The Roles of Multiparametric Magnetic Resonance Imaging, PCA3 and Prostate Health Index—Which is the Best Predictor of Prostate Cancer after a Negative Biopsy?

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Abbreviations and Acronyms

bGS = biopsy Gleason score
DCA = decision curve analysis
DRE = digital rectal examination
DWI = diffusion weighted imaging
%fPSA = free PSA rate
mp-MRI = multiparametric magnetic resonance imaging
MRI = magnetic resonance imaging
PB = prostate biopsy
PCa = prostate cancer
PCA3 = prostate cancer antigen 3
PHI = Prostate Health Index
PSA = prostate specific antigen
RB = repeat biopsy
tPSA = total PSA

Purpose: In patients with a negative prostate biopsy and persistent suspicion of prostate cancer, additional analyses such as the PCA3 score, PHI and multiparametric magnetic resonance imaging have been proposed to reduce the number of unnecessary repeat biopsies. In this study we evaluate the diagnostic accuracy of PCA3, PHI, multiparametric magnetic resonance imaging and various combinations of these tests in the repeat biopsy setting.

Materials and Methods: A total of 170 patients with an initial negative prostate biopsy and persistent suspicion of prostate cancer were enrolled in this prospective study. The patients underwent measurements of the total prostate specific antigen and free prostate specific antigen rate, along with PHI, PCA3 tests and multiparametric magnetic resonance imaging before standard repeat biopsy that was performed by urologists blinded to the multiparametric magnetic resonance imaging results. Multivariate logistic regression models with various combinations of PCA3, PHI and multiparametric magnetic resonance imaging were used to identify the predictors of prostate cancer with repeat biopsy, and the performance of these models was compared using ROC curves, AUC analysis and decision curve analysis.

Results: In the ROC analysis the most significant contribution was provided by multiparametric magnetic resonance imaging (AUC 0.936), which was greater than the contribution of the PHI+PCA3 model ($p < 0.001$). In the multivariate logistic regression analysis only multiparametric magnetic resonance imaging was a significant independent predictor of prostate cancer diagnosis with repeat biopsy ($p < 0.001$). The results of the decision curve analysis confirmed that the most significant improvement in the net benefit was provided by multiparametric magnetic resonance imaging.

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For another article on a related topic see page 252.

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Conclusions: Multiparametric magnetic resonance imaging provides high diagnostic accuracy in identifying patients with prostate cancer in the repeat biopsy setting compared with PCA3 and PHI.

Key Words: prostatic neoplasms; biopsy; magnetic resonance imaging; prostate cancer antigen 3, human

In cases of suspicion of prostate cancer, patients are currently subjected to prostate biopsy, which remains the gold standard for diagnosis.[1] This approach has its limits because in 25% to 30% of patients with PCa the neoplastic tissue is not included in the samples.[2] Moreover in patients with persistently increased PSA and negative PB, the repetition of biopsies does not increase the detection rate of PCa, which indeed decreases progressively.[3] Because of the additional number of samples there is a significant risk of complications (infection, bleeding, acute urinary retention), anxiety and social-sanitary costs.[4]

Recently various biomarkers have been studied to increase the ability to predict PCa diagnosis, especially in patients with persistent suspicion of cancer and a previous negative PB. The most promising biomarkers are PCA3 and [-2]proPSA (p2PSA), along with its derivative, the Prostate Health Index.[5–9] Other authors have emphasized the role of mp-MRI in PCa diagnosis, taking advantage of the anatomical, morphological and functional information that it provides.[10–15]

To evaluate the role of new biomarkers and mp-MRI in this setting we conducted a prospective observational study to evaluate the diagnostic accuracy of PCA3, PHI, mp-MRI and various combinations of the 3 tests in patients undergoing a standard repeat biopsy with an initial negative PB who maintained a high suspicion of harboring PCa.

MATERIALS AND METHODS

Study Design and Population

The study was performed between March 2011 and April 2013, after obtaining the approval of the ethics committee of our institution, San Luigi Hospital in Orbassano, Italy. Patients were prospectively included in the study if they had a negative initial PB (12 samples) and if they had a high suspicion of harboring PCa that warranted RB.

The inclusion criteria were persistently increased PSA and/or positive DRE. The exclusion criteria were contraindications for undergoing PB (ie cannot interrupt anticoagulant therapy) or mp-MRI (ie claustrophobia, presence of magnetically activated implanted devices, metallic implants in sensitive areas) or previous prostate treatment (ie transurethral prostate resection). Moreover patients suspected of having anteriorly located PCa on mp-MRI were noted by the radiologist and were excluded from the study.

Biomarkers

All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access® assays (Beckman Coulter, Brea, California)[16] after processing with a Unicel® DxI 800 Immunoassay System analyzer (Beckman Coulter). All men underwent PCA3 testing before RB via a Progensa® PCA3 assay (Gen-Probe Inc, San Diego, California) according to the manufacturer's specific instructions.

Prostate mp-MRI

All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil (Medrad, Warrendale, Pennsylvania). The prostate and seminal vesicle anatomy was assessed on T2-weighted images in the axial, coronal and sagittal planes. T1 fast spin echo axial images were generated to identify areas of intraprostatic hemorrhage and to evaluate the pelvic nodes and bones. Functional information was obtained by DWI and dynamic contrast enhanced MRI. DWI was performed using axial echo planar imaging sequences at different b-values. The sequence parameters satisfied the recommendations from a European consensus meeting that were published after the beginning of this study.[17] Further details on technical parameters are reported in the supplementary Appendix (http://jurology.com/).

All MR images were sent to a workstation and post-processed (Functool v. 9.4.05a, GE Healthcare). A single experienced radiologist analyzed the mp-MRI findings. The radiologist was blinded to the pathologist biopsy reports and to the biomarker results. For the purpose of this study the radiologist had to choose between suspicion of PCa (positive mp-MRI) or no suspicion of PCa (negative mp-MRI). The signs considered suspicious for PCa are reported in the supplementary Appendix.[10,14,18] Overall the mp-MRI finding was considered positive if at least 2 of the 3 MR sequences (T2-weighted, DWI and dynamic contrast enhanced MRI) produced suspicious findings.

Prostate Biopsy and Pathology

All patients then underwent RB under transrectal ultrasound guidance in an ambulatory setting. Biopsies were performed according to the Rodríguez-Covarrubias et al protocol using a Hawk Ultrasound scanner 2102 EXL with a biplanar transducer 8808 (B-K Medical, Herlev, Denmark) and a disposable core biopsy instrument (MaxCore®) with an 18G needle and 18 mm length of sample notch.[19] When the prostate volume was less than 60 cc the RB consisted of 18 needle biopsy cores, whereas when the prostate volume was 60 cc or greater a 24-sample biopsy scheme was adopted. Two dedicated urologists blinded to

the mp-MRI reports and to the biomarkers results performed all repeat biopsies. RB complications were recorded. Histological examination was conducted by a dedicated uropathologist who was blinded to the biomarkers and to the mp-MRI results according to a standardized protocol.[20]

Patients with a persistently high suspicion of PCa and negative RB were followed according to our clinical practice. In particular, patients with positive mp-MRI underwent a cognitive biopsy under transrectal ultrasound guidance based on mp-MRI findings. The results of this followup were not considered in this study.

Statistical Analysis

Multivariate logistic regression models were used to identify the predictors of PCa when performing RB. The tested models used various combinations of predictors including base (DRE, age), base + PCA3, base + PHI, base + mp-MRI, base + PHI + PCA3, base + PHI + mp-MRI, base + PCA3 + mp-MRI, and full (base, PCA3, PHI and mp-MRI). The performance of these models was compared using 1) ROC and AUC analysis, and 2) decision curve analysis.[21] Since %fPSA, tPSA and PHI are not independent by construction, we included in the base model DRE and age only.

The calibration of the fitted models was measured using the Cessie-van Houwelingen-Copas-Hosmer statistic. The AUCs were compared with DeLong's test for 2 correlated ROC curves. The cutoffs providing the best combination of sensitivity and specificity in the ROC curves were determined following the Youden criterion. Modeling and statistical analyses were performed using the R statistical system (R Foundation for Statistical Computing, Vienna, Austria) version 3.0.1. All tests were 2-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Population Results

A total of 187 patients were eligible according to the inclusion criteria but 17 (9.1%) presented 1 or more exclusion criteria. In particular, 4 patients (2.1%) were excluded due to anteriorly located prostate cancer on mp-MRI. Finally, the overall population consisted of 170 patients. The demographic and clinical characteristics of the cohort are shown in table 1. Only 6 patients (3.5%) underwent a 24-sample RB. The RB complication rate was 5.3% (3 urinary acute retention and 6 acute prostatitis cases). The pathological details are listed in table 2.

Multiparametric MRI missed 5 of 52 (9.6%) tumors (3 bGS 6 and 2 bGS 7). PCA3 missed 22 of 52 (42.3%) tumors (10 bGS 6, 10 bGS 7 and 2 bGS 8 or greater), whereas PHI missed 30 of 52 (57.7%) tumors (16 bGS 6, 12 bGS 7 and 2 bGS 8 or greater).

Statistical Results

The cutoffs for PCA3 and PHI in our cohort were obtained using ROC analysis and were 32.5 (sensitivity 0.659, specificity 0.750) and 48.9 (sensitivity 0.409, specificity 0.780), respectively. In the ROC analysis, as shown in figure 1, the most significant contribution was provided by mp-MRI. Indeed, when added to the base model, mp-MRI had an AUC value of 0.936, which was significantly higher than the value of the base + PHI + PCA3 model ($p < 0.001$). Moreover when adding biomarkers to models containing mp-MRI, there was not a significant improvement of AUC value as shown in figure 1.

In the multivariate logistic regression analysis in the full model only mp-MRI was a significant independent predictor of PCa diagnosis on RB (table 3). PCA3 was an independent predictor only in the absence of mp-MRI, whereas PHI reached a marginal significance only in the base + PHI model.

The specificity at a fixed sensitivity (80%, 90% and 95%) and the sensitivity at a fixed specificity

Table 1. *Demographic and clinical characteristics*

	Pos RB	Neg RB	Overall	p Value
Total No. (%)	52 (30.6)*	118 (69.4)	170	
Median age (IQR)	66 (61–70.5)	64.5 (59–70)	65 (60–70)	0.378
Median ng/ml tPSA (IQR)	7.7 (5.6–10.2)	6.8 (5.1–9.6)	6.9 (5.2–9.8)	0.238
Median %fPSA (IQR)	15.5 (12.2–20.1)	17.1 (13.1–21.2)	16.4 (12.5–21.0)	0.404
No. DRE (%):				0.026†
Neg	44 (84.6)	113 (95.8)	157 (92.4)	
Pos	8 (15.4)	5 (4.2)	13 (7.6)	
Median ml prostate vol (IQR)	42 (39–51)	42 (36–48)	42 (36–50)	0.698
Median PHI (IQR)	43.9 (29.4–57.2)	36.3 (27.8–48.0)	37.8 (28.4–50.9)	0.016†
Median PCA3 (IQR)	43 (23.5–67)	20 (12–36)	27 (13–49)	0.004†
No. mp-MRI (%):				<0.001†
Neg	5 (9.6)	107 (90.7)	112 (65.9)	
Pos	47 (90.4)	11 (9.3)	58 (34.1)	

The chi-square test and Kruskal-Wallis test were used to compare the difference between proportions and medians, respectively, between the positive and negative RB groups.

* The 52 lesions were found in 52 patients.

† $p < 0.05$.

Table 2. *Pathological characteristics*

Pos for PCa		
No. pos for PCa (%)	52	(30.6)
No. bGS (%):		
6 or Less	28	(16.4)
7 (3+4)	19	(11.2)
7 (4+3)	2	(1.2)
8 or Greater	3	(1.8)
Median pos cores (IQR)	2	(1—3)
Median % pos tissue (IQR)	3	(1.2—6.1)
Neg for PCa		
No. neg for PCa (%)	118	(69.4)
No. high grade prostatic intraepithelial neoplasia (%)	10	(5.9)
No. atypical small acinar proliferation of prostate (%)	7	(4.1)
No. high grade prostatic intraepithelial neoplasia with atypical small acinar proliferation of prostate (%)	3	(1.8)
No. atypical adenomatous hyperplasia/adenosis (%)	4	(2.4)
No. chronic inflammation (%)	39	(22.9)
No. benign/neg for malignancy (%)	55	(32.3)

(80%, 90% and 95%) are reported in the supplementary table (http://jurology.com/). The best combination of sensitivity and specificity was displayed by all models containing mp-MRI. At a high sensitivity or specificity the association of the biomarkers with mp-MRI displayed results comparable to those of mp-MRI alone.

The results of DCA, plotted in figure 2, confirm that the most significant improvement in the net benefit was provided by mp-MRI. The inclusion of PCA3 and/or PHI to models containing mp-MRI did not substantially improve the net benefit according to DCA. Moreover the DCA models with mp-MRI indicated a considerable net reduction in avoidable biopsies compared with the biopsy all patients strategy (fig. 3). For example, at a threshold probability of 30% (PCa prevalence of the study 30.3%), the net reduction in avoidable biopsies was greater than 90%.

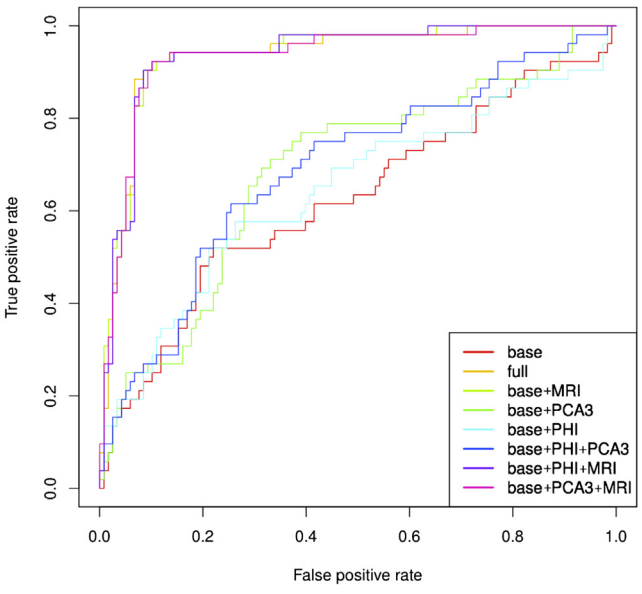

Figure 1. ROC analysis of various combinations of predictors in overall population.

DISCUSSION

The parameters traditionally used to assess the risk of PCa, such as tPSA, %fPSA and DRE, have low sensitivity and specificity.[1] PCA3 score is considered a better biomarker to select patients who could benefit from a RB compared with tPSA.[22] Moreover recent studies have indicated that p2PSA and its derivative PHI significantly improve the accuracy in PCa detection with prostate biopsy.[6,23]

To date 2 studies have reported on head-to-head comparisons between PCA3 and PHI to establish which test has the highest accuracy in predicting prostate cancer with RB.[7,8] In the first study the performance of the 2 biomarkers was compared in a cohort of 246 patients undergoing initial or repeat biopsy.[7] In the RB cohort the PCA3 results were more discriminating. In the second study Scattoni et al evaluated the results of the 2 biomarkers in 95 patients who underwent RB.[8] The authors concluded that both examinations offer a significant increase in diagnostic accuracy with a predominant role for PHI.

Multiparametric MRI has also acquired a significant role in the RB setting. Cirillo et al obtained high positive (70%) and negative (90%) predictive values from RB performed after mp-MRI in a cohort of 54 consecutive men with persistent suspicion of PCa.[24] More recently Sciarra et al demonstrated that the use of mp-MRI to direct biopsies can significantly improve the sensitivity of the PCA3 score.[25]

Mp-MRI is also currently gaining importance in PCa diagnosis because of the possibility that it offers in performing cognitive[26] or visually guided targeted prostate biopsy.[27—29] Moreover, in addition to identifying the presence of a tumor, in positive cases mp-MRI can localize the lesions, assess their local extent and provide insights on their aggressiveness.

To contribute to this field we planned this study to compare the roles of mp-MRI, PCA3 and PHI in the repeat biopsy setting. Because mp-MRI supplies greater clinical information than serum or urine biomarkers, comparing laboratory test results and imaging findings might appear controversial. Therefore, to overcome the possible limitations of the study design, we placed biomarkers and mp-MRI on the same level by dichotomizing the latter so that it could only be assessed as positive or negative for PCa, as occurred in the other tests.

Furthermore, to avoid bias the radiologist who evaluated the mp-MRI findings, the urologists who performed the RBs and the uropathologist who

Table 3. *Multivariate logistic regression models in the overall population*

	Age	Pos DRE	PCA3	PHI	Pos mp-MRI	Hosmer statistics (8 df)
Base model:						
OR (95% CI)	1.339 (0.598–3.053)	4.007 (1.264–13.918)	Not applicable	Not applicable	Not applicable	8.559
p Value	0.479	0.020*	Not applicable	Not applicable	Not applicable	0.380
Base + PCA3:						
OR (95% CI)	0.975 (0.411–2.324)	3.565 (1.093–12.663)	3.878 (1.273–12.947)	Not applicable	Not applicable	17.138
p Value	0.955	0.037*	0.020*	Not applicable	Not applicable	0.028
Base + PHI:						
OR (95% CI)	1.391 (0.615–3.211)	3.393 (1.041–11.992)	Not applicable	3.517 (1.040–14.140)	Not applicable	10.371
p Value	0.430	0.045*	Not applicable	0.053	Not applicable	0.239
Base + mp-MRI:						
OR (95% CI)	2.473 (0.665–9.680)	2.962 (0.467–21.490)	Not applicable	Not applicable	99.521 (34–363.165)	6.134
p Value	0.179	0.275	Not applicable	Not applicable	1.22e −14*	0.632
Base + PCA3 + mp-MRI:						
OR (95% CI)	2.151 (0.536–8.954)	2.863 (0.431–21.569)	1.847 (0.257–9.901)	Not applicable	94.546 (32.138–346.543)	5.846
p Value	0.280	0.301	0.503	Not applicable	3.91e −14*	0.664
Base + PHI+ PCA3:						
OR (95% CI)	1.015 (0.423–2.448)	3.096 (0.916–11.207)	3.873 (1.247–13.225)	3.438 (1.009–13.866)	Not applicable	8.589
p Value	0.973	0.070	0.023*	0.057	Not applicable	0.378
Base + PHI + mp-MRI:						
OR (95% CI)	2.448 (0.655–9.615)	3.070 (0.479–22.261)	Not applicable	0.763 (0.172–4.399)	103.473 (34.489–387.452)	6.350
p Value	0.185	0.260	Not applicable	0.732	2.71e −14*	0.608
Full model:						
OR (95% CI)	2.138 (0.531–8.915)	2.943 (0.441–22.143)	1.837 (0.251–9.950)	0.777 (0.175–4.492)	98.096 (32.525–396.153)	6.803
p Value	0.285	0.289	0.511	0.749	6.78e −14*	0.558

* $p < 0.05$.

reported the pathological analysis were all blinded to the each other's results and to the collected biomarker results. Patients with anteriorly located PCa were excluded from the study because they are rarely diagnosed in a RB setting with ultrasound guided transrectal approach. Only 4 patients were excluded for this reason and, thus, we believe the results were not affected by this choice.

To our knowledge this is one of the first studies in which mp-MRI and biomarkers are compared in RB candidates. Our results demonstrate that the addition of mp-MRI to the base model produces the highest AUC value (0.936) and that the performance of the model is better than that of other models, including base + PCA3 and/or PHI models. On multivariate analysis mp-MRI reached an OR of 99.521 ($p < 0.0001$). In the full model mp-MRI also

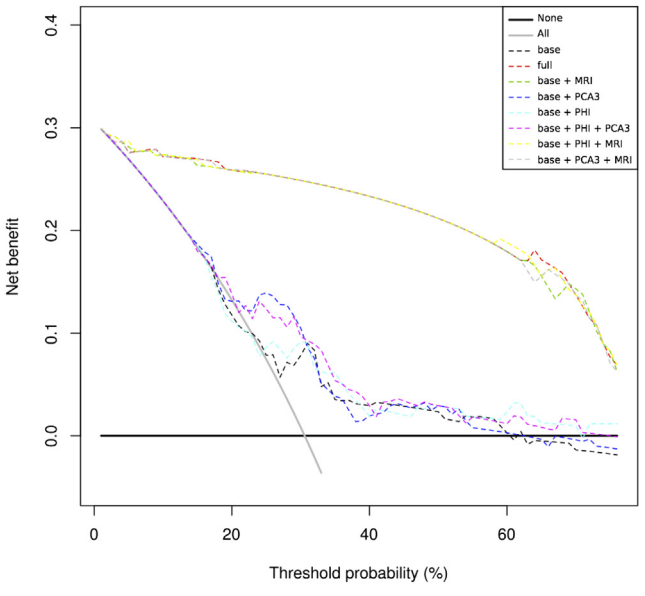

Figure 2. DCAs of effect of various models on PCa detection. Threshold probability to undergo biopsy is reported vs net benefit. Broken black line represents assumption that all patients will harbor PCa (biopsy all patients). Horizontal line represents assumption that no patients will harbor PCa (biopsy no patients).

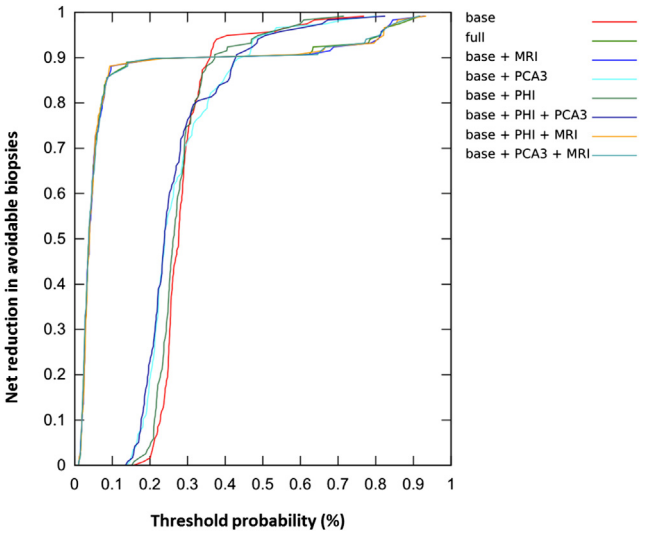

Figure 3. Net reduction in avoidable biopsies reported vs various threshold probabilities (PCa prevalence of study 30.3%).

displayed the highest net benefit according to DCA, with a considerable net reduction in avoidable biopsies. In terms of the biomarkers, PCA3 appeared to be an independent predictor only when mp-MRI was not considered, yielding an OR of 3.878 ($p = 0.021$) in the base + PCA3 model, as happened with PHI in the base + PHI model (OR 3.517, $p = 0.053$). Although we put the imaging to the same level of a PCa marker in this study, interestingly mp-MRI performed better than the laboratory tests in terms of the detection rate.

Our study is not free of limitations. The study was limited by the relatively small number of cases examined and further studies with a larger number should be performed to confirm our findings. Considering RB as reference standard could be a limitation because the chance of missing tumors is still present. Obviously the best reference is the prostatectomy specimen, but this was not possible in our setting. Moreover the inclusion of a single expert uroradiologist who interpreted all of the multiparametric MR images may affect the reproducibility of our results in clinical practice. The results may actually underestimate the true capabilities of mp-MRI at a center of excellence using 3T machines and modern software, even if the imaging protocol used satisfied the recommendations from a European consensus meeting.[17] This effect would be less if a standardized reporting scheme is used like the PI-RADS classification,[14,30] but this prospective study started in 2011 when the classification was not yet published. Finally, the study does not include any discussion of costs and logistics. Given the current health care crisis, these issues are of key importance and further studies should be advised.

Notwithstanding these limitations, we believe that our results are noteworthy and could be immediately transferable to the urological community. Multiparametric MRI should be considered a promising tool for avoiding unnecessary biopsies. PCA3 and PHI do not appear to add further information in a clinical setting with availability and expertise in mp-MRI, suggesting a possible limitation of their widespread use in this clinical scenario. In light of these results we can imagine that the future of PCa diagnosis in the RB setting is closely related to mp-MRI.

CONCLUSIONS

Our results indicate that mp-MRI has a high diagnostic accuracy in identifying patients with prostate cancer in the RB setting compared with PCA3 and PHI. Therefore, mp-MRI should be considered a valid tool for avoiding unnecessary biopsies in patients with an initial negative PB and persistent suspicion of PCa. If these data are confirmed by other studies, the additional value of biomarkers in this setting should be reconsidered.

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