4Kscore Test as a Predictor of Reclassification in Prostate Cancer Active Surveillance.

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INTRODUCTION AND OBJECTIVES:

- Active surveillance (AS) in low-risk prostate cancer (PCa) patients could be improved with new biomarkers such as the 4KscoreTest (4KsT).
- We analyze its ability to predict tumor reclassification at the confirmatory biopsy (cBx) at 6 months after initial biopsy (iBx).

METHODS:

- Observational, prospective, blinded, and non-randomized study, within the Spanish National Registry on AS (AEU/PIEM/2014/0001;NCT02865330) with 137 patients included after iBx.
- Central pathological review confirmed inclusion criteria at iBx and reclassification ones at cBx.
- Plasma was collected 6 months after iBx just before cBx to determine 4KsT. Family history, prostate volume (PV), body mass index, and positive core ratio were also analyzed.
- Reclassification was defined as Gleason>7 and/or higher PCa volume.
- We used logistic regression analysis, calibration plots, area under the receiver operating characteristic curve (AUC), and probability density functions (PDF) to assess discriminatory capacity, and clinical utility curves for decisión making.

RESULTS, univariate and multivariate analysis of patients' characteristics. Combined nomogram generated (4KsT + PV).

- One hundred thirty-seven patients were finally evaluated. Fifty-one patients (37.2%) were reclassified at cBx.

Characteristics of the 137 Patients on Active Surveillance before the Confirmatory Biopsy, including Global Distribution, Stratified by Reclassification Status

	Global distribution		No reclassification		Reclassification		p value
Sample size (n)	137		86	(63)	51	(37)	
Age at cBx (yr)	64.3	(60.2-69.9)	63.7	(59.6-69.0)	66.8	(61.8-72.0)	0.069
Time from iBx (mo)	6.5	(6.2-7.6)	6.4	(7.1-7.2)	6.7	(6.2-8.0)	0.133
Family history of PCa							0.930
· Yes	21	(15.3)	13	(15.1)	8	(15.7)	
· No	112	(81.8)	71	(82.6)	41	(80.4)	
· N/A	4	(2.9)	2	(2.3)	2	(3.9)	
Digital rectal examination							0.424
· Normal	130	(94.9)	83	(96.5)	47	(92.2)	
· Abnormal	7	(5.1)	3	(3.5)	4	(7.8)	
Prostate volume (mL)	41	(30-58)	43.8	(31.0-63.0)	34	(30-46.5)	0.012
PSAD (ng/mL)	0.13	(0.09-0.18)	0.13	(0.08-0.16)	0.16	(0.11-0.20)	0.002
Total PSA (ng/mL)	5.55	(4.02-7.04)	5	(3.82-6.59)	5.94	(4.54-7.12)	0.098
Free PSA (ng/mL)	0.79	(0.55-1.14)	0.81	(0.57-1.14)	0.71	(0.46-1.13)	0.276
Percentage Free/Total PSA (%)	15.4	(10.6-20)	17.2	(12.8-20.7)	13.8	(9.9-18.4)	0.013
Intact PSA	0.404	(0.281-0.579)	0.409	(0.310-0.608)	0.404	(0.254-0.564)	0.475
hK2	0.068	(0.046-0.106)	0.065	(0.044-0.106)	0.078	(0.052-0.106)	0.367
BMI (kg/m²)	27.0	(25.5-29.0)	27.0	(25.5-29.1)	27.0	(25.7-28.6)	0.931
Core ratio	0.08	(0.08-0.12)	0.08	(0.08-0.11)	0.08	(0.08-16.7)	0.155
Negative Bx previous to iBx							0.026
· 0	115	(83.9)	67	(77.9)	48	(94.1)	
· 1	20	(14.6)	17	(19.8)	3	(5.9)	
· 2	2	(1.5)	2	(2.3)	-	-	
4Kscore Test (Probability of High Risk PCa)	14.41	(6.95-28.51)	11.32	(5.64-19.34)	24.94	(12.98-40.74)	<0.001

Data are presented as median (percentile 25-percentile 75) for continuous variables and as n (%) for categorical variables. Progression is considered in volume and/or grade as defined in text.
Core ratio is defined as the number of biopsy cores containing cancer divided by the total number of biopsy cores in the iBx.

- Prostate volume, PSA-density, %f/tPSA, previous negative biopsies, and 4KsT were associated with reclassification.
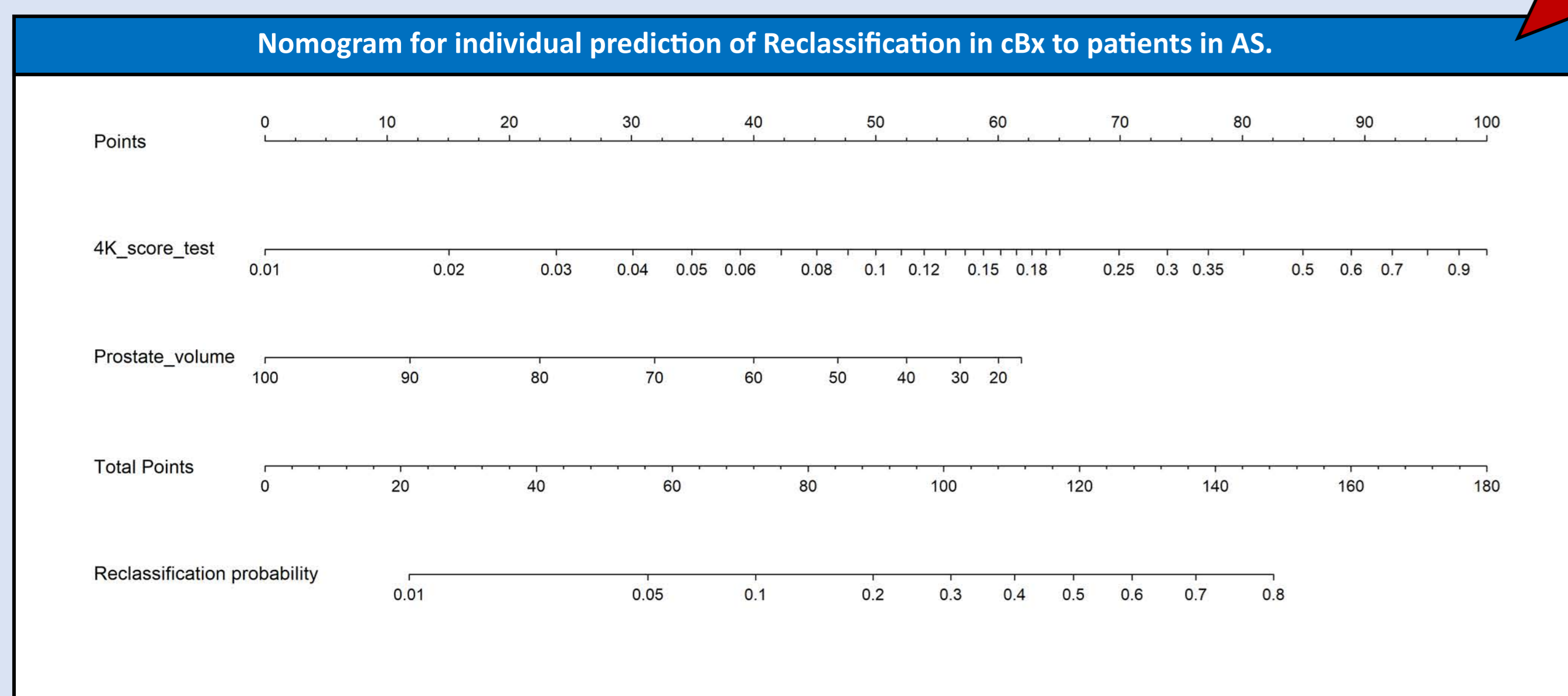
Odds ratio (OR) and Area Under the Curve (AUC) for Predictive Models

Univariate models	OR (95% CI)	P value	AUC
4Kscore Test (OR by 1%)	1.06 (1.03-1.09)	< 0.001	0.733
PSA (OR by 1 ng/mL)	1.09 (0.94-1.28)	0.236	0.585
Free PSA (OR by 0.1)	0.96 (0.89-1.04)	0.371	0.556
Intact PSA (OR by 1)	0.63 (0.14-2.41)	0.517	0.535
hK2 (OR by 0.01)	1.03 (0.97-1.09)	0.337	0.548
Age (OR by 1 year)	1.05 (0.99-1.11)	0.059	0.593
DRE (Ref. Normal)	2.35 (0.51-10.97)	0.275	0.522
Family history (Ref. No)	1.02 (0.33-2.94)	0.973	0.501
Prior Biopsy (Ref. None)	0.22 (0.05-0.69)	0.019	0.581
Core Ratio (OR by 0.01)	1.06 (0.98-1.15)	0.136	0.571
BMI (OR by 1 Kg/m²)	0.97 (0.87-1.09)	0.645	0.501
Prostate volume (OR by 1 mL)	0.97 (0.95-0.99)	0.007	0.628
PSAD (OR by 0.01)	2.88 (1.25-6.63)	0.013	0.656
Percentage Free PSA (OR by 1%)	0.94 (0.88-0.99)	0.023	0.627

Combined models		OR (95% CI)	P value	AUC
Clinical combined model	PSA	1.07 (1.30-1.61)	0.009	
	Prostate volume	0.96 (0.94-0.98)	0.002	
	Age	1.07 (1.01-1.13)	0.034	0.759
	Prior Biopsy	0.14 (0.02-0.55)	0.011	
4Kscore Test combined model	4Kscore Test	2.77 (1.76-4.75)	< 0.001	
	Prostate volume	0.99 (0.99-0.99)	0.014	0.773

Nomogram for individual prediction of Reclassification in cBx to patients in AS.


CONCLUSIONS:

- A nomogram combining 4KsT and PV can aid individual decision-making to indicate a cBx in patients in AS management.
- These results should be externally validated.

RESULTS, internal validation and cut-off points for clinical decission.

4K Score Test			PSA + Prostate volume + Age + Prior Bx			4K Score Test + Prostate volume		
Cut-off	Saved Bx (%)	Undetected Re-classifications (%)	Cut-off	Saved Bx (%)	Undetected Re-classifications (%)	Cut-off	Saved Bx (%)	Undetected Re-classifications (%)
5	21 (15)	1 (2)	11	15 (11)	1 (2)	10	18 (13)	1 (2)
6	31 (23)	4 (8)	12	18 (13)	2 (4)	14	29 (21)	2 (4)
7.5	35 (26)	5 (10)	21	39 (28)	5 (10)	25	49 (36)	5 (10)
11	51 (37)	9 (18)	29	54 (39)	9 (18)	30	60 (44)	9 (18)
13	62 (45)	13 (25)	36	68 (50)	13 (25)	35	68 (50)	13 (25)
15	73 (53)	18 (35)	42	80 (58)	18 (35)	40	74 (54)	17 (33)
19	82 (60)	19 (37)	43	86 (63)	19 (37)	45	86 (63)	19 (37)
20	87 (64)	21 (41)	47	92 (67)	21 (41)	50	90 (66)	21 (41)
100	137 (100)	51 (100)	100	137 (100)	51 (100)	100	137 (100)	51 (100)

Total number of biopsied patients: 137. Total number of reclassified patients at cBx: 51
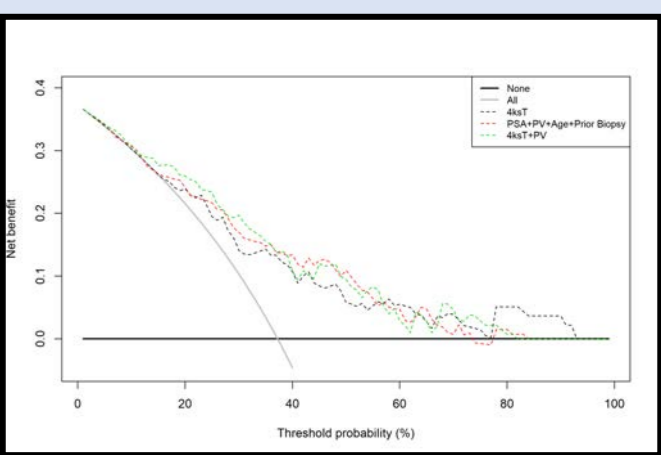
Probability density functions of the 4Kscore Test (a), clinical combined model (b) and the combination of 4Kscore Test with prostate volume (c), from the probabilities of reclassification at cBx offered for the different models, and distributed for their actual situation of reclassified versus non-reclassified patients in our cBx analysis.
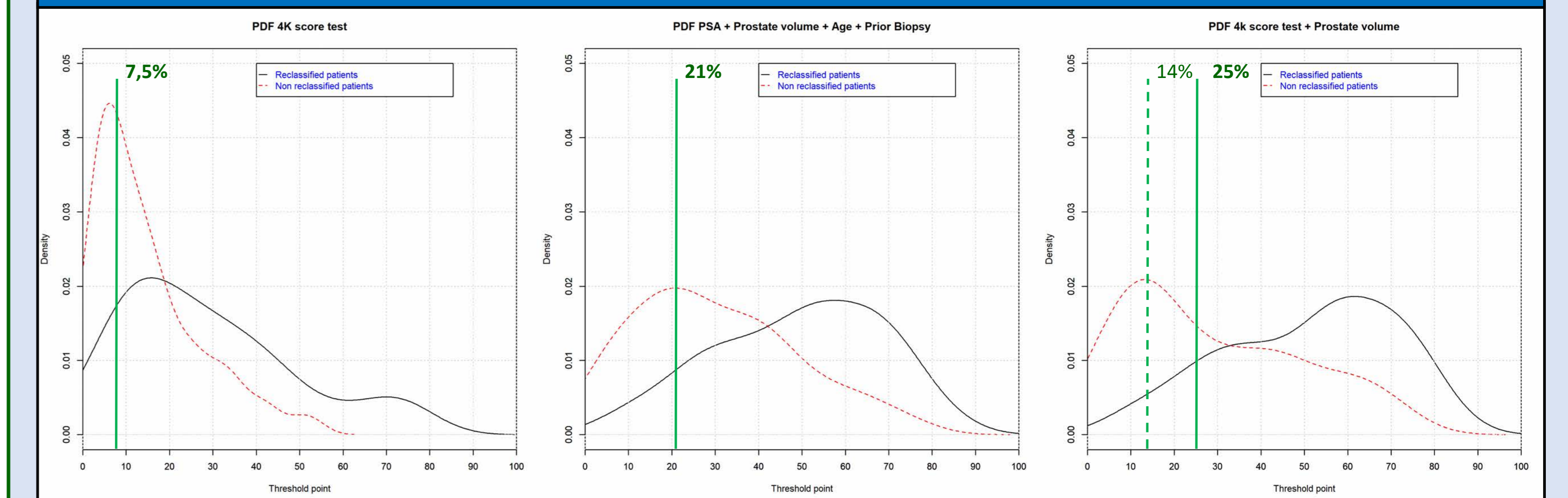
Clinical Utility Curves of 4Kscore Test and Prostate Volume model, showing saved biopsies from total cohort and missed undetected reclassification from subcohort of reclassified patients at cBx, for different cut-off points of probabilities