FDUS 2019

Genetics in Biomarkers for Prostate and Bladder Cancer

Leonard G. Gomella, MD
Chairman, Department of Urology
Sidney Kimmel Cancer Center
Thomas Jefferson University
Philadelphia, PA

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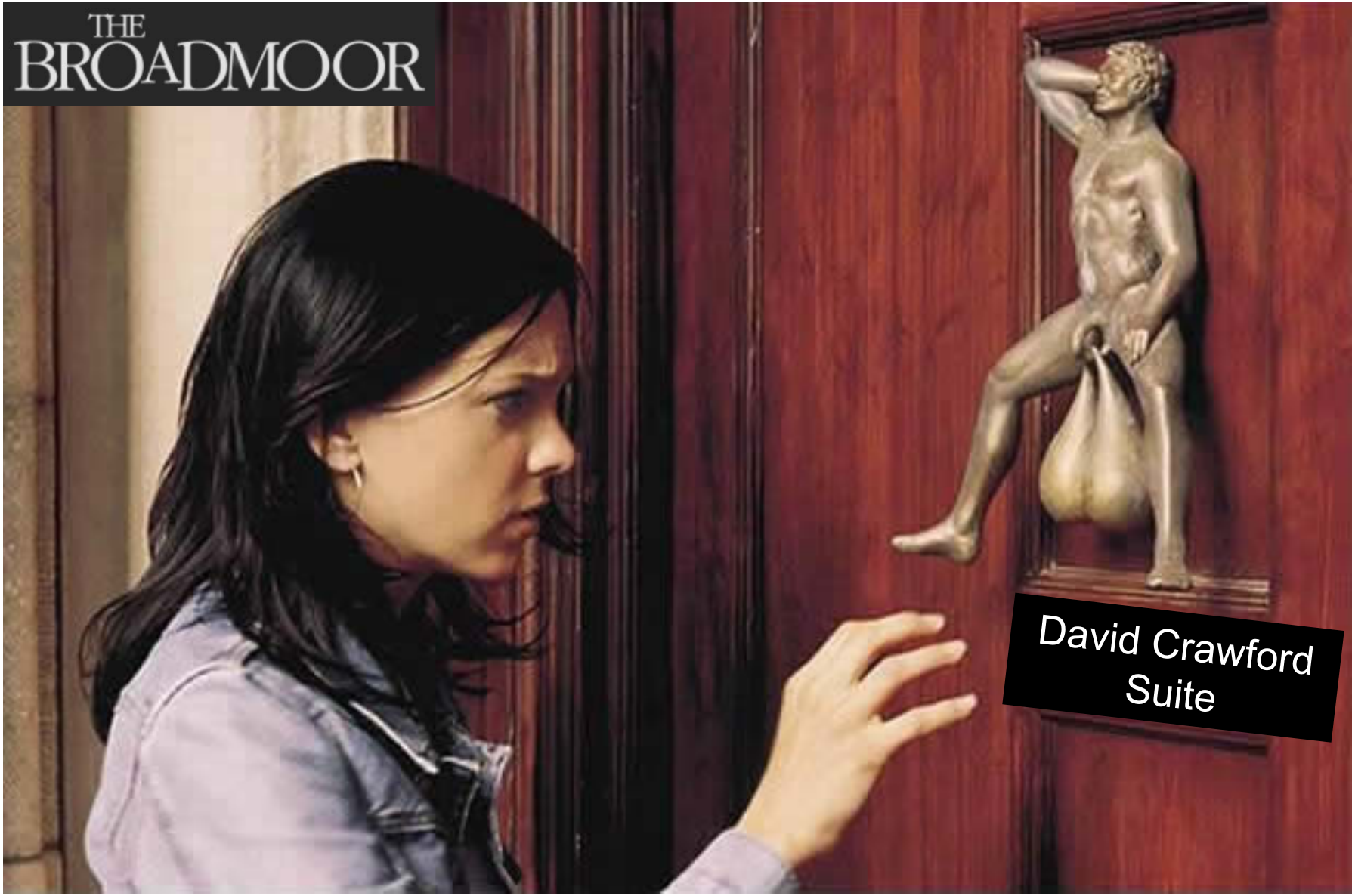
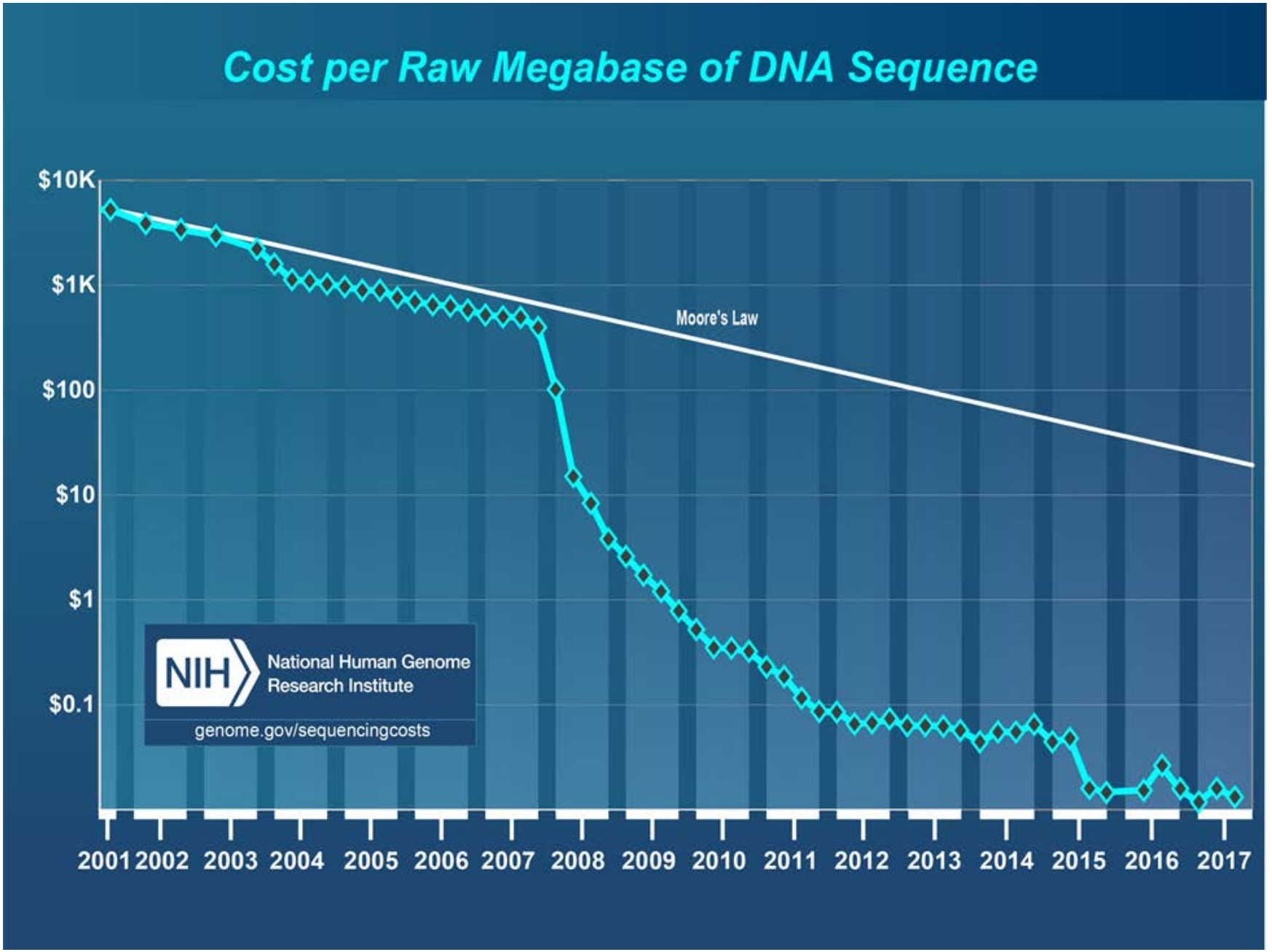
HEALTH IS ALL WE DO

BEST HOSPITALS
U.S.News & WORLD REPORT
NATIONAL
UROLOGY
2018-19


THE
BROADMOOR
David Crawford
Suite

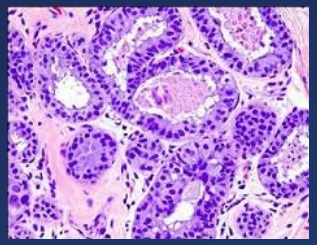

Cost per Raw Megabase of DNA Sequence
$10K
$1K
$100
$10
$1
$0.1
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017

GEORGE FREY/REUTERS

For 23andMe, using genetic data for drug research 'was always part of the vision,' an official says.

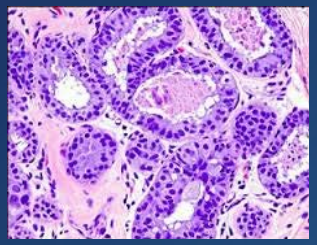
Clinical "Genetic" Testing

Genomic Testing
- Performed in tissues
- Molecular signatures
  (Decipher, Prolaris, OncotypeDX, ConfirmMDX)



Decision-making treatment, and management

Tumor Sequencing
- Performed in tissues
- Tumor-specific mutations
  (Foundation Medicine, Caris)



Inform targeted therapies

~15-20% inherited

Inherited/Germ line Cancer Testing
- Mutations are inherited
- Substantially higher lifetime cancer risk
  (Myriad, Invitae, GeneDX, Color, Strand, others)

Blood or saliva

-Inform cancer screening and prevention
-Genetic testing in blood relatives
-Informing treatment and clinical trials

Genomic/Genetic Testing for Prostate Cancer Risk

- Background:
  - 10-15% PCa are hereditary
  - Inherited mutated genes (BRCA 1/2) do not cause cancer but increase risk
  - These pathogenic genes interact with other genes/environment to increase PCa risk
  - Increased risk for other cancers (Breast, ovarian, pancreatic, others).
  - Evolving evidence on how to best use these genes for screening/therapy.

- Why do Genomic/Genetic Germ Line Testing?
  - Potential impact on therapeutic options
    - So called "actionable genes"
    - If identified may guide treatment
  - Potential to screen/prevent for other at-risk cancers:
    - in the patient
    - in the family

Based on data in Nicolosi, et al ASCO Abstract 5009 2017 Chicago;
https://www.ncbi.nlm.nih.gov/gene/

Genomic/Genetic Testing for Prostate Cancer Risk

Some mutated genes associated with prostate cancer

Most appear to be related to defects in DNA repair mechanisms

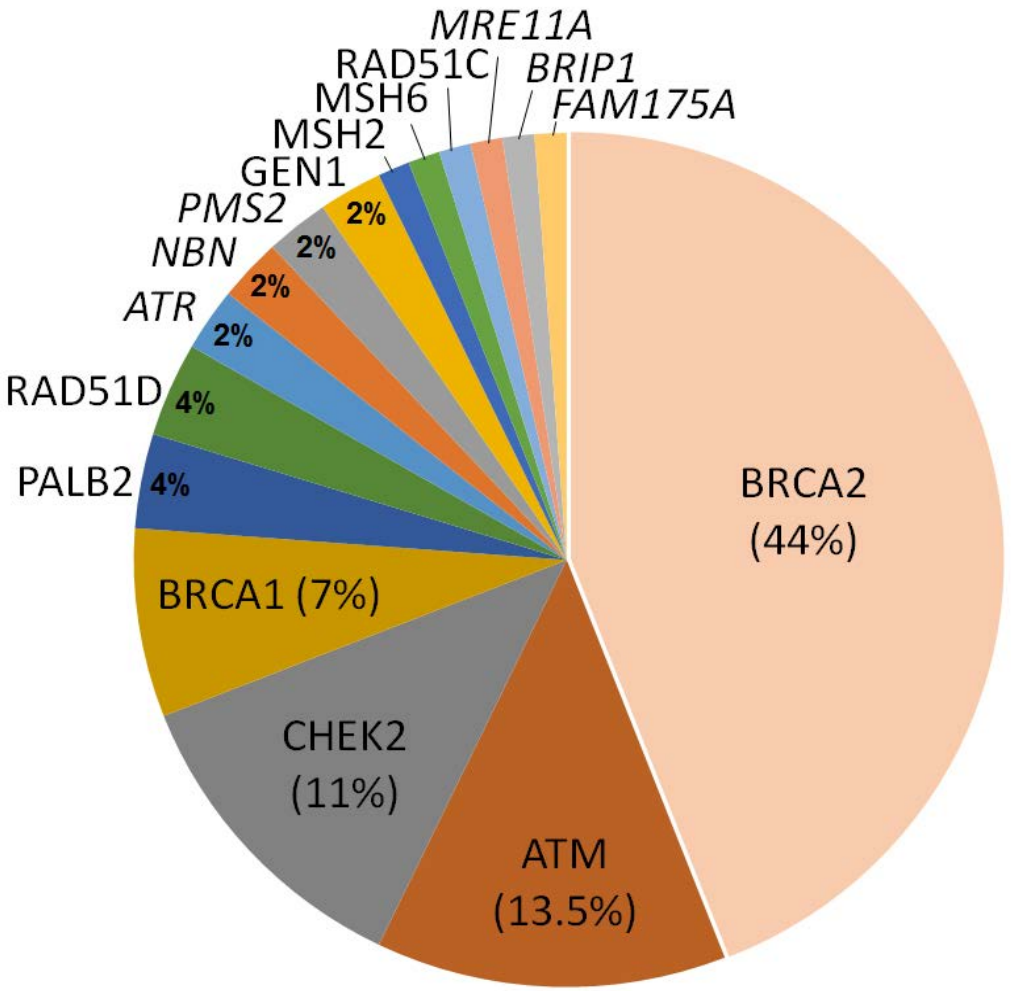
HOXB13 is the gene linked with clearly defined inherited prostate cancer

Gene	PCa Risk	Mechanism
ATM	elevated	DNA damage response
BRCA1	~ 20%	DNA damage repair
BRCA2	~ 20%	DNA damage repair
CHEK2	elevated	DNA repair through phosphorylation of BRCA2
EPCAM	up to 30%	Upregulate c-myc
HOXB13	up to 60%	AR repressor
MLH1	up to 30%	DNA repair
MSH2	up to 30%	DNA repair
MSH6	up to 30%	DNA repair
NBN	elevated	DNA repair
PMS2	up to 30%	DNA mismatch repair
TP53	unknown	Tumor suppressor
PALB2	preliminary	Tumor suppressor
RAD51D	preliminary	DNA repair

Based on data in Nicolosi, et al ASCO Abstract 5009 2017 Chicago;
https://www.ncbi.nlm.nih.gov/gene/

Germline mutations in metastatic PCa

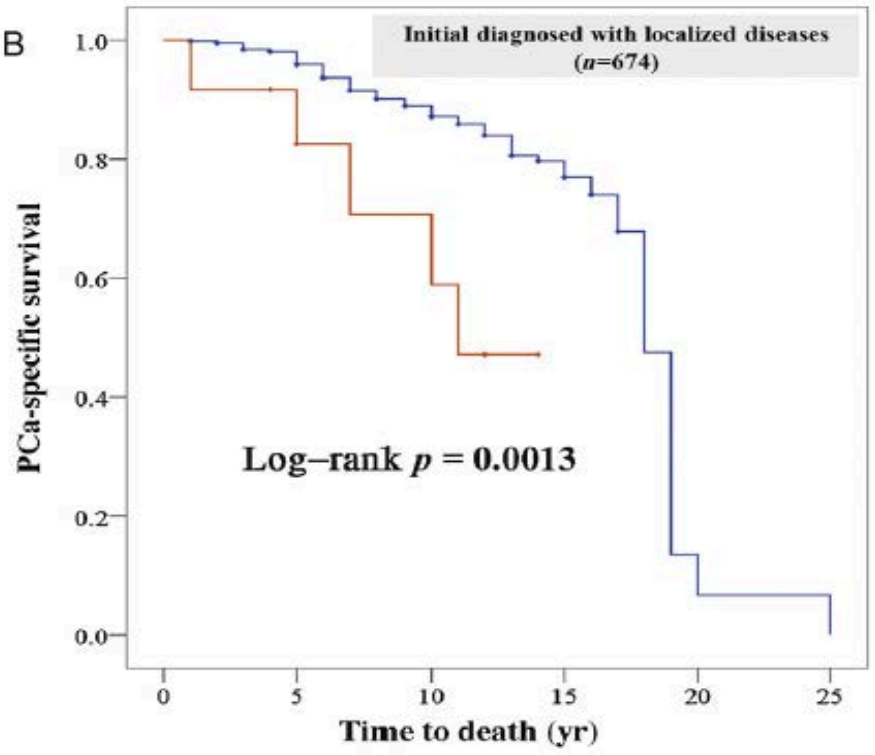
- BRCA-2 best studied for potential screening and treatment
- PCa males with BRCA-2 have more aggressive disease
- More work is needed on the other PCa genes identified
- Germline mutations in 11.8% of metastatic vs. 4.6% localized disease



Pritchard, N Engl J Med. 2016 Aug 4;375(5):443-53

Germline Mutations in *ATM* and *BRCA1/2* Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death

Rong Na [a,b,†], S. Lilly Zheng [b,c,†], Misop Han [d,†], Hongjie Yu [b,e], Deke Jiang [b,e], Sameep Shah [b], Charles M. Ewing [d], Liti Zhang [d], Kristian Novakovic [b,c], Jacqueline Petkewicz [b,c], Kamalakar Gulukota [g], Donald L. Helseth Jr [g], Margo Quinn [b,c], Elizabeth Humphries [d], Kathleen E. Wiley [d], Sarah D. Isaacs [d], Yishuo Wu [a], Xu Liu [b,e], Ning Zhang [a,b], Chi-Hsiung Wang [b], Janardan Khandekar [g], Peter J. Hulick [f], Daniel H. Shevrin [f], Kathleen A. Cooney [h], Zhoujun Shen [b], Alan W. Partin [d], H. Ballentine Carter [d], Michael A. Carducci [i], Mario A. Eisenberger [i], Sam R. Denmeade [i], Michael McGuire [c], Patrick C. Walsh [d], Brian T. Helfand [b,c], Charles B. Brendler [b,c], Qiang Ding [a,], Jianfeng Xu [a,b,c,e,*], William B. Isaacs [d,i,*]*



	Median survival (yr)	95%CI
Mutation carrier	11.0	N/A
Nonmutation carrier	18.0	17.2–18.8

Eur Urol http://dx.doi.org/10.1016/j.eururo.2016.11.033

What proportion of patients with localized disease have germline mutations predisposing to PCa?

- *BRCA1* mutations: ~ 0.5%
- *BRCA2* mutations: ~ 1.0%
- *ATM* mutations: ~ 0.4%
- Much more common in lethal than in nonlethal localized PCa . . .

Na Eur Urol 2017, Kote-Jarai Br J Cancer 2011, Leongamornlert Br J Cancer 2012

Localized PCa in germline BRCA 2+ patients "looks" more like metastatic disease

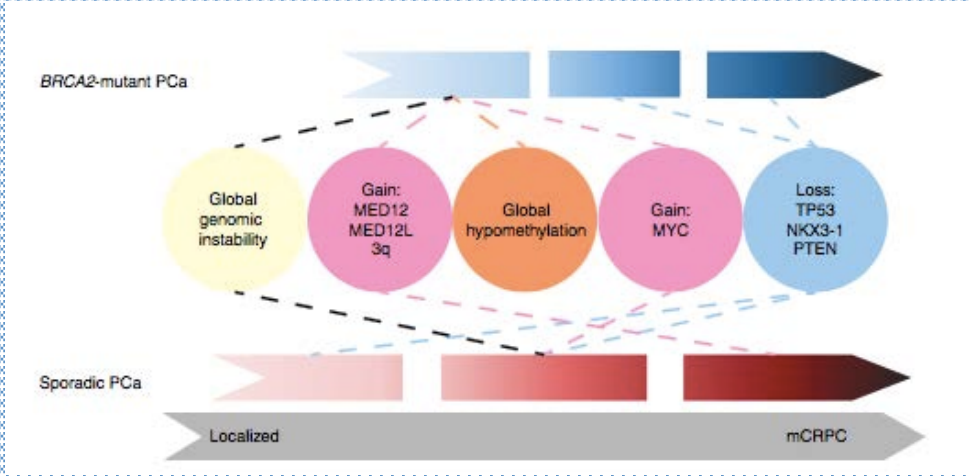
ARTICLE

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

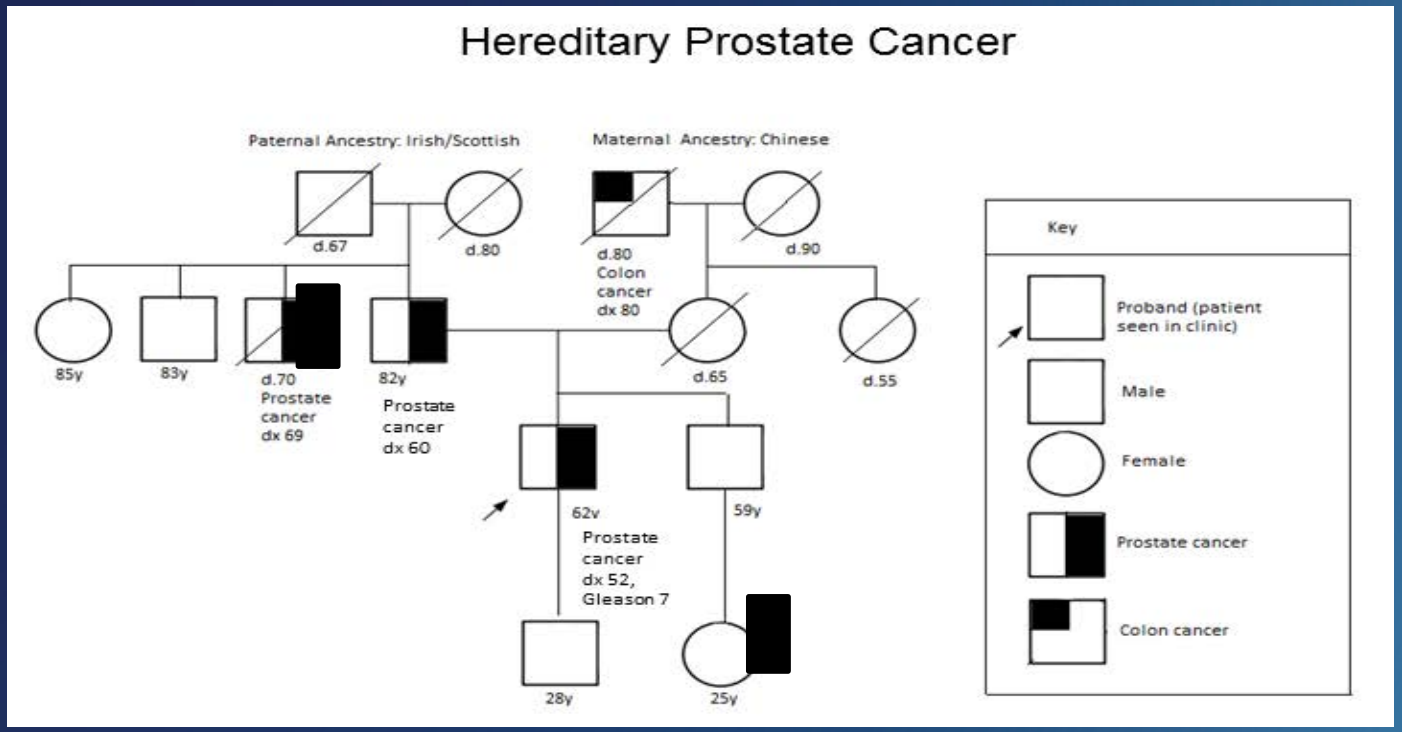
Common Prostate Cancer Specific Panels

- **Ambry Genetics "ProstateNext" (14 gene)**
  - ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53
- **Fulgent "Prostate Cancer Panel" (12 gene)**
  - ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53
- **GeneDx "Prostate Cancer Panel" (12 gene)**
  - ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53
- **Invitae "Prostate Cancer Panel" (up to 15 genes)**
  - ATM BRCA1 BRCA2 CHEK2 EPCAM HOXB13 MLH1 MSH2 MSH6 NBN PMS2 TP53; ADD ON FANCA, PALB2, RAD51D
  - HOXB13: Analysis is limited to the NM_006361.5:c.251G>A, p.Gly84Glu variant.
- **NeoGenomics "Hereditary DNA Repair Panel for Prostate Cancer" (20 genes)**
  - ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, GEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, and XRCC2
- **Strand Diagnostics "UroSeq" (12 gene)**
  - BRCA1/2, ATM, CHEK2, RAD51D, HOXB13, PALB2, MLH1, MSH2, MSH6, PMS2, and EPCAM

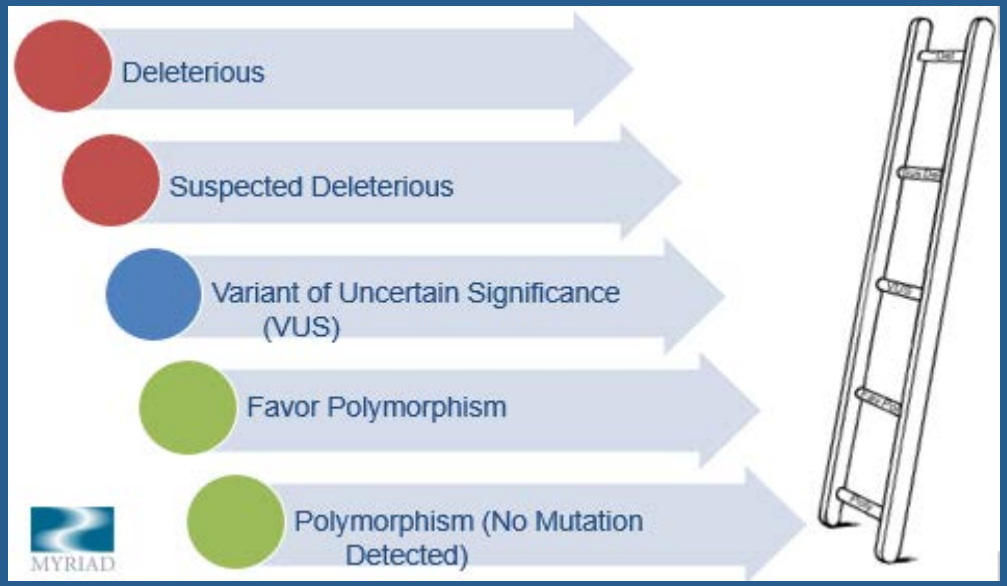
Other Common Cancer Panels

- **Myriad- No prostate panel but "myRisk" 28 gene screen for:**
  Breast,Ovarian,Colorectal,Endometrial,Melanoma,Pancreatic,Gastric,Prostate,Others
  - APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1,HOXB13, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, POLD1, POLE, RAD51C, RAD51D, SMAD4, STK11, TP53

- **Color Genomics/Genome Dx- No prostate panel but "Hereditary Cancer Panel" 30 gene screen for:**
  Breast,Ovarian,Colorectal,Endometrial,Melanoma,Pancreatic,Gastric,Prostate,Others
  - APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, POLD1, POLE, RAD51C, RAD51D, SMAD4, STK11, TP53



- Who in family should be offered “cascade testing”?
- Urology should become more focused on detailed family history: breast, ovarian, prostate, melanoma, Lynch Syndrome, male breast cancer, etc. to inform the need for genetic testing/counselling in men with prostate cancer.
- Expanding role of genetic counsellors

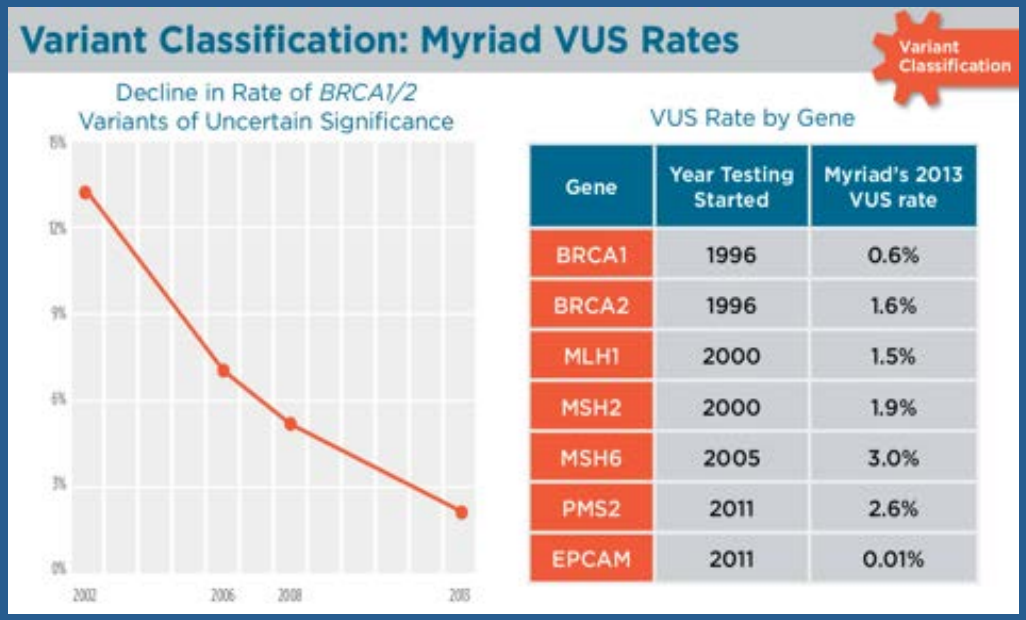


Genetic Variant of Uncertain Significance (VUS)

Can be reported on a patients genetic analysis

Definition: inconclusive
Interpretation: a genetic change that is different from normal control. Most VUS results are ultimately given definitive classifications.

Management: based on personal and family history; clinical single site testing for a VUS in relatives is not recommended



Gene	Year Testing Started	Myriad's 2013 VUS rate
BRCA1	1996	0.6%
BRCA2	1996	1.6%
MLH1	2000	1.5%
MSH2	2000	1.9%
MSH6	2005	3.0%
PMS2	2011	2.6%
EPCAM	2011	0.01%

Richards CS, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. Genet Med 2008: 10: 294;
https://www.myriadpro.com/blog/variants-of-uncertain-significance-what-you-need-to-know

Genetic Information Nondiscrimination Act (GINA) November 2009

Title I

- Prohibits genetic discrimination in health insurance

Title II

- Prohibits genetic discrimination in employment.

BUT….

- GINA does not protect against discrimination in life, disability, or long-term care insurance.
- Employer with fewer than 15 employees, other settings.

Gomella LG. Before Ordering a Genetic Test Get to Know GINA. Can J Urol. 2018 Dec;25(6):9569

Emerging Role of Genetic Testing in Prostate Cancer

- Screening
  - Individual
  - Family members "cascade testing"
- Active surveillance
- Treatment decisions all stages
- Prostate biopsy confirmation
- Precision medicine for advanced therapeutics

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Prostate Cancer Early Detection

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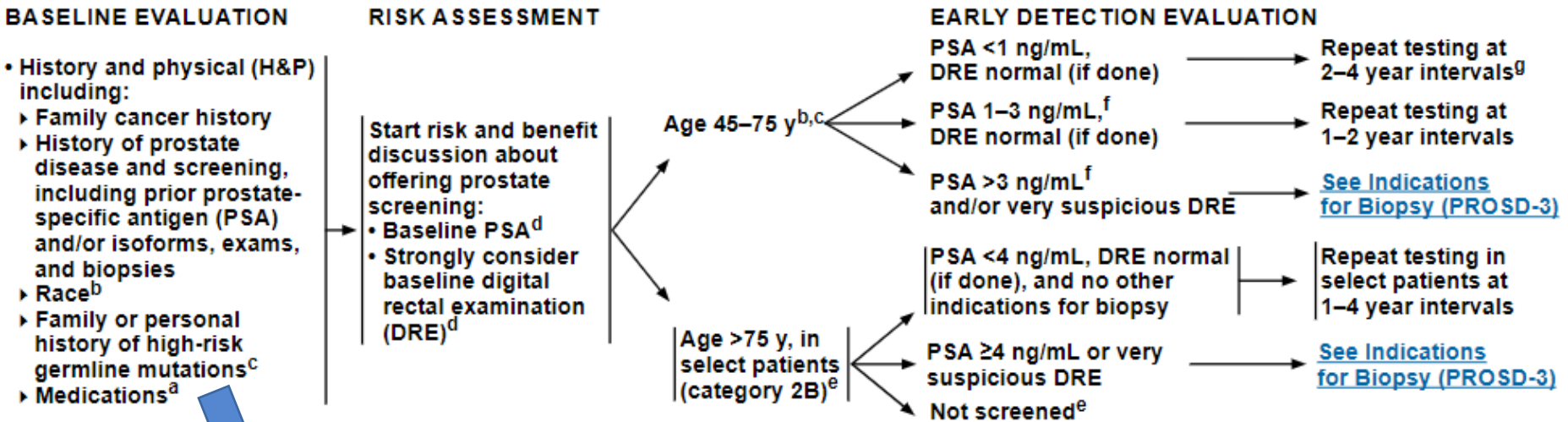

[c] If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. *BRCA1/2* pathogenic mutation carriers have an increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality. Consequently, it is reasonable for men with germline *BRCA1/2* mutations to consider beginning shared decision-making about PSA screening at age 40 and to consider screening at annual intervals rather than every other year.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Prostate Cancer

NEW 2018

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RISK STRATIFICATION AND STAGING WORKUP

Risk group	Clinical/pathologic features	Imaging[i,j]	Molecular testing of tumor	Germline testing	Initial therapy[p]
Very low[g]	• T1c AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[h] AND • PSA density <0.15 ng/mL/g	Not indicated	Not indicated	Consider if strong family history[c]	See PROS-4
Low[g]	• T1-T2a AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL	Not indicated	Consider if life expectancy ≥10y[l]	Consider if strong family history[c]	See PROS-5
Favorable intermediate[g]	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 OR • PSA 10–20 ng/mL AND • Percentage of positive biopsy cores <50%	• Bone imaging[k]: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Consider if life expectancy ≥10y[l]	Consider if strong family history[c]	See PROS-6
Unfavorable intermediate[g]	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR • PSA 10–20 ng/mL	• Bone imaging[k]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider if strong family history[c]	See PROS-7
High	• T3a OR • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 OR • PSA >20 ng/mL	• Bone imaging[k]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider[o]	See PROS-8[p]
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Gleason score 8–10/ grade group 4 or 5	• Bone imaging[k]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider[o]	See PROS-8[p]
Regional	Any T, N1, M0	Already performed	Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)[m,n]	Consider[o]	See PROS-9
Metastatic	Any T, Any N, M1	Already performed	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR[m,n]	Consider[o]	See PROS-13

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See footnotes on next page

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Prostate Cancer

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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

Many new recommended germline testing than before

Genomics and Precision Medicine

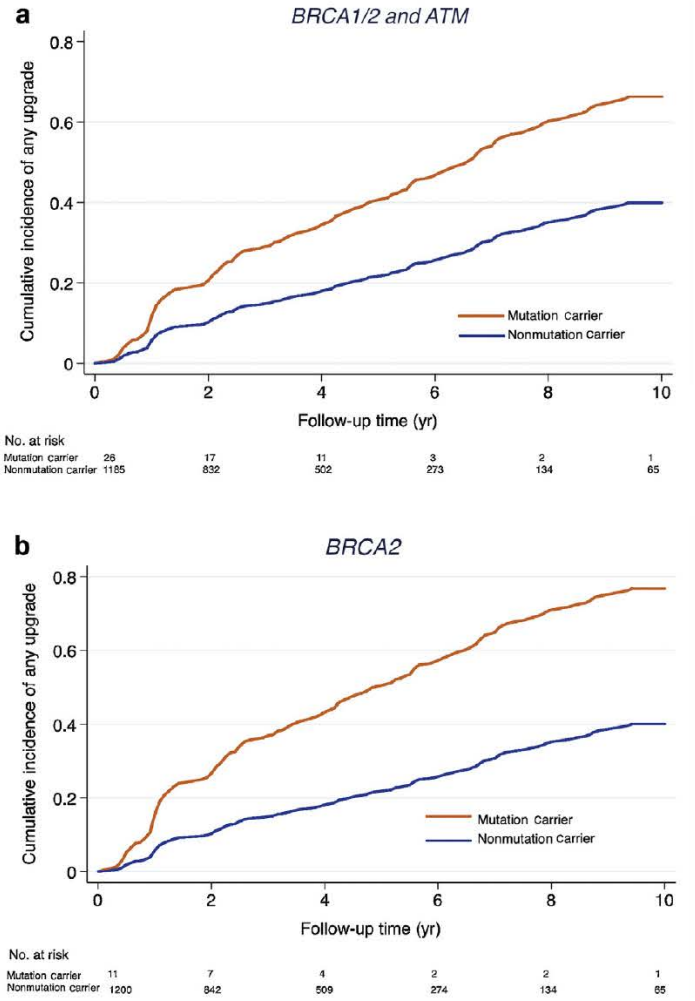


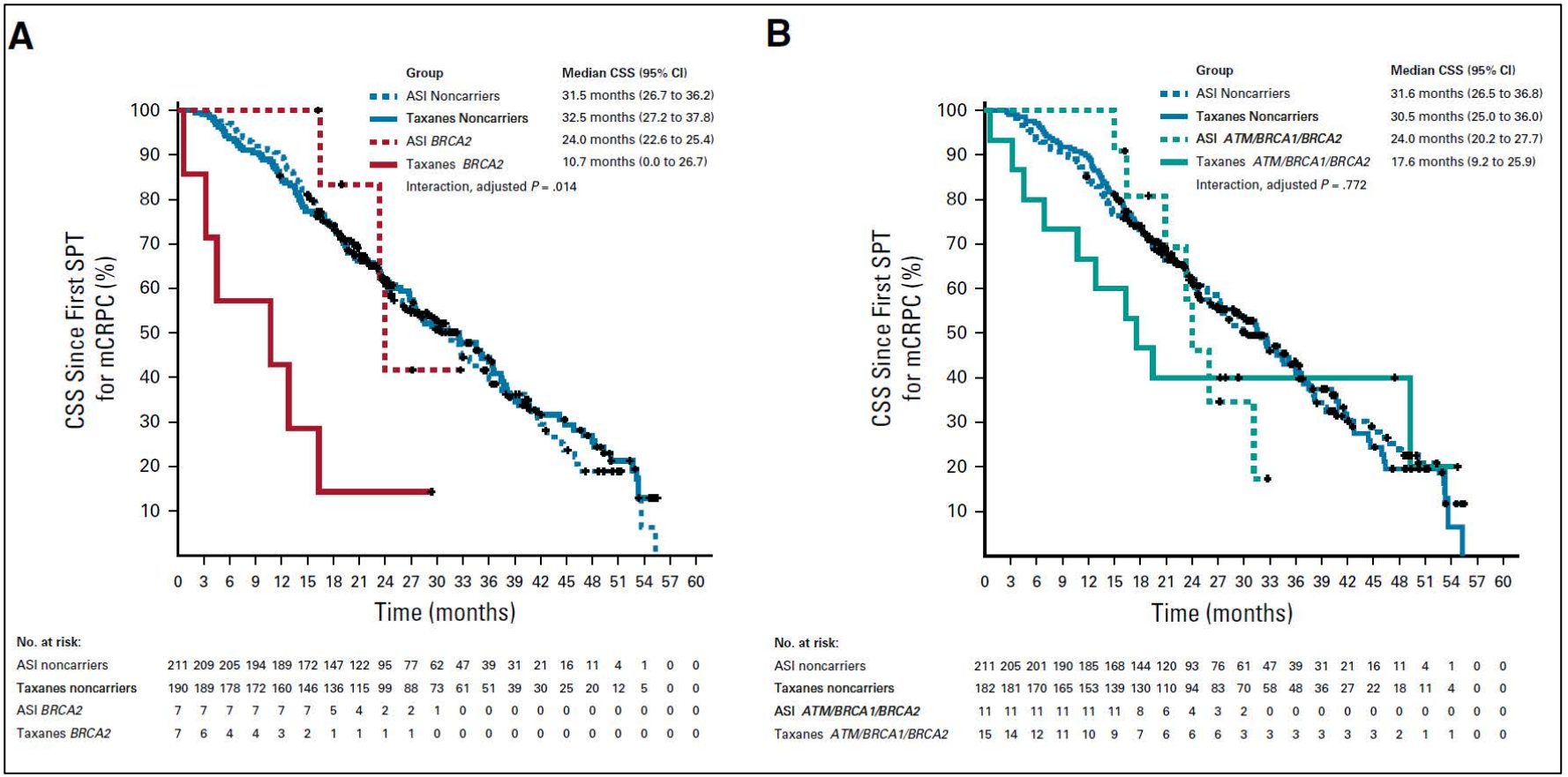
Fig. 1 – Cumulative incidence of upgrading on biopsies after the diagnostic biopsy in (A) carriers and noncarriers of mutations in *BRCA1/2* and/or *ATM*; (B) carriers and noncarriers of mutations in *BRCA2* only. Cumulative incidence based on competing risk analysis. Upgrading refers to any grade group (GG) or Gleason score higher than diagnostic biopsy GG irrespective of initial grade at biopsy.

ACTIVE SURVEILLANCE

Upgrading of biopsies of men on active surveillance for early-stage prostate cancer --> among *BRCA2* carriers

Carter et al. *Eur Urol* 2018

Genomics and Precision Medicine



PROREPAIR-B study: improved survival in mCRPC and *BRCA2* mutations treated with first-line with abiraterone or enzalutamide vs. taxanes

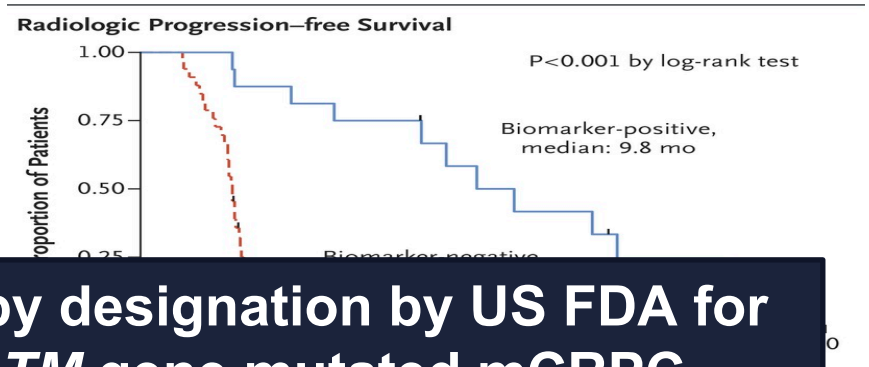
Castro et al. *JCO* 2019

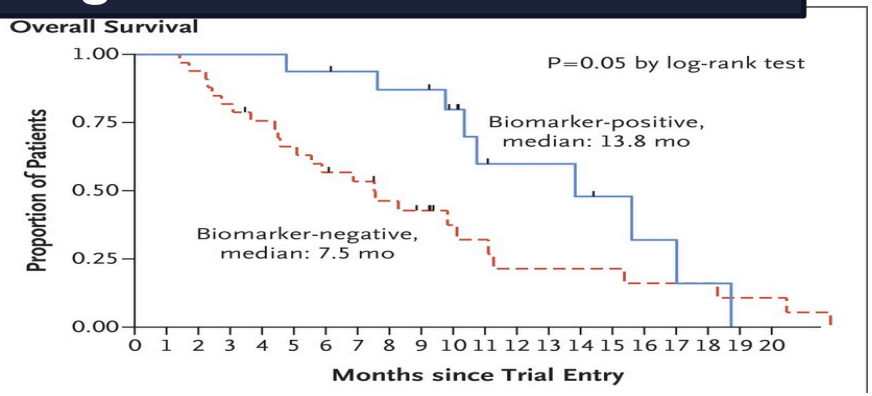
Phase 2 Study of Olaparib in mCRPC (TOPARP-A)

- Mutations
  - 14/16 (88%) of patients **with** a DNA repair alteration had a response
  - 2/33 (6%) of patients **without** a DNA repair alteration had a response

Granted Breakthrough Therapy designation by US FDA for treatment of *BRCA1/2* or *ATM* gene mutated mCRPC

Me	
Median OS	16.1 months
ORR (partial or complete)	32.7%
Duration of response	9 months
Reduction of PSA ≥50%	22% (14/49)
Confirmed reduction in CTC < 5 cells/7.5 mL	29% (14/49)





Mateo, et al. *N Engl J Med.* 2015; 373:1697-1708.

GENetic Testing for Men With Metastatic Prostate Cancer
www.gentlemenstudy.org

Dr. Heather Chang PI University of Washington

- Objective: Remove barriers to genetic testing that may provide critical information for men with metastatic prostate cancer[a]
- Web-based informed consent and patient survey on family history, knowledge, behavior, distress; allows patients to upload supporting data to verify metastatic prostate cancer, such as PSA, pathology reports, scans
- Patients receive Color Genomics saliva kit in the mail; cost covered by study
- Color Genomics pre-test video and post-test telephone access to counselors
- Patients receive results, are invited to follow-up additional genetic counseling, cascade testing, opportunities for research/registry participation, etc

[a] Study has been amended to allow for men in any state within the US, except New York, to participate.

Genetic Testing/Counseling for PCa

American College of Medical Genetics and Genomics (ACMG)

National Society of Genetic Counselors (NSGC)

Philadelphia Prostate Cancer Consensus 2017

NCCN 2019

- ≥ 2 cases of PCa age ≤55 in close relatives
- ≥ 3 FDRs with PCa
- Aggressive (Gl >7) PCa and ≥2 cases of breast, ovarian, and/or pancreatic cancer in close relative
- Metastatic PCa
- Intraductal PCa (regardless of stage only in NCCN 2019)
- Tumor sequencing w/mutations in hereditary cancer genes

Giri JCO 2018; NCCN.org; American College of Medical Genetics and Genomics (ACMG)/National Society of Genetic Counselors (NSGC) practice guidelines.: https://www.acmg.net/docs/ACMG_Practice_Guideline_Referral_Indications_for_cancer_predisposition.pdf

"Implementation of Genetic Testing for Inherited Prostate Cancer"

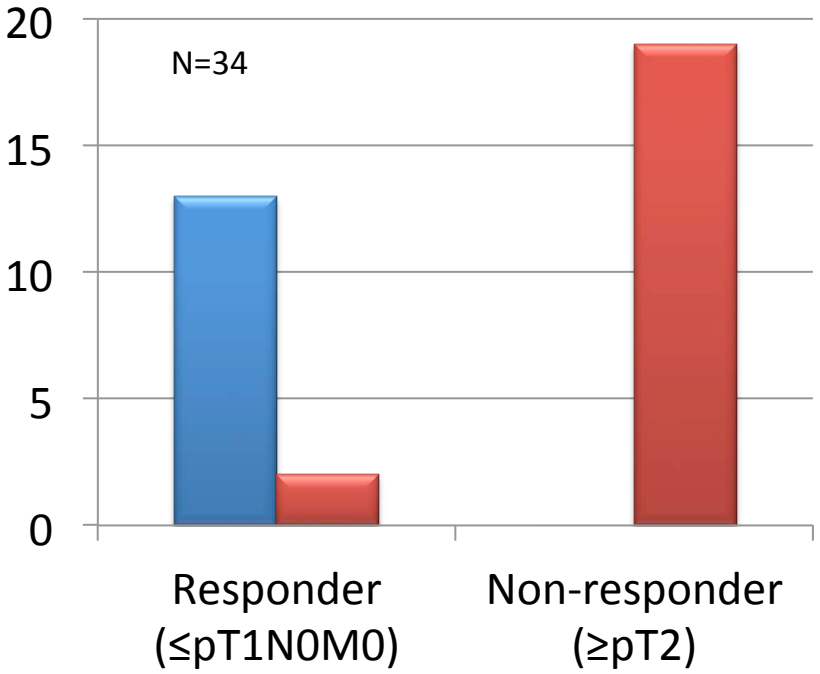
2019 Consensus Conference

October 4,5 2019

Sidney Kimmel Cancer Center, Thomas Jefferson University

Sidney Kimmel Cancer Center at Jefferson
NCI – designated

Dose Dense MVAC: Alterations in ATM, RB1 or FANCC predict pathologic response DD-MVAC (p<0.001)



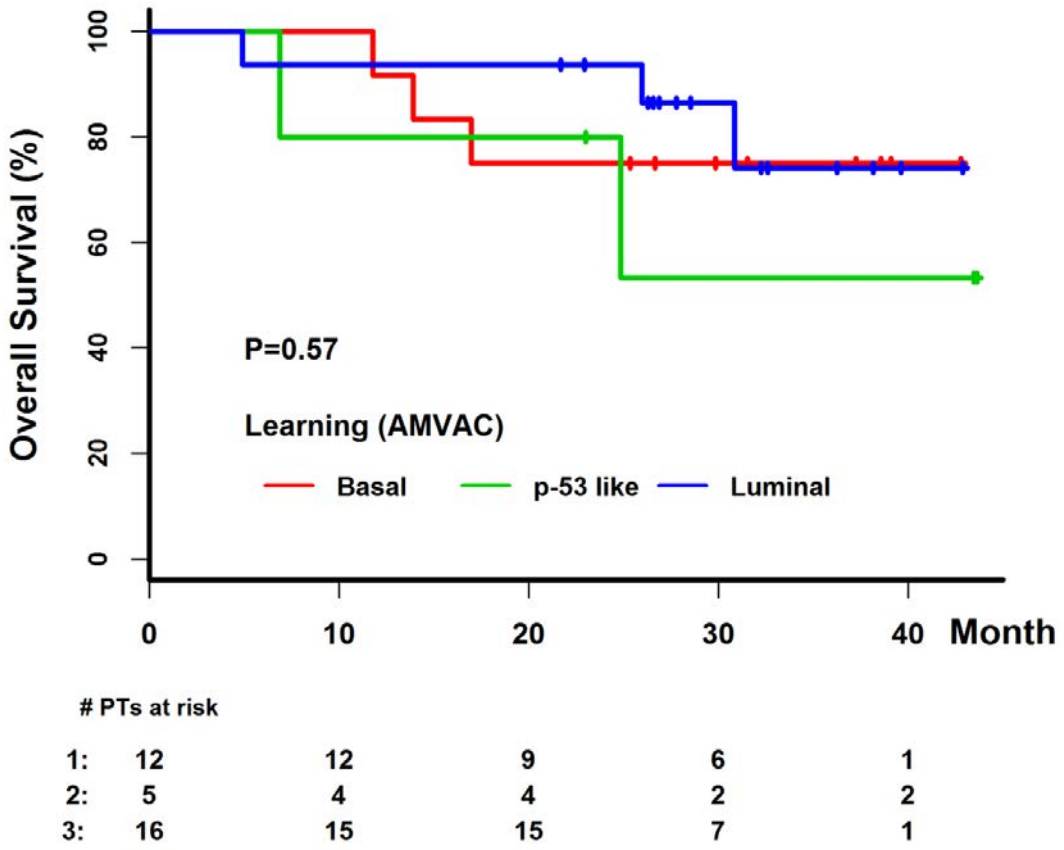
ATM/RB1/
FANCC mut

Sensitivity = 87%
Specificity = 100
PPV = 100%

P<0.001

Courtesy Dr. Plimack, FCCC

Bladder cancer subtypes and survival: BASAL/LUMINAL/p53 like



BLADDER PRESERVATION FOLLOWING NAC BASED ON cT0 + GENOMICS

Daniel Geynisman, Fox Chase Cancer Center

Major Inclusion Criteria:
- cT2-T3 N0M0
- ECOG 0-1
- Urothelial Predominant Histology

- **MFS is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (e.g., >cT4a) or M1 disease.**

TURBT #1 → AMVAC x 3 → TURBT #2

Sequencing
(Caris)
Mutation positive
defined as any
alterations in:
- ATM
- RB1
- FANCC
- ERCC2

No residual tumor/cT0 **AND** Mutation Pos (+)		**Active Surveillance**
cTa or cTis or cT1 or Pos (+) cytology or cT0 mutation Neg (-)	Patient & Physician Choose	**Intravesicle Tx OR Chemo-RT OR Cystectomy**
cT2	Patient & Physician Choose	**Chemo-RT OR Cystectomy**
≥cT3		**Cystectomy**

Primary Endpoint: Metastasis-free survival (MFS) at 2 years.
Non-inferiority design with a 14% margin between risk-adapted design (MFS=78%) and standard-of-care (MFS=64%).
Sample size=70 with an 82% power, Type I error=0.045

Conclusions

- Well established PCa genomic tissue testing
- Evolving recommendations for PCa genetic testing and decision making
- Most critical inherited genes today:
  - –BRCA 1/2, HOXB13, ATM, CHEK2
- Strongly consider referral for genetic testing AND counselling if high risk/family concerns
- Many new PCa genetic panels/genes are being made available commercially, need validation

San Diego Union Tribune:
“Undocumented urologist attempts to enter state of California”