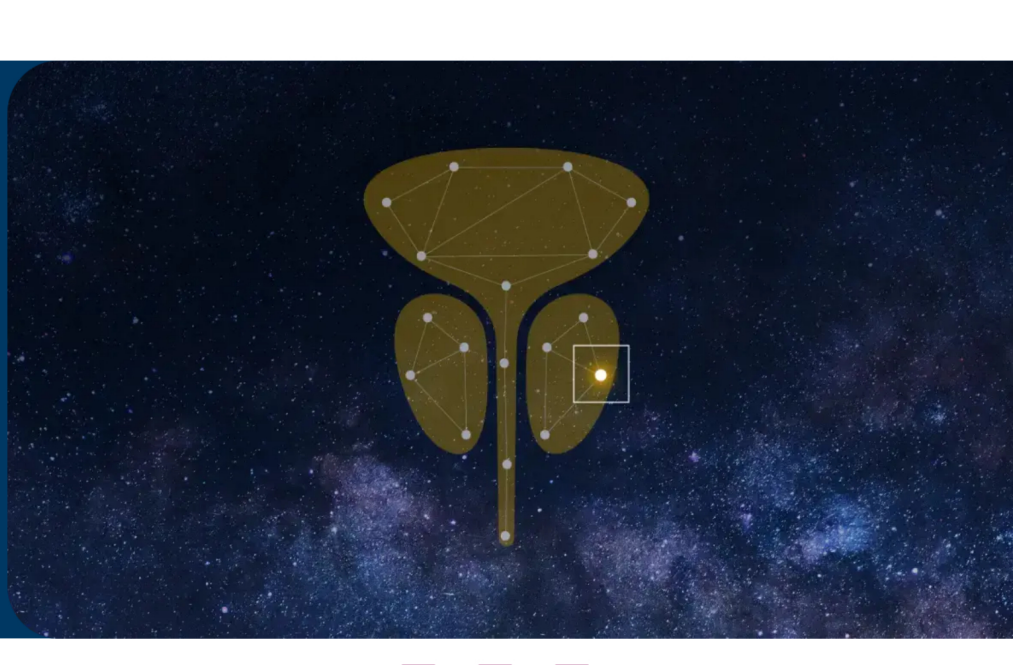
HRR Mutations, Including *BRCA1/2* in Prostate Cancer

Optimize HRRm testing in prostate cancer with guideline recommendations and actionable best practices.



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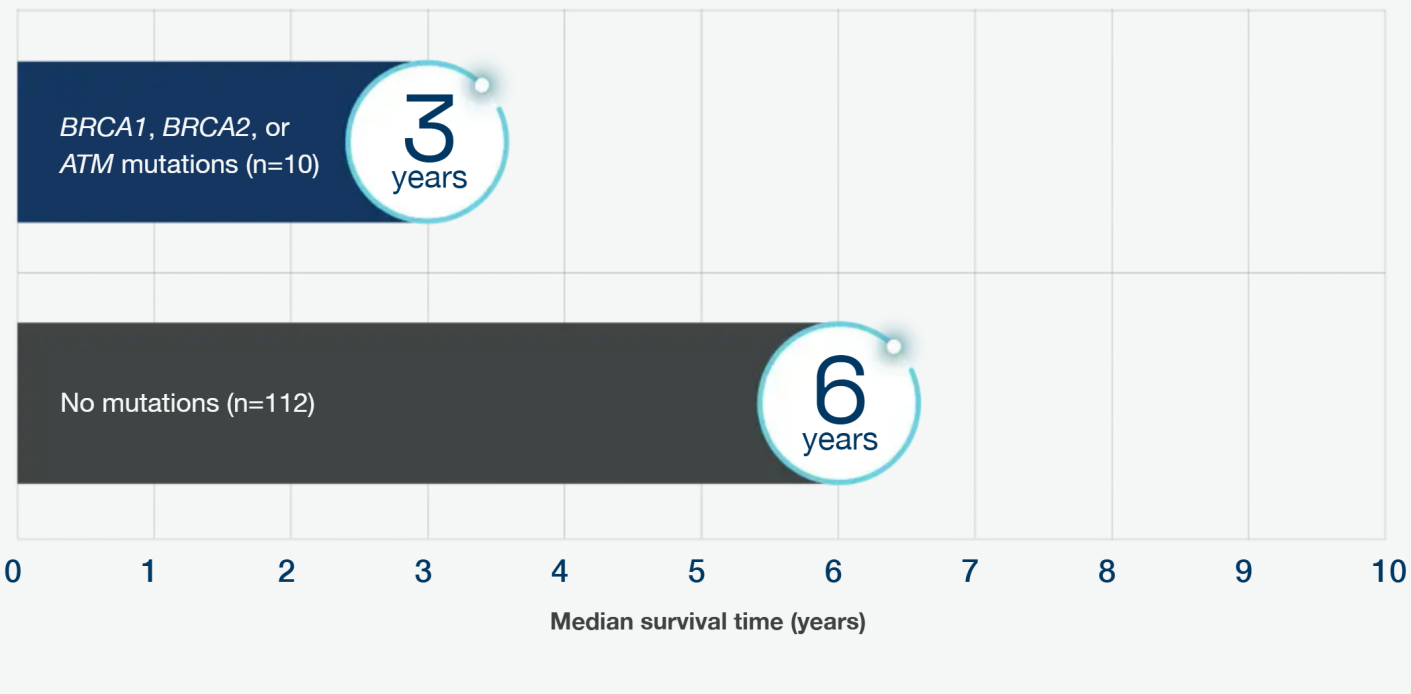
Jump to: Clinical Relevance · Testing Recommendations · Prevalence · Sample Type Considerations · Plasma ctDNA · Diagnostic Assays · Interpreting & Reporting · Considerat

Clinical Relevance of HRR Mutations, Including *BRCA1/2*

In the presence of homologous recombination repair (**HRR**) gene mutations, tumor cells are unable to effectively repair double-strand breaks (**DSBs**) in DNA, leading to the persistence of DSBs, accumulation of mutations, and ultimately, carcinogenesis.[1,2] In prostate cancer, one way to assess HRRm status is through individual mutations in *BRCA1* or *BRCA2*.[3]

Patients with metastatic prostate cancer and certain HRR mutations risk poorer outcomes[4,5]

Median survival time for patients with and without *BRCA1*, *BRCA2*, or *ATM* mutations[4]



ATM, ataxia-telangiectasia mutated; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; DNA, deoxyribonucleic acid; DSB, double-strand break; HRR, homologous recombination repair.

HRR Mutation Testing Recommendations

NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Prostate Cancer recommend tumor testing for all patients with metastatic prostate cancer[3]

Why test[3]	Whom to test[3]	What to test[3]	How to test[6]
To aid in treatment decisions, clinical trial enrollment, and/or familial risk counseling	All patients with metastatic prostate cancer at metastatic or initial diagnosis	Somatic HRR gene mutations[a] including *BRCA1/2*	FDA-approved assay: • FoundationOne®CDx (Foundation Medicine, Inc.)
		Germline mutations in *BRCA1/2*	FDA-approved assay: • BRACAnalysis CDx® (Myriad Genetic Laboratories, Inc.)
		When metastatic biopsy is unsafe or unfeasible, ctDNA assay is an option	FDA-approved assay: • FoundationOne® Liquid CDx (Foundation Medicine, Inc.)

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Footnotes

[a] HRR genes such as: *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*.[3]

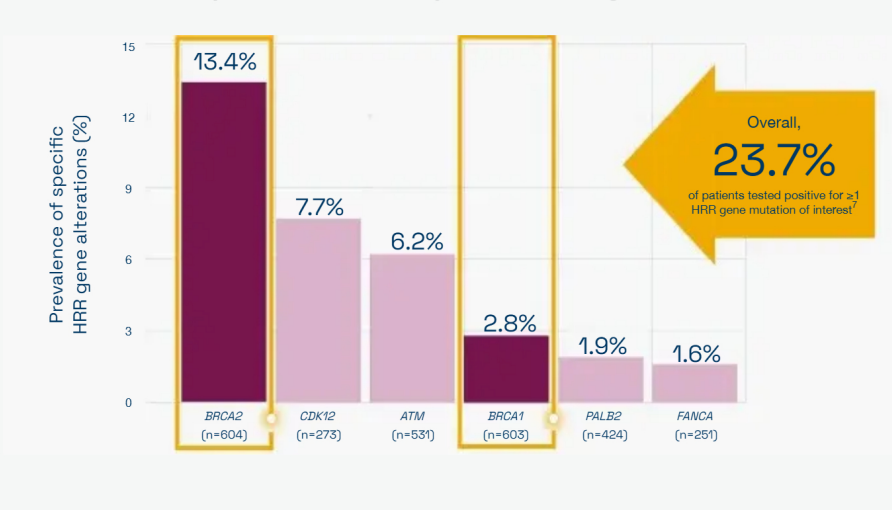
ATM, ataxia-telangiectasia mutated; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; *CDK12*, cyclin-dependent kinase 12; CDx, companion diagnostic; *CHEK2*, checkpoint kinase 2; ctDNA, circulating tumor deoxyribonucleic acid; *FANCA*, fanconi anemia complementation group A; FDA, US Food and Drug Administration; HRRm, homologous recombination repair mutation; NCCN, National Comprehensive Cancer Network® (NCCN®); *PALB2*, partner and localizer of *BRCA2*; *RAD51D*, RAD51 paralog D.

Nearly a Third of Patients Have an HRR Mutation[7]

~15% of patients have *BRCA1/2* mutations[7]

- A retrospective multicenter observational cohort study of patients with advanced prostate cancer in the United States from 2013 to 2019[7]
- 674 patients were tested for 1 or more of 6 HRR gene mutations of interest – *ATM*, *BRCA1*, *BRCA2*, *CDK12*, *PALB2*, and *FANCA*[7]

As supported by real-world evidence, a substantial proportion of patients with advanced prostate cancer may have an HRR gene alteration[7,8]

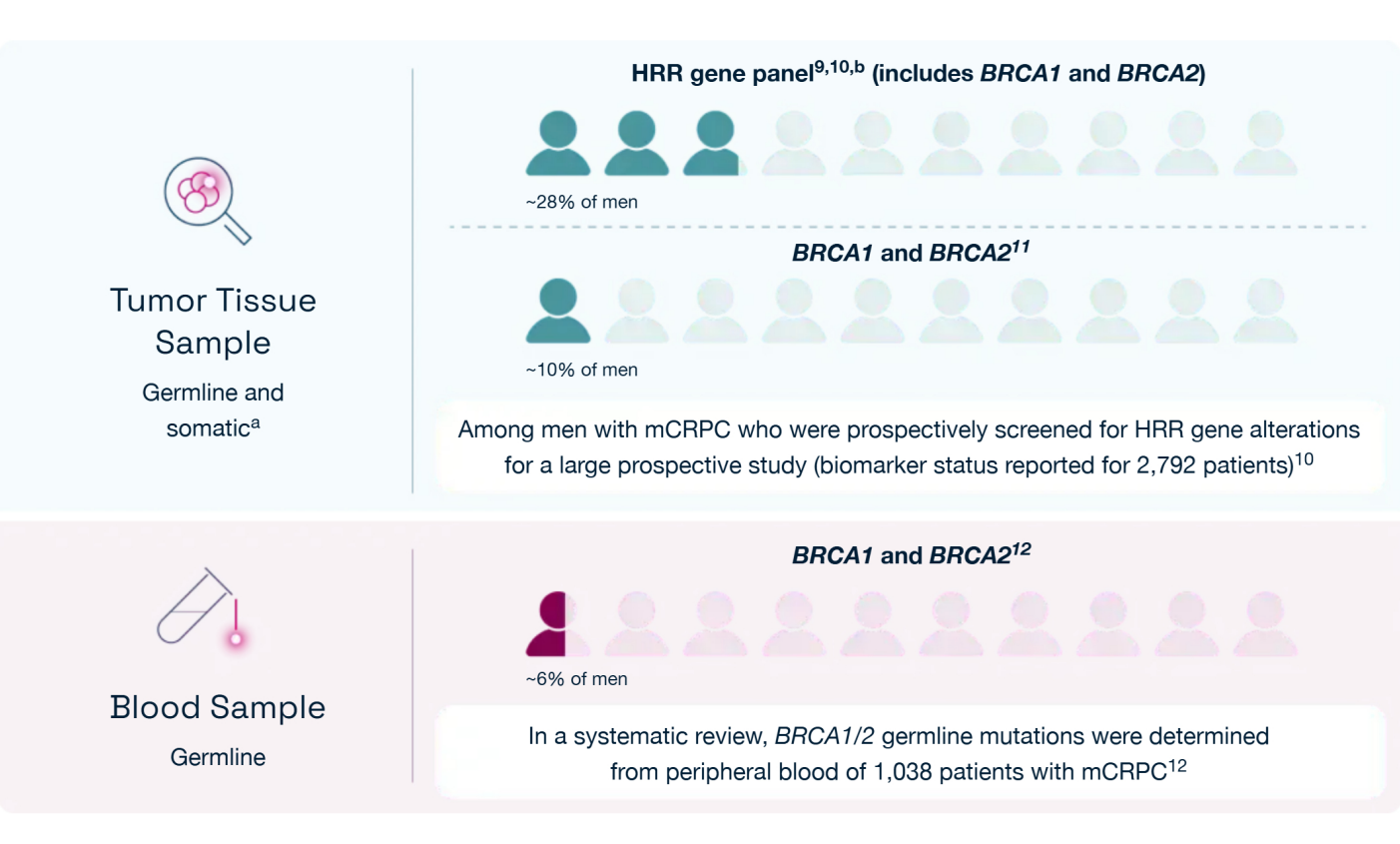


In a separate study, real-world data were analyzed from routine prospective clinical genomic profiling in a US institution[8]

- Using a validated assay of 395 genes (including *BRCA1/2*, *CDK12*, *ATM*, *CHEK2*, *FANCA*, and *ATR*, among others) on 3,476 unmatched primary and metastatic prostate cancer tissue samples, **DNA repair pathway genomic alterations were identified in 31% of samples**[8]

ATM, ataxia-telangiectasia mutated; *ATR*, ataxia telangiectasia and Rad3-related; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; *CDK12*, cyclin-dependent kinase 12; *CHEK2*, checkpoint kinase 2; *FANCA*, Fanconi anemia group A; HRR, homologous recombination repair; HRRm, homologous recombination repair mutations; *PALB2*, partner and localizer of BRCA2.

Sample Type Determines Somatic and/or Germline HRR Mutation Identification



Among men with mCRPC who were prospectively screened for HRR gene alterations for a large prospective study (biomarker status reported for 2,792 patients)[10]

In a systematic review, *BRCA1/2* germline mutations were determined from peripheral blood of 1,038 patients with mCRPC[12]

Sample type	Type of mutation identified	Special considerations/limitations
Tumor tissue[13]	Germline and somatic mutations	• Positive results should be followed by familial risk assessment (germline testing) • Tissue testing does not distinguish between somatic and germline mutations
Plasma ctDNA[14,15]	Germline and somatic mutations	• Dependent on adequate levels of ctDNA • Does not distinguish between somatic and germline mutations
Blood or saliva[16]	Germline mutations	• Does not identify somatic mutations • May have familial implications

Tumor testing identifies both germline and somatic mutations, without differentiation[7,13,16]

Tissue samples may be collected from the primary tumor site or sites of metastasis[13]

- The TRUS-guided 12-core systematic biopsy method is considered gold standard for prostate tissue sample collection; however, this may yield false negatives[17]
- Interventional radiologists use imaging to guide biopsy collection from a non-bone metastatic site[18]
- Bone-only metastases are often sclerotic and require decalcification. Bone scans and CT imaging can identify lesions more suitable for biopsy[19]
- In the event of failed tissue acquisition, archival tissue samples may be used; however, they may not reflect the current tumor molecular status[13]

Consider Plasma ctDNA if Tumor Tissue Is Unavailable

- Minimally invasive option to assess HRRm in mCRPC[20]
- As the amount of ctDNA may correlate with disease progression, sample collection should coincide with progressive disease and not during therapeutic response[20–22]
- High concordance between ctDNA and tissue testing for *BRCA1*, *BRCA2*, and *ATM*[15]

A Positive

mutation result from ctDNA testing alone is actionable[15,21]

A Negative

result requires confirmation with tissue-based testing[15,21]

Perform germline testing to assess familial risk, if tumor test is HRRm-positive[13,16,23,24]

Germline and somatic HRR mutations in patients with advanced prostate cancer are associated with shorter survival time than those without such mutations.[4,5] As *BRCA1/2* mutations in prostate cancer can be either germline or somatic, testing for both identifies all patients affected.

Footnotes

[a] Tumor testing cannot distinguish between germline and somatic mutations.[9] [b] Gene panel testing was conducted in a large prospective study to identify the following genes in the DNA repair process: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.[10]

ATM, ataxia-telangiectasia mutated; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; *CDK12*, cyclin-dependent kinase 12; *CHEK1/2*, checkpoint kinase 1 and/or 2; CT, computed tomography; ctDNA, circulating tumor deoxyribonucleic acid; *FANCL*, fanconi anemia complementation group L; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; *PALB2*, partner and localizer of *BRCA2*; *RAD51B/C/D*, RAD51 paralog B, C and/or D; *RAD54L*, RAD54 paralog L; TRUS, transrectal ultrasound scan.

Diagnostic Assays for HRR Mutations, Including *BRCA1/2* Mutations

Results can take between 7 to 21 days from receiving samples

Tissue testing

Laboratory and test name	FDA approval	Genes or alterations assessed	Minimum sample requirements	Turnaround time
Caris[25–27] Molecular Intelligence® Tumor Seek™ (NGS analysis)	No	HRRm (including *BRCA1/2*), dMMR, MSI	FFPE block or 10 unstained slides (positively charged, unbaked) with a ≥20% tumor nuclei. Needle biopsy (4–6 cores), FNA, malignant fluid cell block, and bone/bone metastasis are also acceptable	~10–14 days
Foundation Medicine[9,28,29] FoundationOne® CDx	Yes	HRRm (including *BRCA1/2*), dMMR, MSI	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
NeoGenomics[30] NeoTYPE® HRR Profile	No	HRRm (including *BRCA1/2*)	Paraffin block preferred	14 days
NeoGenomics[31] BRCA1/2 Mutations Analysis for Tumors	No	*BRCA1/2*	Paraffin block is preferred OR 1 H&E slide + 5–10 unstained slides (positively charged) cut at ≥5 microns	14 days
Tempus[32–35] Tempus xT (Solid tumor)	No	HRRm (*BRCA1/2*), dMMR, MSI	FFPE block with a minimum of 20% tumor content	9 days from receipt

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BRCA1/2, BReast CAncer susceptibility gene 1/2; CDx, companion diagnostic; dMMR, deficient mismatch repair; DNA, deoxyribonucleic acid; FDA, US Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; FNA, fine needle aspiration; H&E, hematoxylin and eosin; HRRm, homologous recombination repair mutation; MSI, microsatellite instability.

Plasma (ctDNA) testing

Laboratory and test name	FDA approval	Genes or alterations assessed	Minimum sample requirements	Turnaround time
Foundation Medicine[36–38] FoundationOne® Liquid CDx	Yes	HRRm (including *BRCA1/2*), dMMR, MSI	2 tubes of peripheral whole blood (8.5 mL per tube)	≤10 days from receipt
Tempus[39,40] Tempus xF	No		2 Streck tubes of peripheral blood (8.5 mL per tube)	7 days from receipt
Guardant Health[41,42] Guardant360® CDx	No	HRRm (including *BRCA1/2*), dMMR	≥5 mL whole blood in Streck Cell-Free DNA BCT®	7 days

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BCT, blood collection tube; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; CDx, companion diagnostic; ctDNA, circulating tumor deoxyribonucleic acid; dMMR, deficient mismatch repair; DNA, deoxyribonucleic acid; FDA, US Food and Drug Administration; HRRm, homologous recombination repair mutation; MSI, microsatellite instability.

Germline testing

Laboratory and test name	FDA approval	Genes or alterations assessed	Minimum sample requirements	Turnaround time
Ambry[43–45] Cancer Next®	Yes	HRRm (including *BRCA1/2*), dMMR	3–4 mL whole blood, EDTA tube (purple top) or PAXgene® DNA tube (blue top) preferred[a]	14–21 days
GenPath[46–48] OnkoRisk™ Oncology Management Panel	No		2–5 mL whole blood, lavender-top EDTA tube	14 days
GeneDx[49,50] OncoGene Dx: Hereditary Prostate Cancer Panel	No		2–5 mL blood, lavender-top tube	2 weeks
Invitae[51,52] Common Hereditary Cancers Panel	No		3 mL whole blood in a purple-top EDTA tube	10–21 calendar days
Invitae[53,54] Multi-Cancer Panel	No		3 mL whole blood in a purple-top EDTA tube	10–21 calendar days
Myriad[55,56] BRACAnalysis CDx® (*BRCA1/BRCA2*)	Yes	*BRCA1/2*	~7 mL peripheral whole blood in a BCT-containing EDTA	<2 weeks
Myriad[57–59] MyRisk® Hereditary Cancer	No	HRRm (including *BRCA1/2*), dMMR	7 mL peripheral blood or buccal saliva sample	≤14 days
Tempus xG[33,60,61] (powered by GeneDx) Common Hereditary Cancers	No		8 mL peripheral blood in a lavender-top EDTA tube or buccal saliva sample	14–21 days from receipt

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Footnotes

[a] NGS sequencing panels and clinical exome sequencing require 6–10 mL.[43]

BCT, blood collection tube; *BRCA1/2*, BReast CAncer susceptibility gene 1/2; CDx, companion diagnostic; dMMR, deficient mismatch repair; DNA, deoxyribonucleic acid; EDTA, ethylenediaminetetraacetic acid; FDA, US Food and Drug Administration; HRRm, homologous recombination repair mutation; NGS, next-generation sequencing.

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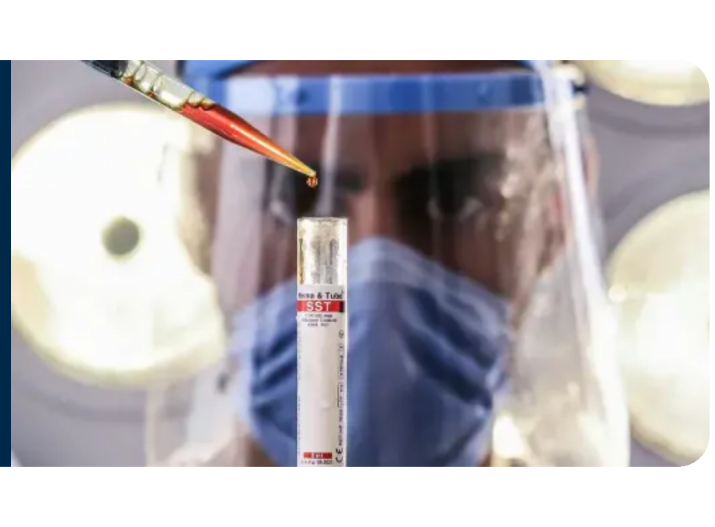

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Interpreting and Reporting Biomarker Test Results

HRRm testing aids in systemic treatment decisions, clinical trial enrollment, and/or genetic counseling on familial risk[62]

Testing for HRRm, including *BRCA1/2*, may:

- Reveal patients who have an increased risk for hereditary cancers.[63,64] Genetic counselors may be required to discuss germline testing in the pre-test setting, allowing patients to make informed decisions. Genetic counselors also play a key role in evaluating genetic testing results[64]
- Offer prognostic insights on patients with metastatic prostate cancer and mutations in genes such as *BRCA1/2* who are at risk for more aggressive disease and poorer outcomes[4,65]
- Provide predictive insights which aid in the development of a comprehensive treatment plan[66,67]
- Open opportunities for patients to be enrolled onto clinical trials to receive upcoming, biomarker-specific treatments[62]

BRCA1/2, BReast CAncer susceptibility gene 1/2; HRRm, homologous recombination repair mutation.

Considerations for Your Practice

Consider HRRm status for treatment decision-making, clinical trial enrollment, and genetic counseling:

- Test for HRRm at metastatic diagnosis
- Re-evaluate HRR genes upon progression
- Consider sample type and age when using tumor tissue for HRRm testing
- Utilize plasma ctDNA testing for cases where tumor testing is not feasible
- Explore solutions to common challenges you may face

ctDNA, circulating tumor deoxyribonucleic acid; HRRm, homologous recombination repair mutation.

Helpful Resources

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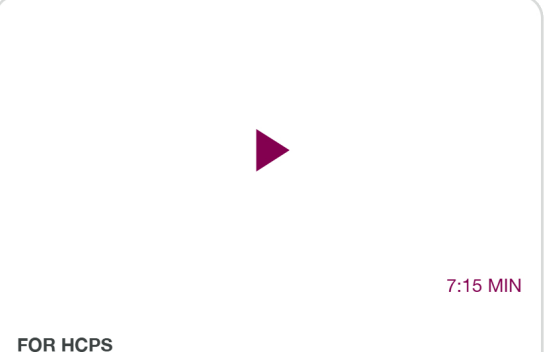

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FOR HCPS

Optimizing biomarker testing for patients with metastatic prostate

Learn how biomarker testing for mutations in homologous recombination repair (HRR) genes, such as BReast CAncer susceptibility gene 1/2 (*BRCA1/2*) may be used to help guide treatment decisions.

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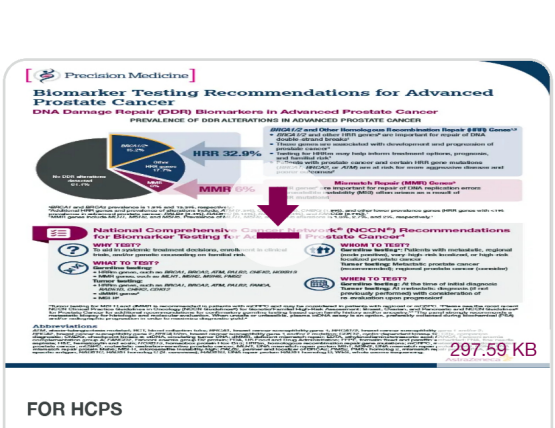

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Biomarker testing recommendations for advanced

Review guideline-recommended testing for BReast CAncer susceptibility gene 1/2 (*BRCA1/2*) and other homologous recombination repair (HRR) gene mutations to help inform treatment decision-making.

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Understanding best practices for homologous recombination repair

Download this resource to help guide tissue testing approaches for biomarkers for patients with advanced prostate cancer.

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