of extrapulmonary cancer, known metastatic bone disease, pregnancy or age less than 19 years were exclusion criteria. Criteria were used to estimate whether a lesion was a bone metastasis or a focus of arthritis. Patients were defined as having no bone metastasis when BS, NaF-18 PET, and FDG PET/CT showed no bone metastasis. Lesions not detectable on BS but showing typical BM findings or NaF-18 PET or FDG PET/CT were considered to be BM. Lesions that were unclear were further evaluated by other imaging techniques, including MRI. Comparisons were performed on a patient basis. The authors found that, of 126 patients studied, 92 showed only degenerative changes, either on FDG PET/CT, BS, or NaF-18 PET. In 34% of patients, bone metastasis lesions were diagnosed. All metastases were osteolytic in nature. In 68 patients both FDG PET/CT and NaF-18 PET were used for imaging, as shown in the following table.

Finding	NaF-18 PET	FDG PET/CT
True-positive	17	14
False-positive	0	0
Equivocal	0	0

Finding	NaF-18 PET	FDG PET/CT
True-negative	50	50
False-negative	1	4
Total	68	68

The authors concluded that integrated FDG PET/CT is superior to BS in detection of osteolytic BM in NSCLC. NaF-18 PET seems to be at least as sensitive in detecting BM as FDG PET/CT. They suggested that a prospective, controlled trial should confirm their findings, including a cost-effectiveness analysis.

Ota N, Kato K, Iwano S, et al. Comparison of NaF PET/CT, FDG PET/CT, and bone scintigraphy (planar and SPECT) in detection of bone metastases of differentiated thyroid cancer: a pilot study. Br J Radiol 2014; 87 (1034): 2013044.

In this small retrospective case series the authors compared the sensitivity and accuracy of NaF-18 PET/CT, FDG PET/CT, and bone scintigraphy (planar and SPECT) in the detection of bone metastases of differentiated thyroid cancer (DTC). Patients were eligible for inclusion if they had undergone total thyroidectomy and were suspected of DTC. The presence of a metastasis in bone was verified based on a combination of imaging studies (I-131 scintigraphy, CT, and MRI). The authors found that the eleven patients included eight females and three males, and that the mean age of the participants was 62 years (range: 47 – 75 years). Abnormal uptake findings were mainly observed at the joints and edges of vertebral bodies, were considered false positive findings, and were excluded from further analysis. Nine of eleven patients had at least one bone metastasis. Sensitivities of the four modalities were not significantly different on a per patient basis. However, when analyzed on a skeletal segment basis, sensitivities and accuracies of NaF-18 PET/CT and SPECT BS were significantly higher than FDG PET/CT or planar BS. The authors concluded that further studies with increased numbers of patients will be needed.

4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

In an evidence-based guideline published in 2013, combined medical societies in Great Britain concluded that indications for use of NaF-18 PET included:

1) Assessment of benign and malignant diseases of bone in selected patients;

2) Sodium 18F-fluoride produces very high quality images of the skeleton with high uptake in bone and rapid clearance from blood.18F-Fluoride has been evaluated against 99mTc-MDP planar and SPECT imaging in patients with suspected or known metastatic bone disease. These studies show it to be more sensitive and specific than 99mTc-MDP scintigraphy, and the addition of CT increases further the specificity of the test; and

3) uptake times are shorter than conventional bone scintigraphy, 15–30 minutes versus 3–4 hours, and imaging times are shorter 15–30 minutes versus 30–60 minutes suggesting that 18F-fluoride imaging for some patients with bone disease may be an appropriate use of PET-CT.

Source: The Royal College of Physicians and the Royal College of Radiologists. Evidence-based indications for the use of PET-CT in the UK. London: RCP, RCR, 2013.

6. Professional Society Recommendations/Concensus Statements/Other Expert Opinion

The Society of Nuclear Medicine and Molecular Imaging submitted a statement in support of the request to end prospective data collection requirements under NOPR as did the US Oncology Network, the Medical Imaging & Technology Alliance and the World Molecular Imaging Congress.

7. Public Comments

Initial Comment Period: March 16, 2015 through April 15, 2015

CMS received 61 public comments during the first public comment period. All supported the request to end CED for all oncologic indications for NaF-18 PET and favored coverage. Comments were received from nuclear medicine and radiation oncology practices, individual physicians, professional societies, advocacy organizations, industry groups, researchers, and cancer treatment centers. Ten commenters suggested that CMS also cover non-oncologic indications for NaF-18 PET, but these comments are outside the scope of our current reconsideration. This decision specifically addresses ending CED for NaF-18 PET to identify bone metastasis of cancer. Any articles submitted with these public comments were not unique to those submitted by the requestor or identified by CMS during its literature review. Comments for this period can be viewed at: http://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=279&ExpandComments=n&bc=AiAAAAAAAgAAAA%3d%3d&#Results.

Second Public Comment Period: September 16, 2015 through October 16, 2015

CMS received 221 public comments regarding the proposed NCD decision memorandum during the second public comment period. Of this number 208 favored coverage of NaF-18 PET without mention of CED. Of those 208, 171 comments were identical word-for-word submissions, that is form letters, that expressed their opinions that this test should continue to be covered by CMS. They provided no evidence or supporting studies. Those commenters also stated its value in patient management. Similarly, an additional 19 form letters favored coverage of NaF-18 PET. Twelve comments specifically favored ending CED and its associated data collection by the National Oncologic PET Registry, and one commenter agreed with the need to continue CED and "to see further evidence in publications on the value of NaF over Tc99m." Several comments had concerns with the lack of availability of 99mTc used for conventional bone scintigraphy. These commenters stated that continued acces to NaF-18 for bone scans, because it is readily available and no shortage unlike 99mTc for conventional bone sicintigraphy. CMS received three comments requesting coverage for non-oncologic indications for NaF-18 at the discrestion of the local Medical Administrative Contractors. Three comments stated that the continued CED requirement be extended from 12 to 18 months. These comments can be read in their entirety at: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=279&ExpandComments=n&bc=AiAAAAAAAgAAAA%3d%3d&.

Comment: Several commenters claimed that NaF-18 bone scan for metastasis in cancer is more sensitive and specific than 99mTc bone scan and magnetic resonance imaging (MRI).

Response: NaF-18 PET is one of a number of technologies that have been used for detection of bone metastasis. A search of the medical literature revealed that 99mTc bone scan and MRI have also been used. Currently, 99mTc bone scan is the gold standard. We note there are some studies that have shown that NaF-18 PET/CT may have a higher measures of accuracy. However, while test characteristics such as sensitive and specificity measured in a cross-sectional study are important to show that a particular test has analytic and clinical validity, these measures alone do not provide evidence that use of the test to guide clinical management leads to improved health outcomes. In addition, since almost all PET scans are now combined with a CT scan, test characteristics should be better, vastly better, than any one test using older technology but that is one of several factors under consideration. Importantly there was no published evidence to address the original 2010 CED question presented in the initial decision - Does the addition of NaF-18 PET imaging lead to: a change in patient management to more appropriate palliative care; or a change in patient management to more appropriate curative care; or improved quality of life; or improved survival?

Comment: Several comments expressed concerns about the continued availability of 99mTc used for conventional bone scintigraphy. The commenters believe that continued approval of NaF-18, because

it is readily available, could eliminatethe shortage concerns.

Response: Currently there is no shortage of 99mTC. Further, we are continuing the same coverage of NaF-18 for the next 24 months. If the completed analysis answers the questions posed in section I of this decision positively, we expect to reconsider this NCD within the next 2 years.

Comment: The NOPR, along with 2 other commenters, oppose the CMS proposed requirement that CED continue for only an additional 12 months. These commenters suggest that the data submitted are sufficient for coverage. If, however, additional study were to be required, each suggests that this time allotment be extended to 18 months to allow adequate time to gather, analyze and publish findings.

Response: As noted above, there were no published studies that definitely answered the original question from the initial 2010 decision allowing CED. As noted in our analysis, while test characteristics such as sensitive and specificity measured in a cross-sectional study are important to show that a particular test has analytic and clinical validity, there are additional factors to consider since these measures alone do not provide evidence on clinical utility.

With respect to the time for extending CED beyond 12 months, CMS agrees with the commenters, and we have finalized the policy to allow for 24 months. We want to ensure that stakeholders have enough time to complete the analysis and CMS to complete a reconsideration of the NCD. The analysis to be performed and resulting evidence published in a peer-reviewed journal should definitely answer the questions initially proposed in the 2010 NCD. The questions are as follows:

Does the addition of NaF-18 PET imaging lead to:

- *A change in patient management to more appropriate palliative care; or*
- *A change in patient management to more appropriate curative care; or*
- *Improved quality of life; or*
- *Improved survival?*

Comment: The NOPR, and others, believed that eliminating CED is warranted based on their published data and that the studies have answered the initial CED question.

Response: We do not agree. As with other diagnostic tests, CMS considers evidence on technical performance (analytic validity), the ability of the test to accurately and reliably identify the disorder of interest as reflected in the test sensitivity, specificity, positive predictive value and negative predictive value (clinical validity), and importantly evidence that demonstrates that use of the test changes patient management resulting in improved health outcomes (clinical utility).

There was no published evidence to address the original 2010 CED question presented in the initial decision - Does the addition of NaF-18 PET imaging lead to: a change in patient management to more appropriate palliative care; or a change in patient management to more appropriate curative care; or improved quality of life; or improved survival? While test characteristics such as sensitive and specificity measured in a cross-sectional study are important to show that a particular test has analytic and clinical validity, these measures alone do not provide evidence that use of the test to guide clinical management leads to improved health outcomes. The published studies reported intended changes in management. While important, we believe as we noted in the analysis that additional confirmatory analyses are needed to show that actual changes in management occurred ideally with improvements in health outcomes to answer the initial CED question.

Comment: NOPR commented that CMS removed the CED requirement for FDG PET on the basis of NOPR's data and should do the same for NaF-18 PET.

Response: The research questions in this NCD address the use of NaF-18 PET. The questions are designed to document actual change in patient management based on the results of the NaF-18 PET, or documentation of improved health outcomes based on patient management. The studies submitted by NOPR, as well as other studies found in the medical literature, failed to demonstrate that the use of NaF-18 PET in patients suspected of bony metastasis results in either actual change in patient management or improvement in patient outcomes. The NCD on FDG PET is a different NCD with a different, more supportive evidence base. For instance, in the FDG PET decision memorandum, studies were found that FDG PET imaging actually did result in physician management changes, and based on those studies, CMS concluded that physicians were able to uses the results of this diagnostic test in the treatment of patients with brain, pancreas, prostate, soft tissue sarcoma and other solid tumors. Analytic as well as clinical validitly requirements were noted, and these studies provided support for clinical utility. CMS concluded that FDG PET was reasonable and necessary to gude anti-tumor strategy in beneficiaries with these various types of cancer after completion of initial anti-tumor therapy, and therefore was appropriate for coverage under §1862(a)(1)(A).

Comment: The NOPR, and other commenters, believes that coverage for NaF-18 scans should be allowed beyond one initial scan used for initial treatment strategy.

Response: Under our existing NCD, an individual may reveive more than one scan so long as the patient meets the criteria stated in 220.6.19.

Comment: The NOPR believes that conventional bone scintigraphy should not be used as a

comparator to FDG PET/CT or NaF-18 PET/CT to inform this National Coverage Analysis.

Response:As noted above, conventional bone scintigraphy is the standard of care for symptomatic patients suspicious of bone disease. When evaluating technologies, it is appropriate to compare modalities that are designated for the same purpose. CMS often uses technology assessments in determining the value of a technology for the Medicare population in the creation of a National Coverage Analysis. The hallmark of a technology for diagnostic tests is to compare available modalities and determine the measure of association (e.g., sensitivity, specificity, positive/negative predictive value) between the technologies.

Comment: The NOPR believes that CMS should consider their concern that NaF-18 PET/CT involves higher radiation risk than conventional bone scan, considering that many patients undergo additional high-dose studies (e.g., chest, abdomen and pelvic CT) for comparison with the bone scan.

Response: CMS acknowledges the concern about the amount of radiation patients may receive from diagnostic imaging and supports the "as low as reasonably achievable" (ALARA) concept on minimum level of radiation needed for imaging. CMS urges providers to be mindful of the cumulative effects of radiation and that they use such imaging techniques in the most efficient manner possible.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Social Security Act.

In addition to § 1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(1)(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]

Section 1142 of the Act describes the authority of the Agency for Healthcare Research and Quality (AHRQ) to conduct and support research on outcomes, effectiveness, and appropriateness of services and procedures to identify the most effective and appropriate means to prevent, diagnose, treat, and manage diseases, disorders, and other health conditions. That section includes a requirement that the Secretary assure that AHRQ research priorities under Section 1142 appropriately reflect the needs and priorities of the Medicare program.

CED is a paradigm whereby Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data. In making coverage decisions involving CED, CMS decides after a formal review of the medical literature to cover an item or service only in the context of an approved clinical study or when additional clinical data are collected to assess the appropriateness of an item or service for use with a particular beneficiary.

See, **Guidance for the Public, Industry, and CMS Staff Coverage with Evidence Development Document, November 20, 2014.** https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27.

CMS expects that results of all CED approved studies under 1862(a)(1)(E) will be analyzed and published in peer reviewed clinical journals. CMS has used and will continue to use the results of published CED studies to inform new or revised coverage decisions.

Section 220.6.19 of the National Coverage Determination (NCD) Manual establishes the requirement for prospective data collection under Coverage with Evidence Development (CED) for NaF-18 PET or bone metastasis in cancer. The clinical studies were required, among other things, to answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the NaF-18 PET study is needed to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy, does the addition of NaF-18 PET imaging lead to:

- A change in patient management to more appropriate palliative care; or
- A change in patient management to more appropriate curative care; or
- Improved quality of life; or
- Improved survival?

Based on the legal framework set forth above, this section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions posed above. As previously noted, PET using NaF-18 to identify bone metastasis of cancer is a diagnostic test.

The Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of a NaF-18 PET imaging test for cancer metastasis to bone in order to assist in initial treatment planning and in identification of symptomatic bone metastases in the anticancer management of patients who are known to have cancer based on clinical findings and preliminary diagnostic testing.

We considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. We believe that evidence of improved health outcomes is more persuasive than evidence of test characteristics.

In evaluating diagnostic tests, Mol and colleagues (2003) reported: "Whether or not patients are better off from undergoing a diagnostic test will depend on how test information is used to guide subsequent decisions on starting, stopping, or modifying treatment. Consequently, the practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes." When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

As a diagnostic test, NaF-18 PET would not be expected to directly change health outcomes, i.e., there is no evidence that administration of NaF-18 is, in and of itself, therapeutic. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available management alternatives.

Since this is a reconsideration of a CED NCD, we have aligned our analytic questions to the questions of the CED study to appropriately address the results obtained from the CED study.

As was done in the evidence section, summaries of articles are grouped by trial design.

Meta-Analyses:

In their meta-analysis, the authors concluded that NaF-18 PET/CT showed better diagnostic accuracy in detecting bone metastases compared with Tc-MDP BS or FDG PET/CT (Shen, Qiu, Han, et al. 2015). But the authors also noted that all the eligible patients lacked histopathological verification of the metastatic lesion, so a multimodal approach was used as the reference. They also noted that due to limited data on different types of cancer a subgroup analysis of results by cancer could not be performed. Both of these deficiencies could call into question the validity of the study.

In the meta-analysis performed by Tateishi et al., the authors concluded that when compared with the diagnostic performance of BS or SPECT, that of NaF-18 PET was excellent in detecting metastatic bone tumors (Tateishi, Morita, et al. 2010). But as noted in the analysis, after identifying eligible studies, only five of the eleven studies were prospective in nature (45%), and the eleven studies included in the analysis varied by diagnostic modality, histology of the primary tumor, and methods used as reference diagnostic standards. Due to the heterogeneity of study design as well as parameters, this could limit the validity of the findings.

Prospective Case Series:

There were a number of prospective case series studies; some of these prospective studies evaluated the effect of NaF-18 PET on anticipated patient management, while the other prospective studies compared NaF-18 PET to other diagnostic imaging methods. Those studies that evaluated the use of NaF-18 PET on anticipated patient management used a Pre Test/Post Test (Before and After) research design (Hillner et al. 2014a, Hillner et al. 2014b, Hiller et al. 2015). Limitations of this research design that can cause violations of internal validity include maturation effect, testing effect, history (Events outside of the participant can change the participant) and instrument decay. Also this particular research design sacrifices external validity, making it difficult to generalize to other populations. Also because randomization is not possible with this design, selection bias is a potential.

A number of prospective case series studies evaluated NaF-18 PET compared to other diagnostic imaging methods (Bortot et al. 2012, Chakraborty et al. 2013, Iagaru et al. 2012, Jadvar et al. 2012). One limitation of these studies is the small sample size. Also the study by Chakraborty failed to report specificity, though sensitivity was reported. This could result in inaccuracies in measures of association.

Retrospective Case Series:

There were two studies that used the retrospective research design (Krueger et al. 2009, Ota et al. 2014). Like all retrospective research designs, potential limitations include selection as well as information bias, confounding, and the introduction of threats to validity such as memory recall, history, and regression to the mean.

Summary of Evidence pertinent to key questions:

1. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully alter the treatment for beneficiaries who have cancer?

Three published studies (Hillman et al., 2014A, 2014B, 2015) of the National Oncologic PET Registry (NOPR) reported that findings of NaF-18 PET imaging on intended or planned change in management. One study reported that by incorporating the use of NaF-18 PET as an option, though 67% of patients continued on their current management course, a planned change in management was reported for almost 25% of patients to switch to another therapy, 7% had planned change in dose of scheduled therapy, and in almost 1%, patient's systemic therapy was planned to be discontinued with an intended switch to supportive care (Hillman et al. 2015).

Another study by Hillman and associates showed that for patients with non-prostate cancer, during initial staging (IS) almost 50% of patients studied had a change in intended management from treatment to non-treatment or vice versa; for patients suspected of first osseous metastasis (FOS), almost 30% of patients studied had a change in intended management from treatment to non-treatment or vice versa; and for patients with suspected progression of osseous metastasis (POM), almost 56% of patients studied had a change in intended management from treatment to non-treatment or vice versa (Hillman et al. 2014b).

Another study of suspected of prostate bone metastasis demonstrated that for IS 47% of patients studied had a change in intended management from treatment to non-treatment or vice versa, for FOM 44% of patients had a change in intended management from treatment to non-treatment or vice versa, and for POM 52% of patients had a change in intended management from treatment to non-treatment or vice versa (Hillman et al. 2014a).

The three studies by Hillman et al. were sequential analyses of the NOPR data and used self-reported pre-test and post-test surveys to evaluate change in intended patient management. Results from self-reported data occasionally may be subject to limitations and then generally should be confirmed with subsequent analyses or more rigorous studies. Since we did not find confirmatory studies of the Hillman results on NaF-18 PET, it is difficult to determine the extent of actual change in patient managed occurred. We encourage further analyses to confirm that actual change in management occurred. In addition, subsequent testing and evaluation which may have associated benefits and risks after PET scans were not reported. This data would be useful and may provide supportive evidence on outcomes. With the published evidence, it is unclear if first objectives of the CED decision (a change in patient management to more appropriate palliative care or a change in patient management to more appropriate curative care;) were met.

2. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully improve patient centered health outcomes for beneficiaries who have cancer?

To answer this evidentiary question, there are several parts to consider: (a) ability of NaF-18 to accurately and reliably detect bone metastases of cancer (test characteristics); (b) benefits and harms of testing and subsequent evaluation; and (c) improved meaningful health outcomes.

As with other diagnostic tests, CMS considers evidence on technical performance (analytic validity), the ability of the test to accurately and reliably identify the disorder of interest as reflected in the test sensitivity, specificity, positive predictive value and negative predictive value (clinical validity), and importantly evidence that demonstrates that use of the test changes patient management resulting in improved health outcomes (clinical utility).

In evaluating whether NaF-18 PET can accurately and reliably detect bone metastasis of cancer, test characteristics, such as sensitivity, specificity and predictive values, provide data on the strength of clinical correlation between test results and presence of bone metastases, often referred to as clinical validity. A pre-specification is acceptable technical performance which is typically an FDA consideration. For FDA approved tracers, technical performance has generally been established (in this case, NaF-18 ion has been shown to accumulate in the bone and the imaging test has been shown to detect NaF-18).

Several published studies (Chakraborty, 2013; Iagaru, 2012; Krueger, 2009; Ota 2014 Shen, 2015) reported test characteristic for NaF-18 PET/CT. Findings were generally similar across studies that sensitivity of NaF-18 PET/CT was higher but specificity was lower than FDG PET/CT. Predictive values were inconsistently reported; one study (Iagaru, 2012) reported comparable positive predictive value (92.0% NaF-18 PET/CT and 94.1% FDG PET/CT) and higher negative predictive value (96.3% NaF-18 PET/CT compared to 77.1% FDG PET/CT).

While PET/CT (NaF-18 and FDG) can detect bone metastases of cancer, it is unclear why BS alone was used as the comparator to a combination of PET and CT. Since almost all PET scans are now combined with a CT scan, test characteristics such as sensitivity and specificity should be better than any one test using older technology such as bone scan; however, there are other factors to consider. In addition, the radiation exposure from combined PET/CT is a concern. In a meta-analysis, Tateishi et al. (2010) reported "18F-Fluoride PET or PET/CT has excellent diagnostic performance for the detection of metastatic bone tumor, but the estimated effective dose and average cost-effective ratio are at a disadvantage compared with BS planar or BS planar and SPECT." PET may have similar limitations in false positive results from reactive processes other than bone metastases of cancer. False positives may lead to additional diagnostic tests which in turn may have associated benefits and/or harms. False negatives may lead to incorrect prognosis and planning and other harms. It is unclear whether or not benefits and/or harms of subsequent testing and evaluation after PET scans were considered. While test characteristics such as sensitive and specificity measured in a cross-sectional study are important to show that a particular test has analytic and clinical validity, there are additional factors to consider since these measures alone do not provide evidence on clinical utility. The key to answering this specific evidentiary question is an analysis of the evidence to determine improved health outcomes. A consideration of improved health outcomes is important to determine whether an item or service is reasonable and necessary. None of the published studies showed that use of NaF-18 PET to guide patient management significantly improved health outcomes such as mortality and morbidity. But, due to the potential severity of disease associated with bone metastases, life expectancy may not be adequately long in a large enough sample to be able to show significant improvements in overall mortality. Yet other meaningful health outcomes like avoidance of hospitalizations, avoidance of invasive procedures or other diagnostic tests, other benefits and harms, and quality of life were also not reported. The National Oncologic PET Registry provided data on intended patient management but actual changes in patient management were not confirmed in subsequent analyses. While NOPR may not have been structured to collect health outcomes data, the registry data could be linked to administrative claims data to provide some information on important outcomes. This linkage and analysis would not necessarily require continuation of the registry itself

but we recognize that continuing NOPR CED may generate additional evidence and facilitate performance of additional analyses and publication of results. Without further analysis, it is also unclear if the last objectives of the CED studies (improved quality of life or improved survival) were met.

CMS received 220comments on the proposed decision memorandum that supported ending CED and favored a positive decision; of this number, 190 were form letters. CMS did receive one comment supporting the proposed DM with continuation of CED. However, with no published studies to definitely address our CED question set in the 2010 NCD, the evidence is insufficient to determine that NaF-18 PET scan for bone metastasis of cancer is reasonable and necessary under §1862(a)(1)(A). Thus, CMS proposes to continue the requirement for CED under §1862(a)(1)(E) of the Social Security Act for NaF-18 PET to identify bone metastasis of cancer contained in section 220.6.19B of the Medicare NCD Manual for 24 months from the final date of this decision. This extension is to allow confirmatory analyses to be performed and the resulting evidence to be published to definitely answer the following question:

Does the addition of NaF-18 PET imaging lead to:

- A change in patient management to more appropriate palliative care; or
- A change in patient management to more appropriate curative care; or
- Improved quality of life; or
- Improved survival?

CED Extension for NaF-18 PET for Bone Metastasis of Cancer

We propose that 24 months is an appropriate duration for continued CED coverage for NaF-18 PET to identify bone metastasis of cancer. Studies have been underway since this CED decision was posted over five years ago. While we recognize the usefulness of the NOPR data and publications that have produced evidence on clinical validity and change in intended patient management, we are perplexed why additional analyses were not performed and published to confirm actual changes in patient management that improves health outcomes occurred.

Health Disparities

Articles discussed above in this decision memorandum do not analyze diagnostic performance or outcome by racial or ethnic categories. Any inference about relative benefits positron emission tomography in specific racial or ethnic groups would be speculative. CMS also notes that generally, evidence is absent about benefits or harms related to other population classifiers that have been associated historically with healthcare access or outcome disparities, such as gender, sexual orientation, religion and age, and encourages additional studies in which such associations might be studied.

Results of cancer therapy continue to demonstrate racial/ethnic as well as socio-economic disparities. The authors of ACS 2012 stated that lack of health insurance and other barriers prevents many Americans from receiving optimal health care. This included, according to a US Census Bureau study in 2009, no health insurance coverage for one-third of Hispanics and one in ten children. Uninsured patients and those from ethnic minorities are more likely to be diagnosed with cancer at a later stage. At this point in the disease, treatment must be more extensive to be effective (ACS 2012).

African Americans are more likely to develop and die from cancer than any other racial or ethnic group. African American men have higher incidence and mortality rates than whites for each of the six most frequent cancer sites (colorectal, kidney, liver and intrahepatic bile duct, lung and bronchus, prostate and stomach (ACS 2012).

Persons with lower socioeconomic status (SES) have disproportionately higher death rates than those with higher SES. Lower SES is also associated with lower access to preventive services and to lower literacy rates. Behaviors that increase cancer risk, including tobacco use, lack of physical activity, and poor diet are more likely among those with lower SES. Progress in reducing cancer death rates has been slower in persons with lower SES (ACS 2012).

CMS concludes that there is a need for additional evidence about racial and ethnic factors. In our view this evidence gap should be considered by trial designers when proposing future clinical trial designs. All other factors being equal, CMS will prefer clinical study proposals in which data on racial and ethnic factors are specifically collected and analyzed.

CMS has reviewed all the comments submitted during the initial as well as the second comment period, and would like to thank those who contributed for their input. There were no new studies or data submitted. Several commenters requested we increase the CED study period from 12 months to 18 months. CMS in this final decision extends the CED study period to 24 months. The additional time will allow confirmatory analysis to be performed so that results can be published in a peer-reviewed journal and a final NCD could be completed. CMS further notes, that we have had several discussions with stakeholders about possible research designs that might be appropriate to demonstrate change in patient management and/or improved health outcomes. Once the studies have been peer reviewed and published, CMS will assess them to determine if changes in coverage should be made. In the meantime, due to lack of sufficient studies demonstrating improved health outcomes or change in patient management, CMS will continue its current policy of covering NaF-18 PET to identify bone metastasis of cancer under coverage with evidence development.

IX. Conclusion

A. The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to determine that use of a NaF-18 positron emission tomography (PET) scan to identify bone metastasis of cancer is not reasonable and necessary to diagnose or treat an illness or injury or to improve the functioning of a malformed body member and, therefore, is no covered under § 1862(a)(1)(A) of the Social Security Act.

B. CMS shall continue the requirement for coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act for NaF-18 PET to identify bone metastasis of cancer contained in section 220.6.19B of the Medicare National Coverage Determinations Manual for 24 months from the final date of this decision. This extension is to allow confirmatory analyses to be performed and resulting evidence to be published to definitely answer the following question:

Does the addition of NaF-18 PET imaging lead to:

- A change in patient management to more appropriate palliative care; or
- A change in patient management to more appropriate curative care; or
- Improved quality of life; or
- Improved survival?

CMS will reconsider the NCD at such time when the evidence has been published in a peer-reviewed journal.

All other uses and clinical indications for NaF-18 PET are nationally non-covered.

See Appendix B for final National Coverage Determination manual language.

APPENDIX A
General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
Differential assessment of outcome (detection bias).
Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies

Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix B

220.6.19 – Positron Emission Tomography NaF-18 (NaF-18 PET) to Identify Bone Metastasis of Cancer
(Effective December 15, 2015)
(Rev.)

A. General

Positron Emission Tomography (PET) is a non-invasive, diagnostic imaging procedure that assesses the level of metabolic activity and perfusion in various organ systems of the body. A positron camera (tomograph) is used to produce cross-sectional tomographic images, which are obtained from positron-emitting radioactive tracer substances (radiopharmaceuticals) such as F-18 sodium fluoride.

The Centers for Medicare & Medicaid Services (CMS) has determined that the available evidence is sufficient to determine that the use of a NaF-18 PET scan to identify bone metastasis of cancer is reasonable and necessary under §1862(a)(1)(E) of the Social Security Act (the Act) through Coverage with Evidence Development (CED). CMS shall continue coverage under CED for 24 months from the final date of this decision to demonstrate that the use of NaF-18 PET scan results in meaningfully altered treatments or improved patient-centered outcomes in beneficiaries who have suspected bone metastasis of cancer.

B.   Nationally Covered Indications

Effective *December 15, 2015,* CMS will *continue to* cover NaF-18 imaging *for 24 months from the final date of this decision* when the beneficiary's treating physician determines that the NaF-18 PET study is needed to inform the initial antitumor treatment strategy, or to guide subsequent antitumor treatment strategy, after the completion of initial treatment, and when the beneficiary is enrolled in, and the NaF-18 PET provider is participating in, the following type of prospective clinical study:

A NaF-18 PET clinical study that is designed to collect additional information at the time of the scan to assist in initial antitumor treatment planning, or to guide subsequent treatment strategy by the identification, location, and quantification of bone metastases in beneficiaries in whom bone metastases are strongly suspected based on clinical symptoms or the results of other diagnostic studies. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and, all patient confidentiality, privacy, and other Federal laws must be followed.

The *24-month extension of this* clinical *study is to allow confirmatory analyses to be performed and resulting evidence to be published to definitely* answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the NaF-18 PET study results are needed, does the addition of NaF-18 PET imaging lead to:

- A change in patient management to more appropriate palliative care; or,

- A change in patient management to more appropriate curative care; or,
- Improved quality of life; or,
- Improved survival?

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.

b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

c. The research study does not unjustifiably duplicate existing studies.

d. The research study design is appropriate to answer the research question being asked in the study.

e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.

g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.

h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.

i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the www.ClinicalTrials.gov Web site by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured, including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability, or Medicaid eligibility.

Consistent with section 1142 of *the Act,* the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that *CMS* determines meet the above-listed standards and address the above-listed research questions.

CMS will reconsider the NCD at such time when the evidence has been published in a peer-reviewed journal.

C. Nationally Non-Covered Indications

N/A

D. Other

The only radiopharmaceutical diagnostic imaging agents *nationally* covered by Medicare for PET cancer imaging are 2-[F-18] Fluoro-D-Glucose (FDG) and NaF-18 (sodium fluoride-18). *However, other PET tracers for cancer can be paid at local contractor discretion when used according to their FDA-approved indication(s).*

(This NCD last reviewed *December 2015*.)

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