The Role of genetic Testing for Inherited Prostate Cancer Risk

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Thomas Jefferson University
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I have the following financial interests or relationships to disclose:

<table>
<thead>
<tr>
<th>I have the following financial interests or relationships to disclose:</th>
<th>Disclosure code</th>
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<tbody>
<tr>
<td>Astellas/Pfizer, Bayer, Janssen, Merck, MDxHealth, Strand Diagnostics</td>
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<td>Thomas Jefferson University</td>
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<td>FKD, Janssen</td>
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</table>
60,000 Genetic Tests!!!

FDA to Finalize LDT Guidance Amid Uncertainty on Number of Genetic Tests Impacted

Feb 04, 2016 | Turna Ray

NEW YORK (GenomeWeb) – An analysis conducted by Tennessee-based healthcare IT firm NextGxDx suggests there may be around 60,000 genetic testing products currently on the market, comprising more than half of the US laboratory-developed test market.

Moreover, depending on the criteria used, NextGxDx has projected that around 7,600 of these genetic testing products could be deemed high risk by the US Food and Drug Administration, for which labs may have to meet premarket review requirements. Since the agency intends to finalize its draft oversight plan for LDTs this year, it's critical that the FDA and industry players have an accurate estimate of currently marketed tests.

Recreational Genomics????
Neanderthal Ancestry

Neanderthals were ancient humans who interbred with modern humans before becoming extinct 40,000 years ago. This report tells you how much of your ancestry can be traced back to Neanderthals.

You have 291 Neanderthal variants.

You have more Neanderthal variants than 70% of 23andMe customers. However, your Neanderthal ancestry accounts for less than 4% of your overall DNA.
Human Genome Project
1990-2003

3.2 billion base pairs

https://www.mun.ca/biology/scarr/Human_Genome_Project_timeline.html
Opinion of SCALIA, J.

SUPREME COURT OF THE UNITED STATES

No. 12–398

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL., PETITIONERS v. MYRIAD GENETICS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 13, 2013]

Justice Scalia, concurring in part and concurring in the judgment.

I join the judgment of the Court, and all of its opinion except Part I–A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. It suffices for me to affirm, having studied the opinions below and the expert briefs presented here, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that complementary DNA (cDNA) is a synthetic creation not normally present in nature.
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:**
  - BRCA1/2/ATM/CHEK2
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

4/2018
Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017

Co-Chairs:
Leonard G. Gomella, MD
Veda N. Giri, MD
Karen E. Knudsen, PhD

Sidney Kimmel Cancer Center, Thomas Jefferson University
and
The Foundation for Breast and Prostate Health
Philadelphia, Pennsylvania
March 3 & 4, 2017
Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017


Representation: Urology (National and International), Medical Oncology, Radiation Oncology, Clinical Cancer Genetics, Genetic Counseling, Health Policy, Bioethics, Population Science, Molecular Epidemiology, Pathology, Breast/GI/Gyn Oncology, Genetic Basic Science Research, Patient Advocates, Patient Stakeholders, NCCN, NCI, ACS
Philadelphia 2017 Consensus-Driven Framework for Multigene Testing for Inherited Prostate Cancer

Which men should consider genetic counseling and genetic testing for prostate cancer?
- Shared decision-making encouraged
- FH of HBOC, HPC, or Lynch syndrome
- FH of 2 close relatives with these cancer syndromes
- Tumor sequencing with mutations in inherited cancer genes
- All men with mCRPC

Which genes should be tested?
Family History:
- BRCA1/2 (HBOC)
- HOXB13 (HPC)
- DNA MMR genes (LS)

Tumor Sequencing:
- BRCA1/2
- DNA MMR genes
- HOXB13
- ATM

mCRPC:
- BRCA1/2
- ATM

Which genes should be factored into management considerations regarding:
- Prostate cancer Screening:
  - BRCA2
  - HOXB13

- Early-stage Disease:
  - BRCA2

- Advanced Disease:
  - BRCA2
  - ATM

- mCRPC:
  - BRCA1
  - BRCA2
  - ATM

Key
- High consensus agreement
- Moderate consensus agreement

Considerations:
- Need greater insights into genetic predisposition to lethal PCA.
- mCRPC could be given stronger consideration for testing to inform cancer risks for men and their families.
- Need more data in African American males.
- Cost-effectiveness and QOL research needed.
- Need more data in screening/early-stage disease.
- Clinical trials enrollment is important.

Giri, JCO 2018. Graphic Courtesy of Gomella, Giri and Knudsen
## 3 Main Genomic Applications

<table>
<thead>
<tr>
<th>Gene, Gene/Drug, Test, or Family History</th>
<th>Disorder/Indication</th>
<th>Use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>family history of breast/ovarian or other types of BRCA-related cancer</td>
<td>hereditary breast and ovarian cancer in women</td>
<td>risk prediction for referral for BRCA genetic counseling</td>
</tr>
<tr>
<td>first-degree family history of breast cancer</td>
<td>hereditary breast and ovarian cancer in women</td>
<td>risk prediction, chemoprevention</td>
</tr>
<tr>
<td>family history of known breast/ovarian cancer with deleterious BRCA mutation</td>
<td>hereditary breast and ovarian cancer in women</td>
<td>risk prediction; referral to counseling for BRCA genetic testing</td>
</tr>
<tr>
<td>HER2/trastuzumab</td>
<td>invasive breast cancer</td>
<td>PGx</td>
</tr>
<tr>
<td>ER and PgR</td>
<td>invasive breast cancer, breast cancer recurrences</td>
<td>PGx</td>
</tr>
<tr>
<td>Oncotype DX® adjuvant chemotherapy</td>
<td>ER+/LN- HER2-breast cancer, intermediate risk of recurrence</td>
<td>prognostic; guiding decision-making: adjuvant chemotherapy</td>
</tr>
</tbody>
</table>

Risk and screening  
Pharmacogenomics  
Decision making: treatment and adjuvant therapy

http://www.cdc.gov/genomics/gtesting/tier.htm
EVOLUTION OF CANCER EVALUATION

Imaging

Gross Path

Histology Path

Cell

Nucleus

Chromosomes

DNA

Base Pairs
Our understanding of genomics relies on computational biology support.

**BRCA2 gene section**

- 27 exons total
- Coding region
- 10,433 base pairs
- 12 pages long
- Image is a very small portion of exon 11
Genomic Tissue Testing

- 5 x 5µ FFPE sections (0.5-1.0mm length) + H&Es
- Most through Pathology
- Price: $3000-5000
- > 90% success (Warn patients!)

Germ Line Genetic Testing

- Buccal saliva (common) or blood
- “Recreational” tests unlikely to deep sequence
- Medical labs: beware low cost

Deep sequencing (hours to days):
- Aka: Next Gen Sequencing (NGS)
- Sequencing a region many times
- Minimizes errors
- More sequencing = more expensive = more accurate
# Prostate Cancer Genomic Tissue Tests

<table>
<thead>
<tr>
<th></th>
<th><strong>ConfirmMDx (MDxHealth)</strong></th>
<th><strong>Decipher (GenomeDx)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>To reduce unnecessary repeat biopsies. Performed on previous negative biopsy tissue. (3 genes Epigenetic methylation)</td>
<td>Prostate Biopsy Treatment decisions after radical prostatectomy (22 genes)</td>
</tr>
<tr>
<td><strong>Outcome Predicted</strong></td>
<td>Presence or absence of occult cancer detection; direct follow up biopsy based on “halo” effect</td>
<td>Risk of clinical metastasis following RP High Grade Disease (Gleason Grade 4/5) 5 year metastasis 10 year PCSM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>Prolaris (Myriad)</strong></th>
<th><strong>Oncotype DX (Genomic Health)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Biopsy and post RP risk of disease progression; active surveillance decision (46 genes)</td>
<td>Risk assessment on biopsy; active surveillance decision Risk on RP (3+3 and 3+4) (17 genes)</td>
</tr>
<tr>
<td><strong>Outcome Predicted</strong></td>
<td>PCA-specific mortality, metastasis, recurrence, progression (10 year)</td>
<td>Adverse Bx pathology : Primary Gleason 4, any 5, pT3 Risk of Death and Metastasis on RP</td>
</tr>
</tbody>
</table>
All Cancer is Genetic
Not All Cancer is Hereditary

First mutation → Second mutation → Third mutation → Fourth mutation

Malignant cells tumor growth
Hereditary/Familial/Sporadic Cancer

• **Hereditary** (5-10% of cases)
  - Usually due to a single inherited genetic mutation
  - Greatly **increases** lifetime risk
    - BRCA1, BRCA2, Lynch syndrome
    - HOXB13: Inherited prostate cancer

• **Familial** (15-20% of cases)
  - Some features of hereditary cancer
  - No detectable mutation identified
  - Possible genetic + environmental risk
  - Close family members increased risks

• **Sporadic** (70-80% of cases)
  - Exact cause unknown
  - No features of hereditary or familial cancers
  - No increased risks for close family members
Genomic/Genetic Testing for Prostate Cancer Risk

• Background:
  • 10-15% PCa are hereditary.
  • Inherited genes such as BRCA 1/2 do not cause cancer but increase risk
  • These pathogenic genes interact with other gens/environment to lead to increased risk of PCa.
  • Also increased risk for other cancers
  • Evolving evidence on how to best use these genes for screening

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

Based on data in Nicolosi, et al ASCO Abstract 5009 2017 Chicago;
Some 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>
BRCA 1/2 and Prostate Cancer

- DNA damage response (DDR) genes
- 2-6 fold ↑ lifetime risk (BRCA2 > BRCA1)
- 8.6-fold ↑ risk by age 65 (BRCA2)
- PCa: Likely to be aggressive: Gleason 8 or higher, node +, mets, poor survival
- ↑ self and family risk for other hereditary cancers: breast, ovarian, melanoma, pancreatic, Lynch Syndrome, colon, gastric
- May direct mCRPC therapy (PARP inhibitors)
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 Gulu kota 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 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,*

B

![Graph showing PCa-specific survival]

Initial diagnosed with localized diseases (n=674)

Log–rank p = 0.0013

<table>
<thead>
<tr>
<th>Median survival (yr)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation carrier</td>
<td>11.0</td>
</tr>
<tr>
<td>Nonmutation carrier</td>
<td>18.0</td>
</tr>
</tbody>
</table>
## BRCA and Cancer

Although the risk of cancer is greater for women than men with BRCA 1/2 gene mutations, both sexes face elevated lifetime chances of several types of cancer. **Risk of cancer as a percentage, by gender.**

<table>
<thead>
<tr>
<th>MEN</th>
<th>Cancer type</th>
<th>U.S. white</th>
<th>BRCA1 mutation carriers</th>
<th>BRCA2 mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
<td>0.1%</td>
<td>1-5%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>16</td>
<td>*</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>2</td>
<td>N.S.</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>1</td>
<td>Up to 3</td>
<td>3-5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WOMEN</th>
<th>Cancer type</th>
<th>U.S. white</th>
<th>BRCA1 mutation carriers</th>
<th>BRCA2 mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
<td>13%</td>
<td>60-80%</td>
<td>50-70%</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>1-2</td>
<td>20-45</td>
<td>10-20</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>2</td>
<td>N.S.</td>
<td>Up to 5</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>1</td>
<td>Up to 3</td>
<td>3-5</td>
</tr>
</tbody>
</table>

N.S. = Not significant; * Some evidence of an increased risk for men younger than 65

**SOURCE:** Penn Medicine’s Basser Research Center for BRCA

MIKE PLACENTRA / Staff Artist
Cancer risks for patients with a hereditary cancer syndrome:

**FOR MEN:**
- Breast Cancer Risk up to 68x the general population.
- Prostate Cancer Risk up to 1.5x the general population.
- Pancreatic Cancer Risk up to 7x the general population.
- Increased risk for Melanoma and Colon Cancer

**FOR WOMEN:**
- Breast Cancer Risk up to 11x the general population.
- Ovarian Cancer Risk up to 44x the general population.
- Uterine Cancer Risk up to 47x the general population.
- Increased risk for Melanoma, Pancreatic Cancer and Colon Cancer

https://new.myriadpro.com/medical-specialties/urology/
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+ 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
First time that NCCN for PCa noted BRCA

NCCN Guidelines Version 1.2017
Prostate Cancer Early Detection

**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
  - Family or personal history of BRCA1/2 mutations

**RISK ASSESSMENT**
- Start risk and benefit discussion about offering prostate screening:
  - Baseline PSA
  - Strongly consider baseline digital rectal examination (DRE)

**EARLY DETECTION EVALUATION**
- PSA <1 ng/mL, DRE normal (if done)
  - Repeat testing at 2-4 year intervals
- PSA 1-3 ng/mL, DRE normal (if done)
  - Repeat testing at 1-2 year intervals
- PSA >3 ng/mL or very suspicious DRE
  - 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)

---

**Discussion**

- African-American men have a higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to Caucasian-American men. This is attributable to a greater risk of developing preclinical prostate cancer and a higher likelihood that a preclinical tumor will spread. Consequently, it is reasonable for African-American men to begin discussing PSA screening with their providers several years earlier than Caucasian-American men. Options for early detection of prostate cancer in African-American men may include extended screening years, screening at age 45, and testing for prostate cancer susceptibility genes.

- BRCA1/2 pathogenic mutation carriers are associated with 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. Information regarding BRCA1/2 gene status should be used as part of the discussion about prostate cancer screening. See Discussion.

---

The reported median PSA values for men aged 40–49 y range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Therefore, the PSA value of 1.0 ng/mL selects for the upper range of PSA values. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and for the aggressive form of the disease. The higher above the median, the greater the risk.

Men age ≥80 years with serum PSA <1.0 ng/mL have a very low risk of metastases or death due to prostate cancer and may not benefit from further testing. A PSA cut point of 3.0 ng/mL at age 75 years also carries a low risk of metastases, and may help avoid harms of prostate biopsy and treatment. Therefore, for men age ≥75 years, and in those under age 75 who have underlying comorbidity, a lower cut point of 2.5 ng/mL may be a reasonable alternative.
Hereditary Prostate Cancer

NCCN now recommends referral to genetic counseling for all men with metastatic (NOTE HBOC Guidelines!!!)
HBOC (Hereditary Breast and Ovarian Cancer Syndrome)

NCCN Guidelines Version 1.2018
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA MUTATION-POSITIVE MANAGEMENT

MEN
- Breast self-exam training and education starting at age 35 y
- Clinical breast exam, every 12 mo, starting at age 35 y
- Starting at age 45 y: (See Guidelines for Prostate Early Detection)
  - Recommend prostate cancer screening for BRCA2 carriers
  - Consider prostate cancer screening for BRCA1 carriers

MEN AND WOMEN
- Education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene mutations.
- No specific screening guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers observed in the family.

RISK TO RELATIVES
- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

REPRODUCTIVE OPTIONS
- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.
- Biallelic mutations in some genes, such as BRCA2 and certain other genes included on gene panels, may be associated with rare autosomal recessive conditions. Thus, for these types of genes, consideration would be given to carrier testing the partner for mutations in the same gene if it would inform reproductive decision-making and/or risk assessment and management.
<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&lt;br&gt;• Gleason score ≤6/grade group 1 AND&lt;br&gt;• PSA ≤10 ng/mL AND&lt;br&gt;• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND&lt;br&gt;• PSA density =0.15 ng/mL</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Consider if strong family history&lt;br&gt;See PROS-4</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>• T1-T2a AND&lt;br&gt;• Gleason score ≤6/grade group 1 AND&lt;br&gt;• PSA ≤10 ng/mL</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Consider if life expectancy ≥10y&lt;br&gt;See PROS-5</td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>• T2b-T2c OR&lt;br&gt;• Gleason score 3+4=7/grade group 2 OR&lt;br&gt;• PSA 10–20 ng/mL&lt;br&gt;• Percentage of positive biopsy cores ≤50%</td>
<td>Bone imaging:&lt;br&gt;- not recommended for staging&lt;br&gt;- Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Consider if life expectancy ≥10y&lt;br&gt;See PROS-6</td>
<td>Consider if strong family history&lt;br&gt;See PROS-7</td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>• T2b-T2c OR&lt;br&gt;• Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR&lt;br&gt;• PSA 10–20 ng/mL</td>
<td>Bone imaging:&lt;br&gt;- recommended if T2 and PSA &gt;10 ng/mL&lt;br&gt;- 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&lt;br&gt;See PROS-8</td>
<td></td>
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<tr>
<td>Intermediate</td>
<td>• T3a OR&lt;br&gt;• Gleason score 8/grade group 4 or Gleason score 4+6/grade group 5 OR&lt;br&gt;• PSA &gt;20 ng/mL</td>
<td>Bone imaging:&lt;br&gt;- recommended&lt;br&gt;- Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Not routinely recommended</td>
<td>Consider&lt;br&gt;See PROS-9</td>
<td></td>
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<tr>
<td>High</td>
<td>• T3b-T4 OR&lt;br&gt;• Primary Gleason pattern 5 OR&lt;br&gt;• ≥4 cores with Gleason score 8–10/ grade group 4 or 5</td>
<td>Bone imaging:&lt;br&gt;- recommended&lt;br&gt;- Pelvic ± abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Not routinely recommended</td>
<td>Consider&lt;br&gt;See PROS-10</td>
<td></td>
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<tr>
<td>Regional</td>
<td>Any T, N1, M0</td>
<td>Already performed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metastatic</td>
<td>Any T, Any N, M1</td>
<td>Already performed</td>
<td></td>
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</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.
### RISK STRATIFICATION AND STAGING WORKUP FOOTNOTES

<table>
<thead>
<tr>
<th>Footnote</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>Strong family history consists of: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age; known germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (germline mutations in MLH1, MSH2, MSH6, or PMS2); and/or more than one relative with breast, ovarian, or pancreatic cancer (suggests possibility of BRCA2 mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome).</td>
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<td>d</td>
<td>For asymptomatic patients with life expectancy ≤5 years, no further workup or treatment is indicated until the patient becomes symptomatic.</td>
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<td>h</td>
<td>Patients with a MRI lesion that is biopsied and demonstrates grade group 1 cancer (regardless of percentage core involvement or number of cores involved) who otherwise qualify for very low risk should be considered very low risk.</td>
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<tr>
<td>i</td>
<td>See Principles of Imaging (PROS-B).</td>
</tr>
<tr>
<td>j</td>
<td>Bone imaging should be performed for any patient with symptoms consistent with bone metastases.</td>
</tr>
<tr>
<td>k</td>
<td>Plain films, CT, MRI, or F-18 NaF PET/CT can be considered for equivocal results on initial bone scan. See PROS-B.</td>
</tr>
<tr>
<td>l</td>
<td>Men with low or favorable intermediate risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, Promark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. See Discussion.</td>
</tr>
<tr>
<td>m</td>
<td>DNA analysis for MSI and IHC for MMR are different assays measuring the same biological effect. If MSI-H or dMMR is found, refer to genetic counseling to assess for the possibility of Lynch syndrome. MSI or dMMR indicate eligibility for pembrolizumab in later lines of treatment for CRPC (see PROS-16 and PROS-17).</td>
</tr>
<tr>
<td>o</td>
<td>Consider testing for mutation in these genes (germline and somatic): BRCA1, BRCA2, ATM, PALB2, FANCA; refer to genetic counseling if positive. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g., PARP inhibitors).</td>
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<td>p</td>
<td>The prevalence of inherited homologous recombination gene mutations in men with metastatic or localized high risk was found to be 11.8% and 8.0%, respectively. Therefore, germline genetic testing and genetic counseling should be considered in all men with high risk, very high risk, regional, or metastatic prostate cancer. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2018;379:443-453.</td>
</tr>
<tr>
<td>q</td>
<td>For asymptomatic patients with life expectancy ≤5 years, See PROS-1.</td>
</tr>
</tbody>
</table>
• Started in 2014 clinic is within the existing (1996) GU Multidisciplinary clinic so that men presenting with all stages of prostate cancer can have the opportunity to undergo preliminary genetic evaluation.
• Focus on prostate cancer risk assessment with preliminary discussion.
• Genetics staff: Genetic counselor, Dr. Giri, and research coordinator.
• Supports our GEM (Genetic Evaluation of Men) multigene study.

Giri et al CJU June 2015
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.
Genetic Counseling for Inherited Cancer Risk

Family history → Personal cancer features → Other risk factors →
Determine suspicion for inherited cancer risk →

Discuss:
- Genetic test options
- Types of results
- Cancer risks
- Insurance implications
- Reproductive implications

Affected individuals:
- Identify additional cancer risks
- Inform treatment
- Test relatives for cancer risk

Unaffected individuals:
- Inform screening and prevention
- Test relatives for familial mutation for inherited cancer risk (Cascade Testing)

Patient makes informed decision regarding proceeding with genetic testing

**Advocated by NCCN, ASCO, and NSGC**

Courtesy Dr. Veda Giri
Genetic Counseling for PCa Criterion

American College of Medical Genetics and Genomics (ACMG)
National Society of Genetic Counselors (NSGC)
Philadelphia Prostate Cancer Consensus 2017
NCCN 2018

- > 2 cases of PCa age ≤ 55 in close relatives
- > 3 FDRs with PCa
- Aggressive (GI > 7) PCa and > 2 cases of breast, ovarian, and/or pancreatic cancer in close relative
- Metastatic prostate cancer
- Tumor sequencing w/mutations in hereditary cancer genes

Conclusions

• Well established PCa genomic tissue testing
• Evolving recommendations for PCa genetic testing
• Most critical inherited genes today:
  – BRCA 1/2, HOXB13, ATM, CHEK2
• High prevalence of germ line mutations (>11%): all mCRPC be offered germline testing
  – May direct therapy of metastatic disease
• Strongly consider referral for genetic testing AND counselling if high risk disease or familial concerns
• Expanding role for genetic counsellors in urology care
• Many new prostate cancer genetic panels are being made available commercially, need validation