PSMA in Prostate Cancer:

A PRECISION MEDICINE APPROACH

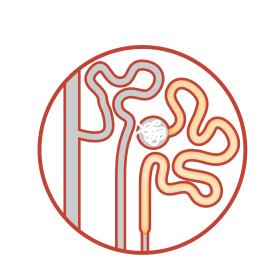
Prostate-specific membrane antigen (PSMA) is expressed in prostate epithelial cells, and expression is further upregulated in prostate cancer^{1,2}

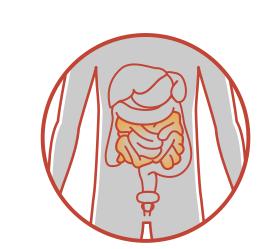
PSMA is highly expressed in the tumor tissue of >80% of men with prostate cancer*1,3-6 and detected in 87% of those with mCRPC⁶



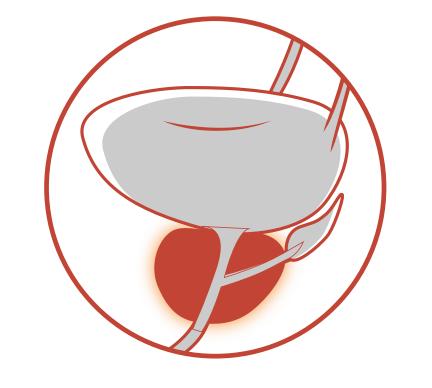
PSMA is also expressed in certain nonprostate tissues, such as the kidneys, small intestine, and salivary glands, at levels



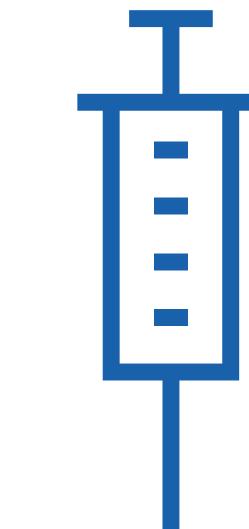








High expression has been demonstrated to be associated with advanced tumor stage^{4,7,8}

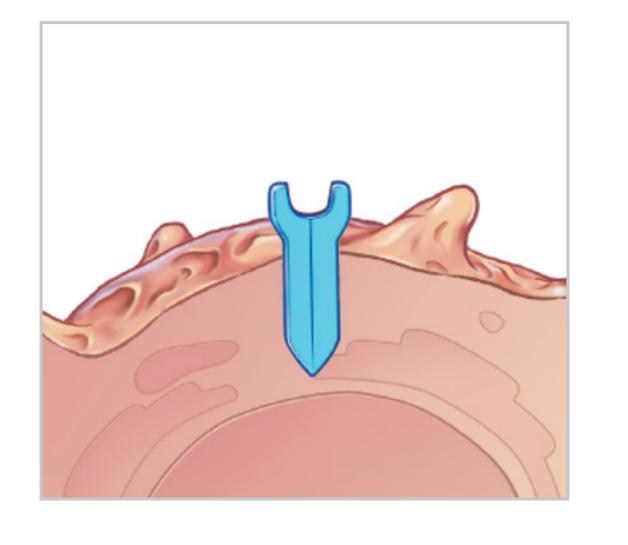


Expression has been demonstrated to remain high in metastases even after hormone therapy¹²

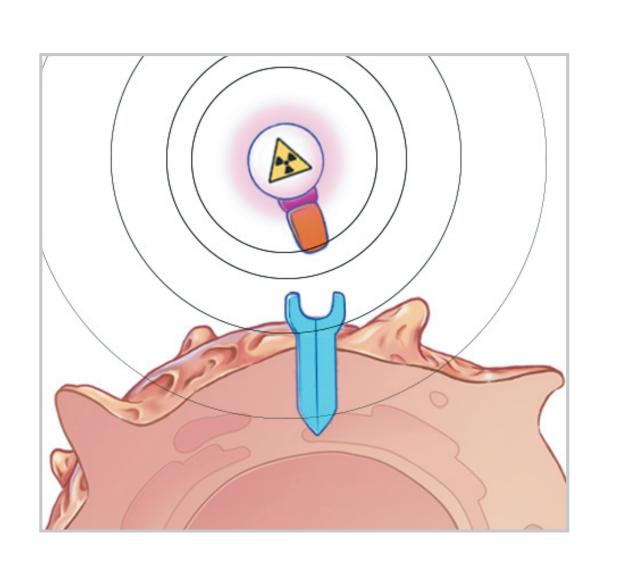


PSMA expression represents an independent indicator of prognosis in early disease and a predictor of disease recurrence^{4,8}

PSMA offers an opportunity to target prostate cancer cells^{13,14}



PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cancer epithelial cells^{1,15,16}

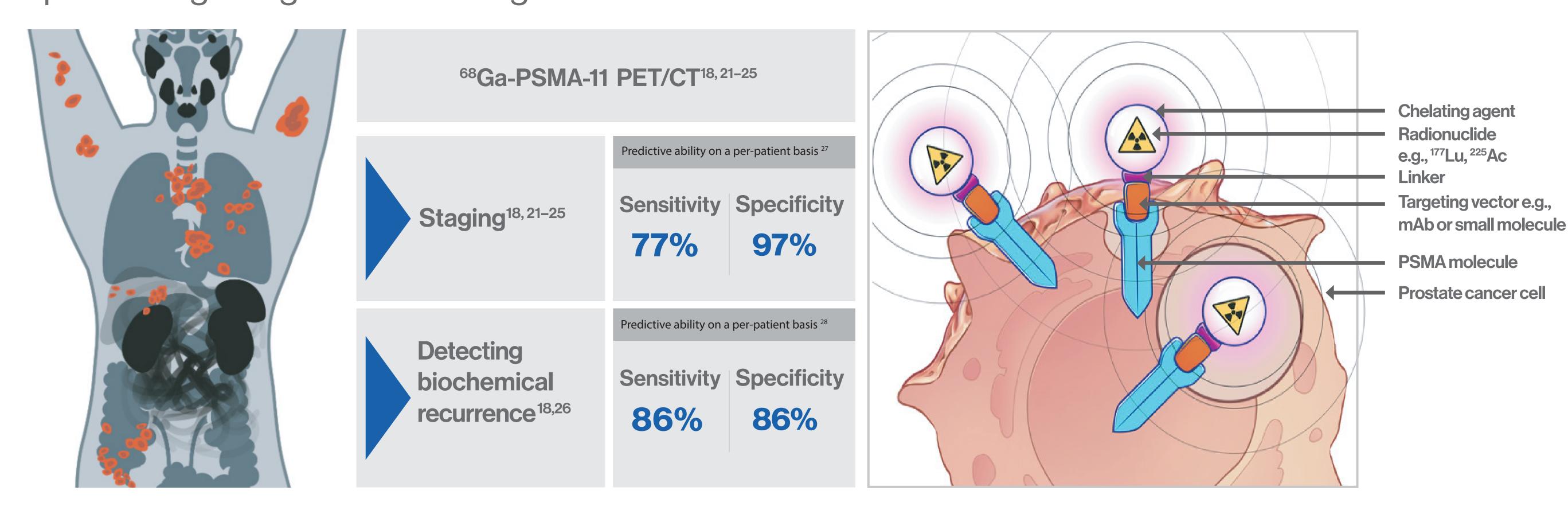


PSMA is expressed on the membrane of prostate cells, making it an accessible target for ligand binding 15,16

The labeling of PSMA ligands has led to the successful development of PSMA-targeted imaging¹⁷

PSMA PET imaging enables the detection of local, distant, and micrometastases^{13,18} and may be increasingly for radioligand therapy^{6,29–33} important in guiding disease management^{19,20}

PSMA is also being evaluated as a target



Ac, actinium; CT, computed tomography; Ga, gallium; Lu, lutetium; mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen. *Compared with benign prostate tissue

benign, and malignant prostate tissues. Urol Oncol. 1995;1(1):18-28; 3. Hope TA, et al. Impact of 68 Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. J Nucl Med. 2017;58(12):1956-1961; 4. Hupe MC, et al. Expression of prostate-specific impact on bone scan guidelines. J Nucl Med. 2020;61(3):405-411; 6. Sartor O, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021 June 23. doi: 10.1056/NEJMoa2107322 [Epub]. 7. Marchal C, et al. Expression of prostate specific membrane antigen (PSMA) in prostatic adenocarcinoma and prostatic intraepithelial neoplasia. Histol Histopathol. 2004;19(3):715–718; 8. Ross JS, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9(17):6357-6362; 9. O'Keefe DS, et al. Comparative analysis of prostate-specific membrane antigen (PSMA) versus a prostate-specific membrane antigen. Prostate. 2004;58(2):200-210; 10. Troyer JK, et al. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. Int J Cancer. 1995;62(5):552-558; 11. Sokoloff RL, et al. A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine. Prostate. 2000;43(2):150-157; 12. Ananias HJ, et al. Expression of the gastrin-releasing peptide receptor, the prostate stem cell antigen and the prostate-specific membrane antigen in lymph node and bone metastases of prostate cancer. Prostate. 2009;69(10):1101–1108; 13. Hofman MS, et al. Prostatespecific 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(10231):1208-1216; 14. Maurer T, et al. Diagnostic efficacy of (68) Gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol. 2016;195(5):1436–1443; 15. Israeli RS, et al. Molecular cloning of a complementary DNA encoding a prostate-specific membrane antigen. Cancer Res. 1993;53(2):227-230; 16. Silver DA, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3(1):81-85; 17. Food and Drug Administration. FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer (accessed July 2021); 18. Vinsensia M, et al. 68 Ga-PSMA PET/CT and volumetric morphology of PET-positive lymph nodes stratified by tumor differentiation of prostate cancer. J Nucl Med. 2017;58(12):1949–1955; 19. Fendler WP, et al. Impact of 68Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. J Nucl Med. 2020;61(12):1793–1799; 20. Müller J, et al. Clinical impact of 68 Ga-PSMA-11 PET on patient management and outcome, including all patients referred for an increase in PSA level during the first year after its clinical introduction. Eur J Nucl Med Mol Imaging. 2019;46(4):889– 900; 21. Herlemann A, et al. 68Ga-PSMA positron emission tomography/computed tomography provides accurate staging of lymph node dissection in patients with prostate cancer. Eur Urol. 2016;70(4):553-557; 22. Budäus L, et al. Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol. 2016;69(3):393–396; 23. Gupta M, et al. A comparative study of 68 Gallium-prostate specific membrane antigen positron emission tomography-computed tomography and magnetic resonance imaging for lymph node staging in high risk prostate cancer patients: an initial experience. World J Nucl Med. 2017;16(3):186–191; 24. Zhang Q, et al. Comparison of 68Ga-PSMA-11 PET-CT with mpMRI for preoperative lymph node staging in patients with intermediate to high-risk prostate cancer. J Transl Med. 2017;15:230; 25. van Leeuwen P, et al. Prospective evaluation of 68 Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. BJU Int. 2017;119(2):209-215; 26.Meredith G, et al. The use of 68Ga-PSMA PET CT in men with biochemical recurrence after definitive treatment of acinar prostate cancer. BJU Int;118(suppl 3):49-55; 27. Perera M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol. 2020;77(4):403–417; 28. Perera M, et al. Sensitivity, specificity, and predictors of positive 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in advanced prostate Cancer: A systematic review and meta-analysis. Eur Urol 2016 Dec;70(6):926-937; 29. Kratochwil C, et al. 225 Ac-PSMA-617 for PSMA-targeted-radiation therapy of metastatic castration-resistant prostate cancer. J Nucl Med. 2016;57(12):1941–1944; 30. ClinicalTrials.gov. NCT04597411. Study of 225 Ac-PSMA-617 in Men with PSMA-positive prostate cancer. https://clinicaltrials.gov/ct2/show/NCT04597411 (accessed July 2021); 31. ClinicalTrials.gov. NCT04689828. 177Lu-PSMA-617 vs. Androgen Receptor-directed Therapy in the Treatment of Progressive Metastatic Castrate Resistant Prostate Cancer (PSMAfore). https://clinicaltrials.gov/ct2/ show/NCT04689828 (accessed July 2021); 32. Clinical Trials.gov. NCT04720157. An International Prospective Open-label, Randomized, Phase III Study Comparing 177Lu-PSMA-617 in Combination With Soc, Versus SoC Alone, in Adult Male Patients With mHSPC (PSMAd dition). https://clinicaltrials.gov/ct2/show/NCT04720157 (accessed July 2021); 33.ClinicalTrials.gov. NCT04597411. Study of 225Ac-PSMA-617 in Men With PSMA-positive Prostate Cancer. https://clinicaltrials.gov/ct2/show/NCT04797411 (accessed July 2021).



A Novartis Company

Advanced Accelerator Applications 1204 Geneva Switzerland

10/22

AAA-NP-GL-0416-22