Prostate Cancer Gene 3 and Multiparametric Magnetic Resonance Can Reduce Unnecessary Biopsies: Decision Curve Analysis to Evaluate Predictive Models

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OBJECTIVE To overcome the well-known prostate-specific antigen limits, several new biomarkers have been proposed. Since its introduction in clinical practice, the urinary prostate cancer gene 3 (PCA3) assay has shown promising results for prostate cancer (PC) detection. Furthermore, multiparametric magnetic resonance imaging (mMRI) has the ability to better describe several aspects of PC.

METHODS A prospective study of 171 patients with negative prostate biopsy findings and a persistent high prostate-specific antigen level was conducted to assess the role of mMRI and PCA3 in identifying PC. All patients underwent the PCA3 test and mMRI before a second transrectal ultrasound-guided prostate biopsy. The accuracy and reliability of PCA3 (3 different cutoff points) and mMRI were evaluated. Four multivariate logistic regression models were analyzed, in terms of discrimination and the cost benefit, to assess the clinical role of PCA3 and mMRI in predicting the biopsy outcome. A decision curve analysis was also plotted.

RESULTS Repeated transrectal ultrasound-guided biopsy identified 68 new cases (41.7%) of PC. The sensitivity and specificity of the PCA3 test and mMRI was 68% and 49% and 74% and 90%, respectively. Evaluating the regression models, the best discrimination (area under the curve 0.808) was obtained using the full model (base clinical model plus mMRI and PCA3). The decision curve analysis, to evaluate the cost/benefit ratio, showed good performance in predicting PC with the model that included mMRI and PCA3.

CONCLUSION mMRI increased the accuracy and sensitivity of the PCA3 test, and the use of the full model significantly improved the cost/benefit ratio, avoiding unnecessary biopsies. UROLOGY 82: 1355–1362, 2013. © 2013 Elsevier Inc.

Currently, the diagnosis of prostate cancer (PC) is mainly based on 2 tests—digital rectal examination (DRE) and prostate-specific antigen (PSA) measurement—and then confirmed using transrectal ultrasound (TRUS)-guided biopsy.[1] The use of the PSA serum level as a predictor of PC has shown a variable range of sensibility and specificity in several clinical experiences. Only a slight increase in specificity has been gained by introducing the density and velocity of the serum PSA values.[2] In recent years, several new biomarkers have been proposed to overcome the current limits of PSA.[2] Since its introduction into clinical practice, the urinary prostate cancer gene 3 (PCA3) assay has shown promising results for PC detection, staging, and prognosis.[3] Marks et al,[4] in a population of 233 patients with previously negative biopsy findings and persistent high PSA serum levels (>2.5 ng/mL), using a PCA3 score cutoff of 35, reported a sensitivity of 58% and specificity of 72%, with an area under the receiving operating characteristic curve (AUC) of 0.68 for the PCA3 score and 0.52 for PSA. In contrast, Goode et al,[5] in a subgroup of 147 patients who had undergone repeated prostate biopsy, reported an AUC of 0.605 for the PCA3 score and 0.500 for the PSA level ($P \leq .2488$), concluding that PCA3 was not superior to PSA in the repeat biopsy population. A recent meta-analysis showed that the sensitivity of the PCA3 test was 46.9%-82.3%

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and the specificity was 56.3%-89%.[6] The variable results of the PCA3 test in terms of sensitivity and specificity can be explained by the low diagnostic performance of TRUS-guided biopsy in detecting PC. The latter has been reported to miss ≤30% of cancer cases.[7] Recent publications on this topic have emphasized that the use of secondary diagnostic imaging, such as magnetic resonance imaging (MRI), to guide prostate biopsy could increase the probability of a positive repeated biopsy and the sensitivity and specificity of the PCA3 test.[8-10] Despite this clinical evidence and that the test has recently been approved by the American Food and Drug Administration, according to the European Association of Urology guidelines, PCA3 remains an experimental examination. The optimal cutoff point also has not yet been well established.

Recently, some studies[10,11] revealed high diagnostic accuracy for multiparametric MRI (mMRI), combining anatomic imaging with magnetic resonance spectroscopic imaging (MRSI), diffusion-weight imaging (DWI), and dynamic contrast-enhanced imaging (DCEI). In particular, mMRI has the ability to better describe several aspects of the natural history of PC and can better guide the biopsy because of the better characterization of cancer foci in patients with a previously negative TRUS-guided biopsy.

With these considerations, the aim of the present study was to evaluate the role of the PSA serum level, mMRI, PCA3, and DRE in identifying patients with PC who had previously had negative findings on TRUS-guided prostate biopsy.

MATERIAL AND METHODS

The idea for the study began from the results of a previous trial conducted by our group, in which we concluded that mMRI can increase the sensitivity of a marker such as PCA3 and can also increase the accuracy of prostate biopsy.[12] We performed a prospective single-center study, from March 2010 to July 2012, of 171 consecutive patients with clinically suspected PC, who had previously had negative TRUS-guided prostate biopsy findings but had persistent high PSA serum levels (4-10 ng/mL).

Each enrolled patient provided written informed consent, and our institutional board committee approved the study protocol.

The inclusion criteria were a first random TRUS-guided prostate biopsy that was negative for PC or high-grade prostatic intraepithelial neoplasm and a PSA level of 4-10 ng/mL. The exclusion criteria were previous hormonal, surgical, or radiotherapy for prostatic disease; inadequate PCA3 samples; all the cases in which MRSI, DWI, and DCEI were not possible; an inadequate prostate biopsy with <10 cores; and declined consent to participate in the study.

To evaluate the PCA3 score, we collected urine specimens from each patient after an attentive prostate massage (3 compressions for each lobe). Next, all patients underwent mMRI with MRSI, DWI, and DCEI, before TRUS-guided biopsy. The biopsy protocol was a 10-core, laterally directed, random TRUS-guided biopsy.[13]

PCA3 Test

To increase the number of prostate cells shed into the urine, the PCA3 test requires urine collection after an attentive DRE,[14] applying firm pressure on the prostate from the base to the apex and from the lateral to the median lobe, with 3 strokes per lobe and sufficient pressure to slightly depress the prostate surface.[4,15] A total of 20-30 mL of urine was collected from each patient's initial void, and PCA3 and PSA messenger ribonucleic acid (RNA) was isolated from 2.5 mL for transcription-mediated amplification (Progensa PCA3 assay, Gen-Probe, San Diego, CA). PCA3 scores were obtained by normalizing PCA3 to the amount of prostate RNA present in the urine sample (quantitative PCA3/PSA messenger RNA ratio × 1000). A PCA3 score of ≥35 was considered positive (per laboratory standard).

MRSI Examination

All examinations were performed using a 3T scanner (Magnetom Vario, Siemens Medical Solutions, Erlangen, Germany; gradient strength 45 mT/m; slew rate 346 T/m/s; rise time 400 μ/s), equipped with a surface-phased array (Body Matrix, Siemens Medical Solutions) and using an endorectal coil (e-Coil, Medrad, combined with an Endoan-interface; Siemens Medical Solutions). Prostatic gland morphologic imaging was achieved by acquiring turbo spin echo T_2-weighted sequences in the axial, sagittal, and coronal planes. The technique used for imaging with MRSI, DWI, and DCEI has been previously described.[11,16] It allowed a comparison of the imaging findings with the pathologic data; in particular, the peripheral zone of the prostate was divided into a sextant using fixed criteria. The location of the MRSI voxels and the DCEI/DWI areas used for analysis were correlated with the sextant defined by mMRI. Spatial correspondence between the mMRI findings and the pathologic evaluation was achieved using the x- and z- coordinates derived from T_2-weighted MRI and the sextant division of the peripheral zone of the prostate.

TRUS-guided Biopsy

All biopsies were performed using an end-fire ultrasound transducer and biopsy gun with an 18-gauge needle (Esaote Technos MP with a C10-5 transducer). We applied to every patient a standard random, laterally directed, 10-core biopsy (2 cores from the basal portion, lateral and paramedial; 2 from the midgland, lateral and paramedial; and 1 from the apex, on each side of the gland). In those cases with areas described by MRSI, DWI, and DCEI as suspicious for PC, 2 additional TRUS-guided cores were taken from each site considered abnormal.

Statistical Analysis

TRUS-guided biopsy has been considered the clinical reference standard for the diagnosis of PC; therefore, PC and no PC refers to positive and negative findings for TRUS-guided biopsy, respectively.

The accuracy and reliability of PCA3, mMRI, and DRE vs the reference standard were evaluated for each test separately, and 3 cutoff values (27, 35, 44) were considered for PCA3. For each diagnostic test, the accuracy index, sensitivity, specificity, Cohen's κ, positive and negative predictive value, and diagnostic odds ratio, with the 95% confidence intervals (CIs) were evaluated.

The association between the Gleason score and the PCA3 score was evaluated using the Pearson chi-square test. For this analysis, the Gleason score was classified into 3 classes: no cancer, Gleason score ≤6, and Gleason score ≥7; and the PCA3 result into 4 classes: <27, 27-35, 35-43, and ≥44.

To evaluate the capability of the addition of PCA3 and mMRI, compared with the base clinical variables (ie, age, PSA level, and DRE findings), to better diagnose PC in patients with previous negative biopsy findings but with persistent high PSA serum levels, 4 multivariate logistic models were estimated. The first model was developed using the base clinical variables; in the next 2 models, mMRI and PCA3 were added separately. Finally, a model that included mMRI, PCA3, and the base clinical variables was developed. The predictive accuracy of each model was evaluated using the AUC. The 95% CIs and inference statistics for the differences between AUCs were computed using the method of DeLong.[17]

A cost-effective analysis, recently proposed by Vickers and Elkin,[18] was performed for each model using decision curve analysis. The decision curve analysis estimates the net benefit of a model by the difference between the number of true-positive and false-positive results, weighted by the odds of the selected threshold probability of risk. The net benefit of a model compared with the reference net benefit or with another model can be interpreted as the net increase in the proportion of cases identified. The reference was calculated by assuming that all patients had undergone biopsy for PC; in contrast, no patient undergoing biopsy was set to a zero net benefit. For any given threshold probability cutpoint, the risk model with the greater net benefit would be the preferred model.[19]

Using an approach in which patients would undergo biopsy if their predicted probability of PC was ≥20%, the number of patients who would undergo biopsy and the number of patients with PC that would be missed was calculated for each estimated model.[20]

The decision curve analysis and plots were implemented using the statistical software STATA for Windows, version 11 (StataCorp, College Station, TX); all other statistical analysis were done using Statistical Analysis Systems for Windows, version 9.2 (SAS Institute, Cary, NC).

RESULTS

We enrolled 171 consecutive patients in the present study. Two patients (1.2%) were excluded from the analysis because of insufficient PSA messenger RNA to evaluate the PCA3 test. Another 2 patients (1.2%) were excluded because of the impossibility of performing mMRI, and 4 patients (2.3%) declined informed consent.

The mean patient age was 66.4 ± 5.3 years; the mean PSA serum level was 6.8 ± 1.6 ng/mL. The DRE findings were identified as positive and uncertain for PC for 34 and 48 patients (20.9% and 29.4%), respectively.

Repeated TRUS-guided biopsy identified 68 new patients with PC (41.7%); 95 patients (58.3%) were not evaluated using the Gleason score because the biopsy findings were negative.

The mean PCA3 value was 57.0 ± 55.3, and 94 patients (57.7%) had PCA3 score of ≥35.

The characteristics of the analyzed patients, stratified by TRUS-guided biopsy outcome (PC vs no PC), are listed in Table 1.

The indexes of accuracy and reliability of the PCA3 test for 3 cutoff levels (27, 35, and 44) and mMRI compared with TRUS-guided biopsy are reported in Table 2. Of the considered PCA3 cutoffs, the cutoff of 44 showed the best general accuracy (accuracy index 0.67, κ = 0.33, diagnostic odds ratio 5.56). In contrast, the 27 cutoff exhibited the best sensitivity and negative predictive value (0.90 and 0.84 respectively), and mMRI had the best performance in detecting PC.

Table 1. Patient characteristics

Characteristic	PC (n = 68; 41.7%)	No PC (n = 95; 58.3%)
Age (y)	65.9 ± 5.8	66.9 ± 4.8
PSA (ng/mL)	6.9 ± 1.7	6.7 ± 1.5
PCA3 value	76.1 ± 52.1	43.2 ± 53.6
PCA3 >35 (+)	46 (67.6)	48 (50.5)
mMRI (+)	61 (89.7)	36 (37.9)
Gleason score		
3+2	4 (5.9)	—
3+3	32 (47.1)	—
3+4	15 (22.1)	—
4+3	6 (8.8)	—
4+4	9 (13.2)	—
4+5	2 (2.9)	—
DRE findings		
Uncertain	19 (27.9)	29 (30.5)
Positive	17 (25.0)	17 (20.6)

DRE, digital rectal examination; mMRI, multiparametric magnetic resonance imaging; PC, prostate cancer; PCA3, prostate cancer gene 3; PSA, prostate-specific antigen.

+ indicates that a particular evaluation is suspected for cancer presence.

Data presented as mean ± standard deviation or n (%).

The PCA3 result was significantly associated with the Gleason score ($P < .001$, chi-square = 71.27), with the patients with the greatest Gleason score also having the highest PCA3 score.

The predictive accuracy of the 4 analyzed predictive models is presented in Table 3.

An AUC of 0.551 (95% CI 0.461-0.640) was estimated for the clinical base model (age, PSA level, and DRE findings). This value increased to 0.742 (95% CI 0.664-0.821) with the addition of PCA3 to the model. The best discrimination (AUC 0.808, 95% CI 0.742-0.874) was obtained using the full model (base clinical model plus mMRI and PCA3). The AUC for the base clinical model plus MRSI resulted in an AUC of 0.781 (95% CI 0.664-0.821).

The enhancement of the models with addition of either PCA3 or mMRI, or both, in terms of the AUC, was statistically significant (Table 3).

Decision curves for PC diagnosis, using the 4 analyzed models, were plotted in Figure 1 to estimate these results in a clinical context. The net benefit of the base model was always equal to, or lower than, the net benefit of the other models. The base model plus PCA3 compared with the base model resulted in a greater net benefit for every probability threshold starting from 19%; however, it was always equal to, or lower than, the net benefit of the other 2 analyzed models. Both the base model plus MRSI and the full clinical model showed a superior net benefit, starting from a 6% probability threshold compared with the other 2 models.

Choosing a predicted probability threshold of 20% and applying the full clinical model would have resulted in

Table 2. Performance of prostate cancer antigen 3 score and magnetic resonance imaging as predictors of transrectal ultrasound biopsy outcome

Parameter	PCA3 ≥27	PCA3 ≥35	PCA3 ≥44	mMRI	DRE
Accuracy	0.60 (0.53-0.68)	0.57 (0.49-0.65)	0.67 (0.60-0.74)	0.74 (0.67-0.80)	0.58 (0.51-0.66)
Sensitivity	0.90 (0.82-0.97)	0.68 (0.57-0.79)	0.68 (0.57-0.79)	0.90 (0.82-0.97)	0.25 (0.15-0.35)
Specificity	0.39 (0.29-0.49)	0.49 (0.39-0.60)	0.66 (0.57-0.76)	0.62 (0.52-0.72)	0.82 (0.74-0.90)
PPV	0.51 (0.42-0.60)	0.49 (0.39-0.59)	0.59 (0.48-0.70)	0.63 (0.53-0.73)	0.50 (0.33-0.67)
NPV	0.84 (0.73-0.95)	0.68 (0.57-0.79)	0.74 (0.65-0.83)	0.89 (0.82-0.97)	0.60 (0.52-0.69)
Cohen's κ	0.26 (0.14-0.37)	0.16 (0.02-0.31)	0.33 (0.19-0.48)	0.49 (0.36-0.61)	0.08 (-0.06-0.21)
AUC	0.64 (0.58-0.70)	0.59 (0.51-0.66)	0.67 (0.60-0.74)	0.76 (0.70-0.82)	0.54 (0.47-0.60)
DOR	5.56 (2.30-13.46)	2.05 (1.07-3.91)	4.12 (2.12-7.99)	14.28 (5.89-34.61)	1.53 (0.72-3.27)

AUC, area under receiver operating characteristic curve; DOR, diagnostic odds ratio; NPV, negative predictive value; PPV, positive predictive value; other abbreviations as in Table 1.

Data in parentheses are 95% confidence intervals.

Table 3. Area under ROC curves of various models with 95% confidence intervals and comparison with base clinical model

Predictor	AUC	95% CI	*P* Value (vs Base)
Base clinical model	0.551	0.461-0.640	—
Base clinical model + PCA3	0.742	0.664-0.821	.0002
Base clinical model + MRSI	0.781	0.710-0.851	<.0001
Full clinical model	0.808	0.742-0.874	<.0001

CI, confidence interval; MRSI, magnetic resonance spectroscopic imaging; other abbreviation as in Tables 1 and 2.

66% fewer patients undergoing biopsy of those with a persistent high PSA serum level, missing only 9% of PC cases of the actual number of patients with PC. Similar results were obtained applying the base clinical model plus MRSI, but no evaluable clinical gain was obtained by applying the other 2 analyzed models.

COMMENT

Random TRUS-guided biopsy is now the preferred method for the histologic diagnosis of PC. Some studies have emphasized that random biopsy cores miss about 30% of cancer cases.[7] Men with persistently elevated serum PSA levels after a negative first random TRUS-guided prostate biopsy represent a great diagnostic challenge for urologists.

Since its introduction into clinical practice, the PCA3 test has been tested in several studies, with a wide range of sensitivity and specificity reported in detecting PC both in patients with previously negative prostate biopsy findings and in those with persistently high PSA serum levels as the first diagnostic test in a prescreened population.[3] Despite the promising initial results that highlighted the utility of the PCA3 test in reducing the number of unnecessary biopsies,[8] the optimal clinical utility of PCA3 remains unclear. Also, on the basis of the available studies on this topic, the European Association of Urology guidelines consider PCA3 still experimental and not recommended for clinical practice, probably because of the low accuracy of the test using prostate biopsy as standard reference and because an optimal cutoff value has not yet been well established.[20] Several investigators have proposed the combination of several biomarkers to improve the prediction rate of PC but reported only a slight increase in accuracy.[21] Similarly, to increase the predictive accuracy of the biopsy outcome and to identify men at risk of PC, a novel biopsy nomogram has been proposed. Chun et al[22] have validated, internally, a novel biopsy nomogram that includes the PCA3 score as a variable. They reported only a slight increase in the predictive accuracy for the PCA3 nomogram vs the basal Kattan nomogram (0.73 vs 0.68). Similar results were reported from a study by Auprich et al[23] that, for an externally validated PCA3 nomogram, reported an accuracy range of 0.72-0.75, using 4 different PCA3 codings. Likewise, other groups[24] have emphasized that incorporating PCA3 improves the diagnostic accuracy of the prediction tools such as the Prostate Cancer Prevention Trial calculator. The investigators[25] reported an AUC-receiver operating characteristic that was higher for the updated Prostate Cancer Prevention Trial calculator than for Chun's nomogram (79.6% vs 71.5%; $P = .043$), emphasizing that this difference could be explained by the use of a ≥12 laterally directed core biopsy vs the ≥10 core biopsy in the study by Chun et al.[22]

The hypothesis in our study was that the potential value of PCA3 as a biomarker for PC diagnosis could be improved using mMRI to direct the prostate biopsy to overcome the current limits of random prostate biopsy. In particular, it is possible that some cases detected as PCA3 false-positive results using random biopsy could become true positive using mMRI to direct the biopsy.[11,26] In our trial, for a PCA3 score of ≥35 alone, as a predictor of PC, we reported a sensitivity and specificity of 68% and 49%, respectively and an AUC of 0.59, which appears similar to other studies in the same population of patients (persistently elevated PSA serum levels and first negative biopsy findings), and therefore not very useful as a biomarker to detect PC.

On multivariate analysis, the introduction of PCA3 as a continuous variable, in addition to the base clinical model, resulted in a statistically significant increase in the AUC (0.74 vs 0.55, $P = .0002$), an increase that became

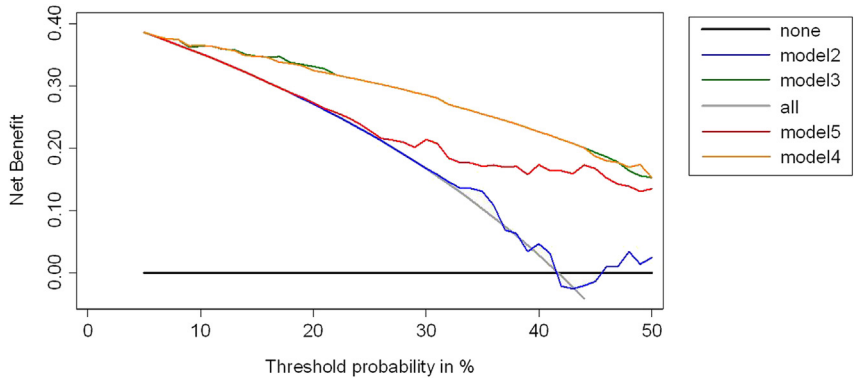

Figure 1. Decision curve analysis. The blue line indicates the base clinical model (age, digital rectal examination, and prostate-specific antigen); the red line indicates the base clinical model plus prostate cancer gene 3 (PCA3) assay; the green line indicates the base clinical model plus multiparametric magnetic resonance imaging (mMRI); and the gold line indicates the base clinical model plus PCA3 and mMRI.

even more evident with the further addition of mMRI (AUC 0.81, $P < .001$; Table 3).

Reading the decision curve analysis is useful to assess the cost/benefit ratio; however, the application of the base clinical model plus PCA3 resulted in no net benefit gain with a cutoff of 20%. Using the clinical base model plus MRSI and, even more, the full clinical model (same cutoff), a large number of unnecessary biopsies could be avoided at the cost of only a small number of patients with PC being advised not to undergo biopsy. Starting from a cutoff of 26%, the net benefit gain of using the base clinical model plus PCA3 without mMRI starts to be remarkable (Fig. 1).

To reduce the ever increasing number of unnecessary biopsies, we applied this new statistical evaluation to help us to better understand the cost/benefit ratio and the number of procedures not required at the expense of only a small number of men with PC being advised against biopsy. Furthermore, most of these men would have low-grade and low-stage PC that could be treated with active surveillance. It is also important to note that the use of this decision analytic method could improve clinical decision-making.

Some limits of our study must be underlined. First, the study was not randomized, and our findings were based on a relatively small sample size. Second, we did not use MRI-guided biopsy. It is difficult to ensure the correspondence of the TRUS-guided biopsy spatial accuracies with areas suspicious using mMRI. However, the correspondence between the localization of PC on histologic examination and the site indicated by mMRI, in those cases with suspicious mMRI findings, who were positive for PC at biopsy, supported our method. Moreover, the results of studies concerning MRI-guided biopsy were similar to our results in terms of the PC detection rate and percentage of clinically significant PC.[27]

The most important problem reported with the use of PSA as a screening test has been overdiagnosis, rather than unnecessary biopsies.[28] Our model led to fewer PC diagnoses but the PC cases not detected were a low grade and stage, which are exactly the type labeled as overdiagnosis.

CONCLUSION

According to our experience, the use of mMRI to drive TRUS-guided prostate biopsy can increase both the accuracy of this procedure and the sensitivity of the PCA3 test.

Promising results from studies on predictive models that have incorporated the PCA3 test as a variable or new biomarkers such a [−2]pro-PSA and the promising results of a new imaging modality for PC diagnosis, such as mMRI, could lead in the near future to better accuracy when predicting PC, allowing patients to avoid unnecessary biopsies. Furthermore, the use of the full model, including the base clinical variables plus mMRI and PCA3, can significantly improve the cost/benefit ratio. Adding mMRI is advisable because of its high performance. In contrast, adding PCA3 can only be recommended in association with other tests.

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EDITORIAL COMMENT

The authors evaluated the role of PCA3 and mMRI to improve the diagnostic accuracy of a repeat prostate biopsy in a cohort of 171 men with a previous negative prostate biopsy and persisting suspicion of harboring PC. The PC detection rate was 41.7% with the repeat biopsy, resulting in a potentially unnecessary biopsy rate of 58.3%. The authors developed multivariate logistic regression models to identify whether a base clinical model (PSA, DRE, age), the addition of PCA3, the addition of mMRI, and the combination of all markers would result in the best discrimination to perform a repeat prostate biopsy. The base model had an AUC of only 0.551, which increased to 0.742 and 0.781 when adding PCA3 and mMRI, respectively. The combination of all markers resulted in an additional statistically significant improvement in the AUC of 0.808. The authors conclude that the full model should be applied to patients who are scheduled for repeat prostate biopsies to decrease the risk of unnecessary biopsies.

Although the conclusions of the prospective study are in line with the statistics of their report, the study had some drawbacks that should be addressed in detail.

Apparently, only the PSA level, DRE findings, and patient age were considered in the decision-making process to perform a repeat prostate biopsy. However, the prostate volume, PSA velocity, PSA doubling time, percentage of free PSA were not considered. It has already been shown by Auprich et al[1] that a percentage of free PSA <15% and a PCA3 score with a cutoff of ≤44 basically result in the same diagnostic accuracy, with an AUC of 0.737 and 0.797, respectively, for men who undergo their first repeat biopsy, resulting in the avoidance of 73% of unnecessary biopsies. In men who are scheduled for a second or even third repeat biopsy, a percentage of free PSA of <12% and <14% outperformed PCA3 (AUC 0.819 vs 0.697 and 0.702 vs 0.616, respectively) and avoided 67% and 45% unnecessary biopsies, respectively. Therefore, the PCA3 score adds only a little value in the decision-making process to perform a repeat prostate biopsy in daily routine practice. This valuation has recently been adopted by Bradley et al,[2] who performed a comparative effectiveness review of PCA3 for the diagnosis of PC and concluded that the diagnostic accuracy of PCA3 was greater than PSA alone but at a very low level of evidence such that the routine use of PCA3 could not be recommended. Therefore, the European Association of Urology guidelines on the diagnosis and management of PC still consider PCA3 to be experimental.[3]

Based on the method used, I am unsure about the false-negative rate of PC. The authors did not use an MRI-guided biopsy, which is available using the transrectal and perineal route, even without using the techniques of MRI—TRUS fusion techniques.[3] The authors somehow transferred the MRI findings to the TRUS images and performed a TRUS-guided biopsy based on the predefined sextant. However, even when using MRI−TRUS fusion-guided biopsy, it has been recommended to target the suspicious lesions and to always supplement the targeted biopsy cores with random biopsy cores to increase the detection rate.[4,5] If a suspicious lesion on mMRI is targeted by a MRI-guided biopsy, 80%-85% of the lesions will

contain PC. If, however, only the sextant hosting the suspicious lesion is targeted, the detection rate will be much lower, depending on the volume of the PC area. We do not have any information on the volume and the intraprostatic location of the lesions identified on mMRI, making it quite difficult to assess the validity of the results. PCA3, however, will not help to increase or decrease the rate of biopsies if we are faced with a typical lesion on MRI.

Aside from mMRI with or without PCA3 scores, the role of transperineal biopsies should not be neglected, because they have the advantage of targeting the anterior zone of the prostate.[3] In a recent meta-analysis evaluating 46 clinical studies, no significant differences with regard to the PC detection rates could be identified when transperineal (PC detection rate 36.8%) and MRI-guided repeat biopsies (PC detection rate 37.6%) were compared.[6]

Furthermore, it seems unclear which cutoff PCA3 level should be used to avoid unnecessary biopsies and not overlook significant PC cases. The most frequently used cutoff score of <35 was present in about 50% of all men who were not diagnosed with PC. A PCA3 score of ≥44 had the highest diagnostic odds ratio of 4.12, but it still was significantly lower than the diagnostic odds ratio of 14.28 achieved using mMRI. Using even higher threshold values to perform a biopsy would result in the risk of overlooking a high number of PC cases. Lower threshold values will result in a high number of unnecessary biopsies, which has recently been shown by Wu et al,[7] who evaluated 103 patients scheduled for repeat biopsy of the prostate. Although PCA3 was independently associated with PC (odds ratio 1.02, 95% confidence interval 1.01-1.04), the AUC of 0.64 was quite low and could be significantly improved to an AUC of 0.82 by adding clinical variables such as the PSA density, PSA level, and DRE and TRUS findings.

Taking into consideration the small additional improvement of the multivariate logistic regression models of only 2.7%, the additional costs of the PCA3 test for the individual patient not covered by insurance and the low scientific evidence, and in accordance with the European Association of Urology guidelines, the use of PCA3 should not be recommended for daily routine use, even in the situation of repeat biopsies.

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REPLY

Recently, some investigators pointed out the need to perform predictive models using new imaging tools and biomarkers to overcome the current limits of PSA and its derivates, and thus avoid doing unnecessary biopsies.[1]

In the past, free PSA (fPSA) and the free/total PSA ratio (% fPSA) were introduced in an attempt to discriminate between benign prostatic hyperplasia and PC, in particular in those men with a total PSA (tPSA) value of 4-10 ng/mL. It is, nonetheless, important to underline that the use of fPSA and %fPSA has some limitations owing to fPSA instability, variable assay characteristics, and large prostate size (dilution effect).[2] Stephan et al,[3] analyzing the influence of prostate volume on the ratio of fPSA with tPSA in patients with PC and benign prostatic hyperplasia, concluded that %fPSA will yield significant results only in men with a normal prostate volume. A statistically significant difference ($P < .01$) will be found in the %fPSA value between patients affected by benign prostatic hyperplasia or PC only when the prostate volume is <40 cm^3.[3] In a recent multicenter study, conducted on a large cohort of 1026 patients (PROMEtheuS project), the investigators analyzed the ability of PSA to predict PC during biopsy. Considering PSA as a predictor of PC, the results were disappointing, with an AUC of tPSA, fPSA, and %fPSA of 0.549, 0.489, and 0.600, respectively.[4]

In contrast, PCA3 has been superior to tPSA and %fPSA in detecting PC, with a favorable AUC for a first repeated biopsy.[5]

In our trial, we focused on a cost/benefit analysis. Applying the full model decision curve analysis, the results of our trial showed that it is possible to avoid ≤66% of biopsies, missing only 9% of PC cases among the actual number of PC cases detected. However, in a trial by Catalona et al[6] that included 773 men who had undergone %fPSA evaluation, only a small decrease in the biopsies performed was reported. In particular, using a %fPSA cutoff of 25% resulted in a PC detection rate of 95%, avoiding only 20% of prostate biopsies.[6] Moreover, Scattoni et al[7] concluded that the prostate health index and PCA3 provide a significant increase in sensitivity and specificity compared with all other examined markers (ie, fPSA) and could help to guide the biopsy decision-making process.

One limitation of our study was that the biopsies were not MRI guided. Using this new technique, we certainly can see an improvement in the targeting of suspicious lesions, as reported by several recent studies.[8] This has been confirmed by the difficulties in ensuring the correspondence of TRUS biopsy spatial accuracies to suspicious areas on mMRI. In our analysis,

however, the peripheral zone of the prostate was divided in sextant according to strict criteria. The 100% correspondence between the localization of PC on histologic examination and the site indicated by mMRI support our method.

We believe that our model, combining a new biomarker (PCA3) with mMRI, that helps in targeting biopsies, can represent a valid tool to reduce unnecessary biopsies.

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