PCA3 Molecular Urine Test for Predicting Repeat Prostate Biopsy Outcome in Populations at Risk: Validation in the Placebo Arm of the Dutasteride REDUCE Trial

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Purpose: We determined the performance of PCA3 alone and in the presence of other covariates as an indicator of contemporaneous and future prostate biopsy results in a population with previous negative biopsy and increased serum prostate specific antigen.

Materials and Methods: Urine PCA3 scores were determined before year 2 and year 4 biopsies from patients in the placebo arm of the REDUCE trial, a prostate cancer risk reduction study evaluating men with moderately increased serum prostate specific antigen results and negative biopsy at baseline. PCA3, serum prostate specific antigen and percent free prostate specific antigen results were correlated with biopsy outcome via univariate logistic regression and ROC analyses. Multivariate logistic regression was also performed including these biomarkers together with prostate volume, age and family history.

Results: PCA3 scores were measurable from 1,072 of 1,140 subjects (94% informative rate). PCA3 scores were associated with positive biopsy rate ($p < 0.0001$) and correlated with biopsy Gleason score ($p = 0.0017$). PCA3 AUC of 0.693 was greater than serum prostate specific antigen (0.612, $p = 0.0077$ vs PCA3). The multivariate logistic regression model yielded an AUC of 0.753 and exclusion of PCA3 from the model decreased AUC to 0.717 ($p = 0.0009$). PCA3 at year 2 was a significant predictor of year 4 biopsy outcome (AUC 0.634, $p = 0.0002$), whereas serum prostate specific antigen and free prostate specific antigen were not predictive ($p = 0.3281$ and 0.6782, respectively).

Conclusions: PCA3 clinical performance was validated in the largest repeat biopsy study to date. Increased PCA3 scores indicated increased risk of contemporaneous cancers and predicted future biopsy outcomes. Use of PCA3 in combination with serum prostate specific antigen and other risk factors significantly increased diagnostic accuracy.

Key Words: prostate cancer antigen 3, human; prostate-specific antigen; prostatic neoplasms; ROC curve; logistic models

Abbreviations and Acronyms

% fPSA = percent free prostate specific antigen

PCa = prostate cancer

PCA3 = prostate cancer gene 3

PSA = prostate specific antigen

PV = prostate volume

REDUCE = Reduction by Dutasteride of Prostate Cancer Events

sPSA = serum prostate specific antigen

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For another article on a related topic see page 2158.

MEN with prostate cancer risk factors and 1 or more previous negative prostate biopsies present numerous questions to the urological practitioner. Is the patient in a precancerous state that will progress? Is there an undetected cancer and, if so, is the cancer of clinical significance? Should a fol-

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lowup biopsy be performed? A related and emerging question is whether some form of chemoprevention is indicated.

PCA3 measured in urine specimens is a PCa specific marker[1–3] associated with the likelihood of biopsy detectable PCa in at risk populations. The marker is insensitive to pre-analytical factors,[4] unaffected by factors that can compromise sPSA performance,[5] increased in confirmed PCa,[4–7] correlated with tumor volume[8,9] and complementary to traditional risk factors on multivariate analysis.[3,5] Recent studies of PCA3 in populations with previous negative biopsies and moderately increased sPSA have demonstrated significant associations of PCA3 with biopsy outcome, and predictive power exceeding sPSA and other covariates.

The REDUCE trial evaluated dutasteride for the prevention of biopsy detectable PCa in men with negative biopsies and increased sPSA.[10] With a placebo arm enrollment greater than 4,000 subjects the REDUCE trial represents an excellent cohort for the study of PCA3. Thus, we validated the performance of PCA3 previously observed in smaller studies. Specifically we determined the diagnostic accuracy of PCA3 alone and in the presence of covariates as an indicator of current and future biopsy outcomes.

MATERIALS AND METHODS

Study Population

The REDUCE trial was an international, multicenter, double-blind, placebo controlled chemoprevention study designed to determine if dutasteride administered at 0.5 mg daily decreased the risk of biopsy detectable PCa.[10] The study enrolled 8,121 men (4,072 and 4,049 in the placebo and dutasteride arms, respectively) 50 to 75 years old with prostate volume 80 ml or less. Men were required to have a recent sPSA of 2.5 to 10 ng/ml (younger than 60 years) or 3 to 10 ng/ml (60 years old or older). Additionally, men had to have had a single previous prostate biopsy (within 6 months of enrollment) of 6 to 12 cores without evidence of cancer, high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation. Enrolled subjects were followed for 4 years with clinical evaluations, laboratory sampling (including sPSA determinations every 6 months), and 10-core biopsies performed at 2 and 4 years. For cause biopsies were allowed if needed. Subjects diagnosed with a positive biopsy were considered to have reached the primary study end point and study participation was discontinued. A total of 1,516 cancers were observed (857 and 659 in the placebo and dutasteride arms, respectively).

A subset of 1,140 subjects from the REDUCE study cohort provided urine samples for PCA3 analysis before year 2 and/or year 4 biopsy (average time between urine collection and biopsy was 2 days, maximum 50 days). Samples for PCA3 analysis were not collected at baseline or at for cause biopsy. REDUCE trial sites that were able to obtain and process post-digital rectal examination urine specimens were included in this substudy. No other site selection criteria were used.

Urine Sampling and PCA3 Measurement

Following a digital rectal examination of 3 strokes per prostate lobe, each subject provided 20 to 30 ml urine in a first catch specimen using a standard urine collection cup. Samples were maintained on ice and processed within approximately 4 hours of collection by mixing with equal volumes of Gen-Probe® urine transport medium to lyse the prostate cells and stabilize the RNA. Samples were frozen at −70C then batch shipped on ice packs to Caris Diagnostics/Molecular Profiling Institute, Phoenix, Arizona for PCA3 determinations. Operators were blinded with respect to biopsy results and study arm (placebo vs dutasteride). Quantification of PCA3 and PSA mRNA levels has been described.[6] The PCA3 score is calculated as the ratio of PCA3 mRNA copies-to-PSA mRNA copies × 1,000.

Statistical Analyses

Nonparametric assessment of differences in PCA3 scores grouped by biopsy outcome was performed using the Wilcoxon rank sum test. Sensitivity and specificity were determined via ROC analysis. AUCs were compared via the method of DeLong et al.[11] Multivariate logistic regression models were developed to evaluate the independence of PCA3 scores in the presence of sPSA, % fPSA and traditional risk factors.

The last variable values and corresponding last biopsy results for a given subject were used for most analyses, ie for subjects with variable results only at 1 point these results were used, whereas for subjects with results at years 2 and 4 the year 4 variables were used. PCA3 scores for predicting future biopsy outcome in comparison to sPSA and % fPSA were evaluated in univariate logistic regression using year 2 values as indicators of biopsy outcome at year 4. NCSS 2004 (NSCC Inc., Kaysville, Utah), JMP® 5.01 and Analyze-It® v2.07 software packages were used for the analyses.

RESULTS

Subject Characteristics, and Correlations of PCA3 and sPSA With Prostate Volume

Pathological, clinical and marker findings were associated with subjects at the last study visit. Of the 1,140 specimens 1,072 provided sufficient mRNA for PCA3 analysis (94% informative rate). The 10-core biopsies detected PCa in 190 of the 1,072 informative subjects (17.7%) throughout the 4-year followup. The majority of cancers were Gleason score 6 or 7 (69.5% and 28.9%, respectively). Serum PSA ranged from 0.30 to 33.9 ng/ml. PCA3 scores ranged from 0.40 to 287.5 with 26.3% of subjects exceeding the cutoff of 35 used in previous studies.

Median PCA3 scores were 15.9 at year 2 and 18.0 at year 4 in subjects tested at both points. Subjects with negative biopsy at both visits displayed median PCA3 values of 15.3 and 16.9 at years 2 and 4, respectively. Statistically higher PCA3 medians were ob-

served at year 2 ($p = 0.0013$) and year 4 ($p = 0.0050$) if cancer was diagnosed at year 4.

Serum PSA values increased with increasing PV. Median values for sPSA were 4.2 ng/ml for PV less than 30 ml, 5.5 ng/ml for PV 30 to 50 ml and 6.4 ng/ml for PV greater than 50 ml ($p < 0.0001$ across categories). In contrast PCA3 scores demonstrated no significant trend with median values of 20.5, 18.5 and 18.8 in subjects with PV less than 30, 30 to 50 and greater than 50 ml, respectively ($p = 0.0621$).

Associations With Current Prostate Cancers

Median PCA3 scores were 33.8 for biopsy confirmed PCa and 16.7 for subjects completing the study without positive findings ($p < 0.0001$). Sensitivity and specificity for detection of cancer at biopsy for different PCA3 cutoffs were examined. At a cutoff of 35 sensitivity and specificity was 48.4% (95% CI 41.1–55.8) and 78.6% (75.7–81.2), respectively. Figure 1 shows biopsy positive rates for various PCA3 score ranges. The percent biopsy positive increased from 6% (7 of 116) at PCA3 scores less than 5 to 57.1% (28 of 49) at scores greater than 100 ($p < 0.0001$ across categories). These results demonstrate a direct correlation of PCA3 score with the probability of positive biopsy for PCa.

For the 190 cancers detected PCA3 scores correlated with biopsy Gleason score expressed as a binary categorical variable, with median values of 31.8 and 49.5 for Gleason score 6 or less vs greater than 6, respectively ($p = 0.0017$), indicating an association with cancer significance. PCA3 scores were also higher for other indicators of clinically significant PCa, although these correlations did not reach statistical significance. Median PCA3 scores were 33.2 and 50.6 for biopsies with 33% or less and more than 33% positive cores ($p = 0.1899$), 33.8 and 48.8 for 50% or less and more than 50% maximum core involvement ($p = 0.2435$), and 31.8 and 36.3 for PSA density 0.15 ng/ml/cm^3 or less and greater than 0.15 ng/ml/cm^3 ($p = 0.1390$).

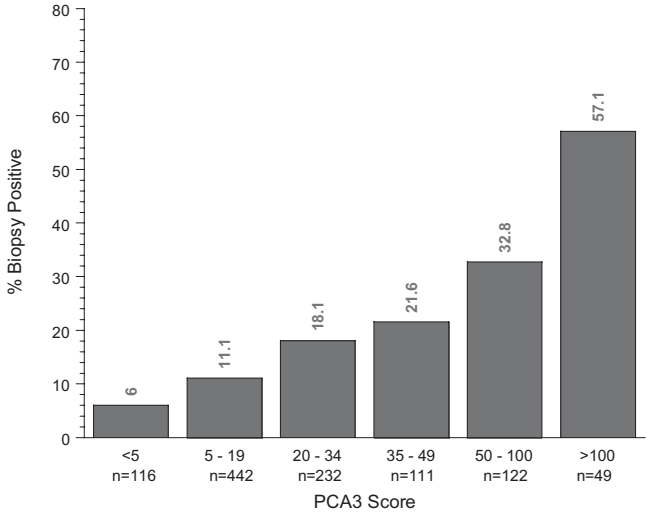

Figure 1. Percent of subjects with positive biopsy findings by PCA3 score range (Pearson chi-square $p < 0.0001$).

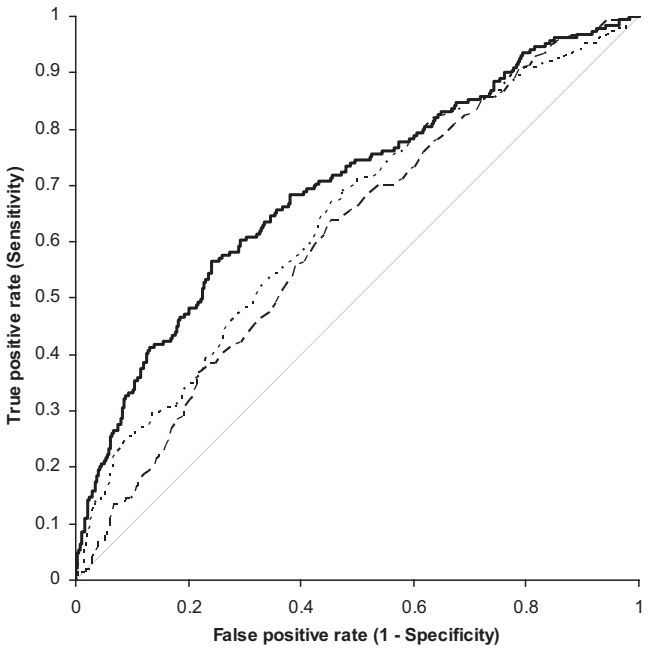

Figure 2. Univariate ROC curves for PCA3 (solid line), sPSA (broken line) and % fPSA (dotted line). Plot displays sensitivity for association with biopsy detectable PCa (any grade) as function of false-positive rate (1 – specificity). Diagonal line indicates no discrimination of biopsy outcomes.

ROC analysis was used to directly compare the univariate performance of PCA3, sPSA and % fPSA for predicting biopsy detectable PCa (any grade). PCA3 as a continuous variable demonstrated an AUC of 0.693 (95% CI 0.649–0.736) compared to 0.612 (0.570–0.655) and 0.637 (0.593–0.681) for sPSA and % fPSA, respectively (fig. 2). The difference in AUC between PCA3 and sPSA reached significance ($p = 0.0077$), although the PCA3 to % fPSA comparison did not ($p = 0.0645$). Univariate logistic regression for these markers and PCA3 expressed as a binary categorical variable with a cutoff at 35 demonstrated significant odds ratios (all $p < 0.0001$) for association with biopsy result (table 1). When expressing PCA3 as a binary variable the magnitude of the odds ratio indicated a 3.5-fold increased risk of biopsy detectable cancer for subjects with PCA3 exceeding the cut point of 35 (95% CI 2.50–4.81).

Prediction of Future Biopsy Detectable Prostate Cancers

For subjects with negative biopsies at year 2, PCA3, sPSA and % fPSA values from year 2 were correlated with year 4 biopsy outcome using univariate

Table 1. *Univariate logistic regression*

	OR (95% CI)	p Value	ROC-AUC (95% CI)
Prediction of current biopsy outcome:			
PCA3 score (continuous)	1.0188 (1.01–1.02)	<0.0001	0.693 (0.649–0.736)*
PCA3 (binary, cutoff 35)	3.4676 (2.50–4.81)	<0.0001	0.634 (0.596–0.673)
sPSA (ng/ml, continuous)	1.1061 (1.06–1.16)	<0.0001	0.612 (0.570–0.655)
% fPSA (continuous)	0.9237 (0.90–0.95)	<0.0001	0.637 (0.593–0.681)
Prediction of yr 4 biopsy outcome based on yr 2 biomarker values:			
PCA3 score (continuous)	1.0103 (1.00–1.02)	0.0002	0.634 (0.564–0.704)†
PCA3 (binary, cutoff 35)	2.0134 (1.12–3.61)	0.0188	0.570 (0.505–0.635)
sPSA (ng/ml, continuous)	1.044 (0.96–1.14)	0.3281	0.535 (0.458–0.611)
% fPSA (continuous)	0.9914 (0.95–1.03)	0.6782	0.519 (0.434–0.603)

* p = 0.0077 vs sPSA and 0.0645 vs % fPSA.
† p = 0.0842 vs sPSA and 0.0402 vs % fPSA.

logistic regression and ROC analysis (572 total subjects, 57 biopsy detected cancers at year 4). For PCA3 as a continuous variable the point estimate and 95% CI of the odds ratio were similar to the association displayed for contemporaneous cancers (OR 1.01, 95% CI 1.00–1.02), which was significant at p = 0.0002 (table 1). sPSA and % fPSA were not significant predictors (p = 0.3281 and 0.6782, respectively). The AUC for PCA3 was 0.634 (95% CI 0.564–0.704). When expressing PCA3 as a binary categorical variable a 2-fold increase in risk was demonstrated for subjects (20) with PCA3 scores greater than 35 who were biopsy negative at year 2 but in whom biopsy detectable PCa subsequently developed at year 4 (OR 2.0134, 95% CI 1.12–3.61). As was observed for the association of PCA3 scores with contemporaneous cancers the percent of positive biopsy findings for predicted year 4 cancers increased rapidly from 1.4% (1 of 74) at a PCA3 score range of less than 5 to 35.7% (5 of 14) at scores greater than 100 (p = 0.0024 across categories).

Multivariate Logistic Regression Models

Multivariate logistic regression was performed to determine the performance of PCA3 in the presence of traditional risk variables including sPSA, % fPSA, age, family history and prostate volume. In model 1 PCA3 expressed as a continuous variable retained its significant association with biopsy result (table 2). The point estimate and CI for odds ratio closely approximated the univariate results (1.0152 vs 1.0188, 95% CI for both 1.01–1.02), indicating that PCA3 retained predictive power despite the independent and significant associations of all other variables in the model with biopsy outcome. In model 2 PCA3 expressed as a binary categorical variable with a cutoff at 35 also retained its significance, although the point estimate for odds ratio decreased from a 3.5-fold increased risk of PCa on univariate assessment to a 2.65-fold risk (95% CI 1.86–3.79) on multivariate assessment. Because the univariate and multivariate CIs overlap this difference is insignificant.

Area under the ROC curve for multivariate model 1 was 0.753 (95% CI 0.712–0.793), which represented a significant improvement (p = 0.0009) compared to the same model after the exclusion of PCA3 (AUC 0.717, 95% CI 0.675–0.759). Model 1 AUC was superior to univariate PCA3 (p = 0.0025) and sPSA (p <0.0001) (fig. 3). Multivariate model 2 AUC was 0.738 (95% CI 0.697–0.779), indicating the minimal effect of conversion of PCA3 to a binary categorical variable. Comparison of model 2 AUC to the model after exclusion of PCA3 did not reach significance (p = 0.0558), likely due to sacrifice of some AUC that naturally occurs when converting a continuous variable to a binary categorical variable. Thus, although PCA3 by itself represents a major contribution to the overall power of the multivariate model, sPSA and the other factors provide additional information that refines the risk assessment.

DISCUSSION

In this study we examined the performance of the PCA3 test in a population at risk for PCa. The results

Table 2. *Multivariate logistic regression*

	OR (95% CI)	p Value
Model 1:*		
Age	1.0675 (1.03–1.10)	<0.0001
Family history (yes/no)	1.7776 (1.12–2.83)	0.0154
PCA3 score (continuous)	1.0152 (1.01–1.02)	<0.0001
% fPSA	0.9426 (0.91–0.97)	0.0003
Prostate vol (ml)	0.9861 (0.98–0.99)	0.0007
sPSA (ng/ml)	1.0870 (1.03–1.15)	0.0024
Model 2:†		
Age	1.0732 (1.04–1.11)	<0.0001
Family history (yes/no)	1.7359 (1.09–2.76)	0.0194
PCA3 (binary, cutoff 35)	2.6527 (1.86–3.79)	<0.0001
% fPSA	0.9445 (0.91–0.98)	0.0005
Prostate vol (ml)	0.9849 (0.98–0.99)	0.0002
sPSA (ng/ml)	1.0902 (1.03–1.15)	0.0016

* Model AUC 0.753 (0.712–0.793).
† Model AUC 0.738 (0.697–0.779).

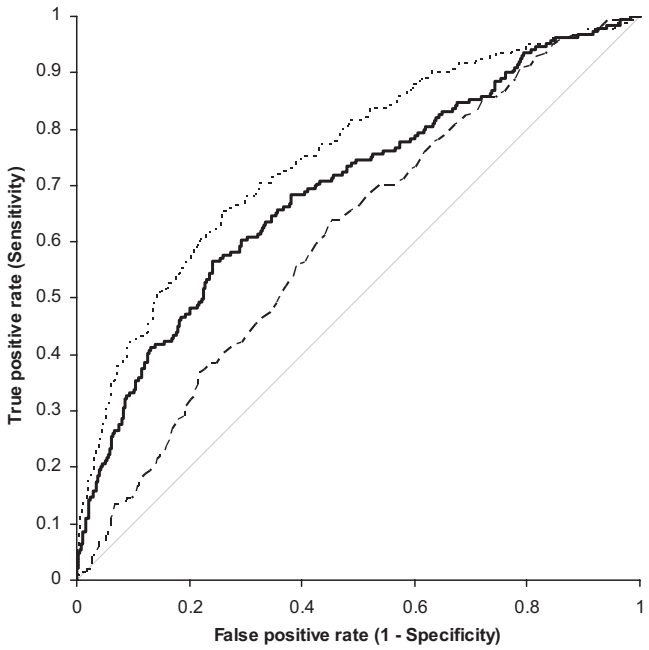

Figure 3. ROC curve analysis for multivariate logistic model (includes PCA3 as continuous variable, sPSA, % fPSA, prostate volume, age and family history of PCa) (dotted line) compared to univariate PCA3 (continuous) (solid line) and sPSA (broken line).

are particularly important as they arise from the REDUCE trial, a major phase 3 pharmaceutical study providing a study cohort approximately 4-fold larger than prior studies of PCA3 in men with previous negative biopsy and moderately increased sPSA.

The results demonstrate that the PCA3 test displays a high informative rate, is insensitive to the confounding variable of prostate volume, correlates with the probability of positive biopsy and displays associative power for biopsy result. These results confirm and expand on those of previous studies using smaller cohorts. To our knowledge Deras et al were the first to demonstrate the insensitivity of PCA3 to prostate volume ($p = 0.54$).[5] Additionally Marks[7] and Haese[12] et al demonstrated the strong relationship of PCA3 score with the probability of positive repeat biopsy. In the study by Marks et al the probability of positive biopsy at PCA3 scores less than 5 and greater than 100 was 12% and 50%, respectively, similar to the 6% and 57% in the present study.[7] Also using univariate ROC analysis the studies by Deras[5] and Marks[7] et al yielded AUC 0.68 for the association of PCA3 with biopsy result, similar to the value of 0.693 reported here. Furthermore, in the study by Marks et al a univariate odds ratio of 3.6 was reported for PCA3 as a binary categorical variable with a cut point at 35, nearly identical to the value of 3.5 observed in this study.[7]

PCA3 was incrementally increased in cancers of significant Gleason score (greater than 6), a finding consistent with the study by Haese et al.[12] In contrast, Deras[5] and Marks[7] et al did not observe an association between PCA3 score and biopsy Gleason score. This finding may be driven by the markedly increased size and power of the present study. Alternatively the lack of correlation in the previous studies may reflect the limitations of biopsy in terms of sampling and accurate Gleason scoring. The latter explanation is supported by Nakanishi et al, in whose study PCA3 correlated with post-prostatectomy but not biopsy Gleason score.[8]

This study also demonstrated for the first time to our knowledge that PCA3 predicts biopsy outcomes 2 years in the future. PCA3 may be detecting cancers that were missed by biopsy or it is possible that PCA3 is related to precancerous states that progress. In either scenario PCA3 was the only marker capable of such prediction as sPSA and % fPSA displayed no significant predictive power in this analysis.

Another major finding of this study is the independence of PCA3 in the presence of traditional risk variables. In the models explored all traditional variables were strong and independent variables associated with biopsy outcome, yet the power of PCA3 was not markedly attenuated. This finding suggests that PCA3 is a complementary predictor for the clinical management of patients at risk for PCa. It is important to note that the study population consisted of a high risk group of men with previous negative biopsies, so the results cannot be extrapolated to a screening setting. PCA3 does not replace sPSA and other factors that are still informative for cancer assessment. Rather PCA3 provides an additional risk evaluation tool to be used by practitioners within the context of all other available information.

CONCLUSIONS

PCA3 performance for predicting repeat biopsy outcome in men with moderately increased sPSA was validated in the largest study to date. Furthermore, PCA3 scores correlated with Gleason score and PCA3 was able to predict biopsy outcome 2 years later. These results confirm that PCA3 can be used in combination with other clinical information to help guide prostate biopsy decisions.

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EDITORIAL COMMENTS

This is the largest study to date evaluating the performance of the PCA3 assay in the setting of a previously negative biopsy. The reader needs to be mindful that these comparisons to PSA are not necessarily transferable to the general prostate cancer screening population. These men all had an increased PSA and previous negative biopsy at baseline. Thus, the men for whom PSA performed well, ie those who had an increased PSA and a positive biopsy, had already been culled out of this population. This significantly reduces the AUC for the PSA group and provides an easier comparison for the PCA3 test. On the other hand, this test clearly provides prognostic value that is independent of PSA and prostate volume. It is a valuable tool for evaluating men with an increased PSA and previous negative biopsy, and should be compared with PSA in the screening setting.

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Although several studies independently suggested that the urinary PCA3 test is helpful for prostate biopsy decision, its use in routine practice is still under debate. Aubin et al expand on previous studies dealing with patients with prior negative biopsies in an important way in that patients arise from an international multicenter cohort and, therefore, the data are likely to be reliable (references 7 and 12 in article). This study represents the largest cohort published to date and definitively confirms that the PCA3 test can determine those patients who will benefit from re-biopsy. Furthermore, it is the first study demonstrating that patients with simultaneous negative biopsies and increased PCA3 score have an increased risk of future prostate cancer. It remains to be determined whether or to what extent these future cancers are significant, but it can be assumed that this study actually generates a new category of patients who require close followup.

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