COR2ED

THE HEART OF MEDICAL EDUCATION

PRECISION ONCOLOGY ANIMATED VIDEO

SAMPLE COLLECTION, TEST REQUEST, GUIDELINES, DIAGNOSTIC MODALITIES PROSTATE CANCER

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September 2024

EDUCATIONAL OBJECTIVES

1. Know how to navigate pre-analytical phase challenges, including how to collect, store, process and prepare the samples
2. Be able to include all relevant biomarkers in the test request and tests
3. Understand the diagnostic modalities, and the role of biomarkers in oncology
4. Be able to implement or improve the leading role of the pathologist on the MDT

MDT, Multidisciplinary team

CLINICAL TAKEAWAYS

- It is important to consider that different types of samples are needed for somatic and germline testing
- Genomic biomarker testing is required to help with treatment decision making and for understanding inherited cancer risk
- Next-generation sequencing of multiple genes is the gold-standard method for both germline and tumour (somatic) testing in prostate cancer
- Alterations in HRR genes and MMR pathway genes in advanced prostate cancer can predict response to targeted therapies

HHR, homologous recombination repair; MMR, mismatch repair

DEVELOPED BY PRECISION ONCOLOGY CONNECT

This programme is developed by PRECISION ONCOLOGY CONNECT, an international group of experts in the field of oncology.

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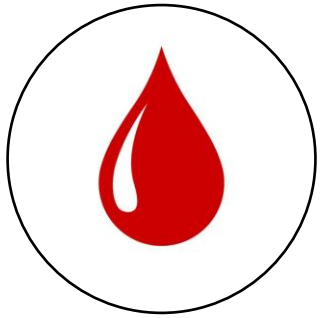
PROSTATE CANCER PRECISION ONCOLOGY TESTING LANDSCAPE

GENOMIC TESTING

GERMLINE VERSUS SOMATIC TESTING

- **Genomic testing** is a broad and non-specific term that describes multiple types of tests performed on part or all of the genome. Typically refers to somatic tests but may be used to describe some germline / genetic tests
- **Germline testing** – DNA test looking for **inherited alterations** present in every cell in the body. *Also called* ***genetic testing***
- **Somatic testing** – DNA test looking for **alterations in cancer DNA**. Typically requires tumour tissue. *Commonly called* ***tumour testing***

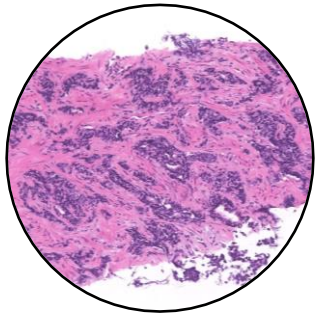
Genetic / germline testing



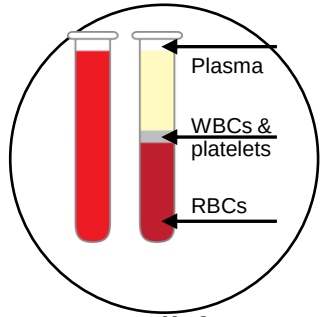
Whole blood or saliva

Will not identify cancer only alterations

Somatic / tumour testing



Tumour tissue sample



Plasma cell-free DNA

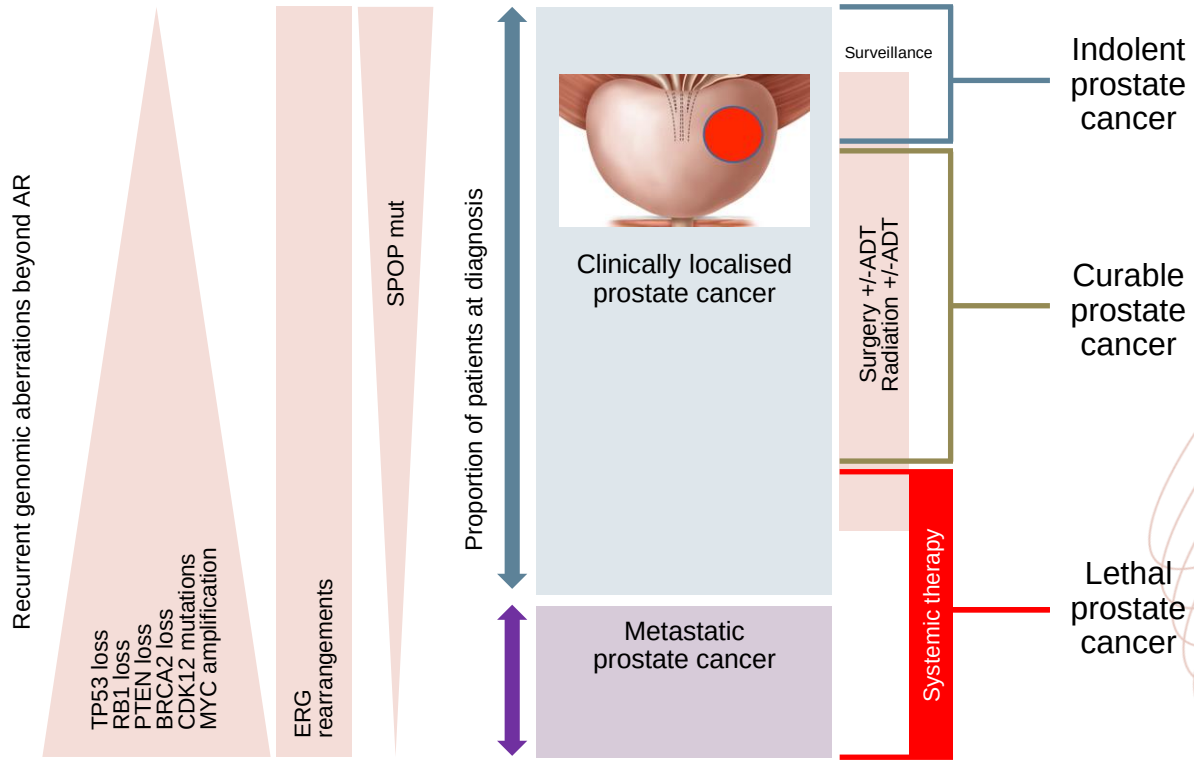
May not identify or discriminate all relevant germline alterations

DNA, deoxyribonucleic acid; RBC, red blood cell; WBC, white blood cell

COMMON GENOMIC ALTERATIONS IN PROSTATE CANCER

- Relatively **low** mutation rate
- Frequent **copy number alterations** and structural rearrangements
- Most classes of alterations are **more frequent in advanced** disease than localised (e.g. DNA repair alterations)
- **AR** gene alterations are only present in **castration-resistant prostate cancer**

Alterations get more frequent in advanced disease



ADT, androgen-deprivation therapy; AR, androgen receptor; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; DNA, deoxyribonucleic acid; ERG, ETS family transcription factor ERG; ETS, erythroblast transformation-specific; MYC, MYC proto-oncogene; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma protein; SPOP, speckle-type POZ; TP53, tumour protein p53

Adapted from Mateo J, et al. Nature Cancer. 2021;1(11):1041-53

BRCA2 AND OTHER DNA DAMAGE REPAIR GENES ARE FREQUENTLY ALTERED IN METASTATIC PROSTATE CANCER

	Germline		Somatic & Germline combined	
	Localised	**Metastatic**	**Localised**	**Metastatic**
All DDR genes	2 - 4%	6 - 12%	8 - 12%	20 - 25%
BRCA2	1 - 2%	4 - 5%	2 - 3%	8 - 12%
ATM	0.5 - 1%	1 - 2%	1 - 2%	3 - 7%
BRCA1	<1%	<1%	<1%	1%
MMRd	<1%	~1%	1%	3-5%
CDK12	Only somatic	Only somatic	1-2%	5%

Overall, DNA damage repair gene alterations (germline and somatic, combined) are found in **~10% of localised prostate cancer** but up to **25% of metastatic prostate cancer**

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer 1 and 2;DDR, DNA damage repair; DNA, deoxyribonucleic acid; MMRd, mismatch repair deficient

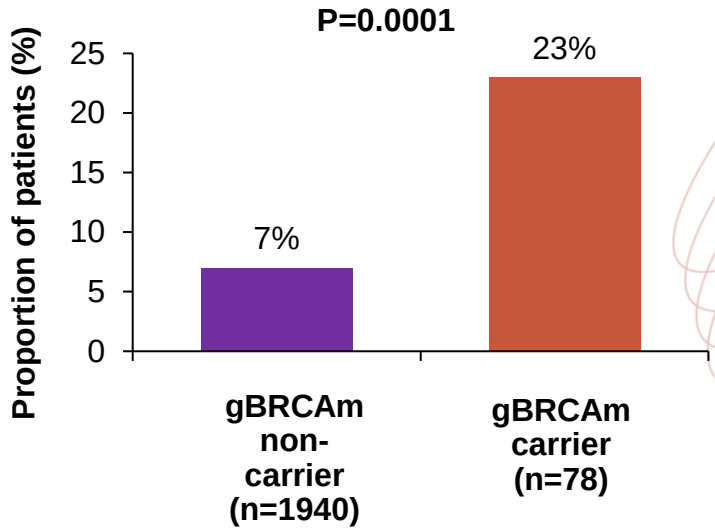
Darst B et al. J Natl Cancer Inst 2021 113(5):616-25; Lee D et al. Eur Urol 2022 81(6):559-67; Warner E et al. Clin Cancer Res 2021 27(6):1650-62; Nicolosi P et al. JAMA Oncol. 2019 5(4):523-8; Pritchard C et al. N Engl J Med. 2016 375:443-53; Abida W et al, JCO Precis Oncol. 2017; Abida W et al, JAMA Oncol. 2019 5(4):471-478, Valsecchi AA et al, Cancers 2023, 15, 2435

CLINICAL IMPLICATIONS OF TESTING

BRCA2 ALTERATIONS HAVE CLINICAL IMPLICATIONS

- Personal and familial risk of cancer (inherited germline alterations)[1]
- Poor outcomes on standard of care therapies (germline or somatic)[2-4]
- Prognostic marker for aggressive disease (germline or somatic)[5,6]
  - Diagnosis = higher Gleason, advanced stage[6]
  - Local = worse outcomes after RP/RT[5]
  - Met = shorter PFS on systemic treatment[2]
  - Predictive biomarker for PARP inhibitors[7]
    - germline or somatic; bi-allelic loss[3]

Patients who developed metastases within 5 years (based on 5-year MFS in localised PC patients)[6]

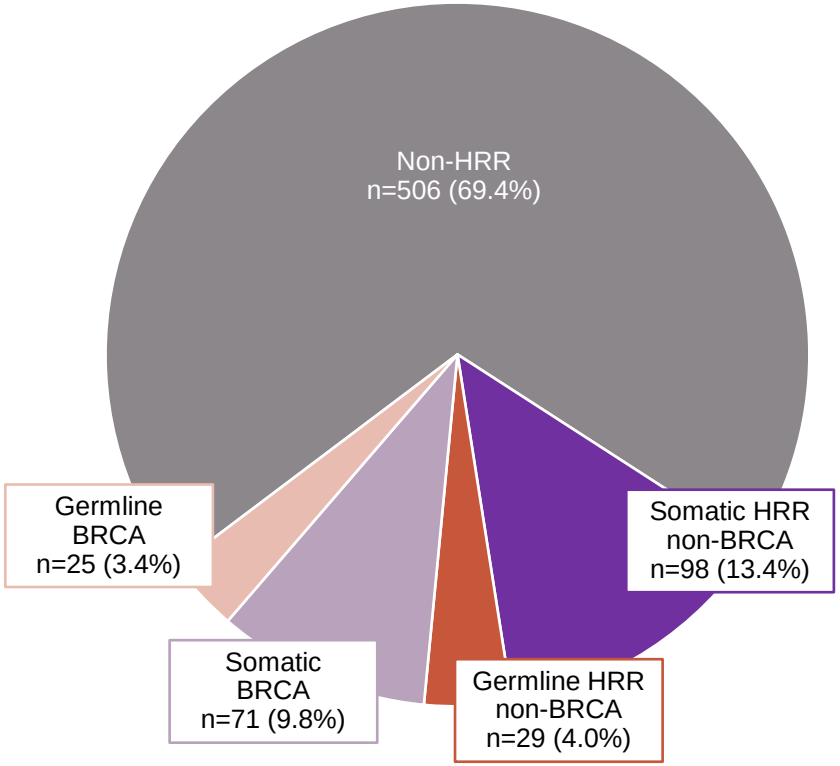


BRCA 2, breast cancer gene 2; met, metastasis; MFS, metastasis-free survival; PARP, poly-ADP ribose polymerase; PC, prostate cancer; PFS, Progression-free survival; RP, radical prostatectomy; RT, radiotherapy

Cheng HH, et al. J Natl Compr Cancer Netw. 2019;17(5):515-21; Castro E, et al. J Clin Oncol. 2019;6:490-503; Annala M, et al. Eur Urol. 2017;72:34-42; Annala M, et al. Cancer Discov. 2018;8(4):444-57; Castro E, et al. Eur Urol. 2015;68:186-93; Castro E, et al. J Clin Oncol. 2013;31:1748-57; Lord CJ and Ashworth A. Nature. 2012;481:287-93

BRCA2 ALTERATIONS HAVE CLINICAL IMPLICATIONS: LATEST DATA

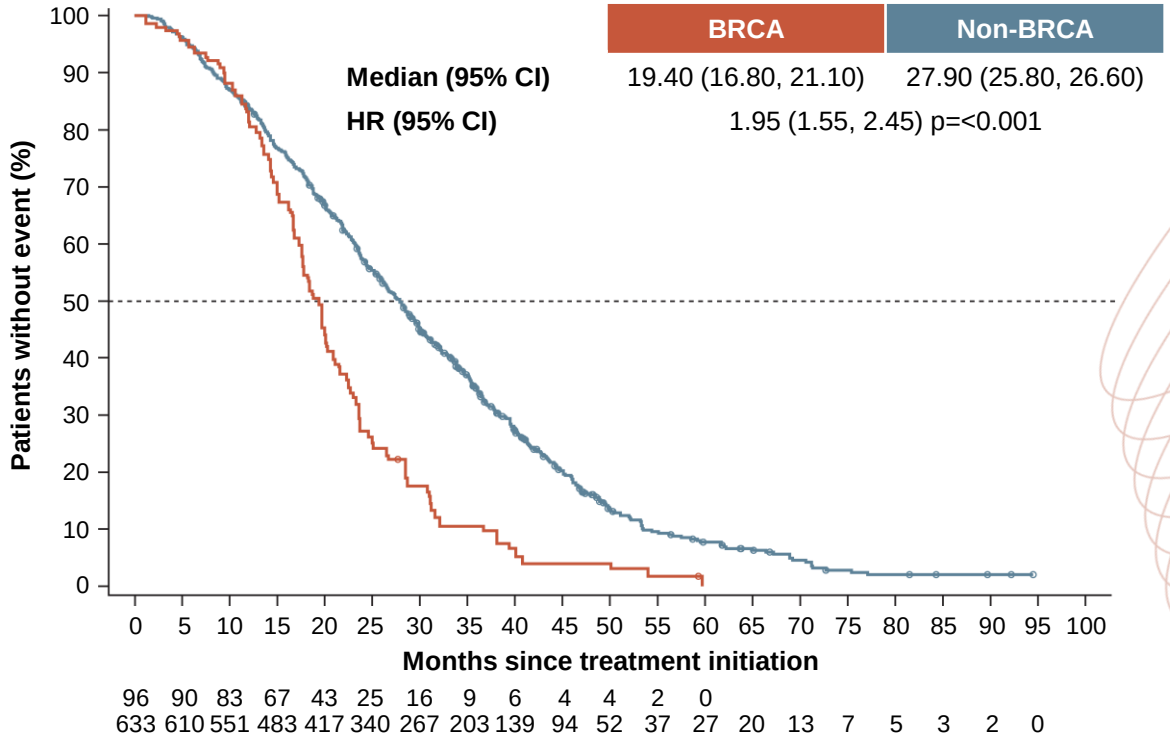
13.2% with ***BRCA1/2*** germline or somatic alterations



Confirmation of worse outcomes with ARPI or taxanes

n=729 mCRPC, 1L Tx ARPI or taxane OS

Poorer OS, rPFS, PFS2 for BRCA1/2 subgroup



1L, first-line; ARPI, androgen receptor pathway inhibitor; HR, hazard ratio; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression free survival; PFS2, second PFS; rPFS, radiographic PFS; Tx, treatment

Adapted from Olmos D et al. Ann Oncol. 2024;35(5):458-72

BRCA2 ALTERATIONS HAVE CLINICAL IMPLICATIONS: LATEST DATA

Confirmation of benefit from PARPi +/- ARPI

mCRPC, pooled analysis of **PARPi** trials

Gene mutation	End point	Arm	No.	No. of events	Median survival, months	HR (95% CI)	HR (95% CI)
*ATM*m (N=268)	rPFS (BICR)	PARPi + ARPI	136	67	19 (16-28)	1.05 (0.74-1.49)	1.02 (0.71-1.45)
		Placebo + ARPI	132	59	19 (16-NE)		
	OS	PARPi + ARPI	136	63	33 (26-NE)	1.18 (0.82-1.71)	1.12 (0.77-1.62)
		Placebo + ARPI	132	55	33 (28-NE)		
*BRCA1*m (N=64)	rPFS (BICR)	PARPi + ARPI	37	14	20 (14-NE)	0.51 (0.23-1.1)	0.52 (0.2-1.33)
		Placebo + ARPI	27	15	12 (4-NE)		
	OS	PARPi + ARPI	37	16	29 (15-NE)	0.74 (0.34-1.61)	0.73 (0.28-1.89)
		Placebo + ARPI	27	13	26 (13-28)		
*BRCA2*m (N=422)	rPFS (BICR)	PARPi + ARPI	199	60	NA (22-NE)	0.31 (0.23-0.42)	0.27 (0.19-0.37)
		Placebo + ARPI	223	144	10 (8-11)		
	OS	PARPi + ARPI	199	77	33 (29-NE)	0.66 (0.49-0.89)	0.6 (0.44-0.82)
		Placebo + ARPI	223	112	24 (22-28)		
*CDK12*m (N=146)	rPFS (BICR)	PARPi + ARPI	73	32	17 (16-NE)	0.5 (0.32-0.8)	0.51 (0.32-0.82)
		Placebo + ARPI	73	44	14 (8-17)		
	OS	PARPi + ARPI	73	32	36 (25-NE)	0.63 (0.39-0.99)	0.64 (0.4-1.03)
		Placebo + ARPI	73	44	27 (20-33)		
*CHEK2*m (N=172)	rPFS (BICR)	PARPi + ARPI	85	37	14 (14-25)	1.06 (0.67-1.66)	1.00 (0.63-1.59)
		Placebo + ARPI	87	43	18 (13-22)		
	OS	PARPi + ARPI	85	39	26 (23-NE)	1.53 (0.95-2.46)	1.48 (0.92-2.4)
		Placebo + ARPI	87	32	34 (26-NE)		
*PALB2*m (N=41)	rPFS (BICR)	PARPi + ARPI	23	12	14 (8-NE)	0.52 (0.23-1.17)	0.43 (0.15-1.21)
		Placebo + ARPI	18	13	9 (2-20)		
	OS	PARPi + ARPI	23	12	25 (15-NE)	0.78 (0.34-1.8)	0.59 (0.21-1.65)
		Placebo + ARPI	18	11	20 (11-NE)		

ATM not strongly linked to outcomes

BRCA2

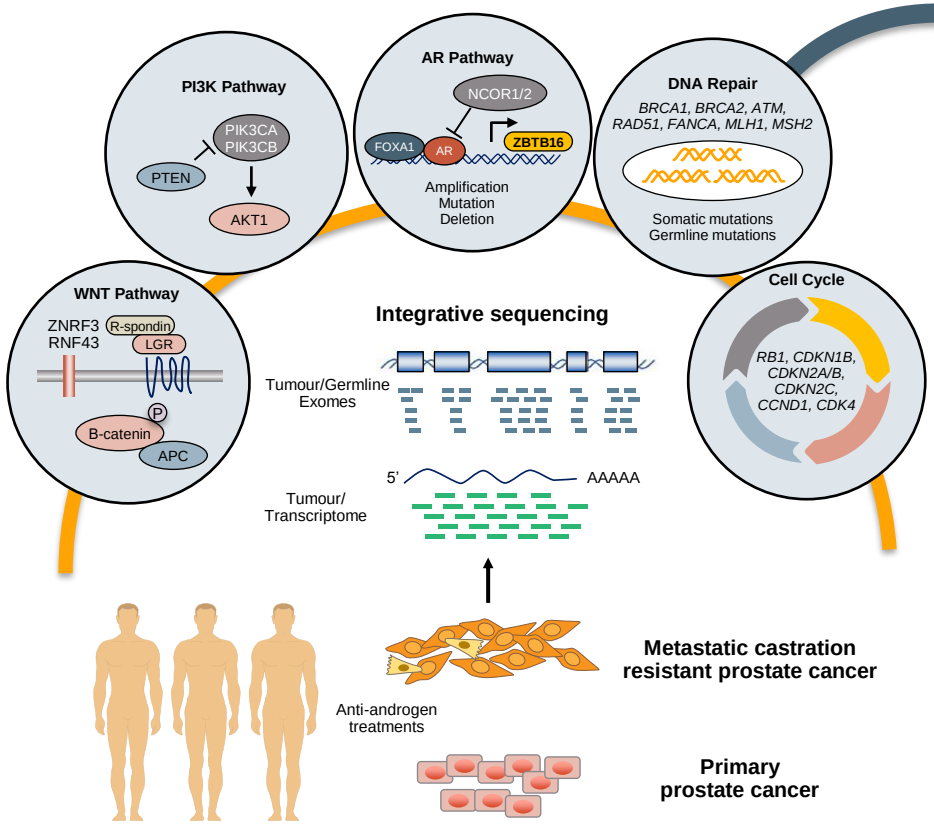
ARPI, androgen receptor pathway inhibitor; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; m, mutation; mCRPC, metastatic castration-resistant prostate cancer; PARPi, poly-ADP ribose polymerase inhibitor; OS, overall survival PFS, progression free survival

Fallah J, et al. J Clin Oncol 2024;42:1687-98

CLINICALLY-RELEVANT GENOMIC ALTERATIONS BEYOND DNA DAMAGE REPAIR PATHWAYS

Correlative studies: non-DNA repair genomic alterations associate with different disease prognosis and may even predict outcomes in some contexts

SPOP, FOXA1
***AR* gene and enhancer**
PTEN*, *PIK3CA*, *AKT1
TP53 and RB1



Clinical guidelines now recommend <u>germline</u> +/- <u>somatic</u> screening of <u>DNA repair genes</u>

hereditary cancers
patient prognosis
treatment selection

Prospective trials are required to prove clinical utility of understanding genomic alterations beyond DNA damage repair defects

Annala M, et al. Cancer Discov. 2018;8(4):444-57; Herberts C, et al. Eur Urol. 2020;78(6):834-44; Annala M, et al. Annals Oncol. 2021;32(7):896-905; Image adapted from Robinson D et al. Cell 2015;161(5):1215-28; Abida W, et al. Proc Natl Acad Sci U S A. 2019;116(23):11428-36; van Dessel LF et al. Nat Commun. 2019;10:5251

WHEN AND WHO TO ORDER BIOMARKER TESTING FOR

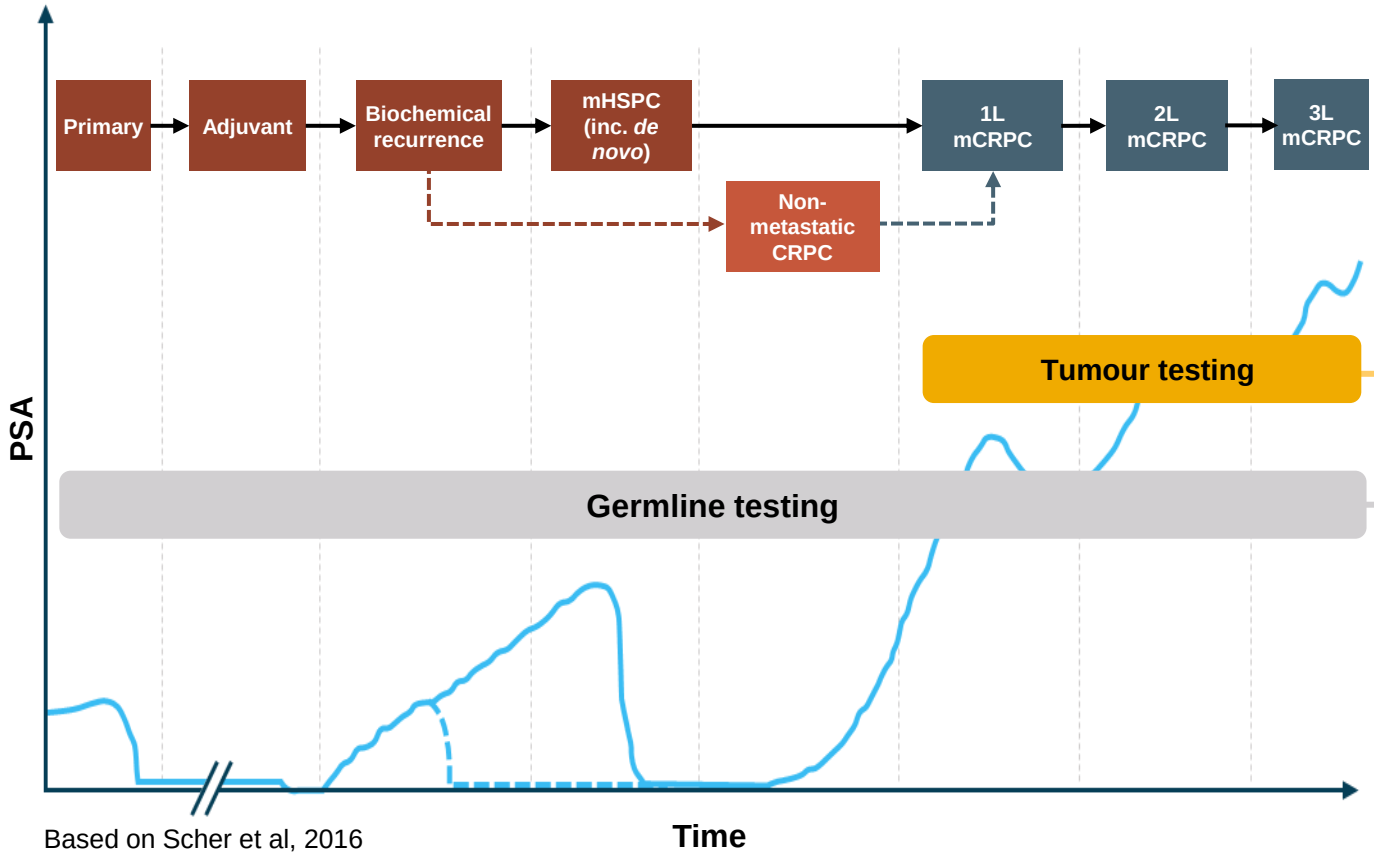
WHO TO TEST FOR DNA REPAIR ALTERATIONS?

- **Germline testing** should be performed in all prostate cancer patients with **metastatic disease**
  - Good practice point: *perform testing as early as possible*.
  - Minimum genes: ***ATM***, ***BRCA1***, ***BRCA2***, *CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2,* ***TP53***, and *RAD51D*
- **Germline testing** should be performed in **selected patients with localised** prostate cancer (family or personal history of related cancers; *high-risk or very-high risk disease*)
- **Tumour/somatic testing** should be performed in patients with **mCRPC** to inform the **selection of therapy**
- **Somatic-only** testing is not adequate for germline conclusions
- Good practice point: *perform testing as early as possible (mCSPC, nmCRPC)*
  - Minimum genes: ***BRCA1***, ***BRCA2***, ***ATM*** (but ideally align with germline panels)
  - Ensure all patients with *de novo* M1 disease have a **tissue biopsy** performed
  - First choice of specimen for testing is tissue, second is ctDNA

ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration resistant prostate cancer; nmCRPC, non-metastatic CRPC

Rendon R, et al. Can Urol Assoc J. 2023;17(10):314-25

CONSIDERATIONS FOR WHEN TO TEST FOR *HRR*m ARE INCLUDED IN INTERNATIONAL GUIDELINES



Based on Scher et al, 2016

ESMO[1]

- Recommended for ***BRCA2*** and other **DDR genes** associated with cancer predisposition in patients with family history of cancer
- Should be considered in all patients with metastatic prostate cancer

- **Consider HRRm** and **MSI dMRR** testing in patients with **mCRPC**

EAU/EANM/ESTRO/ESUR/ISUP/SIOG[2]

- Men with metastatic PCa;
- Men with high-risk PCa and a family member diagnosed with PCa at age <60 years;
- Men with multiple family members diagnosed with csPCa at age <60 years or a family member who died from PCa cancer;
- Men with a family history of high-risk germline alterations or a family history of multiple cancers on the same side of the family.

- **Consider HRRm** and **dMRR** testing in all patients with **mPC**

NCCN[3]

- Individuals where it is likely to impact the prostate cancer treatment and clinical trial options, management of risk of other cancers, and/or potential risk of cancer in family members.
- Men with family history or known germline variants

- Recommend **HRRm** testing in patients with **mPC.** Consider for regional PC
- Recommend testing for **MSI-H, dMMR for mCRPC.** Consider for regional or CSPC
- Consider **TMB** testing for **mCRPC**

AUA/SUO[4]

- Testing for **DDR, MSI dMMR, TMB** and other potential alterations **in mCRPC** patients
- Consider for **mHSPC patients**

- Testing for **DDR, MSI dMMR, TMB and other potential alterations in mCRPC** patients
- Consider for **mHSPC patients**

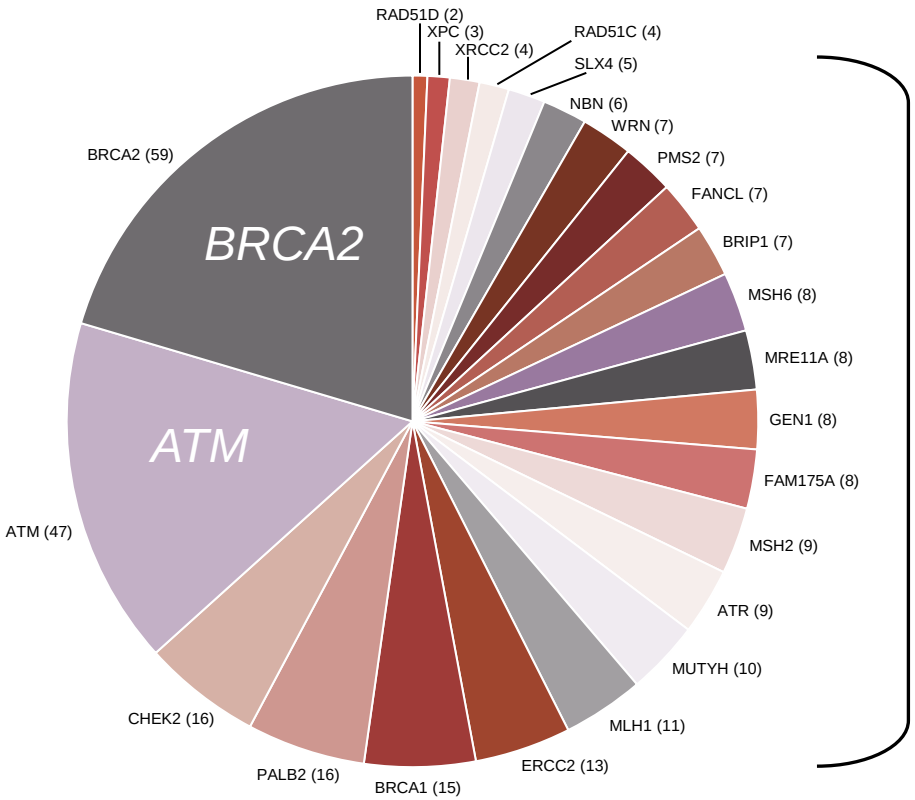
Guidelines differ by jurisdiction:→ be aware of your local guidelines

1L/2L/3L, first/second/third line; BRCA2, breast cancer gene 2; CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer csPCa, clinically significant PCa; DDR, DNA damage repair; dMMR, mismatch repair damage; HRRm, homologous recombination repair mutation; mCRPC, metastatic CRPC; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; MSI(h), microsatellite instability (high); PCa, prostate cancer; PSA, prostate-specific antigen;
TMB, tumour mutational burden

1. Parker C, et al. Ann Oncol. 2020; 31(9): 1119-34; 2. Mottet N, et al. 2023 EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer;
3. National Comprehensive Cancer Network. Prostate Cancer (Version 2024). prostate.pdf (nccn.org).; 4. Lowrance W, et al. J Urol. 2023; 209(6):1082-1090; 5. Scher HI, et al. J Clin Oncol 2016; 34 (12): 1402-1418

DNA DAMAGE REPAIR GENES, BEYOND *BRCA2* (WHAT ADDITIONAL GENES SHOULD BE TESTED)

DNA repair genes with Tier I/II alterations from genetic / germline testing



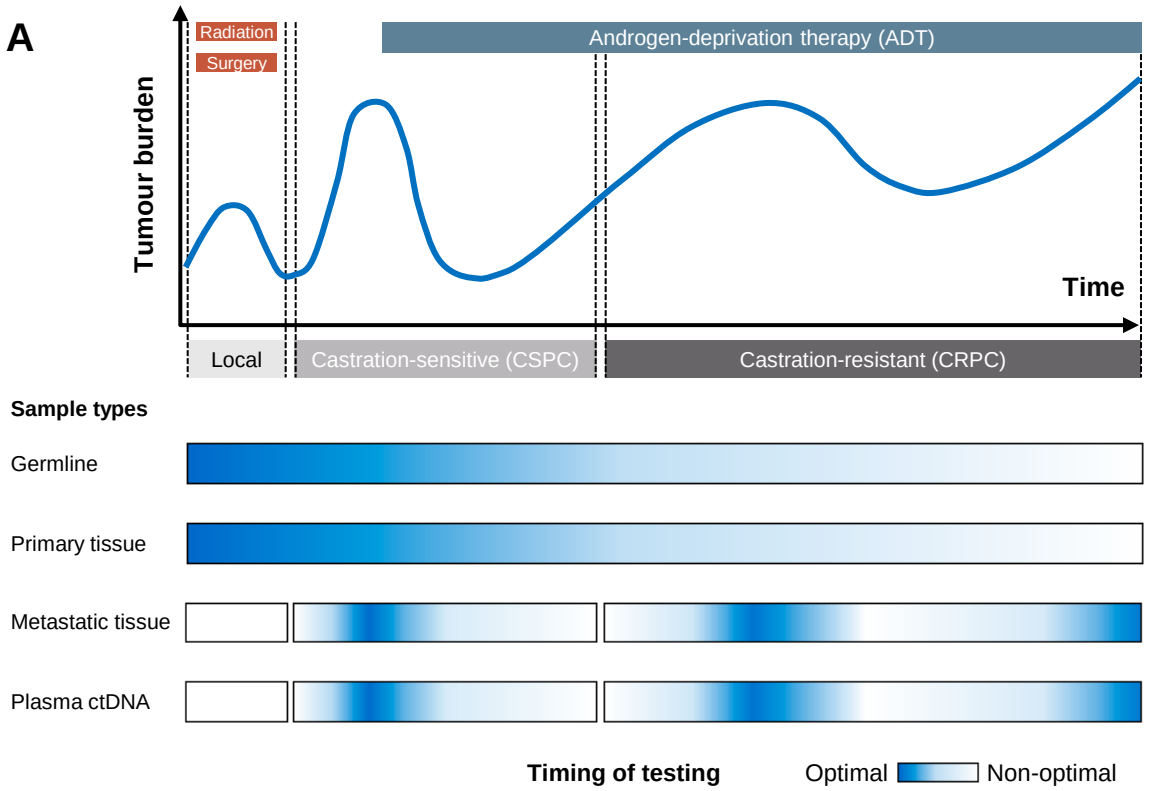
- Rarely altered genes **may not be covered** at all by clinical tests, or may not be reported on even if covered
- Somatic-only testing is not adequate for germline conclusions. Ideally, perform somatic and germline testing in parallel
- It is difficult to predict the familial risk (germline alterations) or the **functional / therapeutic / prognostic relevance** (germline or somatic alterations)
- Rare genes are more likely to be included in a germline test than a somatic test
- Remember that some genes are somatic-only mutated (e.g. *CDK12*)
- Germline testing panels should include genes associated with Lynch syndrome (*MLH1, MSH2, MSH6, PMS2)* and homologous recombination genes (*BRCA1/2, ATM, PALB2, CHEK2*)

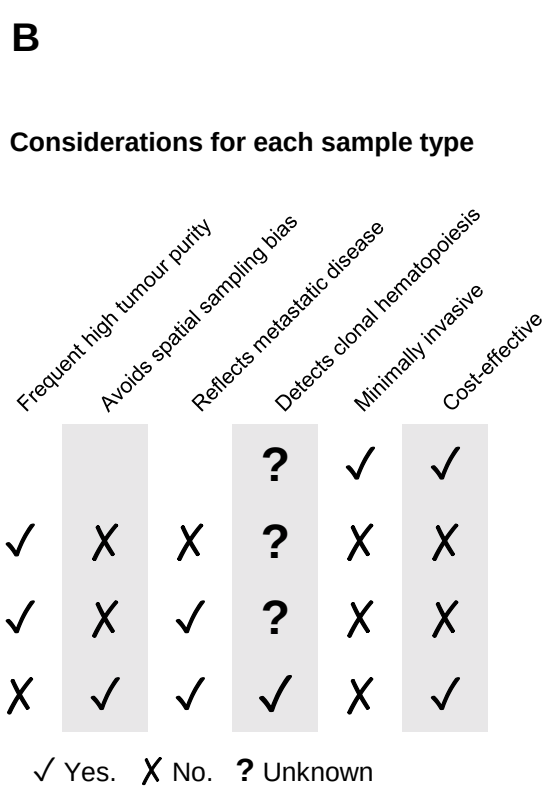
ATM, ataxia telangiectasia mutated; BRCA1/2, BReast Cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK2, checkpoint kinase 2; DNA, deoxyribonucleic acid; FANCA, Fanconi anaemia complementation group A protein; MLH1, mutL homologue 1; MSH2/6, mutS homologue 2/6; PALB2, partner and localiser of BRCA2

Darst B, et al. J Natl Cancer Inst. 2021 113(5):616-25

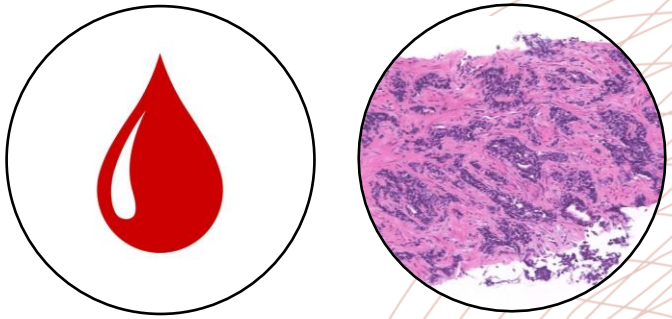
AT WHAT STAGE SHOULD A TEST BE ORDERED?

TEST AS EARLY AS POSSIBLE (ONCE A PATIENT IS ELIGIBLE)

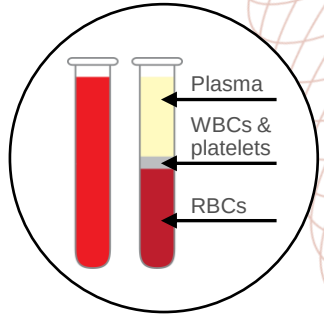




As early as possible:
Germline
(whole blood or saliva)
Somatic (tumour tissue)



Only at disease progression:
Plasma cell-free DNA (ctDNA)

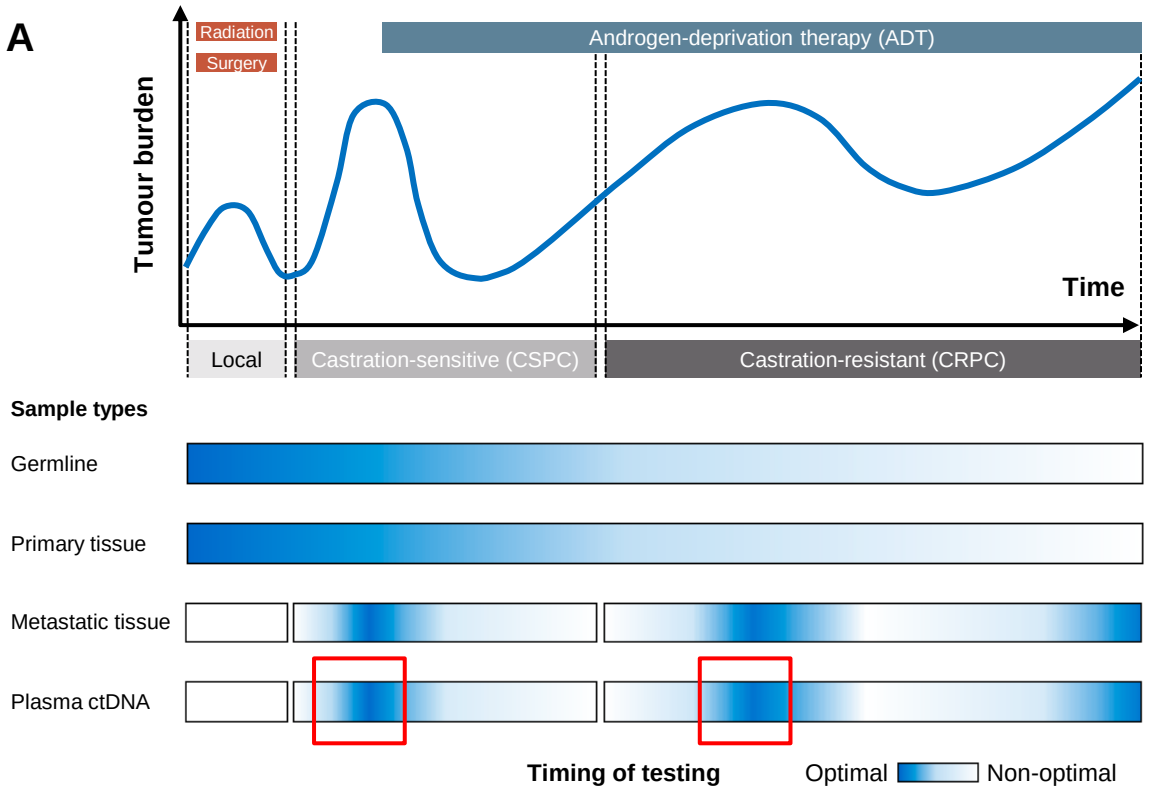


ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; RBC, red blood cell; WBC, white blood cell

Image adapted from Vandekerkhove G, et al. JCO Precis Oncol. 2024;8: e2300654

PLASMA FREE DNA (ctDNA)

- ctDNA fraction is positively associated with progressive disease burden
- The optimal time to order a ctDNA test for cancer genotyping is at times of clinical disease progression
- If ctDNA tests are ordered while cancer is responding to treatment, there is unlikely to be ctDNA present (meaning that the cancer is not being tested)



Only at disease progression:
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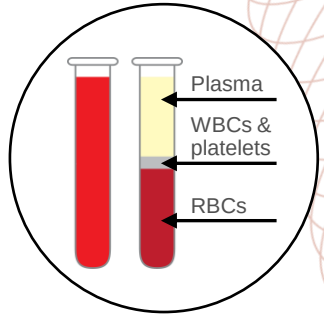
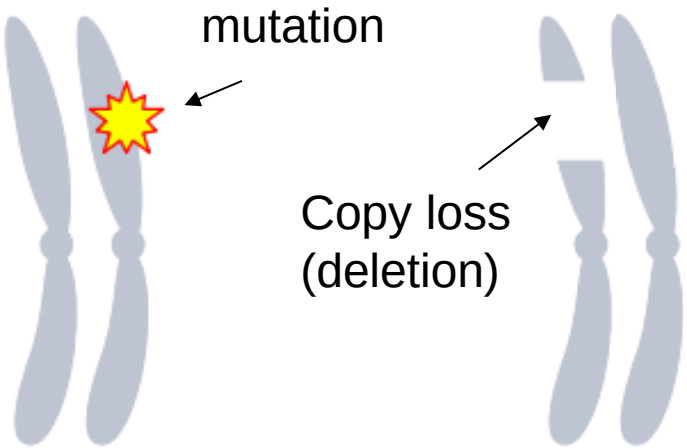


ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; RBC, red blood cell; WBC, white blood cell

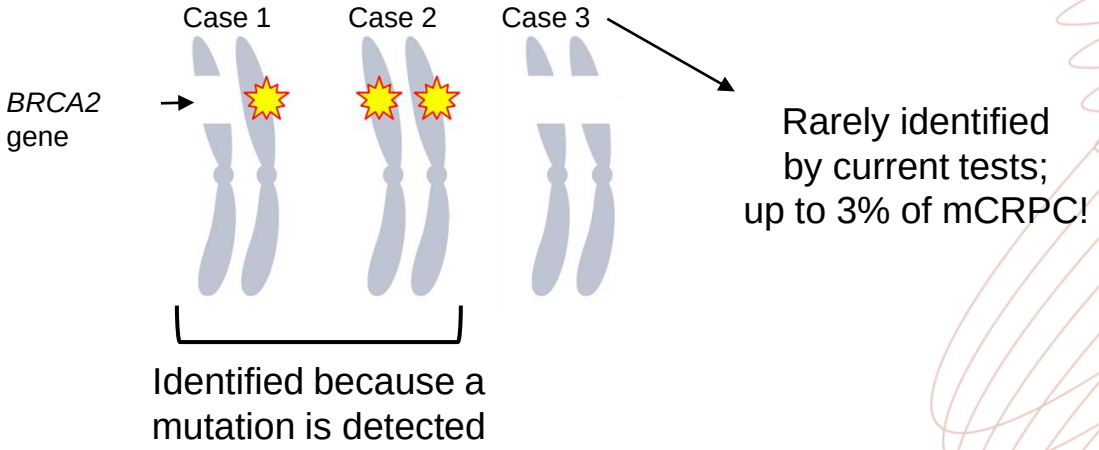
Image adapted from Vandekerkhove G, et al. JCO Precis Oncol. 2024;8: e2300654

MUTATIONS ARE JUST ONE MECHANISM OF GENOMIC ALTERATION (*COPY LOSSES ARE ALSO IMPORTANT*)

- Most **clinical** tests will report a tumour suppressor gene mutation but **not** a copy number deletion (*which can remove one or both parental alleles*)



BRCA2 only relevant if both alleles are lost (bi-allelic loss)



- Key prostate cancer tumour suppressor genes ***BRCA2***, *RB1*, *TP53*, ***MSH2/6***, *PTEN* can be disrupted by copy losses or complex structural rearrangements
- Aim to use tests that report copy number variants in addition to mutations

BRCA2, breast cancer gene 2; mCRPC, metastatic castration-resistant prostate cancer; MSH2/6, mutS homologue 2/6; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma protein; TP53, tumour protein p53

Herberts C and Wyatt A. Trends in Cancer. 2021;7(11):995-1009

CHALLENGES, LIMITATIONS AND RECOMMENDATIONS FOR PROSTATE BIOMARKER TESTING

OPERATIONAL LIMITATIONS OF SOMATIC TESTING

- Tests do not cover all relevant genes / regions
  - *+ huge variability between tests in performance*
- Tests cannot identify or report all possible deleterious alterations
  - *It can also be difficult to know if certain alterations are deleterious / pathogenic*
- Alteration detection is insufficiently sensitive for complex events
  - *Manual curation required even for standard mutations*
- Tumour fraction (purity) may be low, causing false negatives
- Tumour heterogeneity (region to region) may cause false positives or negatives
- Mutations can be sub-clonal (i.e. not present in all tumour cells)
- … & many others!

Remember: tests generally flatten tumour biology into binary presence/absence, and do not always capture/report other relevant biological context that may ultimately be informative for clinical management decisions

COMMON CHALLENGES AND RECOMMENDATIONS IN PROSTATE CANCER GENOMIC TESTING: TEST ORDERING

Access to tissue	• Tumour tissue may not always be accessible – Action: **Source blocks early** or consider re-biopsy
Insufficient tumour content within sample	• Tissue tests have stringent minimum requirements (e.g. cellularity, DNA yield) – Action: Involve a GU-specialist pathologist to help identify optimal tissue regions – Action: Be ready to **pivot to other test** approaches
Insufficient breadth of genes tested	• While all gene panels will include *BRCA1* and *BRCA2*, rare or indirect HRR genes may not be present. Some panels may only report coding region alterations (and not copy number losses) – Action: **Understand your local panel design** (may differ for germline vs somatic testing)
Uncertainty on need for tissue versus liquid biopsy testing	• ctDNA tests can inform on alterations that arose later in disease progression (i.e. that would be missed by archival tissue tests), but can be unclear when a ctDNA test would be helpful – Action: Only order ctDNA tests at times of disease **clinical progression** – Action: Consult with the MDT or local clinical genomics staff
Uncertainty of need for germline versus somatic testing	• ctDNA Optimal testing for metastatic prostate cancer involves somatic and germline testing but guidelines can differ especially for localized prostate cancer – Action: Be aware of the **guidelines** relevant to local practice – Action: **Order** both somatic and germline tests when appropriate (somatic testing does not replace the need for germline testing)

BRCA1.2, breast cancer gene 1/2; ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; GU, genito-urinary; HRR, homologous recombination repair; MDT, multidisciplinary team

COMMON CHALLENGES AND RECOMMENDATIONS IN PROSTATE CANCER GENOMIC TESTING: INTERPRETING RESULTS

False negatives	• Low tumour fraction can result in false negatives, particularly for copy number losses – Action: Recognise the **test-specific limits of detection** for each type of alteration, and when you need to re-test
Allelic status not reported	• Tests may not report tumour allelic status of alterations (i.e. mono vs biallelic loss) – Action: Be aware that most **HRR genes require biallelic loss** for inactivation
Unclear actionability of reported variants	• Test reports can include technical jargon or be ambiguous on clinical actionability of each alteration – Action: seek clarification from the group that operated the test and/or the local **MDT**
No discrimination between somatic and germline alterations	• It can be difficult to resolve a germline variant from tumour tissue testing alone (i.e. without matched germline profiling – Action: if **HRR alterations** are identified by tumour tissue testing (and the patient did not have prior or concurrent germline testing), the alteration may be germline in origin and patients should be referred for genetics counselling and germline testing

HRR, homologous recombination repair; MDT, multidisciplinary team; HRRm homologous recombination repair mutations

CONCLUSIONS

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- Multi-gene germline and somatic testing is required for identification of HRR and MMR gene alterations in advanced prostate cancer.
  - Presence of **HRR/MMR gene alterations** can predict response to targeted therapies
  - Germline alterations should trigger cascade family member testing
- Both tumour tissue and plasma ctDNA can be used for **somatic testing**, but ctDNA tests should only be ordered at times of clinical disease progression
- **Pre-analytical issues** (e.g. tumour tissue availability, quality, and cellularity) and long turn-around times for sourcing and testing tissue can be a barrier to accurate and timely results
- Multi-disciplinary team-based care including **GU-cancer specialised pathologists** and genomics experts are important for optimal precision oncology in prostate cancer

ctDNA, circulating tumour DNA; DNA, deoxyribonucleic acid; GU, genito-urinary; HRR, homologous recombination repair; MMR, mismatch repair

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