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
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)

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

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

- ~15-20% inherited

**Blood or saliva**
- Inform cancer screening and prevention
- Genetic testing in blood relatives
- Informing treatment and clinical trials

**Decision-making**
- Treatment, and management

**Inform targeted therapies**
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

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

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

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

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 h, Janardan Khandekar g, Peter J. Hulick f, Daniel H. Shevrin f, Kathleen A. Cooney h, Zhoujun Shen, Alan W. Partin d, H. Ballentine Carter d, Michael A. Carducci f, Mario A. Eisenberger f, Sam R. Denmeade f, 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,†,*

B

Initial diagnosed with localized diseases
(n=674)

Log-rank p = 0.0013

Median survival (yr) 95%CI

| Mutation carrier | 11.0 | N/A |
| Nonmutation carrier | 18.0 | 17.2–18.8 |
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 . . .

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

- 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

4/2019
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
Gene)c	Variant	of
Uncertain
Significance	(VUS)
Richards	CS,
Can	be	reported	on	a	paJents
geneJc
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
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.

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
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 Guidelines Version 1.2018

## Prostate Cancer

### NEW 2018

## Risk Stratification and Staging Workup

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

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.
Many new recommended germline testing than before.
ACTIVE SURVEILLANCE

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

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.
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

**Efficacy**
- Median follow-up: 14.4 months
- Median OS: 10.1 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)

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

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
- 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

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

Responder (≤pT1N0M0) Non-responder (≥pT2)

N=34

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

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.

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”