## Title

Considerations on Integrating Prostate-Specific Membrane Antigen Positron Emission Tomography Imaging Into Clinical Prostate Cancer Trials by National Clinical Trials Network Cooperative Groups



## Journal

Journal of Clinical Oncology, 40(13)

## ISSN

0732-183X

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## Publication Date

2022-05-01

## DOI

10.1200/jco.21.02440

Peer reviewed

special articles

# Considerations on Integrating Prostate-Specific Membrane Antigen Positron Emission Tomography Imaging Into Clinical Prostate Cancer Trials by National Clinical Trials Network Cooperative Groups

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abstract

**PURPOSE** As prostate-specific membrane antigen (PSMA) positron emission tomography (PET) becomes increasingly available in the United States, the greater sensitivity of the technology in comparison to conventional imaging poses challenges for clinical trials. The NCI Clinical Imaging Steering Committee (CISC) PSMA PET Working Group was convened to coordinate the identification of these challenges in various clinical scenarios and to develop consensus recommendations on how best to integrate PSMA PET into ongoing and upcoming National Clinical Trials Network (NCTN) trials.

**METHODS** NCI CISC and NCI Genitourinary Steering Committee members and leadership nominated clinicians, biostatisticians, patient advocates, and other imaging experts for inclusion in the PSMA PET Working Group. From April to July 2021, the working group met independently and in conjunction with the CISC to frame challenges, including stage migration, response assessment, trial logistics, and statistical challenges, and to discuss proposed solutions. An anonymous, open-ended survey was distributed to members to collect feedback on challenges faced. Representatives from each NCTN group were invited to present an overview of affected trials. From these discussions, the consensus document was developed and circulated for the inclusion of multiple rounds of feedback from both the Working Group and CISC.

**RESULTS** The current consensus document outlines the key challenges for clinical prostate cancer trials resulting from the increasing availability of PSMA PET. We discuss implications for patient selection and definition of end points and provide guidance and potential solutions for different clinical scenarios, particularly with regard to best practices in defining eligibility criteria and outcome measures.

**RECOMMENDATIONS** This article provides guidance regarding clinical trial design and conduct, and the interpretation of trial results.

J Clin Oncol 40:1500-1505. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

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Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 2, 2021 and published at ascopubs.org/journal/jco on January 11, 2022: DOI https://doi.org/10.1200/JCO.21.02440

## INTRODUCTION

As of December 2021, the US Food and Drug Administration (FDA) has approved two prostate-specific membrane antigen (PSMA) imaging agents, $^{68}$Ga-PSMA-11 (PSMA-11, for use at the University of California at Los Angeles and San Francisco; and a commercial product named Illuccix, Telix Pharmaceuticals, Fishers, IN) and $^{18}$F-DCFPyL (Pylarify; Progenics Pharmaceuticals, Inc, N. Billerica, MA), for clinical use in the United States.[1-3] The indications for use on the labels of both PSMA-11 and Pylarify are for the contexts of evaluating suspected prostate cancer metastasis and/or recurrence on the basis of increasing prostate-specific antigen (PSA) levels in the blood. The approval is based on studies showing that PSMA positron emission tomography (PET) imaging was superior to conventional imaging (CI)—which includes computed tomography (CT) of the abdomen and pelvis and Tc99m-MDP bone scans—with detection rates that improve as serum PSA levels rise. The CONDOR study (NCT03739684), using PSMA PET with imaging agent Pylarify, reports cancer detection rates of 36%, 51%, 67%, 85%, and 97% in men with PSA levels of $< 0.5$, 0.51-0.99, 1.0-1.99, 2.0-4.99, and $\geq 5.0$ ng/mL, respectively.[4] Similar rates of 38%, 57%, 84%, 86%, and 97% are reported for PSMA-11 using the same cutoffs in a study using $^{68}$Ga-PSMA.[5] Studies on the use of the agent as an indicator of response are ongoing, including a study with patients receiving taxane-based chemotherapy in which changes in

## CONTEXT

**Key Objective**

How does the increasing availability and high sensitivity of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) affect current and future clinical trials in prostate cancer? This document outlines challenges and possible solutions for trial designs and data management.

**Knowledge Generated**

The PSMA PET Working Group convened experts from across the research community to develop new consensus recommendations to mitigate issues in trial design and conduct. Pragmatic guidance and potential solutions are offered.

**Relevance**

This document outlines three possible options for ongoing trials and encourages clear specification of the option selected in protocol amendments. For future trials, we recommend performing PSMA PET in conjunction with a full-dose computed tomography and address issues related to patient access, regulatory review, reader training, and scan interpretation. Application of these recommendations in clinical trials will help ensure uniform patient management and outcome measurements.

PSA were shown to correlate with changes in disease burden visualized on PSMA PET.[6] Given these advances in disease detection, PSMA PET imaging has been in clinical use at various institutions across the United States under expanded-access protocols for several years; imaging with Pylarify is now also available for commercial clinical use. In addition, some institutions offer PSMA PET imaging for patients with known metastatic disease to help guide therapeutic decisions.

Consequently, men with prostate cancer will increasingly undergo PSMA PET imaging to localize the site(s) of disease outside the prostate gland. Of note, recently, the National Comprehensive Cancer Network has adopted PSMA imaging as part of their updated guidelines,[7] and the first appropriate use criteria for PSMA imaging have been published by a group of international professional organizations.[8]

## METHODS

The NCI Clinical Imaging Steering Committee (CISC) recognizes that the increasing availability and use of PSMA PET imaging pose a challenge for the conduct and analysis of ongoing clinical trials, both in terms of the difference in prognosis and management decisions for patients in the trial on the basis of PSMA PET versus CI, as well as for the recruitment of new patients to trials for recurrent disease. In response to these challenges, the CISC established a PSMA PET Working Group in collaboration with National Clinical Trials Network (NCTN) Cooperative Groups, the NCI Genitourinary Steering Committee (GUSC), and the GUSC Prostate Cancer Task Force (Prostate TF) to discuss the ways in which PSMA PET could potentially compromise the completion and interpretation of the outcomes of ongoing trials using CI only to detect and monitor disease (Table 1). The consensus building process used a comprehensive member-wide survey, five virtual meetings, and three rounds of document review and feedback from a broad and diverse base of Working Group membership to yield the current guidance document (see Appendix 1, online only for additional detail).

## RESULTS

Since PSMA PET is a relatively new imaging test, more data from clinical trials are needed to validate its utility in various clinical settings, including (1) the detection of disease, (2) monitoring for changes as an indicator of response, and (3) as a marker of progression. Although these data are still being collected and it remains to be proven that the integration of PSMA imaging can influence clinical outcomes, PSMA PET is increasingly used in clinical practice, and this may have implications for ongoing and future clinical trials. Several specific considerations pertaining to clinical trial recruitment and end points were discussed:

### Clinical Scenarios

***Stage migration.*** Current criteria for disease detection rely on CT, Tc99m-MDP bone scan, and sometimes pelvic or whole-body magnetic resonance imaging. Given the increased sensitivity and specificity in detecting disease compared with these CI modalities, it is expected that PSMA PET will lead to earlier detection of recurrent disease both at the primary and distant sites. As such, the disease and thus the eligibility status of certain patients considered for, or enrolled in, existing clinical trials may change—eg, from biochemical recurrence only to established metastatic disease. This scenario is termed stage migration since the disease stage advances because of lesions found on PSMA PET but not on CI. In another scenario, response assessment may change from stable disease (on the basis of a lack of change on CI) to progressive disease (on the basis of PSMA PET detecting sites of disease that could not be detected by CI), resulting in potentially premature abandonment of efficacious treatment. Stage migration on the basis of more accurate determination of the presence or absence of metastatic disease will lead to reclassifying patients previously considered low risk to higher risk. However, better characterization of disease state by PSMA PET imaging may lead to more accurate study populations

**TABLE 1.** Clinical Scenarios and Concerns Regarding the Impact of PSMA PET on Existing and Future Clinical Trials in Prostate Cancer

| Clinical Scenario | Potential Effect of PSMA PET | Potential Concerns |
|---|---|---|
| Initial staging (N0 → N1 or M1) | N0 → N1 and/or M1 disease | Stage migration impact on trial populations<br>Changes to trial eligibility status for patients<br>More accurate staging as the earlier detection of disease moves patients from low-risk to higher-risk classification<br>Inaccurate upstaging because of false-positive reporting of PSMA PET findings<br>Advantage: more accurate staging leads to more accurate study populations<br>Outcome of patients with PSMA PET N1 may be better than that of patients with CI N1 disease<br>Impact on treatment decisions<br>Escalation or de-escalation of therapy without proven evidence of clinical benefit<br>As yet unknown whether earlier progression as detected by PSMA PET is clinically meaningful<br>Lack of adherence to treatment guidelines on the basis of CI<br>Morbidity from biopsies or treatment escalation precipitated or deemed necessary by true-positive PSMA PET findings<br>Using PSMA PET as imaging marker may suggest worse course compared with other ongoing or previous trials on the basis of CI alone<br>PFS end points not consistently defined or validated and studies are lacking to relate findings to CI comparable to historical setting<br>Impact on trial logistics<br>May require larger trials and longer follow-up to determine clinically relevant outcome (with associated trials costs) in a truly low-risk group (baseline PSMA-negative)<br>Inconsistencies in coverage provided by third-party payors for the range of clinical use across trial sites<br>Lack of access to PSMA outside of major population centers<br>Possible inconsistencies in reading scans across trial sites |
| Biochemical recurrence | M0 → oligometastatic or polymetastatic disease | As above<br>Additionally,<br>Impact on treatment decisions<br>Omission of empirical local radiotherapy when PSMA PET shows regional or distant disease<br>Increasing use of early salvage procedures and treatment for oligometastatic disease in the absence of data showing benefit from such<br>Possibly high rate of false-positive findings (eg, intraprostatic uptake post-EBRT and brachytherapy; however, PET readers can be trained)<br>Impact on trial logistics<br>Advantage: shorter MFS and rPFS as PSMA PET may detect earlier and more sites of disease than CI studies, potentially reducing trial time, size, and cost<br>Advantage: cleaner cohorts for trials of focal therapy for oligometastatic disease |
| CRPC | M0 → M1 status | As above<br>Additionally,<br>Stage migration with increasing use of therapy for metastatic disease; the true M0 state will become increasingly rare<br>Leads to earlier switch of therapies<br>Role of PSMA PET as response marker needs to be explored and validated (first establish repeatability, multicenter calibration, etc)<br>Sensitivity of PSMA PET may be lower in some advanced CRPC settings<br>Potential change in classification from oligometastatic → polymetastatic<br>Leads to changing protocol eligibility |

Abbreviations: CI, conventional imaging; CRPC, castration-resistant prostate cancer; EBRT, external-beam radiation therapy; M, distant metastasis; MFS, metastasis-free survival; N, regional lymph node; PET, positron emission tomography; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival.

in clinical trials. The number of patients determined to be nonmetastatic by PSMA PET required to show clinical benefit from a therapeutic intervention will increase, as will the follow-up time and cost.

Following stage migration at baseline, the sample size of ongoing clinical trials in the (now truly) lower-risk space may need to increase, with longer follow-up and associated higher costs, to observe a sufficient number of events and maintain adequate power when using CI-defined end points (eg, radiographic progression-free survival [rPFS] and metastasis-free survival [MFS]). Developing PSMA PET databases to assess the magnitude of the impact on trial outcomes is important to both inform and optimize the study design of future clinical trials. Alternatively, risk groups could be defined using previously validated models, with patients then substratified by PSMA PET imaging findings.

***Response assessment.*** Radiographic progression events on the basis of PSMA PET will likely occur earlier than those on the basis of CI. Trial outcome data may not be

comparable with those from the pre-PSMA PET era. It is thus conceivable that end points may be reached earlier, potentially reducing the sample size, increasing the power, or decreasing the needed follow-up time. By contrast, certain patients with locally advanced prostate cancer and at high risk but with negative CI may undergo PSMA-based upstaging. If this occurred, the time to enroll lower-risk (PSMA-negative) patients into trials, the needed sample size, and the required follow-up time would have to increase to observe a statistically meaningful number of events. Trials testing PSMA PET as a valid measure for response will require baseline scans at the time of enrollment and a definition of criteria indicating progression (analogous to Prostate Cancer Working Group [PCWG] criteria for the declaration of progressive disease using bone scan).[9] A major concern for both patients and physicians is whether earlier progression events as detected by PSMA PET will be clinically meaningful—ie, true disease progression versus early detection of an imaging marker that does not necessarily translate into worse overall outcome and survival. Although the detection of new (true-positive) lesions by PSMA PET is probably a manifestation of progression, future studies will need to define appropriate criteria for progression and validate whether this also justifies a change in current therapy. In the extreme, premature acceptance of PSMA PET-determined progression as a clinically meaningful surrogate marker (ie, biologically and quantitatively related to an accepted outcome parameter) could lead to abandoning therapy or commencing new or layered therapy without evidence of survival or clinical benefit. This would be analogous to trials from the 1990s that removed men from study for PSA progression only and without radiographic progression. For instance, metastasis-directed therapy is currently under study in several trials, including therapy to PSMA-positive sites as shown in ORIOLE.[10] Regardless of the potential clinical benefit of these approaches, such data will not be comparable to those from past clinical trials with systemic therapy. Also, in randomized, unblinded trials, some patients assigned to the control arm may be classified as exhibiting progressive disease, potentially introducing bias favoring the treatment arm. Finally, the best frequency of follow-up PSMA scans also needs to be defined. As these data are still being collected, many experts consider it premature to use PSMA PET for routine clinical decision making until the results of prospective studies become available. Of note, the PSMA signal is modulated by androgens and the androgen receptor status (recently reviewed).[11] Short-term androgen deprivation therapy leads to increased PSMA expression, and this has two implications. First, it is not clear whether short-term androgen deprivation should be administered routinely before therapy to boost the PSMA signal to derive an accurate baseline assessment of the extent of disease. Second, a minimum time between baseline and follow-up (a 3 months' time window has been proposed)[12] may be necessary to assess therapy response, avoiding any short-term flare phenomenon. It is not clear whether these concerns similarly apply to modern androgen receptor targeting therapies. Measurement of testosterone levels on the day of imaging will provide information on whether castrate levels of testosterone were achieved.

### Outcome Measures

***MFS.*** MFS, as defined by PCWG2,[13] is a commonly used end point in prostate cancer clinical trials, serving as a validated surrogate for overall survival (OS) in high-risk disease when using current CI.[14,15] MFS may not retain its status or strength of surrogacy when using PSMA PET; this question must be addressed in future phase III clinical trials. For instance, although the PSMA imaging signal correlates with PSA level, the PSA level per se and changes in PSA level are not currently accepted surrogate markers for patient outcome. Investigators have proposed a definition for what constitutes metastatic disease on PSMA-PET as well as PSMA response criteria.[12] For instance, on the basis of expert opinion and depending on clinical scenario, one proposed definition of progression includes two new lesions on a PSMA scan or one new lesion in a location consistent with prostate cancer spread, regardless of RECIST or PCWG criteria (eg, pelvic or retroperitoneal node even if $< 1$ cm; new focal PSMA uptake in bone marrow after exclusion of reasons for false positives, such as post-traumatic or degenerative change).

***OS.*** Whether rPFS as assessed by PSMA PET is an acceptable surrogate for OS needs to be studied. In determining the clinical validity of PSMA-rPFS for assessing OS, both trial-level and patient-level utility should be assessed. Addressing this question should be a priority for current and future prostate cancer clinical trials.

***Statistical implications of adding PSMA PET as a diagnostic tool.*** Cost and power considerations are similar as outlined for the use of the rPFS end point discussed above, if PSMA-positive lesions prove to be clinically significant. Importantly, consistency in monitoring and the use of PSMA PET in both arms of clinical trials is necessary to avoid any potential bias.

## RECOMMENDATIONS

### For Ongoing NCTN Trials

***Integration of PSMA PET imaging.*** Considering the many ways in which PSMA PET can affect disease staging and outcome measures (Table 1), experts discussed several approaches regarding how to integrate PSMA PET into ongoing clinical trials that use CI as an outcome measure, including:

1. Discourage the use of PSMA PET for disease monitoring since the long-term implications of scan findings are currently unclear.
2. Perform PSMA PET at baseline and follow-up, but consider scan findings only as outcome measures for rPFS if confirmed by biopsy; however, this may still alter the traditional end point definition as long as PSMA PET–positive lesions do not meet traditional CI criteria (eg, $< 1$ cm PSMA-positive lymph node).

3. Observe PSMA PET findings until they become positive on the basis of CI criteria, acknowledging that changes in PSMA PET are currently not validated as meaningful end points in clinical trials.

No consensus was reached. Regardless of the final approach taken, the handling of potential PSMA PET results should be specified in protocol amendments to ensure uniform patient management and outcome measurements. Of note, each approach may result in additional psychologic burden to patients.

***Cost and availability considerations.*** The clinical trial cost per patient may increase substantially if and when PSMA PET is made mandatory for study entry and evaluation of outcome. The trial (rather than the patient) should bear this cost. By contrast, the earlier ascertainment of disease outcomes may, in fact, decrease overall study duration and costs. Widespread access to PSMA PET across the country needs to be ensured using different means, including increasing the availability of PSMA outside of major academic hospitals. However, this is likely to occur with the current approval of Pylarify and the imminent approval of other PSMA PET imaging agents. As additional PSMA PET agents are approved, study subjects may need to be stratified if the diagnostic performance of these agents is significantly different.

### For Future NCTN Trials

Given the increasing availability of PSMA PET in the United States, data on PSMA PET from patients in current clinical trials should be collected, according to prespecified protocol criteria, when performed and analyzed as a secondary or exploratory objective independently of the prespecified trial outcome measures. Going forward, criteria for patient preparation (eg, the role of short-term androgen deprivation and radiotracer uptake time), image acquisition, reconstruction, etc, need to be defined, similar to the now established criteria for using FDG PET in clinical trials. In retrospect, statistical analysis can be performed to address the validity of PSMA PET imaging by assessing concordance, or lack thereof, between PSMA PET and traditional CI findings. However, investigators performing subset statistical analysis should be aware that there may be unequal or disparate usage of PSMA PET by sociodemographic group, potentially affecting the analysis. Once PSMA PET becomes widely available across the United States (expected in early 2022), it should be used in addition to but not instead of CI before enrollment and during the study, with ongoing data collection until the clinical utility of PSMA PET becomes better defined. Ultimately, PSMA PET scans may replace other imaging modalities, such as bone scans, and bridge the gaps in clinical care and research, potentially serving as a marker of therapeutic activity of a drug and an indicator of clinical benefit.

***BI.*** As the availability and use of PSMA PET increase, and as both ongoing and future clinical trials are affected, discussing these issues with the appropriate review division at the FDA in the near future will be important. These discussions will be particularly critical if the trial under discussion is designed to support regulatory approval of an investigational product.

***Patient access.*** Investigators need to ensure that diverse populations are enabled to participate in clinical trials and have access to PSMA PET imaging throughout the country, regardless of ability to pay, geographic location, and/or sociodemographic status. Unequal or disparate access to PSMA PET by sociodemographic group must be studied, so that conclusions about the utility of this novel imaging technique can be applied appropriately. Patient-focused communication about PSMA PET must be developed and is essential to (1) ensure that patients understand how their staging and subsequent treatment and risks and benefits may change on the basis of PSMA PET results, (2) reduce stress about lesions identified on PSMA PET but not on CI, (3) adequately explain the potential reasons for and prevalence of false-positive PSMA PET results to patients, and (4) ensure patient understanding that PSMA PET remains an investigational test in clinical trials until its utility in various settings is fully validated. The costs of adding PSMA PET to existing and future clinical trials must be considered during trial design and amendments.

***Recommended technique.*** Ideally, PSMA PET may be performed as PET-CT in conjunction with a full-dose CT (including IV contrast, if and as prespecified by the trial), rather than as a separate, additional test. If this is not feasible, the CT of the PET-CT may be obtained with moderate dose for anatomical localization. Image acquisition protocols need to be standardized.

***Reader training and scan interpretation.*** Since PSMA PET is a new technique, reader training must be implemented to reduce the incidence of false positives.[16,17] Adoption of defined criteria, such as those proposed in the European Association of Nuclear Medicine standardized reporting guidelines for PSMA,[16] may be helpful in the interpretation of PSMA scans and in the standardized reporting of imaging findings. In addition to recording a prespecified number of target lesions on PSMA scans and CI, determination of involved regions and organ systems, as well as assessment of volumes of disease on PSMA PET and CI, may provide valuable and potentially predictive and/or prognostic information.

In conclusion, regardless of clinical state, PSMA PET has high sensitivity for prostate cancer lesions, frequently showing metastatic disease earlier and more extensively than CI does. The clinical implications of such findings and the potential role of PSMA PET as a predictive or prognostic marker in prostate cancer need to be investigated in future clinical trials. Until then, PSMA imaging findings, per se, should not affect patient management and trial outcome; however, retrospective subset analysis may potentially provide meaningful information.

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Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02440.

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## ACKNOWLEDGMENT

The authors thank the National Cancer Institute Clinical Imaging Steering Committee (NCI CISC), the National Cancer Institute Genitourinary Steering Committee (NCI GUSC), and the NCI GUSC Prostate Cancer Task Force. The list of contributing members of the NCI PSMA PET Working Group can be found in Appendix 1.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Patents, Royalties, Other Intellectual Property:** TCGA expression subtype single patient classifier
**Other Relationship:** UpToDate, Bladder Cancer Journal

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**Research Funding:** Dendreon (Inst), Merck (Inst), Seattle Genetics (Inst), Daiichi Sankyo (Inst), Taiho Pharmaceutical (Inst), Blue Earth Diagnostics (Inst), Bayer (Inst), Lantheus Medical Imaging (Inst)

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**Consulting or Advisory Role:** Medivation/Astellas, Accuray, Bayer, Blue Earth Diagnostics, AbbVie, Myovant Sciences, Genentech, Pfizer
**Research Funding:** Accuray

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**Employment:** Emmes Company, LLC

No other potential conflicts of interest were reported.

## APPENDIX 1. WORKING GROUP MEMBERSHIP AND CONSENSUS BUILDING PROCESS

Nominations for PSMA PET Working Group membership were solicited from CISC, GUSC, and Prostate TF leaders, and 36 individuals—including members from each NCTN group, imaging experts, statisticians, patient advocates, and medical and radiation oncologists—accepted the invitation to participate. The Working Group met independently and in conjunction with the CISC on five occasions between April 12, 2021, and July 20, 2021. Initial discussions and formal invited NCTN presentations in these meetings informed the development of an issue outline and corresponding survey, which was circulated to members to collect broad and systematic feedback on the issues faced and potential solutions. The results of the survey (n = 18) were collated and organized to form the foundation of the initial draft document. The draft was subsequently circulated to the entire CISC and Working Group for both written comment and in-meeting discussion, and a revised draft incorporating the suggested changes was distributed for a second round of comment and in-meeting discussion. In total, more than 40 sets of written comments were received from about 26 members, and these were harmonized and integrated to yield the consensus document. The document was circulated a third and final time to ensure there were no outstanding issues or comments.

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