The importance of biology and genetics in prostate cancer (*localized*)

Daniel E. Spratt, MD
Associate Professor
Snow Professor and Vice Chair of Research, Department of Radiation Oncology
Chair, Genitourinary Division of Clinical Research, Rogel Cancer Center

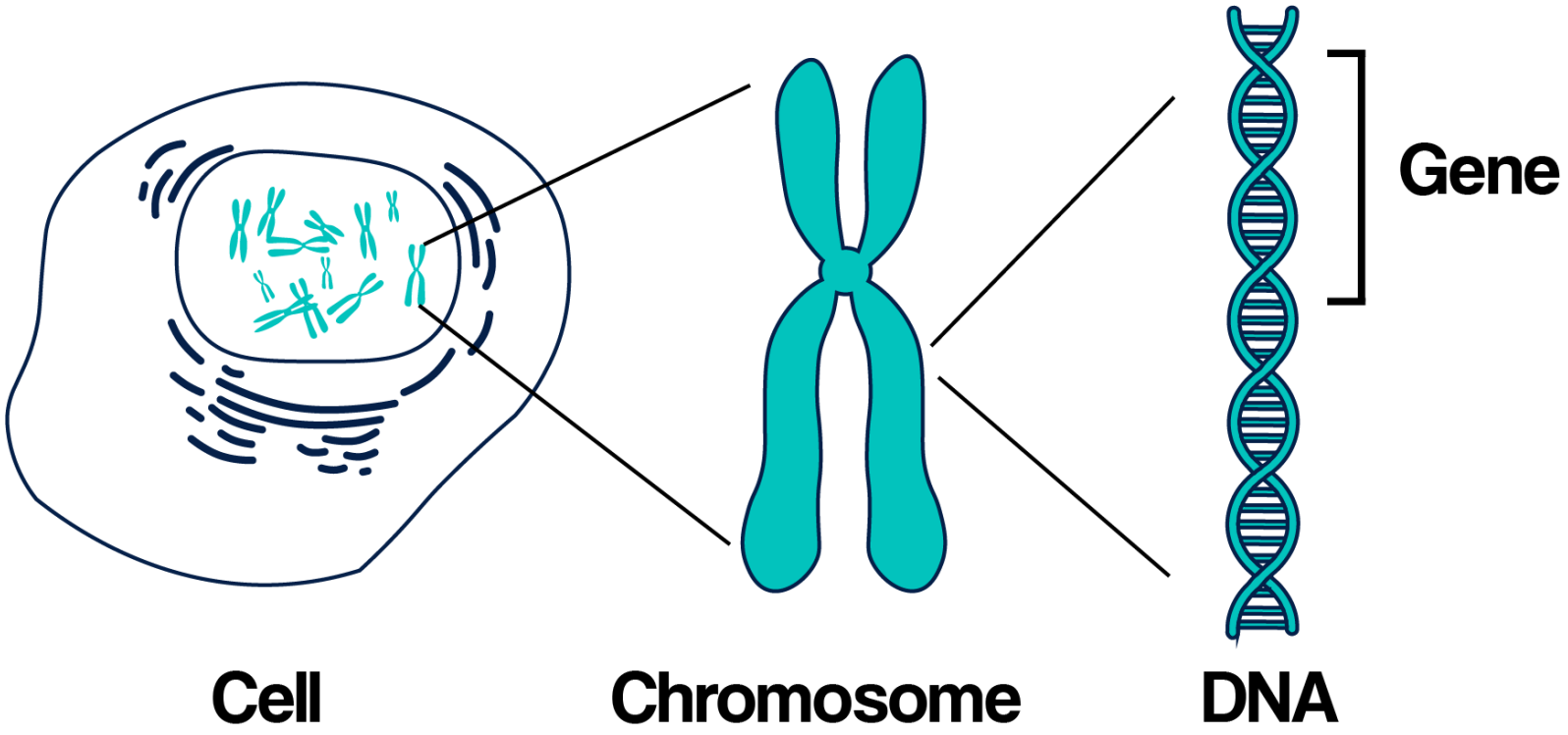
Conflicts of Interest:

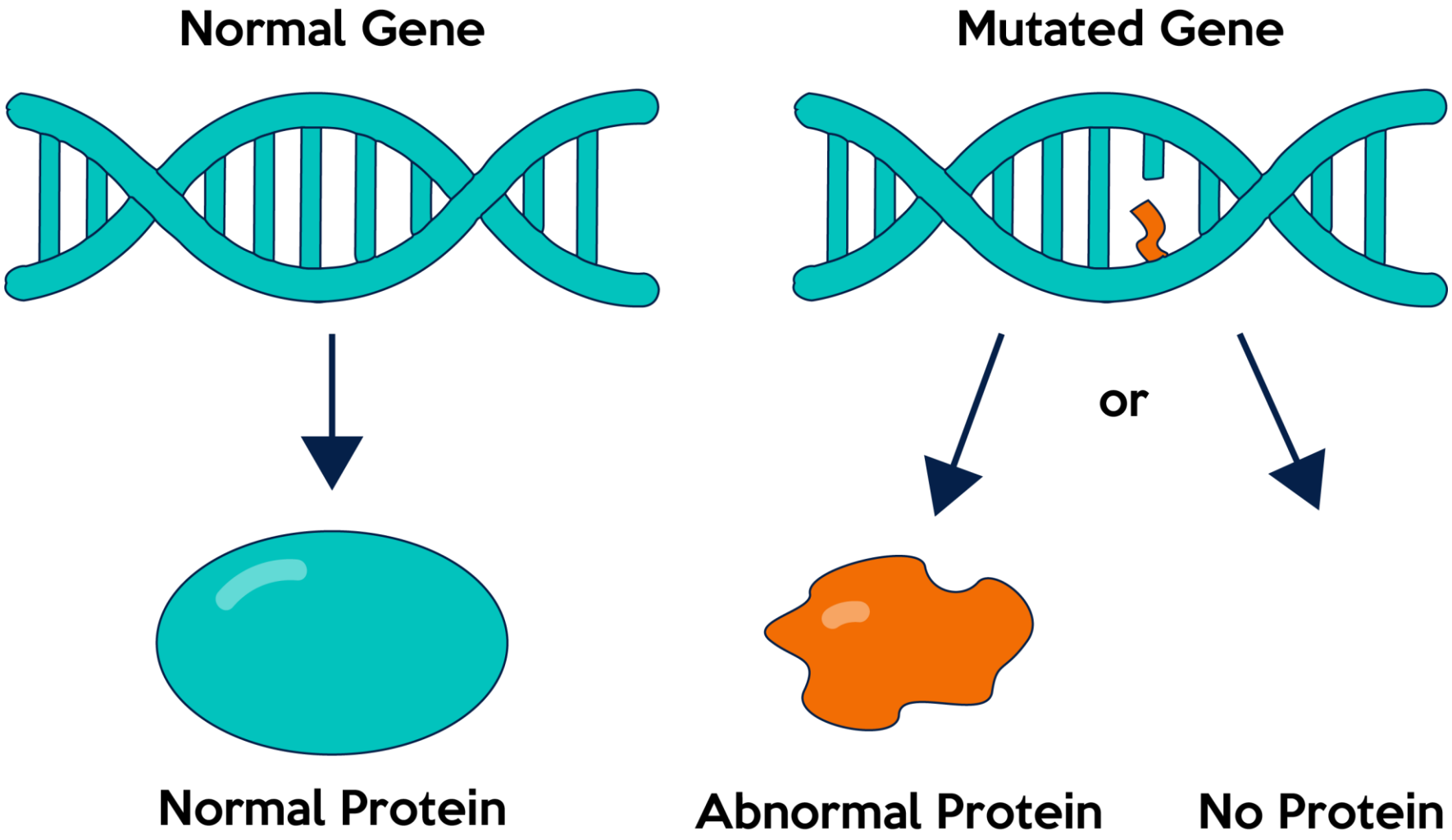
Advisory Board:
Janssen
Blue Earth

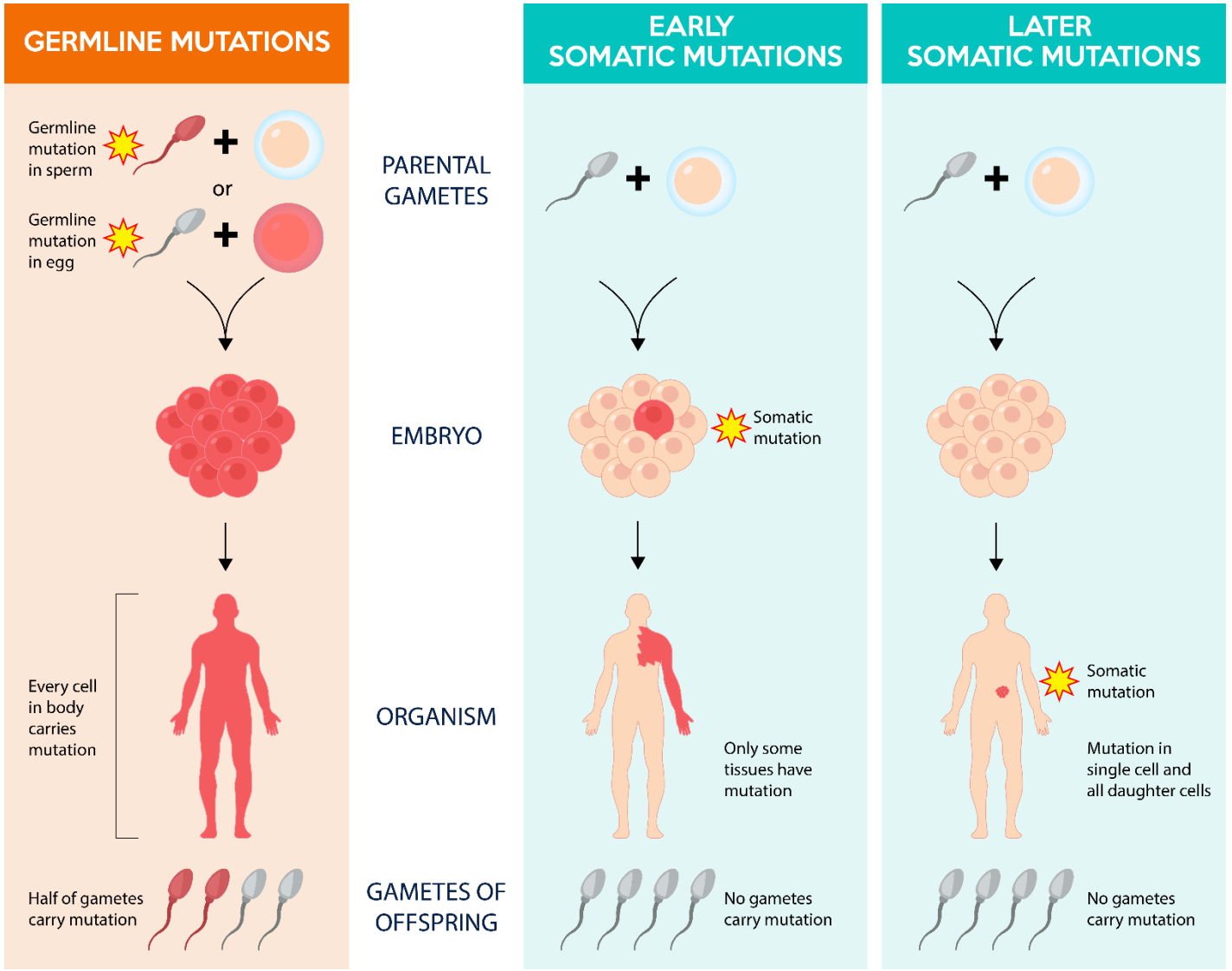
I intentionally refuse any payments from genomics companies

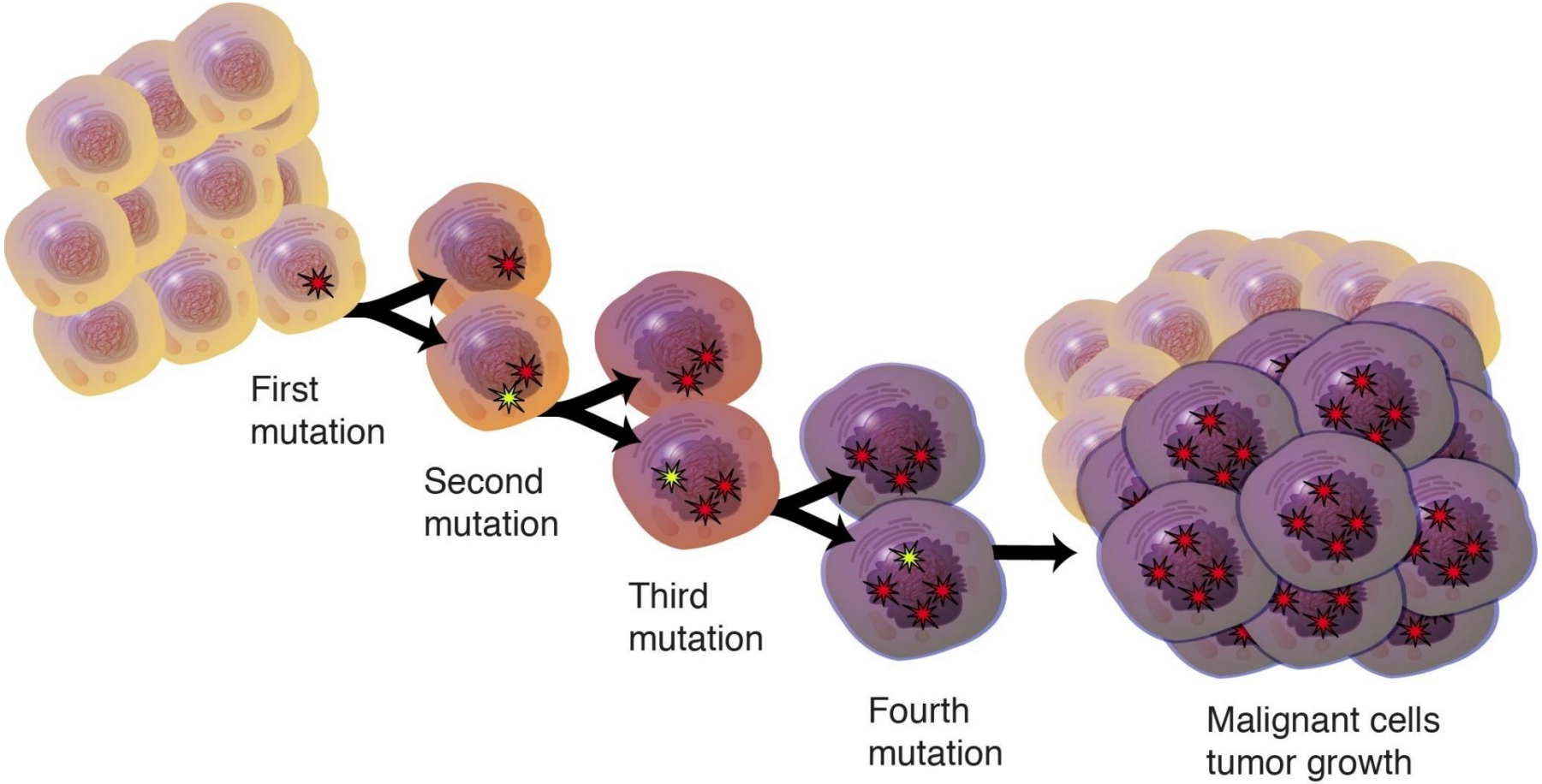
I unfortunately don't own any part of them either

I am the PI of NRG GU006 which uses apalutamide (Janssen) and runs the PAM50 test (GenomeDx)

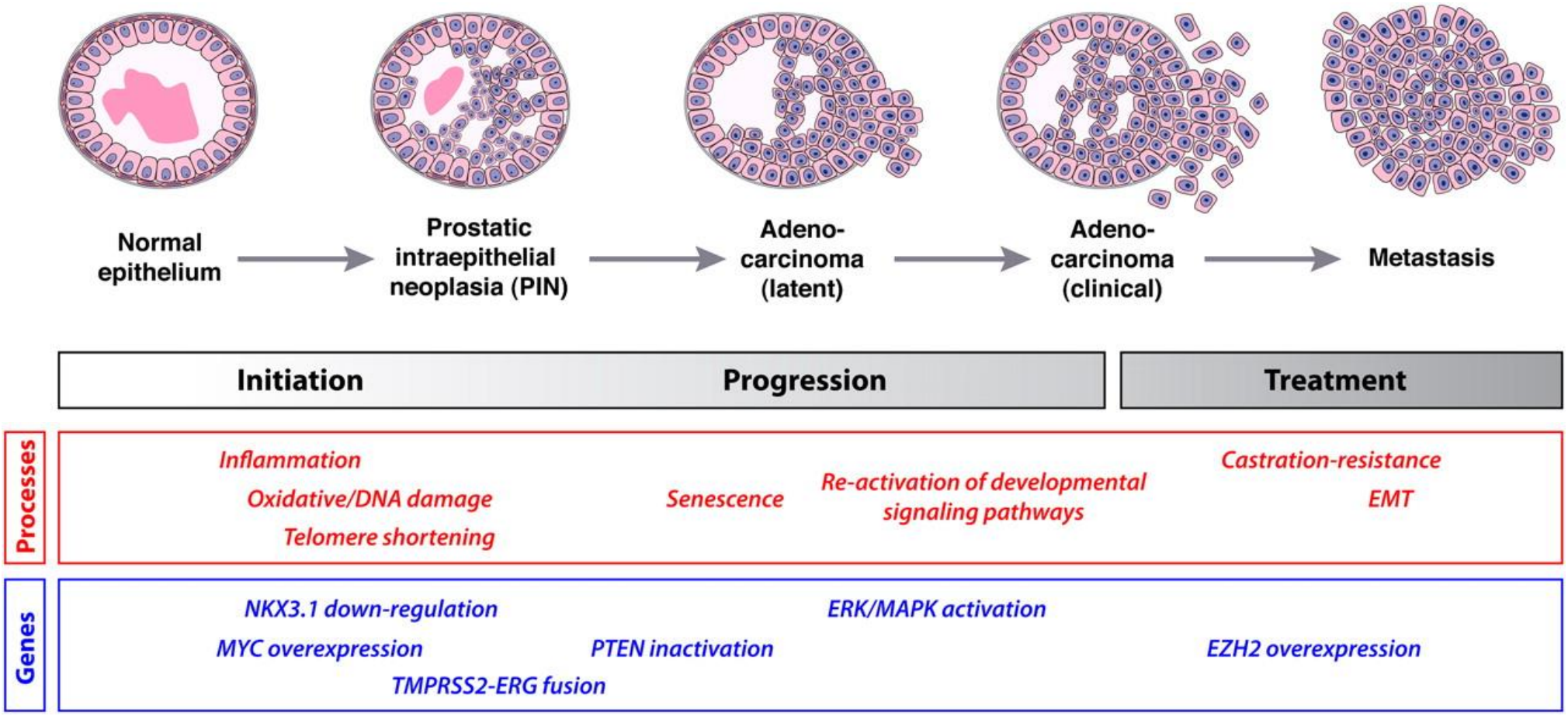

Gene
Cell
Chromosome
DNA


Normal Gene
Mutated Gene
or
Normal Protein
Abnormal Protein
No Protein

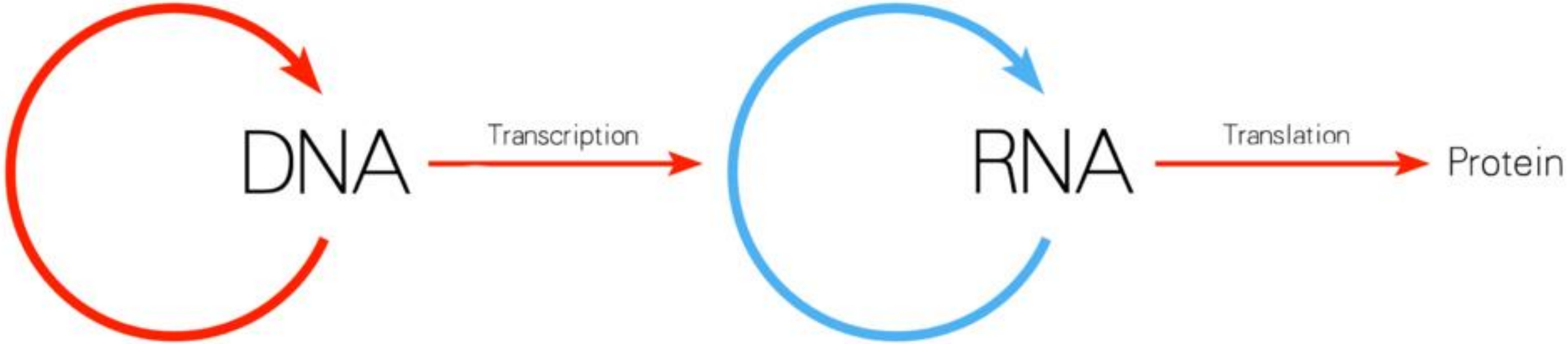

GERMLINE MUTATIONS
EARLY SOMATIC MUTATIONS
LATER SOMATIC MUTATIONS
Germline mutation in sperm
or
Germline mutation in egg
PARENTAL GAMETES
EMBRYO
Somatic mutation
Every cell in body carries mutation
ORGANISM
Only some tissues have mutation
Somatic mutation
Mutation in single cell and all daughter cells
Half of gametes carry mutation
GAMETES OF OFFSPRING
No gametes carry mutation
No gametes carry mutation

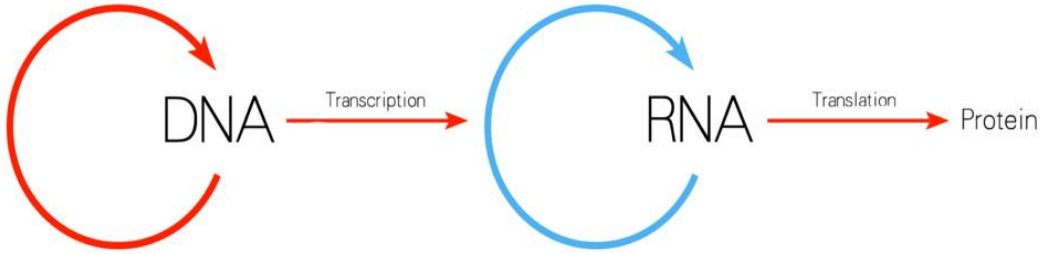

First mutation
Second mutation
Third mutation
Fourth mutation
Malignant cells tumor growth

Important Concepts in Oncology

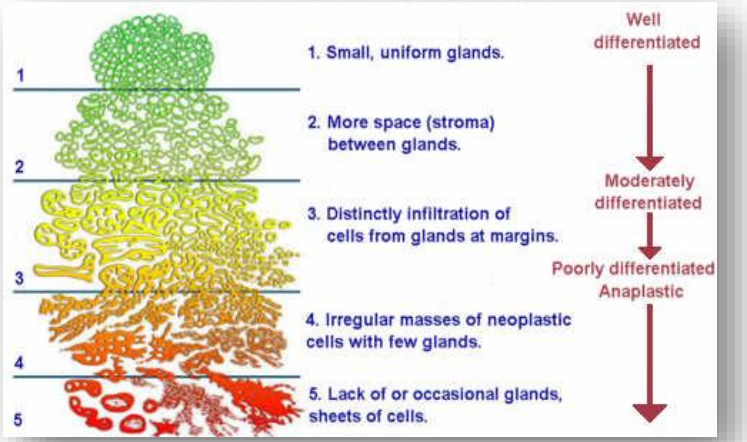


Abate C, Cell 2002

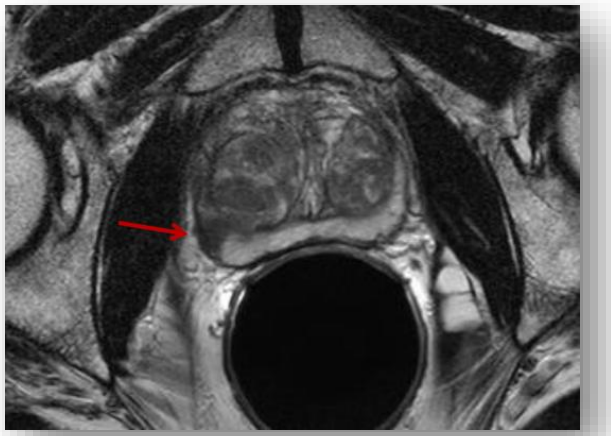

DNA
Transcription
RNA
Translation
Protein



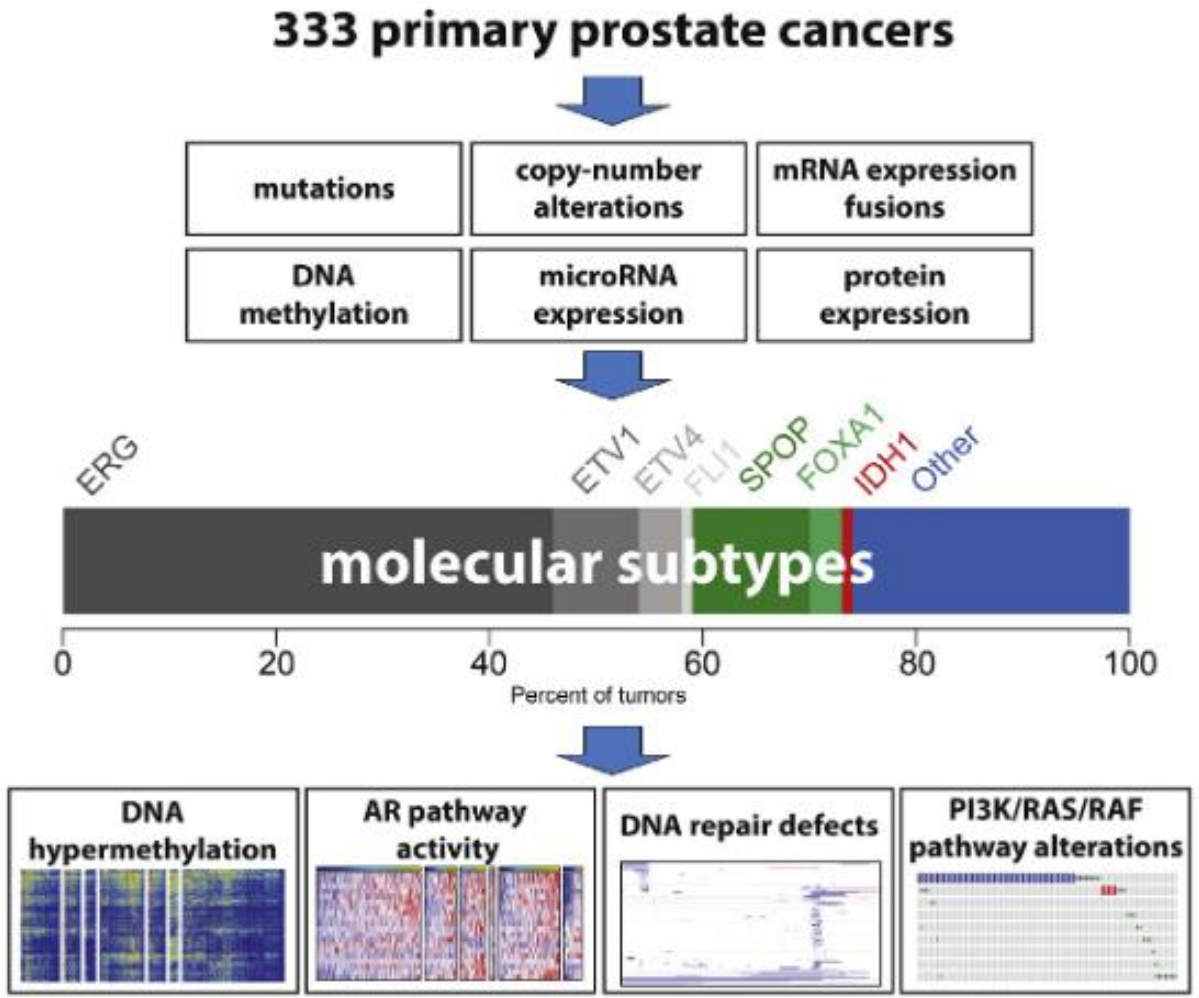
Histology
(Grade)



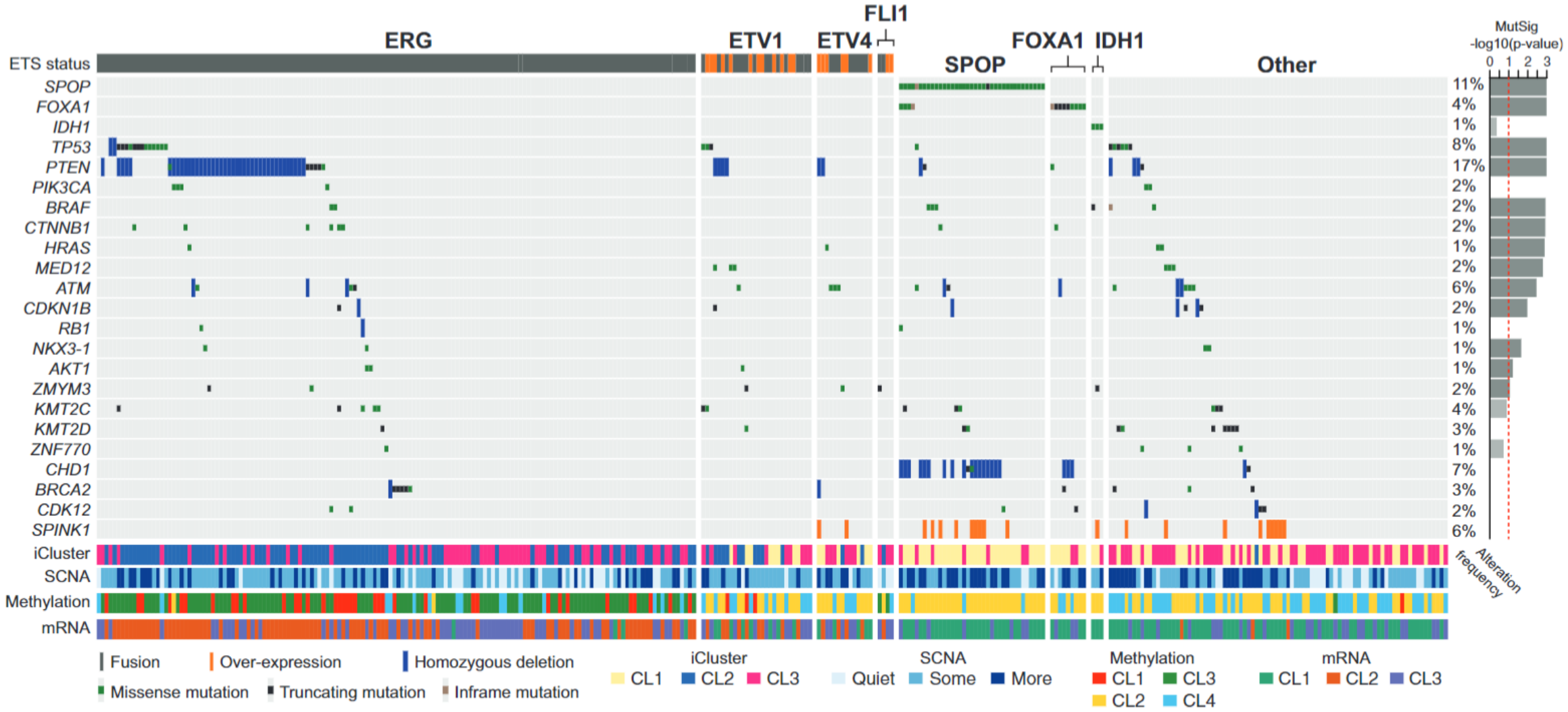
Radiology
(MRI)



DNA mutational landscape of localized prostate cancer



DNA mutational landscape of localized prostate cancer



Clinically relevant genomic alterations?

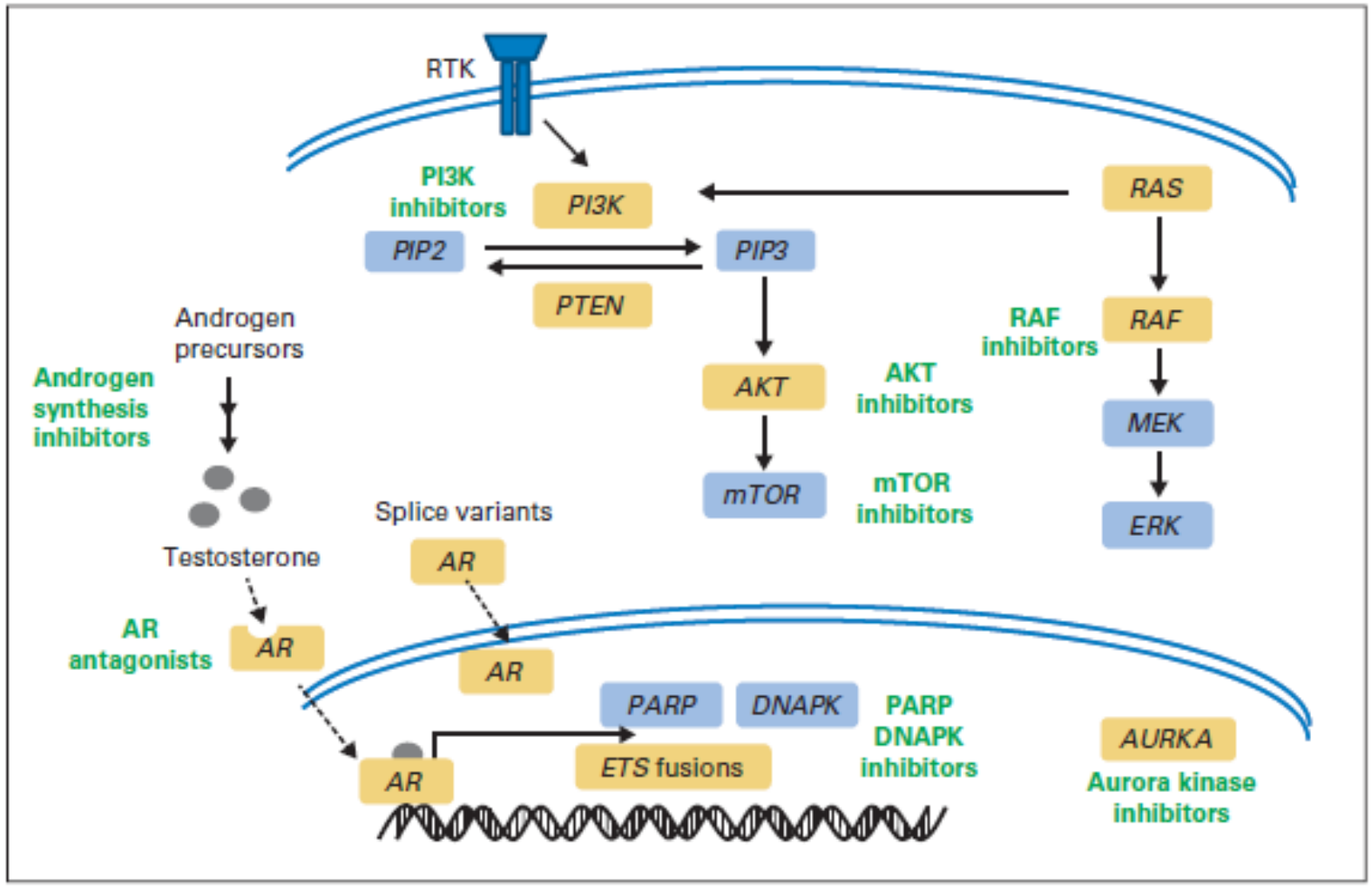
Table 1. Clinically Relevant Genomic Alterations in Prostate Cancer

Gene	Alteration Type	Frequency (%)	Potential Treatment Hypotheses
ETS transcription factors	Rearrangement	50[7]	Indirect targeting of *ETS* gene fusions through *PARP* or *DNAPK* inhibitors[8]
Androgen receptor	Mutation	50[9,10]	Androgen synthesis inhibitors, next-generation androgen receptor antagonists
	Amplification	50[9,10]	
PTEN	Loss	50[9]	PI3K pathway inhibitors[11]
RB1	Loss	25 to 60[9]	Role in disease progression and castrate resistance[12] with potential for targeting
PIK3CA	Amplification	10[10]	PI3K pathway inhibitors[11]
	Mutation	5[10]	
MYC	Amplification	9[9]	Potential for targeting[13]
		40[10]	Neuroendocrine prostate cancer
AURKA	Amplification	5[10]	Aurora kinase inhibitors[14]; co-occurs with *MYC* in 40% of neuroendocrine prostate cancers
AKT	Mutation	1 to 2[15]	AKT inhibitors
RAF	Rearrangement	1 to 2[16]	RAF inhibitors
	Mutation		
KRAS	Mutation	1[9,17,18]	RAF, MEK, or PI3K inhibitors
	Rearrangement		

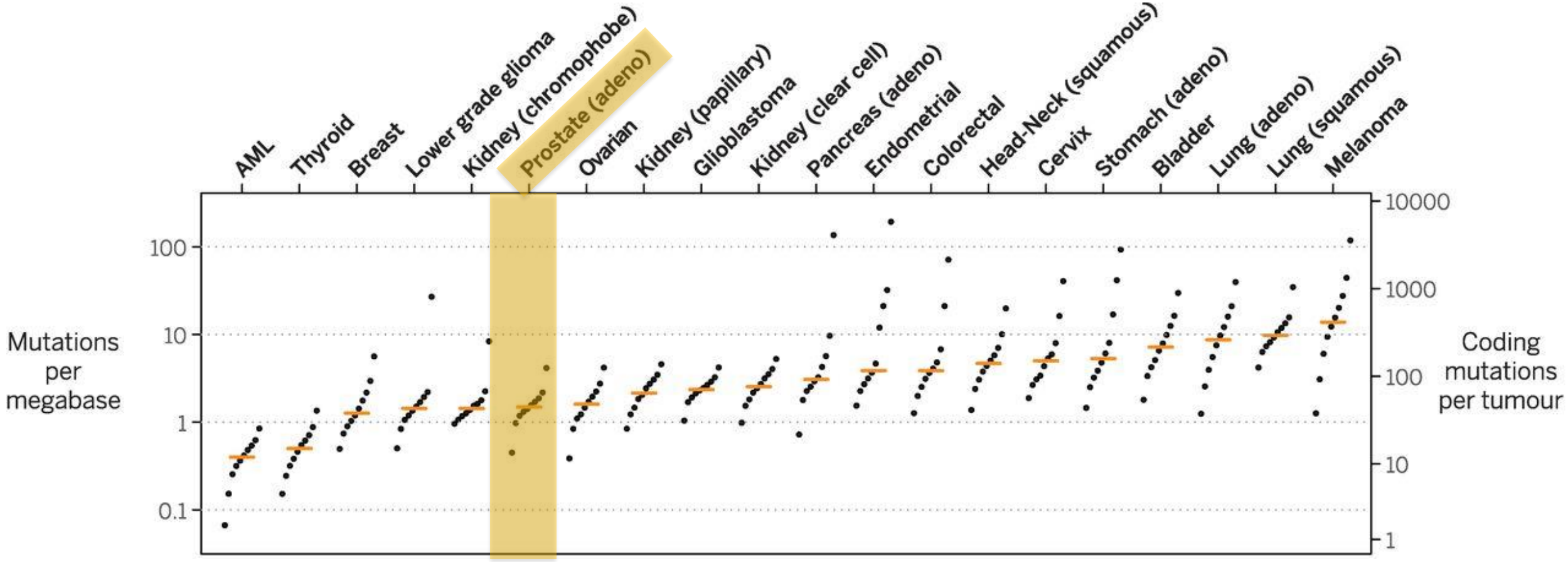
NOTE. Summarizes alterations in prostate cancer that have a treatment hypothesis currently being explored preclinically or in clinical trials. The most common alterations with a treatment hypothesis involve *ETS* rearrangements, androgen receptor, and *PTEN* loss. With only a limited number of samples assessed, a majority of these alterations are not necessarily mutually exclusive.

Abbreviation: PI3K, phosphatidylinositide 3-kinase.

DNA mutations more important in mCRPC



Prostate cancer was low mutational frequency



Is tumor DNA testing clinically ready in localized prostate cancer?

-Many patients wont have a mutation
-Those that do have unclear clinical relevance TODAY in localized prostate cancer (eg ERG, SPINK, SPOP, PTEN)

Somatic DNA testing	Answer	Example
Are the frequency of mutations established?	YES	TCGA
Retrospective data?	YES	MSK IMPACT
Prospective clinical utility data (change management)?	**NO**	
Prospective clinical benefit data (improve outcomes)?	**NO**	
Randomized data?	**NO**	
NCCN Recommended?	**NO**	

PARP inhibitors are starting to enter into localized prostate cancer trials, and somatic testing may prove beneficial

What about **Germline** DNA testing for localized prostate cancer?

Gene	Positive Variants per Requisition, %[a]
BRCA2	4.74
CHEK2	2.88
ATM	2.03
MUTYH	2.37
BRCA1	1.25
HOXB13	1.12
APC	1.28
MSH2	0.69
TP53	0.66
PALB2	0.56
PMS2	0.54
MSH6	0.45
NBN	0.32
RAD50	0.32
BRIP1	0.28
RAD51C	0.21
RAD51D	0.15
CDKN2A	0.13
CDH1	0.12
NF1	0.09
MLH1	0.06

JAMA Oncology | Original Investigation

Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines

tations. In patients with Gleason scores of 6 or lower for a primary tumor (n = 148), positive germline variants were found in 15.1% compared with 16.3% in those with Gleason scores of 7 or higher (n = 1391).

Risk of death from prostate cancer with Gleason 6 with 15-year follow-up = 1%

-15% have them germline variants…yet every single active surveillance series shows phenomenal outcomes
-Immensely questions any clinical relevance
-Will drive up costs substantially

Germline DNA testing	Answer	Example
Are the frequency of mutations established?	**NO**	All cohorts highly selected
Retrospective data?	YES	Invitae data (JAMA Onc 2019)
Prospective clinical utility data (change management)?	**NO**	
Prospective clinical benefit data (improve outcomes)?	**NO**	
Randomized data?	**NO**	
NCCN recommended?	YES	“Consider” or “Recommend”

Guidelines have supported this move without almost any evidence it is clinically relevant

- 11 types of RNA (e.g. mRNA, rRNA, tRNA, snRNA, snoRNA, siRNA, hnRNA, gRNA, tmRNA, telomerase RNA, catalytic RNA)

- Most relevant today clinically is messenger RNA or **mRNA**
  - This represents the gene expression of a cell or tumor

- Other potentially relevant types of RNA that have more recent evidence are long non-coding RNAs or **lncRNAs**
  - Associated with tumor aggressiveness

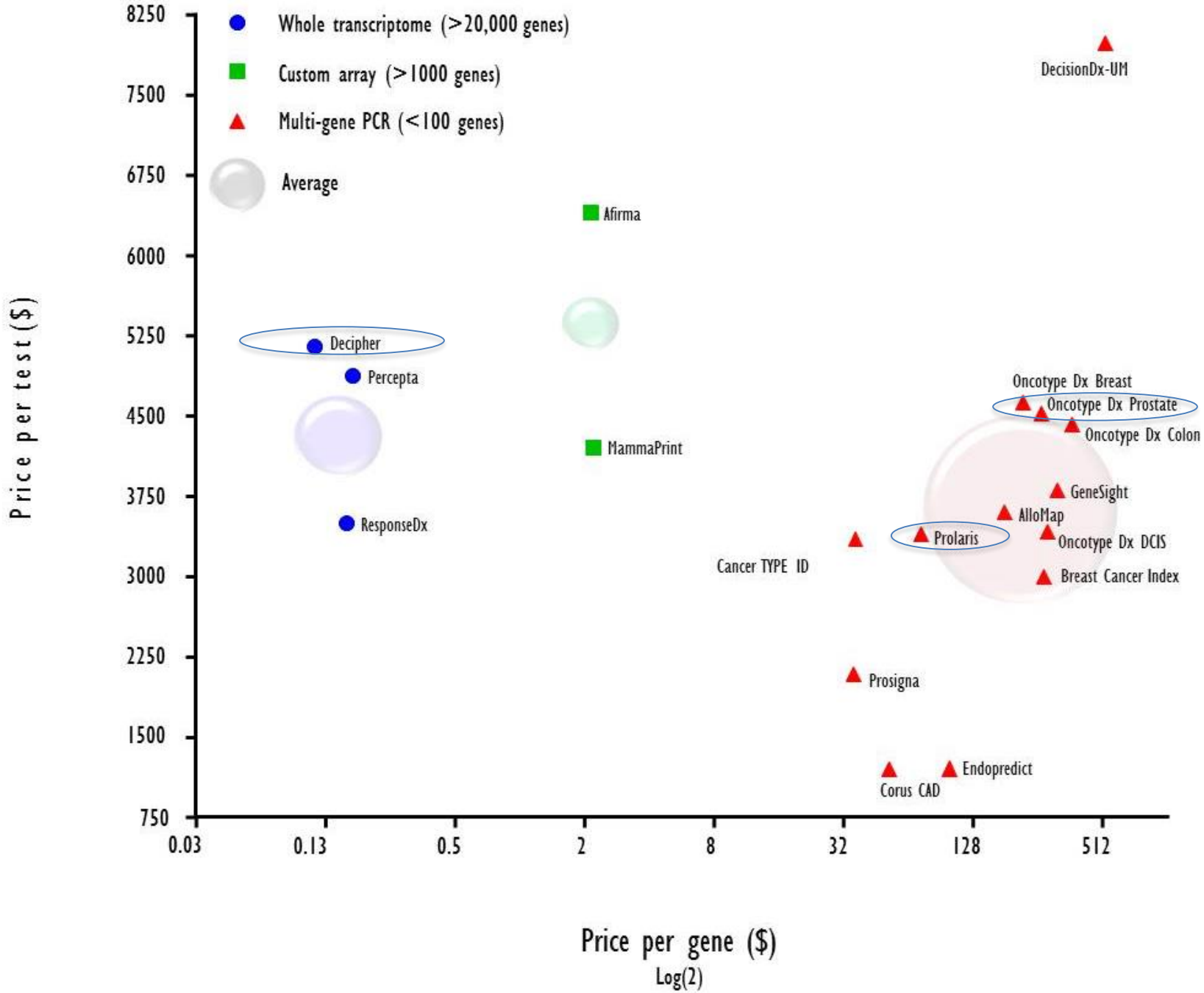
Methods to quantify RNA

- Three common methods:
  - PCR
  - Micro-arrays
  - RNAseq

Nearly every commercial test

Primarily used for research

	Microarray	RNA-seq
Principle	Hybridization	High-throughput sequencing
Thoughput	High	High
Background noise	Higher	Lower
Dynamic range	~100-fold	>8,000-fold
Distinguish different isoforms	Limited	Easier
Cost (perform, store, and analyze data)	Lower	Higher
RNA content required	Higher	Lower
Heterogeneity of read coverage across expressed region	Yes	No
Analysis simplicity	Simple	Complex
Data portability (size of data)	Megabites	Gigabites


Whole transcriptome (>20,000 genes)
Custom array (>1000 genes)
Multi-gene PCR (<100 genes)
Average
Price per test ($)
8250
7500
6750
6000
5250
4500
3750
3000
2250
1500
750
0.03
0.13
0.5
2
8
32
128
512
Price per gene ($)
Log(2)
DecisionDx-UM
Afirma
Decipher
Percepta
MammaPrint
ResponseDx
Oncotype Dx Breast
Oncotype Dx Prostate
Oncotype Dx Colon
GeneSight
AlloMap
Prolaris
Oncotype Dx DCIS
Cancer TYPE ID
Breast Cancer Index
Prosigna
Endopredict
Corus CAD

Utility of RNA biomarkers

- **Prognostic**
- **Predictive**
- **Diagnostic (*rarely*)**
  (usually are DNA or protein-based)

Utility of RNA biomarkers

- **Prognostic-** determines prognosis regardless of treatment
- **Predictive-** determines prognosis specific to a treatment

Routine Clinical and Pathologic Biomarkers	Prognostic Biomarker
Baseline PSA	✓
T-stage	✓
Gleason score (Grade Group)	✓
Percent Positive Biopsy Cores	✓

	Use of Radical Treatment	Dose escalation	Addition of ADT to RT	Addition of Abiraterone
Example	PIVOT	MDACC Trial	RTOG 9408	STAMPEDE
Outcome	OS	BCR	OS	OS
Low	HR all >1	HR all <1	HR all >1	
Int				
High				
N+				HR all >1
M1				

How good are we at determining prognosis without genomics?

C-index for Biochemical Recurrence

Coin Flip:	0.5
PSA:	0.5-0.6
cT-stage:	0.5-0.6
Gleason:	0.6-0.7

C-index for BCR

Gleason grade categorization	Univariate
≤6 vs 7 vs ≥8	0.662
≤6 vs 3 + 4 vs 4 + 3 vs ≥8	0.684
≤6 vs 7 vs 8 vs ≥9	0.666
≤6 vs 3 + 4 vs 4 + 3 vs 8 vs ≥9	0.687

Epstein, Zelefsky et al, Euro Urol 2016

NCCN or CAPRA- have C-index of ~0.65 for predicting the development of metastatic disease

Not great.

Gene expression tests aim to improve this- TONS of prognostic biomarkers

3 have undergone clinical validation

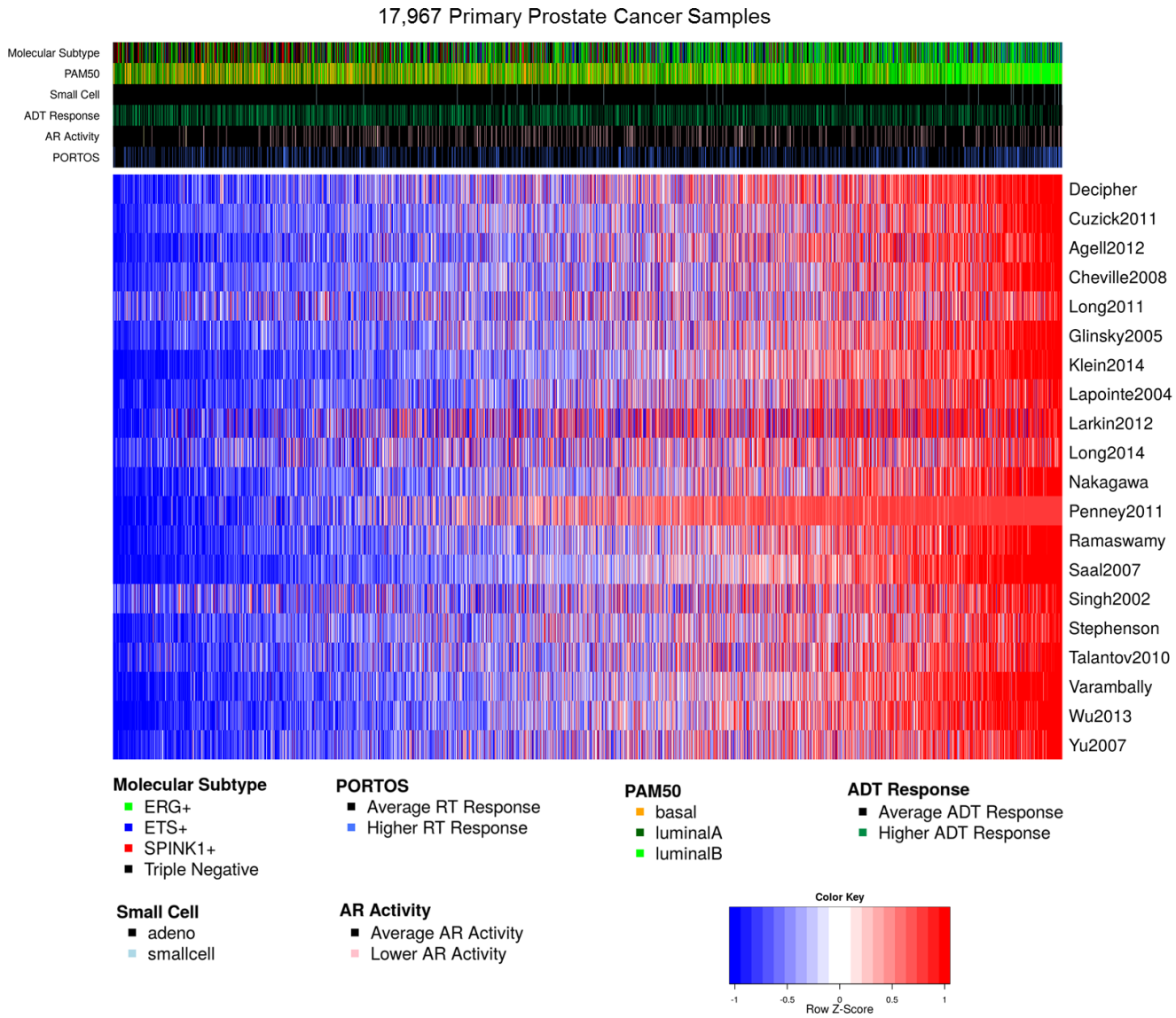
- Decipher
- Prolaris
- Oncotype Dx

Signature	Original Technology*	Number of Features
Erho 2013	Microarray	22
Penney 2011	Microarray	157
Wu 2013	RT-qPCR	30
Bibikova 2007	Microarray	16
Xie 2011	Microarray	71
Ramaswamy 2003	Microarray	17
Agell 2012	Microarray	12
LaPointe 2004	Microarray	22
Nakagawa 2008	Microarray	17
Bismar 2006	Microarray	13
Cheville 2008	Microarray	2
Cuzick 2011	RT-qPCR	31
Yu 2007	Microarray	87
Larkin 2012	RT-qPCR	3
Singh 2002	Microarray	12
Klein 2014	RT-qPCR	17
Larkin 2012	RT-qPCR	10
Saal 2007	Microarray	185
D. Antonio 2008	RT-qPCR	59
Glinsky 2005	Microarray	11
Varambally 2005	Microarray	50
Long 2011	Microarray	12
Stephenson 2005	Microarray	15
Talantov 2010	RT-qPCR	24
Yu 2007	Microarray	14
Roca 2012	Microarray	10
Glinsky 2004	Microarray	5
Stephenson 2005	Microarray	10
Ross 2012	RT-qPCR	6
Glinsky 2004	Microarray	5
Glinsky 2004	Microarray	4
Irshad 2013	Microarray	3
Olmos 2012	Microarray	9

Many perform well to predict the development of metastatic disease

Signature	C-index (95% CI)
Erho 2013 (Decipher)	0.76 (0.65-0.86)
Penney 2011	0.74 (0.64-0.83)
Wu 2013	0.69 (0.61-0.76)
Bibikova 2007	0.68 (0.6-0.77)
Xie 2011	0.68 (0.59-0.75)
Ramaswamy 2003	0.68 (0.6-0.75)
Agell 2012	0.66 (0.58-0.73)
LaPointe 2004	0.64 (0.56-0.72)
Nakagawa 2008	0.64 (0.57-0.72)
Bismar 2006	0.64 (0.56-0.73)
Cheville 2008	0.64 (0.56-0.72)
Cuzick 2011 (Prolaris)	0.63 (0.51-0.74)
Yu 2007	0.63 (0.55-0.69)
Larkin 2012	0.62 (0.56-0.7)
Singh 2002	0.62 (0.54-0.7)
Klein 2014 (Oncotype)	0.62 (0.51-0.74)

RNA captures the immense heterogeneity of localized prostate cancer



Decipher has the strongest data and most relevant to radiation oncology- will be discussed further

Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	83,195,570,625-637	Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Post RP, adjuvant, or salvage radiation	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Biopsy, localized prostate cancer post RP or EBRT	• Metastasis • Prostate cancer-specific mortality • Gleason grade ≥4 disease at RP		
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Gleason grade 4 disease on RP	82,642,643	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	• Prostate cancer-specific mortality	78-81,644-646	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis		
		Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence		
		RP, node-negative localized prostate cancer	• Biochemical recurrence		

Discussion update in progress

Decipher has the strongest data and most relevant to radiation oncology- will be discussed further

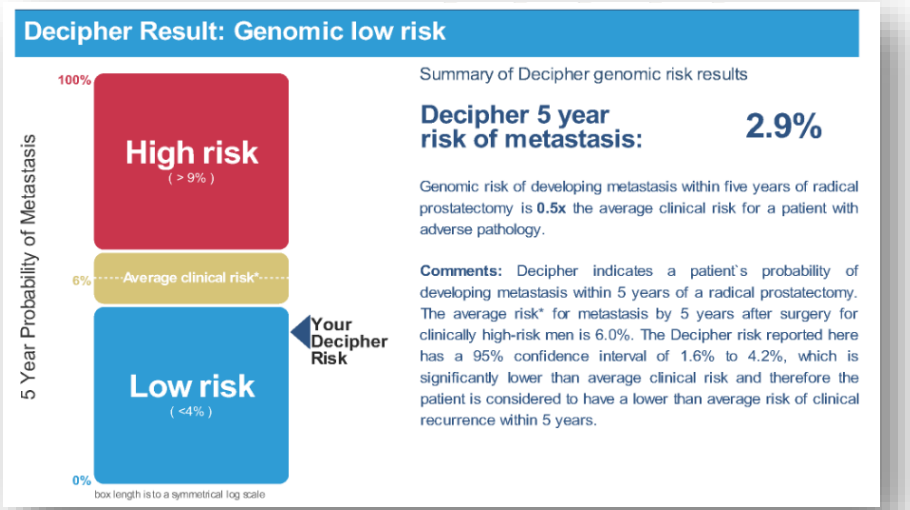
More than 70,000 patient profiles in database

Biomarker for seven prospective Clinical Trials in progress

Broadly Published

Over 130 peer-reviewed publications

Decipher



- The Decipher score is comprised to 22 genes
  - -Scale is 0-1
  - -Also reports score as low/average/high risk

- Also measures 46,000 other coding and non-coding genes

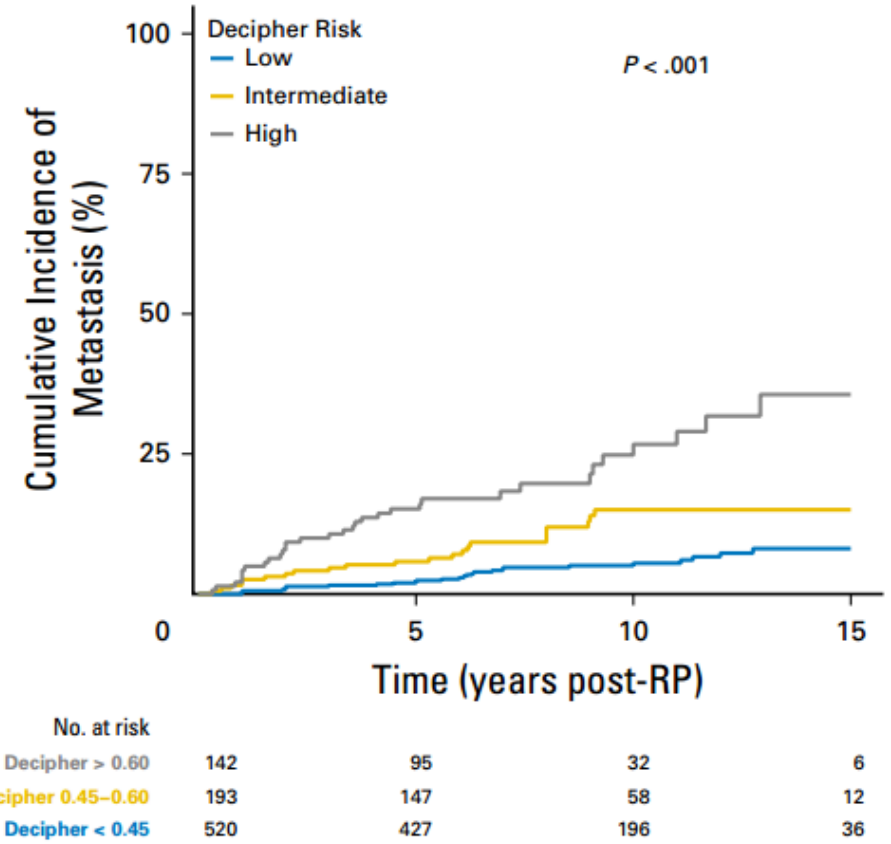
Meta-analysis of ~1000 patients

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

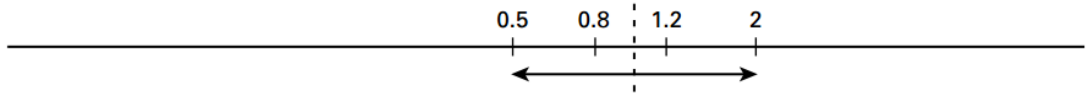
Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease

Spratt DE, JCO 2017

Decipher independently predicts mets across all subgroups

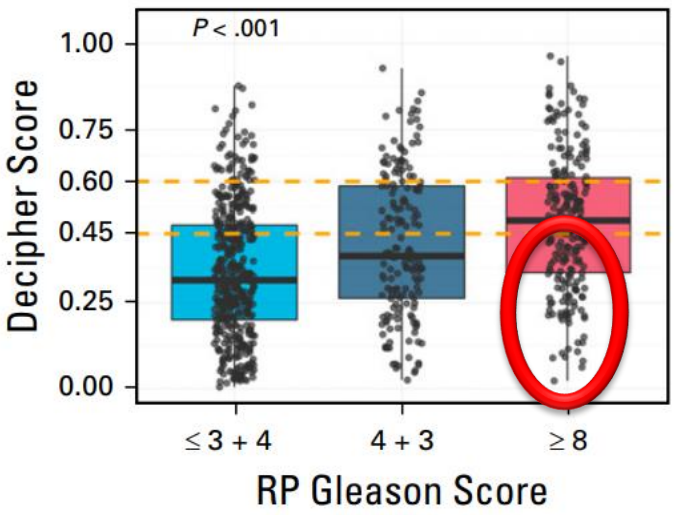


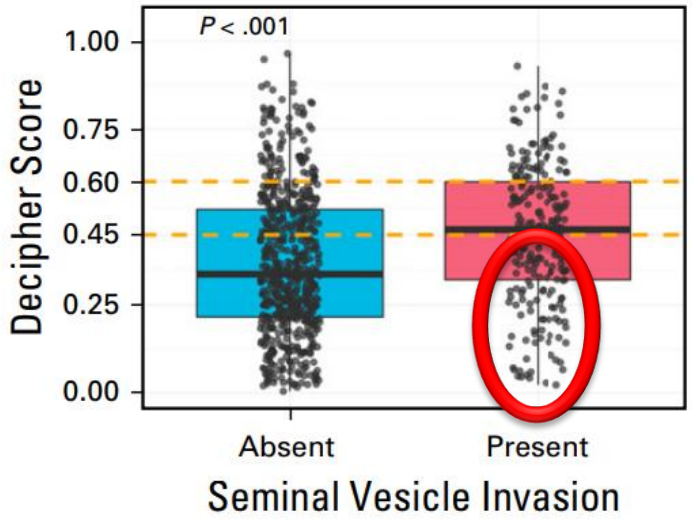
Subgroup	No. of Patients	Hazard Ratio (95% CI)	P
Race			
White	730	1.46 (1.3 to 1.64)	< .001
Black	106	1.43 (0.95 to 2.15)	.087
Preoperative PSA (ng/mL)			
< 5	457	1.91 (1.29 to 2.85)	.001
5-10	277	1.42 (1.19 to 1.7)	< .001
> 10	457	1.47 (1.25 to 1.72)	< .001
RP Gleason score			
≤ 3 + 4	459	1.43 (1.1 to 1.85)	.007
4 + 3	171	1.46 (1.15 to 1.86)	.002
≥ 8	222	1.24 (1.06 to 1.45)	.008
Surgical margins			
Negative	356	1.45 (1.21 to 1.73)	< .001
Positive	499	1.44 (1.25 to 1.66)	< .001
Extraprostatic extension			
Absent	492	1.44 (1.16 to 1.78)	.001
Present	359	1.42 (1.24 to 1.63)	< .001
Seminal vesincle invasion			
Absent	614	1.48 (1.27 to 1.72)	< .001
Present	238	1.37 (1.15 to 1.64)	.001
Lymph node invasion			
Negative	805	1.45 (1.28 to 1.64)	< .001
Positive	49	1.36 (1.06 to 1.76)	.016
Treatment modality			
Prostatectomy alone	421	1.47 (1.24 to 1.73)	< .001
Adjuvant RT	140	1.86 (0.92 to 3.76)	.085
Salvage RT	213	1.44 (1.19 to 1.74)	< .001
Adjuvant ADT	44	1.52 (0.97 to 2.39)	.068
Salvage ADT	116	1.27 (1.02 to 1.59)	.035
ADT	160	1.33 (1.11 to 1.61)	.002



Spratt DE, JCO 2017

Genomic Classifiers Can Help Personalize Risk





Spratt DE, JCO 2017

Making these tests more clinically “useable”

VOLUME 36 · NUMBER 6 · FEBRUARY 20, 2018

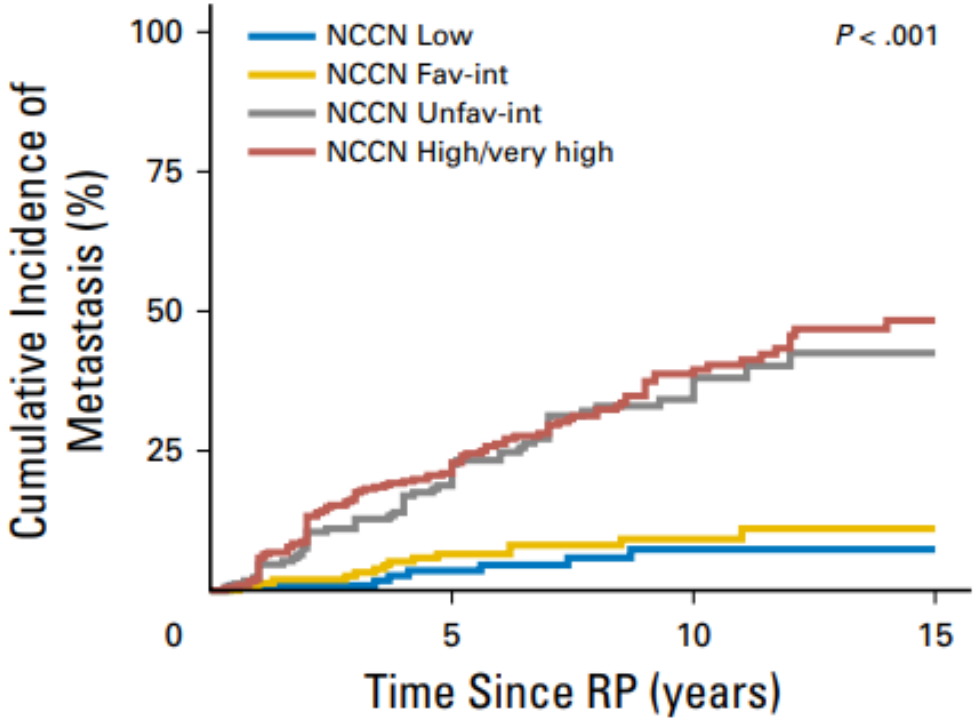
JOURNAL OF CLINICAL ONCOLOGY

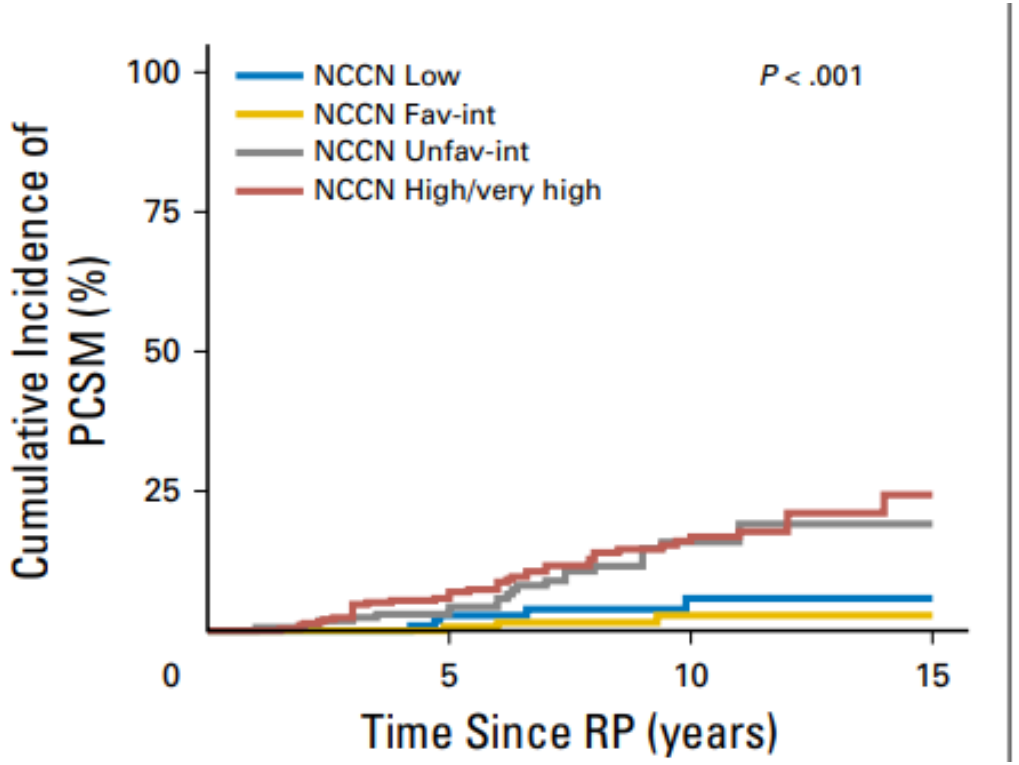
ORIGINAL REPORT

Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer

Daniel E. Spratt, Jingbin Zhang, María Santiago-Jiménez, Robert T. Dess, John W. Davis, Robert B. Den, Adam P. Dicker, Christopher J. Kane, Alan Pollack, Radka Stoyanova, Firas Abdollah, Ashley E. Ross, Adam Cole, Edward Uchio, Josh M. Randall, Hao Nguyen, Shuang G. Zhao, Rohit Mehra, Andrew G. Glass, Lucia L.C. Lam, Jijumon Chelliserry, Marguerite du Plessis, Voleak Choeurng, Maria Aranes, Tyler Kolisnik, Jennifer Margrave, Jason Alter, Jennifer Jordan, Christine Buerki, Kasra Yousefi, Zaid Haddad, Elai Davicioni, Edouard J. Trabulsi, Stacy Loeb, Ashutosh Tewari, Peter R. Carroll, Sheila Weinmann, Edward M. Schaeffer, Eric A. Klein, R. Jeffrey Karnes, Felix Y. Feng, and Paul L. Nguyen

NCCN risk groups DON'T accurately prognosticate patients

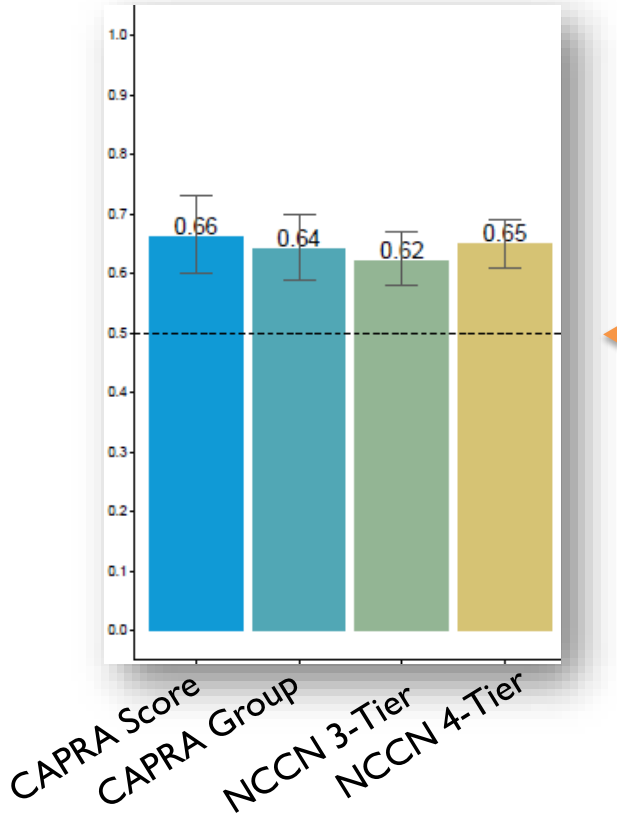




Spratt DE, JCO 2018

NCCN risk groups DON'T accurately prognosticate patients

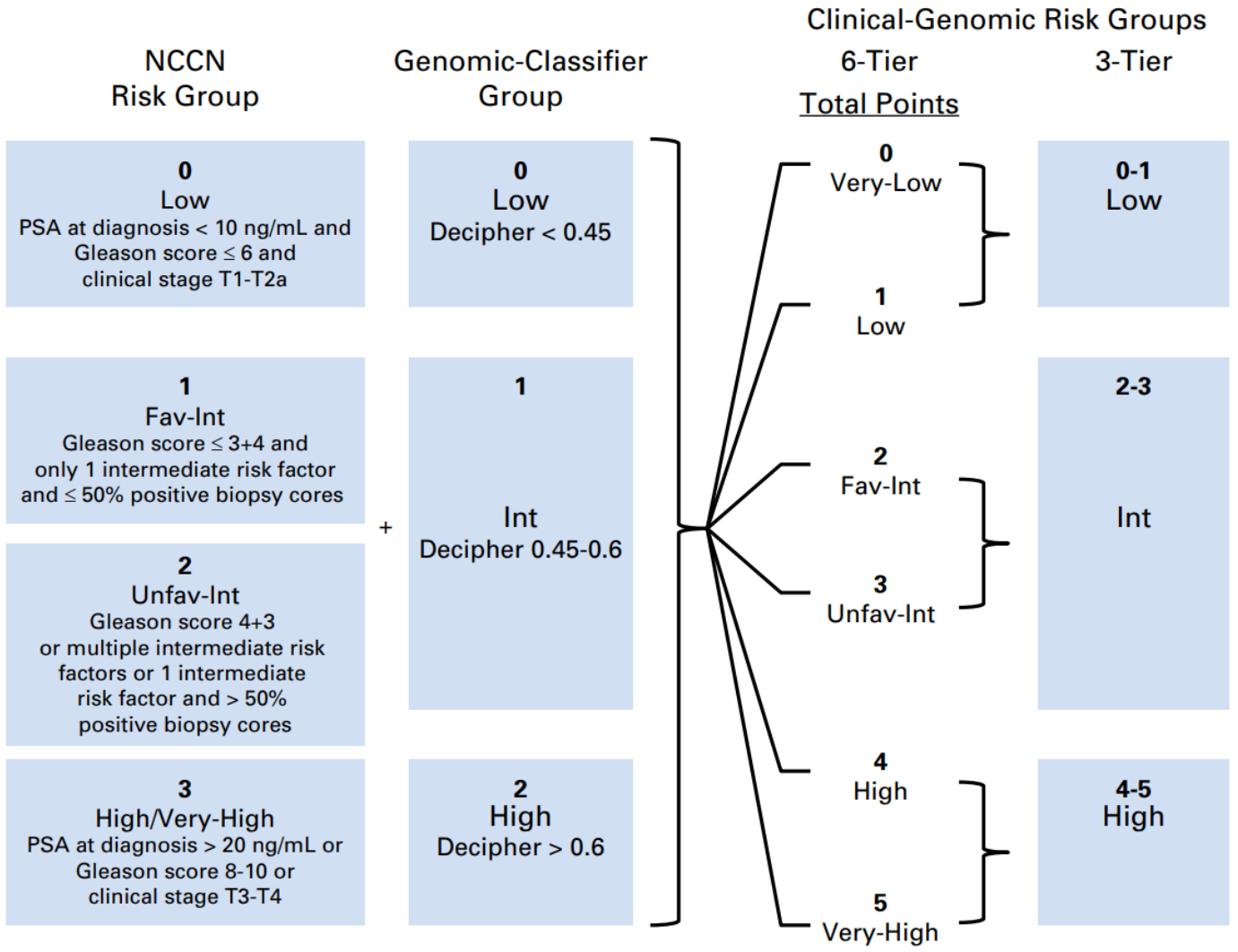
C-index for Metastasis



Coin flip

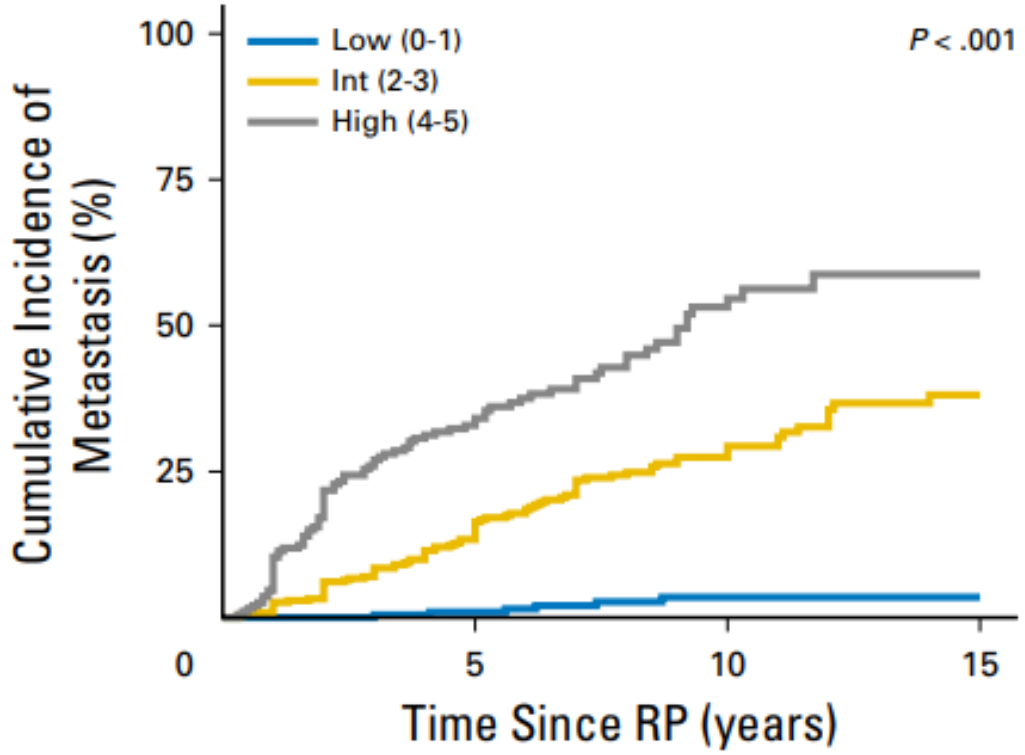
Spratt DE, JCO 2018

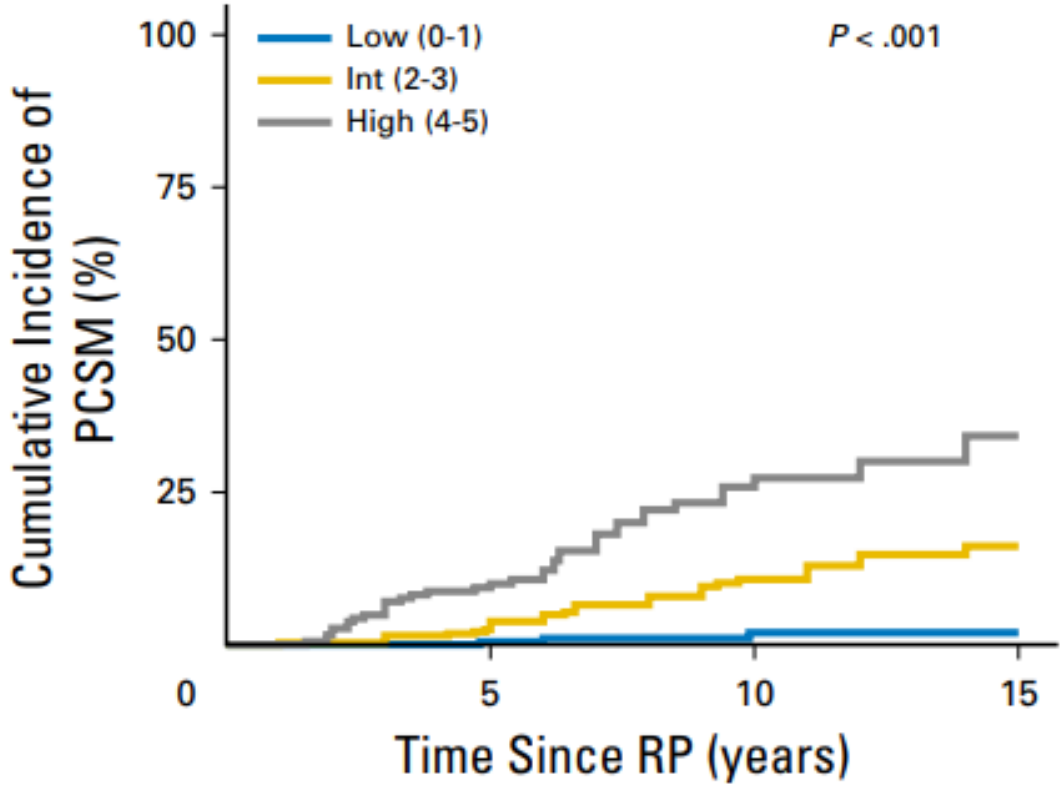
A new NCCN clinical-genomic model



Spratt DE, JCO 2018

A new NCCN clinical-genomic model- highly prognostic

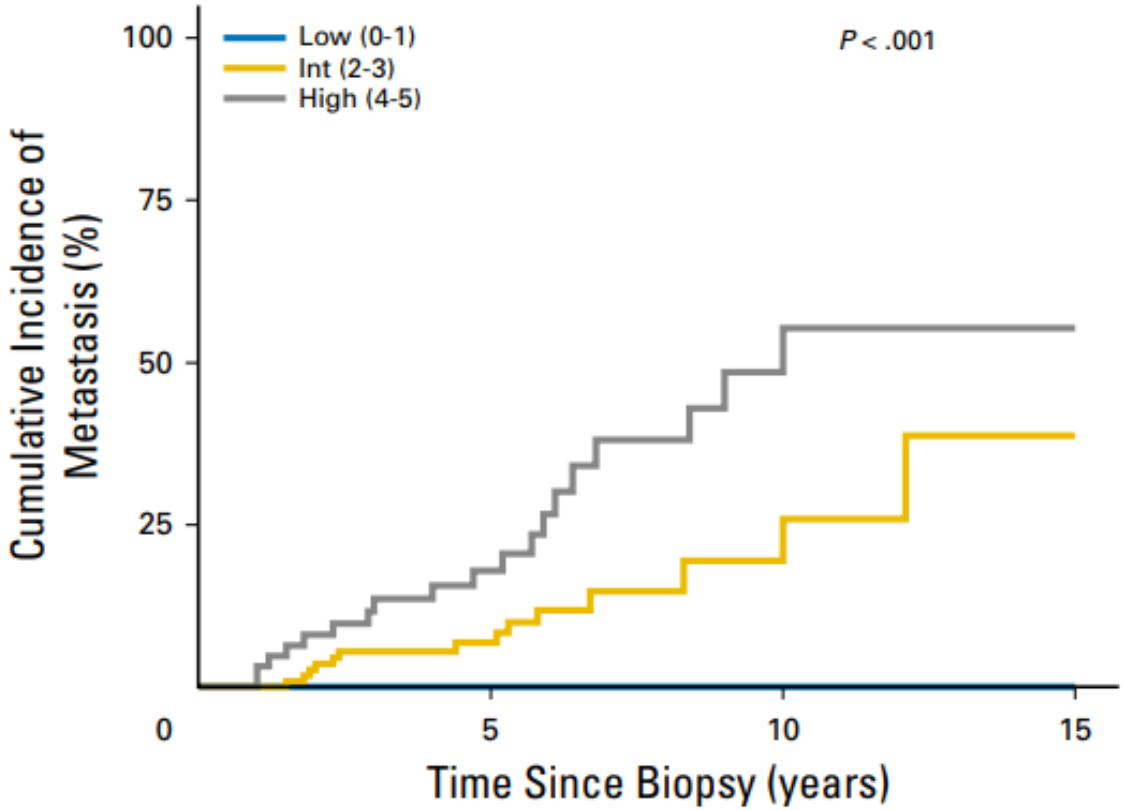




Spratt DE, JCO 2018

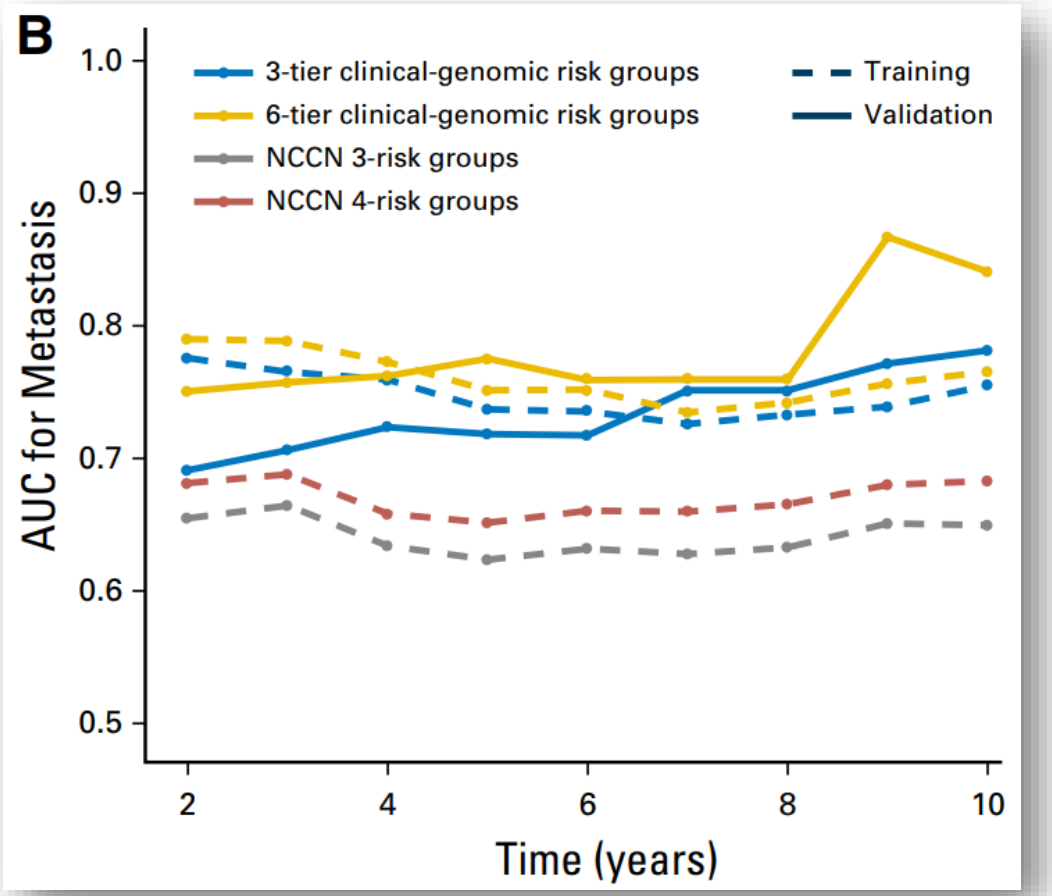
A new NCCN clinical-genomic model- independently validates

Validation Biopsy Cohort



Spratt DE, JCO 2018

A new NCCN clinical-genomic model- AUC of 0.81



Spratt DE, JCO 2018

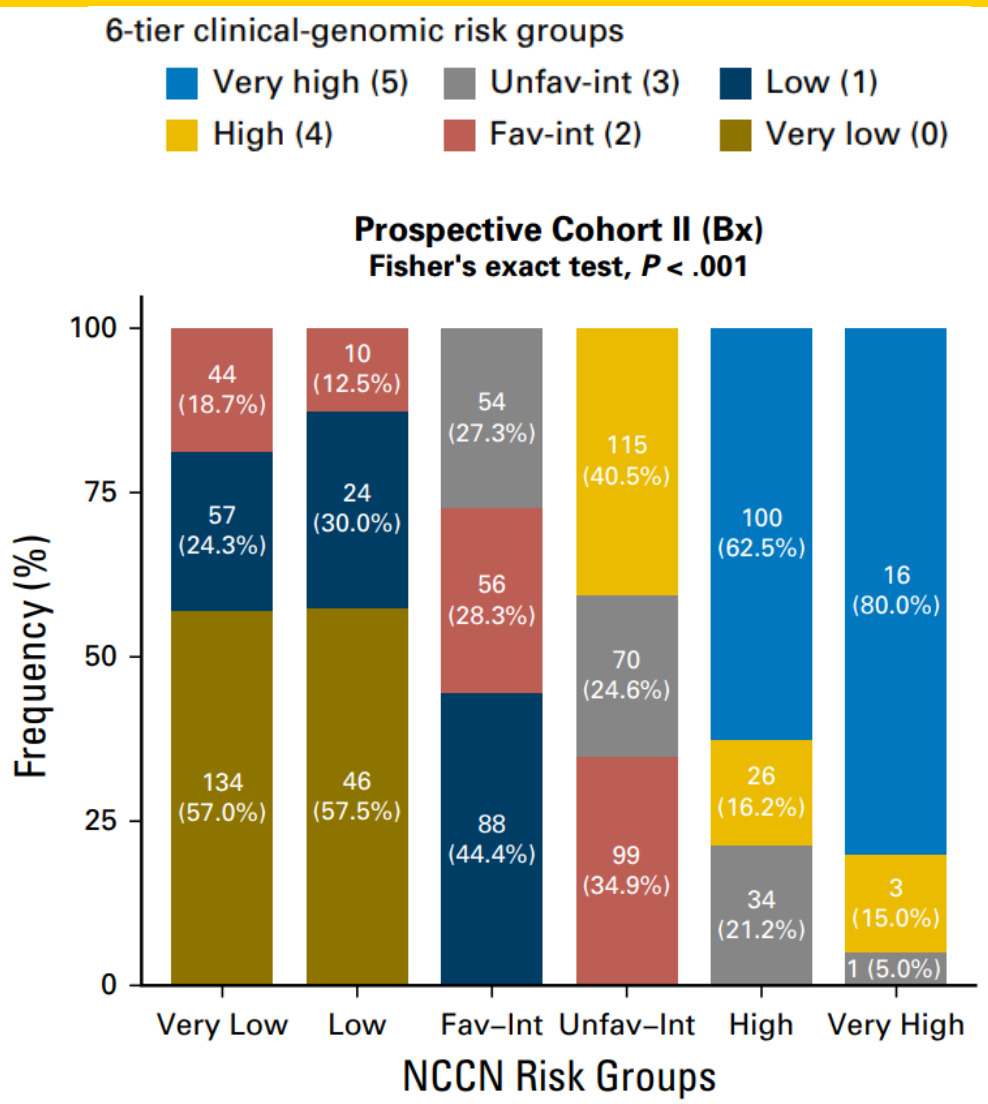
A new NCCN clinical-genomic model- Reclassifies 67% of patients

Reclassifies 67% of patients

-44% of Fav Intermediate → low risk

-41% of Unfav Intermediate → high risk

-63% of high risk → very high risk



Spratt DE, JCO 2018

How can we use these tests?

Decisions in intact prostate cancer:	What do we use to guide our decision?
Treat vs no treat (active surveillance)	Prognosis (NCCN low risk)
RT +/- ADT	Prognosis (NCCN intermediate risk)
RT+ADT +/- long-term ADT	Prognosis (NCCN high risk)

Even though I just showed you these methods don't work well

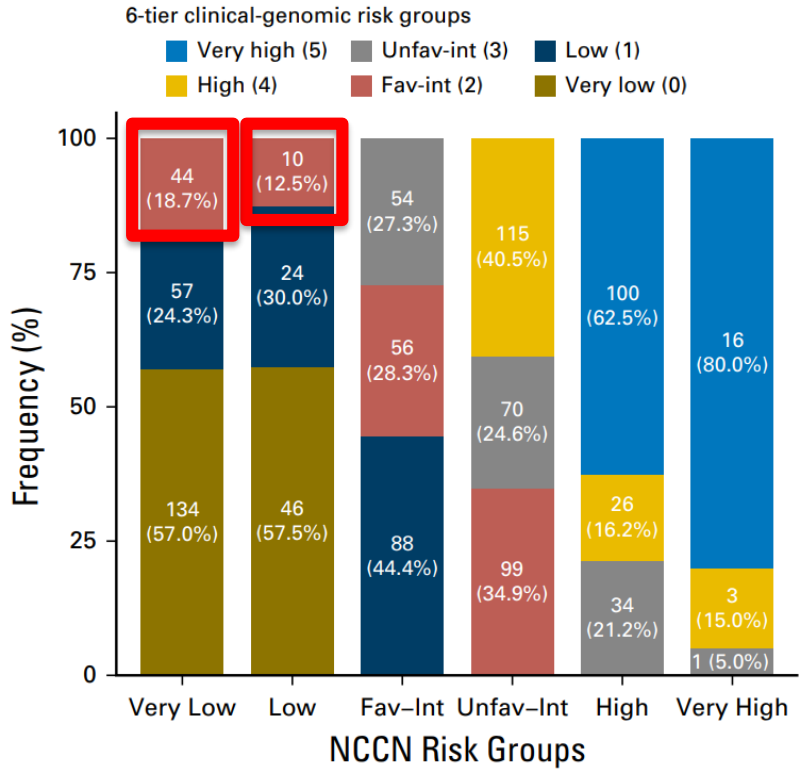
How can we use these tests? Low risk

427 patients "suitable for active surveillance"

"About 15% of low-risk cases—even those defined as lowest risk based on either Gleason group or multivariable CAPRA score—are characterized by higher-risk genomic scores"

Genomic Risk →

	Biochemical recurrence	
	HR (95% CI)	*p* value
CAPRA	1.14 (0.72–1.80)	0.6
PSA density	1.32 (0.99–1.63)	0.06
AGR	1.58 (1.21–2.03)	0.001
CAPRA	1.20 (0.75–1.90)	0.4
PSA density	1.28 (0.95–1.60)	0.1
Genomic cluster 1	REF	
Genomic cluster 2	1.17 (0.45–2.96)	0.7
Genomic cluster 3	0.95 (0.35–2.46)	0.9



Cooperberg, Euro Urol 2018

How can we use these tests? Intermediate risk

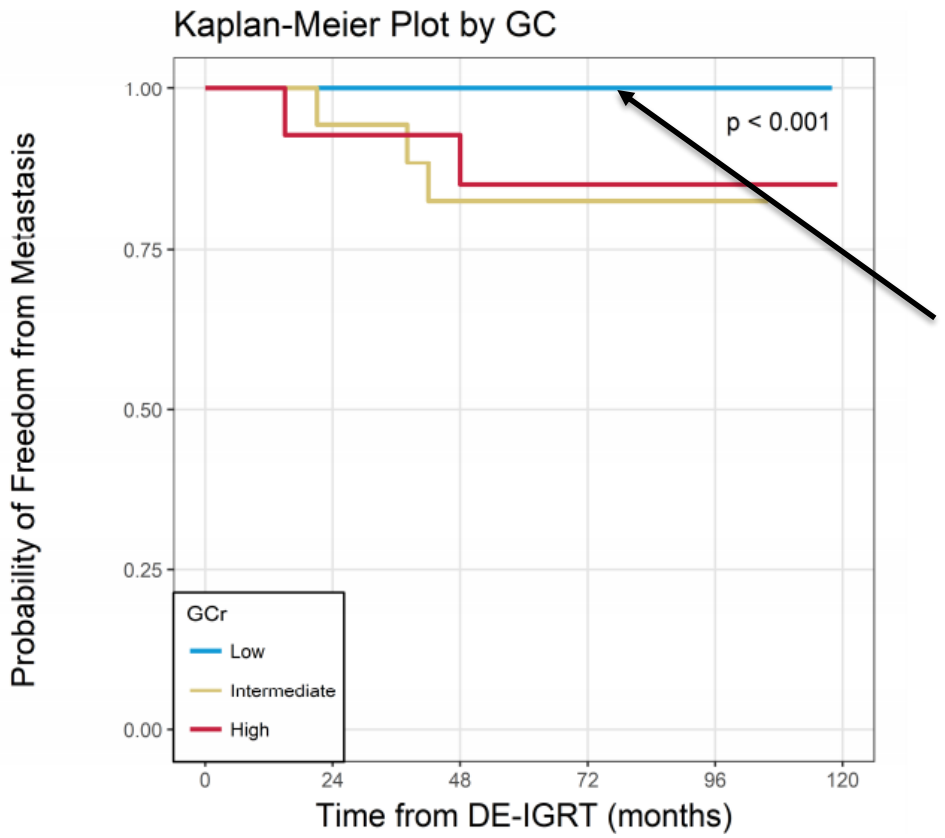
Clinical parameters	N = 121 (%*)
Median follow-up, years (range)	7.7 (0.7-11.2)
Age, years (median, IQR)	72.4 (68.4-75.0)
Pre-diagnostic PSA, ng/ml (median, IQR)	7.8 (5.7-11.2)
Clinical T-category	
cT1c/T2a	95 (78.5)
cT2b/T2c	26 (21.5)
ISUP grade (GS)	
1 (3+3)	12 (9.9)
2 (3+4)	75 (62.0)
3 (4+3)	34 (28.1)
Percentage of positive biopsy cores	
<50%	69 (57.0)
≥50%	48 (39.7)
Unknown	4 (3.3)
NCCN subclassification	
Favorable	33 (27.3)
Unfavorable[#]	87 (71.9)
Unknown	1 (0.8)

PROSPECTIVE cohort

All treated with dose escalated EBRT alone (no brachy boost and no ADT)

Berlin A, IJROBP 2018

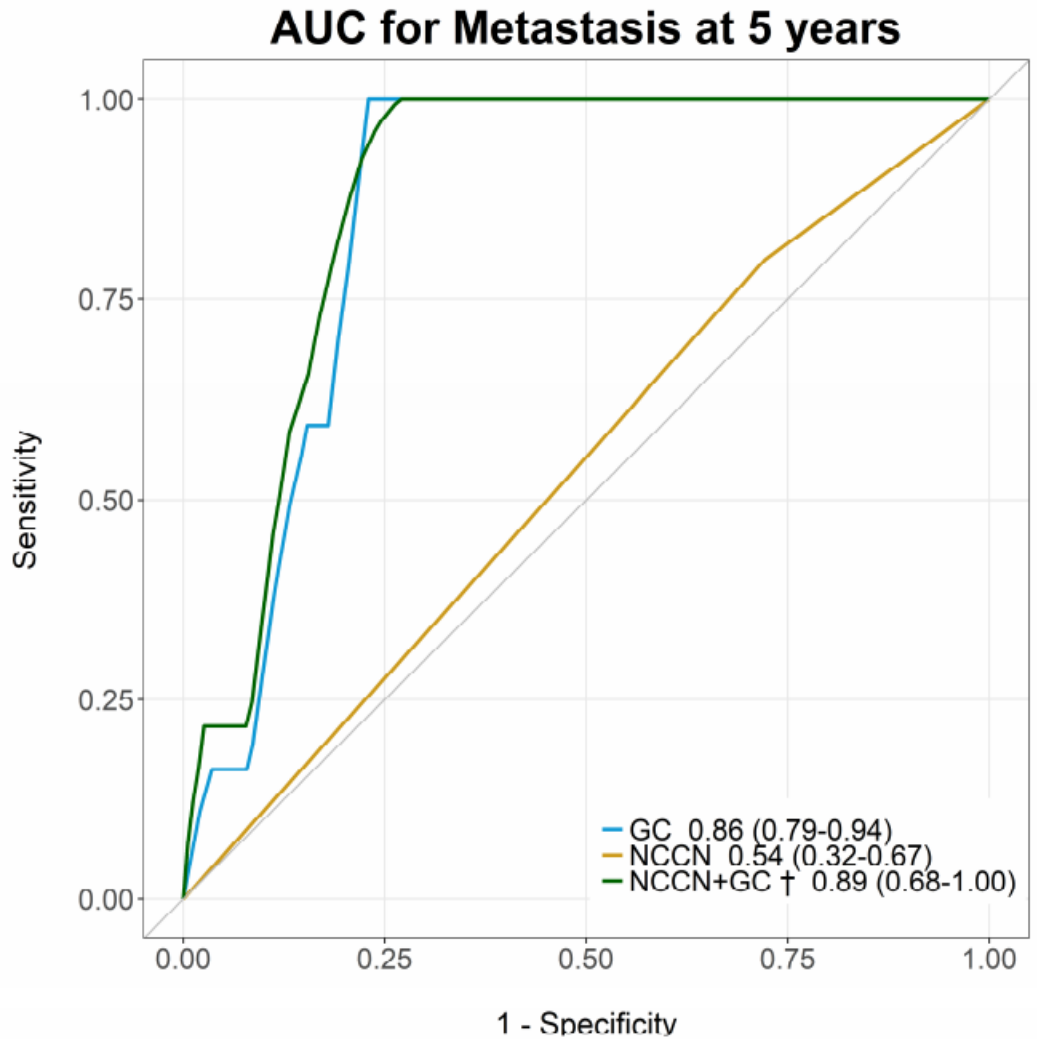
How can we use these tests? Intermediate risk



Low clinical-genomic risk group tumors had no metastatic events

Berlin A, IJROBP 2018

How can we use these tests? Intermediate risk



AUC
Coin flip = 0.50
NCCN = 0.54
Clinical-genomic = 0.89

Berlin A, IJROBP 2018

How can we use these tests? Low/Int Risk Clinical Utility

3,966 low and intermediate risk prostate cancer patients in MUSIC's prospective registry

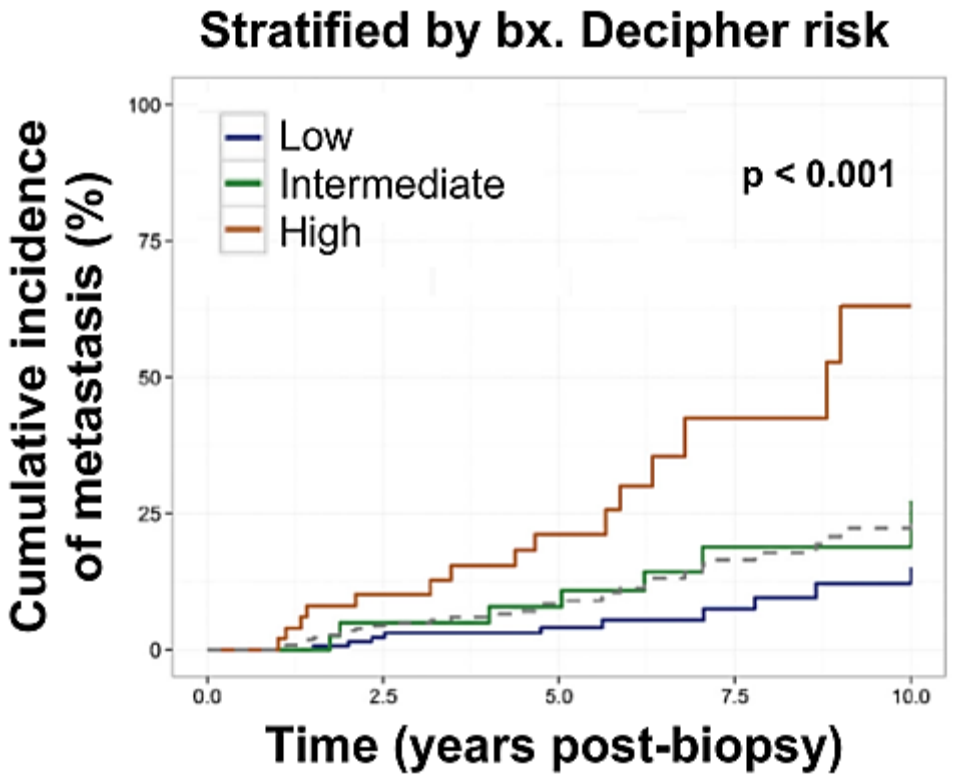
NNT (number needed to test) = 3

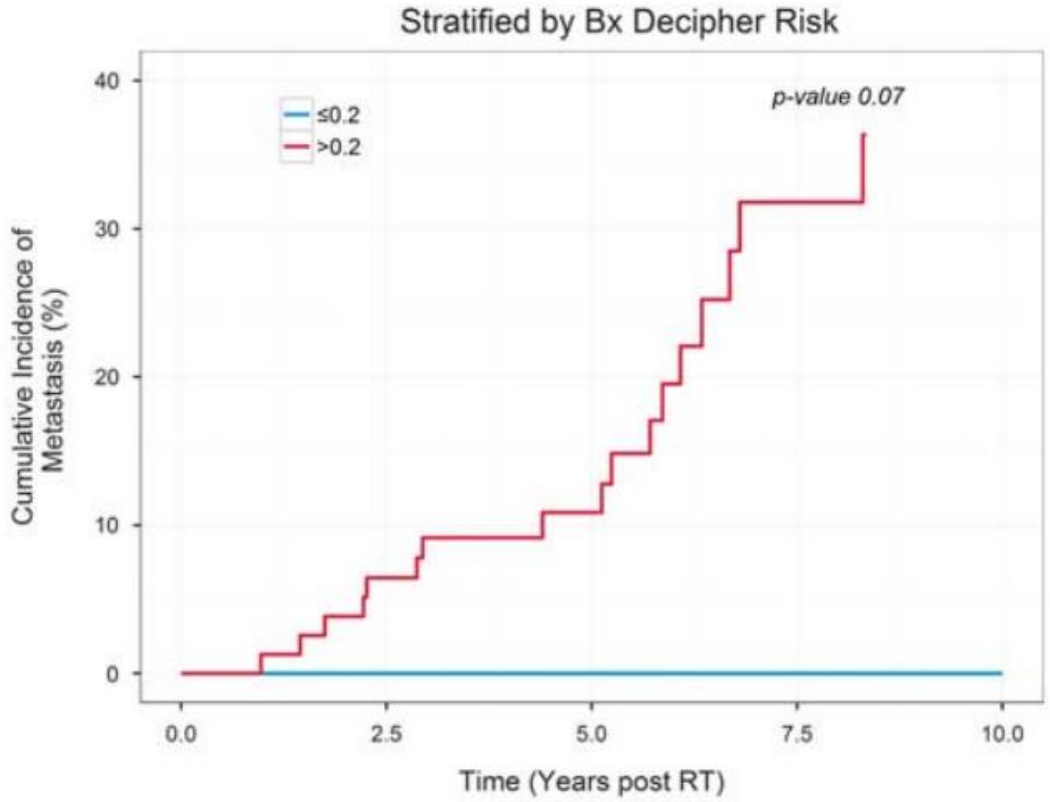
Table 2. Summary of Primary Management According to the Performance and Result of GEC Testing

Test Result by Patient Group	Total	Active Surveillance	Definitive Treatment	No Treatment	P*
All patients					
No GEC test	2,880	742 (25.7)	1,795 (62.3)	343 (11.9)	< .001
GEC test < threshold	264	171 (64.7)	70 (26.5)	23 (8.7)	
GEC test > threshold	423	69 (16.3)	318 (75.2)	36 (8.5)	
Patients with favorable risk					
No GEC test	1167	676 (57.9)	337 (28.9)	154 (13.2)	< .001
GEC test < threshold	203	154 (75.9)	31 (15.3)	18 (8.9)	
GEC test > threshold	117	54 (46.2)	46 (39.3)	17 (14.5)	
Patients with unfavorable risk					
No GEC test	1,713	66 (3.9)	1,458 (85.1)	189 (11.0)	< .001
GEC test < threshold	61	17 (27.9)	39 (63.9)	5 (8.2)	
GEC test > threshold	306	15 (4.9)	272 (88.9)	19 (6.2)	

Hu J, et al, JCO Precision Onc, 2018

How can we use these tests? High risk





Nguyen P, PCAN 2017

How can we use these tests? Post-operative

Adjuvant RT: Prostatectomy +/- Adjuvant RT

Reference	N	Inclusion criteria	Dose (Gy)	Follow-up median (years)	10-year BPFS ART vs. NFT	10-year OS ART vs. NFT	10-year toxicity rate (%) ART vs. NFT
Thompson et al. (5)	425	pT3 cN0/pN0 R0/R1	60–64	12.7	52 vs. 26% $p < 0.001$	74 vs. 66% $p = 0.023$	GI, G3 = 3.3 vs. 0 GU, G3 17.8 vs. 9.5
Bolla et al. (4)	1005	pT2–3 pN0 R0/R1	60	10.6	60 vs. 41% $p < 0.0001$	77 vs. 81% $p = 0.2$	GU > G2 = 21.3 vs. 13.5 ($p = 0.003$) GI > G2 = 2.5 vs. 1.9 ($p = 0.47$)
Wiegel et al. (6)	388 (307)	pT3 pN0 R0/R1 PSA 0	60	9.3	56 vs. 35% $p < 0.0001$	84 vs. 86% $p = 0.59$	ART: GU, G3 = 1 patient, G2 = 2 patients, GI, G2 = 2 patients

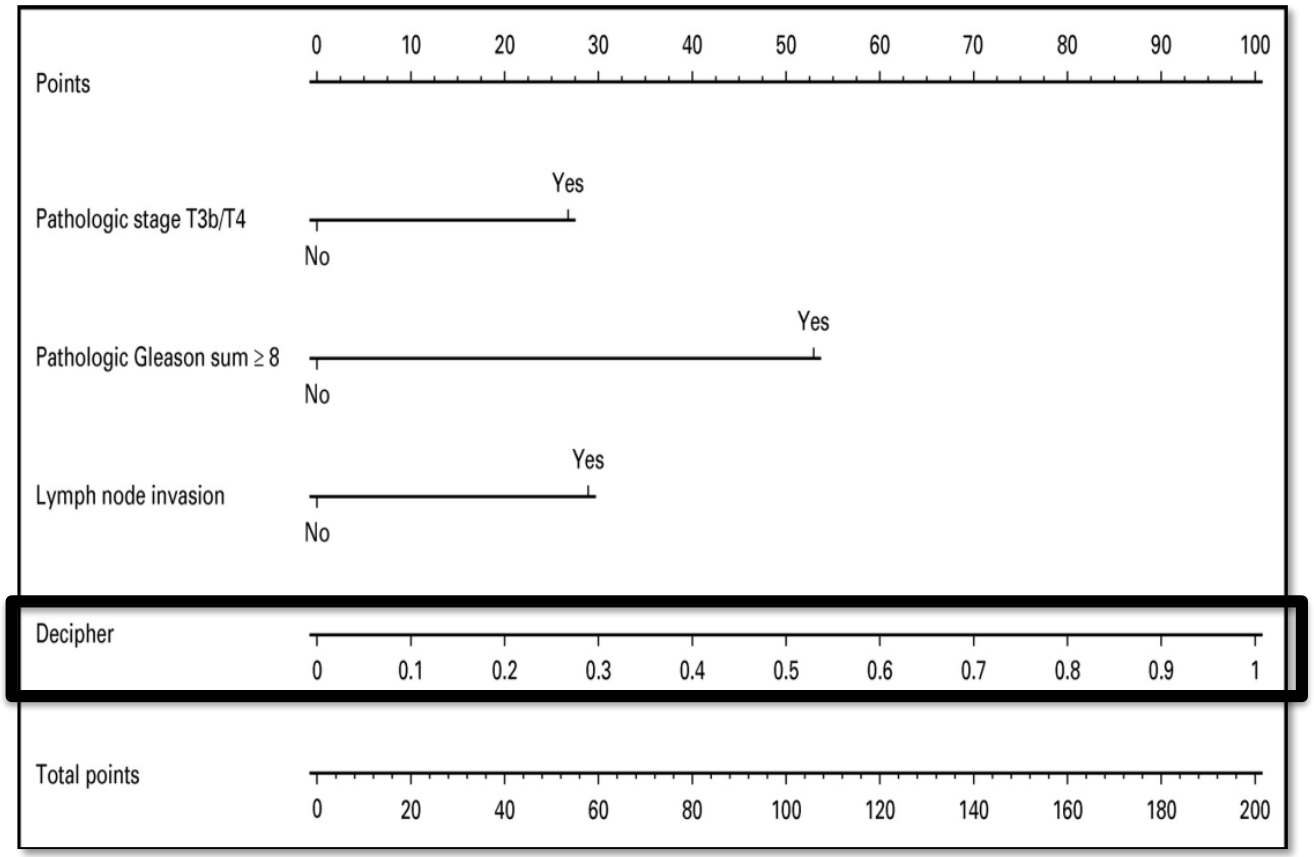
BPFS, Biochemical progression-free survival; OS, overall survival; ART, adjuvant radiation therapy; NFT, no further therapy; GU, genitourinary; GI, gastro-intestinal; G, grade.

Meta-analysis = Decreased BCR with HR of ~0.5

How can we use these tests? Post-operative

Clinicopathologic and Genomic variables

-Guide adjuvant RT

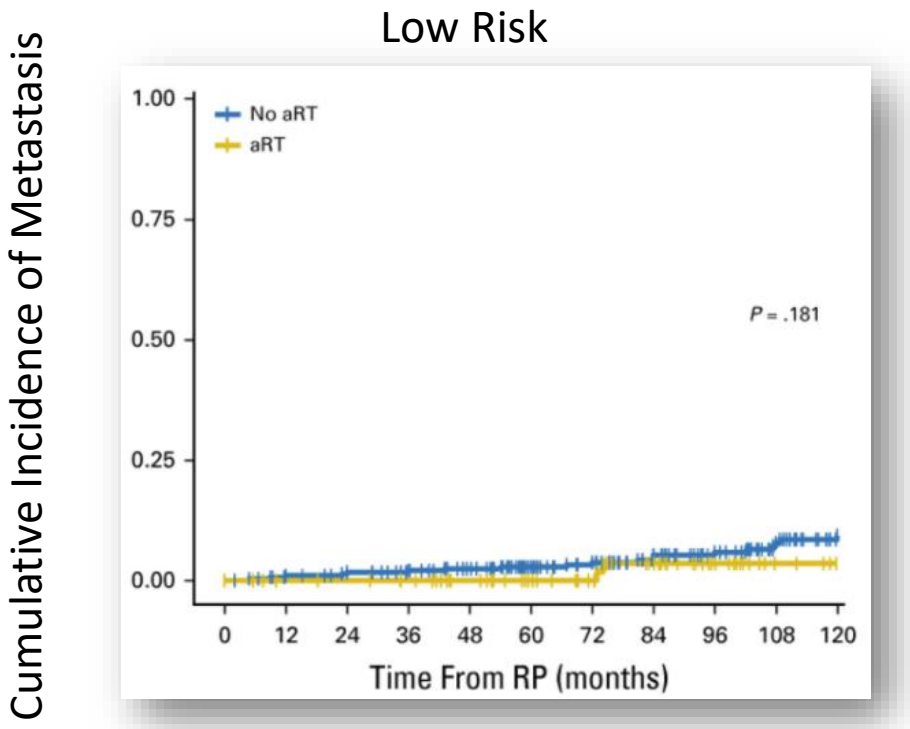


Dalela D, et al, JCO 2017

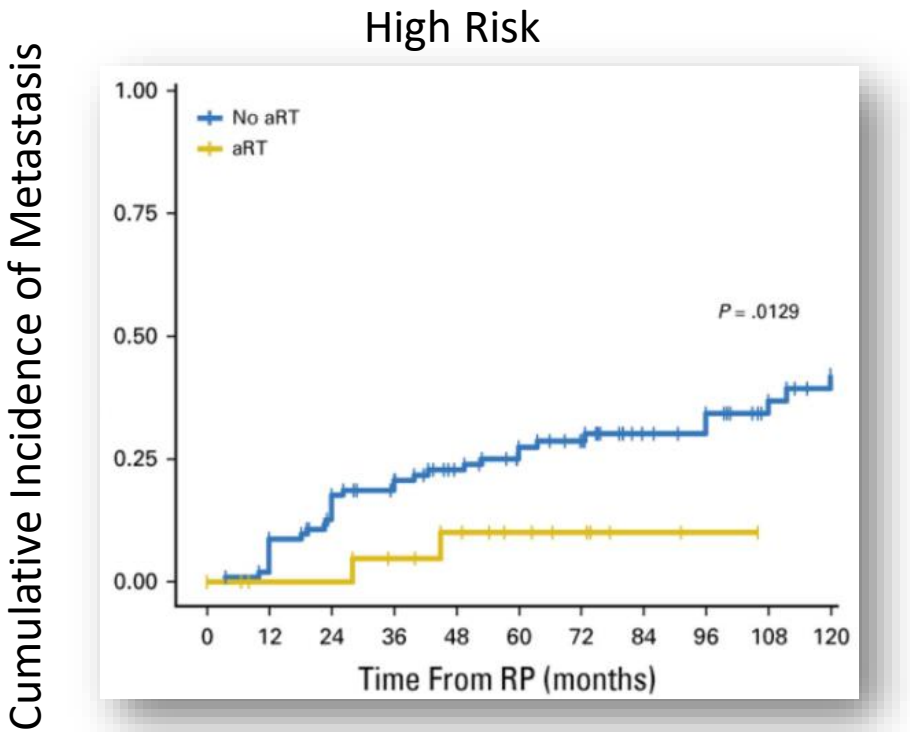
How can we use these tests? Post-operative

Guiding adjuvant RT

Low Risk

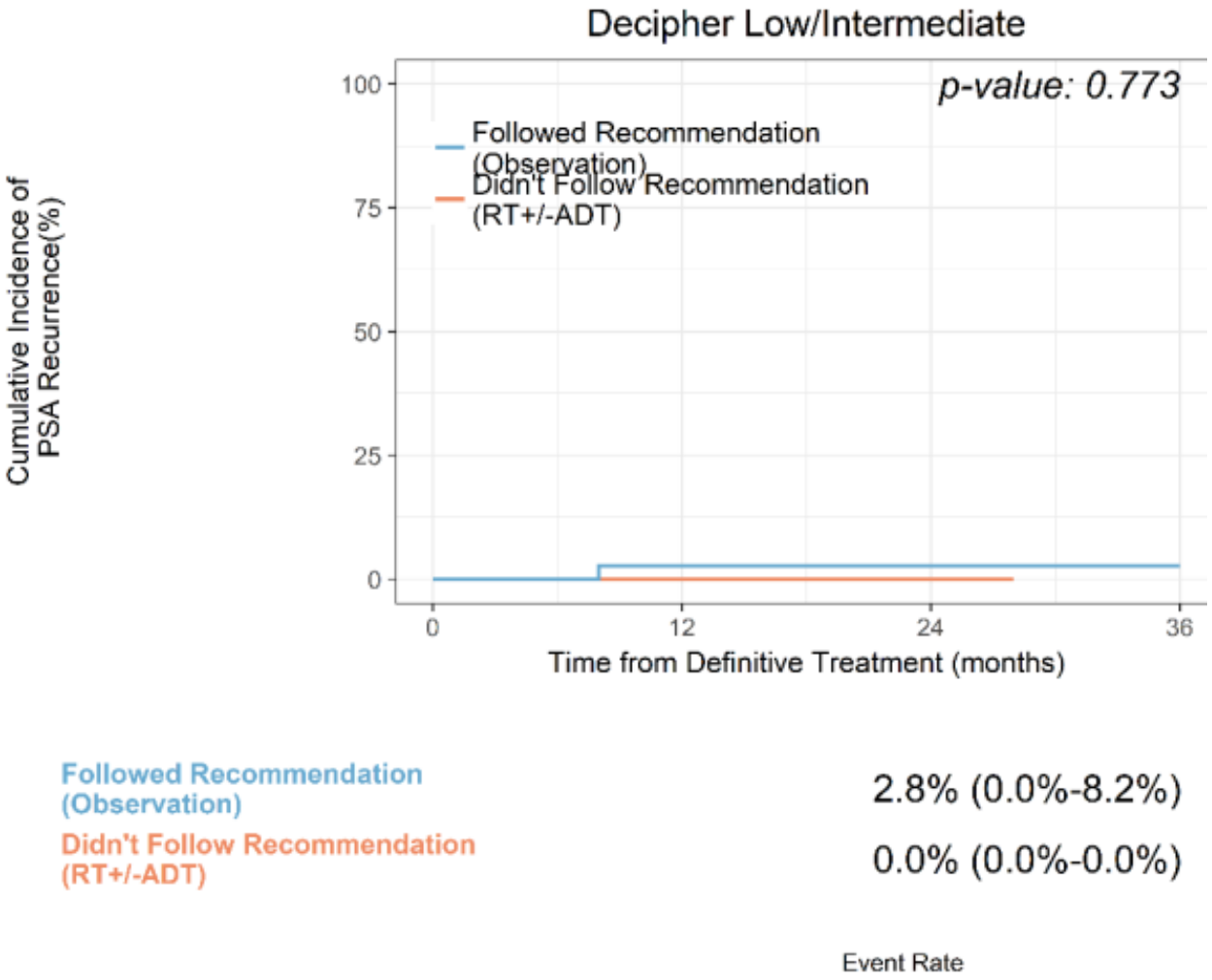


High Risk



Dalela D, et al. JCO 2017

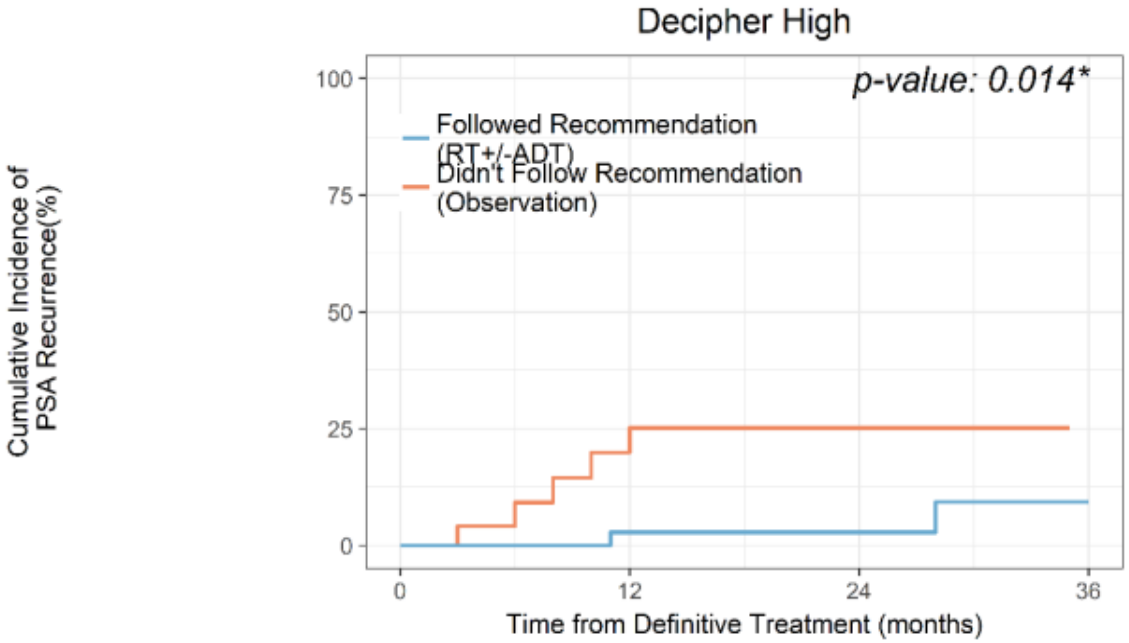
How can we use these tests? Post-operative -Prospective Study from Thomas Jefferson



	MVA	
Variable	**HR (95% CI)**	**P value**
CAPRA-S	1.4 (0.0-1265.0)	0.449
Treated vs Not treated	1.3 (0.0-84.3)	**0.926**

Den R, et al. In submission

How can we use these tests? Post-operative -Prospective Study from Thomas Jefferson



	MVA	
Variable	**HR (95% CI)**	**P value**
CAPRA-S	1.5 (0.9-2.3)	0.093
Treated vs Not treated	0.1 (0.0-0.6)	**0.013**
Yes vs No		

Followed Recommendation (RT+/-ADT) 2.9% (0.0%-8.5%)

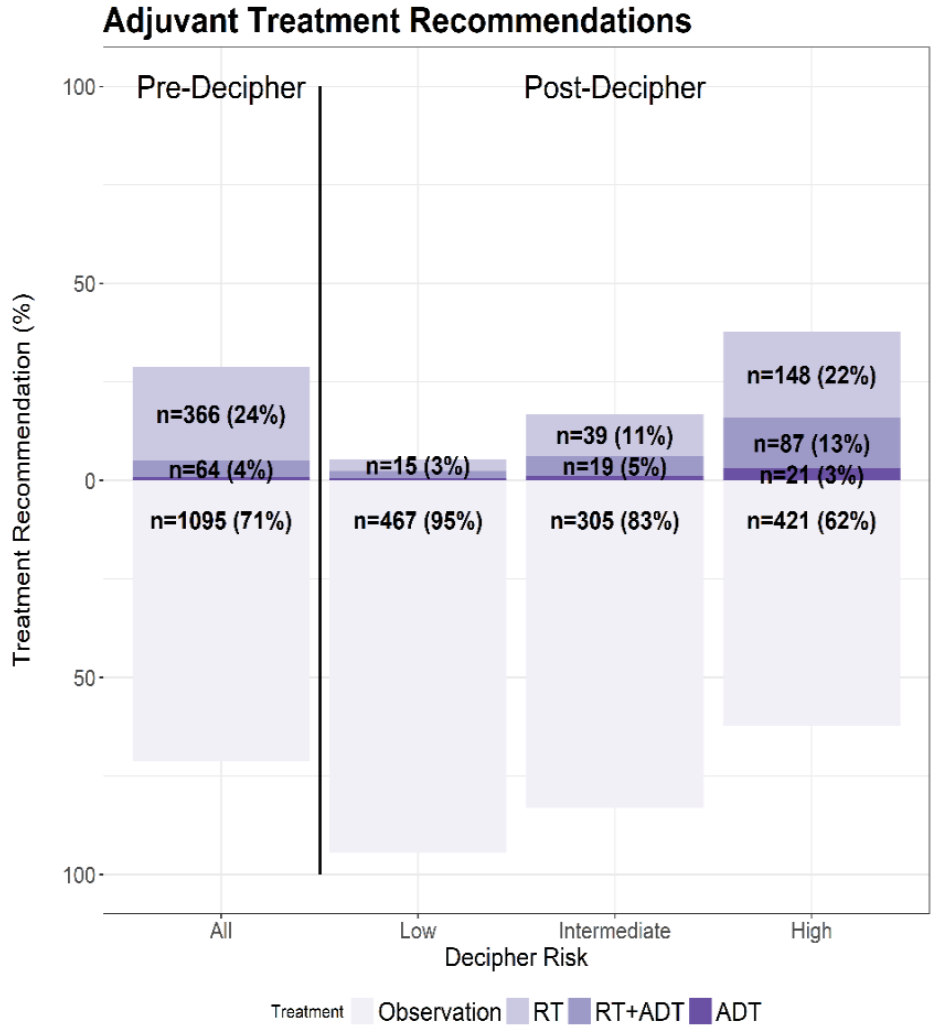
Didn't Follow Recommendation (Observation) 25.2% (5.3%-45.1%)

Event Rate

Den R, et al. In submission

How can we use these tests? Post-op Clinical Utility

Prospective Medicare Registry of ~3000 patients

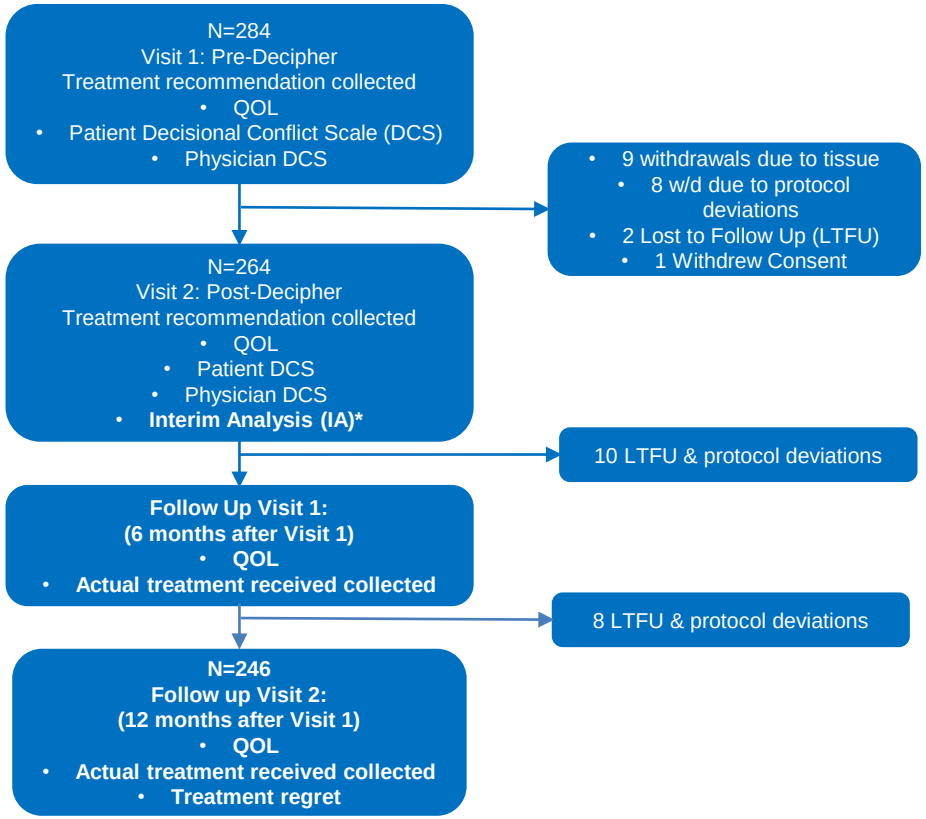


NNT (number needed to test) = 3

Den R, et al. In submission

How can we use these tests? Post-op Clinical Utility

Prospective PRO-IMPACT Trial

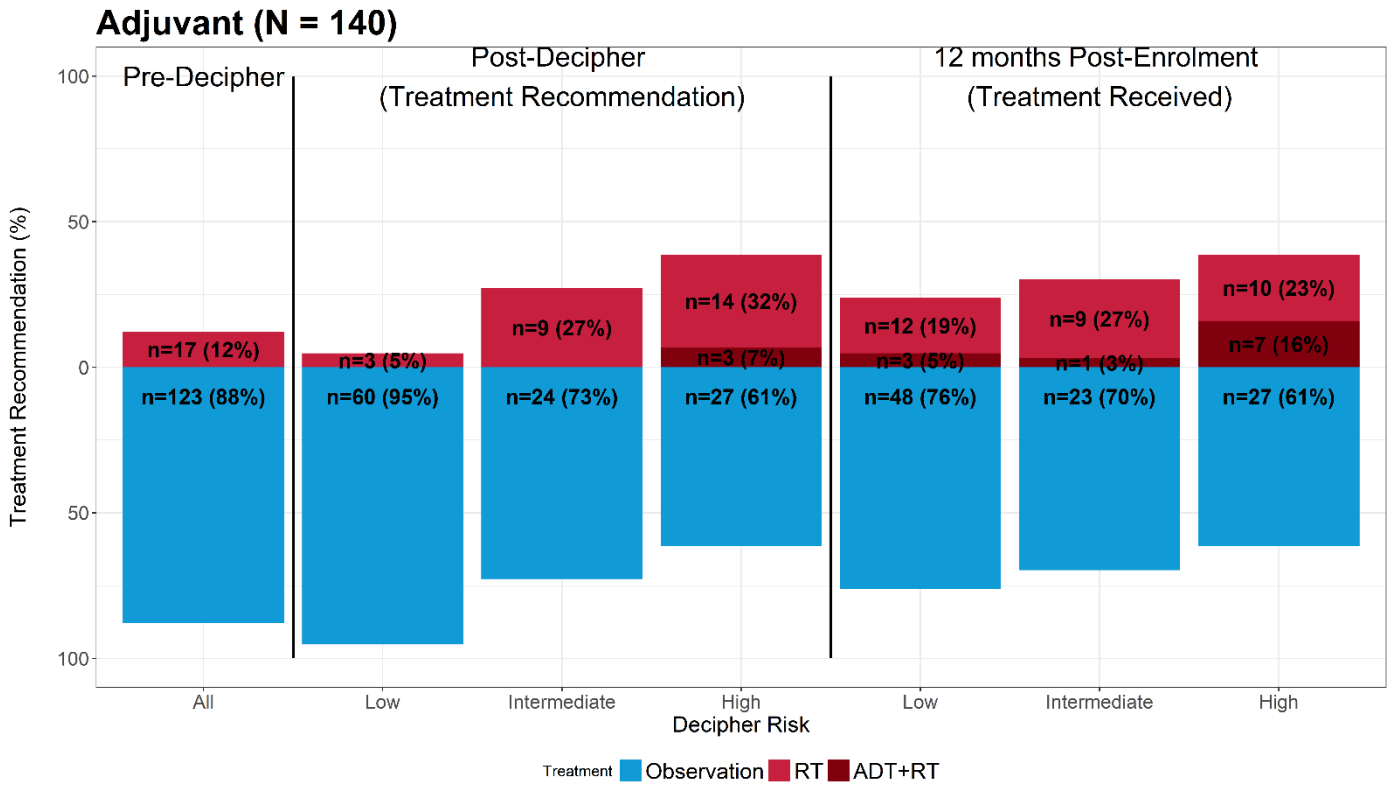


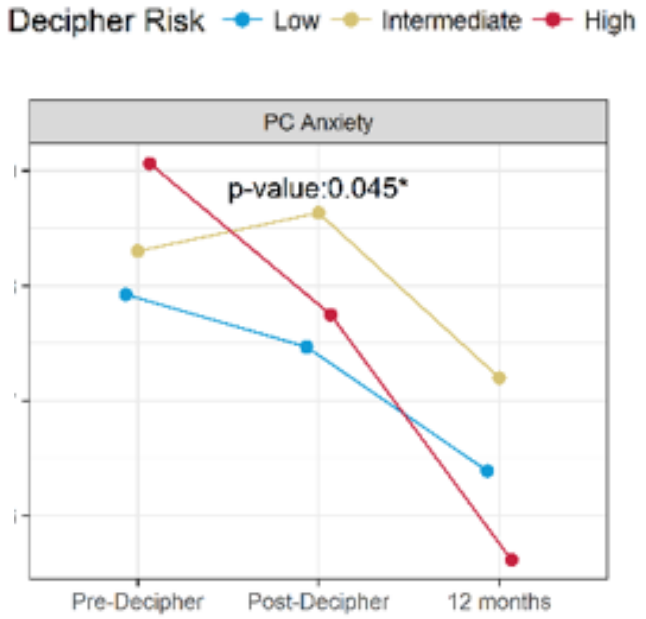
Gore et al. In submission

How can we use these tests? Post-op Clinical Utility

Prospective PRO-IMPACT Trial

NNT (number needed to test) = 4



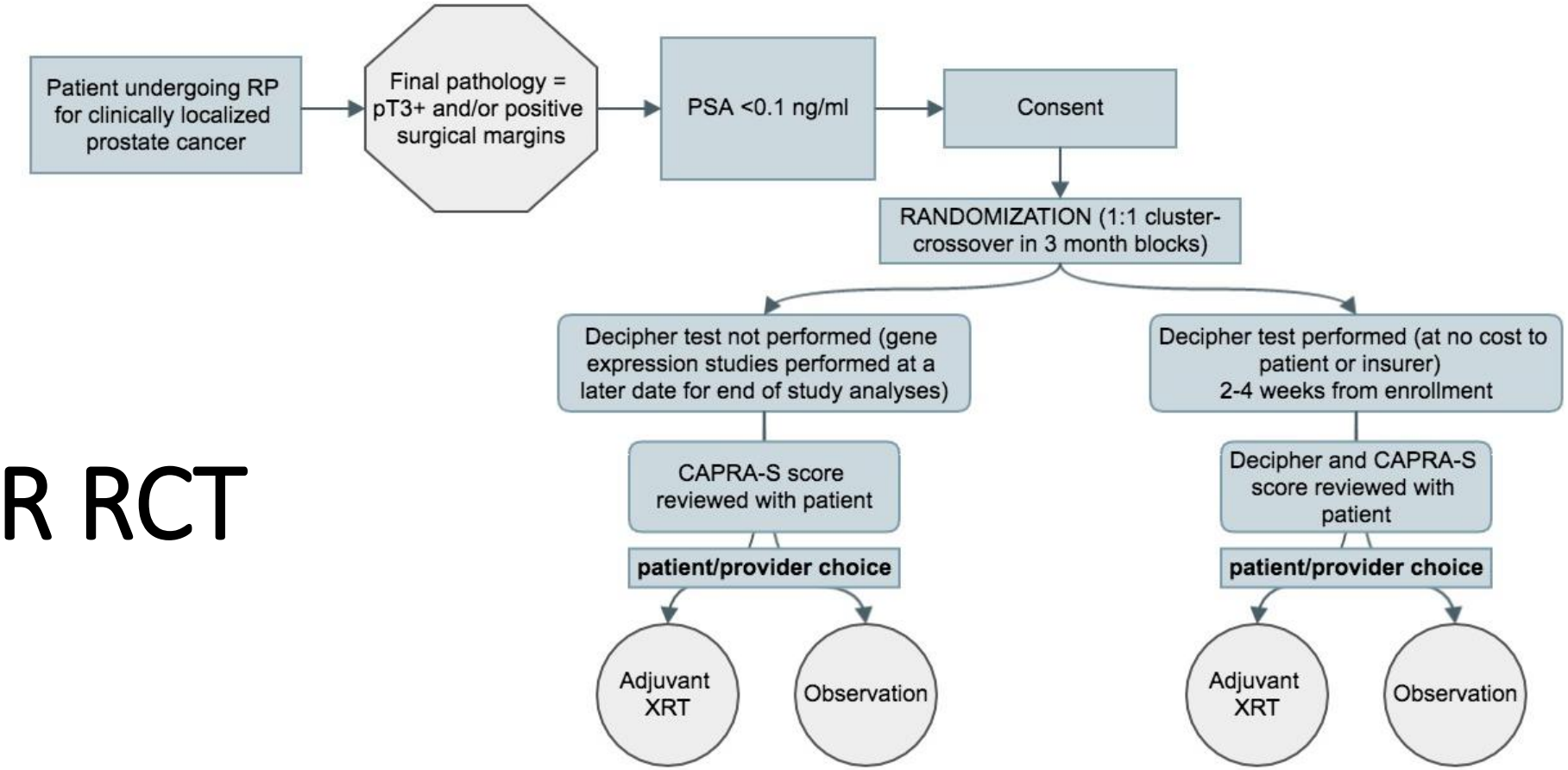


Anxiety decreased

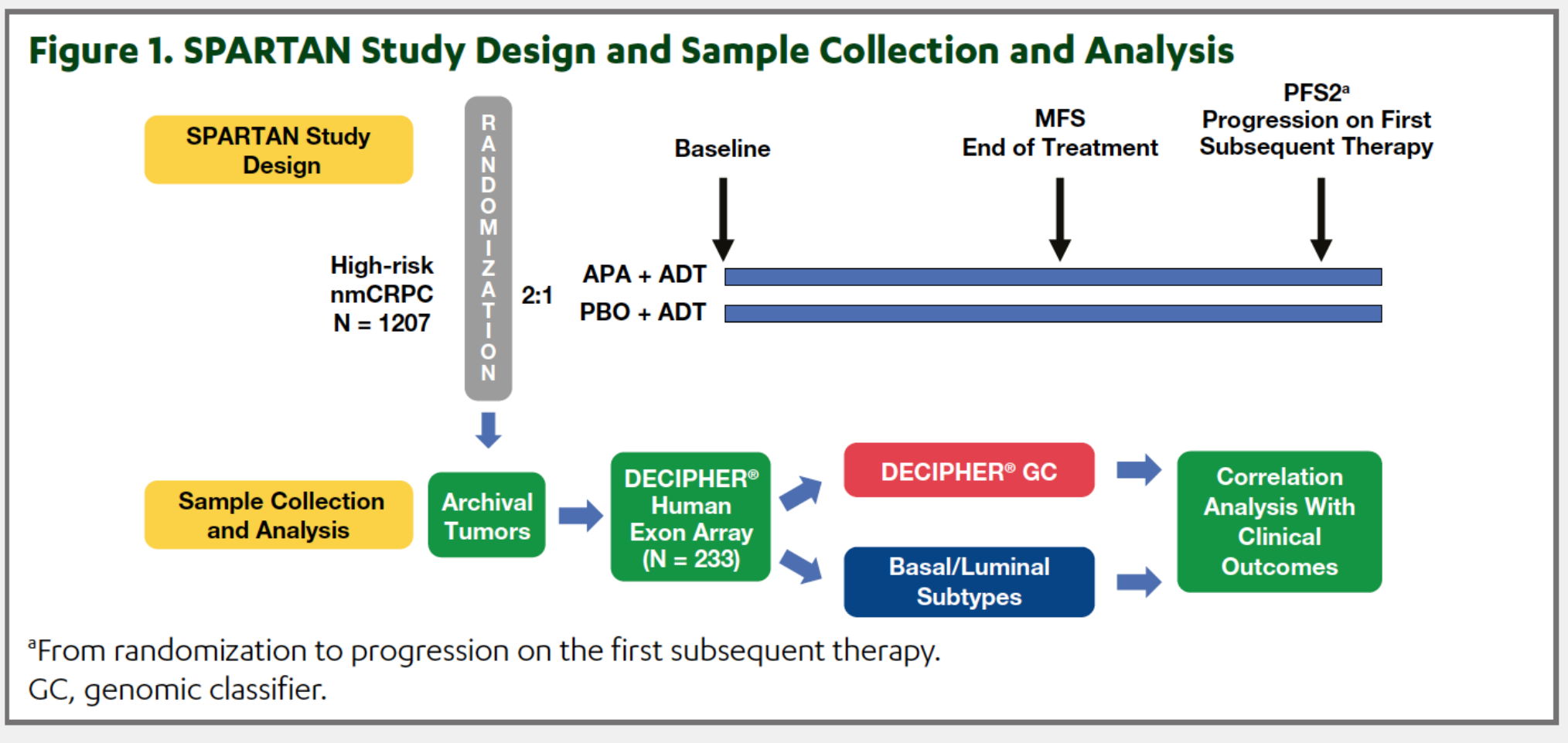
Gore et al. In submission

How can we use these tests? Post-op Clinical Utility

GMINOR RCT

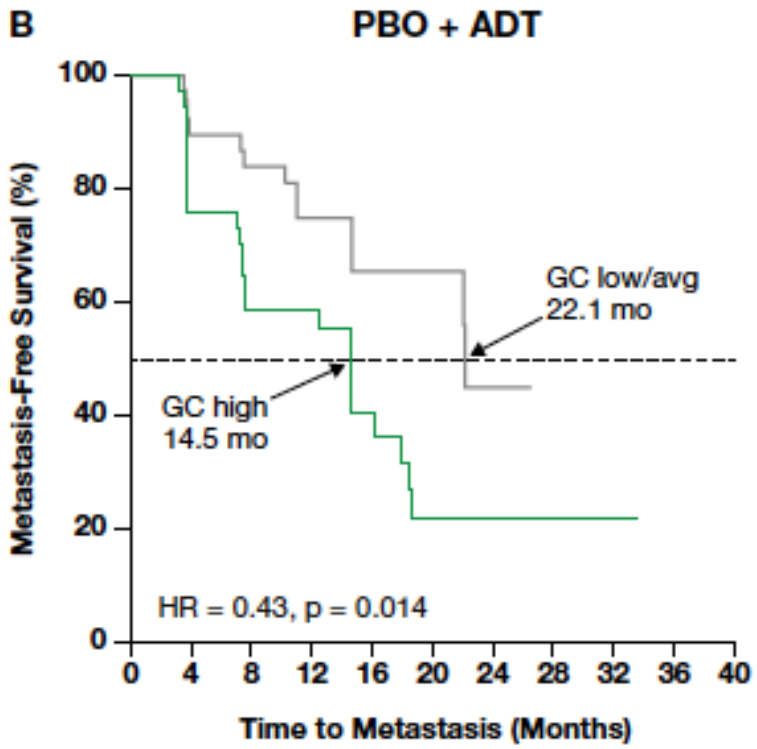


How can we use these tests? M0 CRPC



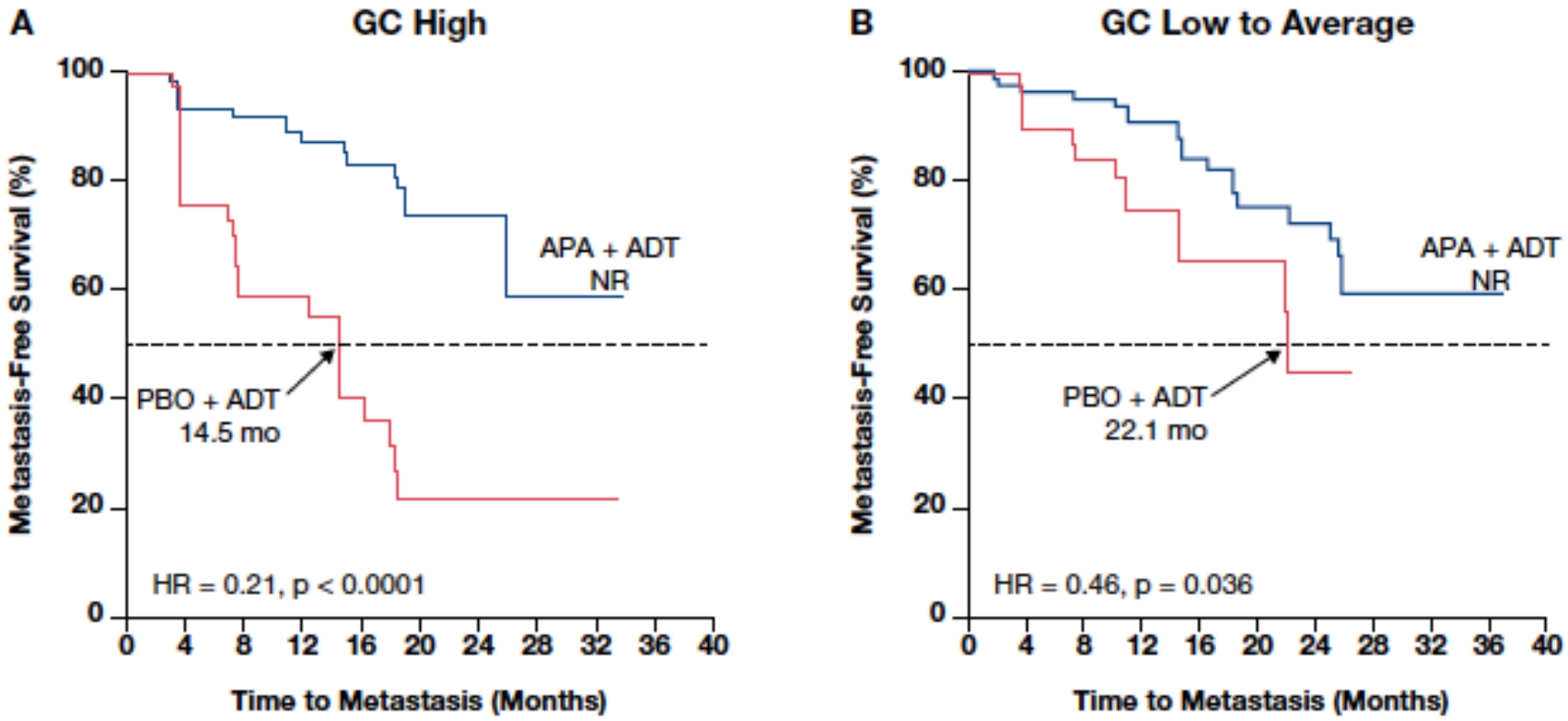
How can we use these tests? M0 CRPC

Figure 2. MFS by DECIPHER GC Score in the APA + ADT (A) and PBO + ADT (B) Treatment Arms of SPARTAN



How can we use these tests? M0 CRPC

Figure 3. MFS by Treatment Arm in Patients With High (A) and Low to Average (B) DECIPHER GC Score



Gene expression testing ready for clinical use?

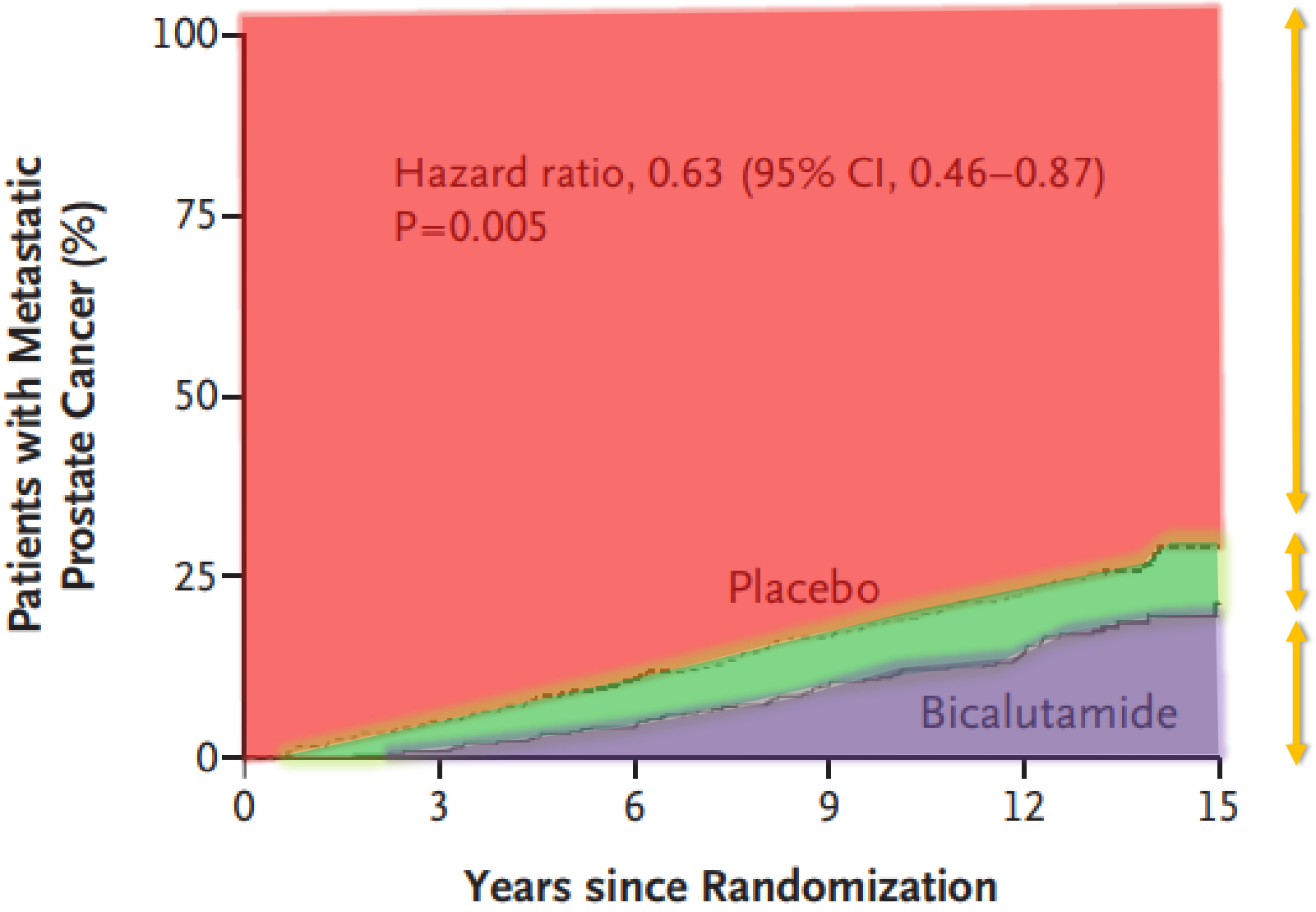
RNA Gene Expression Testing	Answer	Example
Are the frequency of gene expression patterns established?	YES	>20,000 patients
Retrospective data?	YES	>40 papers
Prospective clinical utility data (change management)?	YES	For Biopsy and for RP
Prospective clinical benefit data (improve outcomes)?	YES	For RP
Randomized data?	YES	SPARTAN (much more to come)
NCCN recommended?	**NO**	"Consider" or "Not recommended"

I believe the Decipher test has robust data to support use
Much more than use of MRI or PET in localized prostate cancer

Utility of RNA biomarkers

- Prognostic
- **Predictive**
- Diagnostic (*rarely*)
  (usually are DNA or protein-based)

Which Post-op Patients Need ADT?



Over-treated with AAT
(treatment de-escalation needed)

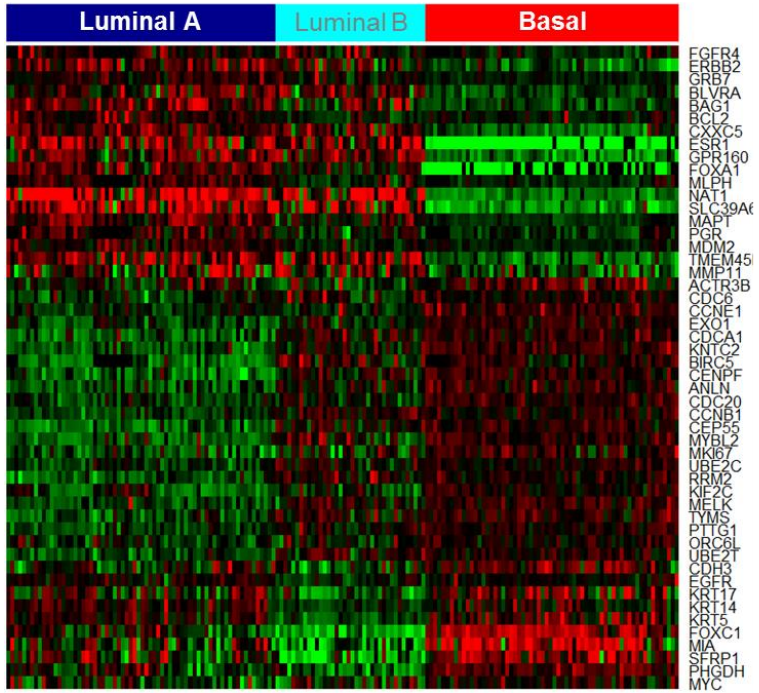
Benefited from AAT

Failed despite AAT
(treatment intensification needed)

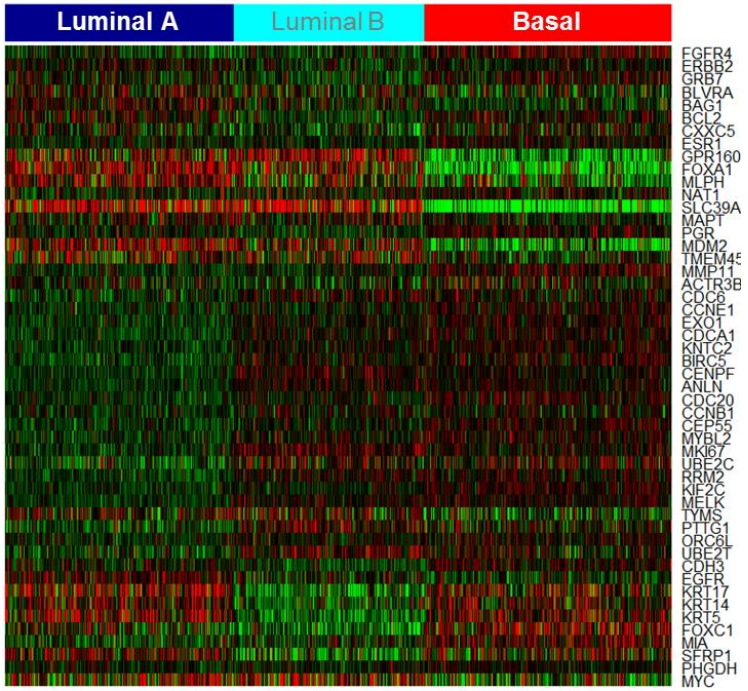
Shipley, NEJM 2017

Luminal and Basal Subtyping in Prostate Cancer

Breast Cohort
N=232
Expression data and PAM50 algorithm obtained from Parker et al.

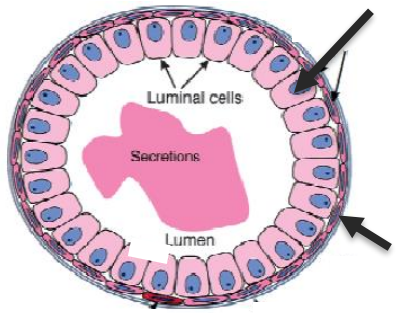


Prostate Cohort
N=1567
Prostatectomy samples on a CLIA-certified platform
Studies included: MCI, MCII, DVA, TJU, JHMI, CCF



Zhao, JAMA Onc, 2017

Tumor Biology

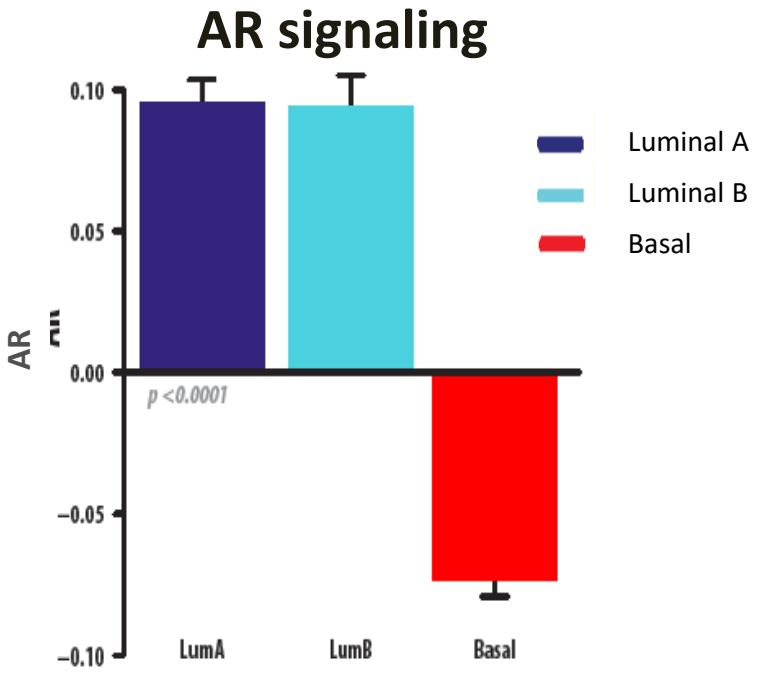


Luminal cells

- Differentiated
- **Hormone sensitive**
- **AR-regulated genes**
- High AR & PSA, low p63

Basal cells

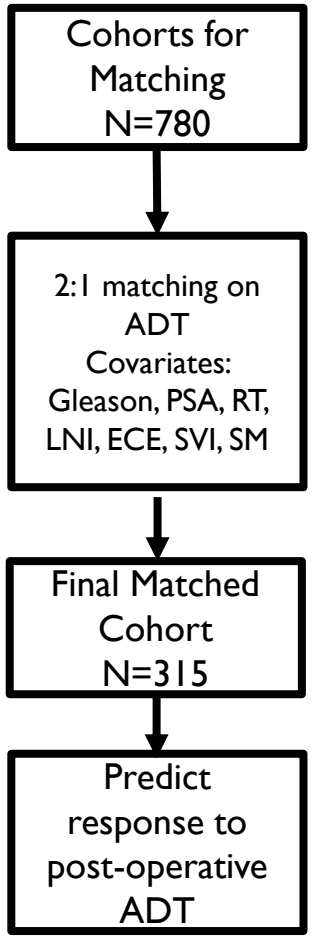
- Undifferentiated
- **Hormone insensitive**
- **Stem cell–like, EMT markers**
- **Neuronal development**
- Low AR, PSA, high MYC

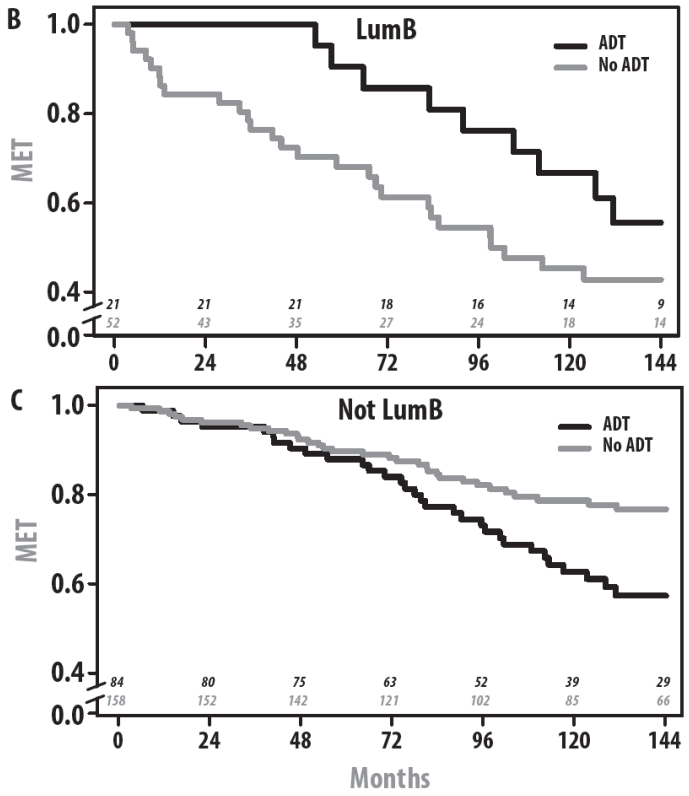


Zhao, JAMA Onc, 2017

Luminal B Cancers are Most Responsive to ADT

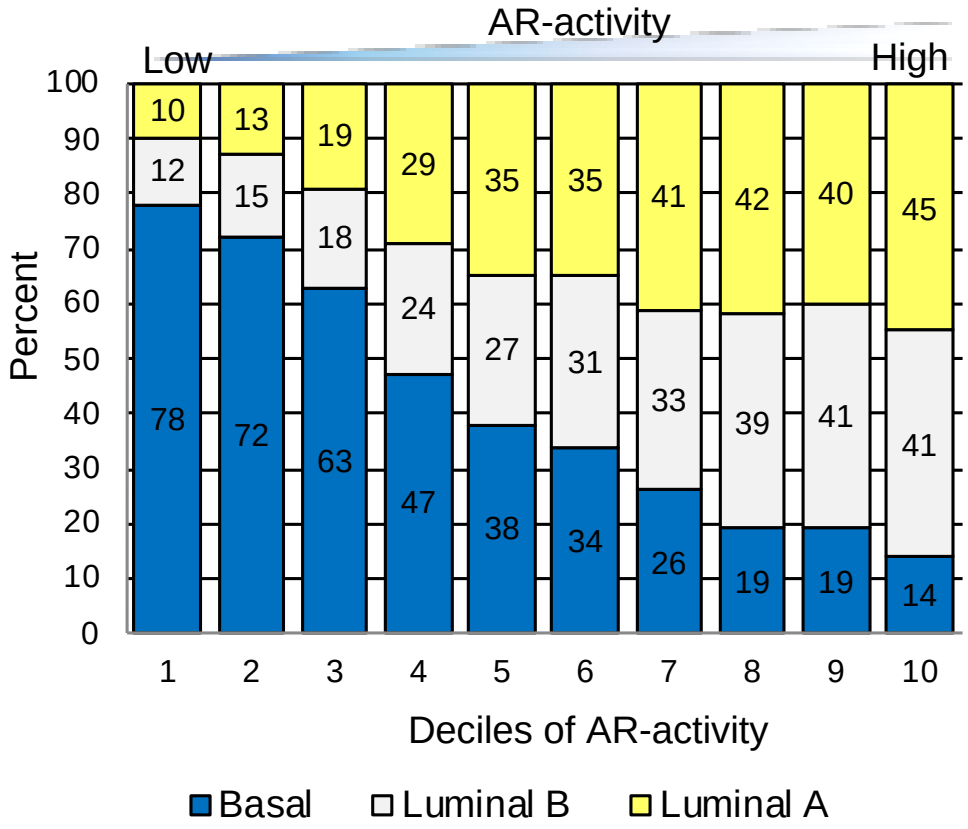
Zhao, JAMA Onc, 2017





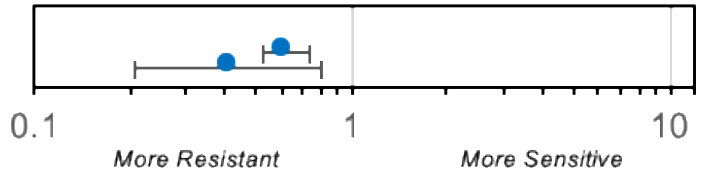
Test for interaction was highly significant p=0.0057

Basal tumors have low androgen receptor activity



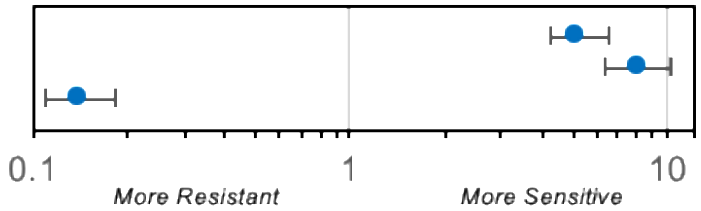
B. Pre-clinical and clinical validation of sensitivity to ADT in low AR-A patients (vs high AR-A)

Drug	OR	Lower	Upper
ADT (preclinical)	0.61	0.52	0.73
ADT (clinical)	0.41	0.21	0.80



C. Pre-clinical drug sensitivity to other oncology drugs in low AR-A patients (vs high AR-A)

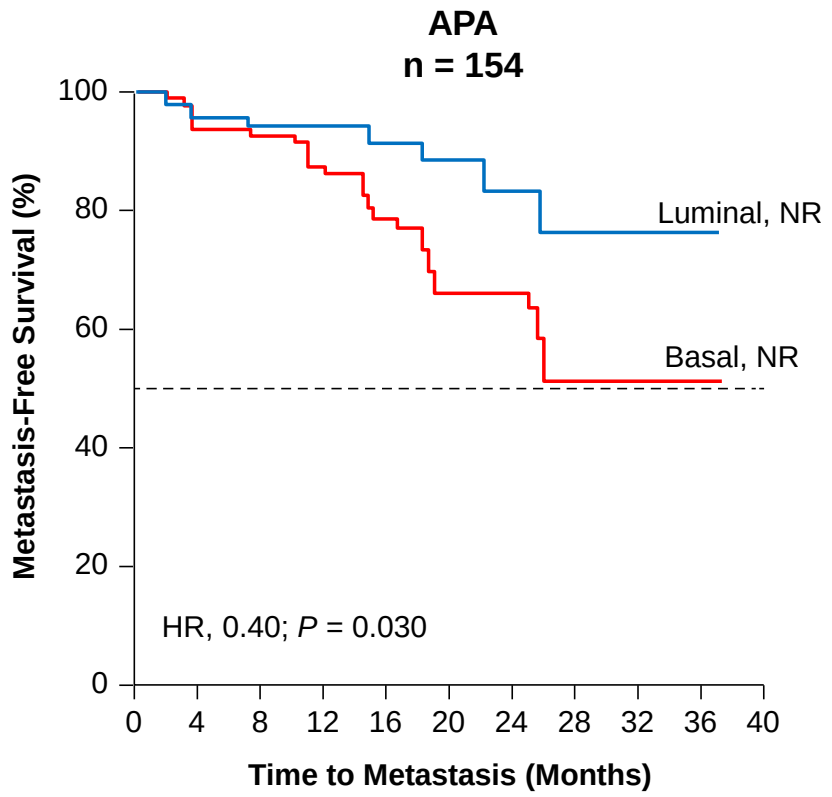
Drug	OR	Lower	Upper
PARP inhibitor	5.24	4.24	6.47
Platinum	8.08	6.36	10.29
Docetaxel	0.14	0.11	0.18



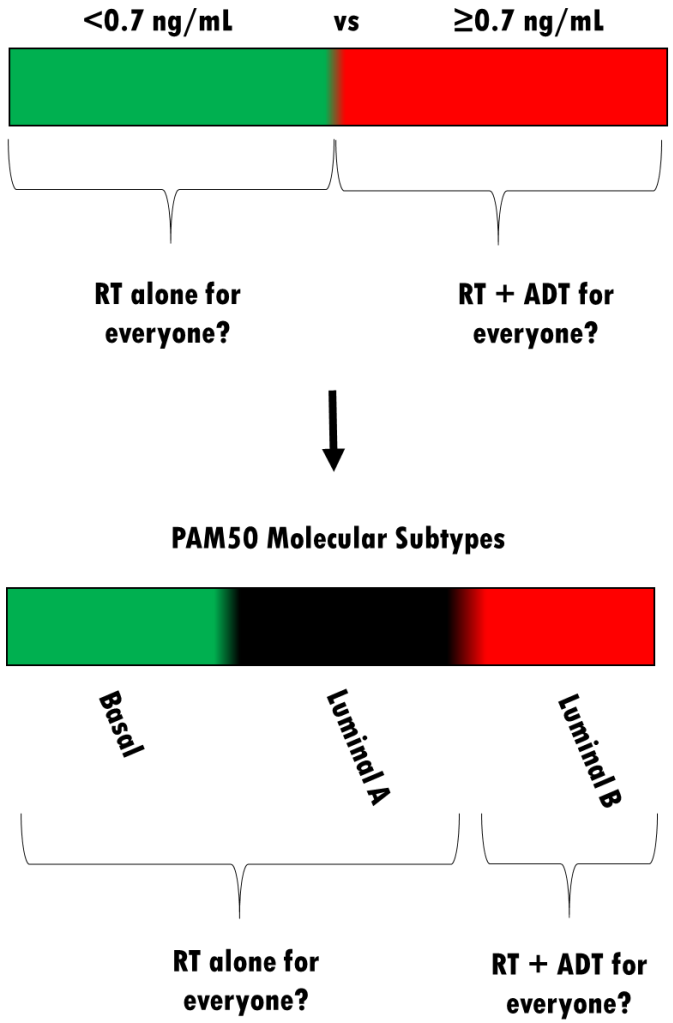
Spratt DE, In submission

Basal tumors more likely to be resistant to ADT

SPARTAN Randomized Controlled Trial



Personalizing ADT Use



Spratt DE, et al. Euro Urol, 2017

Personalizing Therapy

Need biological predictive biomarkers to guide ADT use

NRG GU-006

Post-RP **PSA 0.1-1.0 ng/mL** **And one or more of the following:** • **Gleason 7-10** • **T3-T4** • **Persistently elevated PSA <0.2**	**STRATIFY**	**<u>Surgical Margins</u>** **Positive vs. Negative** **<u>Pre-SRT PSA</u>** **<0.5 ng/mL vs. ≥0.5-1.0 ng/mL** **<u>PAM50 Molecular Subtype</u>** **Luminal B vs. (Luminal A/Basal/Unknown)**	**RANDOMIZE**	**External Beam Radiation:** **64.8 to 70.2, 1.8 Gy/36-39 fractions** **Plus** **Blinded placebo daily for 6 months** **Vs** **Blinded apalutamide daily for 6 months**

Many other promising predictive biomarkers in development

PORTOS- Predicts who benefits most from post-operative radiotherapy (JAMA Onc 2017)

ADT-RS- A neuroendocrine-based biomarker that predicts who benefits from ADT (CCR 2018)

Docetaxel signature

PARP inhibitor signature

RT dose response signature

Gene expression predictive biomarkers

RNA Gene Expression Testing	Answer	Example
Are the frequency of gene expression patterns established?	YES	>5,000 patients
Retrospective data?	YES	
Prospective clinical utility data (change management)?	**NO**	
Prospective clinical benefit data (improve outcomes)?	**NO**	For RP
Randomized data?	YES	SPARTAN (much more to come)
NCCN recommended?	**NO**	

I agree that these tests are not yet ready for prime time

Once SPARTAN data published PAM50 should be available for consumer use

Summary

- Clinically actionable DNA alterations in localized prostate cancer are uncommon
    - There is an unclear role in 2019 to perform routine somatic testing in localized prostate cancer
    - As technology becomes cheaper this may become common place to identify rare alterations to enroll on novel clinical trials

- Germline DNA testing is a "hot topic" and has somehow found its way into guidelines with strong support despite almost no data to support its clinical benefit
    - Will drive up costs, liability of physicians, and lead to over-treatment
    - Unclear impact and unclear which genes clinically matter

Summary

- RNA testing captures tremendous heterogeneity within localized prostate cancer, and has been shown prospectively and retrospectively to outperform standard clinical and pathologic variables and to positively impact treatment decisions and patient QOL.
    - Hopefully guidelines will embrace the benefits shown from these tests, especially in the context of radiotherapy and ADT

Acknowledgements

Funding support

Thank you for coming

@DrSpratticus