Urine Exosome Gene Expression Assay Net Benefit Analysis in a Large Cohort (>1,200)

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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. We developed and published that a non-DRE, urine-based exosome gene expression signature, the ExoDx™ Prostate (IntelliScore) (EPI), 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.[1] In subsequent studies, we validated the threshold of 15.6 in two prospective, independent validation studies.[2,3] In this study, we examined both the accuracy as well as the clinical benefit of ExoDx™ Prostate (IntelliScore) (EPI) results in a large, pooled cohort over a range of probabilities using net benefit analysis.

Prognostic assays are often measured via accuracy parameters that do not always convey an apparent clinical impact. Relevant examples of such statistical metrics include area under the curve (AUC), or concordance index: small improvements in these measurements do not always convey clinical benefit. The net benefit analysis approach makes assumptions about the event probability at which patients would decide upon treatment after evaluating potential benefit versus potential harms. A decision curve is a result of charting the 'net benefit' versus multiple decision probability thresholds.

METHODS

A pooled dataset of two prior validation cohorts and additional cases from an extensive group practice provided a large data set (N=1,212) for net benefit analysis. The pooled population consisted of men ≥ 50 years, scheduled for an initial biopsy and with a PSA measurement. Urine specimens were collected at enrollment using a provided urine collection device, and the EPI tests run at a CLIA-certified central laboratory at Exosome Diagnostics, Waltham, MA. The clinical decision value of the gene expression assay (EPI) was assessed using net benefit analysis and compared EPI results with the standard of care information across a range of probabilities for which a patient might decide on a prostate biopsy. The net benefit is determined by adding the true positive results and subtracting the false negatives across different biopsy probability thresholds.
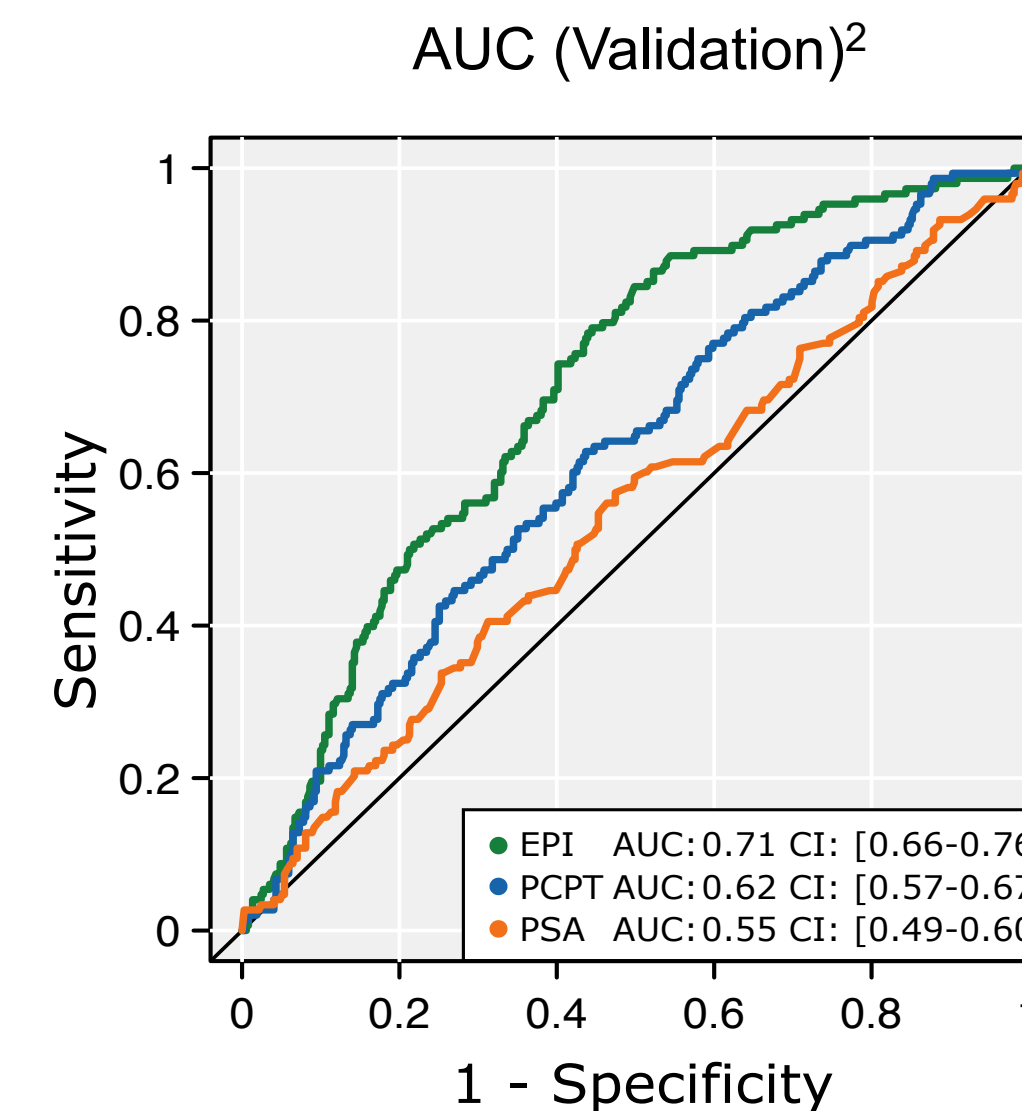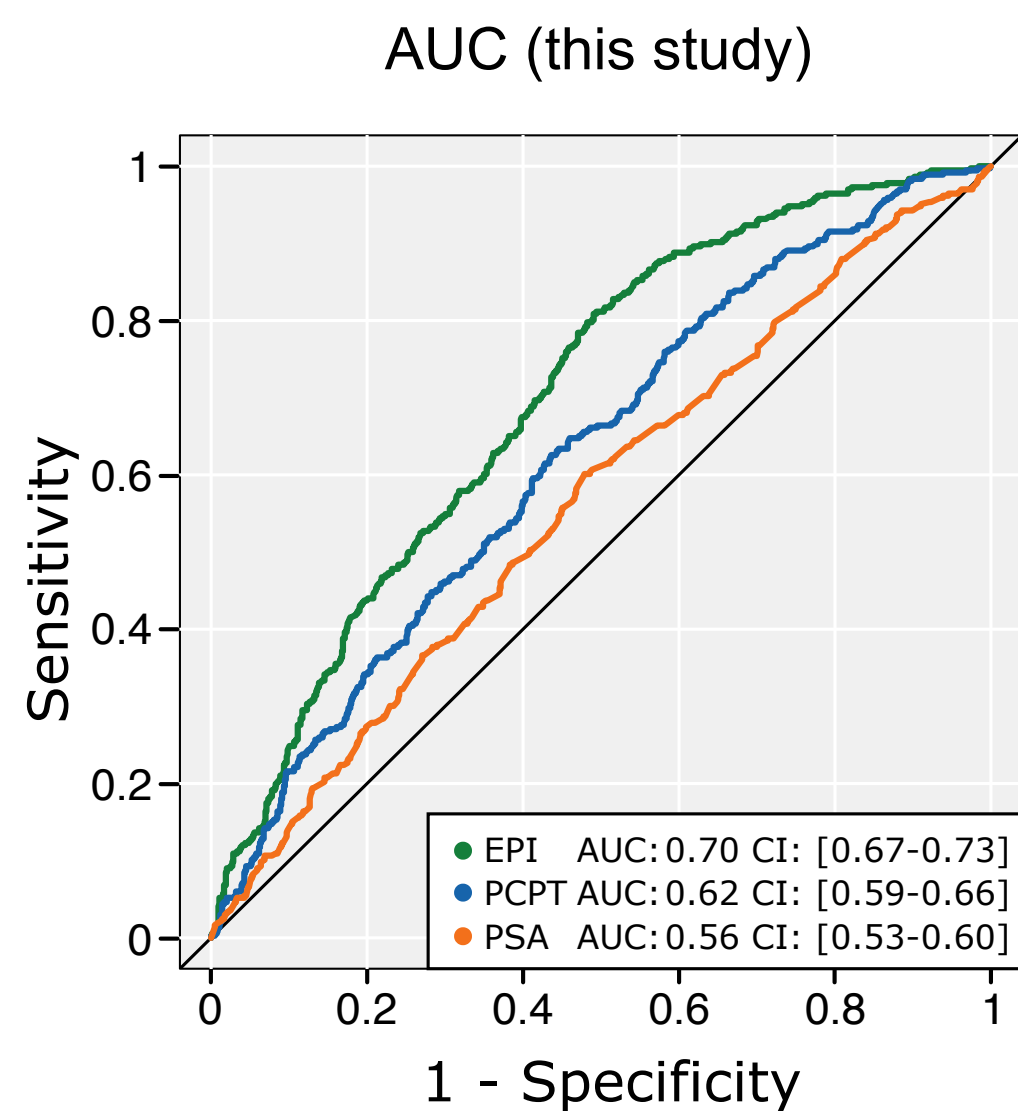
RESULTS

Similar to previous studies the ExoDx™ IntelliScore or EPI assay demonstrated significantly improved accuracy (AUC) compared to PSA or combined clinical features. [2,3]
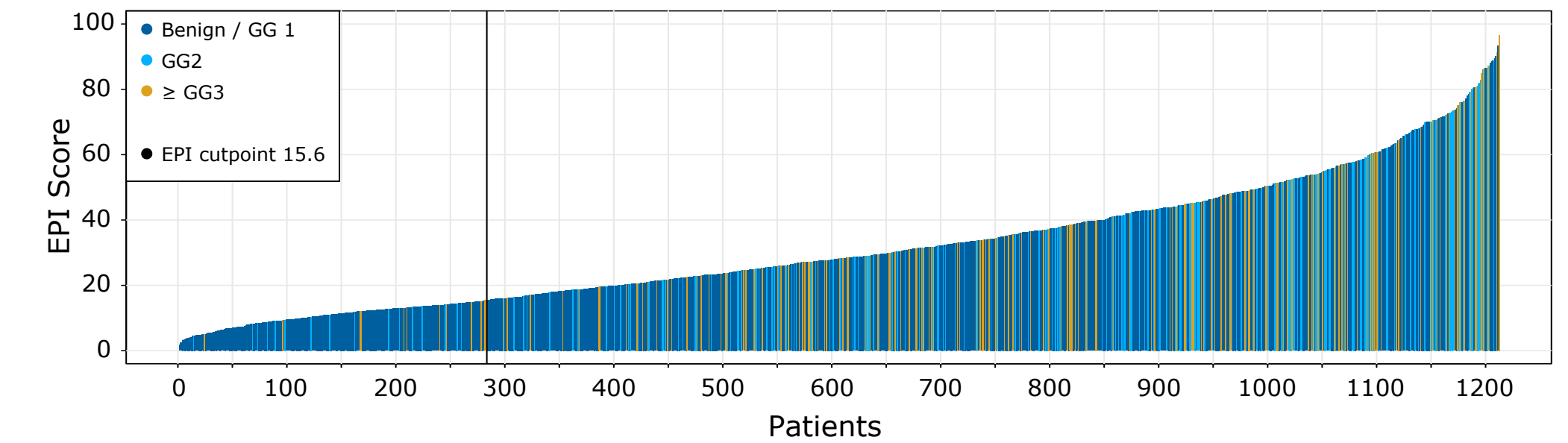
The ExoDx™ IntelliScore (green) demonstrated superior clinical benefit when compared (net benefit analysis) to the Prostate Cancer Prevention Trial (PCPT) prostate cancer risk calculator (blue), or PSA (orange).

Performance (15.6 Threshold)		
	>GG2	>GG3
Cohort size (N)	1212	1212
Prevalence (%)	30.2	13.9
Samples < Cut point (%)	23.3	23.3
Sensitivity (%)	92.3	92.9
NPV (%)	90.1	95.8

Gleason Grade		
	<15.6	>15.6
Benign	220 (77.7%)	365 (39.3%)
GG 1	35 (12.4%)	226 (24.3%)
GG 2	16 (5.6%)	182 (19.6%)
GG 3	8 (2.8%)	76 (8.2%)
GG 4	4 (1.4%)	35 (3.8%)
GG 5	0 (0%)	45 (4.8%)

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AUC (this study)

EPI   AUC: 0.70 CI: [0.67-0.73]
PCPT AUC: 0.62 CI: [0.59-0.66]
PSA AUC: 0.56 CI: [0.53-0.60]

AUC (Validation)[2]

EPI   AUC: 0.71 CI: [0.66-0.76]
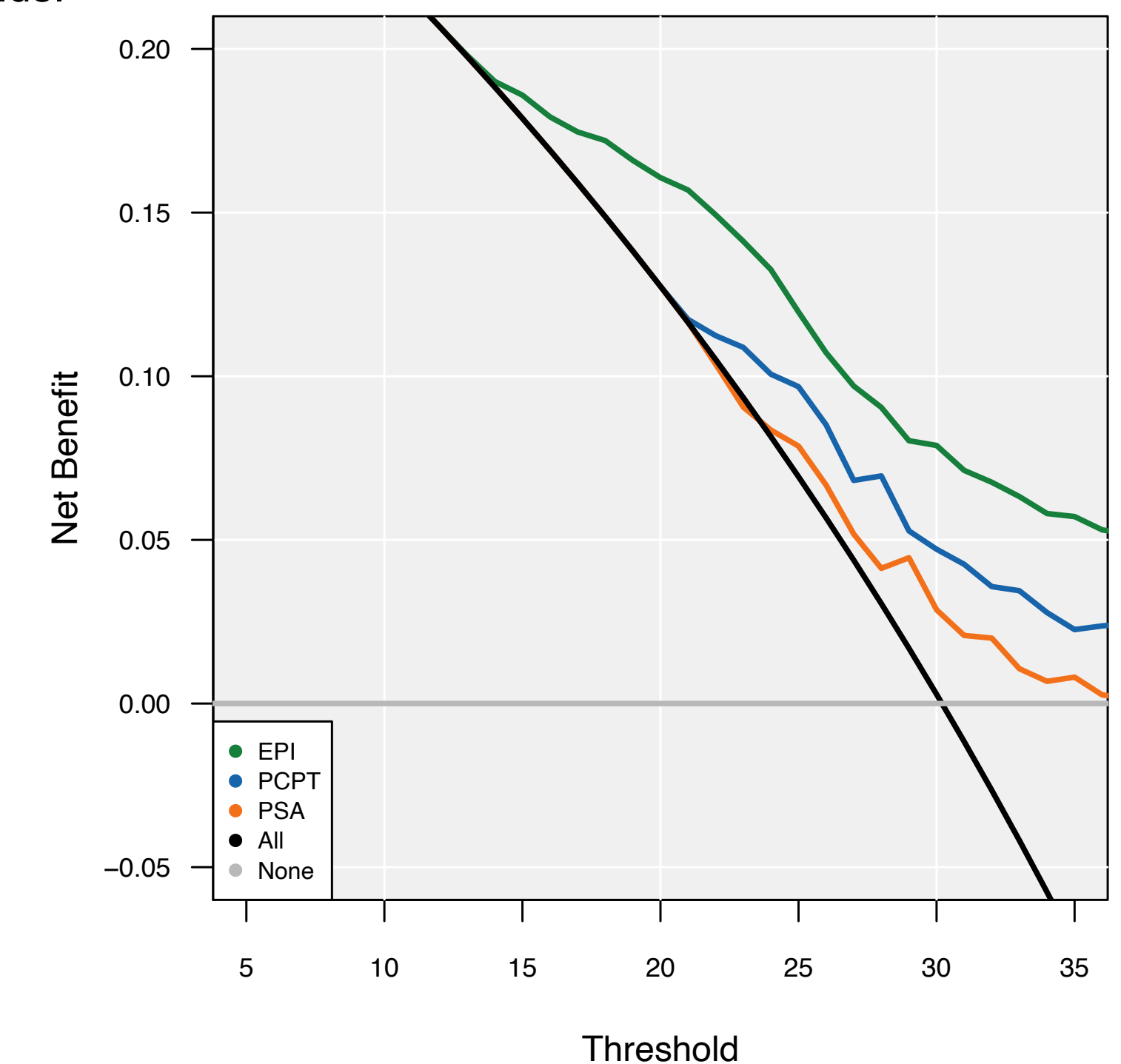PCPT AUC: 0.62 CI: [0.57-0.67]
PSA AUC: 0.55 CI: [0.49-0.60]

WATERFALL

Each individual bar represents a patient's gene expression score and true biopsy diagnosis. The 15.6 cut point is displayed as a vertical black line.

NET BENEFIT ANALYSIS

Net benefit analysis demonstrates that the ExoDx assay (EPI) would provide superior clinical benefit than the prostate cancer prevention trial calculator (PCPT), or PSA over a wide range of decision probability thresholds.

CONCLUSIONS

In this new analysis of a large pooled cohort, the EPI exosome gene expression assay had similar accuracy to prior validation studies. In addition, the exosome-based assay provided the highest clinical net benefit across the 10% - 50% decision threshold compared to decision support methods currently used in the clinic.

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