Understanding Best Practices for HRRm Testing in Patients With Advanced Prostate Cancer

Biomarker Testing Helps Inform Your Clinical Approach[1,2]

Precision Medicine

Predispositional insights
Aid in the assessment of familial risks for cancer[3]

Prognostic insights
Gain knowledge about the course of the disease[3-5]

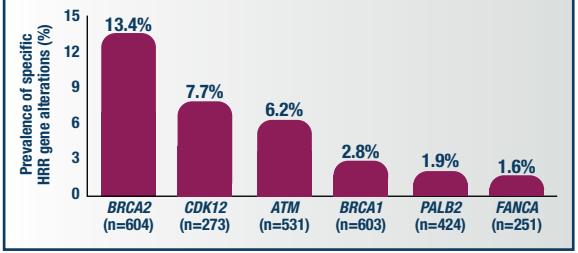
Predictive insights
Aid in the development of a comprehensive treatment plan[4,6]

As Supported by Real-World Evidence, a Substantial Proportion of Patients With Advanced Prostate Cancer May Have an HRR Gene Alteration

- 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]

Overall, 23.7% of patients tested positive for ≥1 HRR gene mutation of interest

Real-world evidence of HRR gene alteration prevalence in advanced prostate cancer[7]



- 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 3476 unmatched primary and metastatic prostate cancer tissue samples, **DNA repair pathway genomic alterations were identified in 31% of samples**[8]

Optimization of Diagnostic Tissue Processing is Crucial in Helping to Improve Testing Completion Rates[1,9]

Up to 70% completion rates reported for strategies relying on tumor tissue testing[10-13]

Tissue testing approaches may be improved by acknowledging challenges to tumor tissue testing, such as[1]

- Limited amount of collected tumor tissue
- Exhaustion of diagnostic material
- Insufficient tumor content
- Suboptimal DNA yield

Recommendations for pre-analytical processing, specimen handling, and analysis[1]

Processing

- Assess total cellularity and neoplastic nuclei content[a]
- Embed multiple cores in 1 FFPE block
- Use EDTA for decalcification of bone samples

Storage and Handling

- Save blocks specifically for molecular testing
- Ensure pathologist is aware of future potential use
- Consider DNA extraction at the time of diagnosis

Analysis

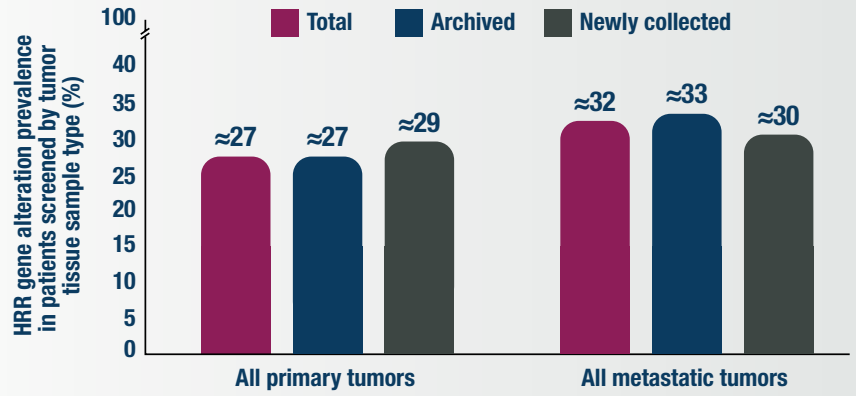
- Use validated DNA extraction protocol for FFPE
- Perform pre-analytical QC of DNA samples
- Use a validated NGS assay

[a]5000 cells contain approximately 30 ng of DNA. At least 10%-20% tumor content is required to reliably detect somatic variants at >5% allele frequency; higher tumor content may be required for detection of large somatic deletions and rearrangements.

Tissue Testing Completion Rates Can Be Influenced by Tumor Type and Sample Age[9]

Central tumor testing of samples from 2792 patients was completed and biomarker status was reported for ≥1 alterations in prespecified genes with a direct or indirect role in HRR, including *ATM*, *BARD1*, *BRCA1/2*, and *BRIP1*, among others[9]

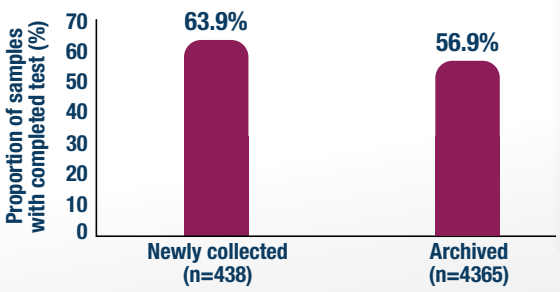
A Prospective, Randomized, Open-label Study in Patients With mCRPC[10,14]



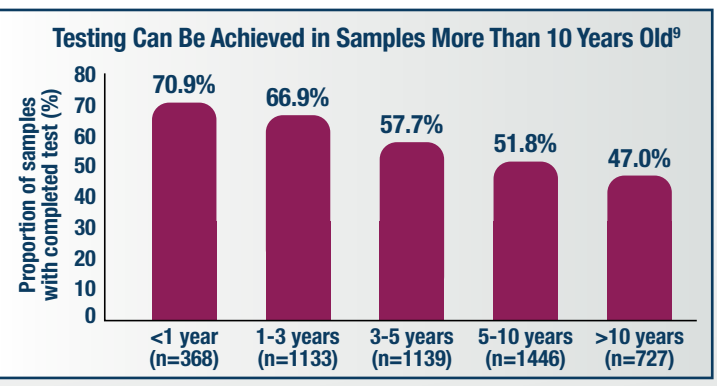
89.9% of samples from screened patients were derived from archived tissue

Similar rates of HRR gene alterations were observed in both primary and metastatic tumor samples[14]

Testing Is Possible With Both Archival and Newly Collected Samples, Regardless of Sample Age[9]



Testing Can Be Achieved in Samples More Than 10 Years Old[9]



10 years for FFPE specimens

The College of American Pathologists recommends that pathology records and materials must be retained for adequate quality control and appropriate care of the patient.[15,16]

Options for HRRm Testing

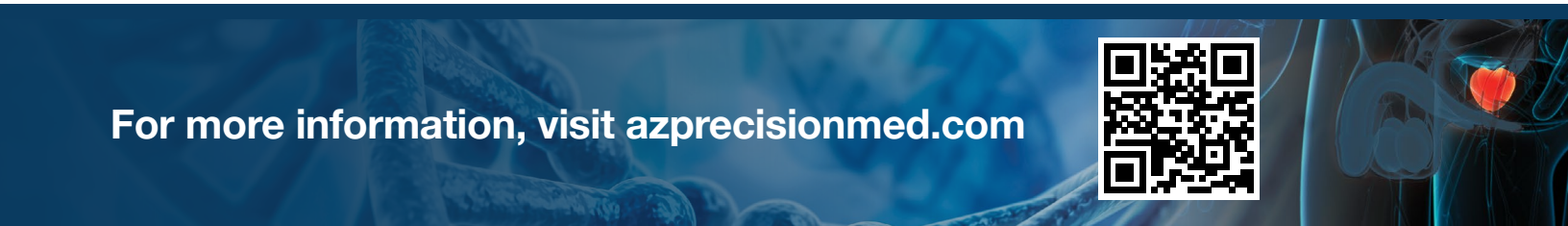
Sample Type	Clinical Relevance	Special Considerations
Tumor Tissue	Determines total mutation status (germline and somatic)[17]	Positive results should be followed by familial risk assessment[17]
Plasma ctDNA (liquid biopsy)	May be used when tumor tissue is unavailable[18]	**Mutation profile dependent on tumor shedding[19]**
Germline (blood or saliva)	Prognostic and predictive value may also have familial implications[17]	**Does not identify patients with somatic mutations[17]**

Abbreviations

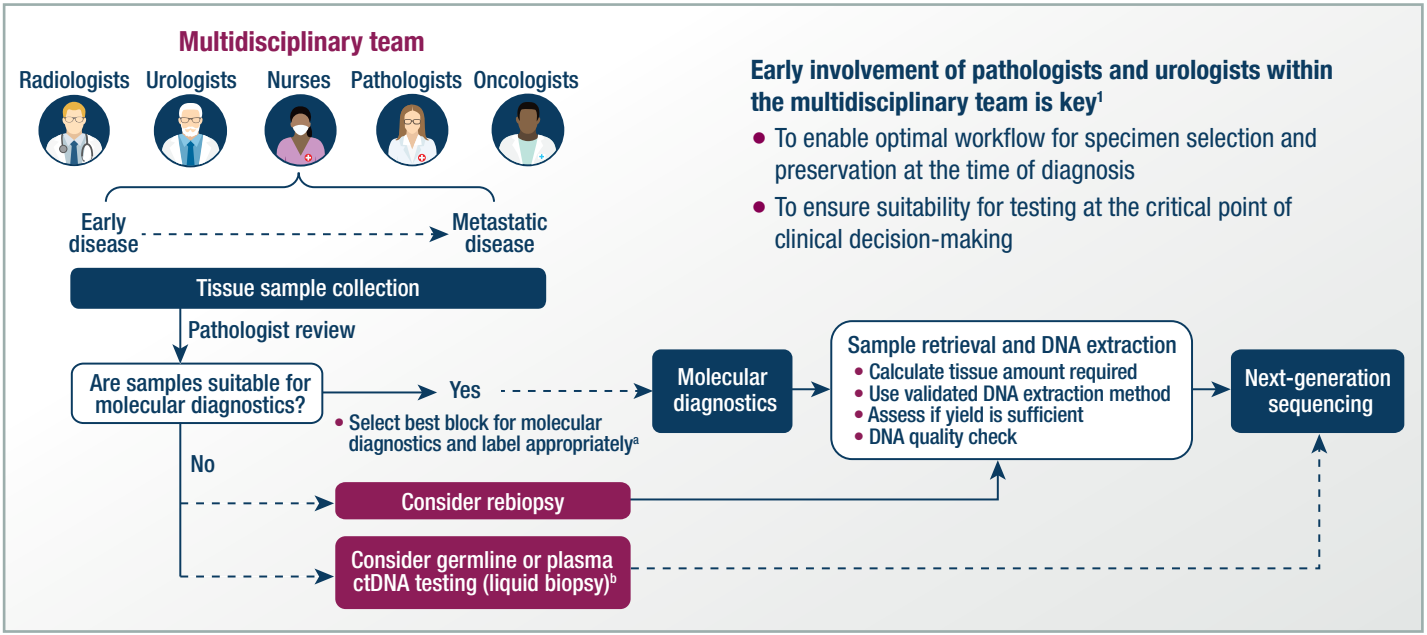
ATM, ataxia-telangiectasia mutated; ***ATR***, ataxia telangiectasia and Rad3-related; ***BARD1***, BRCA-associated RING domain 1; ***BRCA1***, breast cancer susceptibility gene 1; ***BRCA1/2***, breast cancer susceptibility gene 1 or 2; ***BRCA2***, breast cancer susceptibility gene 2; ***BRIP1***, BRCA-interacting protein 1; ***CDK12***, cyclin-dependent kinase 12; ***CHEK2***, checkpoint kinase 2; **ctDNA**, circulating tumor DNA; **EDTA**, ethylenediaminetetraacetic acid; ***FANCA***, Fanconi anemia, complementation group A; **FFPE**, formalin-fixed, paraffin-embedded; **HRR**, homologous recombination repair; **HRRm**, homologous recombination repair mutation; **mCRPC**, metastatic castration-resistant prostate cancer; **NGS**, next-generation sequencing; ***PALB2***, partner and localizer of BRCA2; **QC**, quality control.

References

1. Gonzalez D, et al. *J Pathol Clin Res*. 2021;7(4):311-325. **2.** Cucchiara V, et al. *Eur Urol*. 2018;73(4):572-582. **3.** Heeke AL, et al. *JCO Precis Oncol*. 2018;2018:PO.17.00286. **4.** Tan DS, et al. *J Clin Oncol*. 2008;26(34):5530-5536. **5.** Bolton KL, et al. *JAMA*. 2012;307(4):382-390. **6.** Pellegrino B, et al. *ESMO Open*. 2019;4(2):e000480. **7.** Shore N, et al. *Future Oncol*. 2021;17(22):2907-292. doi:10.2217/fon-2021-0153. **8.** Chung JH, et al. *JCO Precis Oncol*. 2019;3:PO.18.00283. **9.** Hussain M, et al. Poster presented at: Genitourinary Cancers Symposium; February 13-15, 2020; San Francisco, CA. Poster J9. **10.** de Bono J, et al. *N Engl J Med*. 2020;382(22):2091-2102. **11.** Abida W, et al. *JCO Precis Oncol*. 2017;1:PO.17.00029. **12.** Zhu J, et al. *Urol Oncol*. 2019;37(11):813.e1-813.e9. **13.** Abida W, et al. Poster presented at: 21st Annual Meeting of the Society of Urology Oncology; December 3-5, 2020; virtual meeting. Poster 141. **14.** de Bono, et al. Presented at: ESMO Congress; September 27-October 1, 2019; Barcelona, Spain. Abstract 847PD. **15.** Makhlouf H, et al. *Am J Clin Pathol*. 2020;153(2):149-155. **16.** College of American Pathologists. ANP.12500 record retention phase II. In: *Anatomic Pathology Checklist; CAP Accreditation Program*. College of American Pathologists; 2017:25-27. **17.** Cheng HH, et al. *J Natl Compr Canc Netw*. 2019;17(5):515-521. **18.** Chang Y, et al. *Ther Clin Risk Manag*. 2017;13:1363-1374. **19.** Fiala C, Diamandis EP. *BMC Med*. 2018;16(1):166.



Incorporating Molecular Testing Considerations Into the Diagnostic Pathway[1]



[a]If not used immediately, ensure correct storage conditions: 18-25 °C (64.4-77 °F) and low humidity. [b]For liquid biopsies, use cell-stabilization tubes and process within 3 days.

Integrate biomarker testing for patients with advanced prostate cancer in collaboration with your multidisciplinary team.

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