

# Tissue Based Biomarkers for Localized Prostate Cancer

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NASPCC January 2018

# Relevant Disclosures

- Advisory role, ownership interest, previous unrestricted grant support, collaborative research – GenomeDX Biosciences
- Collaborative research – Myriad Genetics
- Dr. Ross' webinar presentation was provide through a generous donation from [Genomic Health](#).

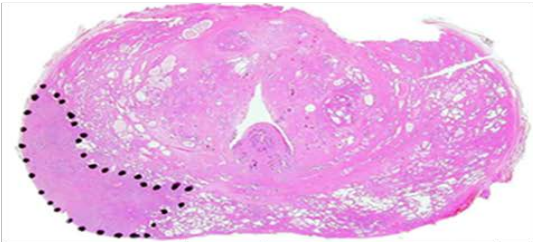


# Molecular Markers Are and Will Continue to Transform Our Ability to Understand Malignancies

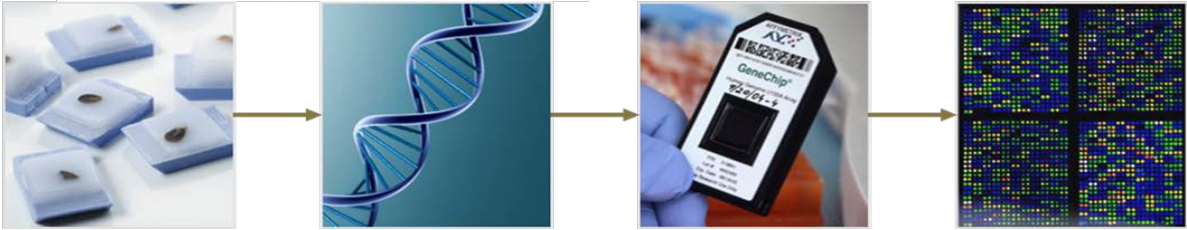
- 1817



- 1917



- 2017



# Biomarkers in Clinical Practice

- Greatest impact will occur in areas of large clinical uncertainty
- Biomarkers can offer prognostic and predictive information
  - Can help us decide who to treat (prognostic, overall risk)
  - Can help us decide what to treat them with (predictive, how will they respond to particular therapies)
- Barriers to Implementation
  - Understanding of the evidence, technology and utilization
  - Willingness to alter current work flow (in the clinic and pathology lab)
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# Outline and Objectives

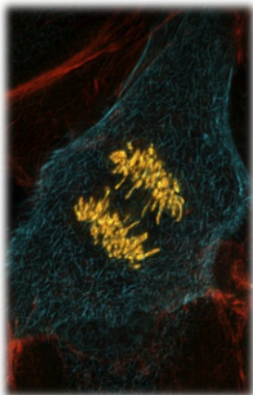
- Review clinically available tissue based biomarkers for localized prostate cancer
- Use of Prognostic Biomarkers
  - At Diagnosis
  - After Treatment
- Predictive Biomarkers
  - Radiation Sensitivity
  - Androgen Response
- Genetics in Prostate Cancer (beyond the scope but particularly important in advanced / metastatic disease)

# Clinically Available Tissue Based Biomarkers in Localized Prostate Cancer (Focusing on Genomics)

Multiplexed RT-PCR Assays FFPE

## Prolaris: CCP

PROLARIS:  
cell cycle  
progression  
(CCP) Score  
  
ratio of 31  
proliferation  
genes to 15  
normal genes



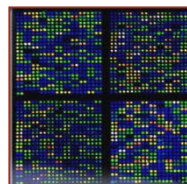
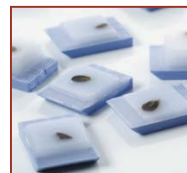
## OncotypeDx Prostate (GPS)

<b>Stromal Response</b>	SFRP4 BGN COL1A1 Stromal Response Group Score
<b>Androgen Signaling</b>	KLK2 SRD5A2 FAM13C1 AZGP1 Androgen Signaling Group Score
<b>Cellular Organization</b>	GSN GSTM2 TPM2 FLNC Cellular Organization Group Score
<b>Proliferation</b>	TPX2

12 Genes / 5 Controls

Genome Wide RNA Profiling FFPE

## Decipher



1.4 million  
probes  
Genome  
Wide  
(coding and  
non coding  
RNAs)



# Prognostic Markers



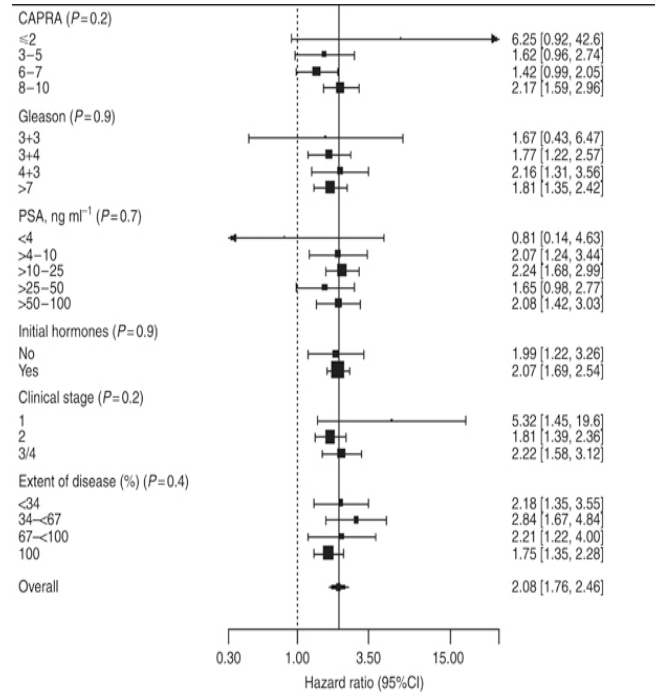
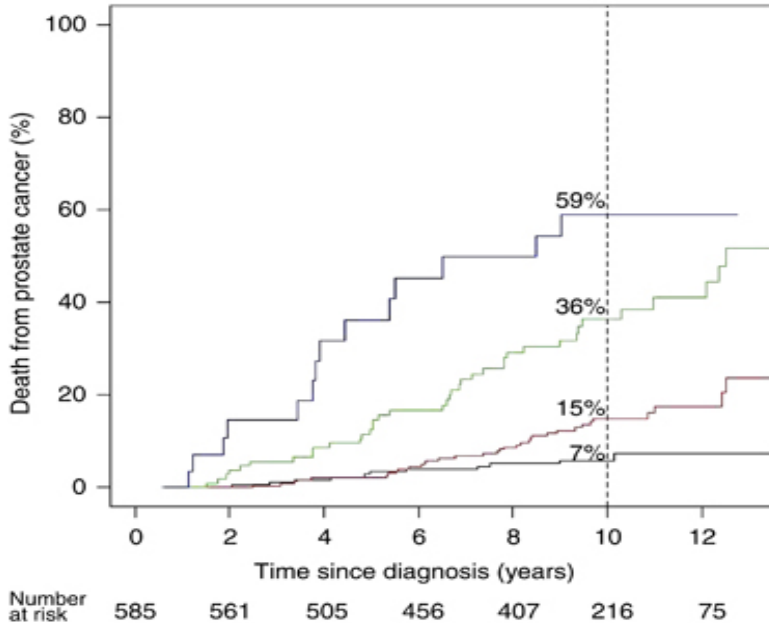
# Prolaris as a Prognostic Marker -- CCP

- Cell cycle abnormalities are common in localized prostate cancer
- Ki-67 IHC has independent prognostic significance after radiation (XRT) or radical prostatectomy (RP) (Khor et al JCO 2004, Tollefson et al Mayo Clin Proc 2014)
- Prolaris
  - qRT-PCR
  - 31 cell cycle genes normalized to 15 house keeping genes
  - Independently prognostic for progression to BCR, Mets and PCSM



# Prolaris as a Prognostic Marker -- CCP

- Transatlantic Prostate Group
- HR death per unit CCP increase ~2 (bivariate analysis with CAPRA)



Cuzick et al Br J Cancer 2015

# OncotypeDX Prostate as a Prognostic Marker - GPS

- qRT-PCR of 12 genes (derived from 732 genes which correlated with poor oncologic outcome) and 5 housekeeping genes

<b>Stromal Response</b>	SFRP4 BGN COL1A1
Stromal Response Group Score	

<b>Androgen Signaling</b>	KLK2 SRD5A2 FAM13C1 AZGP1
Androgen Signaling Group Score	

<b>Cellular Organization</b>	GSN GSTM2 TPM2 FLNC
Cellular Organization Group Score	

<b>Proliferation</b>	TPX2
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- Each 20-point increase (~IQR) in Genomic Prostate Score (GPS) equals ~2 fold risk of adverse pathology ( $\geq 4+3$  ( $\geq$ GG3) or pT3 disease) at RP
- Independently prognostic of adverse pathology, metastatic disease progression and death after radical prostatectomy

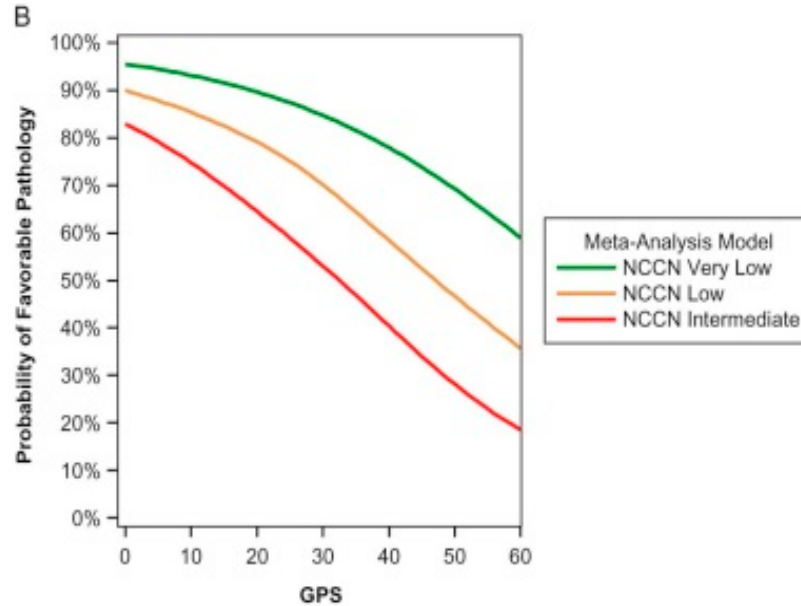
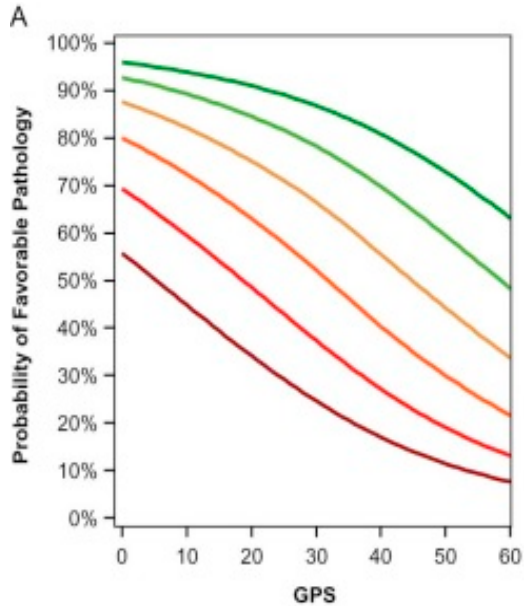
Klein et al Eur Urol 2014

Cullen et al Eur Urol 2014

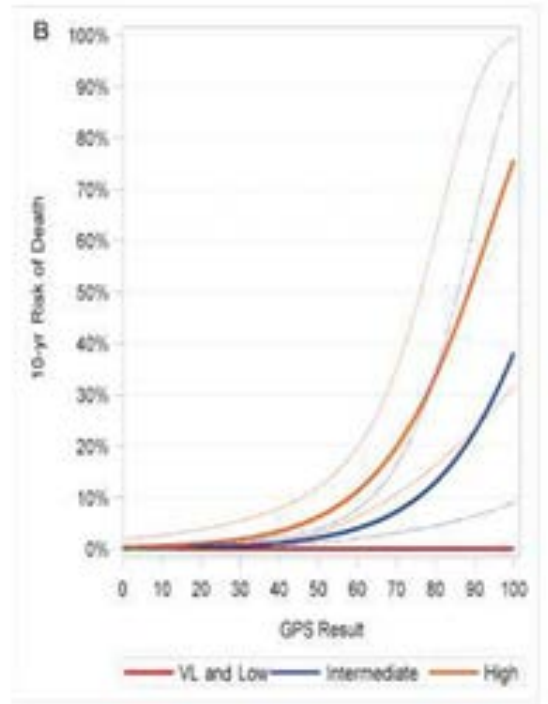
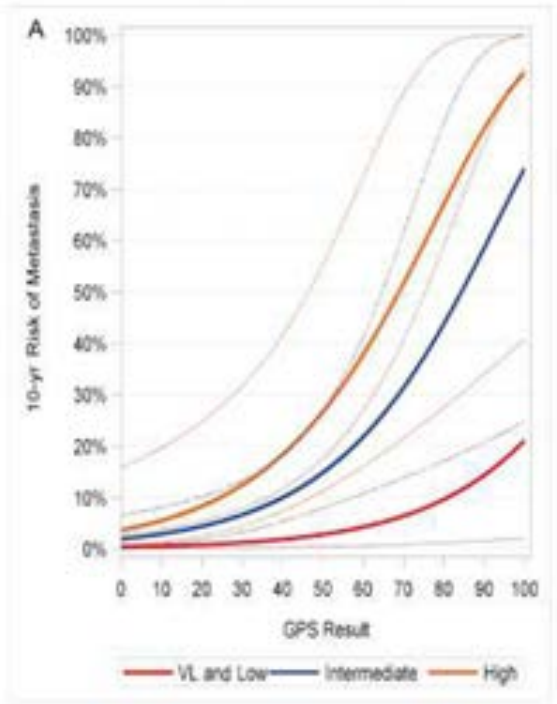
Van Den Eeden et al Eur Urol 2018

# OncotypeDX Prostate as a Prognostic Marker - GPS

- Meta-analysis 732 patients (2 studies, UCSF, CPDR) for prediction of favorable pathology (pT2 and GS 3+4=7 or less)

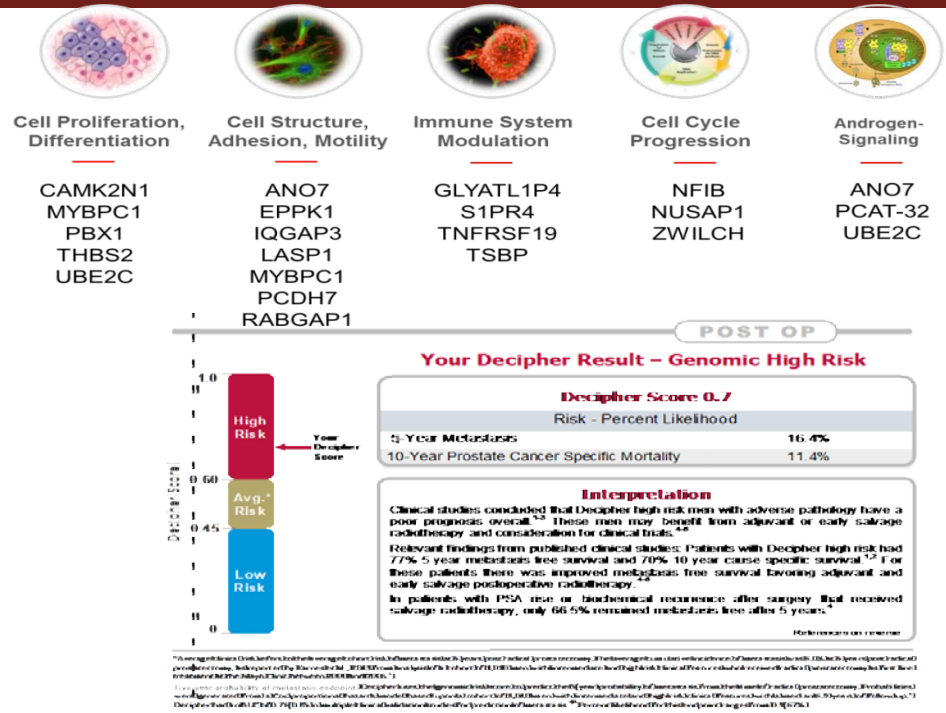


# OncotypeDX Prostate as a Prognostic Marker - GPS



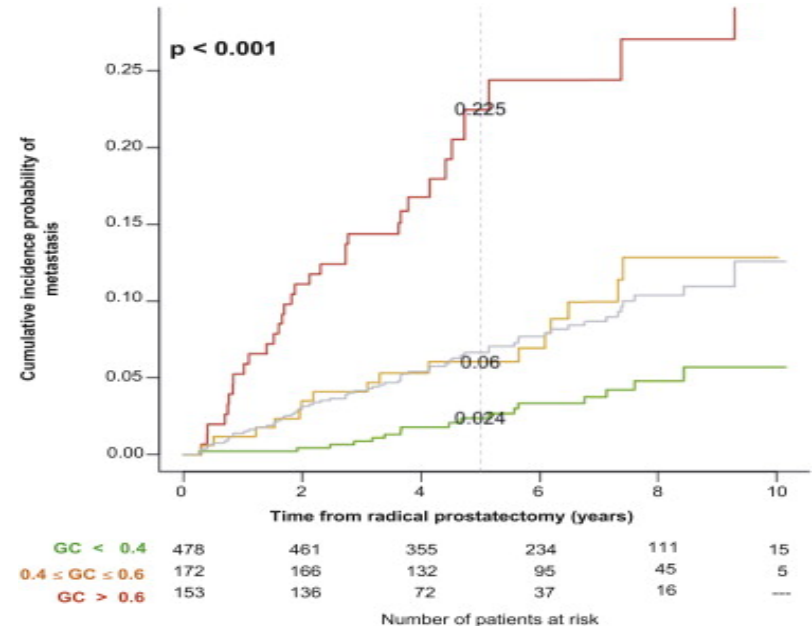
# Decipher as a Prognostic Marker -- GC

- 22 RNA expression based genomic markers selected for their ability to predict rapid metastasis after RP
- Outputs a Genomic Classifier (GC) score that ranges from 0 to 1
- Validated independent prognostic factor for BCR, Metastasis and PCSM



# Genomic Classifier Validation

- Initial validation of the Decipher metastasis signature in 219 high risk men s/p RP at the Mayo Clinic
- Categorical cut-offs for “low”, “intermediate” and “high” Decipher scores are associated with HR for clinical metastasis on multi-variate analysis of 1, 2.4 (1.1-5.2) and 7.3 (3.5-15.1)
- Independently predictive of PCSM as well (HR 1.8 per 0.1 unit increase) with Decipher high patients being 11 times more likely to die of prostate cancer compared to low risk patients ( $p < 0.001$ )
- Caveat: a portion of this cohort underwent adjuvant and salvage therapies

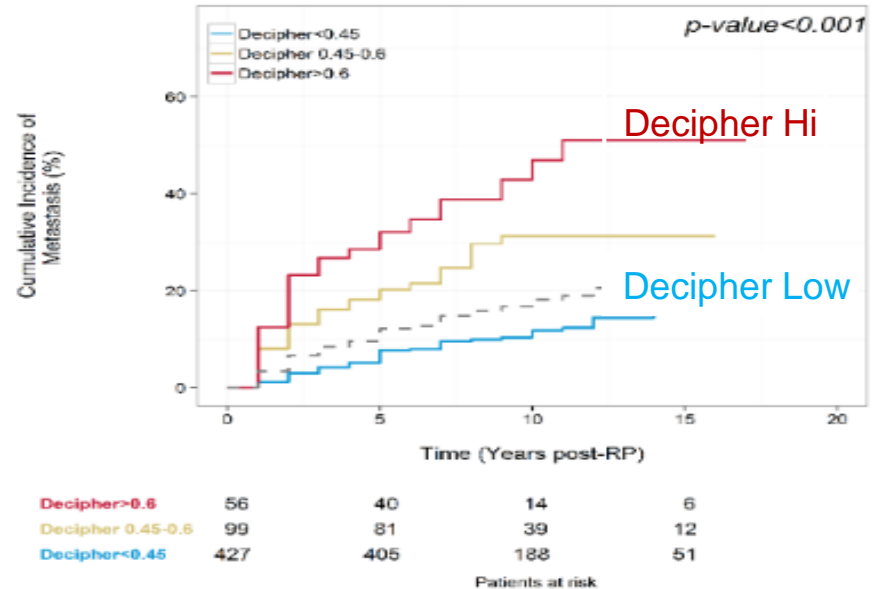


Karnes et al J Urol 2013

Cooperberg et al Eur Urol 2015

# Genomic Classifier Validation

- Subsequent validation in 260 NCCN intermediate and high risk men (99 with metastatic progression) from Johns Hopkins
  - “Natural History” cohort (no post-RP treatment until the time of clinical metastasis)
- HR for clinical metastasis 1.5 (1.3-1.7) per 0.1 unit increase in score on MVA (median score 0.34 IQR 0.22-0.52)
- Similar results found in a third validation cohort from Cleveland Clinic managed without adjuvant radiation
- In a combined cohort from Mayo, JHH, CCF and Durham Vetrans high genomic score (>0.6) was an independent predictor of PCSM on MVA adjusting for CAPRA-S (HR 3.9 (CI 2.4-6.3))



Ross et al Eur Urol 2015  
 Klein et al Eur Urol 2015  
 Karnes et al Eur Urol 2017



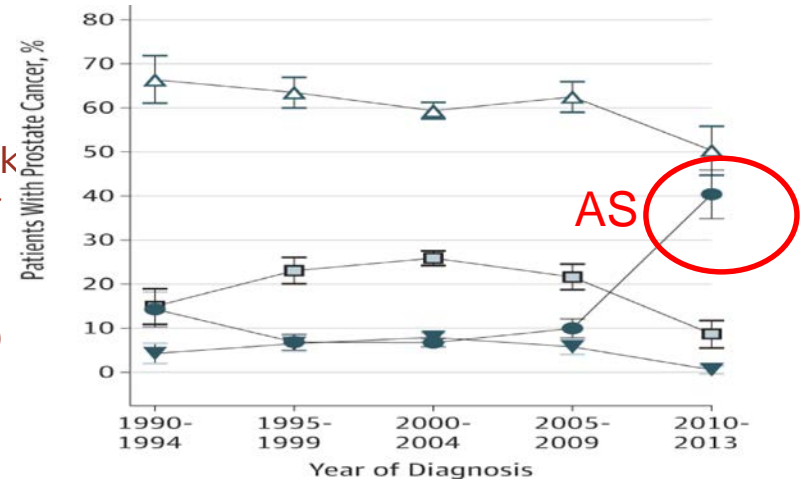
# Use of Prognostic Biomarkers at Diagnosis

## Question 1: When To Treat?

Genomics for Men of Favorable Risk (NCCN VLR, LR, Favorable Intermediate)

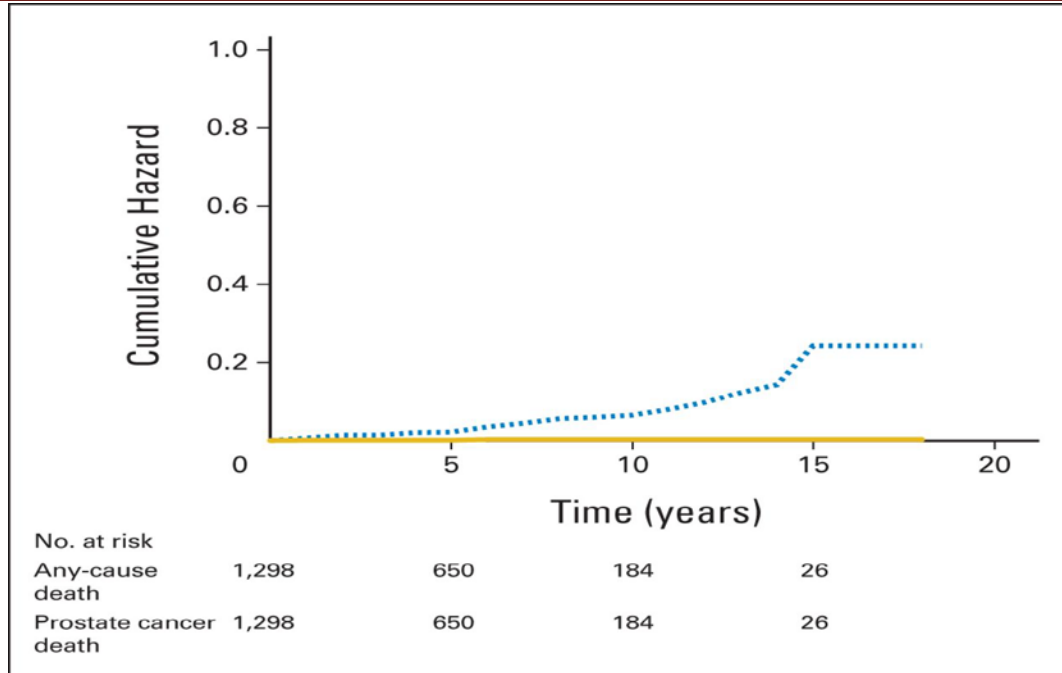
# Active Surveillance and Favorable Risk Prostate Cancer

- Active surveillance (serial biopsy, serum tests, exam, +/-imaging) is a valid treatment strategy for favorable risk men
  - Relatively few men with very low or low risk prostate cancer will progress to die of their disease if immediate local therapy is deferred (Bill-Axelsson et al. NEJM 2014, Hamdy et al. NEJM 2016, Tosoian et al JCO 2015)
- Active surveillance should be considered in very-low, low risk men and some favorable intermediate risk men
  - Rates of progression are higher as clinical risk increases
  - Imaging / Genomic Testing can be considered to qualify candidates



Cooperberg et al JAMA 2015

# Very Low Risk men– Active Surveillance is Standard

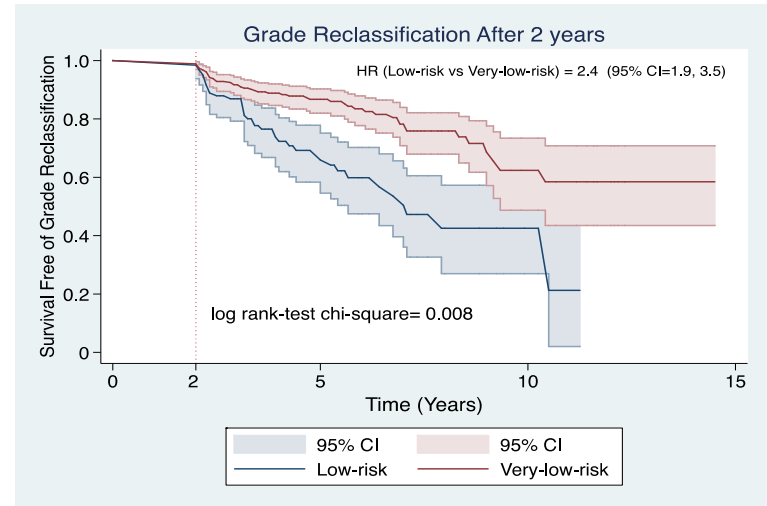


Jeffrey J. Tosoian et al. JCO 2015;33:3379-3385

- Choice of Surveillance
  - Increases mortality by 1.8 months while increasing treatment free interval by 6.4 years (Xia et al CCR 2012)
- Serial PSAs, DRE, biopsy
- Genomics may play a marginal role
  - Exception for understudied populations
    - *Young, AAM, +FamHx*
  - Possibly for aiding in decision of intensity of follow up

# Low and Favorable Intermediate Risk Prostate Cancer – Less Studied, Less Certainty

- Low risk prostate cancer is ~2.5x as likely to be reclassified to  $\geq$  intermediate risk
- 11% reduction in rate of metastasis if treated in SPCG-4 (reduction in PCSM not significant) (Bill-Axelson NEJM 2014)
- ~2.5x increased risk of metastasis at 10 years in ProtecT if initial treatment deferred with many more progressing to incurable disease (Hamdy NEJM 2016)
- Low risk AS patients are NOT indicative of low risk patients (8%  $\geq$  4 cores for AS, 49%  $\geq$  4 cores for RP) (Tosoian et al J Urol 2017)

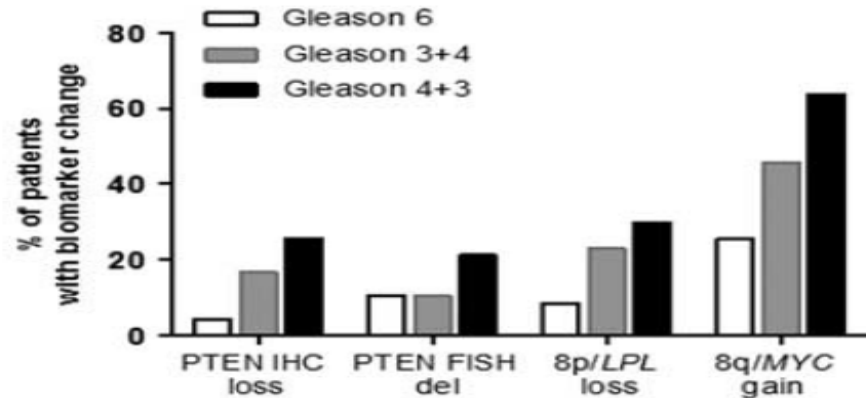
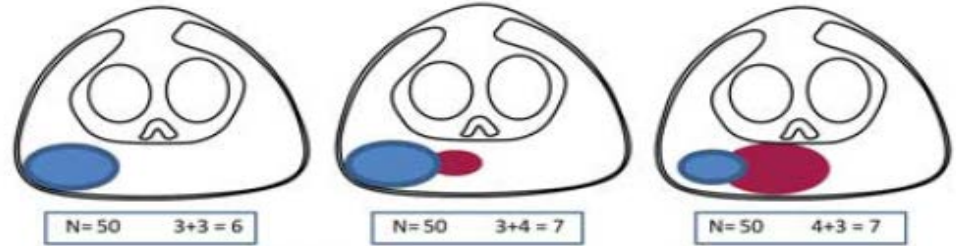


Alam R et al J Urol 2015

**Can we use Genomics to better select LR/F-IR men for AS?**  
**Does GG1 disease have metastatic potential?**

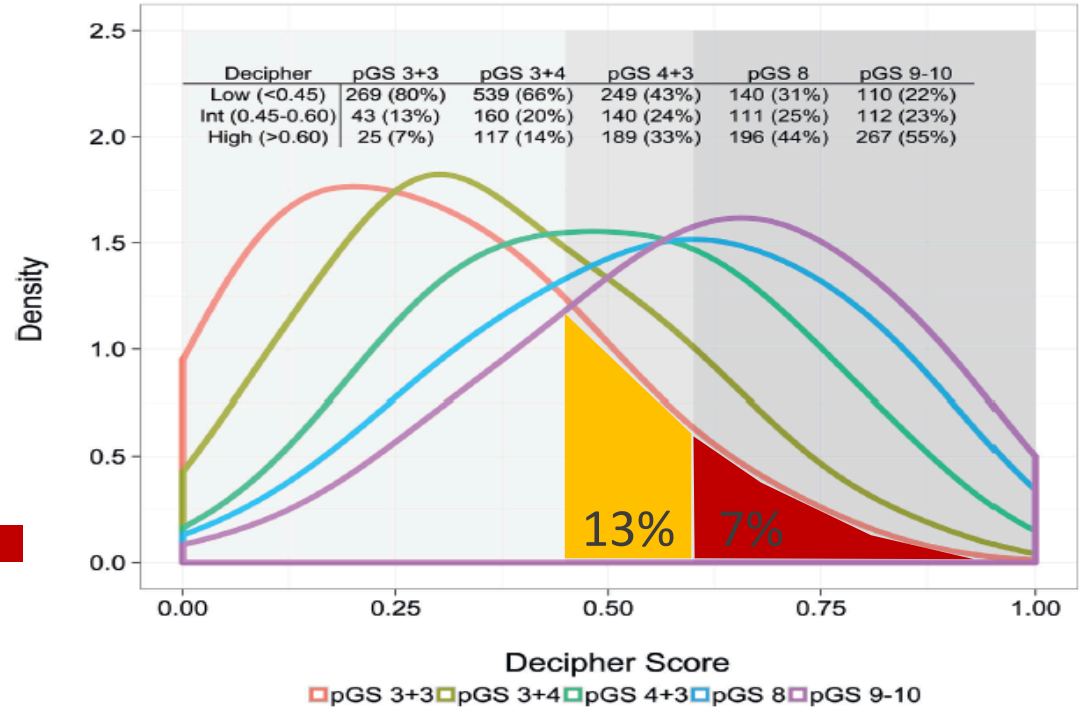
# Genomic markers of aggressive disease in Gleason Pattern 3 tissue from Prostatectomy specimens: PTEN loss, 8p/LPL loss, 8q/MYC gain

- Sampling of **Gleason pattern 3 (G3)** tissue from prostatectomy specimens harboring:
  - -GS 3+3=6
  - -GS 3+4=7
  - -GS 4+3=7
- Evaluation of:
  - -PTEN loss by IHC
  - -PTEN deletion by FISH
  - -LPL/8p loss by FISH
  - -MYC/8q gain by FISH

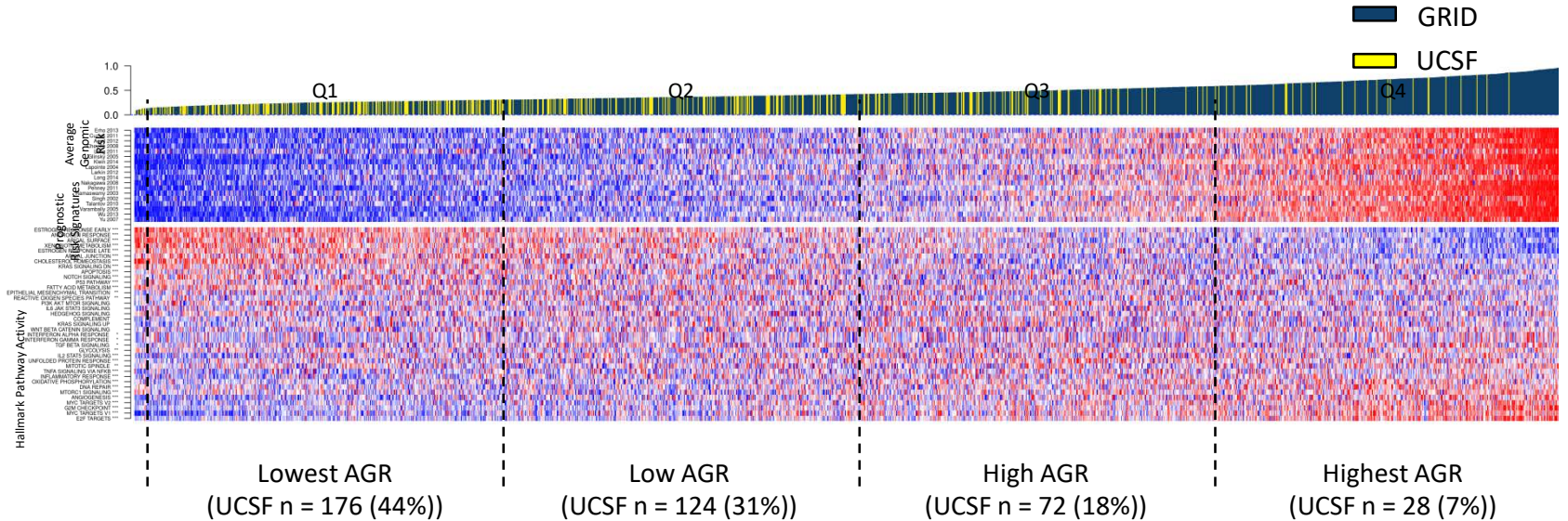


# Genomic classifier for aggressive disease (Decipher metastasis scores) are elevated in a small but not insignificant proportion of pure GG1 tumors

- Tissue obtained from prostatectomy specimens with only GG1 disease:
- 43 (13%) had intermediate risk genomic classifier score ■
- 25 (7%) had high risk genomic classifier score ■



# Genomic patterns of high risk disease cluster together and are found in ~7% of Favorable Risk Patients



- 7% of the UCSF cohort clustered with higher risk patients from GRID, 4<sup>th</sup> quartile, of AGR score of 18 prognostic pathways (Cooperberg AUA 2017)
- High GPS scores were found in 7% of active surveillance candidates and these men had a higher risk of progression after treatment (Klein et al Eur Urol 2014).
- CCP scores >1 found in 8% of favorable risk men (Tosoian et al BJUI 2017)

# Time to BCR for Categorical Decipher (190 NCCN low to favorable intermediate risk patients)

Variable	UVA			MVA		
	HR (95% CI)	P-value	AUC at 5 year	HR (95% CI)	P-value	Opt AUC at 5 year
Age	0.996 (0.923-1.076)	0.920	0.58 (0.36-0.70)	1.022 (0.917-1.138)	0.695	
PSA	1.294 (0.799-2.097)	0.294	0.75 (0.56-0.90)	1.252 (0.658-2.382)	0.494	
% Positive Biopsy Cores	1.211 (0.886-1.655)	0.229	0.64 (0.52-0.79)	1.142 (0.776-1.680)	0.502	
Biopsy Gleason 3+3	--	--	--	--	--	--
Biopsy Gleason 3+4	0.752 (0.206-2.752)	0.667	0.59 (0.46-0.67)	0.708 (0.113-4.429)	0.712	0.73 (0.63-0.87)
Categorical Decipher (Low)	--	--	--			
Categorical Decipher (Int)	3.557 (0.873-14.496)	0.077		3.195 (0.692-14.747)	0.137	
<b>Categorical Decipher (High)</b>	<b>20.968 (4.537-96.915)</b>	<b>&lt;0.001*</b>	<b>0.61 (0.36-0.76)</b>	<b>16.967 (3.076-93.592)</b>	<b>0.001*</b>	<b>0.72 (0.62-0.86)</b>

*Clinical Variable MVA Model includes age, PSA, % positive biopsy cores and biopsy Gleason 3+4 vs. 3+3 and 4+3 or higher vs. 3+3.*

*Decipher MVA Model was adjusted by clinical variables.*

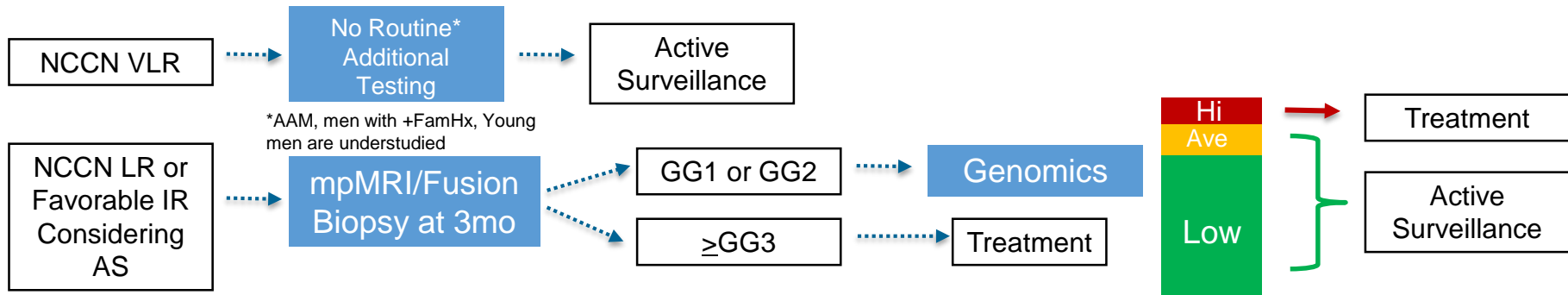
*PSA was on log2 scale.*

*Hazard ratios of the % positive biopsy cores and the Decipher were per 0.1 unit increased.*

Loeb et al in Preparation



# Current Strategies for AS Qualification

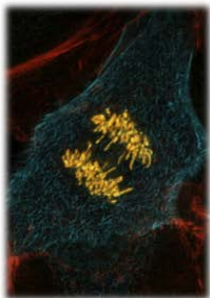


Prolaris: CCP

OncotypeDx Prostate (GPS) Decipher

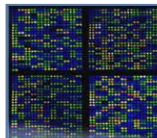
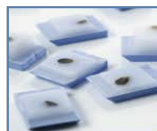
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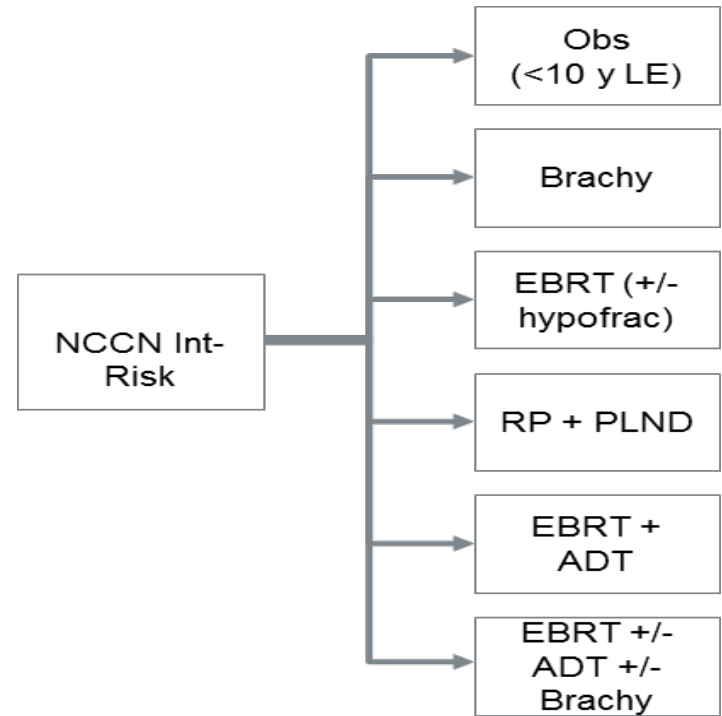
# Use of Prognostic Biomarkers at Diagnosis

## Question 2: What is the Ideal Intensity of Treatment?

Genomics for Men Prioritized to Treatment (NCCN Int)

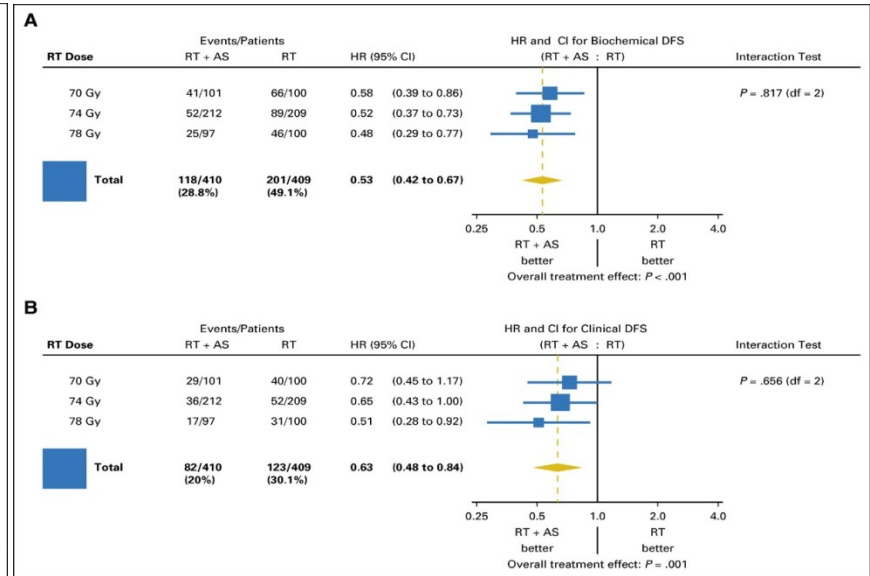
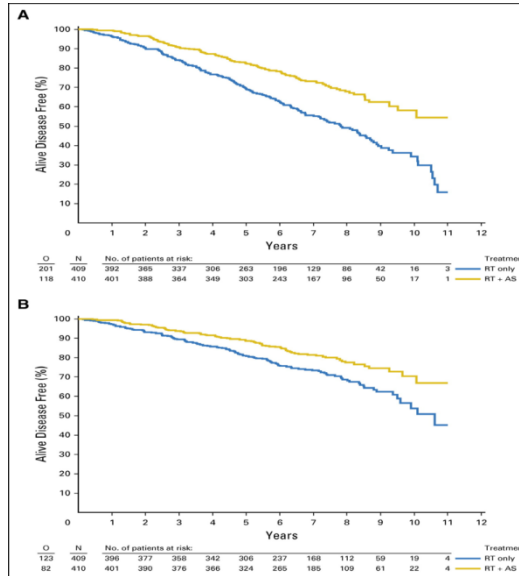
# Intermediate Risk Prostate Cancer – Multiple Treatment Options

- Multiple treatment options, large variance of risk
- For men undergoing radiation based therapy ADT improves progression free survival even with dose escalation (Bolla et al JCO 2016)
- For men undergoing radiation based therapy brachy-boost can improve local control (Morris et al IJROBP 2016)
- For men with <20 years LE, oncological control for RP vs RT based approaches may be similar with RP having higher short term morbidity
- Subtotal gland therapies being investigated / utilized



# ADT Improves Disease Free Survival for Intermediate Risk Men Receiving RT (Bolla et al JCO 2016 EORTC 22991)

- 6 months of ADT improved BFS and clinical DFS even with dose escalation to 78Gy
- 75% patients intermediate risk



# Use of ADT with EBRT in Intermediate Risk Men

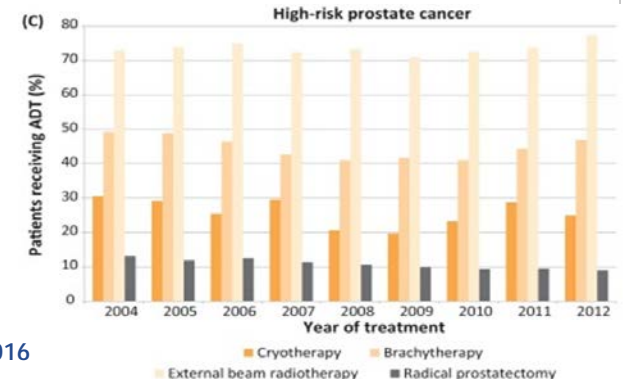
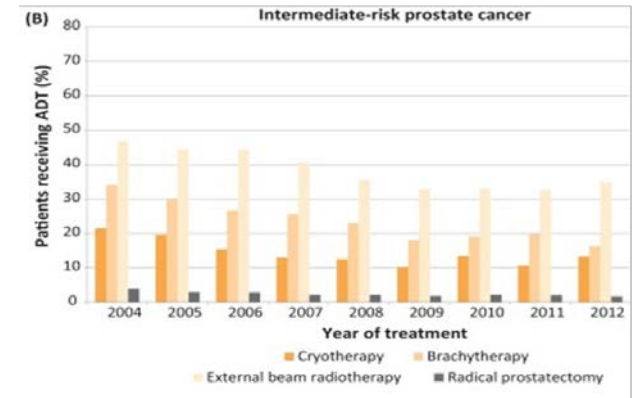
Current use of ADT with EBRT in intermediate risk men is ~35%

Despite level 1 evidence and guideline recommendations, current use of ADT with EBRT for high risk prostate cancer ~75%

Hesitancy regarding ADT:

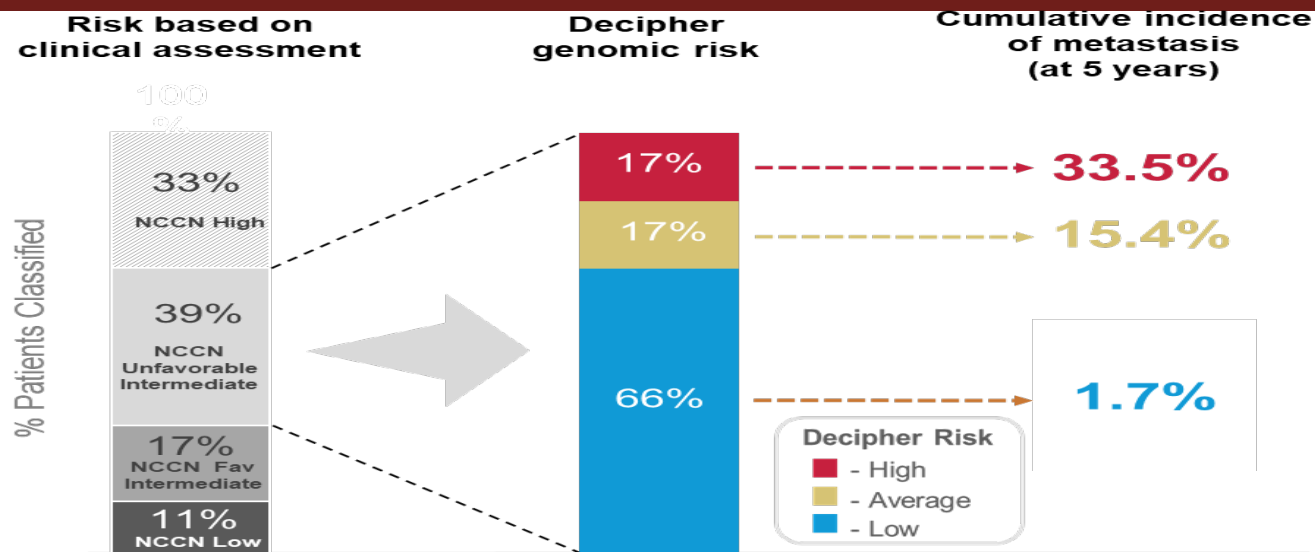
- Cognitive decline (Gonzalez et al JCO 2015, Nead et al JAMA Oncol 2017)
- Cardiovascular risk (O'Farrell et al JCO 2015)
- Sexual dysfunction, reduced energy, weight/fat gain

**Decision regarding intensification of therapy (i.e. use of ADT) should be made based on overall metastatic risk (biological potential) of disease (Lester et al JNCI 2016)**



Gray et al Eur Urol 2016

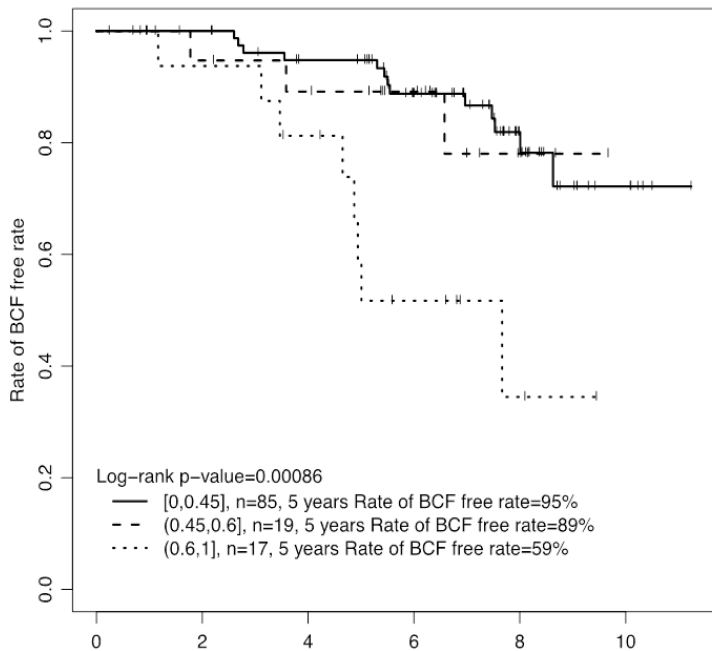
# SUBSET ANALYSIS OF COMBINED BIOPSY COHORT (N=235) SHOWING METASTASIS INCIDENCE RATE FOR UNFAVORABLE INTERMEDIATE NCCN RISK PATIENTS



Variables	UVA		MVA	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Biopsy Grade Group 1-2	Reference	1	Reference	1
Biopsy Grade Group 3	1.7 (0.6 – 5.3)	0.326	0.9 (0.3 – 3.2)	0.923
Log 2 PSA at First Line Treatment	0.8 (0.5 – 1.4)	0.368	1.2 (0.6 – 2.7)	0.546
Age at First line Treatment	1.1 (1.0 – 1.2)	0.012	1.1 (1.0 – 1.2)	0.065
<b>Decipher Biopsy*</b>	<b>1.6 (1.2 – 2.1)</b>	<b>0.001</b>	<b>1.5 (1.1 -2.1)</b>	<b>0.009</b>

# Decipher Biopsy is a significant predictor of progression in intermediate NCCN risk men treated by radiation alone (n=121)

Intermediate risk

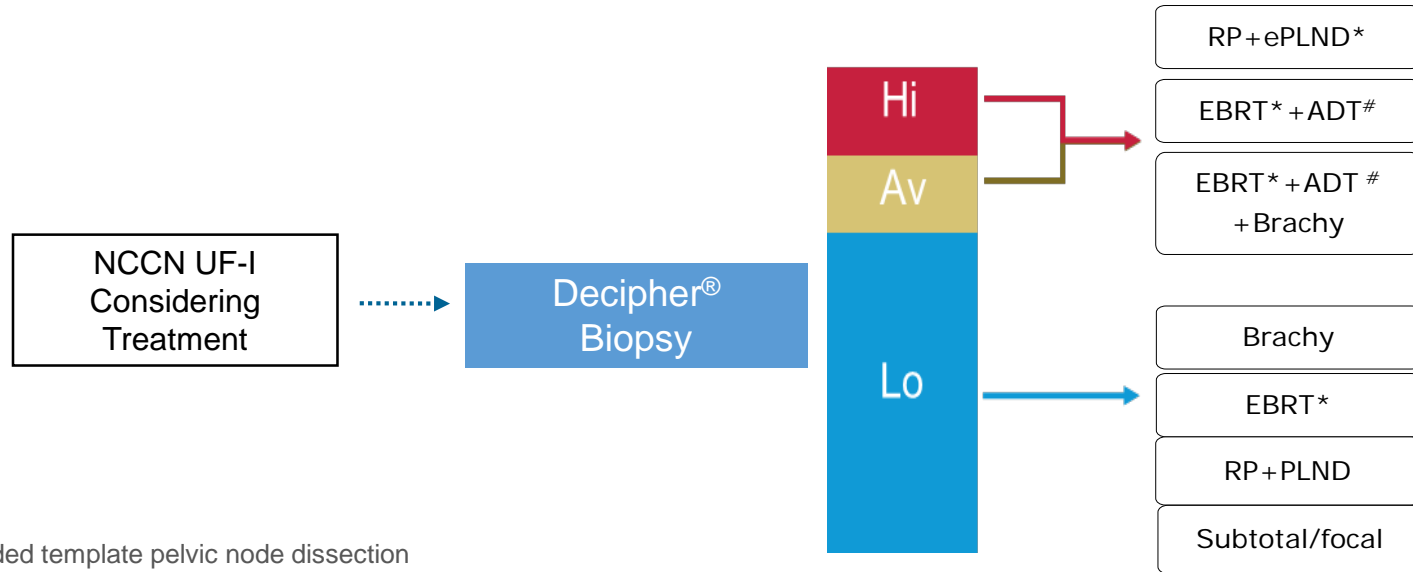


## MVA analysis to predict biochemical failure after RT

	HR (95%CI)	Wald p value
NCCN Risk: Unfav (ref: Fav)	2.58 (0.95-7.03)	0.064
Intraductal Carcinoma: (ref: acinar adenocarcinoma)	1.16 (0.41-3.26)	0.78
<b>Decipher: High risk (ref: low/int)</b>	<b>4.71 (1.81-12.28)</b>	<b>0.0015</b>

*Decipher low risk (82% of men): 5 yr 95% biochemical-free survival when treated with IMRT without any hormone therapy vs. 59% for Decipher high risk (16% of men)*

# How Physicians Can Use Prognostic Biomarkers in the Unfavorable Intermediate (UF-I) Setting



\*Extended template pelvic node dissection

\*Hypofractionation can be considered

#Length of ADT can be adjusted based on risk

-Genomics may also be able to guide staging in UF-I risk men, use of advanced imaging and treatment intensification in HR/VHR men



# Use of Prognostic Biomarkers After Treatment

## Considerations for Adjuvant and Salvage Radiation

Genomics for Men with Adverse Pathological Features at RP

# Treatment Considerations after Radical Prostatectomy

## Considerations for Men with Adverse Pathological Features (APF) after Prostatectomy

- AUA, ASTRO and ASCO Guidelines recommend adjuvant radiotherapy for
  - pT2 with positive margin or any pT3



American  
Urological  
Association

ASTRO  
TARGETING CANCER CARE

**Guideline Statement 3.** Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression. (*Standard\**; Evidence Strength: **Grade A**)

- Supported by level 1 evidence from three RCTs
  - Demonstrated reductions:
    - Biochemical recurrence
    - Local recurrence
    - Clinical progression/metastasis
- Use of ART should be judicious
  - **Many men received NO benefit from the treatment** (SWOG 8794)
  - Control arm - 89% metastasis free survival at 10 years
  - ART arm - more toxicity/side-effects

# Treatment Considerations after Radical Prostatectomy

## Professional Society Opinions

- The American Society of Clinical Oncology (ASCO) has also recently announced its endorsement of guidelines from AUA and ASTRO. However, the endorsement panel highlighted a qualifying statement that:
  - “Not all men who are candidates for adjuvant or salvage radiotherapy have the same risk for recurrence or disease progression, and thus, not all men will derive the same benefit from adjuvant radiotherapy.” (*Freedland et al. Nov 2014, JCO*)
- However, Adjuvant radiation is under-utilized
  - ~10% of men with adverse pathological features
  - Level 1 evidence supporting early salvage radiation is not yet reported
- In the 2017 *National Comprehensive Cancer Network (NCCN) prostate cancer guidelines*, NCCN noted the following:

<sup>b</sup>Men with clinically localized disease may consider the use of tumor-based molecular assays. Retrospective case cohort studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. [See Discussion section.](#)

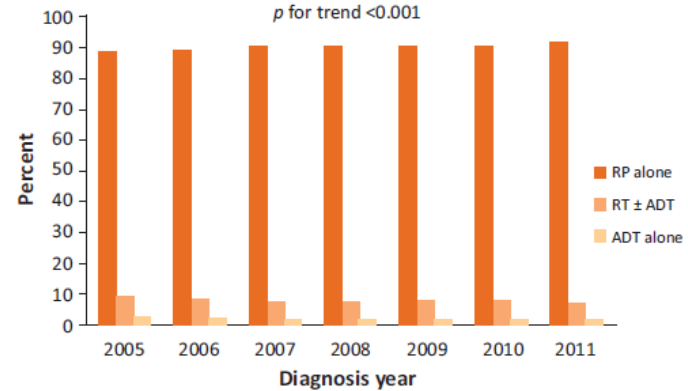
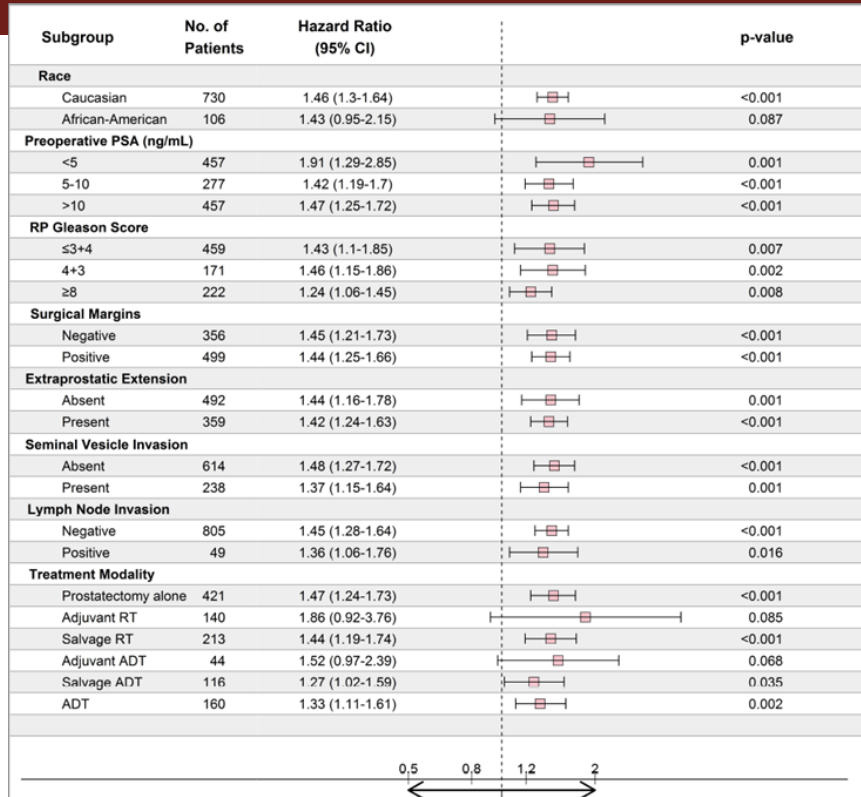


Fig. 1 – Unadjusted patterns of practice within 6 mo of radical prostatectomy for patients with prostate cancer with adverse pathologic features, by year.

Sineshaw et al, Eur Urol 2015

# Meta-analysis of 855 patients from five cohorts shows Decipher is a significant predictor of metastasis across all clinical subgroups



- Hazard ratio per 0.1 (10% increase) in Decipher score
- Decipher improved the ability to predict the cumulative incidence of metastases in nearly all subgroups based on clinicopathologic factors, treatment factors, and demographic factors

Spratt et al., J Clin Onc 2017

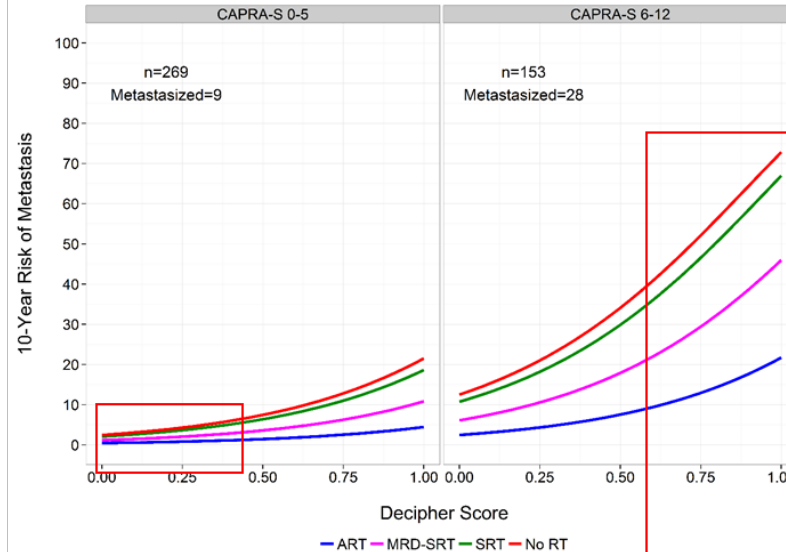
ORIGINAL ARTICLE

# Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk

AE Ross<sup>1,13</sup>, RB Den<sup>2,13</sup>, K Yousefi<sup>3</sup>, BJ Trock<sup>1</sup>, J Tosoian<sup>1</sup>, E Davicioni<sup>3</sup>, DJS Thompson<sup>4</sup>, V Choeng<sup>3</sup>, Z Haddad<sup>3</sup>, PT Tran<sup>5</sup>, EJ Trabulsi<sup>2</sup>, LG Gomella<sup>2</sup>, CD Lallas<sup>2</sup>, F Abdollah<sup>6</sup>, FY Feng<sup>7</sup>, EA Klein<sup>8</sup>, AP Dicker<sup>2</sup>, SJ Freedland<sup>9,10</sup>, RJ Karnes<sup>11</sup> and EM Schaeffer<sup>12</sup>

## Clinical-genomic low risk:

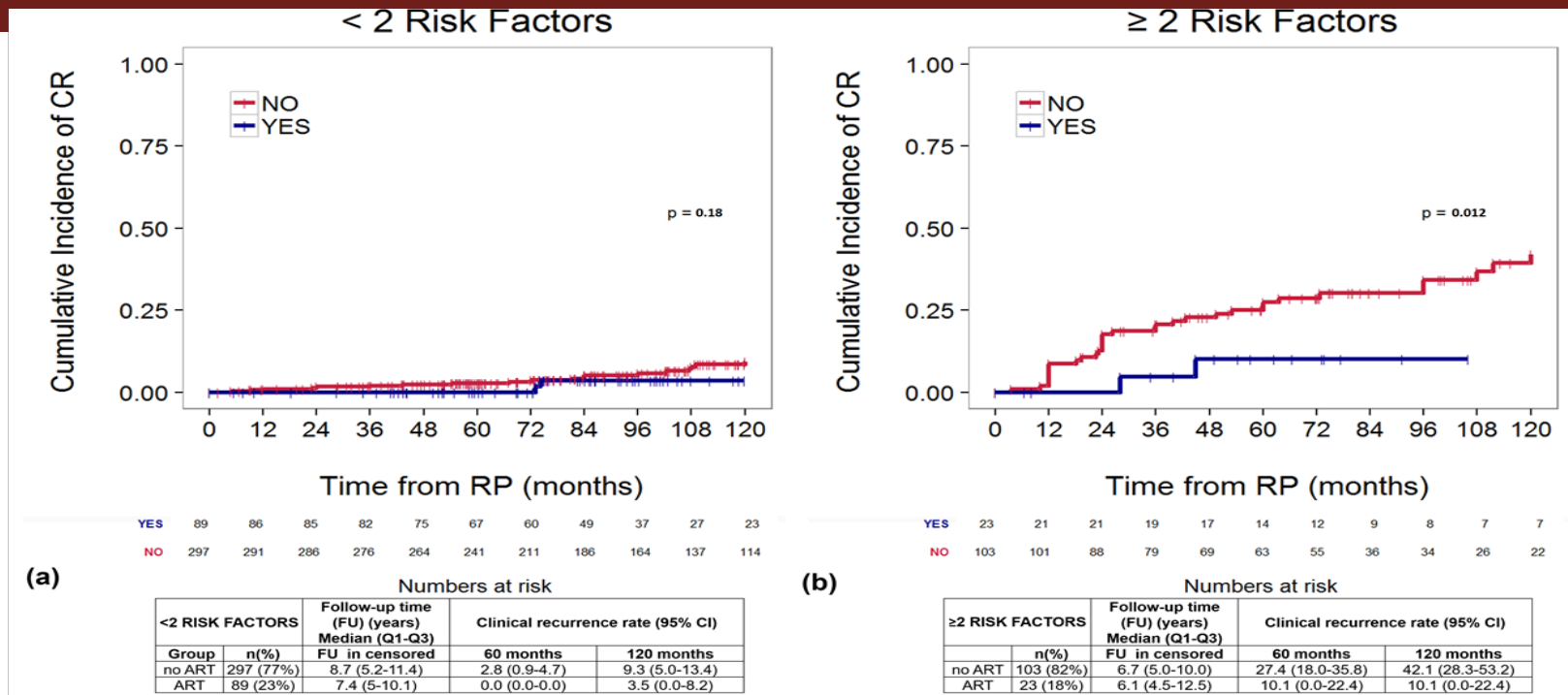
- No difference in 10 yr metastasis between treatment and observation



## Clinical-genomic high risk:

- Earlier RT better than late or never.
- Minimal difference in survival between late salvage and observation

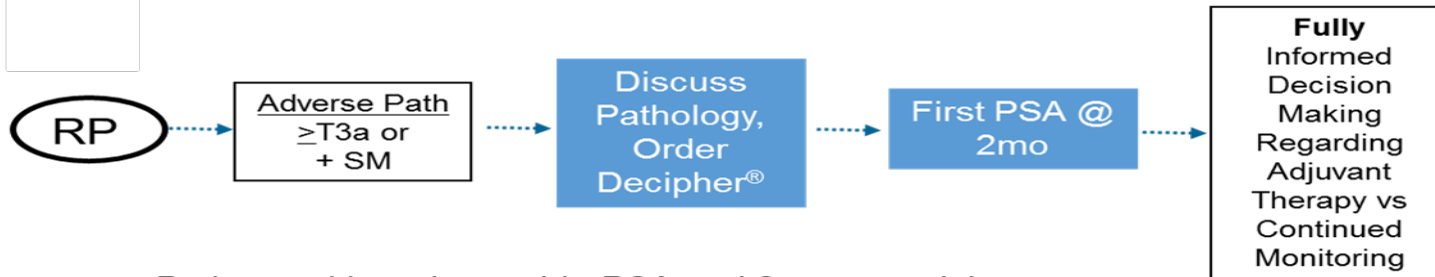
# Patients with $\geq 2$ risk factors benefit from adjuvant radiation (NNT 3)



-Risk Factors: pT3b/T4, GG4-5, pLN+, Decipher GC>0.6  
(Dalela et al JCO 2017)

# Potential use of Genomics (Decipher) in the Post-Op Setting

## Post-Op Prostate Cancer Pathway

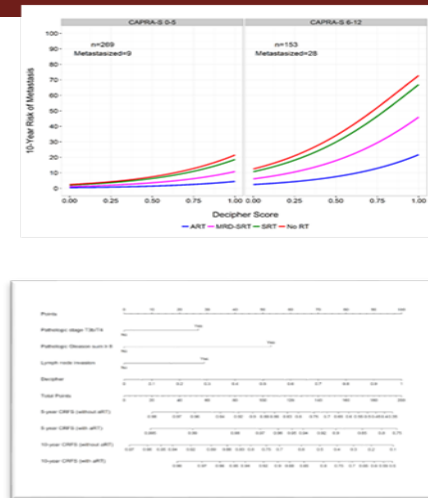


Patients with undetectable PSA and 2 or more risk features may be prioritized to adjuvant therapy

- GC>0.6
- pT3b
- pN1
- GS 8-10

NNT with adjuvant to prevent metastasis is 3 (Dalela et al JCO 2017)

-Genomics may also be able to guide intensification of adjuvant therapy and salvage therapies (i.e. +/- ADT, dense ADT) (Shiple et al NEJM 2017, Spratt et al Eur Urol 2017)





# Predictive Biomarkers



# Most Therapeutics in Prostate Cancer are Biological

## Mechanical

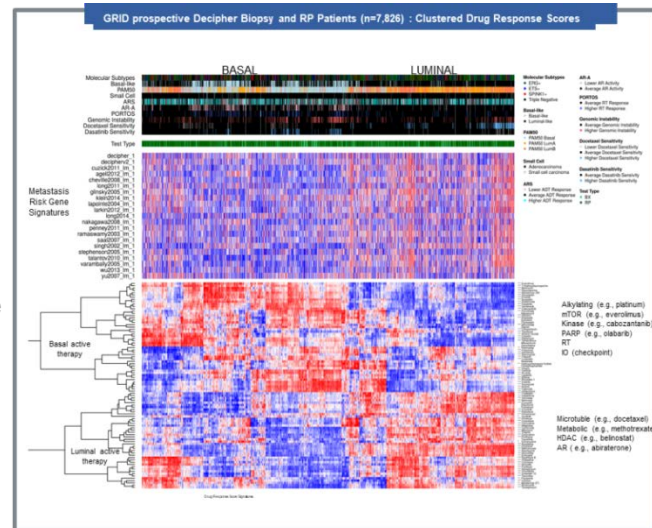
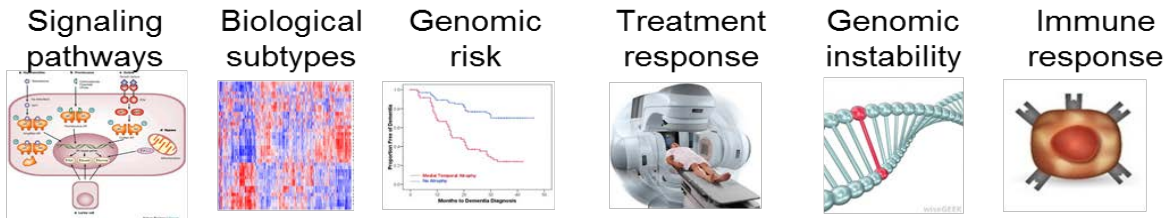
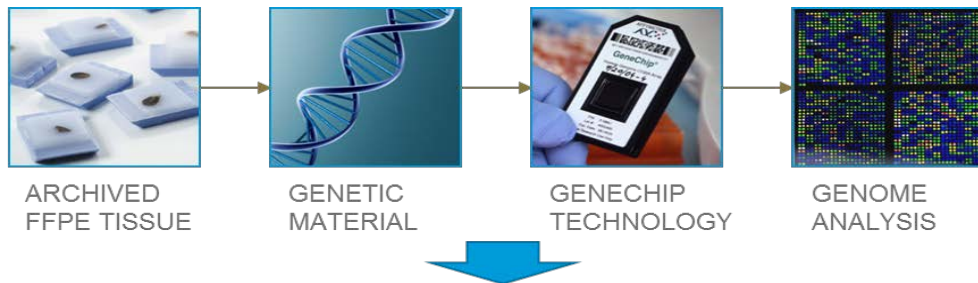
- Surgery
- Ablative therapies

## Biological

- Radiation
- Hormone deprivation
- Chemotherapy
- Immunotherapy

- Response to biology based therapeutics is highly dependent on the molecular make up of the tumor
- Genomics can guide therapeutic choices

# Generation of Clinical Grade Predictive Biomarkers on the Decipher Platform



- Expansive platform provides tremendous flexibility
  - Discovery of cancer biology
  - Development and refinement of prognostic signatures
  - Development of predictive signatures for treatment response

# Generation of Clinical Grade Predictive Biomarkers on the Decipher Platform

## Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis



*Shuang G Zhao\*, S Laura Chang\*, Daniel E Spratt, Nicholas Erho, Menggang Yu, Hussam Al-Deen Ashab, Mohammed Alshalalfa, Corey Speers, Scott A Tomlins, Elai Davicioni, Adam P Dicker, Peter R Carroll, Matthew R Cooperberg, Stephen J Freedland, R Jeffrey Karnes, Ashley E Ross, Edward M Schaeffer, Robert B Den, Paul L Nguyen†, Felix Y Feng†*

### Summary

**Background** Postoperative radiotherapy has an important role in the treatment of prostate cancer, but personalised patient selection could improve outcomes and spare unnecessary toxicity. We aimed to develop and validate a gene expression signature to predict which patients would benefit most from postoperative radiotherapy.

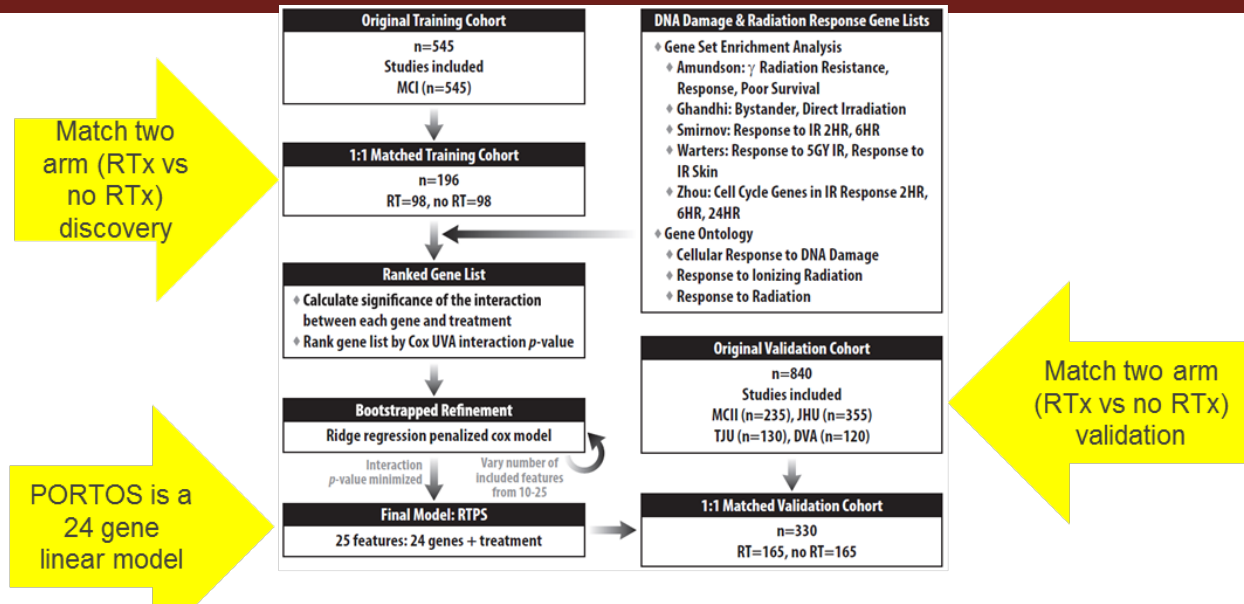
*Lancet Oncol* 2016

Published Online

October 12, 2016

<http://dx.doi.org/10.1016/>

# Development of a Radiation Response Signature (PORTOS)

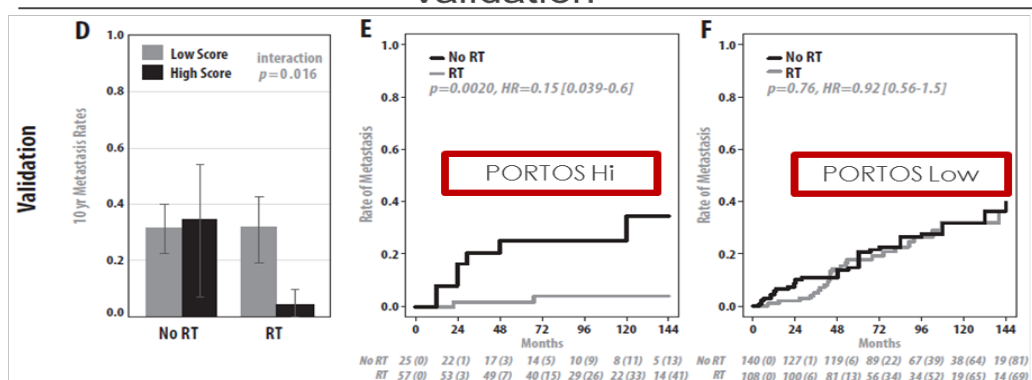


Study design flow diagram depicting the methodology used to create Post-Operative Radiation Therapy Outcomes Score (PORTOS)

# Development of a Radiation Response Signature (PORTOS)

## Patients with high PORTOS have lower rates of metastasis with post-operative radiation

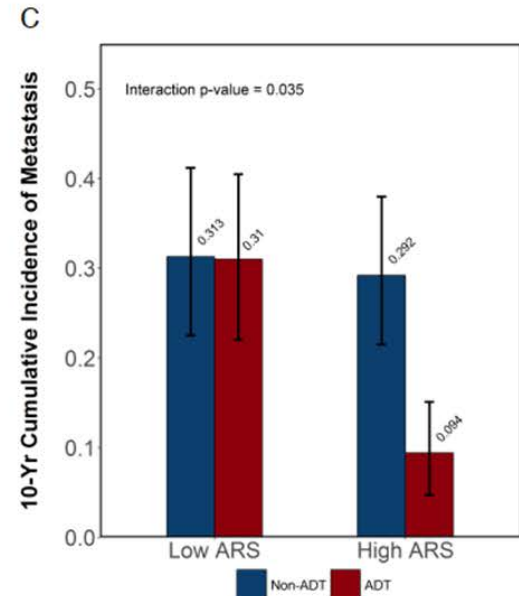
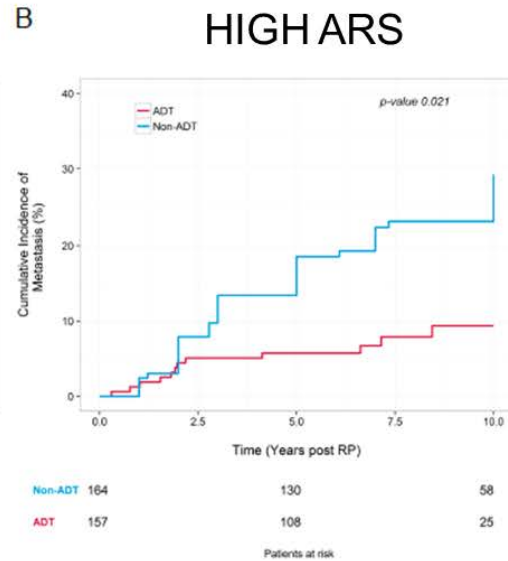
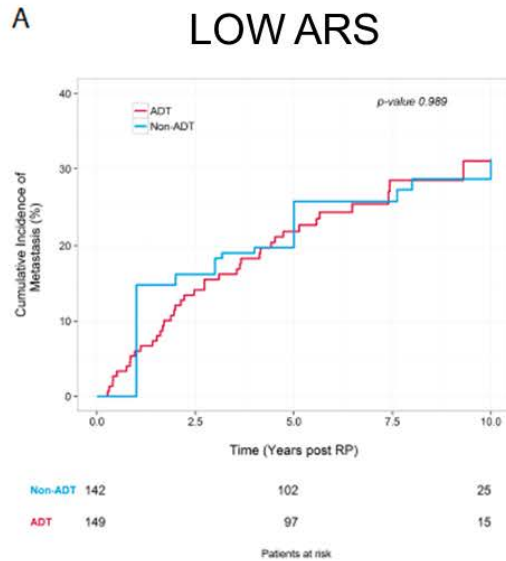
### Validation



High PORTOS Score (top quartile) = 7 fold better response to radiation after RP

PORTOS is NOT prognostic of metastasis in patients NOT treated by radiation

# Development of an Androgen Response Signature (Karnes et al in Review)



# Take Home Messages

- Biomarkers will greatly improve our understanding and treatment of prostate cancer
- Approximately 7% of Gleason Grade Group 1 tumors have molecular features of aggressive disease
  - These men have high GC, GPS or CCP scores
  - Patients with these tumors should approach active surveillance with caution
- Biomarkers can aid in treatment decisions for men in the primary, adjuvant and salvage settings
- Studies primarily utilizing the Decipher platform are beginning to develop predictive biomarkers (i.e. radiation sensitivity, androgen sensitivity)



**Thanks for Your Attention**