

Multicenter validation study of a urine-based molecular biomarker algorithm to predict high-grade prostate cancer.

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BACKGROUND

The major challenge in prostate cancer (PCa) diagnostics is to improve the **early detection of high-grade PCa**. Ideally, PCa-specific biomarkers could be obtained non-invasively, for example derived from urine. Recently, a **promising urinary mRNA biomarker combination** was identified*, that predicts high-grade PCa upon biopsy.

OBJECTIVES

To develop a model combining HOXC6-DLX1 mRNA expression levels and traditional risk factors to accurately predict high-grade PCa upon prostate biopsy.

To assure robustness of the proposed risk score the model was validated in an independent cohort.

MATERIAL & METHODS

Two prospective multicenter studies

- **Cohort A: n=492** (41% PCa of which 51% GS \geq 7)
- **Cohort B: n=371** (47% PCa of which 50% GS \geq 7)

Men scheduled for prostate biopsy

- PSA >3.0 ng/ml / abnormal DRE / family history
- Urine collection first-void, post-DRE
- Biomarker mRNA levels were measured using RT-qPCR.
- Quantification of the mRNA using the Delta Delta Ct method ($\Delta\Delta$ CT).
- Development of the high-grade PCa risk score in training Cohort A and validation in Cohort B.

REFERENCE

*Leyten, G. H. J. M. et al. Identification of a candidate gene panel for the early diagnosis of prostate cancer. Clin. Cancer Res.

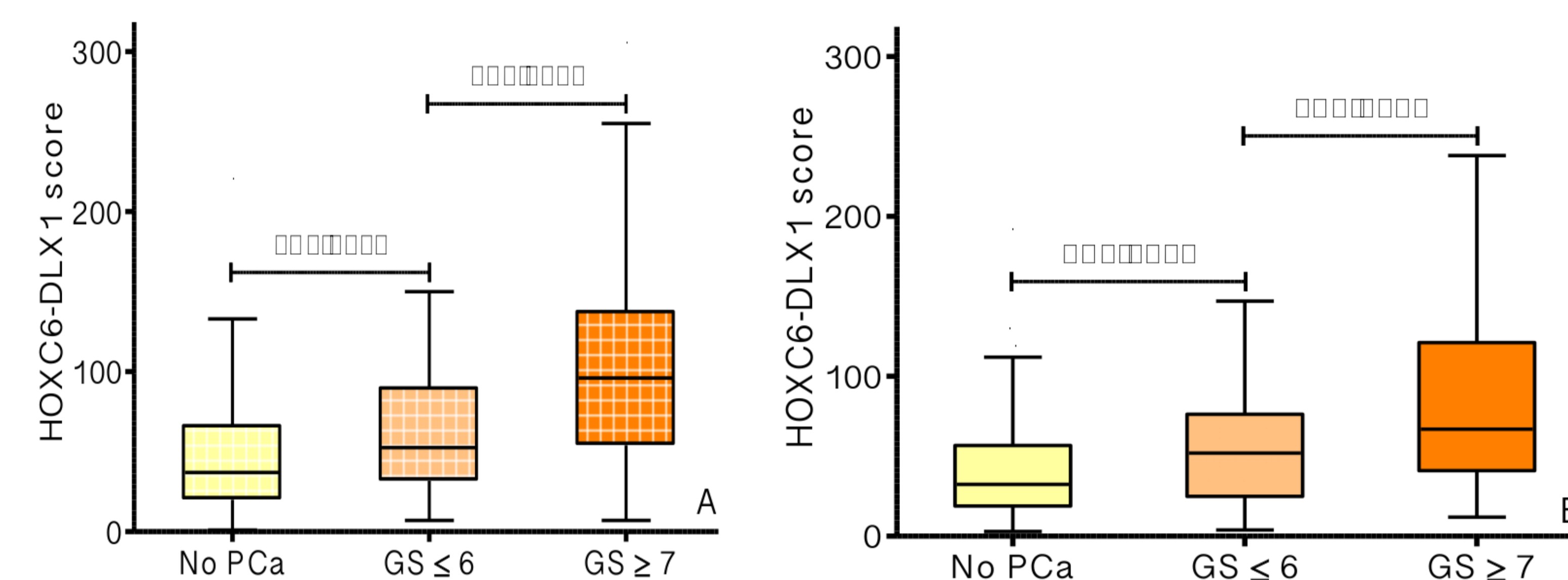
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RESULTS

HOXC6-DLX1 scores in relation to biopsy Gleason scores

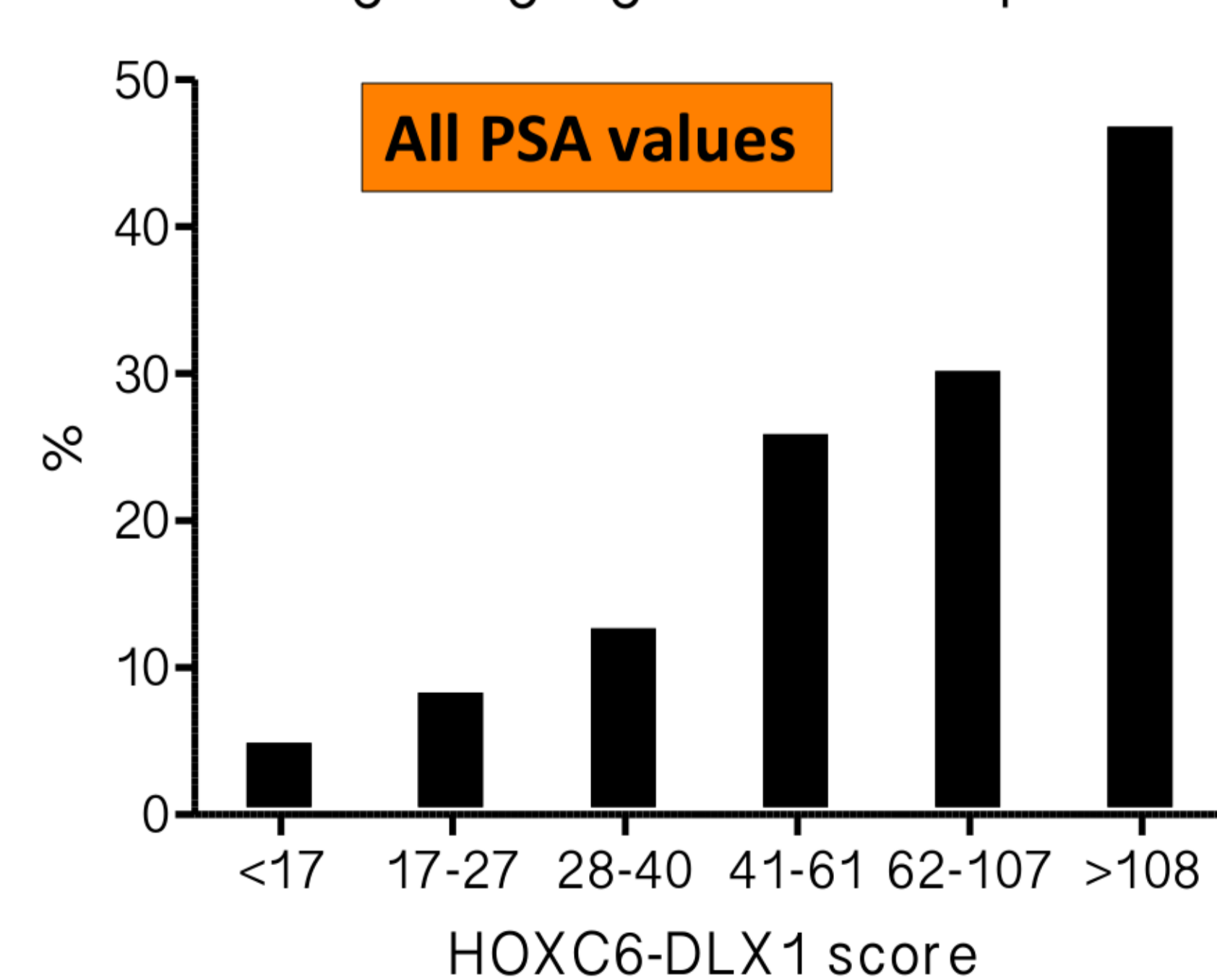
- The HOXC6-DLX1 score was **significant positively associated with the Gleason score** upon biopsy.



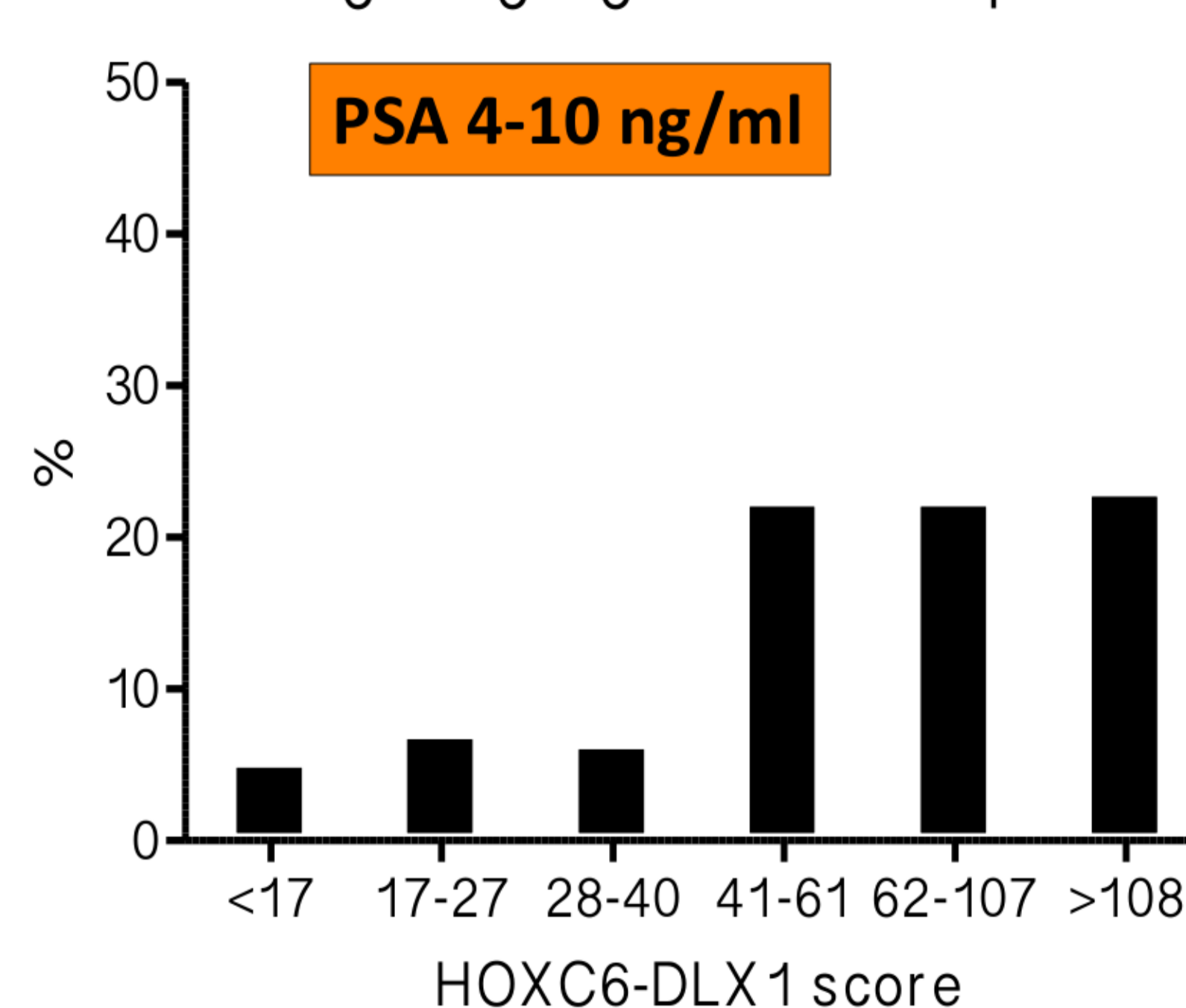
Clinical utility of the HOXC6-DLX1 score

- Elevated HOXC6-DLX1 scores correlated with an increased risk of high-grade PCa detected on biopsy; 47% of men with a score >108 had high-grade PCa as compared to 6% with a score <17.
- Using a HOXC6-DLX1 score cut-off of 27.5, 165 biopsies (31%) could have been avoided, and only 4% of patients with high-grade PCa would have been missed.

Percentage high-grade PCa upon biopsy

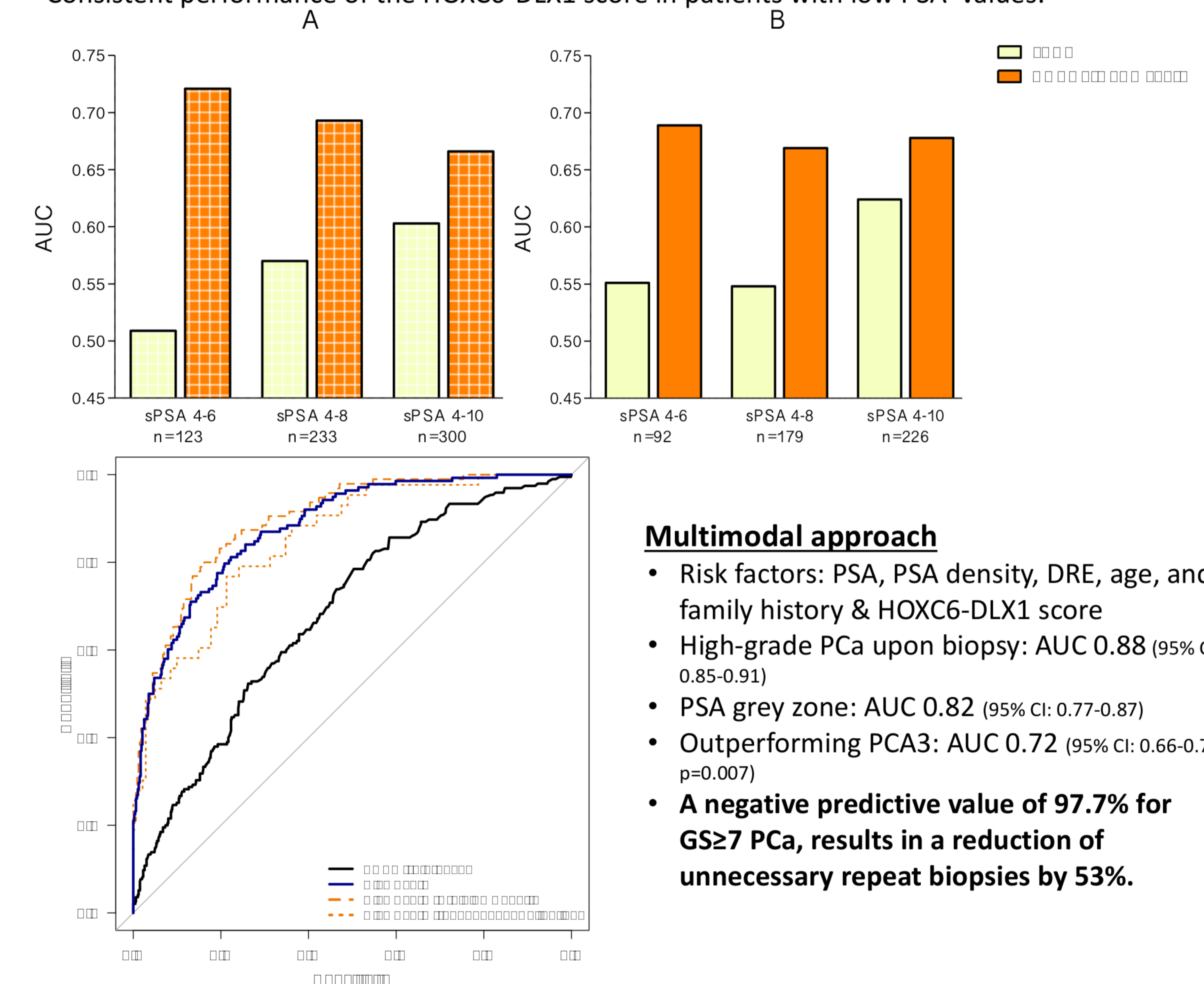


Percentage high-grade PCa upon biopsy



Performance of the HOXC6-DLX1 score in the PSA 'grey zone' (4-10 ng/ml)

- Consistent performance of the HOXC6-DLX1 score in patients with low PSA values.



Multimodal approach

- Risk factors: PSA, PSA density, DRE, age, and family history & HOXC6-DLX1 score
- High-grade PCa upon biopsy: AUC 0.88 (95% CI: 0.85-0.91)
- PSA grey zone: AUC 0.82 (95% CI: 0.77-0.87)
- Outperforming PCA3: AUC 0.72 (95% CI: 0.66-0.77; p=0.007)
- **A negative predictive value of 97.7% for GS \geq 7 PCa, results in a reduction of unnecessary repeat biopsies by 53%.**

CONCLUSION

HOXC6-DLX1 score urine test combined with traditional clinical risk factors:

- Prediction of **high-grade PCa upon prostate biopsy**.
- Positive association with **higher Gleason score**.
- Consistent diagnostic performance in PSA 'grey zone'.

Using the HOXC6-DLX1 risk score: non-invasive solution to select patients for prostate biopsy, and to reduce the amount of unnecessary biopsies.