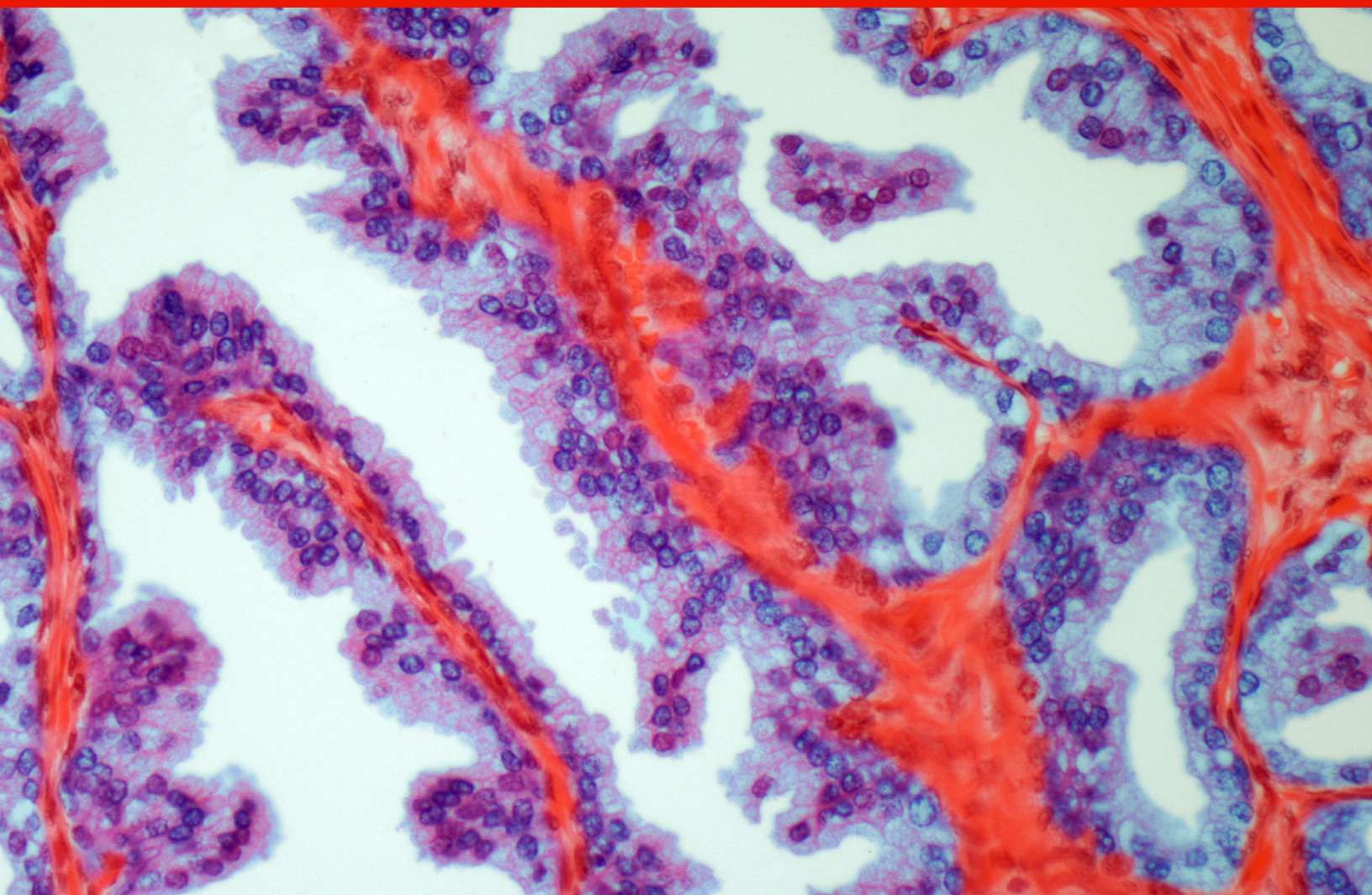
Prostate Cancer Molecular Biomarkers and Guideline Recommendations

J&J
Precision Medicine



Biomarkers have historically played an important role in the diagnosis of prostate cancer[1,2]

PSA isolation and characterization[3]

1970 | **1980** | **1990**

PSA for prostate cancer recurrence approved[1]

PSA for prostate cancer screening approved[1]

Five-year prostate cancer survival[4]

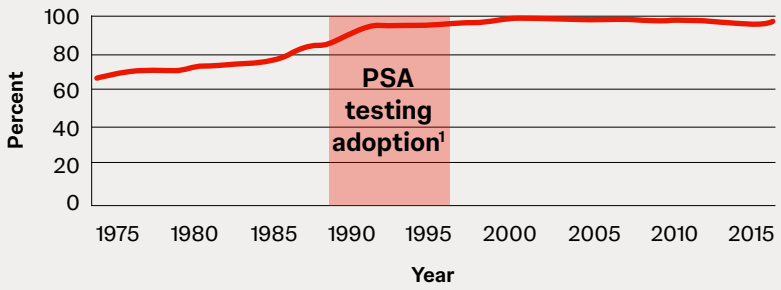


Image adapted from the National Cancer Institute

Introduction of PSA screening led to earlier stage at diagnosis and a **reduction in prostate cancer mortality by 46.0%–63.7%[5]**

PSA is a valuable biomarker[1,2,6]*

- For diagnosing prostate cancer
- For diagnosing recurrence
- As an indicator of treatment response

However, additional biomarkers are needed[1,2]:

- To determine susceptibility for prostate cancer
- To improve risk stratification
- To inform personalized treatment strategies

Tumor-based molecular assays and germline testing are tools which can assist with disease management through risk stratification, diagnosis, and treatment selection[6,7]*

Diagnostic biomarkers | **Predictive biomarkers** | **Genetic predisposition biomarkers** | **Biomarkers for high-risk**

PSAs and transcription factors[6–9]*	DNA repair system and oncosuppressors[6,8,10–14]*						Androgen signaling[6,8,10,15–18]*	
TMPRSS2:ERG	*Rb*	*CHD1*	HRR genes: *BRCA1*	*MSH2*	*p53*	*HOXB1*	*AR* mutations	
PCA3	*PTEN*		*BRCA2*	*MLH1*			*AR* amplification	
PSMA	*SPOP*		*ATM*	*MSH6*			*AR* variants (AR-V7)	
ETV1			*CHEK2*	*PMS2*			*GATA2*	*SRCs*
NKX3.1			*PALB2*	*NBN*			*FOXA1*	*MAGE-11*
			RAD51D					

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Prostate cancer biomarkers may be identified through both germline and somatic testing[6,19]*

Germline testing

Identifies biomarkers in DNA that are **inherited** and expressed in cells from anywhere in the body[10,20]

Blood Saliva

Somatic testing

Identifies new mutations in DNA that are **expressed by cancer cells**[10,20]

Tumor Blood (ctDNA)

There are limitations for performing germline or somatic testing alone:

Up to 50% of actionable DNA damage response (DDR) mutations may be missed by germline testing alone[21]

Up to 20% of patients will have mutations missed by somatic testing alone[20]

Opportunity to optimize

Combining somatic and germline testing may be appropriate for assessing genetic disposition, prognosis, and predicting likelihood of treatment response in some patients with prostate cancer[6,19]*

Prognostic biomarker tests evaluate gene expression to identify aggressive prostate cancer[22]†

	Oncotype Dx GPS[22–24] *Genomic Health*	**ProMark**[9,22,23] *Metamark*	**Decipher®**[22,25,26] *Decipher Bioscience (formally Genome Dx)*	**Prolaris**[22,23,27,28] *Myriad Genetics*
Evaluates	**mRNA expression** levels of **17 genes** across 4 pathways in tumor tissue	**Expression of 8 proteins** in tumor tissue with multiplex immunofluorescence imaging	**mRNA expression** levels of **22 genes** in tumor tissue	**mRNA expression** levels of **10 cell-cycle progression genes** and **6 reference genes** in tumor tissue
Indicates	Tumor aggressiveness	Tumor aggressiveness	Risk of metastasis and death	Likelihood of disease progression and tumor aggressiveness

After positive biopsy[22,23,29]

After definitive therapy[22,23,29]

Prognostic biomarker test results can help determine which patients require treatment[6,23,29]*

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†The presented list of biomarker tests for disease prognosis in prostate cancer is not exhaustive.[22]

Genes with established or emerging potential clinical actionability may impact patient management[10,30]

of metastatic castration-resistant prostate cancer (mCRPC) tumors **contain a potentially actionable mutation**[30]

~ 1 in 4 patients

with advanced prostate cancer **have mutations** in **DDR genes**, which include the HRR and MMR pathways[30,31]

Common MMR pathway biomarkers in prostate cancer[32,33]

Key MMR biomarkers[32,33]:
- *MLH1*
- *MSH2*
- *MSH6*
- *PMS2*

MMR pathway gene mutation

Predict treatment response
- **dMMR can predict response** to immune checkpoint inhibitors[34]

Understand genetic disposition
- **Germline** mutations in these genes can also provide insights into both patient and familial risk for prostate cancer[10]

Mismatch repair deficit

Inform prognosis
- **dMMR** is associated with more aggressive disease and high Gleason scores[34]

MSI or High TMB

Microsatellite instability (MSI)
- Used to evaluate dMMR pathway[33]
- dMMR and MSI-H may be associated with high TMB[34]

HRR pathway mutations are informative prostate cancer biomarkers[10,35]

Key HRR biomarkers[6*†]:
- *BRCA1*
- *BRCA2*
- *ATM*
- *PALB2*
- *RAD51D*
- *CHEK2*
- *FANCA*
- *CDK12*

HRR pathway gene mutation

Predict treatment response
- **Somatic** and/or **germline** mutations in genes such as ***BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D,*** and ***CHEK2*** may guide the use of PARP inhibitors[6,10†]

Understand genetic disposition
- **Germline** mutations in these genes can also provide insights into both patient and familial risk for prostate cancer[6,10†]

Homologous recombination deficiency

Inform prognosis
- Patients with high HRD scores developed CRPC more quickly and had shorter overall survival times[35]

Genomic instability/High TMB

Clinical findings of **high TMB** can be a sign of **HRD**[34]

Among other HRR pathway genes, *BRCA* alterations are informative in prostate cancer[6,36†]

Percent of patients with *BRCA1/2* alterations[36]

	Germline	Somatic
Any stage	4%	7%
mCRPC	5%	11%

Understanding predisposition

7%–26% of males with germline ***BRCA1*** alterations and **19%–61%** of males with germline ***BRCA2*** alterations **will develop prostate cancer**[19,37†]

Prognostic implications

In one retrospective study of 1904 males diagnosed with prostate cancer, 12-year **survival rate in patients with a *BRCA2* alteration was >30% lower** compared with those without a *BRCA* alteration[38]

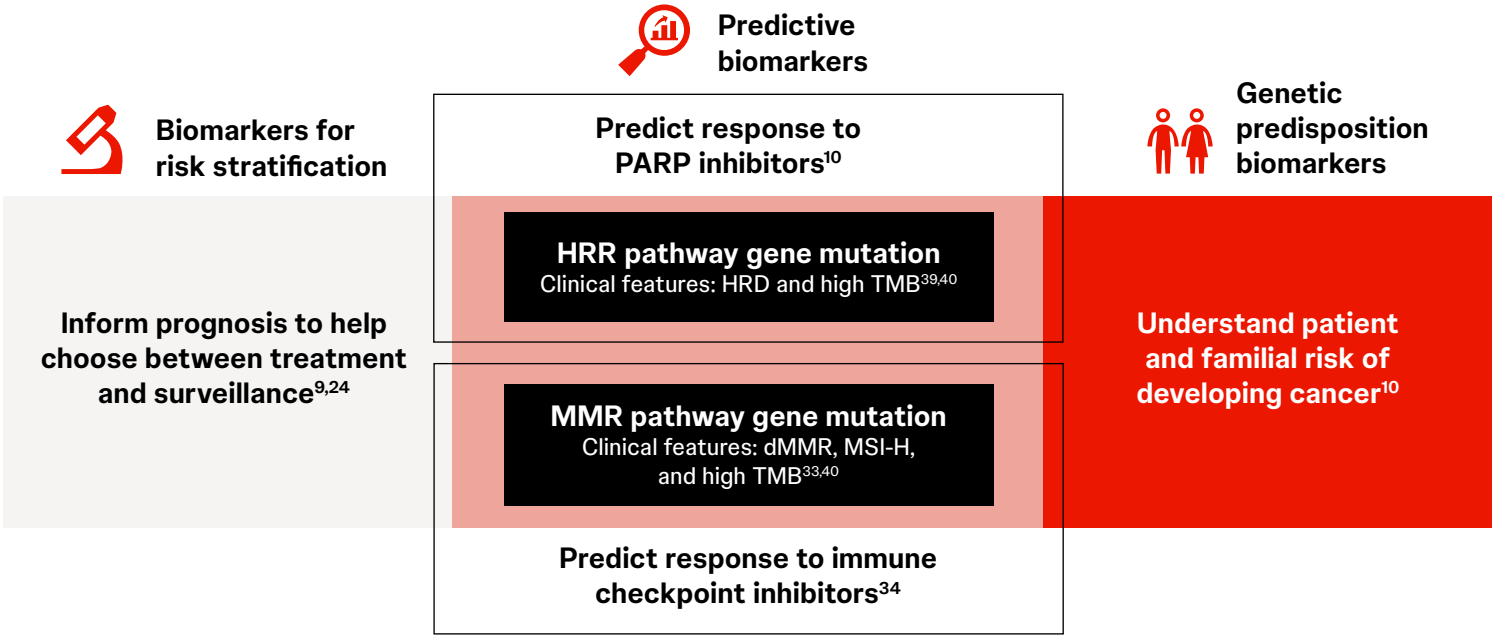
Predictive implications

BRCA alterations may predict **response to PARPis**[6†]

Although mutations in DDR genes are associated with aggressive disease, identification of these biomarkers via both somatic and germline testing can inform treatment decisions and may improve prognosis[6,34†]

*This is not a complete list of all HRR biomarkers in prostate cancer. †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.

Germline and somatic testing for DDR gene mutations can help guide disease management approaches[6,31,35]*



Actionable biomarkers in prostate cancer that can inform treatment decisions may be detected by different assays with unique capabilities[41–47]

	Single-biomarker test[45,48]		Broad-based panel[45,48]
Test type	**Immunohistochemistry (IHC)[41,42]**	**Polymerase chain reaction (PCR)[42–44]**	**Next-generation sequencing (NGS)[42,45–47]**
Alteration type(s) detected	Overexpression/amplification, protein expression	Single-nucleotide variant (SNV), copy number variant (CNV), insertions-deletions (indels), known gene fusions	SNV, CNV, indels, genomic rearrangements
Actionable biomarkers detected	MLH1, MSH2, MSH6, PMS2	MSI, *MLH1, MSH2, MSH6, PMS2*	MSI, TMB, *MLH1, MSH2, MSH6, PMS2, ATM, BRCA1, BRCA2, CDK12, CHEK2, PALB2, FANCA, NBN*

Opportunity to optimize

NGS is an efficient way to test for multiple alterations[42,45]

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Several emerging biomarkers can be used for early prostate cancer detection[49,50]

PSA testing remains the first-line screening test of choice at this time,[51] but may yield false negatives or overdiagnosis and overtreatment[52]

New tests based on other biomarkers may help address these challenges[52]

Extracellular vesicles containing nucleic acids, proteins, and metabolites may serve as highly sensitive biomarkers for the early diagnosis of prostate cancer[49,50]

Analysis of plasma cell-free DNA (cfDNA) methylation is being explored for early detection and tumor classification[49]

A panel of six **multi-omics biomarkers**, *TELO2, ZMYND19*, miR-143, miR-378a, and methylation status of two CpG loci, may be a biomarker for the early detection of recurrent prostate cancer[49]

Many emerging prostate cancer biomarkers can be detected by liquid biopsy[50,53]

Liquid biopsy can detect new biomarkers including ctDNA, ctRNA, CTCs, and EVPs[50,53]

Liquid biopsy is a **non-invasive** tool that can aid in **early detection** and **diagnosis,** understanding **prognosis,** and guiding **treatment selection** for prostate cancer[50,53]

	Circulating tumor DNA (ctDNA)	Circulating tumor RNA (ctRNA)	Circulating tumor cells (CTCs)	Extracellular vesicles and particles (EVPs)
	Emerging biomarkers include DNA methylation, copy number variants, and rearrangements[54–56]	**Primarily noncoding RNAs such as miRNAs[50,54]**	**EpCAM-positive cells circulating in blood that shed from primary/ metastatic tumors[53]**	**Extracellular vesicles and particles that harbor proteins and nucleic acids[50]**
Diagnostic[50]	✓	✓		✓
Distinguishes from BPH[50]		✓		✓
Predicts metastasis[50]	✓		✓	✓
Prognostic[50]	✓	✓	✓	✓
Predicts treatment response[50]	✓	✓		✓

Germline testing guidelines for prognostic and predictive biomarkers and familial risk assessment

		National Comprehensive Cancer Network® (NCCN®)[6,19*]	AUA/ASTRO[57†] (localized)	AUA/SUO[58†] (advanced)	ASCO[59] (metastatic)
Who to test	Patients with prostate cancer and any of the following: • Pathogenic somatic mutations in cancer-risk genes	✓			✓
	• Metastatic prostate cancer	✓		✓	✓
	• (Strong)‡ family history of (related)‡ cancer	✓	✓		
	• Positive family history of germline variants	✓	✓		✓
	• Ashkenazi Jewish ancestry	✓	✓		
	• Strong personal history of related cancers		✓		
	• High-risk§/adverse‡ tumor characteristics	✓	✓		✓
What to test	*BRCA1* and *BRCA2*	✓	✓	✓‖	✓
	ATM and *CHEK2*	✓	✓	✓‖	
	PALB2		✓	✓‖	
	HOXB13 and *TP53*	✓	✓		
	NBN, MLH1, MSH2, MSH6, and *PMS2*		✓		
	RAD51D			✓‖	
When to test	At initial diagnosis, where it is likely to inform treatment and clinical options	✓			✓
	Offer germline testing to inform discussions around prognosis		✓#	✓¶	✓
Additional considerations	Germline testing should include appropriate genetic counseling	✓		✓**	✓

There is consensus across clinical guidelines shown here that **germline testing may include appropriate genetic counseling**[6,19,57–59*]

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Somatic tumor testing guidelines for prognostic and predictive biomarkers

		NCCN[6*]	AUA/SUO[58†] (advanced)	ASCO[59] (metastatic)
Who to test	Patients with metastatic prostate cancer	✓	✓	✓
	Consider for patients with regional (N1) prostate cancer	✓		
Biomarkers to consider	Multigene testing for HRR genes[‡] *BRCA1, BRCA2*	✓	✓	✓
	HRR genes noted by guidelines: *ATM, PALB2, RAD51D, CHEK2*	✓	✓	
	HRR genes noted by guidelines: *FANCA, CDK12*	✓		
	MSI-H or dMMR	✓	✓	✓
	TMB[§]	✓	✓	✓
When to test	At metastatic diagnosis, if not previously tested	✓		✓
	Consider retesting at time of progression	✓		✓

When considering testing, it is important to **check historical records for prior germline and/or somatic testing** to be aligned with guidelines[6*]

Germline and somatic testing may be underutilized in practice[60–63]

Identified barriers to testing[63]

- Access to genetic counselors
- Insurance coverage and cost
- Clinic workflow
- Time and space availability
- Access to resources for provider and patient education

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Summary

Advances in biomarker research have impacted multiple domains of prostate cancer management including **diagnosing** prostate cancer, predicting likelihood of **treatment response**, understanding **genetic disposition**, and identifying and managing **high-risk individuals**[6,7]*

Current clinically actionable prostate cancer biomarkers are **primarily genes involved in DNA repair such as HRR genes** (*BRCA1, BRCA2, ATM, PALB2, RAD51D, CHEK2, FANCA,* and *CDK12*) and **MMR genes** (*MLH1, MSH2, MSH6,* and *PMS2*)[6]*

Combining both somatic and germline testing according to clinical guidelines **can offer a comprehensive view** for genetic disposition, prognosis, and predicting likelihood of treatment response[6,19,57,58]*

Prostate cancer **biomarkers continue to emerge** with emphasis on biomarkers detectable by noninvasive liquid biopsy[50,53]

AR, androgen receptor; ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; *ATM*, ataxia-telangiectasia mutated; AUA, American Urological Association; BPH, benign prostatic hyperplasia; *BRCA*, breast cancer gene; *CDK12*, cyclin-dependent kinase 12; cfDNA, cell-free DNA; *CHEK2*, checkpoint kinase 2; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; ctDNA/RNA, circulating tumor DNA/RNA; DDR, DNA damage response; dMMR, deficient mismatch repair; DNA, deoxyribonucleic acid; EVP, extracellular vesicles and particles; *FANCA*, FA complement group A; GPS, genomic prostate score; *HOXB13*, homeobox B13; HRD, homologous recombination deficiency; HRR, homologous recombination repair; mCRPC, metastatic castration-resistance prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; miRNA, microRNA; *MLH1*, MuTL homolog 1; MMR, mismatch repair; mRNA, messenger RNA; *MSH2/6*, MutS homolog2/6; MSI, microsatellite instability; MSI-H, microsatellite instability–high; *NBN*, nibrin gene; NCCN, National Comprehensive Cancer Network®; *PALB2*, partner and localizer of *BRCA2*; PARPi, poly-ADP ribose polymerase inhibitor; *PMS2*, postmeiotic segregation increased 2; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SUO, Society of Urologic Oncology; TMB, tumor mutational burden.

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Accessed March 17, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer Early Detection V.1.2025 © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed March 17, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org **8.** Fontana F, Anselmi M, Limonta P. Molecular mechanisms and genetic alterations in prostate cancer: from diagnosis to targeted therapy. *Cancer Lett*. 2022;534:215619. doi:10.1016/j.canlet.2022.215619 **9.** Porzycki P, Ciszkowicz E. Modern biomarkers in prostate cancer diagnosis. *Cent European J Urol*. 2020;73(3):300–306. **10.** Cheng HH, Sokolova AO, Schaeffer EM, et al. Germline and somatic mutations in prostate cancer for the clinician. *J Natl Compr Canc Netw*. 2019;17(5):515–521. **11.** Chen WS, Aggarwal R, Zhang L, et al. 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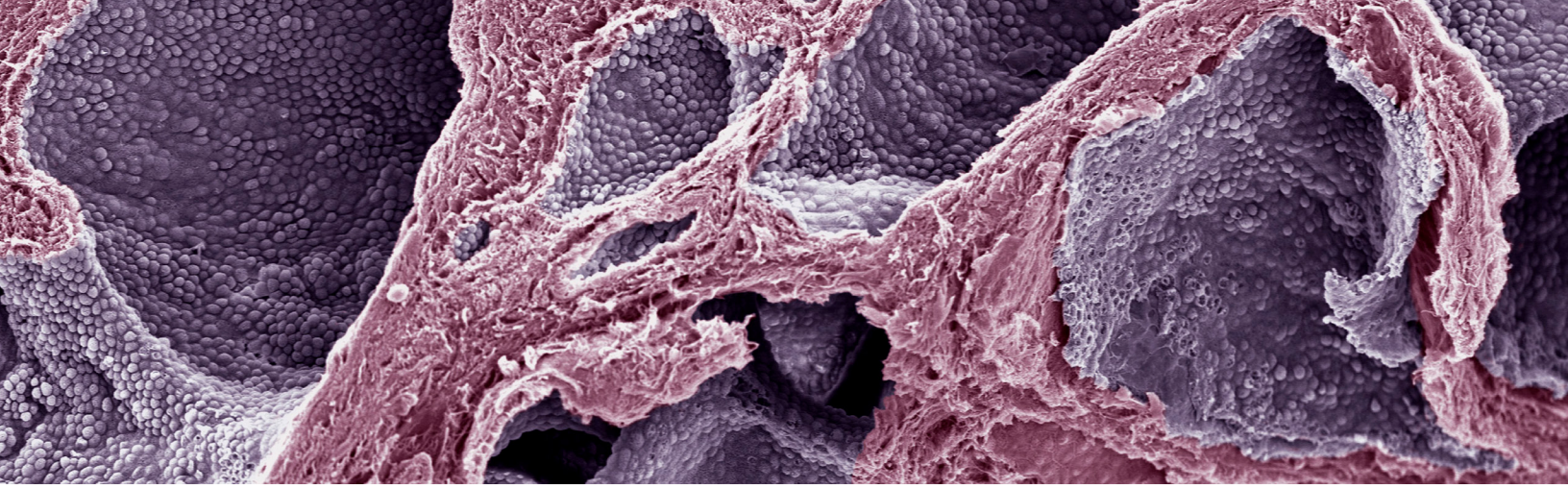

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