Genomics: Next Generation Testing for Prostate Cancer Screening, Prognosis, and Management

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Prostate Cancer Statistics

Each Year in the U.S.

There are **233,000** new cases of prostate cancer.

About **29,480** men will lose their lives to the disease.

1 in 7 men will develop prostate cancer during his lifetime.

http://zerocancer.org/

Prostate Cancer is Clinically Heterogeneous

• **Aggressive vs. Indolent**
  – Some prostate cancers grow and spread quickly
  – Others grow slowly

• Current information (clinical and pathological data) inadequately tell them apart
Figure 3. Screen Detection Capability Based on Tumor Biology and Growth Rates

Esserman et al. 
Prostate Cancer – how bad is it?

- **Stage or amount of cancer**
  - Physical exam
  - Prostate Specific Antigen (PSA)
  - Imaging tests

- **Grade of cancer**
  - Gleason score
Prostate Cancer is Clinically Heterogeneous

Problems with current care

• **Overtreatment** of indolent prostate cancer with radical therapy
  → high morbidity

• **Undertreatment** of lethal prostate cancer
  → continued mortality
Variability of Prostate Cancer: Examples

Patient 1
65 years old
PSA 5
Gleason 7

OBSERVATION
No evidence of progression after 5 years

Patient 2
65 years old
PSA 5
Gleason 7

RADICAL PROSTATECTOMY
(or RADIATION)
Cured
Impotent
Incontinent

Patient 3
65 years old
PSA 5
Gleason 7

RADICAL PROSTATECTOMY
(or RADIATION)
Recurrence
Metastasis
Dies of disease
Genomic Classification

Define distinct classes of prostate cancer based on molecular/genomic characteristics

DNA Abnormalities

Class A

Class B

Class C

Prognosis
Management Strategy
Targeted Therapy: PRECISION MEDICINE
What is genomics?

• Study of the structure and function of the complete set of DNA in a cell or organism
“Genomics” in modern medicine

Can refer to analysis of any molecular information (DNA, RNA, etc) that provides information about biology.

Genome-wide approaches (every single gene) Vs. Targeted
Genomic Testing for Prostate Cancer

1. Patients with no biopsy yet or after a negative biopsy:
   To help initially detect (aggressive) prostate cancer

2. Patients after a positive biopsy:
   To determine if prostate cancer is aggressive or indolent and needs to be treated

3. Tests after a prostatectomy
   To determine if additional therapy may be needed
• **PCA3**: Noncoding RNA overexpressed in > 90% of prostate cancers

• Progenesa PCA3 test
  – FDA approved for men with negative biopsy
Recurrent Fusion of TMPRSS2 and ETS Transcription Factor Genes in Prostate Cancer

Scott A. Tomlins,1 Daniel R. Rhodes,1,2 Sven Perner,7,9 Saravana M. Dhanasekaran,1 Rohit Mehra,1 Xiao-Wei Sun,7 Sooryanarayana Varambally,1,6 Xuhong Cao,1 Joelle Tchinda,7 Rainer Kuefer,10 Charles Lee,7 James E. Montie,3,5,6 Rajal B. Shah,1,3,5,6 Kenneth J. Pienta,3,4,5,6 Mark A. Rubin,7,8 Arul M. Chinnaiyan1,2,3,5,6*

ERG Gene Fusion

- 47%
+ 53%

~10,000 tumors

(Tomlins et al. Science 2005)

Squire, JA. Nature Genetics 41, 509 - 510 (2009)

Detection of Prostate Cancer Cells in Urine

Measure ratio of PCA3 and TMPRSS2-ERG to PSA transcript in urine after DRE

Hessels et al., European Urology 2003
Urine **TMPRSS2:ERG** Fusion Transcript Stratifies Prostate Cancer Risk in Men with Elevated Serum PSA

Scott A. Tomlins,1 Sheila M. J. Aubin,2 Javed Siddiqui,1 Robert J. Lonigro,1,3 Laurie Sefton-Miller,1 Siobhan Mlick,2 Sarah Williamsen,2 Petrea Hodge,2 Jessica Meinke,2 Amy Blase,2 Yvonne Penabella,2 John R. Day,2 Radhika Varambally,1 Bo Han,1 David Wood,4 Lei Wang,1 Martin G. Sanda,5 Mark A. Rubin,6 Daniel R. Rhodes,1 Brent Hollenbeck,4 Kyoko Sakamoto,7 Jonathan L. Silberstein,7 Yves Fradet,8 James B. Amberson,9 Stephanie Meyers,4 Nallasivam Palanisamy,1 Harry Rittenhouse,4 John T. Wei,4 Jack Groskopf,2 Arul M. Chinnaiyan1,3,4,10,*

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Science Translational Medicine 2011

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Urine **TMPRSS2:ERG** Fusion Transcript Integrated With PCA3 Score, Genotyping, and Biological Features Are Correlated to the Results of Prostatic Biopsies in Men at Risk of Prostate Cancer

Jean-Nicolas Cornu,1,2,3,* Géraldine Cancel-Tassin,2,3 Christophe Egrot,1,2 Cécile Gaffory,2,3 François Haab,1 and Olivier Cussenot1,2,3

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The Prostate 2013

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Prospective Multicentre Evaluation of **PCA3** and **TMPRSS2-ERG** Gene Fusions as Diagnostic and Prognostic Urinary Biomarkers for Prostate Cancer

Gisèle H.J.M. Leyten,1 Daphne Hessels2, Sander A. Jannink2, Frank P. Smit2, Hans de Jong2, Erik B. Cornel2, Theo M. de Reijke2, Henk Vergunst4, Paul Kil2, Ben C. Knipscheer2, Inge M. van Oort2, Peter F.A. Mulders2, Christina A. Hulsbergen-van de Kaa2, Jack A. Schalken2,1,*

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European Urology 2012

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Urine **TMPRSS2:ERG** and PCA3 in an Active Surveillance Cohort: Results from a Baseline Analysis in the Canary Prostate Active Surveillance Study


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Clinical Cancer Research 2013
Genomic Testing for Prostate Cancer

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   To determine if prostate cancer is aggressive or indolent and needs to be treated

3. Tests after a prostatectomy
   To determine if additional therapy may be needed
Tests after a positive biopsy:
To determine aggressive or indolent
Oncotype DX® GPS
Specifically Designed to Work in Biopsy Tissue

- Two spatially distinct areas of tumor representing the dominant (primary) and the highest Gleason pattern for each patient were analyzed to identify genes which are predictive regardless of sampled Gleason pattern.
- Selected genes which predict clinical outcome in the face of tumor heterogeneity and biopsy under-sampling and perform well in biopsy tissue.
- Standardized analytical platform for reliable measurement of 17-gene GPS assay in small volume tumor from biopsies.
- Analytical Performance:
  - 96% of biopsies yielded successful GPS results.
  - 99.5% of samples with > 10 ng RNA yielded successful results.
Combining Biologic & Clinical Information Refines Risk Stratification for Individual Patients

Population-Based Clinical Risk Assessment

Very Low Risk: 10% (N=37)
Low Risk: 49% (N=191)
Low-Intermediate Risk: 41% (N=160)

UCSF Validation Study
NCCN Risk Classification

- 10% Very Low-risk
- 49% Low-risk
- 41% Intermediate Risk

GPS Provides Biologic Risk Information

More Individualized Biologic and Clinical Risk Assessment

Very Low Risk: 26% (N=100)
Low Risk: 31% (N=119)
Low-Intermediate Risk: 44% (N=169)

GPS=8: 84%
GPS=25: 75%
GPS=51: 57%

Likelihood of Favorable Pathology

Clinical Utility Study: Actual Treatment Decision

- Patients who had a GPS result pursued AS* more often than those without an Oncotype DX GPS result, highlighting the influence of personalized genomic information on treatment decisions.
- 56% relative increase in patients who pursued AS when GPS was available relative to patients without GPS (AS increased from 43% to 67%).

* Included Active Surveillance/Watchful Waiting
Dall’Era M, PCF 2014.
Testing prostate cancer tissue from a biopsy to evaluate expression of genes that predict aggressive behavior
Genomic Testing for Prostate Cancer

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Do I need more therapy after my prostate has been removed?
Precision genomic technology

Decipher® genomic signature helps physicians assess likelihood of metastasis

- Clinical-grade expression assay
- Analyzes 1.4 million genomic markers
- Provides gene signature for probability of metastasis

Am I a candidate for Decipher?

- Have you had a radical prostatectomy (prostate removal surgery) to treat your prostate cancer?
- Did your doctor indicate that ANY one of the following applied to you after surgery?
  - Positive surgical margins
  - Extraprostatic extension
  - Seminal vesicle invasion
  - PSA started to rise again
  - Pre-surgery PSA 20ng/mL or higher
  - Gleason score 8-10
  - Lymph node involvement

If you answered yes, talk to your physician about Decipher
Tests after prostatectomy:
To determine if additional therapy needed

- Extra prostatic Extension: 0.65
- Gleason Score: 0.64
- Seminal Vesicle Invasion: 0.59
- Lymph Node Invasion: 0.56
- PreOp PSA: 0.56
- Surgical Margins: 0.49

Predictive power measured by Area Under the Curve (AUC)
General overview of prostate cancer management

Order Decipher

Adverse Pathology

Radical Prostatectomy

Decipher High Risk

Radiation (ART Better Results Than SRT)

Excellent prognosis with SRT and may avoid concurrent hormone therapy

Decipher Low Risk

Observation Until Detectable PSA Rise, if any

Excellent prognosis with SRT and may avoid concurrent hormone therapy

PSA Rise/BCR

May require intensification of therapy beyond radiation

PSA Rise/BCR

Excellent prognosis with SRT and may avoid concurrent hormone therapy

Decipher High Risk

Decipher Low Risk
80% reduction in metastasis risk in Decipher high-risk patients who received early (adjuvant) radiation therapy compared to those who received late (salvage) radiation therapy

How to Interpret Decipher Results

60% of men were classified as Decipher low risk, 90% of them opted for observation

Prostate Cancer is Clinically Heterogeneous

- **Indolent** vs. **aggressive**
- Current information inadequately distinguish

**Problems with current care**

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  - → high morbidity

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Genomic Classification

Define distinct classes of prostate cancer based on molecular/genomic characteristics

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Class A

Class B

Class C

Prognosis
Management Strategy
Targeted Therapy: PRECISION MEDICINE
ERG gene fusions: A starting point for molecular classification

TMPRSS2 Gene

ERG Gene

TMPRSS2:ERG Gene Fusion

Gene Fusion

Novel protein

Overexpression leading to disease

~10,000 tumors

47%
7 prostate cancer whole genomes

112 whole exomes
Barbieri et al, *Nature Genetics* 2012

57 whole genomes
Baca et al, *Cell* 2013

WCMC a leader in state-of-the-art DNA sequencing for prostate cancer
$SPOP$ mutations in Prostate Cancer

Prostate Cancer Samples (N=453)

$SPOP$ mutations 10% (45 of 453)
SPOP mutations define a distinct molecular class of prostate cancer

Each column represents a single prostate cancer sample

Type of gene alteration:  
- **Mutation**
- **Deletion**
- **Rearrangement**

Affected Genes

- TP53
- PIK3CA
- PTEN
- ERG
- SPOP

Barbieri et al, Nature Genetics 2012
**SPOP** mutation defines a distinct molecular class of prostate cancer

[Diagram showing Venn diagram with circles labeled **SPOP mutant**, **CHD1**, **TP53**, **PTEN**, **ETS rearranged**, and **TMPRSS2-ERG** intersecting to form the category of *Primary Prostate Cancer*.]
The Cancer Genome Atlas (TCGA)

TCGA et al, Cell 2015 (In Press)
**SPOP** mutation defines a distinct molecular class of prostate cancer

2014 new cases: 233,000

25,000/year

- Brain/Nervous System: 23,130
- Myeloma: 22,350
- Lymphocytic Leukemia: 21,750
- Myeloid Leukemia: 20,510
DNA Rearrangements in Prostate Cancer

Complex patterns of DNA rearrangements

Chromosome numbers
DNA sequencing from 55 clinically localized PCA

DNA Rearrangements in Primary Prostate Cancer

Total Genomic Rearrangements

Number of Prostate Cancers

Total Rearrangements

Primary Prostate Cancer

ETS rearranged

TMPRSS2-ERG

CHD1

SPOP mutant

TP53

PTEN
Timeline of events is critical

*When* do SPOP mutations occur in prostate cancer? Early or Late?

SPOP mutations are present in early lesions
Temporal Relationships: Clonality

SPOP mutation is an early event
SPOP impacts DNA break repair

Double-strand DNA break

Error-free Repair Mechanism

Error-prone Repair Mechanism
DNA Repair as an Achilles Heel in Cancer: Synthetic Lethality

SPOP mutation confers sensitivity to specific DNA damaging agents

Opportunity for novel therapeutic interventions
Prostate cancer can be divided into subclasses based on molecular features. Distinct subclasses may have distinct therapeutic options. Ongoing research in my laboratory will help refine the prostate cancer subclasses and develop improved therapeutic approaches.
CONCLUSIONS

• Prostate Cancer is Heterogeneous
• New genomic tests are becoming available to help:
  – With initial diagnosis
  – Determining how aggressive
  – Need for additional therapy
• Genomic classification is revealing distinct molecular classes
  – Precision medicine approach