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# Imaging Prostate Cancer: Clinical Utility of Prostate-Specific Membrane Antigen

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**Purpose:** Our goal was to review the pathway and pertinent materials leading to approval of prostate-specific membrane antigen (PSMA) scanning by the U.S. Food and Drug Administration (FDA).

**Materials and Methods:** Beginning with the pivotal trials and working backward, we summarize the evolution of PSMA scanning, beginning with the discovery of the molecule, the mechanism of action to identify prostate cancer, the route to the present-day test and some of the major publications leading to each step of the sequence. From the thousands of PSMA articles listed on PubMed®, the present review is focused on the 4 large U.S. trials incorporating university studies of the gallium-68 compound and commercial studies of the fluorine-18 compound. The review further focuses on the role of PSMA scanning for both initial staging of prostate cancer and diagnosis of recurrent prostate cancer.

**Results:** PSMA is a transmembrane-bound glycoprotein which is overexpressed by 100–1,000-fold in prostate cancer cells. Preclinical PSMA studies at Cornell and Johns Hopkins in the 1990s were followed by early human studies in Germany in the early 2010s, then pivotal clinical trials at University of California, Los Angeles and University of California, San Francisco, leading to the first FDA approval in December 2020 ($^{68}$Ga-PSMA-11). In January 2021, a commercially available product ($^{18}$F-DCFPyL) was approved on the basis of multisite registration trials (CONDOR and OSPREY). Sensitivity and specificity of PSMA scanning exceeds that of any other imaging method currently available for initial staging of prostate cancer and diagnosis of recurrent disease. The accuracy of PSMA scanning is attributed to the great image contrast (high signal-to-noise ratio), a property deriving from the high PSMA tracer uptake by prostate cancer cells. That property can be estimated quantitatively by a metric, the standardized uptake value. A follow-on PSMA compound, the theranostic lutetium-177, is currently pending FDA approval for treatment of metastases.

**Conclusions:** PSMA scanning is a disruptive technology that promises to transform the way prostate cancer is initially staged, recurrence is diagnosed and some advanced cases are treated.

**Abbreviations and Acronyms**

BCR = biochemical recurrence
CT = computerized tomography
FDA = U.S. Food and Drug Administration
mpMRI = multiparametric magnetic resonance imaging
MRI = magnetic resonance imaging
NCCN® = National Comprehensive Cancer Network®
PCa = prostate cancer
PET = positron-emission tomography
PPV = positive predictive value
PSA = prostate specific antigen
PSMA = prostate-specific membrane antigen
RLT = radioligand therapy
SUV = standardized uptake value
UCLA = University of California, Los Angeles
UCSF = University of California, San Francisco

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*"BECAUSE of increased sensitivity and specificity, PSMA-PET/CT or PSMA-PET/MRI can serve as an…effective front-line imaging tool for initial staging and to detect biochemical recurrence of prostate cancer."*

NCCN Guidelines®, September 10, 2021[1]

Prostate cancer (PCa) imaging based on prostate-specific membrane antigen (PSMA) is a disruptive innovation; its use has transformed diagnosis, staging and even treatment of PCa. PSMA is over-expressed by the great majority of PCa cells. PSMA-targeting small molecules can be bound to a radionuclide (eg gallium-68 or fluorine-18) and the conjugate can thus be visualized *in vivo* by scanning with positron-emission tomography (PET) scan. Anatomical localization of PSMA uptake is established by computerized tomography (CT) scanning overlay (PSMA PET/CT). Metastases and intra-prostatic cancer, not apparent by conventional imaging, may be seen. Use of PSMA PET/CT has redefined the patterns of PCa spread, resulting in a profound transformation of PCa management. PSMA PET/CT scanning was added to the National Comprehensive Cancer Network® (NCCN®) Guidelines® v1.2022 on September 10, 2021.[1] The following provides an overview of PSMA PET/CT imaging (not a systematic review), which was recently approved by the U.S. Food and Drug Administration (FDA) through use of the radiotracers $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL. Numerous systematic reviews (PRISMA) are available on PubMed® (75 as of January 2022). Herein we focus on the works most directly involved in the path to approval by the FDA.

## BIOLOGY OF PSMA AND BASICS OF PSMA PET/CT IMAGING

PSMA (glutamate carboxypeptidase, folate hydrolase) is a transmembrane-bound glycoprotein, native to prostate epithelial cells and overexpressed by 100−1,000-fold in PCa cells (fig. 1).[2] The normal function of PSMA remains unclear, but it may have a role in signaling and activating molecular pathways.[3] When malignant transformation occurs, PSMA expression increases.[4–7] The PSMA gene is located on the short arm of chromosome 11, a region not commonly deleted in PCa.[8] The molecule has a unique 3-part structure consisting of an extracellular domain (707 amino acids), a transmembrane domain (24 amino acids) and an intracellular domain (19 amino acids; fig. 1).[9] Since 95% of the molecule is extracellular, PSMA is readily accessible for binding of antibodies or low-molecular-weight ligands. PSMA-ligands can be labeled with radionuclides such as gallium-68 or fluorine-18 to form a radiotracer. After injection, the PSMA-targeted radiotracer is rapidly cleared from the blood to the PSMA-binding sites, internalized and accumulated into the PSMA-expressing PCa cells.[10,11]

Physiological PSMA expression may be seen in extraprostatic tissue, such as duodenum, small intestine, colon, kidney, salivary, lacrimal glands, nonmyelinated ganglia and the vascular supply of other cancers,[12] but not in the common sites of PCa metastasis (lymph nodes, bone).[2] Thus, with little background signal, allowing great contrast with PSMA-avid lesions, PET/CT visualization and localization of PCa is possible with accuracy not previously possible. A review by Maurer and associates, who were early investigators, provides extensive detail on the biology of PSMA.[13]

## EVOLUTION OF PSMA-TARGETED IMAGING

Major milestones in the development of today's PSMA scan are shown in figure 2. The proximate forerunner of today's PSMA scan was ProstaScint® (capromab pendetide/7E11-C5).[14] The ProstaScint scan (FDA approved 1996) employed a monoclonal antibody specific to the intracellular epitope of PSMA, radiolabeled with the gamma-emitter indium-111. Using gamma-camera imaging at 3 days of followup, the ProstaScint scan allowed visualization of PCa, including metastases. However, as the target was intracellular and ProstaScint could only bind to dying cells, the low signal/noise ratio reduced accuracy of ProstaScint scans. This and the poor image quality of indium-111 led to limited use and acceptance. The production of ProstaScint was discontinued in the U.S. in 2018.

In 1997, Neil Bander and others at Cornell discovered monoclonal antibodies to the extracellular epitope of PSMA (J591), conferring increased radiotracer uptake.[15,16] At about the same time, Martin Pomper at Johns Hopkins reported that an enzyme in brain was homologous to PSMA and could be targeted with radiolabeled low-molecular weight ligands to image PCa.[17] Thus was born modern interest in PSMA targeted scanning for diagnostic applications. Details of the preclinical discoveries are available elsewhere.[18,19]

In 2012, researchers in Heidelberg, Germany reported the first patient imaged with a $^{68}$Ga-labeled PSMA PET compound using the ligand PSMA-11.[20] Between 2012 and 2020 more than 1,700 studies on PSMA PET were published. On December 1st, 2020, nearly 10 years after its discovery, $^{68}$Ga-PSMA-11 was cleared by the FDA as the first PSMA-targeted radiopharmaceutical for PET imaging of PCa.[21] The FDA approval was originally restricted to the 2 centers where the $^{68}$Ga-PSMA-11 radiotracer was manufactured in the pivotal trials (University of California, Los

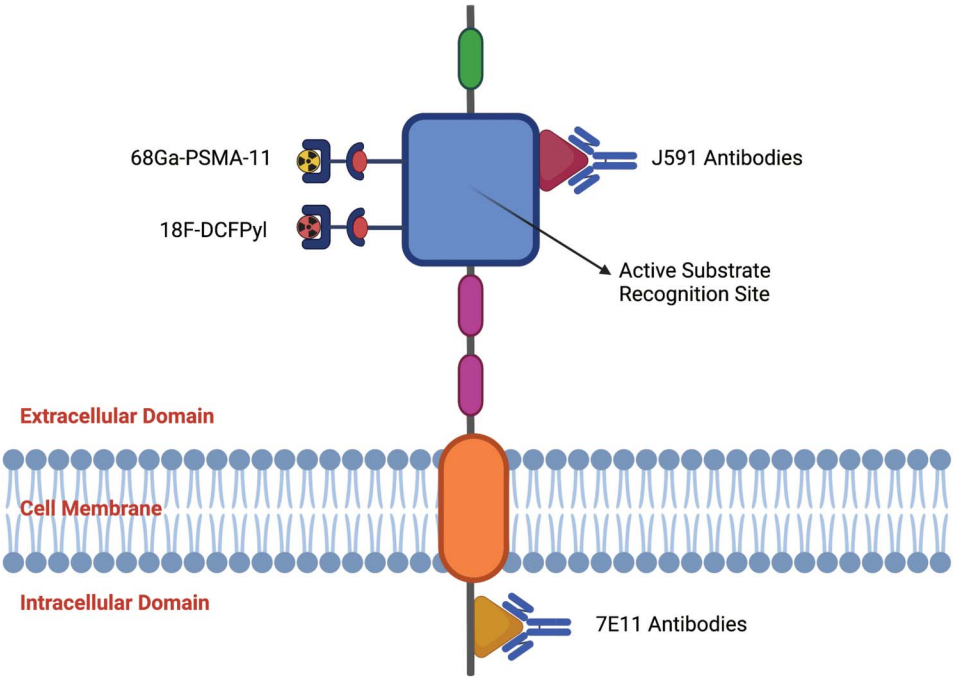


**Figure 1.** Molecular structure of PSMA. The transmembrane molecule consists of 3 parts: a short intracellular domain (19 amino acids), a transmembrane domain (24 amino acids) and a long extracellular domain (707 amino acids). The extracellular domain contains an active substrate-recognition site (blue square) which is targeted by the PSMA ligands, eg $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL. $^{68}$Ga-PSMA-11 and $^{18}$F-DCFPyL attach to the extracellular epitope of the PSMA, like the J591 antibodies. During binding, a process of internalization occurs, resulting in intracellular accumulation of the bound radioligand.[13]

Angeles [UCLA] and University of California, San Francisco [UCSF]). However, widespread availability of PSMA PET imaging is expected, following FDA clearance of the first commercially available PSMA PET radiotracer (Pylarify®, pifluflostat-18, Progenics/ Lantheus) in May 2021.[22] The 4 studies of PSMA PET

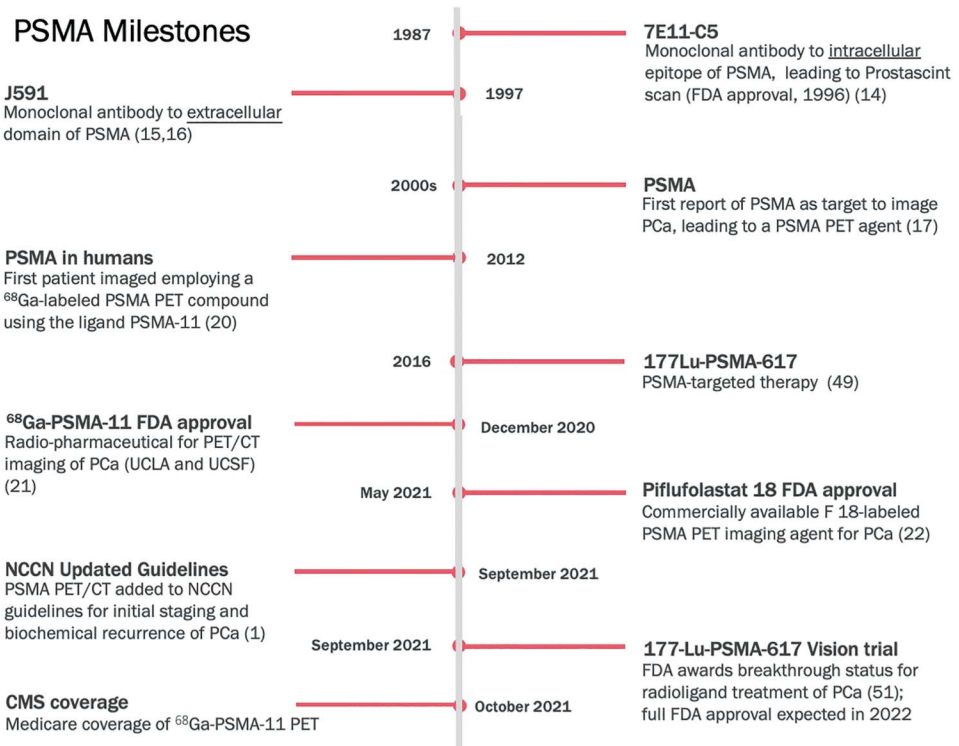


**Figure 2.** Milestones in development of current PSMA PET/CT scan. *CMS*, Centers for Medicare and Medicaid Services.

*Pivotal PSMA studies used in application to FDA*

| Indication | Studies | |
|---|---|---|
| BCR: | | |
| Author | Fendler et al[28] | Morris et al (CONDOR)[39] |
| Yr | 2019 | 2021 |
| No. pts | 635 | 208 |
| Radiotracer | $^{68}$Ga-PSMA-11 | $^{18}$F-DCFPyL |
| Median age (range) | 69 (44–95) | 68 (43–91) |
| Mean ng/ml PSA (range) | 2.1 (0.1–1,154) | 0.8 (0.2–98.4) |
| % Sensitivity | 90–92 | Not available |
| % Specificity | Not available | Not available |
| % PPV by histopathology/correlative imaging/PSA response | 84/not available/not available | 93/89/100 |
| % PPV by composite reference standard | 92 | Not available |
| % PPV by region (prostatic/pelvic/extrapelvic) | Not available | 80/67/67 |
| % Neg predictive value | Not available | Not available |
| Inter-reader agreement (Fleiss κ) | 0.65–0.78 | 0.58–0.73 |
| % Whole body detection rate | 75 | 85–87 |
| Pretreatment staging: | | |
| Author | Hope et al[29] | Pienta et al (OSPREY)[40] |
| Yr | 2021 | 2021 |
| No. pts | 277 | 252 |
| Radiotracer | $^{68}$Ga-PSMA-11 | $^{18}$F-DCFPyL |
| Median age (range) | 69 (63–73) | 64 (46–84) |
| Mean ng/ml PSA (range) | 11.1 (6.5–18) | 9.7 (1.2–125.3) |
| % Sensitivity | 40 | 31–42 |
| % Specificity | 95 | 96–99 |
| % PPV | 75 | 78–91 |
| % Neg predictive value | 81 | 81–84 |
| Inter-reader agreement (Fleiss κ) | 0.46–0.71 | 0.71–0.85 |
| % Accuracy of pelvic nodal metastases detection | 80 | 82–84 |

imaging, which were used in the registration trials for the 2 applications to the FDA, are shown in the table and discussed below.

Examples of PSMA PET/CT scans used for initial staging of PCa and to detect recurrence after treatment are shown in in figure 3 (staging) and figure 4 (recurrence). In figure 5, the sensitivity of PSMA PET/CT for detection of metastatic PCa is contrasted with that of CT scanning alone.

## GENERAL CHARACTERISTICS OF PSMA SCANS

The following are characteristics that apply universally to PSMA PET/CT scans.

### Scan Performance

PET/CT scans are performed in the nuclear medicine department. Radiotracer is administered intravenously. Following tracer uptake (50–100 minutes), PET scanning is performed over the next 20–40 minutes depending on patient size and weight. Fully diagnostic CT is also performed, and the PET/CT images are fused and interpreted. The entire procedure ordinarily takes less than 2 hours including tracer uptake period.[23]

### Safety Profile

PSMA PET scan includes a radiation dose from the isotope of approximately 4 mSv and an average dose from the CT of 12 mSv. For adults over 50 years of age, the low-dose radiation exposure falls below concerning levels. No serious adverse effects of PSMA scanning have been reported.[24]

### PSMA PET Interpretation

Interpretation for PSMA PET imaging relies on standardized criteria (PROMISE criteria, PSMA-RADS,

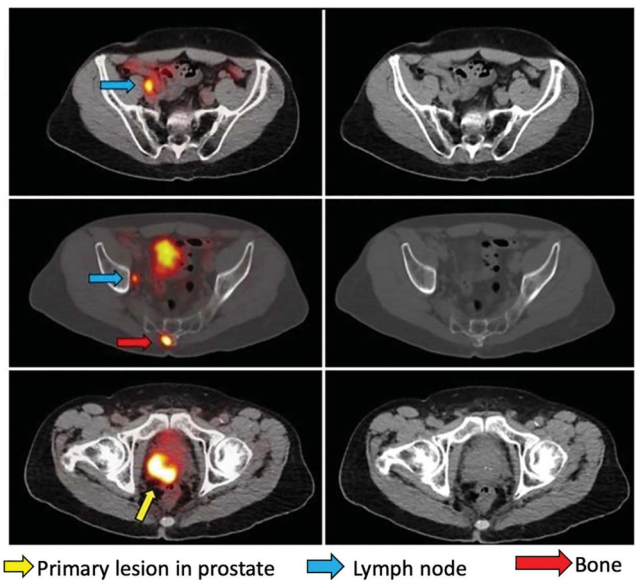


**Figure 3.** $^{68}$Ga-PSMA PET/CT scan (left) and corresponding CT scan (right) obtained for primary staging in a 77-year-old patient presenting with PSA of 7.1 ng/ml and prostate biopsy showing Gleason score of 4+5=9. Note clarity of cancerous lesions on PET/CT scan. PSMA expression is seen in the primary tumor (yellow arrow), lymph nodes (blue arrows) and in bone (sacrum, red arrow). NCCN Guidelines for 2021 have included PSMA PET/CT scanning for initial staging and to detect recurrence after primary treatment.[1]

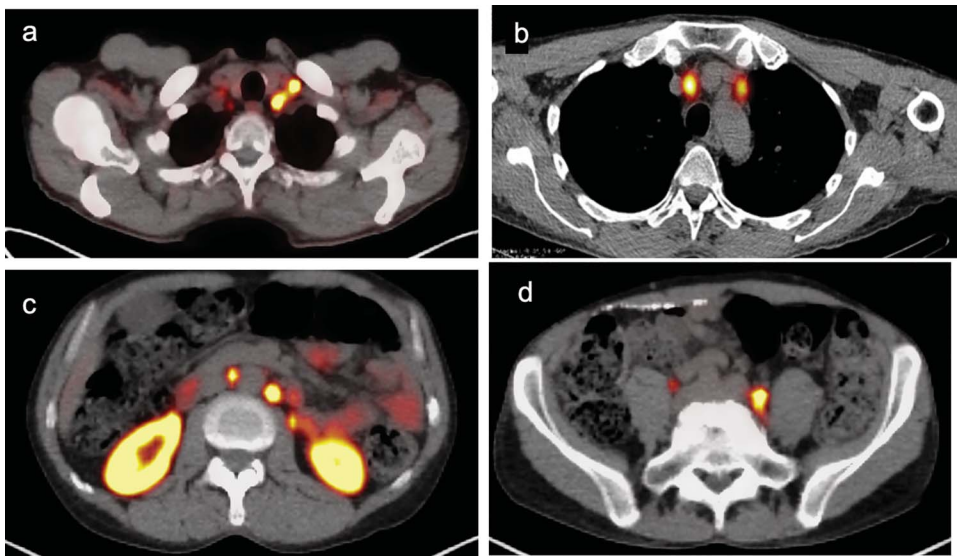


**Figure 4.** Lymph node metastases. $^{68}$Ga-PSMA PET/CT scan obtained for recurrent PCa in a 68-year-old patient with PSA of 24 ng/ml 6 years following radiation therapy for Gleason score 4+4=8 PCa. Note visualization of lymph node metastases in left supraclavicular region (*a*), mediastinum (*b*), retroperitoneum (*c*) and pelvis (*d*). Radiotracers, which bind to the extracellular epitope of PSMA, allow detection of PCa at various sites throughout the body; lymph node involvement by PCa was often undetectable prior to the advent of PSMA scanning. Uptake of $^{68}$Ga in the kidneys (shown here) is physiological.

E-PSMA).[25–27] The PSMA PET reader follows a "TNM-like" structure. PSMA uptake is analyzed visually and compared to the surrounding background and organs of reference (blood, liver, salivary glands).

### Standardized Uptake Value (SUV)

SUV is a metric used to estimate from the PET images the amount of radiotracer in a region. The intensity of PSMA PET signal using SUV can be graded as low (2–4.9), intermediate (5–10) and high (>10). However, SUVs cannot be used as an absolute indicator of PCa. The intensity of PSMA PET signal in a PCa lesion is related to the volume of the lesion and the level of PSMA expression which is correlated with the Gleason score.[4–7] A high SUV (>10) observed in a location compatible with a PCa lesion on CT is highly specific for PCa. On the other hand, in lesions with low SUVs (2–4.9), there is overlap of PCa and other processes (inflammation, bone trauma, granulomatosis, ganglia, other neoplasms). As for any other PET imaging technique, the visual analysis of the signal-to-background ratio is usually more informative than the absolute intensity of the signal. The SUV represents only 1 parameter among others to make a final diagnosis and should only be used as a complement to the visual analysis.

Inter-reader agreement of interpretation of PSMA PET/CT scans among nuclear medicine physicians is substantial (kappa values 0.6–0.8).[28,29] This is explained by the very high signal-to-noise ratio observed in PCa lesions, higher than with any other PET imaging technique.[30]

Reproducibility of PSMA PET signal studies reported that when separate scans were performed some 2 weeks apart, the findings were nearly the same. Within-subject coefficient of variation was 12%–14% for bone and lymph node lesions,[31] establishing that serial scanning may furnish important clinical information, ie in followup and after treatment.

Performance characteristics of PSMA PET/CT scanning are similar with both FDA-approved scans and are directly related to serum prostate specific antigen (PSA) levels (fig. 6 and text below).

## DATA FROM EARLY CLINICAL TRIALS

The peer-reviewed literature on PSMA PET/CT scanning is increasing rapidly, with more than 800 publications listed on PubMed just in the year 2021. Among the first large patient cohorts gathered were those of Afshar-Oromieh[32] and Eiber[33] et al in Germany. The value of PSMA PET/CT scanning has been indicated in these and subsequent large, single-arm studies.[13,34–37] Among the universally-accepted conclusions are that PSMA PET/CT scanning 1) detects PCa lesions—including local recurrences and distant metastases (lymph nodes, bone and viscera)—with greater sensitivity than conventional imaging; 2) demonstrates great specificity for PCa; 3) retains its value during disease progression and androgen deprivation therapy, though with very low serum PSA levels detection rate decreases; 4) identifies intra-prostatic PCa; 5) provides correlation of uptake intensity with PCa disease severity and 6) paves the way for radioligand therapy (RLT) of PCa as a theranostic.

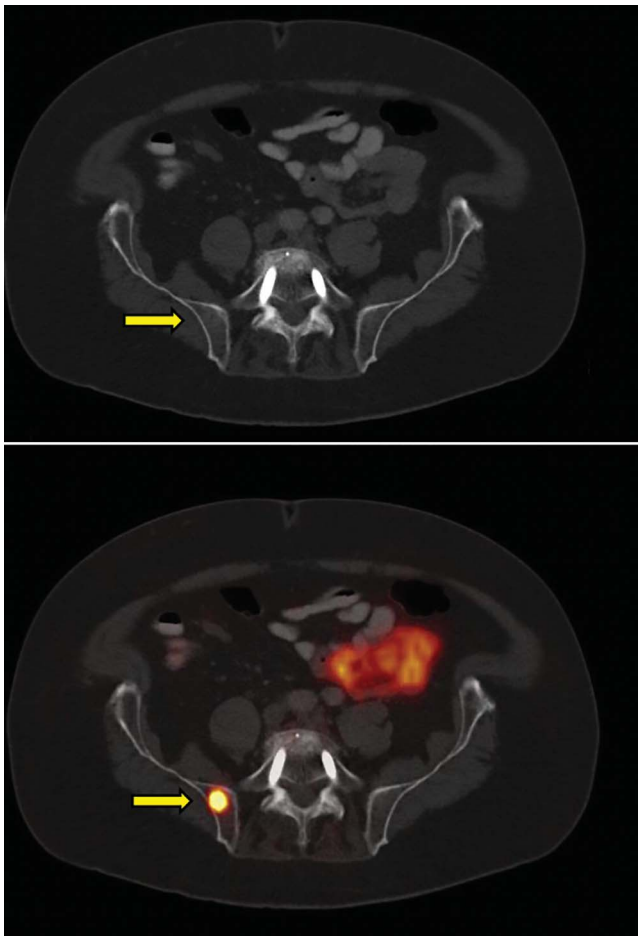

**Figure 5.** Increased sensitivity of PSMA PET/CT for bony lesion (arrows). CT scan (top) shows no abnormalities, but a lesion of PCa with high PSMA expression (bottom) is apparent in the right ileum. Even in retrospect, the CT scan was unrevealing. Because of the increased sensitivity and specificity, PSMA PET/CT has been added to the NCCN Guidelines for 2021.[1]

## PATH TO APPROVAL BY FDA

Among the clinical data most thoroughly vetted are the pivotal trials leading to recent FDA approvals (see table). The original trials, upon which the first FDA clearance was based, comprised a unique co-development effort led by imaging specialists at UCSF (Thomas Hope) and UCLA (Johannes Czernin), who were the primary investigators.[28,29] Fendler reported the UCLA experience with biochemical recurrence (BCR); Hope reported the UCSF experience with pretreatment staging (see table); the imaging agent ($^{68}$Ga-PSMA-11) and the scanning methods were the same at both study sites. For detection of BCR (PSA >0.2 ng/ml), the scan identified the recurrence in 475/635 patients (75%); positive predictive value (PPV) by histopathological validation was 84%.[28] For presurgical staging, the scan identified positive pelvic lymph nodes with a sensitivity of 40% and a specificity of 95%, the low sensitivity attributable to undetected micro-metastases.[29]

Each institution submitted similar Investigational New Drug Applications in late 2016, then matching New Drug Applications in late 2019; $^{68}$Ga-PSMA-11 was manufactured at each place locally. On December 1, 2020 FDA clearance was received by each institution, marking the first PSMA-targeted PET/CT imaging approvals for PCa. The FDA action cleared $^{68}$Ga-PSMA-11 for use in PET imaging for men with PCa and (1) suspected metastases who are candidates for initial therapy (2) suspected recurrence based on elevated serum PSA levels. Full details of the path to original FDA approval are available elsewhere.[38]

## FLUORINE-18 PSMA SCAN (PYLARIFY)

A second form of PSMA PET/CT scan, employing the isotope fluorine-18 with the radiotracer $^{18}$F-DCFPyL, entered U.S. clinical trials in 2016 (CONDOR) and 2018 (OSPREY) under sponsorship of Progenics, Inc. (now Lantheus following merger in 2020). Trial results were similar to those in the $^{68}$Ga-PSMA-11 academic trials above. In the CONDOR trial of BCR (208 patients), detection rate was 59%–66% and PPV was 78%–93%.[39] In the OSPREY trial of metastatic/recurrent patients (93), detection rate was 96% (all biopsied) and PPV was 82%; in the OSPREY trial of men with high-risk PCa at initial staging (252), sensitivity for pelvic lymph node detection was 40% (again micro-metastases) and specificity was 98%.[40] On the basis of these data, FDA clearance was issued to Progenics for $^{18}$F-DCFPyL-PSMA in May 2021 with the same indications as $^{68}$Ga-PSMA-11. A commercial product is now marketed as Pylarify (piflufolastat F-18).

In figure 6, performance characteristics of the gallium-68 and fluorine-18 based PSMA PET radiotracers are compared in results from separate meta-analyses.[41,42] While a head-to-head comparison of the 2 radiotracers is not available, detection rates appear similar and are directly related to serum PSA levels. The 2 compounds $^{18}$F-DCFPyL and $^{68}$Ga-PSMA-11 both target the extracellular domain of PSMA with great affinity, which explains their excellence as imaging agents for PCa. The main difference is the longer half-life of $^{18}$F-DCFPyL (110 minutes) vs that of $^{68}$Ga-PSMA-11 (68 minutes), which favors supply and distribution of the commercialized product. Kit-based approaches are also available permitting on-site production of the $^{68}$Ga-labeled compounds.

### PSMA VS $^{18}$F-FLUCICLOVINE

The 2 PSMA radio-tracers for PET/CT imaging are not to be confused with the PET imaging agent $^{18}$F-fluciclovine (FACBC, Axumin, Blue Earth Diagnostics, Inc., Burlington, Massachusetts), which lacks affinity for PSMA. $^{18}$F-Fluciclovine is an amino acid analog which detects increased amino acid metabolic activity of cancer. It has been commercially available since FDA approval in 2016. A prospective

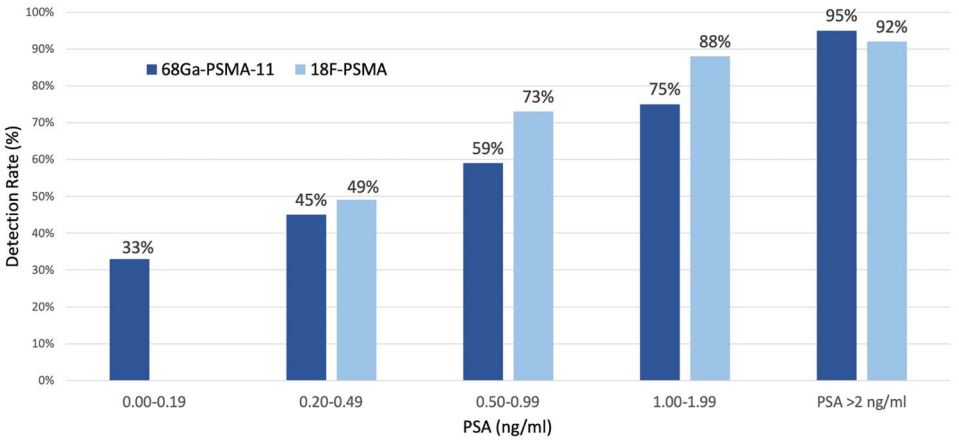


**Figure 6.** Performance characteristics of 2 FDA-approved versions of PSMA scanning. Dark blue bars represent $^{68}$Ga-PSMA (version from UCLA and UCSF) and light blue bars represent $^{18}$F-DCFPyL (version commercialized by Lantheus Corp.). Note that cancer detection rates of the 2 PSMA scans are similar and both are directly related to serum PSA levels. Data compiled from meta-analyses.[41,42]

comparison of $^{18}$F-fluciclovine (Axumin) vs $^{68}$Ga-PSMA-11 PET/CT in 50 patients with early biochemical recurrent PCa after radical prostatectomy (PSA $\leq$2.0 ng/ml) found $^{68}$Ga-PSMA-11 to be a superior imaging modality for overall detection rate of recurrent disease (56% vs 26%).[30] $^{68}$Ga-PSMA-11 also had a significantly better detection rate for pelvic lymph nodes (30% vs 8%), extra-pelvic nodes (6% vs 0%), bone metastases (8% vs 0%), metastases in other organs (4% vs 0%) and extra-pelvic lesions (16% vs 0%). $^{18}$F-fluciclovine was found to have a slightly better detection of lesions in the prostatic bed (18% vs 14%). The lower target-to-background ratio of fluciclovine (up to 8 times lower than for PSMA) is likely to account for differences in diagnostic performance.[30] Thus, PSMA appears to be the preferred PET tracer for diagnosis of recurrent PCa.

## INTRAPROSTATIC LOCALIZATION OF CANCER

In addition to imaging metastases, PSMA PET/CT scanning may also help localize cancer within the prostate. Using whole-mount pathology as a reference standard, Donato and colleagues showed an 80% overall concordance for index lesion detection between PSMA PET scans and magnetic resonance imaging (MRI).[43] PSMA PET/CT scans detected 13% of tumors missed by MRI; MRI detected 4% of tumors missed by PSMA PET/CT; with the combination, only 2% of index tumors were missed.[43] Similar results have been reported in a study employing F-18/PSMA scans.[44] Using the "gold standard" of whole-mount pathology for correlations, Sonni and colleagues recently showed that the combination of PSMA PET/CT+multiparametric MRI (mpMRI) provided intraprostatic tumor delineation better than either modality alone.[45] Thus, pending available technology, PSMA PET/MRI or the fusion of PSMA PET/CT and mpMRI (PSMA PET+mpMRI) deserves further study for localization of primary PCa.

The potential for performing a biopsy, which targets a PSMA-avid spot, was first shown in 2015.[46] Subsequently, a fusion system was used to sample a PSMA-avid spot (PET/CT-ultrasound), thus diagnosing a

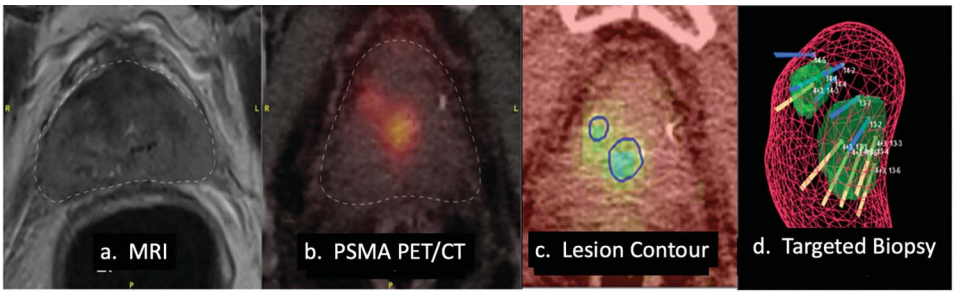


**Figure 7.** Example of PSMA-guided prostate biopsy in a 71-year-old patient with PSA of 8.5 ng/ml and prostate volume of 25 cc. MRI and systematic biopsy were negative (*a*). PSMA PET/CT scan shows 2 $^{68}$Ga-PSMA-expressing lesions in prostate (*b*). CT overlay identifies intraprostatic lesions, which are contoured (*c*). Combining PET/CT with real-time ultrasound allows targeted biopsy using image-fusion device (*d*).[47] Biopsies of larger lesion revealed Grade Group 3 PCa.

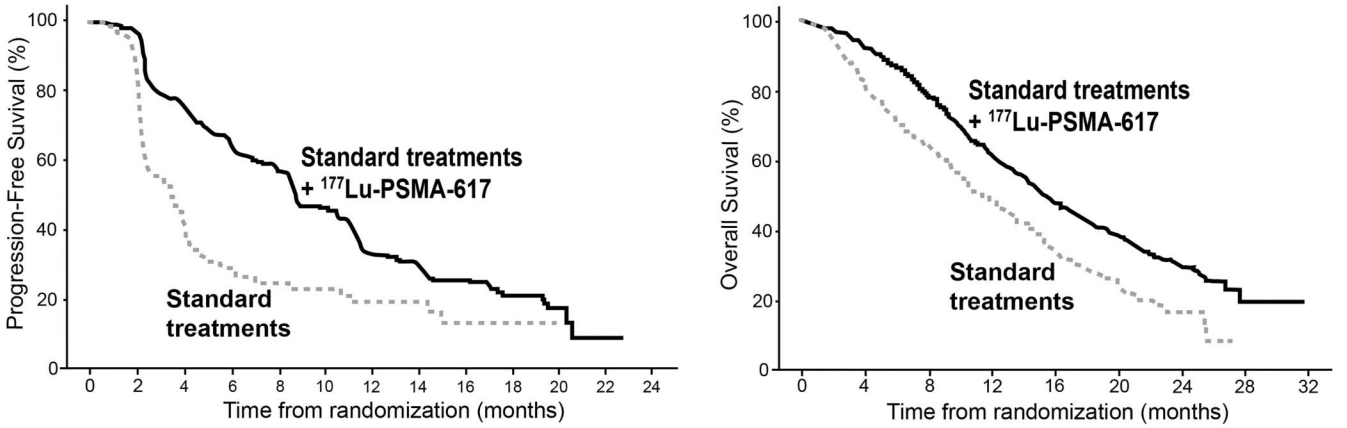


**Figure 8.** RLT for advanced PCa. Survival curves (*A*, progression-free; *B*, overall) show comparison of standard treatments alone (broken lines) and standard treatments with addition of $^{177}$Lu-PSMA-617 (solid lines), the radioligand targeting PSMA. Standard treatments included both androgen deprivation and taxanes in all patients. Addition of the radioligand significantly extended progression-free survival and overall survival ($p < 0.001$). Data are reconstructed from Morris et al[39] and Sartor et al.[51]

serious PCa that could not be detected otherwise.[47] An example of prostate biopsy successfully detecting an occult PCa by targeting a PSMA-avid lesion is shown in figure 7.

In a large prospective trial (PRIMARY) which compared MRI and PSMA-scanning with biopsy results, Emmett and colleagues found the 2 imaging modalities to provide additive information.[35] False-negative rate for clinically significant PCa was 17% with MRI and 10% with PSMA; but only 5/291 men were falsely negative by both, suggesting the possibility of deferring biopsy in such cases. All men with SUV >12 had clinically significant PCa.[35] The value of pre-biopsy imaging, as described in this important paper, deserves further study.

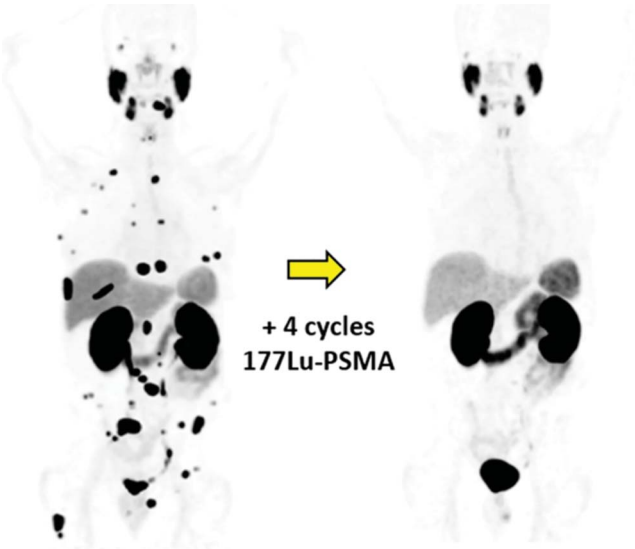


**Figure 9.** Theranostic application of PSMA PET/CT using $^{177}$Lu-PSMA in a 77-year-old patient with castration-resistant, metastatic PCa and PSA of 27 ng/ml (left). After 4 cycles of $^{177}$Lu-PSMA over a 63-week period, metastases are no longer apparent (right), and PSA decreased to 0.02 ng/ml. The theranostic is a beta-emitter, which binds to the extracellular epitope of PSMA like the pure imaging agent. At the time of this writing, the PSMA theranostic is under review at FDA.

## A PSMA-BASED THERANOSTIC

The word "theranostic" is derived from a combination of the words diagnostic and therapeutic, indicating the joint utility of an imaging agent and a therapeutic agent that both target the same receptors. The first theranostic was radioiodine. The gamma-emission of I-131 is detectable by a scanner, and the beta-emission form provides a targeted RLT.[48] Thus theranostics allow the possibility to treat cancer lesions in a specific and tumor-selective manner.

PSMA-617 is a small molecule that, like PSMA-11, binds with high affinity to the extracellular domain of PSMA. It can be labeled with the beta-emitter lutetium-177 ($^{177}$Lu) for RLT. The first prospective results of $^{177}$Lu-PSMA-617 therapy were reported by Hofman and associates in 2018.[49] Retrospective analysis of the German compassionate-use program determined that the RLT was effective in patients with metastatic castration-resistant PCa.[50]

Sartor and colleagues confirmed safety and efficacy of $^{177}$Lu-PSMA-617 therapy in a large multinational, randomized trial.[51] The landmark VISION trial, which involved 831 men with metastatic castration-resistant PCa, compared standard care alone with standard care plus the RLT in men with metastases visible on $^{68}$Ga-PET/CT. Treatment with $^{177}$Lu-PSMA-617 was administered every 6 weeks for 4–6 cycles. When lutetium was added to standard care, significant gains were observed in progression-free survival (8.7 vs 3.4 months) and overall survival (15.3 vs 11.3 months; $p < 0.001$). Survival data from the trial are shown in figure 8. Most commonly reported side effects

of lutetium included dry mouth, nausea and fatigue, but overall quality of life was not affected.[51] With these results the sponsor Novartis filed a "new drug application" with the FDA. On September 28, 2021 the agency granted "breakthrough" status for $^{177}$Lu-PSMA-617—a designation reserved for potentially transformative innovations. An example of a dramatic response to $^{177}$Lu-PSMA-617 is shown in figure 9 (patient not from the trial). Approval of the theranostic is expected in 2022.

## THE FUTURE

Assuming real-world experience resembles the clinical trial outcomes, PSMA PET/CT scanning is likely to be widely adopted. A barrier to adoption is availability of the radiotracer. However, according to the manufacturer of Pylarify (Lantheus Medical Imaging, Inc., North Billerica, Massachusetts), as of January 2022 the product is available in the U.S. within a 2-hour drive of 90% of men who might require it (380 facilities, most in metropolitan areas). In the European Union and Australia, the product is available at approximately 150 sites. Another barrier might be availability of PET scanners, but currently some 2,400 PET scanners are in place in the U.S. (versus 12,000 MRI machines). The affordability barrier should come down soon, as Medicare has issued a permanent HCPCS code (Fluor-18, A9595) for the FDA-approved indications (initial staging and biochemical recurrence), and private payors are expected to follow.

Numerous unmet PCa needs await solutions that may be provided by widespread adoption of PSMA scanning and evaluation in future clinical trials. Improved accuracy of PCa staging is one such need. Use of bone scans and abdominal CT scans would give way to the new imaging procedure, more accurate than the current staging scans. Earlier treatment for recurrent and metastatic disease would be possible, including redefinition of the oligometastatic condition. Some primary cancers, which remain undiagnosed even by MRI, would be found, especially if PET/MRI evolves; earlier curative treatments would be possible. Improved recognition of lesions suitable for partial gland ablation (or not) is another need, which is only partly resolved by current methods. The progression rate of active surveillance might be reduced, if a PSMA scan were negative up-front. For metastatic disease, the armamentarium of treatments would be expanded by theranostics providing reduced toxicity and improved outcomes compared to what is currently available.

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