Appropriate Use Criteria for Bone Scintigraphy in Prostate and Breast Cancer

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EXECUTIVE SUMMARY

Nuclear medicine imaging studies are essential to the diagnosis and management of many diseases, including neoplastic disease (*1*). Modern imaging studies allow noninvasive examination of anatomic and physiologic processes that often change patient management and improve outcomes. The ready availability and high sensitivity of medical imaging in conjunction with concerns about missed diagnoses has, at times, resulted in inappropriate use of the technology. This has resulted in an unnecessary financial burden on the health-care system and in some cases unnecessary exposure to ionizing radiation (*1–5*). Inconsistent use of specific imaging procedures for similar clinical scenarios has prompted a push for consensus documents outlining the most appropriate and cost-effective use of these imaging procedures. It is hoped that this expert guidance will help make the use of bone scintigraphy more consistent and improve health-care outcomes for the intended patient population while minimizing unnecessary imaging costs.

The purpose of this document is to describe the appropriate use of bone scintigraphy in patients with prostate and breast cancer, the two most common diagnoses for which bone scintigraphy is ordered in the adult population. It is hoped that through these recommendations, bone scintigraphy will be used to benefit patients with prostate and breast cancer in the most cost-effective manner.

Representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Nuclear Medicine (EANM), and the American Society of Clinical Oncology (ASCO) assembled as an autonomous workgroup to develop the following appropriate use criteria (AUC). This process was performed in accordance with the Protecting Access to Medicare Act of 2014. This legislation requires that all referring physicians consult AUC using a clinical decision support mechanism before ordering any advanced diagnostic imaging services. Such services are defined as diagnostic MRI, CT, nuclear medicine procedures (including PET), and others as specified by the secretary of Health and Human Services in consultation with physician specialty organizations and other stakeholders (*6*). The AUC in this paper are intended to aid referring medical practitioners in the appropriate use of bone scintigraphy for the more common scenarios encountered in patients with prostate and breast cancer.

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INTRODUCTION

The following document describes the appropriate use of nuclear medicine bone scintigraphy in patients with breast and prostate cancer. The authors have tried to cover the most common clinical scenarios for bone scintigraphy in patients with these two common malignancies. However, the reader is reminded that a patient may present with variations of the scenarios covered here, or with signs or symptoms not described, for which bone scintigraphy may still be indicated. This document is presented to assist health-care practitioners considering bone scintigraphy for patients with breast and prostate cancer; however, each patient is unique, as is each patient's clinical presentation, and therefore this document cannot replace clinical judgement. Bone scintigraphy can also be used for a variety of other conditions, both malignant and benign, for which assessment of osteoblastic activity is important for patient management. These other scenarios are beyond the scope of this document.

Bone scintigraphy is distinguished from conventional radiographic studies by its ability to assess the entire body at a comparatively low financial cost. Bone-seeking agents such as ^{99m}Tc-methylene diphosphonate (MDP) (*7*), ^{99m}Tc-hydroxy-MDP (*8*), and ^{18}F-NaF (*9*) are incorporated into the hydroxyapatite matrix of the bone in proportion to osteoblastic activity. The location of neoplastic disease that has metastasized to bone and caused an increase in osteoblastic activity, such as occurs with most types of breast and prostate cancer, can be discerned from surrounding normal bone osteoblastic activity.

Bone scintigraphy is one of the highest-volume procedures in nuclear medicine imaging facilities. In 2014, approximately 407,000 bone scintigraphy studies were performed on Medicare patients for all indications (*10*). Although bone scintigraphy can be performed on patients with both benign and neoplastic disease, most bone scintigraphy studies are performed for oncologic indications. Of these, patients with breast cancer and prostate cancer make up most of the bone scintigraphy subjects.

A systematic review of the literature for this AUC revealed that strong evidence for this commonly used diagnostic imaging procedure is incomplete. Several factors may be behind the lack of randomized controlled trials supporting bone scintigraphy in breast and prostate cancer.

First, bone scintigraphy was developed more than 40 y ago. At that time, there were few alternatives for the detection of bony metastases, and the development of this unique and sensitive imaging modality was such an obvious improvement in the staging of metastatic prostate and breast disease that the technology was quickly adopted without randomized, controlled trials. Also at that

time, randomized controlled trials looking at patient outcomes were not as common as were trials looking at diagnostic accuracy. Second, the widespread use of bone scintigraphy for staging breast and prostate cancer for so many years has meant that it has become a standard-of-care diagnostic study for staging these types of cancer; thus, there has been little call for expensive, long-term studies demonstrating the importance of a test that is already widely accepted.

Recent refinement of the diagnosis and staging of prostate cancer, along with development of new technologies such as MRI, CT, and ultrasound, have caused referring physicians to reexamine the need for bone scintigraphy in neoplastic disease (*11–14*). In addition, the rising cost of health care and the inconsistencies in the use of bone scintigraphy have encouraged third-party payers to push the medical community to reevaluate the importance of many advanced imaging technologies, including bone scintigraphy.

The rapid advancement of imaging technology has meant that long-term outcome trials are impractical, with results often obsolete by the time the investigation is completed (*15*). Therefore, the Centers for Medicare and Medicaid Services has recognized that expert opinion is often needed in the absence of evidence-based outcome literature. Without published outcome data, the authors of this document have relied on expert opinion from nuclear medicine specialists in the United States and Europe and from the referring oncology community. It is felt that by combining multispecialty expert opinion with the existing literature, the most accurate assessment possible can be made for the clinical utility of bone scintigraphy.

The lack of published evidence for the use of bone scintigraphy in specific clinical scenarios has not yet had a dramatic effect on relative reimbursement for this important test; however, as new regulations take effect requiring referring physicians to consult clinical decision support tools before ordering bone scintigraphy, access to this important technology may become severely limited unless AUC are written for inclusion of this test as an option in clinical decision support tools.

METHODOLOGY

Workgroup Selection

The experts of the AUC workgroup were convened by SNMMI to represent a multidisciplinary panel of health-care providers with substantive knowledge on the use of bone scintigraphy. In addition to SNMMI member representation, an international representative from the EANM and a representative from ASCO were included in the workgroup. Nine physician members were ultimately selected to participate and contribute to the resulting AUC. A complete list of workgroup participants and external reviewers can be found in Appendix A.

AUC Development

The process for AUC development was modeled after the RAND/UCLA appropriateness method (*16,17*) and included the development of a list of common scenarios encountered in the management of patients with prostate and breast cancer, a systematic review of evidence related to these scenarios, and development of an appropriateness score for each scenario using a modified Delphi process. This process strove to adhere to the standards of the Institute of Medicine of the National Academies for developing trustworthy clinical guidance (*18*). The process included a systematic synthesis of available evidence, individual and group ratings of the scenarios using a formal consensus process, and AUC recommendations based on final group ratings and discussions. Development of this AUC based on outcome measures would be desirable, but the literature review did not return significant articles in this area.

Scope and Development of Clinical Scenarios

To begin this process, the workgroup discussed various potential clinical scenarios for which use of bone scintigraphy might be considered (including possible contraindications). The scope of this workgroup was to focus on the appropriate use of bone scintigraphy specifically for the diagnosis and management of breast and prostate cancer. Therefore, the scenarios are specific to these cancers. For all scenarios, the relevant populations were men and women with breast cancer or men with prostate cancer (all at least 18 y old), of any race or geographic location (rural, urban, etc.).

The workgroup identified 16 scenarios for breast cancer patients and 17 for prostate cancer patients. The scenarios are intended to be as representative of the relevant patient population as possible for development of AUC.

A subgroup of interest for bone scintigraphy in breast cancer was pregnant patients. For scenarios related to restaging, the workgroup identified postprostatectomy or postradiation patients as subpopulations of interest.

The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each scenario. Other factors affecting the AUC recommendations were potential harm—including long-term harm that may be difficult to capture—costs, availability, and patient preferences.

Systematic Review

To inform the workgroup, a systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (*19*). The primary purpose of the systematic review was to assess the diagnostic accuracy and comparative effectiveness of bone scintigraphy in clinical decision making and clinical outcomes for breast and prostate cancer.

The key research questions used to guide the systematic review were as follows: In patients with breast or prostate cancer, what is the diagnostic accuracy of bone scintigraphy versus a reference standard (clinical and imaging follow-up, with or without pathologic diagnosis) for identifying patients with metastatic disease (i.e., how does diagnostic accuracy vary according to tumor stage); what are the effects of performing bone scintigraphy versus no bone scintigraphy on use of treatments or decisions regarding end-of-life care (i.e., how do effects vary according to tumor stage); and what are the effects of performing bone scintigraphy on mortality or quality of life (i.e., how do effects vary according to tumor stage)?

The inclusion and exclusion criteria for this review were based on the study parameters established by the workgroup using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. Searches were conducted on the following databases: the Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid Medline (from 1946 through May 2015). These searches were supplemented by reviewing the reference lists of relevant publications.

Two reviewers independently assessed abstracts and full-text articles for inclusion and rated study quality as defined by the

established PICOTS parameters. The quality (based on the risk of bias) of each study was categorized as "good," "fair," or "poor" using the U.S. Preventive Services Task Force criteria (for randomized trials and cohort studies) (*20*), QUADAS-2 (for diagnostic accuracy studies) (*21*), and AMSTAR (for systematic reviews) (*22*). The strength of overall evidence was graded as high, moderate, low, or very low using methods based on quality of evidence, consistency, directness, precision, and reporting bias.

Literature searches resulted in 919 potentially relevant articles. After dual review of abstracts and titles, 294 articles were selected for full-text review and 10 publications were determined to meet the criteria for inclusion in this review.

The researchers at the Pacific Northwest Evidence-Based Practice Center chose good- and fair-quality systematic reviews. Those selected were the most relevant to the key questions and scope parameters, had the most recent search dates, and were of the highest quality. To assess diagnostic accuracy, the workgroup selected systematic reviews that were published after 2012 and evaluated the accuracy of bone scintigraphy against a reference standard. Primary studies beyond those in the systematic reviews were included if they reported diagnostic accuracy and compared the accuracy of bone scintigraphy against a reference standard that, for all patients, included an alternative imaging test and, for patients with negative bone scintigraphy results, included clinical follow-up of at least 6 mo. Studies using a case-control design, or that enrolled only patients known to have metastatic disease, were excluded to reduce spectrum bias. To assess the effects of bone scintigraphy on clinical decision making and clinical outcomes, the researchers selected randomized trials and cohort studies that reported the effects of bone scintigraphy versus no bone scintigraphy (in patients with breast or prostate cancer) on treatment decisions or clinical outcomes (i.e., mortality, morbidity, quality of life, and harm). Additionally, studies of patients with mixed types of cancer that separately reported diagnostic accuracy for breast and prostate cancer were included. Non-English language studies and studies published only as conference abstracts were excluded.

Rating and Scoring

In developing these AUC for bone scintigraphy, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions (*23*): "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics."

On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical scenarios to ensure their accuracy and facilitate consistent interpretation when scoring each scenario for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the benefits and risks of bone scintigraphy for each of the identified scenarios and provide an appropriateness score for each scenario. Workgroup members then convened at a day-long, in-person forum to discuss each scenario and its associated scores from the first round of individual scoring. After deliberate discussion, each member independently provided a second round of scores for each scenario. For each scenario, the mode numeric score was determined and then assigned to the associated appropriate use category. The results of second-round scoring continued to indicate some difference in opinion among members about the appropriateness of certain scenarios. Therefore, the workgroup continued its deliberations and further clarified the criteria for assigning the different scores before conducting a third round of scoring, which reflected a group-level consensus of scores. For this final scoring round, the members were asked to include their expert opinion. All members contributed to the final discussion, and no one was forced into consensus. Once the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA appropriateness method.

The workgroup scored each scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores 1–3 indicate that use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. Additionally, if there was a difference in clinical opinion for a particular scenario such that workgroup members could not agree on a common score, that scenario was given a score of 5 to indicate a lack of agreement on appropriateness based on the available literature and the members' collective clinical opinion, indicating the need for additional research.

PROSTATE CANCER

Introduction

Adequate and appropriate staging is of paramount importance in decision making for initial and subsequent treatment of prostate cancer. Overuse of imaging in patients with a low probability of having metastases results in unnecessary additional expense, not only for bone scintigraphy but for studies such as CT and MRI. At the same time, underuse of imaging studies such as bone scintigraphy in high-risk patients results in misdiagnosis and the resultant morbidity from ineffective local therapies (*5*). Bone scans are used to stage and determine the appropriate therapy for early disease or whether the therapy needs to be changed in advanced disease. A change in therapy is contemplated on the basis of changes in the patient's symptoms, changes in prostate-specific antigen (PSA) doubling time, rapid rises in serum PSA level, and a new appearance of or change in visceral metastases (*24*). The purpose of this section of the AUC is to evaluate the appropriate use of bone scintigraphy in patients with prostate cancer both at initial diagnosis and during the subsequent course of their disease.

Background

Prostate cancer is the most common malignancy diagnosed in men, with an estimated incidence of 220,800 new cases in 2015 (*25*). The incidence of prostate cancer increases with age (*26*).

The development of a serum PSA assay in the 1980s and the Food and Drug Administration approval of screening with PSA in the mid-1990s led to an increase in the detection of prostate cancer. With the widespread use of serum PSA screening in the early 1990s, nonpalpable disease became the most common presentation of prostate cancer. The subsequent decade led to randomized trials using PSA as a screening tool, with controversial results (*27,28*). These controversies led to various organizations rejecting the use of PSA screening. With this change, a stage migration may occur, with more advanced

disease being present at diagnosis, including the increased presence of bone metastases.

Clinical Staging

The TNM (tumor–node–metastasis) staging system for prostate cancer developed by the American Joint Committee on Cancer is used for pretreatment clinical staging and encompasses the primary tumor, the lymph nodes, and any metastases.

Regarding tumor staging, the primary tumor is determined by the findings on digital rectal examination (DRE), the extent of cancer found in the lobes of the prostate on biopsy, and the findings of imaging modalities such as CT and MRI. Most cancers in the PSA screening era were nonpalpable tumors. A metaanalysis of DRE estimated its sensitivity for detecting prostate cancer to be 59%, its specificity 94%, and its positive predictive value 28% (*29*). DRE therefore has limited accuracy in identifying prostate cancer (*30*).

Regarding nodal staging, the presence of nodal metastasis is determined with conventional imaging such as CT scans or MRI. These modalities usually depend on anatomic enlargement of the pelvic nodes. PET tracers in development are showing promise for the detection of metastasis to local nodes before nodal enlargement occurs.

Regarding metastasis staging, the most common site of metastasis is the bone. In addition to having distant nodal disease, 15%–20% of patients have visceral disease to the liver or lungs. Clinical assessment for metastatic disease is done with conventional CT scans or MRI, and bone imaging is done with bone scintigraphy.

Serum PSA testing is used widely in predictive models for staging and assessing risk. In general, a higher PSA level is associated with more advanced disease. In a review of 23 studies that examined the role of staging bone scintigraphy at initial diagnosis, the rates for detection of bone metastases in men with serum PSA levels of less than 10, 10.1–19.9, and 20–50 ng/mL were 2%, 5%, and 16%, respectively (*31*).

Risk Assessment

To determine the likelihood of disease containment within the prostate, risk is assessed in all patients with a new diagnosis of prostate cancer. The factors that determine such risk include serum PSA level, presence or absence of abnormal DRE results, and Gleason grade and score; additional features include the number of positive biopsies and the percentage of cancerous tissue in the biopsy material (*32*). The most widely used classification is the D'Amico classification, which divides patients into low-, intermediate-, and high-risk groups and takes into consideration PSA level, DRE findings, and Gleason score. The National Comprehensive Cancer Network guidelines incorporate the number of positive biopsies and volume of cancer and categorize patients as being at very low risk, low risk, intermediate risk, high risk, or very high risk. The cancer-of-prostate risk assessment tool (*33*) includes the above as well as age at diagnosis.

National Comprehensive Cancer Network Risk Stratification

To be classified as being at very low risk, patients must have a Gleason score of 6 or less on biopsy and a serum PSA level of less than 10 ng/mL. In addition, the extent of disease within the prostate must be limited; that is, fewer than 3 positive biopsy cores with less than 50% involvement in any one core, and a PSA density of less than 0.15 ng/mL/g.

Patients with low-risk, clinically localized prostate cancer either have no apparent tumor in the prostate (i.e., diagnosis based on a biopsy only [T1], with no abnormal findings on imaging or palpation) or limited disease in one lobe of the prostate gland, a serum PSA level of less than 10 ng/mL, and a Gleason score of no more than 6.

Patients with intermediate-risk, clinically localized prostate cancer can have a more extensive tumor in the prostate (i.e., involving more than half of one prostate lobe (*33*) or with bilateral disease on initial examination or imaging [T2]) but without detectable extracapsular extension or seminal vesicle involvement. In addition, patients are classified as having intermediate-risk disease on the basis of a serum PSA level of between 10 and 20 ng/mL or a biopsy Gleason score of 7.

Patients with high-risk, clinically localized prostate cancer have more extensive disease based on the presence of presumed extracapsular extension on DRE (T3a) or a serum PSA level of more than 20 ng/mL or a Gleason score of 8–10.

Patients whose initial evaluation suggests locally advanced disease (T3b or T4) with seminal vesicle involvement, tumor fixation, or invasion of adjacent organs are classified as being at very high risk for progression or recurrence. In addition, patients with a primary Gleason pattern of 4, 5, or more cores and a Gleason score of 8–10 are classified as being at very high risk.

Bone Metastases

Prostate cancer has a high predilection to metastasize to the bones. The incidence of bone metastases correlates with serum PSA level and Gleason score. The incidence of bone metastases ranges from 2% for a PSA level of less than 10 ng/mL to 16% for a PSA level of more than 20 ng/mL. For patients with a PSA level of less than 10 ng/mL who are asymptomatic, the yield of positive bone scintigraphy is too low to warrant routine use for initial staging if the Gleason score is less than 7 (*34,35*). Bone metastases are seen in 5% of patients with a Gleason score of less than 6 versus 30% of those with a Gleason score of more than 7.

A systematic literature review for the appropriate use of bone scintigraphy in the staging of prostate cancer produced few articles published in recent years, possibly because the importance of bone scintigraphy was established years ago through case studies often comparing bone scintigraphy with plain radiography (*36*). Since that time, bone scintigraphy has remained a favored imaging modality despite the interval development of CT and MRI. Although CT and MRI can be more sensitive for metastatic disease in some instances, the cost and radiation dose of CT and the cost and logistics of MRI have limited their clinical use (*37*).

Although clinical practice continues to favor bone scintigraphy as the primary test to screen for bone metastases, particularly in asymptomatic patients, not all patients with a diagnosis of prostate cancer will benefit from bone scintigraphy. The workgroup has therefore considered several common clinical scenarios following the diagnosis of prostate cancer in which bone scintigraphy may or may not be advised.

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of bone scintigraphy and final AUC scores in prostate cancer are presented in Table 1.

Scenario 1: Initial Staging for Asymptomatic Patient with Normal Alkaline Phosphatase Level, PSA < 10, and Gleason Score < 6 (Score 2—Rarely Appropriate). The reasoning behind a rarely appropriate rating is that this scenario represents a very low risk for metastasis of prostate cancer to bone, and therefore patients fitting this clinical picture are unlikely to have true-positive

TABLE 1
Clinical Scenarios for Prostate Cancer

Scenario no.	Description	Appropriateness	Score
1	Initial staging for asymptomatic patient with normal alkaline phosphatase level, PSA $<$ 10, and Gleason score $\leq$ 6	Rarely appropriate	2
2	Initial staging for asymptomatic patient with elevated alkaline phosphatase level, PSA $<$ 10, and Gleason score $\leq$ 6	May be appropriate	4
3	Initial staging for asymptomatic patient with PSA = 10–20 or Gleason score = 7	May be appropriate	6
4	Initial staging for asymptomatic patient with PSA $\geq$ 20 or Gleason score $\geq$ 8 or $\geq$T3 prostate cancer	Appropriate	8
5	Initial staging for asymptomatic patient with PSA $<$ 10, Gleason score $\leq$ 6, and T2 prostate cancer	Rarely appropriate	3
6	Initial staging for asymptomatic patient with PSA $\geq$ 10, Gleason score $\leq$ 6, and T2 prostate cancer	May be appropriate	6
7	Initial staging for asymptomatic patient with PSA $<$ 10, Gleason score = 7, and T2 prostate cancer	May be appropriate	6
8	Initial staging for asymptomatic patient with PSA $\geq$ 10, Gleason score = 7, and T2 prostate cancer	Appropriate	8
9	Initial staging for symptomatic patient with normal alkaline phosphatase level, PSA $<$ 10, and Gleason score $\leq$ 6	Appropriate	8
10	Initial staging for symptomatic patient with elevated alkaline phosphatase level, PSA $<$ 10, and Gleason score $\leq$ 6	Appropriate	8
11	Evaluation of patient (at any clinical stage) presenting with new pathologic fracture	Appropriate	9
12	Initial staging for patient with bone pain	Appropriate	8
13	Restaging for asymptomatic patient when change in treatment is planned	Appropriate	7
14	Restaging for patient with bone pain when change in treatment is planned	Appropriate	8
15	Restaging for patient with bone pain	Appropriate	8
16	In patient with remote history of prostate cancer who has undergone imaging for another clinical reason, evaluation of incidental findings equivocal for osseous metastatic disease	Appropriate	7
17	Evaluation of patient before radionuclide bone therapy	Appropriate	9

PSA levels are in ng/mL.

bone scintigraphy results. The systematic literature review supports a low incidence of bony metastases for these patients and lack of utility for bone imaging in patients with low risk (*19*). A summary of 23 studies evaluating bone imaging to stage prostate cancer found bone metastases in 2.3% of patients with a PSA level of less than 10 ng/mL and in 5% of patients with a low Gleason score (*31,35*). This rating is also consistent with the clinical experience of the workgroup.

Scenario 2: Initial Staging for Asymptomatic Patient with Elevated Alkaline Phosphatase Level, PSA $<$ 10, and Gleason Score $<$ 6 (Score 4—May Be Appropriate). The reasoning behind this rating in this scenario is that an elevated alkaline phosphatase level is considered nonspecific, and although it may be caused by bone metastases, the low PSA level and Gleason score suggest that this scenario still represents low-risk patients. There were very few data from the literature to support bone scintigraphy in the scenario of an elevated alkaline phosphatase level as the sole sign of possible metastatic disease to bone. A retrospective study of 220 patients found that elevation of the alkaline phosphatase level did not correlate with positive bone scintigraphy results in men with an otherwise low risk of prostate cancer (*38*).

Scenario 3: Initial Staging for Asymptomatic Patient with PSA = 10–20 or Gleason Score = 7 (Score 6—May Be Appropriate). A PSA level of between 10 and 20 ng/mL or a Gleason score of 7 suggests that the neoplastic disease may be more aggressive and therefore more likely to metastasize. In a study of 263 patients, the cutoff estimated by receiver-operating-characteristic analysis was a PSA level of 16 ng/mL and a Gleason score of 7. This cutoff yielded a sensitivity of 94.5% and a specificity of 47% for bone scintigraphy in patients with prostate cancer (*39*). Intermediate-risk prostate cancer represents a heterogeneous group of patients, and bone imaging may be appropriate in those with a predominantly Gleason 4 pattern (*40*).

Scenario 4: Initial Staging for Asymptomatic Patient with PSA $>$ 20 or Gleason Score $>$ 8 or $\geq$T3 Prostate Cancer (Score 8—Appropriate). Patients in this scenario have high-risk disease and are considered at risk for metastases. A study of 155 patients revealed an odds ratio of 7.2 and a 29% increased risk of metastases in patients with a Gleason score of more than 8 (*41*). This is consistent with the recommendations of most guidelines and with best practices.

Scenario 5: Initial Staging for Asymptomatic Patient with PSA $<$ 10, Gleason Score $\leq$ 6, and T2 Prostate Cancer (Score

3—Rarely Appropriate). The reasoning behind a "rarely appropriate" rating in this scenario is that it represents a very low risk and that patients with these clinical signs are unlikely to have true-positive results on bone scintigraphy. A prospective trial of 645 patients revealed no bone metastases in patients with a PSA level of less than 10 ng/mL independently of T stage and Gleason score (*42*).

Scenario 6: Initial Staging for Asymptomatic Patient with PSA ≥ 10, Gleason Score ≤ 6, and T2 Prostate Cancer (Score 6—May Be Appropriate). This scenario represents patients at low intermediate risk who are elevated to a higher risk category by a PSA level of 10 ng/mL or higher. However, the low Gleason score makes the presence of bone metastases unlikely and was the main rationale behind the workgroup's recommendation. Recent data suggest that of the 567 patients with low intermediate risk who underwent preoperative bone imaging, 5% had a positive scan result and very few had progression during subsequent follow-up (*43*). Despite these data, there is high use of bone scintigraphy for this group of patents (*5,44*).

Scenario 7: Initial Staging for Asymptomatic Patient with PSA < 10, Gleason Score = 7, and T2 Prostate Cancer (Score 6—May Be Appropriate). In a review of 683 patients, no patient with a PSA level of less than 10 ng/mL and cT2 prostate cancer had true-positive findings on bone scintigraphy (*45*). However, the workgroup feels that a Gleason score of 7, especially if there is a dominant Gleason 4 pattern, raises the chance of bone metastasis enough to warrant bone scintigraphy in some patients despite the low PSA level and low T stage.

Scenario 8: Initial Staging for Asymptomatic Patient with PSA ≥ 10, Gleason Score = 7, and T2 Prostate Cancer (Score 8—Appropriate). This scenario represents intermediate-risk patients, and the PSA level of 10 ng/mL or higher and Gleason score of 7 pose a higher risk of bone metastases (*45*). For patients presenting with new-onset bone pain, irrespective of PSA level, stage, Gleason score, or alkaline phosphatase level, the workgroup recommends bone scintigraphy per good clinical practice. This is applicable to scenarios 9, 10, 11, 12, 14, and 15.

Scenario 9: Initial Staging for Symptomatic Patient with Normal Alkaline Phosphatase Level, PSA < 10, and Gleason Score ≤ 6 (Score 8—Appropriate). The low Gleason score and low PSA may not suggest metastatic disease; however, the consensus of the workgroup is that bone symptoms, particularly new symptoms, should be investigated further. Although other imaging studies can be used for investigating localized bone pain, MRI can be logistically difficult to obtain, and plain radiographs and CT are not as sensitive as bone scintigraphy. In addition, bone scintigraphy can more easily evaluate the entire skeleton for additional sites of disease. Normal bone scintigraphy is helpful to rule out metastasis in patients with symptoms of bone pain.

Scenario 10: Initial Staging for Symptomatic Patient with Elevated Alkaline Phosphatase Level, PSA < 10, and Gleason Score ≤ 6 (Score 8—Appropriate). Although there are no data to discretely delineate how to proceed with this scenario, the workgroup feels that if a patient has bone-related symptoms and an elevated bone marker, additional work-up is warranted. Even though this scenario represents low-risk disease, symptoms mandate that the patient be evaluated.

Scenario 11: Evaluation of Patient (at Any Clinical Stage) Presenting with New Pathologic Fracture (Score 9—Appropriate). Although no evidence was found in the systematic review, the workgroup feels that the presence of a pathologic fracture warrants further examination. This would help exclude other areas of future pathologic fracture and clarify the extent of disease.

Scenario 12: Initial Staging for Patient with Bone Pain (Score 8—Appropriate). In any patient presenting with bone pain, or any patient with a known history of prostate cancer who develops bone pain, bone imaging for staging purposes is warranted before the start of therapy.

Scenario 13: Restaging for Asymptomatic Patient When Change in Treatment Is Planned (Score 7—Appropriate). Although there are no data to discretely delineate how to proceed with this scenario, the workgroup feels that if there is a clinical need to change treatment, knowledge of the current disease status is helpful to guide therapy, and bone scintigraphy is therefore appropriate.

Scenario 14: Restaging for Patient with Bone Pain When Change in Treatment Is Planned (Score 8—Appropriate). With more options available now for patients with advanced metastatic disease, restaging before the start of new therapy is appropriate and consistent with good clinical practice.

Scenario 15: Restaging for Patient with Bone Pain (Score 8—Appropriate). Patients who present with bone pain need imaging studies per good clinical practice to determine the optimal therapy, such as radiation planning.

Scenario 16: In Patient with Remote History of Prostate Cancer Who Has Undergone Imaging for Another Clinical Reason, Evaluation of Incidental Findings Equivocal for Osseous Metastatic Disease (Score 7—Appropriate). Although evidence for this scenario was not found in the systematic review of the literature, the workgroup members feel that, on the basis of their clinical judgment, this scenario is similar to a restaging after clinical evidence of recurrence and is consistent with good clinical practice. MRI may be helpful to additionally characterize a focal abnormality; however, bone scintigraphy is better suited to evaluate the entire bony skeleton.

Scenario 17: Evaluation of Patient Before Radionuclide Bone Therapy (Score 9—Appropriate). According to the SNMMI procedure standard for palliative treatment of painful bone metastases, bone scintigraphy is required before treatment with bone-seeking radionuclide therapy. Package inserts for the radionuclide therapies for osseous metastatic disease require this imaging before therapy.

Summary of Recommendations

Bone scintigraphy is usually appropriate for initial staging in patients with intermediate-risk disease (stage T2, PSA level > 10 ng/mL, or Gleason score ≥ 7); for initial evaluation of patients with high-risk disease (stage T3, PSA level > 20 ng/mL, or Gleason score > 8); for evaluation of patients with symptoms referable to the bones regardless of stage or risk; for evaluation of patients in whom a change in treatment is anticipated; for evaluation of patients presenting with a pathologic fracture; and for evaluation of patients who are to undergo radium or other radionuclide bone therapy.

Bone scintigraphy is usually not appropriate for initial staging in patients with a low risk of metastatic disease (PSA level < 10 ng/mL, Gleason score < 6, and no other clinical signs or symptoms of disease).

BREAST CANCER

Introduction

Like prostate cancer, breast cancer does not require bone scintigraphy in all patients at the time of diagnosis. Breast neoplastic disease discovered at an early stage is unlikely to metastasize to bone; therefore, unless there are signs or symptoms suggesting metastasis in early-stage disease, bone imaging is not necessary (*46*). If bone scintigraphy is felt necessary, imaging of pregnant patients requires special

consideration. Recommendations for the appropriate use of bone scintigraphy in breast cancer are described in this section.

Background

Worldwide, breast cancer is the most common malignancy in women, regardless of their ethnicity (*47*). The prevalence in the United States is almost 3 million patients (*48*). The American Cancer Society estimated that in 2015, 231,840 new cases of invasive breast cancer would be diagnosed and that 40,290 women would die from breast cancer (*8*). The lifetime risk that a woman in the United States will develop breast cancer is 12.3% (*8*). The fact that the number of new cases per year has increased since 1975 may be secondary to more sensitive and widespread screening techniques (*48*). Conversely, the overall number of deaths has decreased (*48*), suggesting that lifesaving therapies have improved. Hispanic women are more likely than women of other ethnicities to die from breast cancer (*48*).

Information about the prognosis of breast cancer can be obtained through staging at initial diagnosis. The 5-y survival rate for localized, or in situ, breast carcinoma is 98.6%. However, when regional lymph node involvement is present, 5-y survival drops to 84.9%, and when there is distant disease, survival decreases to 25.9% (*8*). Accurately establishing the stage early in the course of disease is helpful for directing therapy and improving individual outcomes.

Male breast cancer is less common, with an estimated incidence of 2,350 and an estimated death toll of 440 in 2015 (*49*). The overall survival is similar to that in women with breast cancer, but at stage IV (distant disease), 5-y survival drops to 20% in men (*50*).

Clinical Staging

Presurgical information is used to identify the TNM stage. The collected information includes a thorough patient history, physical examination, mammography, and sometimes advanced breast imaging, such as ultrasound, MRI (*51*), or breast scintimammography. The tumor and node stages can often be determined by these means.

The metastasis stage can be more difficult to determine. If prompted by patient signs or symptoms, further evaluation may be performed using liver function tests; alkaline phosphatase tests; bone scintigraphy; cross-sectional imaging of the chest, abdomen, or pelvis; or ^{18}F-FDG PET imaging (*49*).

Risk Assessment

The Gail model, developed by Dr. Mitchell Gail at the National Cancer Institute, is the classic algorithm used to assess breast

TABLE 2
Clinical Scenarios for Breast Cancer

Scenario no.	Description	Appropriateness	Score
1	Evaluation of patient with prior ^{18}F-FDG PET/CT study showing avid bone lesions	Rarely appropriate	2
2	Evaluation of patient with prior ^{18}F-FDG PET/CT study showing nonavid bone lesions	May be appropriate	4
3	Evaluation of patient with prior ^{18}F-FDG PET/CT study showing no bone lesions	Rarely appropriate	2
4	Initial staging for asymptomatic patient with elevated alkaline phosphatase level and clinical stage I or II breast cancer	Appropriate	7
5	Initial staging for symptomatic patient	Appropriate	8
6	Initial staging for patient with clinical stage IV breast cancer	Appropriate	8
7	Initial staging for patient with clinical stage III breast cancer	Appropriate	8
8	Initial staging for patient with clinical stage 0 breast cancer	Rarely appropriate	2
9	Restaging for asymptomatic patient with change in treatment plan	Appropriate	7
10	Restaging for patient with new bone pain	Appropriate	8
11	Restaging for asymptomatic patient with increase in alkaline phosphatase level	Appropriate	8
12	Restaging for suspicion of nonosseous recurrence	Appropriate	7
13	Evaluation of patient (at any clinical stage) presenting with new pathologic fracture	Appropriate	9
14	Evaluation of patient before radionuclide bone therapy	Appropriate	9
15	In patient with remote history of breast cancer who has undergone imaging for another clinical reason, evaluation of incidental findings equivocal for osseous metastatic disease	Appropriate	7
16	Routine surveillance in patient with history of breast cancer and no prior evidence of bone metastasis	Rarely appropriate	1

cancer risk (*52*). This algorithm uses a woman's personal medical history, reproductive history, and family history in first-degree relatives to determine her risk for developing invasive breast cancer. The Gail model was first used in Caucasian women and has also been validated in the Asian and Pacific Islander population but may underestimate risk in African American women (*53,54*). Other tools include the International Breast Cancer Intervention Study risk evaluation tool (*55*), which assumes the presence of other genetic factors in addition to the breast cancer susceptibility genes, and the "breast and ovarian analysis of disease incidence and carrier estimation" algorithm (*56*). These individually developed tools have been incorporated into a single breast cancer risk assessment tool designed by the National Cancer Institute (*57*). Still other models are available for risk assessment, including the Claus, Ford, Tyrer-Cuzick, and Manual models (*58*).

Although breast cancer testing and familial risk models have been found to be helpful, the efficacy of extensive genetic screening remains unknown. More evidence is required before widespread genetic screening for breast cancer can be advocated (*59*). To this end, a multicenter study conducted by the Centers for Disease Control, North American Association of Central Cancer Registries, American Cancer Society, and National Cancer Institute is examining genetic associations between breast cancer subtypes and age, race/ethnicity, poverty level, and other factors. The 4 major molecular subtypes of breast cancer are determined by hormone receptor (HR) status and expression of the human epidermal growth factor receptor 2 (HER2) gene: HR+/HER2−, HR+/HER2+, HR−/HER2+, and HR−/HER2− (*60*). Because the HR and HER2 receptor sites are targets for molecularly directed therapies, absence of their expression portends a poorer prognosis. Another prognostic parameter is the presence of Ki-67, a nuclear protein associated with cellular proliferation. The higher this proliferation index, the more aggressive the malignancy and, consequently, the poorer the prognosis (*61*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of bone scintigraphy and final AUC scores in breast cancer are presented in Table 2.

Scenario 1: Evaluation of Patient with Prior ^{18}F-FDG PET/CT Study Showing Avid Bone Lesions (Score 2—Rarely Appropriate). In one study, the median sensitivity of ^{18}F-FDG PET for bone lesions was similar to that of bone scintigraphy, and its specificity was somewhat higher (*62*). Another study found that ^{18}F-FDG PET/CT had a higher sensitivity and specificity than bone scintigraphy (*63*). These studies suggest that if bone lesions are found on metabolic imaging, bone scintigraphy does not contribute to patient management in most situations.

Scenario 2: Evaluation of Patient with Prior ^{18}F-FDG PET/CT Study Showing Nonavid Bone Lesions (Score 4—May Be Appropriate). Although this scenario is less clear-cut than the first scenario, the same references apply. The workgroup's opinion is that ^{18}F-FDG PET is less sensitive than bone scintigraphy for osteoblastic breast cancer lesions. Management of patients with osteoblastic breast cancer lesions may therefore be assisted by bone scintigraphy (*64,65*).

Scenario 3: Evaluation of Patient with Prior ^{18}F-FDG PET/CT Study Showing No Bone Lesions (Score 2—Rarely Appropriate). This scenario once again relies on the concept that ^{18}F-FDG PET is more sensitive and specific than bone scintigraphy for bony lesions, as referenced in the first scenario (*62,63*). If ^{18}F-FDG PET/CT is negative for metastatic disease to bone, bone scintigraphy is not likely to find occult metastatic bone disease.

Scenario 4: Initial Staging for Asymptomatic Patient with Elevated Alkaline Phosphatase Level and Clinical Stage I or II Breast Cancer (Score 7—Appropriate). Patients with stage I or II disease are at a lower risk for disseminated disease than patients with higher stages. Recent studies have demonstrated a 0.2% likelihood of metastatic disease in stage I patients and a 1.2% likelihood in stage II patients (*46*). Another study found that the prevalence of metastatic disease in stage I or II patients is 5% (*66*). An elevated alkaline phosphatase level can be seen with hepatic or bone metastatic disease, and therefore the workgroup feels that an elevated alkaline phosphatase level may be a predictor of mortality in breast cancer (*67*), if this conclusion can be extrapolated from prostate cancer research.

Scenario 5: Initial Staging for Symptomatic Patient (Score 8—Appropriate). The prevalence of metastatic disease increases with symptoms referable to bone (*65*); therefore, further work-up of these patients, such as with bone scintigraphy, is indicated.

Scenario 6: Initial Staging for Patient with Clinical Stage IV Breast Cancer (Score 8—Appropriate). There is evidence that the yield for skeletal scintigraphy increases with increasing stage (*65*). Bone scintigraphy in patients with clinical stage IV breast cancer can confirm clinical suspicion of stage, define the burden of disease, and survey for potential pathologic fracture sites.

Scenario 7: Initial Staging for Patient with Clinical Stage III Breast Cancer (Score 8—Appropriate). There is evidence that the yield for skeletal scintigraphy increases with increasing stage (*65*). Scintigraphy in patients with clinical stage III breast cancer can assist in defining the burden of disease.

Scenario 8: Initial Staging for Patient with Clinical Stage 0 Breast Cancer (Score 2—Rarely Appropriate). The workgroup can infer from the evidence that if a stage I or II patient has a very low probability of osseous metastatic disease, a stage 0 patient should have an even lower probability (*65*). Therefore, it is rarely appropriate to perform bone scintigraphy in this scenario.

Scenario 9: Restaging for Asymptomatic Patient with Change in Treatment Plan (Score 7—Appropriate). Although the systematic review provided no data on which to base a recommendation on how to proceed with this scenario, the workgroup feels that if there is a clinical need to change treatment, knowing the current disease status is helpful in guiding therapy and in determining a new baseline by which treatment-response decisions can be made. Therefore, a recommendation for use of bone scintigraphy is appropriate in this scenario.

Scenario 10: Restaging for Patient with New Bone Pain (Score 8—Appropriate). The workgroup can infer from the literature that use in this scenario is appropriate because symptomatic patients have been shown to have more extensive disease (*65*).

Scenario 11: Restaging for Asymptomatic Patient with Increase in Alkaline Phosphatase Level (Score 8—Appropriate). This scenario has no discrete supporting data based on the systematic review but is supported by workgroup consensus. The workgroup considers a rise in alkaline phosphatase level to be an indication for evaluation of the bony skeleton. Skeletal scintigraphy is an excellent modality for a broad skeletal survey and is highly sensitive (*62*).

Scenario 12: Restaging for Suspicion of Nonosseous Recurrence (Score 7—Appropriate). Although there are no data in the literature to advise how to proceed with this scenario, the

workgroup feels that if there is a clinical need to change treatment, knowing the current disease status is helpful in guiding therapy.

Scenario 13: Evaluation of Patient (at Any Clinical Stage) Presenting with Pathologic Fracture (Score 9—Appropriate). Although there is no evidence in the literature, the workgroup feels that the presence of a pathologic fracture warrants further examination to look for other areas of potential pathologic fracture and to clarify the extent of disease.

Scenario 14: Evaluation of Patient Before Radionuclide Bone Therapy (Score 9—Appropriate). The SNMMI procedure guideline for palliative treatment of painful bone metastases and the package inserts for therapeutic radionuclides state that bone scintigraphy is required before treatment. Therapeutic tracer localizes to the bone in a pattern similar to that of bone scintigraphy agents (*68*). If there is no metastatic disease to bone causing increased uptake on bone scintigraphy, therapy with bone-seeking agents would expose a patient to radiation without a therapeutic benefit (*69,70*). Although ^{223}Ra-chloride is not currently Food and Drug Administration–approved for breast cancer metastasis, ongoing trials may soon demonstrate clinical benefit. Pretherapy bone scintigraphy would be needed for the same reasons as in prostate cancer patients (*71*).

Scenario 15: In Patient with a Remote History of Breast Cancer Who Has Undergone Imaging for Another Clinical Reason, Evaluation of Incidental Findings Equivocal for Osseous Metastatic Disease (Score 7—Appropriate). Although evidence for this scenario is unavailable, the workgroup feels that this scenario is similar to those for restaging. The sensitivity of bone scintigraphy for active metastatic disease would provide useful information about osteoblastic activity at a suspected site and would provide a survey of the remainder of the skeleton for other sites of osteoblastic activity.

Scenario 16: Routine Surveillance in Patient with History of Breast Cancer and No Prior Evidence of Bone Metastasis (Score 1—Rarely Appropriate). Unless there are signs or symptoms of bone metastasis, the workgroup considers using bone scintigraphy for routine surveillance of patients who do not have prior evidence of bone metastasis to rarely be appropriate. There is no evidence in the literature to support routine surveillance in these patients.

Summary of Recommendations

Bone scintigraphy is appropriate for initial staging in patients with node-positive disease; for patients at any stage or risk who have symptoms referable to the bones; and for patients who are to undergo bone-directed radionuclide therapy.

Bone scintigraphy is usually appropriate for breast cancer patients who present with a pathologic fracture, require a change in treatment plan, or are suspected of having nonosseous or osseous disease progression.

Bone scintigraphy is usually not appropriate for initial staging in patients with low-risk disease (clinical stage 0 or I) and no other clinical signs or symptoms of disease.

BENEFITS AND HARMS OF IMPLEMENTING THE AUC GUIDANCE

Some providers have raised the concern that AUC for medical imaging might inappropriately limit access to health-care services (*72*). For example, several authors in the reviewed literature suggested that AUC might lead to denial of reimbursement for needed imaging services because of incomplete AUC or lack of strong evidence for a particular procedure (*73*). It is hoped that besides providing recommendations for the appropriate use of bone scintigraphy, this document will demonstrate gaps in the literature and subsequently encourage new investigations to address these gaps.

Integration of an AUC into clinical decision support tools can assist health-care providers and offer a way to track comparisons between the AUC model and the payer's reimbursement policy (*73,74*). Ultimately, this may lead to a more efficient approval process for advanced diagnostic imaging procedures, including radiology and nuclear medicine procedures, saving time and effort for the referring provider and the imaging facility. However, the difficult task of writing AUC for all scenarios and keeping these AUC current remains a large obstacle to the effective use of the clinical decision support model.

QUALIFYING STATEMENTS

Study/Evidence Limitations

Although the medical community has relied on bone scintigraphy for decades, the workgroup found the body of medical literature regarding its use to be limited when rigorous inclusion criteria were applied to the systematic literature review. Studies that initially validated this technique do not meet the methodologic standards that have come about as the medical literature has evolved. Because bone scintigraphy for breast and prostate cancer has been a well-accepted and frequently used diagnostic study for many years, there has been little impetus to conduct new studies. As a result, the workgroup found only 4 reviews and 6 trials of good and fair quality written since 2012 (*19*). Furthermore, methodologic shortcomings limit many studies of the diagnostic accuracy of bone scintigraphy. Although no studies directly commented on the accuracy of bone scintigraphy with respect to tumor stage or grade, useful data were found on the low prevalence of skeletal metastases in early-stage prostate and breast cancer from which inferences could be drawn regarding the appropriate use of bone scintigraphy in these clinical settings (*75*). Decades of extensive clinical experience also played a role in assessing the appropriateness of many scenarios.

No studies of bone SPECT/CT or ^{18}F-NaF PET/CT met the inclusion criteria; however, these newer imaging techniques show promise to replace conventional bone scintigraphy in the assessment of skeletal metastatic disease (*65,76*).

SPECT/CT combines bone SPECT imaging and CT imaging, resulting in improved accuracy over conventional planar scintigraphy. Some investigations have demonstrated that the proportion of indeterminate bone lesions can be significantly decreased from a rate of 48%–72% with whole-body scintigraphy or SPECT to a rate of 0%–15% with additional SPECT/CT. Sensitivity can also be improved by SPECT/CT through improved image contrast (*65,76–78*). Furthermore, the number of additional diagnostic imaging tests such as plain radiography, CT, and MRI to characterize unclear findings can be significantly reduced from a rate of 25%–60% with planar whole-body scintigraphy to a rate of 0%–5% with SPECT/CT (*65,76–78*). The new technique of whole-body SPECT/CT can improve management through more accurate staging, better definition of the extent of metastatic disease, and a lower number of additional diagnostic procedures. With low-dose CT technique as part of the SPECT/CT study, a significant improvement in diagnostic accuracy can occur without substantially increasing the radiation dose (*65*).

^{18}F-NaF PET/CT is another promising alternative to conventional whole-body bone scintigraphy. ^{18}F-NaF is a positron-emitting agent that was historically used as a skeletal tracer for planar scintigraphy before the advent of ^{99m}Tc-labeled agents. A fluorine atom (as found in NaF) is an analog of the hydroxyl group found in hydroxyapatite bone crystals and therefore an avid bone seeker. As with ^{99m}Tc-based bone scintigraphy radiopharmaceuticals, which are bound to bone by chemical adsorption, fluorine is directly incorporated into the bone matrix, converting hydroxyapatite to fluoroapatite. Although uptake of ^{99m}Tc-MDP and uptake of ^{18}F-fluoride both reflect the osteoblastic reaction of bone, ^{18}F-fluoride is considered to have superior pharmacokinetic characteristics (*79–85*). The advantages of ^{18}F-NaF PET/CT include superior image quality with higher sensitivity and higher bone uptake. Furthermore, the direct correlation of PET and CT findings allows improved specificity because many benign osteoblastic processes can be discerned by their CT appearance (*79–85*).

The expanded availability of dedicated PET/CT cameras and the subsequent recent adoption, by several centers, of ^{18}F-FDG PET/CT for the initial detection and staging of various cancers and for monitoring response to therapy has generated early literature discussing the benefits of ^{18}F-NaF PET imaging over single-photon tracers (*82,84*).

Publications have validated the use of ^{18}F-NaF PET/CT in multiple clinical scenarios such as initial staging, suspected first osseous metastasis, and suspected progression of osseous metastasis for prostate cancer and other cancers. ^{18}F-NaF is widely available and has a relatively low cost.

In a recent metaanalysis, ^{18}F-NaF PET/CT showed a high level of overall accuracy in detecting bone metastases, with pooled sensitivity and specificity of 92% (95% confidence interval, 89%–95%) and 93% (95% confidence interval, 91%–95%), respectively (*83*). When compared with ^{99m}Tc-MDP bone scintigraphy, ^{18}F-NaF PET/CT showed not only better sensitivity but also better specificity. When compared with ^{18}F-FDG PET/CT, ^{18}F-NaF PET/CT showed higher sensitivity, whereas no significant difference was observed in specificity for bone metastases of prostate origin (*84*) or of other origin (*82*). On the basis of the excellent diagnostic capacity of ^{18}F-NaF PET/CT, in future it might be indicated as the first-line diagnostic imaging method for the detection of bone metastases. Coadministration with ^{18}F-FDG may also represent an appealing approach in selected cancer patients. The clinical impact of ^{18}F-NaF PET/CT when used to monitor treatment response, however, remains uncertain. Emerging clinical applications such as PET/MR also warrant further investigation.

Considerations for Pregnant Patients

The pregnancy status of female patients of child-bearing age should be determined. Radiation exposure to the fetus from ^{99m}Tc-MDP, ^{99m}Tc-hydroxy-MDP, and ^{18}F-NaF is low and may be decreased further with special precautions such as increased hydration and catheterization (*86*). Physicians involved in the care of the patient and fetus should weigh the benefits of the examination against the potential risk of radiation exposure. There is also risk to both mother and fetus with inaccurate staging of breast cancer. It should be noted that no harmful effects from bone scintigraphy have ever been identified in a pregnant patient or her fetus.

The effective dose from bone scintigraphy using 740 MBq (20 mCi) of ^{99m}Tc-MDP or ^{99m}Tc-hydroxy-MDP is approximately 4.22–4.44 mSv (422–444 mrem) (*87–89*). For bone scintigraphy using 370 MBq (10 mCi) of ^{18}F-NaF, the effective dose is 8.9 mSv (890 mrem) (*87*).

IMPLEMENTATION OF THE AUC GUIDANCE

To develop broad-based multidisciplinary clinical guidance documents, SNMMI has been working with several other medical specialty societies. This collaboration will foster the acceptance and adoption of this guidance by other specialties.

SNMMI has developed a multipronged approach to disseminate the AUC for bone scintigraphy in malignant diseases to all relevant stakeholders—referring physicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will be a mix of outreach and educational activities and will be targeted to each of these audiences.

SNMMI will create detailed case studies for its members as well as for referring physicians and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of bone scintigraphy, as well as some cases in which the results of bone scintigraphy are equivocal.

Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on the AUC, factsheets, and other didactic materials will be made available on the SNMMI webpage dedicated to bone scintigraphy AUC. Live sessions will be held at the SNMMI annual and midwinter meetings, as well as at the relevant societal meetings of referring physicians, to highlight the importance of these AUC.

SNMMI also aims to create a mobile application for the bone scintigraphy AUC for both Apple and Android platforms. Mobile applications are becoming increasingly popular in the health-care industry and can be used to push updates to all users.

In addition to the above activities, SNMMI will also undertake patient-focused outreach to provide education on how AUC can play an invaluable role in achieving a more accurate diagnosis.

APPENDIX A: WORKGROUP MEMBERS AND EXTERNAL REVIEWERS

Workgroup

The members of the workgroup are Kevin J. Donohoe, MD (chair), Beth Israel Deaconess Medical Center, Boston, MA (SNMMI); Erica J. Cohen, DO, MPH, CCD, Edward Hines Jr. Veterans Administration Hospital, Hines, IL (SNMMI); Francesco Giammarile, MD, PhD, International Atomic Energy Agency, Vienna, Austria (EANM); Erin Grady, MD, CCD, FACNM, Christiana Care Health System, Newark, DE (SNMMI); Bennett S. Greenspan, MD, FACNM, FACR, Medical College of Georgia, Augusta, GA (SNMMI); Robert E. Henkin, MD, FACR, Loyola University Medical Center, Maywood IL (retired), Chicago, IL (SNMMI); John Millstine, MD, Scottsdale Medical Imaging, Ltd., Scottsdale, AZ (SNMMI); Gary T. Smith, MD, Tennessee Valley Healthcare System, Nashville, TN (SNMMI); and Sandy Srinivas, MD, Stanford University School of Medicine, Stanford, CA (ASCO).

External Reviewers

The external (peer) reviewers are Tobias Bäuerle, Universitätsklinikum Erlangen, Erlangen, Germany; A. Cahid Civelek, University of Louisville Medical Center, Louisville, KY; Edward B. Silberstein, University of Cincinnati Medical Center, Cincinnati, OH; Helena R. Balon, William Beaumont Hospital, Royal Oak, MI; John Buscome, University of Cambridge, Cambridge, U.K.; and Robert Dreicer, University of Virginia, Charlottesville, VA.

Patient Advocate

The patient advocate is Susan Davis, outreach coordinator at FORCE (Facing Our Risk of Cancer, Empowered).

SNMMI

The staff support from SNMMI is Sukhjeet Ahuja, MD, MPH, director, Evidence & Quality Department; and Julie Kauffman, associate program manager, Evidence & Quality Department.

APPENDIX B: DEFINITION OF TERMS AND ACRONYMS

AMSTAR: Assessing the Methodological Quality of Systematic Reviews.

ASCO: American Society of Clinical Oncology.

AUC: appropriate use criteria.

Bone scintigraphy (*90*): a diagnostic imaging test in which a radiotracer accumulates predominantly in the bones and is detected by an imaging device. The resulting 2- or 3-dimensional images can reveal various processes such as bony fractures, infection, inflammation, and changes secondary to the presence of cancer cells. Bone scintigraphy refers to planar imaging unless specified otherwise.

Cancer stage grouping (*91*): a system by which the stage of cancer is determined by combining the tumor, node, and metastasis classifications. Most types of cancer have 4 stages. Some also have a stage 0, which describes cancer in situ—literally, "in place." Stage 0 tumors are still located where they started and have not invaded nearby tissues. This stage is often highly curable, usually by removing the entire tumor through surgery. Stage I, often called early-stage cancer, is typically a small tumor that has not grown deeply into nearby tissue and has not spread to the lymph nodes or other parts of the body. Stage II and III tumors are larger, have grown more deeply into nearby tissue, and have spread to lymph nodes but not to other parts of the body. Stage IV, also referred to as advanced or metastatic cancer, has spread to other organs or parts of the body (*92*).

CT: radiography in which a 3-dimensional image of a body structure is constructed by computer from a series of planar cross-sectional images acquired along an axis.

DRE (*93*): digital rectal examination, a screening test. It allows a physician to check the lower rectum, pelvis, and lower belly for cancer and other health problems, including prostate cancer in men, rectal or lower-colon cancer in men and women, and (along with a vaginal examination) uterine or ovarian cancer in women. A physician may perform a DRE as part of a routine medical examination or if a patient has symptoms such as rectal bleeding, a change in bowel habits, urethral discharge or bleeding, or a change in urine stream.

EANM: European Association of Nuclear Medicine.

^{18}F-FDG (*90*): ^{18}F-fluorodeoxyglucose (also referred to as fluorine-18 FDG or F-18 FDG), a frequently used radiotracer in PET scanning. ^{18}F-FDG is a compound in which the radioactive isotope ^{18}F is attached to a molecule of glucose. Once in the body, ^{18}F-FDG is absorbed by various tissues and can be detected by a PET scanner. The resulting images show how the radiotracer is distributed within the body, helping physicians diagnose various medical conditions and assess how well the body is functioning.

Gleason grade (*92*): a grade given to each of the two most prevalent patterns of cancer cells in prostate tumor biopsy specimens. The Gleason grade is based on a scale of 1 to 5, with 1 to 3 corresponding to well-differentiated cancer cells similar in appearance to normal cells and 4 to 5 corresponding to poorly differentiated cancer cells that look abnormal.

Gleason score (*92*): a score that is the sum of the two Gleason grades assigned to a prostate tumor. The Gleason score is on a scale of 2 to 10, with lower numbers indicating a slow-growing tumor unlikely to spread and higher numbers indicating an aggressive tumor.

HR: hormone receptor.

HER2: human epidermal growth factor receptor 2 gene.

MDP: methylene diphosphonate.

PET (*90*): positron emission tomography, which involves an imaging device and injection of a radiotracer into a patient's bloodstream. A frequently used PET radiotracer is ^{18}F-FDG, which the body treats like glucose. It usually takes between 30 and 60 min for the ^{18}F-FDG distribution throughout the body to become fixed.

PET/CT (*90*): a combination device that provides detail on both function and anatomy by superimposing the precise location of abnormal metabolic activity (from PET) on a detailed anatomic image (from CT).

PICOTS (*94*): population, intervention, comparison, outcome, timing, and setting. The PICOT format is a helpful approach for summarizing research questions that explore the effect of therapy. *Population* refers to the sample of subjects to be recruited for a study. There may be a fine balance between defining the sample that is most likely to respond to an intervention (e.g., no comorbidity) and the sample that can be generalized to patients likely to be seen in actual practice. *Intervention* refers to the treatment to be provided. *Comparison* refers to a reference group. The outcomes of the reference group (no intervention applied) are compared with the outcomes of the population to which the intervention was applied. *Outcome* refers to a measurement that will determine the effectiveness of the intervention. Familiar and validated outcome measurement tools relevant to common patient populations include the Neck Disability Index 6 and the Roland-Morris Questionnaire 7. There are typically a multitude of outcome tools available for different clinical populations, each having strengths and weaknesses. *Timing* describes the duration of data collection.

Prostate gland (*95*): a gland in male individuals that surrounds the neck of the urinary bladder and the urethra. It secretes a substance that liquefies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum.

PSA (*95*): prostate-specific antigen, a glycoprotein that is a kallikrein-like serine proteinase and an esterase, produced by both normal and malignant prostate epithelial cells. PSA is an important marker for the diagnosis of prostate cancer.

Prostatectomy (*90*): surgical removal of part or all of the prostate gland.

QUADAS-2 (*21*): Quality Assessment of Diagnostic Accuracy Studies, version 2. The QUADAS tool was first developed in 2003. Experience, anecdotal reports, and feedback suggested areas for improvement, leading to QUADAS-2. The tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concern about applicability. Signaling questions are included to help judge risk of bias. The tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability. The tool allows for more transparent rating of bias and of the applicability of primary diagnostic accuracy studies.

TABLE 1C
Bone Scintigraphy Radiation Dose (from SNMMI Procedure Standard for Sodium ^{18}F-Fluoride PET/CT Bone Scans 1.0)

Compound	Stage of gestation	Estimated mean dose	Estimated dose range
^{18}F-fluoride*	Early	0.022 mGy/MBq (0.081 rad/mCi)	4.1–8.1 mGy (0.41–0.81 rad; 410–810 mrem)
	3 mo	0.017 mGy/MBq (0.063 rad/mCi)	3.1–6.3 mGy (0.31–0.63 rad; 310–630 mrem)
	6 mo	0.0075 mGy/MBq (0.028 rad/mCi)	1.4–2.8 mGy (0.14–0.28 rad; 140–280 mrem)
	9 mo	0.0068 mGy/MBq (0.025 rad/mCi)	1.3–2.5 mGy (0.13–0.25 rad; 130–250 mrem)
^{99m}Tc-MDP†	Early	0.0061 mGy/MBq (0.023 rad/mCi)	1.1–2.3 mGy (0.11–0.23 rad; 110–230 mrem)
	3 mo	0.0054 mGy/MBq (0.020 rad/mCi)	1.0–2.0 mGy (0.10–0.20 rad; 100–200 mrem)
	6 mo	0.0027 mGy/MBq (0.010 rad/mCi)	0.5–1.0 mGy (0.050–0.10 rad; 50–100 mrem)
	9 mo	0.0024 mGy/MBq (0.0089 rad/mCi)	0.44–0.89 mGy (0.044–0.089 rad; 44–89 mrem)

*No information about possible placental crossover of this compound was available.
†Information about possible placental crossover of this compound was available and was considered in estimates of fetal doses.

TABLE 1D
Reported Relationships with Industry and Other Entities

Workgroup member	Reported relationships
Cohen, Erica	None
Donohoe, Kevin	None
Giammarile, Francesco	None
Grady, Erin	None
Greenspan, Bennett	None
Henkin, Robert	None
Millstine, John	None
Smith, Gary	None
Srinivas, Sandy	None

Radiation therapy (*90*): the use of high-energy waves or particles of radiation to kill cancer cells and shrink tumors.

Restaging (*90*): a reevaluation of the extent of disease, after a round of treatment, that provides the basis for ongoing management. The results of restaging may indicate the need to alter a patient's treatment.

SNMMI: Society of Nuclear Medicine and Molecular Imaging.

SPECT: single-photon emission computed tomography, which involves injection of a radiotracer and detection by a γ-camera. The camera rotates over a 360° arc around the patient, allowing for reconstruction of an image in 3 dimensions.

SPECT/CT: a combination device that provides detail on both function and anatomy by superimposing the precise location of abnormal metabolic activity (from SPECT) on a detailed anatomic image (from CT).

TNM (*90*): tumor–node–metastasis, the staging system of the American Joint Committee on Cancer. This system examines the size and location of the tumor, whether cancer cells have spread to lymph nodes near the tumor, and whether the tumor has spread to other parts of the body. The letter T plus a number (0 to 4) describes the size and location of the tumor, including how far it has grown into nearby tissues. A larger tumor or one that has grown more deeply into the surrounding tissue is given a higher number. For some types of cancer, lowercase letters such as "a," "b," or "m" (multiple) are added to the T stage to provide more detail. The letter N plus a number (0 to 3) describes whether cancer is in the lymph nodes and, in some types of cancer, how many of them contain cancer. Most often, the more lymph nodes with cancer, the larger the number assigned. However, for some types of tumors, it is the location of the cancerous lymph nodes that determines the N stage. The letter M indicates whether the cancer has metastasized—M0 if it has not and M1 if it has.

APPENDIX C: 2010 SNMMI PROCEDURE STANDARD FOR ^{18}F-NAF PET/CT BONE SCANS (*86*)

A summary of the 2010 SNMMI procedure standard for ^{18}F-NaF PET/CT bone scans can be found in Table 1C.

APPENDIX D: DISCLOSURES AND CONFLICTS OF INTEREST (COIs)

SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 2A. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-mo period. In addition, if an external reviewer was either the principle investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC. All external reviewers were asked about any potential COI.

APPENDIX E: PUBLIC COMMENTARY

The workgroup solicited information from all communities through the SNMMI website and through direct solicitation of

SNMMI members. The comments and input helped to shape the development of these AUC on the appropriate use of bone scintigraphy for prostate cancer and breast cancer.

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