

Model-Based Prebiopsy Risk Estimation and Systematic Core Omission During Transrectal Rigid Magnetic Resonance Imaging–Ultrasound Fusion Biopsy

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Abstract

Purpose

Whether systematic cores can be omitted once a multiparametric magnetic resonance imaging (mpMRI) target is sampled depends on biopsy technique, yet existing evidence pools routes and registration methods. We identified prebiopsy determinants of clinically significant prostate cancer (csPCa) and quantified the cost of omitting systematic cores in a technically uniform cohort.

Methods

In this retrospective dual-centre study, 902 men with ≥ 1 Prostate Imaging Reporting and Data System (PI-RADS) ≥ 3 lesion underwent same-session targeted (TBx) and systematic biopsy transrectally with rigid software coregistration. Multivariable logistic regression identified factors associated with csPCa (International Society of Urological Pathology [ISUP] grade group ≥ 2) and high-grade cancer (hgPCa, ISUP ≥ 3), with Harrell's c-index, bootstrap validation, calibration and decision-curve analysis. TBx performance against overall biopsy was expressed absolutely, all biopsied men, and conditionally, men with csPCa.

Results

csPCa was detected in 338/902 men (37%), hgPCa in 91 (10%). Age, PSA density (PSAD), digital rectal examination (DRE) stage and maximum PI-RADS independently predicted csPCa; the optimism-corrected c-index was 0.80, exceeding each variable alone (0.70–0.74), with net benefit across 5–85% thresholds. For hgPCa, only PSAD and DRE remained independent. TBx sensitivity was 76% (71–81); the absolute miss rate, csPCa found only by systematic cores, was 8.9% (80/902), corresponding to a conditional rate of 24% (19–29), highest in PI-RADS 3 (35%) and at PSAD < 0.10 ng/ml/cm³ (43%).

Conclusion

Under transrectal rigid fusion, systematic cores should be retained. Imaging category alone does not identify high-grade disease; reduced sampling should be judged on the absolute rather than the conditional miss rate.

1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) reported with the Prostate Imaging Reporting and Data System (PI-RADS) is the gateway investigation for clinically significant prostate cancer (csPCa) [1, 2]. PRECISION showed that targeting increases csPCa detection while reducing detection of clinically insignificant disease [3], the paired MRI-FIRST design found targeted and systematic sampling

complementary rather than substitutable [4], and screening trials confirmed reduced overdiagnosis at population level [5, 6].

Two questions remain unresolved once mpMRI is positive. First, risk stratification: csPCa probability varies widely among men with a visible lesion, and PI-RADS alone does not capture this heterogeneity. PSAD combined with PI-RADS stratifies risk better than either alone [7, 8], and PSAD thresholds and lesion-level modifiers have since been refined, particularly within PI-RADS 3 [9–13]. Second, sampling strategy: whether systematic biopsy (SBx) can be omitted once the target is sampled. Paired designs and meta-analyses show targeted biopsy (TBx) and SBx to be complementary, a residual fraction of csPCa being detected only by systematic cores [14–16].

That residual fraction is conditioned by the technical circumstances of targeting rather than fixed. Platforms differ in rigid versus elastic coregistration, and concordance between biopsy and final International Society of Urological Pathology (ISUP) grade differs materially with elastic fusion in biopsy-naïve men [17]. Route is a second determinant, though evidence divides by design: randomized comparisons show no detection advantage for transperineal access [18, 19], whereas matched series report higher detection, most consistently for anterior lesions [20, 21]. A multicentre PI-RADS 3 cohort found the absolute cost of omitting systematic cores lowest with transperineal access, PSAD below 0.10 ng/ml/cm³ and greater targeted sampling intensity, but pooled routes and registration methods, leaving unresolved how targeted-only sampling behaves within one technical environment [22].

We therefore evaluated men with a positive prebiopsy mpMRI undergoing same-session targeted and systematic fusion biopsy under uniform conditions, transrectal access with software-assisted rigid coregistration, to identify independent prebiopsy determinants of csPCa and quantify, on conditional and absolute scales, what a targeted-only strategy would miss.

2. Patients and methods

2.1 Study Design, Setting and Population

This retrospective dual-centre study included men whose prebiopsy mpMRI showed at least one PI-RADS 3 or greater lesion and who underwent an index fusion biopsy comprising overall biopsy (OBx; TBx + SBx) in the same session by the transrectal route between July 2017 and October 2022. Men with a highest-scoring lesion of PI-RADS 2 or lower, those biopsied transperineally and those with previous positive biopsies were excluded. Cases came from two institutional databases; reporting followed the Standards of Reporting for MRI-targeted Biopsy Studies [23].

mpMRI was acquired locally on 1.5-T or 3-T scanners with standard sequences and reported by PI-RADS version 2, version 2.1 applied after local adoption [1, 2]. Examinations were read by radiologists with dedicated prostate expertise; mpMRI centre was retained as a covariate in all models to account for residual interpretive variability.

The mpMRI dataset was uploaded to a software-assisted fusion platform (Arietta 30 with Real-time Virtual Sonography; Hitachi Ltd, Tokyo, Japan) on which lesions were delineated for real-time coregistration and targeted sampling. Coregistration was rigid throughout, aligning the segmented mpMRI prostate to the ultrasound volume by translation and rotation without deformation to intraprocedural gland shape. Targeted cores preceded systematic cores and were submitted in separately labelled containers, so pathology was reported independently. Procedures were performed by experienced urologists (> 100 fusion biopsies); specimens were assessed by board-certified uropathologists using ISUP grade group standards.

Analysis required complete prebiopsy data (DRE stage, PSAD, lesion number) and complete histopathology for both components. Of 922 men screened, 20 were excluded, yielding 902 evaluable patients, with complete-case data for 891 in multivariable models and 897 in PSAD-stratified analyses (Online Resource 1). Radical prostatectomy specimens were unavailable, restricting grading to biopsy ISUP assignments.

The primary design feature was a within-patient comparison of two classifications from the same procedure: TBx-only, from targeted cores alone, versus OBx, from any TBx or SBx core.

2.2 Outcomes

Prespecified outcomes addressed two questions: which prebiopsy variables identify men harbouring csPCa, and what TBx-only classification misses relative to TBx + SBx. csPCa was defined a priori as ISUP grade group 2 or greater, hgPCa as grade group 3 or greater, each on the highest grade across cores of the relevant classification. Analyses were at patient level. Prespecified strata were maximum PI-RADS (3, 4, 5) and PSAD (< 0.10, 0.10–0.15, 0.15–0.20, ≥ 0.20 ng/ml/cm³), the bands used in published risk-adapted pathways [24].

2.2.1 Primary Outcome

The primary outcome was csPCa on OBx. Candidate predictors were restricted to variables available before the biopsy decision is taken.

2.2.2 Secondary Outcomes

Secondary outcomes were (1) independent prebiopsy factors associated with hgPCa on OBx, analyzed identically to the primary outcome, and (2) the cost of omitting systematic cores, overall and within prespecified strata.

That cost was expressed on two scales answering different questions. The conditional scale: the proportion of men with csPCa on OBx in whom TBx alone failed, equal to one minus TBx sensitivity, describes the reliability of targeting once cancer is known present. The absolute scale: the proportion of all biopsied men in whom systematic cores yielded a csPCa missed by targeting, describes what is lost

per patient exposed to the decision, the quantity relevant to a policy of omission; its reciprocal gives the number needed to sample systematically for one additional csPCa.

2.3 Statistical analysis

Continuous variables are described as median and interquartile range (IQR), qualitative variables as absolute and relative frequencies (%).

Multivariable logistic regression identified independent factors associated with odds of csPCa on OBx. Predictors were selected a priori based on clinical relevance: age, PSA density, DRE result, PI-RADS, previous biopsy status, index lesion diameter and mpMRI centre; with age and mpMRI centre retained as covariates for demographic and inter-centre variability. The multivariable model was fitted on complete cases (missing rate 1.2% across candidate predictors). Linearity condition of continuous predictors was assessed with restricted cubic splines in the rms R package [25]; PSA density showed a non-linear association and was log2-transformed. Discrimination ability was evaluated with Harrell's c-index, apparent and optimism-corrected [25], internal validation using 500 bootstrap samples for the corrected c-statistic and calibration slope and intercept. Effect sizes are reported as odds ratios (OR) with 95% confidence intervals.

The minimum required sample size was calculated using the pmsampsize R package [26], based on 13 candidate predictors, an expected c-statistic of 0.80 and an expected csPCa prevalence of 30%, yielding a minimum requirement of 448 patients (events = 135, events per predictor EPP = 10.34). The final study cohort (N = 891, events = 337, 11 potential predictor parameters included in the model) exceeded this minimum requirement, corresponding to an observed EPP of 30.6.

The clinical utility of the multivariable logistic model was evaluated using decision curve analysis [27], and net benefit was estimated across a range of threshold probabilities and compared against models including only PI-RADS, PSAD or DRE, with age and mpMRI centre as covariates.

The diagnostic performance of TBx alone was evaluated using overall biopsy as the reference standard, reporting TBx-only sensitivity for detecting csPCa and the proportion of missed csPCa cases if SBx had been omitted, each with a 95% confidence intervals calculated using the Clopper-Pearson exact method.

All statistical analyses were performed in R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 denoted statistical significance.

3. Results

3.1 Description of the study cohort characteristics

Of 922 men who underwent transrectal mpMRI–transrectal ultrasound (TRUS) fusion biopsy, 902 met the eligibility criteria and constitute the analytic cohort (Online Resource 1). Demographic and clinical characteristics are summarised in Table 1. The cohort was predominantly biopsy-naïve (769, 83%). Any

prostate adenocarcinoma was detected on the current biopsy in 490 men (54%), csPCa in 338 (37%) and hgPCa in 91 (10%). According to DRE findings, the clinical TNM stage was T1c in 534 patients (59%), whereas 368 patients (41%) had stage T2 or higher.

Table 1
Cohort characteristics

Characteristic	Cohort (N = 902)
Age (years)	65 (61, 70)
PSA (ng/mL)	7.3 (5.3, 11)
Prostate volume (mL, N = 897)	50 (37, 68)
PSAD (ng/mL/cm ³ , N = 897)	0.15 (0.10, 0.25)
DRE stage, n (%)	
Negative	534 (59)
Positive	368 (41)
Prior biopsy history, n (%)	
Naïve	769 (83)
Repeat-benign	121 (13)
Repeat -pre-malignant (ASAP/HGPIN)	32 (3.6)
Number of MRI lesions, n (%)	
1	647 (72)
2	228 (25)
3	27 (3)
Maximum PI-RADS, n (%)	
3	210 (23)
4	383 (43)
5	309 (34)
Number of PI-RADS ≥ 3 lesions	
1	657 (73)
2	219 (24)
3	26 (2.9)
<p>PSA: Postate Specific Antigen; PSAD: PSA density; DRE: Digital Rectal Exanination; ASAP: Atypical Small Acinar Proliferation; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; PI-RADS: Prostate Imaging Reporting and Data System; TBx: targeted biopsy; SBx: systematic biopsy; csPCa : clinically significant prostate cancer defined as ISUP grade goup ≥ 2 on the combined targeted-plus-systematic biopsy; hgPCa: high grade prostate cancer defined as ISUP grade group ≥ 3 on the combined targeted-plus-systematic biopsy; N: number of cases; Estimates were given as median (IQR: quartile 1, quartile 3) or absolute frequency (relative frequency, %).</p>	

Characteristic	Cohort (N = 902)
Index-lesion diameter (mm)	14 (10, 19)
Total cores taken on combined biopsy	16 (15, 16)
Targeted total cores	4 (3, 4)
Systematic total cores	12 (12, 12)
Positive cores on combined biopsy, among men with a positive combined biopsy	6 (3, 8)
Positive cores on TBx, among men with a positive TBx	4 (2, 6)
Positive cores on SBx, among men with a positive SBx	3 (2, 4)
Positive pathologic result	490 (54)
Overall ISUP grade group, n (%)	
0- No cancer	412 (46)
1	152 (17)
2	247 (27)
3	65 (7.2)
4	14 (1.6)
5	12 (1.3)
csPCa detected, n (%)	338 (37)
hgPCa detected, n (%)	91 (10)
<i>PSA: Postate Specific Antigen; PSAD: PSA density; DRE: Digital Rectal Examination; ASAP: Atypical Small Acinar Proliferation; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; PI-RADS: Prostate Imaging Reporting and Data System; TBx: targeted biopsy; SBx: systematic biopsy; csPCa : clinically significant prostate cancer defined as ISUP grade group ≥ 2 on the combined targeted-plus-systematic biopsy; hgPCa: high grade prostate cancer defined as ISUP grade group ≥ 3 on the combined targeted-plus-systematic biopsy; N: number of cases; Estimates were given as median (IQR: quartile 1, quartile 3) or absolute frequency (relative frequency, %).</i>	

3.2 Pre-biopsy logistic regression model for estimating odds of csPCa

On multivariable analysis, age, PSA density, DRE stage and PI-RADS remained independently associated with the odds of csPCa (Table 2). Each doubling of PSA density doubled the odds (adjusted OR = 2.00, 95% CI: 1.69–2.38, $p < 0.0001$) after adjustment for the other covariates. Relative to PI-RADS 3, the odds rose for PI-RADS 4 (adjusted OR = 2.35, 95% CI: 1.46–3.80, $p = 0.00046$) and further for PI-RADS 5 (adjusted OR = 3.69, 95% CI: 2.06–6.60, $p < 0.0001$).

A Prior biopsy history × Maximum PI-RADS interaction did not improve model fit (likelihood ratio $\chi^2(4) = 4.63$, $p = 0.3$); although 2 individual interaction coefficients reached significance ($p = 0.041$ and $p = 0.046$), the term was not retained in the final model.

The final model achieved an apparent c-statistic of 0.81 (95% bootstrap CI: 0.78–0.83), an optimism-corrected c-statistic of 0.80 and a calibration slope of 0.95, outperforming single-predictor models of PSA density (AUC = 0.74, 95% bootstrap CI: 0.70–0.77), DRE stage (0.72, 0.68–0.75) and PI-RADS (0.70, 0.67–0.74; DeLong $p < 0.0001$ for each), all adjusted for age and mpMRI centre.

Table 2
Multivariable logistic regression results for odds of csPCa (N = 891, events = 337)

Variable	Adjusted OR	95% CI	p-value
Age (per 5-yr increase)	1.20	1.07, 1.35	0.0021
PSAD (per doubling, ng/mL/cm ³) ^a	2,00	1.69, 2.38	< 0.0001
DRE			
Negative	Reference	–	
Positive-unilateral right	3.19	2.14, 4.76	< 0.0001
Positive -unilateral left	4.19	2.75, 6.39	< 0.0001
Positive-Bilateral	2.66	1.27, 5.57	0.0092
Prior biopsy history, n (%)			
Naïve	Reference	–	
Repeat-benign	0.78	0.48, 1,28	0.3
Repeat -pre-malignant (ASAP/HGPIN)	0.96	0.41, 2.25	0.9
Maximum PI-RADS			
3	Reference	–	
4	2.35	1.46, 3.80	0.00046
5	3.69	2.06, 6.60	< 0.0001
Index lesion diameter (per 10-mm increase)	0.98	0,72, 1.33	0.9
mpMRI Center			
University centre	Reference	–	
Secondary centre	1.15	0.82, 1.59	0.4
<p>OR: Odds Ratio; 95% CI: 95% Confidence Interval; PSA: Postate Specific Antigen; PSAD: PSA density; DRE: Digital Rectal Exanination; ASAP: Atypical Small Acinar Proliferation; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; PI-RADS: Prostate Imaging Reporting and Data System; csPCa : clinically significant prostate cancer defined as ISUP grade group ≥ 2 on the combined targeted-plus-systematic biopsy;^aPSAD was log2-transformed to satisfy the linearity assumption; the reported adjusted OR (odds ratio) corresponded to a doubling of PSAD value. Other continuous predictors were linearly rescaled for interpretability.</p>			

The nomogram (Online Resource 2) described the probability of csPCa for any combination of the studied predictors. Decision-curve analysis showed that the full model yielded a positive incremental net benefit across the threshold probability range 5% – 85% and reduced unnecessary biopsies compared to biopsy-all strategy (Fig. 1).

3.3 Pre-biopsy logistic regression model for estimating odds of hgPCa

The refitted model for hgPCa (Table 3) retained good discrimination (apparent c-statistic = 0.78, 95% bootstrap CI: 0.73–0.82; optimism-corrected 0.75), with 2 independent predictors: PSAD (adjusted OR = 1.45, 95% CI: 1.17–1.81) and abnormal DRE, unilateral right-lobe (adjusted OR = 3.35, 95% CI: 1.83–6.12) and left-lobe (adjusted OR = 4.48, 95% CI: 2.51–7.99).

Table 3
Multivariable logistic regression results for odds of hgPCa (N = 891, events = 91)

Variable	Adjusted OR	95% CI	p-value
Age (per 5-yr increase)	1.14	0.96, 1.35	0.1
PSAD (per doubling, ng/mL/cm ³) ^a	1.45	1.17, 1.81	0.0008
DRE			
Negative	Reference	–	
Positive-unilateral right	3.35	1.83, 6.12	0.00009
Positive -unilateral left	4.48	2.51, 7.99	< 0.00001
Positive-Bilateral	2.05	0.70, 5.98	0.2
Prior biopsy history, n (%)			
Naïve	Reference	–	
Repeat-benign	1.34	0.70, 2.59	0.4
Repeat -pre-malignant (ASAP/HGPIN)	1.72	0.63, 4.69	0.3
Maximum PI-RADS			
3	Reference	–	
4	2.22	0.90, 5.50	0.085
5	2.05	0.74, 5.65	0.2
Index lesion diameter (per 10-mm increase)	1.38	0.93, 2.03	0.1
mpMRI Center			
University centre	Reference	–	
Secondary centre	1.08	0.67, 1.74	0.8
<p>OR: Odds Ratio; 95% CI: 95% Confidence Interval; PSA: Prostate Specific Antigen; PSAD: PSA density; DRE: Digital Rectal Examination; ASAP: Atypical Small Acinar Proliferation; HGPIN: High-Grade Prostatic Intraepithelial Neoplasia; PI-RADS: Prostate Imaging Reporting and Data System; hgPCa : high-grade prostate cancer defined as ISUP grade group ≥ 3 on the combined targeted-plus-systematic biopsy;^a PSAD was log2-transformed to satisfy the linearity assumption; the reported adjusted OR (odds ratio) corresponded to a doubling of PSAD value. Other continuous predictors were linearly rescaled for interpretability.</p>			

3.4 Per-route diagnostic sensitivity of targeted biopsy (TBx) alone relative to the combined biopsy as reference standard

TBx sensitivity against combined biopsy as reference standard was 76% (95% CI: 71–81%) for the whole cohort, so 24% (95% CI: 19–29%) of csPCa would have been missed had SBx been omitted. The conditional miss rate was highest in PI-RADS 3 (35%) of any PI-RADS group (Table 4) and was inversely related to PSAD (Fig. 2), reaching 43% below 0.10 ng/mL/cm³ (Table 4).

Table 4

TBx sensitivity relative to the combined biopsy as reference standard stratified by PI-RADS index and PSA density

Groups	N	Combined csPCa, n (%)	TBx-only sensitivity (%)	95% CI	Missed csPCa if SBx was omitted (%)	95% CI
All cohort	902	338	76.3	71.4, 80.8	23.7	19.2, 28.6
PI-RADS 3	210	29	65.5	45.7, 82	34.5	17.9, 54.3
PI-RADS 4	383	137	74.4	66.3, 81.5	24.6	17.8, 32.9
PI-RADS 5	309	172	79.7	72.9, 85.4	20.3	15.1, 27.8
PSAD (ng/mL/cm ³ , N = 897)						
< 0.10	244	35	57.1	39.4, 73.7	42.9	26.3, 60.6
0.10–0.15	212	67	70.1	57.7, 80.7	29.9	19.3, 42.3
0.15–0.20	139	65	75.4	63.1, 85.2	24.6	14.8, 36.9
≥ 0.20	302	171	83	76.6, 88.3	17	11.7, 23.4
TBx: targeted biopsy; SBx: systematic biopsy; PSA: Prostate Specific Antigen; PSAD: PSA density; 95% CI: 95% Confidence Interval; csPCa : clinically significant prostate cancer defined as ISUP grade group ≥ 2 on the combined targeted-plus-systematic						

4. Discussions

This study identifies age, PSA density, DRE stage and maximum PI-RADS as independent determinants of csPCa in MRI-positive men undergoing transrectal rigid fusion biopsy, and quantifies the diagnostic cost of a targeted-only strategy on two complementary scales: 8.9% of all men biopsied (1 in 11) had csPCa detected only by systematic cores, the absolute miss rate, corresponding to 24% of the csPCa actually present; the conditional miss rate. The absolute rate is the more clinically intuitive, since it is the

risk a man accepts when systematic sampling is omitted. The findings pull in opposite directions: prebiopsy variables discriminate csPCa well enough, with net benefit at plausible thresholds, to be offered as an individualized probability rather than a PI-RADS category or PSAD cut-point, yet that discrimination does not make systematic sampling dispensable, omitting it would forfeit a quarter of detectable csPCa, disproportionately where prebiopsy risk was lowest.

The predictors themselves are established; the contribution lies in their handling. PSAD entered the model per doubling rather than as a fixed cut-point, since its accuracy varies with prostate volume and thresholds transport poorly across cohorts [12]. Index-lesion diameter and prior biopsy status added no independent information, in line with series restricted to MRI-positive men [9, 10, 12], though one unrestricted cohort reported an association [13]. Two features distinguish this model: DRE coded by laterality rather than as binary, and mpMRI centre as a covariate. Its discrimination (c-statistic 0.81) sits within the 0.77–0.93 range of comparable prebiopsy models [9, 11, 28, 29]; the contribution of this cohort is therefore not a superior statistic but a technically uniform setting, in which the cost of omitting systematic cores can be estimated without pooling heterogeneous techniques.

The csPCa and hgPCa models diverge. Maximum PI-RADS was ordinally associated with csPCa yet lost independent significance for hgPCa, for which PSAD and abnormal DRE remained predictive: increasing imaging suspicion tracks the presence of grade group 2 or greater disease more closely than its aggressiveness, so a PI-RADS-led pathway is better calibrated to detecting grade group 2 cancer than to identifying the men who most need treatment. Externally validated calculators combine the same variables; PI-RADS, PSAD and DRE [30, 31]; and risk-adapted mpMRI-plus-PSAD pathways avoided 54% of biopsies while missing 1.6% of csPCa in 2055 biopsy-naïve men [24]. Our model is not intended to replace these tools; it describes how risk distributes under one specific technique, transrectal rigid fusion.

The absolute miss rate of 8.9% is about double the pooled Cochrane estimate for biopsy-naïve MRI-positive men [15]. How that cost distributes across subgroups depends on the denominator, and the two denominators; men with csPCa (conditional) versus all men biopsied (absolute); rank subgroups in opposite orders. On the conditional scale, targeting failed most often in PI-RADS 3 lesions (35%), the equivocal category in which practice varies most widely [32, 33], and at PSAD below 0.10 ng/mL/cm³ (43%). Brisbane and colleagues offer the spatial explanation: the radius capturing 90% of csPCa around a target widens from approximately 5 mm at PI-RADS 5 to 16 mm at PI-RADS 3 [34], so targeted cores most often miss where the lesion is least confidently drawn; pooled PI-RADS 3 data show the same deficit [35]. On the absolute scale the order reverses, because low-risk groups contain few cancers to miss: derived from Table 4, systematic cores detected an otherwise-missed csPCa in 4.8% of PI-RADS 3, 8.9% of PI-RADS 4 and 11.3% of PI-RADS 5 patients. The conditional rate states how far a negative targeted result can be trusted in a man who has cancer; the absolute rate states what omission costs per patient biopsied, and policy should follow the absolute rate.

What is missed also matters. Systematic-only cancers concentrate at grade group 2: all 10 in GÖTEBORG-2 were Gleason 3 + 4, mostly with minimal pattern 4 and mostly managed by surveillance [6], and in MRI-FIRST the incremental yield of systematic biopsy fell from 5.2% at grade group 2 or greater to 1.2% at grade group 3 or greater [4]. Our hgPCa model shows the same asymmetry. A targeted-only strategy therefore forfeits mainly grade group 2 disease, much of it destined for surveillance, and considerably less high-grade disease; whether that trade is acceptable depends on the value placed on diagnosing grade group 2 cancer.

Beyond whether to retain full systematic sampling, the practical question is whether a smaller template around the lesion suffices, and perilesional biopsy has been proposed as the answer. The rationale is quantitative: 90% of csPCa cores lie within 10 mm of the lesion boundary [34]. Retrospective series report detection equivalent to combined sampling with fewer cores [36, 37], a randomized trial met noninferiority against targeted plus 12-core systematic biopsy with fewer complications [38], and prospective multicentre data indicate that once perilesional cores are taken, distant cores add more grade group 1 than grade group 2 disease [39].

That evidence, however, was generated under conditions absent here, transperineal access, cognitive or elastic registration, and the trial's 15% noninferiority margin is wide against the deficit measured in this cohort (8.9% absolute, 24% conditional) [36–38]. The technique-matched evidence points the other way: in the only prospective surgeon-blinded transrectal comparison using software fusion from our manufacturer, perilesional cores added under 2 percentage points and the authors recommended retaining the 12-core template [40]; multicentre data show perilesional sampling failing in PI-RADS 3 and on surveillance [41], and even the series endorsing omission of distant cores found no perilesional gain in PI-RADS 3 or after negative biopsy [39]. Perilesional substitution is therefore supported where registration is elastic or access transperineal, and unproven under transrectal rigid fusion, the setting of most fusion biopsies currently performed.

Limitations include the absence of whole-mount pathology and core-level spatial mapping: missed csPCa was defined on biopsy alone, and although the standardized 12-core bilateral template means most systematic cores sampled tissue remote from the index lesion, perilesional extension cannot be excluded for cores from the target-bearing sextant. Because all men had a positive mpMRI, csPCa prevalence exceeds that of an unselected population, affecting calibration in lower-prevalence settings while largely preserving discrimination. The study evaluated a single route and registration method and cannot address other combinations; validation was internal, and performance against published calculators remains to be established. The hgPCa model used the same predictors as the csPCa model on 91 events and is exploratory; subgroup estimates carry wide confidence intervals, and the PSAD tiers were adopted from published pathways for description rather than re-validated here.

5. Conclusions

Men with a positive mpMRI should be counselled with an individualized probability combining age, PSAD, DRE stage and maximum PI-RADS rather than any single variable. Because maximum PI-RADS lost independent significance for hgPCa, imaging category alone should not identify the men who most need treatment. Under transrectal rigid fusion, systematic cores should be retained; these estimates should not be extrapolated to other routes or registration methods. Reduced sampling should be judged on the absolute miss rate, cancers missed per patient biopsied, rather than the conditional rate among men with known cancer, since the 2 scales rank subgroups in opposite directions.

Declarations

Conflict of interest:

The authors declare no conflicts of interest.

Ethics statement

This study was approved by the local ethics committee and conducted in line with the principles of the Declaration of Helsinki; informed consent was obtained.

Funding/support and role of the sponsor

None.

Author Contribution

Nicolae Crisan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Buhas, Iancu, Ploussard.

Acquisition of data: Buhas, Andras, Buzoianu, Borz, Crisan. Analysis and interpretation of data: Buhas, Uleri, Iancu. Drafting of the manuscript: Buhas, Iancu. Critical revision of the manuscript for important intellectual content: Uleri, Diamand, Mjaess, Abou Chakra, Brown. Administrative, technical, or material support: None. Statistical analysis: Iancu. Supervision: Ploussard, Crisan. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. Conflict of interest: The authors declare no conflicts of interest. Ethics statement: This study was approved by the local ethics committee and conducted in line with the principles of the Declaration of Helsinki; informed consent was obtained. Funding/support and role of the sponsor: None. Data availability: Data are available on reasonable request from the corresponding author.

Data availability:

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Figures

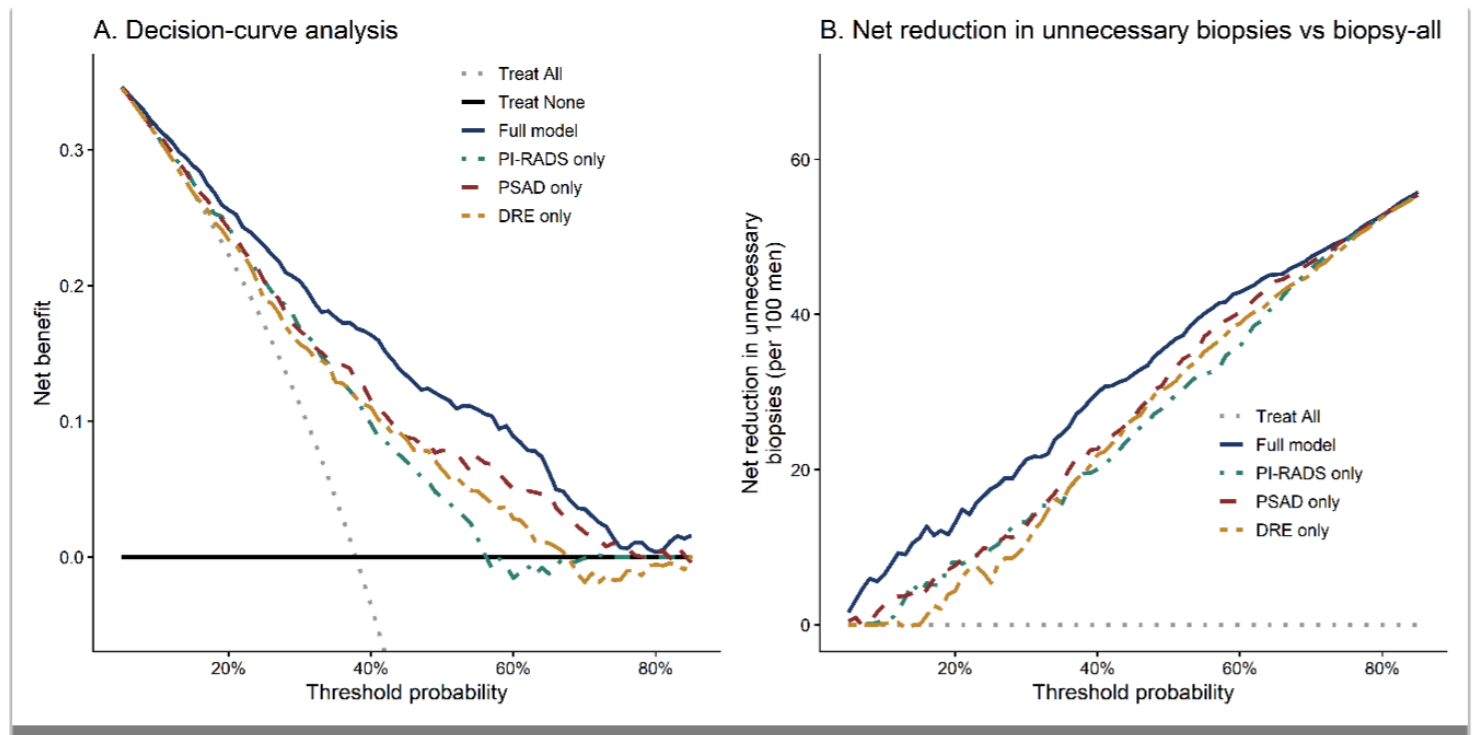


Figure 1

Clinical utility of the multivariable logistic model for the csPCa detection – decision curve analysis. A. Net Benefit across the threshold range of the tested model, model with PI-RADS only, PSA density-only and DRE-only, all models adjusted for age and mpMRI centre. B. Net reduction in unnecessary MRI-TRUS fusion biopsies per 100 men relative to a biopsy-all strategy

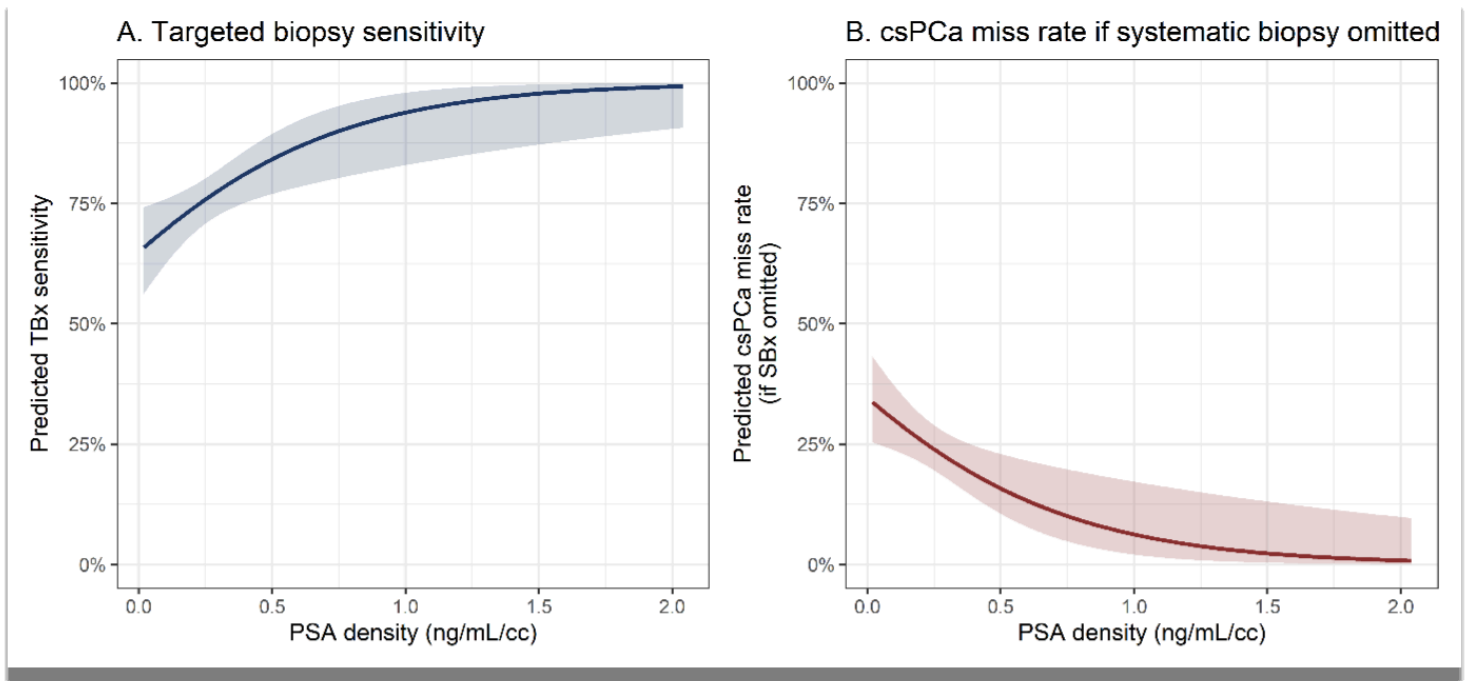


Figure 2

Diagnostic performance of TBx across PSAD values: A. sensitivity for detecting csPCa and B. miss csPCa rate if SBx were omitted. Univariable logistic models were fitted on patients with positive combined biopsy results (N = 338). Lines represented predicted probabilities derived from these models and shaded areas represented corresponding 95% confidence intervals.