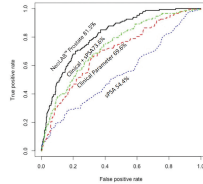


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Background

Distinguishing between low-grade and high-grade prostate cancer (PCa) as detected by biopsy results is very important, not only for diagnosis, but also for monitoring patients on active surveillance. However, biopsy results may underestimate the actual grade of the PCa when prostatectomy is performed. We previously developed a urine/plasma assay and algorithm to predict high grade prostate cancer and determined it performed better than sPSA alone.



Objective

To determine whether our previously developed noninvasive test may predict tumor grade as well or better than biopsy, we tested the algorithm using cell-free RNA (cfRNA) levels of UAP1, PDLIM5, IMPDH2, HSPD1, PCA3, PSA, TMPRSS2-ERG, AR, PTEN, and ERG genes in both urine and peripheral blood plasma against the results of biopsy and prostatectomy for the presence of high-grade PCa as measured by Gleason Score.

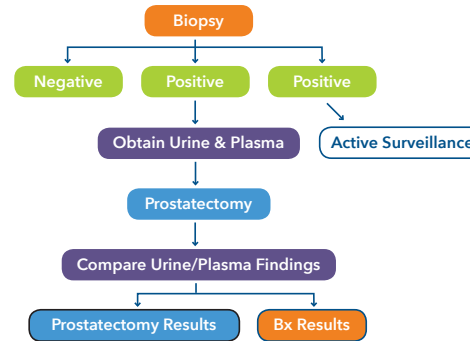
Patients and Methods

- This prospective blinded study was conducted in a community based setting at six different large urology groups.
- Urine and blood samples from 306 patients were collected and tested prior to prostatectomy and at least 2 months after biopsy.
- All recruited patients were treatment naïve and without metastases.
- Most patients were Caucasian (80.4%), while 16.3% were African American.
- The majority of patients were staged at T1c or lower (91.7%).
- Digital rectal exam was normal in 202 (66%) of patients.
- More than half (61.4%) of patients had no family history of prostate cancer.
- The RNA levels of PDLIM5, HSPD1, IMPDH2, PCA3, TMPRSS2, ERG, UAP1, PTEN, AR, GAPDH, and B2M genes were quantified in urine and plasma using qRT-PCR as previously detailed.
- An algorithm incorporating RNA levels with clinical information, previously developed, was used for predicting high-risk, standard-risk, and low-risk advanced prostate cancer (Gleason \geq 3+4).

Participant Characteristics

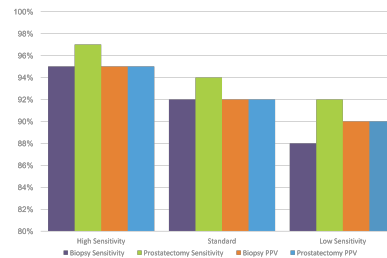
Age (Median, Min-Max)	61 (36-77)	Race	Caucasian 246 (80.4%) African American 50 (16.3%) Hispanic 1 (0.3%) Asian 1 (0.3%) Missing 8 (2.6%)	Family Hx	No 188 (61.4%) Yes 93 (30.3%) Unknown 25 (8.2%)	Bx Performed By	Ultrasound 304 (99%) MRI 2 (1%)
Prostate size (gm) (Median, Min-Max)	34 (9.22-160)	DRE	Normal 202 (66%) Abnormal 64 (21%) Unknown 40 (13%)	Stage	T1 90 (29%) T1a 50 (16%) T1b 20 (7%) T1c 122 (40%) T2 1 (0.3%) T2a 5 (2%) T2b 14 (5%)	Prostate Size Determined By	TRUS-Ultrasound 293 (96%) MRI 10 (3%) Unknown 3 (1%)
Gleason	3+3 90 (29.4%) 3+4 122 (39.8%) 4+3 50 (16.3%) 3+5, 4+4, 4+5, 5+4 44 (14.4%)						
sPSA (ng/ml) (Median, Min-Max)	\leq 4 62 (20%) 4 to 10 198 (65%) >10 46 (15%)						

Participant Selection



Sensitivity of the Urine/Plasma Test in Predicting Biopsy and Prostatectomy Results

Prostatectomy		Value	Biopsy
97%	High Sensitivity	Value	95%
94%		Lower Limit	91%
99%		Upper Limit	98%
94%	Standard Sensitivity	Value	92%
90%		Lower Limit	87%
96%		Upper Limit	95%
92%	Low Sensitivity	Value	88%
87%		Lower Limit	83%
95%		Upper Limit	92%



Sensitivity and Specificity of Biopsy in Predicting Prostatectomy Results

	Estimated	95% Confidence Interval	
	Value	Lower Limit	Upper Limit
Sensitivity	78%	72%	83%
Specificity	71%	55%	83%
PPV	94%	90%	97%
NPV	36%	26%	46%

Gleason Score Changes After Prostatectomy

Upgraded		Downgraded	
Gleason Score	No (%)	Gleason Score	No (%)
3+3 to 3+4	49 (16%)	3+4 to 3+3	11 (4%)
3+3 to 4+3	9 (3%)	4+3 to 3+3	1 (0.3%)
3+4 to 4+3	14 (5%)	4+4 to 3+3	1 (0.3%)
3+4 to 4+4	2 (1%)	4+4 to 3+4	2 (0.7%)
3+4 to 4+5	2 (1%)	4+4 to 4+3	11 (4%)
4+3 to 4+4	3 (1%)	4+5 to 4+3	8 (3%)
4+3 to 5+4	1 (0.3%)	5+4 to 4+5	1 (0.3%)
4+4 to 4+5	1 (0.3%)	5+5 to 4+5	1 (0.3%)
4+5 to 5+4	1 (0.3%)	Total	36 (12%)
Total	82 (27%)		

Results

- The algorithms and urine/plasma test used in this study resulted in predicting the presence of high-grade PCa with sensitivity (92-97%) and specificity (36-57%).
- Prediction of Gleason \geq 4+3: Sensitivity 96-99% with specificity 37-59%.
- Diagnosis of Gleason \geq 3+4 was missed in 1% to 3% of tested patients and of Gleason \geq 4+3 in 0.2% to 1%.
- Testing 306 samples with prostatectomy data demonstrated accurate prediction of cancer missing only 2.6% to 7% of Gleason \geq 3+4 and 1 to 3% of \geq 4+3, dependent on which cut-off point is used.

Conclusion

We show that this algorithm is highly reliable in predicting high grade (Gleason \geq 3+4) PCa based on biopsy results in 306 patients who underwent prostatectomy. Taking advantage of urine/plasma biomarkers, serum PSA, prostate size, and prior history of biopsy, we were able to predict high grade prostate cancer with negative predictive value (NPV) of 97% to 90% for Gleason \geq 3+4 and 99% to 98% for Gleason \geq 4+3. Furthermore, this test was further proved to be highly sensitive as confirmed by prostatectomy data.