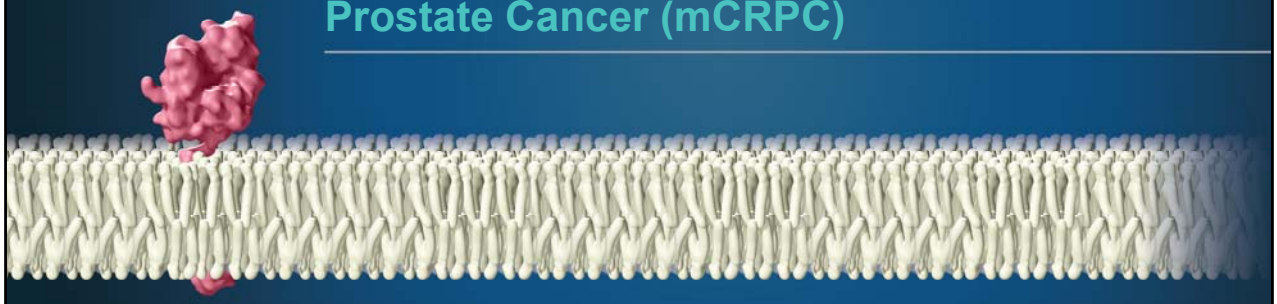
PSMA–A Clinically Validated Target in Metastatic Castration-Resistant Prostate Cancer (mCRPC)



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CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

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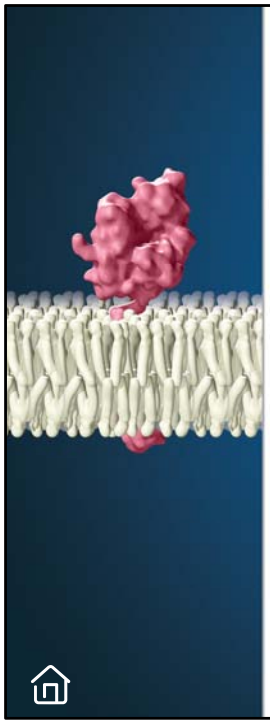

Unmet Need in mCRPC With Standard-of-Care Therapies

mCRPC, metastatic castration-resistant prostate cancer.

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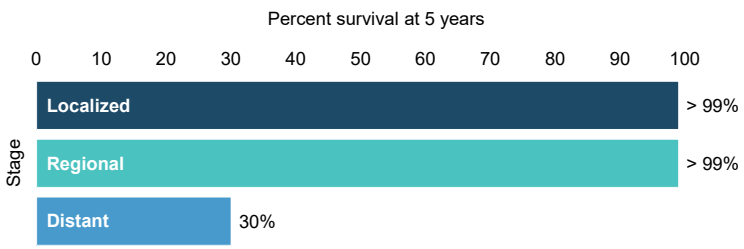
Prostate Cancer Is the Second Leading Cause of Cancer-Related Death in Men in the US[1]

~250,000 new patients diagnosed and **34,100 estimated deaths**
due to prostate cancer in the **US** in 2021[1]

Metastatic Prostate Cancer Is Associated With Reduced Survival[1,*]



- The stage at which men are diagnosed with prostate cancer varies globally[2]
- Because of the limited screening for early disease detection in developing countries, men in these countries are more likely to be diagnosed at an advanced stage compared with men in developed countries[2,†]

*5-year relative survival rates from 2010–2016 in the US.[1] †Screening is not recommended in men who are asymptomatic.[3]

1. Siegel RL, et al. *CA Cancer J Clin.* 2021;71:7-33. **2.** Taitt HE. *Am J Mens Health*. 2018;12:1807-1823. **3.** US Preventive Services Task Force. *JAMA.* 2018;319:1901-1913.

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Prostate Cancer Is a Continuum of Progressive Disease, With Most Patients Progressing to Advanced Disease[1,2]

Up to 20% of men advance to castration-resistant prostate cancer (CRPC) and no longer respond to hormonal therapy[1,2,*]

Of the men who advance to CRPC,
≥ 84% will have metastases[2,†]

Progression to mCRPC Is Associated With Poor Outcomes[3,4]

- Predicted survival rate is only **~24 months** following progression to mCRPC[3,4]
- **Quality of life** may be decreased[2,3]
- **Skeletal-related events**, such as bone pain and fractures, are increased[2,3]

*When CRPC is defined in terms of a rise in PSA levels following castration.[1] †Sites of metastases typically include bone, lymph nodes, liver, and lung.[3]
mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

1. Crawford ED, et al. *Urol Oncol*. 2017;35S:S1-S13. **2.** Kirby M, et al. *Int J Clin Pract*. 2011;65:1180-1192. **3.** Frieling JS, et al. *Cancer Control*. 2015;22:109-120. **4.** Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.

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Innovative Mechanisms of Action Are Needed to Treat mCRPC, Especially in 3L Where Treatment Options Are Limited[1-4]

- For ~20 years, the mainstay of treatment in mCRPC has been taxanes and hormonal therapy, which slow disease growth but do not significantly shrink tumors and do not improve disease-related symptoms[1,3,4]

is the average length of ADT treatment prior to progression to CRPC[3,5]

Despite recent advances and the impact of immunotherapy use in solid tumors, the majority of men with prostate cancer have not benefited and mCRPC remains an incurable and difficult to treat disease, highlighting the need for novel therapies[1,2,6-8]

However, targeted immuno-oncology therapies, designed to engage patients' own T cells and tumor-associated antigens on prostate cancer cells, may offer a potential new approach to treat mCRPC[9-12]

Emerging targeted immuno-oncology therapies may delay disease progression in patients with mCRPC who have not benefited from current SOC[1,2,12]

3L, third line; ADT, androgen-deprivation therapy; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; SOC, standard-of-care.

1. Crawford ED, et al. *Urol Oncol*. 2017;35S:S1-S13. **2.** Frieling JS, et al. *Cancer Control*. 2015;22:109-120. **3.** Sumanasuriya S, et al. *Cold Spring Harb Perspect Med*. 2018;8:a030635. **4.** Sartor O, et al. *N Engl J Med*. 2018;378:645-657. **5.** Petrylak DP, et al. *N Engl J Med*. 2004;351:1513-1520. **6.** Morsch R, et al. *BMC Cancer*. 2020;20:230. **7.** Reimers MA, et al. *Curr Urol Rep*. 2019;20:64. **8.** Subudhi SK, et al. *Sci Trans Med*. 2020;12:eaaz3577. **9.** Yuraszeck T, et al. *Clin Pharmacol Ther*. 2017;101:634-645. **10.** Baeuerle PA, et al. *Cancer Res*. 2009;69:4941-4944. **11.** Frankel SR, et al. *Curr Opin Chem Biol*. 2013;17:385-392. **12.** Tran B, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. Abstract 609O.

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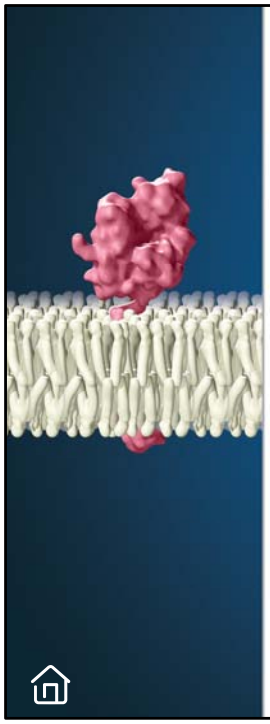

PSMA: A Clinically Validated Target in mCRPC

mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

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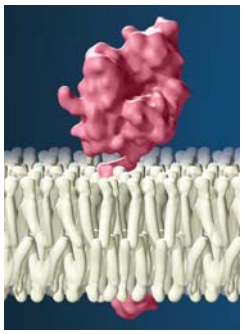
PSMA Is a Clinically Validated Therapeutic Target That Is Highly Expressed in Prostate Cancer Cells[1,2]

PSMA



- PSMA is a type II integral membrane protein that is expressed on the surface of prostate epithelial cells[1,3]
  - PSMA is also located in the cytoplasm; however, the membrane bound form of PSMA is more clinically relevant[4]
- PSMA is upregulated in most prostate tumors, with **> 90% of advanced prostate cancer cells being PSMA-positive**[5-8]
- PSMA is also expressed on the vasculature of non-prostate tumors, including lung cancer[6,7]

- In prostate cancer, PSMA expression levels increase with:
  - Disease progression and the transition to mCRPC[5,6]
  - Increasing grade of lesions and metastases[9-11]
    - PSMA expression correlates positively with Gleason score (GS) and differs significantly between grades[9-11,*]
- In prostate cancer, mPSMA overexpression is an indicator of poor prognosis[4,9,11-13]

PSMA is an attractive target for the treatment of prostate cancer and potentially other solid tumors[5-7]

*GS is used to stage prostate cancers.[11]

mCRPC, metastatic castration-resistant prostate cancer; mPSMA, membranous prostate-specific membrane antigen; PSMA, prostate-specific membrane antigen.

1. Caromile LA, et al. *Sci Signal*. 2017;10:eaag3326. **2.** Tran B, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. Abstract 609O. **3.** Wright GL Jr, et al. *Urol Oncol*. 1995;1:18-28. **4.** Paschalis A, et al. *Eur Urol*. 2019;76:469-478. **5.** Wright GL Jr, et al. *Urology*. 1996;48:326-334. **6.** Ross JS, et al. *Clin Cancer Res*. 2003;9:6357-6362. **7.** Van de Wiele C, et al. *Histol Histopathol*. 2020;35:919-927. **8.** Food and Drug Admistration. www.fda.gov. Accessed February 4, 2021. **9.** Bouchelouche K, et al. *Discov Med*. 2010;9:55-61. **10.** Cimadamore A, et al. *Front Oncol*.2018;8:653. **11.** Bravaccini S, et al. *Sci Rep*. 2018;8:4254. **12.** Chang SS. *Rev Urol*. 2004;6(suppl 10):S13-S18. **13.** Hupe MC, et al. *Front Oncol*. 2018;8:623.

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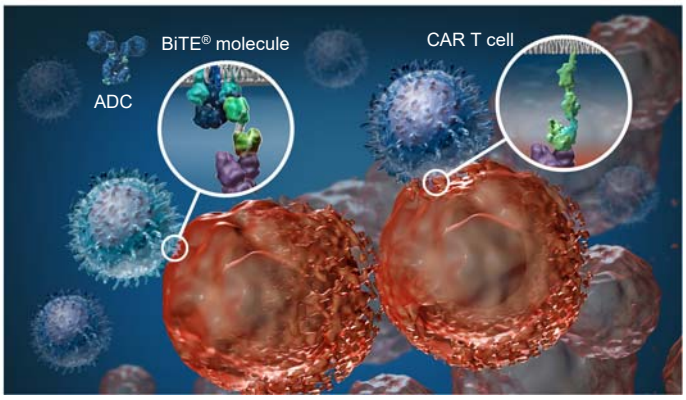
Several Modalities Are Being Investigated to Target PSMA[1]

- As PSMA expression levels increase with disease progression and in the transition to mCRPC, clinical trials are investigating modalities that target PSMA[1-4]
  - **Investigational radiolabeled compounds**: bind to the extracellular domain of PSMA, delivering beta-particle therapy to prostate cancer cells[5]
  - **Investigational antibody-drug conjugates**: specifically bind extracellular PSMA and deliver a cytotoxic drug into the cell[6]
  - **Immune cell–targeted therapies**: selectively target PSMA on tumor cells[7-10]
    - Anti-PSMA chimeric antigen receptor (CAR): natural killer (NK) cell and CAR T cell platforms are designed such that NK or T cells isolated from patients' blood are genetically engineered to target the extracellular domain of PSMA, and infused back into patients[7,8]
    - Investigational PSMA-directed vaccines: target T cells to the extracellular domain of PSMA[9]
    - Investigational BiTE® (Bispecific T-cell Engager) molecules: engage patients' own T cells and PSMA[10]



ADC, antibody-drug conjugate; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

1. Donin NM, et al. *J Nucl Med*. 2018;59:177-182. **2.** Hupe MC, et al. *Front Oncol*. 2018;8:623. **3.** Wright GL Jr, et al. *Urology*. 1996;48:326-334. **4.** Ross JS, et al. *Clin Cancer Res*. 2003;9:6357-6362. **5.** Hofman MS, et al. *Lancet Oncol*. 2018;19:825-833. **6.** Wang X, et al. *Mol Cancer Ther*. 2011;10:1728-1739. **7.** Junghans RP, et al. *Prostate*. 2016;76:1257-1270. **8.** Brand LJ, et al. *Cancer Res*. 2017;77(suppl 13):LB-185. **9.** Slovin SF. *Expert Opin Ther Targets*. 2005;9:561-570. **10.** Tran B, et al. Presented at: The European Society for Medical Oncology; September 2020; Virtual Congress. Abstract 609O.

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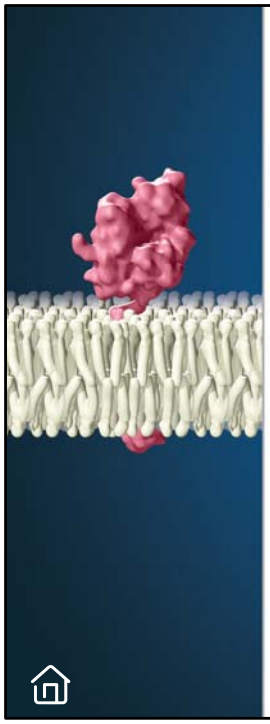

PSMA PET-CT Imaging as an Emerging Diagnostic and Treatment Management Tool for Patients With mCRPC

CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

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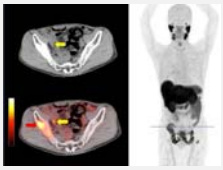
There Has Been a Shift in How Treatment Decisions Are Made in Aggressive Prostate Cancers[1]

- Until recently, treatment decisions in prostate cancers that progressed were based on clinical features (eg, PSA velocity, GS, and time from primary treatment) and conventional imaging techniques (eg, bone scan and CT)[1]
- Conventional imaging techniques rarely detect the location of disease recurrence, whereas emerging imaging techniques, such as PSMA PET-CT, can detect the site of recurrence following primary therapy[1]

PSMA PET-CT Imaging Can Be Used for Diagnosing and Monitoring Treatment Responses in Prostate Cancer[1-5]



- Clinical guidelines recommend the use of imaging techniques for diagnosis and treatment management only for intermediate- to high-risk patients with prostate cancer[6,7]
- PSMA PET-CT, which combines CT and PET scans, is becoming the **new gold standard** for detecting aggressive prostate cancers[2,8]

The clinical validation of PSMA as a target in prostate cancer has led to the utilization of PET-CT imaging to identify PSMA-positive lesions to guide diagnosis and management of patients with mCRPC[9]

CT, computed tomography; GS, Gleason score; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

1. Dorff TB, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:321-330. **2.** National Cancer Institute. www.cancer.gov. Accessed February 4, 2021. **3.** Verburg FA, et al. *Nat Rev Urol.* 2016;13:498-499. **4.** Naka S, et al. *EJNMMI Radiopharm Chem.* 2020;5:18; **5.** Liu C, et al. *Cancer Med.* 2020;9:3278-3286. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer. v.1.2021. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed February 4, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **7.** Hofman MS, et al. *Radiographics.* 2018;38:200-217. **8.** Food and Drug Administration. www.fda.gov. Accessed February 4, 2021. **9.** Evans JD, et al. *Pract Radiat Oncol.* 2018;8:28-39.

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Various PSMA-Targeted Imaging Radiotracers Can Guide Assessment of Prostate Cancer[1-3]

- Cyclotrons or generators produce radionuclides, which are attached to a biologically active molecule forming a PET radiotracer[3]

Overview of Prostate Cancer–Specific Radiotracers

Radionuclide	Examples of PET-CT Radiotracers	Half-Life (min)	Production Method	Advantages	Disadvantages	Country Utilization
^{68}GA[1-7]	• ^{68}GA-PSMA-11 • ^{68}GA-PSMA-617 • ^{68}GA-PSMA-I&T	67.7	Generator/ Cyclotron	• Long shelf-life and simple to use • Provide a steady source of the radionuclide for medical centers without cyclotrons • Tracer production can be performed every hour or up to 3 productions within 1 working day • Do not require special premises with radiation shielding constructions	• Lower positron yield, higher positron energy, and increased imaging noise • Limiting shipping range and challenging to deliver from a centralized facility • Presence of cationic metal ion impurities (eg, Al, Fe, Cu, Zn, Ti, Sn)	• ^{68}GA-PSMA-11: US – FDA-approved for suspected prostate cancer metastasis potentially curable by surgery or radiation therapy and for suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) levels • AU – all approved for routine use in many Australian hospitals
^{18}F[3,4,7-9]	• ^{18}F-FACBC • ^{18}F-DCFBC • ^{18}F-FDG* • ^{18}F-DCFPyL* • ^{18}F-10a • ^{18}F-PSMA-1007	109.8	Cyclotron	• Supports centralized production and distribution to satellite centers • Higher positron yield and lower positron energy • Allows for delayed imaging protocols and flexibility in study design	• May detect more benign lesions vs ^{68}GA-PSMA-11 • Reduced binding affinity in vitro	• ^{18}F-FACBC: US – FDA-approved for PET imaging of suspected prostate cancer recurrence based on elevated PSA levels following prior treatment
^{11}C[3]	• Choline C-11	20.3	Cyclotron	• Superior to MRI for pelvic lymph node metastases	• Decreased pooled sensitivity for detection of local recurrence	• US – FDA-approved for PET imaging of suspected prostate cancer recurrence

*Under investigation in Amgen's clinical trials.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

1. National Cancer Institute. www.cancer.gov. Accessed February 4, 2021. **2.** Food and Drug Administration. www.fda.gov. Accessed February 4, 2021. **3.** Evans JD, et al. *Pract Radiat Oncol.* 2018;8:28-39. **4.** Czarniecki M, et al. *Transl Androl Urol.* 2018;7:831-843. **5.** Velikyan I, et al. *Molecules.* 2015;20:12913-12943. **6.** Dash A, et al. *Am J Nucl Med Mol Imaging.* 2019;9:30-66. **7.** Werner RA, et al. *Theranostics.* 2020;10:1-16. **8.** Rauscher I, et al. *J Nucl Med.* 2020;61:51-57. **9.** NCT04631601. https://clinicaltrials.gov/ct2/show/NCT04631601. Accessed February 19, 2021.

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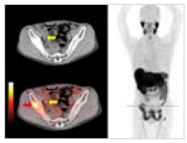
Overview of the Production Process for PSMA-Targeted PET-CT Imaging

Radionuclide is produced in a high energy cyclotron[1,2]

PSMA-targeted radiotracers can be produced in commercially available automated synthesis units[2,3,*]

The PSMA-targeted radiotracer is injected into the patient[1,4]

The patient undergoes the PSMA-targeted radiotracer PET/CT scan[4]



Tumor load is determined by PSMA-targeted radiotracer PET/CT scan[2,5]

*Examples include TracerLab FXFN and TracerLab MX (GE Healthcare), NEPTIS® mosaic-RS (ORA), SYNTHERA®+ (IBA), and CFN-MPS200 (Sumitomo Heavy Industries).[2,3]
CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

1. Evans JD, et al. *Pract Radiat Oncol.* 2018;8:28-39. **2.** Naka S, et al. *EJNMMI Radiopharm Chem.* 2020;5:18. **3.** Bouvet V, et al. *EJNMMI Res.* 2016;6:40. **4.** King's College Hospital NHS Foundation Trust. https://www.kch.nhs.uk/service/cancer/tests-and-investigations/nuclear-medicine-scan. Accessed February 2, 2021. **5.** Czarniecki M, et al. *Transl Androl Urol.* 2018;7:831-843.

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PSMA-Based Imaging May Aid in Diagnosis, Treatment Assessment, and Predict Clinical Outcomes in Patients With mCRPC[1,2]

Clinical Trials Have Demonstrated Positive Outcomes With PSMA PET-CT Imaging

Diagnosis

- PSMA PET-CT imaging was **27% more accurate in detecting any metastases** compared with conventional imaging[3]

Treatment Assessment

- Incorporation of PSMA PET-CT imaging resulted in a **treatment plan change for 15%** of men who underwent conventional imaging initially[3]

Clinical Outcomes

- PSMA PET-CT imaging identified patients with higher levels of PSMA expression who experienced **longer mPFS** following long-term hormonal treatment than nonresponders (12.1 months vs 6.8 months, $P = 0.012$)[1]

CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; mPFS, median progression-free survival; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

1. Liu C, et al. *Cancer Med.* 2020;9:3278-3286. **2.** Hofman M. *Clin Adv Hematol Oncol.* 2019;17:370-373. **3.** National Cancer Institute. www.cancer.gov. Accessed February 4, 2021.

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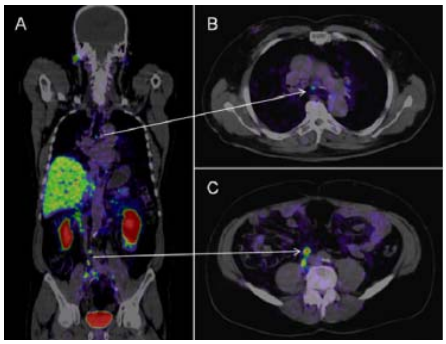
PSMA PET-CT Imaging Is Evolving Practice in Aggressive Prostate Cancers[1,2]

^{68}GA PSMA PET-CT Results in a Patient With Prostate Cancer[3]



- PSMA PET-CT imaging has demonstrated superior accuracy over conventional imaging techniques for staging high-risk patients[1,3]
  - **Superior sensitivity (66% vs 44%)** and **specificity (99% vs 85%)** compared to conventional imaging[1,4]
  - Detects lesions as small as **3 mm** across lymph nodes, which are undetectable with conventional imaging[1]
  - **Does not detect benign lesions** that may look like prostate cancer[1,3]
- PSMA PET-CT imaging can identify patients with distant metastatic disease and may be utilized to downstage patients inaccurately diagnosed with conventional imaging[1,4]

PSMA PET-CT imaging may more accurately detect metastatic disease compared with conventional imaging in patients with prostate cancer[3]

CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

1. Hofman M. *Clin Adv Hematol Oncol.* 2019;17:370-373 **2.** Dorff TB, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:321-330. **3.** National Cancer Institute. www.cancer.gov. Accessed February 4, 2021. **4.** Hofman MS, et al. *Radiographics.* 2018;38:200-217.

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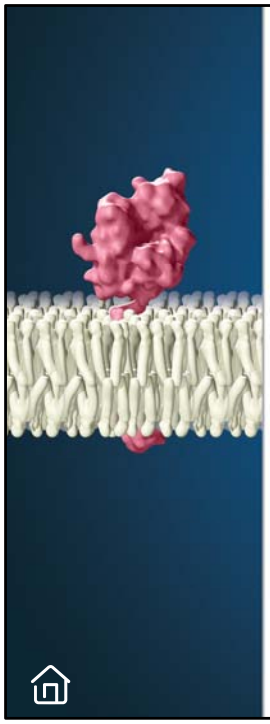

Summary

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Summary

- mCRPC remains an incurable and difficult to treat form of prostate cancer[1]
- PSMA expression levels increase with disease progression and in the transition to mCRPC; therefore, PSMA is an attractive target for the treatment of prostate cancer and potentially other solid tumors[2-4]
- Several treatment modalities are being investigated that target PSMA[5]
- PSMA PET-CT imaging is becoming the gold standard for imaging in prostate cancer, as it may aid in diagnosis, treatment assessment, and predict clinical outcomes in patients with mCRPC[6-9]

CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

1. Frieling JS, et al. *Cancer Control.* 2015;22:109-120. **2.** Wright GL Jr, et al. *Urology.* 1996;48:326-334. **3.** Ross JS, et al. *Clin Cancer Res.* 2003;9:6357-6362. **4.** Van de Wiele C, et al. *Histol Histopathol.* 2020;35:919-927. **5.** Donin NM, et al. *J Nucl Med.* 2018;59:177-182. **6.** National Cancer Institute. www.cancer.gov. Accessed February 4, 2021. **7.** Food and Drug Administration. www.fda.gov. Accessed February 4, 2021. **8.** Liu C, et al. *Cancer Med.* 2020;9:3278-3286. **9.** Hofman M. *Clin Adv Hematol Oncol.* 2019;17:370-373.

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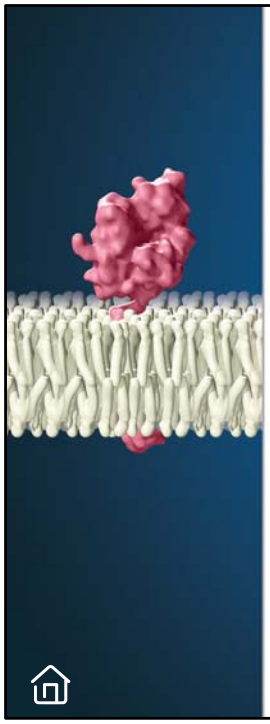

User Guide

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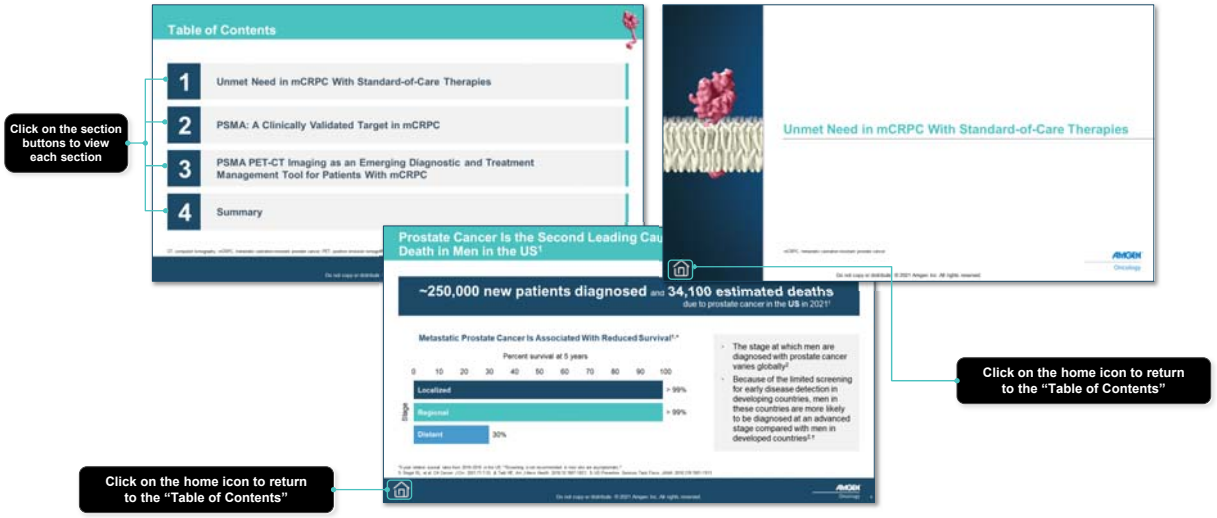
User Guide Instructions



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