

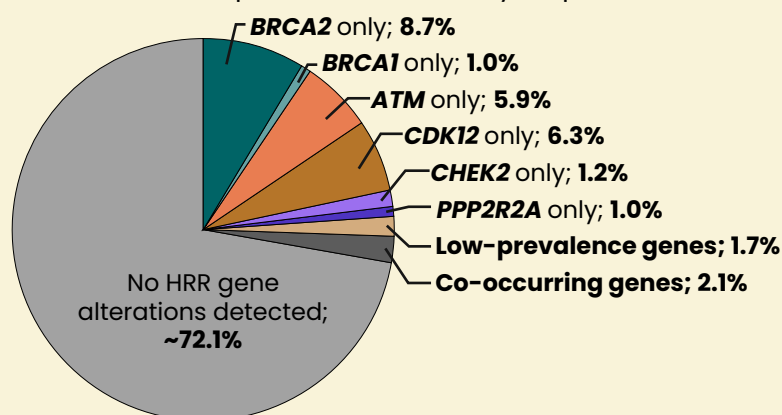
An APP Guide to Optimal Integration of Biomarker Testing: Prostate Cancer

Rationale for Molecular Testing in Prostate Cancer

- ▲ Germline genetic testing and somatic tissue/liquid biopsy testing are important to inform the care of patients with prostate cancer^{1,2}
- ▲ Homologous recombination repair (HRR) mutations are prevalent in prostate cancer: ~20%–30%^{3–6}
 - The prognosis of patients with HRR alterations suggests approximately 1.5 times higher likelihood of lower survival in patients with HRR alterations (*ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK1*), including worse prognosis for patients with *BRCA*/HRR mutations regardless of treatment^{7,8}

Prevalence of Tumor HRRm Identified From Screened mCRPC Population

(N = 2792 patients successfully sequenced)



Prevalence of Germline HRRm in Patients With Early or Advanced Prostate Cancer

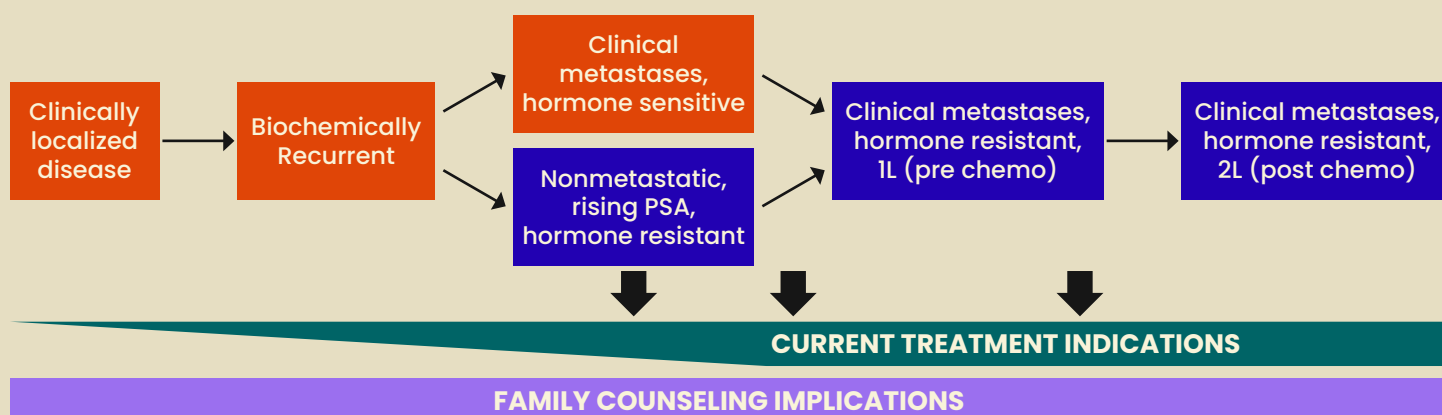
Gene	Prevalence Range
<i>BRCA2</i>	3.5% to 5.3%
<i>BRCA1</i>	0.9% to 1.3%
<i>ATM</i>	0.3% to 2.0%
<i>PALB2</i>	0.4% to 0.6%

- ▲ Deficient DNA mismatch repair/microsatellite instability-high (dMMR/MSI-H; including mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2*) occur in ~2.8% to 3.1% of prostate cancers, whereas high tumor mutational burden (TMB-H) occurs in ~1.5% to 4.7%, and higher rates in metastatic castration-resistant prostate cancer (mCRPC)⁷
- ▲ Biomarker testing in early prostate cancer can help inform the presence of hereditary conditions,⁸ and in patients with advanced/metastatic disease can inform the use of novel therapies and/or clinical trial eligibility^{8–10}

Biomarker Testing Workflow in Prostate Cancer

- ▲ Patients should be assessed earlier in the disease course vs later to ensure timely consideration of targeted therapy choice (and clinical trials), particularly for those patients with advanced/metastatic disease and MMR genes, *BRCA1* and *BRCA2*, and other HRR gene alterations.¹¹
- ▲ NCCN and ASCO guidelines recommend germline and somatic testing for^{2,11}:
 - Patients who develop mCRPC should consider referral to genetic counselor if dMMR/MSI-H status
 - Consider germline testing for mutation in HRR genes if not done previously

When to Test: Prostate Cancer Disease States



Other Considerations Affecting Molecular Testing

Identifying patients to test: In younger patients, consider asking open-ended questions about potential for family history and educating about germline and somatic testing options¹²

Liquid biopsy testing success: The success of blood-based circulating DNA assays can depend heavily on total metastatic disease burden¹³⁻¹⁵

- ▲ Low volume: may lead to false negative or inconclusive test results for HRR gene assays
- ▲ Clonal Hematopoiesis of Indeterminate Potential poses a significant risk of false-positive results in prostate cancer liquid biopsies (ie, age related mutations)

Sample quality and availability: Increased success with larger sample volume, fresh formalin-fixed paraffin embedded tissue sample blocks, and non-/brief decalcification of bone metastases¹³

Loss of PSMA antigen in patients with metastatic disease: PSMA antigen loss in metastatic prostate cancer occurs in 15% to 20% of mCRPC, causing resistance to PSMA-targeted therapies¹⁶⁻¹⁸

- ▲ Evaluating and re-assessment for PSMA status is primarily done through PSMA PET/CT imaging

Report on Available Biomarkers

- ▲ Laboratory reports on germline or somatic tumor tissue may indicate the presence of pathogenic HRR variants, and MMR status may help with prognosis and treatment selection
- ▲ Patients with *BRCA1* or *BRCA2* gene alteration as well as other HRR genes (pathogenic biallelic loss) may be eligible for PARP inhibitors or immunotherapy for dMMR/MSI-H status
- ▲ If reports are unclear, APPs are encouraged to talk to the pathologist or their molecular lab technician to clearly identify the meaning of a statement for “deleterious” or “variant of undetermined significance”

Treatment Implications for Available Biomarkers in Prostate Cancer²

- ▲ Initial therapy in patients with nonmetastatic prostate cancer with HRR or BRCA gene alterations often follows standard of care options, including radical prostatectomy or radiation therapy with hormonal therapy as appropriate, but may require intensified management due to higher risk of progression in these patients²

Useful biomarkers in patients with metastatic prostate cancer and their use for informing therapy options.*

Biomarker(s)	Patient Population	FDA-Approved Targeted Agent
<i>BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHECK1, CHECK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L</i>	mCRPC with progressive disease following previous enzalutamide or abiraterone	Olaparib
<i>BRCA1, BRCA2</i>	mCRPC previously treated with androgen-receptor directed therapy and taxane-based chemotherapy	Rucaparib
<i>BRCA1, BRCA2</i>	mCRPC	▲ Olaparib + Abiraterone ▲ Niraparib + Abiraterone
<i>BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C</i>	mCRPC	Talazoparib + enzalutamide
PSMA-positive metastases	mCRPC	Lutetium Lu-177 vipivotide tetraxetan (Lu-177-PSMA-617)

*Approved therapies and professional guidelines change frequently. Experts advise reviewing the most recently approved indications and guidelines based on biomarker test results.

- ▲ According to the latest clinical guidelines, patients with systemic disease and no actionable biomarker may receive an androgen receptor pathway inhibitor (abiraterone, enzalutamide, apalutamide, or darolutamide) based on approved indications^{2,19}
- ▲ For patients with mCRPC harboring dMMR/MSI-H or high tumor mutational burden, immunotherapy options might be considered based on tissue-agnostic approvals; however, there are limited data specific to prostate cancer²⁰

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