Precision Medicine in Advanced Prostate Cancer

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Precision Medicine Is an Approach That Utilises Diagnostic Tools to Select Therapies for Appropriate Patients to Optimise Outcomes and Minimise Adverse Events[1-10]

- The concept of **precision medicine** is based on the detailed evaluation of an individual patient's disease in order to…[1-6]
  - Gain insight into the disease diagnosis
  - Tailor a treatment approach to the patient
- The **goal** of precision medicine is to efficiently and accurately guide clinical management by[6-10]:
  - Assisting in predicting the most appropriate course of action
  - Simplifying management of complex diseases

Application of precision medicine is underpinned by a detailed understanding of the **molecular characteristics** of the patient's disease[1,3,4,6-10]

Strategy for Developing Personalised Medicine[8-10]

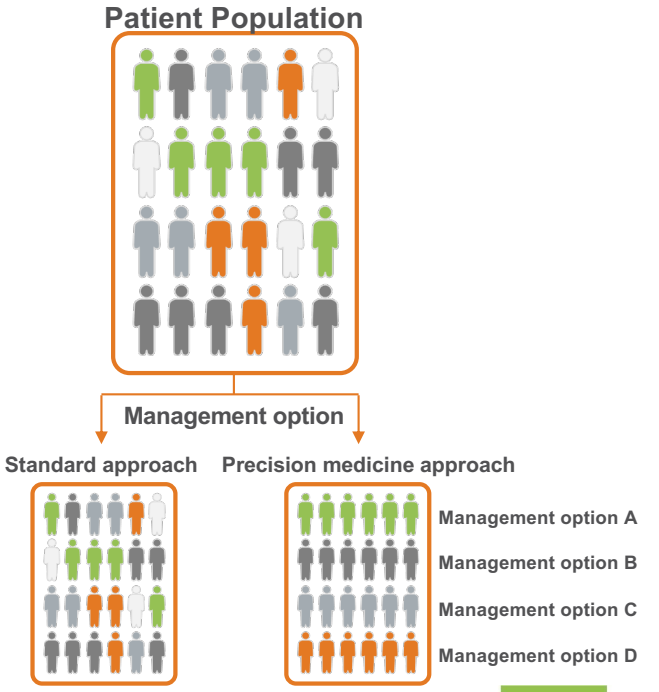

Figure modified from Yu K et al. *Sci Rep*. 2017;7:43294.

References: 1. Yates LR et al. *Ann Oncol*. 2018;29(1):30-35. **2.** Jameson J et al. The practice of medicine. In: *Harrison's Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill Education; 2018:1-20. **3.** Kratochwil C et al. *J Nucl Med*. 2016;57(8):1170-1176. **4.** Rodriguez-Rodriguez L et al. Preface: introduction to precision medicine oncology. In: *Precision Medicine Oncology: A Primer*. New Brunswick, NJ: Rutgers University Press; 2019:ix-xiii. **5.** National Cancer Institute. Precision Medicine. Accessed May 18, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/precision-medicine. **6.** Ku SY et al. *Nat Rev Urol*. 2019;16(11):645-654. **7.** Aronson SJ, Rehm HL. *Nature*. 2015;526(7573):336-342. **8.** Calais J et al. *J Nucl Med*. 2018;59(3):434-441. **9.** Müller J et al. *Eur J Nucl Med Mol Imaging*. 2019;46(4):889-900. **10.** Zang S et al. *Oncotarget*. 2017;8(7):12247-12258.

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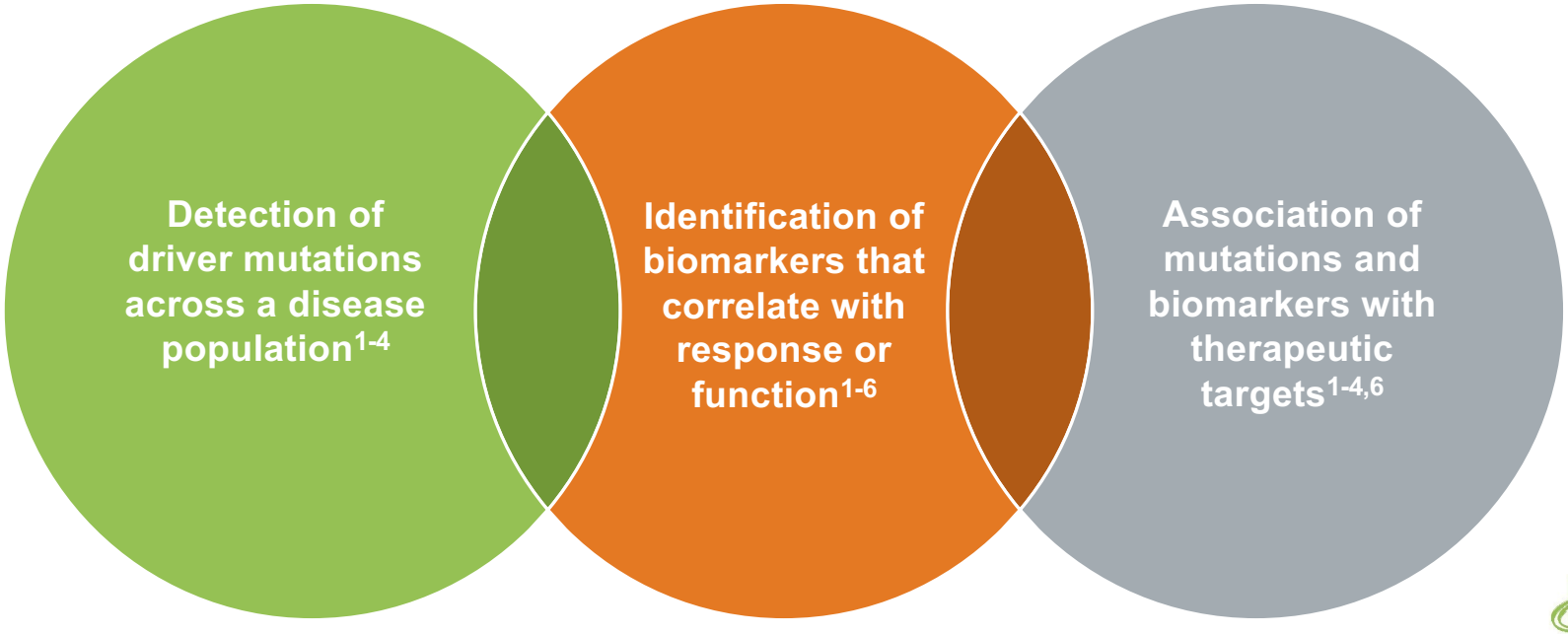
Precision Medicine Requires Several Key Components for Successful Translation to Clinical Practice[1-6]

Key Components for a Successful Translation of Precision Medicine to Clinical Practice[1-6]



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Reference: 1. Senft D et al. *Trends Mol Med.* 2017;23(10):874-898. **2.** Cobleigh MA et al. *J Clin Oncol.* 1999;17(9):2639-2648. **3.** Huziak RM et al. *Proc Natl Acad Sci USA*. 1987;84(20):7159-7163. **4.** Lynch TJ et al. *N Engl J Med*. 2004;350(21):2129-2139. **5.** Vargas AJ, Harris CC. *Nat Rev Cancer.* 2016;16(8):525-537. **6.** de Bono J et al. *N Engl J Med*. 2020;382(22):2091-2102.

Breast Cancer as a Model for Precision Medicine in Oncology

- Management of breast cancer includes:
  - Surgery: local management of primary; regional management of axilla[1]
  - Radiation: postlumpectomy, postmastectomy, palliative radiation for metastatic disease[1]
  - Medical: chemotherapy, HER2-targeted therapy, endocrine therapy, other targeted therapies (eg, PARP inhibitors, PI3K inhibitors, CDK4/6 inhibitors)[1,2,4-8]

Molecular classification based on complex patterns of gene expression provides a **link** between **molecular biology** and **behavior of breast cancer cells** in different subtypes[3]

Actionable Mutations Identified in Breast Metastases Inform Targeted Therapies

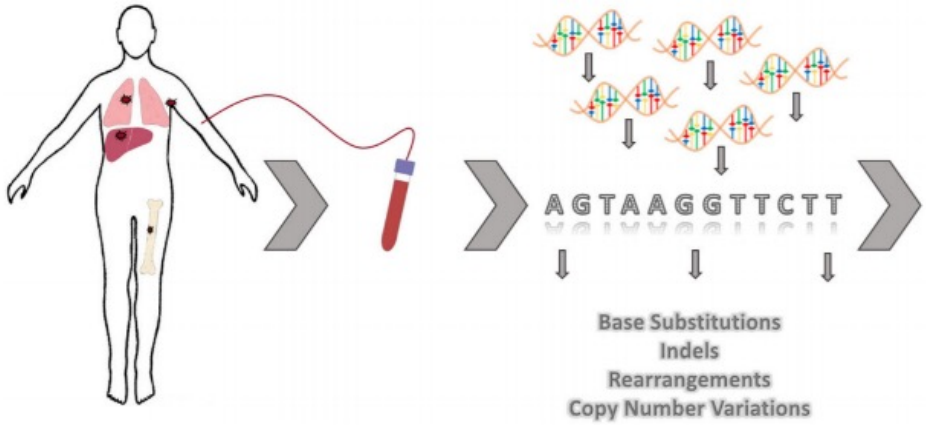

Figure modified from Ivanova E et al. *Front Mol Biosci.* 2020;7:134.

Detected genes	Drug/-s	Clinical trial
CD274 (PD-L1), TP53, MDM2, MAP2K1 (MEK1), MAP2K2 (MEK2)	Atezolizumab, Cobimetinib, Idasanutlin	NCT0356648
PTEN, AKT1, MTOR, RHEB, P1K3CA	Gedatolisib	NCT01920061
PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, FANCA, FANCC	Talazoparib	NCT02401347
TP53, ESR1, PIK3CA, AKT1, GATA3, PTEN, TBX3	Ipatasertib	NCT04253561
CDK2, CDK4, CDK6	PF-06873600	NCT03519178

CDK, cyclin-dependent kinases; HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol 3-kinase.

References: 1. McDonald ES et al. *J Nucl Med.* 2016;57(Suppl 1):9S-16S. **2.** Jazieh K et al. *Ann Transl Med.* 2020;8(14):907. **3.** Miladinova D. *Nucl Med Mol Imag.* 2019;53(5):313-319. **4.** Robson M et al. *N Engl J Med.* 2017;377(6):523-533. **5.** André F et al. *N Engl J Med.* 2019;380(20):1929-1940. **6.** Finn RS et al. *N Engl J Med.* 2016;375(20):1925-1936. **7.** Im SA et al. *N Engl J Med.* 2019;381(4):307-316. **8.** Sledge GW Jr et al. *JAMA Oncol.* 2020;6(1):116-124.

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Precision Medicine in Prostate Cancer Is Not Widely Used Due to the Lack of Actionable Biomarkers, Which Are a Critical Component of Precision Medicine[1-17]

- A **biomarker** is a disease- or host-related indicator that is objectively evaluated to characterise normal biologic processes, pathogenic processes, or responses to medical interventions[11-13]
- Biomarkers provide clinicians with important disease information to inform evidence-based decision making[5,13-16]

Examples of Biomarker Types[17]

Biomarker	Definition
Diagnostic	Primarily to assist diagnosis; most commonly using immunohistochemistry (IHC) on tissue sections but may also be a liquid test (using serum)
Prognostic	Primarily as a guide to characterise the course and prognosis of disease (therapy unspecified)
Predictive	Specifically for classification of responders vs nonresponders for a defined therapy; assay and threshold developed jointly in clinical trial with the specified drug

References: 1. Mullane SA, Van Allen EM. *Curr Opin Urol.* 2016;26(3):231-239. **2.** Friedlander TW et al. *Am Soc Clin Oncol Educ Book*. 2017;37:358-369. **3.** Romero Otero JR et al. *Urol Oncol.* 2014;32(3):252-260. **4.** Senft D et al. *Trends Mol Med.* 2017;23(10):874-898. **5.** FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Food and Drug Administration (US); 2016. https://www.ncbi.nlm.nih.gov/books/NBK326791. **6.** Tian S et al. *Cancer Cell Int*. 2020;20:409. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **8.** Kantoff PW et al. *N Engl J Med*. 2010;363(5):411-422. **9.** Kelly WK et al. *J Clin Oncol*. 2012;30(13):1534-1540. **10.** Parker C et al. *N Engl J Med*. 2013;369(3):213-223. **11.** National Cancer Institute. Biomarker. Accessed August 29, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biomarker. **12.** Millner LM, Strotman LN. *Clin Lab Med*. 2016;36(3):557-573. **13.** Saini S. *Cell Oncol (Dordr)*. 2016;39(2):97-106. **14.** Selleck MJ et al. *Biomark Insights*. 2017;12:1177271917715236. **15.** Calais J et al. *J Nucl Med*. 2018;59(3):434-441. **16.** Müller J et al. *Eur J Nucl Med Mol Imaging*. 2019;46(4):889-900. **17.** Taylor CR. Introduction to predictive biomarkers: definitions and characteristics. In: Badve S, Kumar GL, eds. *Predictive Biomarkers in Oncology*. Cham, Switzerland: Springer Nature; 2019:3-18.

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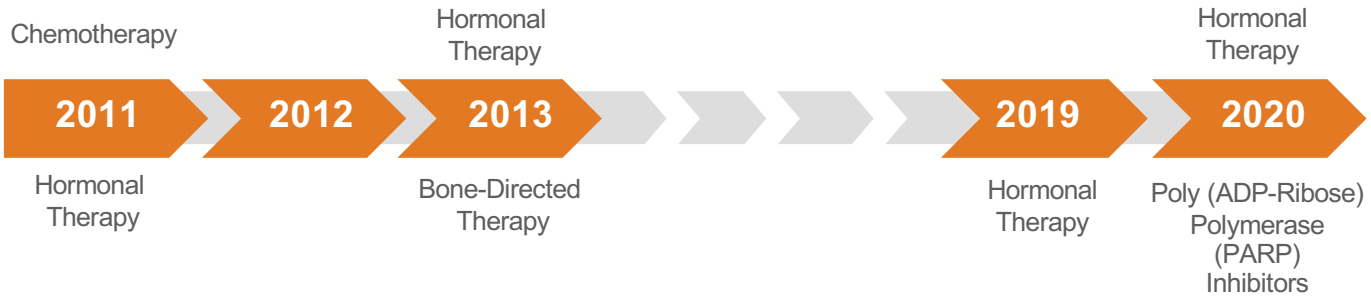
Precision Medicine in Advanced Prostate Cancer Is Not Yet Widely Used: PARP Inhibitors Approved Into an Already Complex Treatment Landscape[1-5]

- Treatment options for prostate cancer have expanded over the last decade[5-12]

Timeline of New Drug Approvals in Advanced Prostate Cancer[5-12]



- Selecting and sequencing among the available treatment options is challenging[3,4]

ADP, adenosine diphosphate.

References: 1. Mullane SA, Van Allen EM. *Curr Opin Urol.* 2016;26(3):231-239. **2.** Friedlander TW et al. *Am Soc Clin Oncol Educ Book.* 2017;37:358-369. **3.** Teo MY et al. *Annu Rev Med.* 2019;70:479-499. **4.** Huang X et al. *J Hematol Oncol.* 2012;5:35. **5.** Lynparza [summary of product characteristics]. Södertälje, Sweden: AstraZeneca AB; 2021. **6.** Jevtana [summary of product characteristics]. Paris, France: Sanofi-aventis groupe; 2015. **7.** Zytiga [summary of product characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2011. **8.** Xtandi [summary of product characteristics]. Leiden, Netherlands: Astellas Pharma Europe BV; 2013. **9.** Xofigo [summary of product characteristics]. Leverkusen, Germany: Bayer AG; 2013. **10.** Erleada [summary of product characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2019. **11.** Nubeqa [summary of product characteristics]. Leverkusen, Germany: Bayer AG; 2020. **12.** Committee for Medicinal Products for Human Use. *Summary of opinion (post authorisation): Lynparza, olaparib.* Amsterdam, Netherlands: European Medicines Agency; 2020.

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Challenges With Traditional Biomarkers in Advanced Prostate Cancer

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PSA Is the Most Commonly Used Biomarker but Is Not Ideal for Precision Medicine[1-6]

- Clinical applications for prostate-specific antigen (PSA)[2]:
  - **Initial diagnosis** of prostate cancer
  - **Risk-stratifying** disease
  - **Monitoring** biochemical recurrence
- PSA is not a predictive biomarker and **does not** provide guidance for selecting treatments in advanced prostate cancer due to a disconnect between change in PSA levels and survival outcomes[2-6]

Prostate Cancer Progression

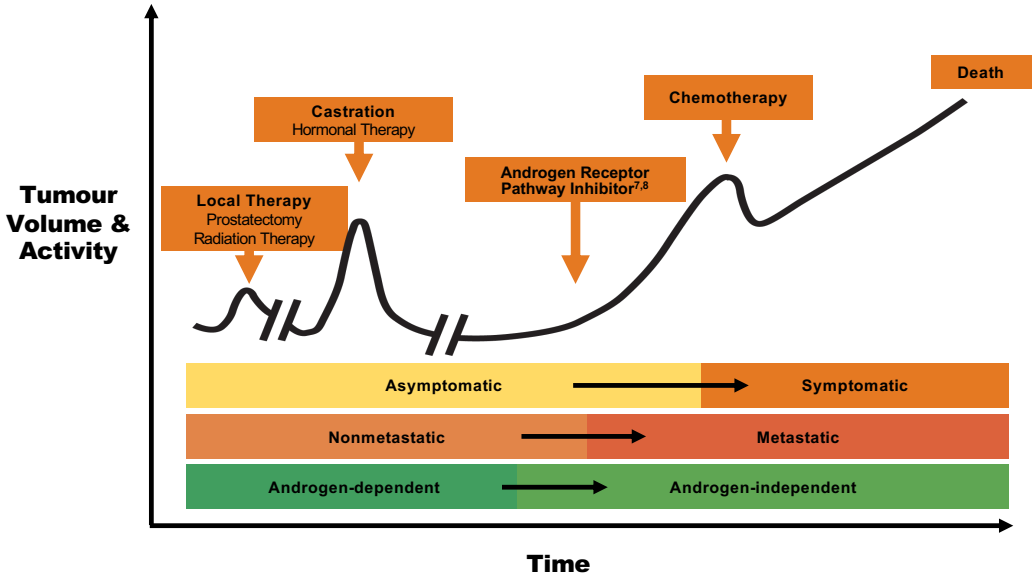

Figure modified from Higano CS et al. In: Figg W et al. (eds.) *Drug Management of Prostate Cancer*. New York, NY: Springer; 2010:321-327.

References: 1. Lorente D et al. *Eur Urol Focus.* 2016;2(5):488-498. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** Tian S et al. *Cancer Cell Int.* 2020;20:409. **4.** Kantoff PW et al. *N Engl J Med.* 2010;363(5):411-422. **5.** Kelly WK et al. *J Clin Oncol.* 2012;30(13):1534-1540. **6.** Parker C et al. *N Engl J Med.* 2013;369(3):213-223. **7.** Kulkarni HR et al. *Br J Radiol.* 2018;91(1091):20180308. **8.** Abou D et al. *Front Oncol.* 2020;10:884.

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Identifying Optimal Biomarkers in Advanced Prostate Cancer Through Traditional Genetic Sequencing Modalities Is Challenging[1-24]

There are *various challenges* in implementing precision medicine using genotypic biomarkers. Examples include:

Biologic Challenges

Disease heterogeneity[1-4]

Treatment-induced genetic alterations[1,5,6]

Few widespread mutations identified[7,8]

Clinical Challenges

Biopsies are technically difficult and associated with morbidity[3,9-20]

Complexity of interpreting biopsies due to tumour heterogeneity[2-4,9-11,21,22]

Operational Challenges

Determining timing and type of molecular testing and interpretation of test results[21-24]

Appropriately counselling patients and families[21,23]

References: 1. Testa U et al. *Medicines (Basel)*. 2019;6(3):82. **2.** Carm KT et al. *Sci Rep*. 2019;9(1):13579. **3.** Mateo J et al. *Nat Cancer*. 2020;1(11):1041-1053. **4.** Haffner MC et al. *Nat Rev Urol*. 2021;18(2):79-92. **5.** Venkatesan S et al. *Cold Spring Harb Perspect Med*. 2017;7(8):a026617. **6.** Li Q et al. *Nat Commun*. 2018;9(1):3600. **7.** Armenia J et al. *Nat Genet*. 2018;50(5):645-651. **8.** The Cancer Genome Atlas Research Network. *Cell*. 2015;163(4):1011-1025. **9.** Friedlander TW et al. *Am Soc Clin Oncol Educ Book*. 2017;37:358-369. **10.** Mullane SA, Van Allen EM. *Curr Opin Urol*. 2016;26(3):231-239. **11.** Ku SY et al. *Nat Rev Urol*. 2019;16(11):645-654. **12.** Van Allen EM et al. *Prostate Cancer Prostatic Dis*. 2014;17(1):23-27. **13.** Spritzer CE et al. *Radiology*. 2013;269(3):816-823. **14.** Holmes MG et al. *J Vasc Interv Radiol*. 2017;28(8):1073-1081. **15.** Lukaszewski B et al. *Contemp Oncol (Pozn)*. 2017;21(2):98-103. **16.** Minervini A et al. *Asian J Androl*. 2014;16(3):415-417. **17.** Wagenlehner FM et al. *Eur Urol*. 2013;63(3):521-527. **18.** Kahriman G et al. *J Clin Ultrasound*. 2011;39(5):270-273. **19.** Forsvall A et al. *Scand J Urol*. Published online June 7, 2021. doi:10.1080/21681805.2021.1933169. **20.** Evans R et al. *Open Forum Infect Dis*. 2017;4(1):ofw265. **21.** Ersek JL et al. *Am Soc Clin Oncol Educ Book*. 2018;38:188-196. **22.** Levit LA et al. *J Oncol Pract*. 2019;15(6):325-329. **23.** Giri VN et al. *J Clin Oncol*. 2020;38(24):2798-2811. **24.** Hahn AW et al. *Cancer Treat Res Commun*. 2019;19:100120.

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Heterogeneity in Advanced Prostate Cancer Makes the Use of Precision Medicine Challenging[1-4]

- Heterogeneity in prostate cancer is attributed to[1,5-7]:
  1. Genomic instability of advancing disease[1,5,7]
  2. Treatment-induced selective pressures[1,5,6]
- Together, these factors lead to the development of the genetic complexity that is characteristic of advanced prostate cancer[1-4]

Increasing Tumour Heterogeneity With Progressive Disease

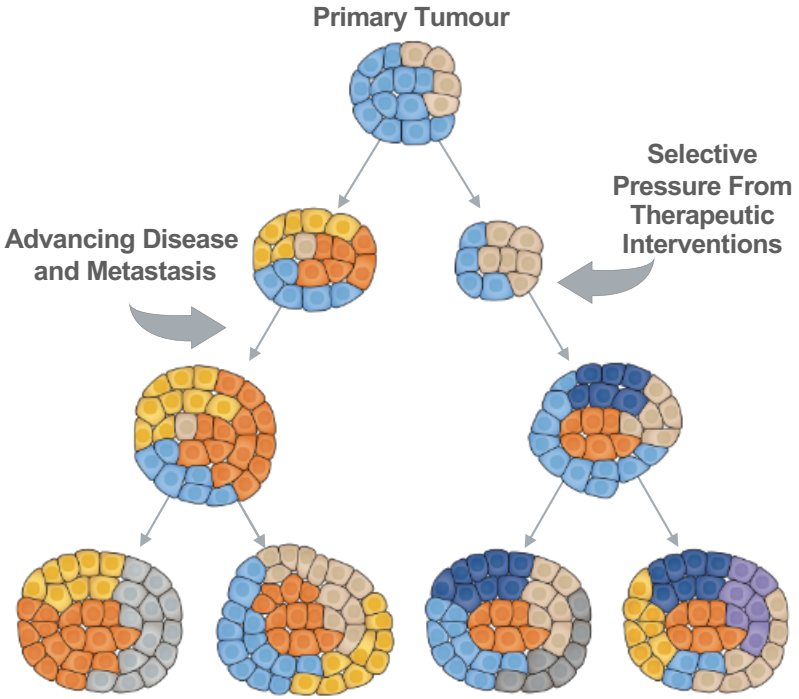

Figure modified from Maia MC et al. *Nat Rev Urol.* 2020;17(5):271-291.

References: 1. Testa U et al. *Medicines (Basel).* 2019;6(3):82. **2.** Carm KT et al. *Sci Rep*. 2019;9(1):13579. **3.** Mateo J et al. *Nat Cancer*. 2020;1(11):1041-1053. **4.** Haffner MC et al. *Nat Rev Urol.* 2021;18(2):79-92. **5.** Venkatesan S et al. *Cold Spring Harb Perspect Med*. 2017;7(8):a026617. **6.** Li Q et al. *Nat Commun*. 2018;9(1):3600. **7.** Karanika S et al. *Oncogene*. 2015;34(22):2815-2822.

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Few Widespread Mutations Have Been Identified Due To Heterogeneity of Prostate Cancer, Further Complicating Use of Targeted Therapies[1,2]

- The genomic heterogeneity of mutations in prostate cancer is characterised by a long tail of driver mutations[1,2]
- Traditional cancer gene screening panels may not be effective for identifying actionable driver mutations[3,4]
- Next-generation sequencing (NGS) modalities, which can potentially capture individualised genomic data, may be complex and expensive to perform[5-8]

Long Tail of Driver Mutations in Advanced Prostate Cancer[a]

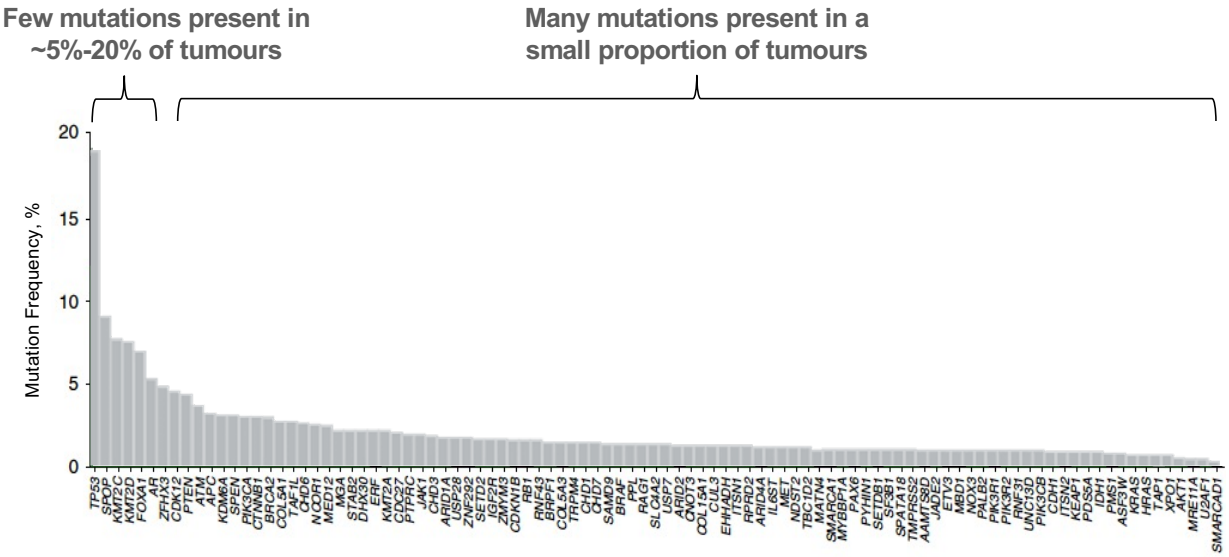

Figure modified from Armenia J et al. *Nat Genet.* 2018;50(5):645-651.

[a]In an exome sequencing analysis study, data from 1013 prostate cancers (primary, n=680; metastatic, n=333) were aggregated and uniformly analysed to identify recurrently mutated genes that occur at lower frequencies.[1]

References: 1. Armenia J et al. *Nat Genet.* 2018;50(5):645-651. **2.** The Cancer Genome Atlas Research Network. *Cell.* 2015;163(4):1011-1025. **3.** Zehir A et al. *Nat Med.* 2017;23(6):703-713. **4.** Mullane SA, Van Allen EM. *Curr Opin Urol.* 2016;26(3):231-239. **5.** Hovelson DH, Tomlins SA. *Cancer J.* 2016;22(5):357-361. **6.** Van Allen EM et al. *Nat Med.* 2014;20(6):682-688. **7.** Cheng HH et al. *Prostate.* 2016;76(14):1303-1311. **8.** Hovelson DH et al. *Neoplasia.* 2015;17(4):385-399.

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Genetic Biomarkers Can Be Clinically Challenging to Obtain and Measure in Prostate Cancer Due to Biopsy Limitations[1-17]

Comparison of Liquid and Tissue Biopsies

Biopsy Type	Definition	Advantages	Disadvantages
Tissue 	Direct sampling and evaluation of tumour tissue[1]	• Pathologic gold standard[2] • Histology and phenotypic changes easily assessed[2]	• Morbidity associated with biopsy of primary and metastatic lesions[2-8] • Difficult to biopsy bone metastases (technically challenging, lesions frequently sclerotic)[2,9-12] • Primary tumour biopsy results may not be representative of metastatic tumour genetic profile and may not capture disease heterogeneity[2,9,13-15]
Liquid 	Measuring tumour cells or circulating tumour DNA in the blood; may also apply to other measurements in the blood, urine, or saliva[16]	• Noninvasive and less morbid[2,17] • May provide a better reflection of the heterogeneity of disease[2]	• Challenging to establish a prognosis, especially in the metastatic setting; modest clinical utility[2]

References: 1. Taylor CR. Introduction to predictive biomarkers: definitions and characteristics. In: Badve S, Kumar GL, eds. *Predictive Biomarkers in Oncology*. Cham, Switzerland: Springer Nature; 2019:3-18. **2.** Friedlander TW et al. *Am Soc Clin Oncol Educ Book*. 2017;37:358-369. **3.** Lukaszewski B et al. *Contemp Oncol (Pozn)*. 2017;21(2):98-103. **4.** Minervini A et al. *Asian J Androl*. 2014;16(3):415-417. **5.** Wagenlehner FME et al. *Eur Urol*. 2013;63(3):521-527. **6.** Kahriman G et al. *J Clin Ultrasound*. 2011;39(5):270-273. **7.** Forsvall A et al. *Scand J Urol*. 2021. Published online June 7, 2021. doi:10.1080/21681805.2021.1933169. **8.** Evans R et al. *Open Forum Infect Dis*. 2017;4(1):ofw265. **9.** Mullane SA, Van Allen EM. *Curr Opin Urol*. 2016;26(3):231-239. **10.** Mateo J et al. *Nat Cancer*. 2020;1(11):1041-1053. **11.** Spritzer CE et al. *Radiology*. 2013;269(3):816-823. **12.** Holmes MG et al. *J Vasc Interv Radiol*. 2017;28(8):1073-1081. **13.** Olson EM et al. *Nat Rev Clin Oncol*. 2011;8(10):620-625. **14.** Carm KT et al. *Sci Rep*. 2019;9(1):13579. **15.** Haffner MC et al. *Nat Rev Urol*. 2021;18(2):79-92. **16.** Di Meo A. *Mol Cancer*. 2017;16(1):80. **17.** Ku SY et al. *Nat Rev Urol*. 2019;16(11):645-654.

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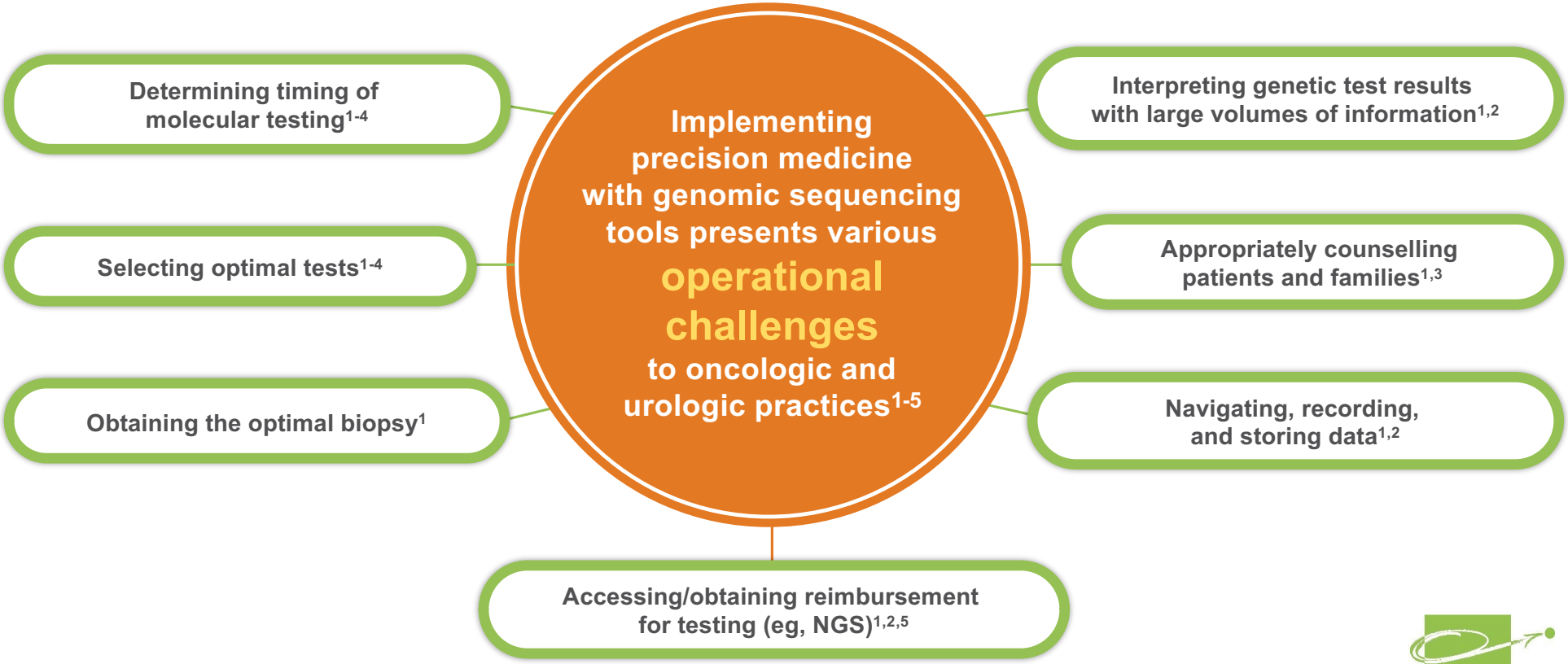
Operational Challenges Associated With Genotypic Biomarker-Based Precision Medicine



References: 1. Ersek JL et al. *Am Soc Clin Oncol Educ Book*. 2018;38:188-196. **2.** Levit LA et al. *J Oncol Pract*. 2019;15(6):325-329. **3.** Giri VN et al. *J Clin Oncol*. 2020;38(24):2798-2811. **4.** Hahn AW et al. *Cancer Treat Res Commun*. 2019;19:100120. **5.** Horgan D et al. *Biomed Hub*. 2020;5(3):511209.

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Challenges Associated With the Use of Genotypic Biomarkers in Advanced Prostate Cancer Underscore the Need for a Novel Approach[1-9]

Optimal biomarkers should be[6,10]

Clinically significant

Noninvasive

Highly sensitive and specific

References: 1. Friedlander TW et al. *Am Soc Clin Oncol Educ Book*. 2017;37:358-369. **2.** Mullane SA, Van Allen EM. *Curr Opin Urol*. 2016;26(3):231-239. **3.** Testa U et al. *Medicines (Basel)*. 2019;6(3):82. **4.** Ersek JL et al. *Am Soc Clin Oncol Educ Book*. 2018;38:188-196. **5.** Giri VN et al. *J Clin Oncol*. 2020;38(24):2798-2811. **6.** Jedinak A et al. *Oncotarget*. 2018;9(65):32534-32550. **7.** Kulkarni HR et al. *Br J Radiol*. 2018;91:20180308. **8.** Abou D et al. *Front Oncol*. 2020;10:884. **9.** Tian S et al. *Cancer Cell Int*. 2020;20:409. **10.** Taylor CR. Introduction to predictive biomarkers: definitions and characteristics. In: Badve S, Kumar GL, eds. *Predictive Biomarkers in Oncology*. Cham, Switzerland: Springer Nature; 2019:3-18.

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Understanding the Role of Phenotypes in Precision Medicine

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Imaging Phenotypes May Provide a Novel Biomarker Approach[1-4]

A **phenotypic trait** is defined as an observable characteristic that is produced through the interaction of genotype and environment (eg, the physical expression of genes)[5]

While genotypes require biologic samples for genetic sequencing,[6,7] phenotypes can be characterised by **noninvasive diagnostics**[1-4,8,9]:

- **Conventional imaging**—ie, computed tomography (CT) or bone scan[8,9]
- **Next-generation imaging**—ie, positron emission tomography (PET)/CT[8,9]

References: 1. Rowe SP et al. *J Nucl Med*. 2015;56(7):1003-1010. **2.** Osborne JR et al. *J Urol*. 2014;191(5):1439-1445. **3.** Kratochwil C et al. *J Nucl Med*. 2016;57(8):1170-1176. **4.** Lee DY, Li KC. *AJR Am J Roentgenol*. 2011;197(2):318-324. **5.** National Cancer Institute. Phenotype. Accessed June 7, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/phenotype. **6.** Ku SY et al. *Nat Rev Urol*. 2019;16(11):645-654. **7.** de Bono J et al. N Engl J Med. 2020;382(22):2091-2102. **8.** Ghafoor S et al. *J Nucl Med*. 2019;60(10):1350-1358. **9.** Crawford ED et al. *J Urol*. 2019;201(4):682-692.

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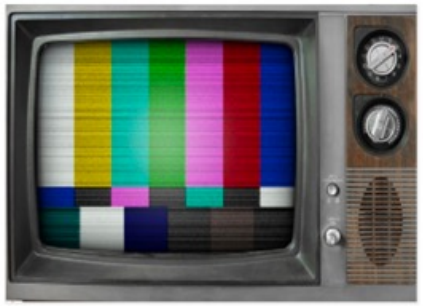
Next-Generation Imaging Can Detect Phenotypic Biomarkers[1-11]

- Phenotypic assessment through next-generation imaging is improving the ability to detect prostate cancer by enhancing the sensitivity and specificity compared to other available options[1-11]
- PET imaging leverages radiotracers to detect molecules that may be highly expressed in prostatic cancer cells[6,7,12-14]
- Examples of radiotracers used in prostate cancer imaging:
  - **^{18}F-fluciclovine:** amino acid transport[6,7,15]
  - **^{11}C-choline:** cell membrane synthesis[6,7,16]
  - **^{68}Ga-PSMA, ^{18}F-DCFBC, ^{18}F-DCFPyL:** targets prostate-specific membrane antigen (PSMA)[6,7,17]
  - **^{18}F-NaF:** bone matrix[6,7,18]

Conventional Imaging
(CT, bone scan)[7,19]



VS

Novel noninvasive diagnostics
(Radiolabeled PET/CT)[7,19]

References: 1. Rowe SP et al. *J Nucl Med*. 2015;56(7):1003-1010. **2.** Osborne JR et al. *J Urol*. 2014;191(5):1439-1445. **3.** Hofman MS et al. *Lancet*. 2020;395(10231):1208-1216. **4.** Hofman MS et al. *Lancet Oncol*. 2018;19(6):825-833. **5.** Zang S et al. *Oncotarget*. 2017;8(7):12247-12258. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Crawford ED et al. *J Urol*. 2019;201(4):682-692. **8.** Perera M et al. *Eur Urol*. 2020;77(4):403-417. **9.** Perera M et al. *Eur Urol*. 2016;70(6):926-937. **10.** Afshar-Oromieh A et al. *Eur J Nucl Med Mol Imaging*. 2015;42(2):197-209. **11.** Afshar-Oromieh A et al. *Eur J Nucl Med Mol Imaging*. 2017;44(8):1258-1268. **12.** Wright GL et al. *Urology*. 1996;48(2):326-334. **13.** Sweat SD et al. *Urology*. 1998;52(4):637-640. **14.** Hupe MC et al. *Front Oncol*. 2018;8:623. **15.** Axumin [summary of product characteristics]. Dublin, Ireland: Blue Earth Diagnostics Ireland Ltd; 2017. **16.** Choline C11 injection [prescribing information]. Rochester, MN: Mayo Clinic; September 2012. **17.** FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. U.S. Food & Drug Administration [press release]. December 1, 2020. Accessed June 28, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer. **18.** Sodium fluoride (18F) [guideline on core summary of product characteristics]. London, UK: Committee for Medicinal Products for Human Use; 2015. **19.** Ghafoor S et al. *J Nucl Med*. 2019;60(10):1350-1358.

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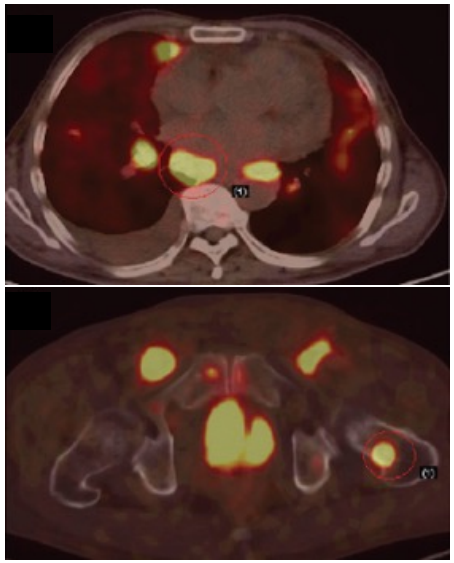
Genotyping vs Phenotyping in Advanced Prostate Cancer[1,2]

- PET imaging with radiotracers offers a phenotypic approach that may facilitate decision making and the use of precision medicine in advanced prostate cancer[2-7]

Genotyping in Advanced Prostate Cancer[1]

Phenotyping in Advanced Prostate Cancer[2]



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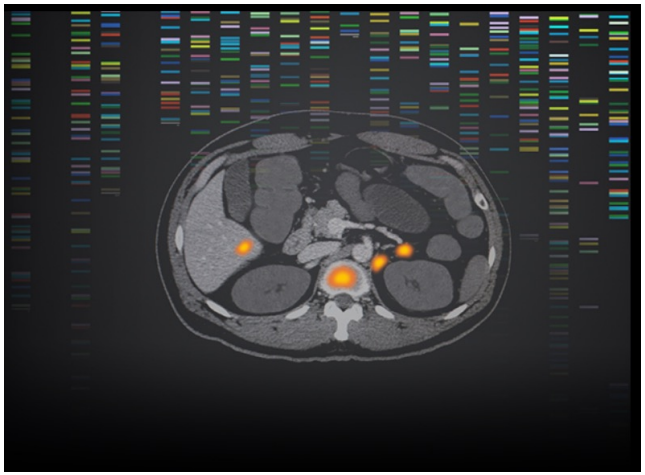
Phenotypic Biomarkers May Facilitate the Use of Precision Medicine in Advanced Prostate Cancer[1-14]

- Phenotypic precision medicine is an approach that utilises noninvasive diagnostic imaging to characterise observable traits in order to select therapies for appropriate patients with the goal of optimising outcomes while minimising adverse events[1-10]
- Prostate-specific membrane antigen (PSMA) is an example of a phenotypic biomarker whose detection by positron emission tomography (PET) represents a potential phenotypic precision medicine approach[3,5-14]



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Most Recently, PSMA PET Has Emerged as an Example of a Sensitive and Specific Imaging Technique in Prostate Cancer[1-6]

Radiotracers Used in Prostate Cancer Imaging (EU)

Radiotracer	Characteristics
^{18}F-FDG[7]	• Widely available[8] • Meaningful prognostic indicator in advanced prostate cancer[9] • Prostate cancer has low glucose metabolism, resulting in low sensitivity[8]
^{11}C-choline[10]	• Higher diagnostic sensitivity than FDG-PET/CT[11,a] • Variable sensitivity and specificity for biochemical recurrence, especially at low PSA levels[2,12] • Short half-life of 20.4 minutes requires an on-site cyclotron[2,13]
^{18}F-choline[14-25]	• High diagnostic performance for accurate staging and restaging in patients with prostate cancer[26,b] • Long half-life of 109.8 minutes does not require an on-site cyclotron[14,27] • Higher urinary excretion than ^{11}C-choline, which necessitates continuous bladder irrigation to eliminate bladder radioactivity[28] • Approved in 12 countries in Europe[14-25]
^{18}F-fluciclovine[29]	• Useful for detection of recurrent disease, particularly for patients with higher PSA values[30] • Lesion detection rate superior to choline[31,c] • Potential variability in sensitivity and specificity related to location of metastases[2]
PSMA-targeting radiotracers	• High specificity and sensitivity, even at low PSA levels[2,4,32,33,d-f] • May provide better biochemical recurrence detection than ^{18}F-fluciclovine[32,d] • ^{68}Ga-PSMA-11 was approved[g] in December 2020 and ^{18}F-DCFPyL was approved in May 2021 for use in the USA as radioactive diagnostic PET imaging agents in men with prostate cancer with suspected metastasis who are potentially curable by surgery or radiation therapy, or with suspected recurrence based on elevated serum PSA level[34,35]

^{18}F-FDG, ^{18}F-fluorodeoxyglucose; CT, computed tomography; EU, European Union; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

[a]In a meta-analysis of the diagnostic performance of ^{18}F/^{11}C-choline or PET/CT carried out on 8 selected studies including 276 patients.[11]

[b]In a meta-analysis of the staging/restaging performance of ^{18}F-choline carried out on 16 patient-based and 4 lesion-based studies in 2122 patients and 1039 lesions, respectively.[26]

[c]In a head-to-head comparison performed in 50 patients treated with radical prostatectomy for prostate cancer and presenting with rising PSA levels.[31]

[d]In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels 0.2-2.0 ng/mL.[32]

[e]In a meta-analysis of reported predictors of positive ^{68}Ga-PSMA and corresponding sensitivity and specificity profiles in 16 studies involving 1309 patients.[4]

[f]In a single-arm prospective trial of 635 patients with biochemically recurrent prostate cancer who underwent ^{68}Ga-PSMA-11 PET.[36]

[g]Available at 2 sites, the University of California, Los Angeles and the University of California, San Francisco.[34]

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** Crawford ED et al. *J Urol*. 2019;201(4):682-692. **3.** Perera M et al. *Eur Urol*. 2020;77(4):403-417. **4.** Perera M et al. *Eur Urol*. 2016;70(6):926-937. **5.** Afshar-Oromieh A et al. *Eur J Nucl Med Mol Imaging*. 2015;42(2):197-209. **6.** Afshar-Oromieh A et al. *Eur J Nucl Med Mol Imaging*. 2017;44(8):1258-1268. **7.** Fludeoxyglucose (18F) [guideline on core summary of product characteristics]. London, UK: Committee for Medicinal Products for Human Use; 2012. **8.** Wallitt KL et al. *Radiographics*. 2017;37(5):1512-1536. **9.** Jadvar H et al. *J Nucl Med*. 2013;54(8):1195-1201. **10.** Choline C11 injection [prescribing information]. Rochester, MN: Mayo Clinic; September 2012. **11.** Evangelista L et al. *Clin Transl Imaging*. 2013;1:99-109. **12.** Nanni C et al. *Eur J Nucl Med Mol Imaging*. 2016 Aug;43(9):1601-1610. **13.** Czernin J et al. *PET Clin*. 2009;4(2):163-172. **14.** AAACholine [Information destinée aux professionnels - Suisse]. Genève, Suisse: Advanced Accelerator Applications Switzerland SA; 2016. **15.** CHOLSCAN [Resume des caracteristiques du produit - Belgique]. Saint-Genis-Pouilly, France: Advanced Accelerator Applications; 2017. **16.** CHOLSCAN [Ficha técnica o resumen de las características del product - España]. Esplugues de Llobregat, España: Advanced Accelerator Applications Ibérica; 2017. **17.** CHOLSCAN [Riassunto delle caratteristiche del prodotto - Italia]. Saint Genis Pouilly, Francia: Advanced Accelerator Applications; 2017. **18.** CHOLSCAN [Preparato charakteristikų santrauka - Lietuva]. Saint Genis Pouilly, Prancūzija: Advanced Accelerator Applications; 2017. **19.** CHOLSCAN [Samenvatting van de productkenmerken - Nederland]. Saint Genis Pouilly, Frankrijk: Advanced Accelerator Applications SA (AAA); 2017. **20.** Cholview [Resumo das características do medicamento, rotulagem e folheto informative - Portugal]. Saint Genis Pouilly, França: Advanced Accelerator Applications SA (AAA); 2018. **21.** FLUROCHOL [Zusammenfassung der merkmale des arzneimittels - Österreich]. Saint Genis Pouilly, Frankreich: Advanced Accelerator Applications; 2017. **22.** FLUROCHOL [Zusammenfassung der merkmale des arzneimittels - Deutschland]. Saint-Genis-Pouilly, Frankreich: Advanced Accelerator Applications; 2017. **23.** FLUROCHOL [Resume des caracteristiques du produit - France]. Saint Genis Pouilly, France: Advanced Accelerator Applications; 2015. **24.** FLUROCHOL [Resume des caracteristiques du produit - Luxembourg]. Saint Genis Pouilly, France: Advanced Accelerator Applications; 2017. **25.** FLUROCHOL [Charakterystyka produktu leczniczego – Polska]. Saint Genis Pouilly, Francja: Advanced Accelerator Applications; 2016. **26.** Lin CY et al. *Clin Nucl Med*. 2019;44(5):365-376. **27.** DeGrado TR et al. *J Nucl Med*. 2001;42(12):1805-1814. **28.** Hara T et l. *J Nucl Med*. 2002;43(2):187-199. **29.** Axumin [summary of product characteristics]. Dublin, Ireland: Blue Earth Diagnostics Ireland Ltd; 2017. **30.** Savir-Baruch B et al. *AJR Am J Roentgenol*. 2019;213(4):851-858. **31.** Nanni C et al. *Clin Nucl Med*. 2015;40(8):e386-e391. **32.** Calais J et al. *Lancet Oncol*. 2019;20(9):1286-1294. **33.** Fendler WP et al. *JAMA Oncol*. 2019;5(6):856-863. **34.** FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. U.S. Food & Drug Administration [press release]. December 1, 2020. Accessed June 28, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer. **35.** FDA approves second PSMA-targeted PET imaging drug for men with prostate cancer. U.S. Food & Drug Administration [press release]. May 27, 2021. Accessed October 8, 2021. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-second-psma-targeted-pet-imaging-drug-men-prostate-cancer. **36.** Fendler WP et al. *J Nucl Med*. 2020;61(12):1793-1799.

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PSMA as a Diagnostic, Prognostic, and Clinically Relevant Biomarker in Prostate Cancer

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The Role of PSMA in Prostate Cancer

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PSMA Is a Transmembrane Protein That Is Highly Expressed in Prostate Cancer[1-8]

- PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cells[1,2]
- Despite the name, PSMA is not specific to the prostate gland and is found in[3-5]:
  - Normal tissues: renal tubules, prostate epithelium, duodenum, and colon
  - Tumour-associated neovasculature: eg, renal, bladder, and colon
  - Prostatic tumour tissues: primary prostate, and lymph node and bone metastases
- However, PSMA is expressed at much higher levels in prostate cancer cells[5-8]

PSMA Is a Transmembrane Protein With a Signalling Role

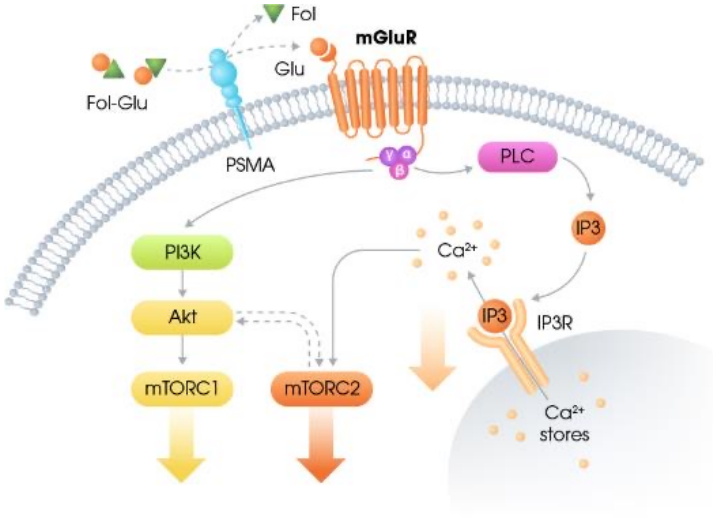

Figure modified from Kaittanis C et al. *J Exp Med*. 2018;215(1):159-175.

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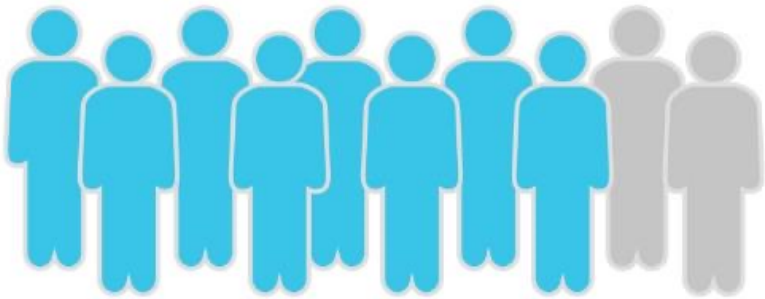
PSMA Is Highly Expressed in >80% of Men With Prostate Cancer[1-5]

- PSMA is a transmembrane protein that is anchored in the cell membrane of prostate cells[6,7]
- Ligand binding to the extracellular portion of PSMA enables detection or targeting of tumour cells[8-14]
- Expression is significantly higher in tumour tissue compared to benign tissue[1,4]
- Expression is associated with:
  - Higher tumour stage and positive nodal status[1,4]
  - Metastatic disease[1]
  - Disease progression[15]
  - Disease recurrence[1,4,16]



PSMA is highly expressed in >80% of men with prostate cancer[1-5]

References: 1. Hupe MC et al. *Front Oncol.* 2018;8:623. **2.** Hope TA et al. *J Nucl Med.* 2017;58(12):1956-1961. **3.** Pomykala KL et al. *J Nucl Med.* 2020;61(3):405-411. **4.** Minner S et al. *Prostate.* 2011;71(3):281-288. **5.** Bostwick DG et al. *Cancer.* 1998;82(11):2256–2261. **6.** Israeli RS et al. *Cancer Res.* 1993;53(2):227-230. **7.** Bařinka C et al. *Curr Med Chem.* 2012;19(6):856-870. **8.** Mesters JR et al. *EMBO J.* 2006;25(6):1375-1384. **9.** Fendler WP et al. *JAMA Oncol.* 2019;5(6):856-863. **10.** Hofman MS et al. *Lancet Oncol.* 2018;19(6):825-833. **11.** Kinoshita Y et al. *Prostate Cancer Prostatic Dis.* 2005;8(4):359-363. **12.** Perera M et al. *Eur Urol.* 2020;77(4):403-417. **13.** Sartor O et al. *N Engl J Med.* Published online June 23, 2021. doi: 10.1056/NEJMoa2107322. **14.** Yordanova A et al. *Onco Targets Ther.* 2017;10:4821-4828. **15.** Emmett L et al. *J Nucl Med.* 2019;61(6):866-872. **16.** Perner S et al. *Hum Pathol.* 2007;38:696-701.

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PSMA Is an Imaging Target in Prostate Cancer Due to Its High Expression in Malignant Tissues[1-7]

PSMA is highly expressed in prostate cancer cells, suggesting a large potential patient population that could be appropriate for PSMA imaging[5-12]

PSMA Is Highly Expressed in Prostate Cancer Cells[8,a]

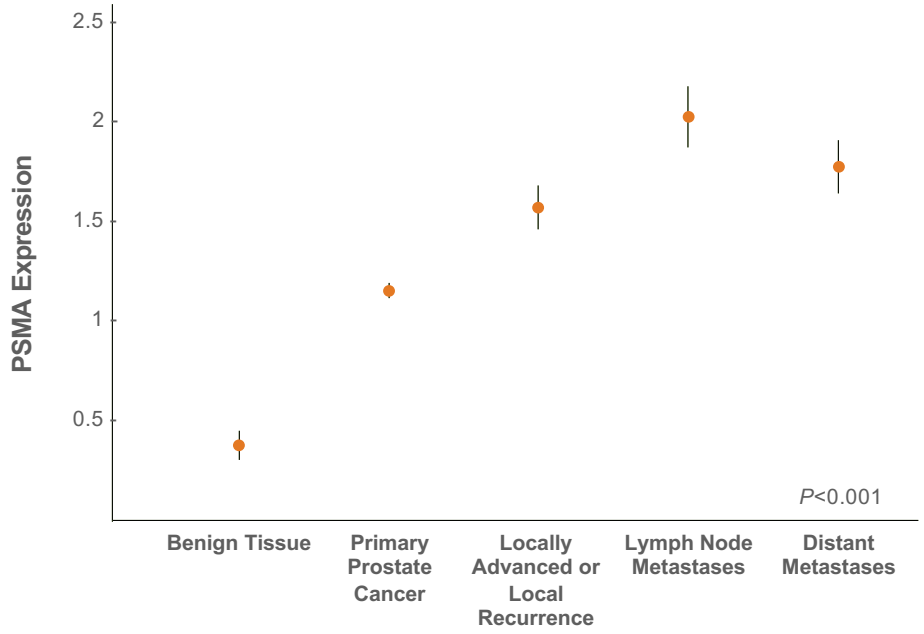

Figure modified from Hupe MC et al. *Front Oncol.* 2018;8:623.

PSMA, prostate-specific membrane antigen.

[a]PSMA expression was assessed by immunohistochemistry in 294 preoperative biopsies, 621 primary tumour foci from 242 radical prostatectomies, 43 locally advanced or recurrent tumours obtained from transurethral prostate resection, 34 lymph node metastases, and 52 benign prostatic samples from patients who underwent surgery for prostate cancer in the Hospital of Goeppingen, Germany between 2002 and 2014. An additional 78 distant metastases of patients who were treated at the University Hospital Schleswig-Holstein, Campus Luebeck, Germany, were included in the study. PSMA expression was categorised as no expression (score of 0), low expression (1), medium expression (2), or high expression (3).[8]

References: 1. Hofman MS et al. *Lancet*. 2020;395(10231):1208-1216. **2.** Hofman MS et al. *Lancet Oncol.* 2018;19(6):825-833. **3.** Zang S et al. *Oncotarget*. 2017;8(7):12247-12258. **4.** Calais J et al. *Lancet Oncol.* 2019;20(9):1286-1294. **5.** Wright GL et al. *Urology*. 1996;48:326-334. **6.** Sweat SD et al. *Urology*. 1998;52:637-640. **7.** Perner S et al. *Hum Pathol.* 2007;38:696-701. **8.** Hupe MC et al. *Front Oncol.* 2018;8:623. **9.** Hope TA et al. *J Nucl Med*. 2017;58(12):1956-1961. **10.** Pomykala KL et al. *J Nucl Med.* 2020;61(3):405-411. **11.** Minner S et al. *Prostate*. 2011;71(3):281-288. **12.** Bostwick DG et al. *Cancer*. 1998;82(11):2256-2261.

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PSMA as a Diagnostic Biomarker in Prostate Cancer

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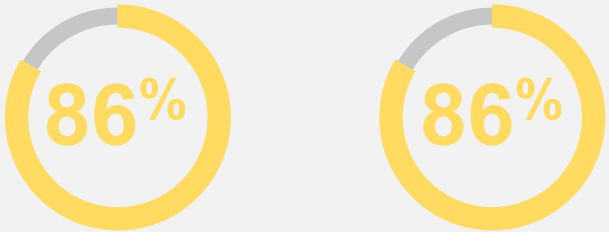
PSMA Is a Sensitive and Specific Diagnostic Biomarker for Primary and Recurrent Prostate Cancer[1,2]

Meta-analysis[1,a]

PSMA PET trials assessing prediction of primary and recurrent prostate cancer

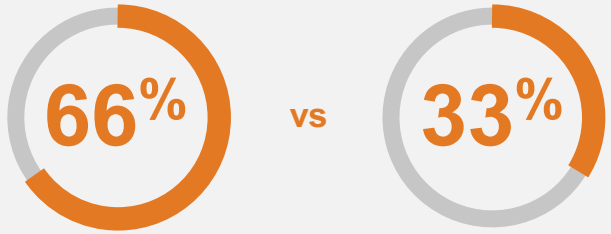
Per-patient sensitivity **Per-patient specificity**



Head-to-head trial[2,b]

PET/CT with PSMA-based radiolabeled ligands or ^{18}F-fluciclovine for localisation of biochemically recurrent disease after RP

Per-patient sensitivity



PSMA PET/CT ^{18}F-fluciclovine

CT, computed tomography; PET, positron emission tomography; FACBC, fluciclovine; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy.

[a]In a meta-analysis of 16 articles including 1309 patients, the sensitivity and specificity values were calculated for patients who underwent ^{68}Ga-PSMA PET. Studies evaluating the utility of ^{68}Ga-PSMA PET in detecting metastatic disease in advanced prostate cancer were included in the overall meta-analysis.[1]

[b]In a prospective, single-center, open-label comparative study, 50 adults with biochemical recurrence after radical prostatectomy and PSA levels 0.2 to 2.0 ng/mL received ^{18}F-fluciclovine or PSMA-based PET/CT. The primary end point was identification of tumour locations, at the patient level and by anatomical region. Per-patient sensitivity was 33% (95% CI, 15–58; five true positives and ten false negatives) for ^{18}F-fluciclovine and 66% (42–85; ten true positive and five false negative) for PSMA PET-CT (odds ratio, 3.5 [95% CI, 0.67–34.5], *P*=0.18).[2]

References: 1. Perera M et al. *Eur Urol*. 2016;70(6):926-937. **2.** Calais J et al. *Lancet Oncol*. 2019;20(9):1286-1294.

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In the ProPSMA Study, PSMA PET/CT Was Superior to Conventional Imaging for Diagnosis of Metastases

- The ProPSMA study was a multicenter randomised controlled trial of men with high-risk apparently localised prostate cancer
- Three hundred two men were randomly assigned to receive either CT and bone scan (conventional imaging) or ^{68}Ga PSMA-11 PET/CT
- PSMA PET/CT had 27% absolute greater area under the curve (AUC) for accuracy compared to conventional imaging (92% vs 65%; *P*<0.0001)
  - PSMA PET/CT was 32% more accurate for pelvic nodal metastases and 22% more accurate for distant metastases (AUC 91% vs 59% and 95% vs 74%, respectively)

Comparison of PSMA PET/CT and Conventional Imaging in 2 Men With Normal Conventional Imaging Results[a]

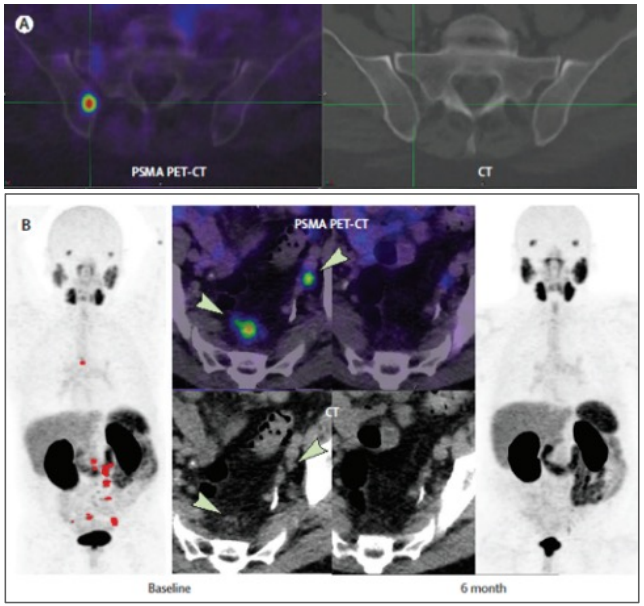

Figure modified from Hofman MS et al. *Lancet*. 2020;395(10231):1208-1216.

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

[a]Images show PSMA PET/CT and conventional imaging results for 2 patients with (A) a right iliac bone metastasis (at baseline) and (B) multiple sub-cm pelvic and distant nodal metastasis. Six-month follow-up imaging is shown in (B) after systemic treatment and disease regression.

Reference: Hofman MS et al. *Lancet*. 2020;395(10231):1208-1216.

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PSMA as a Prognostic Biomarker in Prostate Cancer

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PSMA PET/CT Shows Utility As a Prognostic Biomarker

- PSMA PET/CT results have been associated with freedom from progression after salvage radiotherapy[a]

PSMA PET Positivity Was More Independently Predictive of Freedom From Progression Than Established Clinical Factors

	Hazard Ratio	95.0% CI for Exp(B)		Significance
		Lower	Higher	
PSMA	**2.73**	**1.45**	**5.14**	**0.002**
PSA	1.17	0.82	1.68	0.38
T stage at RP	0.71	0.11	4.45	0.71
Gleason score	0.69	0.23	2.06	0.50

CT, computed tomography; Exp(B), exponentation of the B coefficient; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatatectomy; T, testosterone.

[a]In a prospective multicenter study of 260 men with rising PSA following radical prostatectomy who were considered for salvage radiotherapy were enrolled. Median PSA was 0.26 ng/mL Of the 90 men with negative PSMA PET, 32% did not receive treatment. Freedom from progression was defined as serum PSA remaining ≤0.2 ng/mL above the post salvage radiotherapy nadir, without either the initiation of androgen deprivation therapy or additional radiation therapy after completion of salvage radiotherapy.

Reference: Emmett L et al. *J Nucl Med*. 2019;61(6):866-872.

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PSMA as a Prognostic Biomarker Is Also Demonstrated by a Negative Association With 5-Year PSA Recurrence-Free Survival

- Higher PSMA expression level, as detected by IHC on preoperative biopsy, was associated with shorter 5-year PSA recurrence-free survival
  - The 5-year PSA recurrence-free survival rates are 88.2%, 74.2%, 67.7%, and 26.8% for patients exhibiting no, low, medium or high PSMA expression on preoperative biopsy, respectively

Recurrence-Free Survival According to PSMA Level at Diagnosis[a,b]

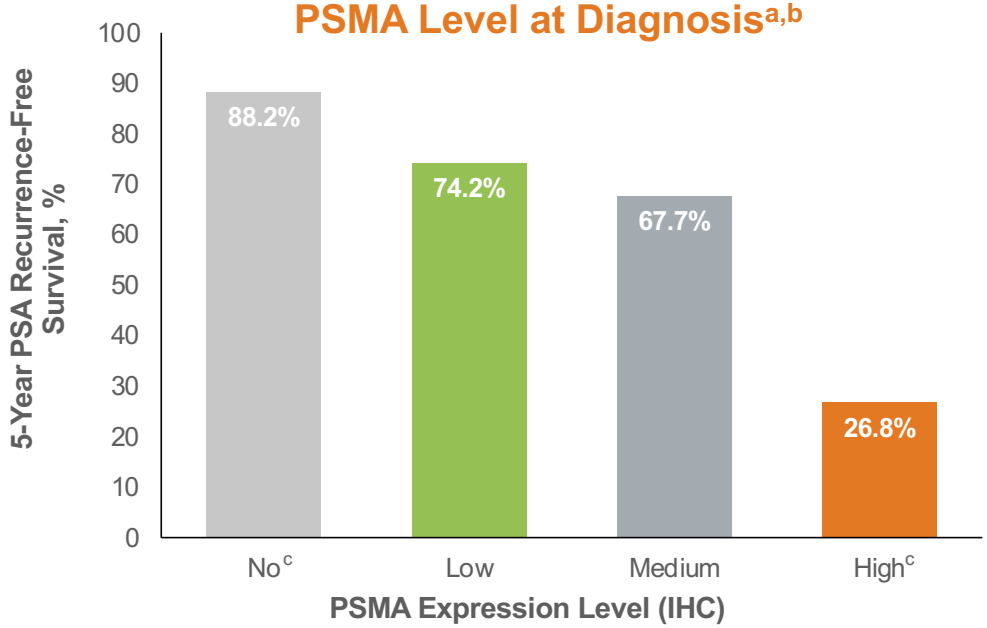

Figure modified from Hupe MC et al. *Front Oncol.* 2018;8:623.

IHC, immunohistochemistry; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

[a]PSMA expression was assessed in a retrospective study by IHC in 294 preoperative biopsies, 621 primary tumour foci from 242 radical prostatectomies, 43 locally advanced or recurrent tumours obtained from transurethral prostate resection, 34 lymph node metastases, 78 distant metastases, and 52 benign prostatic samples from patients who underwent surgery. PSMA expression was categorised as no expression (score of 0), low expression (1), medium expression (2), or high expression (3).

[b]Disease recurrence was defined as biochemical recurrence (prostate-specific antigen increase above the postoperative nadir following radical prostatectomy) and used as the end point for survival analysis.

[c]Log rank $P<0.001$ by univariate analysis for PSMA negative vs PSMA high expression.

Reference: Hupe MC et al. *Front Oncol.* 2018;8:623.

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PSMA as a Clinically Relevant Biomarker in Prostate Cancer

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PSMA PET/CT Provides Clinically Relevant Insights to Guide Treatment Plans With a Tailored Approach[1,2]

- In real-world studies and clinical trials of PSMA PET/CT, changes in management plans have been made after PSMA PET/CT[1,2]
  - PSMA PET/CT contributed to management changes in up to 60% of patients[1-3]
  - PSMA PET/CT results were used for metastasis-targeted treatment, and radiotherapy with or without systemic treatment was the most frequently selected option[1]
  - Use of systemic therapy with or without local treatment was less frequent after PSMA PET/CT than it would have been according to guidelines (before PSMA PET/CT)[1]

Change in Therapy Options With and Without PSMA PET/CT[1,a]

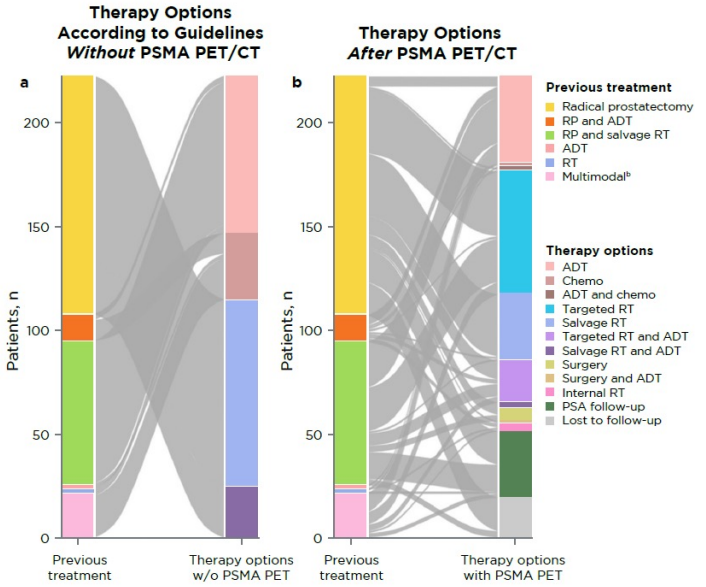

Figure modified from Müller J et al. *Eur J Nucl Med Mol Imaging*. 2019;46(4):889-900.

ADT, androgen deprivation therapy; chemo, chemotherapy; CT, computed tomography; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.

[a]The aim of the retrospective study from Switzerland was to assess the effect of PSMA PET/CT on management and outcome in all patients imaged during the first year after its introduction into clinical practice. The rate of detection of recurrence was determined from review of patient charts. In the 203 patients with follow-up 6 months after PSMA PET/CT, the therapies effectively implemented as well as follow-up PSA levels were evaluated, with a PSA value of <0.2 ng/mL representing a complete response and a decrease in PSA valued of at least 50% from baseline at the time of the scan representing a partial response.[1]

[b]Multimodal included surgery, salvage radiation therapy (RT), ADT, and/or chemotherapy combined.[1]

References: 1. Müller J et al. *Eur J Nucl Med Mol Imaging*. 2019;46(4):889-900. **2.** Fendler WP et al. *J Nucl Med*. 2020;61(12):1793-1799. **3.** Calais J et al. *J Nucl Med*. 2018;59(3):434-441.

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PSMA Upregulates Several Key Oncogenic Pathways* and Is a Potential Therapeutic Target in Prostate Cancer[1-6]

- PSMA has emerged as an attractive potential therapeutic target due to its role in several oncogenic signalling pathways[1-6]
- PSMA has been linked with a number of pathways that promote oncogenic cell growth and tumour progression[1-6]
- Expression of PSMA in the vasculature of some tumour types has been reported to be linked with worse survival[7,8]

PSMA Association With Oncogenic Signalling Pathways:

Cell proliferation and survival[1-4]

Cell migration[4]

Angiogenesis[5,6]

*In *in vitro* and animal studies.

References: 1. Kaittanis C et al. *J Exp Med*. 2018;215(1):159-175. **2.** Colombatti M et al. *PLoS One*. 2009;4(2):e4608. **3.** Perico ME et al. *Oncotarget*. 2016;7(45):74189-74202. **4.** Zhang Y et al. *Prostate*. 2013;73(8):835-841. **5.** Conway RE et al. *Mol Cell Biol*. 2006;26(14):5310-5324. **6.** Conway RE et al. *Angiogenesis*. 2016;19(4):487-500. **7.** Jiao D et al. *Clin Transl Gastroenterol*. 2019;10(5):1-7. **8.** Haffner MC et al. *Mod Pathol*. 2012;25(8):1079-1085.

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European Society for Medical Oncology Guidelines on PSMA PET/CT

- **Staging and risk-assessment**
  - Technetium bone scan and thoraco-abdominal CT scan or whole-body magnetic resonance imaging (MRI) or **PSMA PET/CT**
  - Men with intermediate- or high-risk disease should have imaging for nodal or metastatic disease
  - Whole-body MRI, choline PET/CT and **PSMA PET/CT have better sensitivity and specificity than CT or bone scan**
    - However, they have not been shown to improve clinical outcomes
    - Evidence regarding PET and whole-body MRI in this setting is not adequate to make a recommendation concerning their use
- **Treatment of relapse after radical local treatment**
  - Re-staging: for patients with biochemically recurrent prostate cancer, **PSMA PET imaging is replacing conventional imaging, based on its superior sensitivity and specificity**
    - Nevertheless, there are no trials indicating that the earlier detection of recurrence and subsequent change in management improves outcomes
    - The study of modern imaging methods has focused on their diagnostic performance, not their effect on care pathways

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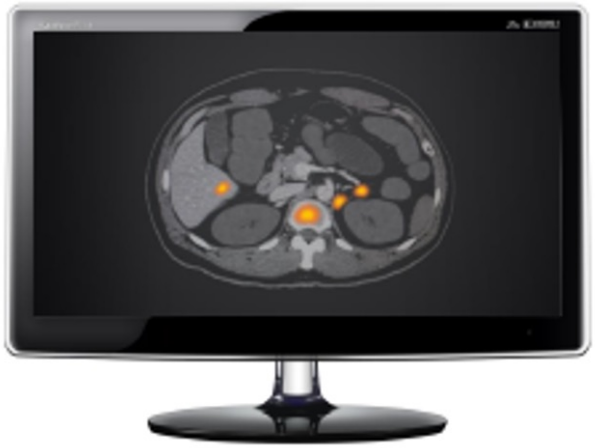
Reference: Parker C et al. *Ann Oncol.* 2020;31(9):1119-1134.

PSMA Is a Key Phenotypic Biomarker That May Facilitate the Use of Precision Medicine in Advanced Prostate Cancer[1-11]

- PSMA is a **diagnostic biomarker and potential therapeutic target**, enabling a phenotypic precision medicine approach to help guide patient selection for therapy in advanced prostate cancer[1-6]
  - Detection of a clinically relevant biomarker using a noninvasive imaging tool[2,5,6-11]
  - Optimisation of patient selection to help inform management decisions[1,2,4]
  - Utilisation of phenotypic precision medicine with the goal of improving outcomes[4,5]



References: 1. Calais J et al. *J Nucl Med*. 2018;59(3):434-441. **2.** Hofman MS et al. *Lancet*. 2020:395(10231):1208-1216. **3.** Hupe MC et al. *Front Oncol*. 2018;8:623. **4.** Müller J et al. *Eur J Nucl Med Mol Imaging*. 2019;46(4):889-900. **5.** Hofman MS et al. *Lancet Oncol*. 2018;19(6):825-833. **6.** Zang S et al. *Oncotarget*. 2017;8(7):12247-12258. **7.** Kratochwil C et al. *J Nucl Med*. 2016;57(8):1170-1176. **8.** Lee DY, Li KC. *AJR Am J Roentgenol*. 2011;197(2):318-324. **9.** Rowe SP et al. *J Nucl Med*. 2015;56(7):1003-1010. **10.** Osborne JR et al. *J Urol*. 2014;191(5):1439-1445. **11.** Calais J et al. *Lancet Oncol*. 2019;20(9):1286-1294.

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