Duke Prostate Center
DUKE UNIVERSITY HEALTH SYSTEM

WE PUT MEN BACK ON COURSE

15th NASPCC-2019: Low Risk Localized Prostate Cancer Panel: Genomic Tests

Judd W. Moul, M.D. FACS
James H Semans Professor of Surgery -Duke Cancer Institute
Duke University Medical Center
Durham, NC---Oct 19, 2019

What Causes Cancer?

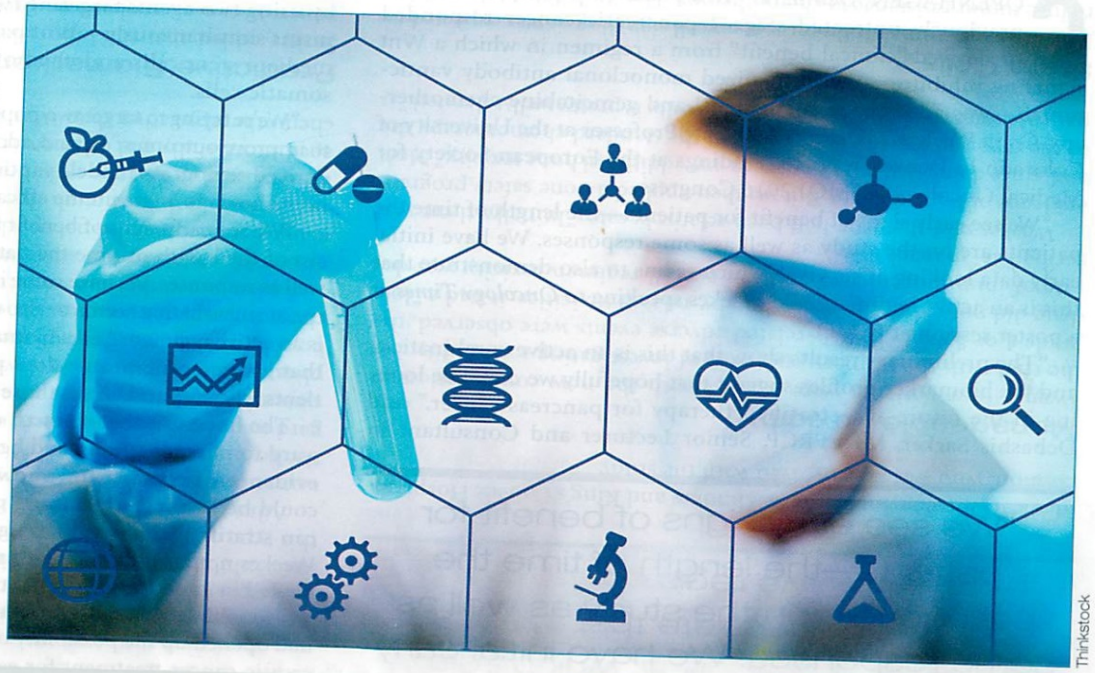
Genetics are major cause of cancer

Genomic Testing Issues in the Era of Precision Medicine

BY PEGGY EASTMAN

As cancer care evolves into a field where genomic testing is used routinely to pinpoint diagnoses and determine treatments for specific subpopulations, a growing number of molecular tests are becoming available to oncologists. Invited speakers examined issues related to the role of these tests in precision medicine at a Senate briefing on Capitol Hill sponsored by the Friends of Cancer Research (FOCR) and the Deerfield Institute, which develops and analyzes data to enhance the understanding of innovation, emerging products, and trends within health care.

Concerns have been raised that some of the tests used, specifically laboratory-developed tests (LDTs), may not be as high in quality as FDA-approved tests sold as diagnostic kits and known



Thinkstock

Genomics and Cancer-Hot Topic!

Personalized, Genomic-Based Care Could Mean a Paradigm Shift

BY JIANFENG XU, MD, DRPH, CHARLES B. BRENDLER, MD, & CARLY CONRAN, BS

Genomic-based personalized cancer care strategies are being developed to better assess one's inherited risk for various types of cancer, a development that could lead to more effective ways to screen for, prevent, and treat the disease, all critical to reducing cancer mortality.

Currently, inherited cancer risk assessment is based primarily on family history. For a small subset of patients with an exceptionally strong family history of a cancer, or cancers, genetic testing of inherited (germline) impactful alterations in high-penetrance genes (HPGs) such as BRCA1/2 may be performed to further assess inherited risk. However, this current standard of care is insufficient because most individuals are either unaware or possess an incomplete understanding of their family history.

Indeed, about 50 percent of individuals who harbor mutations in HPGs do not have a known family history of the associated disease, and, similarly, many individuals without a known family history or HPG mutations may still have an increased inherited cancer risk.

Thinkstock

Genetic Risk Score

The NorthShore University HealthSystem (NorthShore) Genetic Risk Score (GRS) is a novel tool for measuring inherited risk beyond HPGs and can identify additional subjects in the general population who have an elevated risk of developing specific types of cancer. The GRS is based on cancer risk-associated single nucleotide polymorphisms (SNPs) that have been discovered

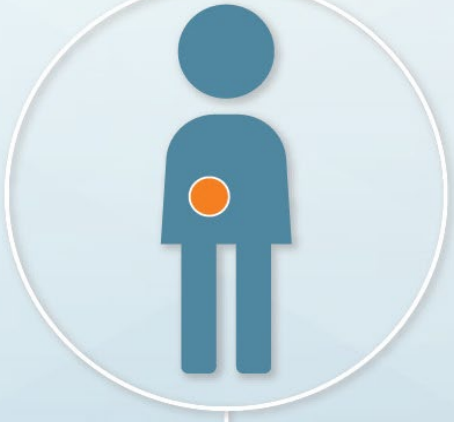
JIANFENG XU, MD, DRPH, is Vice President of Translational Research & Director, Program for Personalized Cancer Care, NorthShore University HealthSystem. **CHARLES B. BRENDLER, MD,** is Vice Chairman of Surgery & Executive Research Director, Program for Personalized Cancer Care, NorthShore University HealthSystem. **CARLY CONRAN, BS,** is Research Coordinator, Program for Personalized Cancer Care, NorthShore University HealthSystem.

includes both cancer-associated HPGs and SNPs. This panel, called the NorthShore Inherited Cancer Panel (ICP), eliminates the need to perform two separate assays for HPGs and GRS. In this way, it is both simple and cost-effective. A potential clinical utility of the ICP may include inherited risk assessment among asymptomatic subjects for developing targeted cancer prevention and screening strategies. The ICP may also be used among known cancer patients for predicting prognosis and personalizing treatment strategies.

Testing With Clinical Trials

To evaluate the clinical utility of our inherited cancer risk assessment strategy, we have recently initiated two clinical trials at NorthShore. The first trial is a study of our GRS for breast, prostate, and colorectal

Somatic vs. Germline Mutation



SOMATIC MUTATION

- Every cancer has many somatic mutations.
- A **somatic mutation** is a change in the gene that arose in the tumor and is confined to the tumor.
- Most cancer is sporadic (i.e., it happened by chance).

GERMLINE MUTATION

- A **germline mutation** is a change in the gene that was inherited and therefore causes an increased risk for cancer.
- This is also known as **hereditary cancer**.
- Only around 10% of cancer is hereditary.

Genetic Tests Remain Controversial- Prostate

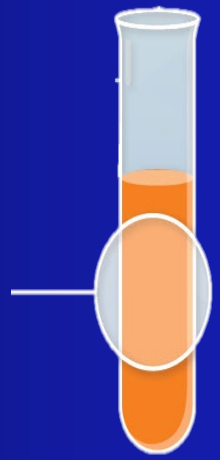
- Germline/Hereditary: Legal Privacy Concerns; limited targeted therapeutics; accuracy and cost of current multi-gene tests and “which one is best”
- Somatic: lack of prospective RCTs; expense; accuracy; “which one is best”; lack of clear guidelines

Tumor Testing vs. Germline Testing

Tumor testing can help guide treatment options (e.g., Prolaris, Oncotype, Decipher)

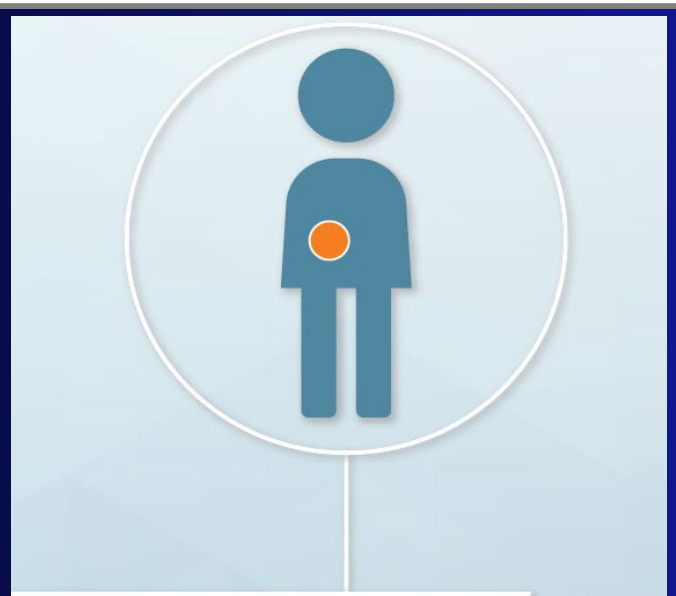
Tumor Biopsy

Germline testing (blood/saliva) can help determine if a mutation was inherited and help guide treatment and risk management options for patient and family members



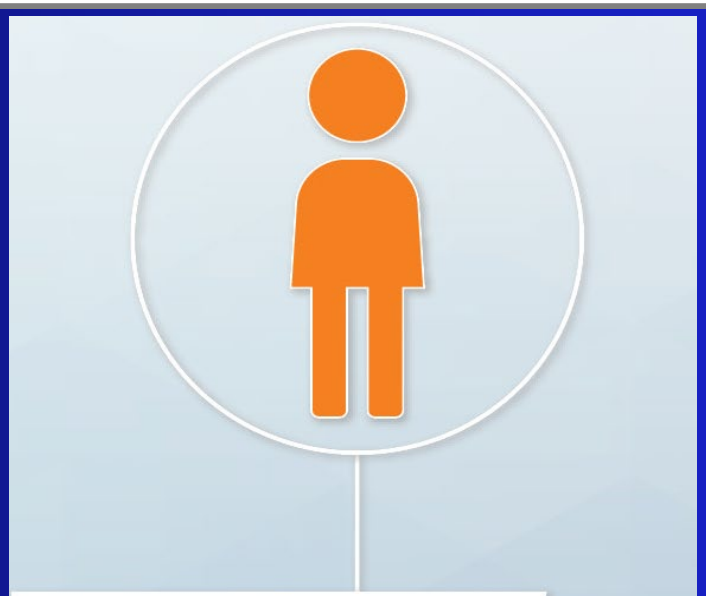
Blood or Saliva Test

Somatic vs. Germline Mutation



SOMATIC MUTATION

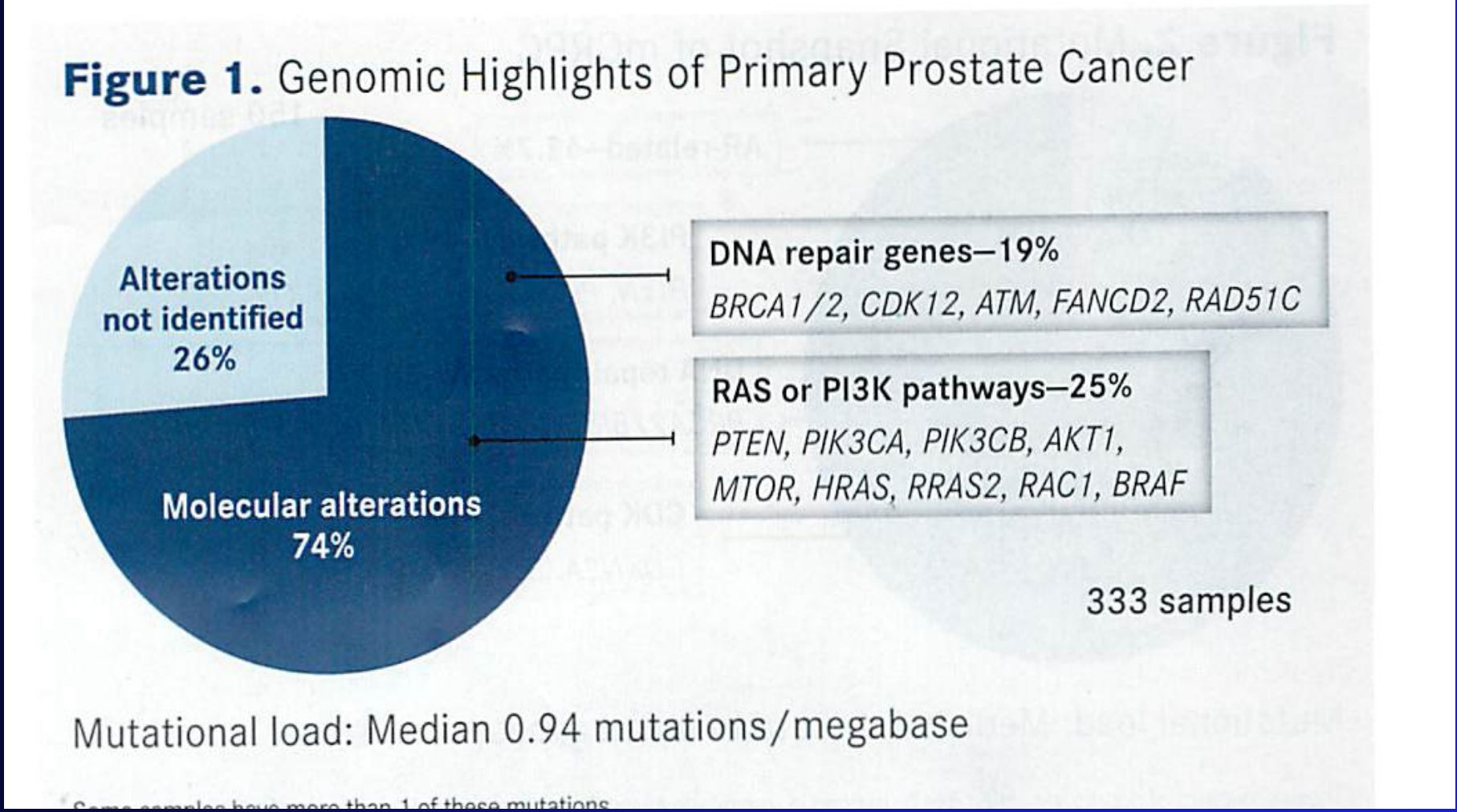
- Every cancer has many somatic mutations.
- A **somatic mutation** is a change in the gene that arose in the tumor and is confined to the tumor.
- Most cancer is sporadic (i.e., it happened by chance).



GERMLINE MUTATION

- A **germline mutation** is a change in the gene that was inherited and therefore causes an increased risk for cancer.
- This is also known as **hereditary cancer**.
- Only around 10% of cancer is hereditary.

Localized CaP: Molecular Alterations in 74% of Patients



Molecular Risk Tools-2019

- Serum Markers

  -PHI (Beckman Coulter)

  -4K Score (Opko Labs)

- Prostate Biopsy Tissue

  -Confirm MDx (MDx Health)

  -Prolaris (Myriad Genetics)

  -Oncotype GPS (Genomic Health)

  -Decipher (Genome Dx)

Radical Prostatectomy Tissue

-Prolaris (Myriad Prolaris)

-Decipher (Genome Dx)

Genetic testing at Duke Prostate Center-Duke Cancer Institute

- Duke Diagnostic Technology Committee (multi-D) must approve all "send-out" molecular/genetic tests
- Myriad Prolaris approved 12/19/2012
- Oncotype Dx GPS approved 9/10/14
- 4K score rejected 12/2014
- Decipher (post RP) approved 6/2015
- PHI "in house" Duke Labs 1/2016
- Confirm MDx- approved 5/12/2016

Guidelines: Molecular Testing of Tumor

2018 NCCN Prostate Cancer Guidelines

- Very low risk- Not generally indicated
- Low risk- consider if >10 year life-expectancy
- Favorable intermediate- " " " "
- Unfavorable intermediate- not indicated
- High Risk- not indicated
- Very High Risk-not generally indicated
- Regional metastases- consider: MSI; dMMR
- Distant metastases- consider: " "

Myriad Prolaris

CCP Gene Function

THE PROLARIS 46-GENE PANEL

FOXM1	CDC20	CDKN3	CDC2
KIF11	KIAA0101	NUSAP1	CENPF
ASPM	BUB1B	RRM2	DLGAP5
BIRC5	KIF20A[BP1]	PLK1	TOP2A
TK1	PBK	ASF1B	C18or∫24
RAD54L	PTTG1	MCM10	PRC1
DTL	CEP55	RAD51	CENPM
CDCA3	CDCA8	ORC6L	

31 Cell Cycle Progression Genes
Highly correlated and provide a reproducible measure of cell proliferation

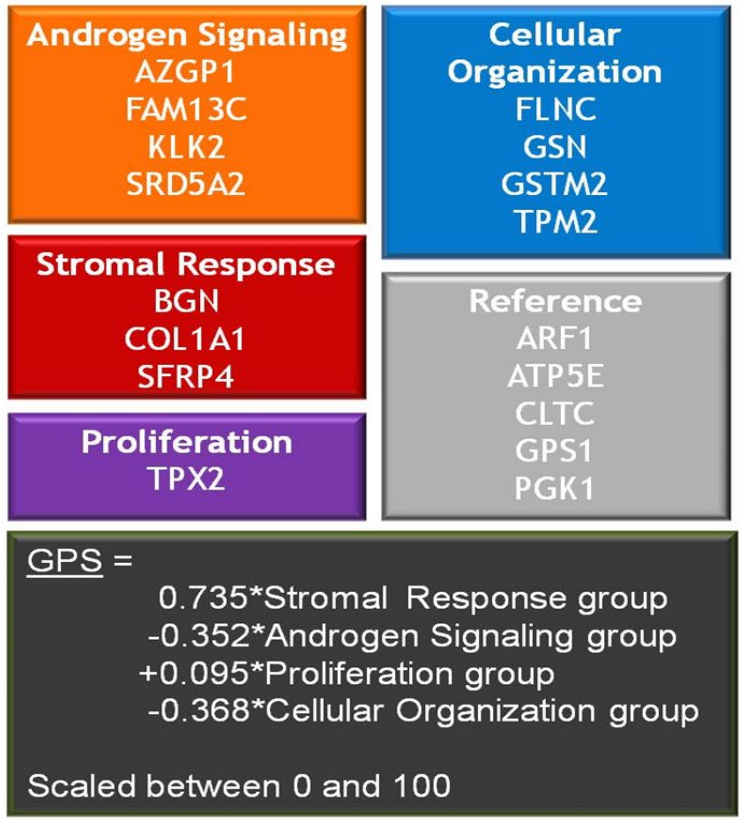
RPL38	UBA52	PSMC1	RPL4
RPL37	RPS29	SLC25A3	CLTC
TXNL1	PSMA1	RPL8	MMADHC
RPL13A	PPP2CA	MRFAP1	

15 Housekeeper Genes
Normalize the expression of the cell proliferation genes

Genomic Health Oncotype Dx GPS

Oncotype DX Prostate

- Quantitative 17-gene RT-PCR assay on manually micro dissected tumor tissue from needle biopsy
- Genes and biological pathways predictive of multiple endpoints, with emphasis on clinical recurrence
- Optimized for very small tissue input: six 5 micron sections of single needle biopsy block with as little as 1 mm tumor length



Cooperberg MR, et al. Development and valdiation fo the biopsy-based genomic prostate score (GPS) as a predictor of high grade or extracapsular prostate cancer to improve patient selection for active surveillance. Presented at AUA 2013

Comparison of two genetic tissue tests

Myriad Prolaris

- RNA expression cell cycle progression (CCP) genes
- 31 genes across cell cycle progression pathways
- 15 housekeeper genes
- Each 1 unit change in Prolaris score equals a doubling (or halving) of risk
- Biopsy tissue
- Radical prostatectomy tissue
- Can be ordered- all grades

Genomic Health GPS

- RNA expression of multiple cellular pathways
- 12 genes across multiple varied cellular pathways
- 5 housekeeper genes
- GPS results range from 0-100
- Newly diagnosed men with low to low-intermediate risk prostate cancer (GS 3+3, low volume 3+4) who have had a biopsy within the past 12 months

Limitations of Prolaris/Oncotype

- Neither have been prospectively validated in an active surveillance population
- Unclear which of the two is “better”
- Costly ($3,000-3,500 USD) but Medicare covered
- How the information is presented to the patient is not standardized and physician biases and patient wishes will invariably affect treatment decisions
- Not globally available

NASPCC 2019:Genetic Tests Prostate -Summary

- Must differentiate germline vs. somatic testing
- Hereditary testing: Fam Hx; advanced disease
- Hereditary mutation: candidate for AS?
- Somatic Localized: Myriad Prolaris and Genomic Health Oncotype GPS - Biopsy tissue based mRNA multi-gene expression/ archival tissue: AS vs Active Rx- do they really make any long term difference?