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Performance of a validated urine exosome gene expression assay to predict high-grade prostate cancer utilizing the 'International Society of Urological Pathology' (ISUP) 2014 grading system

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Introduction:

Overdetection and overtreatment of indolent prostate cancer (PCa) remains a significant health issue requiring noninvasive assays to guide the prostate biopsy decision process. We demonstrated that the ExoDx™ *Prostate (IntelliScore)* (EPI) derived from a urine exosome gene expression assay (**Figure 1**) discriminates GS 7 PCa from GS 6 and benign disease in the PSA gray zone, potentially reducing the number of unnecessary biopsies [1].

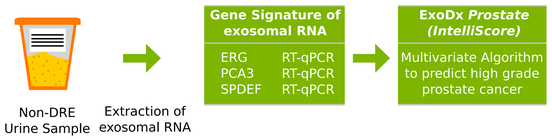

Figure 1: Schematic overview of the ExoDx™ Prostate IntelliScore (EPI) assay.

The International Society of Urological Pathology (ISUP) proposed a prognostic PCa grading system to accurately reflect the biology of PCa; ISUP separates GS 7 PCa into group 2 (GS 3 +4) and group 3 (GS 4+3) (**Table 1**) [2]. We sought to evaluate the performance of the EPI test according to the newly proposed ISUP system in two different population definitions A and B. The demographic properties of the intended use population are shown in **Table 2**.

Table 1: Histological Definition of the ISUP Grading System

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

Methods:

The urine test results and clinical data from the ExoDx™ *Prostate (IntelliScore)* validation cohort (N=519) was re-annotated using the ISUP group grading system shown in **Table 1**. Here, we analyze the performance of EPI to discriminate:

A **ISUP 1 (GS ≤ 6) from ISUP 2-5 (GS ≥ 7)**

B **ISUP 1+2 (GS ≤ 3+4) from ISUP 3-5 (GS ≥ 4+3)**

We used two different cut-points ('Validated' (EPI 15.6) and 'Adjusted' (EPI 20)) to assess the performance of EPI by %avoided biopsies, AUC, sensitivity, specificity and negative predictive value (NPV). In addition, we tested if ExoDx™ *Prostate (IntelliScore)* values are significantly different in the defined groups (**Figure 3**).

Table 2: Demographic Properties

Demographics	Intended Use Cohort PSA 2-10 ng/mL
Cohort Size	512
Age (Median)	63 years
PSA (Median)	5.12 ng/mL
African American	87 (17%)
Familyhistory - Yes	117 (23%)
Biopsy Result (GS ≥ 6)	251 (49%)
Prevalence HGPCa (GS ≥ 7)	148 (29%)

Results:

A

Applying the Validated cut-point on the ISUP-labeled cohort to discriminate ISUP 1 from ISUP 2-5 leads to 27% avoided biopsies and a NPV of 91.3% which is equivalent to our previously reported results based on Gleason score labeled data. The Adjusted cut-point leads to an improved rule-out rate of 37% biopsies avoided, while maintaining the NPV at 90% (**Figure 2A**, **Table 3)**.

B

Utilizing the same two cut-points to discriminate ISUP 1+2 from ISUP 3-5 (dominant pattern 4) results in 26% and 37% biopsies are avoided, respectively, with an improved NPV of 98% in both cases (**Figure 2B**, **Table 3, Figure 4**).

Higher EPI scores are significantly associated with ISUP categories (**Figure 3**). In this analysis EPI is significantly different in ISUP 1 compared to EPI in ISUP ≥ 2. Even the union of ISUP1+2 is different from ISUP ≥3; supporting accurate discrimination in high grade PCa.

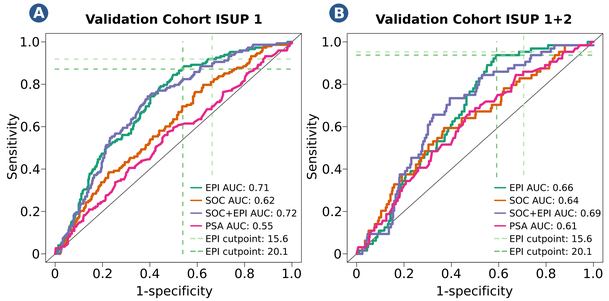

Figure 2: Comparison of receiver-operator-characteristics (ROC) and area under the curve (AUC) for different models. EPI is compared with standard-of-care (SOC), standard-of-care + EPI (SOC+EPI) and PSA. (**A**) Comparison for discriminating ISUP 1 from ISUP 2. (**B**) Comparison for discriminating ISUP 1+2 from ISUP 3.

Table 3: ExoDx™ Prostate IntelliScore Performance Characteristics

	A ISUP 1		B ISUP 1+2	
Cutpoint	**Validated**	**Adjusted**	**Validated**	**Adjusted**
Cohort Size	512	512	512	512
Prevalence	28.5%	28.5%	12.3%	12.3%
Biopsies Avoided	26.6%	36.6%	26.6%	36.6%
Sensitivity	91.9%	87.2%	95.3%	93.8%
Specificity	34.0%	46.1%	29.7%	40.9%
NPV	91.3%	90.0%	97.8%	97.9%

ExoDx™ *Prostate (IntelliScore)* Distributions

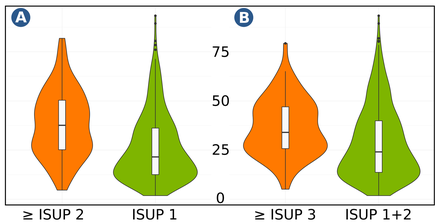

Figure 3: Comparison of ExoDx™ *Prostate (IntelliScore)* distributions in the validation cohort (N=512). ISUP 1 is significantly different from ISUP 2 and ISUP 1+2 differs significantly from ISUP 3 (p-value < 2.1×10^{-8})

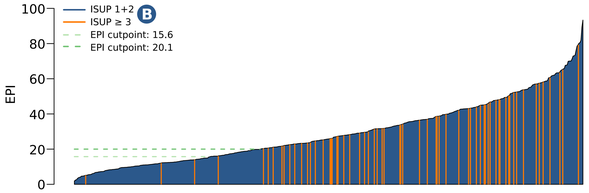

Figure 4: Waterfall plot of all patients in the intended use population highlighting the discrimination of ISUP 1+2 and ISUP ≥ 3. The validated cut-point for the ExoDx™Prostate IntelliScore rules out 27% ofpatients from biopsy, with a NPV of 98%. Adjusting the cut-point avoids 37% of biopsies, while maintaining a NPV of 98%.

Conclusions:

The ExoDx™ *Prostate (IntelliScore)* is a noninvasive, first-catch non-DRE gene expression assay that accurately discriminates low-grade from high-grade PCa in both PCa definitions (**Table 3**). The test has the potential to reduce the number of unnecessary biopsies and performs equally well in contemporary approaches to PCa stratification.

ExoDx™ *Prostate (IntelliScore)*:

- non-DRE, first-catch urine sample to predict high-grade PCa in men with PSA 2-10 ng/mL presenting for initial biopsy
- NPV of 91.3% while avoiding 26.9% of biopsies when separating ISUP 1 from ISUP 2-5 A
- NPV of 98% while avoiding 26.9% of biopsies when separating ISUP 1+2 from ISUP 3-5 B

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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