Genetic Testing in Advanced Prostate Cancer

Leonard G. Gomella, MD, FACS
Emeritus Chair, Department of Urology
Senior Director for Clinical Affairs
Sidney Kimmel Comprehensive Cancer Center
Thomas Jefferson University
Philadelphia, PA
May, 2026

1

Onflict of Interest

- Advisory board for Merck/Astellas
- Patent rights with Thomas Jefferson University

2

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Genetic Testing in Advanced Prostate Cancer

Background: Genomic and Genetic Testing

Prostate Cancer Genetic Testing: Basic Concepts

Prostate Cancer and Inherited Risk

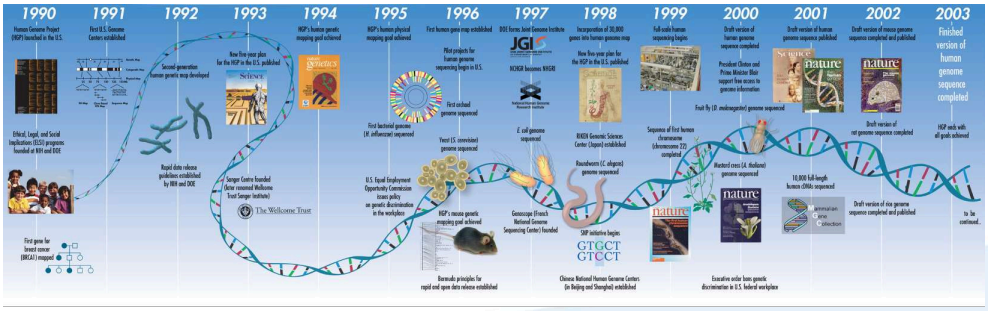
Practical Considerations in Genetic Testing

Precision Medicine for Advanced Prostate Cancer

3

Human Genome Project

1990-2003



3.2 billion base pairs

https://www.mun.ca/biology/scarr/Human_Genome_Project_timeline.html

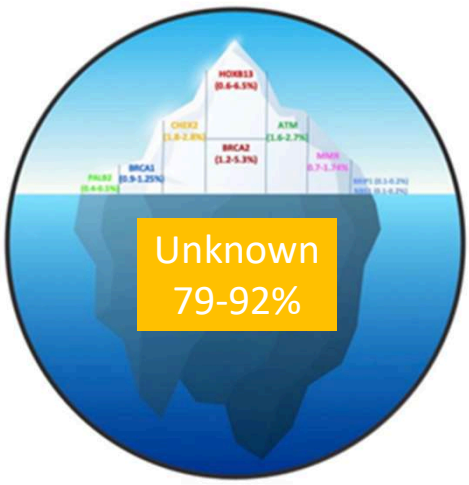
American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

4

Science April 1, 2022
"Filling in the gaps of the last 8% of the Human genome"

RESEARCH ARTICLE
HUMAN GENOMICS
The complete sequence of a human genome



Int. J. Mol. Sci. 2021, 22(7), 3753; https://doi.org/10.3390/ijms22073753

5

"Breast Cancer Linkage Consortium" Prostate Cancer in 1999:

Male *BRCA1/2* carriers: 30%-39% lifetime risk

Germline mutation of *BRCA1*

- Males heterozygous for a m*BRCA1* with a relative **risk of approximately 1.8**
- Risk may vary significantly depending on the location of the *BRCA1* variant
- Such cancers do not typically demonstrate a younger than usual age at diagnosis

---

Germline mutation of *BRCA2*

- The relative risk for **prostate cancer** in males with a **m*BRCA2* is 4.6**
- In contrast to *BRCA1 PCa* , it may demonstrate a younger-than-usual age and be more aggressive

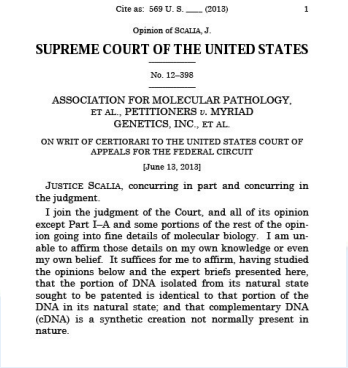
[Breast**Cancer** Linkage Consortium 1999, Risch et al 2001, Thompson & Easton 2002, Giusti et al 2003, Tryggvadóttir et al 2007, Cybulski et al 2008, Edwards et al 2010.

6

Spring 2013: Everything Changed

BRCA inherited cancer risk

May 13, 2013



Cite as: 569 U. S. ____ (2013) 1

Opinion of SCALIA, J.

SUPREME COURT OF THE UNITED STATES

No. 12–398

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS *v.* MYRIAD GENETICS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 13, 2013]

JUSTICE SCALIA, concurring in part and concurring in the judgment.

I join the judgment of the Court, and all of its opinion except Part I–A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. It suffices for me to affirm, having studied the opinions below and the expert briefs presented here, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that complementary DNA (cDNA) is a synthetic creation not normally present in nature.

DNA cannot be patented

June 13, 2013

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

7

Rapid Advances in Prostate Cancer Genetic Testing: NCCN 2016-2020

- **Before 2016**: Prostate cancer and BRCA only discussed in Hereditary Breast and Ovarian Cancer (HBOC) Guidelines
- **2016 Early Detection**: First mention of Family History BRCA1/2 for screening
- **2017 Prostate Cancer**: First Familial/Hereditary genetic considerations for screening

> [a]The following should be considered: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age, germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (germline mutations in MLH1, MSH2, MSH6, or PMS2) and/or strong family history for breast or ovarian cancer (suggests possibility of BRCA2 mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, *small bowel, urothelial, kidney, or bile duct cancer (suggests* possibility of Lynch syndrome).

- **2017.2 Prostate Cancer:** First mention of PARP and DNA repair for therapy
- **2018.1 Prostate Cancer**: First "consideration" for germ line testing based on risk
- **2020.1 Prostate Cancer**: Germ line testing now "recommended" based on risk

www.nccn.org

8

Rapid Advances in Prostate Cancer Genetic Testing: NCCN 2016-2020

- **Before 2016**: Prostate cancer and BRCA only discussed in Hereditary Breast and Ovarian Cancer (HBOC) Guidelines
- **2016 Early Detection**: First mention of Family History BRCA1/2 for screening
- **2017 P**
- **2017.**
- **2018.**
- **2020.1 Prostate Cancer**: Germ line testing now "recommended" based on risk

10 years AUA SUO Advanced Prostate Cancer Program

www.nccn.org

9

Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017

Sidney Kimmel Cancer Center at Jefferson
NCI – designated

Sidney Kimmel Cancer Center, Thomas Jefferson University
and
The Foundation for Breast and Prostate Health
Philadelphia, Pennsylvania
March 3 & 4, 2017

Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

Conference Co-Chairs:
- Leonard Gomella, MD
- Veda N. Giri, MD
- Karen E. Knudsen, PhD, MBA

Giri, et al J Clin Oncol. 2018 Feb 1; 36(4): 414–424; Giri et al. J Clin Oncol. 2020 Aug 20;38(24):2798-2811.

10

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Genetic Testing in Advanced Prostate Cancer

Background: Genomic and Genetic Testing

Prostate Cancer Genetic Testing: Basic Concepts

Prostate Cancer and Inherited Risk

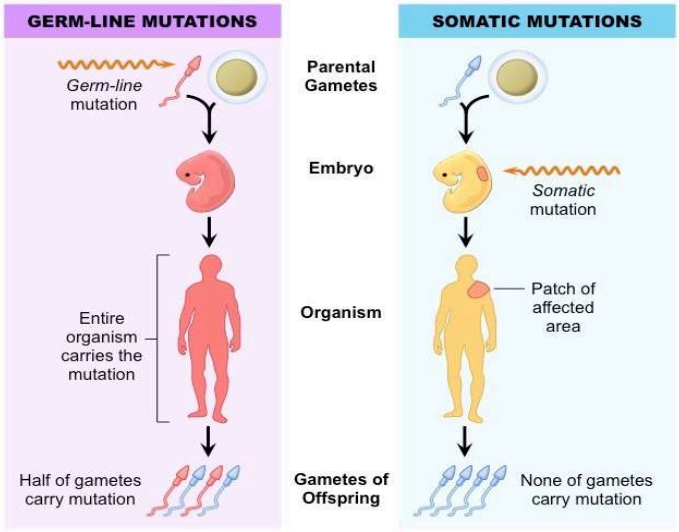
Practical Considerations in Genetic Testing

Precision Medicine for Advanced Prostate Cancer

11

Inherited germ line mutations from parents

Blood or saliva sample



Mutation may only be found in tumor, but germ line mutations may also be detected.

Fresh or archival tumor, metastasis or liquid biopsy

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

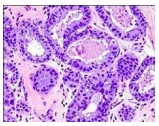
http://ib.bioninja.com.au

12

Prostate Cancer "Genetic/Genomic" Testing

Genomic "Profiling"
- Tissue based biopsies
- Proprietary molecular signatures

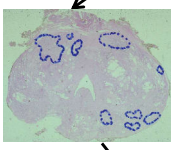
(Decipher, Prolaris, OncotypeDX, ConfirmMDX, Prostatype)

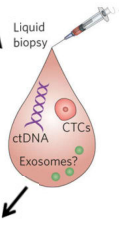


-Outcomes, treatment, management decisions

Genomic Tumor Sequencing
- **Somatic testing**
  - Tissue or "liquid biopsy"
  - Extensive testing tumor-specific mutations (300+)

(Foundation Medicine, Caris)

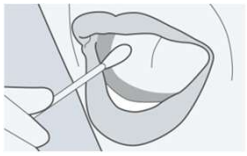




-Direct targeted therapies
-Clinical trial eligibility

Inherited Cancer Risk Testing
- **Germline testing**
  - Identify inherited mutations by buccal/blood testing
  - Increased cancer risk

(Ambry, Myriad, Invitae, GeneDX, Color, others)



-Cancer screening and prevention
-Genetic testing in close relatives
-Informing treatment and clinical trials

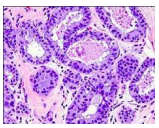
Courtesy Dr. Leonard Gomella

13

Prostate Cancer "Genetic/Genomic" Testing

Genomic "Profiling"
- Tissue based biopsies
- Proprietary molecular signatures

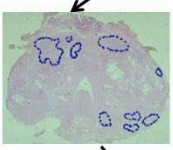
(Decipher, Prolaris, OncotypeDX, ConfirmMDX, Prostatype)

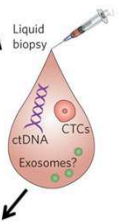


-Outcomes, treatment, management decisions

Genomic Tumor Sequencing
- **Somatic testing**
  - Tissue or "liquid biopsy"
  - Extensive testing tumor-specific mutations (300+)

(Foundation Medicine, Caris)

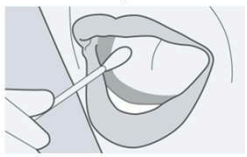




-Direct targeted therapies
-Clinical trial eligibility

Inherited Cancer Risk Testing
- **Germline testing**
  - Identify inherited mutations by buccal/blood testing
  - Increased cancer risk

(Ambry, Myriad, Invitae, GeneDX, Color, others)



-Cancer screening and prevention
-Genetic testing in close relatives
-Informing treatment and clinical trials

Courtesy Dr. Leonard Gomella

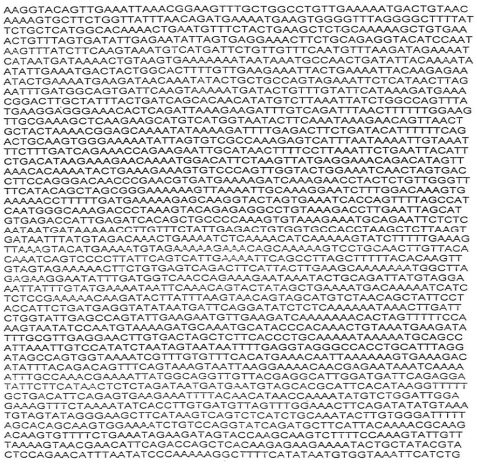
14

Deep sequencing
Next Generation Sequencing (NGS)

- Takes hours to days
- Sequencing a region many times; Minimizes errors
- “Gene Chip” technology assays many genes at once
- More sequencing = more expensive = more accurate
- “Recreational” tests unlikely to deep sequence
- Medical labs: beware low cost

15

Genomic testing relies on computational biology



Example:

<u>Normal BRCA2 gene</u>

- 27 exons total, 12 pages long
- coding region 10,433 base pairs
- image is small portion of exon 11

<u>mBRCA2 gene</u>

- Mutated genes such as mBRCA2 can have several hundred different reported sequences**
- Not just ONE mutated gene sequence
- GenBank ® is the NIH genetic sequence database (www.ncbi.nlm.nih.gov › genbank)

** Note “recreational” gene testing (e.g. 23 and Me) only test for a couple of “founder” genes and not all mutations

16

NIH National Institutes of Health
Turning Discovery Into Health

- **BRCA is an abbreviation for "BReast CAncer gene"**
- **20,000 +** unique BRCA1 and BRCA2 mutation variants.
- 6,100 variants classified by an expert panel.
- **3,700** of these variants are known to cause disease.
- CAUTION: Direct to consumer genetic testing screens limited number of mutations

www.brcaexchange.org Accessed January 31, 2026

17

Example Mutated Germline Testing

Hereditary Cancer Risk Test ***(Color Genomics)***

A pathogenic mutation was identified in the *BRCA2* gene.

DETAILS

A pathogenic mutation is a variant in the DNA sequence of a gene that affects its ability to function and is also referred to as a mutation in this report

GENE	MUTATION	CLASSIFICATION
BRCA2	**c.1813delA (p.Ile605Tyrfs*9)** *Alternate name(s): chr13.GRCH37:g.32907428delA* *Transcript: ENST00000544455* *Zygosity: Heterozygous*	**Pathogenic**

American Urological Association Education & Research, Inc.
SUO Society of Urologic Oncology, Inc.

18

Genomic/Genetic Testing for Prostate Cancer Risk

- Background:
  - 10-15% PCa are hereditary
  - Inherited mutated genes (BRCA 1/2) do not cause cancer but increase risk
  - These pathogenic genes interact with other genes/environment to increase PCa risk
  - Increased risk for other cancers (breast, ovarian, pancreatic, others).
  - Rapidly evolving evidence on how to use these genes for screening/therapy.

- Why do Genomic/Genetic Germ Line Testing?
  - Potential impact on therapeutic options
    - Identify "actionable genes"
    - May guide treatment in era of "precision medicine"
  - Potential to screen/prevent other at-risk cancers:
    - in the patient
    - in the family

American Urological Association Education & Research, Inc.

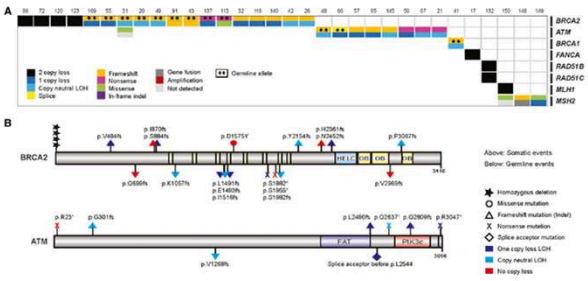
SUO Society of Urologic Oncology, Inc.

19

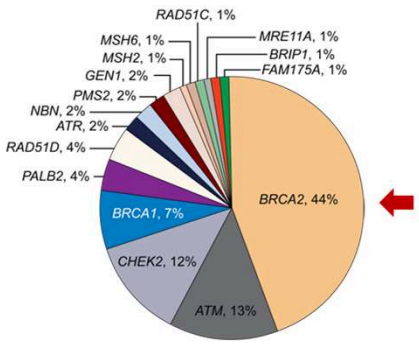
Major Impact: DNA repair Gene Mutations and PCa

Somatic

- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations increases in metastatic disease vs. localized disease



Germline



- 12% of men with metastatic prostate cancer have a germline DNA repair defect

Robinson D et al. *Cell.* 2015;161:215-28. Pritchard CC et al. *N Engl J Med.* 2016;375: 443-53.

20

Genomic/Genetic Testing for Prostate Cancer Risk

Most mutated genes in PCa are HRR Genes (Homologous Recombination Response) that repair double-stranded DNA damage

<u>Most important mutations related to defects in DNA repair mechanisms</u>

HOXB13: gene linked with clearly defined inherited prostate cancer (young age, high grade, multiple family members)

Modified from Nicolosi P, JAMA Oncol. 2019 Apr 1;5(4):523-528.

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Some genes when mutated (i.e. mBRCA2) associated with prostate cancer

Gene	PCa Risk	Mechanism
ATM	elevated	DNA damage response
BRCA1	~ 20%	DNA damage repair
BRCA2	~ 20%	DNA damage repair
CHEK2	elevated	DNA repair through phosphorylation of BRCA2
EPCAM	up to 30%	Upregulate c-myc
HOXB13	up to 60%	AR repressor
MLH1	up to 30%	DNA repair
MSH2	up to 30%	DNA repair
MSH6	up to 30%	DNA repair
NBN	elevated	DNA repair
PMS2	up to 30%	DNA mismatch repair
TP53	unknown	Tumor suppressor
PALB2	preliminary	Tumor suppressor
RAD51D	preliminary	DNA repair

21

DNA damage response (DDR) mutations and PCa

- Most are mHRR Genes (Homologous Recombination Response)
  - 2-6 fold ↑ lifetime risk (BRCA2 > BRCA1)
  - 8.6-fold ↑ risk by age 65 (BRCA2)
- PCa: Usually aggressive:
  - > Gleason 7-8, node +, mets, poor survival
- ↑ risk for other hereditary cancers in self and family:
  - <u>Breast, ovarian, melanoma, pancreatic, Lynch Syndrome, colon</u>
- Identification of mutations direct screening and mCRPC therapy (e.g., PARP inhibitors)

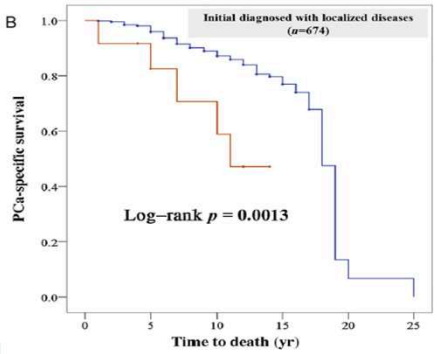
American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Eur Urol Open Sci. 2023 Jan 25;49:23-31

22

Germline Mutations in *ATM* and *BRCA1/2* Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death



	Median survival (yr)	95%CI
Mutation carrier	11.0	N/A
Nonmutation carrier	18.0	17.2–18.8

American Urological Association Education & Research, Inc.

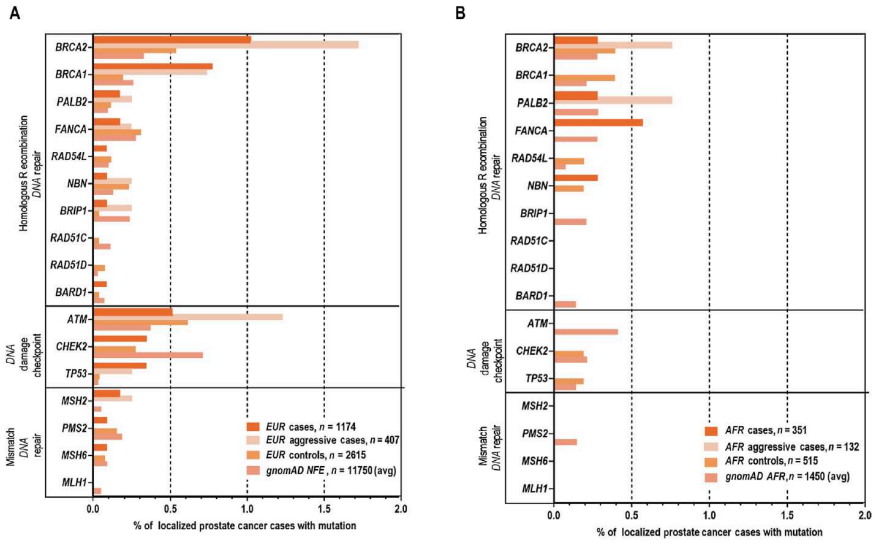
SUO Society of Urologic Oncology, Inc.

Eur Urol 2016 Na et al ;http://dx.doi.org/10.1016/j.eururo.2016.11.033

23

Low incidence of germ line mutations in localized Dz (European vs African American)

Mutation rates in identified PCa genes >2.0% only in high-risk disease



Lee European Urology 2022

24

Polygenetic Risk Score (PRS)

- SNP (single nucleotide polymorphism) single nucleotide DNA sequence variation in at least 1% of the population.
  - SNPs cause variations in genes (eye and hair color, etc)
- Over 140 PCa SNPs reported (WBSCR22, PRMT2, SRD5A1, etc)
  - PRS: tool utilizing PCa-associated SNPs identified from genome-wide association study (GWAS)
  - Multiple PCa-associated SNPs may explain 33% of the risk of developing Pca
  - May improve PSA screening
- Interaction of SNP and germline factors under investigation
- BARCODE1 study: PRS improved CaP screening over PSA and MRI

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Am J Transl Res 2021;13(4):3868-3889; Urol Clin North Am. 2021 Aug;48(3):387-399; NEJM. 2025 Apr 10;392(14):1406-1417.

25

Polygenetic Risk Score (PRS)

- SNP (single nucleotide polymorphism) single nucleotide DNA sequence variation in at least 1% of the population.
  - SNPs cause variations in genes (eye and hair color, etc)
- Over 140 PCa SNPs reported (WBSCR22, PRMT2, SRD5A1, etc)
  - PRS: tool utilizing PCa-associated SNPs identified from genome-wide association study (GWAS)
  - Multiple PCa-associated SNPs may explain 33% of the risk of developing Pca
  - May improve PSA screening
- Interaction of SNP and germline factors under investigation
- BARCODE1 study: PRS improved CaP screening over PSA and MRI

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Am J Transl Res 2021;13(4):3868-3889; Urol Clin North Am. 2021 Aug;48(3):387-399; NEJM. 2025 Apr 10;392(14):1406-1417.

26

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Genetic Testing in Advanced Prostate Cancer

Background: Genomic and Genetic Testing

Prostate Cancer Genetic Testing: Basic Concepts

Prostate Cancer and Inherited Risk

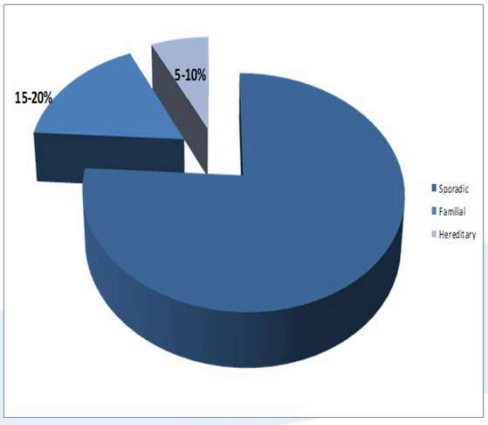
Practical Considerations in Genetic Testing

Precision Medicine for Advanced Prostate Cancer

27

Prostate Cancer: Hereditary/Familial/Sporadic

- **Hereditary (10-15% of cases)**
  - Often due to a single inherited genetic mutation
  - Greatly **increases** lifetime risk
  - BRCA1, BRCA2, Lynch syndrome
  - HOXB13: Inherited prostate cancer
- **Familial (15-20% of cases)**
  - Some features of hereditary cancer
  - No detectable mutation identified
  - Possible genetic + environmental risk
  - Close family members increased risks
- **Sporadic (70-80% of cases)**
  - Exact cause unknown
  - No features of hereditary or familial cancers
  - No increased risks for close family members



American Urological Association Education & Research, Inc.

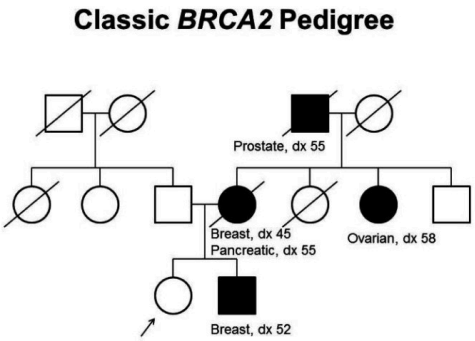
SUO Society of Urologic Oncology, Inc.

Klein EA, et al Prostate Cancer and Prostatic Diseases (1998) 1, 297-300

28

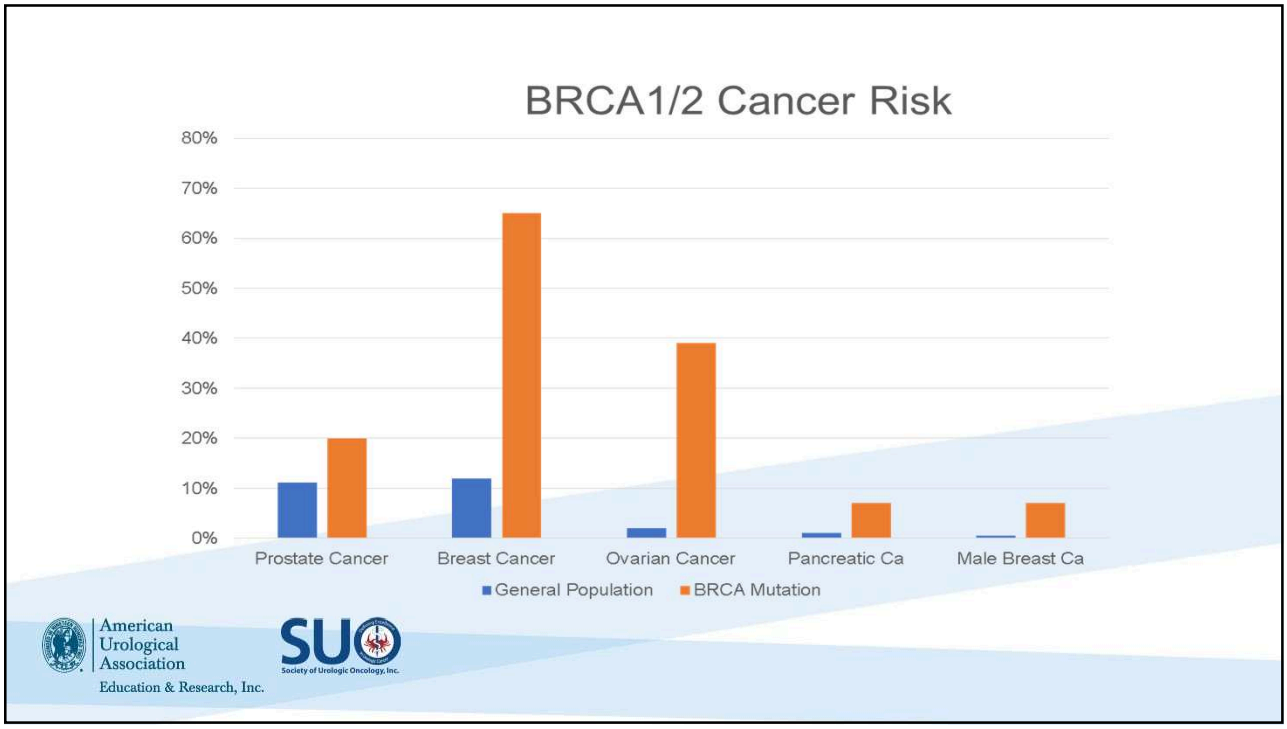
Familial vs Hereditary CaP

- **Familial** PCa: simple clustering.
- **Hereditary** PCa: is a more specific
  - A subtype of familial PCa consistent with mendelian inheritance of a susceptibility gene.
  - Age is important for hereditary PCa:
    - PCa relative Dx < 53 yo lifetime risk: 40%
    - Pca relative Dx >65yo lifetime risk: 18%
- Importance of **genetic counsellors**



Walsh and Partin, Cancer November 1, 1997 / Volume 80 / Number 9
Carter BS, Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A. 1992 Apr 15;89(8):3367-71;
https://www.ncbi.nlm.nih.gov/books/NBK65767/

29



30

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Genetic Testing in Advanced Prostate Cancer

Background: Genomic and Genetic Testing

Prostate Cancer Genetic Testing: Basic Concepts

Prostate Cancer and Inherited Risk

Practical Considerations in Genetic Testing

Precision Medicine for Advanced Prostate Cancer

31

Testing for Germline Mutations

Result	Interpretation
"Pathogenic" or "likely pathogenic" mutation • Hundreds of mutations have been identified for a specific gene Example: • *BRCA2* c.1411G>T/(p.Glu471Ter)	• Should be referred for genetic counseling • Consider detailed review of family history • May recommend testing of family members for so called "cascade" testing
"Benign" or "Likely benign"	• No pathogenic mutations definitively identified
"VUS" (variant of unknown significance)	• Can be considered a "negative" test but requires follow up • Ongoing review for newly identified mutations • GenBank (https://www.ncbi.nlm.nih.gov/genbank/) maintains central repository of reported genes

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Richards S, et al. *Genet Med*. 2015;17:405-424.

32

Common Genetic Germ Line Testing Panels

- **Fulgent "Prostate Cancer Panel" (20 gene)**
  - ABRAXAS1, ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, GEN1, HOXB13, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53
- **OncoGeneDx "Hereditary Prostate Cancer Panel" (16 gene)**
  - ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM*, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53
- **Invitae "Hereditary Cancer Panel" (12+ select up to 16 genes)**
  - ATM BRCA1 BRCA2 CHEK2 EPCAM HOXB13 MLH1 MSH2 MSH6 NBN PMS2 TP53; ADD ON ATR,BRIP1, GEN1, NBN
- **Color Health "Hereditary Cancer Genetic Test" (30 genes based on test ordered)**
  - Includes common prostate cancer genes: BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2
- **Ambry/Labcorp VistaSeq**: Focuses on key high-risk genes including ATM, BRCA1/2, and Lynch syndrome markers.
- **ProstateNow (GoPath Diagnostics):** (23 genes) plus a Genetic Risk Score (GRS) and the HSD3B1 gene (resistance to ADT)
- **Myriad:** No prostate panel, but "myRisk" (48 genes)

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Manufacturers web sites Accessed March 15, 2026

33

Common Genetic Germ Line Testing Panels

- **Fulgent "Prostate Cancer Panel" (20 gene)**
  - ABRAXAS1, ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, GEN1, HOXB13, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53
- **OncoGeneDx "Hereditary Prostate Cancer Panel" (16 gene)**
  - ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM*, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53
- **Invitae**
  - ATM
- **Color H**
  - Incl
- **Ambry/**
  markers
- **Prostat**
  (resistance to ADT)
- **Myriad:** No prostate panel, but "myRisk" (48 genes)

Prostate Cancer "Core" Genes

ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Manufacturers web sites Accessed March 15, 2026

34

Somatic Tumor DNA Testing

- Used to identify “actionable” genes for clinical trials and drug approvals
- Primary tumor, lymph node, liver, bone common
  - Becoming more common“Liquid biopsy”: ctDNA (circulating tumor cell DNA)
- If germline mutation noted, perform germline testing if not previously done
- Therapeutic approvals:
  - Multiple PARP Inhibitors: Rucaparib, Olaparib, PARP combinations through FDA approved “Companion Diagnostics”
  - Pembrolizumab: If microsatellite instability-high (MSI-H) or mismatch repair deficient or tumor mutational burden > 10 Mb

Companion Diagnostics

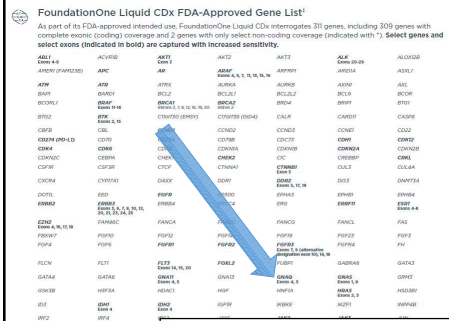
- **Myriad BRACAnalysis CDx:** BRCA 1/2 germline companion diagnostic for olaparib
- **FoundationOne Liquid CDx:** Analyses over 300 genes
  - BRCA 1/2 + ATM is companion diagnostic for olaparib and rucaparib
- **FoundationOne CDx:** Analyses over 300 genes
  - Also 14 gene companion for olaparib
  - BRCA 1/2 is tissue companion for niraparib and abiraterone (AKEEGA)

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Moreno JG, Gomella LG .*Urology*. 2019;132:1-9. doi: 10.1016/j.urology.2019.06.006.
Tuffaha H, Prostate Cancer Prostatic Dis (2023). doi.org/10.1038/s41391-023-00676-0

35


FoundationOne Liquid CDx FDA-Approved Gene List[1]

As part of its FDA-approved intended use, FoundationOne Liquid CDx interrogates 311 genes, including 309 genes with complete exonic (coding) coverage and 2 genes with only select non-coding coverage (indicated with *). **Select genes and select exons (indicated in bold) are captured with increased sensitivity.**

Somatic testing evaluates > 300 potentially actionable genes, **TMB** (tumor mutational burden), **MSI** (microsatellite instability)

CDx Somatic Testing available for both solid tumors and liquid biopsy of circulating cell free DNA (cfDNA)

ABL1 Exons 4-9	ACVR1B	**AKT1** Exon 3	AKT2	AKT3	**ALK** Exons 20-29	ALOX12B
AMER1 (FAM123B)	**APC**	**AR**	**ARAF** Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1
ATM	**ATR**	ATRX	AURKA	AURKB	AXIN1	AXL
BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6	BCOR
BCORL1	**BRAF** Exons 11-18	**BRCA1** Introns 2, 7, 8, 12, 16, 19, 20	**BRCA2** Intron 2	BRD4	BRIP1	BTG1
BTG2	**BTK** Exons 2, 15	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8
CBFB	CBL	**CCND1**	CCND2	CCND3	CCNE1	CD22
CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	**CDH1**	**CDK12**
CDK4	**CDK6**	CDK8	CDKN1A	CDKN1B	**CDKN2A**	CDKN2B

36

Somatic Mutation Testing in Prostate Cancer

- Identify "**actionable**" mutations.
  - HRR genes: e.g. *BRCA1, BRCA2, PALB2*
    - → PARP inhibitors/combo therapy
      - Up to 30% of mCRPC with increasing use
  - MMR (mismatch repair) genes: e.g. *MLH1, MSH2, MSH6 Or MSH high*
  - *High Tumor Mutational Burden (TMB)*
    - → Pembrolizumab
      - 3-5% of mcrpc

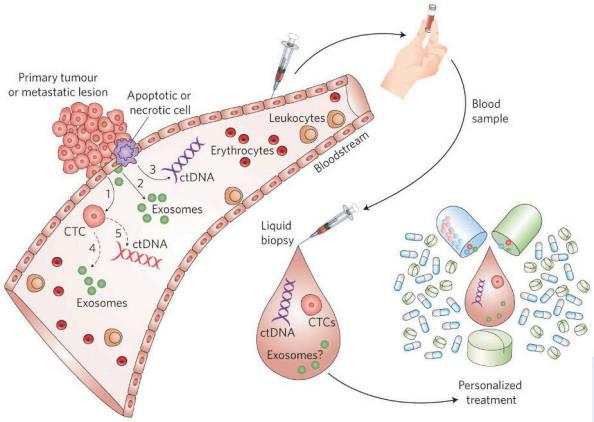
American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Germline and Somatic Genomic Testing for Metastatic Prostate Cancer: ASCO Guideline. J Clin Oncol. 2025 Feb 20;43(6):748-758.

37

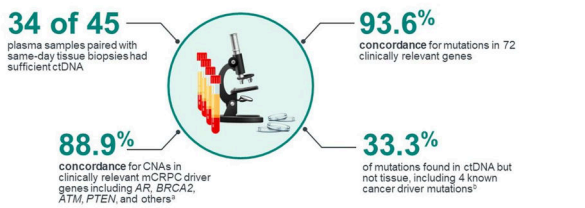
Clinical Utility of Liquid Biopsies



Matched tissue and liquid biopsies show high concordance in patients with mCRPC and evidence of disease progression

Wyatt, AW
J Natl Cancer Inst. 2017 Dec; 109(12)

Concordance between solid tissue (S) and liquid (L) biopsy in select clinically relevant genes in mCRPC



American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Moreno JG, Gomella LG. Urology. 2019 Oct;132:1-9. Alix-Panabières C et al. *Nat Biomed Eng*. 2017;1(4):1-3; Moreno JG et al. *Urology*. 2001;58(3):386-392.; Wyatt AW, JNCI 2017 Dec; 109 (12)

38

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Genetic Testing in Advanced Prostate Cancer

Background: Genomic and Genetic Testing

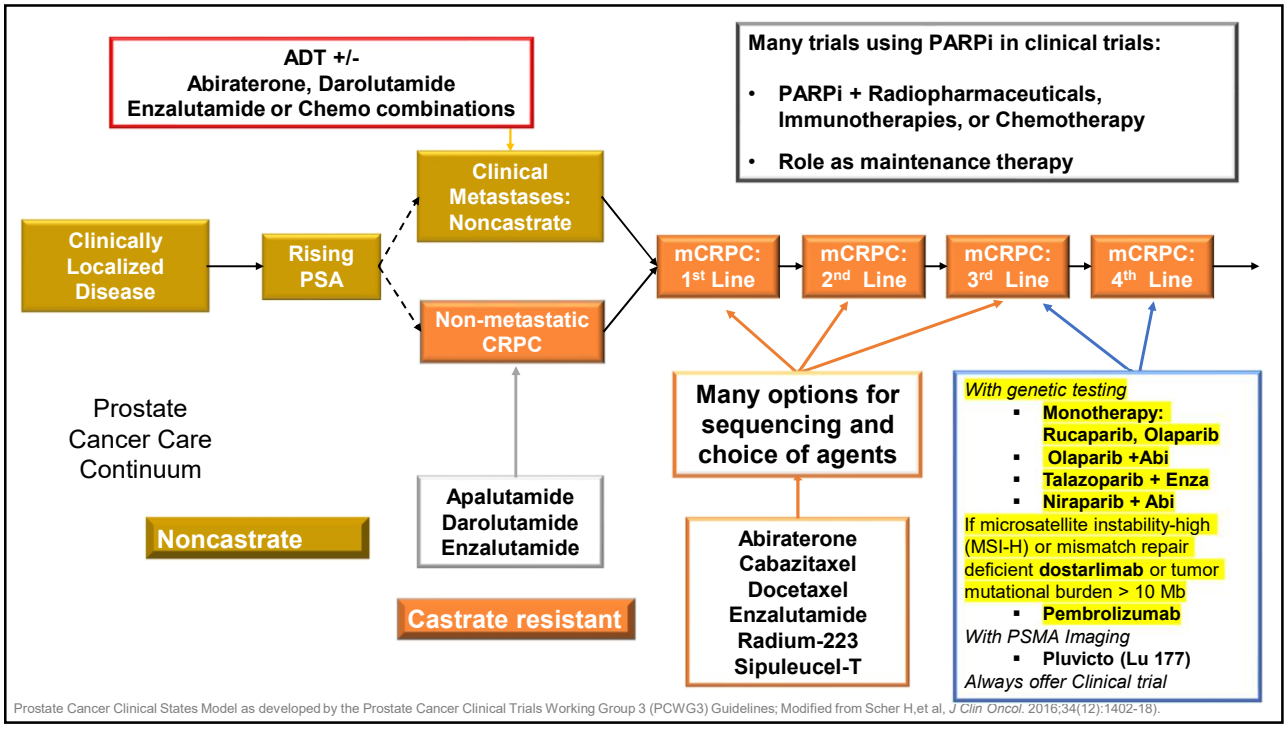
Prostate Cancer Genetic Testing: Basic Concepts

Prostate Cancer and Inherited Risk

Practical Considerations in Genetic Testing

Precision Medicine for Advanced Prostate Cancer

39



40

Genomic Profiling To Guide Treatment: *DNA Repair Genes*

- DNA repair genes (e.g., BRCA2, BRCA1, ATM) make proteins that repair double stranded DNA breaks (homologous recombination repair, HRR)
  - When mutated errors in DNA repair that cause neoplastic growth
  - Mutated in up to ~20%-25% of all advanced prostate cancers
- Poly (ADP-ribose) polymerase (PARP) enzymes repair single-strand DNA breaks
  - Drugs that inhibit PARP1 cause multiple double-strand breaks
  - These double-strand breaks cannot be easily repaired, cell death results

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Antonarakis ES, Gomella LG, Petrylak DP. Eur Urol Oncol. 2020 Aug 17:S2588-9311

41

PCa Genomic Profiling To Guide Treatment Decisions: DNA Repair Genes

- Precision medicine applications in mCRPC
- If the germline or somatic testing is positive for *BRCA2/BRCA1*, we now have FDA-approved therapies specifically targeting these mutations/alterations
  - Poly (ADP-ribose) polymerase (PARP) inhibitors
    - PARP inhibitors work at the DNA level during replication by inhibiting PARP1 and PARP2 enzymes leading to unrepaired DNA breaks and cancer cell death (synthetic lethality).
    - With *BRCA1/BRCA2*-mutated prostate cancer have a 50%- 70% chance of response to PARP inhibitors; other genes like *ATM* and *CHEK2* may not respond as well.
    - **Multiple new approvals for PARPi w/wo ARPB**

American Urological Association Education & Research, Inc.

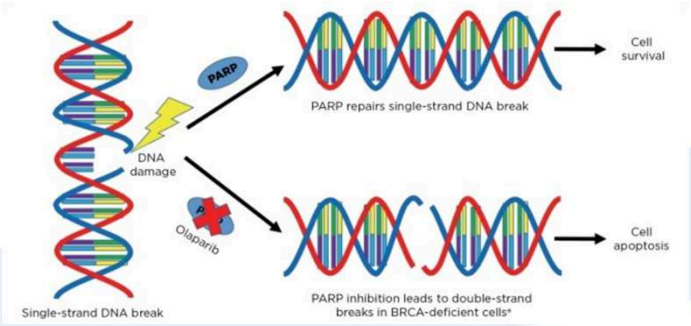
SUO Society of Urologic Oncology, Inc.

Adashek J, et al. Cells. 2019; 8(8). Criscuolo D, et al. International Journal of Molecular Sciences. 2019;20,3100

42

Genomic Profiling To Guide Treatment: *DNA Repair Genes and Synthetic lethality*

- **"Synthetic lethality":** a combination of deficiencies in two or more genes leads to cell death, whereas a deficiency in only one of these genes does not; this is PARP inhibitor MOA
- Patients with *BRCA1/BRCA2*-mutated have a > 50% response to PARP inhibitors



American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Antonarakis ES, Gomella LG, Petrylak DP. Eur Urol Oncol. 2020 Aug 17:S2588-9311

43

Earliest PARP inhibitors for HRR-mutated mCRPC

OLAPARIB: In **May 2020,** based on data from the **PROfound study,** the FDA granted **full approval olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

FoundationOne Liquid CDx and BRACAnalysis CDx Companion diagnostic

[a]*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.*
[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.
1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

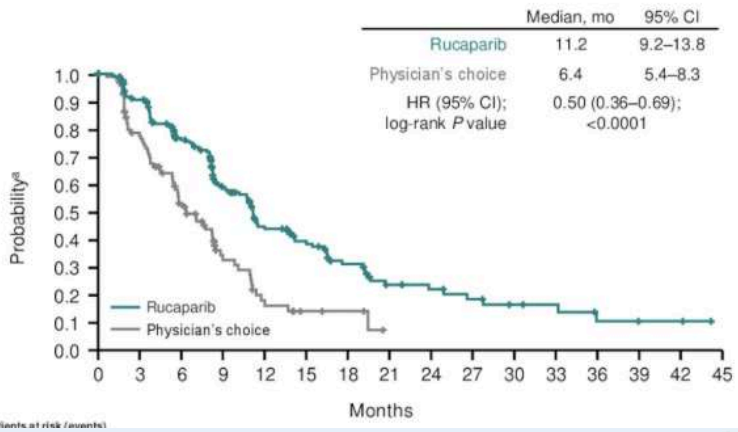
RUCAPARIB: In **May 2020,** based on data from the **TRITON2 study,** the FDA granted **accelerated approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy.[1]**

FoundationOne Liquid CDx companion diagnostic for BRCA1/2

1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.

44

Overall Survival TRITON 3 TRIAL: Parp Inhibitor Example in mBRCA subgroup



American Urological Association Education & Research, Inc.

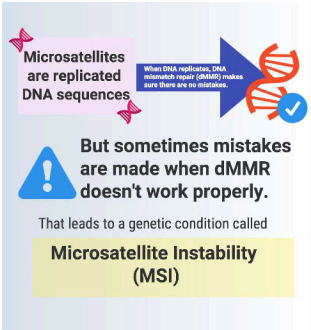
SUO Society of Urologic Oncology, Inc.

Bryce, et al 2025 ASCO GU Annual Meeting, San Francisco, CA,

45

Microsatellite instability (MSI)

- MSI: marker associated when the proteins that are responsible for repairing errors in genes do not fix DNA replication errors
- Also known as DNA mismatch repair (dMMR)
- **Pembrolizumab** approved for previously-treated patients with (MSI-H) or mismatch repair deficient (dMMR) cancer.



- **MSS**: Same number of repeats in normal and tumor
- **MSI-Low**: <30% of MS markers show instability
- **MSI-High:** >30% of MS markers show instability

American Urological Association Education & Research, Inc.

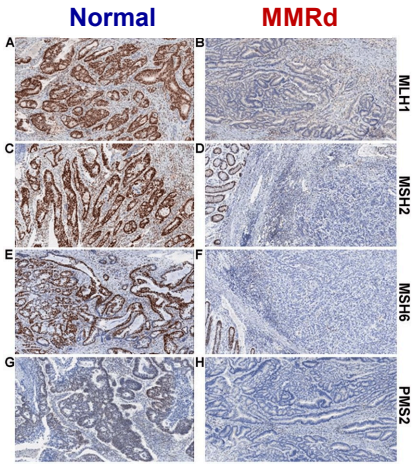
SUO Society of Urologic Oncology, Inc.

https://www.curetoday.com/view/three-fast-facts-on-microsatellite-instability; Accessed March 15, 2026

46

Direct evaluation of MMR Genes
(MLH1, MSH2, MSH6, PMS2)

- Mismatch repair genes (MMR genes) can also be assessed by Immunohistochemistry (IHC)
- Lynch Syndrome genes increase risk of endometrial, colon and prostate cancer



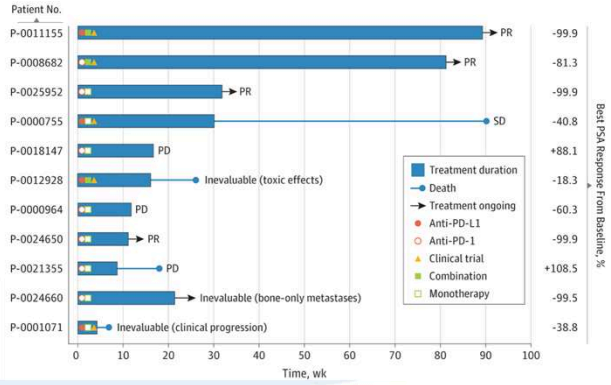
Richman S. Deficient mismatch repair: Read all about it (Open Access https://www.spandidos-publications.com/10.3892/ijo.2015.3119)

47

47

MSI-H and dMMR uncommon, but actionable with anti-PD1 and PD-L1 agents

- Prevalence of MSI-H or dMMR in prostate cancer is 3.1% (32/1033)
- Of these, 21.9% (7/32) with germline Lynch Syndrome mutation.
- 5/11 pts who received anti-PD-1/PD-L1 agent had durable clinical benefit.



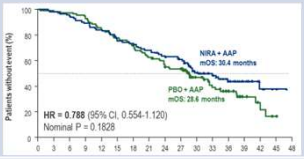
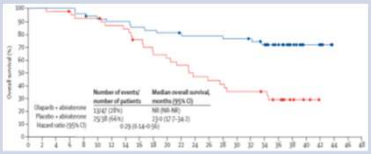
American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

W. Abida, et al. JAMA Oncol. 2019;5(4):471-478.

48

PARP inhibitors plus ARPB recent studies

		MAGNITUDE Abi + Niraparib N = 225	PROPEL Abi+ Olaparib N = 85	TALAPRO-2 N = 158
				N/A
OS	**Median**	**30.4 vs 28.6 months**	**NR vs 23.0 months**	**N/A**

Results with mBRCA1/2

Chi KN et al. *Annals Oncol.* 2023;34(9):772-782. Chi KN et al. 2023 ESMO Annual Meeting. Abstract LBA 85.
Saad F et al. *Lancet Oncol.* 2023;24(10):1094-1108. Fizazi K et al. *Nature Med.* 2024;30:257–264.

49

Drug	Relevant Genetic Alteration	Clinical Setting
FDA-approved therapies		
Olaparib	*BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*	mCRPC after abiraterone/ prednisone or enzalutamide
Rucaparib	*BRCA1, BRCA2*	mCRPC after abiraterone/ prednisone or enzalutamide and one taxane
Pembrolizumab	MSI-high	No satisfactory alternative treatments
Pembrolizumab	TMB ≥10	No satisfactory alternative treatments
MAGNITUDE, PROPEL, and TALAPRO-2 clinical trial populations		
Niraparib + abiraterone/ prednisone (MAGNITUDE)	*ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2,* or *PALB2*	First-line mCRPC after ADT ± docetaxel for mCNPC
Olaparib + abiraterone/ prednisone (PROPEL)	*ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*	First-line mCRPC after ADT ± docetaxel for mCNPC
Talazopraib + enzalutamide (TALAPRO-2)	*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MRE11A,* and *CDK12*	First-line mCRPC after ADT ± docetaxel or abiraterone for mCNPC

Abbreviations: FDA, US Food and Drug Administration; mCNPC, metastatic castration-naïve prostate cancer; mCRPC, metastatic castratio prostate cancer; MSI, microsatellite instability; TMB, tumor mutational burden.

ascopubs.org/journal/jco on April 25, 2023:DOI https://doi.org/10.1200/JCO.23.00350

50

Drug	Relevant Genetic Alteration	Clinical Setting
FDA-approved therapies		
Olaparib	*BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*	mCRPC after abiraterone/ prednisone or enzalutamide
Rucaparib	*BRCA1, BRCA2*	mCRPC after abiraterone/ prednisone or enzalutamide and one taxane
Pembrolizumab	MSI-high	No satisfactory alternative treatments
Pembrolizumab	TMB ≥10	No satisfactory alternative treatments
MAGNITUDE, PROPEL, and TALAPRO-2 clinical trial populations		
Niraparib + abiraterone/ prednisone (MAGNITUDE)	*ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2,* or *PALB2*	First-line mCRPC after ADT ± docetaxel for mCNPC
Olaparib + abiraterone/ prednisone (PROPEL)	*ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*	First-line mCRPC after ADT ± docetaxel for mCNPC
Talazopraib + enzalutamide (TALAPRO-2)	*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MRE11A,* and *CDK12*	First-line mCRPC after ADT ± docetaxel or abiraterone for mCNPC

Abbreviations: FDA, US Food and Drug Administration; mCNPC, metastatic castration-naïve prostate cancer; mCRPC, metastatic castratio prostate cancer; MSI, microsatellite instability; TMB, tumor mutational burden.

ascopubs.org/journal/jco on April 25, 2023:DOI https://doi.org/10.1200/JCO.23.00350

51

Decision Making in Prostate Cancer: Which Genetic Testing Guidelines to Follow?

52

Advanced Prostate Cancer: AUA/SUO Guideline 2020; Amended 2023

Genetic testing related statements

- **mHSPC:** offer germline testing, and consider somatic testing and genetic counseling.
- **mCRPC:** offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, microsatellite instability (MSI) status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk, as well as direct any targeted therapies.
- **Offer a PARP inhibitor** to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enza or abir, and/or a taxane-based chemo. Platinum based chemo as an alternative to PARP inhibitor.
- **Mismatch repair deficient or microsatellite instability-high (MSI-H) mCRPC**: offer pemrolizumab.

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Lowrance W, Dreicer R, Jarrard DF, et al. Updates to advanced prostate cancer: AUA/SUO guideline (2023). J Urol. 2023;209(6):1082-1090.

53

Conclusions

- All mCRPC/high-risk PCa should have germline and somatic testing
  - High prevalence of germ line/somatic mutations (over 30%) in mCRPC
  - Direct therapy of metastatic disease (i.e. PARP inhibitors)
- Most critical PCa genes today: **BRCA 1/2, HOXB13, ATM, CHEK2**
- New role for somatic tumor testing including liquid biopsy of cfDNA
- Consider referral for genetic testing AND counselling if high risk/family concerns; Need more genetic counsellors in urology care
- <40% of mCRPC get germline or somatic testing; How to increase?
  - TARGET study: use of patient-driven digital webtools for genetic education
  - HELIX: On Line Tool

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

JAMA Oncology July 2024 Volume 10, Number 7; Clin Genitourin Cancer. 2022 Apr;20(2):e104-e113

54

Thank you for your attention

55

Supplemental slides

Genetic Testing in
Advanced Prostate Cancer

56

DNA Damage Terminology Review

- **DDR Genes:** DNA Damage Repair Genes (BRCA1/2, many others etc) maintain genomic stability
- **HRR Genes:** Homologous Recombination Response/Repair genes repair double-stranded DNA damage.
  - ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54
  - Most critical in mCRPC
- **HRD Tumor:** Homologous Recombination Deficient tumors, contain mutated BRCA 1/2, etc.
- **MMR genes:** Mismatch repair genes fix limited DNA damage that occurs during cell division.
  - MLH1, MSH2, MSH6, PMS2, EPCAM (Lynch syndrome genes)
- **dMMR or MMR-D Tumors:** Mismatch repair deficient /mutated tumors
- **MSI-high:** Microsatellite instability occurs in tumors with dMMR
- **TMB:** Tumor mutational burden number of mutations measured per megabase (mut/Mb)

57

Homologous Recombination Response (HRR)

- Maintenance of genomic stability relies on accurate duplication of the genome and on continuous monitoring of chromosomal integrity
  - HRR deficiency causes genomic instability, a hallmark of cancer
- **HRR is the main DNA rescue pathway and repairs double-strand DNA breaks**
- The error-free repair of a ds-break in DNA in which the broken DNA molecule is repaired using homologous sequences
  - A strand in the broken DNA searches for a homologous region in an intact chromosome to serve as the template for DNA synthesis
  - The restoration of two intact DNA molecules results in the exchange, reciprocal or nonreciprocal, of genetic material between the intact DNA molecule and the broken DNA molecule
- The HRR pathway includes many cellular factors, such as *BRCA1/2*
- **A mutated *BRCA* or another gene coding for HRR factor results in HR deficiency (HRD), compromised DNA repair, and tumorigenesis**

Chartron E, et al. *Crit Rev Oncol Hematol*. 2019;133:58-73. Konstantinopolous PA, et al. Cancer Discov. 2015;5(11):1137-1154.

58

Common homologous recombination repair (HRR) genes

- ATM: ataxia telangiectasia mutated
- BRCA 1 and BRCA 2: breast cancer susceptibility gene
- CDK12: cyclin-dependent kinase 12
- CHEK: checkpoint kinase
- FANCA: Fanconi anemia complementation group A
- PALB2: partner and localizer of BRCA2
- RAD51: DNA Repair Protein RAD51

59

DNA Damage Repair (DDR) Prevalence Estimates in Advanced Prostate CA

	GERMLINE	SOMATIC	COMBINED	ENHANCED WITH
BRCA2	5%	5%	**10%**	• Family History Breast/Ovarian • Ductal and Intraductal Histology
BRCA1	1%	1%	**2%**	• Family History Breast/Ovarian • Ductal and Intraductal Histology
ATM	2%	2%-3%	**4%-5%**	• Family History Breast/Ovarian
MSH 2/6 (Mismatched Repair)	1.5%	4%-5%	**5%-6%**	• Family History Colon/Endometrial/Lynch Syndrome • Ductal Histology/Gleason 5

Courtesy Dr Colin Pritchard at 2019 APCCC conference

60

HRR In Advanced Prostate Cancer

- DNA damage is ongoing and requires a variety of repair pathways to maintain genomic integrity.
- In normal cells, DNA double-strand breaks (DSBs) are repaired via the homologous recombination repair (HRR) pathway.
- With HRR gene mutations (HRRm), cells are unable to repair DSBs; other pathways (eg, BER,NHEJ), are less efficient, leading to the persistence of DSBs, an accumulation of mutations, and increasing carcinogenesis.

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Pilié P, et al. Nat Rev Clin Oncol. 2019;16(2):81-104; Frey MK, Pothuri B. Gynecol Oncol Res Pract. 2017;4:4; O'Connor MJ. Mol Cell. 2015;60(4):547-560. 3.

61

Genetics vs Genome vs Genomics

- **Genetics:**
  - **TRADITIONAL**: study of individual genes and their inheritance
    - Eg, sickle cell anemia and cystic fibrosis, a single gene
  - **MODERN:** study of multiple genes and inheritance pattern
- **Genome:** Entire set of genes in an organism
- **Genomics:**
  - **COMPLEX:** refers to the analysis of multiple genes interacting with each other and the environment (i.e. cancer, diabetes)

MODERN GENETIC TESTING RELIES ON GENOMICS

62

Examples of Commercial Assays for Somatic HRR Gene Panels

Tissue Assays

TEST NAME	EXAMPLES OF HRR GENES INCLUDED
Molecular Intelligence® Comprehensive Tumor Profiling	*ATM, ATR, BARD1, BRCA1/2, BRIP1, CHEK1/2, FANCA, FANCL, PALB2, RAD51B*
FoundationOne® CDx	*ATM, ATR, BRCA1/2, CHEK1/2, FANCA, PALB2, RAD51D*
NeoTYPE® HRD+ Profile	*ATM, ATR, BARD1, BRCA1/2, BRIP1, CDK12, CHEK1/2, FANCA, PALB2, RAD51B/C/D*
Tempus xT	*ATM, ATR, BARD1, BRCA1/2, CKD12, CHEK1/2, FANCA, FANCL, PALB2, RAD51B/C/D, RAD54L*

Liquid Biopsy Assays

TEST NAME	EXAMPLES OF HRR GENES INCLUDED
FoundationOne® Liquid	*ATM, ATR, BARD1, BRCA1/2, BRIP1, CDK12, CHEK1/2, FANCA, FANCL, PALB2, RAD54L*
Guardant360®	*ATM,† BRCA1/2, CDK12†*
Tempus xF	*ATM, ATR, BRCA1/2, PALB2, RAD51C*

https://www.azprecisionmed.com/content/dam/open-digital/precisionmed-hcp/en/pdf/US-40459-Dx-Pathology-Tissue-Testing-ctDNA-Leave-Behind.pdf Accessed March 16, 2025

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

63

Ideal sequence to identify PCa HRR alterations

Fresh metastatic tumor biopsy > Circulating tumor DNA > Archival biopsy/ primary tumor tissue > Blood or saliva (germline testing only)

Order of preference

Germline-only testing

May underestimate important somatic HRR mutations

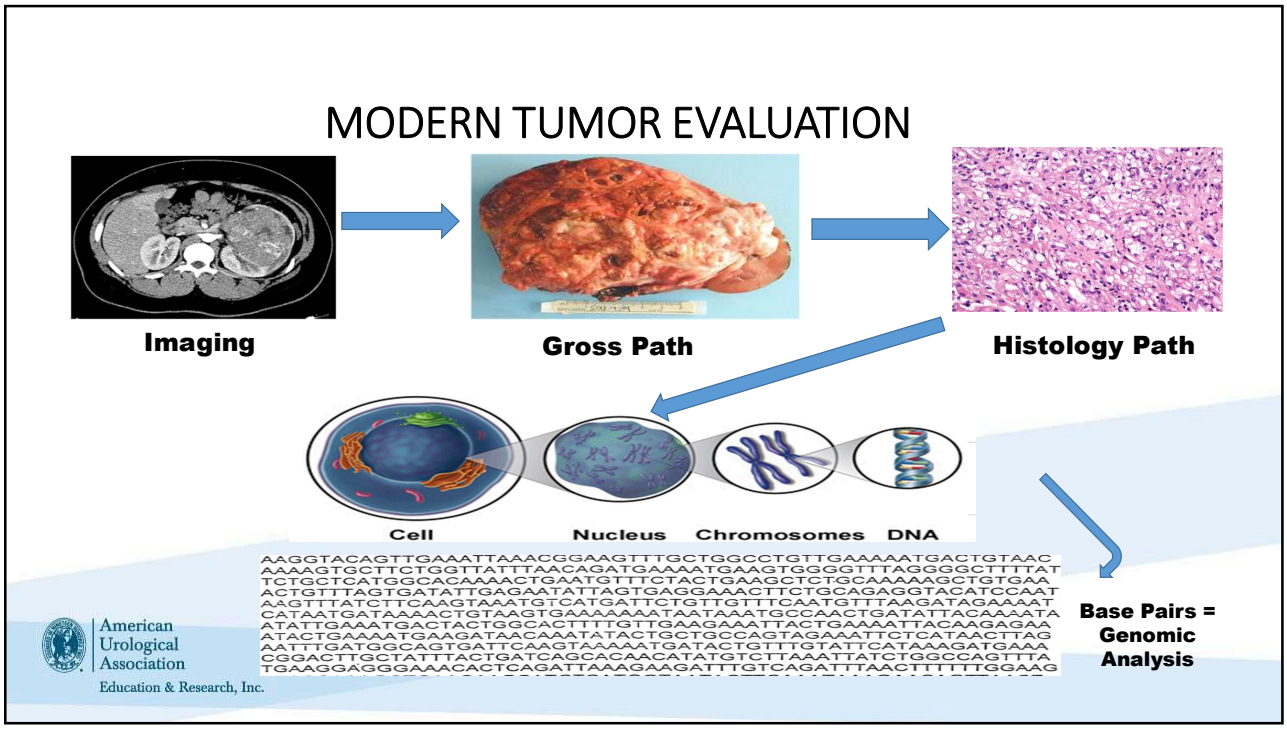
Unable to discern monoallelic from biallelic HRR mutations

Recommended to have both germline and somatic testing in advanced Pca

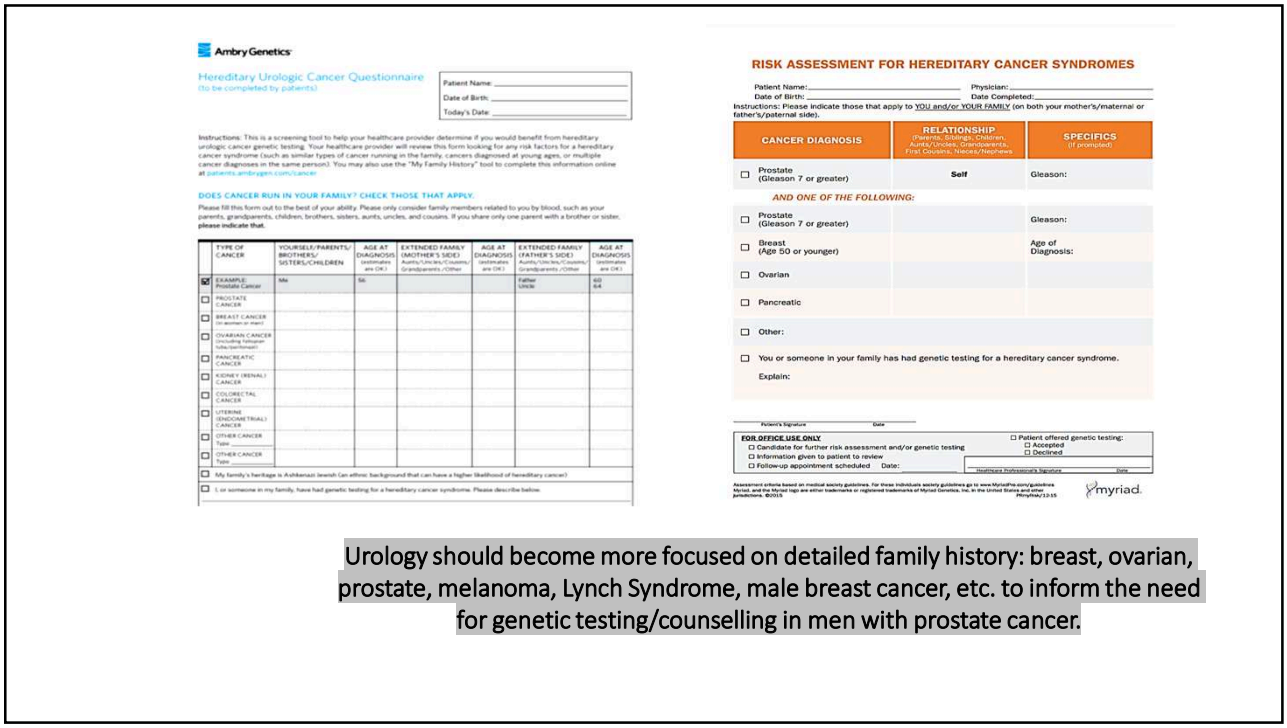
Biallelic mutations more aggressive than mono allelic

Antonarakis ES, Gomella LG, Petrylak D et al. *Eur Urol Oncol* 2020;3:594-611.

64



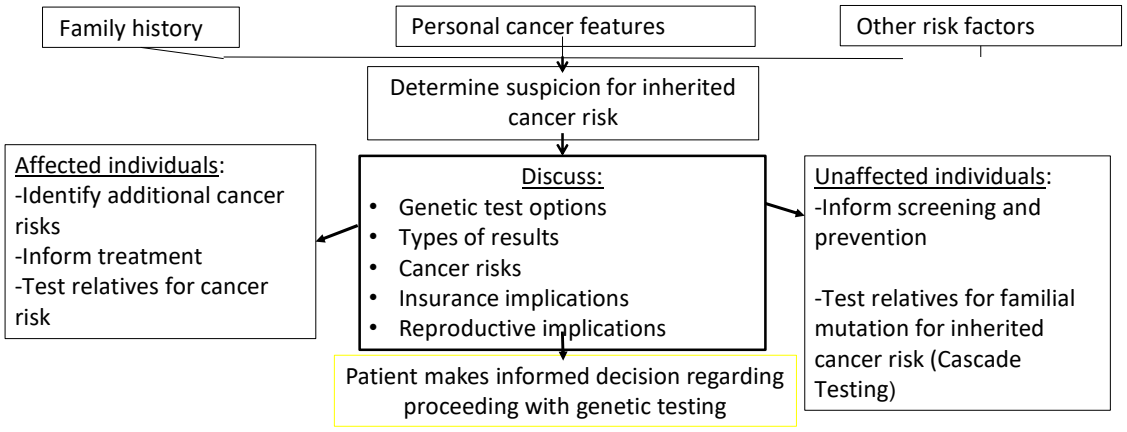
65



Urology should become more focused on detailed family history: breast, ovarian, prostate, melanoma, Lynch Syndrome, male breast cancer, etc. to inform the need for genetic testing/counselling in men with prostate cancer.

66

Genetic Counseling for Inherited Cancer Risk



Advocated by NCCN, ASCO, and NSGC** ;Giri VN, Prostate. 2019 Mar;79(4):333-339.

67

Genetic Germ Line Testing/Counseling for PCa

- ≥ 2 cases of PCa age ≤55 yrs in close relatives regardless of risk category
- ≥ 3 FDRs with PCa regardless of risk
- Aggressive (Gl >7) PCa
- ≥2 cases of breast, ovarian, and/or pancreatic cancer in close relative
- Metastatic PCa or mCRPC
- Intraductal/Cribiform PCa (NCCN 2020)
- Consider with Active Surveillance
- Ashkenazi Jewish
- Somatic tumor sequencing w/mutations in hereditary cancer genes
- Family history of cancer at early age of diagnosis:
  - Breast Ca <45 years
  - Uterine or Colon Cancer <50
  - Ovarian Cancer <60 years

Key Organizations
American College of Medical Genetics and Genomics (ACMG)
National Society of Genetic Counselors (NSGC)
Philadelphia Prostate Cancer Consensus 2017/2019
NCCN 2024

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

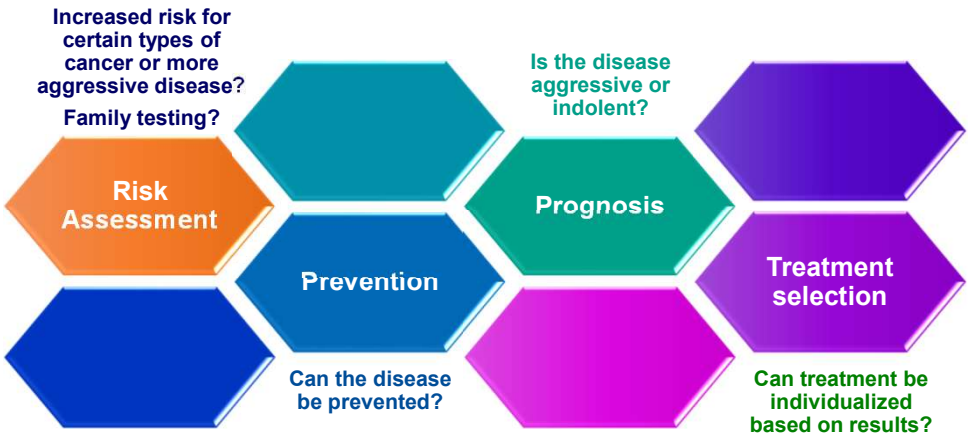
Giri JCO 2018, Giri JCO 2019 NCCN.org; American College of Medical Genetics and Genomics (ACMG)/National Society of Genetic Counselors (NSGC) practice guidelines.:
https://www.acmg.net/docs/ACMG_Practice_Guideline_Referral_Indications_for_cancer_predisposition.pdf

68

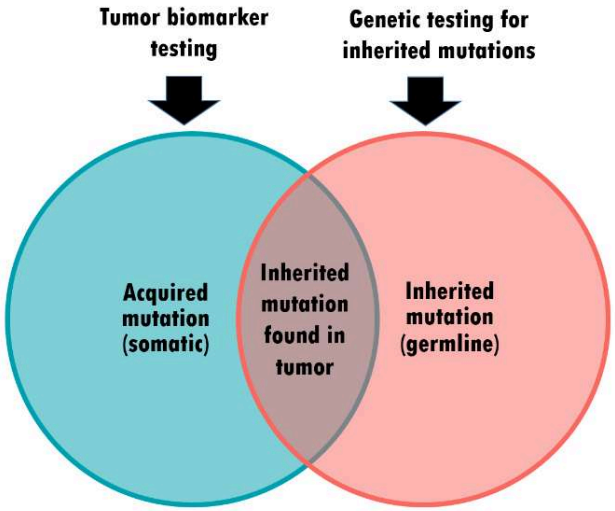
Criteria to recommend germline genetic testing	Supporting guideline(s)[6-12]
Metastatic (castration resistant or castration sensitive) prostate cancer at any age	NCCN Prostate Cancer v1 2023 AUA/ASTRO/SUO: advanced prostate cancer 2020 Philadelphia Consensus 2019
Regional (node positive), high-risk or very high–risk localized Prostate cancer at any age	NCCN Prostate Cancer v1 2023 AUA/ASTRO: clinically localized prostate cancer 2022
Ashkenazi Jewish ancestry	NCCN Prostate Cancer v1 2023 AUA/ASTRO: clinically localized prostate cancer 2022 Philadelphia Consensus 2019
Personal history of breast cancer	NCCN Prostate Cancer v1 2023 Philadelphia Consensus 2019
≥ 1 FDR, SDR, or TDR with: • Prostate cancer from one of the risk categories above at any age • Breast cancer at age ≤ 50 • Colorectal or endometrial cancer at age ≤ 50 • Male breast cancer at any age • Ovarian cancer at any age • Exocrine pancreatic cancer at any age	NCCN Prostate Cancer v1 2023
≥ 1 FDR with prostate cancer (except grade group 1) at age ≤ 60	NCCN Prostate Cancer v1 2023 AUA/ASTRO: clinically localized prostate cancer 2022 Philadelphia Consensus 2019
≥ 2 FDR, SDR, or TDR with: • Breast cancer at any age • Prostate cancer (except grade group 1) at any age	NCCN Prostate Cancer v1 2023
≥ 3 FDR or SDR with Lynch syndrome–related cancers, especially if diagnosed < 50[a]	NCCN Prostate Cancer v1 2023
Tumor sequencing showing variants in cancer risk genes, especially with a family history	Philadelphia Consensus 2019
Known family history of cancer risk mutation (such as those listed below)	NCCN Prostate Cancer v1 2023 AUA/ASTRO: clinically localized prostate cancer 2022
Germline multigene testing to include at least *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*	NCCN Prostate Cancer v1 2023
Criteria to consider germline genetic testing	
Intermediate-risk prostate cancer with intraductal/cribriform histology	NCCN Prostate Cancer v1 2023 AUA/ASTRO: clinically localized prostate cancer 2022 Philadelphia Consensus 2019
Prostate cancer and a prior personal history of any of the following cancers: exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal	NCCN Prostate Cancer v1 2023

69

Why Germline and Somatic Testing Are Important

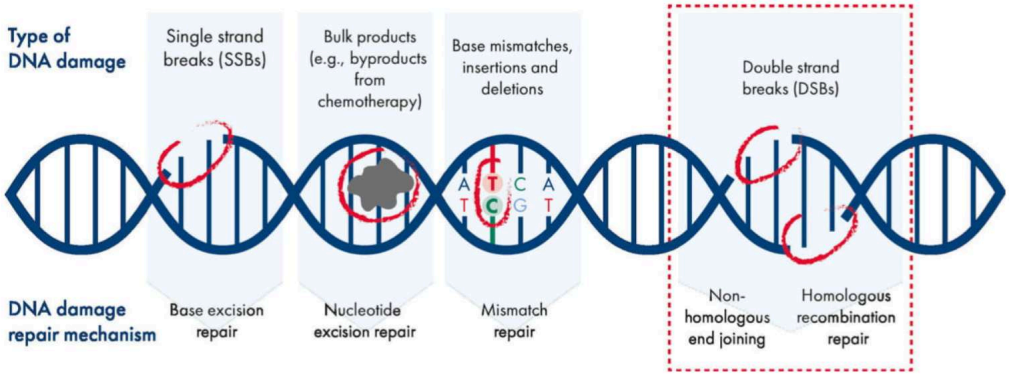


70



https://www.facingourrisk.org/info/risk-management-and-treatment/biomarker-testing-dna-damage-repair
Accessed March 3 2024

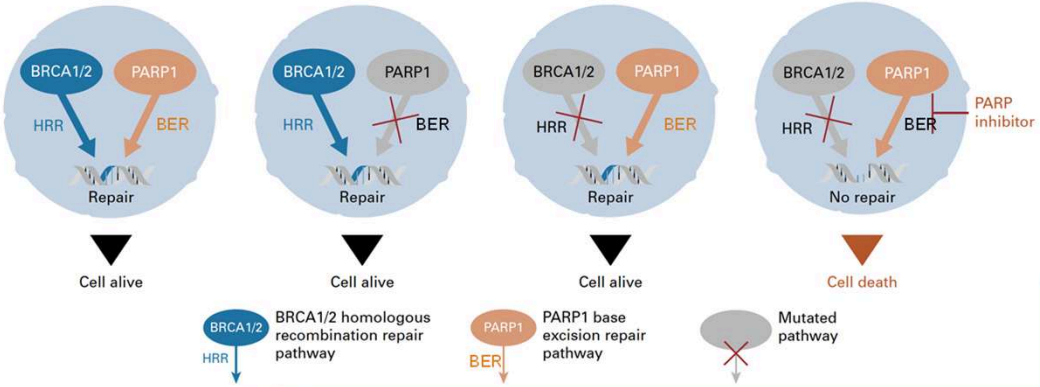
71



https://www.qiagen.com/us/applications/oncology/solid-tumor/dna-damage-response Accessed March 14, 2024

72

PARP Inhibition causes "Synthetic Lethality"



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

After Gourley C et al. *J Clin Oncol*. 2019

73

IMPACT: Prostate Screening in *BRCA1/2* Families

1. International, multicenter men (40-69y) in families with known mutations (BRCA1/2, Lynch Syndrome).
2. Annual PSA screening.
3. Biopsy if PSA >3, re-biopsy if ASAP or PIN, or PSA doubling >50%.

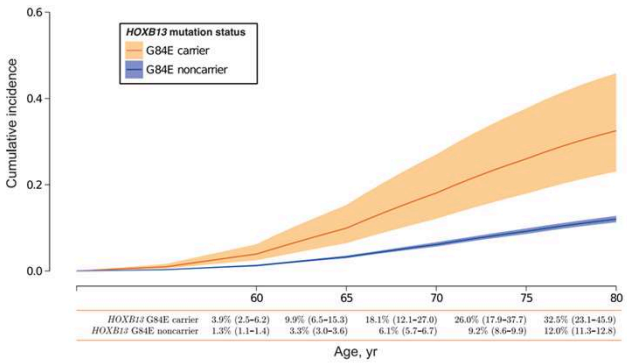
	BRCA-1 carrier N=791	BRCA-1 control N=531	BRCA-2 carrier N=731	BRCA-2 control N=428
PCa incidence	**2.3%**	1.9%	**3.3%**	1.6%
PPV of biopsy	**41%**	23%	**48%**	33%
Intermediate/ high risk PCa	**61%**	60%	**68%**	43%

Bancroft, et al (2014) Eur Urol

74

HOXB13: First Specific Inherited PCa Gene

- Men with this G84E mutation
  - **33% to 60% risk of PCa to age 80** vs. 12% in the general population.
- Families with G84E:have men with early-onset PCa or multiple cases of PCa.
- Mutation in ~5% of PCa, mostly European descent.
- Normal gene: Tumor suppressor, prostate and skin development.



Ewing CM, Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366:141–9
MacInnis RJ, Population-based estimate of prostate cancer risk for carriers of the HOXB13 missense mutation G84E. PLoS One. 2013;8:e54727
Karlsson R, A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. Eur Urol. 2014;65:169-176.

Germline Testing Guidelines Summary

- Family history of cancer at early age of diagnosis:
  - Breast Ca <45 years; Uterine or Colon Cancer <50
  - Ovarian or Prostate Cancer <60 years, others
- Multiple prior cancers
- Male Breast Cancer- usually *BRCA2*
- Ashkenazi Jew hertiage
- Multiple generations of prostate cancer <60 years
- Personal history of metastatic prostate cancer
- Personal high grade PCA Gleason ≥ 7 and 2 or more syndrome related cancers: pancreatic, melanoma, breast, colon, uterine

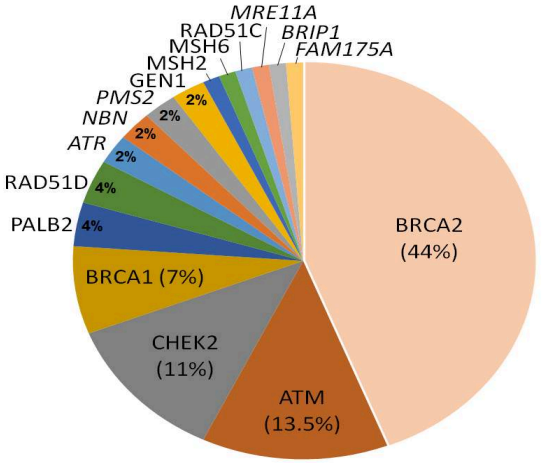
American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

NCCN Practice Guidelines: Prostate Cancer. Version 1.2024. Accessed 02/28/2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Germline Mutations in Metastatic PCa

- BRCA-2 best studied for potential screening and treatment
- PCa males with BRCA-2 have more aggressive disease
- More work is needed on the other PCa genes identified
- **Germline mutations in 11.8% of metastatic vs. 4.6% localized disease**
- Later data may be up to 25% of mCRPC



Pritchard, N Engl J Med. 2016 Aug 4;375(5):443-53; Cindamore A, Future Oncology VOL. 16, NO. 5 Online:9 Jan 2020

77

Studies of PARP Inhibitor-Based Combinations

Why? Synergy between PARP and AR signalling in DNA repair

NCT03732820: Phase 3 Study of Olaparib + Abiraterone vs Abiraterone in mCRPC
(PROpel)

NCT03748641: Phase 3 Study of Niraparib + Abiraterone vs Abiraterone in mCRPC
(MAGNITUDE)

NCT03395197: Phase 3 Study of Talazoparib + Enzalutamide vs Enzalutamide in mCRPC
(TALAPRO-2)

NCT04497844: Phase 3 Study of Abiraterone ± Niraparib in HRR mHSPC
(AMPLITUDE)

NCT04455750: Phase 3 Study of Enzalutamide ± Rucaparib in mCRPC
(CASPAR)

78

Latest PARPi + ARPI Phase 3 Trials

		MAGNITUDE	PROPEL	TALAPRO-2
Intervention	ARPI	Abiraterone	Abiraterone	Enzalutamide
	PARPi	+/- Niraparib 200 mg PO OD	+/- Olaparib 300 mg BID	+/- Talazoparib
Design	Primary Endpoint	rPFS by BICR	rPFS by investigator	rPFS by BICR
	Analysis	Separate cohorts	Retrospective	Stratified and separate cohorts
	Biomarker Testing	Prospective	Retrospective	Prospective
Eligibility	Qualifying genes	ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, or PALB2	ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12
Population	N	656	796	All comers: 805 HRR cohort: 399
	BRCA1/2	225	85	All comers: 59 HRR cohort: 158
	HRR/non-BRCA	198	141	All comers: 110 HRR cohort: 241
	Non-HRR/unknown	233	570	All comers: 642

Chi KN et al. *J Clin Oncol.* 2023;41(18):3339-3351. Saad F et al. *Lancet Oncol.* 2023;24(10):1094-1108.
Agarwal N et al. *Lancet.* 2023;402(10398):291-30. Fizazi K et al. *Nature Med.* 2024;30:257–264.

79

DNA Tumor Tissue testing

If stored under optimal conditions, tumor DNA may be viable for several Years but if available, more recent samples are preferred

ADVANTAGES

- Can be done using archived tissue or new tissue samples from the primary site or from sites of metastasis
- Usually provides ample material for genomic testing

CHALLENGES

- Tissue sampling may cause patient morbidity and difficulties in obtaining sufficient tissue from metastasis such as bone
- Tumor heterogeneity may cause false negatives

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Friedlander TW et al. Am Soc Clin Oncol Educ Book. 2017;37:358-369; Wyatt AW et al. J Natl Cancer Inst. 2017;109(12):djx118

80

Liquid biopsy allows for ctDNA plasma blood sample

ADVANTAGES

- Is minimally invasive and not hindered by limitations in tumor access
- Permits assessment of diverse inter- and intratumor heterogeneity
- Can detect alterations from the primary site and distant sites of metastasis

CHALLENGES

- The mutation profile provided by ctDNA analysis depends on tumor shedding
- Tumor shedding may be limited following recent androgen deprivation therapy
- Cannot distinguish between somatic and germline mutations

American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Stewart CM et al. J Pathol. 2018;244(5):616-627;
Cheng HH et al. J Natl Compr Canc Netw. 2019;17(5):515-521.

81

Prostate NCCN Guidelines v1.2024

Germline Testing	Somatic Tumor Testing

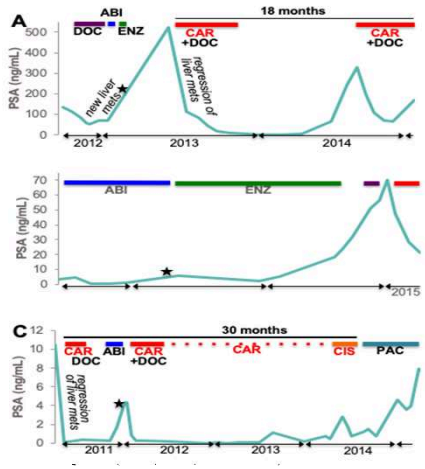
Germline testing <u>is recommended</u> in patients with a personal history of prostate cancer who:
• Have metastatic, regional (N+), very-high-risk localized, or high-risk localized prostate cancer
• Have family history and/or ancestry with:
  • ≥1 first, second, or third degree relative with
  • Breast cancer at age ≤50 years
  • Colorectal or endometrial cancer at age ≤50 years
  • Male breast cancer at any age
  • Ovarian cancer at any age
  • Pancreatic cancer at any age
  • Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age
  • ≥1 first degree relative with prostate cancer at age ≤60 years
  • ≥2 first, second, or third degree relatives with:
  • Breast cancer at any age
  • Prostate cancer at any age
  • ≥3 first or second degree relatives with:
  • Lynch syndrome-related cancers, especially if diagnosed at age <50 years
  • A known family history of a familial cancer risk mutation
  • Ashkenazi Jewish ancestry
  • Personal history of male breast cancer
 	
Germline testing <u>may be considered</u> in patients with a personal history of PCa who:
• Have intermediate-risk prostate cancer with intraductal/cribriform histology
• Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer
 	
Germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended; additional genes may be appropriate based on clinical context
	Tumor testing for alterations in HRR DNA repair genes such as ***BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,*** and ***CDK12*** is recommended in patients with <u>metastatic</u> prostate cancer, and may be considered for patients with regional (N+) prostate cancer
	
	Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC, and may be considered for patients with mCSPC
	
	TMB testing may be considered in patients with mCRPC

NCCN Practice Guidelines: Prostate Cancer. Version 1.2024. Accessed 02/28/2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

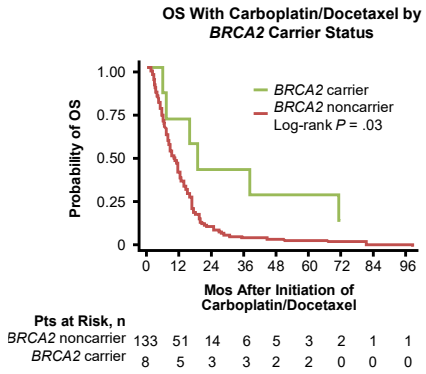
82

BRCA2 mutations and Response to Carboplatin-based therapy

Therapeutic responses in HRR mutations not only limited to PARP inhibitors in advanced PCa



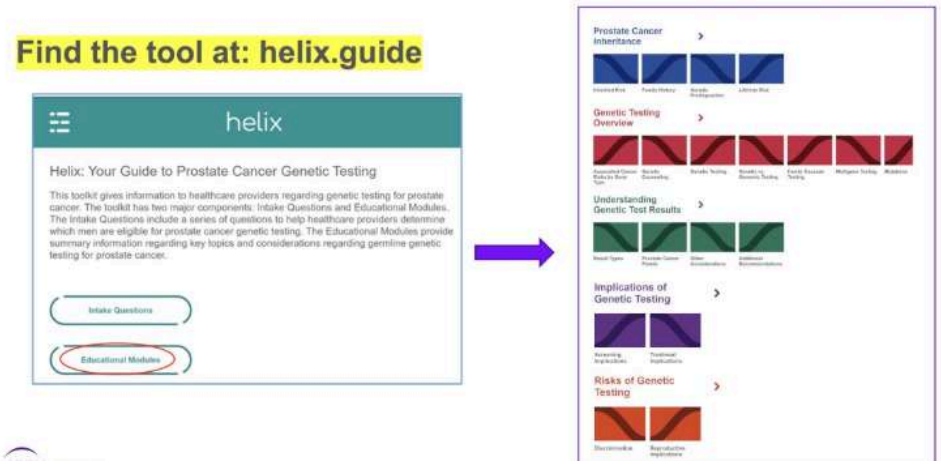
8/141 (5.7%) men with mCRPC had pathogenic germline *BRCA2* variants



Cheng,HH, et al Eur Urol, 2016; Pomerantz MM, et al. Cancer. 2017.

83

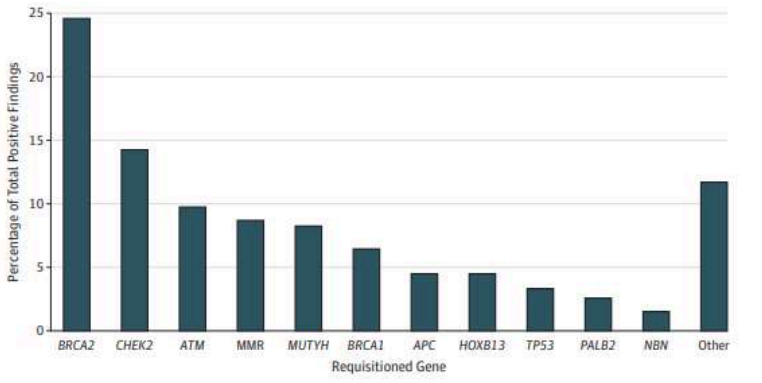
Helix: Your Guide to Prostate Cancer Genetic Testing



Giri VN, Walker A, Gross L, Helix: A Digital Tool to Address Provider Needs for Prostate Cancer Genetic Testing in Clinical Practice. Clin Genitourin Cancer. 2022 Apr;20(2):e104-e113

84

Figure. Frequency by Gene of Pathogenic, Likely Pathogenic, and Increased-Risk Allele Variants Detected in This Study



All positive variants detected in a gene were combined and divided by the total number of pathogenic variants detected (n = 674). Mismatch repair (MMR) genes included *MLH1, MSH2, MSH6, and PMS2* (no *MSH1* variants were detected in this cohort).

American Urological Association Education & Research, Inc.

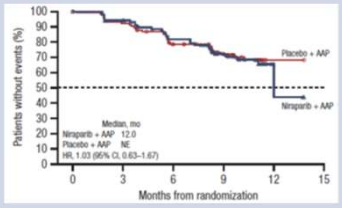
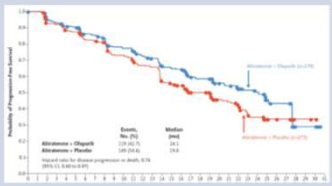
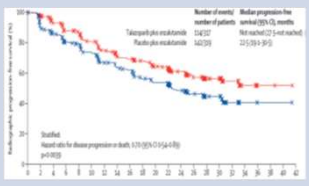
SUO Society of Urologic Oncology, Inc.

JAMA Oncology April 2019 Volume 5, Number 4

85

Results: Non-HRR Mutated

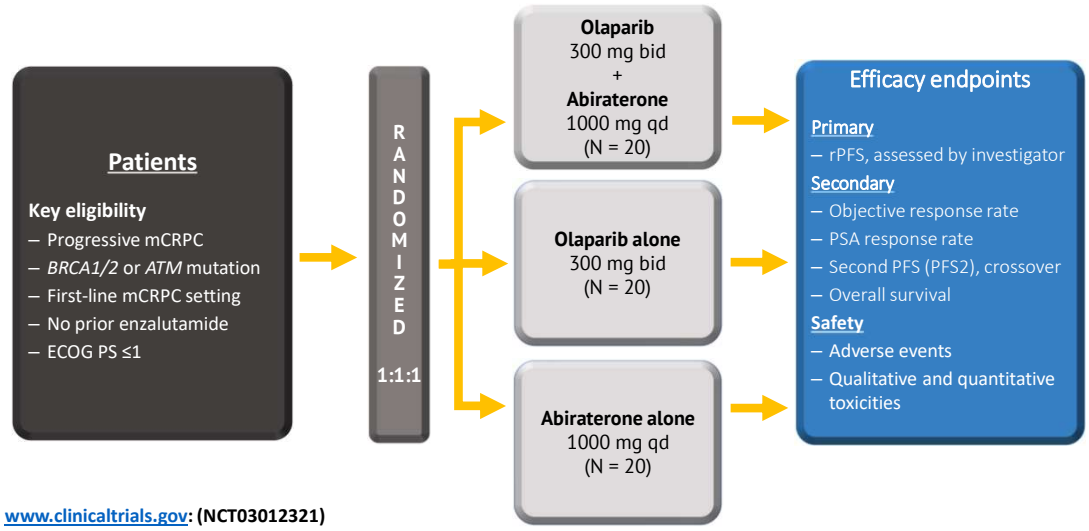
Equivocal Benefit, rPFS

		MAGNITUDE Abi + Niraparib N = 225	PROPEL Abi+ Olaparib N = 85	TALAPRO-2 Enza + Talazopaib N = 158
				
rPFS	**Medians**	**12.0 vs NE months**	**24.1 vs 19.0**	**NR vs 22.5 months**
	HR (95% CI)	**1.09 (0.75-1.57)**	**0.76 (0.60–0.97)**	**0.70 (0.54-0.89)**
OS	**Median**	**N/A**	**42.1 vs 38.9**	**N/A**

Chi KN et al. *J Clin Oncol.* 2023;41(18):3339-3351. Clarke NW et al. *NEJM Evid*. 2022;1(9).
Saad F et al. *Lancet Oncol.* 2023;24(10):1094-1108. Agarwal N et al. *Lancet.* 2023;402(10398):291-30.

86

BRCAaway: Randomized Phase 2 Trial in HRRm CRPC



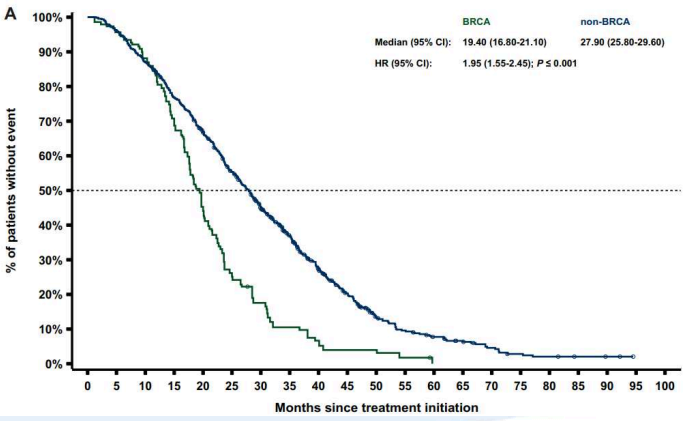
www.clinicaltrials.gov: **(NCT03012321)**

Hussain MHA et al. *J Clin Oncol.* 2024;42(suppl 4;Abstract 19.

87

Treatment patterns and outcomes in mCRPC with and without somatic or germline alterations

- 1/3 of mCRPC had ≥1 HRR alterations; 13% had alterations in *BRCA1/2* genes.
- With *BRCA1/2* alterations, irrespective of somatic/germline origin, had worse outcomes than those without.
- **With *BRCA1/2* alterations outcomes did not significantly differ by 1L treatment choice (ARSi or taxanes).**
- Identification of somatic/germline HRR alterations (*BRCA1/2*), is key for targeted therapy



American Urological Association Education & Research, Inc.

SUO Society of Urologic Oncology, Inc.

Olmos, D. et al. Annals of Oncology, Volume 35, Issue 5, 458 – 472 (2024)

88