GERMLINE GENETIC TESTING IN PROSTATE CANCER

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DISCLOSURES

- Grant/Sponsorship Support: Bayer, Janssen, Hybridine, Astellas,Verity, Point Biopharma
- Honorarium/Consulting Fees/Speaker Fees: Bayer, AbbVie, Janssen, Astellas, Sanofi,

GREETINGS

GREETINGS

U.S. News and World Report released its annual 2019 Best Global Universities rankings on Oct. 30 for the fifth straight year.

For the rankings, *U.S. News* evaluated 1,250 universities and colleges across 75 countries. The U.S. saw the highest number of universities on the list with 227, followed by China (130 schools), the U.K. (78 schools), Japan (67 schools) and Germany (62 schools).

The latest edition of the list includes rankings by country, region and in 22 areas of study. Clarivate Analytics InCites provided *U.S. News* with the data and metrics used in the subject rankings. The publication also analyzed several other sources, including publications and citations, and indicators for the institution's global and regional reputation in each subject area. Scores were provided on a zero to 100 scale, with the highest-performing universities earning a subject score of 100.

Here are the *U.S. News* top 10 universities in the world for clinical medicine along with their rating, including ties:

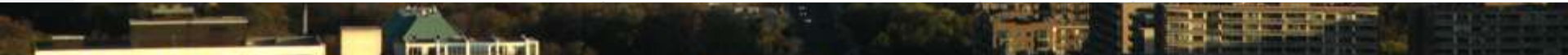
1. Harvard University (Cambridge, Mass.) — 100
2. Johns Hopkins University (Baltimore) — 90.7
3. UC San Francisco — 87.4
4. University of Oxford (U.K.) — 86.5
5. University of Toronto (Canada) — 85.7

GREETINGS

Newsweek SIGN IN

WORLD'S BEST HOSPITALS - TOP 10 GLOBAL

RANK	HOSPITAL	CITY COUNTRY
1	Mayo Clinic - Rochester	Rochester, MN USA
2	Cleveland Clinic	Cleveland, OH USA
3	Singapore General Hospital (SGH)	Singapore Singapore
4	The Johns Hopkins Hospital	Baltimore, MD USA
5	Charité – Universitätsmedizin Berlin	Berlin Germany
6	Massachusetts General Hospital	Boston, MA USA
7	Toronto General Hospital	Toronto, ON Canada
8	The University of Tokyo Hospital	Tokyo Japan
9	CHUV Centre Hospitalier Universitaire Vaudois	Lausanne Switzerland
10	Sheba Medical Center Tel HaShomer	Ramat Gan Israel



GERMLINE GENOMICS IN 2020

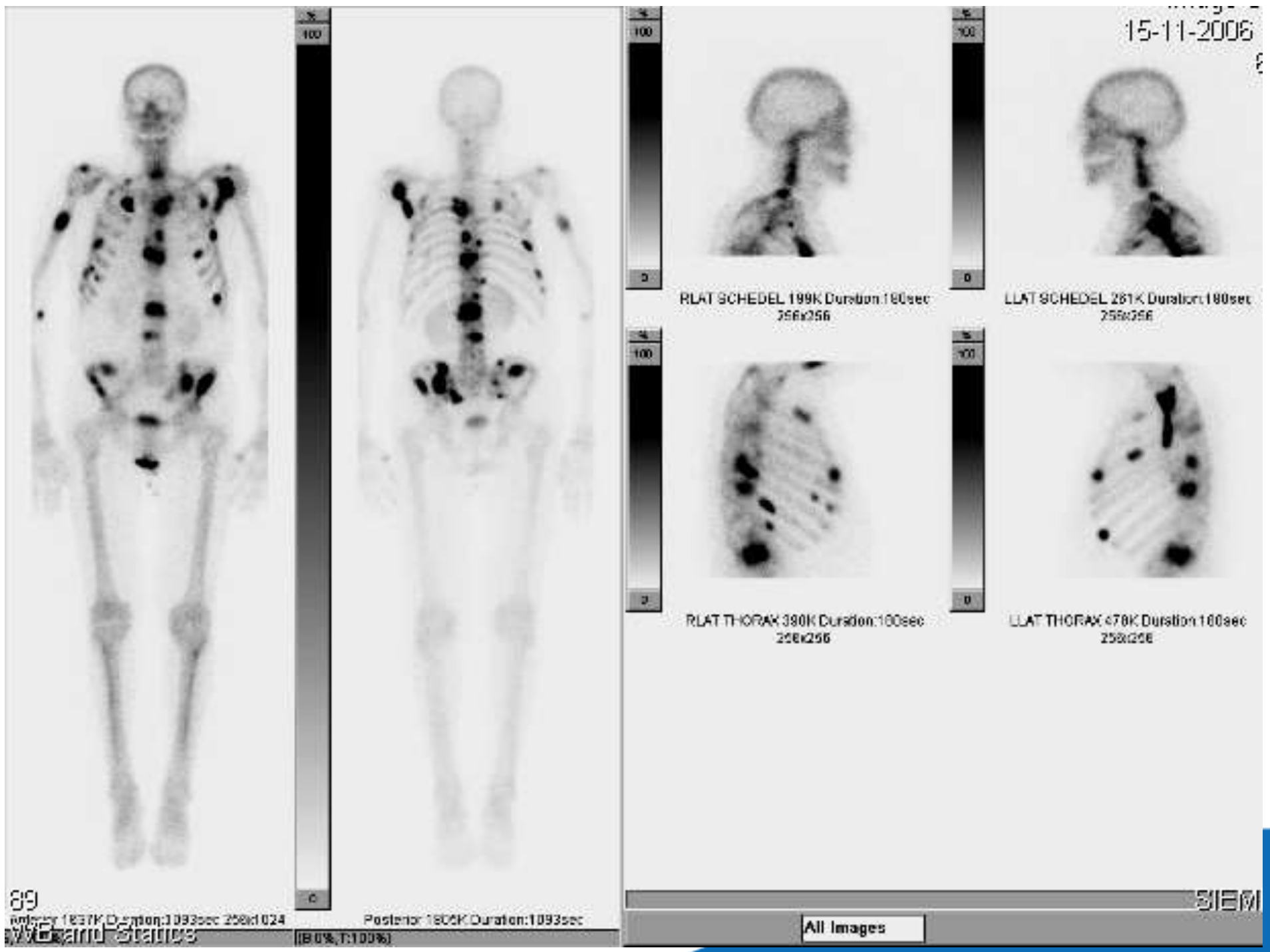
- Understanding of their relevance has increased
- Testing has become very inexpensive
- Testing no longer has jeopardy

MR FP

- 58 yr old male
- PSA 2.3 ng/ml
- Father-prostate CA
- Mom- breast CA
- Sister- ovarian ca
- Biopsy--- negative

6 months later

- Mr P – pain and NFW
- PSA 868 ng/ml
- Bone scan—diffuse metastatic disease in bones and liver
- Color Test—Br CA 1 positive


15-11-2006
RLAT SCHEDEL 199K Duration:180sec
256x256
LLAT SCHEDEL 261K Duration:180sec
256x256
RLAT THORAX 380K Duration:100sec
256x256
LLAT THORAX 478K Duration:100sec
256x256
Posterior 1805K Duration:1093sec
All Images

MR AF: 62 years old

- PSA 11.2 ng/ml
- T1C
- Gleason ¾
- RRP in March 2018
- Final Pathology
  - pT3B, R0
  - Post op PSA follow up……

MR AF: 62 years old

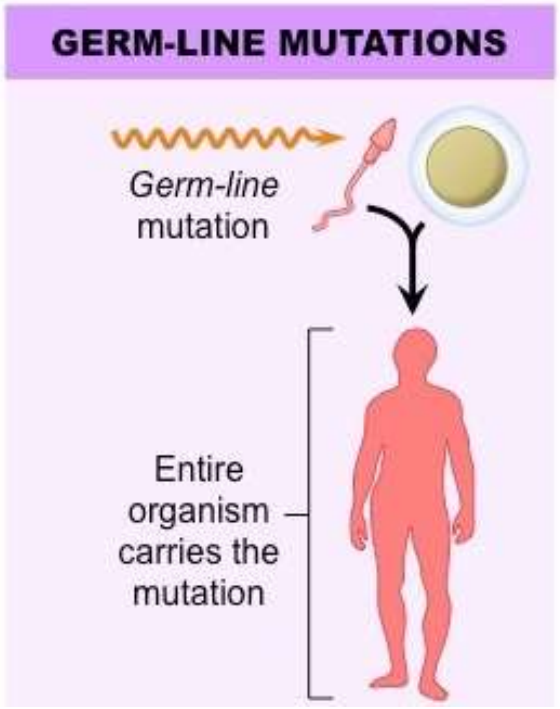
- PSA 11.2 ng/ml
- T1C
- Gleason ¾
- RRP in March 2018
- Final Pathology
  - pT3B, R0
  - Post op PSA follow up……31.6 ng/ml
  - I reassured him it's the wrong test " come back in 2 weeks" with another PSA

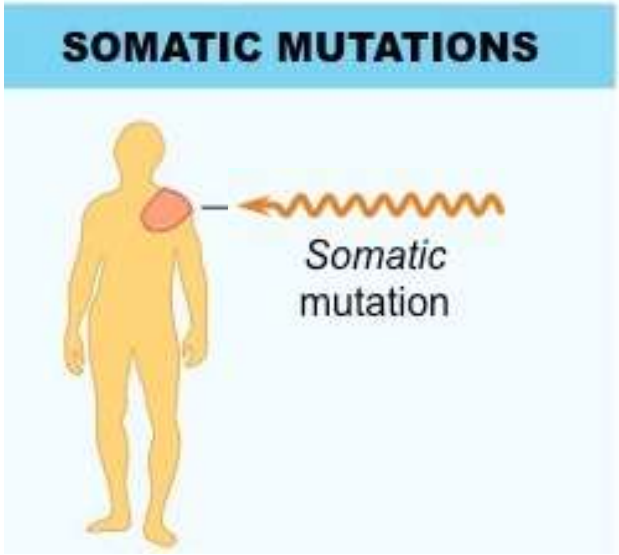
AF: 62 years old

- PSA—103.7 ng/ml

- Color test
- BRCA2

Germline vs. Somatic Genetics

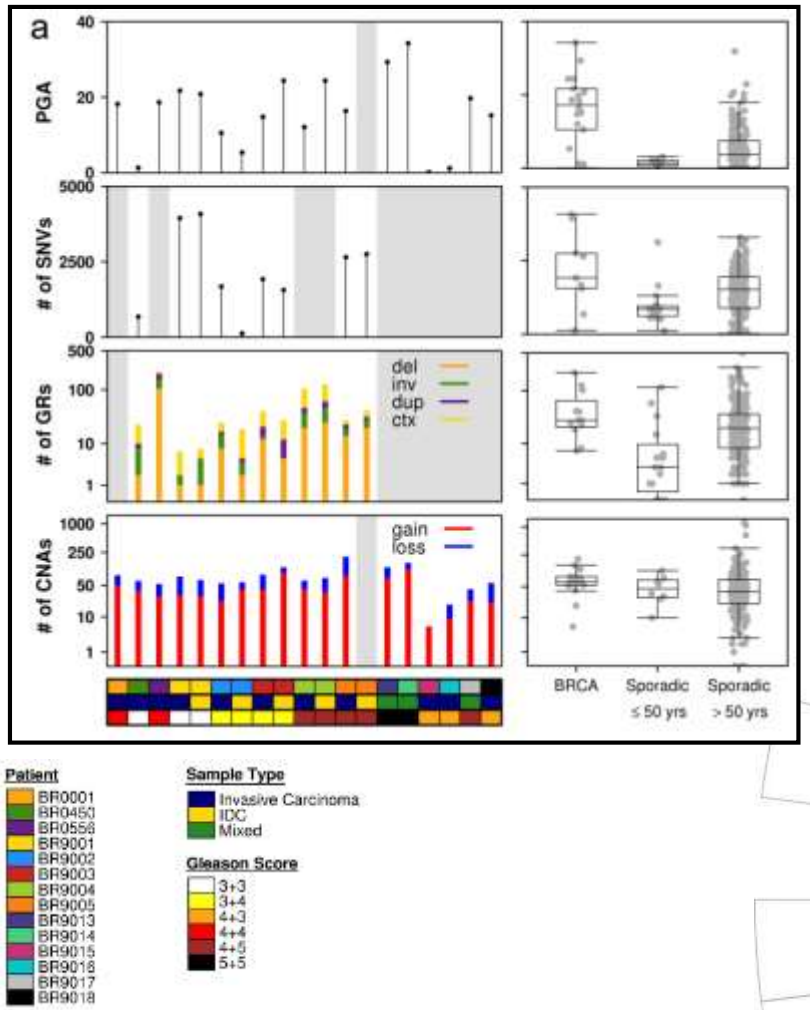


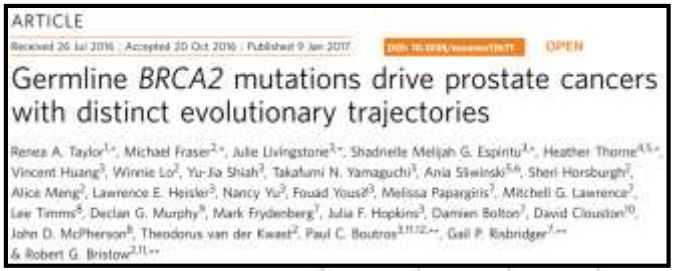


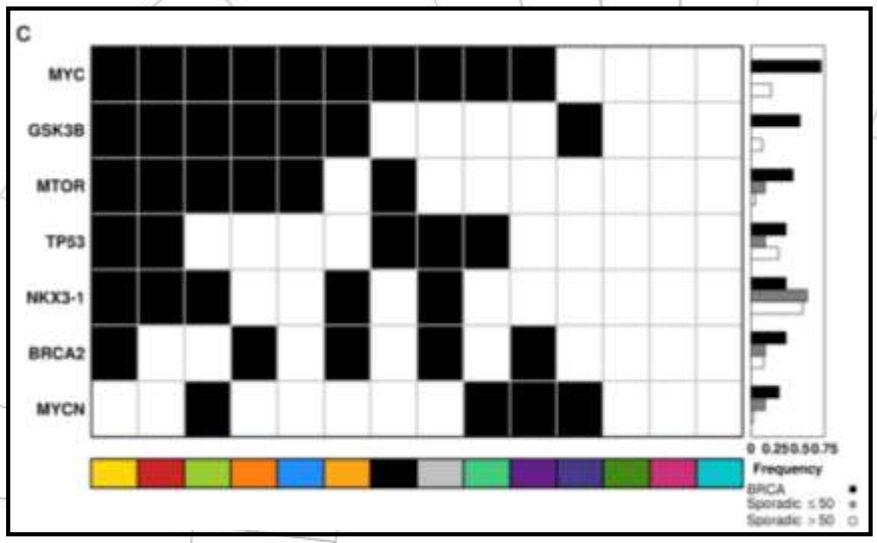
- Present in every cell in body
- Fixed (present throughout life)
- Passed on to offspring
- Obtained via sputum/blood
- E.g. BRCA mutation

- Only present in the tumour
- Variable (can change over time)
- Not passed on to offspring
- Obtained via biopsy
- E.g. PTEN loss

The germline matters!







Taylor et al, Nature Comms, 2017

Pritchard et al., NEJM 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

CONCLUSIONS

In our multicenter study, the incidence of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was 11.8%, which was significantly higher than the incidence among men with localized prostate cancer. The frequencies of germline mutations in DNA-repair genes among men with metastatic disease did not differ significantly according to age at diagnosis or family history of prostate cancer. (Funded by Stand Up To Cancer and others.)

Pritchard et al., NEJM 2016

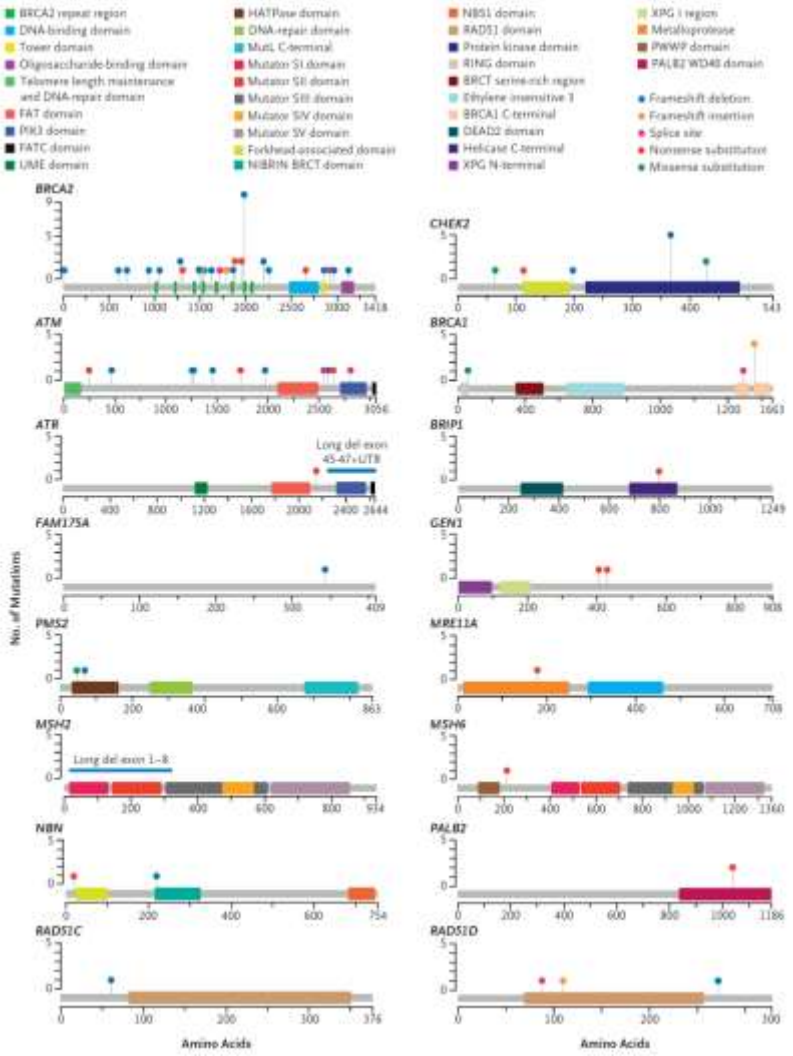
Table 2. Germline Mutations in Metastatic Cases as Compared with the General Population and Primary Cases.

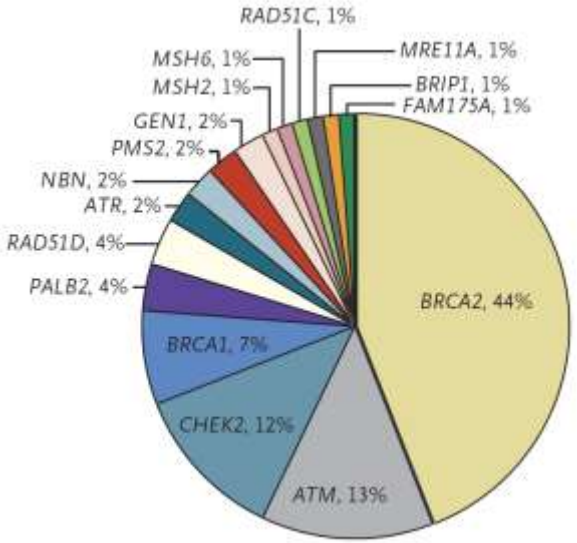
Gene	Metastatic Prostate Cancer (N=692)*	Exome Aggregation Consortium (N=53,105)†	TCGA Cohort with Primary Prostate Cancer (N=499)	Metastatic Prostate Cancer vs. Exome Aggregation Consortium		Metastatic Prostate Cancer vs. TCGA Cohort	
	No. of Mutations (% of Men)			Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
ATM	11 (1.59)	133 (0.25)	5 (1.00)	6.3 (3.2–11.3)	<0.001	1.6 (0.8–2.8)	0.12
ATR	2 (0.29)	43 (0.08)	0	3.6 (0.4–12.8)	0.11	—	—
BAP1‡	0	1	0	—	—	—	—
BARD1‡	0	38 (0.07)	1 (0.20)	—	—	—	—
BRCA1	6 (0.87)	104 (0.22)	3 (0.60)	3.9 (1.4–8.5)	0.005	1.4 (0.5–3.1)	0.32
BRCA2	37 (5.35)	153 (0.29)	1 (0.20)	18.6 (13.2–25.3)	<0.001	26.7 (18.9–36.4)	<0.001
BRIP1‡	1 (0.18)	100 (0.19)	1 (0.20)	0.9 (0.02–5.3)	1.0	0.9 (0.0–4.9)	1.0
CHEK2‡	10 (1.87)	314 (0.61)	2 (0.40)	3.1 (1.5–5.6)	0.002	4.7 (2.2–8.5)	<0.001
FAM175A‡	1 (0.18)	52 (0.10)	0	1.8 (0.05–10.1)	0.42	—	—
GEN1‡	2 (0.46)	42 (0.08)	0	5.8 (0.7–20.8)	0.048	—	—
MLH1	0	11 (0.02)	0	—	—	—	—
MRE11A	1 (0.14)	36 (0.07)	1 (0.20)	2.1 (0.1–11.8)	0.38	0.7 (0.0–4.0)	1.0
MSH2	1 (0.14)	23 (0.04)	1 (0.20)	3.3 (0.1–18.5)	0.26	0.7 (0.0–4.0)	1.0
MSH6	1 (0.14)	41 (0.08)	1 (0.20)	1.9 (0.05–10.4)	0.41	0.7 (0.0–4.0)	1.0
NBN	2 (0.29)	61 (0.11)	1 (0.20)	2.5 (0.3–9.1)	0.19	1.4 (0.2–5.2)	0.40
PALB2	3 (0.43)	65 (0.12)	2 (0.40)	3.5 (0.7–10.3)	0.05	1.1 (0.2–3.1)	0.76
PMS2	2 (0.29)	56 (0.11)	1 (0.20)	2.7 (0.3–9.8)	0.17	1.4 (0.2–5.2)	0.40
RAD51C	1 (0.14)	59 (0.11)	2 (0.40)	1.3 (0.03–7.2)	0.54	0.4 (0.0–2.0)	0.54
RAD51D	3 (0.43)	40 (0.08)	1 (0.20)	5.7 (1.2–16.7)	0.02	2.2 (0.4–6.3)	0.16
XRCC2	0	23 (0.04)	0	—	—	—	—

* The denominators for genes for which data were censored were 561 (*BAP1*, *BARD1*, *BRIP1*, and *FAM175A*), 437 (*GEN1*), and 534 (*CHEK2*).
† Data are for the persons in the Exome Aggregation Consortium, minus the patients included in the TCGA studies. The percent with a mutation was calculated on the basis of the total number of persons for whom sequence coverage was adequate for the given allele, which differed slightly from the total of 53,105 persons, depending on the specific mutation.
‡ Data for metastatic cases with inadequate sequencing for this gene were censored.

Pritchard et al.: Inherited DNA-repair gene mutations in prostate cancer;
N Engl J Med 375(5), 2016

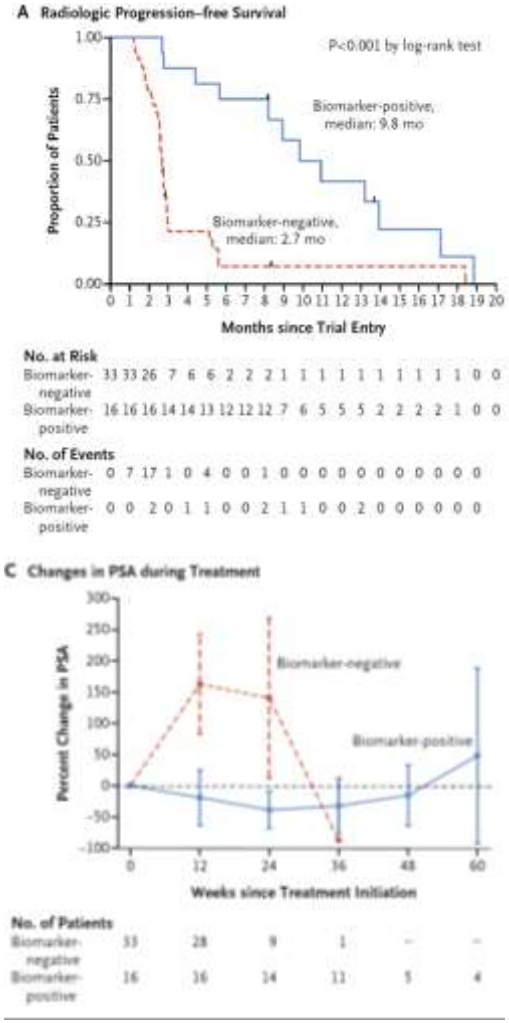
Pritchard et al., NEJM 2016





Pritchard et al.: Inherited DNA-repair gene mutations in prostate cancer; N Engl J Med 375(5), 2016

Mateo et al., NEJM 2015



Mateo et al.: DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer; N Engl J Med 375 (5), 2016

Mateo et al., NEJM 2015

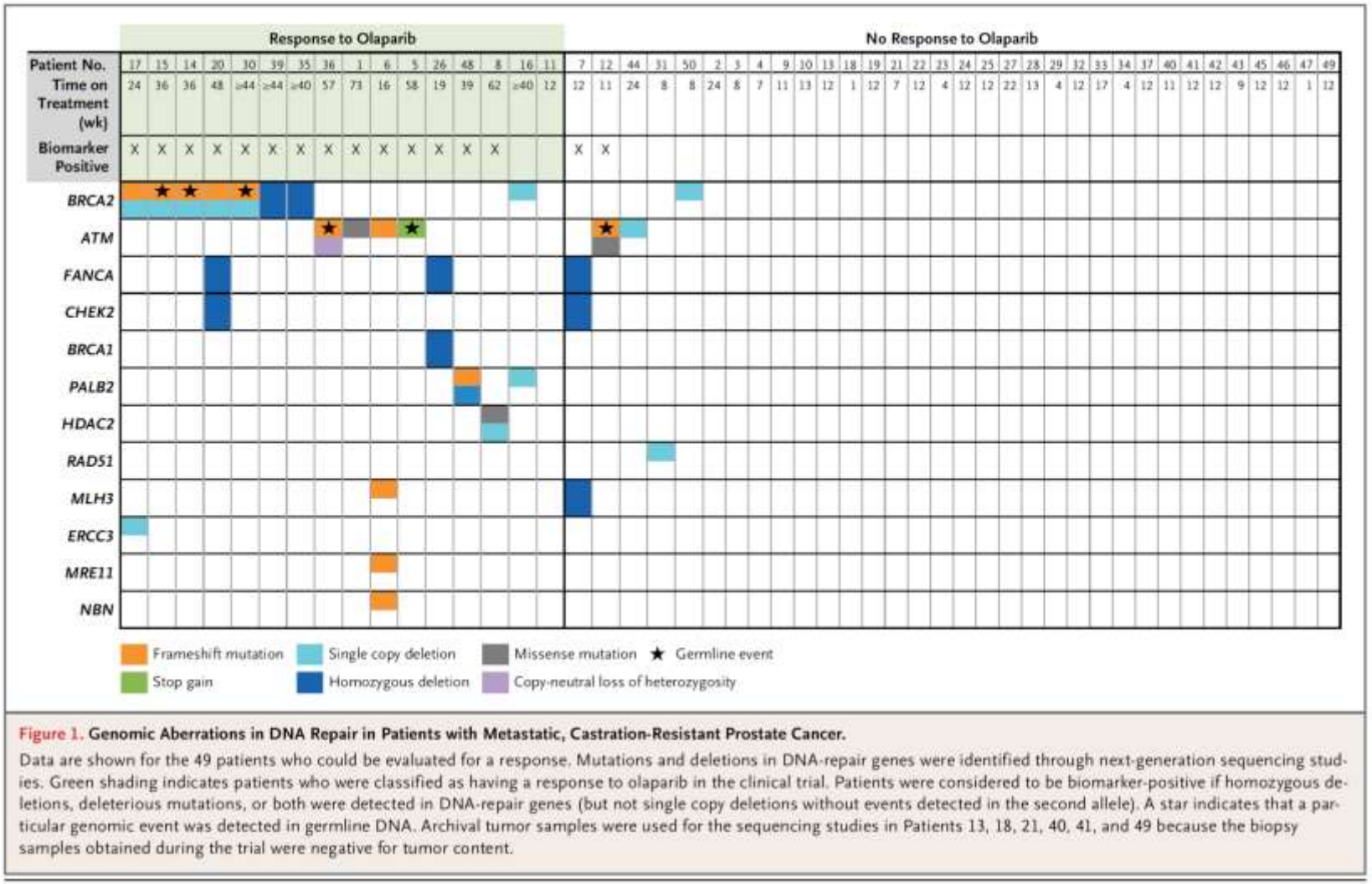
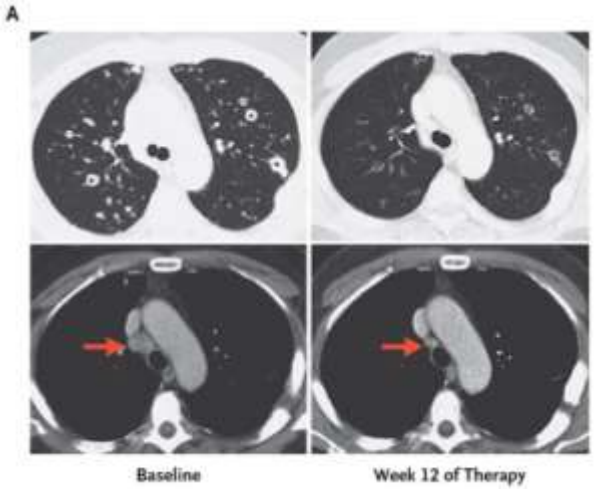


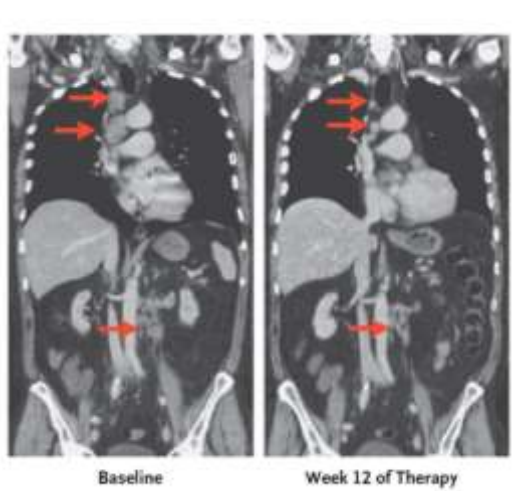
Figure 1. Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

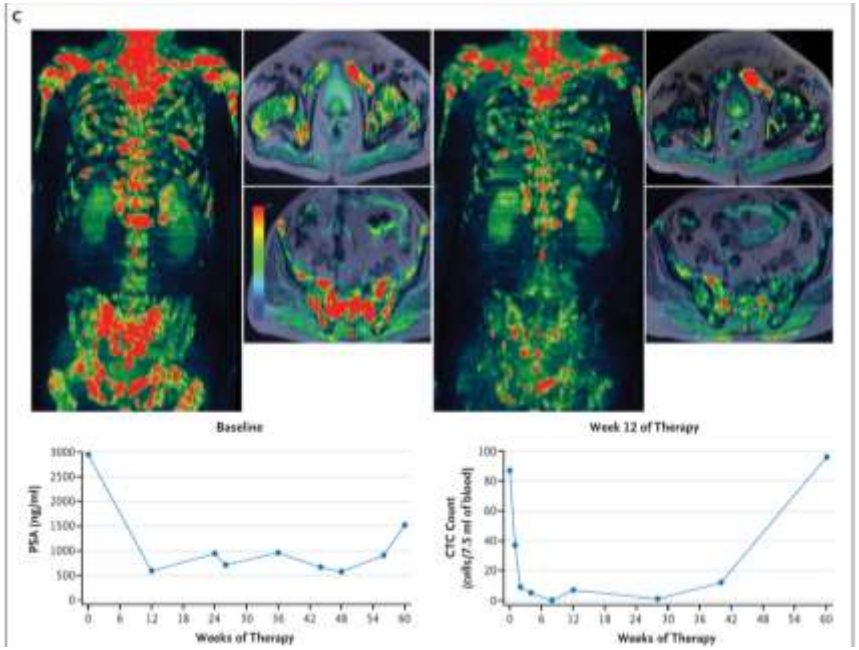
Data are shown for the 49 patients who could be evaluated for a response. Mutations and deletions in DNA-repair genes were identified through next-generation sequencing studies. Green shading indicates patients who were classified as having a response to olaparib in the clinical trial. Patients were considered to be biomarker-positive if homozygous deletions, deleterious mutations, or both were detected in DNA-repair genes (but not single copy deletions without events detected in the second allele). A star indicates that a particular genomic event was detected in germline DNA. Archival tumor samples were used for the sequencing studies in Patients 13, 18, 21, 40, 41, and 49 because the biopsy samples obtained during the trial were negative for tumor content.

Mateo et al.: DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer; N Engl J Med 375 (5), 2016

Mateo et al., NEJM 2015

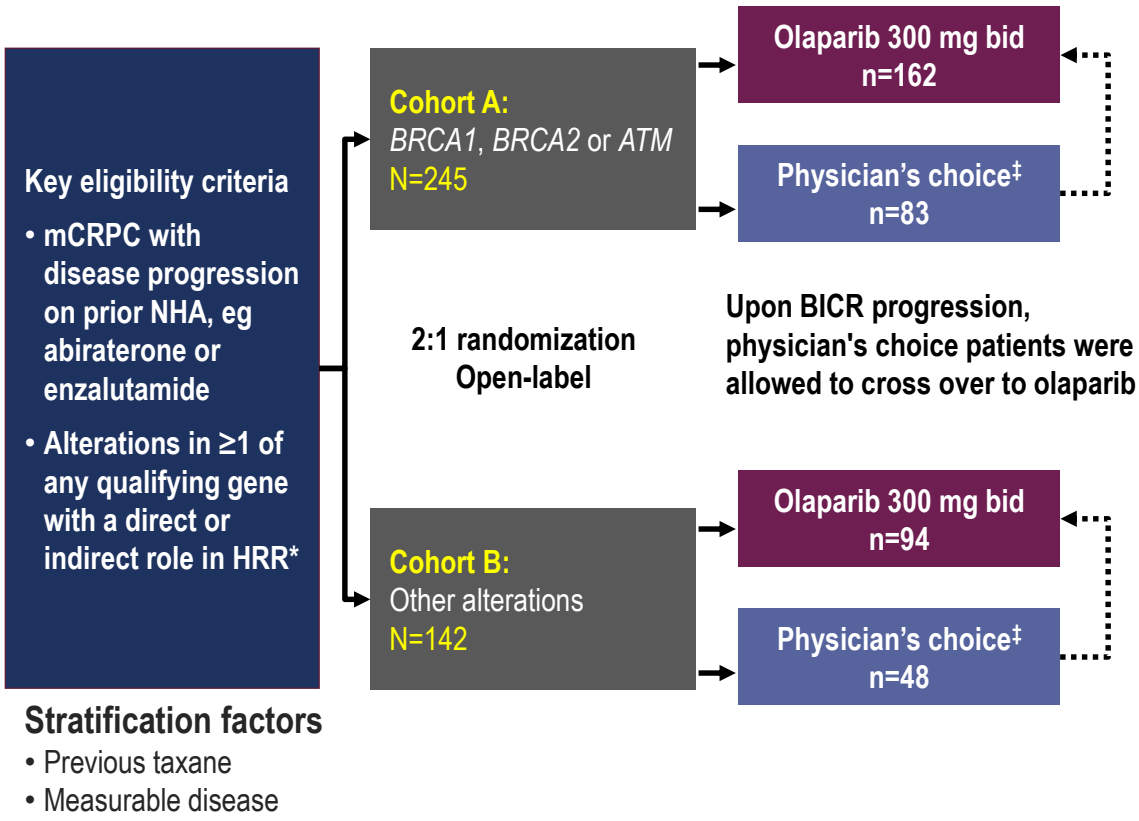






Mateo et al.: DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer; N Engl J Med 375 (5), 2016

PROfound STUDY DESIGN



Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints

- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

***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

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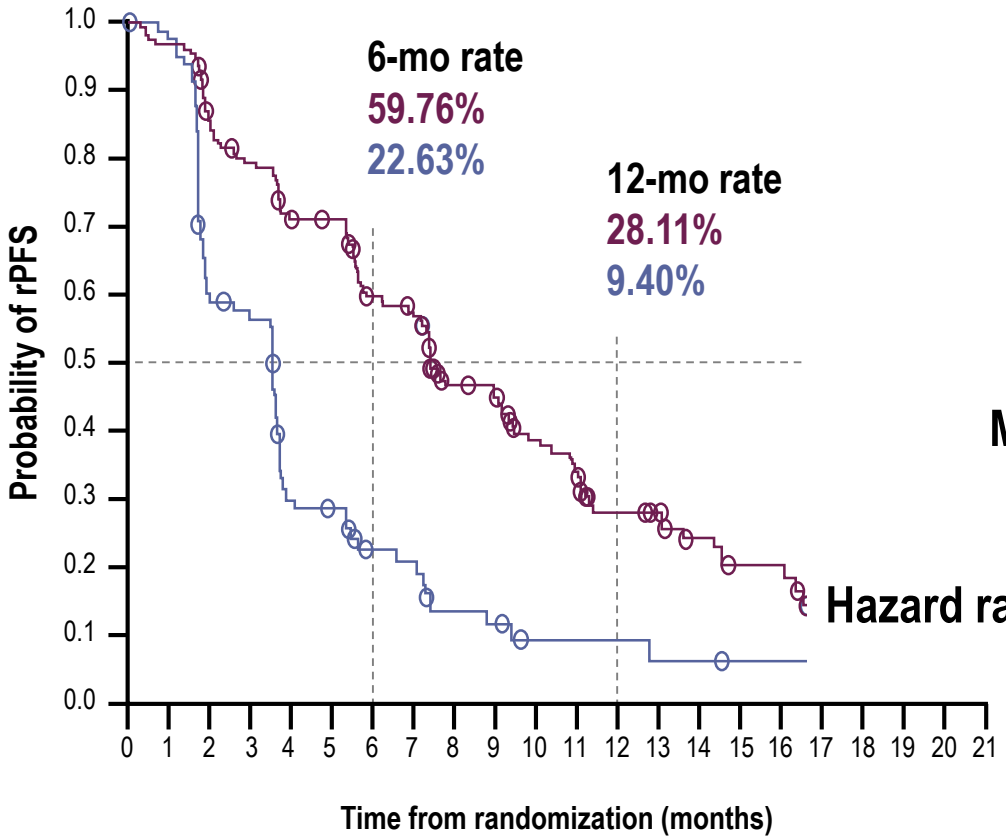
‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

PATIENT CHARACTERISTICS *

		Cohort A		Cohorts A+B †	
		Olaparib (N=162)	Physician's choice (N=83)	Olaparib (N=256)	Physician's choice (N=131)
Patients with alteration(s) in a single HRR gene, n (%)	*BRCA1* or *BRCA2*	88 (54.3)	52 (62.7)	89 (34.8)	52 (39.7)
	ATM	60 (37.0)	24 (28.9)	62 (24.2)	24 (18.3)
	Others	-	-	88 (34.4)	44 (33.6)
Patients with co-occurring alterations, n (%)		14 (8.6)	7 (8.4)	17 (6.6)	11 (8.4)
Median (range) age, years		**68 (47–86)**	**67 (49–86)**	**69 (47–91)**	**69 (49–87)**
Metastatic disease at initial diagnosis, n (%)		**38 (23.5)**	**19 (22.9)**	**66 (25.8)**	**25 (19.1)**
Site of metastases, n (%)	Bone only	57 (35.2)	23 (27.7)	86 (33.6)	38 (29.0)
	Visceral (eg lung/ liver)	46 (28.4)	32 (38.6)	68 (26.6)	44 (33.6)
	Other	49 (30.2)	23 (27.7)	88 (34.4)	41 (31.3)
Measurable disease at baseline, n (%)		95 (58.6)	46 (55.4)	149 (58.2)	72 (55.0)
Median (Q1, Q3) baseline PSA, µg/L		**62.2 (21.9, 280.4)**	**112.9 (34.3, 317.1)**	**68.2 (24.1, 294.4)**	**106.5 (37.2, 326.6)**
ECOG performance status, n (%)	0–1	151 (93.2)	80 (96.4)	243 (94.9)	126 (96.2)
	2	11 (6.8)	3 (3.6)	13 (5.1)	4 (3.1)
Prior new hormonal agent	Enzalutamide only	68 (42.0)	40 (48.2)	105 (41.0)	54 (41.2)
	Abiraterone only	62 (38.3)	29 (34.9)	100 (39.1)	54 (41.2)
	Abiraterone + enzalutamide	**32 (19.8)**	**14 (16.9)**	**51 (19.9)**	**23 (17.6)**
Previous taxane use, n (%)	**Yes**	**106 (65.4) ‡**	**52 (62.7)**	**170 (66.4)**	**84 (64.1)**
	Docetaxel only	74 (45.7)	32 (38.6)	115 (44.9)	58 (44.3)

Primary endpoint

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

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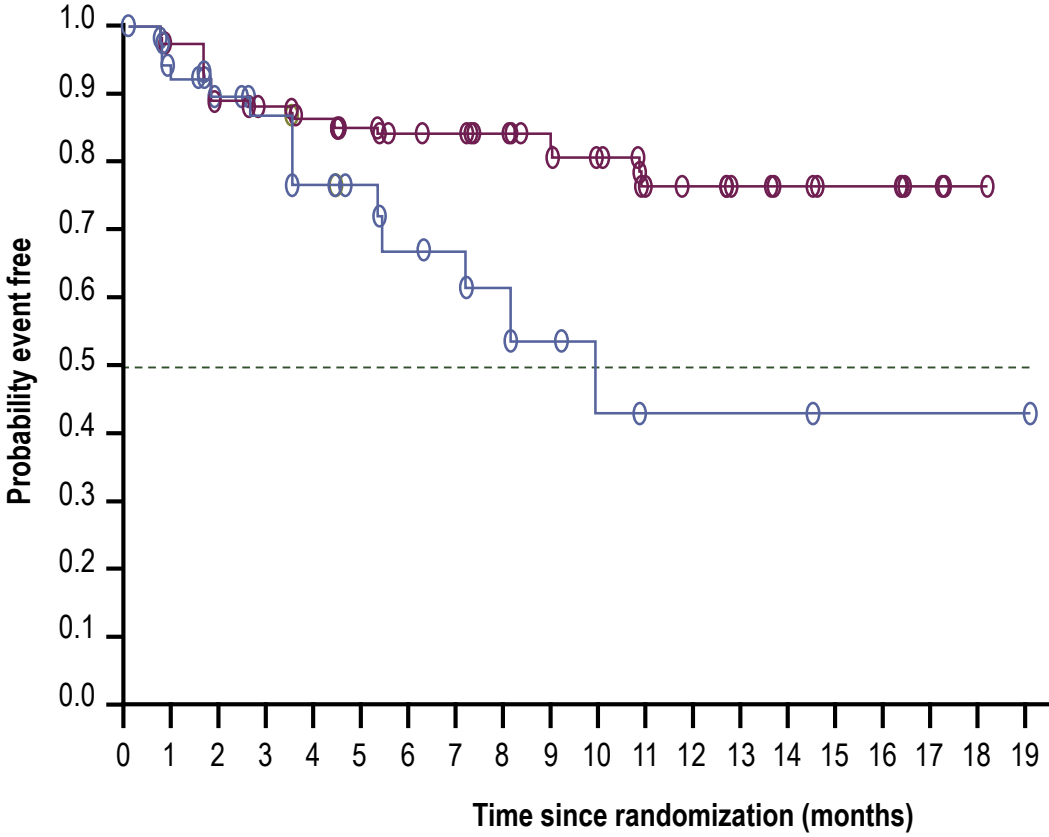
Key secondary endpoint

TIME TO PAIN PROGRESSION* IN COHORT A



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	21 (13.0)	14 (16.9)
Median TTPP (months)	NR	9.92
Hazard ratio (95% CI)	0.44 (0.22, 0.91) *P*=0.0192	

No. at risk																					
Olaparib	162	109	94	91	82	77	73	69	58	50	41	31	26	21	19	12	12	6	4	0	0	0
Physician's choice	83	46	35	29	22	17	13	12	8	6	4	3	3	3	3	1	1	1	1	1	0	0

*Based on the Brief Pain Inventory-Short Form (BPI –SF) worst pain [Item 3] and opioid use

For the overall population (Cohorts A+B), median time to pain progression was NR in either arm (HR 0.64 [95% CI 0.35, 1.21])

NR, Not reached

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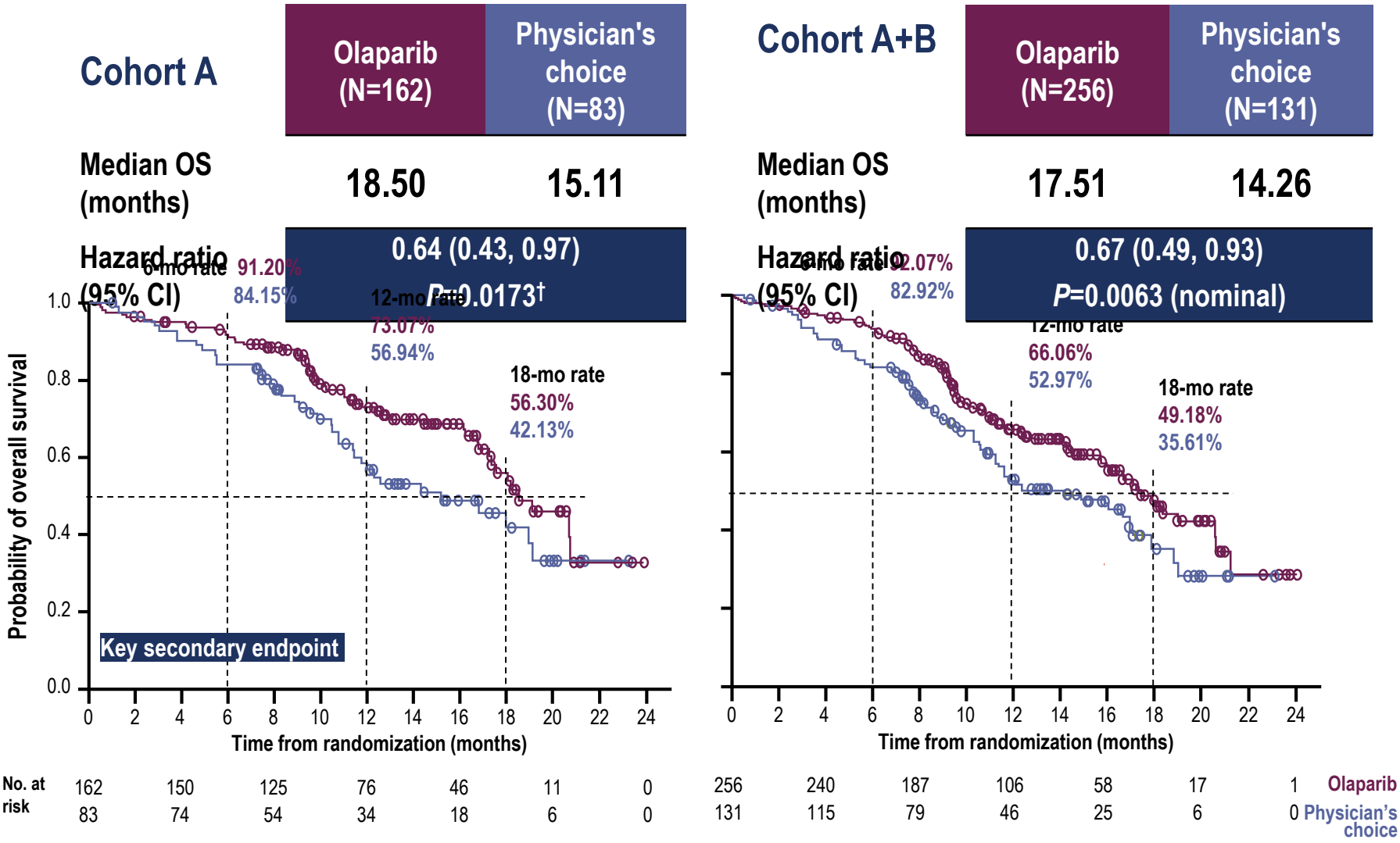
INTERIM* OVERALL SURVIVAL



Of the physician's choice arm patients who progressed, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib

*38% maturity in Cohort A; 41% maturity in Cohort A+B; final analysis planned after ~146 deaths in Cohort A (60% maturity)

†Alpha spend at interim was 0.01; statistical significance not reached

CONCLUSIONS

- In patients with mCRPC with disease progression on prior NHA, olaparib provided a statistically significant and clinically meaningful improvement in BICR rPFS compared with physician's choice of enzalutamide or abiraterone + prednisone in:
  - Patients with alterations in *BRCA1, BRCA2* and/ or *ATM* (primary endpoint)
  - The overall population with alterations in any qualifying gene with a direct or indirect role in homologous recombination repair
- Olaparib improved multiple clinical and patient-reported endpoints (rPFS, ORR, time to pain progression)
  - Despite >80% cross-over, at interim analysis olaparib had a favorable trend in OS for patients with alterations in *BRCA1*, *BRCA2* and/ or *ATM* (HR=0.64), and in the overall population (HR=0.67)
- Olaparib was well tolerated, with a safety profile generally consistent with that seen in other cancers
- **PROfound is the first positive biomarker-selected Phase III study evaluating a molecularly-targeted therapy in men with mCRPC – and highlights the importance of genomic testing in this population**

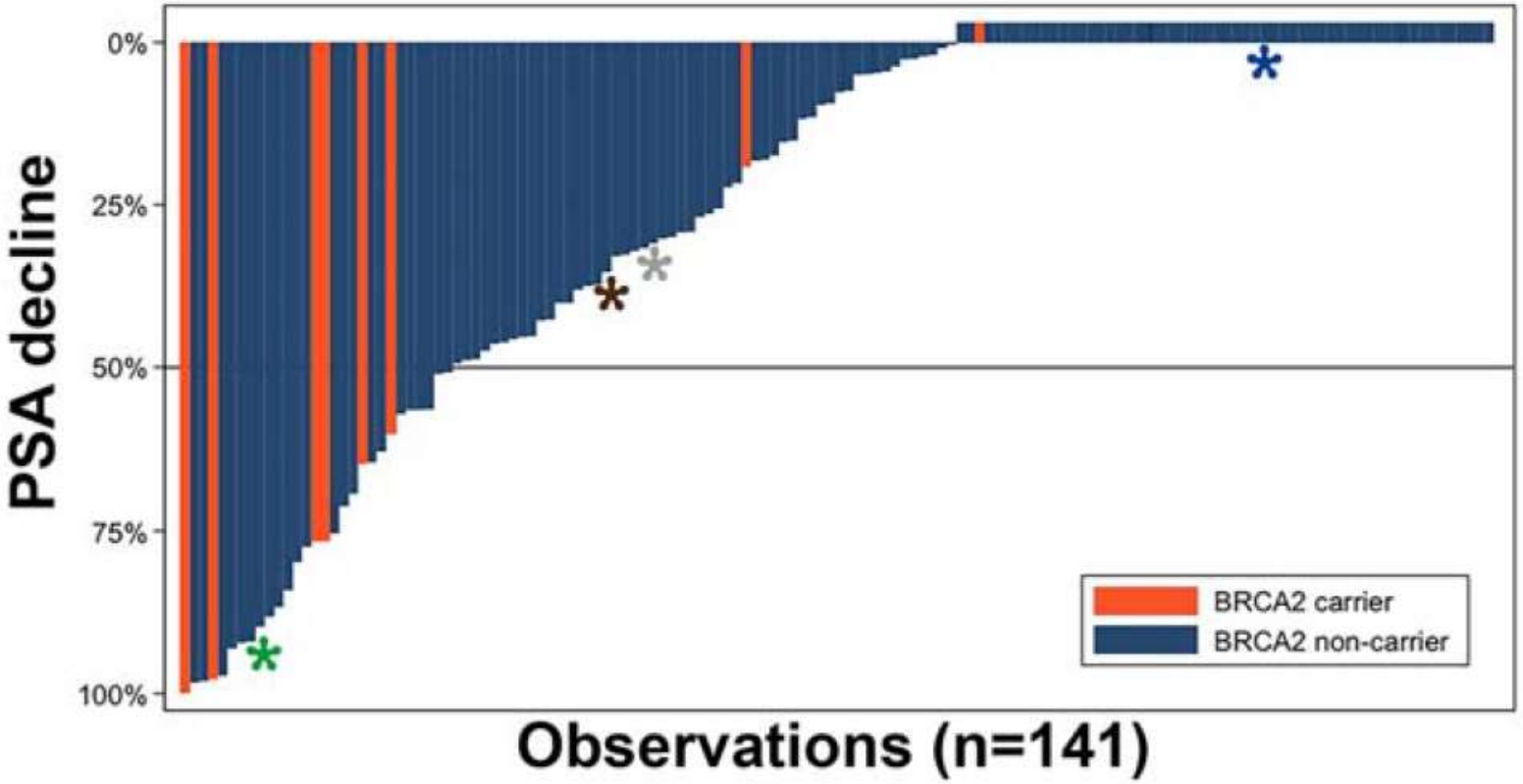
Cancer

Original Article

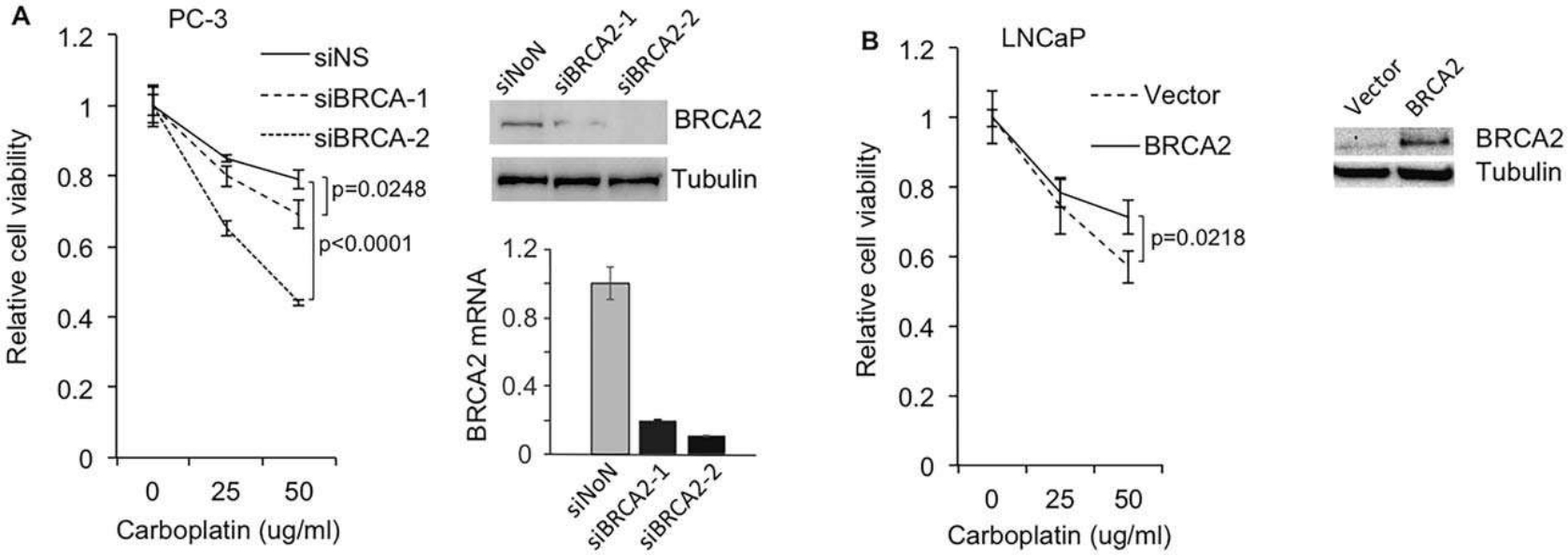
The Association Between Germline *BRCA2* Variants and Sensitivity to Platinum-Based Chemotherapy Among Men With Metastatic Prostate Cancer

Mark M. Pomerantz, MD[1]; Sandor Spisák, PhD[1]; Li Jia, PhD[2]; Angel M. Cronin, PhD[3]; Istvan Csabai, PhD[4]; Elisa Ledet, PhD[5]; A. Oliver Sartor, MD[5]; Irene Rainville, PhD[3]; Edward P. O'Connor, BA[1]; Zachary T. Herbert, PhD[1]; Zoltan Szállási, PhD[6]; William K. Oh, MD[7]; Philip W. Kantoff, MD[8]; Judy E. Garber, MD[3]; Deborah Schrag, MD[3]; Adam S. Kibel, MD[2]; and Matthew L. Freedman, MD[1]

Pomerantz et al., 2017



Pomerantz et al., 2017



Testing of Relevant Genes (Color)

Cancer	Breast	Ovarian	Uterine	Colorectal	Melanoma	Pancreatic	Stomach	Prostate*
BRCA1	●	●				●		●
BRCA2	●	●			●	●		●
MLH1		●	●	●		●	●	
MSH2		●	●	●		●	●	
MSH6		●	●	●			●	
PMS2***		●	●	●				
EPCAM**		●	●	●		●	●	
APC				●		●	●	
MUTYH				●				
MITF**					●			
BAP1					●			
CDKN2A					●	●		
CDK4**					●			
TP53	●	●	●	●	●	●	●	●
PTEN	●		●	●	●			
STK11	●	●	●	●		●	●	
CDH1	●						●	
BMPR1A				●		●	●	
SMAD4				●		●	●	
GREM1**				●				
POLD1**				●				
POLE**				●				
PALB2	●	●				●		
CHEK2	●			●				●
ATM	●					●		●
NBN	●							●
BARD1	●	●						
BRIP1	●	●						
RAD51C		●						
RAD51D		●						

Genetic Non-Discrimination Act

First Session, Forty-second Parliament,
64-65-66 Elizabeth II, 2015-2016-2017

STATUTES OF CANADA 2017

CHAPTER 3

An Act to prohibit and prevent genetic discrimination

ASSENTED TO

MAY 4, 2017

BILL S-201

CHAPTER 3

An Act to prohibit and prevent genetic discrimination

[*Assented to 4th May, 2017*]

Her Majesty, by and with the advice and consent of the Senate and House of Commons of Canada, enacts as follows:

Short Title

Short title

1 This Act may be cited as the *Genetic Non-Discrimination Act*.

SUMMARY

This enactment prohibits any person from requiring an individual to undergo a genetic test or disclose the results of a genetic test as a condition of providing goods or services to, entering into or continuing a contract or agreement with, or offering specific conditions in a contract or agreement with, the individual. Exceptions are provided for health care practitioners and researchers. The enactment provides individuals with other protections related to genetic testing and test results.

The enactment amends the *Canada Labour Code* to protect employees from being required to undergo or to disclose the results of a genetic test, and provides employees with other protections related to genetic testing and test results. It also amends the *Canadian Human Rights Act* to prohibit discrimination on the ground of genetic characteristics.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk group	Clinical/pathologic features			Imaging[h,i]	Germline testing	Molecular and biomarker analysis of tumor[l]	Initial therapy
Very low[f]	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Not indicated	See PROS-4
Low[f]	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-5
Intermediate[f]	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive[g]	• Bone imaging[j]: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-6
		Unfavorable intermediate	• 2 or 3 IRFs and/or • Grade Group 3 and/or • ≥50% biopsy cores positive[g]	• Bone imaging[j]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Not routinely recommended	See PROS-7
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8

UROLOGY GENETICS RISK ASSESSMENT PROGRAM (GRASP)AT UHN

- Dedicated clinic to genetic carriers
- Color/Invitae test if criteria not fulfilled
- Cohorts
  - All high grade cancers and their family if relevant
  - All active surveillance
  - All metastatics
  - All young patients with UC

GRASP CLINIC

- Patients will be tested for free (if they cant pay)
- If positive
  - Take into account for their case
  - Invite relatives
- Bespoke follow up/monitoring plan
  - Annual
    - Skin exam
    - Pancreas Ultrasound
    - PSA/Prostate testing

CONCLUSION

- Genes your born with matter
- Although uncommon—major impact on Prostate cancer death
- New clinic will aim to streamline care and be a living laboratory for these patients and their families