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How will new biomarkers change prostate cancer management

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BAUS Section of Oncology Annual Meeting
Cardiff, UK

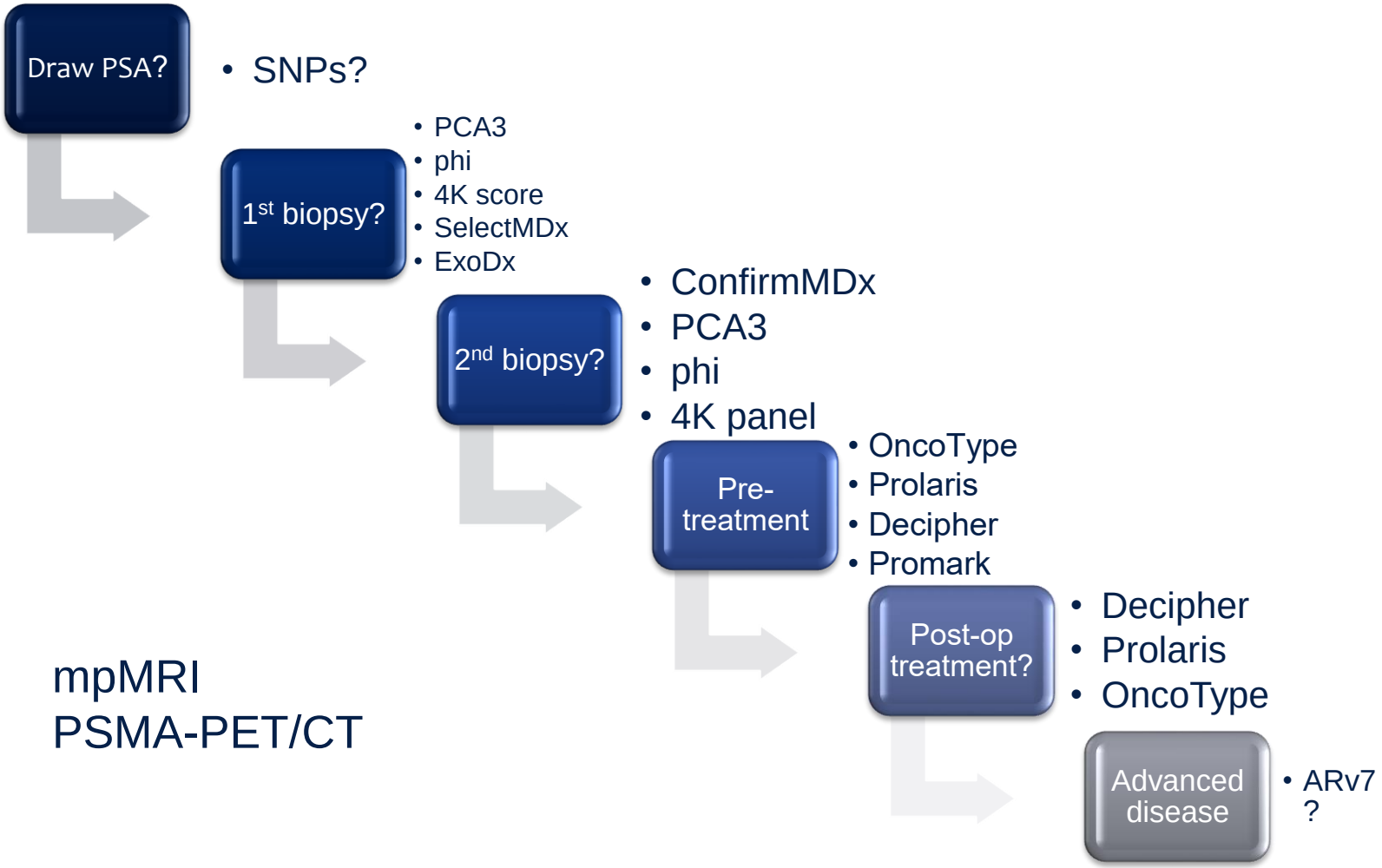
15 November 2016

@dr_coops

Disclosures

- Consulting relationships with:
  - Astellas
  - Dendreon
  - Myriad
- Institutional research support:
  - GenomeDx
  - Genomic Health
  - Myriad

Prostate cancer 2016: *Decision, decisions…*



Pre-diagnosis principles

1. Any candidate marker has to improve on an existing multivariable gold standard (not just PSA).
   Risk calculators: e.g. PCPT, ERSPC, Sunnybrook

2. High-quality methodology is absolutely critical, especially for retrospective studies.
   - **REporting of tumor MARKer (REMARK)** guidelines – McShane et al. JCO 2005; 23:9067
   - **P**rospective-specimen collection, **R**etrospective **B**linded **E**valuation (**PROBE**) - Pepe et al. JNCI 2008; 100:1432

3. The goal is *not* identification of prostate cancer. The goal is identification of potentially lethal prostate cancer.

Should we consider *pre-PSA* testing in the population?

Evaluation of Multiple Risk–Associated Single Nucleotide Polymorphisms Versus Prostate-Specific Antigen at Baseline to Predict Prostate Cancer in Unscreened Men

Robert J. Klein [a,], Christer Hallden [b,†], Amit Gupta [c,†], Caroline J. Savage [d], Anders Dahlin [e], Anders Bjartell [f], Jonas Manjer [g], Peter T. Scardino [c], David Ulmert [c,f], Peter Wallström [h], Andrew J. Vickers [d], Hans Lilja [b,c,i]*

	Any prostate cancer	Aggressive or advanced prostate cancer (clinical stage ≥T3, evidence of metastasis, WHO grade 3, or Gleason stage ≥8 at diagnosis)	Advanced prostate cancer (clinical stage ≥T3 or evidence of metastasis at diagnosis)
PSA alone	0.792 (0.774–0.810)	0.823 (0.792–0.855)	0.800 (0.771–0.830)
PSA plus SNPs	0.791 (0.773–0.809)	0.811 (0.777–0.844)	0.788 (0.757–0.818)
SNPs alone	0.571 (0.548–0.594)	0.498 (0.455–0.541)	0.499 (0.460–0.538)

WHO = World Health Organization; SMP = single nucleotide polymorphism.

† All estimates have been corrected for overfit using 10-fold repeated cross-validation and are reported as area under the curve (95% confidence interval).

Klein et al. Eur Urol 2012; 61:471

Tests to *consider* before a first biopsy

PCA3

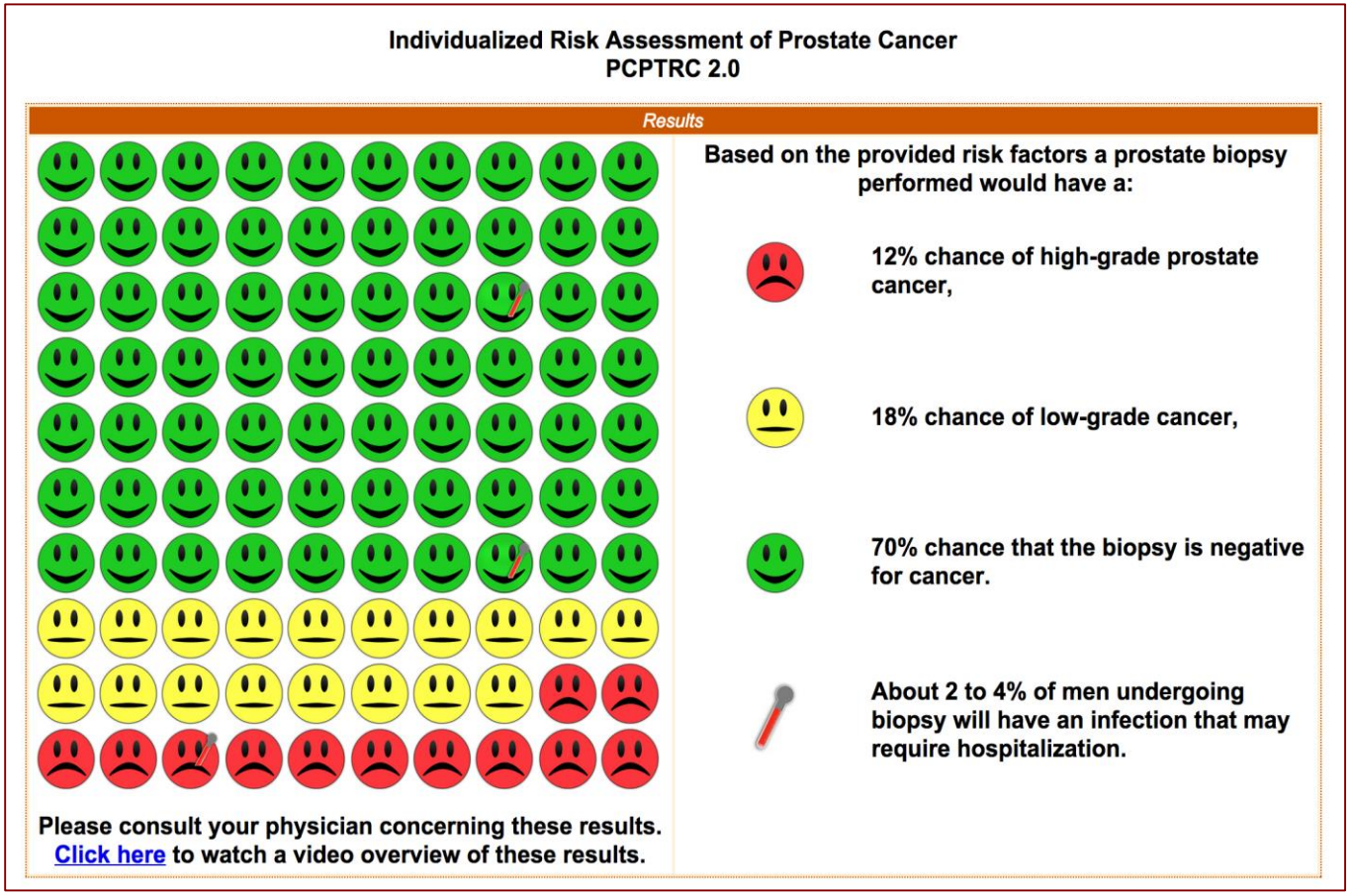
4K

phi

SelectMDx

ExoDx

mpMRI



4K and phi

Prostate Cancer

Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer

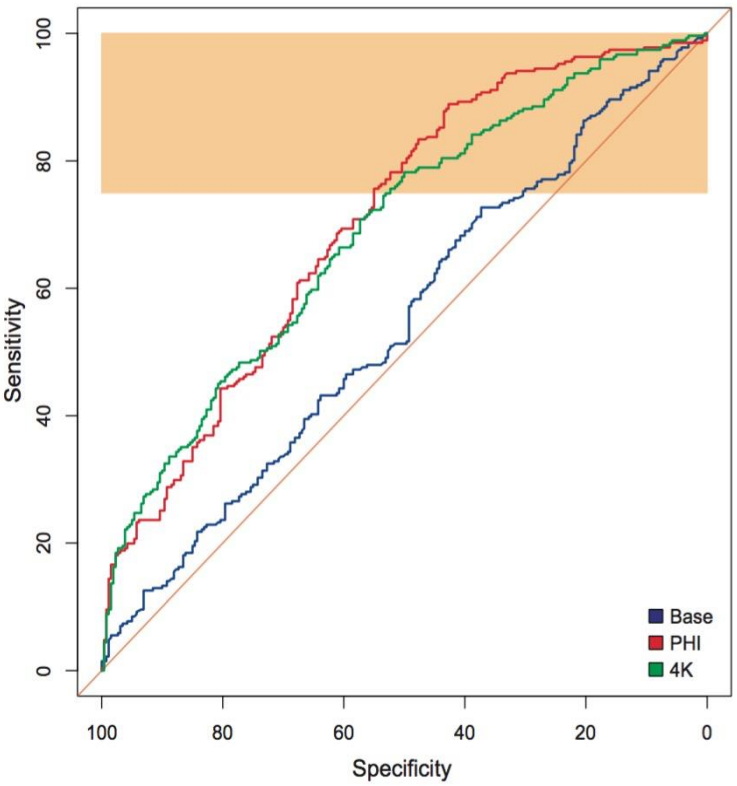
Tobias Nordström[a,b,*], *Andrew Vickers*[c], *Melissa Assel*[c], *Hans Lilja*[d,e,f], *Henrik Grönberg*[b], *Martin Eklund*[b,g]

phi: PSA, fPSA, -2proPSA
4K: PSA, fPSA, iPSA, HK2

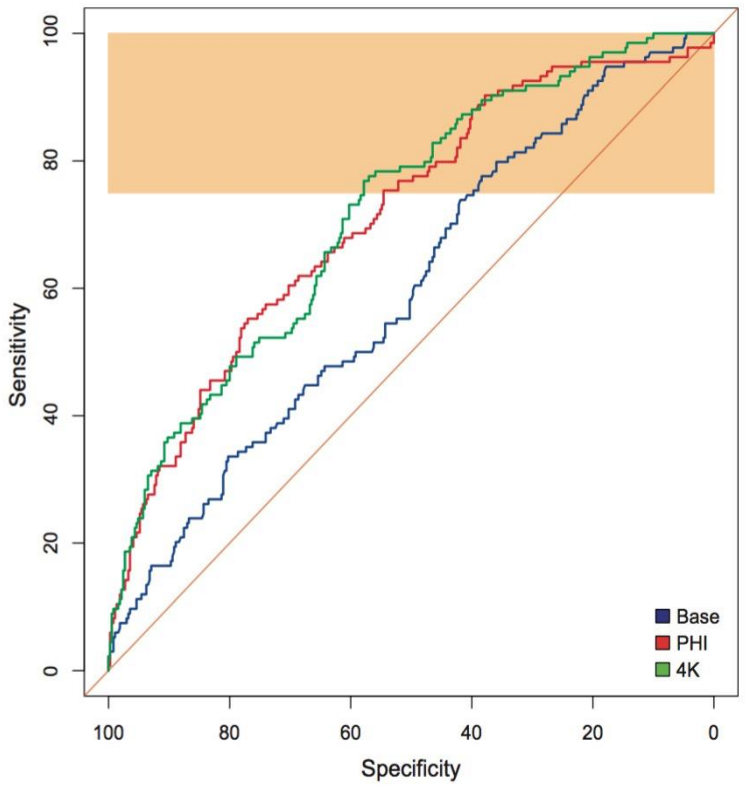
Conclusions: The four-kallikrein panel and PHI similarly improved discrimination when predicting PCa and high-grade PCa. Both are simple blood tests that can reduce the number of unnecessary biopsies compared with screening with total PSA, representing an important new option to reduce harm.

4K and phi

Any cancer



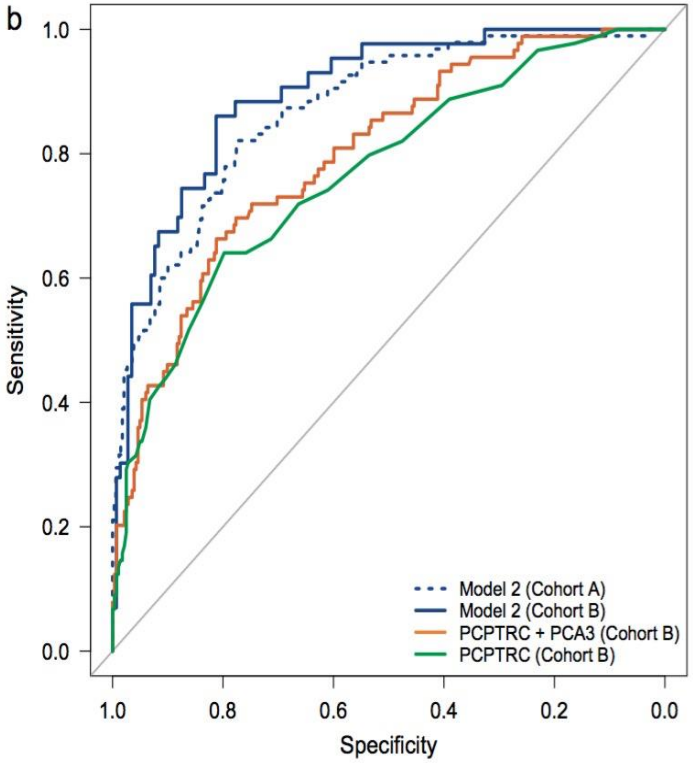
High-grade cancer



Nordström et al. Eur Urol 2015; 68:139

SelectMDx

- Urinary assay for *HOXC6* and *DLX1* mRNA transcripts
- Validated in 2 multicenter cohorts across 6 centers in the Netherlands (N=519, N=386), mixed de novo and repeat biopsy



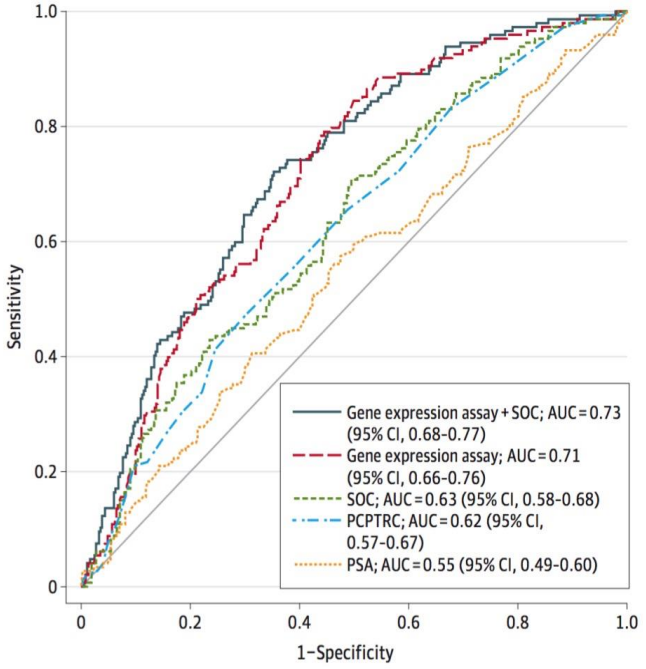
ExoDX

- Assessment of urinary exosomal RNA (PCA3, TMPRSS2:ERG, SPDEF as control) without prior DRE
- N=255 training, N=519 validation

Table 1. Performance of Gene Expression Assay[a] in the Training Cohort

	Biopsy Result				
	High Grade	Negative and Low Grade	Total	Performance, % (SE)	(95% CI)
ExoDx Prostate IntelliScore > cut point	76	128	204	Sensitivity, 97.44 (1.79)	(93.93-100)
ExoDx Prostate IntelliScore ≤ cut point	2	49	51	Specificity , 27.68 (3.36)	(21.09-34.28)
Total	78	177	255	PPV, 37.25 (3.39)	(30.62-43.89)
				NPV, 96.08 (2.72)	(90.75-100)
High-grade biopsy prevalence %	30.59	Fraction predicted negative	20.00		

Figure 2. Area Under Receiver Operating Characteristic Curve (AUC) for Performance of Gene Expression Assay Score Plus Standard of Care (SOC), Gene Expression Assay Score, or SOC in the Intended Use Validation Cohort (N = 519)



Tests to consider before a *repeat* biopsy

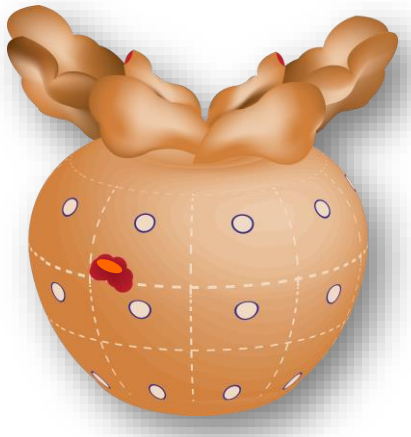
PCA3

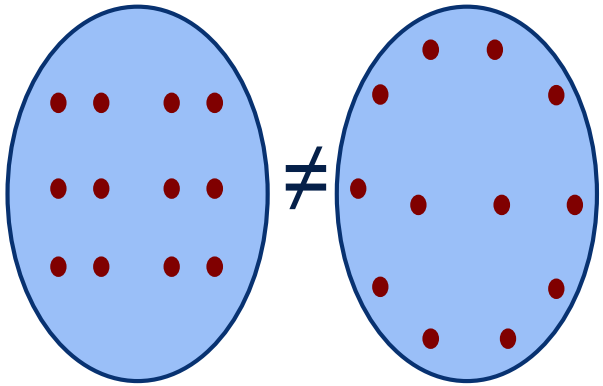
4K

phi

ConfirmMDx

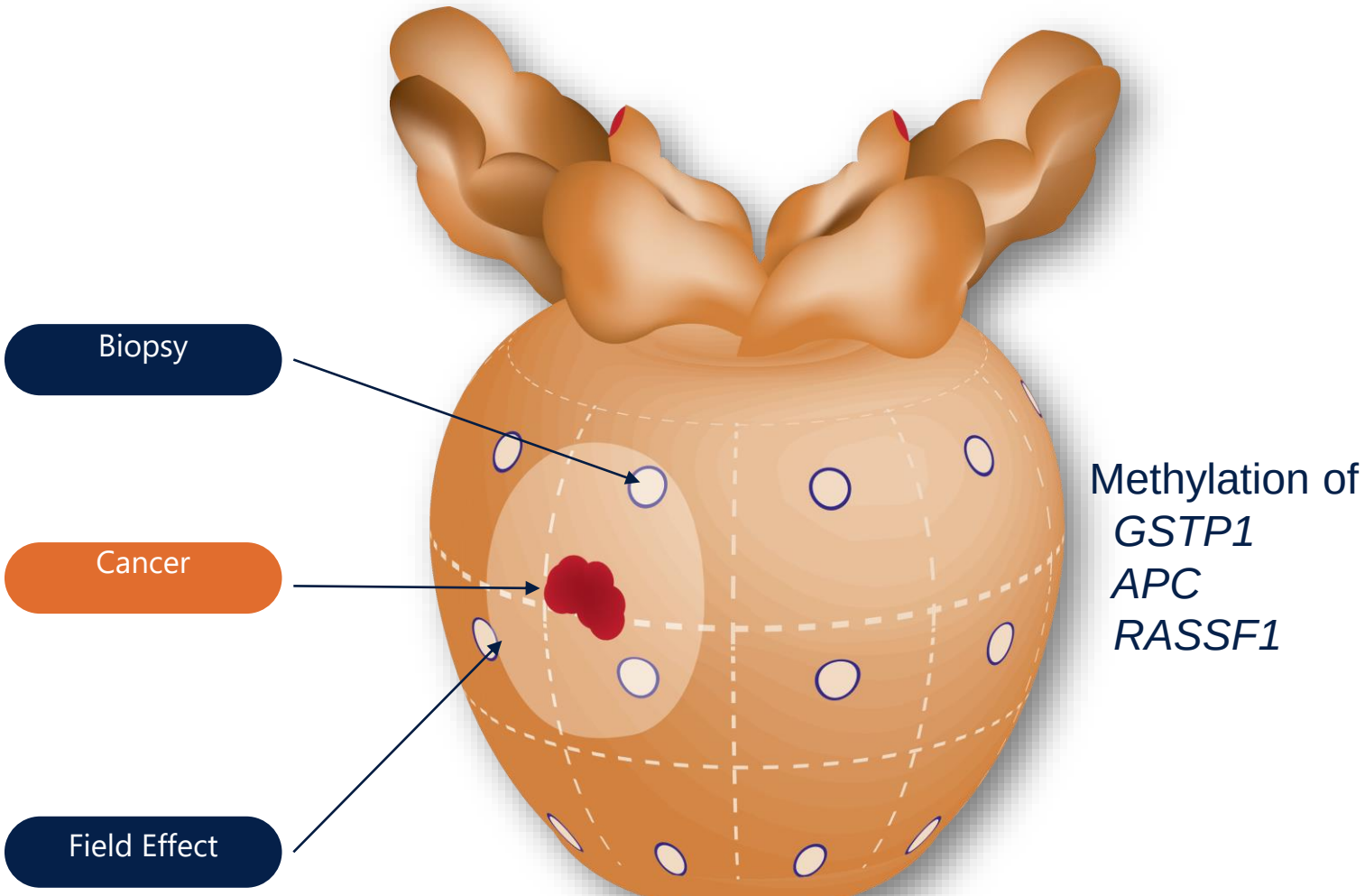
mpMRI



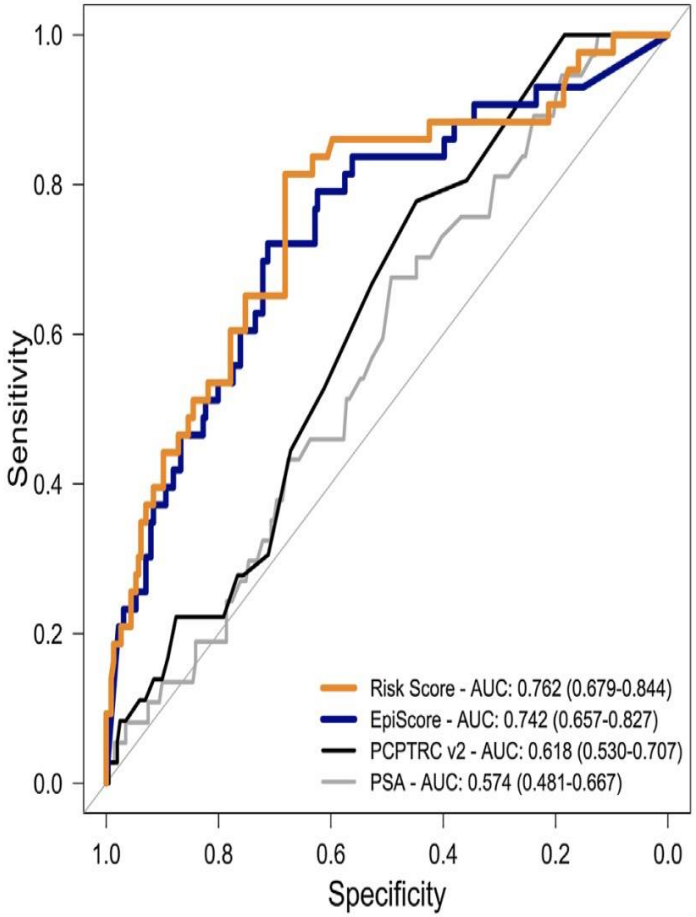


Routinely include anterior cores

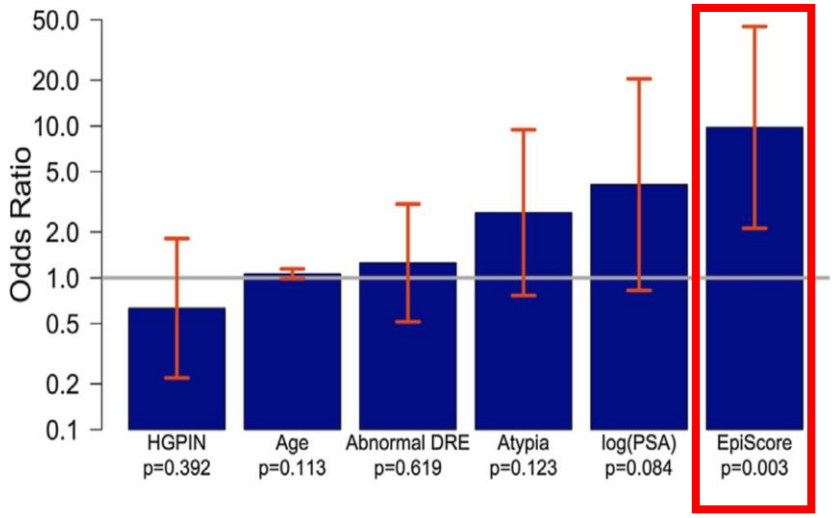
ConfirmMDx


Biopsy
Cancer
Field Effect
Methylation of
GSTP1
APC
RASSF1

ConfirmMDx Risk Profile Score



Outperforms traditional score methods like PSA and Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator 2.0 (PCPTRC2)



NPV for high-grade disease: 96%

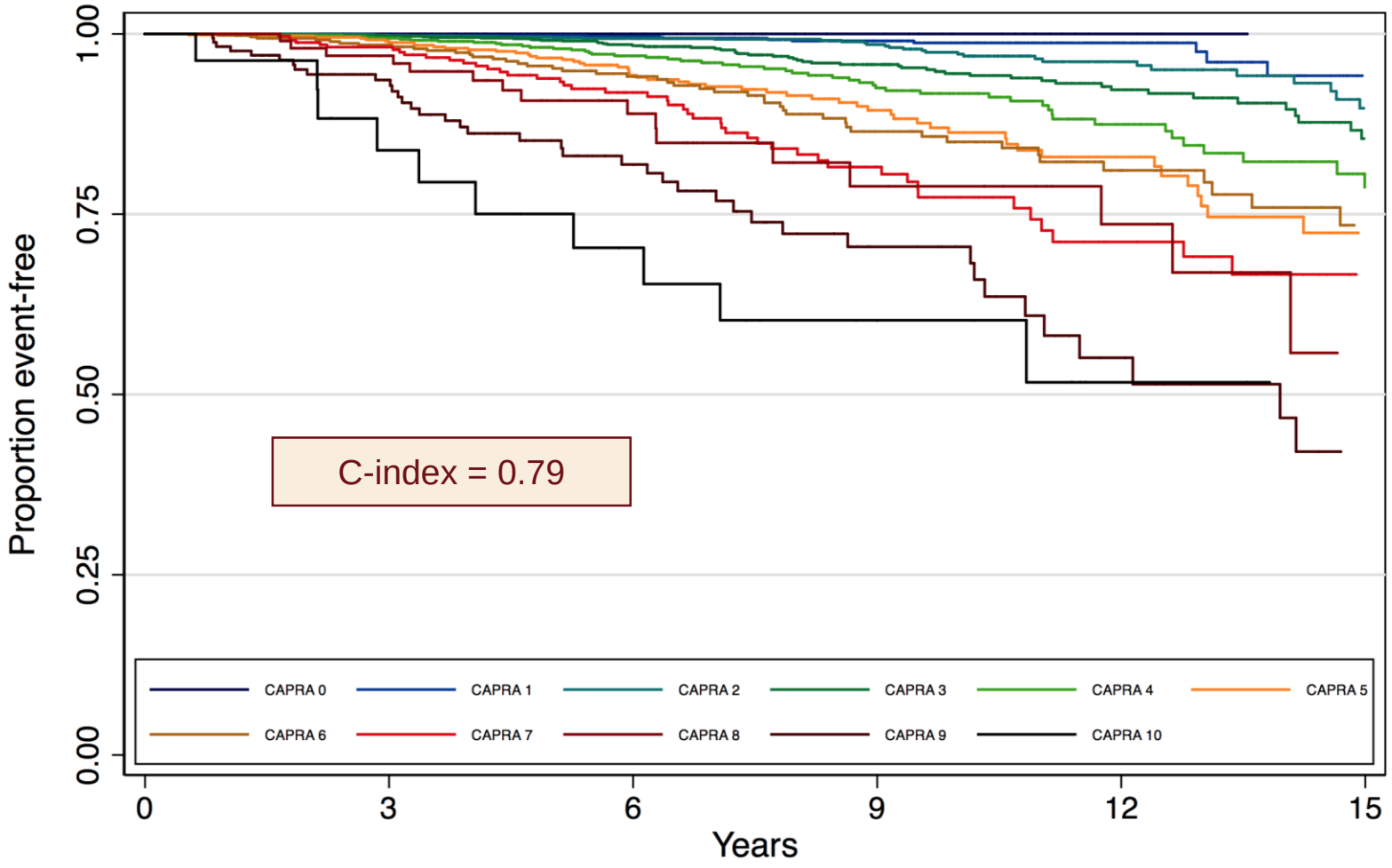
Post-diagnosis: similar principles

A putative biomarker must improve on an existing, *multivariable* clinical model, ideally a previously validated one

Nomograms
CAPRA / CAPRA-S

Not just Gleason score alone or the D'Amico / NCCN risk groups

The bar is high for improved accuracy



Prolaris (Myriad Genetics)

Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study

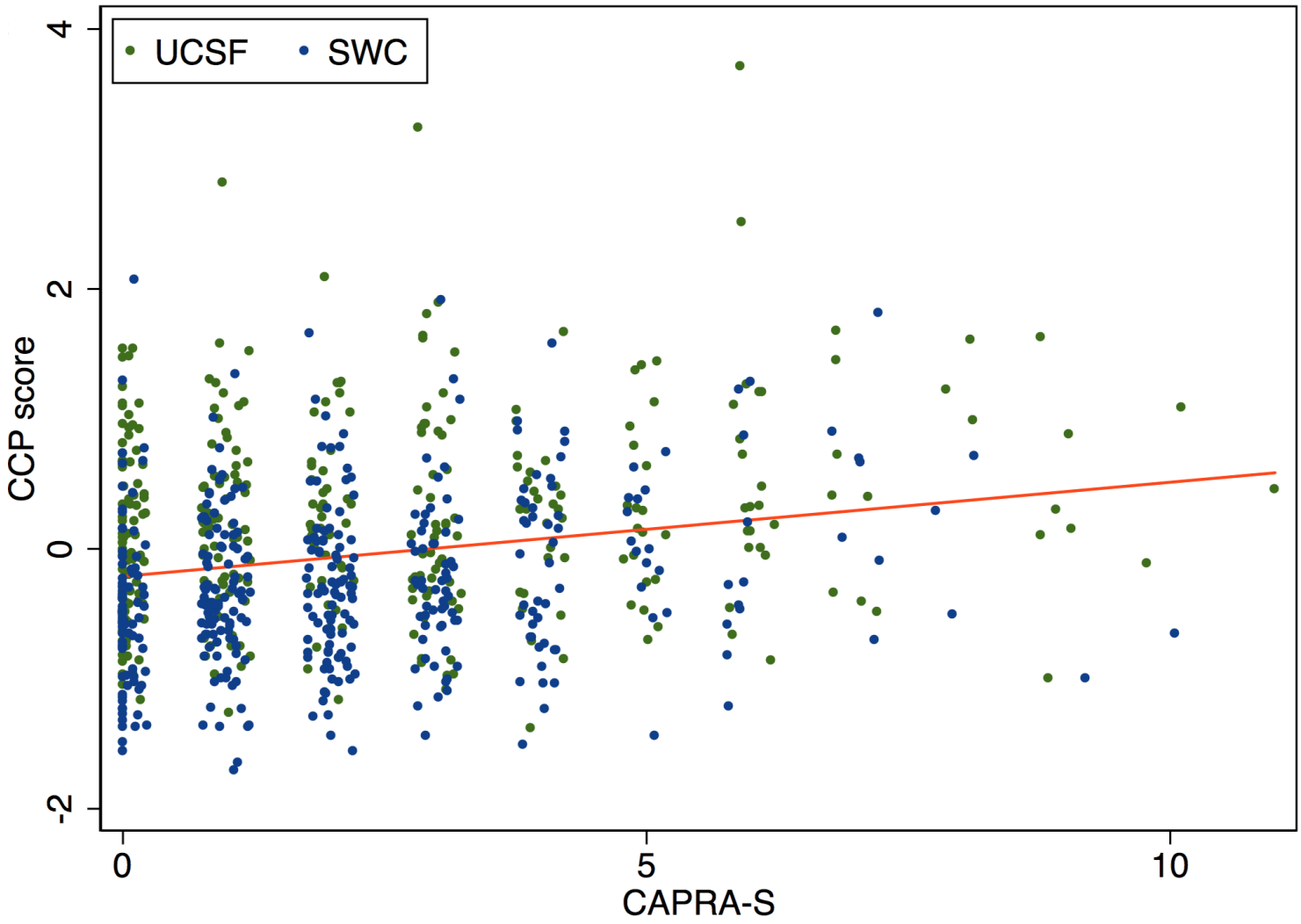
Jack Cuzick, Gregory P Swanson*, Gabrielle Fisher, Arthur R Brothman, Daniel M Berney, Julia E Reid, David Mesher, V O Speights, Elzbieta Stankiewicz, Christopher S Foster, Henrik Møller, Peter Scardino, Jorja D Warren, Jimmy Park, Adib Younus, Darl D Flake II, Susanne Wagner, Alexander Gutin, Jerry S Lanchbury, Steven Stone, on behalf of the Transatlantic Prostate Group*

31 cell cycle progression (CCP) genes, normalized to 15 housekeeper genes

Score is expressed as average centered expression of CCP genes relative to housekeeper genes; negative scores = less active CCP, positive scores = more active CCP

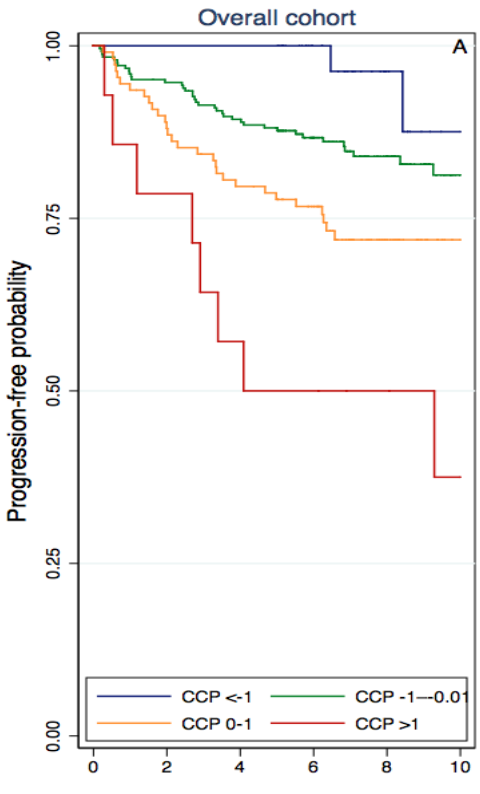
Predicts mortality from biopsy

Biomarkers vs. clinical parameters



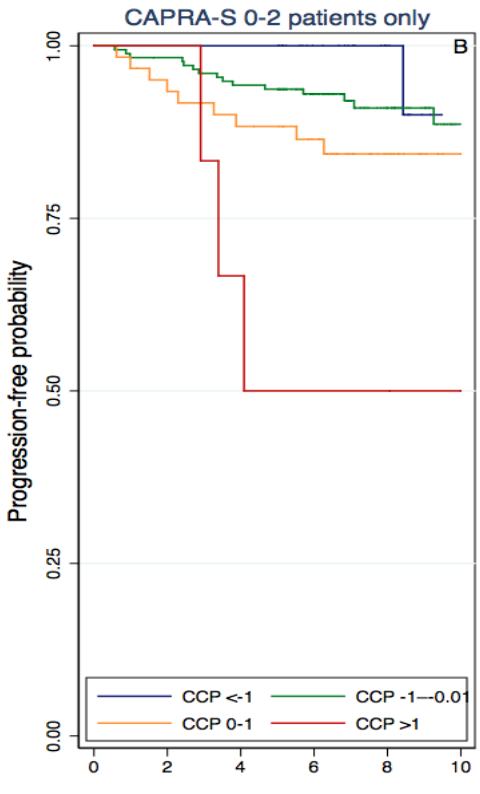
Cooperberg et al, JCO 31:1428, 2013

CCP score stratifies outcomes



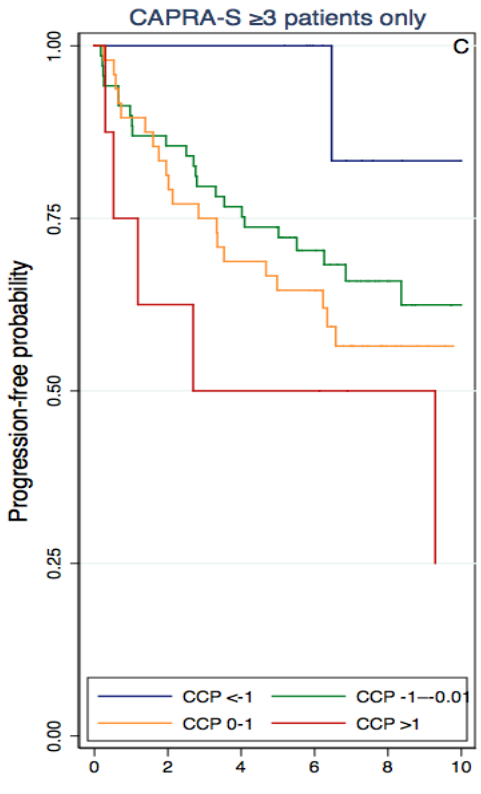
Number at risk

CCP score <-1	43	43	43	29	13	2
CCP score -1—-0.01	245	231	217	154	88	37
CCP score 0-1	109	95	85	72	33	14
CCP score >1	14	11	8	7	5	2



Number at risk

CCP score <-1	32	32	32	22	11	2
CCP score -1—-0.01	176	172	165	118	68	26
CCP score 0-1	61	56	52	44	24	11
CCP score >1	6	6	4	3	3	1



Number at risk

CCP score <-1	11	11	11	7	2	0
CCP score -1—-0.01	69	59	52	36	20	11
CCP score 0-1	48	39	33	28	9	3
CCP score >1	8	5	4	4	2	1

Cooperberg et al, JCO 31:1428, 2013

Cox model of PGP

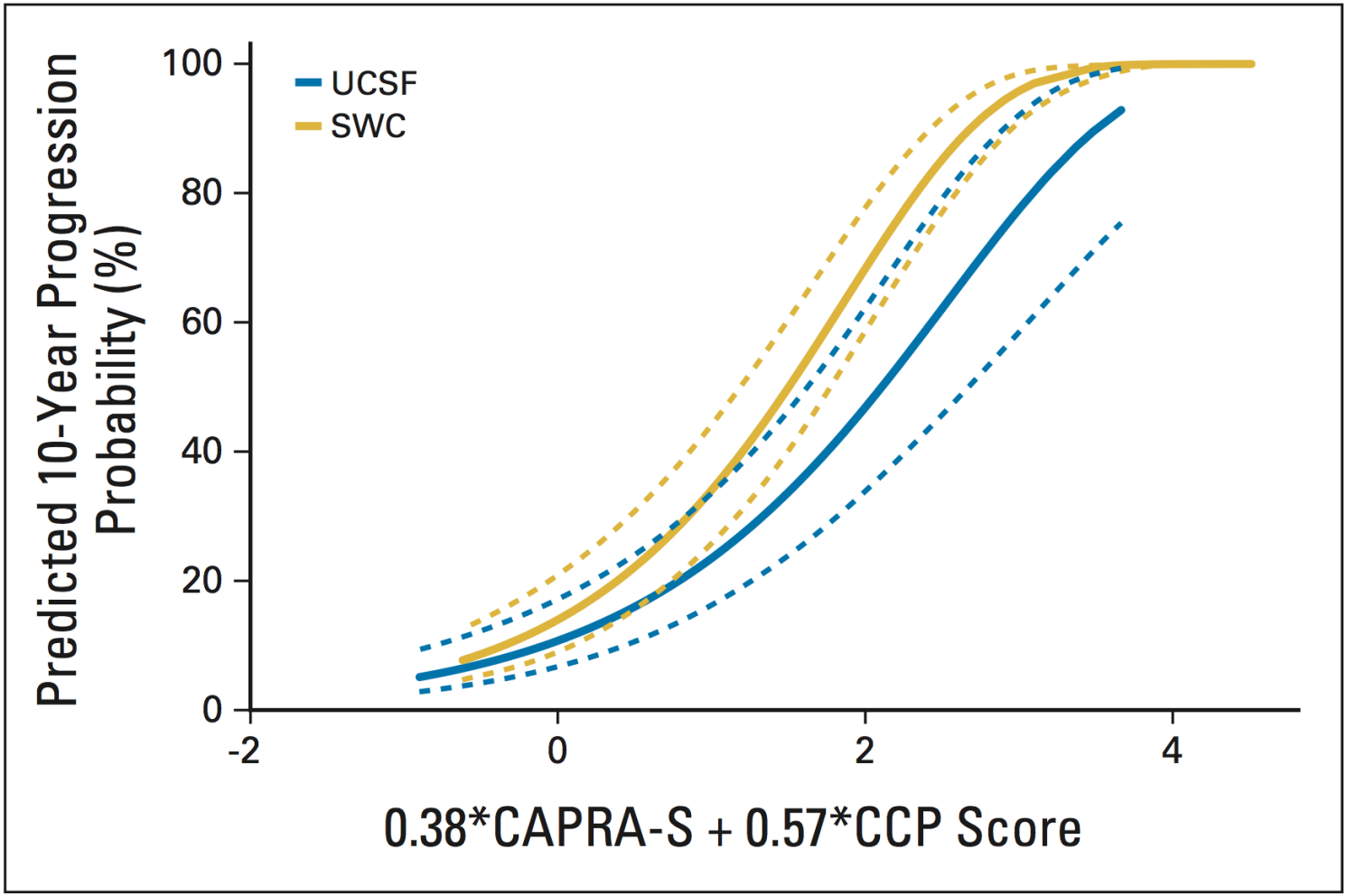
	Univariate			Adjusted model 1			Adjusted model 2		
CCP score	HR	p	95% CI	HR	p	95% CI	HR	p	95% CI
≤-1	ref								
>-1 – 0	3.5	0.08	0.9 – 14.6	3.3	0.10	0.8 –13.6	2.9	0.15	0.7 – 12.0
>0 – 1	6.8	0.009	1.6 – 28.3	5.1	0.03	1.2 – 21.4	4.7	0.04	1.1 – 19.8
>1	14.9	0.001	3.1 – 70.3	9.4	0.005	2.0 – 44.7	12.7	0.002	2.5 – 63.3

Model 1 = adjusted by CAPRA-S

Model 2 = adjusted by individual clinical variables

C-index 0.73 for CAPRA-S vs. 0.77 for combined model

10-year PGP predictions



Cooperberg et al, JCO 31:1428, 2013

Oncotype DX GPS (Genomic Health)

- Quantitative 17-gene RT-PCR assay on manually microdissected tumor tissue from needle biopsy
- Genes and biological pathways predictive of multiple endpoints, with emphasis on clinical recurrence
- Optimized for very small tissue input: six 5 micron sections of single needle biopsy block with as little as 1 mm tumor length

Androgen Signaling
AZGP1
FAM13C
KLK2
SRD5A2

Cellular Organization
FLNC
GSN
GSTM2
TPM2

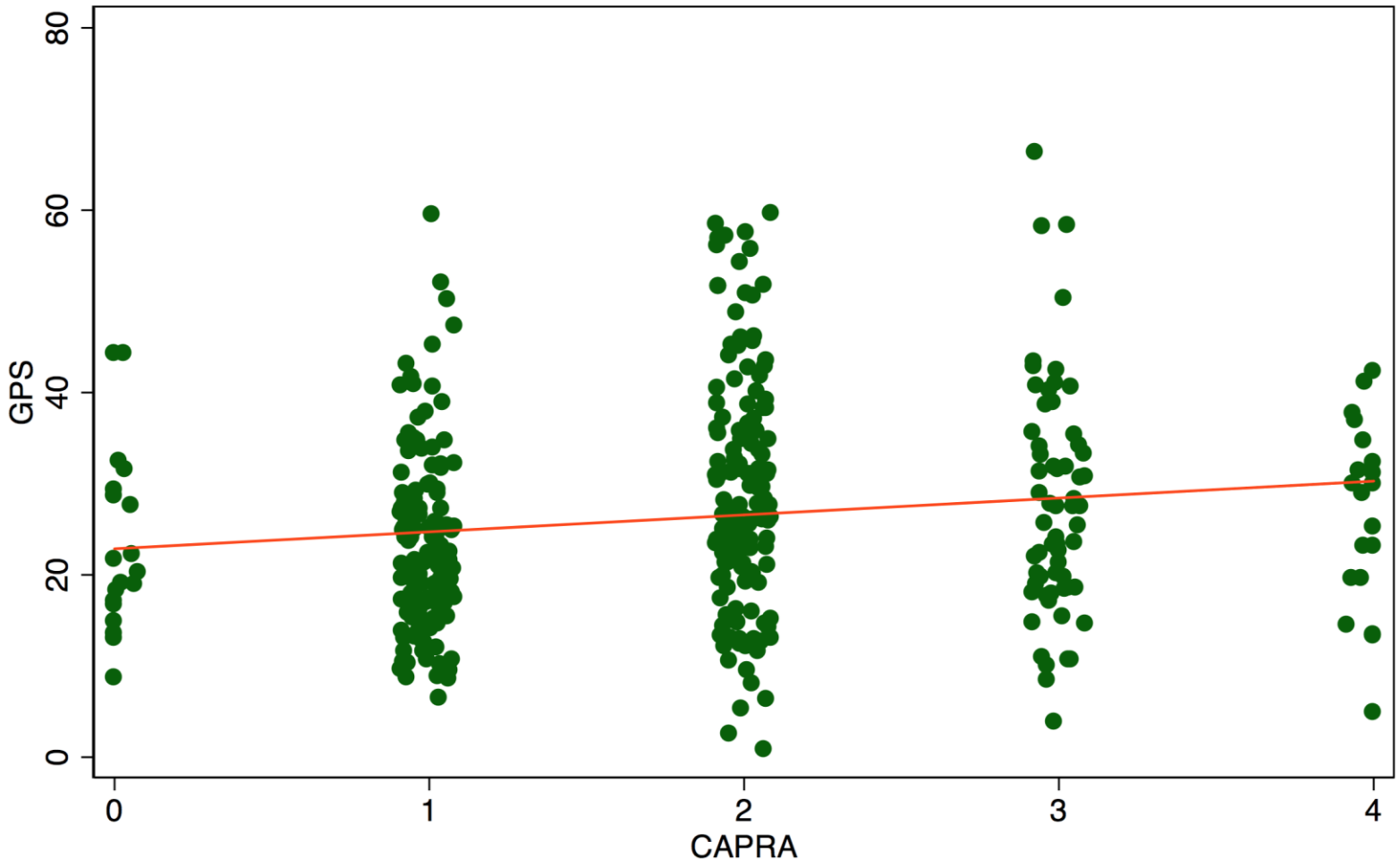
Stromal Response
BGN
COL1A1
SFRP4

Reference
ARF1
ATP5E
CLTC
GPS1
PGK1

Proliferation
TPX2

GPS =
0.735*Stromal Response group
-0.352*Androgen Signaling group
+0.095*Proliferation group
-0.368*Cellular Organization group
Scaled between 0 and 100

Weak correlation between CAPRA and GPS



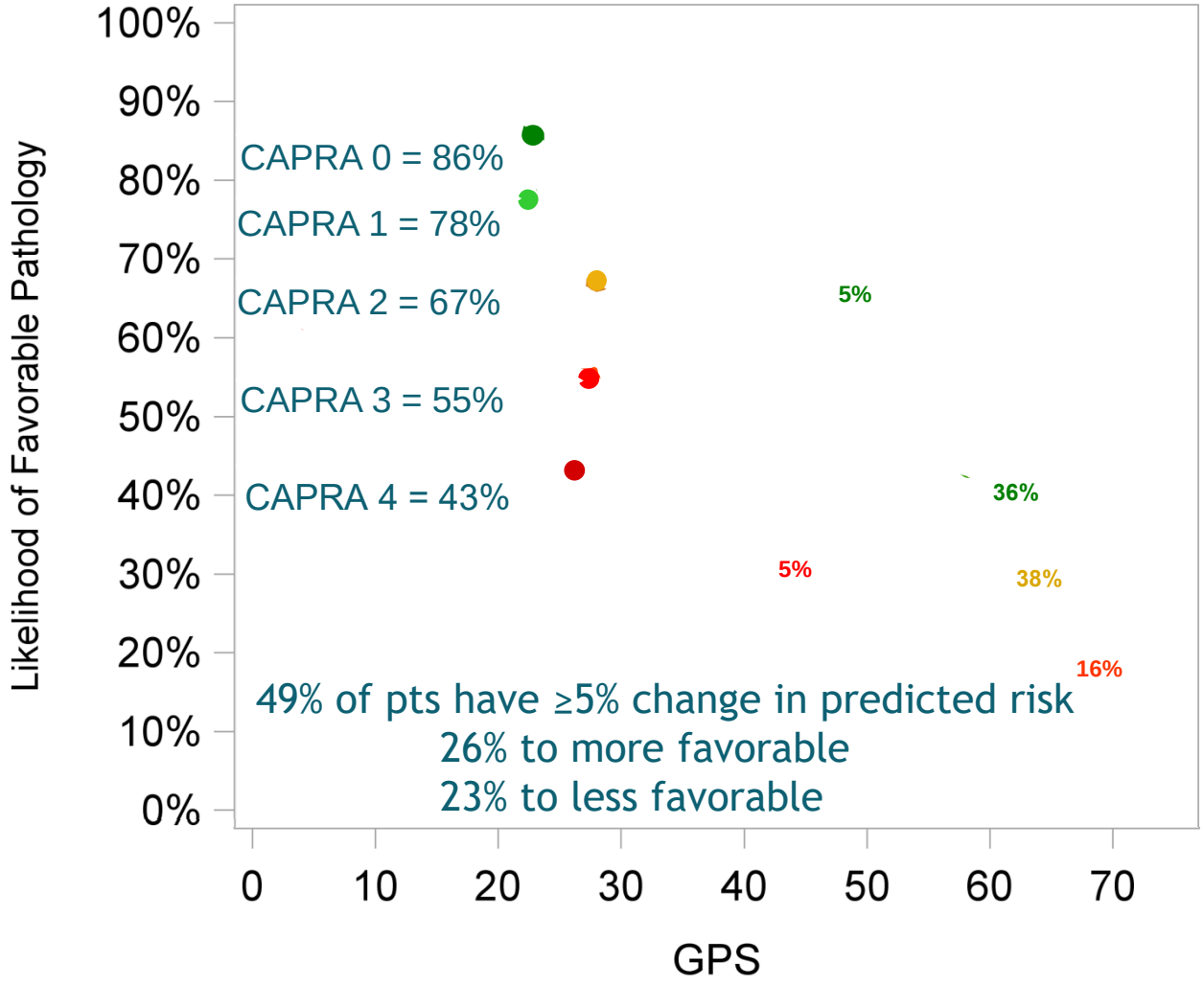
Klein, Cooperberg et al. Eur Urol 66:550, 2014

Multivariable Performance of GPS

Model	Variable	Odds Ratio	95% CI	P-value
1	**GPS (per 20 units)**	**1.85**	**(1.23, 2.81)**	**0.003**
	Age (continuous)	1.05	(1.01, 1.09)	0.004
	PSA (continuous)	1.11	(1.04, 1.18)	0.002
	Clinical Stage T2 vs. T1	1.57	(0.98, 2.51)	0.059
	Biopsy Gleason Score (7 v. 6)	1.70	(1.00, 2.88)	0.050
2	**GPS (per 20 units)**	**2.13**	**(1.44, 3.16)**	**<0.001**
	CAPRA	1.58	(1.24, 2.02)	<0.001

Klein, Cooperberg et al. Eur Urol 66:550, 2014

Adding GPS to CAPRA: predicting pathology



Klein, Cooperberg et al. Eur Urol 66:550, 2014

Additional validation studies

Prolaris

- Predicting BCR and mets following surgery based on biopsy (Bishoff J Urol 2014)
- Predicting BCR after EBRT (Freedland IJROBP 2013)
- Prolaris as outcome in fish oil diet study (Galet, Cancer Prev Res 2014).

OncoType GPS

- Prediction of adverse pathology and BCR following prostatectomy in CPDR cohort (Cullen Eur Urol 2014)

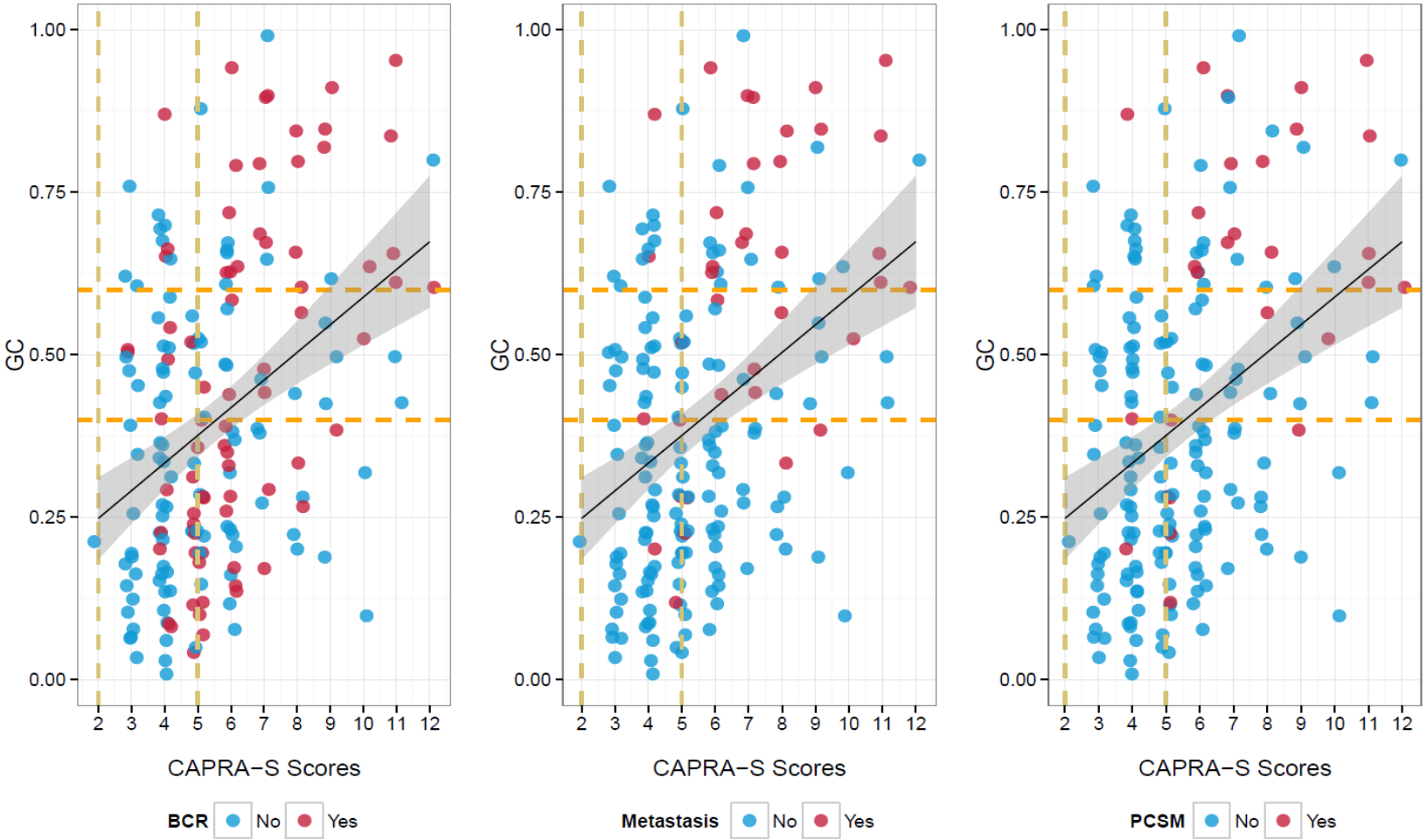
Decipher (GenomeDx Biosciences)

22-gene genomic classifier, with genes chosen purely by statistical selection to predict metastasis among high-risk RP patients, no pathway analysis (includes non-coding genes, 3 unknowns)

Rather than RT-PCR on established gene set, clinical assay is run using Affymetrix Human Exon 1.0ST GeneChip (1.4M probe sets interrogating 5.5M features of whole exome)

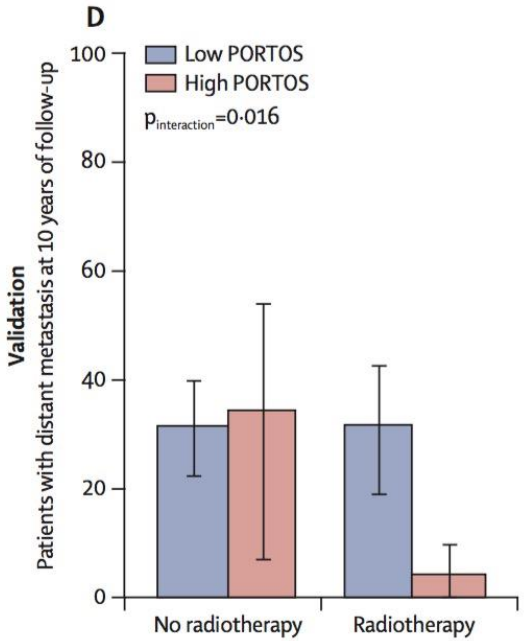
Decipher score is calculated, but a large trove of data is kept in the databank for ongoing / future discovery

Genomic reclassification

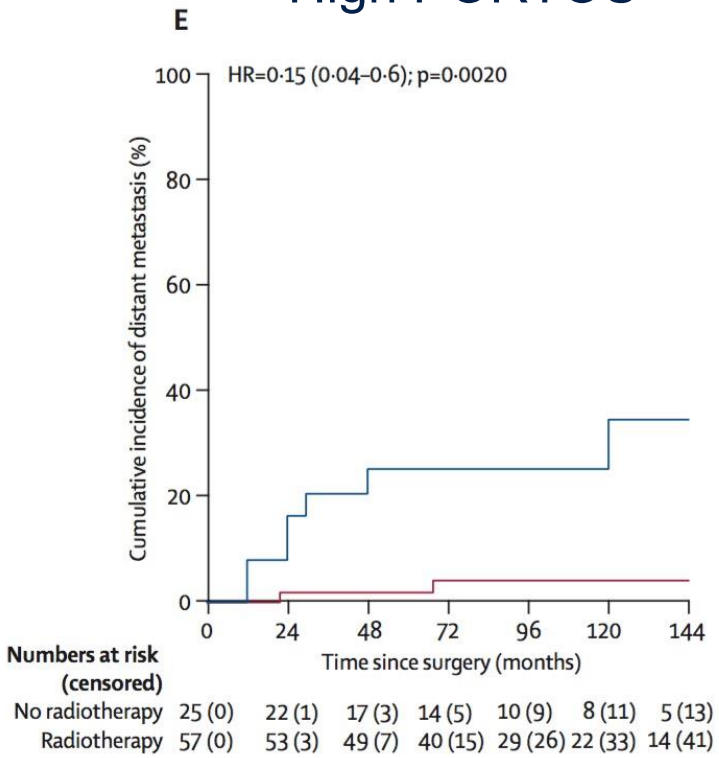


Cooperberg et al. Eur Urol 67:326, 2015

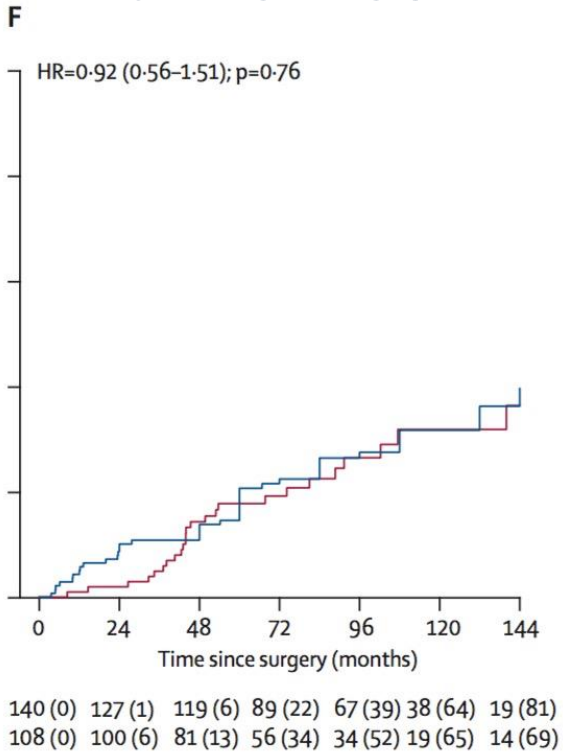
PORTOS score for post-op radiation



High PORTOS

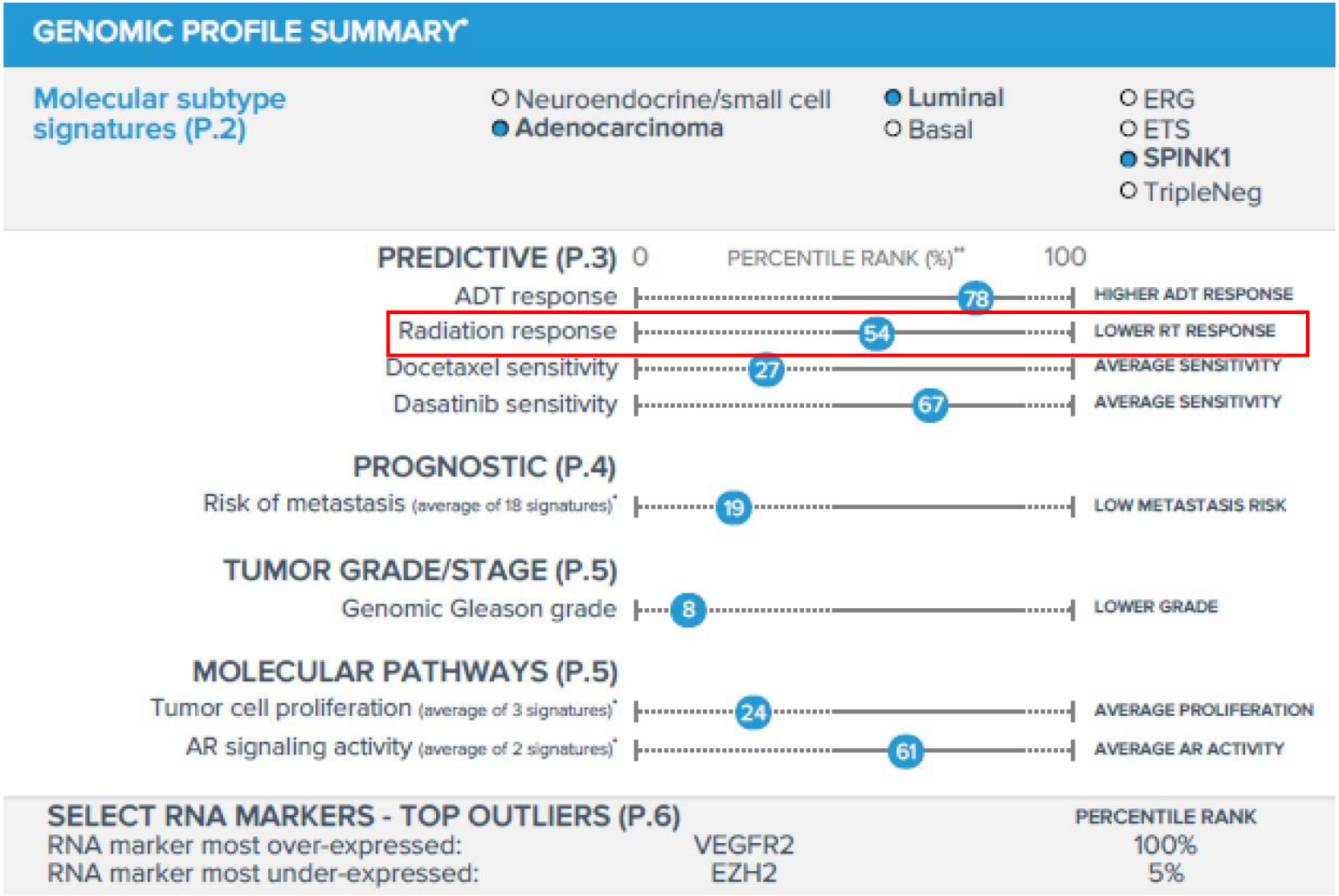


Low PORTOS



Zhao et al. Lancet Oncol 2016 epub

Decipher GRID



“Next generation” liquid biopsy

Coming soon:

Plasma miRNA

CTC enumeration/sequencing

Cell-free DNA

Stay tuned…!

Conclusions and future questions

Emerging biomarkers offer improved *prognostic* information compared to clinical parameters alone

How to (really) use these tests in clinical practice is mostly unclear

Can we do a better job *customizing* active surveillance (Can some men be stratified to watchful waiting? Can a subset be "undiagnosed"?)

Are these tests cost-effective?

Molecular subtyping is finally in sight for prostate cancer

We are barely even at the "end of the beginning"

Thank you — UCSF Urologic Oncology

Peter Carroll

June Chan

Katsuto Shinohara

Max Meng

Kirsten Greene

Sima Porten

Hao Nguyen

Jeff Simko

Robert Blelloch

Felix Feng

Janet Cowan

Stacey Kenfield

Imelda Tenggara

Jenny Broering

Nannette Perez

Pamela Paris

Sarah Joost

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University of California
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Questions?