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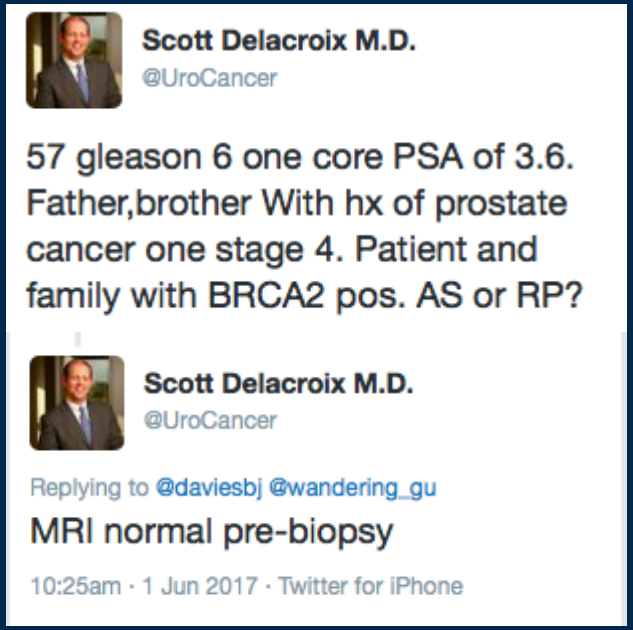
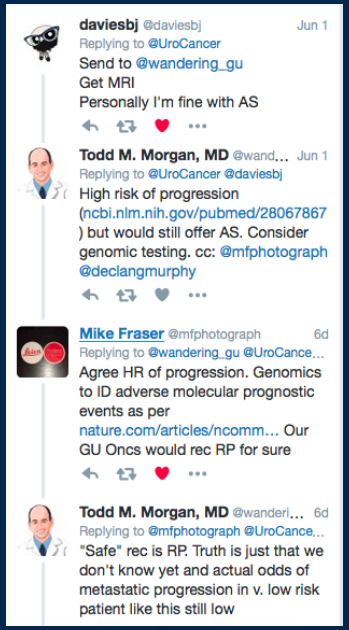
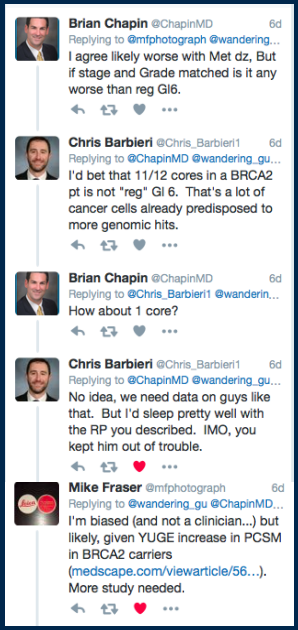
When you need Twitter to help crowdsource patient care. . .







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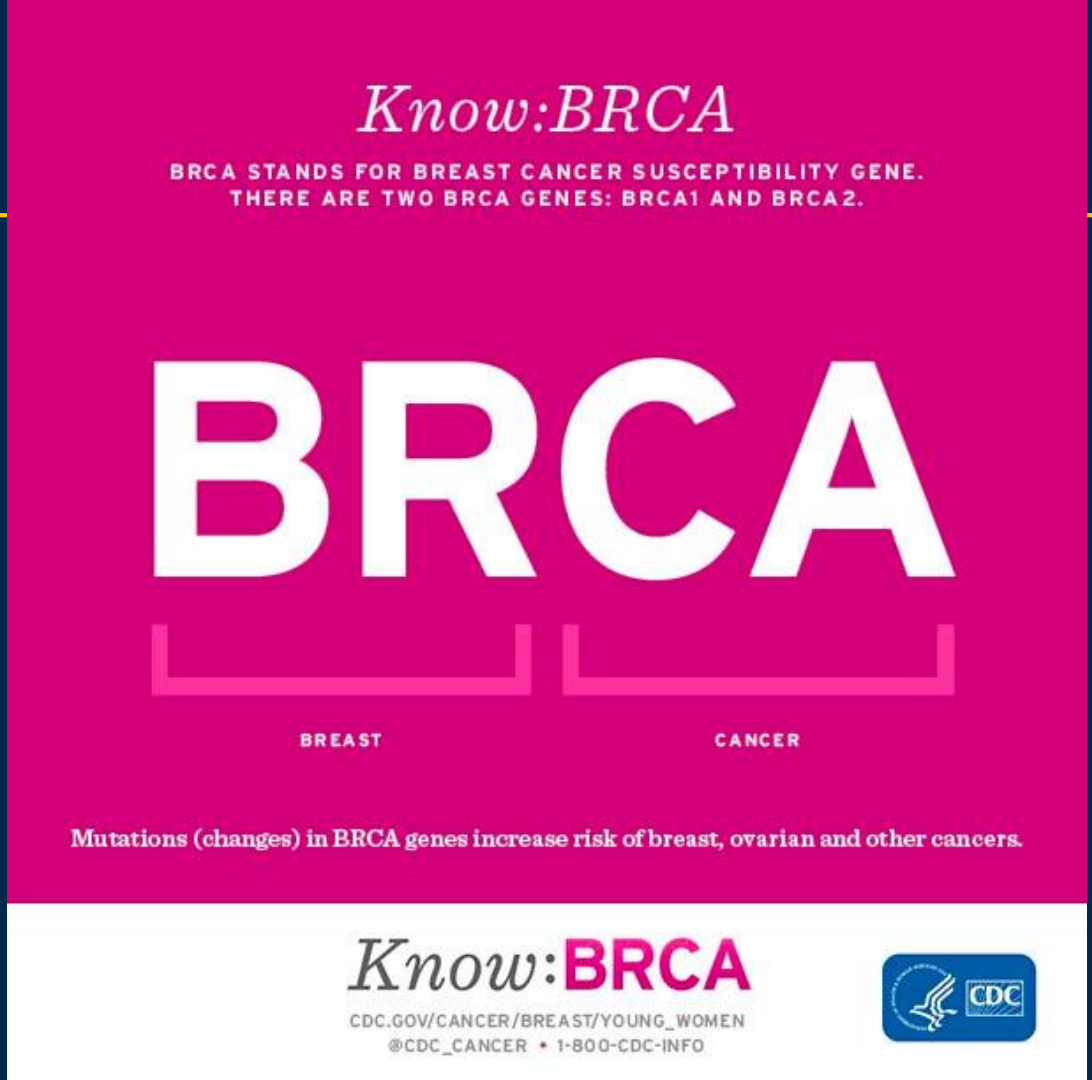

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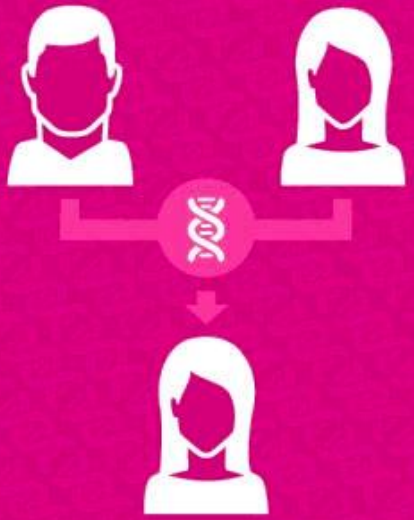
Know:Your Risk

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

CDC

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Questions from a Urologist's perspective

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- 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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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

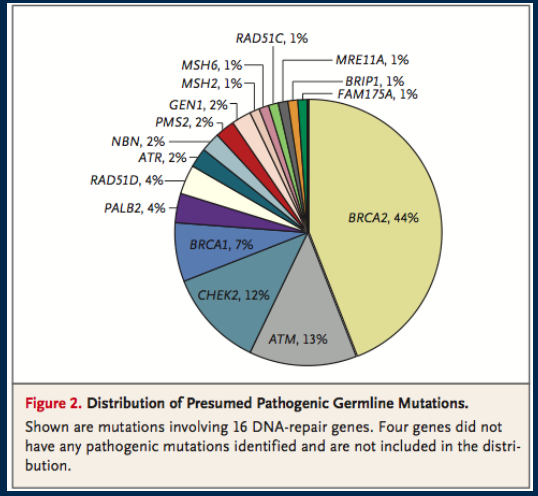

Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

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

Pritchard, NEJM, 2016

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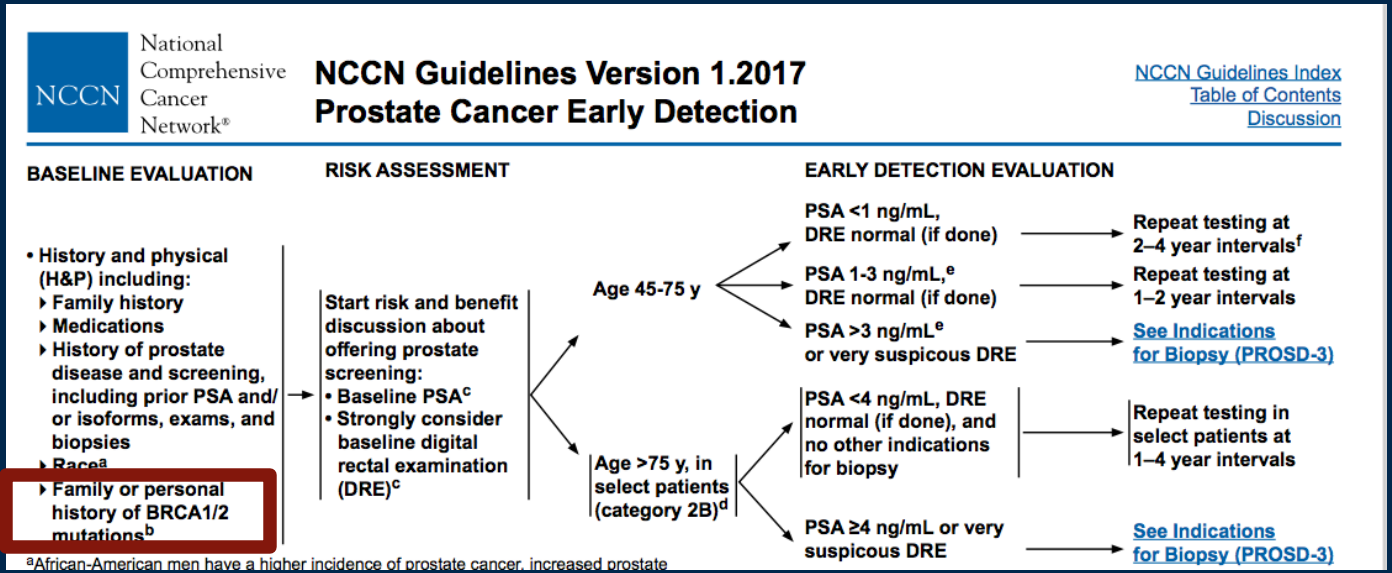
NCCN Early Detection Guidelines



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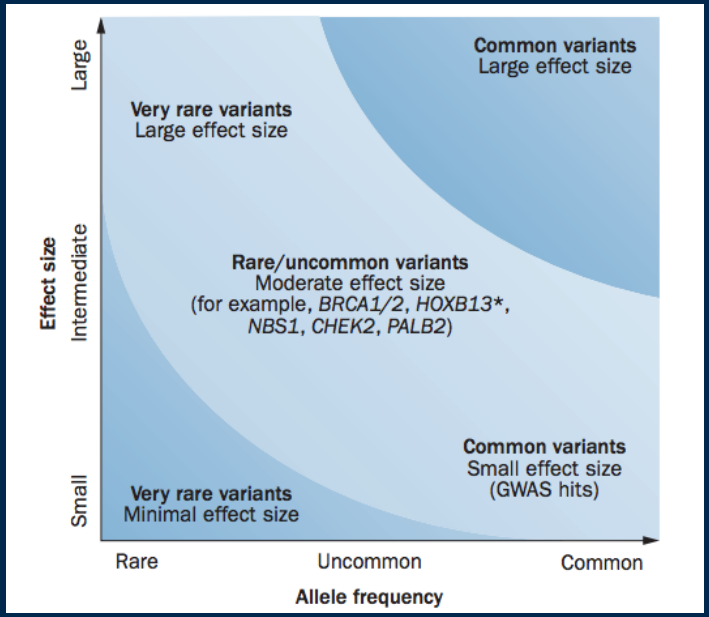
Heritable PCa risk



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

Eeles, Nat Rev Urol 2014

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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	—

Giri, Sem Oncol, 2016

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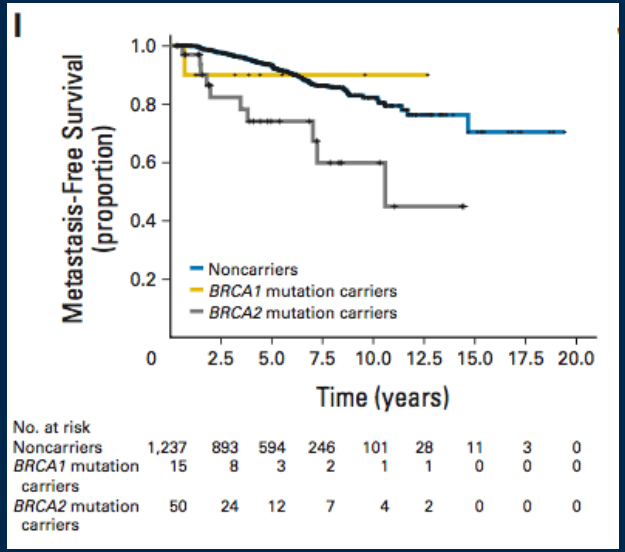
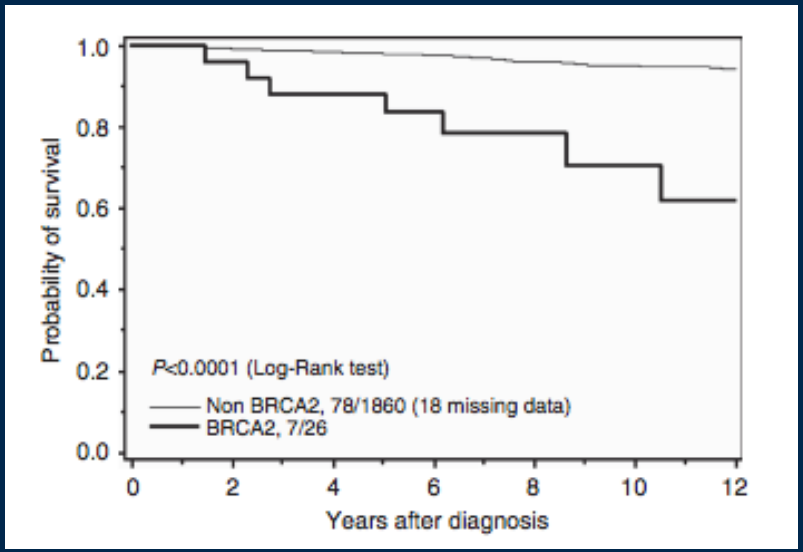
BRCA2 and PCa aggressiveness





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

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

Akbari, Br J Cancer, 2014; Castro, JCO, 2013

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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)

Kicinski, PloS One, 2011

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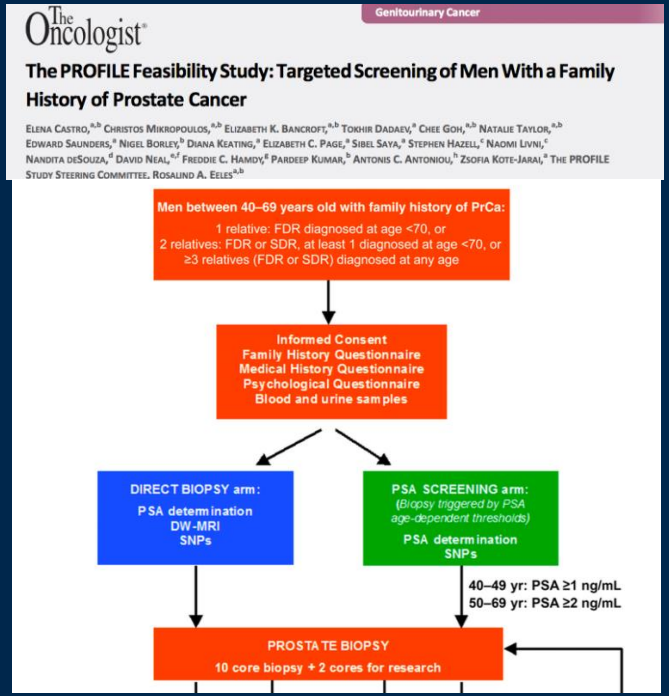
Early detection in high risk patients: PROFILE study



- 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

Castro, The Oncologist, 2016

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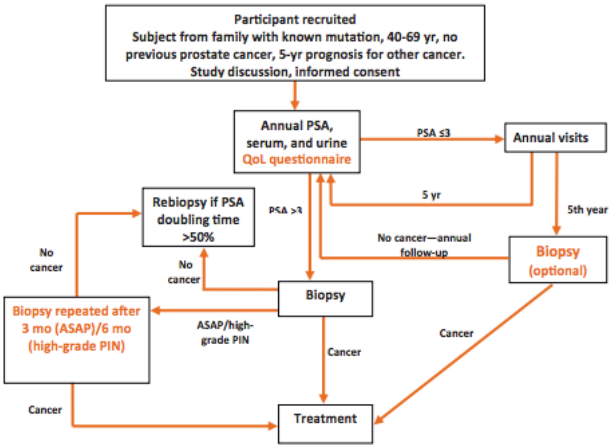
Early detection in high risk patients: IMPACT study

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

Bancroft, Eur Urol, 2014

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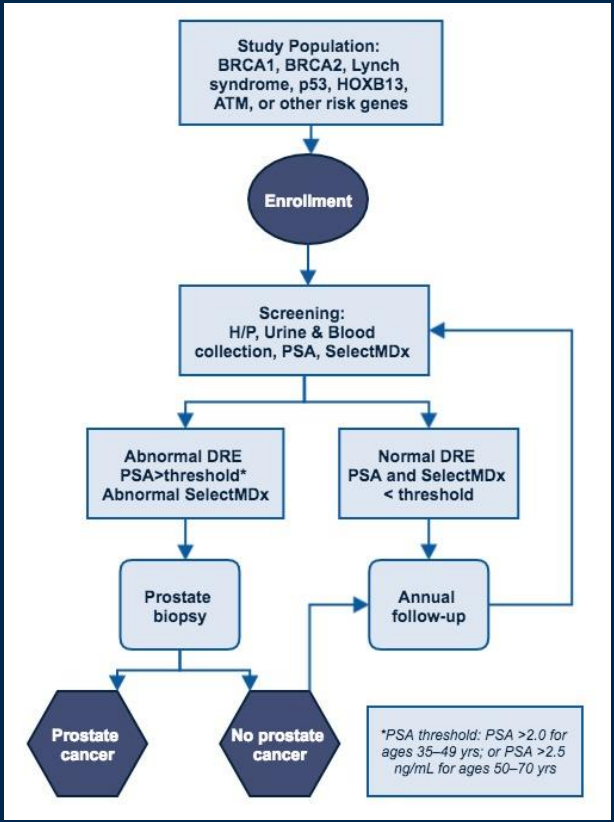
UMich Prostate Cancer Risk Clinic



- 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

FOR MORE INFORMATION, CONTACT:

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

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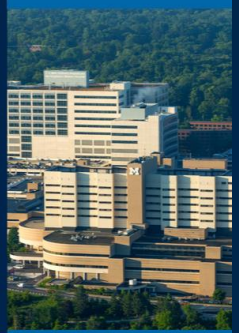
PROSTATE CANCER RISK CLINIC

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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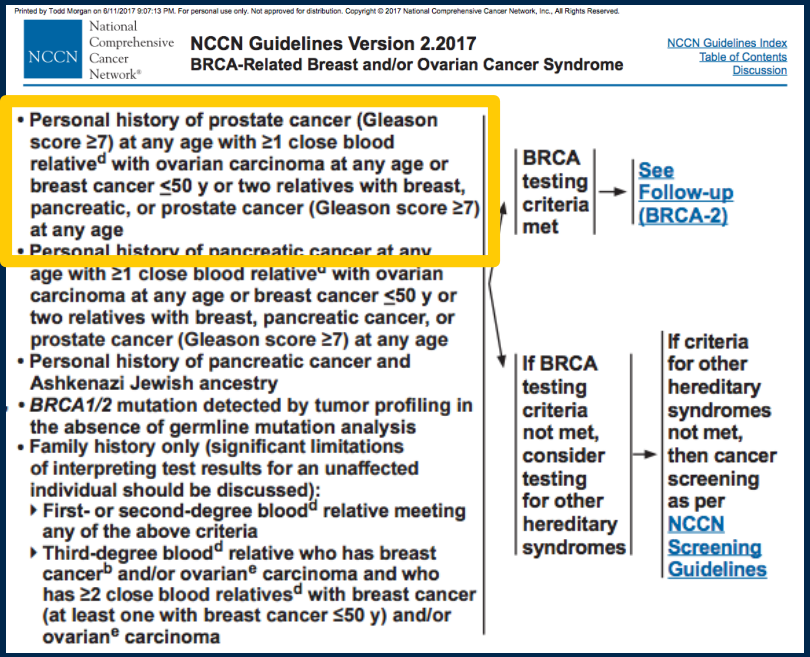
Questions from a Urologist's perspective

- 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?

NCCN breast and ovarian risk assessment 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

Na R, Zheng 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 (307, 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."

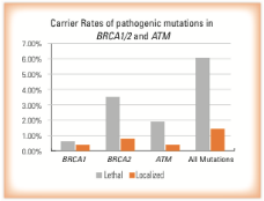
CLINICAL COHORT DESCRIPTION

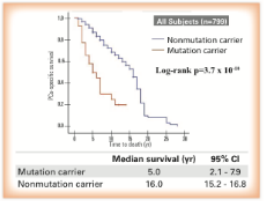
799 men undergoing prostate cancer treatment from three institutions. 313 of these patients had lethal prostate cancer, which is defined as death due to metastatic prostate cancer. 486 of these patients were diagnosed with low-risk localized prostate cancer that underwent active surveillance. Among them 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





	Median survival (yr)	95% CI
Mutation carrier	5.0	2.1 - 7.9
Nonmutation carrier	16.0	15.2 - 16.8

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.

myriad.

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

For more information, Clinical Support, Healthcare Information and Customer Services: **Prolaris.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)
☐ Prostate (Gleason 7 or greater)	**Self**	Gleason:
AND ONE OF THE FOLLOWING:		
☐ Prostate (Gleason 7 or greater)		Gleason:
☐ Breast (Age 50 or younger)		Age of Diagnosis:
☐ Ovarian		
☐ Pancreatic		
☐ Other:		

☐ 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

PRmyRisk/12-15

myriad.

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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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Localized PCa in germline BRCA+ patients is more aggressive

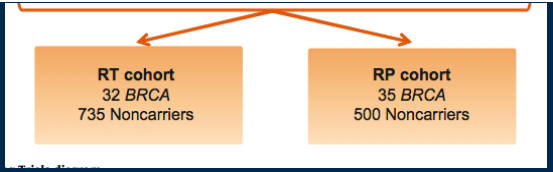
European Association of Urology

Platinum Priority – Prostate Cancer

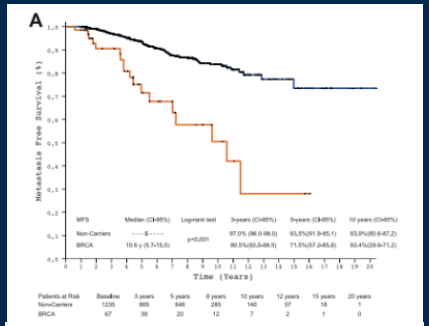
Editorial by Ola Bratt and Niklas Loman on pp. 194–195 of this issue

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

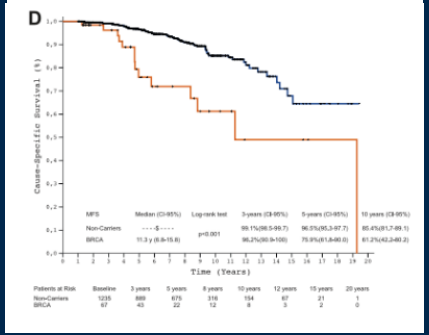
Elena Castro[a,b,], Chee Goh[b], Daniel Leongamornlert[b], Ed Saunders[b], Malgorzata Tymrakiewicz[b], Tokhir Dadaev[b], Koveela Govindasami[b], Michelle Guy[b], Steve Ellis[c], Debra Frost[c], Elizabeth Bancroft[b], Trevor Cole[d], Marc Tischkowitz[e], M. John Kennedy[f], Jacqueline Eason[g], Carole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



Metastasis



PCSM



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

Castro, Eur Urol, 2015

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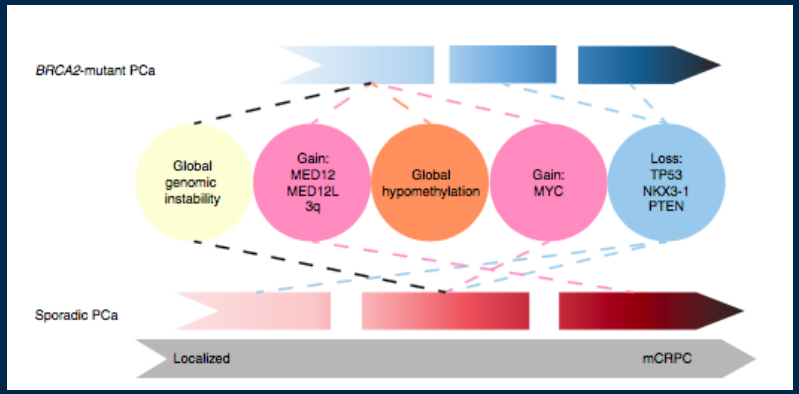
Localized PCa in germline BRCA+ patients "looks" more like metastatic disease

ARTICLE
Received 26 Jul 2016 | Accepted 20 Oct 2016 | Published 9 Jan 2017
DOI: 10.1038/ncomms13671 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 Huang[3], Winnie Lo[2], Yu-Jia Shiah[3], Takafumi N. Yamaguchi[3], Ania Sliwinski[5,6], Sheri Horsburgh[2], Alice Meng[2], Lawrence E. Heisler[3], Nancy Yu[3], Fouad Yousif[3], Melissa Papargiris[7], Mitchell G. Lawrence[7], Lee Timms[8], Declan G. Murphy[9], Mark Frydenberg[7], Julia F. Hopkins[3], Damien Bolton[7], David Clouston[10], John D. McPherson[8], Theodorus van der Kwast[2], 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

Taylor, Nat Commun, 2017

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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

Castro, Eur Urol, 2015

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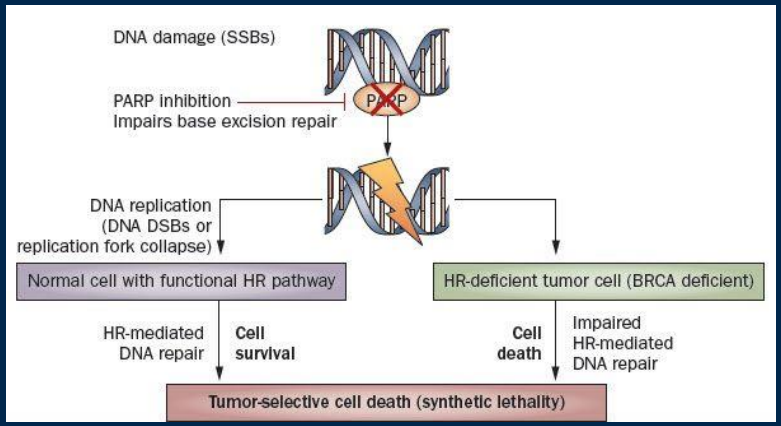
What does this mean for management of high-risk BRCA+ patients?

- 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?

Martini-Klinik
Prostatakrebszentrum

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“

Slide courtesy of Alex Haese

- 4 MDs, 1 EngD

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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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