Performance of a clinically validated urine exosome gene expression test to predict high grade prostate cancer in men with a prior negative biopsy

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Introduction:

The over-diagnosis of low grade, indolent prostate cancer (PCa) initiates significant patient anxiety regarding treatment options and health risk. To address this clinical need, we developed and subsequently validated a noninvasive, easy to administer, supportive diagnostic test (ExoDx™ *Prostate (IntelliScore)*, EPI) to guide the initial prostate biopsy decision process for men with PSA 2-10ng/mL [1]. The EPI test is a urine exosome gene expression assay to discriminate high-grade prostate cancer (HGPCa, ≥ GS 7 PCa / ISUP 2) from low-grade PCa (GS 6 / ISUP 1) and benign disease, thereby potentially reducing the number of unnecessary biopsies **(Figure 1)**. As many men have had prior negative biopsies, we sought to understand the performance of EPI in this selected population.

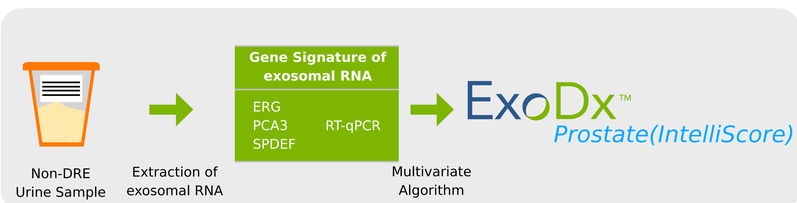

Figure 1: Schematic overview of the ExoDx™ *Prostate (IntelliScore)* (EPI) assay.

Methods:

Utilizing men with prior negative biopsies from two clinical trials we evaluated performance of the EPI test with respect to subsequent biopsy outcomes. We used the previously validated and alternative EPI cut-points of 15.6 and 20, respectively, to assess performance with AUC, sensitivity, and NPV. An explorative cutpoint is tested on the prior negative biopsy cohort only, to optimize the number of biopsies avoided while ensuring a high negative predictive value. Performances of EPI are compared against the Prostate Cancer Prevention Trial (PCPT) Risk Calculator (PCPTRC) version 2 [2] and PSA by area under the receiver operator characteristic curve (AUC).

Table 1: Histological Definition of the ISUP System

ISUP	Benign	1	2	3	4	5
Gleason	Benign	6 (3+3)	7 (3+4)	7 (4+3)	8 (4+4) (5+3) (3+5)	≥ 9

Results:

Results are obtained from a total of N = 286 patients with a prior negative biopsy; median age 65 years, median PSA 6.1 ng/mL, 22% positive family history, 15% African American; 32% positive biopsy rate: 20% GS6 (ISUP1) and 12% ≥ GS7 PCa (ISUP ≥ 2). EPI achieved an AUC of 0.68 vs. AUC 0.59 for the PCPT (i.e. PSA, age, race, family history) and AUC 0.51 for PSA alone. By comparison the EPI initial biopsy AUC was 0.71. Using the previously validated EPI cut-points of 15.6 (or alternative 20) yielded NPVs of 92% and 95%, and number of avoided biopsies of 23% and 32%, respectively, and sensitivity of 85.7% for both cut-points. Notably, EPI in the initial biopsy setting had a sensitivity of 92 vs. 87% and an NPV of 91 vs. 90%, for the 15.6 and 20 cut-points, respectively.

Initial Biopsy Cohort:

Table 2: EPI Performance

Cohort Size	519	
Age (Median)	63 years	
PSA (Median)	5.1 ng/mL	
African American	16.8%	
Familyhistory - Yes	22.5%	
	Validated	Alternative
Prevalence HGPCa	28.5%	28.5%
Biopsies Avoided	26.6%	36.6%
Sensitivity	91.9%	87.2%
Specificity	34.0%	46.1%
NPV	91.3%	90.0%

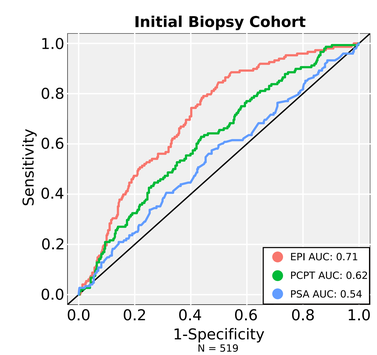

Figure 2: Comparison of receiver-operator-characteristics (ROC) and area under the curve (AUC) of ExoDx™ Prostate (IntelliScore), PCPTRC and PSA in the inital biopsy cohort. **Table 2** shows the demographic properties and EPI test performances in the initial biopsy cohort for the validated and alternative EPI cutpoints.

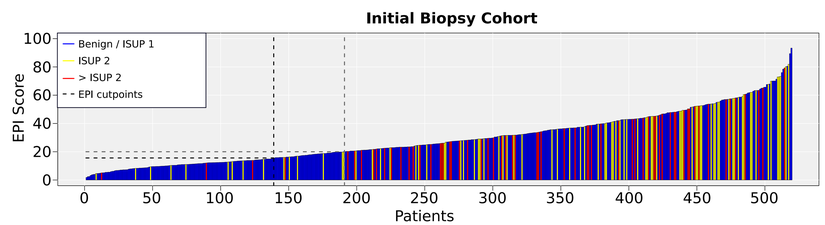

Figure 3: Waterfall plot showing all patients (N = 519) of the initial biopsy cohort (x-axis), their EPI score (y-axis) and their ISUP group based on prostate biopsy. The validated and alternative EPI cut-points are shown as dashed lines.

Conclusion:

The EPI test is a noninvasive, first-catch, non-DRE gene expression array that accurately discriminates low-grade and benign biopsy outcomes from high-grade prostate cancer. The test performs well in both the initial and prior negative biopsy patients and has the potential to reduce the overall number of unnecessary biopsies in both settings.

Prior Negative Biopsy Cohort:

Table 3: EPI Performance

Cohort Size	286		
Age (Median)	65 years		
PSA (Median)	6.1 ng/mL		
African American	15.4%		
Familyhistory - Yes	22.0%		
	Validated	Alternative	Explorative
Prevalence HGPCa	12.2%	12.2%	12.2%
Biopsies Avoided	23.1%	31.8%	55.6%
Sensitivity	85.7%	85.7%	74.3%
Specificity	24.3%	34.3%	59.8%
NPV	92.4%	94.5%	94.3%

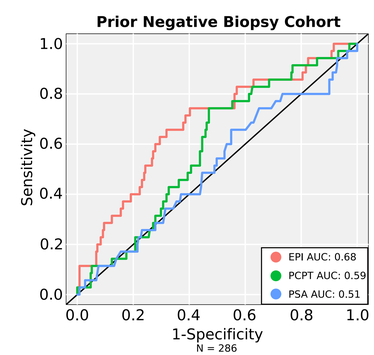

Figure 4: Comparison of receiver-operator-characteristics (ROC) and area under the curve (AUC) of ExoDx™ Prostate (IntelliScore), PCPTRC and PSA in the prior negative biopsy cohort. **Table 3** shows the demographic properties and EPI test performances in the prior negative biopsy cohort for the validated and alternative EPI cutpoints as well as for an explorative cutpoint specifically chosen for a prior negative biopsy cohort.

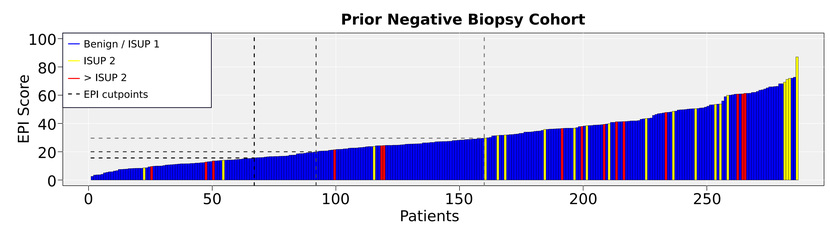

Figure 5: Waterfall plot showing all patients (N = 286) of the prior negative biopsy cohort (x-axis), their EPI score (y-axis) and their ISUP group based on prostate biopsy. The validated, alternative and explorative EPI cut-points are shown as dashed lines.

References:

[1] McKiernan, J., Donovan, M. J., O'Neill, V., Bentink, S., Noerholm, M., Belzer, S., ... & Brown, G. (2016). A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. *JAMA oncology*, 2(7), 882-889.

[2] Ankerst, D. P., Hoefler, J., Bock, S., Goodman, P. J., Vickers, A., Hernandez, J., ... & Thompson, I. M. (2014). Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low-vs high-grade prostate cancer. Urology, 83(6), 1362-1368.

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