FDUS August 2018

The Role of Genetic Testing for Prostate Cancer Risk

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BEST HOSPITALS
U.S.News
NATIONAL
UROLOGY
2017-18


PHILADELPHIA
EAGLES

CANCER AWARENESS

Genomics, studies try to uncover prostate cancer

By Paul Jablow
FOR THE INQUIRER

or researchers, physicians — one cancer from another. Now researchers at Thomas Jefferson University and elsewhere think they

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

60,000 Genetic Tests!!!

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

THE WALL STREET JOURNAL.

HEALTH | HEALTH & WELLNESS

August 8, 2018

The Genetic Test Some Men Don't Know They Need

Women are far more likely to get tested for inherited BRCA and other gene mutations, even though they also pose a cancer risk for men and their children

Recreational Genomics????

23andMe

ancestry.com

Spring 2013: Everything Changed

May 13, 2013

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.

June 13, 2013

3 Main Genomic Applications

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

http://www.cdc.gov/genomics/gtesting/tier.htm

Risk and screening

Pharmacogenomics

Decision making: treatment and adjuvant therapy

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

Sidney Kimmel Cancer Center at Jefferson
NCI – designated

Sidney Kimmel Cancer Center, Thomas Jefferson University

and

The Foundation for Breast and Prostate Health

Philadelphia, Pennsylvania

March 3 & 4, 2017

FOUNDATION FOR Breast & Prostate Health

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

www.phillyprostate.com

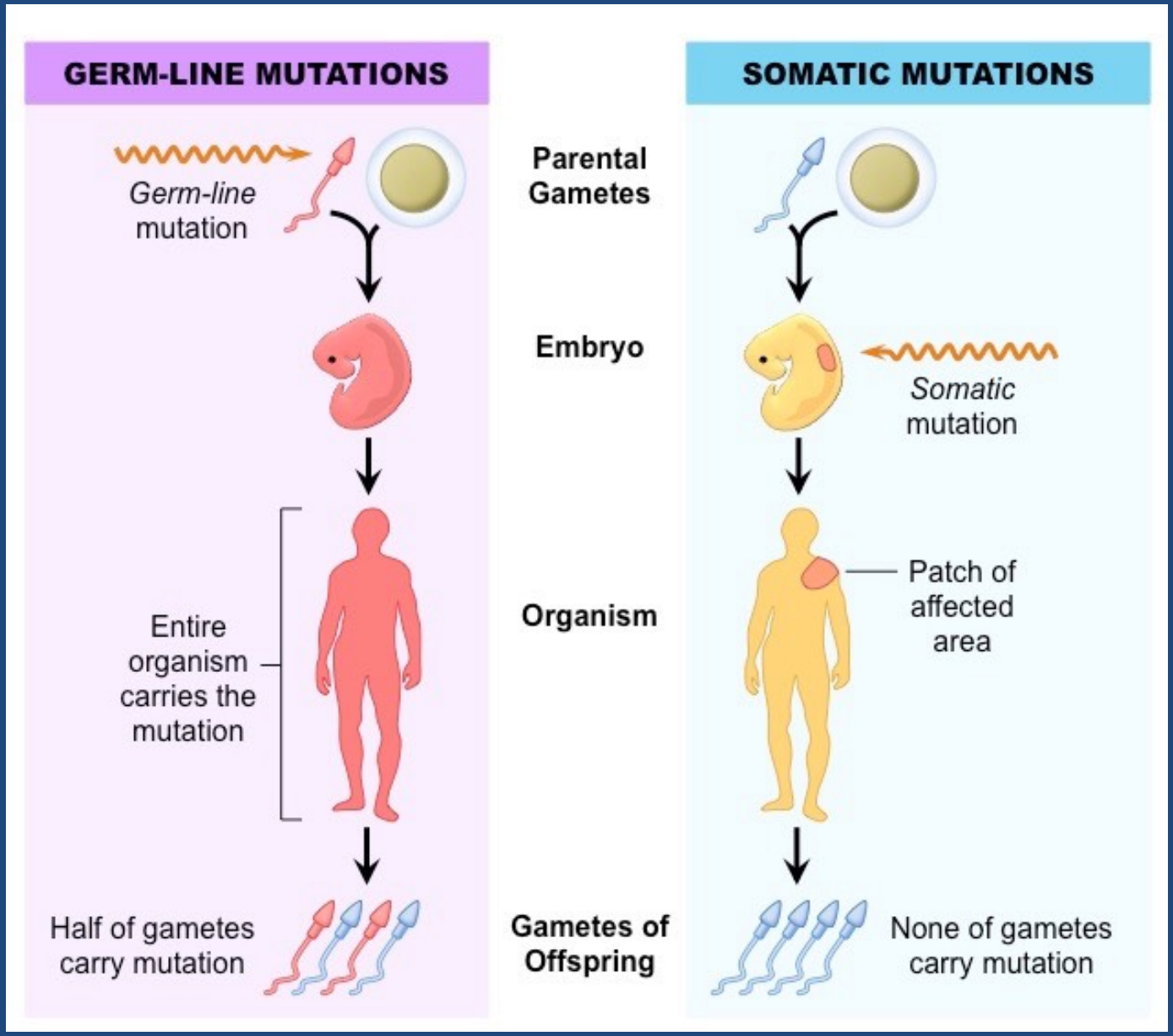
JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

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

Veda N. Giri, Karen E. Knudsen, William K. Kelly, Wassim Abida, Gerald L. Andriole, Chris H. Bangma, Justin E. Bekelman, Mitchell C. Benson, Amie Blanco, Arthur Burnett, William J. Catalona, Kathleen A. Cooney, Matthew Cooperberg, David E. Crawford, Robert B. Den, Adam P. Dicker, Scott Eggener, Neil Fleshner, Matthew L. Freedman, Freddie C. Hamdy, Jean Hoffman-Censits, Mark D. Hurwitz, Colette Hyatt, William B. Isaacs, Christopher J. Kane, Philip Kantoff, R. Jeffrey Karnes, Lawrence I. Karsh, Eric A. Klein, Daniel W. Lin, Kevin R. Loughlin, Grace Lu-Yao, S. Bruce Malkowicz, Mark J. Mann, James R. Mark, Peter A. McCue, Martin M. Miner, Todd Morgan, Judd W. Moul, Ronald E. Myers, Sarah M. Nielsen, Elias Obeid, Christian P. Pavlovich, Stephen C. Peiper, David F. Penson, Daniel Petrylak, Curtis A. Pettaway, Robert Pilarski, Peter A. Pinto, Wendy Poage, Ganesh V. Raj, Timothy R. Rebbeck, Mark E. Robson, Matt T. Rosenberg, Howard Sandler, Oliver Sartor, Edward Schaeffer, Gordon F. Schwartz, Mark S. Shahin, Neal D. Shore, Brian Shuch, Howard R. Soule, Scott A. Tomlins, Edouard J. Trabulsi, Robert Uzzo, Donald J. Vander Griend, Patrick C. Walsh, Carol J. Weil, Richard Wender, and Leonard G. Gomella

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



http://ib.bioninja.com.au/

Prostate Cancer Genomic Tissue Tests

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

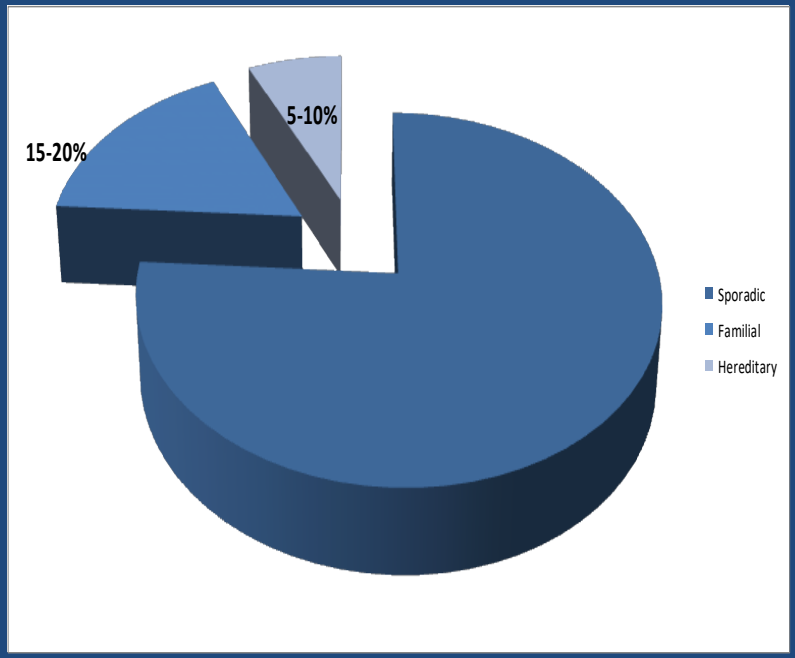
	Prolaris (Myriad)	Oncotype DX (Genomic Health)
Indications	Biopsy and post RP risk of disease progression; active surveillance decision (46 genes)	Risk assessment on biopsy; active surveillance decision Risk on RP (3+3 and 3+4) (17 genes)
Outcome Predicted	PCa-specific mortality, metastasis, recurrence, progression (10 year)	Adverse Bx pathology : Primary Gleason 4, any 5, pT3 Risk of Death and Metastasis on RP

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 genes/environment to increased risk of PCa.
  - Also increased risk for other cancers
  - Evolving evidence on how to best use these genes for screening
- Why do 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 or their 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 genes associated with prostate cancer BUT DO NOT CAUSE 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

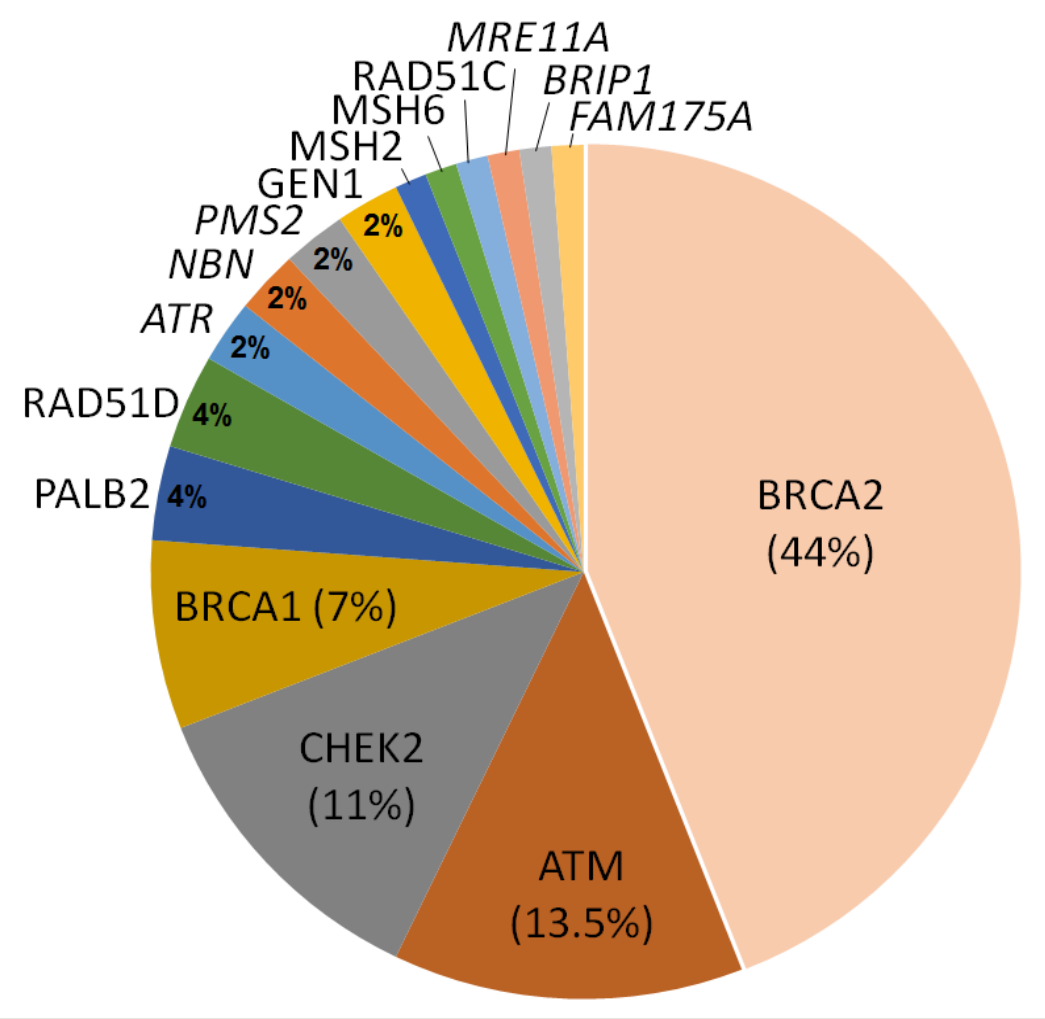
Based on data in Nicolosi, et al ASCO Abstract 5009 2017 Chicago;
https://www.ncbi.nlm.nih.gov/gene/

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

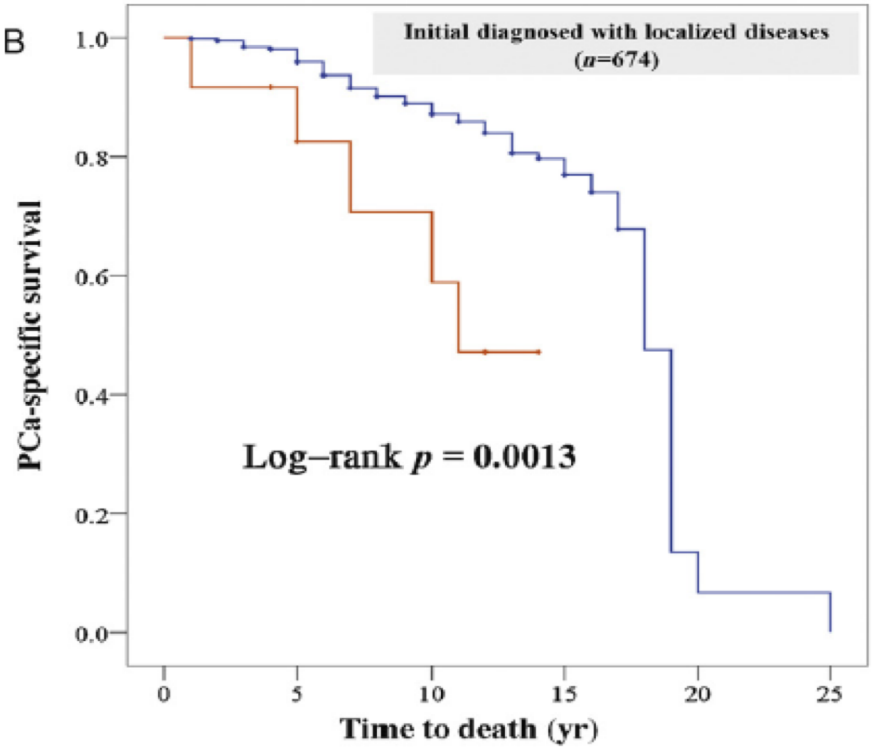
- BRCA-2 best studied for screening and treatment
- PCa males with BRCA-2 have more aggressive disease
- More work is needed on the other PCa genes identified
- Germline mutations in 11.8% of metastatic vs. 4.6% localized disease



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

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.*

Cancer type	U.S. white	BRCA1 mutation carriers	BRCA2 mutation carriers
MEN			
Breast	0.1%	1-5%	7%
Prostate	16	*	25
Melanoma	2	N.S.	5
Pancreas	1	Up to 3	3-5
WOMEN			
Breast	13%	60-80%	50-70%
Ovary	1-2	20-45	10-20
Melanoma	2	N.S.	Up to 5
Pancreas	1	Up to 3	3-5

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

http://pinkhope.org.au/what-it-means-for-men-who-carry-a-brca-gene-fault/

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" (7 gene)**
  - ATM, BRCA1, BRCA2, CHEK2, HOXB13, PALB2, RAD51D

7/2018

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
- **Strand Diagnostics – "98 Gene Panel" screen for:**
  Breast, Ovarian, Colorectal, Endometrial, Melanoma, Pancreatic, Gastric, Prostate, Others
  (UroSeq PLUS 91 Other genes)
  - AIP, ALK, APC, ATM, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, BUB1B, CDC73, CDH1, CDK4, CDKN1C, CDKN2A, CEBPA, CEP57, CHEK2, CYLD, DDB2, DICER1, DIS3L2, EGFR, EPCAM, ERCC2, ERCC3, ERCC4, ERCC5, EXT1, EXT2, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FH, FLCN, GATA2, GPC3, HNF1A, HOXB13, HRAS, KIT, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, NSD1, PALB2, PHOX2B, PMS1, PMS2, PPM1D, PRF1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL4, RET, RHBDF2, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SLX4, SMAD4, SMARCA4, SMARCB1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, WT1, WRN, XPA, XPC

STRAND DIAGNOSTICS
know error

UroSeq™

PROSTATE GENE PANEL TEST

To Help Assess Prostate Cancer Risk

Test Consent and Family History Form
BRCA1/BRCA2/ATM/CHEK2/PALB2/
HOXB13/RAD51D Gene Panel

Today's date	Patient Name (First and Last Printed)	Patient Date of Birth Month / Day / Year

Personal History of Cancer: ☐ No personal history of cancer

Have you ever been diagnosed with:

- ☐ Bladder cancer. If so, what age? _____
- ☐ Brain tumor. If so, what age? _____
- ☐ Colon/Rectal cancer. If so, what age? _____
- ☐ Colon/Rectal adenoma polyps. If so, what age? _____ How many? _____
- ☐ Gastric (stomach) cancer. If so, what age? _____
- ☐ Kidney cancer. If so, what age? _____
- ☐ Prostate cancer. What age? ___ Gleason score? __
- ☐ Leukemia. If so, what age? _____
- ☐ Male breast cancer. If so, what age? _____
- ☐ Melanoma (skin cancer). If so, what age? _____
- ☐ Pancreatic cancer. If so, what age? _____
- ☐ Sarcoma. If so, what age? _____
- ☐ Thyroid cancer. If so, what age? _____
- ☐ Other? _____

Patient Family History of Cancer: ☐ No known family history of cancer

If any of your relatives have had cancer, please indicate below (including parents, brother/sister, children, grandparents, grandchildren, uncles, nephews, half-brother/sister, great grandparents, great grandchildren, or first cousins).

Relative	Mother's Side?	Father's Side?	Cancer Type (or if adenoma polyp, how many?)	Age at Diagnosis
	☐	☐		
	☐	☐		
	☐	☐		
	☐	☐		
	☐	☐		
	☐	☐		

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
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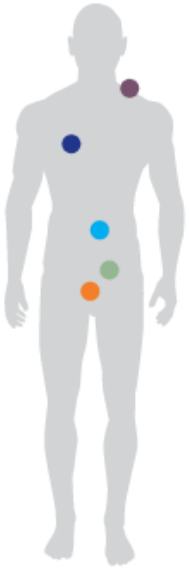
myriad

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.

Cancer risks for patients with a hereditary cancer syndrome:[2]



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 . . .

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

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

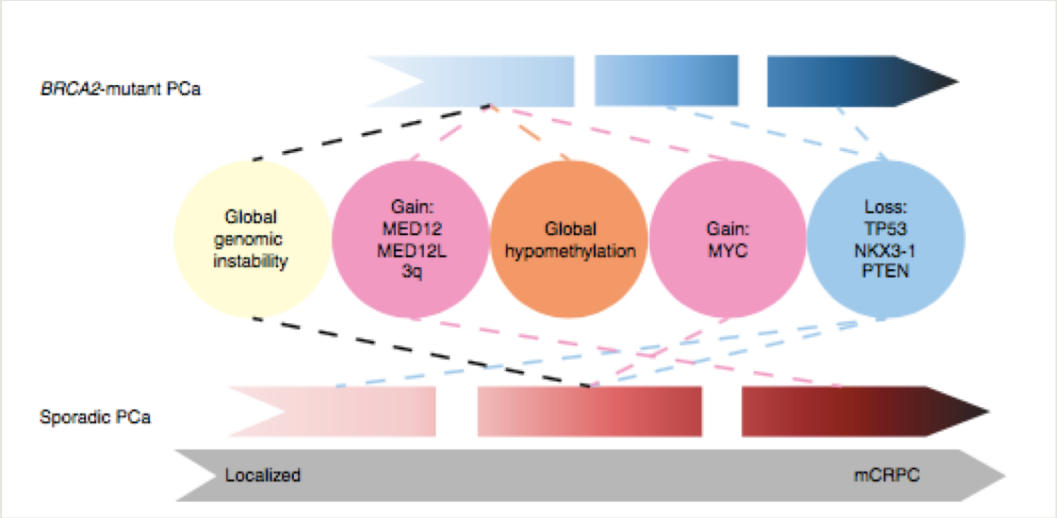
ARTICLE

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

First time that NCCN for PCa noted BRCA

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Prostate Cancer Early Detection

NCCN Guidelines Index
Table of Contents
Discussion

BASELINE EVALUATION

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

RISK ASSESSMENT

Start risk and benefit discussion about offering prostate screening:
- Baseline PSA[c]
- Strongly consider baseline digital rectal examination (DRE)[c]

EARLY DETECTION EVALUATION

Age 45-75 y:
- PSA <1 ng/mL, DRE normal (if done) → Repeat testing at 2–4 year intervals[f]
- PSA 1-3 ng/mL,[e] DRE normal (if done) → Repeat testing at 1–2 year intervals
- PSA >3 ng/mL[e] or very suspicous DRE → See Indications for Biopsy (PROSD-3)

Age >75 y, in select patients (category 2B)[d]:
- 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 suspicous DRE → See Indications for Biopsy (PROSD-3)

[a]African-American men have a higher in[illegible]f 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 and to consider screening at annual intervals rather than every other year.

[b]If there is a known or suspected cancer susceptibility gene, referral to a cancer-genetics professional is recommended. 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.

[c]The best evidence supports the use of serum PSA for the early detection of prostate cancer. DRE should not be used as a stand-alone test, but should be performed in those with an elevated serum PSA. DRE may be considered as a baseline test in all patients as it may identify high-grade cancers associated with "normal" serum PSA values. Consider referral for biopsy, if DRE is very suspicious. Medications such as 5α-reductase inhibitors (finasteride and dutasteride) are known to decrease PSA by approximately 50%. PSA values in these men should be corrected accordingly. Halpern JA, Shoag JE, Mittal S, et al. Prognostic significance of digital rectal examination and prostate specific antigen in the prostate, lung, colorectal and

[d]Testing above the age of 75 years of age should be done with caution and only in very healthy men with little or no comorbidity as a large proportion may harbor cancer that would be unlikely to affect their life expectancy, and screening in this population would substantially increase rates of over-detection. However, a clinically significant number of men in this age group may present with high-risk cancers that pose a significant risk if left undetected until signs or symptoms develop. Very few men above the age of 75 years benefit from PSA testing.

[e]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.

[f]Men age ≥ 60 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

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

Genitourinary Cancer Genetics Clinic

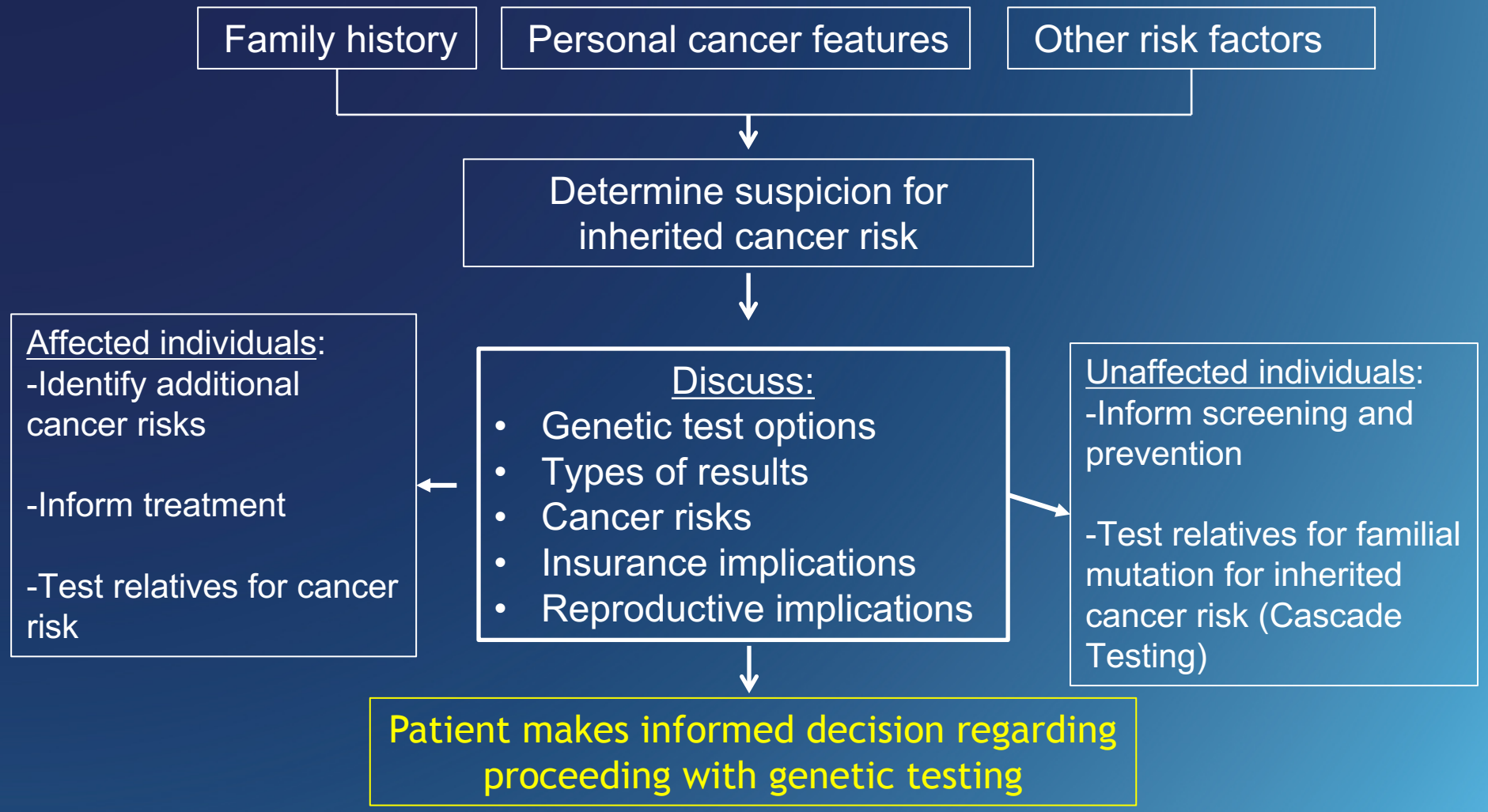
- Started in 2014 clinic is within the existing (1996) GU Multidisciplinary clinic so that men presenting with all stages of prostate cancer can have the opportunity to undergo preliminary genetic evaluation.
- Focus on prostate cancer risk assessment with preliminary discussion.
- Genetics staff: Genetic counselor, Dr. Giri, and research coordinator.
- Supports our GEM (Genetic Evaluation of Men) multigene study.

Jefferson™ Kimmel Cancer Center NCI-designated

BEST HOSPITALS U.S.News NATIONAL UROLOGY 2017-18

Giri et al CJU June 2015

Genetic Counseling for Inherited Cancer Risk



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
- Gleason 8/9/10 regardless of fam hx or stage (NCCN)
- 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

Conclusions

- 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
- Many new prostate cancer genetic panels are being made available commercially