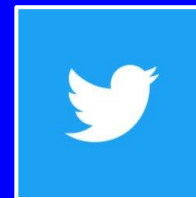


# Genomic Risk Assessment for Active Surveillance

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**Professor and Chair Emeritus**  
**Glickman Urological and Kidney Institute**  
**Cleveland Clinic**



**@CleClinicUro**  
**@EricKleinMD**

**Disclosures: None**

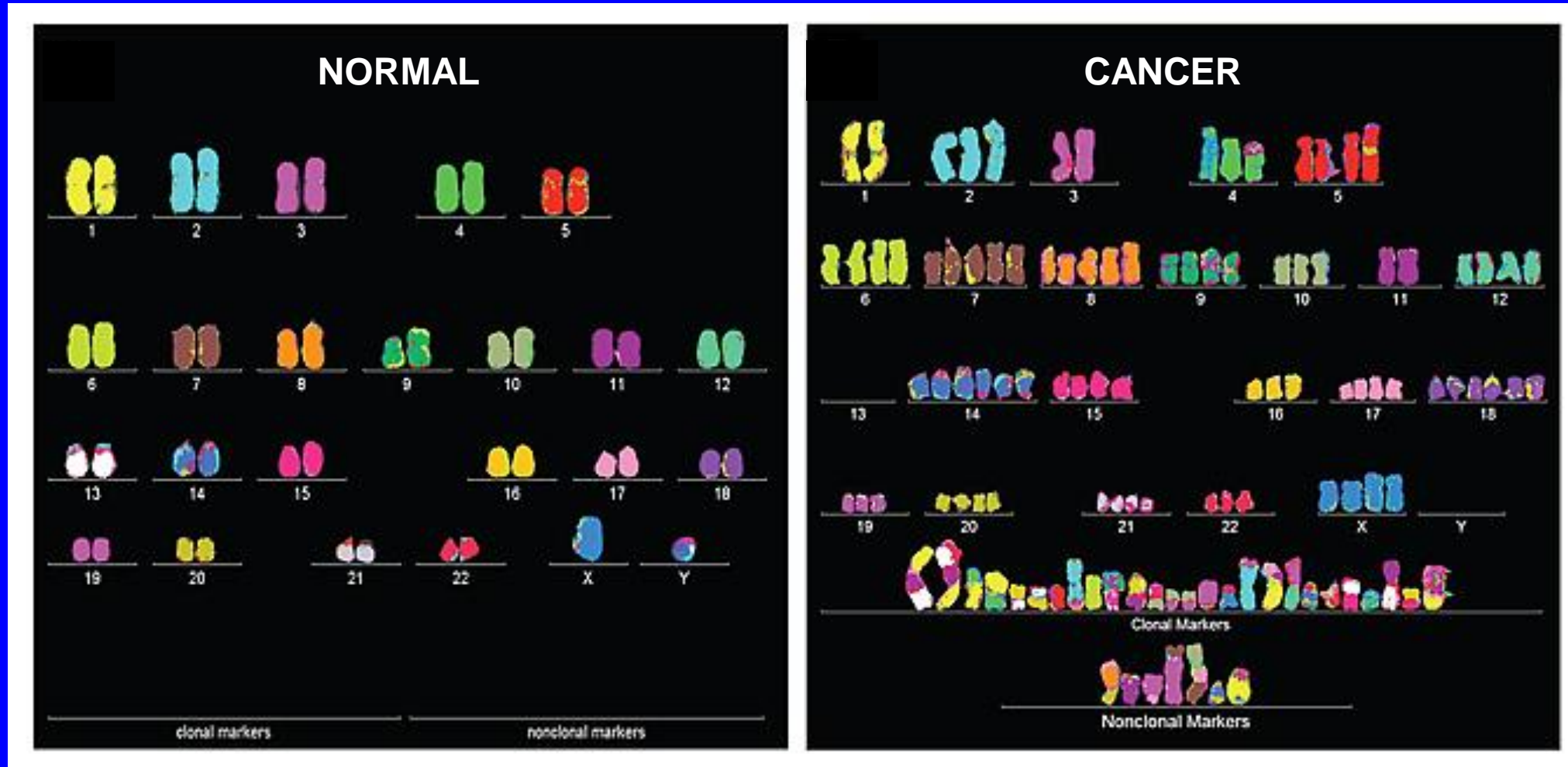
# Prostate Cancer in 2022

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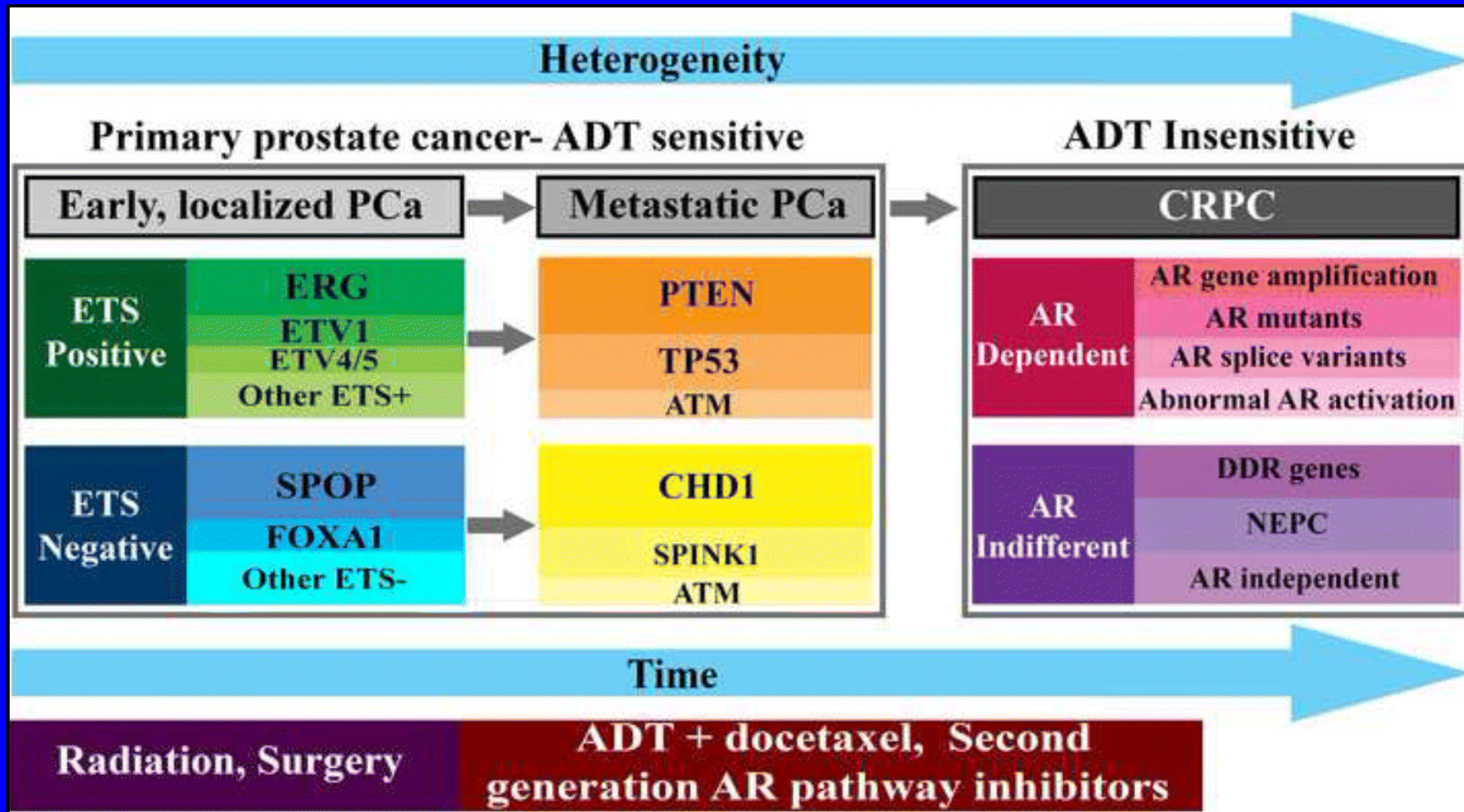
## Aspirational Goals

- **Treat only those cancers that have metastatic or lethal potential**
- **Put everyone else on Active Surveillance**

# Cancer is a genetic disease



# Molecular Taxonomy of Prostate Cancer

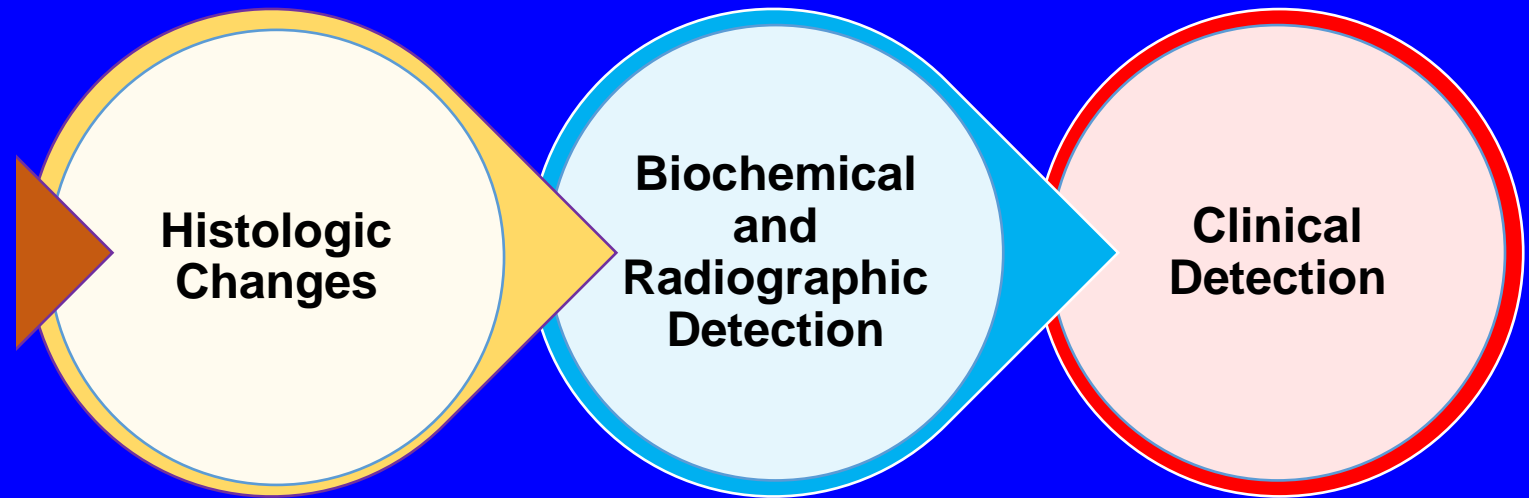


# **Think Biology, Not Histology**

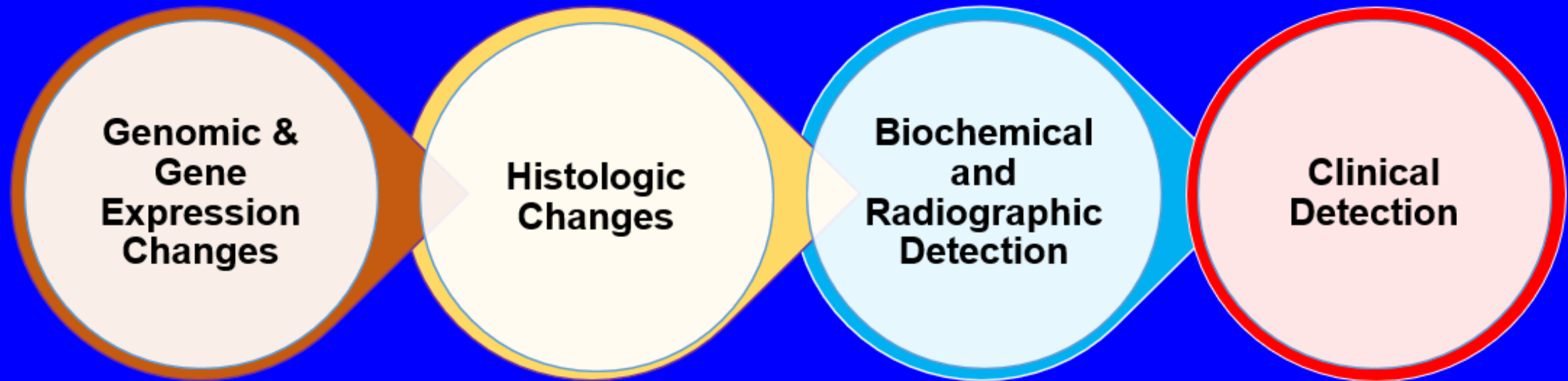
**Histology is informative about biology,  
but does not tell the whole story**

**Ditto for MRI**

# Think Biology, Not Histology



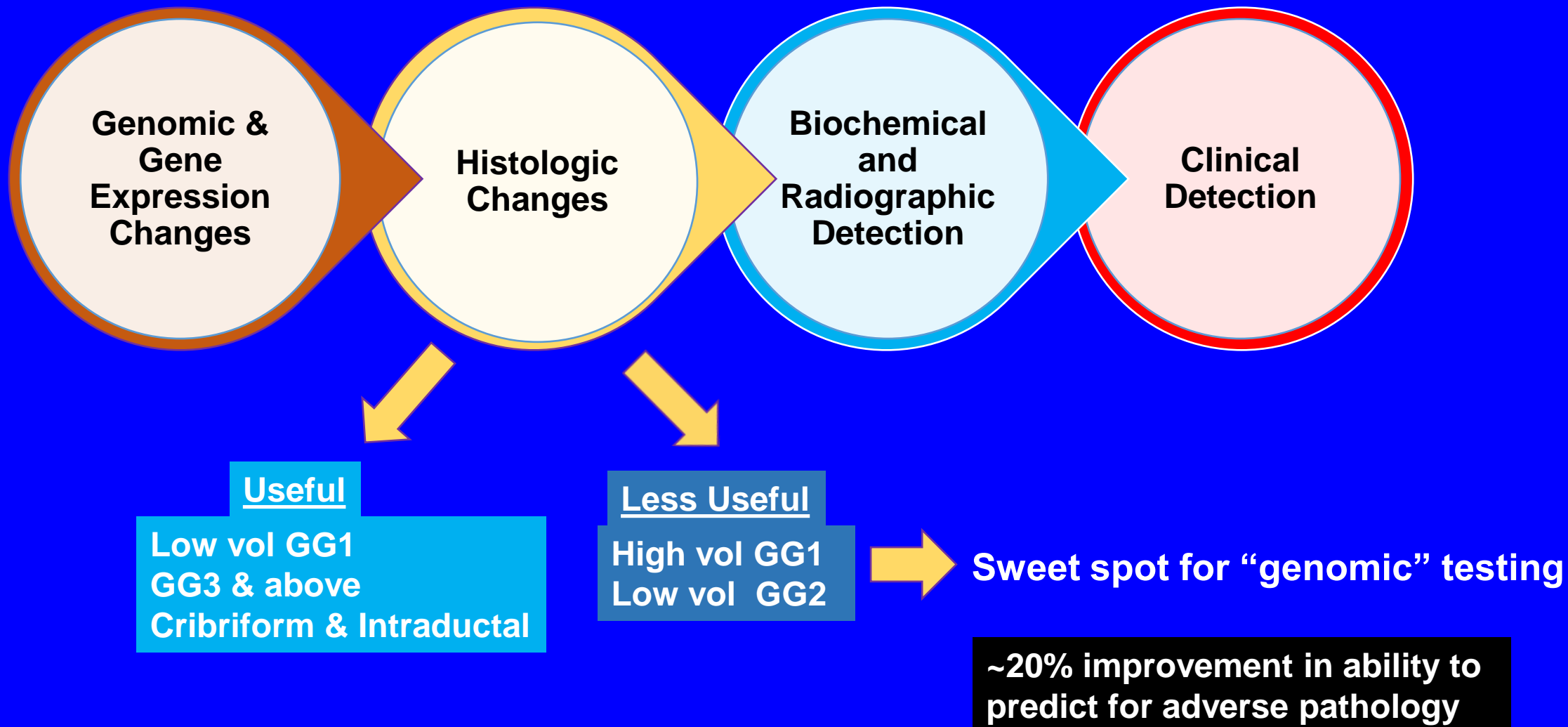
# Spatially resolved clonal copy number alterations in benign and malignant tissue



**Conclusion: Genomic changes (CNV) and gene expression changes characteristic of the nearby cancer are present in histologically benign appearing tissue**



# Think Biology, Not Histology



# What is Adverse Pathology?

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**Gleason score 4 + 3 (Grade group 3)**

**Disease outside the prostate (non-organ confined)**

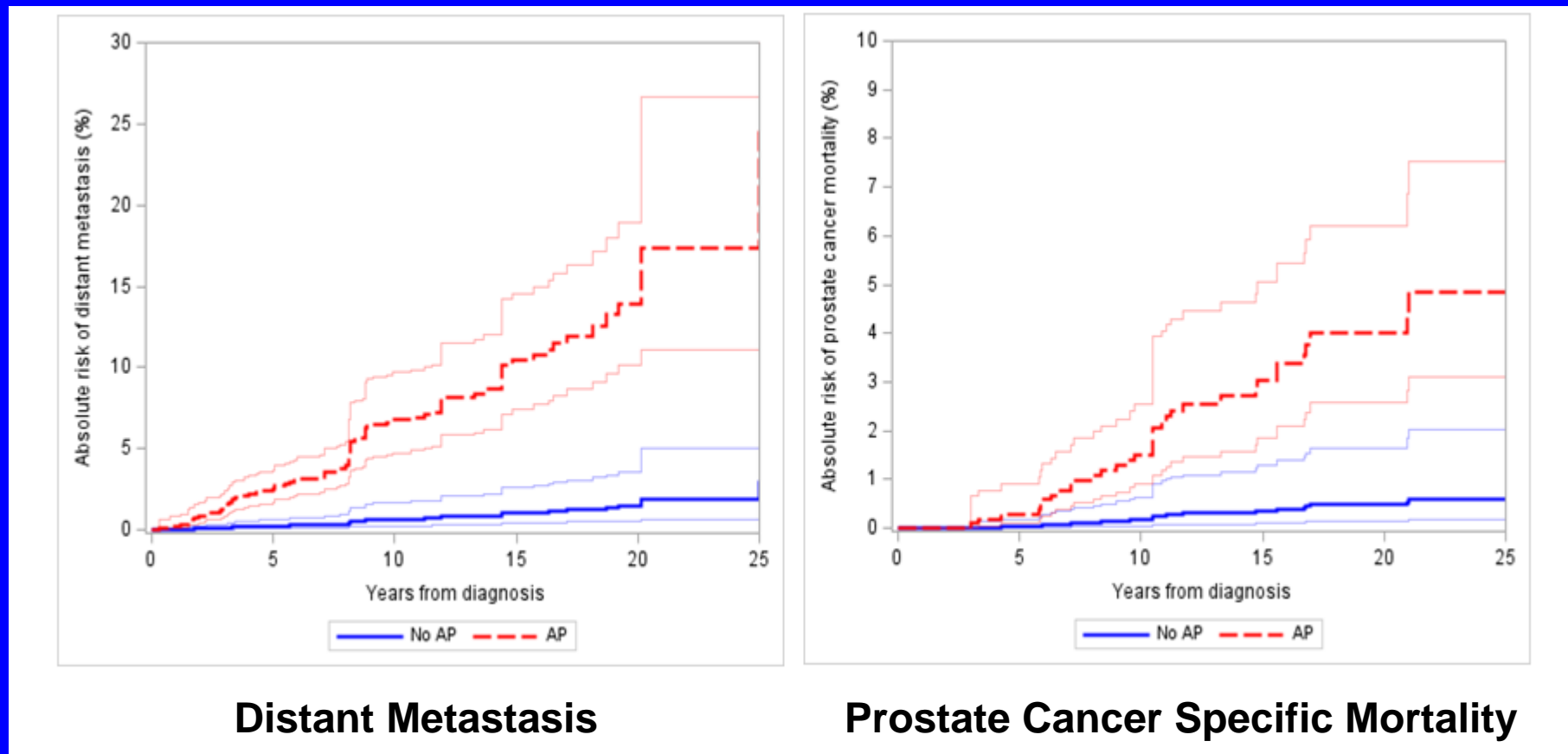
- **Extraprostatic extension**
- **SV invasion**
- **Node +**

**Generally speaking these features exclude a patient from active surveillance, whether**

- **Present at initial evaluation**
- **Progress to this while on surveillance**

# Impact of Adverse Pathology on Long Term Outcomes

## AUA Low and Intermediate Risk



# Which is Better in Predicting Adverse Pathology in Men on AS?

Adverse pathology = GI  $\geq$  4+3 or higher, disease outside the prostate

MRI or Gene Expression Profiling?

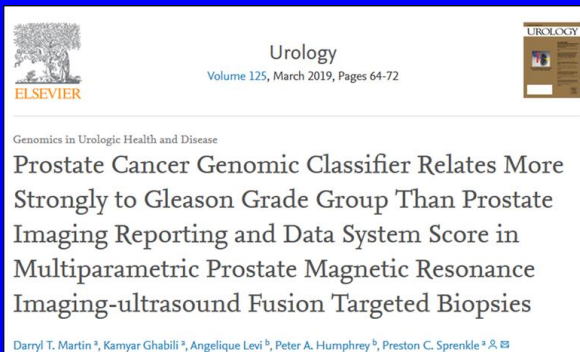
UCSF  
(Oncotype)

Genomic Prostate Score, PI-RADSv2, and Progression in Men with Prostate Cancer on Active Surveillance

Zachary Kornberg <sup>1</sup> ✉, Janet E. Cowan <sup>1</sup>, Antonio C. Westphalen <sup>3</sup>, Matthew R. Cooperberg <sup>1,2</sup>, June M. Chan <sup>1,2</sup>, Shoujun Zhao <sup>1</sup>, Katsuto Shinohara <sup>1</sup>, Peter R. Carroll <sup>1</sup>  
J Urol 2018

Gene expression profiling

YALE  
(Decipher)



Prostate Cancer Genomic Classifier Relates More Strongly to Gleason Grade Group Than Prostate Imaging Reporting and Data System Score in Multiparametric Prostate Magnetic Resonance Imaging-ultrasound Fusion Targeted Biopsies

Darryl T. Martin <sup>\*</sup>, Kamyar Ghabili <sup>3</sup>, Angeliqve Levi <sup>3</sup>, Peter A. Humphrey <sup>3</sup>, Preston C. Spenkle <sup>3</sup> ✉

Gene expression profiling

UCLA  
(Oncotype)

A 17-Genic Prostate Score Assay Provides Independent Information on Adverse Pathology in the Setting of Combined Multiparametric Magnetic Resonance Imaging Fusion Targeted and Systematic Prostate Biopsy

Amirali Salmasi, Jonathan Said, Alan W. Shindel,\* Pooria Khoshnoodi, Ely R. Felker, Anthony E. Sisk, Jr., Tristan Grogan, Debbie McCullough,\* John Bennett,\* Helen Bailey,\* H. Jeffrey Lawrence,\* David A. Elashoff, Leonard S. Marks, Steven S. Raman, Phillip G. Febbo\* and Robert E. Reiter†  
J Urol 200:564, 2018

Gene expression profiling

# MRI



# GENOMICS

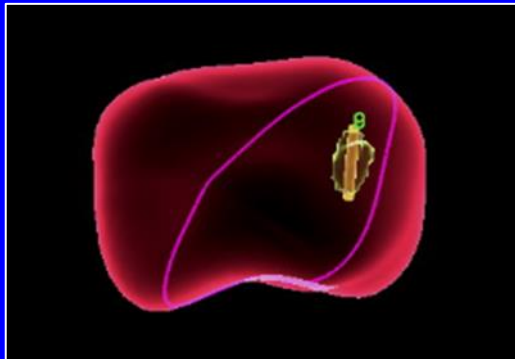


# The Problem of Undersampling

## Biopsy undersampling

– Was the highest grade tumor sampled?

- Tools to address this
  - MRI guided biopsy

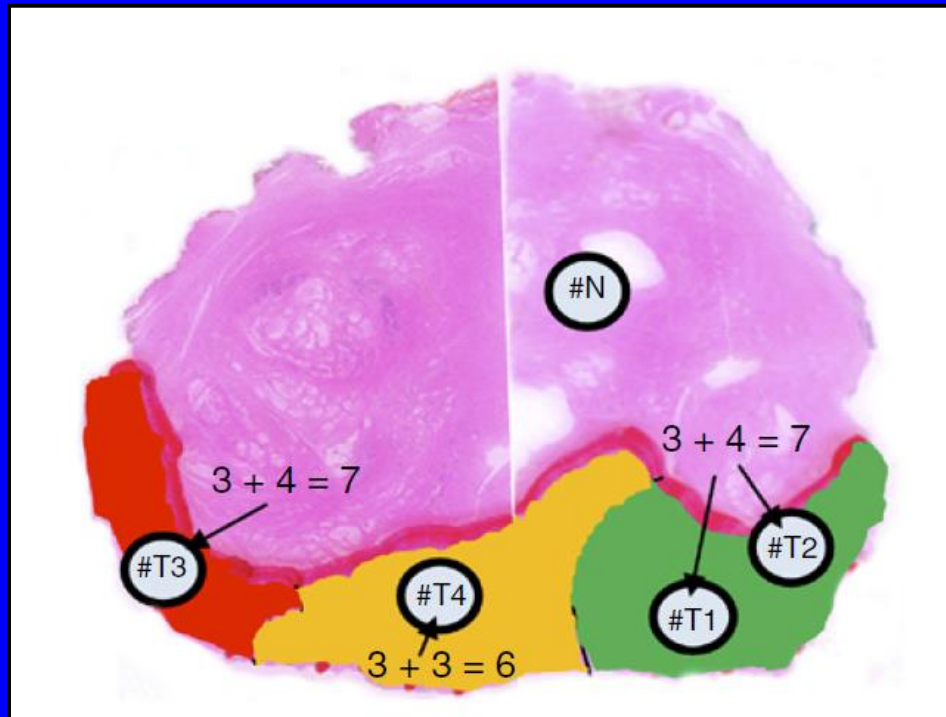


- Tools to address this
  - Genomic tests



# Limitations of Genomic Testing

Genomics could be wrong if the prostate has clonally distinct tumors that are geographically separated



Genomics always correct

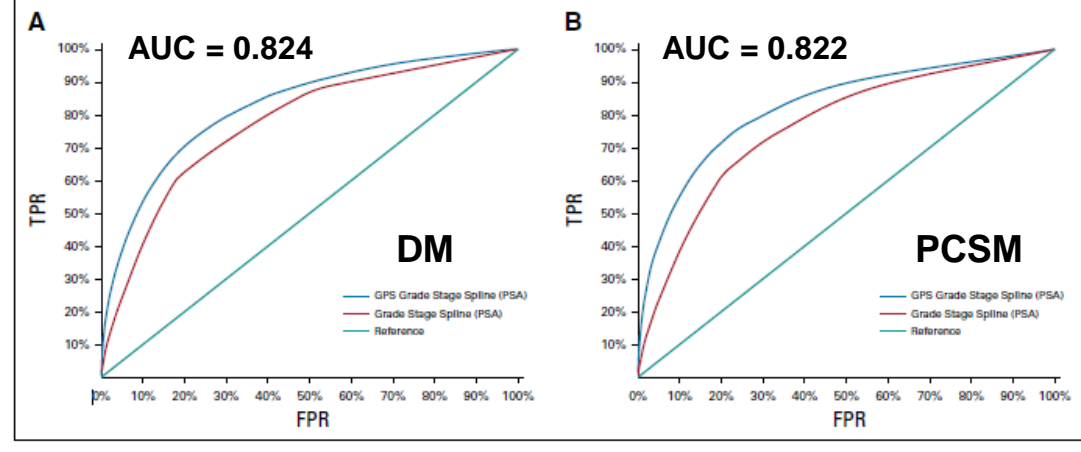
Genomics usually correct

Genomics potentially wrong

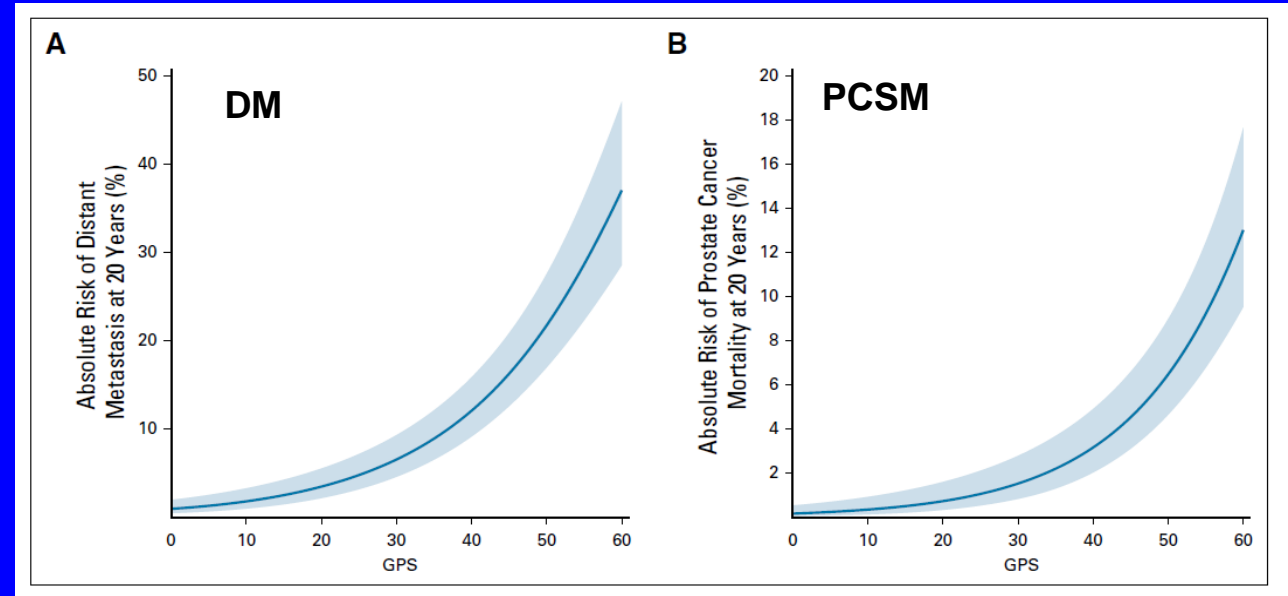
**CANCER GENOMICS**

# GPS Assay Association With Long-Term Cancer Outcomes: Twenty-Year Risk of Distant Metastasis and Prostate Cancer-Specific Mortality

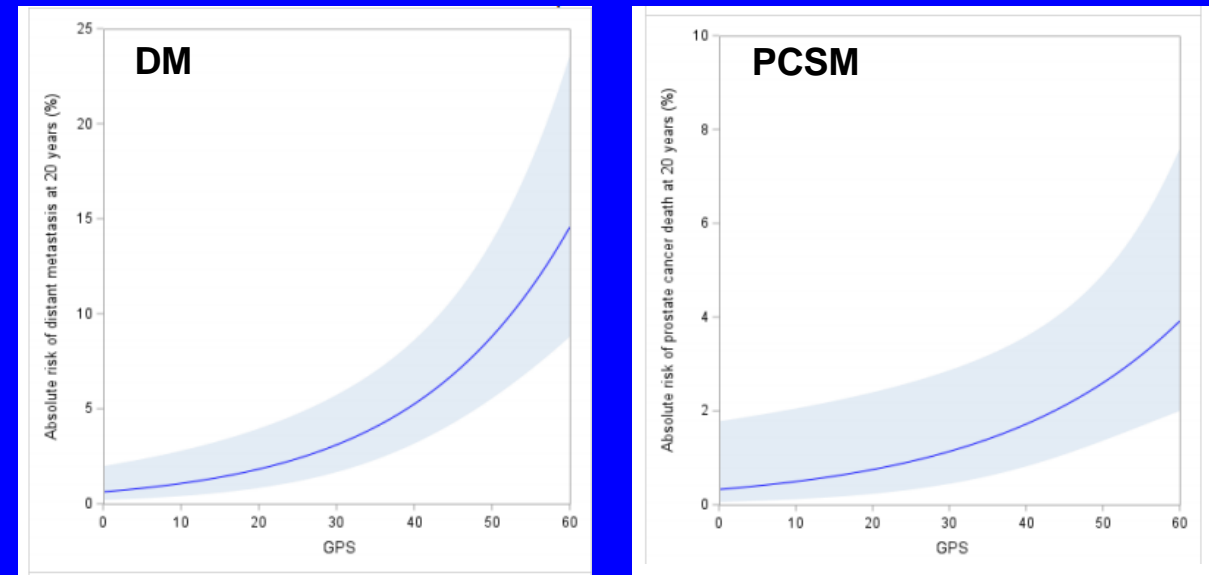
Michael A. Brooks, MD<sup>1</sup>; Lewis Thomas, MD<sup>2</sup>; Cristina Magi-Galluzzi, MD, PhD<sup>3</sup>; Jianbo Li, PhD<sup>4</sup>; Michael R. Crager, PhD<sup>5</sup>; Ruixiao Lu, PhD<sup>5</sup>; John Abran, MD, PhD<sup>5</sup>; Tamer Aboushwareb, MD, PhD<sup>5</sup>; and Eric A. Klein, MD<sup>2</sup>



## All Patients



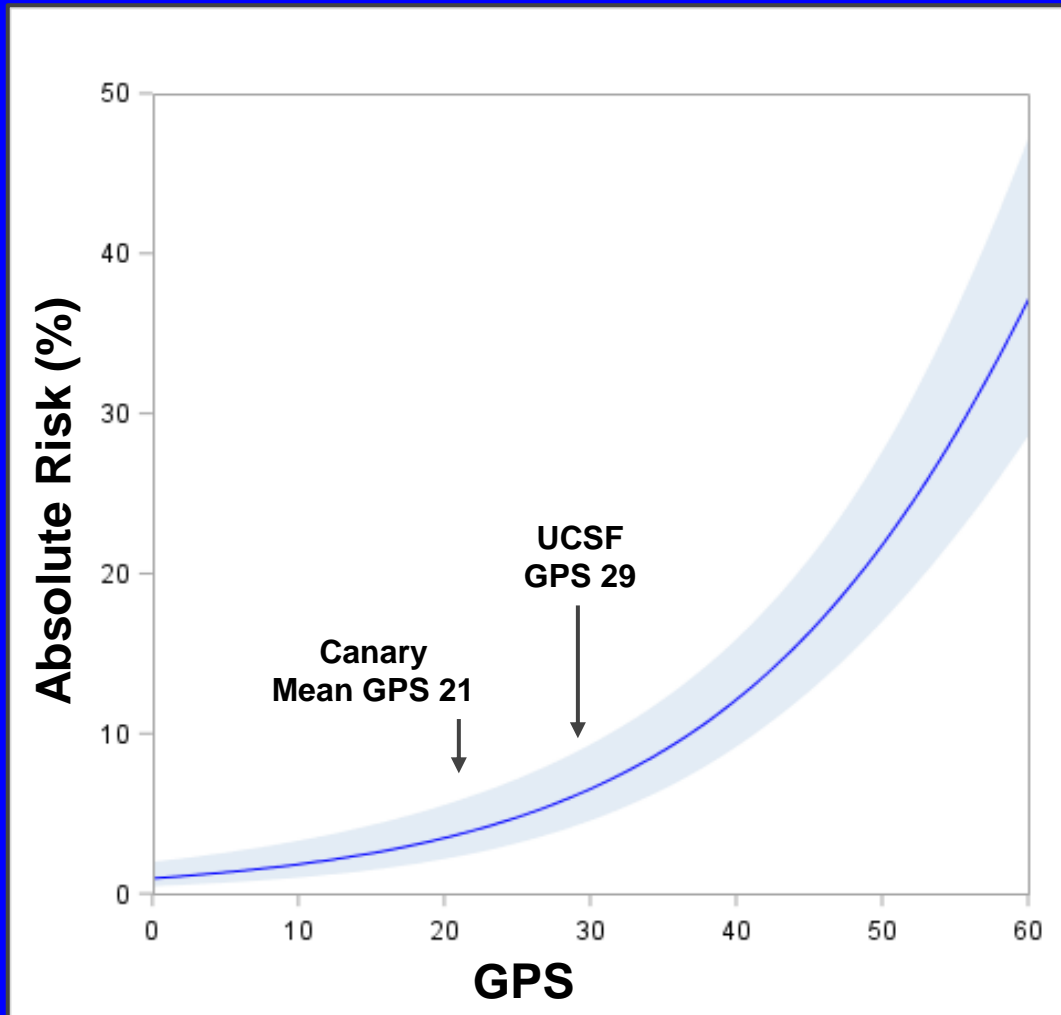
## Low and Favorable Intermediate Risk



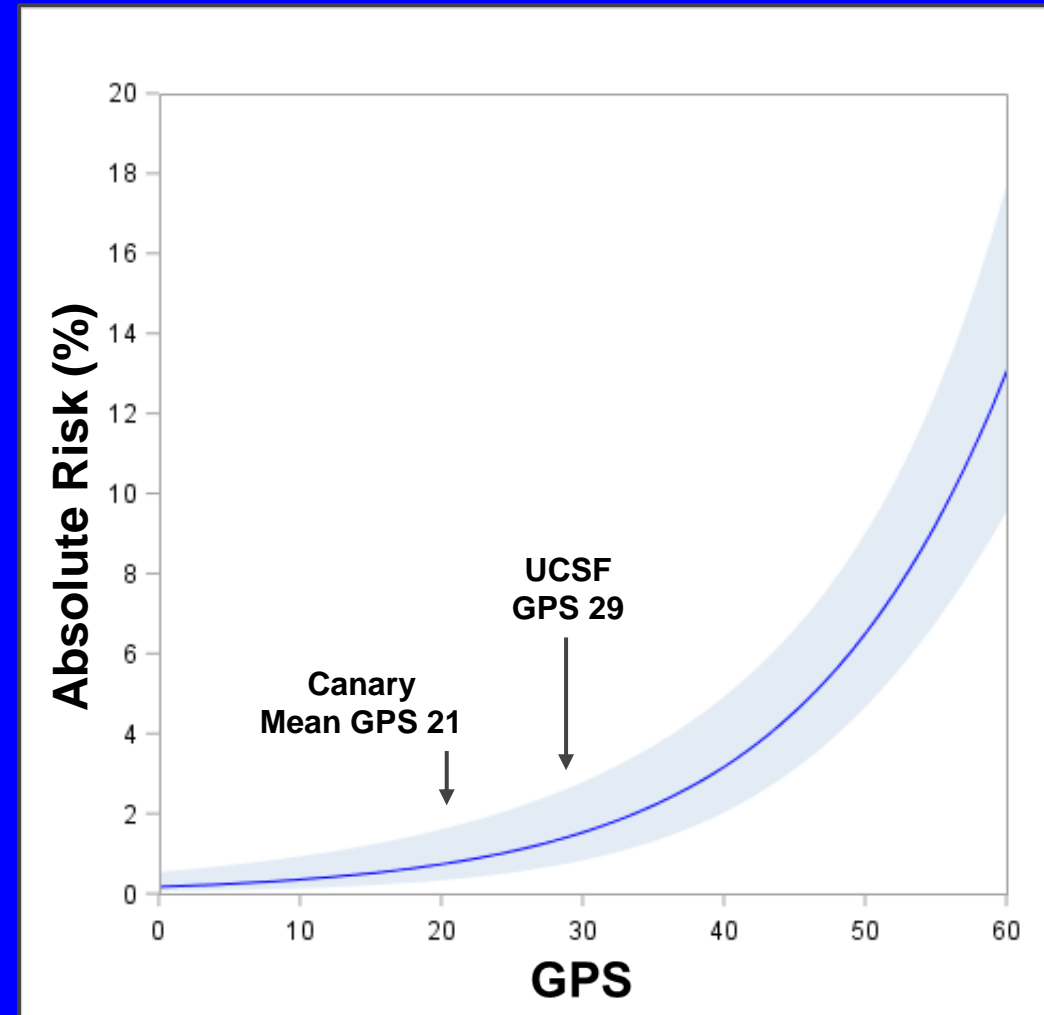


# Oncotype GPS Predicts Outcome 20 Years after RP

## Metastasis



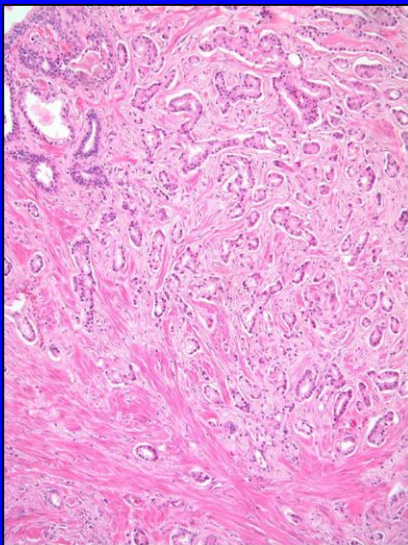
## Prostate Cancer Death



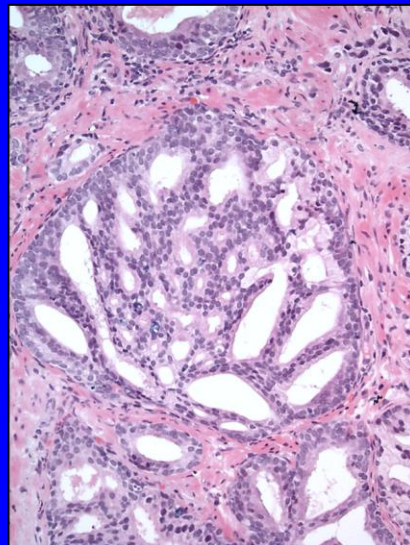
# Histologic Grading of Prostatic Adenocarcinoma Can Be Further Optimized

*Analysis of the Relative Prognostic Strength of Individual Architectural  
Patterns in 1275 Patients From the Canary Retrospective Cohort*

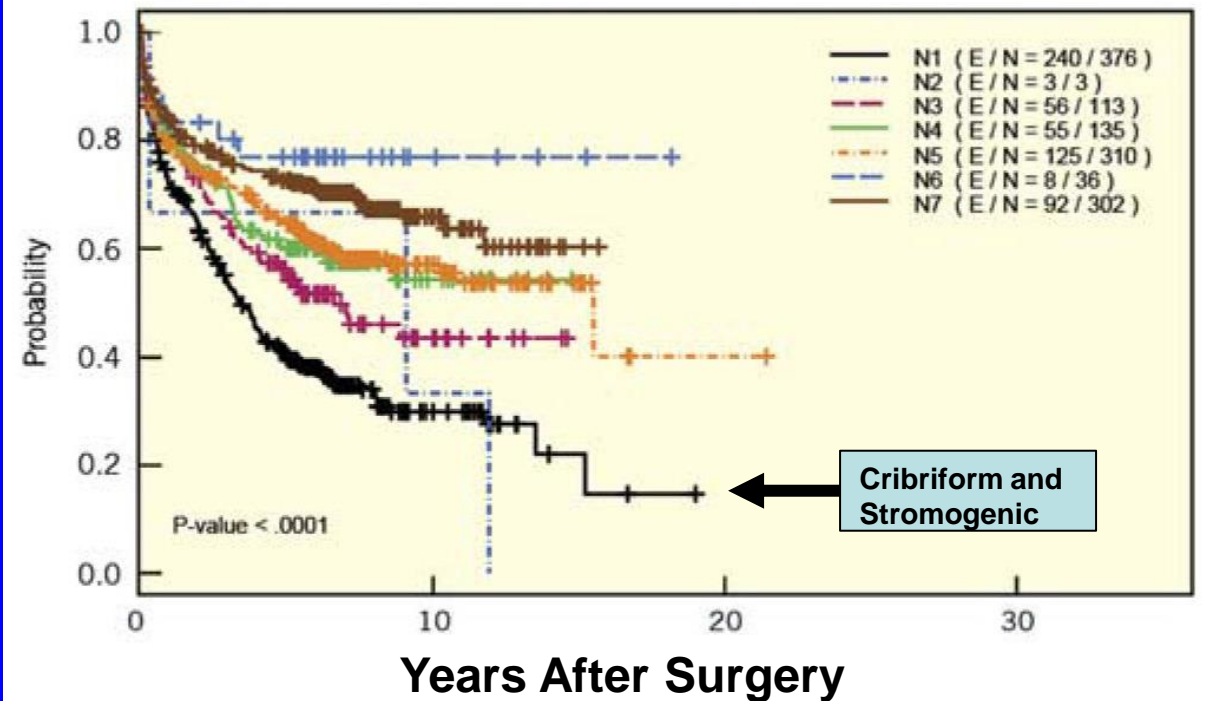
**Stromogenic**



**Cribriform**

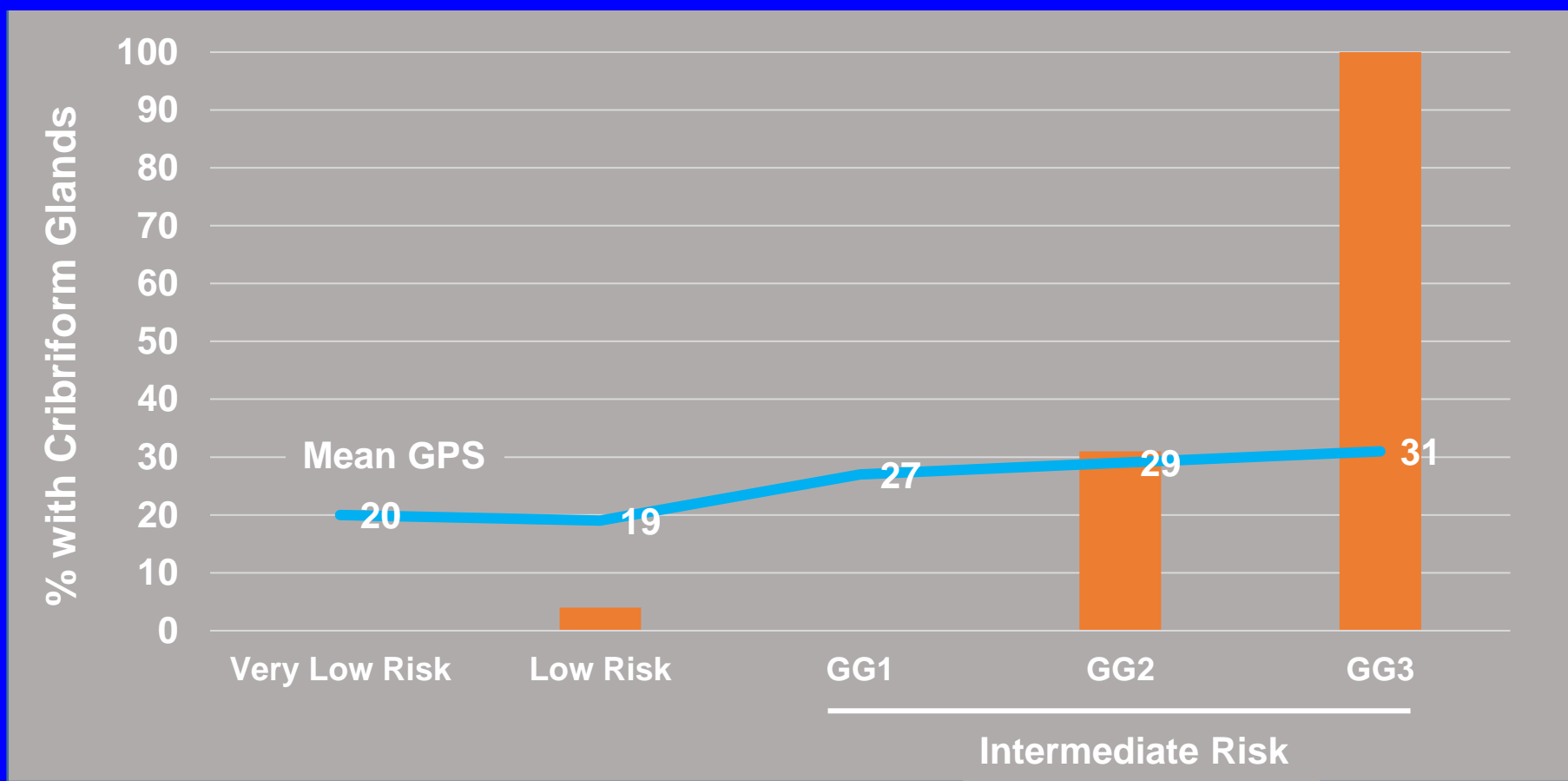


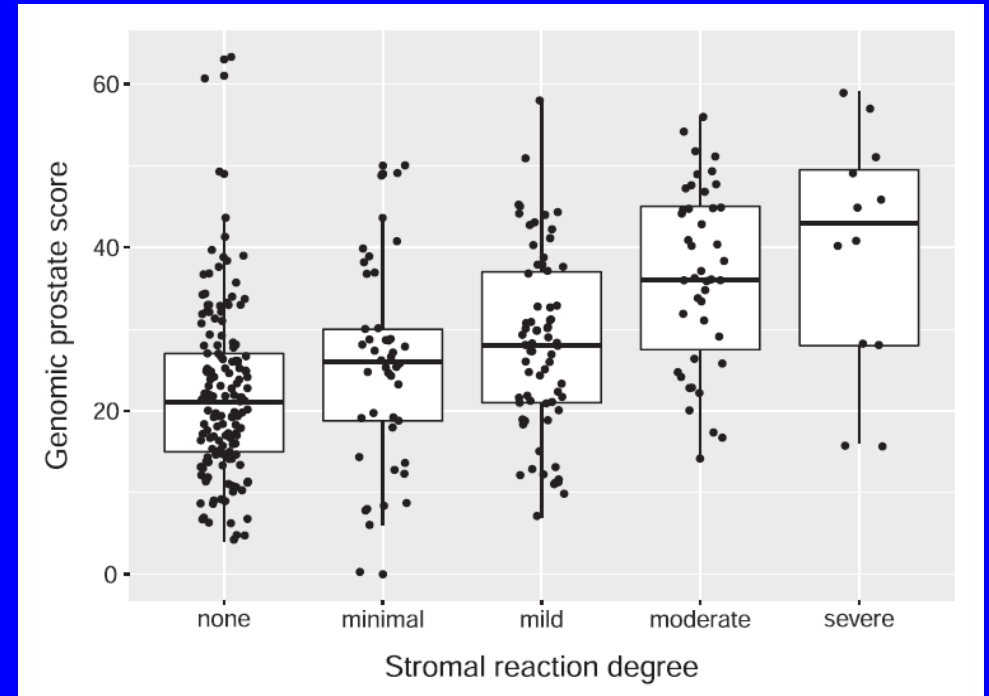
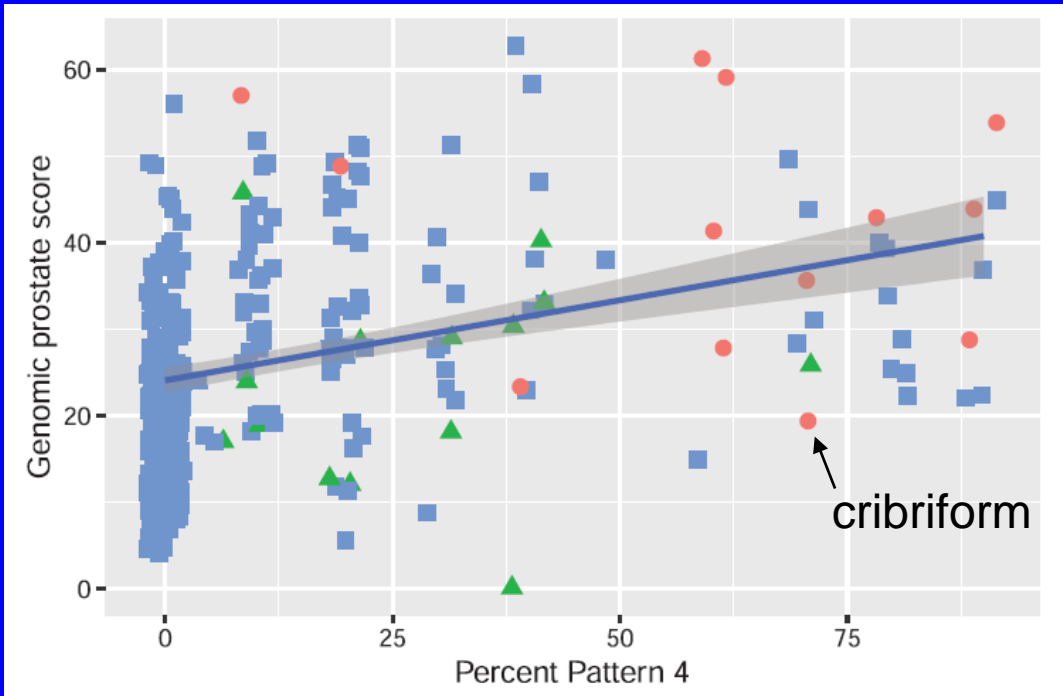
## Recurrence Free Survival



# Higher Oncotype GPS is Associated with Cribriform Histology on Biopsy

N = 189 on surveillance

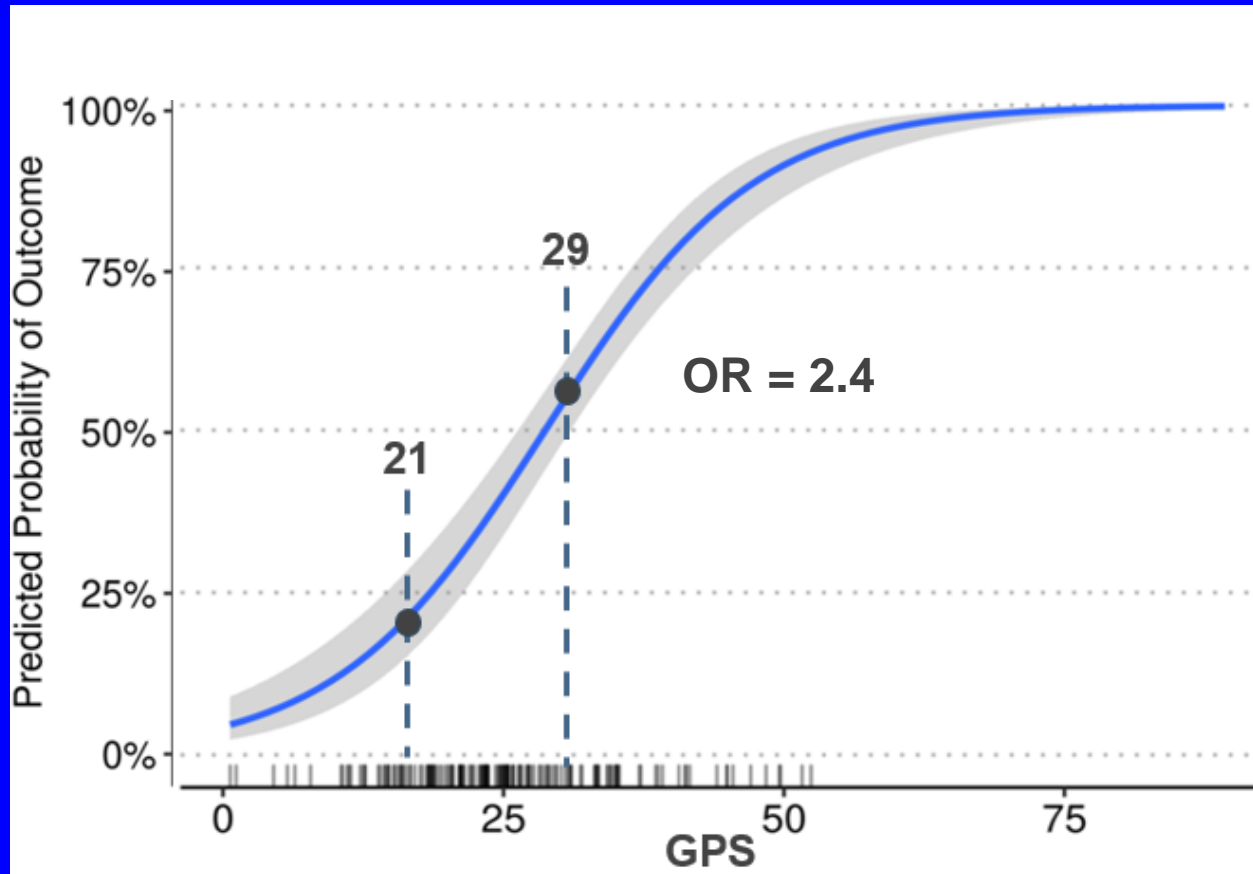




**“...given that these histologic features are subjective, and that molecular testing is both objective and reproducible, ...use of a molecular profile such as GPS as an adjunct to standard histopathologic assessment would likely improve upon current patient prognostication.”**

# Oncotype Validated for New Definition of Adverse Pathology

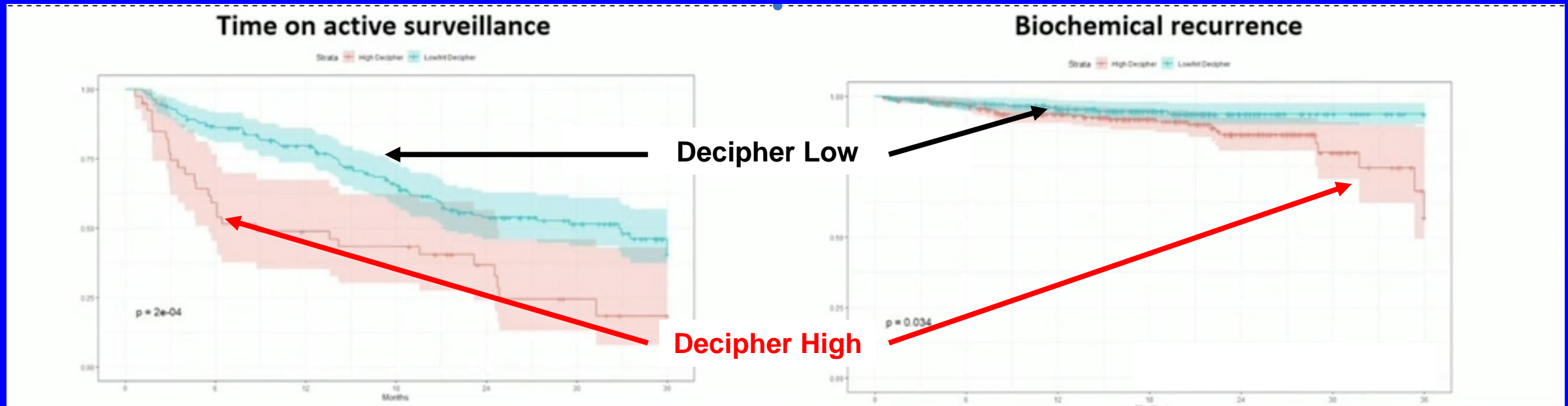
Adverse Pathology defined by Cribriform Histology



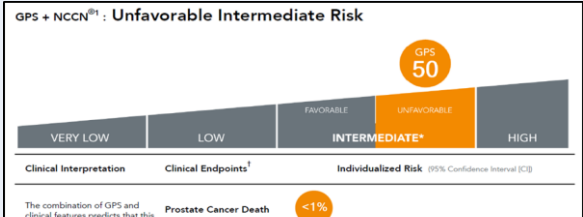
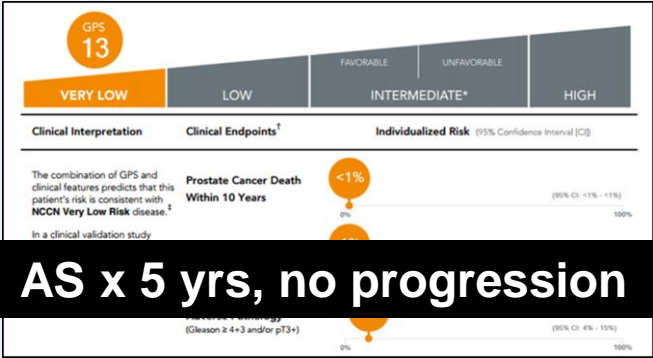
Cohorts: Training = Canary, Validation = Oncotype

# Prospective outcomes from clinical use of Decipher in men treated with active surveillance

MUSIC Active Surveillance Genomics Study (N = 800)



# NCCN Low Risk Disease

Case 1	Case 2
<p><b>56yo WM</b></p> <p><b>PSA 4.1      DRE benign</b></p> <p><b>Px vol 54cc    PSAD 0.07</b></p>	<p><b>63yo WM</b></p> <p><b>PSA 1.6      DRE nodule</b></p> <p><b>Px vol 32cc    PSAD = 0.05</b></p>
 <p><b>GPS + NCCN<sup>®1</sup>: Unfavorable Intermediate Risk</b></p> <p>GPS 50</p> <p>VERY LOW    LOW    INTERMEDIATE*    HIGH</p> <p>Clinical Interpretation    Clinical Endpoints<sup>†</sup>    Individualized Risk (95% Confidence Interval [CI])</p> <p>The combination of GPS and clinical features predicts that this patient's risk is consistent with NCCN Very Low Risk disease.<sup>‡</sup></p> <p>Prostate Cancer Death Within 10 Years &lt;1% (95% CI: -1% - 1%)</p> <p><b>RP: multifocal 3+4 (40% 4), crib, focal EPE</b></p> <p><b>Margins, SV, LNs negative</b></p>	 <p><b>GPS 13</b></p> <p>VERY LOW    LOW    INTERMEDIATE*    HIGH</p> <p>Clinical Interpretation    Clinical Endpoints<sup>†</sup>    Individualized Risk (95% Confidence Interval [CI])</p> <p>The combination of GPS and clinical features predicts that this patient's risk is consistent with NCCN Very Low Risk disease.<sup>‡</sup></p> <p>Prostate Cancer Death Within 10 Years &lt;1% (95% CI: -1% - 1%)</p> <p><b>AS x 5 yrs, no progression</b></p> <p>In a clinical validation study</p> <p>Prostate Cancer Death Within 10 Years (Gleason ≥ 4+3 and/or pT3+) 0% (95% CI: -6% - 10%)</p>

# The Precision Medicine Era

Then



Now

**“No decision without precision!”**

**Jonathon Simons**