



# **State of the art on molecular characterization in advanced prostate cancer (APC)**

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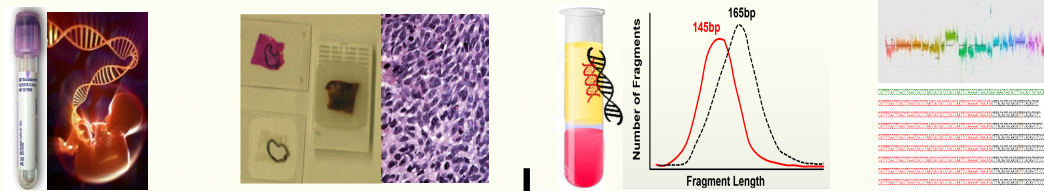
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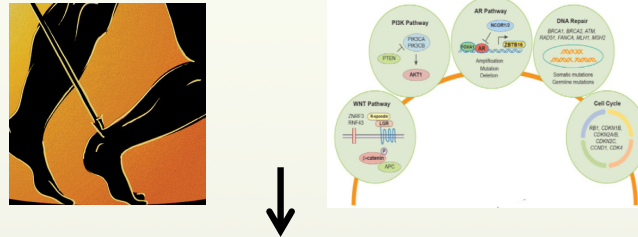
August 29, 2019

# Emerging Model For Advanced Prostate Cancer

Germline, tumor, liquid biopsy evaluated



Therapy guided by germline and somatic findings



Genetic counseling based on somatic and germline findings



# DNA Repair in Prostate Cancer

DNA Repair Pathway	Key Genes	Germline Syndrome	Treatment
Homologous Recombination Repair (HR)	<i>BRCA1</i> , <i>BRCA2</i>	King	PARPi, platinum
Mismatch Repair (MMR)	<i>MSH2</i>	Lynch	Anti-PD1/ PDL-1

# DDR Mutation Prevalence Estimates (Advanced Prostate Cancer)

	Somatic	Germline	Combined	Enriched In
<i>BRCA2</i>	5%	5%	10%	Family history breast/ovarian, Ductal + Intraductal histology
<i>BRCA1</i>	1%	1%	2%	Family history breast/ovarian, Ductal + Intraductal histology
<i>ATM</i>	2-3%	2%	4-5%	Family history breast/ovarian
<i>MSH2/6</i>	4-5%	1.5%	5-6%	Family history colon/endometrial, Ductal histology, Gleason pattern 5

Estimates based on Robinson 2015, Prtichard 2016, Na 2017, Annala 2017, Giri 2018, Nava Rodriguez 2018, Nicolosi 2019



# Not All DDR Genes Are the Same

Gene	Pathway	Germline Prostate Cancer Risk?	PARP/platinum (~level of evidence)	Anti PD1/PDL1 (~level of evidence)
<b>BRCA2</b>	<b>HR</b>	<b>High</b>	+++++	-
<b>BRCA1</b>	<b>HR</b>	<b>Moderate</b>	++++	-
<b>ATM</b>	<b>HR</b>	<b>Moderate</b>	++	-
<b>CHEK2</b>	<b>HR</b>	<b>Moderate</b>	+	-
<b>PALB2</b>	<b>HR</b>	<b>Emerging (High?)</b>	+++	-
<i>NBN</i>	HR	Some data	+/-	-
<i>RAD51C</i>	HR	Unknown	+/-	-
<i>RAD51D</i>	HR	Unknown	+/-	-
<i>BRIP1</i>	HR	Unknown	+/-	-
<i>FANCA</i>	HR	Unknown	+	-
<b>MSH2</b>	<b>MMR</b>	<b>High</b>	-	+++++++
<b>MSH6</b>	<b>MMR</b>	<b>Moderate</b>	-	+++++
<b>MLH1</b>	<b>MMR</b>	<b>Moderate</b>	-	++++
<i>PMS2</i>	MMR	Some Data	-	++

# Lynch: The Specific Gene Matters

## *Cumulative Prostate Cancer Incidence by Gene (%)*

Age	<i>MLH1</i>	<i>MSH2</i>	<i>MSH6</i>	<i>PMS2</i>
50	0.3	0.8	0	4.6
60	3.2	6.3	0	4.6
70	7	15.9	4.8	4.6
75	13.8	23.8	8.9	4.6

Adapted from: *Genetics in Medicine* (2019) <https://doi.org/10.1038/s41436-019-0596-9>



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## NCCN Guidelines Version 3.2019 Prostate Cancer

- Consider **metastatic biopsy**
- Consider **tumor testing for MSI-H or dMMR**
  - Use MSI test ***specifically-validated*** for prostate cancer
- Consider **germline AND tumor testing for HR DNA repair**
  - *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*

MSI-H: microsatellite instability high; dMMR: deficient mismatch repair; HR: homologous recombination

# ISUP 2019 Recommendations

- **Germline** panel testing for DNA repair genes in:
  - Metastatic AND high-risk localized
- **Somatic** tumor DNA testing in all metastatic:
  - dMMR** by either IHC and/or MSI/gene sequencing *AND*
  - dHR** by sequencing of *BRCA1/2* at minimum

Testing on **metastatic tissue** or, if unavailable, **primary tissue** is acceptable



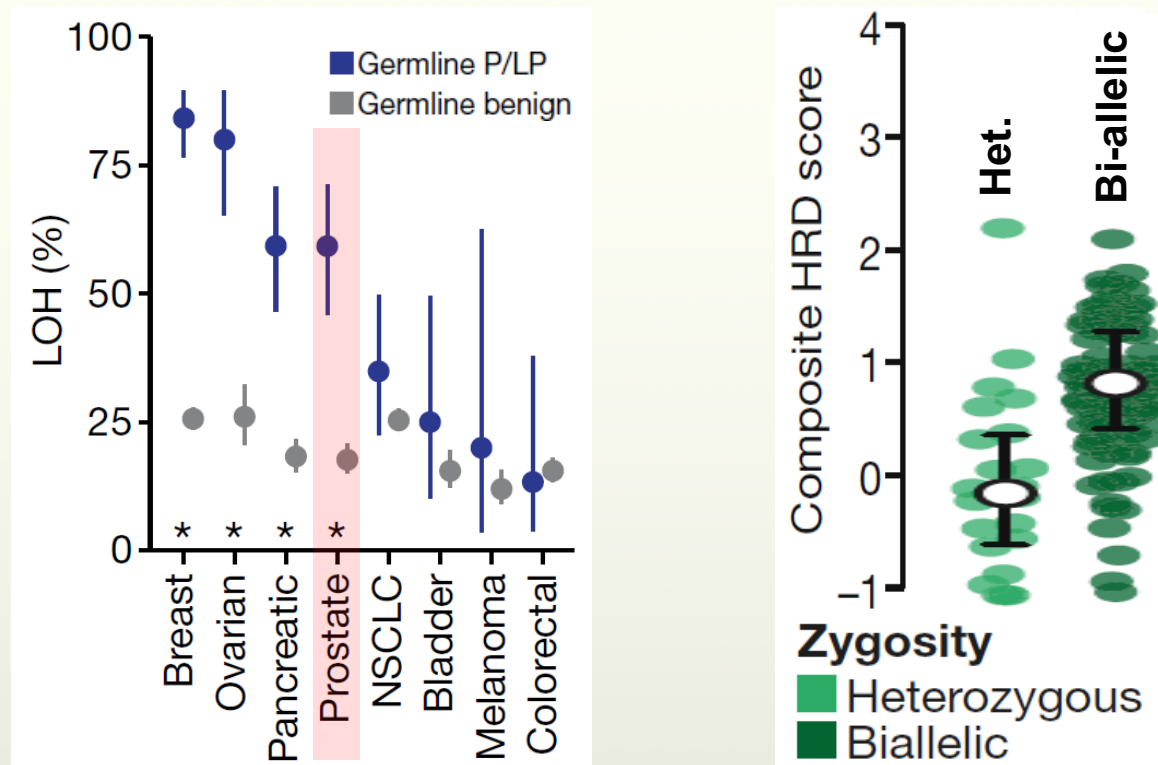
# HR DDR Testing: Issues

- **Confirming bi-allelic** inactivation
  - HR signature analysis (*BRCA1/2*)
  - IHC (ATM protein)
- **Variant interpretation**
  - Commercial labs still struggling

HR DDR= Homologous Recombination DNA Damage Repair

# Bi-allelic Inactivation Matters

***BRCA1* and *BRCA2* (combined)**



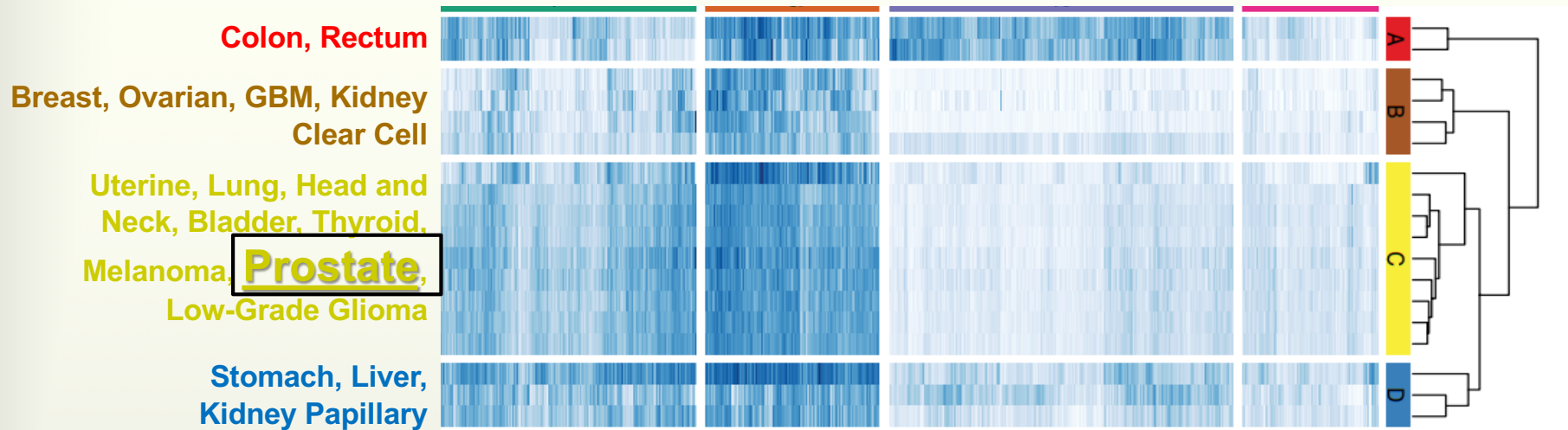
Adapted from Jonsson et al. *Nature*. 2019 571:576-579.

# MMR DDR Testing: Issues

- Accuracy of MSI
- Accuracy of IHC
- Technically challenging to detect underlying mutation(s)

MMR DDR= Mismatch Repair DNA Damage Repair

# MSI Patterns Are Not The Same Between Cancer Types



Hause et al. 2016 *Nat. Med.* PMID:27694933





# Prostate Cancer-*Validated* MSI by NGS Outperforms Traditional Methods

**MSI-PCR (5-marker)**

Fraction Unstable Loci

MMR-deficient

MMR-intact

8 False Negatives

**MSIplus (18-marker NGS)**


Fraction Unstable Loci

MMR-deficient

MMR-intact

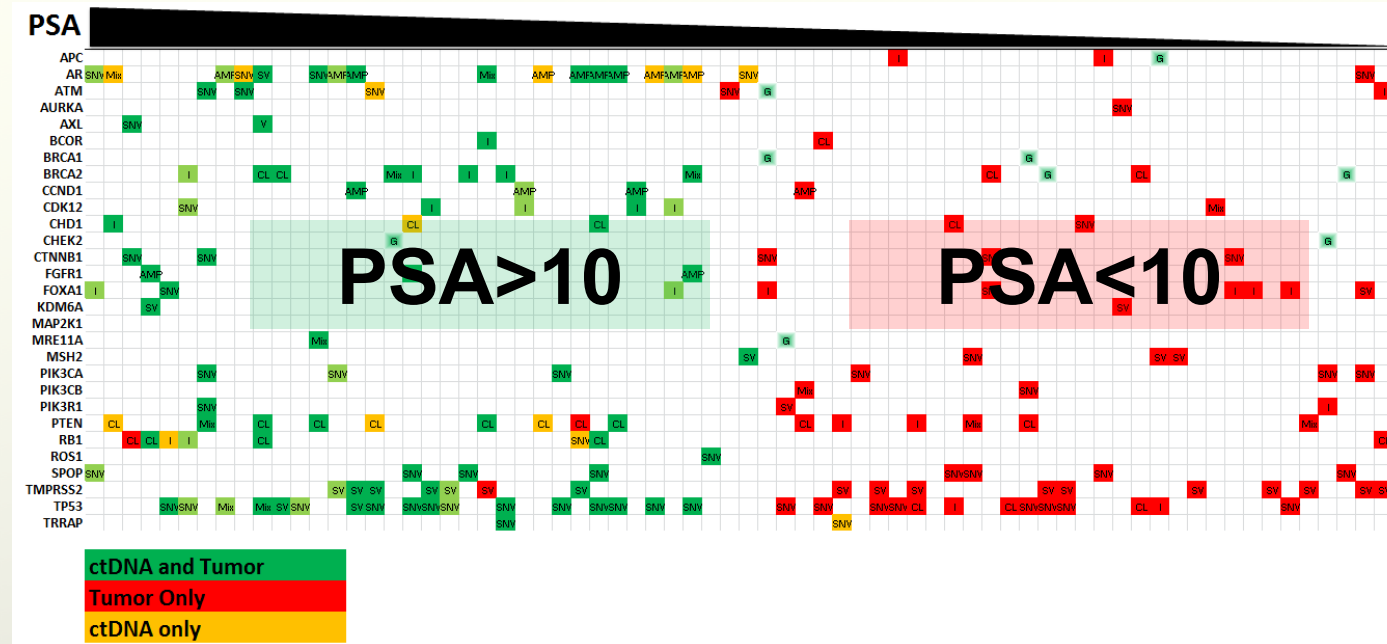
1 False Negative

Hempelmann et al. (2018) *JITC*.

A circular portrait of Dr. Sarah E. Hill, a woman with light brown hair pulled back, smiling slightly. She is wearing a dark blue jacket over a light-colored top.

# Liquid Biopsy

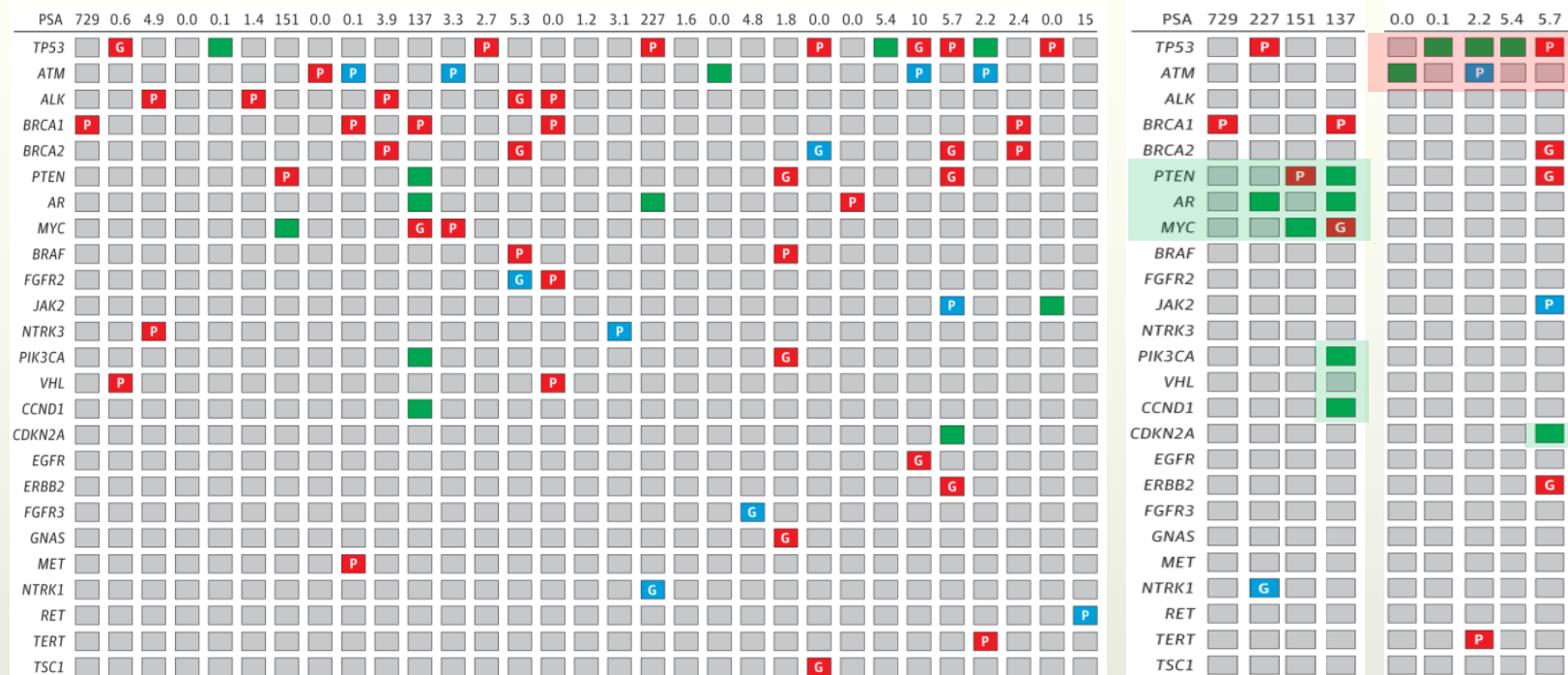
Adequate testing in advanced prostate cancer depends on disease burden



Adapted from Schweizer et al. *Prostate* (2019) 79:701-708.

# Liquid Biopsy: Pitfalls

Poor congruence between two commercial labs in 40 mPC patients



CHIP?

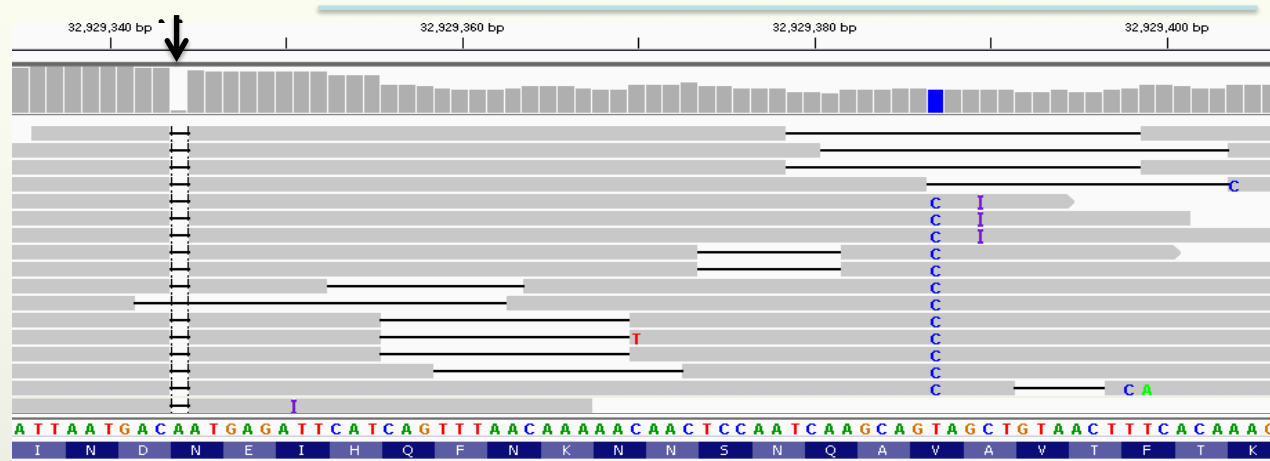
Adapted from Torga and Pienta, *JAMA Oncol.* 2018;4(6):868-870.

# Liquid Biopsy: Treatment Resistance

Example: Following Platinum Treatment  
**Reversion Mutations** Restore Reading Frame

*BRCA2* c.7355del

*Reversion Mutations*



***BRCA2* Exon 14**

Cheng et al. (2018) *JCO Precision Oncology*





# Summary

- **Germline and tumor NGS** testing of DNA repair genes is increasingly **recommended to guide advanced prostate cancer treatment**
- **Liquid biopsy (ctDNA)** testing increasingly **used in place of tissue testing** and useful when patients are carefully selected with adequate disease burden
- **Sample, methods, and interpretation matter, increasing molecular pathologist roles**

# Thank You!

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