Appropriate Use Criteria for Prostate-Specific Membrane Antigen PET Imaging

Hossein Jadvar[1], Jeremie Calais[2], Stefano Fanti[3], Felix Feng[4], Kirsten L. Greene[5], James L. Gulley[6], Michael Hofman[7], Bridget F. Koontz[8], Daniel W. Lin[9], Michael J. Morris[10], Steve P. Rowe[11], Trevor J. Royce[12], Simpa Salami[13], Bital Savir-Baruch[14], Sandy Srinivas[15], and Thomas A. Hope[16]

[1]Department of Radiology, University of Southern California, Los Angeles, California; [2]Department of Molecular and Medical Pharmacology, University of California, Los Angeles, California; [3]University of Bologna, Bologna, Italy; [4]Department of Radiation Oncology, University of California, San Francisco, California; [5]Department of Urology, University of Virginia, Charlottesville, Virginia; [6]National Institutes of Health, Bethesda, Maryland; [7]Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Center, Melbourne, Victoria, Australia and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria Australia; [8]Department of Radiation Oncology, Duke University, Durham, North Carolina; [9]Department of Urology, University of Washington, Seattle, Washington; [10]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, New York; [11]Department of Radiological Sciences, Johns Hopkins University, Baltimore, Maryland; [12]Department of Radiation Oncology, University of North Carolina, Chapel Hill, North Carolina; [13]Department of Urology, University of Michigan, Ann Arbor, Michigan; [14]Department of Radiology, Loyola University, Maywood, Illinois; [15]Department of Medicine (Oncology), Stanford University, California; and [16]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California

Prostate cancer is the most common cancer diagnosis in men in the United States and a leading cause of cancer-related morbidity and mortality (1). It can exist along a wide spectrum of aggressiveness and severity, from indolent, very-low-risk, localized prostate cancer to life-threatening, very-high-risk, metastatic prostate cancer. For a newly diagnosed patient in a given clinical state, especially early in the disease, the spectrum of appropriate therapeutic options may range from no intervention to multimodality therapy. Accurate assessment of the extent of disease (e.g., metastatic vs. localized prostate cancer) is essential for guiding treatment decisions. Decision making for the clinical use of imaging and for the development of new imaging technology can both be organized by the framing principles outlined in Prostate Cancer Working group 3 (2).

Imaging plays a critical role in that assessment, which has traditionally been done in men at high risk for metastatic disease using a ^{99m}Tc-methylene diphosphate bone scan and CT (3). Significant advances toward developing more sensitive imaging techniques for detecting the extent of prostate cancer include PET radiopharmaceuticals. Although useful across a wide variety of cancer types, ^{18}F-FDG PET has had limited applicability in prostate cancer staging (4). Novel radiopharmaceuticals such as ^{18}F-fluciclovine and choline PET have been used increasingly in the biochemical recurrence (BCR) setting but have limited specificity (5,6).

INTRODUCTION

Prostate-Specific Membrane Antigen (PSMA) PET

The increasing use of radiopharmaceuticals that target the PSMA is based on growing scientific evidence that supports their favorable imaging performance. Many PSMA-targeted imaging agents are being evaluated, and 2 are currently approved by the U.S. Food and Drug Administration: ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. Additional agents are being evaluated in phase III trials in the United States, including ^{18}F-PSMA-1007 (NCT04239742 and NCT04487847), ^{18}F-rhPSMA-7.3 (NCT04186819 and NCT04186845), ^{18}F-CTT1057 (NCT04838626), ^{68}Ga-PSMA-R2 (NCT03490032), and ^{64}Cu-SAR-bisPSMA (NCT04868604). Although there may be small differences between each radiopharmaceutical, there is no evidence to date that one specific radiopharmaceutical has improved diagnostic characteristics compared with another (7,8). For the purpose of this appropriate use criteria (AUC) document, we will treat all PSMA PET radiotracers as equivalent and refer to them as a class (e.g., PSMA PET).

Safety and Dosimetry of PSMA PET

Given the subpharmacologic mass dose and high specific activity administered, PSMA PET radiotracers, similar to other radiopharmaceuticals, have an excellent safety profile. For ^{68}Ga-PSMA-11, the proPSMA study showed no adverse events, and a safety evaluation from 2 prospective multicenter trials reported only minor changes in vital signs such as blood pressure and heart rate, with no medical interventions required (9). A similar safety profile has been observed with ^{18}F-DCFPyL, with no adverse events attributable to the radiotracer reported from the first-in-human trial (10).

The dosimetry for both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL is comparable to that of other radiotracers in terms of whole-body exposure (Table 1). ^{68}Ga-PSMA-11 has a calculated effective dose of 0.017 mSv/MBq, equating to 4.4 mSv for a 259 MBq (7 mCi) injected dose, with the highest uptake organ being the kidney at 0.37 mGy/MBq (11). The total effective dose of ^{18}F-DCFPyL per mCi is similar to that of ^{68}Ga-PSMA-11 per mCi, coming in at 0.011 mSv/MBq, equating to 4.3 mGy for an injected dose of

370 MBq (10 mCi) (*10,12*). The highest exposure organ for ^{18}F-DCFPyL is the kidney, with a dose of 0.123 mGy/MBq. Although the differences in dosimetry partly dictate different injected doses (generally 148–259 MBq [4–7 mCi] for ^{68}Ga-PSMA-11 vs. 296–370 MBq [8–10 mCi] for ^{18}F-DCFPyL), those differences are also due to the different physical half-lives of the radionuclides used (68 min for ^{68}Ga vs. 109 min for ^{18}F) (*13*).

PSMA PET Imaging Protocols and Reporting

The recommended imaging protocols for ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL are similar. In short, the administered activity, based on the prescribing information, is 111–259 MBq (3–7 mCi) for ^{68}Ga-PSMA-11 and 296–370 MBq (8–10 mCi) for ^{18}F-DCFPyL. The uptake time for ^{68}Ga-PSMA-11 is 50–100 min and for ^{18}F-DCFPyL is 60 min. A helpful resource for PSMA-11 PET is provided in the joint European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure guidelines (*14*). Delayed imaging can be valuable in patients with high bladder urine activity in selected cases. Some sites use furosemide or oral hydration, which can be useful in some cases to decrease bladder activity but is limited by potential incontinency and patient compliance. Similarly, the use of iodinated contrast in the urogram phase may be beneficial in some cases, particularly for separating ureteric activity from small nodal abnormalities and characterizing local recurrence (*15*). PSMA PET can be performed with both PET/CT and PET/MRI, although the added value of PET/MRI is yet to be delineated. Overall, PSMA PET imaging from PET/MRI and PET/CT is equivalent, with a possible improvement in local disease detection with PET/MRI (*16*). The CT protocol may be devised according to the clinical requirements, which may comprise low-dose CT (for anatomic correlation and attenuation correction) or diagnostic-dose CT with or without intravenous or oral contrast agents. As with any new modality, training and experience is required to appreciate normal patterns, pitfalls, and typical and atypical patterns of disease spread. For reporting, E-PSMA standardized reporting guidelines provide a consensus statement from a panel of experts in structured reports to harmonize diagnostic interpretation criteria (*17*).

Consideration of Prognostic Factors in Patient Selection

Prostate cancer is segmented into discrete clinical states, which now have regulatory recognition in the approval of both drugs and imaging agents (*2*). Each state has specific risk-stratifying criteria that have been validated for predicting not only state-to-state transitions, but also the risk of dying of disease. These disease-related risks must account for the health and viability of the patient, as comorbid disease (i.e., competing risks) in an older patient population may represent more risk than prostate cancer.

For men with localized disease, risk stratification has long been dependent on a variety of factors, including Gleason score/Grade Group, pretreatment prostate-specific antigen (PSA), and local extent of disease. One of the most commonly used is the D'Amico risk model, which predicts the risk of biochemical failure after definitive local therapy (*18*). Another approach has been to incorporate these factors into nomogram-based models for ease of clinical use, which now exist for preoperative patients, postoperative patients, and preradiation patients when newly diagnosed with localized disease (*19–21*). More recently, genomic classifiers have been introduced that can further risk stratify patients to refine risk identification more granularly than prior risk models could, both

TABLE 1
Dosimetry for ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL

	^{68}Ga-PSMA-11	^{18}F-DCFPyL
Organ		
Kidneys (mSv/MBq)	0.371	0.123
Liver (mSv/MBq)	0.041	0.037
Spleen (mSv/MBq)	0.065	0.027
Bladder wall (mSv/MBq)	0.098	0.007
Dose		
Effective dose (mSv/MBq)	0.017	0.011
Typical injected activity		
MBq	259	370
mCi	7	10
Estimated effective dose per scan (mSv)	4.4	4.3

before primary therapy and in the postoperative setting, in determining the need for adjuvant or salvage treatment (*22–25*). Blood-based tests of kallikrein levels can also offer robust predictions of aggressive disease and distant metastases (*26*).

Risk stratification schema for biochemically relapsed patients after definitive initial therapy have used characteristics such as original distribution of disease, Gleason score/Grade Group, time from primary therapy to BCR, PSA doubling time (PSADT), and trigger PSA levels to predict freedom from disease, metastasis-free survival, and overall survival (*27–29*). PSADT has been key to understanding the likelihood of developing metastatic disease in the rising PSA population who have relapsed while receiving androgen deprivation therapy (ADT) (nonmetastatic castration-resistant prostate cancer [nmCRPC or M0 CRPC]) (*30*). As large-scale genomic profiling of patients with prostate cancer is now standard in men with a history of familial genetic disorders, high-grade disease, or metastatic disease, the implications of these findings for the clinical course of those with DNA repair defects or high microsatellite instability disease will need to be better defined and ultimately incorporated into future prognostic models.

For the purpose of this AUC document, we have chosen to mirror National Comprehensive Cancer Network (NCCN) definitions for patients with localized disease and have chosen not to incorporate risk stratification into the selection of imaging for recurrent patients. It is important that the individual patient factors described above be incorporated into the decision about when to image patients with PSMA PET.

PSMA PET and Stage Migration

Whether one uses the TNM staging system or the disease states model, the presence of metastatic disease indicates a clinically distinct entity with clear clinical treatment and prognostic implications. However, the bedrock of clinical data that supports this comes from less sensitive and specific techniques such as CT and bone scintigraphy. The more sensitive and more specific PSMA PET has introduced a lead-time bias known as the "Will Rogers phenomenon" (*31*). This phenomenon happens when the disease state of patients is reclassified on the basis of more sensitive tools (*31,32*) and may happen with changes in staging classification systems (*33*). For example, PSMA PET M1 disease was detected in

45% of early CRPC (PSA $\leq$ 3 ng/mL) (*34*) and 55% of high-risk nmCRPC (PSA > 2 ng/mL, PSADT $\leq$ 10 mo or Gleason score $\geq$ 8) (*35,36*). Merely identifying metastasis earlier with a more sensitive measure can lead to longer survival with this newly defined metastatic disease without affecting the natural history of the patient. This lead-time bias affects prognostic values and limits cross-trial comparisons that use different techniques unless there is also a common set of tools used in the studies on which to anchor the results (e.g., bone scintigraphy and CT).

Oligometastatic Disease and the Role of PSMA PET

Oligometastatic disease is defined as limited metastatic sites and locations, with consensus publications recommending an upper limit of either 3 or 5 lesions in up to 2 organ types (*37–39*). This disease has long been recognized, but has recently been critically scrutinized as an opportunity to change the natural history of metastatic prostate cancer (*37,40*). For example, the STAMPEDE M1 RT trial has changed practice after finding that prostate irradiation improves failure-free and overall survival in men with 3 or fewer metastases on bone scan (*41*). Notably, the improved specificity of PSMA PET may reclassify some oligometastatic bone scan findings as false-positive and downstage patients with these findings to M0 (*42*).

The advent of molecular imaging has allowed patients in BCR to be reclassified as PET-oligometastatic. Several PET tracers (^{18}F-NaF, ^{11}C-choline, and ^{18}F-fluciclovine) are currently recommended by the NCCN for imaging, although the guideline also notes that "the Panel remains unsure of what to do when M1 is suggested by these PET tracers but not on conventional imaging" (*43*). ^{68}Ga-PSMA-11 had higher detection rates than ^{18}F-fluciclovine did in a prospective trial of these 2 PET tracers (*44*), and with U.S. Food and Drug Administration approval of PSMA PET, PSMA radiopharmaceuticals are anticipated to be added to treatment guidelines.

There has been increased interest in metastasis-directed therapy (MDT), often ablative-dose radiation, to delay systemic therapy with earlier detection of metastatic disease. The phase II STOMP trial randomized men with BCR and 1–3 choline PET-detected metastases to observation versus MDT, finding a significant improvement in ADT-free survival and delay in development of castration resistance with MDT (*45*). POPSTAR, a single-arm pilot study, demonstrated a 48% 2-y freedom from ADT using ^{18}F-NaF PET/CT to direct MDT (*46*). The ORIOLE trial, phase II study reported a 6-mo progression-free survival (PFS) of 95% with PSMA PET–guided MDT versus 62% with conventional imaging–guided MDT (*47*). Recently developed larger randomized phase III trials such as ECOG-ACRIN 8191 (NCT04423211), PEACE-V (STORM, NCT03569241), *VA STARPORT* NCT04787744, NCT04619069, *PRESTO* NCT04115007, and *PILLAR* NCT03503344, which are evaluating the roles of MDT and ADT for oligometastatic disease, rely on PET imaging for identification of this new risk group and targeting of treatment.

PSMA PET and ADT

The expression of PSMA is known to be modulated by treatments that inhibit the androgen receptor (AR). In patients with hormone-sensitive metastatic prostate cancer, AR inhibition may rapidly decrease PSMA expression in patients. However, in patients with hormone-resistant disease, AR blockers such as enzalutamide and bicalutamide may increase expression of PSMA (*48–51*). Because of the complex modulation of PSMA

expression, the clinical use of PSMA PET imaging to evaluate therapy response in the setting of ADT is not well defined. One retrospective study showed that patients with BCR had a higher detection rate while receiving ADT (*52*). Although assessment criteria for response to systemic therapy were proposed, the clinical impact of PSMA expression due to AR inhibition remains unclear (*53*). Accordingly, the intensity of uptake alone should be used with caution when assessing response to treatment.

Studies of PSMA-Targeted Radioligand Therapy That May Affect Scenarios

Current clinical indications for PSMA PET primarily revolve around the detection of metastatic disease at initial staging before definitive therapy and at the time of BCR. PSMA PET can be used as a biomarker for patient selection for PSMA-targeted radioligand therapy (RLT). The results of the TheraP trial (*54*) and the VISION trial (NCT03511664), as well as the potential subsequent approval of ^{177}Lu-PSMA-617, will support the use of PSMA in patients with metastatic CRPC for the purpose of patient selection. Additional studies in earlier stages before chemotherapy (PSMAfore NCT04689828, SPLASH NCT04647526, ARROW NCT03939689) and in castration-sensitive prostate cancer (CSPC) (PSMAddition NCT04720157, UpFrontPSMA) will further expand the number of patients who may benefit from PSMA PET. Optimal PSMA PET criteria for patient selection are not yet well established and studies are warranted. ^{18}F-FDG PET/CT may provide additional value in identifying ^{18}F-FDG–positive, PSMA-negative sites of disease (*54*).

METHODOLOGY

Workgroup Selection

The experts of the AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health-care providers with substantive knowledge of prostate cancer. In addition to SNMMI members, international representatives from the American College of Nuclear Medicine (ACNM), American College of Physicians (ACP), American Society of Clinical Oncology (ASCO), American Urological Association (AUA), Australian and New Zealand Society of Nuclear Medicine (ANZSNM), and EANM were included in the workgroup. Sixteen physician members were ultimately selected to participate and contribute to the resulting AUC. A complete list of workgroup participants can be found in Appendix A. Appendix B is a summary of definitions of terms and acronyms, and Appendix C provides the disclosures and conflicts of interest statement.

AUC Development

The process for developing AUC was modeled after the RAND/UCLA Appropriateness Method (*55,56*) and included the development of a list of common scenarios encountered in the management of patients with prostate cancer, a systematic review of evidence related to these scenarios, and the 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 (*57*). 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 these AUC based on traditional outcome measures would have

been optimal, but a literature review did not find significant numbers of articles with this information.

Scope and Development of Clinical Scenarios (or Indications)

To begin this process, the workgroup discussed various potential clinical scenarios for which the use of PSMA PET might be considered. The scope of this workgroup was to focus on the appropriate use of PSMA PET, specifically for the diagnosis and management of prostate cancer. For all scenarios, the relevant populations were men of any age, race, or socioeconomic status who had prostate cancer.

The workgroup identified 11 scenarios for patients with prostate cancer. The scenarios are intended to be as representative of the relevant patient population as possible for development of AUC. 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

ASCO conducted a systematic review to develop a comprehensive clinical practice guideline for optimum imaging strategies for advanced prostate cancer, and the same systematic review was used by this AUC workgroup (58). The inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. A protocol for each systematic review defined parameters for a targeted literature search. Additional parameters included relevant study designs, literature sources, types of reports, and prespecified inclusion and exclusion criteria for the literature identified. The protocol for this guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee's Genitourinary Cancer Guideline Advisory Group. and the Cochrane Collaboration Library electronic databases (with or without meeting abstracts) were searched for evidence that reported on outcomes of interest. Since the publication of the ASCO clinical practice guideline (58), we have updated this review to include recent literature.

Rating and Scoring Process

In developing these AUC for PSMA PET, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances the risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics" (59).

At the beginning of the process, workgroup members convened virtually to develop the initial scenarios. 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 PSMA PET for each of the identified scenarios and provide an appropriateness score for each scenario. 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 of 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 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. After 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 of 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores of 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores of 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and is generally 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. In addition, 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.

CLINICAL SCENARIOS AND AUC SCORES

Clinical scenarios for the use of PSMA PET and final AUC scores in patients with prostate cancer are presented in Table 2.

Initial Staging

PSMA PET imaging has a higher accuracy in the initial staging evaluation of men with newly diagnosed prostate cancer than conventional imaging (bone scan and CT) does. In the multicenter randomized ProPSMA trial of conventional imaging versus ^{68}Ga-PSMA-11 PET for staging of men with high-risk prostate cancer, PSMA PET had a 27% greater accuracy than conventional imaging did (60). In another study of men with high-risk prostate cancer undergoing radical prostatectomy, ^{18}F-DCFPyL PET/CT demonstrated high specificity (median 97.9%) for detection of pelvic lymph node metastasis, although with a limited sensitivity of 40% (61). These data support the utility of using PSMA PET imaging to facilitate accurate risk stratification in men with newly diagnosed high-risk prostate cancer.

Scenario 1: Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) to evaluate for targeted biopsy and detection of intraprostatic tumor (Score 3 – Rarely Appropriate). Currently, evidence is limited for the use of PSMA PET for patients before the pathologic diagnosis of prostate cancer. There may be some settings, for example, when MRI results are inconclusive or biopsy results are negative (62), in which further supportive evidence may emerge to support the use of PSMA PET in this setting, although such evidence is currently lacking. Moreover, because PSMA expression is highly heterogeneous, in some cases, the results may be negative both in primary tumors and metastases (63). The multicenter, prospective, cross-sectional clinical trial PRIMARY will provide further evidence on the added value of PSMA PET to multiparametric MRI for detecting clinically significant prostate cancer in men

TABLE 2
Clinical Scenarios for PSMA PET

Scenario no.	Description	Appropriateness	Score
1	Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) evaluated for targeted biopsy and detection of intraprostatic tumor	Rarely appropriate	3
2	Patients with very-low, low-, and favorable intermediate-risk prostate cancer	Rarely appropriate	2
3	Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer	Appropriate	8
4	Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging	Appropriate	8
5	Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging	May be appropriate	4
6	PSA persistence or PSA rise from undetectable level after radical prostatectomy	Appropriate	9
7	PSA rise above nadir after definitive radiotherapy	Appropriate	9
8	PSA rise after focal therapy of the primary tumor	May be appropriate	5
9	nmCRPC (M0) on conventional imaging	Appropriate	7
10	Posttreatment PSA rise in the mCRPC setting	May be appropriate	6
11	Evaluation of response to therapy	May be appropriate	5

undergoing initial biopsy for suspected prostate cancer (*64*). With the current paucity of evidence in this clinical space, the panel recommended PSMA PET as rarely appropriate in this clinical scenario.

Scenario 2: Patients with very-low, low-, and favorable intermediate-risk prostate cancer (Score 2 – Rarely Appropriate). The NCCN guidelines for prostate cancer stratify the initial risk for clinically localized disease as very low, low, intermediate (favorable, unfavorable), high, and very high on the basis of several clinical and pathologic features (*3*). For very-low, low-, and intermediate- (favorable) risk disease, imaging is generally not indicated and may be considered only in certain circumstances. Moreover, observation or active surveillance is often the preferred initial management for patients with these risk levels, depending on expected survival. In accordance with the NCCN guidelines, the paucity of relevant evidence, and the morbidity and financial cost associated with screening for clinically insignificant prostate cancer, the panel recommended PSMA PET as rarely appropriate in this clinical scenario.

Scenario 3: Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer (Score 8 – Appropriate). To align with the NCCN categories and because of the potentially important role of imaging in depicting the extent of disease, the panel decided to include unfavorable intermediate- along with high-risk and very-high-risk categories in relation to the relevance of PSMA PET. There is supportive evidence in this clinical setting that PSMA PET is more informative than conventional imaging and so may be considered the "new" conventional imaging. Prospective trials of both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL have demonstrated a sensitivity of 40% for PSMA PET for the detection of pelvic node metastasis in comparison with pathology at the time of radical prostatectomy and pelvic node dissection (*65,66*). In addition, the proPSMA randomized trial compared PSMA PET and conventional imaging for staging high-risk prostate cancer before curative intent surgery or radiotherapy. PSMA PET was more accurate than conventional imaging, with fewer equivocal

imaging results, lower radiation exposure to the patient, and greater treatment impact (*60*). Moreover, a decision tree analysis of the cost per accurate diagnosis demonstrated that PSMA PET/CT was also less costly than conventional imaging for detection of disease spread (*67*). In view of supportive high-level evidence, the panel recommended PSMA PET as appropriate in this clinical scenario.

Scenario 4: Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging (Score 8 – Appropriate). The panel acknowledges that clinicians may continue to use conventional imaging in their management algorithms and that it will take some time before new-generation imaging such as PSMA PET is adopted as first-line imaging. Randomized trials such as ProPSMA have demonstrated the superiority of PSMA PET over conventional imaging in staging high-risk localized prostate cancer. PSMA PET may demonstrate sites of disease that are not identified or are equivocal on conventional imaging. Moreover, because of the higher sensitivity of PSMA PET, metastatic disease will be detected earlier. In addition, oligometastatic disease as identified on conventional imaging may in fact be polymetastatic disease, which can have an impact on subsequent clinical management decisions (e.g., MDT vs. systemic therapy) (*45,47*). In keeping with the supportive evidence in this clinical space, the panel recommended PSMA PET as appropriate in this clinical scenario.

Scenario 5: Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging (Score 4 – May Be Appropriate). There is little evidence that PSMA PET adds additional value in the setting of known widespread metastatic disease identified on conventional imaging, given that the detection of additional disease sites will likely have no major clinical management implications. A phase 3 trial on metastatic CSPC that compares ^{177}Lu-PSMA-617 and AR therapy is currently under way (NCT04689828). Until approval of PSMA RLT in this setting is obtained, the panel recommended PSMA PET as may be appropriate for this clinical scenario.

Biochemical Recurrence

BCR is experienced by about 40% of patients who undergo local definitive therapy within 10 y of surgery (68). After successful radical prostatectomy, the PSA level is anticipated to fall to undetectable levels; otherwise, the condition is termed PSA persistence. After prostatectomy, BCR is defined as a PSA rise of $\geq$ 0.2 ng/mL measured at 6–13 wk after surgery and confirmed by a second determination of the PSA level of > 0.2 ng/mL (69). In patients who receive definitive radiation therapy, BCR is defined as a PSA rise of $\geq$ 2 above the nadir achieved after radiotherapy, regardless of ADT (70). BCR signals locally recurrent disease, metastatic disease, or both. Accurate identification of disease sites on imaging allows for the selection of an appropriate intervention.

The sensitivity of conventional imaging is limited in localizing disease in many patients, with either falsely negative findings or underestimation of disease burden, compared with that of new-generation imaging techniques. Evidence for the utility of PSMA PET in the setting of BCR is robust, including prospective studies with ^{68}Ga-PSMA-11 (44,71) and ^{18}F-DCFPyL (72), which have demonstrated high patient-level detection rates, positive predictive values, and sensitivities for the localization of disease in the setting of BCR after definitive therapy.

Scenario 6: PSA persistence or PSA rise from undetectable level after radical prostatectomy (Score 9 – Appropriate). The consensus was that PSMA PET should be used to localize disease in patients with BCR or persistence after radical prostatectomy. There was some debate about whether a PSA threshold should be used to determine the time at which patients should be imaged with PSMA PET, and it was decided that a threshold should not be defined. One reason is that the absolute PSA value does not include consideration of other risk factors for disease such as PSADT or genomic risk scores. In addition, salvage treatments are often used at PSA values below the standard AUA definition of BCR (69), and PSMA PET has been shown to localize recurrent disease at lower PSA levels. The panel agreed that patient-specific risk factors, as discussed above, should determine whether or not PSMA PET should be considered. The high sensitivity of PSMA PET in localizing recurrent disease has also been shown to significantly affect clinical management (73–75). Trials are currently under way to determine whether this change in management improves patient outcomes (76,77). The panel recommended PSMA PET as appropriate in this clinical scenario on the basis of high-quality supportive evidence.

Scenario 7: PSA rise above nadir after definitive radiotherapy (Score 9 – Appropriate). The supportive evidence for this scenario is similar to that presented for Scenario 6. Also similar to that for Scenario 6, the group consensus was to not limit the utility of PSMA PET to only BCR as defined by the ASTRO-Phoenix criteria, because treatment of patients frequently occurs before the threshold criteria for BCR is met. Additional patient-specific factors beyond the PSA level should be considered, including PSADT. The panel recommended PSMA PET as appropriate in this clinical scenario on the basis of high-quality supportive evidence.

Scenario 8: PSA rise after focal therapy of the primary tumor (Score 5 – May Be Appropriate). There was significant debate regarding this indication. Overall, it was acknowledged that there are scarce data on using PSMA PET in this setting. In addition, after focal therapy, it is unclear what the definition of biochemical failure is, given that normal prostate parenchyma is present. Finally, as most patients who are treated with focal therapies have low-grade disease, it was not clear whether patients should be staged using PSMA PET. Therefore, the panel was not fully supportive of this indication. They

recommended that the role of PSMA PET should be determined from the initial risk stratification provided in indications 1–5.

Castration-Resistant Prostate Cancer

CRPC is defined as progressive disease despite low levels of testosterone; it can exist with or without metastases. The modalities available for assessment include bone scans to assess osseous metastases and CT and MRI to assess nodal, soft-tissue, and visceral metastases. ^{18}F-FDG PET scans are not recommended by NCCN for staging prostate cancer but are recognized by the Centers for Medicare and Medicaid Studies as having a possible role in assessing response to therapy in metastatic disease. Conventional imaging is used when symptoms change, when there is a change in systemic therapy to establish a new baseline, or to assess response to therapy in addition to serum PSA levels. Assessing response in bone-only disease continues to be challenging (58,78). At this time, ^{18}F-fluciclovine PET is not used in CRPC.

Many life-prolonging therapies have been approved in CRPC. For patients with nmCRPC (M0 CRPC), 3 next-generation androgen axis inhibitors (enzalutamide, apalutamide, and darolutamide) have been approved (79–81). Several classes of drugs are available for metastatic castration-resistant prostate cancer (mCRPC): hormonal agents (enzalutamide and abiraterone), chemotherapies (docetaxel and cabazitaxel), immunotherapies (sipuleucel-T and pembrolizumab), poly(-ADP-ribose) polymerase inhibitors (olaparib and rucaparib), and ^{223}Ra dichloride for patients with bone-dominant disease. Radioligand therapies such as ^{177}Lu-PSMA-617 are likely to be approved soon in this space. Optimum sequencing of these agents is unclear. Overall, given that these therapies are systemic, the role of imaging is to evaluate progression rather than localize metastatic disease.

Scenario 9: nmCRPC (M0) on conventional imaging (Score 7 – Appropriate). PSMA PET has been studied in the M0 CRPC population. Nearly all patients who were categorized as M0 CRPC on the basis of conventional imaging had PSMA-positive disease and 55% were categorized as M1 by PSMA PET (36). There was some discussion by the panel regarding final scoring for this scenario, primarily because it was unclear how PSMA PET would change management, as all drugs approved in the M0 CRPC space are also approved for the metastatic setting (79,80). Overall, there is an appreciation that external beam radiation is being used to treat patients with oligometastatic CRPC, with some preliminary data on its effectiveness (82); therefore, PSMA PET is important for correctly characterizing disease in these patients. On this basis, the panel decided to support PSMA PET as appropriate in this clinical scenario.

Scenario 10: Posttreatment PSA rise in the mCRPC setting (Score 6 – May Be Appropriate). There was general consensus that PSMA PET provides improved staging in patients with mCRPC compared with that of conventional imaging, but it was unclear how this improved staging would result in improved management of patients with metastatic disease demonstrated on conventional imaging. Although the panel acknowledged the role of MDT in the M0 CRPC population in Scenario 9, in the mCRPC setting, this role was less clear.

The VISION trial, which randomized PSMA RLT to the best standard of care, showed that radiographic PFS was improved to 8.7 mo with PSMA RLT versus 3.4 mo for standard of care (hazard ratio 0.40), with an associated improvement in overall survival (15.3 vs. 11.3 mo, respectively, hazard ratio 0.62) (83). The TheraP trial (PSMA RLT vs. cabazitaxel) demonstrated that PSMA RLT was associated with higher PSA response, longer PFS, and fewer grade 3 or 4 adverse events than with cabazitaxel

(*54*). With the anticipated approval of PSMA-based RLTs, given the results of the VISION study, PSMA PET will likely have an important role in this disease setting, and the scoring of this indication will then be revisited. However, at this time, the panel recommended PSMA as may be appropriate for this clinical scenario.

Scenario 11: Evaluation of response to therapy (Score 5 – May Be Appropriate). The panel agreed that data are limited regarding how PSMA PET should be used for response assessment. Although there are preliminary response assessment criteria (*84*), they have not been validated in clinical trials. With the approval of PSMA-based RLTs, PSMA PET may have an important role in assessing response. Also important is that therapies that target the androgen axis affect PSMA expression, which may not correlate with response, confounding the ability for PSMA PET to be used as a response biomarker (*51,85*). The effect of various other current and emerging therapies on PSMA expression will also need additional studies. At this time, the panel recommended PSMA as may be appropriate for this clinical scenario.

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 (*86*). For example, several authors of papers included in our metaanalysis suggested that the AUC might lead to denial of reimbursement for needed imaging services because of incomplete AUC or lack of strong evidence for a particular procedure (87). It is hoped that besides providing recommendations for the appropriate use of PSMA PET, this document will demonstrate gaps in the literature and subsequently encourage new investigations to address these gaps.

Integration of 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 (*87,88*). 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 the AUC current remains a large obstacle to the effective use of the clinical decision support model.

QUALIFYING STATEMENTS

Study/Evidence Limitations

Although a large body of literature focuses on PSMA PET, the workgroup found the body of medical literature regarding the use of PSMA PET to be limited when rigorous inclusion criteria were applied to the systematic literature review. Most articles did not use pathologic findings or patient follow-up to assess accuracy, and so sensitivity and specificity measurements were often limited. Information was also scarce on the role of PSMA PET in patients with low-grade disease at initial staging and in patients with CRPC. In addition, little data were available on how PSMA PET can be used to predict and evaluate response to RLT. Preliminary studies have shown that PSMA PET patterns are prognostic of outcome after radical prostatectomy (*89,90*), after stereotactic radiation therapy (SRT), or after oligo-MDT (*91*). Prospective randomized studies powered for clinical outcome that use PSMA PET will give guidance to clinicians on how to act on the PSMA PET information. PSMA PET may improve patient outcomes by better definition of the extent and location of the disease (treatment planning), but more

important, by acting as a biomarker tool for patient selection for specific treatment. The positive randomized trial EMPIRE-1 (standard salvage radiotherapy vs. fluciclovine PET-based SRT) provides some evidence that patient selection and treatment planning-based PET imaging can improve patient clinical outcome (*76*). Similar or even superior results can be expected with PSMA PET. Several randomized studies are ongoing for initial therapy (NCT04457245 and NCT04557501), salvage therapy (NCT03582774, NCT035252880, and NCT04794 777), FACBC-based versus PSMA-based SRT (NCT03762759), and oligometastatic-directed therapy (standard systemic therapy vs. systemic therapy + PSMA-based oligo-MDT) in CSPC (NCT04787744, NCT04619069, NCT04115007) and CRPC (NCT03503344).

Implementation of This AUC Guidance

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

SNMMI has developed a multipronged approach to disseminate the AUC for PSMA PET in prostate cancer 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 and for referring physicians and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of PSMA PET, as well as some cases in which the results of PSMA PET are equivocal.

Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on these AUC, factsheets, and other didactic materials will be made available on the SNMMI webpage dedicated to the PSMA PET 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 PSMA PET AUC for both Apple and Android platforms. Mobile applications are becoming increasingly popular in the health-care industry and can be used to distribute updates to all users.

In addition to these activities, SNMMI will 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 Hossein Jadvar, MD, PhD, MPH, MBA (Cochair), University of Southern California, Los Angeles, CA (SNMMI); Jeremie Calais, MD, University of California, Los Angeles, CA (SNMMI); Stefano Fanti, MD, University of Bologna, Bologna, Italy (EANM); Felix Feng, MD, University of California, San Francisco, CA; Kirsten L. Greene, MD, University of Virginia, Charlottesville, VA (AUA); James L. Gulley, MD, PhD, National Institutes of Health, Bethesda, MD (ACP); Michael Hofman, MD, Peter MacCallum Cancer Center and University of Melbourne, Melbourne, Victoria, Australia (ANZSNM); Bridget F. Koontz, MD, Duke University, Durham, NC; Daniel W. Lin, MD, University of Washington, Seattle, WA (AUA); Michael J. Morris, MD, Memorial Sloan Kettering Cancer Center,

New York, NY(ASCO); Steve P. Rowe, MD, PhD, Johns Hopkins Medical Institutions, Baltimore, MD (SNMMI); Trevor J. Royce, MD, MPH, University of North Carolina, Chapel Hill, NC; Simpa Salami, MD, University of Michigan, Ann Arbor, MI (AUA); Bital Savir-Baruch, MD, Loyola University, Maywood, IL (ACNM); Sandy Srinivas, MD, Stanford University, Stanford, CA (ASCO); and Thomas A. Hope, MD (Cochair), University of California, San Francisco, CA (SNMMI).

External Reviewers

The external reviewers are Andrei H. Iagaru, MD (Stanford University, Stanford, CA); Ambros J. Beer, MD (Ulm University Hospital, Ulm, Germany); Francesco Ceci, MD, PhD (European Institute of Oncology, Milan, Italy); Steve Y. Cho, MD (University of Wisconsin-Madison, WI); Wolfgang P. Fendler, MD (University of Duisburg, Essen, Germany); and Morand R. Piert, MD (University of Michigan, Ann Arbor, MI).

SNMMI

The supporting staff from SNMMI are Sukhjeet Ahuja, MD, MPH, Sr. Director, Health Policy & Quality Department; Teresa Ellmer, MIS, CNMT, Senior Program Manager, Health Policy & Quality Department; and Julie Kauffman, Program Manager, Health Policy & Quality Department.

APPENDIX B: SUMMARY OF DEFINITIONS OF TERMS AND ACRONYMS

ACNM: American College of Nuclear Medicine
ACP: American College of Physicians
ADT: androgen deprivation therapy
ANZSNM: Australian and New Zealand Society of Nuclear Medicine
AR: androgen receptor
ASCO: American Society of Clinical Oncology
AUA: American Urological Association
AUC: appropriate use criteria
BCR: biochemical recurrence
CRPC: castration-resistant prostate cancer
CSPC: castration-sensitive prostate cancer
CT: computed tomography
EANM: European Association of Nuclear Medicine
E-PSMA: EANM standardized reporting guidelines for PSMA-PET
^{18}F-FDG: ^{18}F-fluorodeoxyglucose
M0 CRPC: nonmetastatic castration-resistant prostate cancer
mCRPC: metastatic castration-resistant prostate cancer
MDT: metastasis-directed therapy
MRI: magnetic resonance imaging
NCCN: National Comprehensive Cancer Network
nmCRPC: nonmetastatic castration-resistant prostate cancer
PET: positron emission tomography
PFS: progression-free survival
PICOTS: population, intervention, comparisons, outcomes, timing, and setting
PSA: prostate-specific antigen
PSADT: prostate-specific antigen doubling time
PSMA: prostate-specific membrane antigen
RLT: radioligand therapy
SNMMI: Society of Nuclear Medicine and Molecular Imaging
SRT: stereotactic radiation therapy
TNM: tumor, node, metastasis

APPENDIX C: DISCLOSURES AND CONFLICTS OF INTEREST

Relationships with Industry and Other Entities

Workgroup member	Reported relationships
Jadvar, Hossein	• ImaginAb, Research • Subtle Medical, Research • Ming Hsieh Institute, Research • National Institutes of Health, Research • RadioMedix, Advisory Board • Blue Earth Diagnostics, Consultant • Telix, Consultant
Calais, Jeremie	• AAA, Research • Progenics, Research • Curium, Research • Janssen, Research • GE Healthcare, Research • SNMMI, Grant
Fanti, Stefano	• European Association of Nuclear Medicine
Feng, Felix	• American Society of Radiation Oncology, Research • American Society of Clinical Oncology, Research • American Association of Cancer Research, Research • PFS Genomics, Stock • Serimmune, Stock
Greene, Kirsten L.	• None
Gulley, James L.	• None
Hofman, Michael	• Endocyte, Research • AAA (Novartis Companies), Research • ANSTO, Nonfinancial support • Astellas, Personal fees • AstraZeneca, Personal fees • Janssen, Personal fees • Mundipharma, Personal fees • Merck/MSD, Personal fees
Hope, Thomas A.	• Curium, Consulting • Ipsen, Consulting
Koontz, Bridget F.	• Janssen, Research • Merck, Research • Blue Earth Diagnostics, Research, Consulting • Rytus Therapeutics, Consulting • Myovant, Consulting
Lin, Daniel W.	• Society of Urologic Oncology, Board of Directors • Southwest Oncology Group, Board of Directors
Morris, Michael J.	• None
Rowe, Steve P.	• Progenics, Research • Precision Molecular, Consulting, Stock • Plenary.ai, Consulting
Royce, Trevor J.	• None
Salami, Simpa	• None
Savir-Baruch, Bital	• American College of Nuclear Medicine • BED, Research
Srinivas, Sandy	• None

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin.* 2021;71:7–33.
2. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34:1402–1418.
3. Schaeffer E, Srinivas S, Antonarakis ES, et al. NCCN guidelines insights: prostate cancer, version 1.2021. *J Natl Compr Canc Netw.* 2021;19:134–143.
4. Jadvar H. Imaging evaluation of prostate cancer with ^{18}F-fluorodeoxyglucose PET/CT: utility and limitations. *Eur J Nucl Med Mol Imaging.* 2013;40(suppl 1): S5–S10.
5. Fanti S, Minozzi S, Castellucci P, et al. PET/CT with ^{11}C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. *Eur J Nucl Med Mol Imaging.* 2016;43:55–69.
6. Kim S-J, Lee SW. The role of ^{18}F-fluciclovine PET in the management of prostate cancer: a systematic review and meta-analysis. *Clin Radiol.* 2019;74:886–892.
7. Dietlein F, Kobe C, Neubauer S, et al. PSA-stratified performance of ^{18}F- and ^{68}Ga-PSMA PET in patients with biochemical recurrence of prostate cancer. *J Nucl Med.* 2017;58:947–952.
8. Kuten J, Fahoum I, Savin Z, et al. Head-to-head comparison of ^{68}Ga-PSMA-11 with ^{18}F-PSMA-1007 PET/CT in staging prostate cancer using histopathology and immunohistochemical analysis as a reference standard. *J Nucl Med.* 2020;61:527–532.
9. Nielsen JB, Zacho HD, Haberkorn U, et al. A comprehensive safety evaluation of ^{68}Ga-labeled ligand prostate-specific membrane antigen 11 PET/CT in prostate cancer: the results of 2 prospective, multicenter trials. *Clin Nucl Med.* 2017;42: 520–524.
10. Szabo Z, Mena E, Rowe SP, et al. Initial evaluation of [^{18}F]DCFPyL for prostate-specific membrane antigen (PSMA)-targeted PET imaging of prostate cancer. *Mol Imaging Biol.* 2015;17:565–574.
11. US Food and Drug Administration. Gallium Ga 68 PSMA-11 injection [prescribing information label]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212642s000lbl.pdf. Accessed November 28, 2021.
12. US Food and Drug Administration. PYLARIFY® (piflufolastat F 18) injection [prescribing information label]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214793s000lbl.pdf. Accessed November 28, 2021.
13. Werner RA, Bundschuh RA, Bundschuh L, et al. Semiquantitative parameters in PSMA-targeted PET imaging with [^{18}F]DCFPyL: impact of tumor burden on normal organ uptake. *Mol Imaging Biol.* 2020;22:190–197.
14. Fendler WP, Eiber M, Beheshti M, et al. ^{68}Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2017;44:1014–1024.
15. Iravani A, Hofman MS, Mulcahy T, et al. ^{68}Ga PSMA-11 PET with CT urography protocol in the initial staging and biochemical relapse of prostate cancer. *Cancer Imaging.* 2017;17:31.
16. Guberina N, Hetkamp P, Ruebben H, et al. Whole-body integrated [^{68}Ga]PSMA-11-PET/MR imaging in patients with recurrent prostate cancer: comparison with whole-body PET/CT as the standard of reference. *Mol Imaging Biol.* 2020;22: 788–796.
17. Ceci F, Oprea-Lager DE, Emmett L, et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. *Eur J Nucl Med Mol Imaging.* 2021;48: 1626–1638.
18. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA.* 1998;280:969–974.
19. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst.* 1998;90:766–771.
20. Kattan MW, Zelefsky MJ, Kupelian PA, et al. Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. *J Clin Oncol.* 2003;21:4568–4571.
21. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst.* 2006;98:715–717.
22. Marascio J, Spratt DE, Zhang J, et al. Prospective study to define the clinical utility and benefit of Decipher testing in men following prostatectomy. *Prostate Cancer Prostatic Dis.* 2020;23:295–302.
23. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol.* 2014;66:550–560.
24. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. *Eur Urol.* 2015;67:778–786.
25. Shore ND, Kella N, Moran B, et al. Impact of the cell cycle progression test on physician and patient treatment selection for localized prostate cancer. *J Urol.* 2016;195:612–618.
26. Punnen S, Pavan N, Parekh DJ. Finding the wolf in sheep's clothing: the 4Kscore is a novel blood test that can accurately identify the risk of aggressive prostate cancer. *Rev Urol.* 2015;17:3–13.
27. Antonarakis ES, Chen Y, Elsamanoudi SI, et al. Long-term overall survival and metastasis-free survival for men with prostate-specific antigen-recurrent prostate cancer after prostatectomy: analysis of the Center for Prostate Disease Research National Database. *BJU Int.* 2011;108:378–385.
28. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA.* 2005;294:433–439.
29. Van den Broeck T, van den Bergh RCN, Briers E, et al. Biochemical recurrence in prostate cancer: the European Association of Urology prostate cancer guidelines panel recommendations. *Eur Urol Focus.* 2020;6:231–234.
30. Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol.* 2005;23:2918–2925.
31. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med.* 1985;312:1604–1608.
32. Albertsen PC, Hanley JA, Barrows GH, et al. Prostate cancer and the Will Rogers phenomenon. *J Natl Cancer Inst.* 2005;97:1248–1253.
33. Woodward WA, Strom EA, Tucker SL, et al. Changes in the 2003 American Joint Committee on Cancer staging for breast cancer dramatically affect stage-specific survival. *J Clin Oncol.* 2003;21:3244–3248.
34. Bergamin S, Eade T, Kneebone A, et al. Interim results of a prospective prostate-specific membrane antigen-directed focal stereotactic reirradiation trial for locally recurrent prostate cancer. *Int J Radiat Oncol Biol Phys.* 2020;108:1172–1178.
35. Weber M, Kurek C, Barbato F, et al. PSMA-ligand PET for early castration-resistant prostate cancer: a retrospective single-center study. *J Nucl Med.* 2021;62: 88–91.
36. Fendler WP, Weber M, Iravani A, et al. Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2019;25:7448–7454.
37. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol.* 2020;148:157–166.
38. Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic prostate cancer: results of a Dutch multidisciplinary consensus meeting. *Eur Urol Oncol.* 2020; 3:231–238.
39. D'Angelillo RM, Francolini G, Ingrosso G, et al. Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: a position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO). *Crit Rev Oncol Hematol.* 2019;138:24–28.
40. Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol.* 2020;77:508–547.
41. Ali A, Hoyle A, Haran ÁM, et al. Association of bone metastatic burden with survival benefit from prostate radiotherapy in patients with newly diagnosed metastatic prostate cancer: a secondary analysis of a randomized clinical trial. *JAMA Oncol.* 2021;7:555–563.
42. Lenis AT, Pooli A, Lec PM, et al. Prostate-specific membrane antigen positron emission tomography/computed tomography compared with conventional imaging for initial staging of treatment-naïve intermediate- and high-risk prostate cancer: a retrospective single-center study. *Eur Urol Oncol.* September 2020:S2588-9311 (20)301395.
43. National Comprehensive Cancer Network. Prostate cancer. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed November 28, 2021.
44. Calais J, Ceci F, Eiber M, et al. ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol.* 2019; 20:1286–1294.
45. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol.* 2018;36:446–453.
46. Siva S, Bressel M, Murphy DG, et al. Stereotactic abative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. *Eur Urol.* 2018;74:455–462.
47. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol.* 2020;6:650–659.

48. Evans MJ, Smith-Jones PM, Wongvipat J, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. *Proc Natl Acad Sci USA.* 2011;108: 9578–9582.

49. Hope TA, Truillet C, Ehman EC, et al. ^{68}Ga-PSMA-11 PET imaging of response to androgen receptor inhibition: first human experience. *J Nucl Med.* 2017;58:81–84.

50. Ettala O, Malaspina S, Tuokkola T, et al. Prospective study on the effect of short-term androgen deprivation therapy on PSMA uptake evaluated with ^{68}Ga-PSMA-11 PET/MRI in men with treatment-naïve prostate cancer. *Eur J Nucl Med Mol Imaging.* 2020;47:665–673.

51. Emmett L, Yin C, Crumbaker M, et al. Rapid modulation of PSMA expression by androgen deprivation: serial ^{68}Ga-PSMA-11 PET in men with hormone-sensitive and castrate-resistant prostate cancer commencing androgen blockade. *J Nucl Med.* 2019;60:950–954.

52. Brumberg J, Beckl M, Dierks A, et al. Detection rate of ^{68}Ga-PSMA ligand PET/CT in patients with recurrent prostate cancer and androgen deprivation therapy. *Biomedicines.* 2020;8:511.

53. Fanti S, Hadaschik B, Herrmann K. Proposal for systemic-therapy response-assessment criteria at the time of PSMA PET/CT imaging: the PSMA PET progression criteria. *J Nucl Med.* 2020;61:678–682.

54. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet.* 2021;397:797–804.

55. Fitch K, Bernstein SJ, Aguilar MD, Burnand B. *The RAND/UCLA Appropriateness Method User's Manual.* Santa Monica, CA: RAND; 2001.

56. Hendel RC, Patel MR, Allen JM, et al. Appropriate use of cardiovascular technology: 2013 ACCF appropriate use criteria methodology update: a report of the American College of Cardiology Foundation appropriate use criteria task force. *J Am Coll Cardiol.* 2013;61:1305–1317.

57. Institute of Medicine of the National Academy. *Clinical Practice Guidelines We Can Trust.* Washington, DC: National Academies Press; 2011.

58. Trabulsi EJ, Rumble RB, Jadvar H, et al. Optimum imaging strategies for advanced prostate cancer: ASCO guideline. *J Clin Oncol.* 2020;38:1963–1996.

59. Society of Nuclear Medicine and Molecular Imaging. Appropriate use criteria (AUC) development process. https://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=15665. Accessed September 9, 2021.

60. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet.* 2020;395:1208–1216.

61. Pienta KJ, Gorin MA, Rowe SP, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with ^{18}F-DCFPyL in prostate cancer patients (OSPREY). *J Urol.* 2021;206:52–61.

62. Buisset J, Norris JM, Puech P, et al. Negative prebiopsy magnetic resonance imaging and risk of significant prostate cancer: baseline and long-term followup results. *J Urol.* 2021;205:725–731.

63. Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009;15:167–172.

64. Amin A, Blazevski A, Thompson J, et al. Protocol for the PRIMARY clinical trial, a prospective, multicentre, cross-sectional study of the additive diagnostic value of gallium-68 prostate-specific membrane antigen positron-emission tomography/computed tomography to multiparametric magnetic resonance imaging in the diagnostic setting for men being investigated for prostate cancer. *BJU Int.* 2020;125:515–524.

65. Gorin MA, Rowe SP, Patel HD, et al. Prostate specific membrane antigen targeted ^{18}F-DCFPyL positron emission tomography/computed tomography for the prospective staging of high risk prostate cancer: results of a prospective, phase II, single-center study. *J Urol.* 2018;199:126–132.

66. Hope TA, Armstrong WR, Murthy V, et al. Accuracy of ^{68}Ga-PSMA-11 for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicenter prospective phase III imaging study. *J Clin Oncol.* 2020; 38(suppl 15):5502.

67. de Feria Cardet RE, Hofman MS, Segard T, et al. Is prostate-specific membrane antigen positron emission tomography/computed tomography imaging cost-effective in prostate cancer: an analysis informed by the proPSMA trial. *Eur Urol.* 2021;79:413–418.

68. Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. *J Urol.* 2012;188:2219–2224.

69. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol.* 2007;177:540–545.

70. Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys.* 2006;65:965–974.

71. Fendler WP, Calais J, Eiber M, et al. Assessment of ^{68}Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. *JAMA Oncol.* 2019;5:856–863.

72. Morris MJ, Rowe SP, Gorin MA, et al. Diagnostic performance of ^{18}F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR phase III, multicenter study. *Clin Cancer Res.* 2021;27:3674–3682.

73. Fendler WP, Ferdinandus J, Czernin J, et al. Impact of ^{68}Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. *J Nucl Med.* 2020;61:1793–1799.

74. Calais J, Fendler WP, Eiber M, et al. Impact of ^{68}Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. *J Nucl Med.* 2018;59:434–441.

75. Han S, Woo S, Kim YJ, Suh CH. Impact of ^{68}Ga-PSMA PET on the management of patients with prostate cancer: a systematic review and meta-analysis. *Eur Urol.* 2018;74:179–190.

76. Jani AB, Schreibmann E, Goyal S, et al. ^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. *Lancet.* 2021;397:1895–1904.

77. Calais J, Armstrong WR, Kishan AU, et al. Update from PSMA-SRT Trial NCT03582774: a randomized phase 3 imaging trial of prostate-specific membrane antigen positron emission tomography for salvage radiation therapy for prostate cancer recurrence powered for clinical outcome. *Eur Urol Focus.* 2021;7:238–240.

78. Froemming AT, Verma S, Eberhardt SC, et al. ACR Appropriateness criteria ® post-treatment follow-up prostate cancer. *J Am Coll Radiol.* 2018;15:S132–S149.

79. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med.* 2018;378:1408–1418.

80. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2018;378:2465–2474.

81. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380:1235–1246.

82. Triggiani L, Alongi F, Buglione M, et al. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. *Br J Cancer.* 2017;116:1520–1525.

83. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* [published online June 23, 2021]. 10.1056/NEJMoa2107322.

84. Fanti S, Goffin K, Hadaschik BA, et al. Consensus statements on PSMA PET/CT response assessment criteria in prostate cancer. *Eur J Nucl Med Mol Imaging.* 2021;48:469–476.

85. Aggarwal R, Wei X, Kim W, et al. Heterogeneous flare in prostate-specific membrane antigen positron emission tomography tracer uptake with initiation of androgen pathway blockade in metastatic prostate cancer. *Eur Urol Oncol.* 2018;1: 78–82.

86. Bettmann MA. The ACR appropriateness criteria: view from the committee chair. *J Am Coll Radiol.* 2006;3:510–512.

87. Thrall JH. Appropriateness and imaging utilization: "computerized provider order entry and decision support. *Acad Radiol.* 2014;21:1083–1087.

88. Sistrom CL. In support of the ACR appropriateness criteria. *J Am Coll Radiol.* 2008;5:630–635, discussion 636–637.

89. Emmett L, Tang R, Nandurkar R, et al. 3-Year freedom from progression after ^{68}Ga-PSMA PET/CT-triaged management in men with biochemical recurrence after radical prostatectomy: results of a prospective multicenter trial. *J Nucl Med.* 2020;61:866–872.

90. Amiel T, Würnschimmel C, Heck M, et al. Regional lymph node metastasis on prostate specific membrane antigen positron emission tomography correlates with decreased biochemical recurrence-free and therapy-free survival after radical prostatectomy: a retrospective single-center single-arm observational study. *J Urol.* 2021;205:1663–1670.

91. Schmidt-Hegemann NS, Kroeze SGC, Henkenberens C, et al. Influence of localization of PSMA-positive oligo-metastases on efficacy of metastasis-directed external-beam radiotherapy-a multicenter retrospective study. *Eur J Nucl Med Mol Imaging.* 2020;47:1852–1863.