# OMICS and AI in PROSTATE CANCER

## Omics driven systemic treatments

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# Disclosures:

| Type of conflict | Sponsor |
|---|---|
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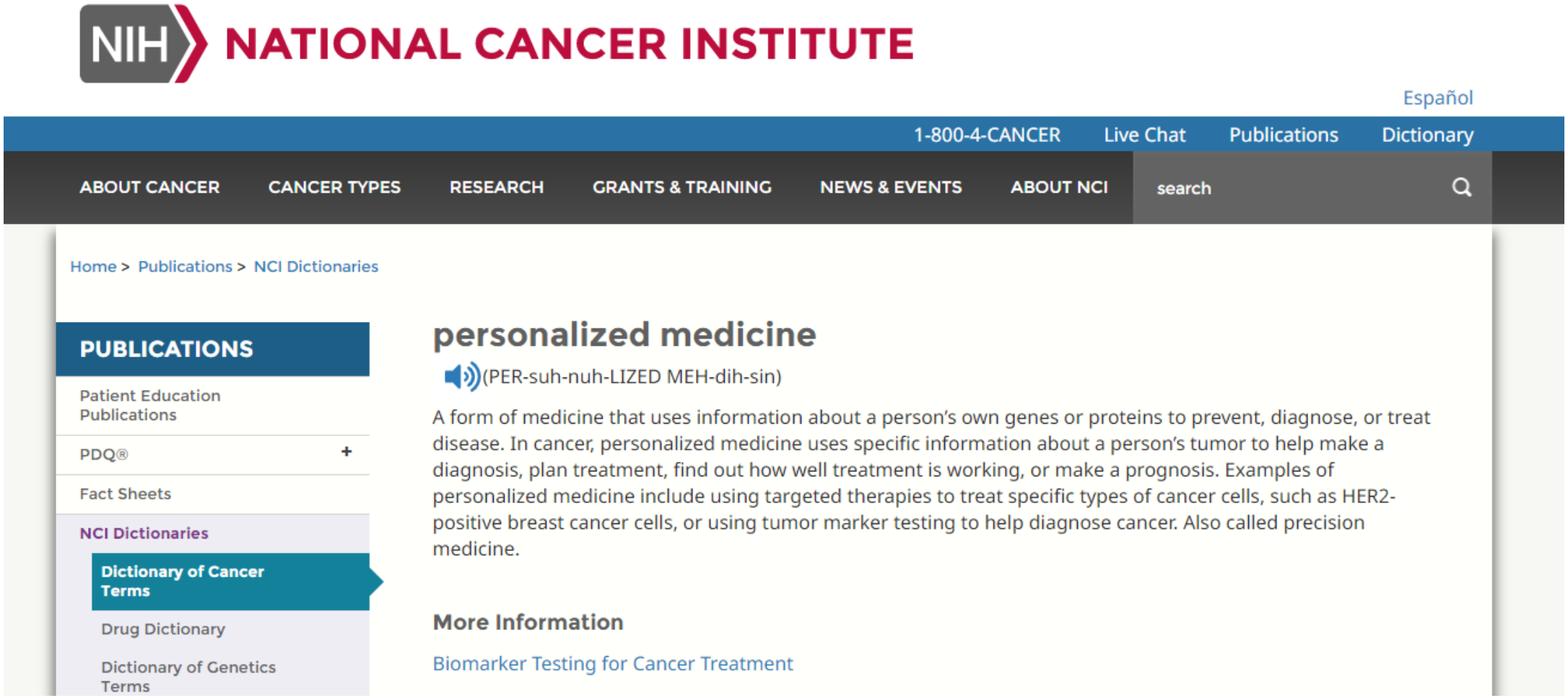
| Research support (inst) | BMS, Pfizer. |
| I am a clinician | Myself |

# Genomics as a way for personalized medicine (also in Pca):

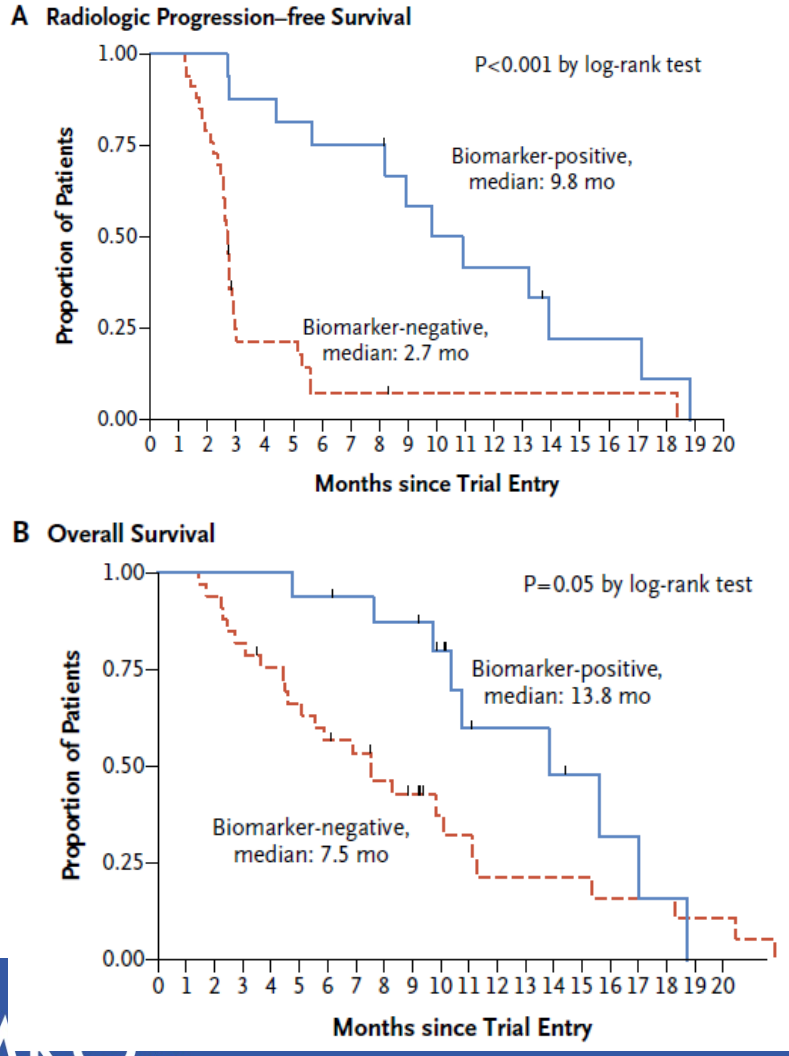


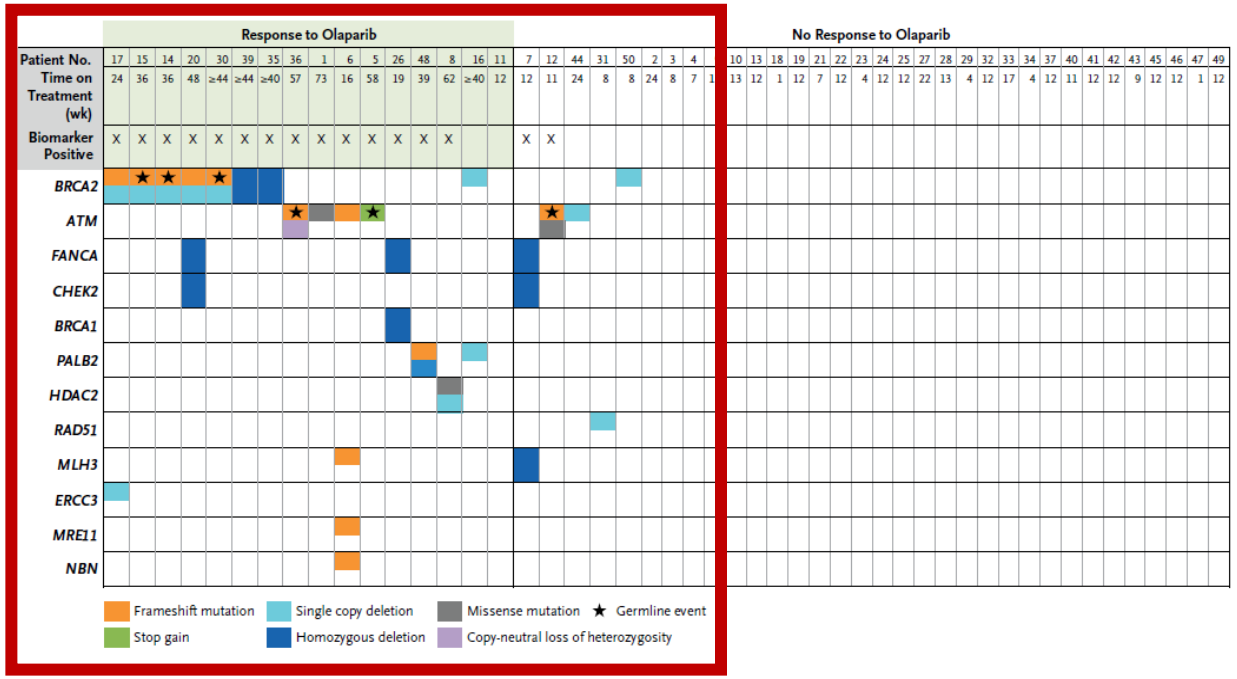
# The clinical point of view when using genomics/genetics:

- How genomic/genetic knowledges have impacted PCa treatment?
- How deeper genomic/genetic knowledges can affect PCa treatment?
- Considerations about the potential of genomics and the role of ctDNA in clinical management of PCa.

# How genomic/genetic knowledges have impacted PCa treatment?

## TOPARP-A study




49 heavily pretreated mCRPC men treated with PARP inhibitor (olaparib 400 mg BID)

Genomic signature of PARP inhibitor sensitivity in 16/49 (33%)

Response to PARP in 14/16 (87,5%)

Mateo J et al. *New Engl J Med*. 2015;373:1697-708

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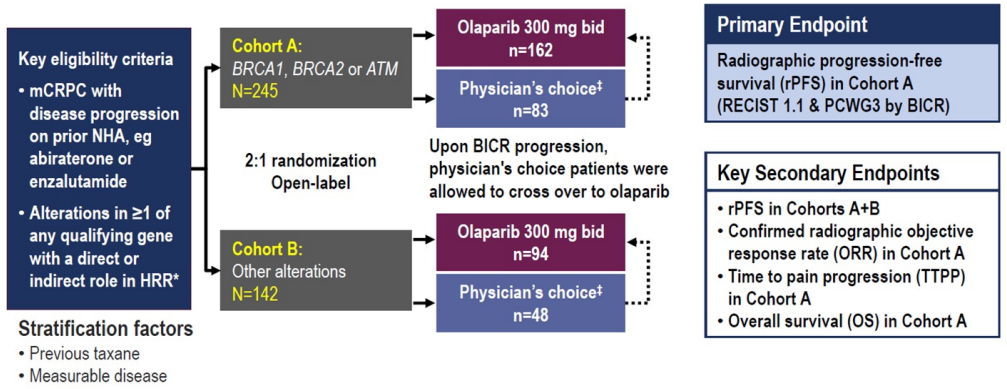
# How genomic/genetic knowledges have impacted PCa treatment?

**PROfound STUDY DESIGN**

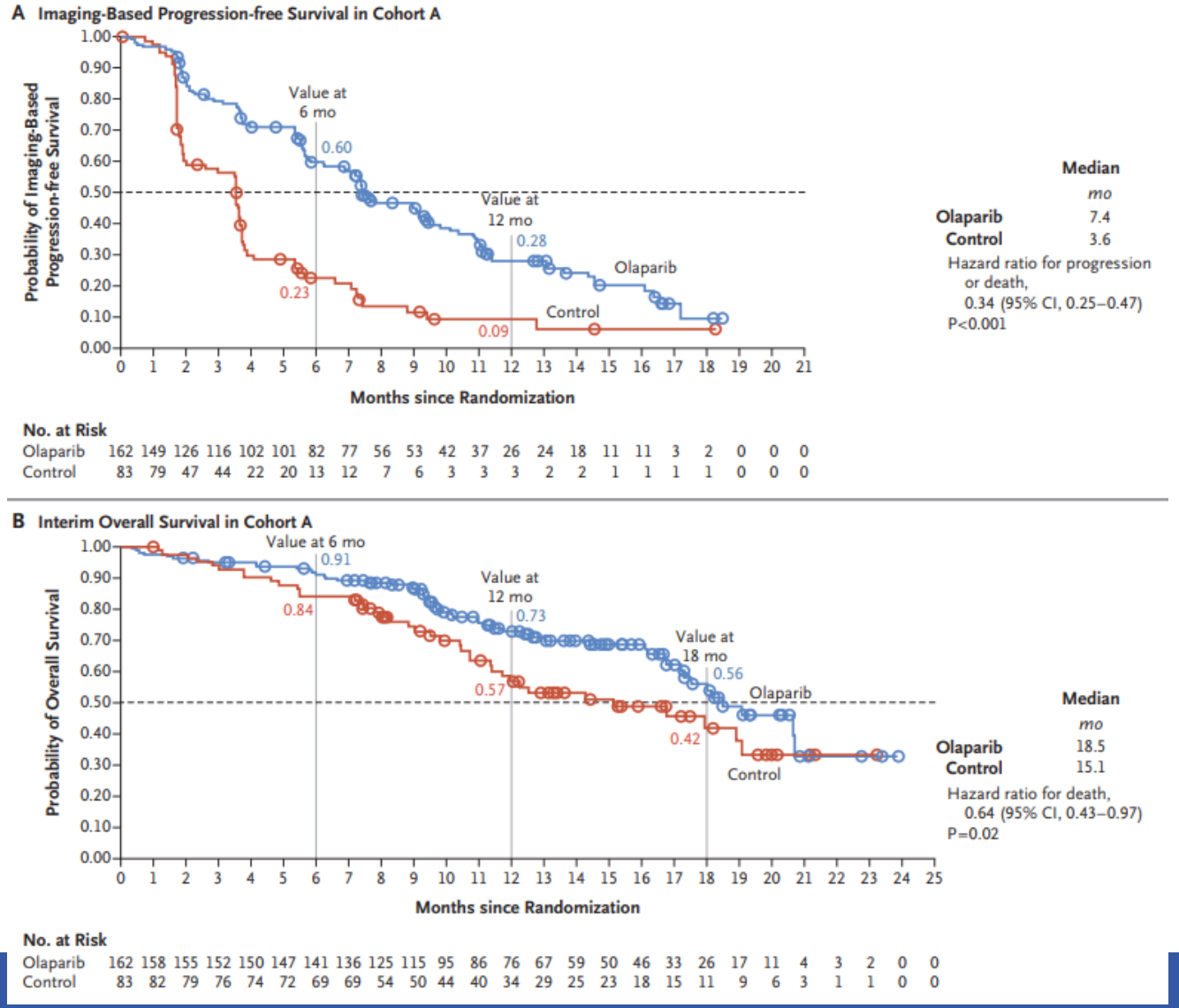



*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

BARCELONA 2019 ESMO congress

‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review




De Bono J, et al. N Engl J Med 2020; 382:2091-2102

# How deeper genomic/genetic knowledges affect PCa treatment?

## PROpel: global randomized double-blind Phase III trial[1]

**Patient population**
- 1L mCRPC
- Docetaxel allowed at mHSPC stage*
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrolment
- ECOG 0–1

**Stratification factors**
- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

1:1

**Abiraterone 1000 mg qd† + olaparib 300 mg bid** n=399
Full dose of abiraterone and olaparib used

**Abiraterone 1000 mg qd† + placebo** n=397
Full dose of abiraterone used

**Primary endpoint**
- rPFS by investigator assessment (sensitivity analysis by BICR)

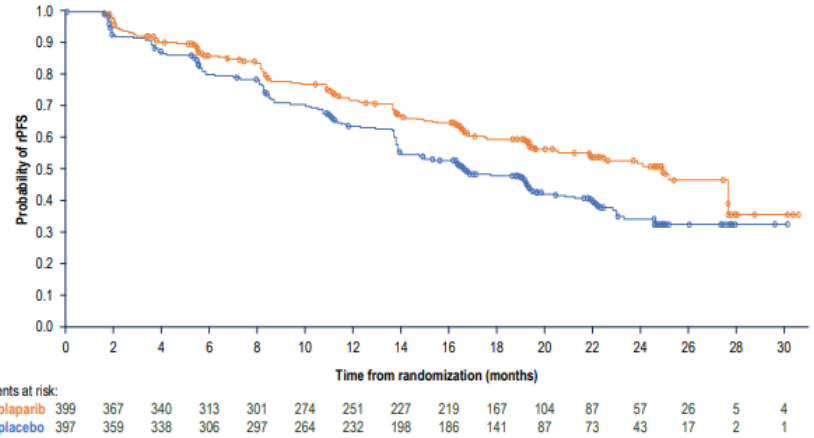
**Key secondary endpoint**
- OS (alpha controlled)

**Additional endpoints**
- TFST
- PFS2
- ORR
- HRRm‡ gene mutation status (by tissue and ctDNA testing)
- Safety and tolerability

First patient randomized: November 2018; Last patient randomized: March 2020; Primary analysis, DCO1: 30 July 2021; Second data cut-off, DCO2: 14 March 2022
A multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS
*Docetaxel during neoadjuvant/adjuvant treatment for localized prostate cancer and mHSPC was permitted. †In combination with prednisone or prednisolone 5 mg bid. ‡HRRm testing conducted after randomization and before primary analysis, including a 14-gene panel, using the FoundationOne®CDx test and FoundationOne®Liquid CDx test
bid, twice daily; BICR, blinded independent central review; ctDNA, circulating tumour DNA; DCO1, primary data cut-off; DCO2, second data cut-off; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone-sensitive prostate cancer; ORR, objective response rate; PFS2, time to second progression or death; qd, once daily; TFST, time to first subsequent therapy or death
1. Clarke N *et al. NEJM Evidence* 2022;EVIDoa2200043

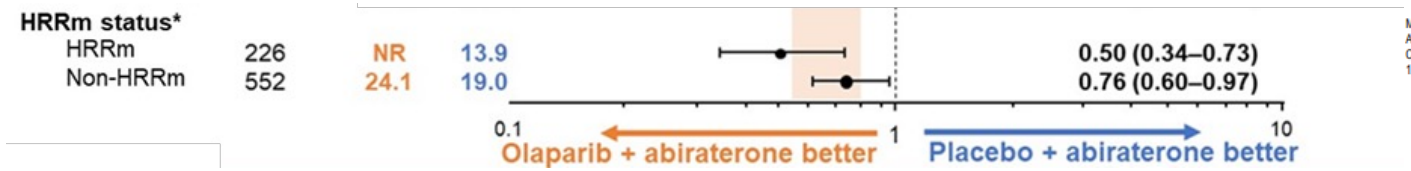
## PROpel primary endpoint: rPFS by investigator assessment in the ITT population

At primary analysis (DCO1) there was a 34% reduction in the risk of radiological progression or death with abiraterone + olaparib[1]




| Number of patients at risk: | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abiraterone + olaparib | 399 | 367 | 340 | 313 | 301 | 274 | 251 | 227 | 219 | 167 | 104 | 87 | 57 | 26 | 5 | 4 |
| Abiraterone + placebo | 397 | 359 | 338 | 306 | 297 | 264 | 232 | 198 | 186 | 141 | 87 | 73 | 43 | 17 | 2 | 1 |

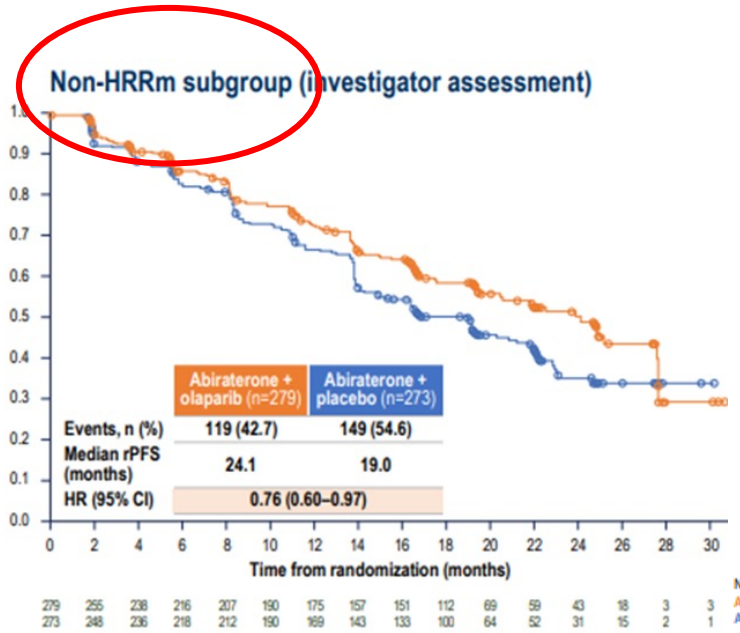
| | Abiraterone + olaparib (n=399) | Abiraterone + placebo (n=397) |
|---|---|---|
| Events, n (%) | 168 (42.1) | 226 (56.9) |
| Median rPFS (months) | 24.8 | 16.6 |
| HR (95% CI) | 0.66 (0.54–0.81); *P*<0.001 | |



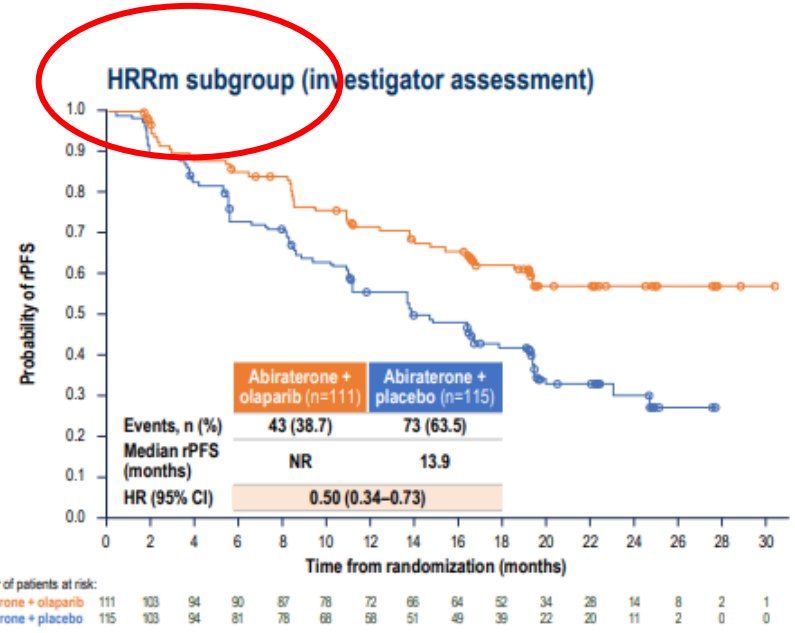

Median duration of follow-up in censored patients was 19.3 months (range 0.03–30.59) in the abiraterone + olaparib arm and 19.4 months (range 0.03–30.16) in the abiraterone + placebo arm.
A circle indicates a censored observation
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat
1. Clarke N *et al. NEJM Evidence* 2022;EVIDoa2200043. 

Saad F, ASCO GU2022
Saad F, ESMO 2022; Presentation number: 1357O

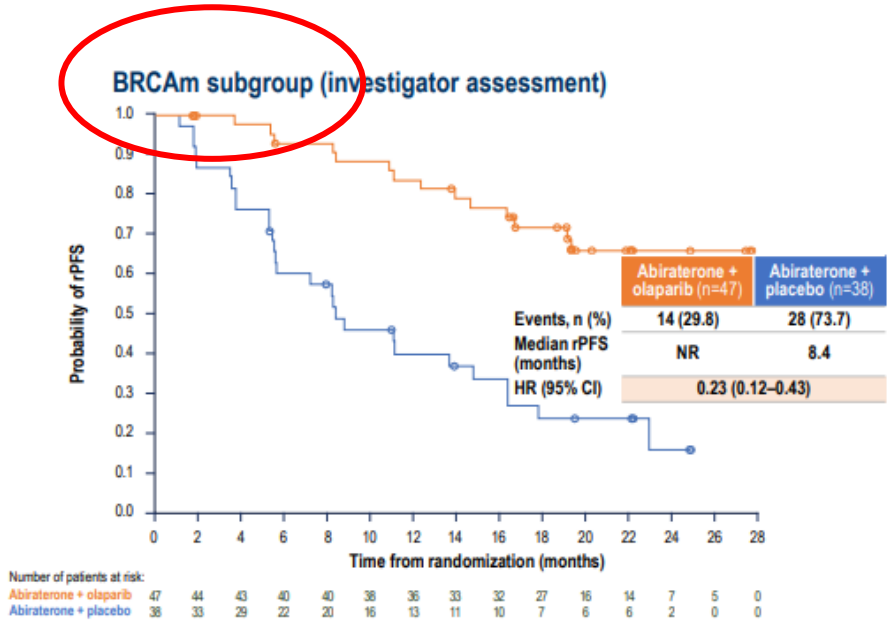
# How deeper genomic/genetic knowledges affect PCa treatment?




Sensitivity analysis by blinded independent central review:[1]
Median 27.6 vs 19.1 months;
HR 0.72, 95% CI 0.56–0.93




Sensitivity analysis by blinded independent central review:[1]
Median 28.8 vs 13.8 months;
HR 0.45, 95% CI 0.31–0.65




Sensitivity analysis by blinded independent central review:
Median NR vs 8.4 months;
HR 0.18, 95% CI 0.09–0.34

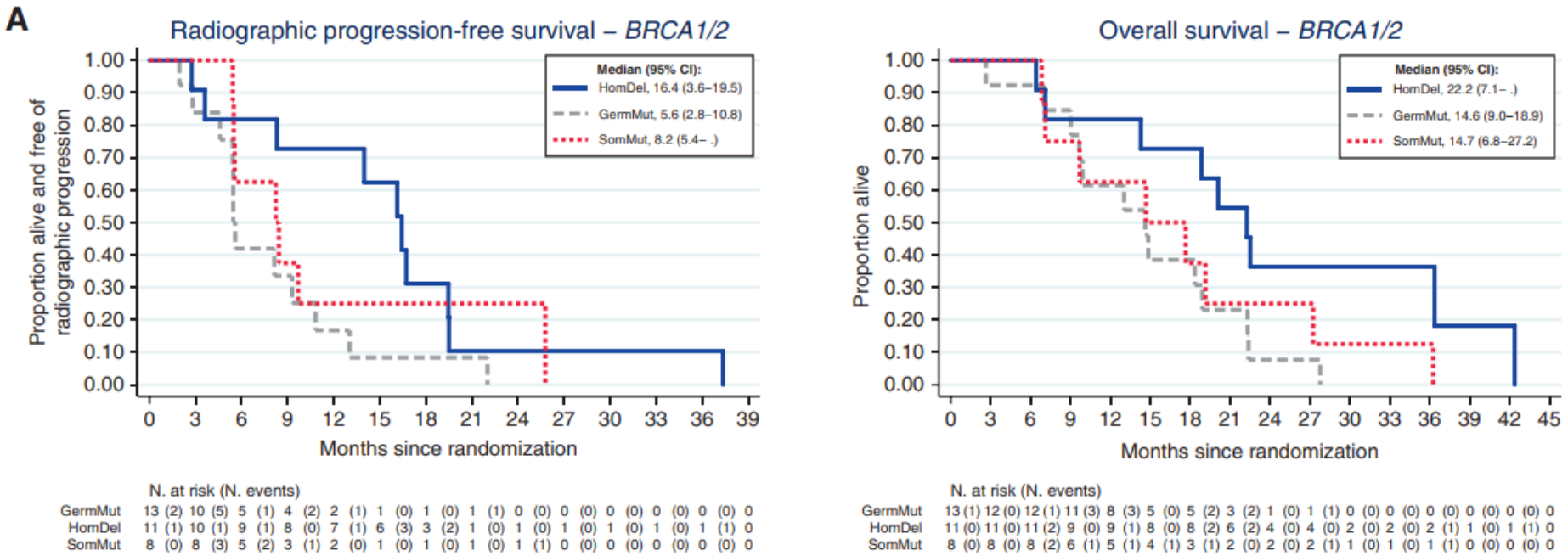
Patients

Personalization of Tx

Saad F, ESMO 2022; Presentation number: 1357O

# How deeper genomic/genetic knowledges affect PCa treatment?

**Patients enrolled in TOPARP-B study and analyzed based on the type of mutation:**

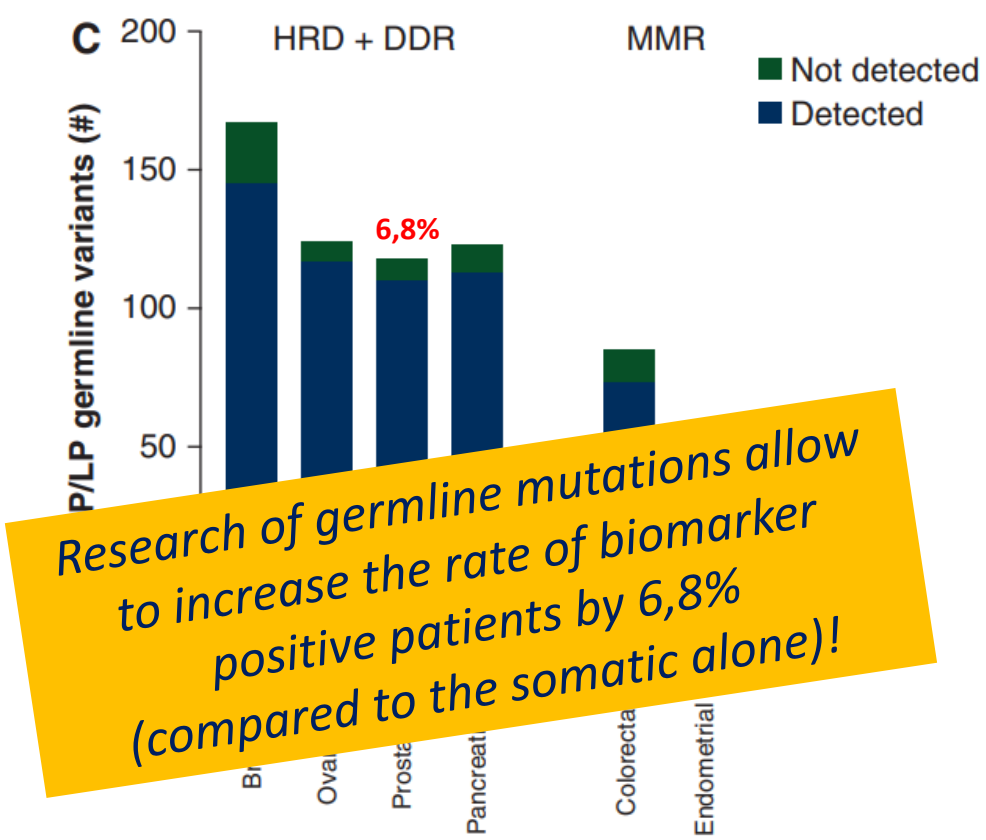



"BRCA1/2 germline and somatic pathogenic mutations associated with similar benefit from olaparib; greater benefit was observed with homozygous BRCA2 deletion".

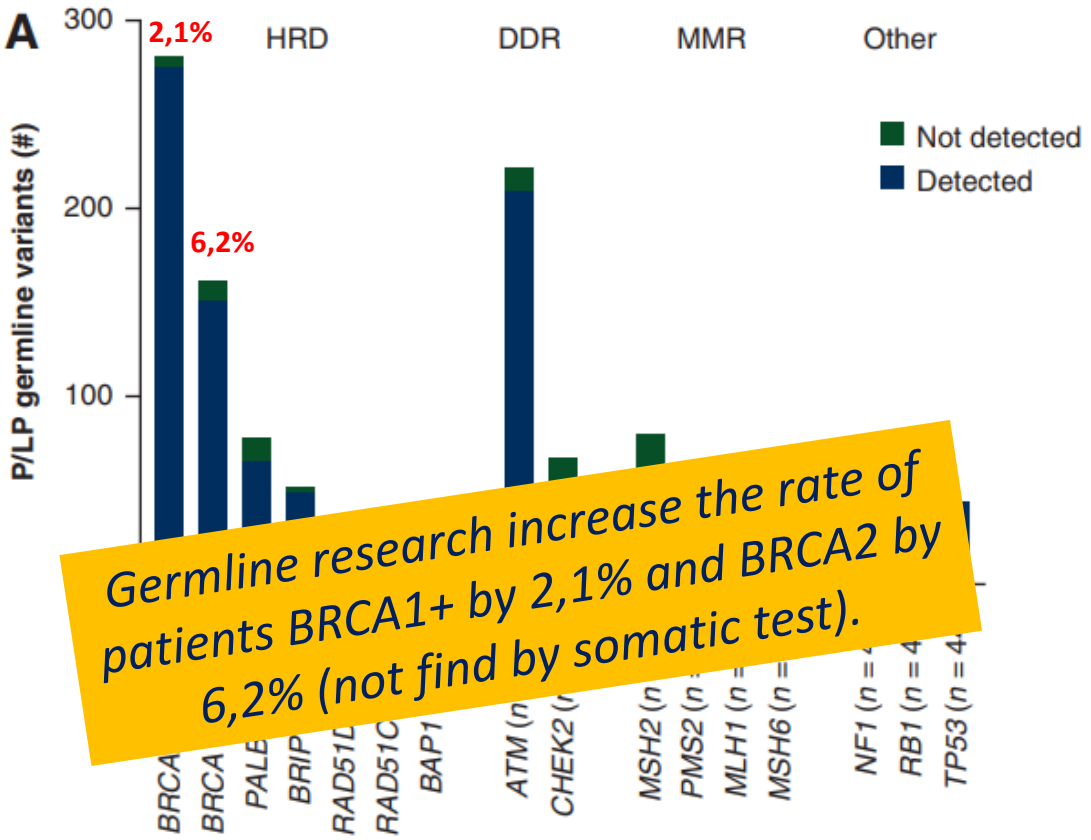
Carreira S, et al. Cancer Discov. 2021;11:2812-2827.

# How deeper genomic/genetic knowledges affect PCa treatment?

De-identified tumor and blood massively parallel sequencing data of 21.333 cancer patients enrolled in the study




*Research of germline mutations allow to increase the rate of biomarker positive patients by 6,8% (compared to the somatic alone)!*

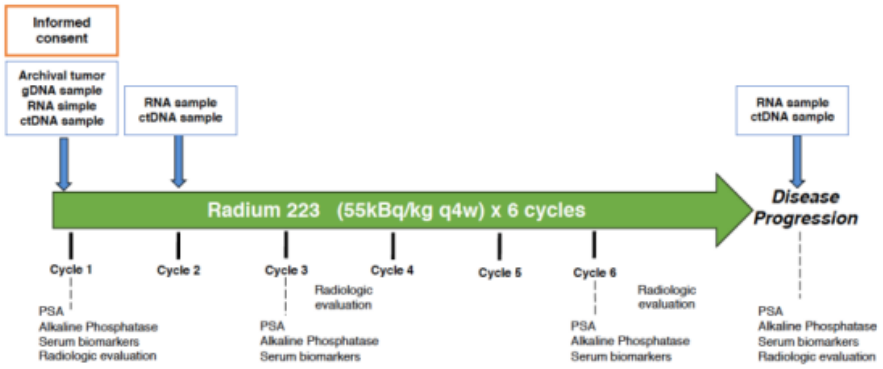


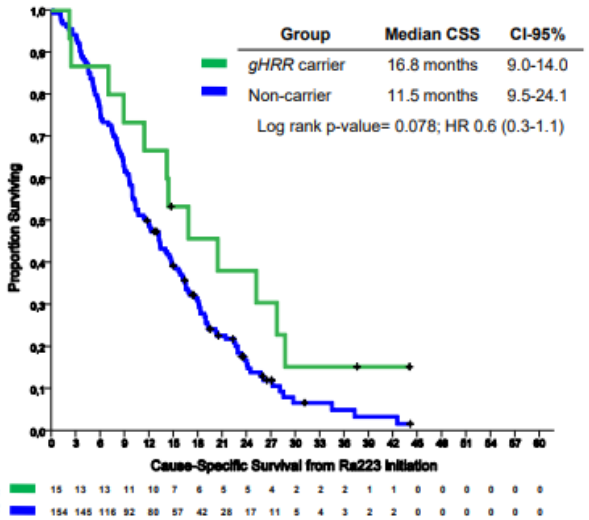

*Germline research increase the rate of patients BRCA1+ by 2,1% and BRCA2 by 6,2% (not find by somatic test).*

Sixteen genes were included in these analyses, including seven HR deficiency (HRD) genes (BRCA2, BRCA1, PALB2, BRIP1, RAD51D, RAD51C and BAP1), two DDR genes (ATM and CHEK2), four MMR genes (MSH2, PMS2, MLH1 and MSH6) as well as NF1, RB1 and TP53.

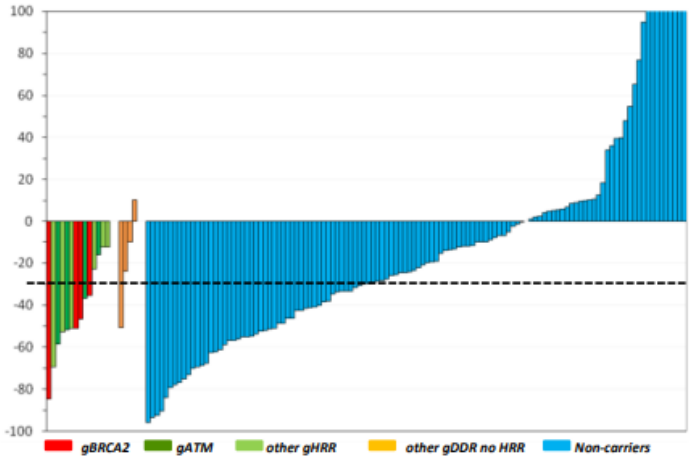
# HRR mutations might select patients more responsive to some therapies…

## Patients with gHR alterations may benefit from Radium-223 more than non-carriers




Kaplan-Meier curve for CSS by gHR status




Change in ALP levels at 12 weeks by HR status

*Presented by Dr Castro at ESMO 2021*

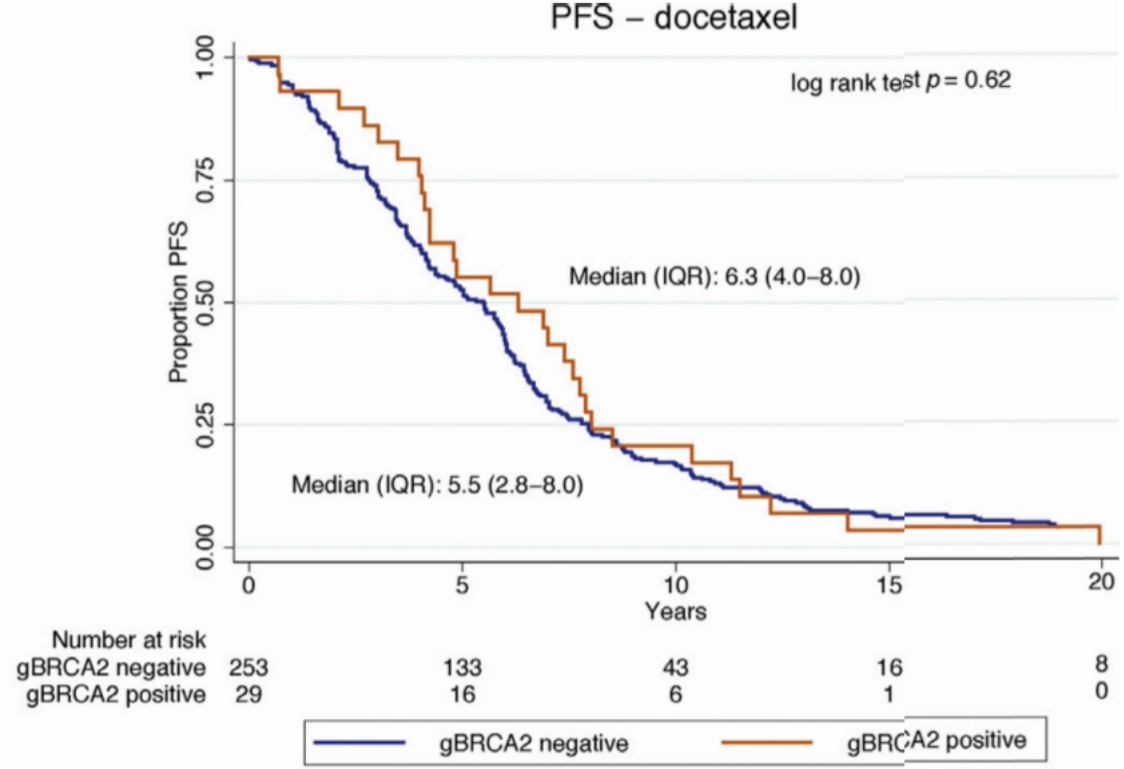
PARIS 2022 ESMO congress

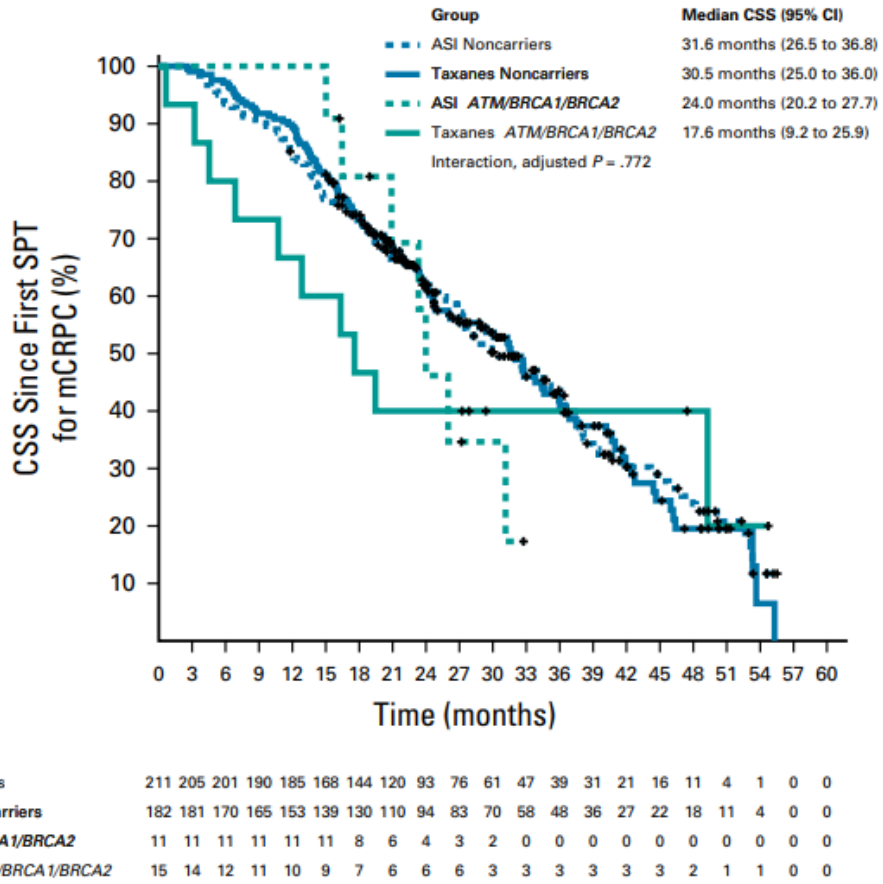
Elena Castro MD PhD



MRO.ART MODERN RADIATION ONCOLOGY

# …but not to all!

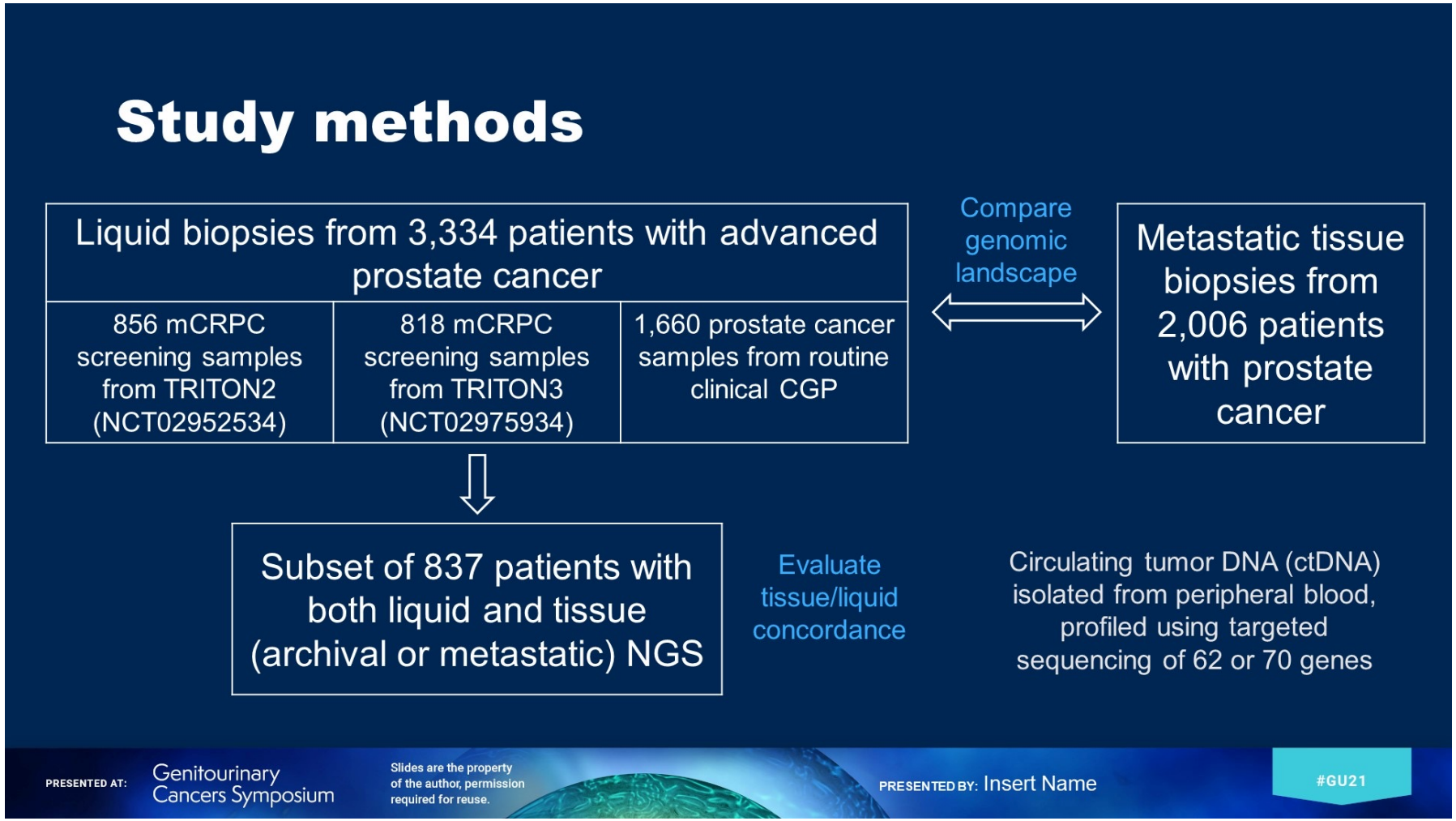



- Mutations of BRCA1/2 and ATM genes did not predict a better response to taxane-based chemo.
- These alteration remain prognostics.

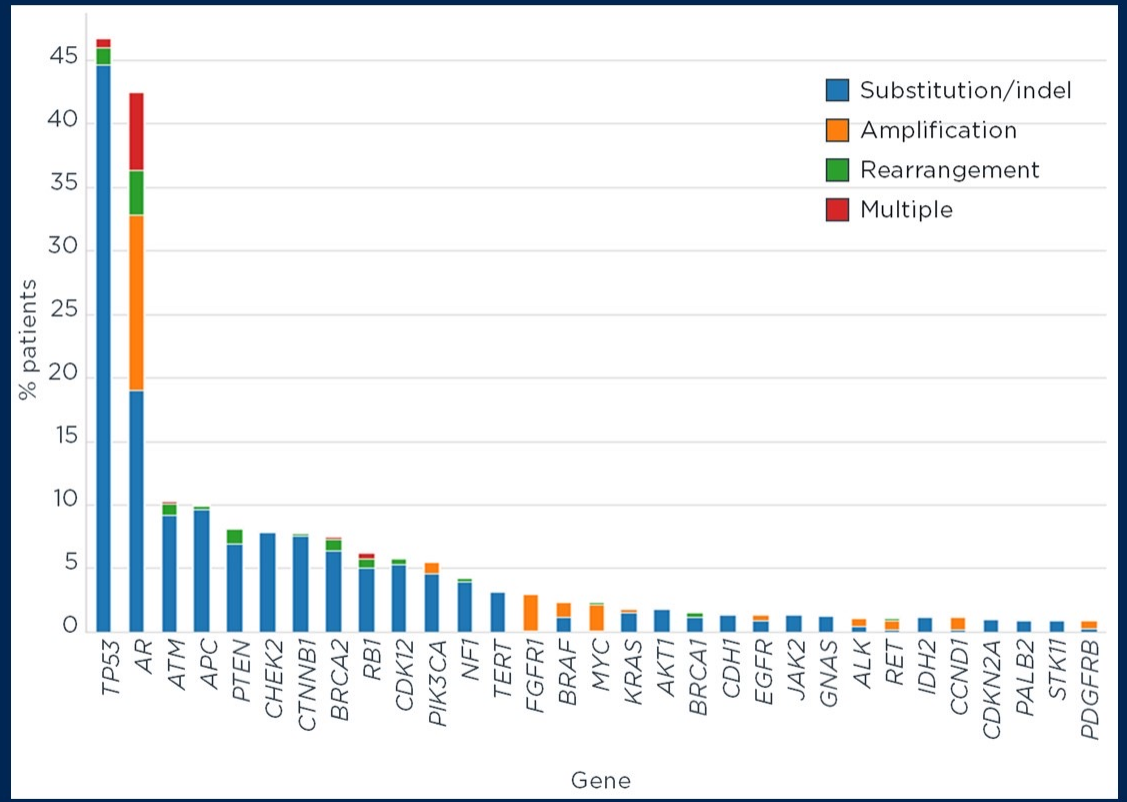

Mateo J, et al. Eur Urol. 2018;73(5):687-693.
Castro E, et al. J Clin Oncol. 2019;37:490-503.

# Considerations about the potential of genomics and the role of test in PCa.



# Considerations about the potential of genomics and the role of test in PCa.

## Figure 1. Genomic landscape of GAs detected in advanced prostate cancer liquid biopsies




**The genomic landscape of prostate cancer ctDNA largely recapitulates that detected by tissue biopsies.**

*BRCA1/2* alterations: 8.8%
*AR* alterations: 42%
PI3K/AKT/mTOR: 14%
WNT/β-catenin: 17%
RAS/RAF/MEK: 5%

Note: homozygous deletions not reported by the assays in this study (affecting *PTEN, RB1, BRCA1/2*). *TMPRSS2-ERG* and *SPOP* were not baited.

PRESENTED AT: Genitourinary Cancers Symposium



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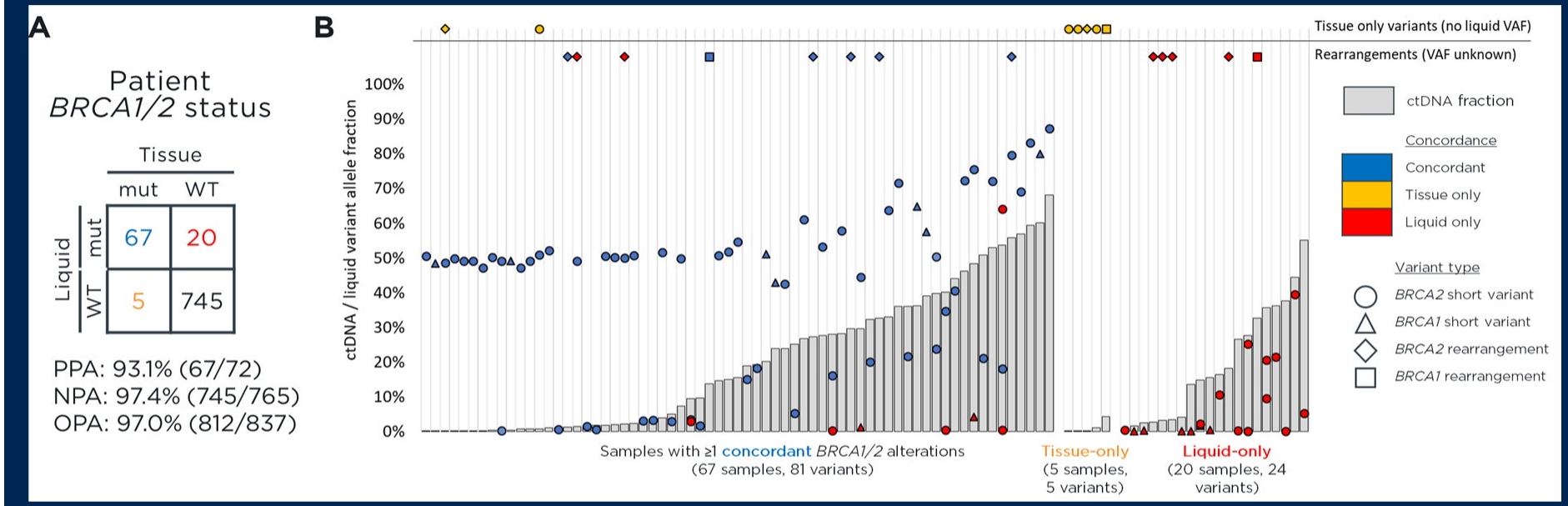
# Considerations about the potential of genomics and the role of test in PCa.

## Figure 3. Concordance of *BRCA1/2* alterations in liquid/tissue biopsy pairs from the same patient




**(A)** Contingency table showing detection of BRCA1/2 short variants and rearrangements by liquid and tissue biopsy. **(B)** ctDNA fractions and variant allele frequencies (VAF) of BRCA1/2 variants detected in 92 tissue/liquid pairs.

PPA: positive percent agreement; NPA: negative percent agreement; OPA: overall percent agreement. Short variant: substitution, short insertion/deletion.

**There was a high level of agreement in detection of *BRCA1/2* alterations between tissue and liquid biopsy. Patients with tissue-only detection of *BRCA1/2* had liquid biopsies with low ctDNA fraction.**

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# Conclusions