The Role of Genetic Testing in Prostate Cancer Risk Assessment

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Director Sidney Kimmel Cancer Network
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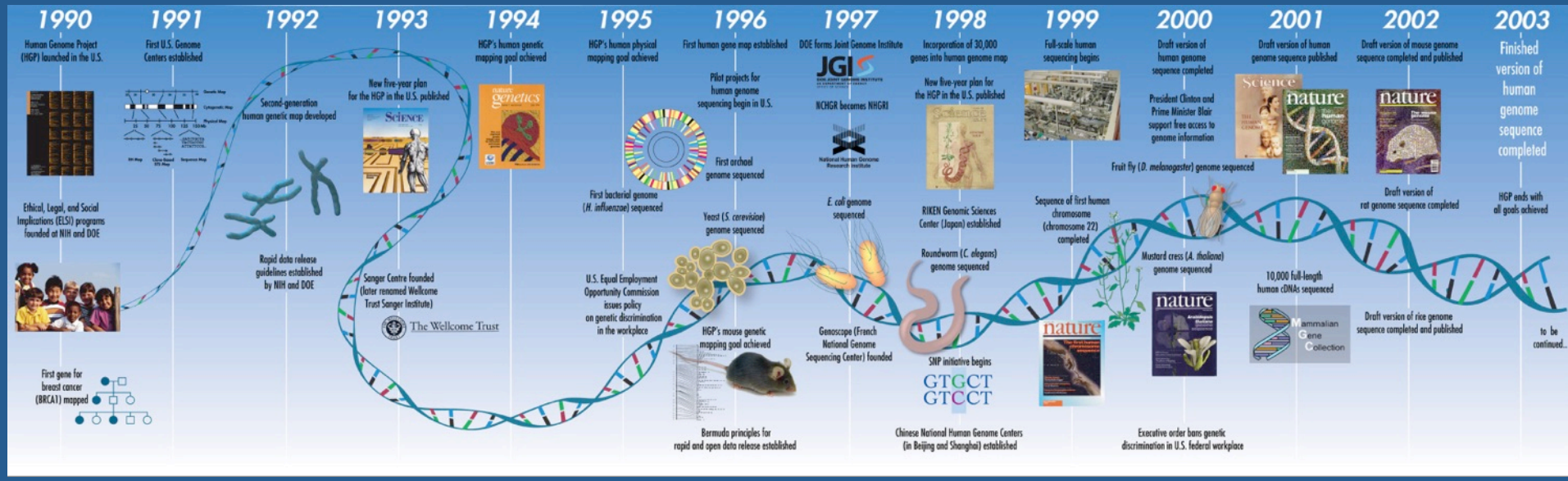
Urology Basics
Prostate Cancer Genetic Testing

1. Recently urology has focused only on tumor genomics
2. Increasing data on importance of inherited genes
3. Familial clustering of PCa has been well known
4. Linkage of PCa to other cancers in families observed
5. PCa has a substantial inherited component identifiable in 12-15% overall estimated at 40-50% (1)
6. Germline PCa predisposition mutations
   A. Localized disease 1-4.6% (TGCA) (2,3)
   B. Metastatic disease >11% (3)
7. Single Gene testing being replaced by panel testing

1. Lichtenstein P, NEJM 2000 2. Agalliu, 2010 3. Pritchard, 2016

Human Genome Project

1990-2003



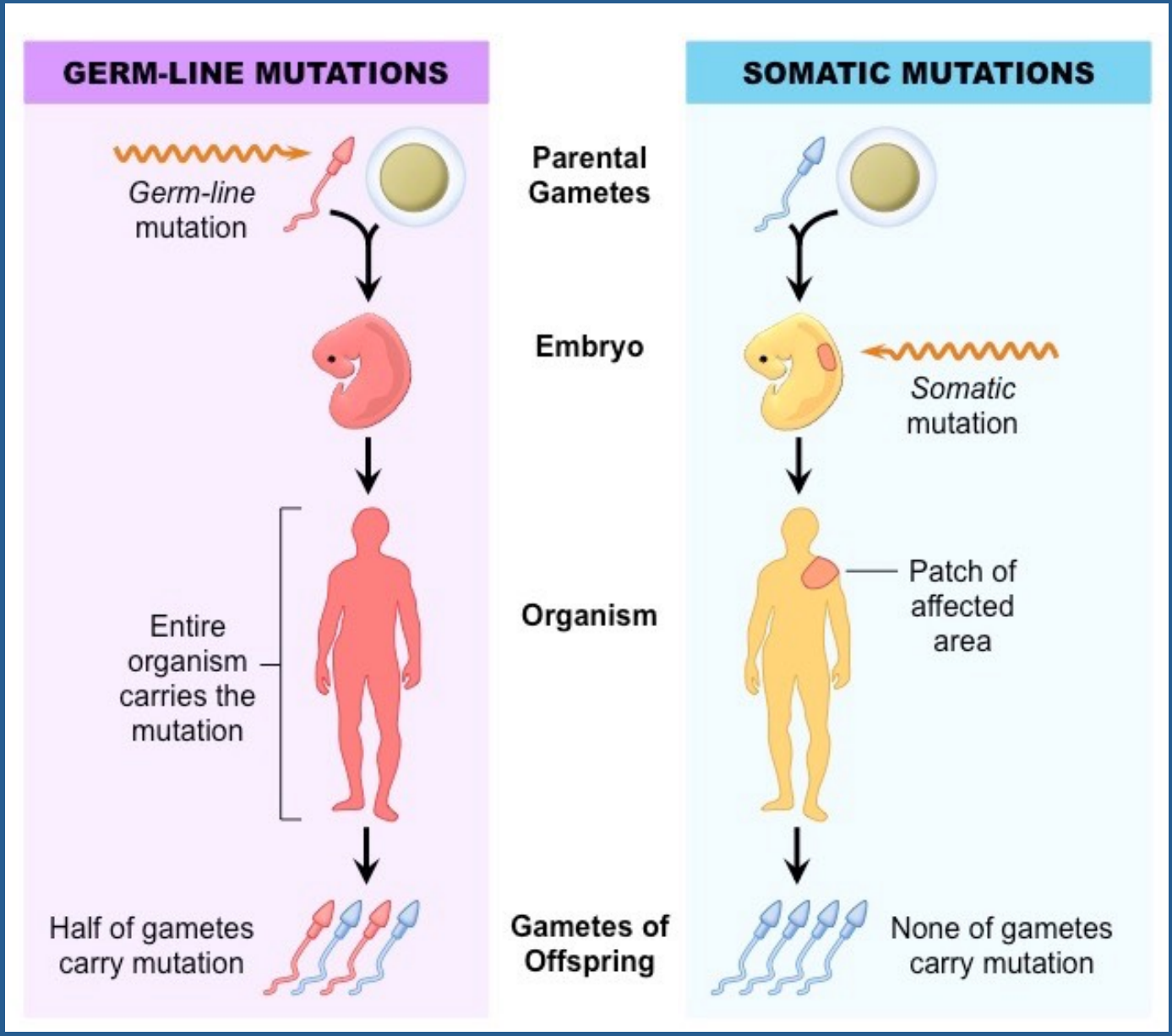
3.2 billion base pairs

https://www.mun.ca/biology/scarr/Human_Genome_Project_timeline.html

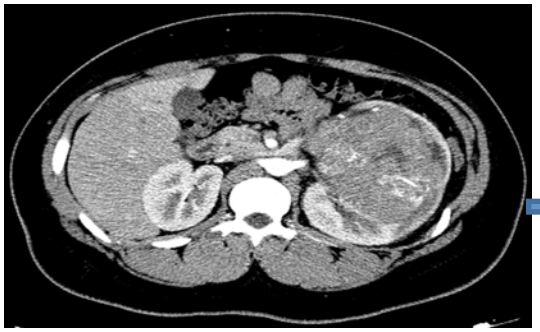
Genetics vs Genomics

- **Genetics:** the study of specific, individual genes and their role in inheritance
  - Eg, sickle cell anemia and cystic fibrosis, often caused by an error in a single gene

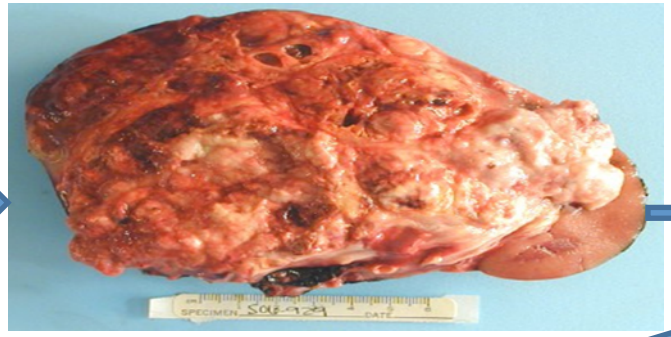
- **Genomics:** more complex and usually refers to an organism's entire genetic makeup (genome) or an extensive number gene
  - Used for diseases caused by variations in more than one gene or by multiple genes interacting with each other and the environment (ie. cancer, diabetes)



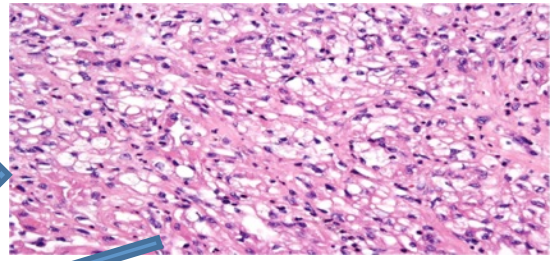
http://ib.bioninja.com.au/



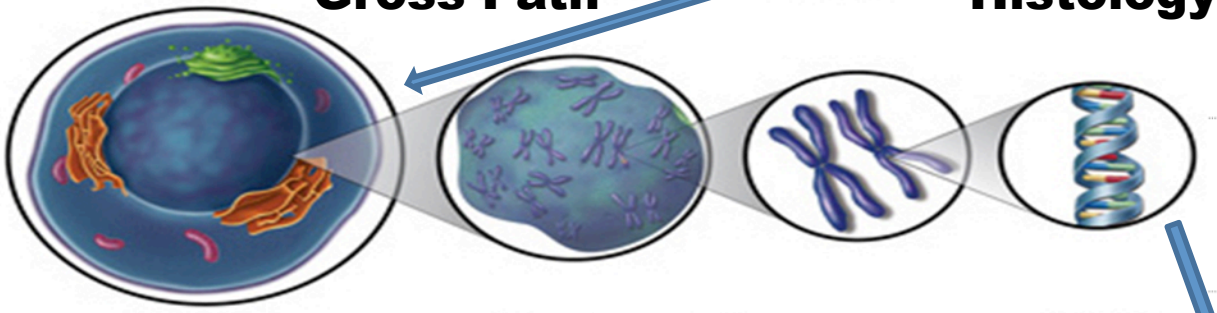
Imaging



Gross Path



Histology Path

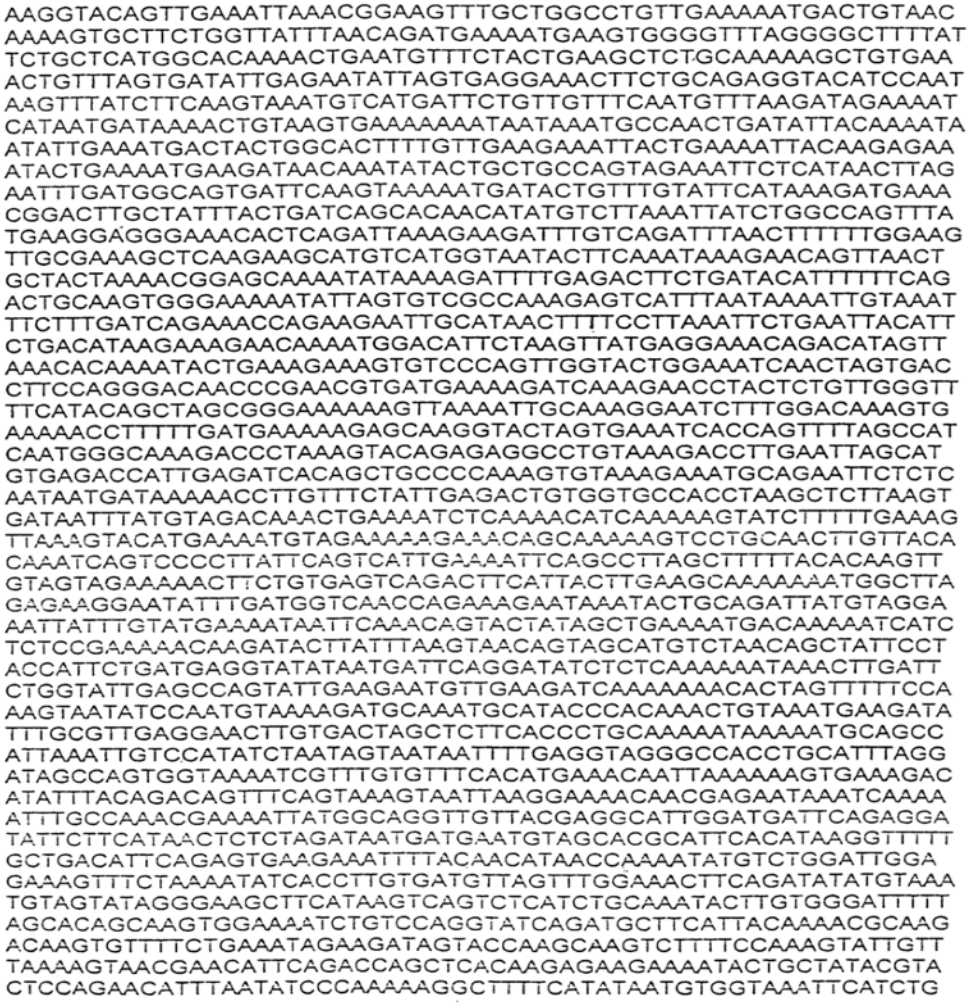


Cell Nucleus Chromosomes DNA

AAGGTACAGTTGAAATTAAACGGAAGTTTGCTGGCCTGTTGAAAAATGACTGTAAC
AAAAGTGCTTCTGGTTATTTAACAGATGAAAATGAAGTGGGGTTTAGGGGCTTTTAT
TCTGCTCATGGCACAAAACTGAATGTTTCTACTGAAGCTCTGCAAAAAGCTGTGAA
ACTGTTTAGTGATATTGAGAATATTAGTGAGGAAACTTCTGCAGAGGTACATCCAAT
AAGTTTATCTTCAAGTAAATGTCATGATTCTGTTGTTTCAATGTTTAAGATAGAAAAT
CATAATGATAAAACTGTAAGTGAAAAAAATAATAAATGCCAACTGATATTACAAAATA
ATATTGAAATGACTACTGGCACTTTTGTTGAAGAAATTACTGAAAATTACAAGAGAA
ATACTGAAAATGAAGATAACAAATATACTGCTGCCAGTAGAAATTCTCATAACTTAG
AATTTGATGGCAGTGATTCAAGTAAAAATGATACTGTTTGTATTCATAAAGATGAAA
CGGACTTGCTATTTACTGATCAGCACAACATATGTCTTAAATTATCTGGCCAGTTTA
TGAAGGAGGGAAACACTCAGATTAAAGAAGATTTGTCAGATTTAACTTTTTTGGAAG

Base Pairs

Computational biology support critical



BRCA2 gene section

-27 exons total
-coding region
10,433 base pairs
-12 pages long
-image is a very small portion of exon 11

Patent Novel coding sequence haplotypes of the human BRCA2 gene US 20060154272 A1

Common PCa Associated Genes and Panel Testing

Prostate cancer panels

	Lab #1	Lab #2	Lab #3
ATM	X	X	X
BRCA1	X	X	X
BRCA2	X	X	X
CHEK2	X	X	X
EPCAM	X	X	X
HOXB13	X	X	X
MLH1	X	X	X
MSH2	X	X	X
MSH6	X	X	X
PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

Giri et al
Submitted
JCO 2017

BRCA Prostate Cancer Risks

- 2-6 fold increased lifetime risk (BRCA2 > BRCA1)
- 8.6-fold increased risk by age 65 (BRCA2)
- PCa Prognosis: More likely to have aggressive features: Gleason 8 or higher, node positive disease, mets, poor survival

	General risk (%)	BRCA1/2 mutation carrier risk (%)
• Fam Hx Breast cancer:	12%	45-87%
• Fam Mx Ovarian cancer:	2%	11-40%
• Male breast cancer:	0.1%	5-10%
• Prostate cancer:	14%	15-20%
• Pancreatic cancer :	1.5%	Increased
• Melanoma:	2%	Increased

- Other hereditary cancers: Lynch Syndrome, Colorectal Ca, Gastric

IMPACT:
Prostate Screening in *BRCA1/2* Families

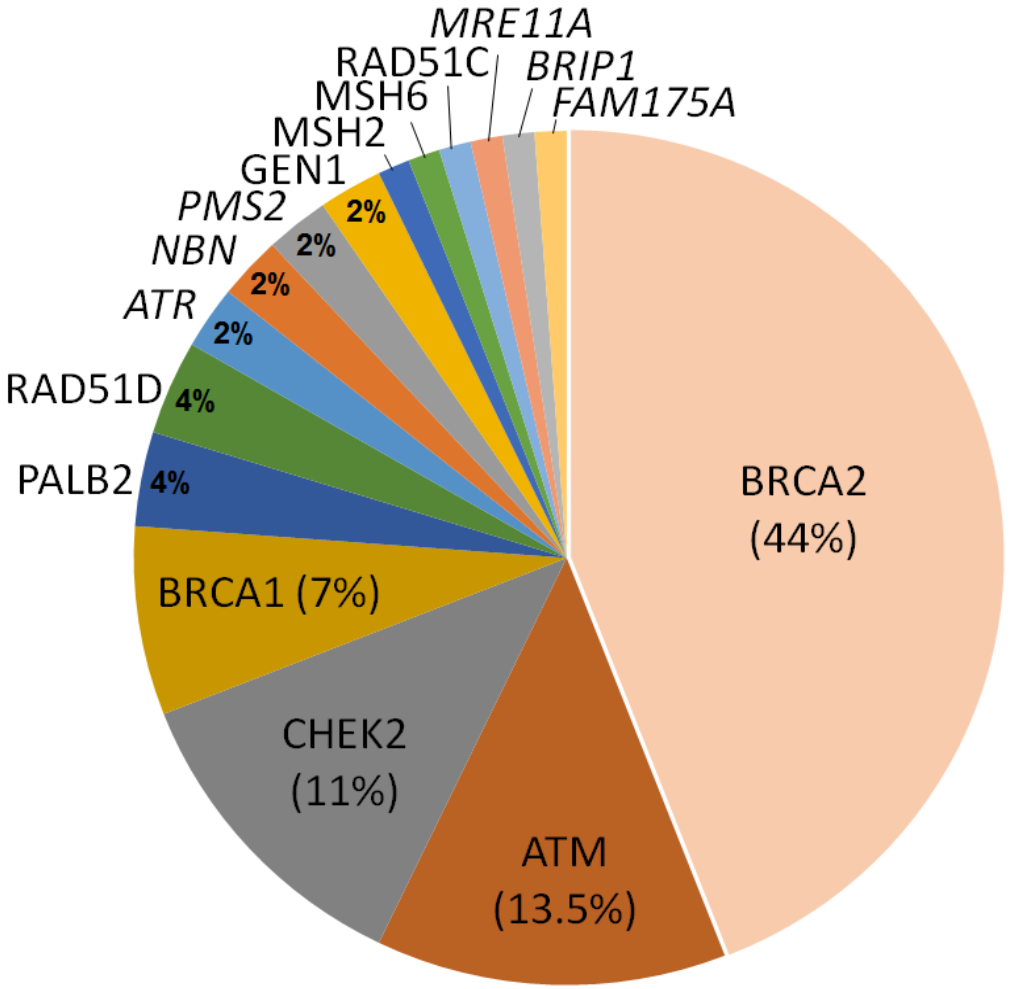
1. International, multicenter trial in men (40-69y) from families with known mutations (BRCA1/2, Lynch Syndrome)
2. Annual PSA screening
3. Biopsy if PSA >3, re-biopsy if ASAP or PIN, or PSA doubling >50%

	BRCA-1 carrier N=791	BRCA-1 control N=531	BRCA-2 carrier N=731	BRCA-2 control N=428
PCa incidence	**2.3%**	1.9%	**3.3%**	1.6%
PPV of biopsy	**41%**	23%	**48%**	33%
Intermediate/ high risk PrCa	**61%**	60%	**68%**	43%

Bancroft, et al (2014) Eur Urol

Germline mutations in metastatic PCa

- BRCA-2 currently best studied for potential screening and treatment of advanced disease
- PCa males with BRCA-2 mutation carriers with prostate cancer have more aggressive disease
- More work is needed on the other PCa genes identified



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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Genetics Table of Contents
Discussion

BRCA MUTATION-POSITIVE MANAGEMENT

MEN[7]

- 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 40 y:
  - Recommend prostate cancer screening for *BRCA2* carriers
  - Consider prostate cancer screening for *BRCA1* carriers

NCCN Guidelines® Insights
Prostate Cancer Early Detection, Version 2.2016

Featured Updates to the NCCN Guidelines

The panel then discussed whether a known *BRCA1* or *BRCA2* mutation would impact prostate cancer screening. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at NCCN.org) recommend that men with *BRCA2* mutations begin prostate cancer screening at age 40 years and that those with *BRCA1* mutations consider the same.[69] Results were recently

fore, the panel noted that although these mutations are clearly risk factors, data supporting a change in the PSA screening and biopsy recommendations for these men relative to those without mutations are insufficient at this time. The panel also noted that, as with race, baseline PSA value is a stronger predictive factor than a positive family history.[52]

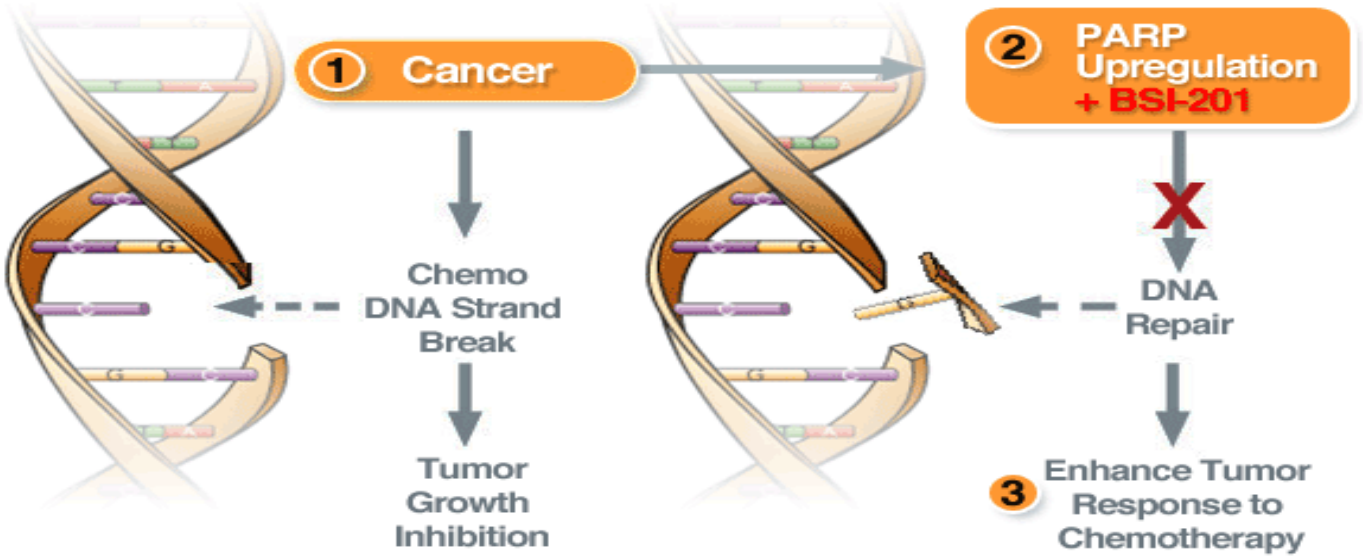
J Natl Compr Canc Netw 2016;14(5):509–519

BRCA Targeting

- Genomic aberrations in the DNA damage repair pathway are common in PC (BRCA1/2)
- More common in late-stage disease, and may direct treatment
  - Genomic defects in DNA repair 20–30% of advanced CRPC
  - Some are germline and heritable
- Support the development of PARP inhibitors and DNA-damaging agents
  - Poly (ADP-ribose) polymerase (PARP)

N Engl J Med. 2015 Oct 29;373(18):1697-708

PARP Inhibitors in mCRPC if BRCA1/2 positive

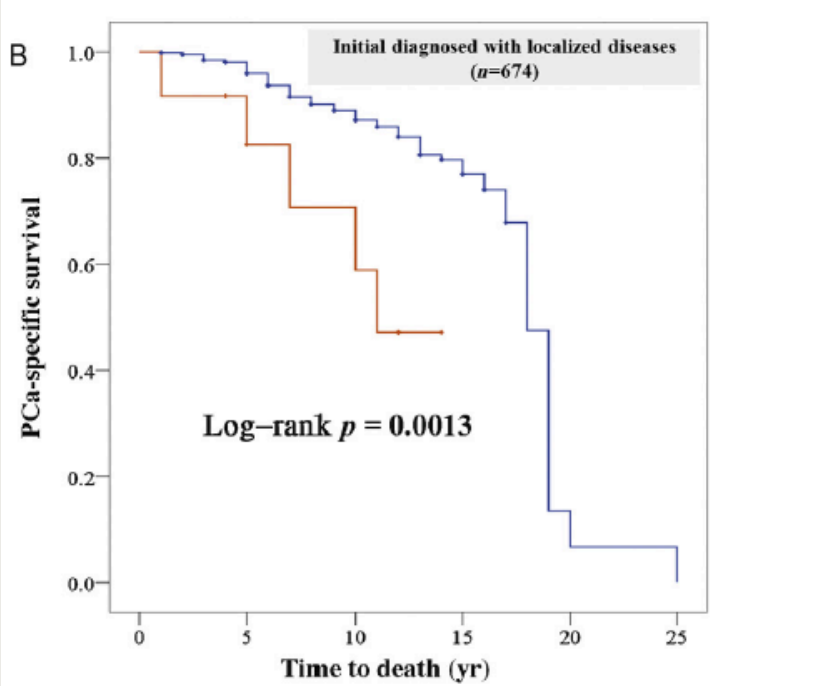


1. Many commonly utilized cancer chemotherapy regimens target tumor cells via fatal DNA lesions
2. Key DNA repair pathways (such as PARP) are upregulated in tumor cells - may lead to resistance
3. Inhibiting PARP may potentiate chemotherapy or be used as monotherapy in conditions with pre-existing DNA repair defects (such as BRCA negative)

http://www.parp-inhibitors.com/

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

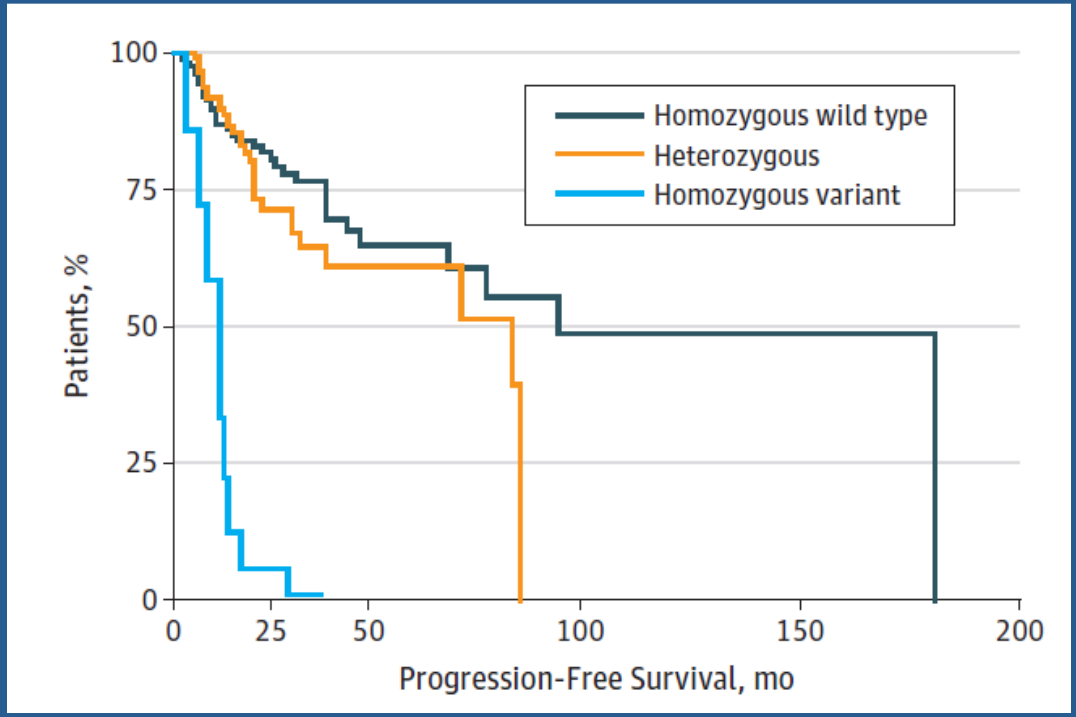
Rong Na [a,b,†], S. Lilly Zheng [b,c,†], Misop Han [d,†], Hongjie Yu [b,e], Deke Jiang [b,e], Sameep Shah [b], Charles M. Ewing [d], Liti Zhang [d], Kristian Novakovic [b,c], Jacqueline Petkewicz [b,c], Kamalakar Gulukota [g], Donald L. Helseth Jr [g], Margo Quinn [b,c], Elizabeth Humphries [d], Kathleen 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 [a], 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

HSD3B1 genotype predicts time to progression on ADT "fast vs slow androgen metabolizers"



Agarwal et al, JAMA Oncol. Feb 16, 2017

Sidney Kimmel Cancer Center MDC Genetics Clinic

Table 1: Spectrum of Cancer Risks for Genes Associated with Prostate Cancer Predisposition

	Prostate	Breast	Ovarian	Pancreatic	Melanoma	Colon	Gastric/ Small bowel	Uterine	Sebaceous carcinoma
BRCA1 and *BRCA2*	x	x	x	x	x				
DNA mismatch repair genes*	x		x			x	x	x	x
HOXB13	x								

*Note: Studies describe higher rates of prostate cancer in Lynch syndrome families. Emerging data implicate DNA mismatch repair genes in prostate cancer predisposition, though definitive studies are warranted.

Table 2: Referral Criteria for Prostate Cancer Patients for Genetic Evaluation

Referral Criteria	***References***
Age at prostate cancer diagnosis ≤65 years	13
Gleason score > 7 and family history of cancers related to HBOC	5
Family history of cancers relevant to HBOC, HPC, or Lynch syndrome particularly in first-degree or second-degree relatives given the implication of prostate cancer in these syndromes	5, 8-11

Giri VN, Gross L, Gomella LG, Hyatt Cow I Do It: Genetic counseling and genetic testing for inherited prostate cancer. Can J Urol. 2016 Apr;23(2):8247-53

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

Cancer Center at Jefferson
NCI – designated

The Foundation for Breast and Prostate Health

Philadelphia, Pennsylvania

March 3 & 4, 2017

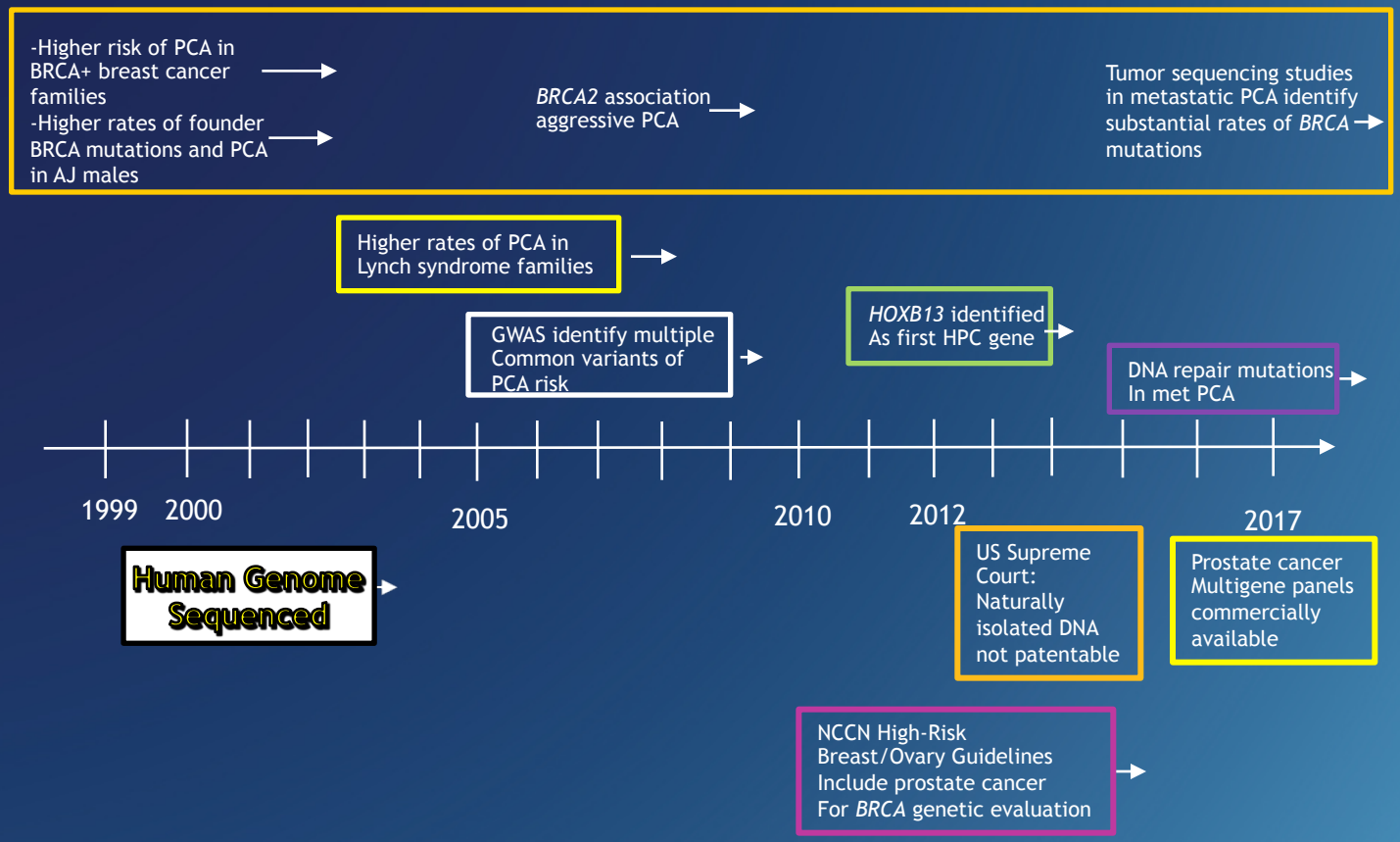
FOUNDATION FOR Breast & Prostate Health

Leonard G. Gomella, MD
Consensus Co-Chair
Professor and Chair, Department of Urology

Veda N. Giri, MD
Consensus Co-Chair
Associate Professor, Medical Oncology and Cancer Biology,

Karen Knudsen, PhD.
Consensus Co-Chair
Director, Sidney Kimmel Cancer Center
Thomas Jefferson University

Why consensus conference was needed in 2017?



Need for Consensus Conference in 2017

Science → Growing knowledge of genetic contribution to inherited prostate cancer

Clinical Testing Capability →

Intersection → Gap in Clinical Application Guidelines for Multigene Panels → **Philadelphia Prostate Cancer Consensus 2017**

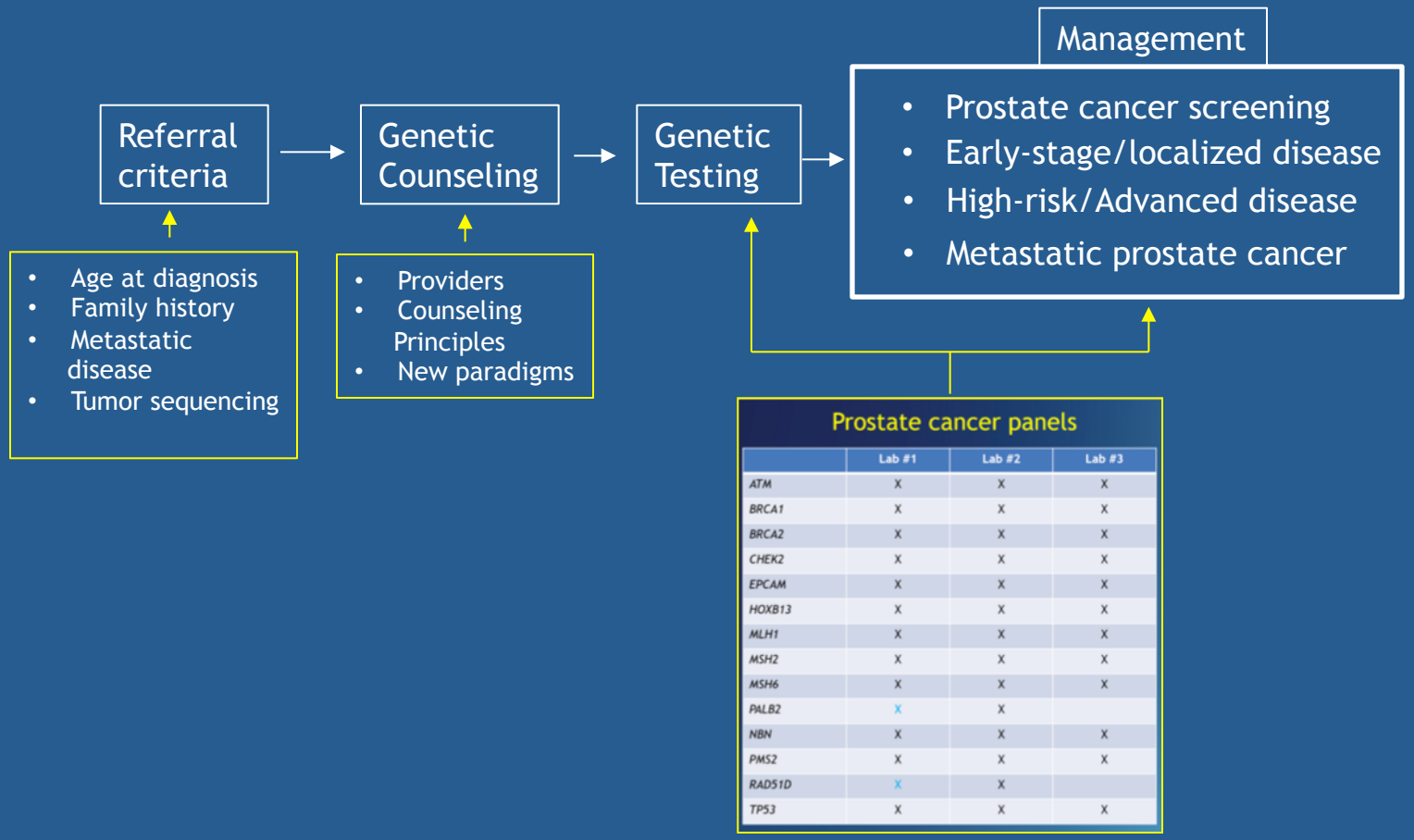
Prostate cancer panels

	Lab #1	Lab #2	Lab #3
ATM	X	X	X
BRCA1	X	X	X
BRCA2	X	X	X
CHEK2	X	X	X
EPCAM	X	X	X
HOXB13	X	X	X
MLH1	X	X	X
MSH2	X	X	X
MSH6	X	X	X
PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

Consensus Panel

- Included ~70 international experts:
  - Urology
  - Clinical Cancer Genetics
  - Genetic Counseling
  - Medical Oncology
  - Radiation Oncology
  - Primary Care
  - Breast and GI Cancer Genetics
  - Gynecologic oncology
  - Molecular Pathology
  - Epidemiology
  - Bioethics
  - Health Services
  - Health disparities
  - Population Science
  - Advocacy Organizations
  - Patient Advocates
- Representation:
  - American Cancer Society
  - National Comprehensive Cancer Network
  - National Cancer Institute
  - Prostate Cancer Foundation

Framework for Genetic Evaluation of Inherited Prostate Cancer



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MSH6	X	X	X
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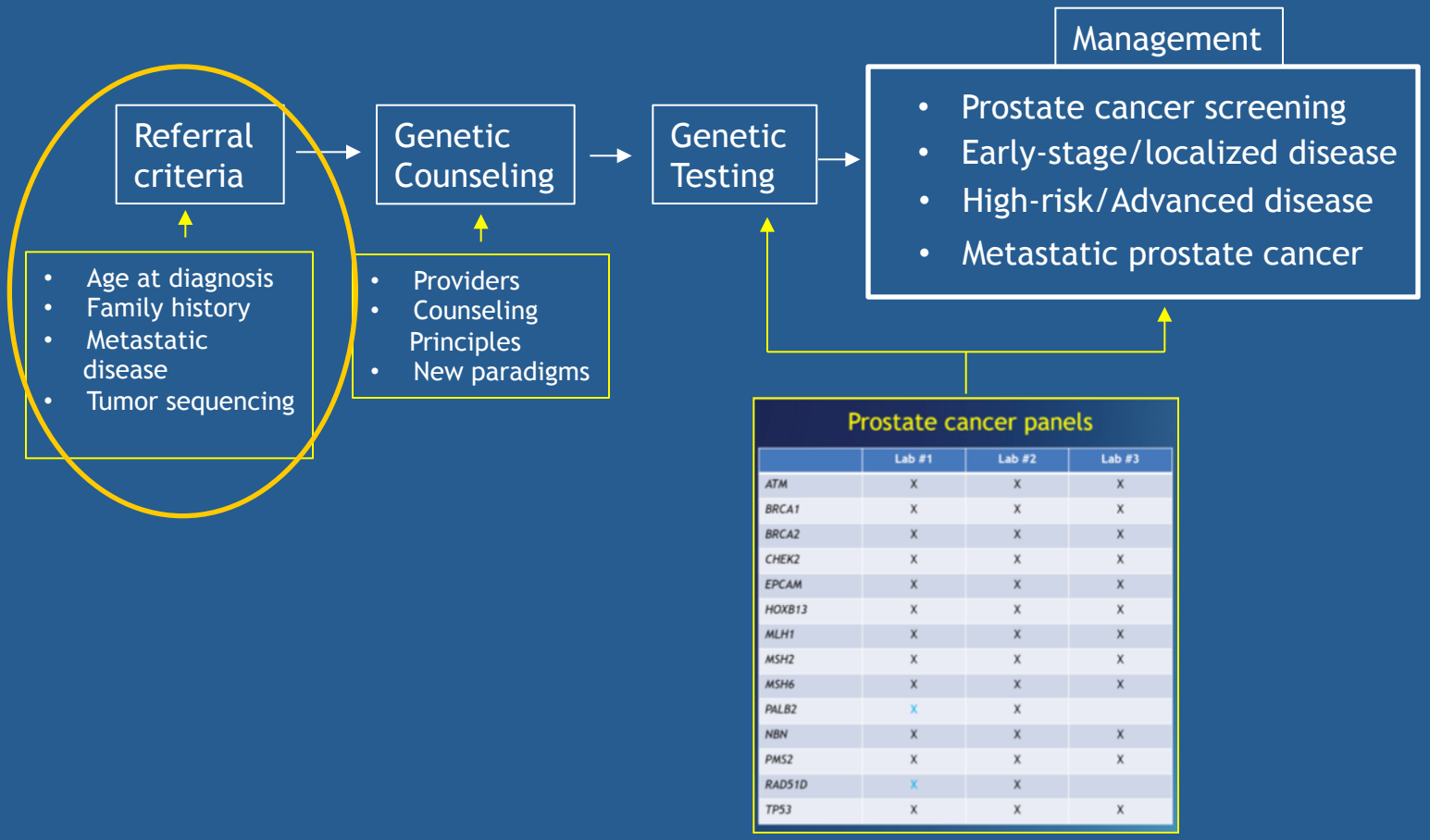
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

Framework for Genetic Evaluation of Inherited Prostate Cancer



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PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

Who should be referred for genetic counseling and consideration of genetic testing to assess for inherited PCA?

- First-degree relative (FDR) diagnosed with PCA <=55 or personal diagnosis of PCA<=55 with FDR diagnosed with PCA at any age or death from PCA in FDR at age<60 (Consensus: 78%)

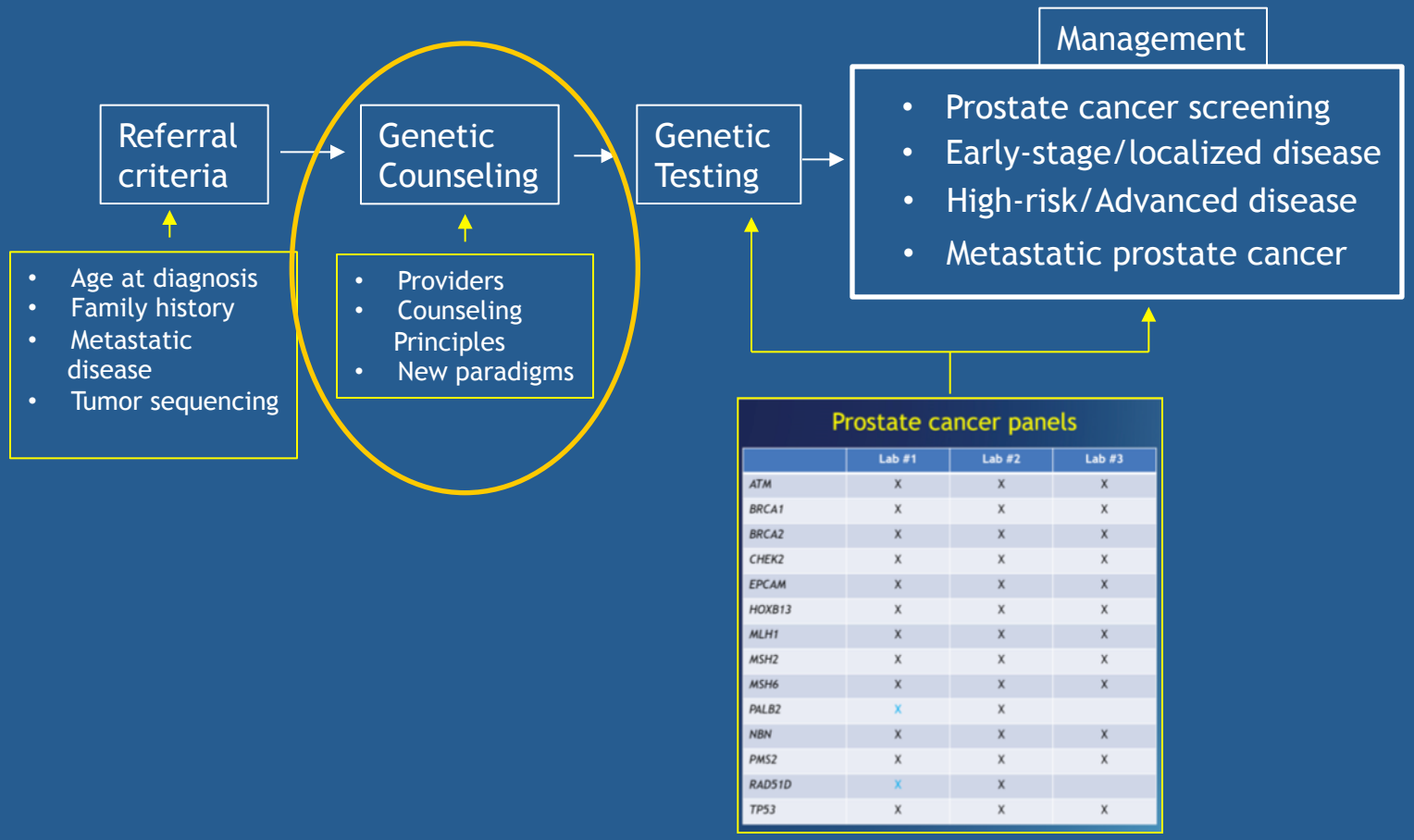
- Two close blood relatives with PCA on same side of family with at least one diagnosed with PCA <=55 (Consensus: 80%)

- Any FDR with cancer in Hereditary Breast and Ovarian Cancer/Lynch Syndrome spectrum diagnosed <50 (Consensus: 83%)

- Tumor sequencing showing mutations in hereditary cancer genes (Consensus: 93%)

Expanded referral criteria to include age at diagnosis, Lynch syndrome cancers, and broader tumor sequencing results

Framework for Genetic Evaluation of Inherited Prostate Cancer



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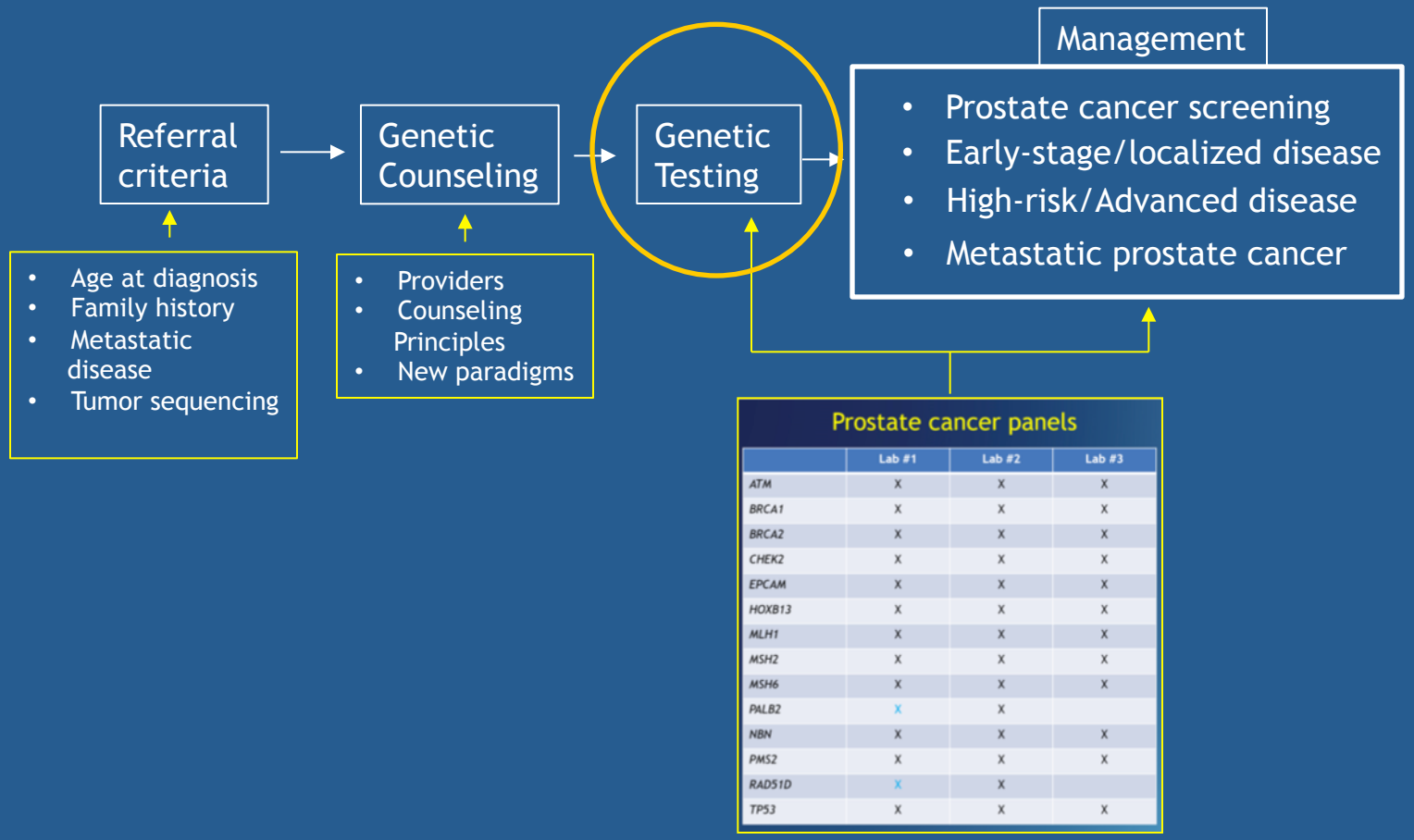
HOXB13	X	X	X
MLH1	X	X	X
MSH2	X	X	X
MSH6	X	X	X
PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

What criteria should be considered to recommend genetic testing for inherited PCA?

- Patients should engage in shared decision-making for genetic testing for PCA (Consensus: 77%)
- All men with PCA from families meeting established testing or syndromic criteria for the following should be considered for genetic testing:
  - Hereditary Breast and Ovarian Cancer (Consensus: 93%)
  - Hereditary Prostate Cancer (Consensus: 95%)
  - Lynch Syndrome (Consensus: 88%)
- Men with PCA with >= 2 or more close blood relatives on the same side of the family with a cancer in the following syndromes should be considered for genetic testing:
  - Hereditary Breast and Ovarian Cancer (Consensus: 93%)
  - Hereditary Prostate Cancer (Consensus: 86%)
  - Lynch Syndrome (Consensus: 86%)
- All men with metastatic castrate-resistant prostate cancer (mCRPC) should undergo genetic testing for PCA (Consensus: 67%)

- Specifically addressed shared decision-making for genetic counseling for prostate cancer
- Expanded testing criteria to encompass hereditary cancer syndromes in which PCA has been implicated
- Addressed genetic testing for metastatic, castration-resistant prostate cancer

Framework for Genetic Evaluation of Inherited Prostate Cancer



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MSH6	X	X	X
PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

A	A	A			C	A			X#
B		A	A	A		A	A	A	
A									
	A		C		C	C		A	
B	A					C			
C	A		A					C	
	A					A			
C	B								
		A							

Giri et al. *JCO Precision Oncology* 2017 DOI: 10.1200/PO

editary Breast and Ovarian Cancer; **LS**-Lynch syndrome; **L**
ncer; **BR**-breast cancer; **OV**-ovarian cancer; **CO**-colon can
A-pancreatic cancer; **GA**-gastric cancer; **OC**-other cancer

ncer risks can vary based on gene and variant

8/

association

What genes should be tested for inherited PCA?

- The following genes should be tested in males suspected of:
  - Hereditary Prostate Cancer: *HOXB13* (Consensus: 95%)
  - Hereditary Breast and Ovarian Cancer: *BRCA1/BRCA2* (Consensus: 97%)
  - Lynch Syndrome: DNA mismatch repair genes (Consensus: 73%)

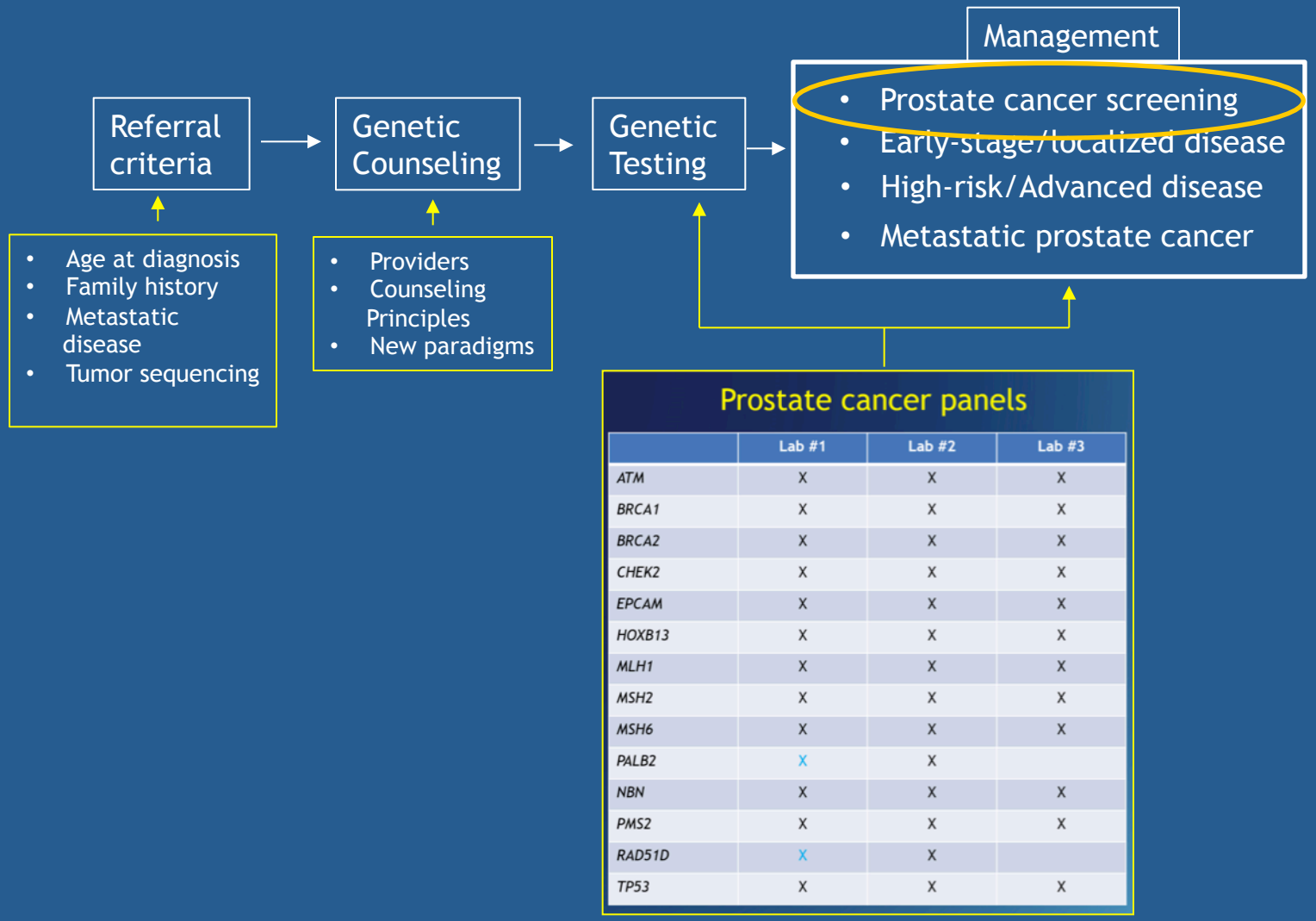
- The following genes should be tested in men with >=2 two close blood relatives on the same side of the family with a cancer in the following:
  - Hereditary Breast and Ovarian Cancer spectrum: *BRCA1/BRCA2* (Consensus: 98%)
  - Lynch Syndrome spectrum: DNA mismatch repair genes (Consensus: 97%)

- Men with prostate tumor sequencing showing mutations in *BRCA1/BRCA2* should have confirmatory germline genetic testing: *BRCA1/BRCA2* (Consensus: 89%)

- If men with metastatic, castration-resistant prostate cancer undergo genetic testing for treatment determination, the following genes should be tested: *BRCA1/2* (Consensus: 88%); *ATM* (Consensus: 62%)

- Expanded genetic testing to include hereditary cancer syndromes or broader family cancer hx
- Provided context of relevance of genes based upon family history or disease aggressiveness

Framework for Genetic Evaluation of Inherited Prostate Cancer



Prostate cancer panels

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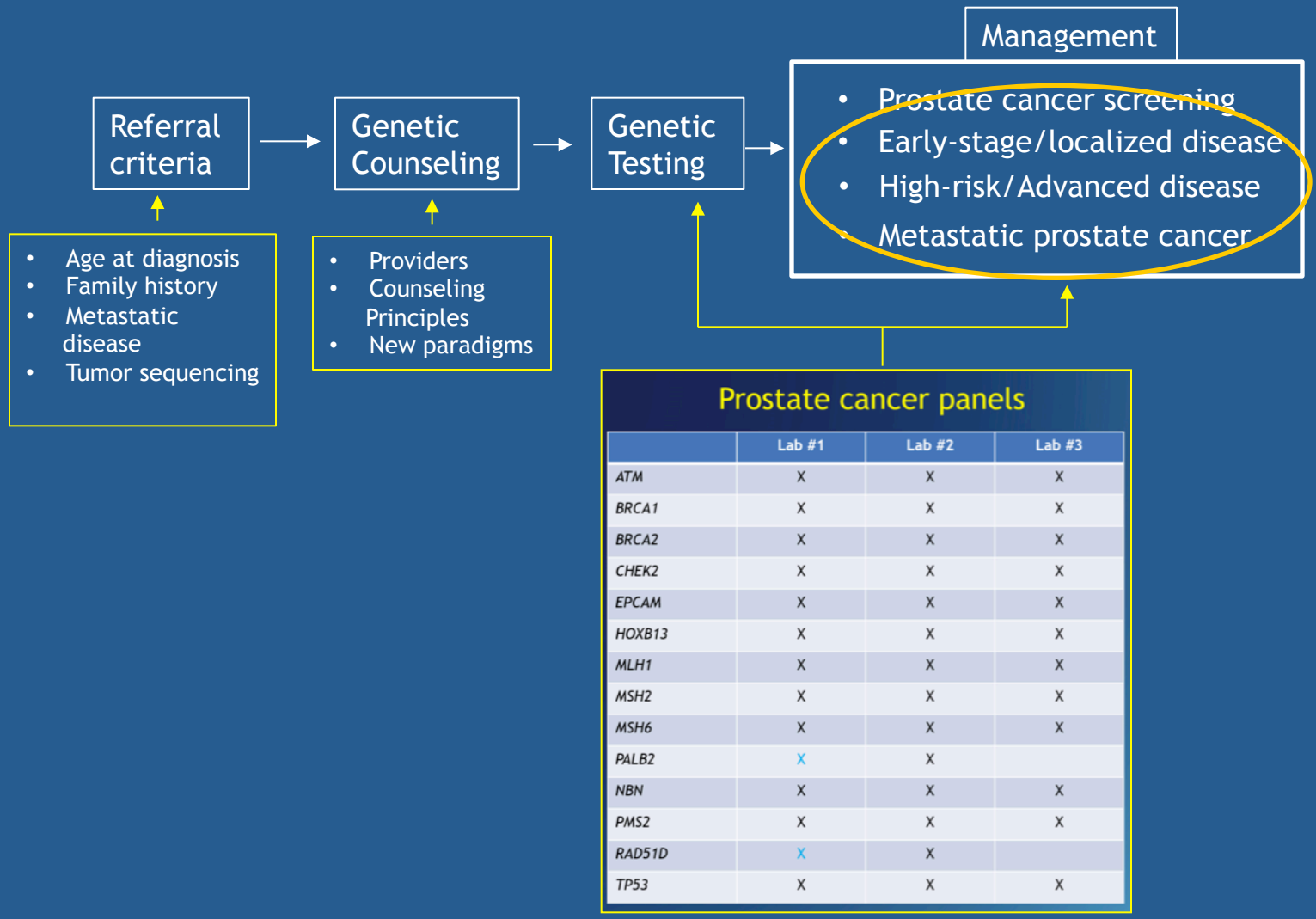
MSH2	X	X	X
MSH6	X	X	X
PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

How should genetic test results inform prostate cancer screening?

- *BRCA2* mutation status should be factored into PCA screening discussions (Consensus: 80%).
  - Screening strategy:
    - Baseline PSA at age 40 or 10 years prior to youngest PCA diagnosed in family (Consensus: 56%)
    - Interval of screening yearly or determined by baseline PSA (Consensus: 76%)
- *HOXB13* mutation status should be factored into PCA screening discussions (Consensus: 53%).
  - Screening strategy:
    - Baseline PSA at age 40 or 10 years prior to youngest PCA diagnosed in family (Consensus: 52%)
    - Interval of screening yearly or determined by baseline PSA (Consensus: 75%)

- Expanded *BRCA2*-informed prostate cancer screening to include consideration of age at diagnosis of prostate cancer in male blood relatives
- First to address *HOXB13* genetic testing and role in prostate cancer screening

Framework for Genetic Evaluation of Inherited Prostate Cancer



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MSH2	X	X	X
MSH6	X	X	X
PALB2	X	X	
NBN	X	X	X
PMS2	X	X	X
RAD51D	X	X	
TP53	X	X	X

Should genetic test results inform management of early-stage/ localized, advanced/high-risk, and metastatic, castration-resistant prostate cancer?

- Of all genes on PCA multigene panels, the following should be factored into management discussion of early-stage/localized PCA: *BRCA2* (Consensus: 64%)

- Of all genes on PCA multigene panels, the following should be factored into management discussion of high-risk/advanced PCA: *BRCA2* (Consensus: 97%); *ATM* (Consensus: 59%)

- The following genes should be factored into discussions of treatment of metastatic, castration-resistant prostate cancer: *BRCA1* (Consensus: 83%), *BRCA2* (Consensus: 88%), *ATM* (Consensus: 56%)

- Inclusion of genetic information in management discussions of early-stage and advanced prostate cancer.
- Emerging role of *ATM* in prostate cancer management discussions.

Considerations and Areas in Need of Research

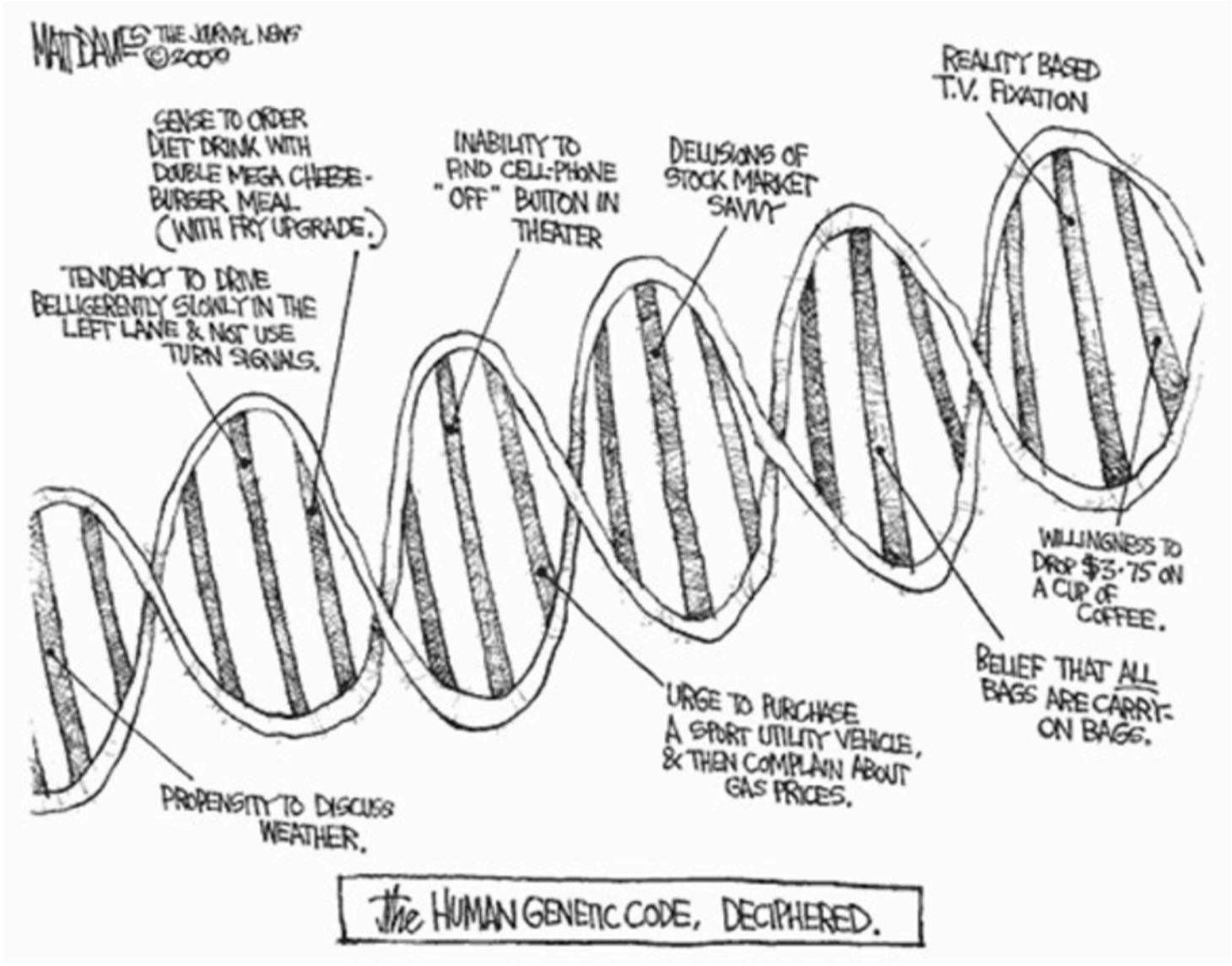
- Breadth of expertise-->
  - Consideration: May have impacted ultimate strength of consensus results
  - Strength: Thought-leaders engaged in prostate cancer care, advocacy, and research--> balanced views
- Need for greater evidence base:
  - Genetic predisposition to lethal prostate cancer
  - Genetic predisposition to prostate cancer in African American males
  - Clinical utility of genetic information in prostate cancer screening and management
  - Health services and health disparities research
  - Community implementation and engagement with primary care
  - Development of new models of genetic counseling and linking with urologic providers

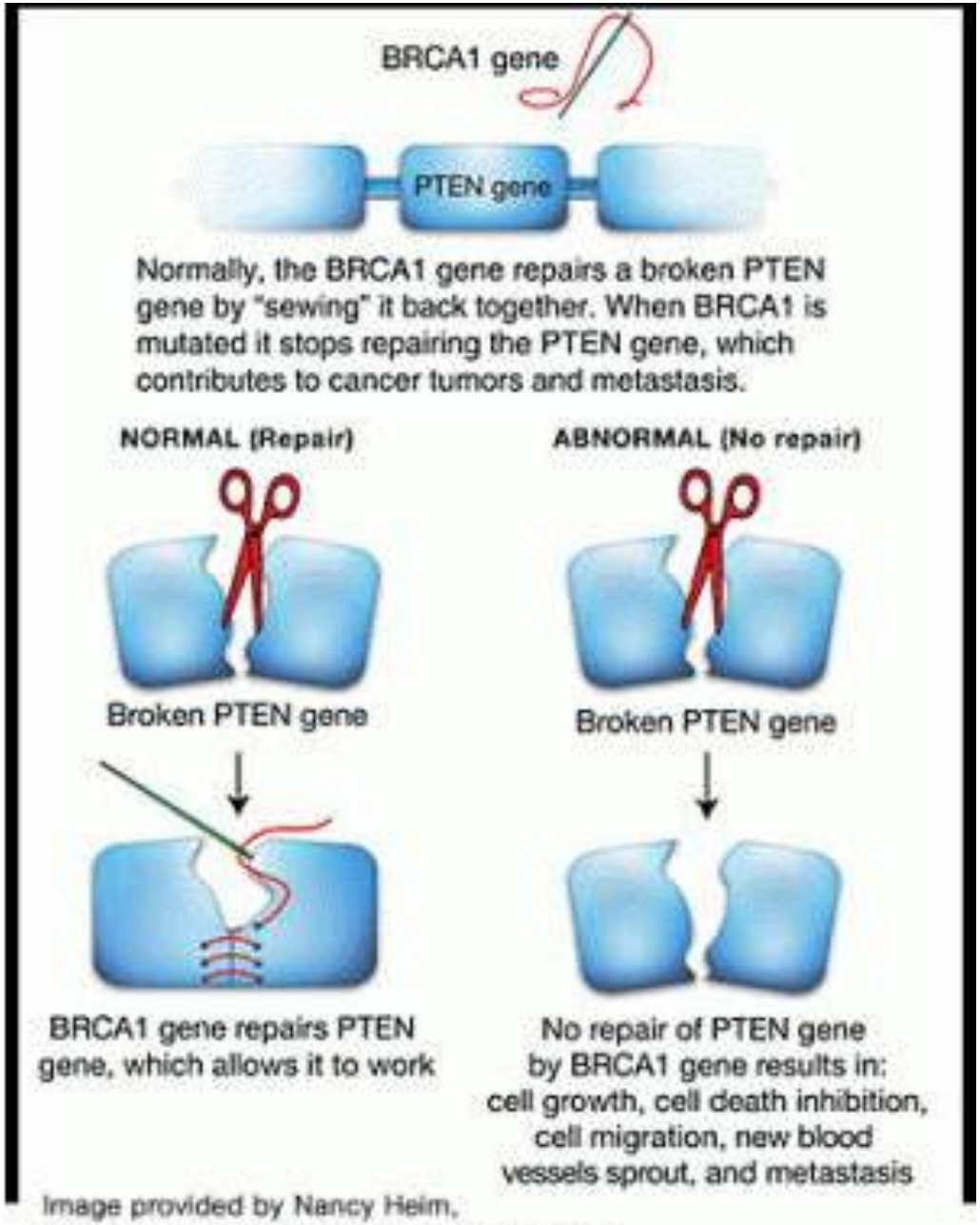
Consensus Summary

- First centralized, comprehensive, and multidisciplinary consensus to address a working framework for genetic evaluation of inherited PCA in the multigene testing era.
- Expert opinion consensus addressed critical gaps in guidelines for multigene testing for prostate cancer with best evidence available at this time.
- Dynamic field and will require updating of guidelines in the future.
- Some significant advances over NCCN guidelines
- Inform national guidelines to move the field forward to enable males to engage in genetic counseling and genetic testing for inherited prostate cancer--> benefit to men and their families.

Guide to Prostate Cancer Genetic Testing: Conclusions

- Evolving recommendations for PCa genetic testing
- Obtain complete family history in all PCa
  - Key cancers breast, ovarian, pancreatic, Lynch Syndrome
- High prevalence of germ line mutations (>11%) suggests that all men with *metastatic* PCa should be offered germline testing
  - Testing may also direct therapy of metastatic disease
- Strongly consider referral for genetic testing AND counselling
- Many new Prostate Cancer Genetic Panels are being made available commercially


MATT DAVIES THE JOURNAL NEWS ©2000
SENSE TO ORDER DIET DRINK WITH DOUBLE MEGA CHEESE-BURGER MEAL (WITH FRY UPGRADE.)
TENDENCY TO DRIVE BELLIGERENTLY SLOWLY IN THE LEFT LANE & NOT USE TURN SIGNALS.
INABILITY TO FIND CELL-PHONE "OFF" BUTTON IN THEATER
DELUSIONS OF STOCK MARKET SAVVY
REALITY BASED T.V. FIXATION
WILLINGNESS TO DROP $3.75 ON A CUP OF COFFEE.
BELIEF THAT ALL BAGS ARE CARRY-ON BAGS.
URGE TO PURCHASE A SPORT UTILITY VEHICLE, & THEN COMPLAIN ABOUT GAS PRICES.
PROPENSITY TO DISCUSS WEATHER.
The HUMAN GENETIC CODE, DECIPHERED.


BRCA1 gene
PTEN gene
Normally, the BRCA1 gene repairs a broken PTEN gene by "sewing" it back together. When BRCA1 is mutated it stops repairing the PTEN gene, which contributes to cancer tumors and metastasis.
NORMAL (Repair)
ABNORMAL (No repair)
Broken PTEN gene
Broken PTEN gene
BRCA1 gene repairs PTEN gene, which allows it to work
No repair of PTEN gene by BRCA1 gene results in: cell growth, cell death inhibition, cell migration, new blood vessels sprout, and metastasis
Image provided by Nancy Heim, Columbia University Medical Center ® 2007