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Implications of BRCA in localized prostate cancer: 4 key questions (and answers)

Todd M. Morgan

University of Michigan



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Disclosures

- Myriad Genetics: Research funding, advisory board
- MDxHealth: Research funding
- GenomeDx: Research funding



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When you need Twitter to help crowdsource patient care...



Scott Delacroix M.D.

@UroCancer

57 gleason 6 one core PSA of 3.6.
Father, brother With hx of prostate
cancer one stage 4. Patient and
family with BRCA2 pos. AS or RP?



Scott Delacroix M.D.

@UroCancer

Replying to @daviesbj @wandering_gu

MRI normal pre-biopsy

10:25am · 1 Jun 2017 · Twitter for iPhone



daviesbj @daviesbj

Replying to @UroCancer

Send to @wandering_gu

Get MRI

Personally I'm fine with AS

↩️ ↗️ ❤️ ...



Todd M. Morgan, MD @wand... Jun 1

Replying to @UroCancer @daviesbj

High risk of progression

(ncbi.nlm.nih.gov/pubmed/28067867

) but would still offer AS. Consider

genomic testing. cc: @mfphotograph

@declangmurphy

↩️ ↗️ ❤️ ...



Mike Fraser @mfphotograph 6d

Replying to @wandering_gu @UroCancer...

Agree HR of progression. Genomics
to ID adverse molecular prognostic
events as per

nature.com/articles/ncomm... Our

GU Oncs would rec RP for sure

↩️ ↗️ ❤️ ...



Todd M. Morgan, MD @wand... 6d

Replying to @mfphotograph @UroCancer...

"Safe" rec is RP. Truth is just that we
don't know yet and actual odds of
metastatic progression in v. low risk
patient like this still low



Brian Chapin @ChapinMD 6d

Replying to @mfphotograph @wandering...

I agree likely worse with Met dz, But
if stage and Grade matched is it any
worse than reg Gl6.

↩️ ↗️ ❤️ ...



Chris Barlieri @Chris_Barlier1 6d

Replying to @ChapinMD @wandering_gu...

I'd bet that 11/12 cores in a BRCA2
pt is not "reg" Gl 6. That's a lot of
cancer cells already predisposed to
more genomic hits.

↩️ ↗️ ❤️ ...



Brian Chapin @ChapinMD 6d

Replying to @Chris_Barlier1 @wandering...

How about 1 core?

↩️ ↗️ ❤️ ...



Chris Barlieri @Chris_Barlier1 6d

Replying to @ChapinMD @wandering_gu...

No idea, we need data on guys like
that. But I'd sleep pretty well with
the RP you described. IMO, you
kept him out of trouble.

↩️ ↗️ ❤️ ...



Mike Fraser @mfphotograph 6d

Replying to @wandering_gu @ChapinMD...

I'm biased (and not a clinician...) but
likely, given YUGE increase in PCSM
in BRCA2 carriers
(medscape.com/viewarticle/56...).
More study needed.

↩️ ↗️ ❤️ ...



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Know:BRCA

BRCA STANDS FOR BREAST CANCER SUSCEPTIBILITY GENE.
THERE ARE TWO BRCA GENES: BRCA1 AND BRCA2.

BRCA



BREAST

CANCER

Mutations (changes) in BRCA genes increase risk of breast, ovarian and other cancers.

Know:BRCA

[CDC.GOV/CANCER/BREAST/YOUNG_WOMEN](https://www.cdc.gov/cancer/breast/young_women)
@CDC_CANCER • 1-800-CDC-INFO



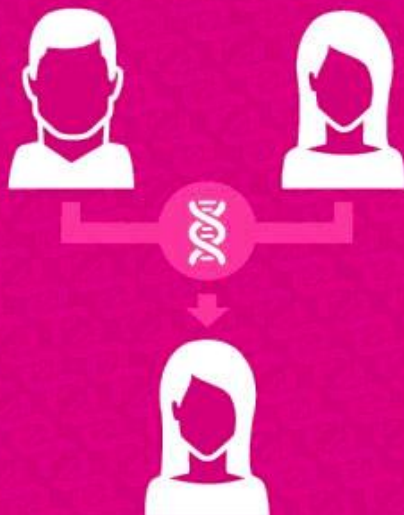


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Know:Your Risk

IF ONE OF YOUR PARENTS HAS A BRCA GENE MUTATION (CHANGE),
THERE'S A 50% CHANCE YOU HAVE IT TOO.



Talk to your doctor about your own risk for having a BRCA mutation.

Know:BRCA

CDC.GOV/CANCER/BREAST/YOUNG_WOMEN

@CDC_CANCER • 1-800-CDC-INFO





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Know:BRCA

@CDC_CANCER • 1-800-CDC-INFO





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Questions from a Urologist's perspective

- Should we screen for PCa differently in healthy men with a BRCA mutation?
- Which patients with localized PCa should undergo genetic testing?
- Should we treat patients with low-risk PCa differently if they have a BRCA mutation?
- Should we treat patients with high-risk localized PCa differently if they have a BRCA mutation?

DNA-repair defects in advanced PCa

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

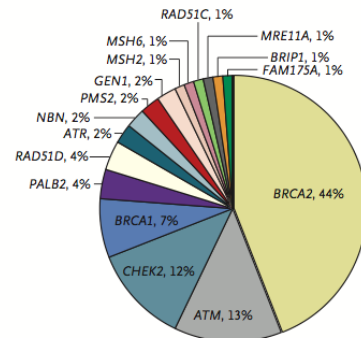


Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

- 11.8% of men with metastatic PCa had germline mutations in DNA repair genes



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NCCN Early Detection Guidelines



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2017 Prostate Cancer Early Detection

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

BASELINE EVALUATION

- History and physical (H&P) including:
 - ▶ Family history
 - ▶ Medications
 - ▶ History of prostate disease and screening, including prior PSA and/or isoforms, exams, and biopsies
 - ▶ Race^a
 - ▶ Family or personal history of BRCA1/2 mutations^b

RISK ASSESSMENT

Start risk and benefit discussion about offering prostate screening:

- Baseline PSA^c
- Strongly consider baseline digital rectal examination (DRE)^c

Age 45-75 y

Age >75 y, in select patients (category 2B)^d

EARLY DETECTION EVALUATION

PSA <1 ng/mL,
DRE normal (if done)

PSA 1-3 ng/mL,^e
DRE normal (if done)

PSA >3 ng/mL^e
or very suspicious DRE

Repeat testing at
2-4 year intervals^f

Repeat testing at
1-2 year intervals

[See Indications
for Biopsy \(PROSD-3\)](#)

PSA <4 ng/mL, DRE
normal (if done), and
no other indications
for biopsy

Repeat testing in
select patients at
1-4 year intervals

PSA ≥4 ng/mL or very
suspicious DRE

[See Indications
for Biopsy \(PROSD-3\)](#)

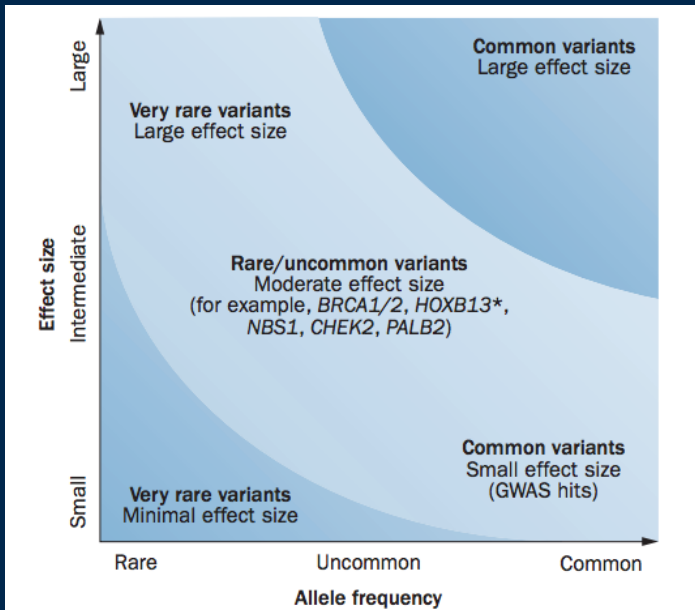
^aAfrican-American men have a higher incidence of prostate cancer, increased prostate



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Heritable PCa risk



- Rare genetic variants confer high risk
 - Small % of familial risk
- Genetic susceptibility more commonly due to variants with smaller effect size



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PCa risk estimates by mutation

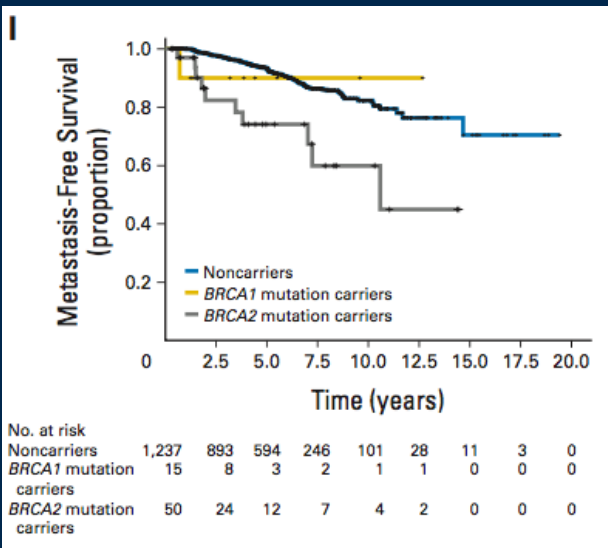
Gene	Risk for PCA	Risk for aggressive PCA features	Risk for early-onset PCA (age at diagnosis <65)	Risk for PCSM
BRCA1	1.07–3.81	—	1.82	5.16
BRCA2	3.18–8.6	3.18–4.38	7.33	2.4–5.48
Mismatch repair genes	1.99–3.67	—	2.48	—
HOXB13	2.8–8.47	—	2.7–10.11	—



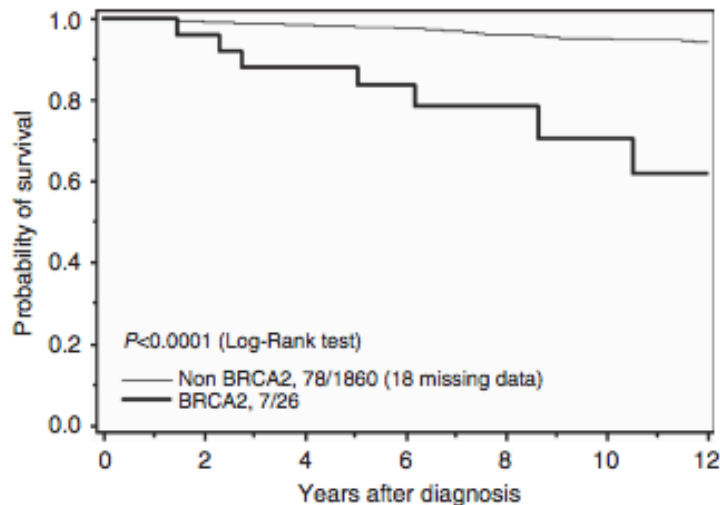
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BRCA2 and PCa aggressiveness



73% vs 93% 5-year MFS in M0 patients



Adjusted HR 3.48 for PCSM (HR 4.38 in high grade subset)



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Questions from a Urologist's perspective

- **Should we screen for PCa differently in healthy men with a BRCA mutation?**
- Which patients with localized PCa should undergo genetic testing?
- Should we treat patients with low-risk PCa differently if they have a BRCA mutation?
- Should we treat patients with high-risk localized PCa differently if they have a BRCA mutation?



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Familial risk factors for PCa

Risk Group	RR for prostate cancer (95% CI)
Brother(s) with prostate cancer diagnosed at any age	3.14 (2.37–4.15)
Father with prostate cancer diagnosed at any age	2.35 (2.02–2.72)
One affected FDR diagnosed at any age	2.48 (2.25–2.74)
Affected FDRs diagnosed <65 y	2.87 (2.21–3.74)
Affected FDRs diagnosed ≥65 y	1.92 (1.49–2.47)
SDRs diagnosed at any age	2.52 (0.99–6.46)
Two or more affected FDRs diagnosed at any age	4.39 (2.61–7.39)



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Early detection in high risk patients: PROFILE study

The
Oncologist[®]

Genitourinary Cancer

The PROFILE Feasibility Study: Targeted Screening of Men With a Family History of Prostate Cancer

ELENA CASTRO,^{a,b} CHRISTOS MIKROPoulos,^{a,b} ELIZABETH K. BANCROFT,^{a,b} TOKHIR DADAEV,^a CHEE GOH,^{a,b} NATALIE TAYLOR,^{a,b} EDWARD SAUNDERS,^a NIGEL BORLEY,^a DIANA KEATING,^a ELIZABETH C. PAGE,^a SIBEL SAYA,^a STEPHEN HAZELL,^a NAOMI LUVIN,^a NANOITA DESOUZA,^a DAVID NEAL,^{a,c} FREDDIE C. HAMDY,^a PARDEEP KUMAR,^a ANTONIS C. ANTONIOU,^a ZSOFIA KOTE-JARAI,^a THE PROFILE STUDY STEERING COMMITTEE, ROSALIND A. EELES^{a,b}

Men between 40–69 years old with family history of PCa:

1 relative: FDR diagnosed at age <70, or
2 relatives: FDR or SDR, at least 1 diagnosed at age <70, or
≥3 relatives (FDR or SDR) diagnosed at any age

Informed Consent

Family History Questionnaire
Medical History Questionnaire
Psychological Questionnaire
Blood and urine samples

DIRECT BIOPSY arm:

PSA determination
DW-MRI
SNPs

PSA SCREENING arm:

(Biopsy triggered by PSA
age-dependent thresholds)
PSA determination
SNPs

40–49 yr: PSA ≥1 ng/mL
50–69 yr: PSA ≥2 ng/mL

PROSTATE BIOPSY

10 core biopsy + 2 cores for research

- Prostate biopsies irrespective of PSA in feasibility study (n=100)
- 25% with PCa detected (**52% with PSA <3 ng/ml**)
- PROFILE main study ongoing
- Evaluating PCa screening in men with fam hx, association with SNPs



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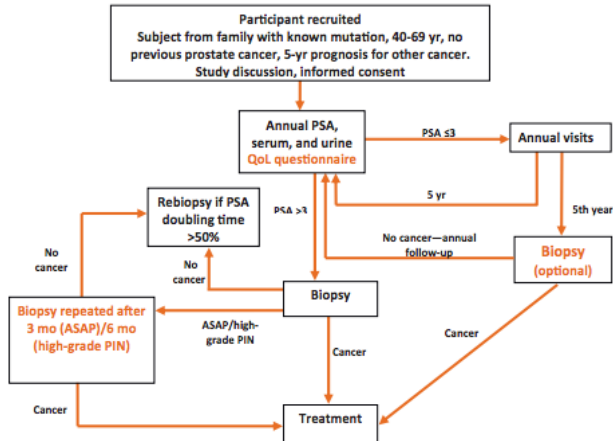
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Early detection in high risk patients: IMPACT study

Platinum Priority – Prostate Cancer

Editorial by Ola Bratt on pp. 500–501 of this issue

Targeted Prostate Cancer Screening in *BRCA1* and *BRCA2* Mutation Carriers: Results from the Initial Screening Round of the IMPACT Study



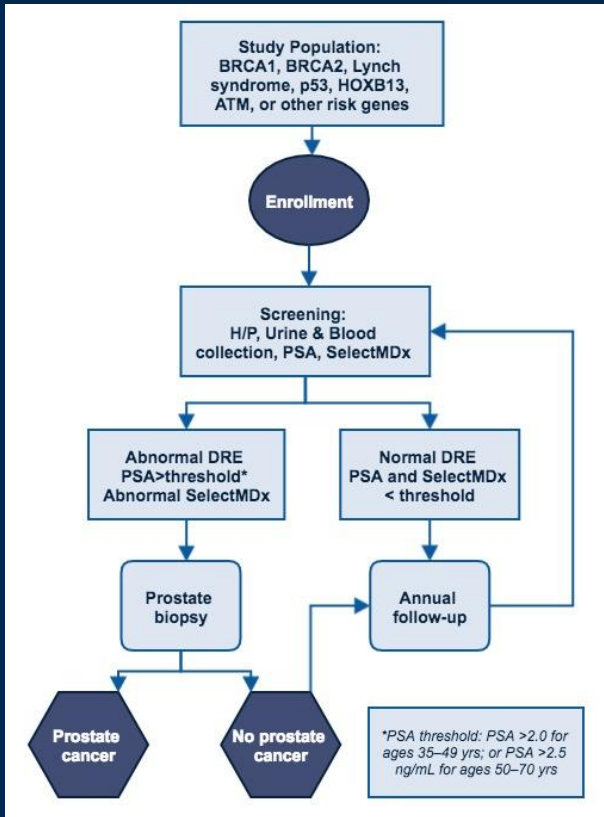
- Men recruited from families with a known BRCA mutation
- Biopsies for PSA > 3 ng/ml
- PCa detection rate:
 - BRCA1 carriers 2.3% vs controls 1.9%
 - BRCA2 carriers 3.3% vs controls 1.6%
 - Intermediate/high-risk in 2.4% BRCA2 carriers vs 0.71% of controls
- PPV of biopsy using a PSA threshold of 3.0 ng/ml:
 - 38% BRCA1 carriers vs 23.3% in controls
 - 48% BRCA2 carriers vs 33% in controls



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UMich Prostate Cancer Risk Clinic



- Eligibility:

- Age 35 - 70 years
- Known PCa-related mutation carrier: *BRCA* 1/2, Lynch syndrome, p53, HOXB13, ATM
- Also: PALB2, CHEK2, RAD51D, ATR, NBN, GEN1, RAD51C, MRE11A, BRIP1, FAM175A

- Clinical care:

- Annual screening with PSA, DRE, SelectMDx
- Survey data: lifestyle, medications, dietary supplements
- Discussion of risk, lifestyle interventions
- Biopsy based on abnormal DRE, SelectMDx, or PSA (**>2 ng/ml for patients <50 years, >2.5 ng/ml for patients 50-70 years**)



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UMich Prostate Cancer Risk Clinic



MICHIGAN MEDICINE
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FOR MORE INFORMATION, CONTACT:

Chaitra Madiyal
Clinical Coordinator
734-232-4863
cmadiyal@umich.edu

PROSTATE CANCER RISK CLINIC

at the University of Michigan



WHAT IS THE PROSTATE CANCER RISK CLINIC?

The Prostate Cancer Risk Clinic at the University of Michigan is intended for men with genetic mutations known or suspected to increase the risk of prostate cancer.

While the increased risk of breast cancer in women with BRCA mutations is more widely known, men with BRCA mutations or other cancer-related mutations are at greater risk of developing prostate cancer. The PCRC is intended for men with these mutations in order to initiate an individualized prostate cancer screening plan and follow-up care.



HOW DO I PARTICIPATE?

Call 734-936-7030 to schedule an appointment with the Prostate Cancer Risk Clinic.



WHAT TO EXPECT?

- Consent to participate in Prostate Cancer Risk Clinic and complete a questionnaire.
- Patient history and physical exam.
- Review of family history, genetic risk, and other lifestyle factors that may contribute to prostate cancer risk.
- Blood and urine testing for individualized assessment of prostate cancer risk.
- Presentation of individualized plan of follow-up care based on test results and discussion of prostate biopsy if indicated.
- Referral to University of Michigan Urologic Oncology clinic for prostate cancer management, if necessary.

WHO CAN PARTICIPATE?

Men who have undergone genetic testing revealing any of the following cancer-related mutations or syndromes:

- BRCA1 or BRCA2
- Lynch Syndrome
- Li-Fraumeni syndrome (p53 gene)
- ATM, PALB2, CHEK2, RAD51D, ATR, NBN, GEN1, RAD51C, MRE11A, BRIP1, FAM175A

This clinic is primarily for men age 35-70 without a prior diagnosis of prostate cancer.

OUR ADDRESS

Urology Clinic at Taubman Center
1500 E. Medical Center Drive Floor 2,
Reception C
Ann Arbor, MI, 48109
734-936-7030

Appointments can be made by
physician or self-referral.



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Questions from a Urologist's perspective

- Should we screen for PCa differently in healthy men with a BRCA mutation?
- **Which patients with localized PCa should undergo genetic testing?**
- Should we treat patients with low-risk PCa differently if they have a BRCA mutation?
- Should we treat patients with high-risk localized PCa differently if they have a BRCA mutation?




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NCCN breast and ovarian risk assessment guidelines

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National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2017
BRCA-Related Breast and/or Ovarian Cancer Syndrome

[NCCN Guidelines Index](#)
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- Personal history of prostate cancer (Gleason score ≥ 7) at any age with ≥ 1 close blood relative^d with ovarian carcinoma at any age or breast cancer ≤ 50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥ 7) at any age
- Personal history of pancreatic cancer at any age with ≥ 1 close blood relative^d with ovarian carcinoma at any age or breast cancer ≤ 50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥ 7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
 - ▶ First- or second-degree blood^d relative meeting any of the above criteria
 - ▶ Third-degree blood^d relative who has breast cancer^b and/or ovarian^e carcinoma and who has ≥ 2 close blood relatives^d with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian^e carcinoma

BRCA testing criteria met → [See Follow-up \(BRCA-2\)](#)

If BRCA testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per [NCCN Screening Guidelines](#)

- Personal history G7+ PCa with:
 - 1+ close blood relative with ovarian cancer (any age) or breast cancer ≤ 50 , or
 - 2 relatives with breast, pancreatic or PCa (G7+)

THE ROLE OF GENETIC TESTING FOR INHERITED PROSTATE CANCER RISK





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Who should be referred for genetic counseling and consideration of genetic testing to assess for inherited PCa?

- First-degree relative (FDR) diagnosed with PCa ≤ 55 or personal diagnosis of PCa ≤ 55 with FDR diagnosed with PCa at any age or death from PCa in FDR at age < 60
- 2 close blood relatives with PCa on same side of family with at least one diagnosed with PCa at age ≤ 55
- Any FDR with cancer in HBOC/LS spectrum diagnosed at age < 50
- 2+ close blood relatives on same side of family with cancer in HBOC/LS spectrum diagnosed at any age
- Tumor sequencing showing mutations in hereditary cancer genes



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Innumerable multigene panels from multiple sources

- Eg. Ambry, Color, Myriad, GeneDx, UW, UMich
- Some prostate-specific:
 - Ambry Genetics
 - Fulgent
 - GeneDx
 - Invitae
 - NeoGenomics



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Direct to Urologist and patient advertising

CLINICAL SUMMARY

GERMLINE MUTATIONS IN *ATM* AND *BRCA1/2* DISTINGUISH RISK FOR LETHAL AND INDOLENT PROSTATE CANCER AND ARE ASSOCIATED WITH EARLY AGE AT DEATH

Ni R, Zhuang S, Han M, et al. Eur Urol (December 2016)

Vol. 4 No. 2

BACKGROUND

While over 1 million men are diagnosed with prostate cancer each year worldwide, a much smaller number (302,500) die from the disease. "Understanding the inherited factors contributing to the progression of prostate cancer to a lethal disease could have an important translational impact on the detection, diagnosis, and prognosis of this common cancer."

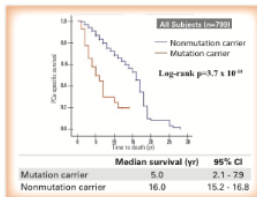
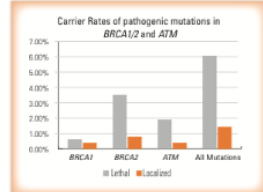
CLINICAL COHORT DESCRIPTION

799 men undergoing prostate cancer treatment from three institutions. 313 of these patients had lethal prostate cancer, which is defined as death due to metastatic prostate cancer. 486 of these patients were diagnosed with low-risk localized prostate cancer that underwent active surveillance. Among them were European American (613), African American (119), and Chinese (67) men.

METHODS

Whole genome sequencing was performed on germline DNA extracted from the blood of 129 lethal prostate cancer patients. Next-generation sequencing was performed on the germline DNA of all the remaining patients. All cases were analyzed using the Fisher's exact test and logistic regression analysis. Kaplan-Meier survival and Cox regression models were also used in comparing clinical and pathological features of mutation carriers and non-carriers.

RESULTS



CONCLUSIONS

The mutation status of *ATM* and *BRCA1/2* distinguishes the risk for lethal and indolent prostate cancer and is associated with earlier age at death and shorter survival time. This may have important clinical implications in genetic testing and prostate cancer screening and treatment. "Another clinical implication of our findings is to consider inclusion of mutation carrier status as another important factor for decision making in active surveillance."

For more information regarding the content in this newsletter, please contact your local Myriad representative.

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Myriad Genetic Laboratories, Inc.
320 Wakara Way, Salt Lake City, UT 84108

For more information, Clinical Support, Healthcare Information and Customer Services: Prolis.com | 855-469-7765

RISK ASSESSMENT FOR HEREDITARY CANCER SYNDROMES

Patient Name: _____ Physician: _____
Date of Birth: _____ Date Completed: _____

Instructions: Please indicate those that apply to YOU and/or YOUR FAMILY (on both your mother's/maternal or father's/paternal side).

CANCER DIAGNOSIS	RELATIONSHIP (Parents, Siblings, Children, Aunts/Uncles, Grandparents, First Cousins, Nieces/Nephews)	SPECIFICS (If prompted)
<input type="checkbox"/> Prostate (Gleason 7 or greater)	Self	Gleason:
AND ONE OF THE FOLLOWING:		
<input type="checkbox"/> Prostate (Gleason 7 or greater)		Gleason:
<input type="checkbox"/> Breast (Age 50 or younger)		Age of Diagnosis:
<input type="checkbox"/> Ovarian		
<input type="checkbox"/> Pancreatic		
<input type="checkbox"/> Other:		
<input type="checkbox"/> You or someone in your family has had genetic testing for a hereditary cancer syndrome.		
Explain:		

Patient's Signature

Date

FOR OFFICE USE ONLY

- ☐ Candidate for further risk assessment and/or genetic testing
☐ Information given to patient to review
☐ Follow-up appointment scheduled Date: _____

☐ Patient offered genetic testing:

- ☐ Accepted
☐ Declined

Healthcare Professional's Signature

Date

Assessment criteria based on medical society guidelines. For these individuals society guidelines go to www.myriadpro.com/guidelines. Myriad and the Myriad logo are either trademarks or registered trademarks of Myriad Genetics, Inc. in the United States and other jurisdictions. ©2015





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Need to develop a urologist-based approach to testing

- Define criteria for testing
- Identify preferred panel test
- Determine insurance/billing options
- Counsel patient and order test
- Refer to genetics only if positive test/VUS



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- **Should we treat patients with high-risk localized PCa differently if they have a BRCA mutation?**



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Localized PCa in germline BRCA+ patients is more aggressive



European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Ola Bratt and Niklas Loman on pp. 194–195 of this issue

Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer

Elena Castro^{a,h,*}, Chee Goh^b, Daniel Leongamornlert^b, Ed Saunders^b,
Malgorzata Tymrakiewicz^b, Tokhir Dadaev^b, Koveela Govindasami^b, Michelle Guy^b,
Steve Ellis^c, Debra Frost^c, Elizabeth Bancroft^b, Trevor Cole^d, Marc Tischkowitz^e,
M. John Kennedy^f, Jacqueline Eason^g, Carole Brewer^h, D. Gareth Evansⁱ, Rosemarie Davidson^j,
Diana Eccles^k, Mary E. Porteous^l, Fiona Douglas^m, Julian Adlardⁿ, Alan Donaldson^o,
Antonios C. Antoniou^c, Zsolt Kote-Jarai^b, Douglas F. Easton^c, David Olmos^{a,*}, Rosalind Eeles^{b,†}

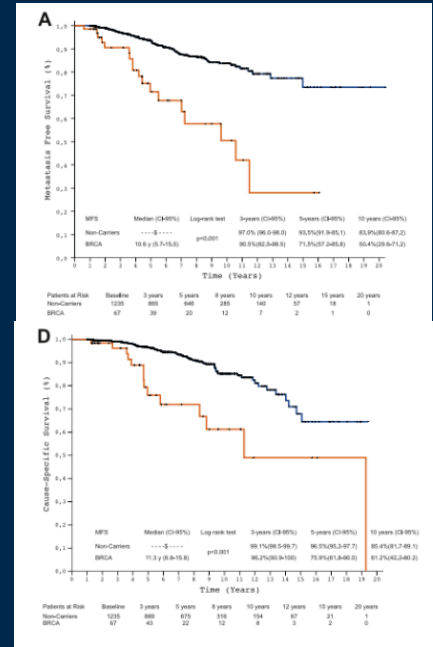
RT cohort

32 BRCA
735 Noncarriers

RP cohort

35 BRCA
500 Noncarriers

Metastasis



PCSM

- BRCA status associated with ~3X increased odds of metastasis and PCSM independent of clinical/path variables



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Localized PCa in germline BRCA+ patients “looks” more like metastatic disease

ARTICLE

Received 26 Jul 2016 | Accepted 20 Oct 2016 | Published 9 Jan 2017

DOI: 10.1038/ncomms13571

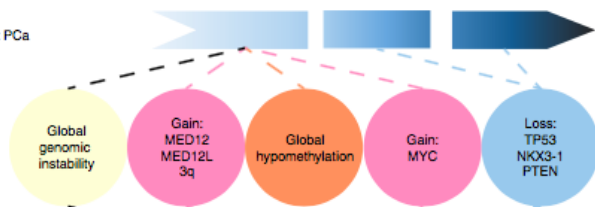
OPEN

Germline *BRCA2* mutations drive prostate cancers with distinct evolutionary trajectories

Renea A. Taylor^{1,*}, Michael Fraser^{2,*}, Julie Livingstone^{3,*}, Shadrielle Melijah G. Espiritu^{3,*}, Heather Thorne^{4,5,*}, Vincent Huang³, Winnie Lo², Yu-Jia Shiah³, Takafumi N. Yamaguchi³, Ania Sliwinski^{5,6}, Sheri Horsburgh², Alice Meng², Lawrence E. Heisler³, Nancy Yu³, Fouad Yousif³, Melissa Papargiris⁷, Mitchell G. Lawrence⁷, Lee Timms⁸, Declan G. Murphy⁹, Mark Frydenberg⁷, Julia F. Hopkins³, Damien Bolton⁷, David Clouston¹⁰, John D. McPherson⁸, Theodorus van der Kwast², Paul C. Boutros^{3,11,12,**}, Gail P. Risbridger^{7,**} & Robert G. Bristow^{2,11,**}

- Localized PCa in 14 BRCA2+ pts profiled
 - Global genomic instability
 - MED12, MYC gains
 - Genotypically similar to mCRPC despite no ADT

BRCA2-mutant PCa



Sporadic PCa

Localized

mCRPC



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What does this mean for AS in low-risk BRCA+ patients?

Table 4 – Multivariable analyses for cause-specific survival

Variables	Multivariable		
	HR	95% CI	p value
BRCA carrier vs noncarriers	2.17	1.16–4.07	0.016
Tumour stage (T)			0.597
T2 vs T1	1.22	0.54–2.77	0.635
T3 vs T1	0.54	0.12–2.44	0.425
T4 vs T1	0.96	0.21–4.30	0.952
Nodes: N1 vs N0			
Gleason score			<0.001
7 vs ≤6	2.50	1.23–5.07	0.011
≥8 vs ≤6	5.99	2.86–12.55	<0.001
PSA level	1.01	1.00–1.02	0.033
Treatment: RP vs RT	0.52	0.28–0.95	0.035
ADT			
≤6 mo vs no ADT	NA	NA	NA
>6 mo vs no ADT			
AJCC stage			0.016
IIa vs I	1.55	0.46–5.18	0.481
IIb vs I	1.27	0.38–4.24	0.696
III vs I	2.07	0.65–6.62	0.218
IV vs I	3.73	1.10–12.66	0.035
Age at diagnosis	NA	NA	NA
Cause-specific survival: Kattan score, treatment, and BRCA (T4 excluded)			
BRCA carrier vs noncarriers	2.78	1.53–5.04	0.001
Kattan score	1.02	1.01–1.02	<0.001
Treatment	0.60	0.34–1.05	0.071

ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; NA = not applicable; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

- Gleason grade still a strong predictor of mets/death
 - Only 22 G6 BRCA+ patients (any mets/PCSM?)
- Would multigene classifiers also predict outcomes in these patients?
- My take: Exercise caution with AS, but not enough data to recommend against AS in these patients

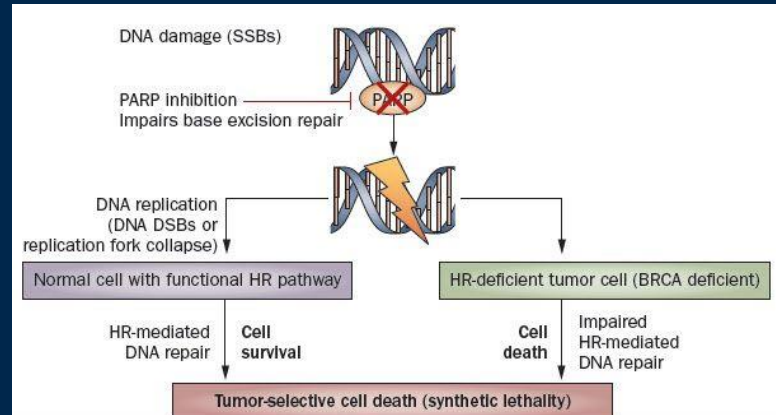


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What does this mean for management of **high-risk** BRCA+ patients?

- Need the best we can offer
 - Multimodality (RP, RT, ADT)
- Need neoadjuvant trials
 - PARP-I
 - Chemotherapy?
 - Immunotherapy?





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Can this all be avoided with prophylactic prostatectomy?



The Martini-Klinik Experience

- 5 preventive prostatectomies so far
- age: 36-52 years
- PSA 0.9-6,1
- 4/5 went through standard (TRUS-Bx) or extensive (MRI-guided) diagnosis
- 3/4 had neg Bx, one had HGPIN
- 1/5: only PSA
- 3/5 PCa (all pT2, 3+3 or 3+4, no cancer <0.5cc)
- no 90 day complications, all continent, all erectile function ≥ 18 on IIEF at 3/12 months
- when asked „ would you do again“ all said „yes“
- 4 MDs, 1 EngD

Slide courtesy of Alex Haese



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Questions from a Urologist's perspective

- Should we screen for PCa differently in healthy men with a BRCA mutation?
- Which patients with localized PCa should undergo genetic testing?
- Should we treat patients with low-risk PCa differently if they have a BRCA mutation?
- Should we treat patients with high-risk localized PCa differently if they have a BRCA mutation?





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Thank You!

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