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# Radical prostatectomy outcomes from a validated urine exosome gene expression assay which predicts high-grade (GS7) prostate cancer suggests utility for men enrolled in Active Surveillance

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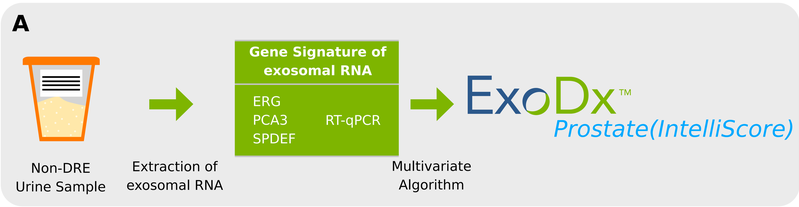
## Introduction:

With over-diagnosis and over-treatment of indolent prostate cancer (PCa), non-invasive screening tools that predict low-grade (≤ Gleason score 6, GS 6) from high-grade (≥ GS 7) PCa will play a significant role in the treatment decision process. Recently, we demonstrated that the urine exosome gene expression assay ExoDx™ *Prostate (IntelliScore)* (EPI) (**Figure 1 A**) could discriminate high-grade (≥ GS 7) from low-grade (GS 6) and benign disease biopsy outcomes, and could potentially reduce the number of unnecessary biopsies (**Figure 1 B**, **Table 1**) [1]. In a parallel study, we also showed that EPI scores were associated with pathologic stage (PS) and radical prostatectomy Gleason score (RP-GS). We now sought to expand these results and further examine outcomes from men enrolled in the EPI validation trial who had selected surgery.




**B**

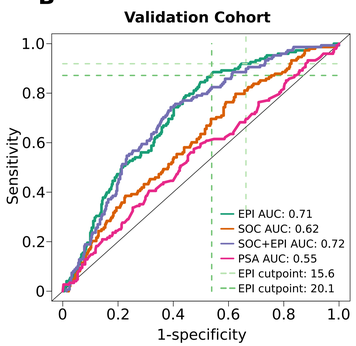



**Table 1: EPI Performance**

| Cutpoint | Validated | Alternative |
|---|---|---|
| **Cohort Size** | 512 | 512 |
| **Prevalence** | 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% |

**Table 2: Histological Definition of the ISUP System**

| ISUP | Gleason Score | Histological Definition |
|---|---|---|
| | Benign biopsies | No abnormalities |
| ISUP 1 | GS ≤ 3+3 | Only individual discrete well-formed glands |
| ISUP 2 | GS 3+4 | Predominantly well-formed glands with lesser component of poorly formed/fused/ cribriform glands |
| ISUP 3 | GS 4+3 | Predominantly poorly-formed fused/cribriform glands with lesser component of well-formed glands |
| ISUP 4 | GS 4+4 | Only poorly-formed/fused cribriform glands *or* Predominantly well-formed glands and lesser component lacking glands *or* Predominantly lacking glands and lesser component of well-formed glands |
| | GS 3+5 | |
| | GS 5+3 | |
| ISUP 5 | GS ≥ 9 | Lacks gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands |

**Figure 1**: **(A)** Schematic overview of the ExoDx™ *Prostate (IntelliScore)* (EPI) assay. **(B)** Comparison of receiver-operator-characteristics (ROC) and area under the curve (AUC) for different models. EPI is compared with standard-of-care (SOC), standard-of-care + EPI (SOC+EPI) and PSA. **Table 1** shows the corresponding classification performances for the EPI model with the Validated (15.6) and Alternative (20) cutpoint.

## Methods:

Urine was collected from a total of 242 patients prior to scheduled radical prostatectomy (RP). The pre-RP EPI score was generated and the tissue status from both a pre-RP biopsy and from final pathology post RP using the ISUP 2014 criteria [2] were reported. Additionally, RP-GS outcomes from 86 men that were enrolled in the 519-patient validation cohort were evaluated [1]. The patients were derived from the two cohorts as follows:

242 patients from a dedicated pre-RP study (previously reported)
86 patients from the EPI validation study, who proceeded to have a RP

Both patient cohorts were merged prior to final analysis (N=328). During pathology evaluation of the prostate after RP, patients often experience up- and down-grading relative to their biopsy status. In this analysis, we are focusing on a subset of 112 out of 328 men with an initial biopsy status of ISUP 1 (i.e. potential candidates for Active Surveillance). We reviewed EPI scores and PSA values for those patients that were ISUP1 by biopsy with their RP pathology outcomes:

- A maintained ISUP 1 status
- B upgraded to ISUP 2
- C upgraded to > ISUP 2

## Results:

The pre-RP cohort (N=242) segregates into 33% ISUP 1 (GS 6), 42% ISUP 2 (GS 3+4) and 25% > ISUP 2 (≥ GS 4+3) patients prior to RP. Comparable ISUP ratios are observed in the EPI-validation cohort (N=86) with 38% ISUP 1, 34% ISUP 2 and 28% > ISUP 2, respectively. 33% of the pre-RP patients exhibited up-grading while 14% were down-graded and 28% of the EPI-validation patients were up- and 10% down-graded. Overall demographic properties of the merged patient cohort (N=328) are shown in **Table 3**.

**Table 3: Demographic Properties**

| Demographics | Intended Use PSA 2-10 ng/ml |
|---|---|
| Cohort Size | 328 |
| Age (Median) | 62 years |
| PSA (Median) | 5.4 ng/ml |
| African American | 28 (8.5%) |
| Familyhistory - Yes | 104 (32%) |
| Prevalence HGPCa (GS ≥ 7) | 216 (66%) |

**Figure 2**: Heatmap is showing up- and down-grading of ISUP grades after RP relative to biopsy based ISUP grading. Absolute number of patients are plotted as text. Relative up- and down-grading of ISUP grades are shown color coded.

EPI scores and PSA values were obtained from all 328 patients. Subsequent analysis focuses on a subset of 112 low-grade PCa patients that were classified as ISUP 1 based on biopsy outcome (**Figure 2**).

Higher urine EPI scores are associated with higher RP-ISUP groups (**Figure 3 A**). **Patients initially classified as ISUP 1 that were re-classified as > ISUP 2 after RP have significantly higher EPI scores (p-value = 0.001) compared to patients that were not up-graded after RP**. In contrast, PSA was not able to discriminate the different patient groups. The distributions of PSA values are very similar between up- and non-upgraded groups (**Figure 3 B**).

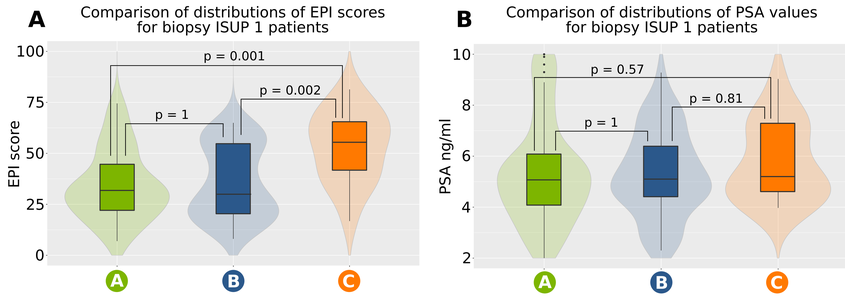



**Figure 3**: **(A)** ExoDx™ *Prostate (IntelliScore)* distributions are shown for biopsy ISUP 1 patients that: A maintained ISUP 1 after RP, B patients that got up-graded to ISUP 2 after RP and C patients that got up-graded to > ISUP 2 after RP. Patients that got up-graded to >ISUP 2 C have significantly higher EPI scores compared to groups A and B. **(B)** Distributions of PSA values are shown instead of EPI scores. PSA cannot discriminate between patient groups.

## Conclusion:

The EPI test is a non-invasive, non-DRE gene expression signature that accurately discriminates low-grade from high-grade PCa in ISUP and traditional Gleason score based grading systems. Improved discrimination for predicting higher ISUP groups suggests a potential role in longitudinal monitoring of patients enrolled in Active Surveillance and warrants further validation.

## 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] Epstein, J. I., Egevad, L., Amin, M. B., Delahunt, B., Srigley, J. R., Humphrey, P. A., & Grading Committee. (2016). The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. *The American journal of surgical pathology*, 40(2), 244-252.

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