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/

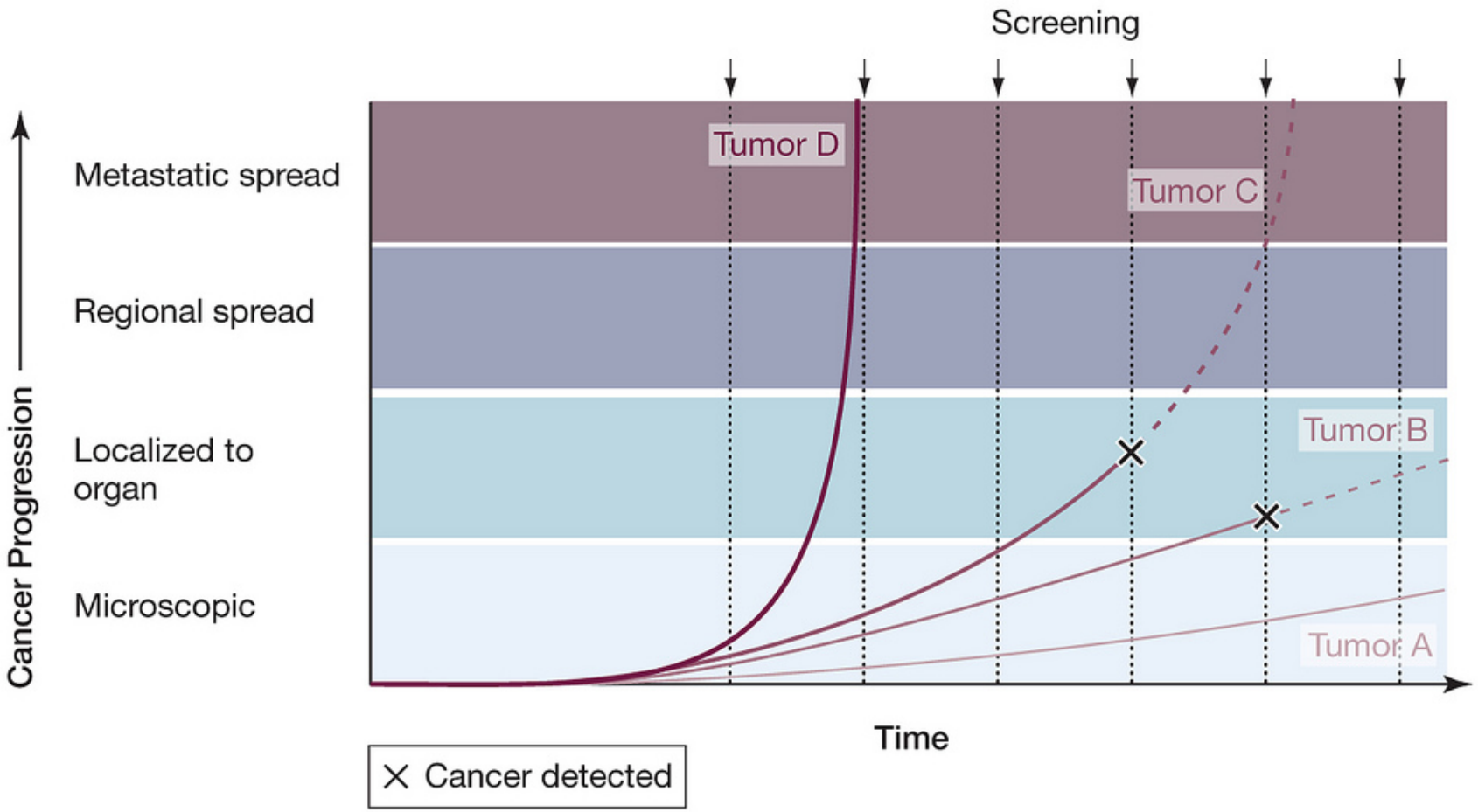
http://www.healthline.com/health/prostate-cancer/facts-statistics-infographic

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

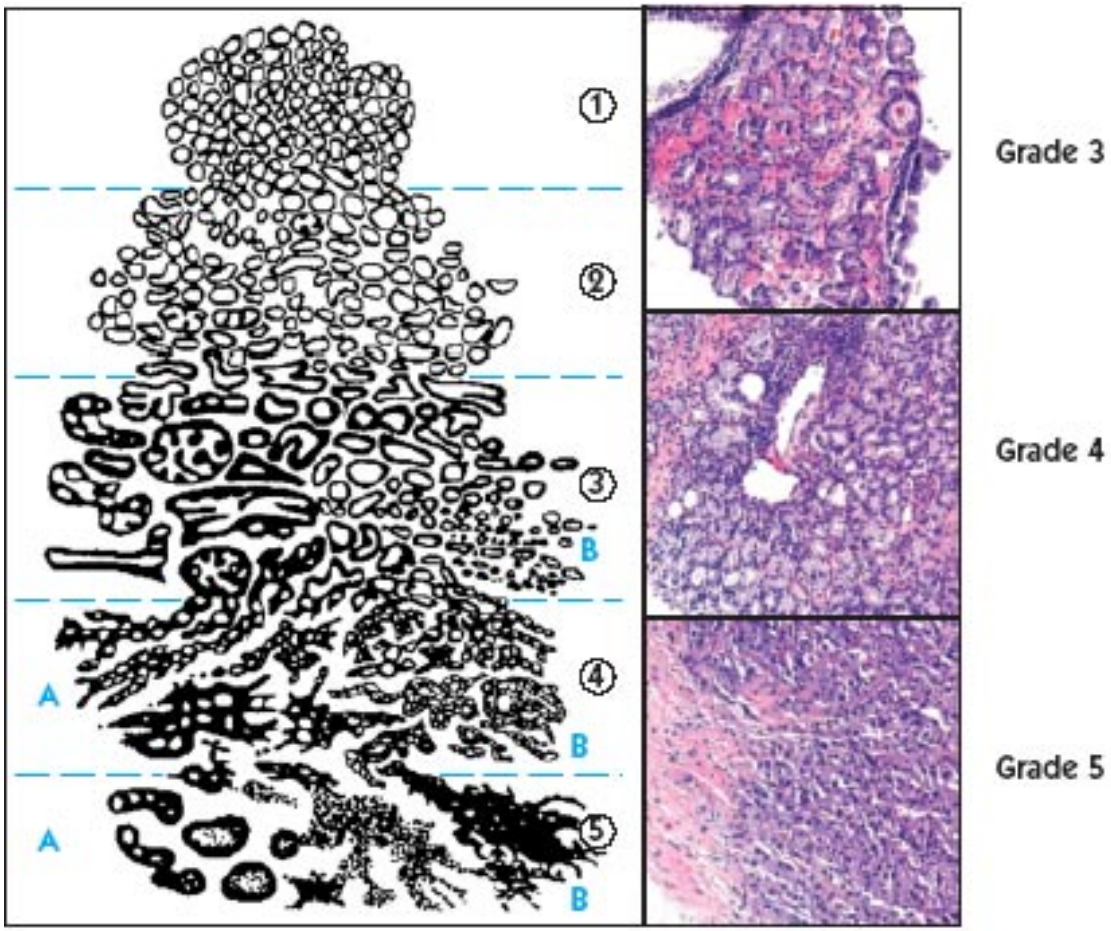
Figure 3. Screen Detection Capability Based on Tumor Biology and Growth Rates



Esserman et al.
JAMA. 2009;302(15):1685-1692. doi:10.1001/jama.2009.1498.

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

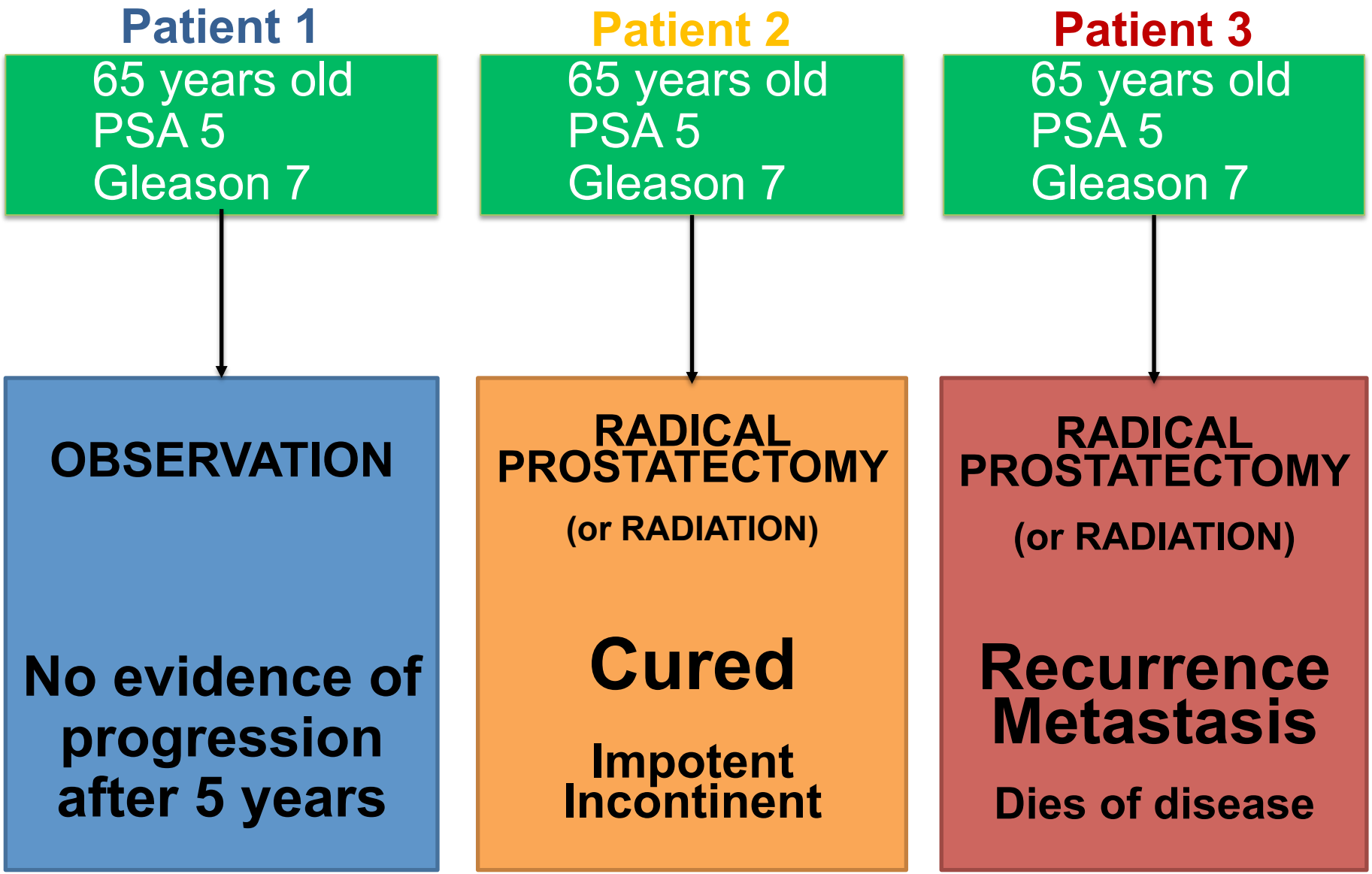
- **Overtreatment** of indolent prostate cancer with radical therapy

  → high morbidity

- **Undertreatment** of lethal prostate cancer

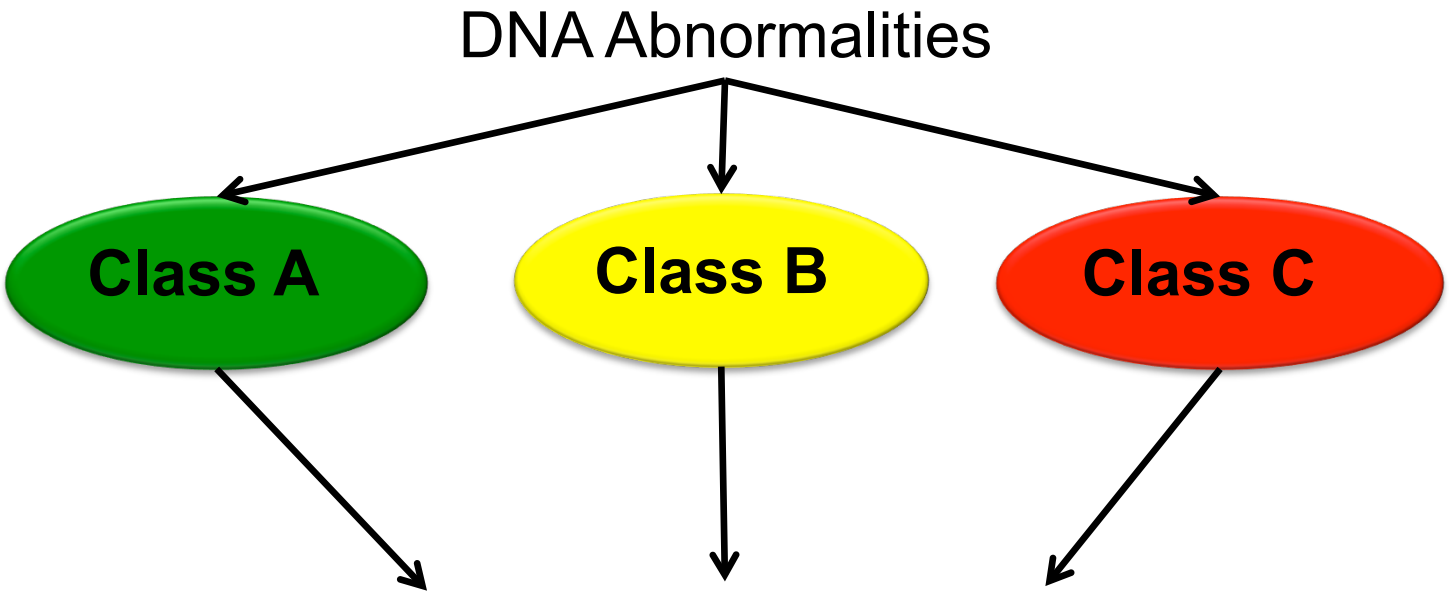
  → continued mortality

Variability of Prostate Cancer: Examples



Genomic Classification

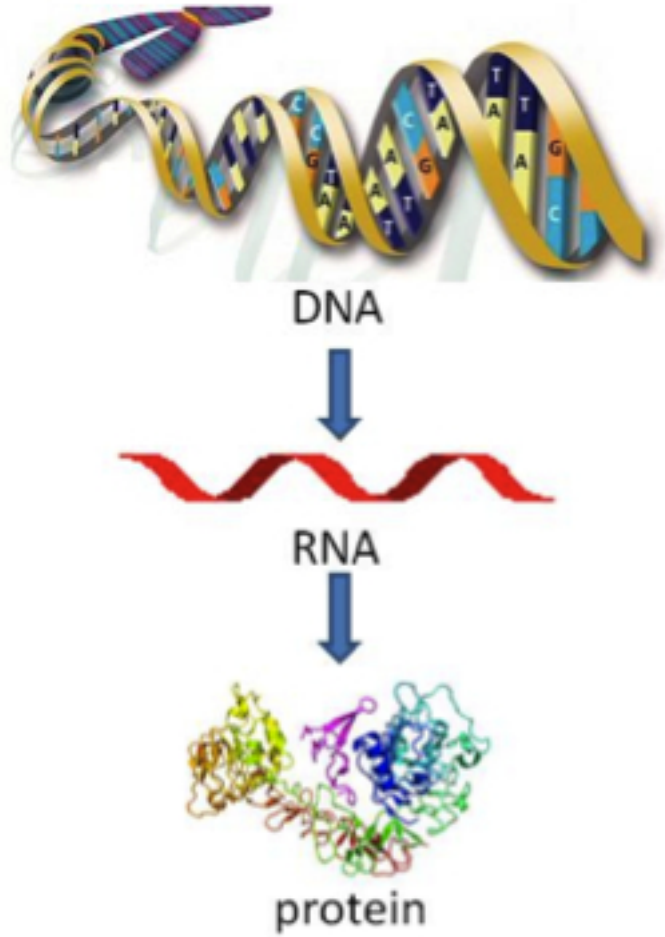
Define distinct classes of prostate cancer based on molecular/genomic characteristics



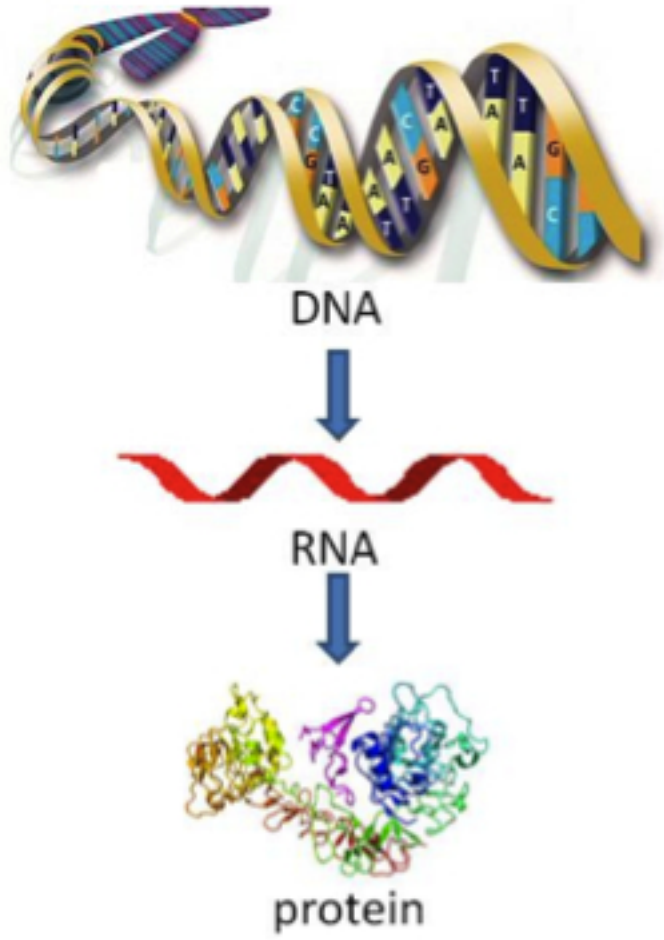
Prognosis
Management Strategy
Targeted Therapy: **PRECISION MEDICINE**

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

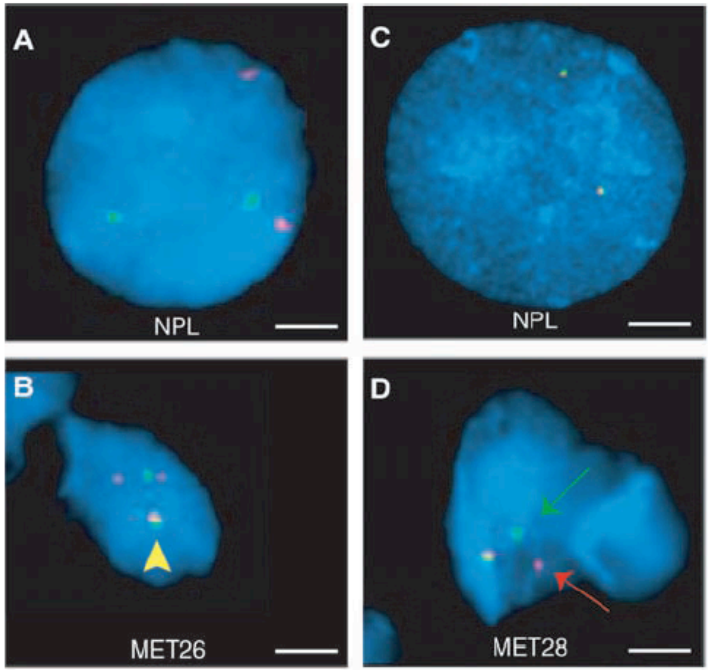
- **PCA3**: Noncoding RNA overexpressed in > 90% of prostate cancers
- Progensa PCA3 test
  - FDA approved for men with negative biopsy

TMPRSS2-ERG

28 OCTOBER 2005 VOL 310 SCIENCE

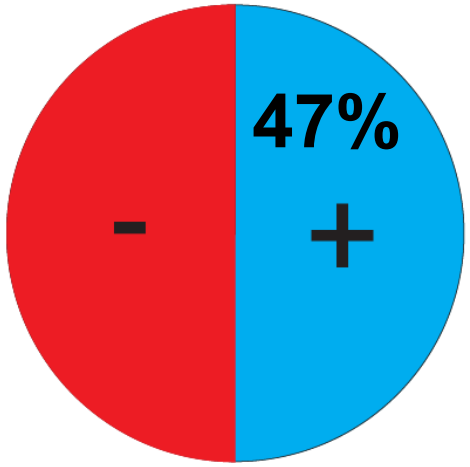
Recurrent Fusion of *TMPRSS2* and ETS Transcription Factor Genes in Prostate Cancer

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. Chinnaiyan[1,2,3,5,6*]



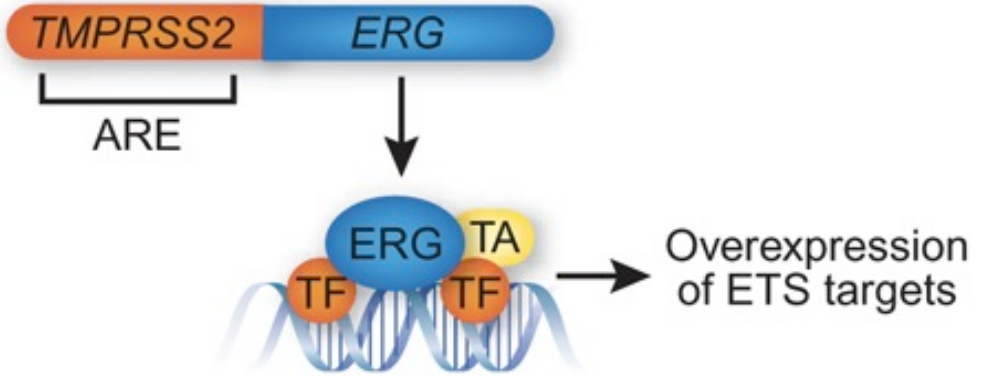
(Tomlins et al. Science 2005)

ERG Gene Fusion



~10,000 tumors

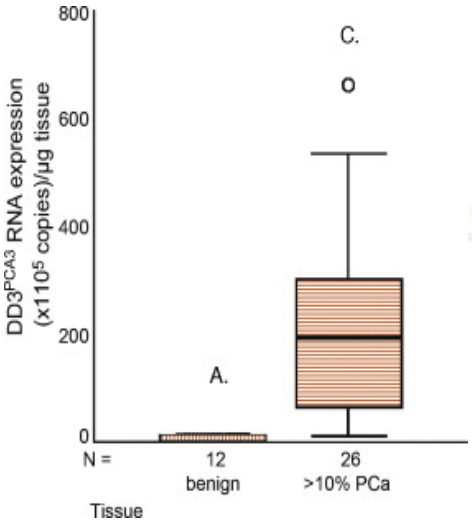
(Pettersson *et al*. Cancer Epid Bio Prev, 2012)



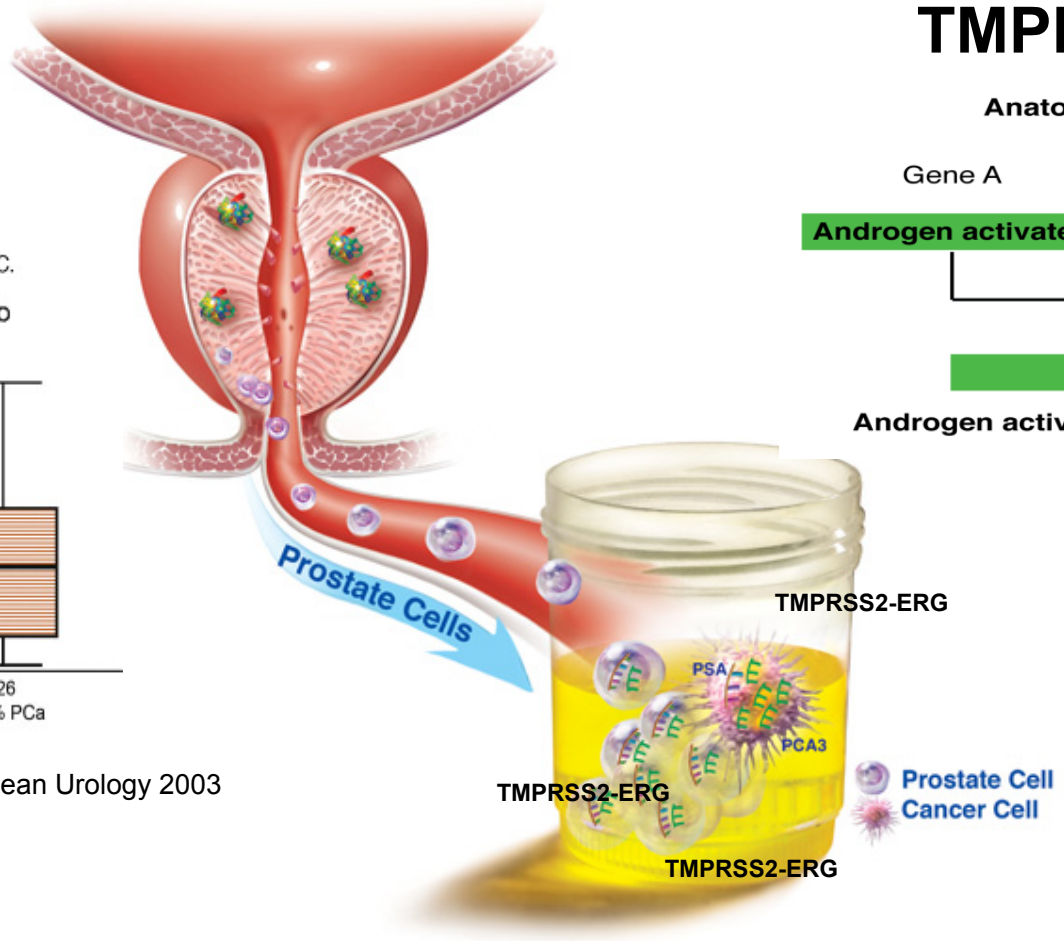
Squire, JA. Nature Genetics 41, 509 - 510 (20

Detection of Prostate Cancer Cells in Urine

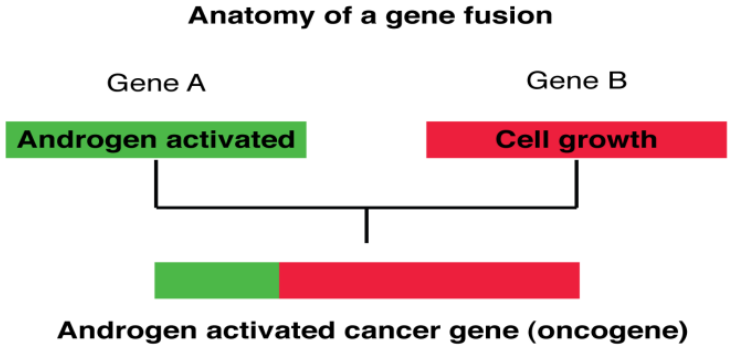
PCA3



Hessels et al., European Urology 2003



TMPRSS2-ERG



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

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 Miick,[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,[2] John T. Wei,[4] Jack Groskopf,[2] Arul M. Chinnaiyan[1,3,4,10]*

Science Translational Medicine 2011

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 Cussenot[1,2,3]

The Prostate 2013

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

Gisele H.J.M. Leyten [a], Daphne Hessels [b], Sander A. Jannink [b], Frank P. Smit [b], Hans de Jong [b], Erik B. Cornel [c], Theo M. de Reijke [d], Henk Vergunst [e], Paul Kil [f], Ben C. Knipscheer [g], Inge M. van Oort [a], Peter F.A. Mulders [a], Christina A. Hulsbergen-van de Kaa [h], Jack A. Schalken [a,]*

European Urology 2012

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

Daniel W. Lin, Lisa F. Newcomb, Elissa C. Brown, et al.

Clinical Cancer Research 2013

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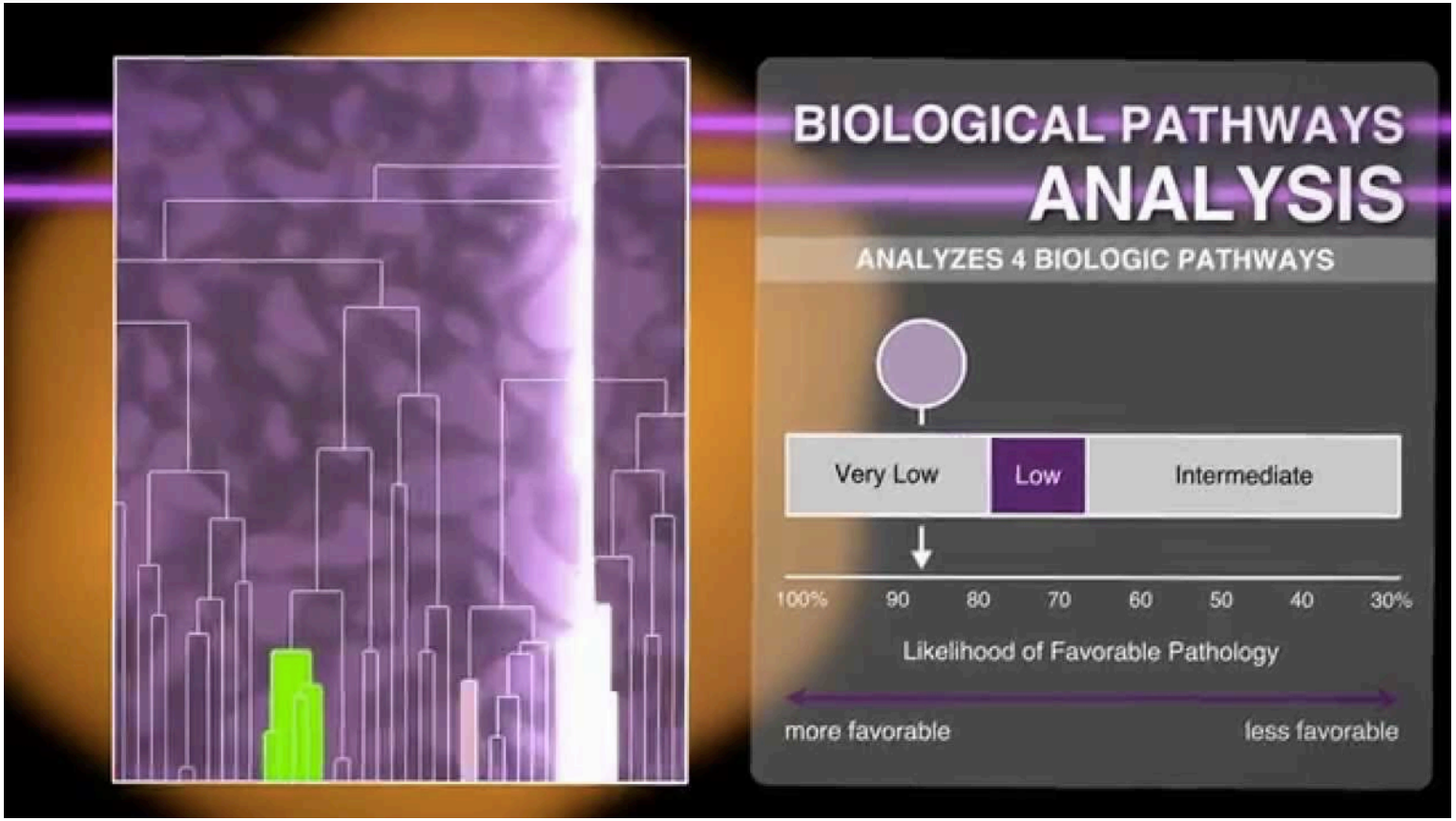
   To determine if prostate cancer is aggressive or indolent and needs to be treated

3. Tests after a prostatectomy

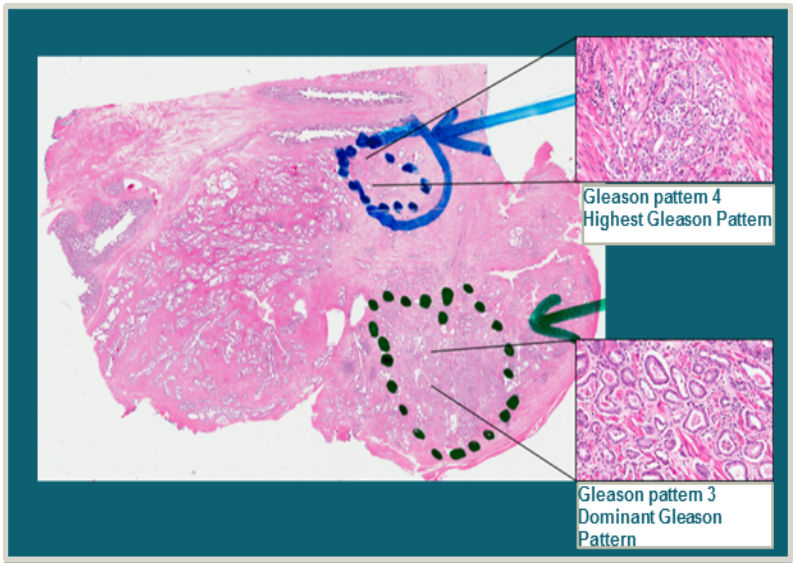
   To determine if additional therapy may be needed

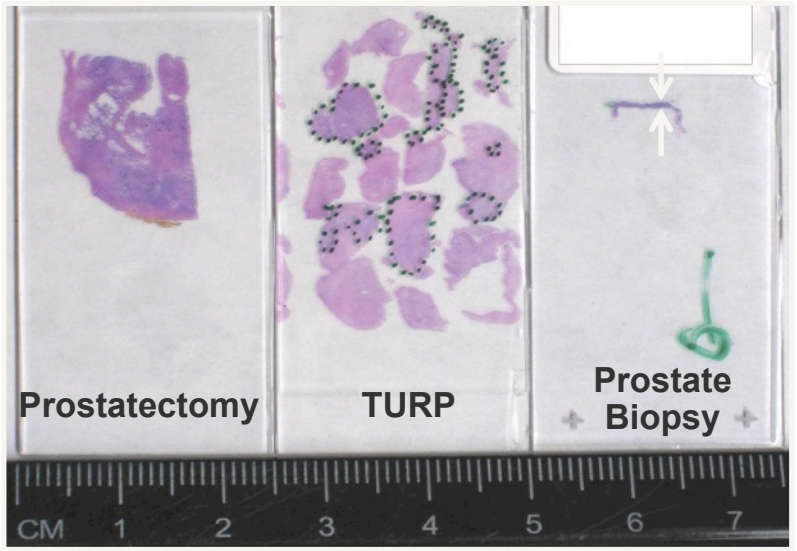
Tests after a positive biopsy:
To determine aggressive or indolent

oncotype DX®
Prostate Cancer Assay



Oncotype DX® GPS
Specifically Designed to Work in Biopsy Tissue

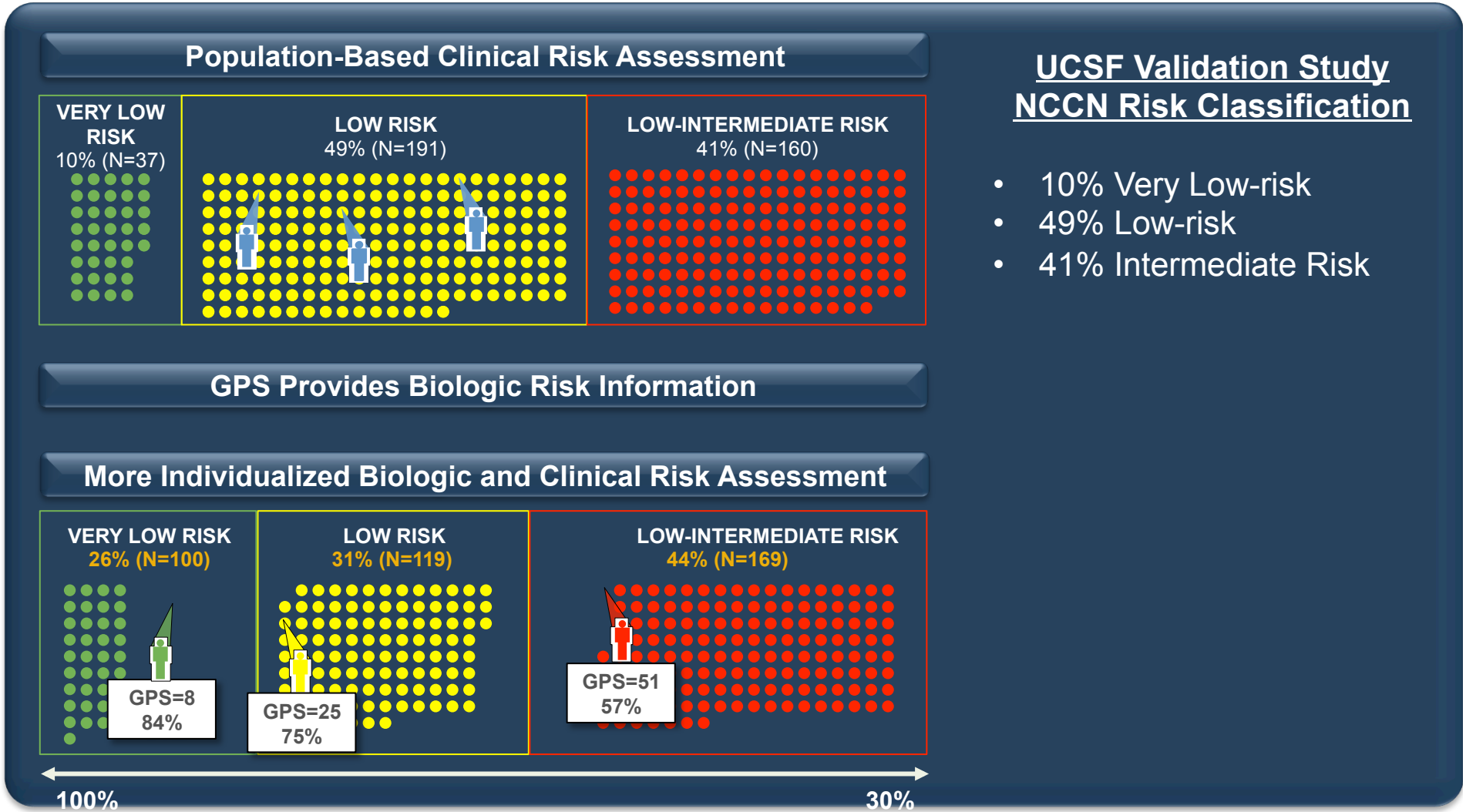




- Two spatially distinct areas of tumor representing the dominant (primary) and the highest Gleason pattern for each patient were analyzed to identify genes which are predictive regardless of sampled Gleason pattern
- Selected genes which predict clinical outcome in the face of tumor heterogeneity and 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



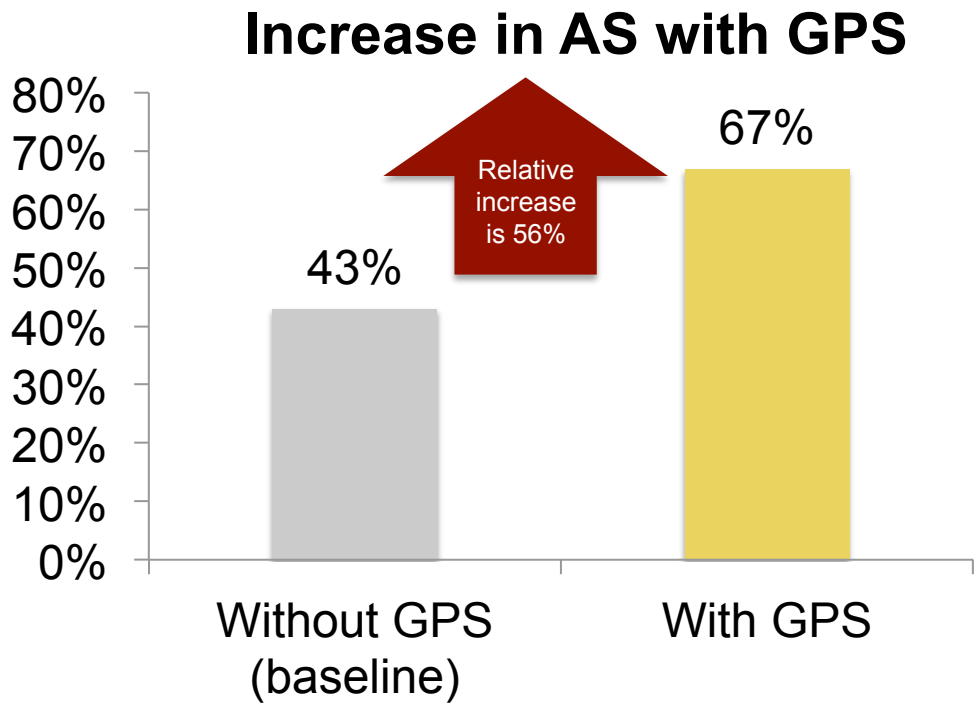
UCSF Validation Study
NCCN Risk Classification

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

Klein, Cooperberg et al, *Euro Urol (2014).*

Clinical Utility Study: Actual Treatment Decision

- Patients who had a GPS result pursued AS* more often than those without an Onco*type* 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.

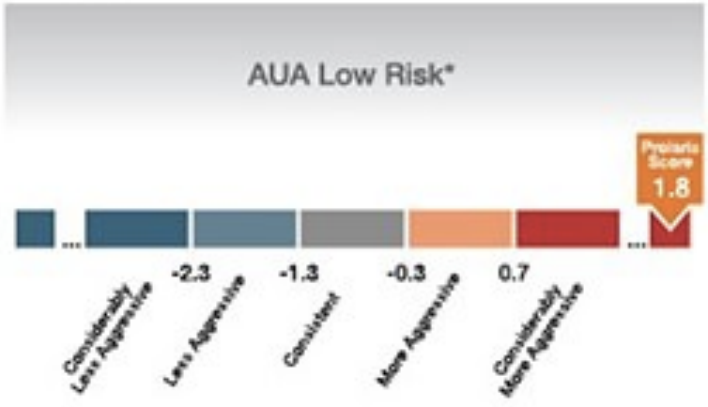
Prolaris®

Testing prostate cancer tissue from a biopsy to evaluate expression of genes that predict aggressive behavior

Prolaris Score: 1.8

▸ **Considerably More Aggressive** Than Average AUA Low Risk

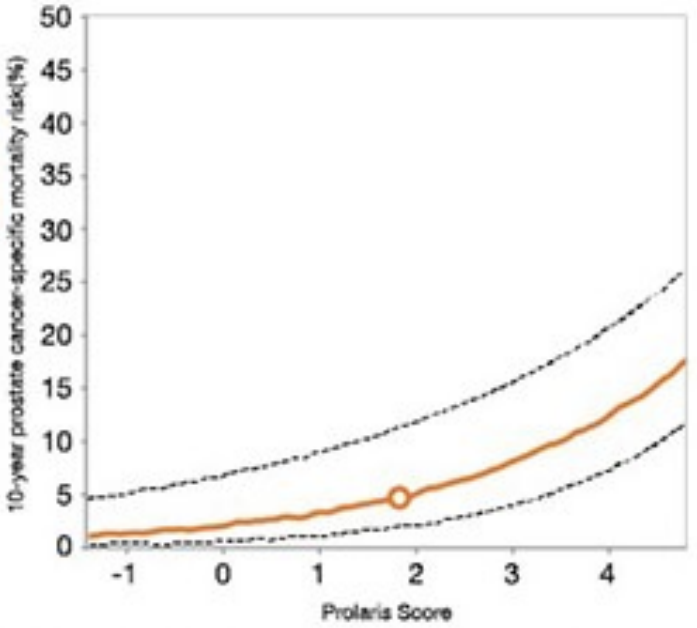
Interpretation: The Prolaris Score of 1.8 indicates that this cancer is considerably more aggressive than the average cancer in the American Urology Association (AUA)' Low Risk category.



The above chart illustrates the AUA Low Risk category, which is composed of patients with varying degrees of cancer aggressiveness. Cancer aggressiveness can be stratified within this category based upon Prolaris Scores, which are indicated below the graph.[2]

▸ 10-Year Prostate Cancer-Specific **Mortality Risk: 5%** (95% CI:2-11%)

Interpretation: The patient has a 10-year mortality risk of 5% if managed conservatively. Mortality risks could be altered by various therapeutic interventions.



Genomic Testing for Prostate Cancer

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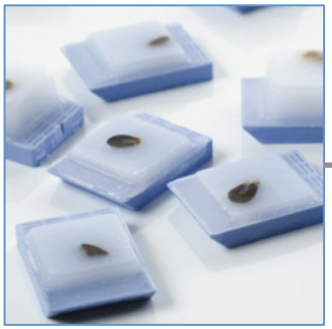
   To determine if additional therapy may be needed

Decipher®
prostate cancer classifier

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

Decipher® genomic signature helps physicians assess likelihood of metastasis



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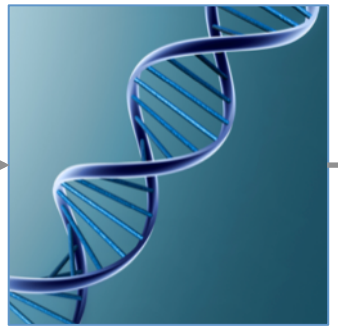
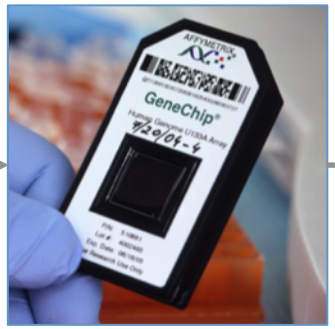
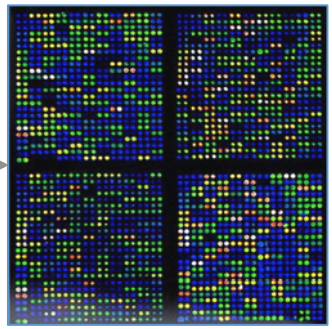
FFPE TISSUE



GENETIC
MATERIAL



GENECHIP
TECHNOLOGY



GENOME
ANALYSIS

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

Abdueva et al., Journal of Molecular Diagnostics 2010, Vergara et al., Frontiers in Genetics 2011, Erho et al., Journal of Oncology 2012

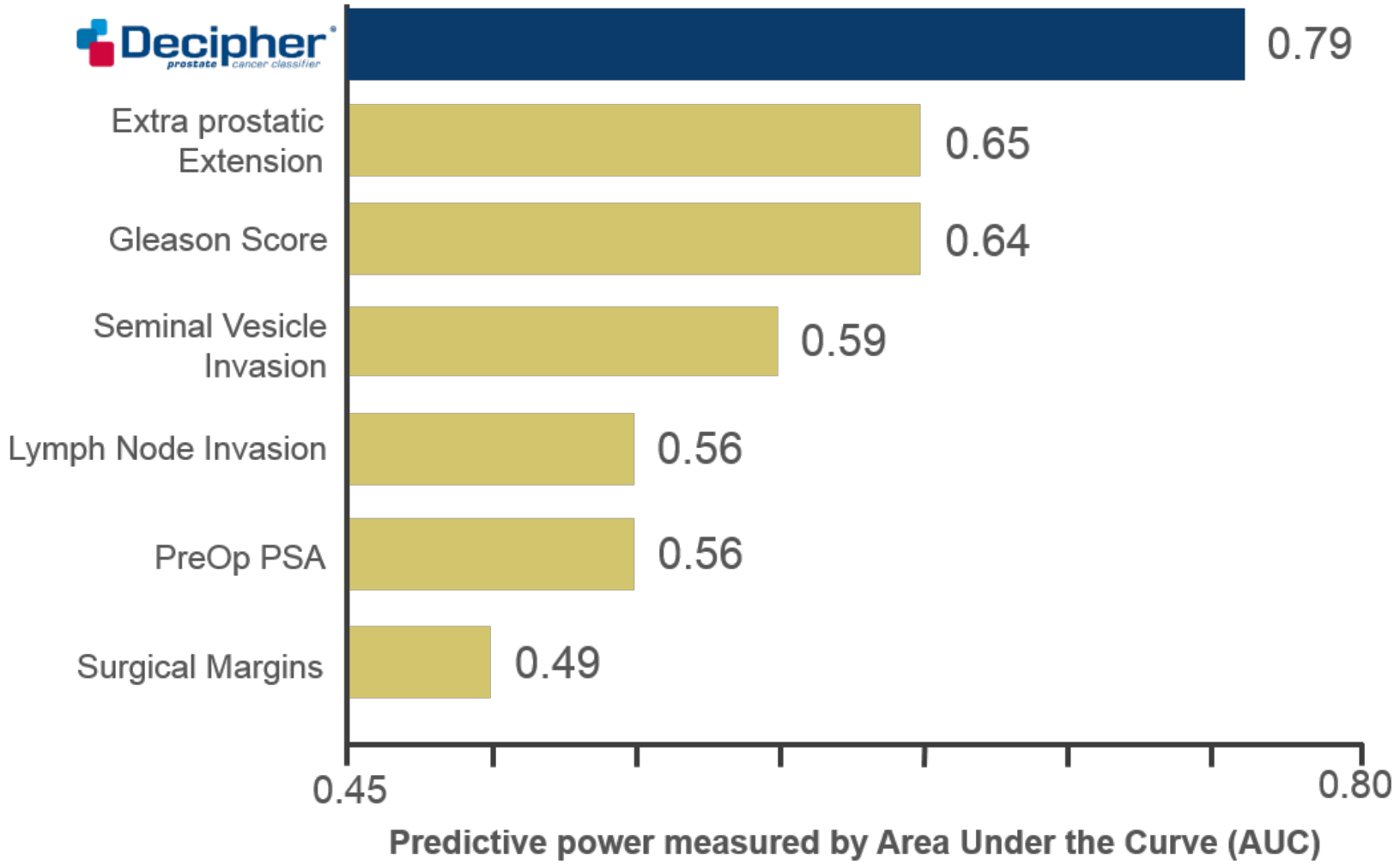
Am I a candidate for Decipher?

- 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

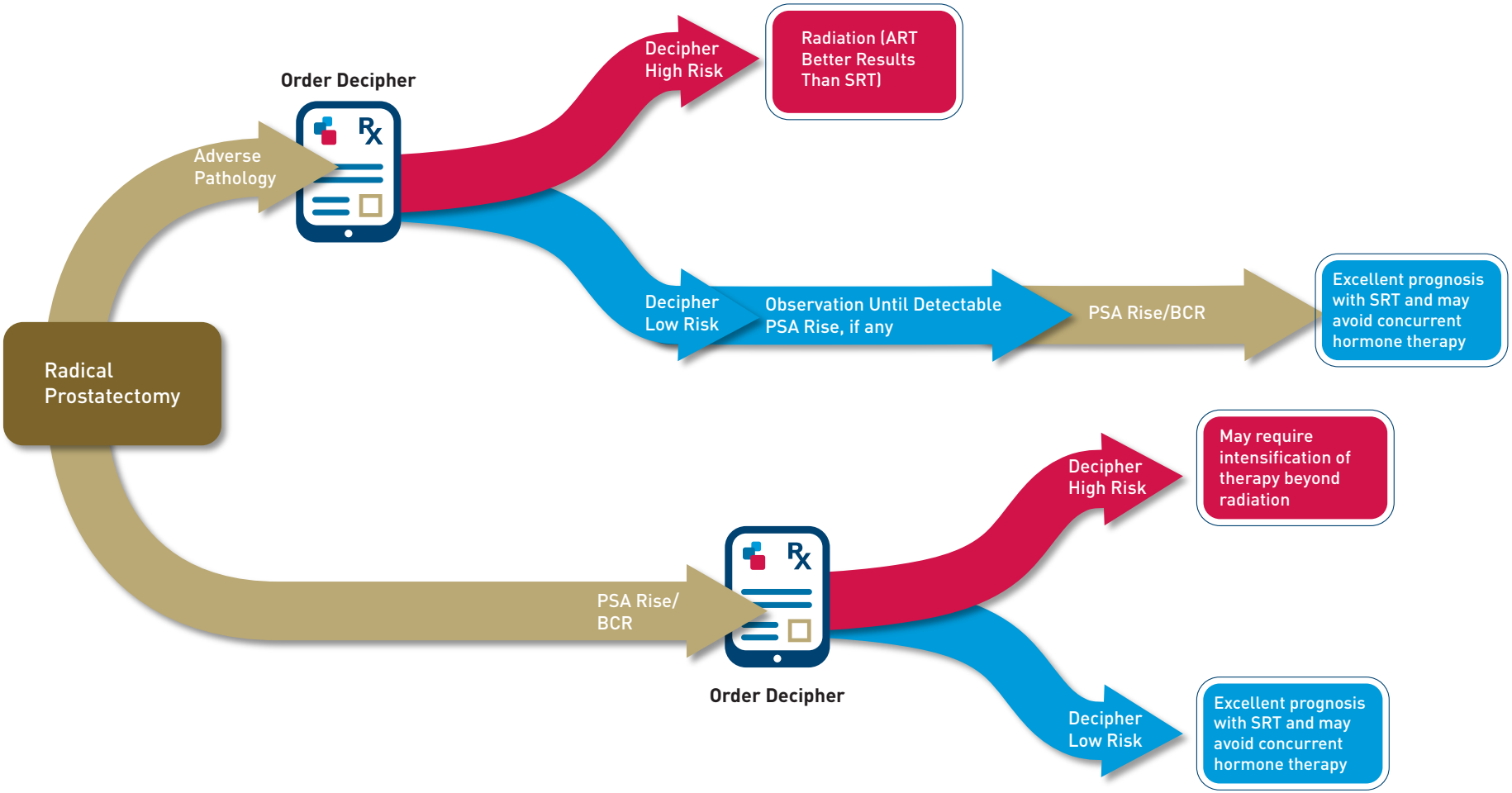
If you answered yes, talk to you physician about Decipher

Tests after prostatectomy:

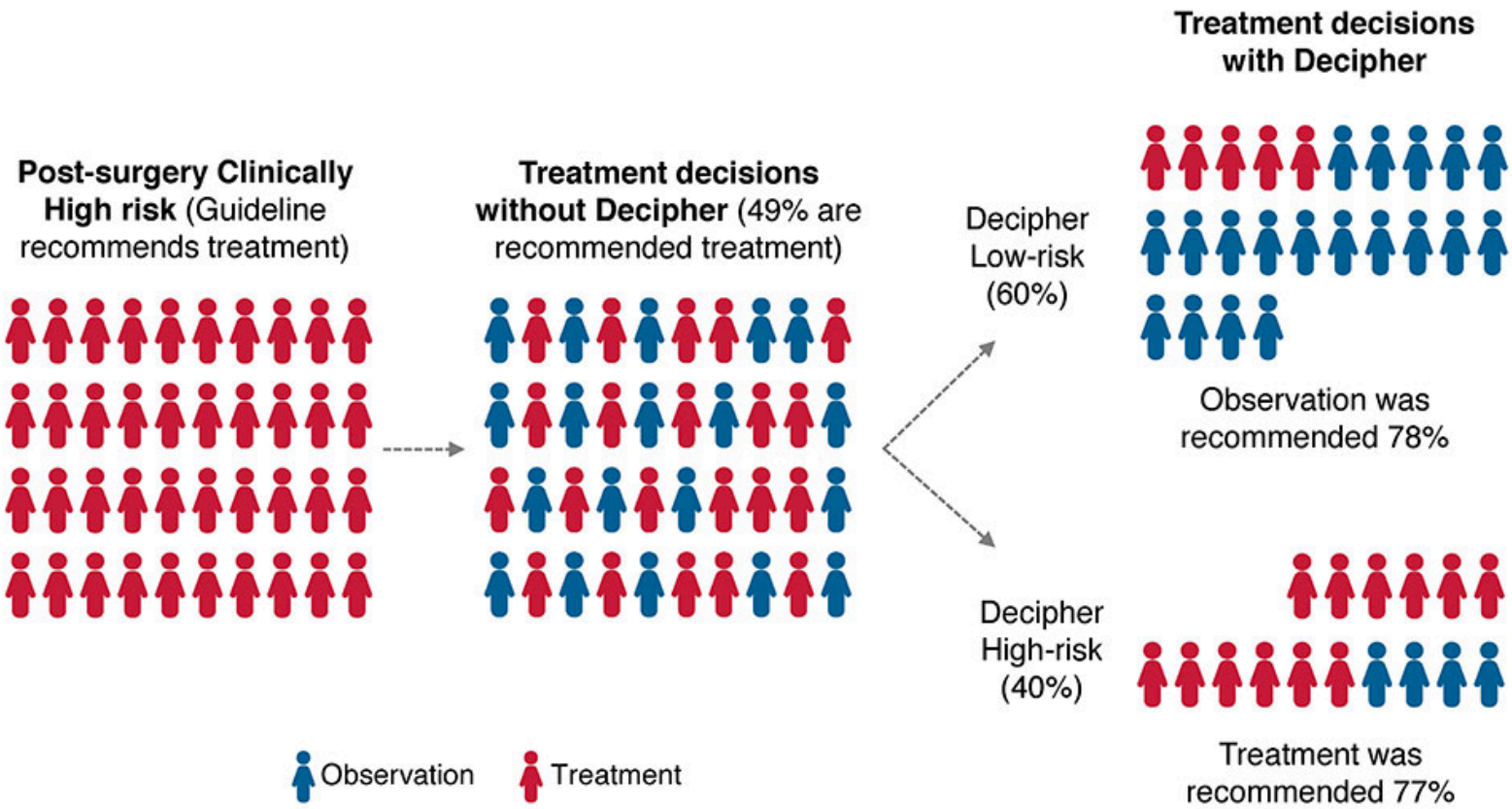
To determine if additional therapy needed



General overview of prostate cancer management

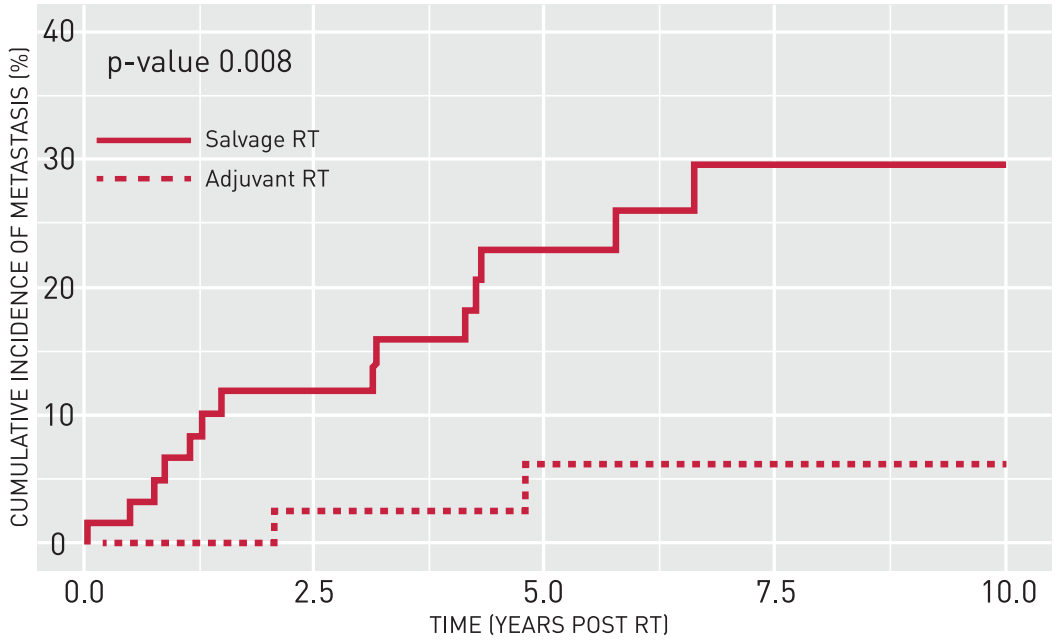


Decipher®
prostate cancer classifier



How to Interpret Decipher Results

High Risk

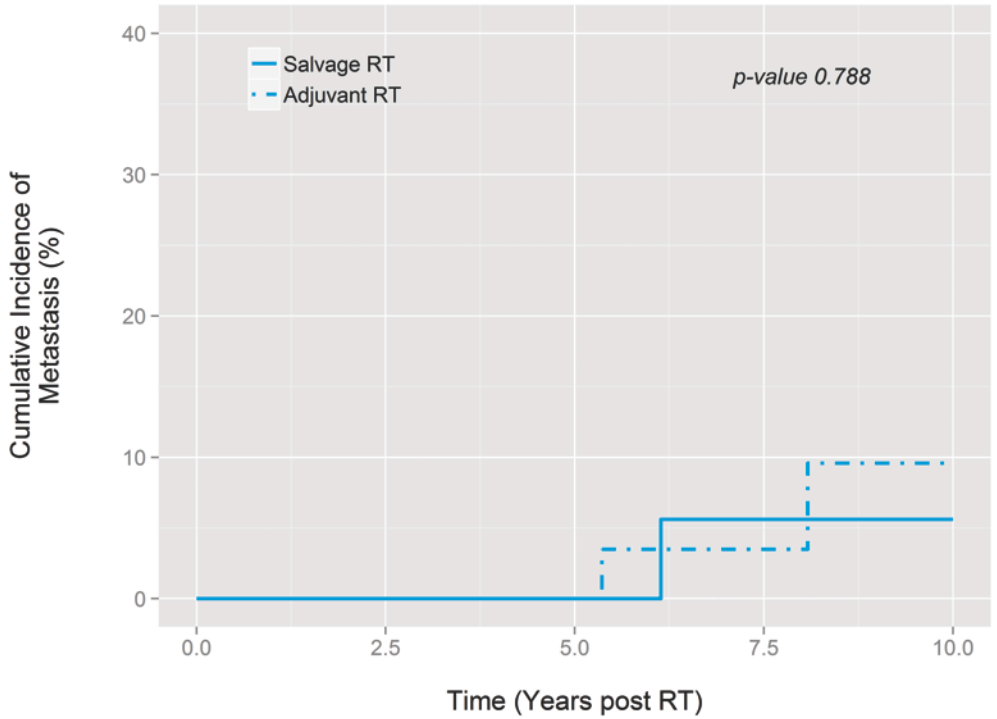


80% reduction in metastasis risk in Decipher high-risk patients who received early (adjuvant) radiation therapy compared to those who received late (salvage) radiation therapy

Den et al, Journal of Clinical Oncology, 2015

How to Interpret Decipher Results

Low Risk



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

Michalopolous, et al. *Curr Med Res Opin* 2014

Prostate Cancer is Clinically Heterogeneous

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

Problems with current care

- **Overtreatment** of indolent prostate cancer with radical therapy

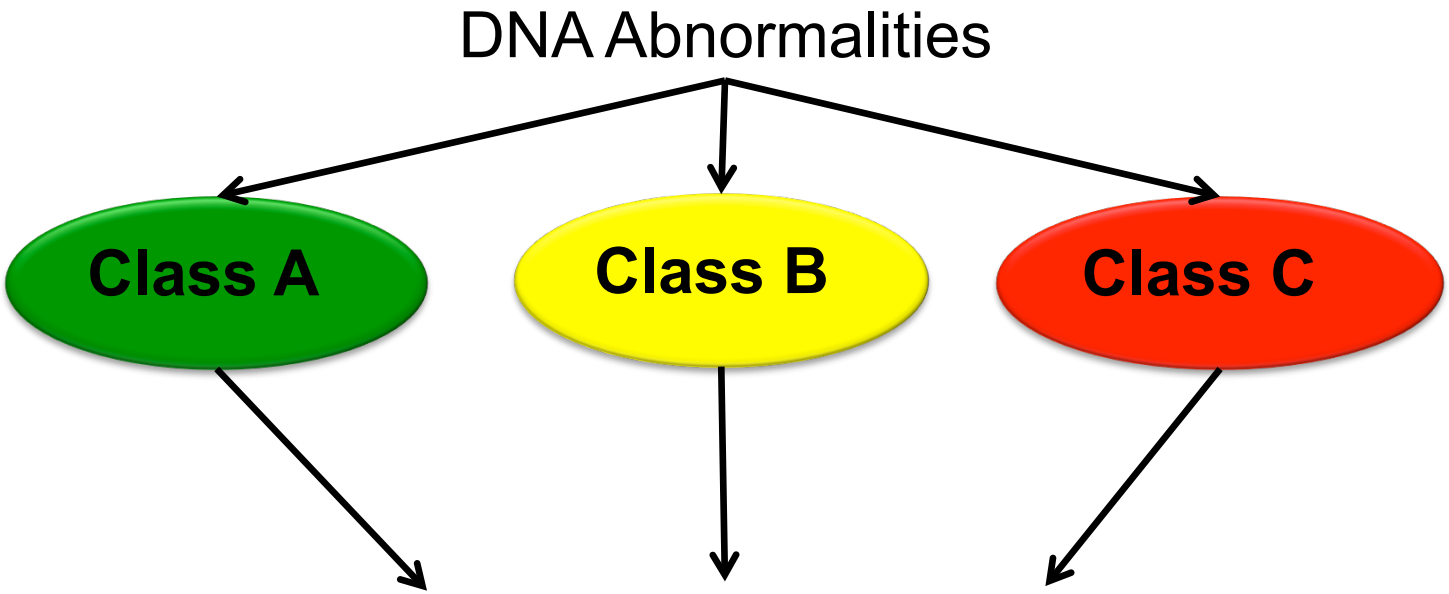
  → high morbidity

- **Undertreatment** of lethal prostate cancer

  → continued mortality

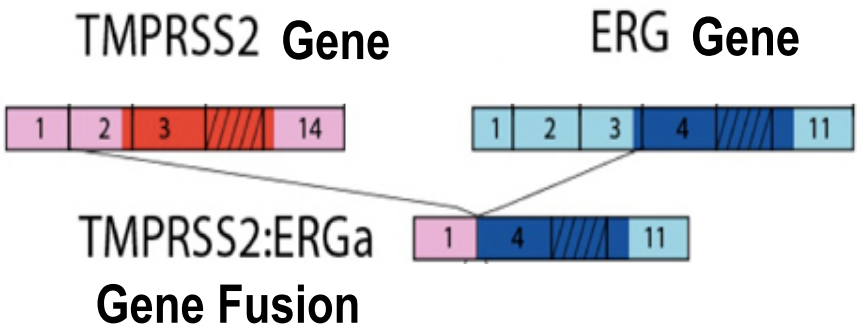
Genomic Classification

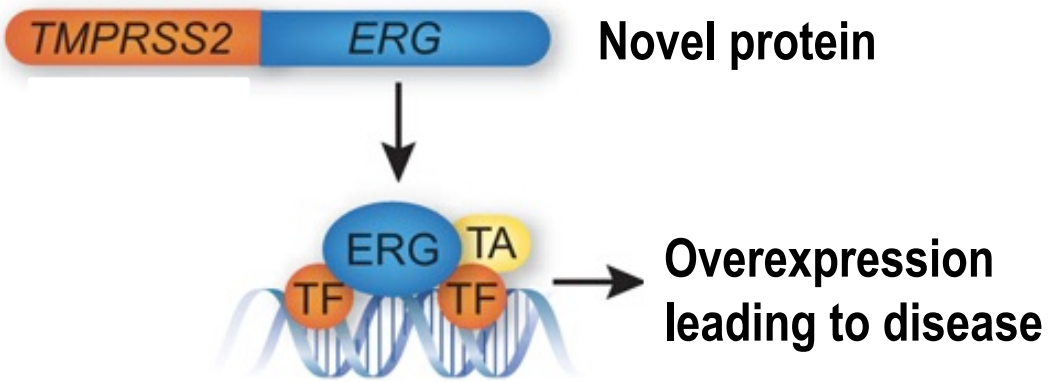
Define distinct classes of prostate cancer based on molecular/genomic characteristics

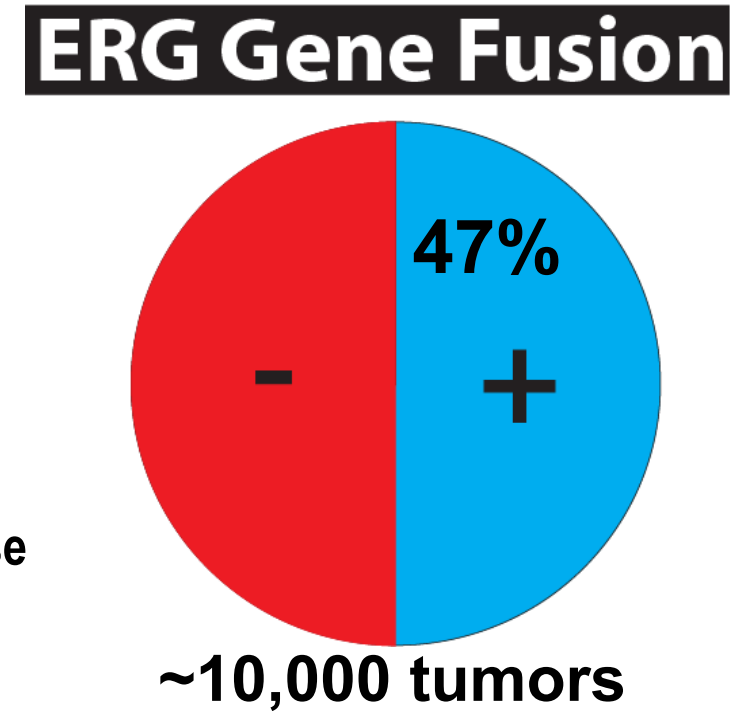


Prognosis
Management Strategy
Targeted Therapy: **PRECISION MEDICINE**

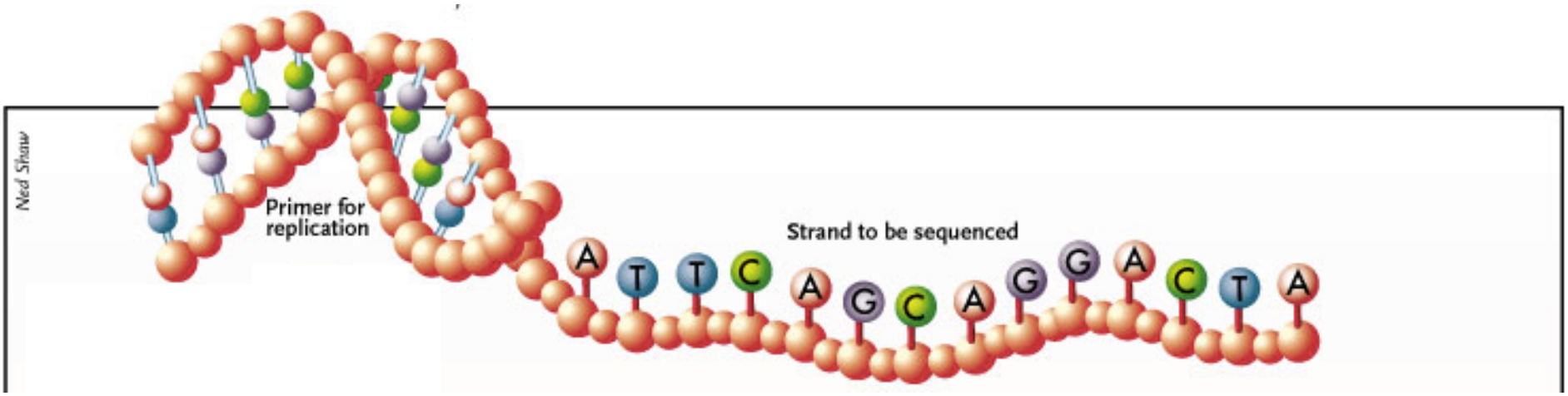
ERG gene fusions:
A starting point for molecular classification







WCMC a leader in state-of-the-art DNA sequencing for prostate cancer



7 prostate cancer whole genomes
Berger et al, *Nature* 2011

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

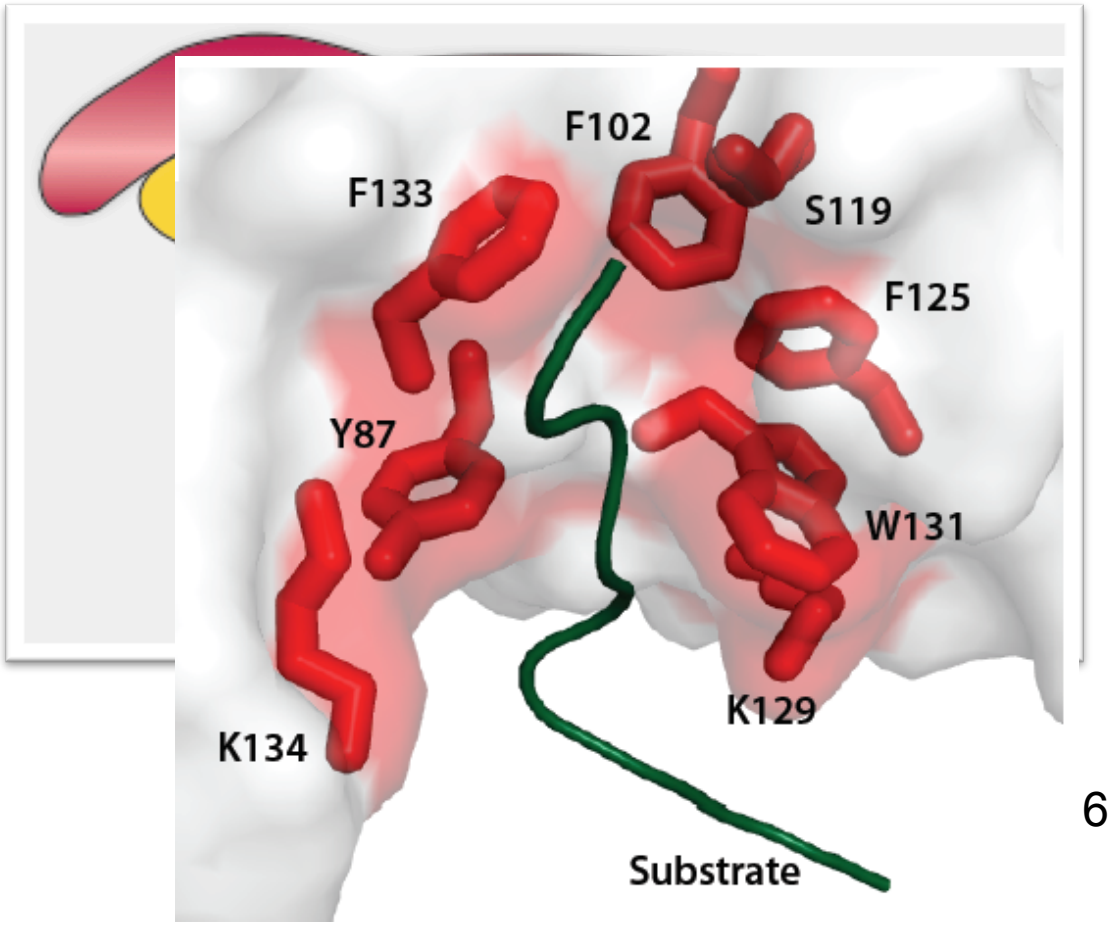
57 whole genomes
Baca et al, *Cell* 2013

SPOP mutations in Prostate Cancer

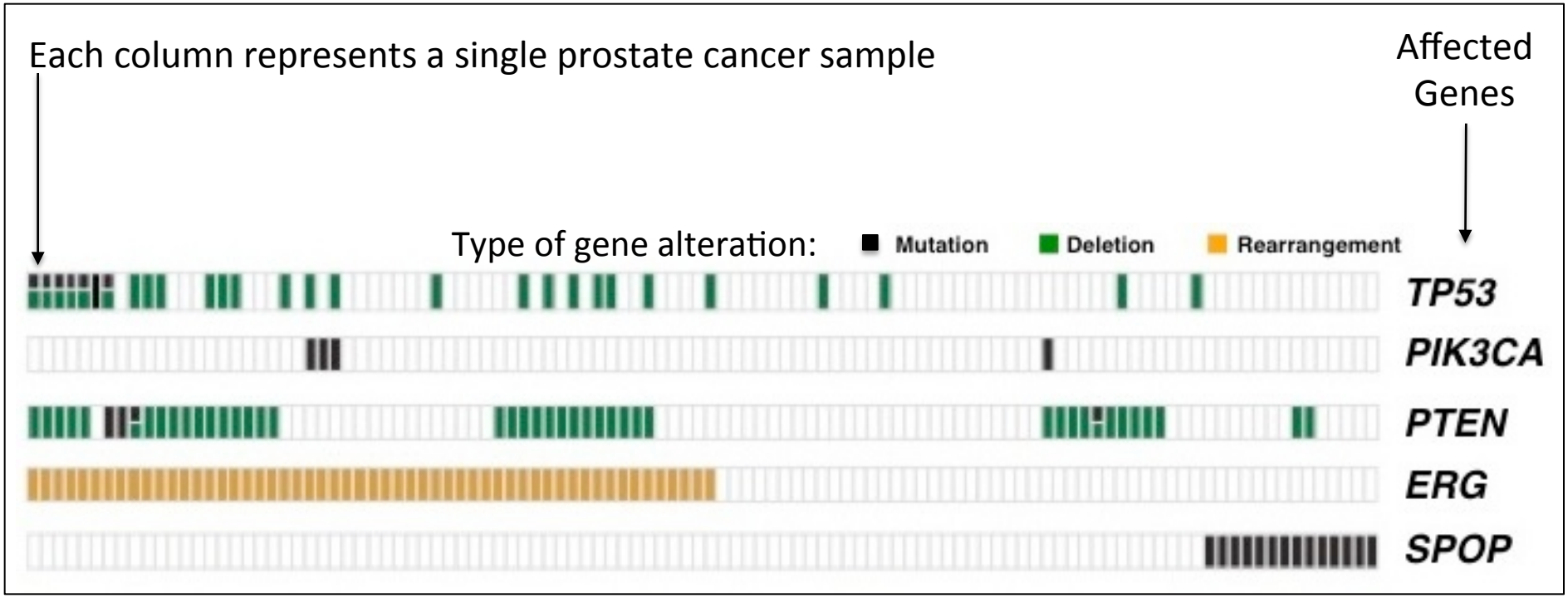
Prostate Cancer Samples (N= 453)

↓

SPOP mutations **10%** (45 of 453)



SPOP mutations define a distinct molecular class of prostate cancer



Barbieri et al, Nature Genetics 2012

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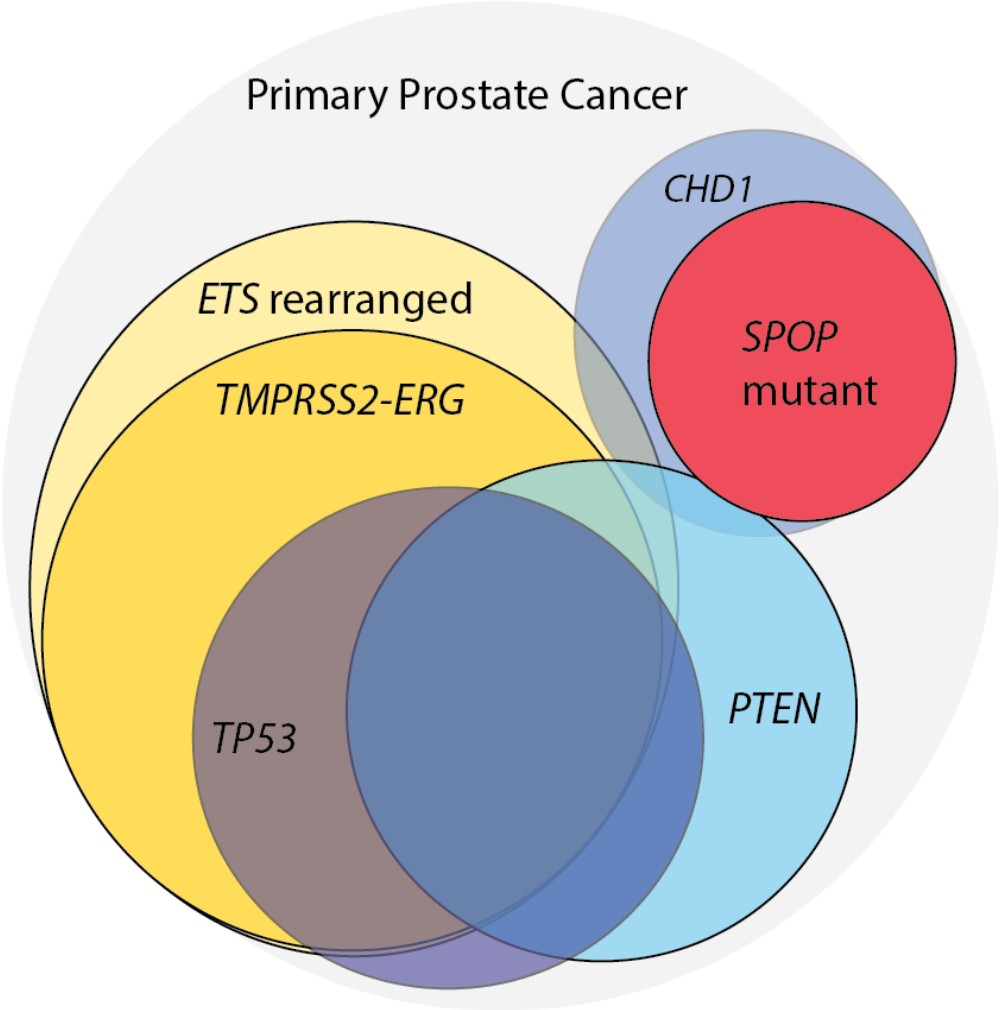
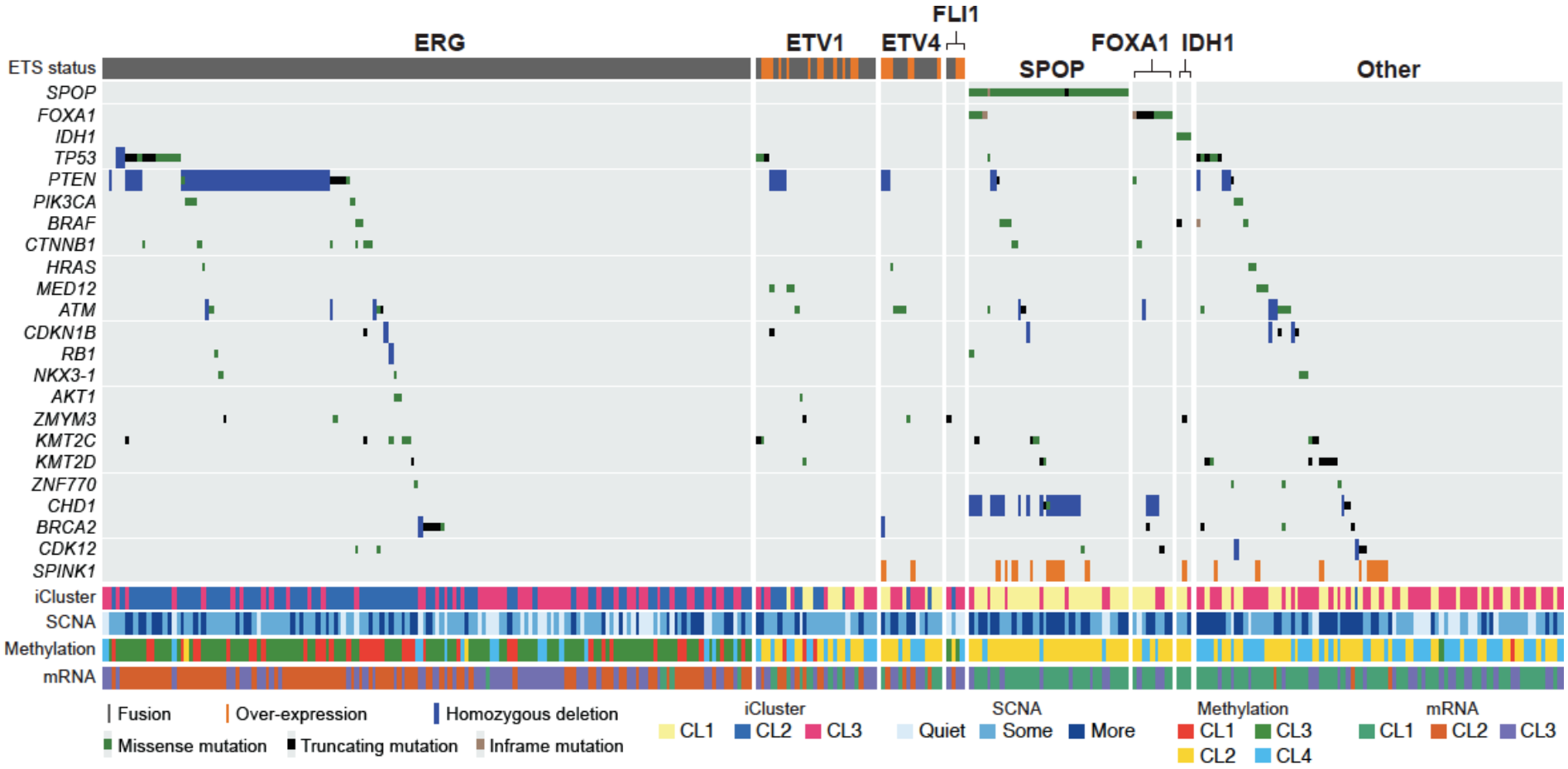


The Cancer Genome Atlas (TCGA)

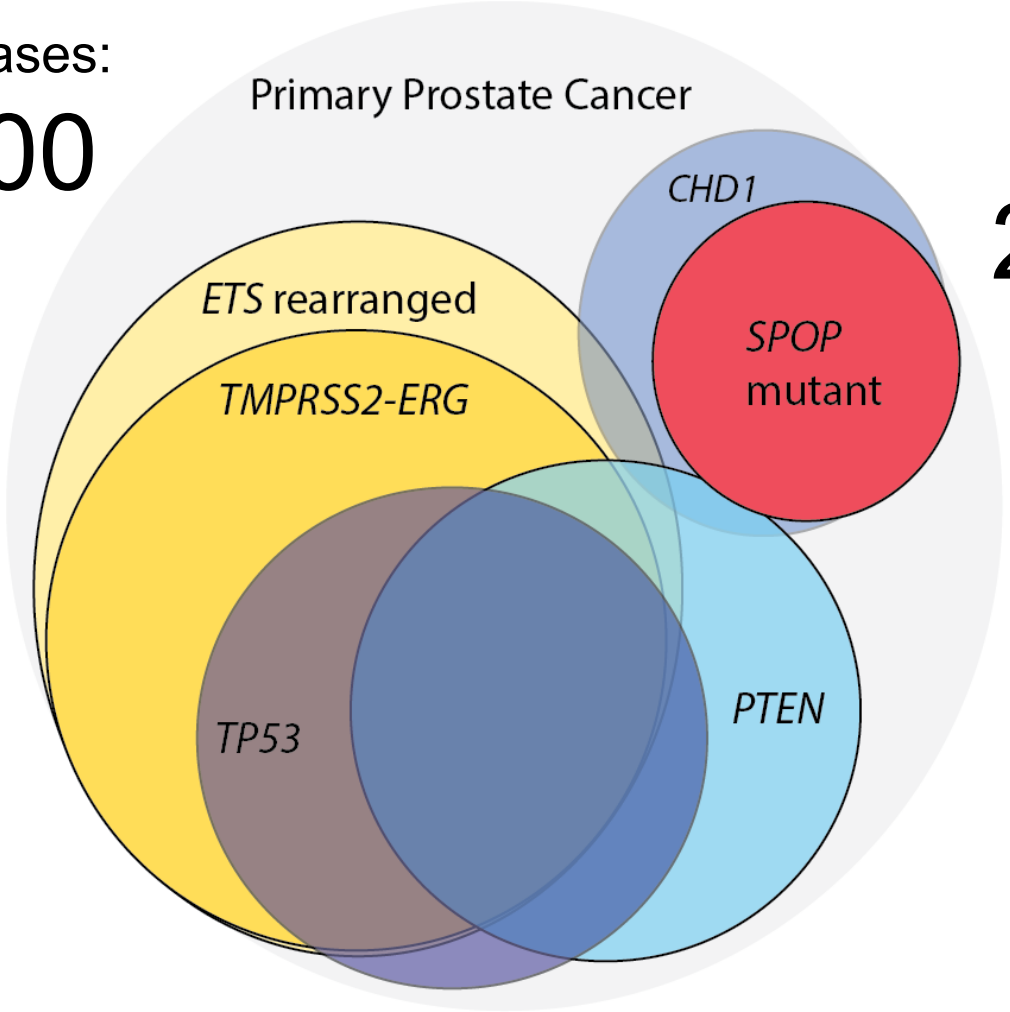


TCGA et al, Cell 2015 (In Press)

SPOP mutation defines a distinct molecular class of prostate cancer

2014 new cases:

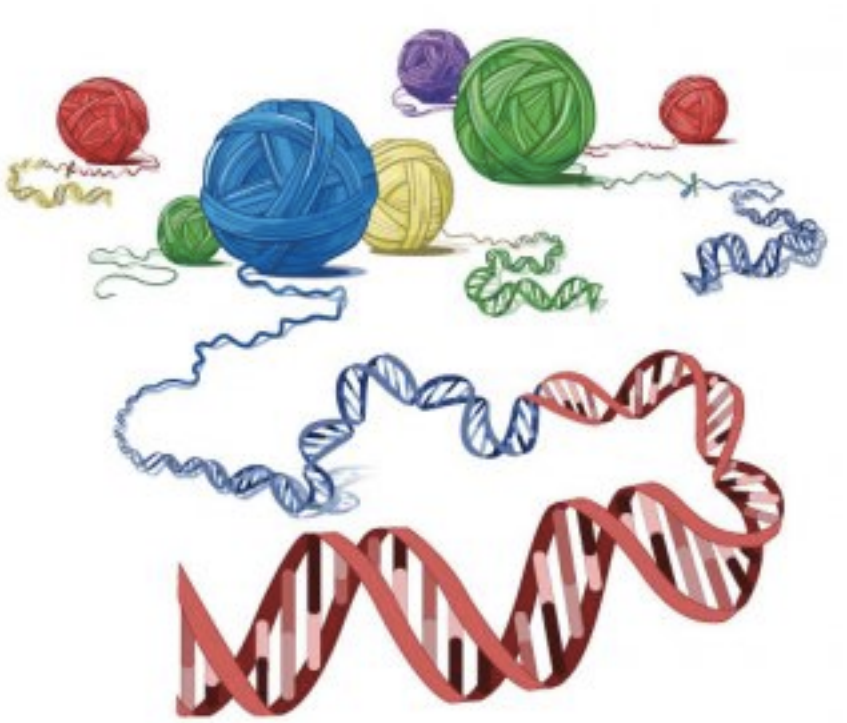
233,000



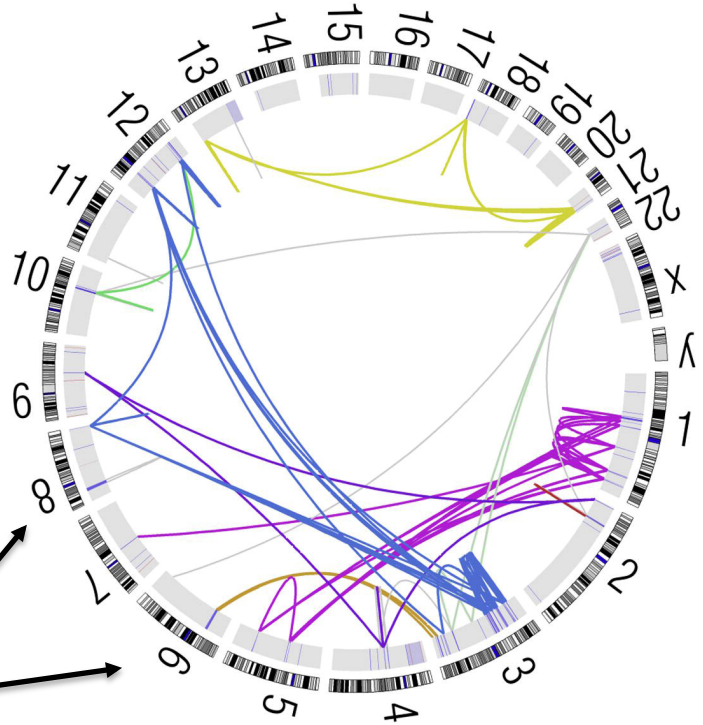
25,000/year

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



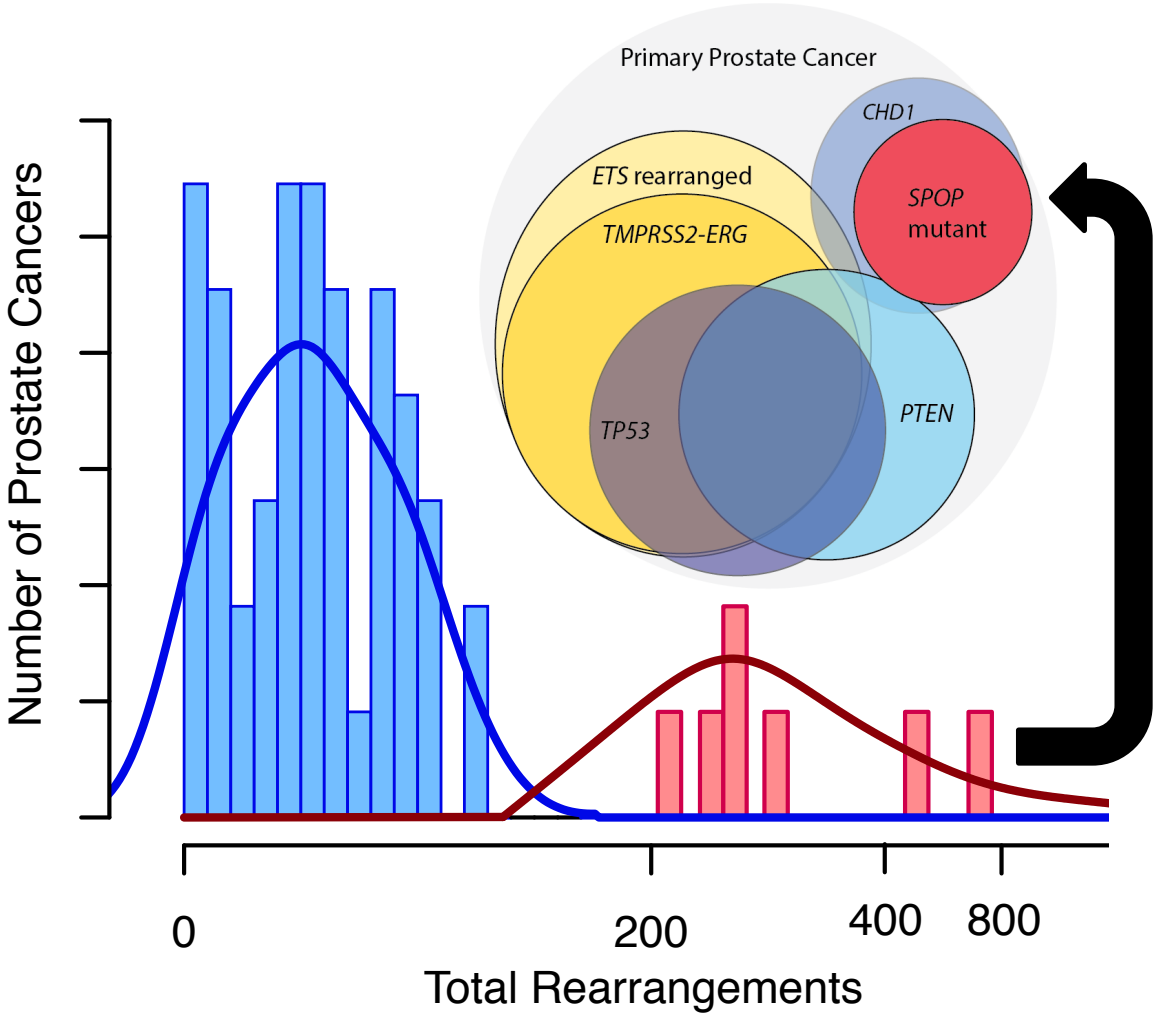
Chromosome numbers

DNA Rearrangements in Primary Prostate Cancer

DNA sequencing from 55 clinically localized PCA

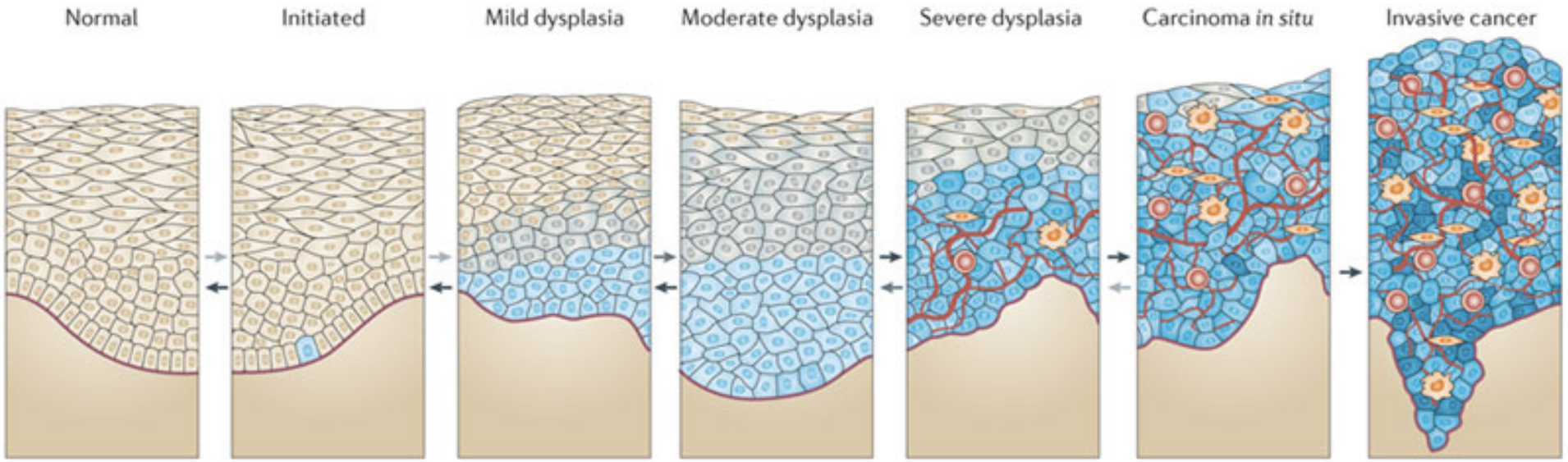
↓

Total Genomic Rearrangements



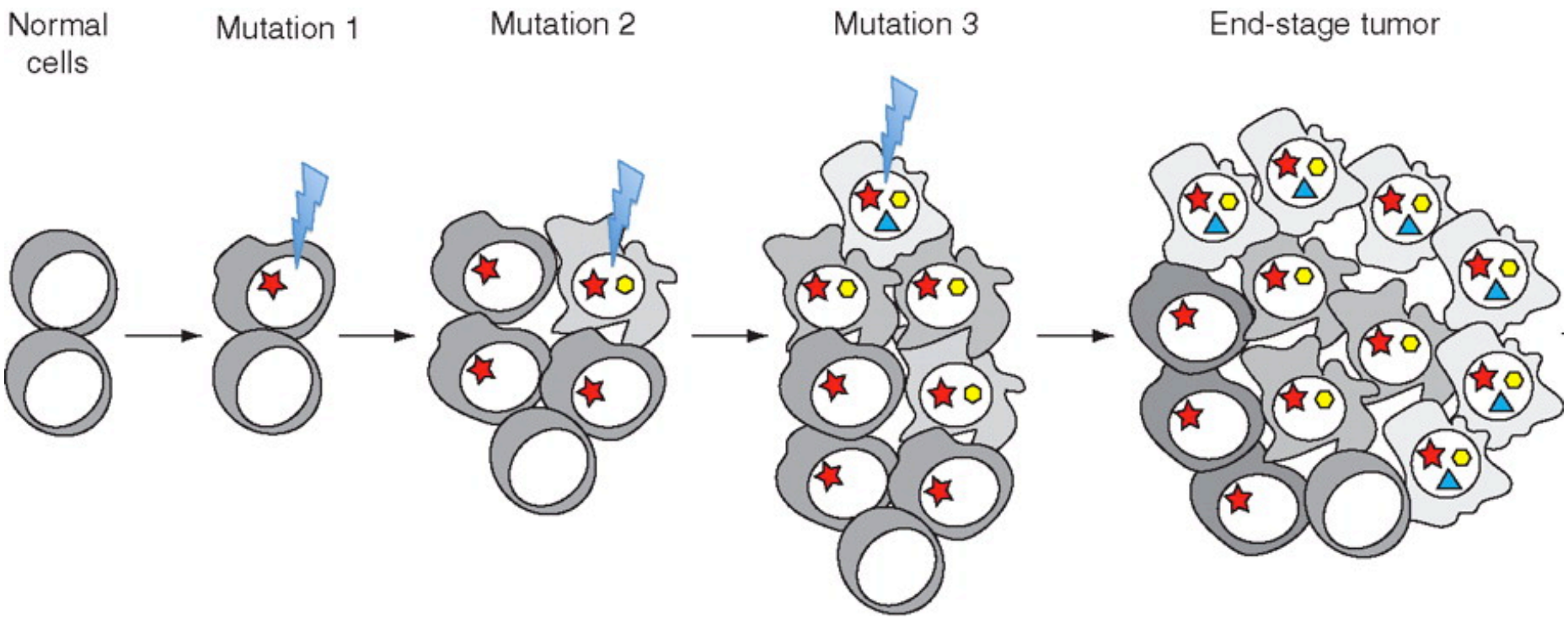
Timeline of events is critical

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



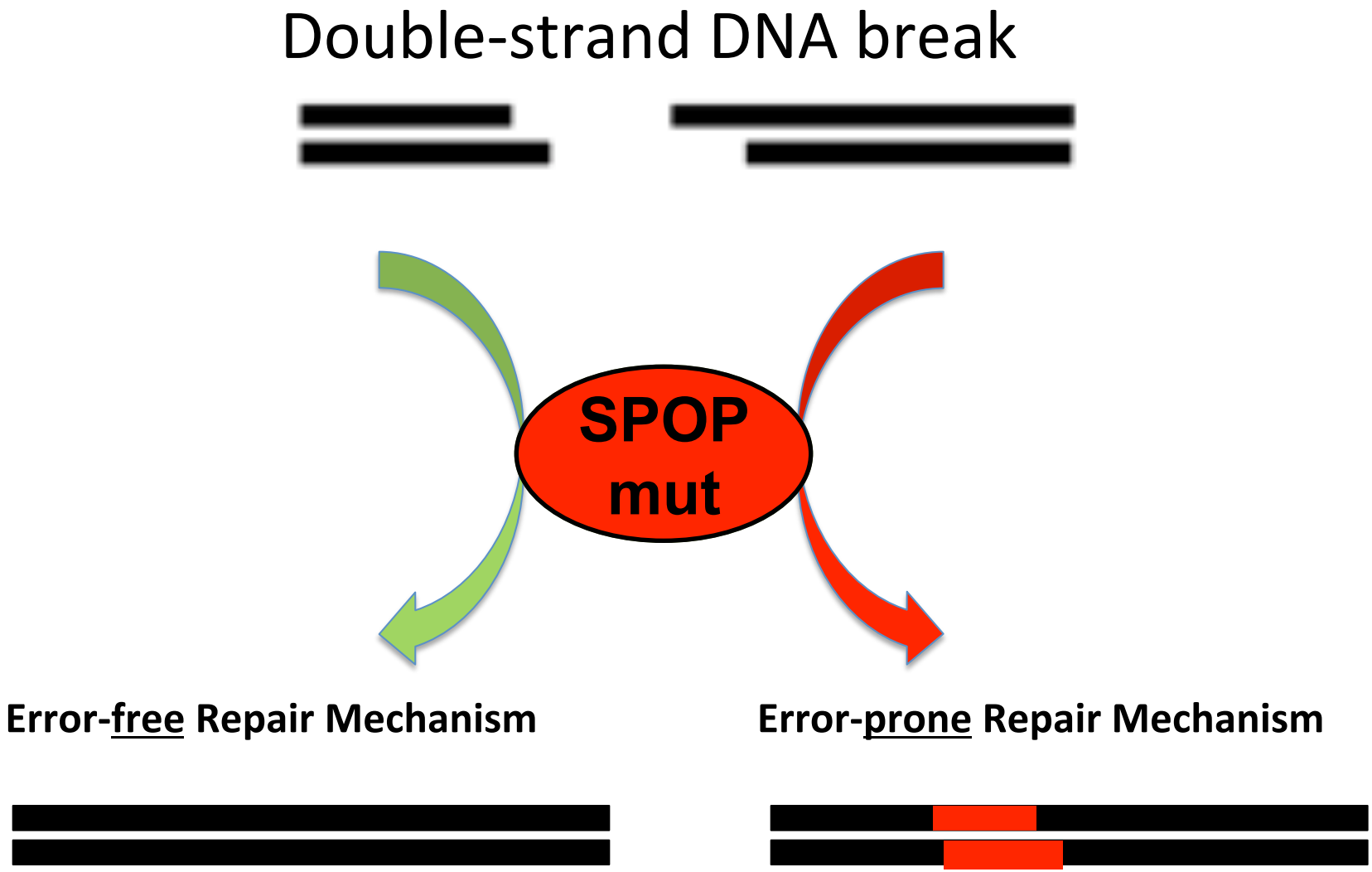
SPOP mutations are present in early lesions

Temporal Relationships: Clonality

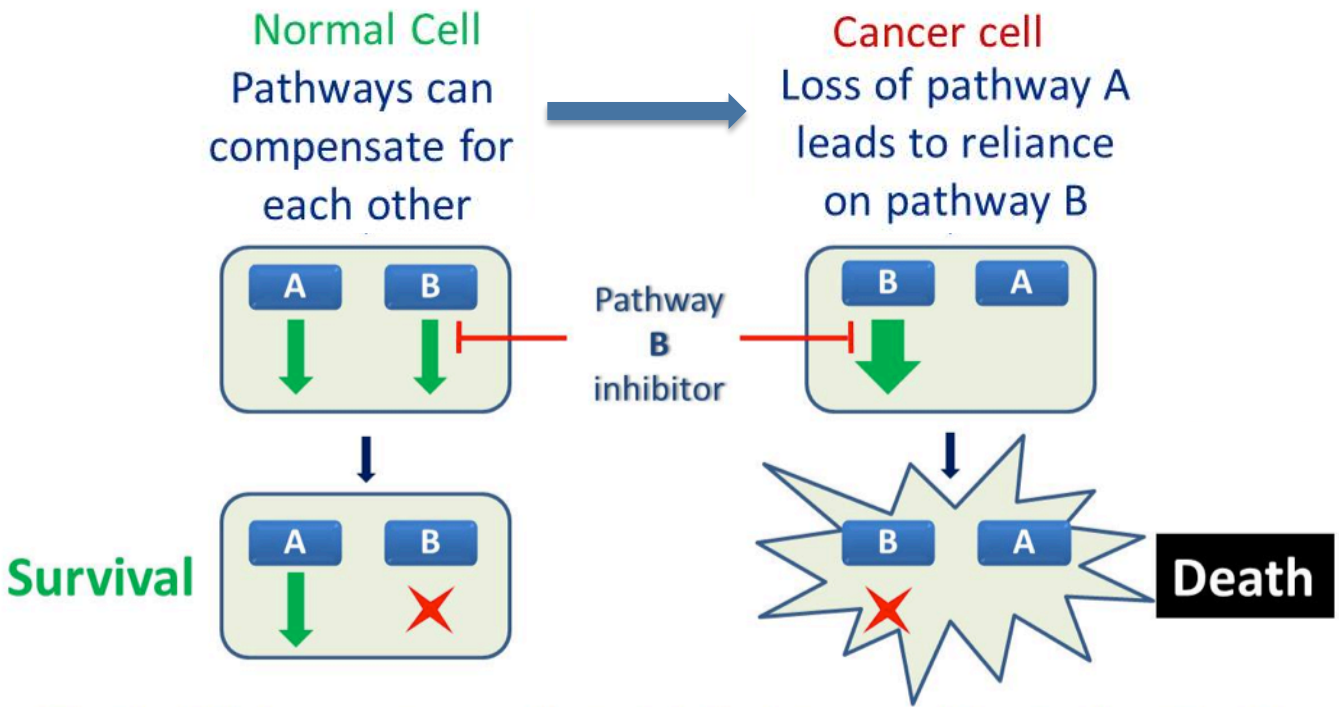


***SPOP* mutation is an *early* event**

SPOP impacts DNA break repair



DNA Repair as an Achilles Heel in Cancer: Synthetic Lethality

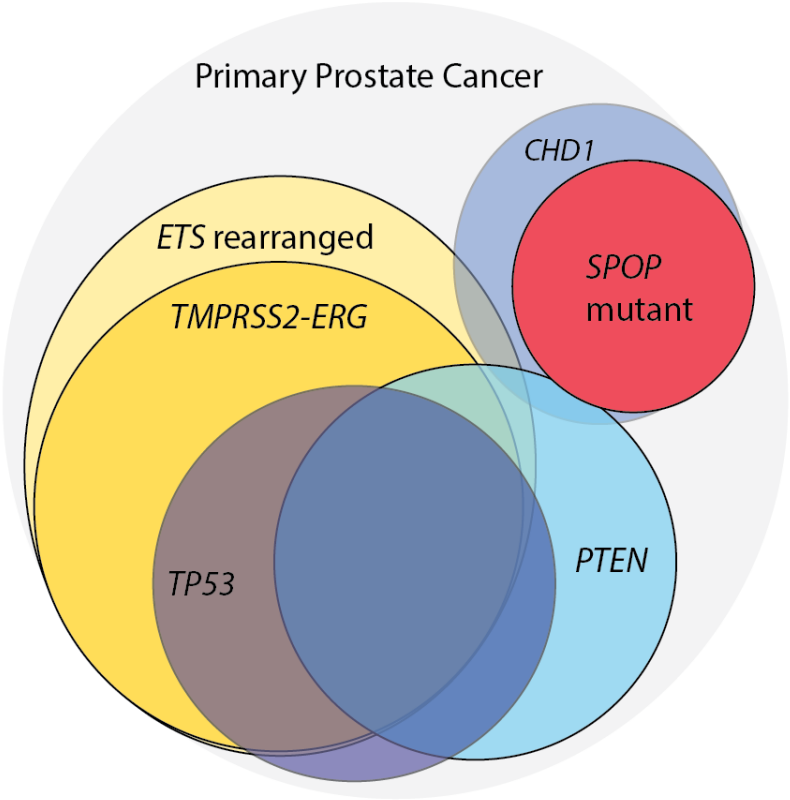


SPOP mutation confers sensitivity to specific DNA damaging agents

Opportunity for novel therapeutic interventions

Distinct molecular classes of prostate cancer

- 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