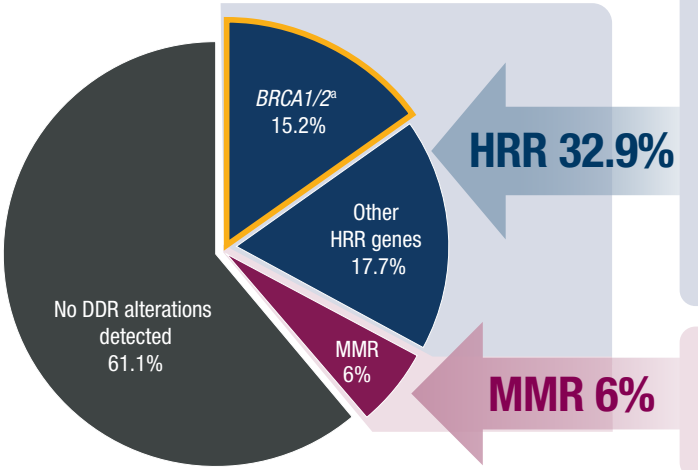
Precision Medicine

Biomarker Testing Recommendations for Advanced Prostate Cancer

DNA Damage Repair (DDR) Biomarkers in Advanced Prostate Cancer

PREVALENCE OF DDR ALTERATIONS IN ADVANCED PROSTATE CANCER



BRCA1/2 and Other Homologous Recombination Repair (HRR) Genes[1,2]

- *BRCA1/2* and other HRR genes[b] are important for repair of DNA double-strand breaks[1]
- These genes are associated with development and progression of prostate cancer[1]
- Testing for HRRm may help inform treatment options, prognosis, and familial risk[1]
- Patients with prostate cancer and certain HRR gene mutations (*BRCA1*, *BRCA2*, or *ATM*) are at risk for more aggressive disease and poorer outcomes[2]

Mismatch Repair (MMR) Genes[3]

- MMR genes[c] are important for repair of DNA replication errors
- Microsatellite instability (MSI) often arises as a result of MMR mutations

[a]*BRCA1* and *BRCA2* prevalence is 1.9% and 13.3%, respectively.[1]
[b]Additional HRR genes and prevalence of alterations include: *ATM* (7.3%), *CDK12* (6.9%), *CHEK2* (1.9%), and other lower prevalence genes (HRR genes with <1% prevalence in advanced prostate cancer: *PALB2* [0.4%], *RAD51C* [0.14%], *RAD51D* [0.4%], and *FANCD2* [0.7%]).[1]
[c]MMR genes include *MLH1, MSH2,* and *MSH6*. Prevalence of *MLH1, MSH2,* and *MSH6* alterations is 1.3%, 2.7%, and 2%, respectively.[1]

National Comprehensive Cancer Network® (NCCN®) Recommendations for Biomarker Testing for Advanced Prostate Cancer[4]

WHY TEST?

To aid in systemic treatment decisions, enrollment in clinical trials, and/or genetic counseling on familial risk

WHAT TO TEST?

Germline testing:

- HRRm genes, such as *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13*
- MMR genes, such as *MLH1, MSH2, MSH6, PMS2*

Tumor testing:

- HRRm genes, such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12*
- dMMR genes[d]
- MSI-H[d]

WHOM TO TEST?

Germline testing[e]: Patients with metastatic, regional (node positive), very-high-risk localized, or high-risk localized prostate cancer

Tumor testing: Metastatic prostate cancer (recommended); regional prostate cancer (consider)

WHEN TO TEST?

Germline testing: At the time of initial diagnosis

Tumor testing: At metastatic diagnosis (if not previously performed) with consideration of re-evaluation upon progression[f]

[d]Tumor testing for MSI-H and dMMR is recommended in patients with mCRPC and may be considered in patients with regional or mCSPC. [e]Please see the most recent NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines® for Prostate Cancer for additional recommendations for confirmatory germline testing based upon family history and/or ancestry.[4,5] [f]The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.[4]

Abbreviations

ATM, ataxia-telangiectasia mutated; BCT, blood collection tube; *BRCA1*, breast cancer susceptibility gene 1; *BRCA1/2*, breast cancer susceptibility gene 1 and/or 2; *BRCA2*, breast cancer susceptibility gene 2; *BRCA1/2*m, breast cancer susceptibility gene 1 and/or 2 mutation; *CDK12*, cyclin-dependent kinase 12; CDx, companion diagnostic; *CHEK2*, checkpoint kinase 2; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; EDTA, ethylenediaminetetraacetic acid; *FANCA*, Fanconi anemia complementation group A; *FANCD2*, Fanconi anemia group D2 protein; FDA, US Food and Drug Administration; FFPE, formalin-fixed and paraffin-embedded; FNA, fine-needle aspirate; H&E, hematoxylin and eosin; *HOXB13*, homeobox protein Hox-B13; HRRm, homologous recombination repair gene mutations; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; *MLH1*, DNA mismatch repair protein Mlh1; *MSH2*, DNA mismatch repair protein Msh2; *MSH6*, DNA mismatch repair protein Msh6; MSI-H, microsatellite instability-high; *PALB2*, partner and localizer of BRCA2; *PMS2*, PMS1 homolog 2, mismatch repair protein; PSA, prostate-specific antigen; *RAD51C*, RAD51 homolog C (*S. cerevisiae*); *RAD51D*, DNA repair protein RAD51 homolog D; WES, whole exome sequencing.

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A Variety of Tests Are Available to Assess Biomarkers in Advanced Prostate Cancer

ASSAYS FOR THE ASSESSMENT OF HRRm, dMMR GENE MUTATIONS, AND MSI IN ADVANCED PROSTATE CANCER[a]

	LABORATORY	ASSAY NAME	BIOMARKERS ASSESSED[b]				MINIMUM SAMPLE REQUIREMENT	TURNAROUND TIME
			*BRCA1/2*m	HRRm	dMMR	MSI		
TISSUE	Caris	Molecular Intelligence® Comprehensive Tumor Profiling (WES analysis)[6-8]	✓	✓	✓	✓	FFPE block or 10 unstained slides (positively charged, unbaked) with ≥20% tumor nuclei. Needle biopsy (4-6 cores), FNA, malignant fluid cell block, and bone/bone metastasis are also acceptable	≈10-14 days
TISSUE	Foundation Medicine	FoundationOne® CDx[9-11,c]	✓	✓	✓	✓	1 block + 1 H&E slide OR 10 unstained slides (positively charged and unbaked at 4-5 microns thick) + 1 H&E slide	≤12 days from receipt
TISSUE	NeoGenomics	NeoTYPE® HRR Profile[12]	✓	✓	✓		Paraffin block preferred	14 days
TISSUE	NeoGenomics	*BRCA1/2* Mutation Analysis for Tumors (*BRCA1/BRCA2*)[13]	✓				Paraffin block is preferred OR 1 H&E slide + 5-10 unstained slides (positively charged) cut at ≥5 microns	14 days
TISSUE	Tempus	Tempus xT (Solid Tumor)[14-17,d]	✓	✓	✓	✓	FFPE block with a minimum of 20% tumor content	10 days from receipt
PLASMA ctDNA	Foundation Medicine	FoundationOne® Liquid CDx[18,19,c,e]	✓	✓	✓	✓	2 tubes of peripheral whole blood (8.5 mL per tube)	≤10 days from receipt
PLASMA ctDNA	Tempus	Tempus xF[20, 21]	✓	✓	✓	✓	2 Streck tubes of peripheral blood (8.5 mL per tube)	7 days from receipt
PLASMA ctDNA	Guardant Health	Guardant360® CDx[22,23,f]	✓	✓	✓		≥5 mL whole blood in Streck Cell-Free DNA BCT®	7 days
GERMLINE	Ambry	ProstateNext®[24,25]	✓	✓	✓		3-5 mL whole blood, EDTA tube (purple top) or PAXgene® DNA tube (blue top) preferred	14-21 days
GERMLINE	GenPath	Hereditary Prostate Cancer Panel[26-28]	✓	✓	✓		2-5 mL whole blood in a lavender-top EDTA tube	14-21 days
GERMLINE	GeneDx	Hereditary Prostate Cancer Panel[29]	✓	✓	✓		2-5 mL blood in a lavender-top tube	2 weeks
GERMLINE	Invitae	Common Hereditary Cancers Panel[30]	✓	✓	✓		3 mL whole blood in a purple-top EDTA tube	10-21 calendar days
GERMLINE	Invitae	Multi-Cancer Panel[31]	✓	✓	✓		3 mL whole blood in a purple-top EDTA tube	10-21 calendar days
GERMLINE	Myriad	BRACAnalysis CDx® (*BRCA1/BRCA2*)[32,33,c]	✓				≈7 mL peripheral whole blood in a BCT-containing EDTA	<2 weeks
GERMLINE	Myriad	MyRisk® Hereditary Cancer[34-36]	✓	✓	✓		7 mL peripheral blood or buccal saliva sample	≤14 days
GERMLINE	Tempus xG (Powered by GeneDx)	Common Hereditary Cancers[15,37,38]	✓	✓	✓		8 mL peripheral blood in a lavender-top EDTA tube or buccal saliva sample	10-21 days from receipt

[a]This document is intended as educational information and is not intended as a complete list of available testing options. AstraZeneca is not responsible for any test provider and does not endorse any particular diagnostic test. The accuracy and results of diagnostic tests vary, and AstraZeneca shall have no liability arising from such testing. Information provided herein should in no way be considered a guarantee of coverage, reimbursement, or patient assistance. Providers should contact third-party laboratories for information on their patient assistance programs. While diagnostic testing may assist providers in identifying appropriate treatment for patients, the decision and action should be decided by a provider in consultation with the patient. All products are trademarks of their respective holders, all rights reserved. [b]Tests listed may include analysis of some, but not all HRR and/or dMMR genes. Additionally, tests may assess for additional genes. Please see product specifications for a full list of genes investigated. [c]FDA-approved diagnostic. [d]Tests tumor and matched normal sample from blood or saliva. [e]The test analyzes 324 genes and is FDA approved to detect and report substitutions, insertions and deletions (indels) in 311 genes, and rearrangements and copy number alterations in 3 genes, including *BRCA1* and *BRCA2*. [f]The test analyzes 74 genes and is FDA approved for the detection and reporting of single-nucleotide variants (SNVs), indels in 55 genes, copy number amplifications (CNAs) in 2 genes, and fusions in 4 genes.

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