

# Comparison of the Diagnostic Performance of Multiparametric Prostate Magnetic Resonance Imaging Results with Classical Parameters for Prostate Carcinoma in Gray Zone Patients

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## What's known on the subject? and What does the study add?

Urology guidelines suggest that multiparametric prostate magnetic resonance imaging should be conducted for all patients before biopsy. However, not all centers can perform a targeted prostate biopsy. Nonetheless, it is beneficial for patients to undergo this imaging method even if a targeted biopsy cannot be performed. In patients with prostate-specific antigen levels between 4–10 ng/mL, classical parameters, such as prostate-specific antigen density and free total prostate-specific antigen ratio, remain crucial in making biopsy decisions.

## Abstract

**Objective:** To compare the diagnostic value of prostate imaging-reporting and data system (mpMRI) version 2.0 with classical parameters for prostate cancer detection in gray zone patients with ultrasonography-guided prostate biopsy as a reference point.

**Materials and Methods:** With the retrospective nature of the study, 438 biopsy-naïve patients in the gray zone with pre-biopsy mpMRI were reviewed. Ultrasonography-guided transrectal prostate biopsy was the reference point. Diagnostic performance of classical parameters compared with mpMRI results for prostate carcinoma and clinically significant prostate carcinoma.

**Results:** The overall cancer detection rate was 30%. Prostate-specific antigen density, free/total prostate-specific antigen ratio, prostate volume, suspicious digital rectal examination, and mpMRI score >3 were independent predictors of clinically significant prostate carcinoma. Prostate-specific antigen density followed by free/total prostate-specific antigen ratio had the largest area under the curve values compared with mpMRI score >3 for prostate carcinoma and clinically significant prostate carcinoma.

**Conclusion:** Classical parameters, prostate-specific antigen density, and f/t prostate-specific antigen ratio were still critical to deciding prostate biopsy in gray zone patients, in whom ultrasonography-guided transrectal prostate biopsy was used as a reference point. In centers where targeted fusion biopsies were unavailable, pre-biopsy mpMRI still had some benefits. However, biopsy decisions should be made according to each patient's individual characteristics.

**Keywords:** Prostate, biopsy, multiparametric prostate magnetic resonance imaging, prostate carcinoma

## Introduction

After skin cancer, prostate cancer (PCa) is the second most frequent malignancy in men (1). The decision to perform a systematic 10–12 core transrectal ultrasonography-guided prostate biopsy (TRUS-PB), which is typically performed in an

outpatient clinic under local anesthesia and has an overall cancer detection rate of 30–40%, has long been based on elevated prostate-specific antigen (PSA) levels and abnormal digital rectal examination (DRE) results (2). Although the widespread use of TRUS-PB and PSA testing helped increase the early detection of PCa, this conventional pathway also resulted

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**Received:** 30.06.2023 **Accepted:** 07.10.2023

**Cite this article as:** Bostancı C, Demir DÖ. Comparison of the Diagnostic Performance of Multiparametric Prostate Magnetic Resonance Imaging Results with Classical Parameters for Prostate Carcinoma in Gray Zone Patients J Urol Surg



in numerous unnecessary treatments for clinically insignificant prostate cancer (CISPCa) and missed up to 30% of clinically significant prostate carcinoma (CSPCa) (3-6).

A prostate-specific antigen (PSA) level above 4 ng/mL is typically considered a threshold for biopsy indication. However, due to the low specificity of PSA in detecting PCa, no absolute cut-off value can entirely rule out the need for a biopsy (7). Additionally, when PSA is used to predict PCa likelihood in the 4-10 ng/mL range, known as the "gray zone", approximately 75% of biopsies yield negative results (8,9). To decrease these unnecessary biopsies, parameters such as PSA density (PSAD), the ratio of free PSA (f PSA) to total PSA (f/t PSA), PSA velocity, prostate volume (PV), and age-related PSA are also used to decide for biopsy in gray zone patients (10).

The traditional method of performing a prostate biopsy has changed with the increasing use of pre-biopsy prostate multiparametric magnetic resonance imaging (mpMRI). Research studies such as PRECISION and PROMIS have demonstrated that mpMRI can be used as a triage test, reducing unnecessary prostate biopsies by 25% and improving diagnostic accuracy for CSPCa (11,12). However, despite being a valuable tool for detecting CSPCa, mpMRI may not always provide accurate results because studies have shown that false negative outcomes can occur in 20-30% of patients with CSPCa (3-13).

According to the latest guidelines of the European Association of Urology (EAU) (14), mpMRI is now regarded as the initial imaging modality used before prostate biopsy in biopsy-naïve and repeat biopsies. According to the EAU guidelines, we aim to obtain pre-biopsy mpMRI from almost all patients who are candidates for biopsy in the gray zone. However, the risk profile of patients who would benefit the most from mpMRI has yet to be clearly defined. Accordingly, the objective of this study was to assess the efficacy of classical diagnostic parameters such as age, PSA levels, f PSA, PSAD, DRE, and f/t PSA when compared with mpMRI prostate imaging-reporting and data system (PI-RADS) scores in predicting PCa and CSPCa in which systematic 12-core TRUS-PB was used as a reference point in grey zone patients. In addition, this study assessed the diagnostic accuracy of classical parameters and mpMRI PI-RADS scores in predicting PCa and CSPCa.

## Materials and Methods

Our hospital's electronic media was used to retrospectively collect data on 820 patients who underwent TRUS-PB between January 2018 and April 2023. PSA >4.0 ng/mL, PI-RADS score  $\geq 3$ , suspicious DRE, prior suspicious biopsy results, and staging of patients with a history of PCa were the biopsy criteria. The study inclusion criteria included biopsy-naïve patients who had undergone at least 12-core TRUS-PB with a PSA level ranging

from 4 to 10 ng/mL with pre-biopsy mpMRI. We eliminated 382 patients from the study without a pre-biopsy mpMRI, had PSA levels outside the gray zone, had a previous biopsy or diagnosis of PCa, had less than 12 core biopsies, or were using 5-alpha reductase inhibitors. As a result, the study included 438 patients.

Although the operator was aware of the PI-RADS score, no mpMRI ultrasound targeted fusion biopsies (MR/USTB) were performed because of a lack of equipment. In addition, cognitive fusion biopsies (CFB) were not conducted because of the lack of high-level MR reading and experience of the operator. However, all patients with PI-RADS scores  $\geq 3$  were referred to another hospital located 250 km away in the closest city where MR/USTB was available. Patients who accepted TRUS-PB in our institution were included in the study.

All systematic 12-core TRUS-PB operations were performed by the same urologist (CB) under local anesthesia in the left decubital position using an 18-gauge single-use biopsy needle and the same ultrasonography device. In all patients, 1 or 2 extra biopsy cores were taken from each suspicious lesion on transrectal ultrasonography in addition to systematic 12-core biopsies.

T2-weighted (T2W), diffusion-weighted, and dynamic contrast-enhanced imaging were used during mpMRI using a 1.5 Tesla MRI system (Magnetom Essenza, Siemens Healthcare Solutions). The radiology specialists contracted by our hospital described the mp-MRI findings using a PIRADS score of 2.0.

Within 4 h of blood collection, serum PSA and f PSA levels were measured in our hospital laboratory using chemiluminescent microparticle immunoassay. The ellipsoid formula was used to determine PV. Using MR images, three prostate dimensions were evaluated.

The core specimens were analyzed by pathologists from the same institution. According to the International Society of Urological Pathology, PCa with a Gleason score (GS) of 7 is classified as CSPCa, whereas those with a GS of 6 are classified as CISPCa (15).

## Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested using the Shapiro-Wilk test. Factors affecting PCa and CSPCa were tested using univariate and multivariate binary logistic regression analysis. ROC curve analysis was used to calculate and compare the variables under the curve. SPSS 22.0 Windows version package program and MedCalc 19.7.1 package program were used in the analysis.  $P < 0.05$  was considered significant.

## Results

Table 1 summarizes the patient's clinical information, including their median age of 66 years, PSA level of 5.9 ng/mL, f PSA level of 1.3 ng/mL, PV of 60.0 mL, PSAD of 0.09 ng/mL/mL, and f/t PSA of 0.23. The median number of biopsy cores was 12, and 31.6% of patients had a suspicious DRE. Of the 438 patients, 131 (29.9%) were diagnosed with PCa and 87 (19.8%) with CSPCa.

Age, PV, PSA level, PV, PSAD, f/t PSA, suspicious DRE, PI-RADS score 3, and PI-RADS score 4-5 were among the parameters identified by univariate logistic regression analysis as significant predictors of PCa. The multivariate analysis assessed the parameters that stood out in the univariate study. Age, PSAD, suspicious DRE, PI-RADS score 3, and PI-RADS score 4-5 were found to be independent predictors of PCa in multivariate analysis. Regarding CSPCa, it was found that age, PSA level, PV, PSAD, f/t PSA, suspicious DRE, PI-RADS 3, and PI-RADS score 4-5 were predictors in univariate analysis. However, upon further multivariate analysis, only age, f/t PSA, suspicious DRE, PI-RADS score 3, and PI-RADS score 4-5 were deemed independent predictors of CSPCa (Table 2).

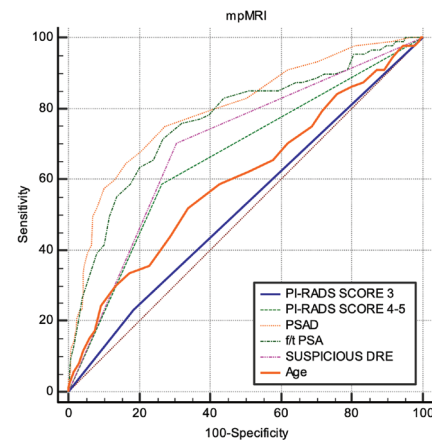
The diagnostic performance of the parameters for PCa and CSPCa was evaluated using ROC curve analysis. The ROC curve analysis for predicting PCa showed that the area under the curve (AUC) values of PSAD (0.771) were the highest, followed by f/t PSA (0.733) compared with other parameters. For CSPCa, PSAD had the highest AUC value (0.798) compared with the other parameters. The f/t PSA ratio had the second highest AUC value (0.768), followed by suspicious DRE (Figure 1).

ROC curve analysis revealed a cut-off value of PSAD of 0.11 ng/mL/mL in predicting PCa. With a cut-off value of 0.11 ng/mL/mL, the sensitivity and specificity were 61.8% and 83.7%, respectively. For CSPCa, the cut-off value of PSAD was calculated to be 0.12 ng/mL/mL with 64.3% sensitivity and 83.7% specificity.

For f/t PSA, using a cut-off value of 0.19 for PCa, the sensitivity and specificity of predicting PCa were 62.6% and 76.2%, respectively. The cut-off value of f/t PSA was the same for CSPCa, with 71.2% sensitivity and 73.5% specificity.

The PV, with a cut-off value of 49 mL, had 59.5% sensitivity and 81.4% specificity for PCa. For CSPCa, the cut-off value was calculated at 50 mL with 66.6% sensitivity and 75.5% specificity.

According to logistic regression analysis, a PI-RADS score of 3 and a PI-RADS score of 4-5 were independent predictors of PCa or CSPCa. A PI-RADS score of 4-5 had a sensitivity of 48.8% and specificity of 74.2% for PCa, whereas it had a sensitivity of 58.6% and specificity of 73.9% for CSPCa. The cut-off values with the sensitivity and specificity results of the parameters for PCa and CSPCa are shown in Supplementary Table 1.



Variable	AUC	SE <sup>a</sup>	95% CI <sup>b</sup>
PI-RADS score 3	0.524	0.0249	0.476 to 0.571
PI-RADS score 4-5	0.662	0.0290	0.616 to 0.706
PSAD	0.798	0.0283	0.757 to 0.834
f/t PSA	0.768	0.0305	0.725 to 0.807
Suspicious DRE	0.698	0.0276	0.653 to 0.741
Age	0.600	0.0358	0.552 to 0.646

**Figure 1.** ROC curves of PI-RADS score 3, PI-RADS score 4-5, PSAD, f/t PSA, suspicious DRE, and age in clinically significant prostate cancer detect

PI-RADS: Prostate Imaging-Reporting and Data System, PSAD: Prostate specific antigen density, DRE: Digital rectal examination, f/t PSA: Free/total prostate specific antigen ratio, AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidence interval, SE:

**Table 1. Main data of pre-biopsy mpMRI applied patients in grey zone with pathology results**

Parameters	Pre-biopsy mpMRI applied patients in grey zone
No. of patients	438
Age, years median (IQR)	66.0 (61.0-70.0)
PSA ng/mL median (IQR)	5.9 (4.9-7.6)
Prostate volume mL median (IQR)	60.0 (46.0-85.0)
Free PSA ng/mL median (IQR)	1.3 (1.0-1.8)
PSAD ng/mL/mL median (IQR)	0.09 (0.06-0.13)
f/t PSA % median (IQR)	0.23 (0.16-0.29)
Suspicious DRE n, (%)	145 (31.6)
No. of biopsy cores median (IQR)	12.0 (12.0-12.0)
<b>Pathology results</b>	
PIN n, (%)	22 (5)
ASAP n, (%)	45 (10.2)
BPH n, (%)	240 (54.7)
PCa n, (%)	131 (29.9)
CISPCa n, (%)	44 (10.0)
CSPCa n, (%)	87 (19.8)
<b>PI-RADS scores</b>	
PI-RADS 1-2 n, (%)	211 (48.2)
PI-RADS 3 n, (%)	84 (19.2)
PI-RADS 4-5 n, (%)	143 (32.6)

PSA: Prostate specific antigen, PSAD: Prostate specific antigen density, f/t PSA: Free/total prostate specific antigen ratio, DRE: Digital rectal examination, PIN: Prostatic intraepithelial neoplasia, ASAP: Atypical small acinar cell proliferation, BPH: Benign prostatic hyperplasia, PCa: Prostate carcinoma, CISPCa: Clinically insignificant prostate carcinoma, CSPCa: Clinically significant prostate carcinoma, PI-RADS: Prostate imaging-reporting and data system, IQR: Interquartile range

**Table 2. Univariate and multivariate analysis of classical parameters and PI-RADS score for the prediction of prostate cancer and clinically significant prostate cancer**

PCa	Univariate a.	p	Multivariate a.	p
Age	1.04 (1.01-1.08)	0.007*	1.07 (1.02-1.12)	<b>0.003*</b>
PSA	1.23 (1.097-1.38)	0.001*	0.93 (0.74-1.18)	0.564
Prostate volume	0.96 (0.95-0.97)	0.001*	0.99 (0.98-1.01)	0.376
PSAD	6.54 (4.16-10.26)	0.001*	3.91 (1.6-9.55)	<b>0.003*</b>
f/t PSA	0.00 (0.00-0.00)	0.001*	0.04 (0-1.01)	0.051
Suspicious DRE	4.52 (2.92-6.97)	0.001*	3.19 (1.86-5.5)	<b>0.001*</b>
No. of biopsy core	1.09 (0.81-1.49)	0.563	1.2 (0.79-1.82)	0.404
PI-RADS 3	2.84 (1.61-5.03)	0.001*	2.46 (1.23-4.95)	<b>0.011*</b>
PI-RADS 4-5	3.93 (2.42-6.41)	0.001*	2.53 (1.35-4.72)	<b>0.004*</b>
CSPCa	Univariate a	p	Multivariate a.	p
Age	1.06 (1.02-1.10)	0.004*	1.08 (1.02-1.13)	<b>0.003*</b>
PSA	1.32 (1.17-1.51)	0.001*	1.09 (0.84-1.41)	0.535
Prostate volume	0.96 (0.95-0.97)	0.001*	0.98 (0.96-1)	0.088
PSAD	4.88 (3.26-7.32)	0.001*	1.84 (0.82-4.13)	0.136
f/t PSA	0.00 (0.00-0.00)	0.001*	0 (0-0.31)	<b>0.013*</b>
Suspicious DRE	5.35 (3.21-8.92)	0.001*	3.22 (1.71-6.06)	<b>0.001*</b>
No. of biopsy core	0.94 (0.64-01.36)	0.732	0.81 (0.5-1.34)	0.415
PI-RADS 3	3.81 (1.83-7.79)	0.001*	3.08 (1.31-7.21)	<b>0.010*</b>
PI-RADS 4-5	6.75 (3.66-12.48)	0.001*	4.85 (2.28-10.32)	<b>0.001*</b>

PSA: Prostate specific antigen, PSAD: Prostate specific antigen density, f/t PSA: Free/total prostate specific antigen ratio, DRE: Digital rectal examination, PI-RADS: Prostate imaging-reporting and data system

## Discussion

Our research aimed to evaluate the effectiveness of mpMRI in predicting PCa and CSPCa compared with classical parameters in gray zone patients. In our study, 29% of the patients were diagnosed with PCa, indicating that unnecessary biopsies were performed in 71% of the patients. Previously, elevated PSA levels were used as the primary indicator for prostate biopsy, but this resulted in overdiagnosis and unnecessary biopsies (16). Our study demonstrated that PSA was not an independent predictor of PCa and CSPCa in multivariate analysis. Nonetheless, PSA derivatives, such as f/t PSA and PSAD, remain widely used in deciding whether to perform a prostate biopsy. Multiple studies have suggested that a prostate biopsy should be recommended when f/t PSA <0.15 and PSAD >0.15 ng/mL (17-19). Our results showed that the cut-off values for PSAD were 0.11 for PCa and 0.12 for CSPCa, whereas for f/t PSA, these values were calculated as 0.19 for both PCa and CSPCa. We also observed that these two parameters had the highest AUC values in the ROC analysis for both PCa and CSPCa. However, we should note that f PSA has been reported to have a summary sensitivity of 70% in gray zone patients, and because of its instability in serum, it is not recommended to use it alone in determining whether to conduct a prostate biopsy or not (20).

Our study demonstrated that using mpMRI with a score of  $\geq 3$  had a lower AUC value for detecting PCa and CSPCa than PSAD, f/t PSA, and suspicious DRE. This may be due to the fact that we did not perform targeted biopsies on patients with a PI-RADS score  $\geq 3$ . The introduction of mpMRI and PI-RADS scoring has changed the traditional PSA and its derivatives approach. According to the latest EAU guidelines, it is recommended to use pre-biopsy mpMRI to locate suspicious lesions or to avoid biopsy in low-risk patients and to perform both targeted and systematic biopsies on patients with suspicious lesions detected by mpMRI (14). The PROMIS study demonstrated that the use of pre-biopsy mpMRI can significantly reduce unnecessary biopsies by 27% while increasing the diagnosis of CSPCa by 18% and reducing the potential over-diagnosis and over-treatment of CSPCa by 5% (11). Similarly, the PRECISION study has shown that targeting biopsy alone is more effective than systematic biopsy for detecting CSPCa (12). However, the MR-FIRST study has indicated that combining systematic and targeted biopsy can yield better results than either method alone (21). Moreover, large randomized controlled trials have supported the combination of targeted and systematic biopsy as the optimal approach for achieving the highest cancer detection rates in patients with suspicious mpMRI lesions (22,23). However, mpMRI fusion targeting biopsies, which are in-bore MRI-targeted and MR ultrasound-targeted fusion biopsies (MR/USTB), are not

available in all hospitals. The alternative technique, CFB, requires no additional equipment but a high level of mpMRI reading knowledge. We opted not to use CFB because of its high reliance on mpMRI readings, despite its simplicity, speed, and lack of necessary equipment. To conduct a CFB, the operator must have a complete understanding of the location of the prostate lesion. This can only be achieved by carefully examining each MRI image, which requires a high level of mpMRI reading knowledge. Although the FUTURE study demonstrated that these three techniques did not have significantly different CSPCa detection rates (24), the success of CFB and MR/USTB heavily depends on the experience of the biopsy operators, making it imperative for skilled urologists proficient in mpMRI reading or a radiologist familiar with prostate MRI to perform cognitive biopsies (25,26).

Even if we did not perform fusion-targeted biopsies, pre-biopsy mpMRI provided two significant benefits. First, it helped us avoid unnecessary biopsies for patients in the gray zone who had no lesions on MRI by using other parameters. Second, patients with lesions in the anterior part of the prostate were referred directly to specialized hospitals for targeted biopsies. In addition, patients requiring repeat biopsies no longer have to wait eight weeks for mpMRI because they already had pre-biopsy mpMRI.

### Study Limitations

One of the study's main limitations was that it was conducted at a single-center and had a retrospective nature. This study did not involve targeted biopsies but used TRUS-PB as a reference point. However, TRUS-PB has been criticized for both underdetecting and overdiagnosing PCa.

### Conclusion

Classical parameters, PSAD, and f/t PSA are essential when deciding on prostate biopsy in gray zone patients. If targeted fusion biopsies are unavailable, pre-biopsy mpMRI can still provide some advantages. Nevertheless, it is essential to consider each patient's unique characteristics before deciding to proceed with a biopsy.

### Ethics

**Ethics Committee Approval:** The study was initiated with the approval of the Karabük University Non-invasive Clinical Research Ethics Committee (date: 07.11.2022, approval no: 2022/1150).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: C.B., D.Ö.D., Concept: C.B., D.Ö.D., Design: C.B., D.Ö.D., Data Collection or Processing: C.B., D.Ö.D.,

Analysis or Interpretation: C.B., D.Ö.D., Literature Search: C.B., D.Ö.D., Writing: C.B., D.Ö.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

### References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-E386 .
2. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev M, Wiegel T, Zattoni F, Mottet N. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014;65:124-137.
3. Pokorny MR, de Rooij M, Duncan E, Schröder FH, Parkinson R, Barentsz JO, Thompson LC. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. *Eur Urol* 2014;66:22-29.
4. Rabbani F, Stroumbakis N, Kava BR, Cookson MS, Fair WR. Incidence and clinical significance of false-negative sextant prostate biopsies. *J Urol* 1998;159:1247-1250.
5. Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, Zerbib M, Muradyan N, Legman P, Cornud F. Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. *J Urol* 2013;189:493-499.
6. Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P, Huang J, Dorey FJ, Reiter RE, Marks LS. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. *Eur Urol* 2014;65:809-815.
7. Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. *J Natl Cancer Inst* 2005;97:1132-1137.
8. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, Feng Z, Parnes HL, Coltman Jr CA. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2006;98:529-534.
9. Yoshida K, Honda M, Sumi S, Arai K, Suzuki S, Kitahara S. Levels of free prostate-specific antigen (PSA) can be selectively measured by heat treatment of serum: free/total PSA ratios improve detection of prostate carcinoma. *Clin Chim Acta* 1999;280:195-203.
10. Liu J, Dong B, Qu W, Wang J, Xu Y, Yu S, Zang X. Using clinical parameters to predict prostate cancer and reduce the unnecessary biopsy among patients with PSA in the gray zone. *Sci Rep* 2020;10:5157.
11. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, Moraes YC, Ward K, Hindley RG, Freeman A, Kirkham AP, Oldroyd R, Parker C, Emberton M. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;389:815-822.
12. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, Briganti A, Budaus L, Hellawell G, Hindley RG, Roobol MJ, Eggener S, Ghei M, Villers A, Bladou F, Villeirs GM, Virdi J, Boxler S, Robert G, Singh PB, Venderink W, Hadashik BA, Ruffion A, Hu JC, Margolis D, Crouzet S, Klotz L, Taneja SS, Pinto P, Gill I, Allen C, Giganti F, Freeman A, Morris S, Punwani S, Williams NR, Graves CB, Deeks J, Takwoingi Y, Emberton M, Moore CM. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018;378:1767-1777.

13. Meng X, Rosenkrantz AB, Mendhiratta N, Fenstermaker M, Huang R, Wysock JS, Bjurlin MA, Marshall S, Deng FM, Zhou M, Melamed J, Huang WJ, Lepor H, Taneja SS. Relationship Between Prebiopsy Multiparametric Magnetic Resonance Imaging (MRI), Biopsy Indication, and MRI-ultrasound Fusion-targeted Prostate Biopsy Outcomes. *Eur Urol* 2016;69:512-517.
14. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati S, Gandaglia G, Gillessen S, Grivas N, Grummet J, Henry AM, van der Kwast TH, Lam TB, Lardas M, Liew M, Mason MD, Moris L, Oprea Lager DE, van der Poel HG, Rouviere O, Schoots IG, Tilki D, Wiegel T, Willemsse PPM, Cornford P. EAUEANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2021;79:243-262.
15. vanLeenders GJLH, van der Kwast TH, Iczkowski KA. The 2019 International Society of urological pathology consensus conference on prostate cancer grading. *Eur Urol* 2021;79:87-99.
16. Alberts AR, Schoots IG, Roobol MJ. Prostate-specific antigen-based prostate cancer screening: past and future. *Int J Uro* 2015;22:524-532.
17. Ha YS, Yu J, Salmasi AH, Patel N, Parihar J, Singer EA, Kim JH, Kwon TG, Kim WJ, Kim IY. Prostate-specific antigen density toward a better cutoff to identify better candidates for active surveillance. *Urology* 2014;84:365-371.
18. Schoots IG, Osses DF, Drost F-JH, Werbeek JFM, Remmers S, van Leenders GJLH, Bangma CH, Roobol MJ. Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PI-RADS and PSA-density, with different thresholds for significant disease. *Transl Androl Urol* 2018;7:132-144.
19. Ujike T, Uemura M, Kawashima A, Nagahara A, Fujita K, Miyagawa Y, Nonomura N. A novel model to predict positive prostate biopsy based on serum androgen level. *Endocr Relat Cancer* 2018;25:59-67.
20. Huang Y, Li ZZ, Huang YL, Song HJ, Wang YJ. Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10ng/mL: A meta-analysis. *Medicine (Baltimore)* 2018;97:e0249.
21. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, Petrucci MD, Chambardel MD, Magaud L, Remontet, Ruffion A, Colombel M, Crouzet S, Schott AM, Lemaitre L, Rabilloud M, Grenier N. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;20:100-109.
22. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, Bloom J, Gurram S, Siddiqui M, Pinsky P, Parnes H, Linehan WM, Merino M, Choyke PL, Shih JH, Turkbey B, Wood BJ, Pinto PA. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. *N Engl J Med* 2020;382:917-928.
23. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, Marks LS. Comparison of Targeted vs. Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. *JAMA Surg* 2019;154:811-818.
24. Wegelin O, Exterkate L, van der Leest M, Kummer JA, Vreuls W, de Bruin PC, Bosch JLHR, Barentsz JO, Somford DM, van Melick HHE. The future trial: a multicenter randomized controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. *Eur Urol* 2019;75:582-590.
25. Puech P, Ouzzane A, Gaillard V, Betrouni N, Renard B, Villers A, Lemaitre L. Multiparametric MRI-targeted TRUS prostate biopsies using visual registration. *Biomed Res Int* 2014;2014:819360.
26. Moldovan P, Udrescu C, Ravier E, Souchon R, Rabilloud M, Bratan F, Sanzalone T, Cros F, Crouzet S, Gelet A, Chapet O, Rouviere O. Accuracy of Elastic Fusion of Prostate Magnetic Resonance and Transrectal Ultrasound Images under Routine Conditions: A Prospective Multi-Operator Study. *PLoS One* 2016;11:e0169120.

## Supplementary Table 1a. The cut-off values of parameters with sensitivity and specificity for PCa

### 1. Age

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.592
Standard error <sup>a</sup>	0.0311
95% confidence interval <sup>b</sup>	0.544 to 0.638
Z-statistic	2.949
Significance level p (area=0.5)	0.0032

Youden index J	0.1879
Associated criterion	>67
Sensitivity	50.38
Specificity	68.40

#### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>67	50.38	41.5-59.2	68.40	62.9-73.6

### 2. PSA

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.612
Standard error <sup>a</sup>	0.0290
95% confidence interval <sup>b</sup>	0.565 to 0.658
Z-statistic	3.861
Significance level p (area=0.5)	0.0001

Youden index J	0.1926
Associated criterion	>6.05
Sensitivity	60.31
Specificity	58.96

#### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>6.05	60.31	51.4-68.7	58.96	53.2-64.5

### 3. PSAD

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.771
Standard error <sup>a</sup>	0.0263
95% confidence interval <sup>b</sup>	0.728 to 0.809
Z-statistic	10.312
Significance level p (area=0.5)	<0.0001

Youden index J	0.4555
Associated criterion	>0.11
Sensitivity	61.83
Specificity	83.71

#### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>0.11	61.83	52.9-70.2	83.71	79.1-87.7

### 4. f/t PSA

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.733
Standard error <sup>a</sup>	0.0280
95% confidence interval <sup>b</sup>	0.689 to 0.774
Z-statistic	8.332
Significance level p (area=0.5)	<0.0001

Youden index J	0.3882
Associated criterion	≤0.19
Sensitivity	62.60
Specificity	76.22

#### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
≤0.19	62.60	53.7-70.9	76.22	71.1-80.9

### 5. PV

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.747
Standard error <sup>a</sup>	0.0268
95% confidence interval <sup>b</sup>	0.704 to 0.788
Z-statistic	9.217
Significance level p (area=0.5)	<0.0001

Youden index J	0.4098
Associated criterion	≤49
Sensitivity	59.54
Specificity	81.43

#### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
≤49	59.54	50.6-68.0	81.43	76.6-85.6

### 6. PI-RADS 4-5

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.616
Standard error <sup>a</sup>	0.0252
95% confidence interval <sup>b</sup>	0.568 to 0.661
Z-statistic	4.582
Significance level p (area=0.5)	<0.0001

Youden index J	0.2312
Associated criterion	>0
Sensitivity	48.85
Specificity	74.27

#### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>0	48.85	40.0-57.7	74.27	69.0-79.1

## 7. PI-RADS 3

### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.532
Standard error <sup>a</sup>	0.0215
95% confidence interval <sup>b</sup>	0.484 to 0.580
Z-statistic	1.485
Significance level p (area=0.5)	0.1374

Youden index J	0.06400
Associated criterion	>0
Sensitivity	23.66
Specificity	82.74

### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>0	23.66	16.7-31.9	82.74	78.0-86.8

## Supplementary Table 1b. The cut-off values of parameters with sensitivity and specificity for CSPCa

### 1. Age

#### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.600
Standard error <sup>a</sup>	0.0358
95% confidence interval <sup>b</sup>	0.552 to 0.646
Z-statistic	2.784
Significance level p (area=0.5)	0.0054

Youden index J	0.1811
Associated criterion	>67
Sensitivity	51.72
Specificity	66.38

### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>67	51.72	40.8-62.6	66.38	61.2-71.3

## 2. PSA

### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.645
Standard error <sup>a</sup>	0.0335
95% confidence interval <sup>b</sup>	0.598 to 0.690
Z-statistic	4.319
Significance level p (area=0.5)	<0.0001

Youden index J	0.2616
Associated criterion	>6.3
Sensitivity	60.92
Specificity	65.24

### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>6.3	60.92	49.9-71.2	65.24	60.0-70.2

## 3. PSAD

### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.798
Standard error <sup>a</sup>	0.0283
95% confidence interval <sup>b</sup>	0.757 to 0.834
Z-statistic	10.523
Significance level p (area=0.5)	<0.0001

Youden index J	0.4813
Associated criterion	>0.12
Sensitivity	64.37
Specificity	83.76

### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>0.12	64.37	53.4-74.4	83.76	79.5-87.5



#### 4. f/t PSA

##### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.768
Standard error <sup>a</sup>	0.0305
95% confidence interval <sup>b</sup>	0.725 to 0.807
Z-statistic	8.792
Significance level p (area=0.5)	<0.0001

Youden index J	0.4477
Associated criterion	≤0.19
Sensitivity	71.26
Specificity	73.50

##### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
≤0.19	71.26	60.6-80.5	73.50	68.6-78.0

#### 5. PV

##### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.757
Standard error <sup>a</sup>	0.0302
95% confidence interval <sup>b</sup>	0.714 to 0.797
Z-statistic	8.525
Significance level p (area=0.5)	<0.0001

Youden index J	0.4217
Associated criterion	≤50
Sensitivity	66.67
Specificity	75.50

##### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
≤50	66.67	55.7-76.4	75.50	70.7-79.9

#### 6. PI-RADS 4-5

##### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.662
Standard error <sup>a</sup>	0.0290
95% confidence interval <sup>b</sup>	0.616 to 0.706
Z-statistic	5.580
Significance level p (area=0.5)	<0.0001

Youden index J	0.3241
Associated criterion	>0
Sensitivity	58.62
Specificity	73.79

##### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>0	58.62	47.6-69.1	73.79	68.9-78.3

#### 7. PI-RADS 3

##### Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.524
Standard error <sup>a</sup>	0.0249
95% confidence interval <sup>b</sup>	0.476 to 0.571
Z-statistic	0.954
Significance level p (area=0.5)	0.3401

Youden index J	0.04755
Associated criterion	>0
Sensitivity	22.99
Specificity	81.77

##### Criterion values and coordinates of the ROC curve [Show]

Criterion	Sensitivity	95% CI	Specificity	95% CI
>0	22.99	14.6-33.2	81.77	77.3-85.7