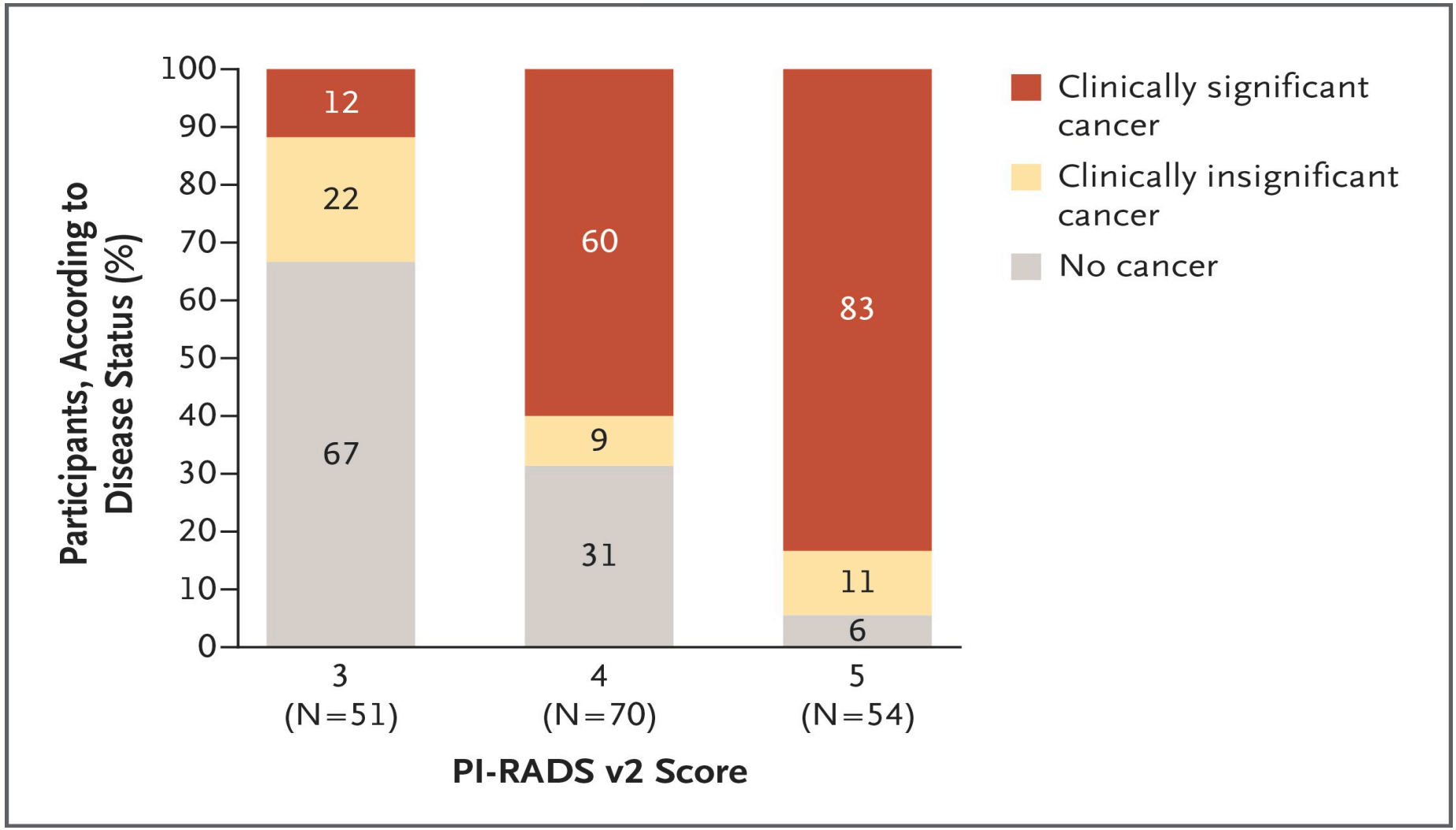
mpMRI as Prostate Cancer Biomarker

Robert E. Reiter MD MBA
Bing Professor of Urologic Oncology
Chief, Division of Urologic Oncology
UCLA

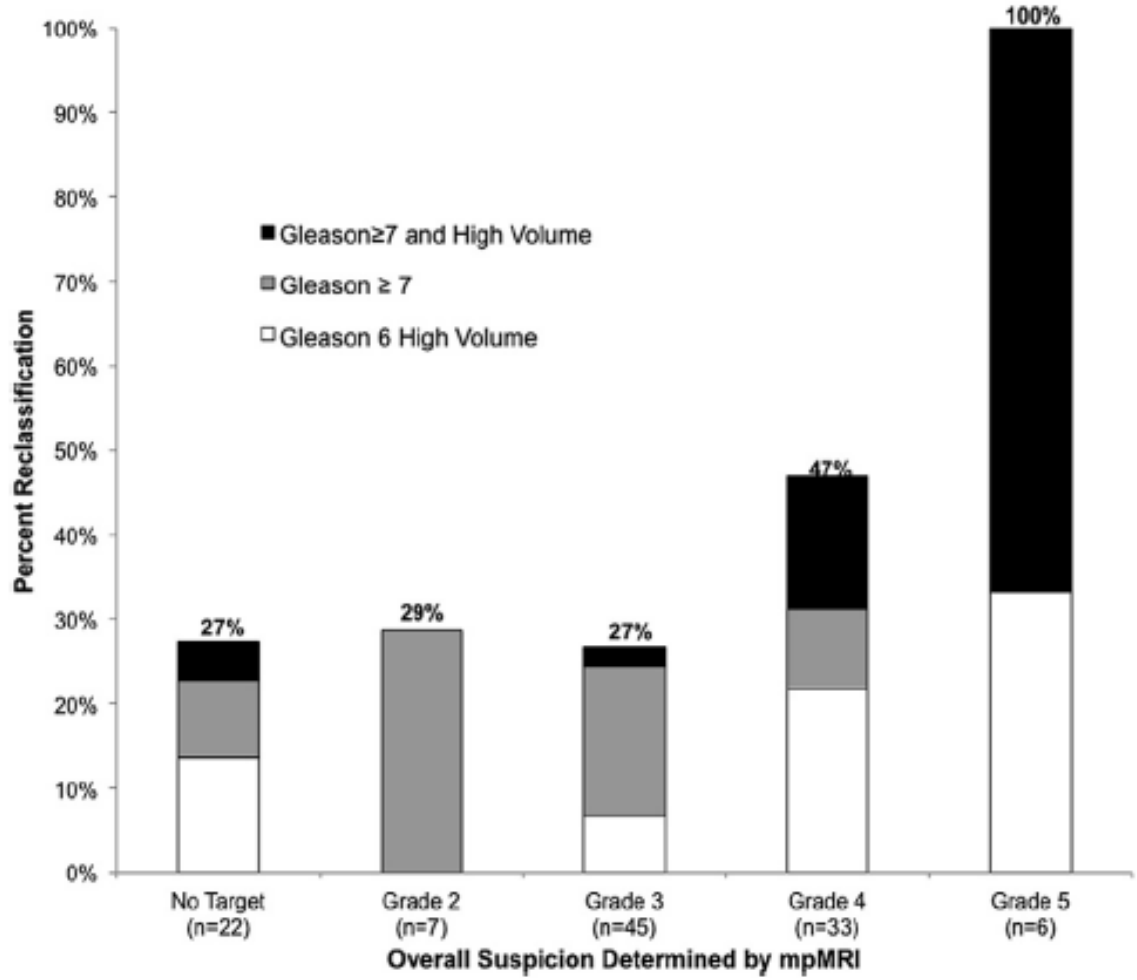
Percentages of Men with Cancer Identified According to PI-RADS v2 Score.



Kasivisvanathan V et al. N Engl J Med 2018;378:1767-1777

The NEW ENGLAND JOURNAL of MEDICINE

Effect of mpMRI on Upgrading/Upstaging in Men with Very Low Risk Prostate Cancer



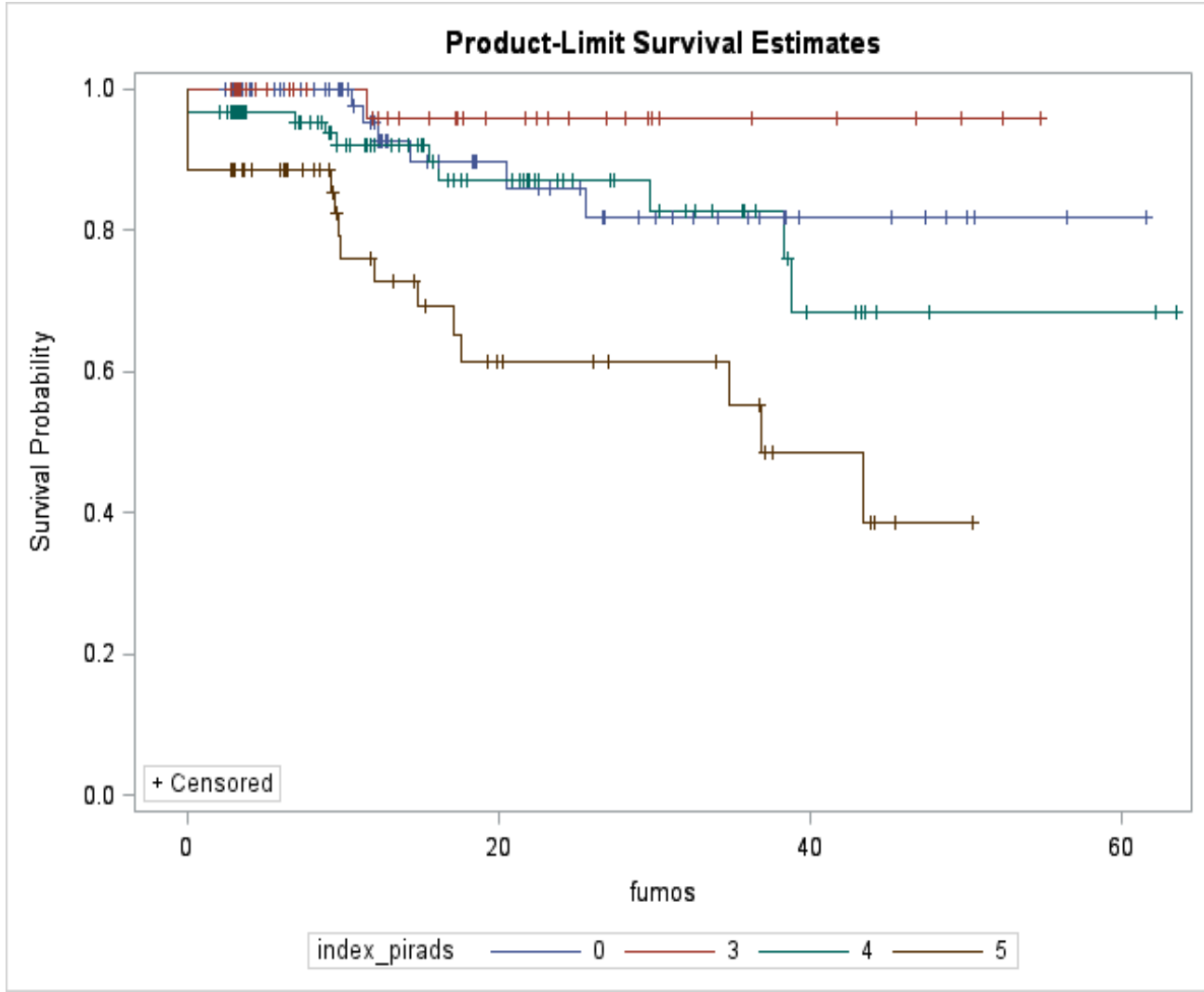
Hu et al Eur. Urol 2014

Predictors of Cancer in 612 Consecutive Men with MRI/Whole Mount Comparison

	All CaP (GS ≥6)	csCAP (GS ≥7)
Sensitivity	45% (42, 47)	65% (61, 69)
PPV	**81% (78, 84)**	**65% (61, 69)**
PI-RADS 3	64% (58, 71)	40% (33, 47)
PI-RADS 4	85% (81, 89)	68% (62, 73)
PI-RADS 5	92% (87, 95)	89% (83, 93)

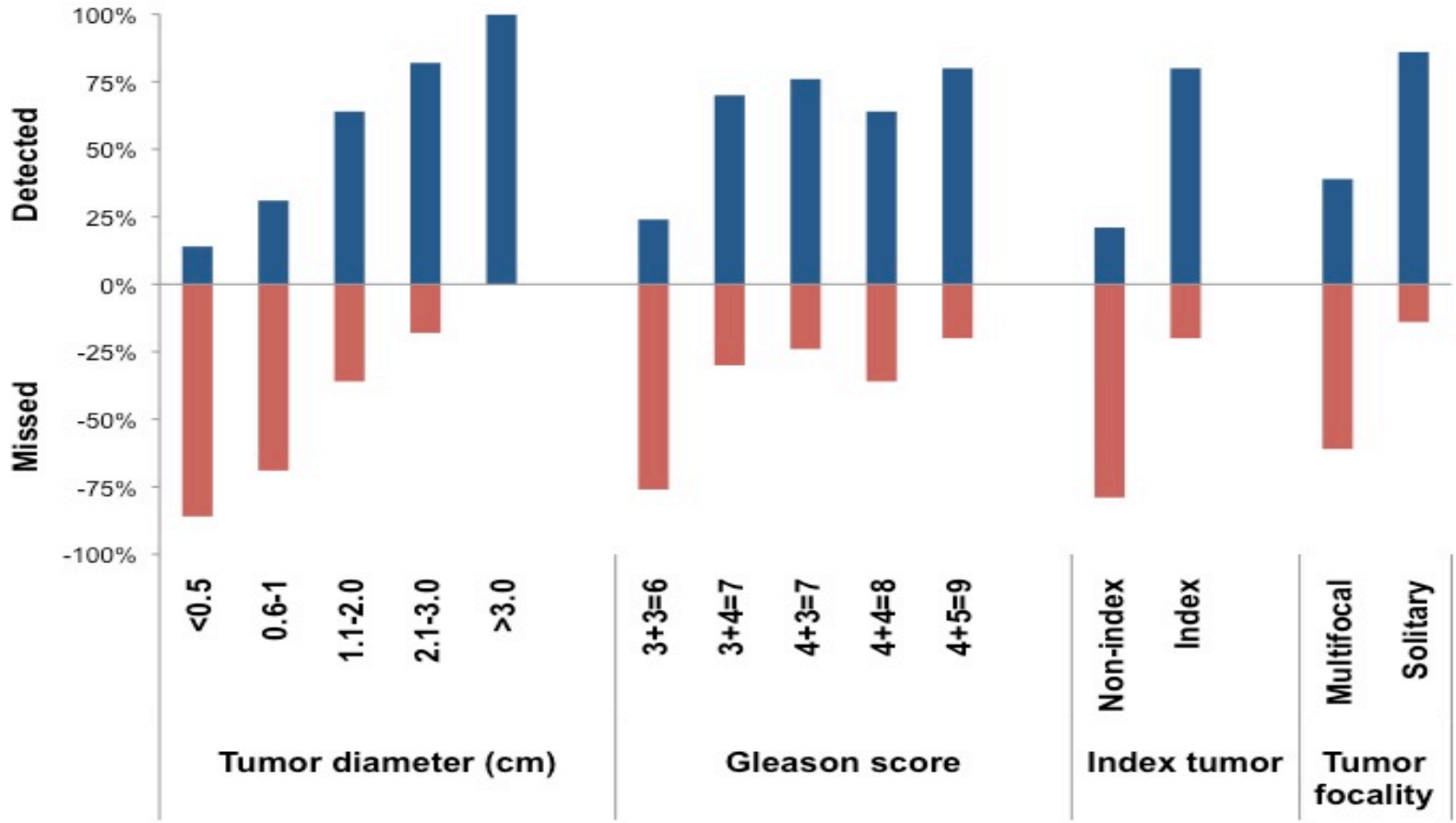
False Positive	**19% (16, 22)**
	PI-RADS 3 56% (n=74)
	PIRADS 4 33% (n=43)
	PIRADS 5 11% (n=15)

PIRAD Predicts BCR Among Patients with (Any) Biopsy Gleason 3+4



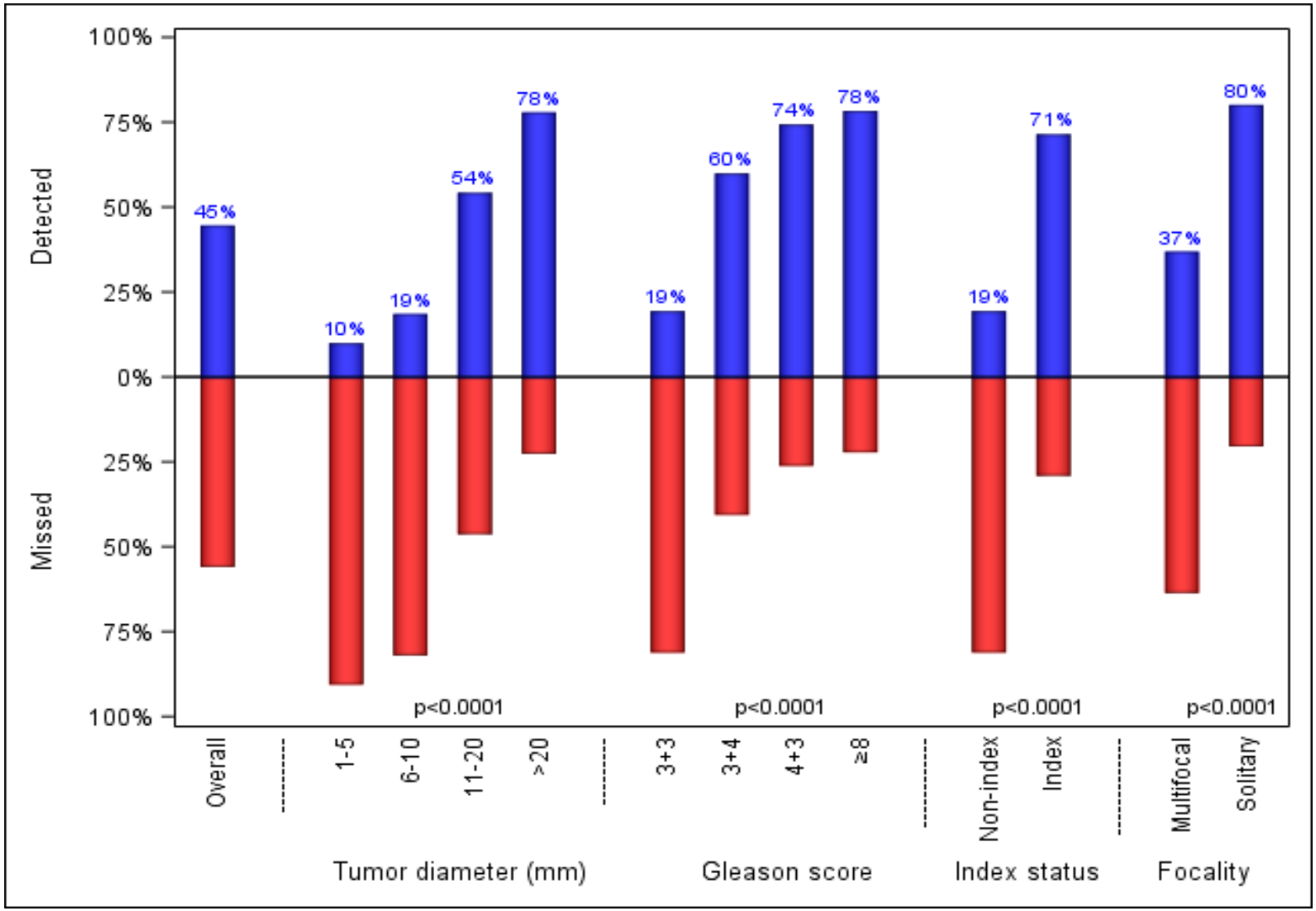
Faena, Unpublished Data

Tumor Detection by MRI: Whole Mount Analysis



Le, Reiter Eur Urol 2014

Summary of Key Results in 612 Patients – Predictors of Detection



Significant predictors of detection (univariate)

- Larger size
- Higher GS
- Index lesion status
- Solitary tumor

Distribution of PIRAD scores by Gleason score of final pathology

	Solitary				Multifocal			
Gleason score	**3+3**	**3+4**	**4+3**	**>=4+4**	**3+3**	**3+4**	**4+3**	**>=4+4**
No MRI lesion (missed)	11	22	6	4	431	152	32	14
PI-RADS 3 (detected)	6	15	5	0	45	46	11	3
PI-RADS 4 (detected)	7	39	14	12	42	88	26	12
PI-RADS 5 (detected)	3	24	27	21	3	48	27	17
Total (from Table 2b)	**27 (40)**	**100 (22)**	**52 (12)**	**37 (11)**	**521 (83)**	**334 (45)**	**96 (33)**	**46 (30)**

Questions

- What are the genomic/biologic determinants of visibility/high PIRAD vs invisibility/low PIRAD?
  - Why is a PIRAD 5 tumor more likely to recur than one that is PIRAD 3?
  - What is the biology being captured by MRI sequences such as diffusion, perfusion?
- Can diagnostic biomarkers assays add biological information to mpMRI that can aid in management decisions?

Summary of Radiomics Studies *(Stoyanova et al.)*

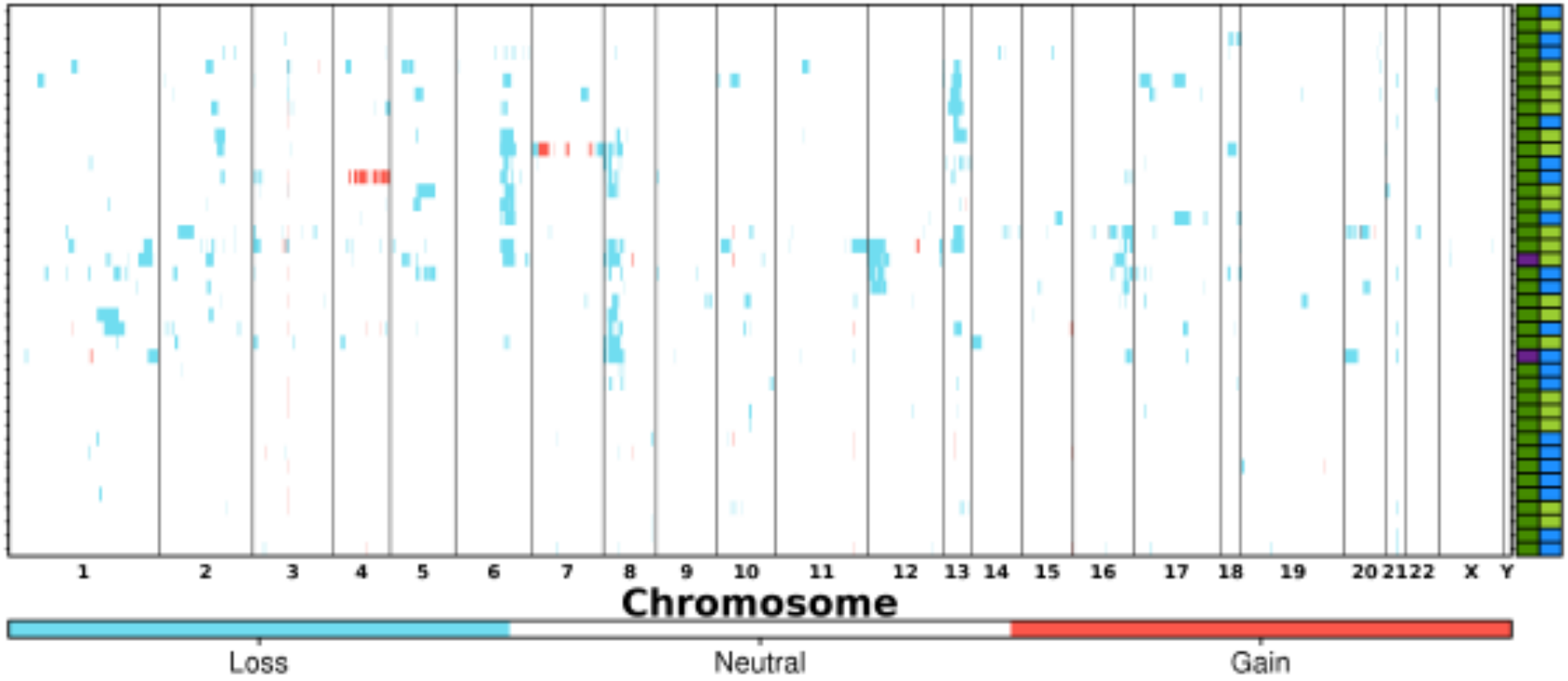
- Compared 49 radiomic features (DWI, Ktrans etc.) to RNA expression data from 17 MRI-targeted biopsies from 6 patients
- Prostate cancer associated signatures (Decipher, GPS and Prolaris) associated with radiomic features
- TZ and PZ have distinct radiomic features that correlate with gene signatures suggesting influence of cancer on radiomic features of normal appearing tissue or that of normal tissue on cancer formation (field effect).
- ADC values most significantly associated with distinct biological processes
- Gene ontology analysis identified specific radiomic features associated with immune/inflammatory response, metabolism, cell and biological adhesion

Genomics of PIRAD 5 and Invisible Gleason Grade Group 2 Tumors

- Methods: 20 PIRAD 5 tumors with final Gleason score 3+4 and 20 non-visualized tumors with final Gleason score 3+4 were identified
- Tumors were matched for tumor size and location
- DNA and RNA from each tumor were isolated
- Copy Number Analysis and RNA sequencing were performed and then analyzed

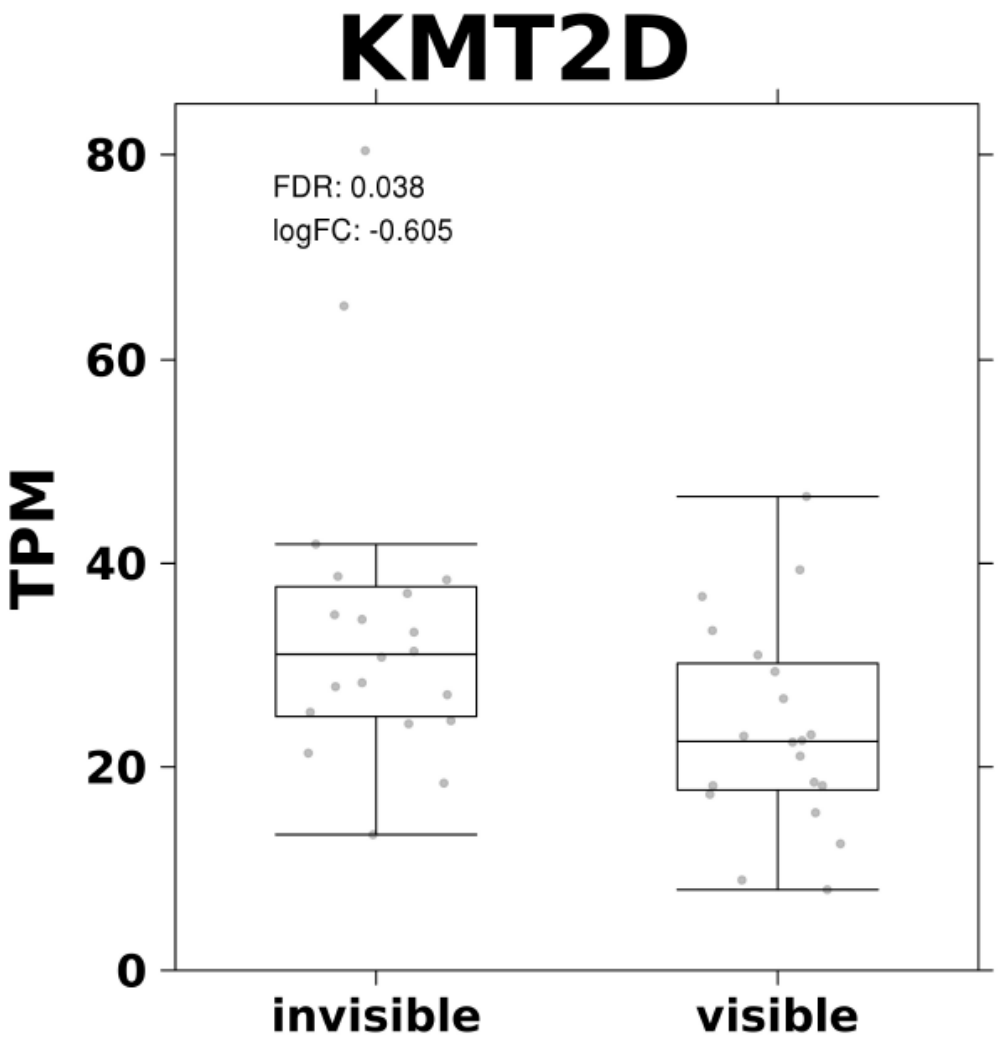
Copy Number Analysis

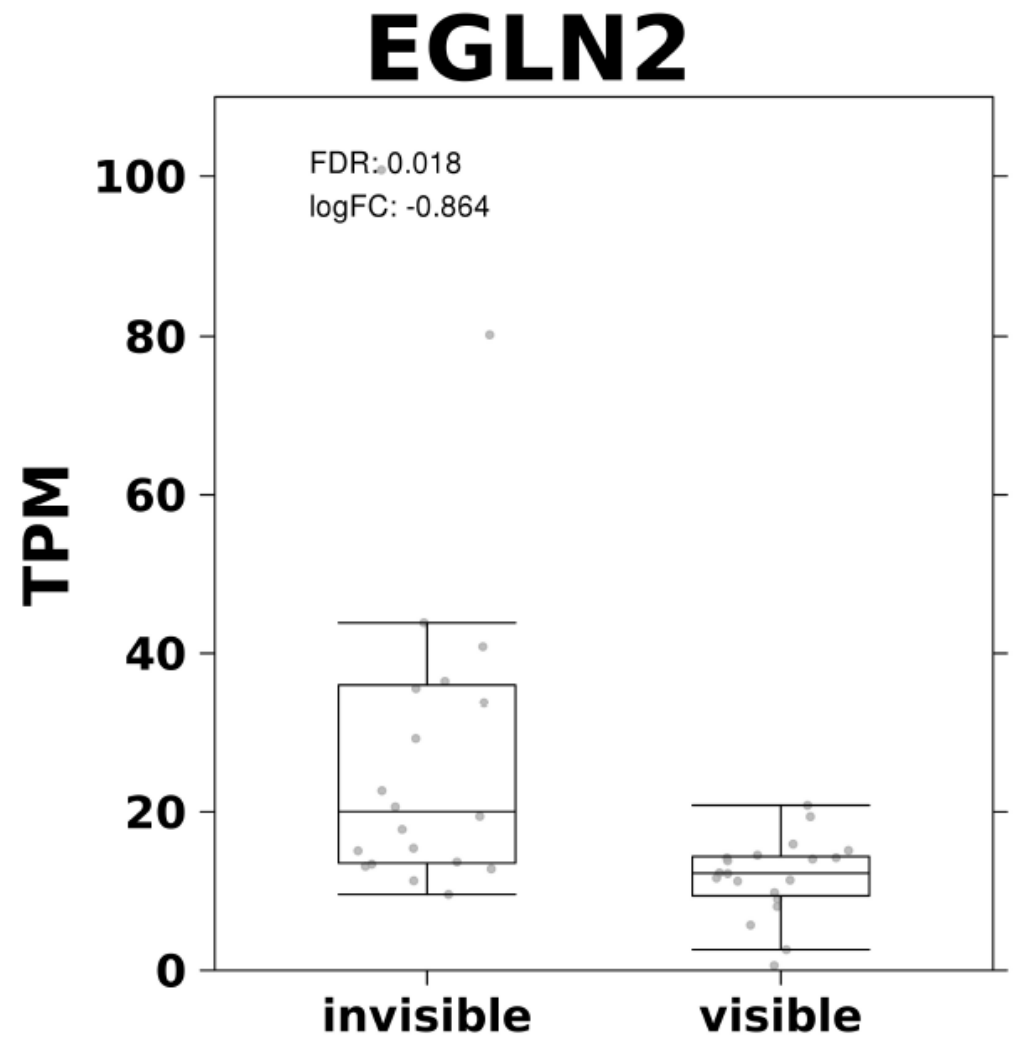
A)



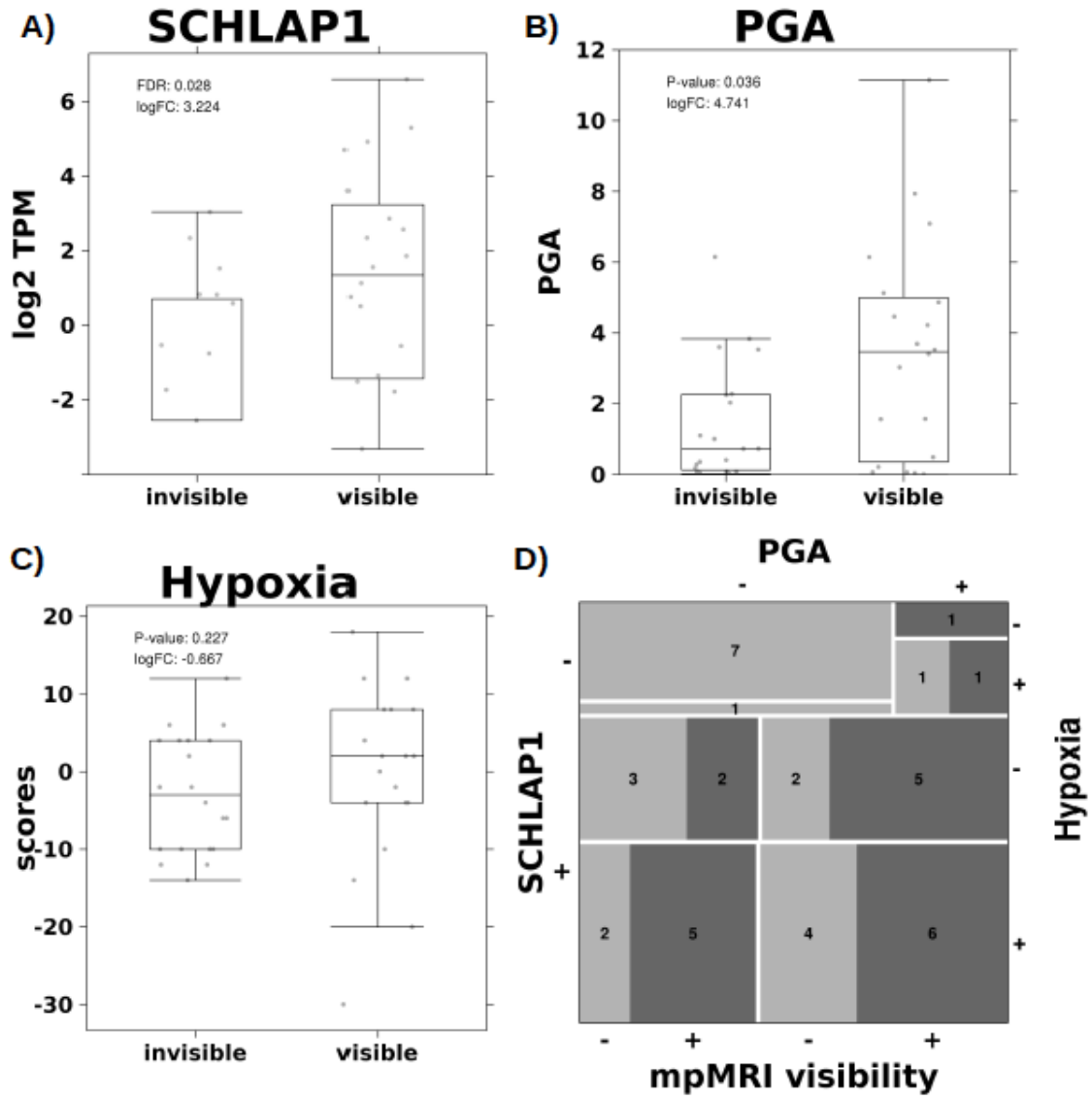
Genomically “silent” tumors consistent with GGG2
No differences between visualized and non-visualized

Genes Downregulated in MRI Visible Tumors

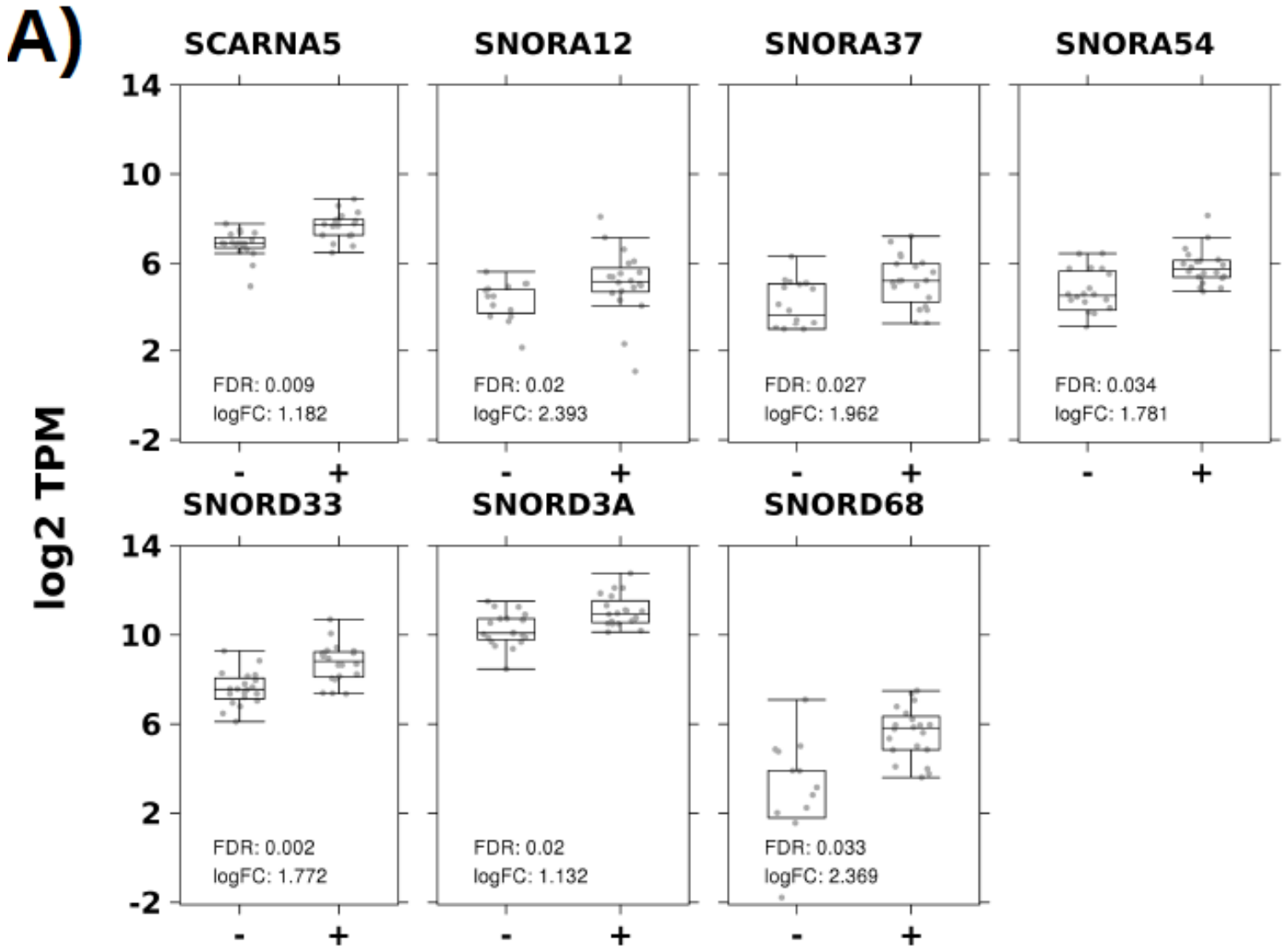




Genes Upregulated in MRI Visible Tumors



Increase Expression of Non-coding RNAs in MRI Visible Tumors



Does Oncotype Dx Score (GPS) Provide Biological Information on GGG1-2 Cancer Detected by Targeted Biopsy

- Primary:
  - To investigate the performance of GPS in predicting AP in men who went to RP after having a simultaneous mpMRI-guided and systematic prostate biopsy.
- Secondary
  - To assess the performance of GPS scores across mpMRI results and in a subgroup of patients with NCCN Intermediate Risk Disease.

Methods

- A cohort of men with low and intermediate risk PCa who were managed with RP was identified.
- Patients were required to have had a simultaneous mpMRI-guided and systematic biopsy and to have undergone RP within 6 months.
- Biopsy tissue of the highest Gleason pattern (systematic or MRI-guided) was used for calculation of GPS.

Results

Predictors of AP at surgery

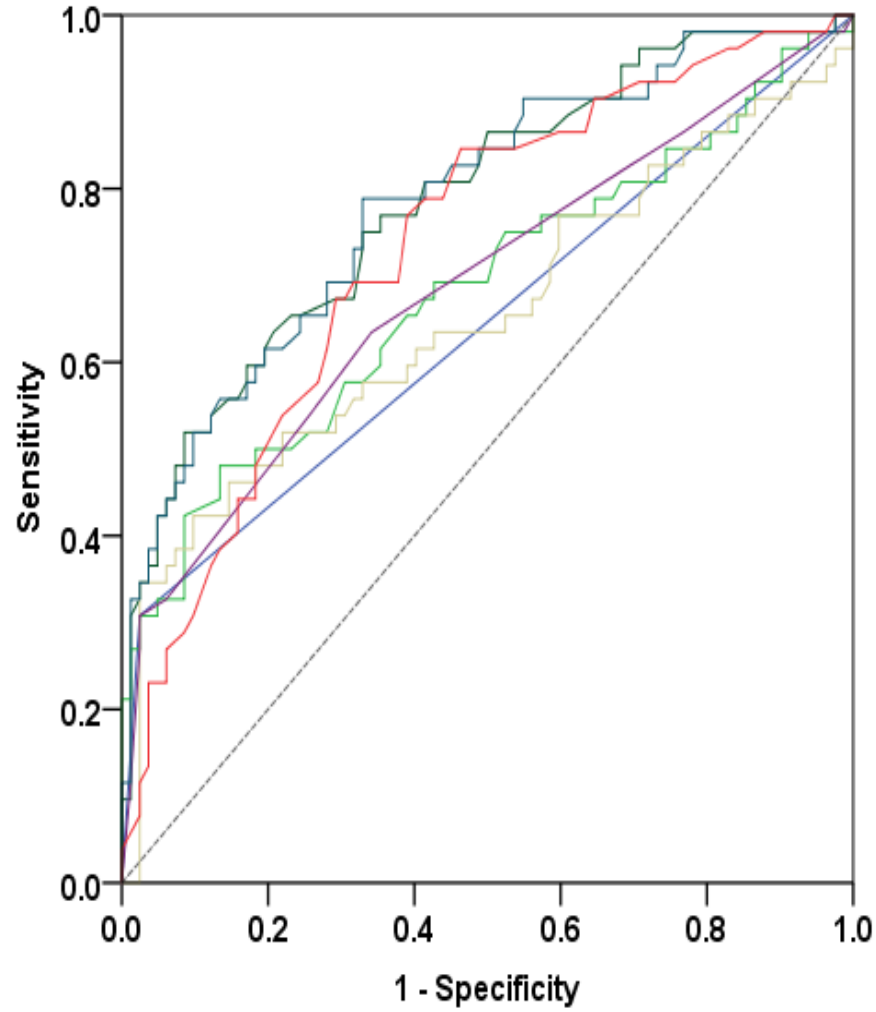
GPS in the Reduced group (OR 3.19, 95% CI 1.66 – 6.11, p<0.001)

Univariable analysis			Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.98 (0.92-1.03)	0.4		
Ethnicity		0.23		
Caucasian	referent			
AA	0.33 (0.09-1.24)			
Hispanic	0.26 (0.03-2.33)			
Asian	0.44 (0.04-4.36)			
NCCN risk				
Low / Very low	referent			
Intermediate	1.13 (0.44-2.92)	0.797		
Rounded GPS (20 units)	3.84 (2.07-7.16)	<0.001	3.22 (1.69-6.12)	<0.001
Highest biopsy Gleason		0.001		0.006
3+3	referent		referent	
3+4	1.02 (0.40-2.61)		0.75 (0.27-2.10)	
4+3	18.0 (3.32-97.5)		9.65 (1.66-56.0)	
MRI PI-RAD		0.525		
2	0.37 (0.04-3.89)			
3	0.51 (0.19-1.35)			
4	0.69 (0.30-1.57)			
5	referent			
ADC	1.00 (1.00-1.00)	0.875		

Results

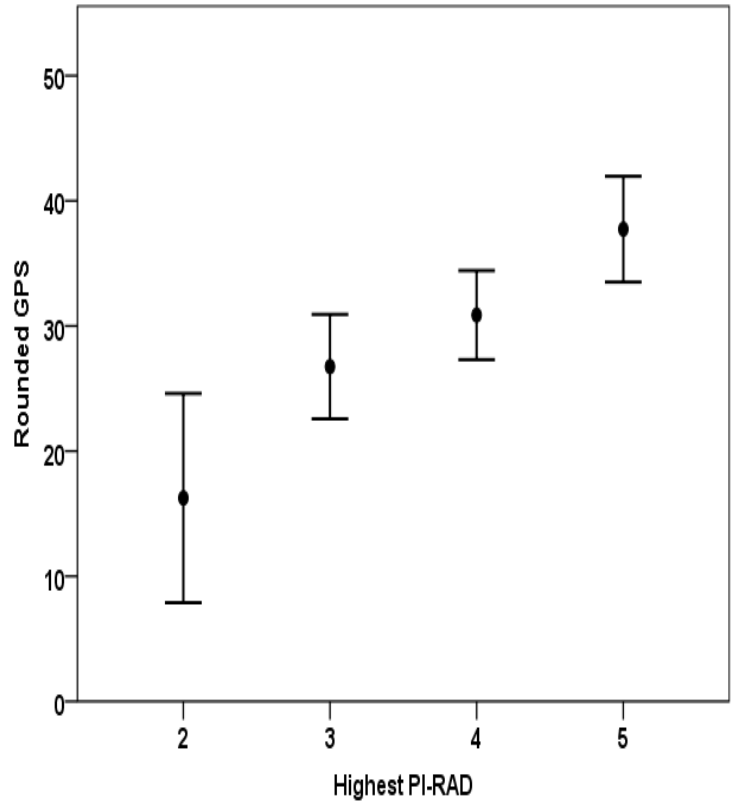
AUC curves to predict AP

Predictors	AUC (95% CI)
GS + GPS + MRI highest PIRAD	0.79 (0.71-0.87)
GS + GPS	0.79 (0.70-0.87)
GPS only	0.73 (0.65-0.82)
GS + MRI highest PIRAD	0.69 (0.59-0.78)
GS + PSA	0.68 (0.58-0.78)
GS + PSA density	0.65 (0.55-0.75)
Gleason score (GS)	0.64 (0.54-0.74)

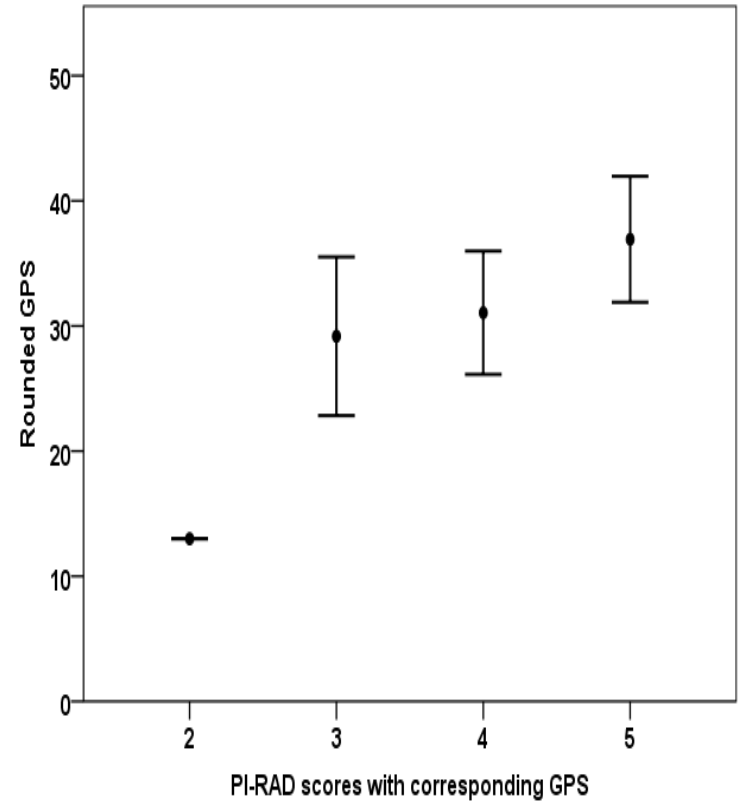


Results

Distribution of GPS across PI-RAD levels



Spearman, r=0.346, p<0.001, n=134



Spearman, r=0.286, p=0.009, n=82

Results

Performance of GPS for each PI-RAD score

PI-RAD Score	GPS mean (SD)	OR of GPS for AP	p-value
Corresponding			
2	13		
3	29.3 (12)	4.49 (0.61-33.1)	0.14
4	31.6 (14.3)	3.33 (1.13-9.84)	0.029
5	36 (12.4)	5 (0.95-26.1)	0.056
Highest PI-RAD			
2	16.2 (5.2)		
3	26.7 (11.6)	4.62 (0.89-23.8)	0.067
4	30.9 (13.7)	3.41 (1.39-8.34)	0.007
5	37.7 (12.8)	4.1 (1.21-13.8)	0.023

Conclusion

- MRI is a biomarkers in prostate cancer
  - Predicts upgrading in men on AS
  - Predicts for biochemical recurrence
- MRI may capture a gene signature reflecting tumor biology
  - Known predictors of aggressive disease such as SCHLAP1 strongly upregulated in PIRAD 5 vs invisible tumors
- The GPS assay provides independent and complementary prognostic information to mpMRI-guided biopsies.
  - Most notable for PIRAD 3 and 4 lesions