PCA3 Score *vs* PSA Free/Total Accuracy in Prostate Cancer Diagnosis at Repeat Saturation Biopsy

PIETRO PEPE and FRANCESCO ARAGONA

Urology Unit, Cannizzaro Hospital, Catania, Italy

Abstract. *Aim. PCA3 score and PSA free/total (F/T) accuracy in PCa diagnosis at repeat saturation prostate biopsy (SPBx) in patients with PSA between 4 and 10 ng/mL was evaluated. Materials and Methods: From October 2009 to September 2011 74 men (median 64 years) with persistent high or increasing PSA values, negative DRE, median PSA values of 8.9 ng/mL and primary negative extended biopsy underwent a SPBx (median 28 cores) for persistent suspicion for PCa. Results: PCA3 >20 and >35, PSA F/T ≤15%, ≤20% and ≤25% identified 25, 21, 18, 23 and 26 out 27 cancer, respectively. PCA3 cut-off of 20 demonstrated the best accuracy with an AUC-ROC curve of 0.73. Conclusion: The NPV equal to 88.9% suggests to use PCA3 cut-off 20 as an exclusion tool; moreover, PCA3 cut-off of 35 combined with PSA F/T ≤15% allows to spare 32.4% of unnecessary repeat biopsies.*

The widespread use of the prostate specific antigen (PSA) test and mass screening protocols (1) have increased the detection rate of prostate cancer (PCa); moreover, many patients after a negative primary biopsy (20-30% of the cases) and persistent suspicion of PCa undergo repeat biopsy with a detection rate for cancer equal to 22-41% (2, 3). Thus, to improve PSA specificity and reduce the number of unnecessary biopsies many molecular forms of PSA (*i.e.* free/total PSA, pro-PSA) have been introduced into clinical practice in the presence of PSA values below 10 ng/mL; recently, in this respect, the urinary prostate cancer gene 3 (PCA3) assay (a gene-based marker) alone (4, 5) or incorporated into multivariable predictive nomograms (6) has been used to select patients to undergo repeat prostate biopsy.

The aim was to compare PCA3 score and PSA free/total (F/T) accuracy in PCa diagnosis at repeat saturation prostate biopsy (SPBx) in patients with PSA between 4 and 10 ng/mL.

Correspondence to: Pietro Pepe, MD, Urology Unit, Cannizzaro Hospital, Via Messina 829, Catania, Italy. Tel: +39 957263285, Fax: +39 957263259, e-mail: piepepe@hotmail.com

Key Words: PCA3, PSA free/total, prostate cancer, saturation prostate biopsy, repeat biopsy, cancer diagnosis.

Materials and Methods

From October 2009 to September 2011 74 consecutive Caucasian men aged between 48 and 74 years (median 64 years) with primary negative extended biopsy (median 18 cores) underwent a SPBx (range: 24-34 cores; median 28) for persistent suspicion of PCa. All the patients underwent digital rectal examination (DRE) and a blood sample was taken for total and free PSA assay (Roche Diagnostics; Mannheim, Germany) and measurement of the PSA F/T ratio. In all cases the DRE was negative and the PSA values were between 4 and 10 ng/mL (median 8.9 ng/mL; range 4.5-10 ng/mL); the indications to repeat biopsy were persistent high or increasing PSA values. SPBx was accomplished transperineally with a tru-cut 18 gauge needle (Bard, Covington, GA) using a GE Logiq 500 PRO ecograph (General Electric; Milwaukee, WI, USA) supplied with a biplanar transrectal probe (5-6.5 MHz) under sedation and antibiotic prophylaxis. The prostate biopsy protocol included a median of 12 cores in the posterior zone of each lobe (apex, median zone and base of the gland) beginning parasagittally to reach the outer edges of the gland (lateral margins) and 2-3 cores in the transition zone (3). Three-ten days before performing the SPBx, first-catch urine samples were collected following DRE (three strokes per lobe) and processed to quantify PCA3 and PSA mRNA concentrations using the Progensa PCA3 assay (Gen-Prob Inc., San Diego, CA, USA); the PCA3 score was calculated as (PCA3 mRNA/PSA mRNA) ×1000.

In the presence of PCa either definitive treatment or active surveillance (AS) was offered. The patients who accepted surgery underwent radical retropubic prostatectomy (RRP) with bilateral obturator and external iliac lymphadenectomy. The volume of cancer was reported as the percentage of prostate cancer in the entire specimen according to Bostwick (7) and the incidence of PCa, that fulfilled the Epstein criteria (8) for pathological indolent PCa (pIPCa) (cancer volume less than 0.5 mL and no Gleason grade 4 or 5 disease) was recorded.

The performance of the PCA3 score (cut-off of 20 *vs* 35) and PSA F/T using different cut-offs (≤25% *vs* ≤20% *vs* ≤15%) was evaluated in terms of diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV); moreover, the detection rate for cancer, number of avoided biopsies and missed PCa using PCA3 cut-off of 20 and 35, PSA F/T and PCA score combined with PSA F/T were recorded. Receiver operating characteristic (ROC) was performed to define the diagnostic performance of PCA3 (cut-off of 20 *vs* 35) and PSA F/T (≤15% *vs* ≤20% *vs* ≤25%) using the calculated area under the curve (AUC); a probability (p) level of less than 0.05 was considered statistically significant.

Table I. *Clinical and pathological characteristics of the 27 patients with prostate cancer.*

Age (yrs)	PSA ng/mL	Biopsy GS	Positive cores	GPC %	PSA F/T %	PCA3 score	pTN	Definitive GS	psm	Cancer volume
60	4.5	6	1	50	10	35	T2c N0	6	–	>0.5 mL
62	8.0	6	1	50	8	37	T2c N0	6	–	>0.5 mL
72	6.8	6	1	50	10	86	T2c N0	6	–	>0.5 mL
70	9.9	6	1	50	15	9	T2b N0	6	–	>0.5 mL
58	8.9	6	1	60	12	119	T2c N0	6	–	>0.5 mL
63	9.6	6	1	50	11	54	T3a N0	6	–	>0.5 mL
62	9.2	6	1	75	12	74	T2c N0	6	+	>0.5 mL
69	9.5	6	1	50	9	32	T2c N0	6	–	>0.5 mL
70	9.5	6	1	50	8	40	T3a N0	6	–	>0.5 mL
64	7.9	6	2	50	9	73	T2c N0	6	–	>0.5 mL
58	6.9	6	1	5	23	41	T2c N0	6	–	>0.5 mL
68	8.3	6	1	5	11	8	T2a N0	6	–	>0.5 mL
65	8.3	6	1	5	27	30	T2a N0	6	–	>0.5 mL
63	10.0	6	1	5	20	79	T2c N0	6	–	>0.5 mL
64	9.0	6	1	5	11	170	T3a N0	6	–	>0.5 mL
62	8.7	6	1	5	11	58	T2c N0	6	–	>0.5 mL
68	9.1	6	4	50	15	30	T3a N0	6	–	>0.5 mL
60	8.8	6	3	75	23	110	T2c N0	6	+	>0.5 mL
70	9.7	6	3	50	19	48	T2c N0	7	–	>0.5 mL
67	9.3	7	8	50	13	45	T2c N0	7	–	>0.5 mL
69	9.1	7	9	100	18	62	T3a N0	7	+	>0.5 mL
61	10.0	7	6	75	19	47	T3a N0	7	+	>0.5 mL
61	10.0	7	5	100	19	73	T3b N1	8	+	>0.5 mL
62	9.3	7	6	75	8	74	T2c N0	7	–	>0.5 mL
61	8.8	7	3	100	8	79	T3a N0	7	+	>0.5 mL
68	9.5	7	2	75	21	38	T2c N0	3	–	>0.5 mL
63	9.5	7	4	100	9	46	T3a N0	7	+	>0.5 mL

PSA: Prostate specific antigen; GS: Gleason score; GPC: greatest percentage of cancer; PSA F/T: free/total; PCA3: prostate cancer gene; psm: positive surgical margin.

Results

All the patients had adequate concentrations of PCA3 and PSA mRNA to calculate a PCA3 score that was equal to 42 (median; range 3-250): 58 (78.4%) *vs* 46 (62.2%) patients had a PCA3 score >20 and >35, respectively. The median PSA F/T value was 13.5% (range: 4-40%): 66 (89.1%), 58 (78.3%) and 43 (58.1%) patients had a PSA F/T ≤25%, ≤20% and ≤15%, respectively.

A T1c PCa was found in 27 (36.5%) patients (median age 64.5 yrs; range: 58-71 yrs) who underwent RRP. Histological specimens showed in all cases the presence of a substantial PCa (Gleason score ≥6 and/or a cancer volume >0.5 mL): 20, 6 and 1 men had a pT2N0, pT3aN0 and pT3bN1 stage, respectively. The clinical and pathological characteristics of the patients are listed in Table I. Out of the remaining 47 men, 44 (59.5%) had a normal parenchyma, 1 (1.3%) and 2 (2.7%) had an high-grade prostatic intraepithelial neoplasia (HGPIN) and a atypical small acinar proliferation (ASAP), respectively.

The PCA3 score was significantly higher in the presence of PCa in comparison with the absence of cancer, 64 (median; range: 7-170) *vs* 39 (median; range: 4-253) (p=0.001), respectively. The PCa detection rate increased from 12.5% at PCA3 scores less than 20 to 50% at scores greater than 100 (Figure 1); a PCA3 score >20 and PCA3 score >35 identified 25 (92.6%) and 21 (77.8%) out of the 27 cancer cases , respectively. In the presence of ASAP and HGPIN the PCA3 score was 83 (median; range: 53-113) and 72, respectively.

The median PSA F/T was 13.5%: 12% *vs* 13.5% (p=0.403) in the presence or absence of PCa, respectively. In the presence of ASAP and HGPIN, the PSA F/T score was 23 (median; range: 19-27%) and 14%, respectively. In the 27 patients with PCa, 18 (66.7%), 23 (85.1%) and 26 (96.2%) had a PSA F/T ≤15%, ≤20% and ≤25%, respectively.

The detection rate for PCa, number of avoidable biopsies and missed cancer using the PCA3 score >20, PCA3 score >35, PSA F/T (≤15% *vs* ≤20% *vs* ≤25%) and PCA score (cut-off of 20 and 35) combined with PSA F/T (≤15%, ≤20% and ≤25%) are listed in Table II. A PCA3 cut-off of 20 combined with PSA F/T ≤15% demonstrated the best performance diagnosing 27 (100%) out of the 27 PCa; on the other hand, a PCA3 score >35 combined with PSA F/T ≤15% allowed the avoidance of the highest percentage of unnecessary biopsies (32.4%) maintaining a sensitivity of 96.3%.

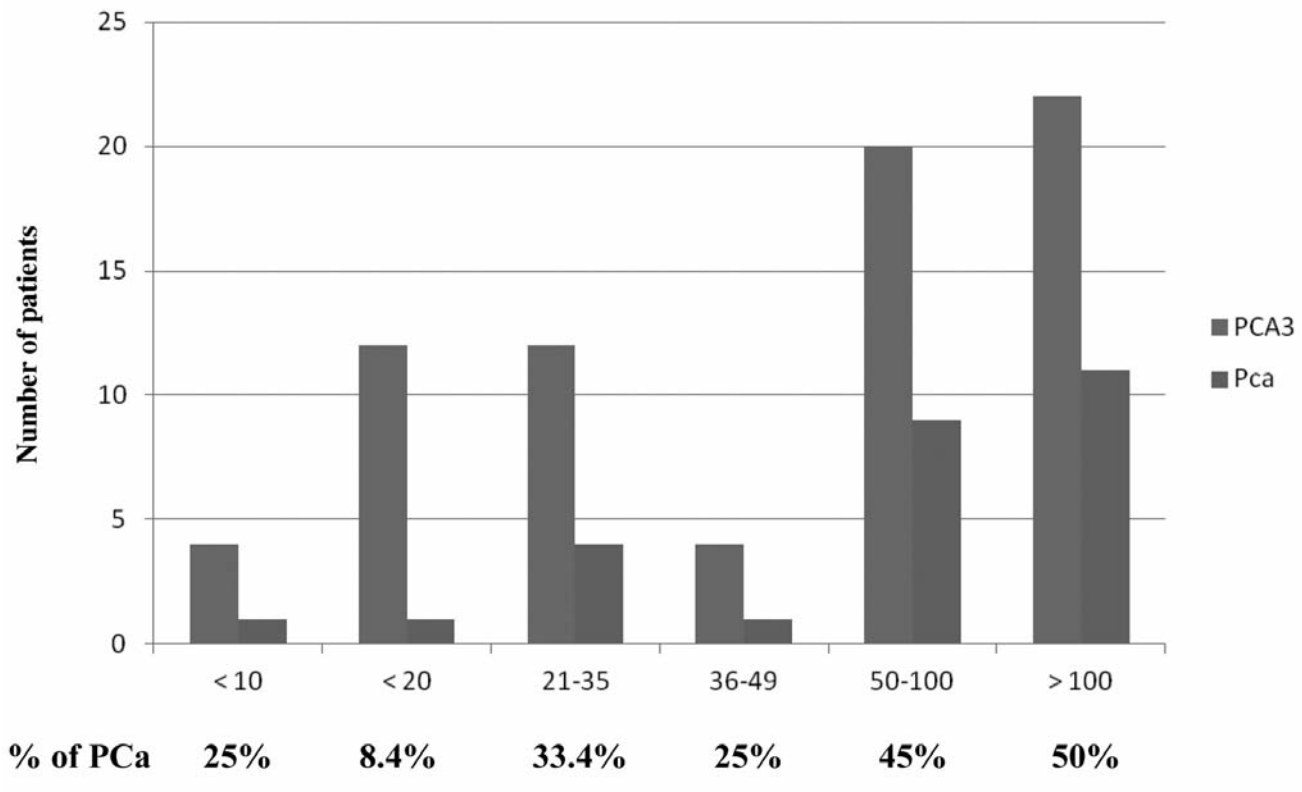

Figure 1. *Prostate cancer (PCa) detection by PCA3 score range in patients submitted to repeat saturation biopsy.*

The diagnostic accuracy, sensitivity, specificity, PPV, NPV and AUC-ROC of the PCA3 score (cut-off of 20 and 35) and PSA F/T (cut-off ≤15% *vs* ≤20% *vs* ≤25%) are listed in Table III.

Discussion

In 1997, Catalona (9) proposed a PSA F/T cut-off for biopsy of 27% in men with PSA 2.6-4.0 ng/mL (90% sensitivity, avoiding 18% of biopsies with a 24% PPV); in a subsequent systematic review, a PSA F/T >25% in men with PSA values of 4.0 to 9.9 ng/mL avoided 20% of biopsies allowing 8% of the carcinomas to be missed (10).

In our experience (11), in 13,782 patients with PSA below 10 ng/mL enrolled in a case-finding protocol a PCa was found in 459 (28.8%) of 1,589 men submitted to biopsy and PSA F/T allowed to spare 33.3% (75 cases) biopsies (PSA F/T *vs* PSA cut-off of 4 ng/mL) in case of repeat biopsy; moreover, the risk of pIPCa detection was equal to 7.7% resulting significantly lower than the pIPCa diagnosed in the European prostate cancer screening (50% of the cases) (1).

Table II. *Detection rate for PCa, number of avoided biopsies and missed cancer cases using PCA3 score (cut-off of 20 vs 35), PSA F/T (≤15% vs ≤20% vs ≤25%) and PCA score combined with PSA F/T.*

	No. of patients	Detection rate for PCa (%)	Missed PCa (%)	Avoided biopsies (%)
PCA3 >20	58	25 (92.6)	2 (7.5)	16 (21.0)
PCA3 >35	46	21 (77.8)	6 (22.2)	28 (37.8)
PSA F/T <15%	43	18 (66.7)	9 (33.4)	31 (41.8)
PSA F/T <20%	58	23 (88.5)	4 (14.7)	16 (21.6)
PSA F/T <25%	66	26 (96.3)	1 (3.7)	8 (10.8)
PCA3 >20 + PSA F/T <15%	63	27 (100)	0	14 (14.9)
PCA3 >20 + PSA F/T ≤20%	61	26 (96.3)	1 (3.7)	16 (21.6)
PCA3 >20 + PSA F/T ≤25%	69	26 (96.3)	1 (3.7)	5 (6.8)
PCA3 >35 + PSA F/T ≤15%	51	26 (96.3)	1 (3.7)	24 (32.4)
PCA3 >35 + PSA F/T ≤20%	58	26 (96.3)	1 (3.7)	16 (21.6)
PCA3 >35 + PSA F/T ≤25%	66	26 (96.3)	1 (3.7)	8 (10.8)

PSA F/T: PSA free/total; PCa: prostate cancer; PCA3: prostate cancer gene.

Table III. *PCA3 score (cut-off 20 vs 35) and PSA free/total (cut-off ≤25% vs ≤20% vs ≤15%) accuracy in PCa diagnosis at repeat saturation biopsy in patients with PSA between 4 and 10 ng/mL.*

	PSA F/T ≤15%	PSA F/T ≤20%	PSA F/T ≤25%	PCA3 score >35	PCA 3 score >20
Sensitivity	66.7%	85.1%	96.3%*	70.4%	92.6%*
Specificity	51.0%*	28.6%	14.3%	43.5%*	21.6%
PPV	42.8%	39.6%	32.9%	42.2%	43.1%
NPV	73.5%	87.5%*	88.9%*	71.5%	88.9%*
Diagnostic accuracy	56.6%	46.6%	44.8%	51.4%	55.5%
AUC-ROC	0.51	0.53	0.70*	0.66	0.73*

PPV: Positive predictive value; NPV: negative predictive value; PSAF/T: free/total PSA; AUC-ROC: area under the curve of receiver operating characteristic. *$p<0.05$ *vs* other parameters in the same row. For PPV and diagnostic accuracy PSA F/T (≤15%/≤20%/≤25%) *vs* PCA3 score (cut-off 20/35) $p>0.05$.

Recent studies have demonstrated that a PCA3 score of 35 provides an optimal balance between sensitivity and specificity in diagnosing PCa (4, 12, 13), although PCA3 was insensitive to prostate volume or prostatitis (14), it correlated significantly with Gleason score (15) and was a predictor of pIPCa (16). Using a PCA3 cut-off of 20 and 35 avoidable repeat biopsies and missed PCa were reported to be 67% and 9% *vs* 44% and 21%, respectively (5). However, PCA3 accuracy at repeat biopsy remains contradictory: sensitivity, specificity, PPV and NPV range between 47 to 76.6% (4), 66.6 to 78.6% (5), 39 to 74% (17) and 62.5 to 87% (18), respectively. Only the NPV demonstrated a good and homogeneous performance (about 80%) (4,7,17) suggesting limiting the use of PCA3 to avoid the risk of unnecessary repeat SPBx (18, 19) due to high number (10-26% of the cases) of false negative results (13).

While the PCA3 score has been reported to be more accurate than PSA F/T (5, 21) reporting a better AUC equal to 0.68 *vs* 0.57; on the contrary, Aubin (14) did not demonstrate a statistical difference in AUC ROC analysis between PCA3 and PSA F/T (0.69 *vs* 0.63). Recent data have underlined the lower sensitivity of PCA3 in comparison with PSA F/T (greater percentage of missed PCa) combined with a greater specificity (lower number of false positive results and unnecessary biopsy) (5, 20).

In the present study, PSA F/T ≤25% and PCA3 >20 provided the best sensitivity (96.3 and 92.6%, respectively), while PSA F/T ≤15% had the best specificity (51%) but, at the same time, the highest percentage of missed cancer (33.4%). The PCA3 cut-off of 20 or 35 combined with PSA F/T ≤15% showed the best performance demonstrating the highest detection rate for PCa (100 *vs* 96.3%) with 15-37% avoidable biopsies (Table II).

Some limitations and considerations of the present study deserve mention. First, it was not known if the false positive results were related to the false negative of SPBx or could predict PCa detection in the future (22): HGPIN (1 case) and an ASAP (2 cases) were included; moreover, 22 (29.7%) out of the 74 patients with negative SPBx had a PCA3 score greater than 100 that is associated with a risk to detect a cancer at repeat biopsy of 30% (23). Second, due to the limited number of cases submitted to RRP the accuracy of PCA3 in diagnosing pIPCa could not be established. Finally, given equal accuracy the costs and benefit should be evaluated, PCA3 is more expensive than PSA F/T assay and still has not been routinely introduced into clinical practice, however any evaluation of the cost should include the number of spared repeat biopsies.

In conclusion, PCA3 score cut-off of 20 demonstrates the best accuracy in PCa diagnosis with a AUC-ROC curve of 0.73, moreover, the high NPV (88.9%) suggests that PCA3 should be used as an exclusion tool. PCA3 score cut-off of 35 combined with PSA F/T ≤15% allows a remarkable number of unnecessary repeat biopsies to be avoided (32.4% of the cases) detecting 96.3% of PCa.

References

1 Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Määttänen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ and Auvinen A: Screening of prostate cancer mortality in randomized European study. N Engl Med *360*: 1320-1328, 2009.

2 Pepe P and Aragona F: Saturation prostate needle biopsy and prostate cancer detection at initial and repeat evaluation. Urology *70*: 1131-1135, 2007.

3 Walz J, Graefen M, Chun FK, Erbersdobler A, Haese A, Steuber T, Schlomm T, Huland H and Karakiewicz PI: High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. Eur Urol *50*: 498-505, 2006.

4 Marks LS, Fradet Y, Deras IL, Blase A, Mathis J, Aubin SM, Cancio AT, Desaulniers M, Ellis WJ, Rittenhouse H and Groskopf J: PCA3 molecular urinary assay for prostate cancer in men undergoing repeat biopsy. Urology *69*: 532-535, 2007.

5 Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Abbou CC, Remzi M, Tinzl M, Feyerabend S, Stillebroer AB, van Gils MP and Schalken JA: Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. Eur Urol *54*: 1081-1088, 2008.
6 Perdonà S, Cavadas V, Di Lorenzo G, Damiano R, Chiappetta G, Del Prete P, Franco R, Azzarito G, Scala S, Arra C, De Sio M and Autorino R: Prostate cancer detection in the "grey area" of prostate-specific antigen below 10 ng/ml: head-to head comparison of the update PCPT calculator and Chun's nomogram, two risk estimators incorporating prostate cancer antigen 3. Eur Urol *59*: 81-87, 2011.
7 Bostwick DG, Grignon DJ, Hammond ME, Amin MB, Cohen M, Crawford D, Gospadarowicz M, Kaplan RS, Miller DS, Montironi R, Pajak TF, Pollack A, Srigley JR and Yarbro JW: Prognostic factors in prostate cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med *124*: 995-1000, 2000.
8 Epstein J, Walsh P and Carmichael M: Pathological and clinical findings to predict tumor extent of non palpable (stage T1c) prostate cancer. JAMA *271*: 368-374, 1994.
9 Catalona W, Smith D and Ornstein D: Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4 ng/ml and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA *277*: 1452-1455, 1994.
10 Hoffman R, Clanon D, Littenberg B, Frank JJ and Peirce JC: Using free-to-total PSA ratio to detect prostate cancer in men with non specific elevations of PSA levels. J Gen Intern Med *15*: 739-748, 2000.
11 Pepe P and Aragona F: Incidence of insignificant prostate cancer using free/total PSA: results of a case-finding protocol on 14453 patients. Prostate Cancer Prostatic Dis *13*: 316-19, 2010.
12 Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, Brentano S, Mathis J, Pham J, Meyer T, Cass M, Hodge P, Macairan ML, Marks LS and Rittenhouse H: APTIMA molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem *52*: 1089-1095, 2006.
13 Vlaemink-Guillem V, Ruffion A, Andrè J, Devonec M and Paparel P: Urinary prostate cancer 3 test: toward the age of reason? Urology *75*: 447-453, 2010.
14 Deras IL, Aubin SM, Blasé A Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H and Groskopf J: PCA3: a molecular urine assay for predicting prostate biopsy outcome. J Urol *179*: 1587-1592, 2008.
15 Aubin SM, Reid J, Sarno MJ Blase A, Aussie J, Rittenhouse H, Rittmaster R, Andriole GL and Groskopf J: PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of dutasteride REDUCE trial. J Urol *184*: 1947-1952, 2010.
16 Auprich M, Chun FK, Ward JF, Pummer K, Babaian R, Augustin H, Luger F, Gutschi S, Budäus L, Fisch M, Huland H, Graefen M and Haese A: Critical assessment of preoperative urinary prostate cancer antigen 3 on the accuracy of prostate cancer staging. Eur Urol *59*: 96-105, 2011.
17 Fradet Y, Saad F, Aprikian A, Dessureault J, Elhilali M, Trudel C, Mâsse B, Piché L and Chypre C: uPM3, a new molecular urine test for the detection of prostate cancer. Urology *64*: 311-15, 2004.
18 Panebianco V, Sciarra A, DE Berardinis E, Busetto GM, Lisi D, Buonocore V, Gentile V, Di Silverio F and Passariello R: PCA3 urinary test *versus* 1H-MRSI and DCEMR in the detection of prostate cancer foci in patients with biochemical alterations. Anticancer Res 31: 1399-05, 2011.
19 Schilling D, Hennenlotter J, Munz M, Bökeler U, Sievert KD and Stenzl A: Interpretation of the prostate cancer 3 in reference to the individual clinical background: implication for daily practice. Urol Int *85*: 159-65, 2010.
20 Vlaeminck-Guillem V, Campos-Fernandes JL, Champetier D, Chikh K, Decaussin-Petrucci M, Devonec M, Gobeaux N, Paparel P, Perrin P, Rodriguez-Lafrasse C and Ruffion A: Value of PCA3 urinary test for prostate biopsy decision: the Lyon-Sud university hospital experience. Ann Biol Clin *69*: 31-39, 2011.
21 Ploussard G, Haese A, Van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Bastien L, Abbou CC, Remzi M, Tinzl M, Feyerabend S, Stillebroer AB, Van Gils MP, Schalken JA and de La Taille A: The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies. BJU Int *106*: 1143-1147, 2010.
22 Remzi M, Haese A, Van Poppel H, De La Taille A, Stenzl A, Hennenlotter J and Marberger M: Follow-up of men with an elevated PCA3 score and negative biopsy: does an elevated PCA3 score indeed predict the presence of prostate cancer? BJU Int *106*: 1138-1142, 2010.
23 Roobol MJ, Schroder FH, van Leenders GL, Hessels D, van den Bergh RC, Wolters T and van Leeuwen PJ: Performance of prostate cancer antigen 3 (PCA3) and prostate-specific antigen in pre-screened men: reproducibility and detection characteristics for prostate cancer patients with high PCA3 score (>100). Eur Urol *58*: 893-899, 2010.

Received September 17, 2011
Revised November 23, 2011
Accepted November 24, 2011