# Extended validation results from a prospective adaptive utility trial confirm performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy

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# Introduction:

The ability to discriminate indolent from clinically significant prostate cancer (PCa) prior to initial biopsy remains an important health issue. Diagnostic assays that have been extensively evaluated in a prospective setting are necessary for efficacy and clinical adoption. We conducted a second independent validation study to assess outcome and cut-point performance of the ExoDx *Prostate(IntelliScore)* (EPI) (**Figure 1**) urine exosome assay vs. a standard of care model (SOCm) (i.e. prostate-specific antigen [PSA], age, race, and family history) for discriminating Grade group (GG) ≥2 PCa from GG1 PCa and benign disease on initial biopsy [1, 2, 3]. Exosomes are small vesicles released from cells into biofluids such as urine. These exosomes contain molecular information, including RNA signatures of tumor cells, which can be used to monitor disease status in real-time.

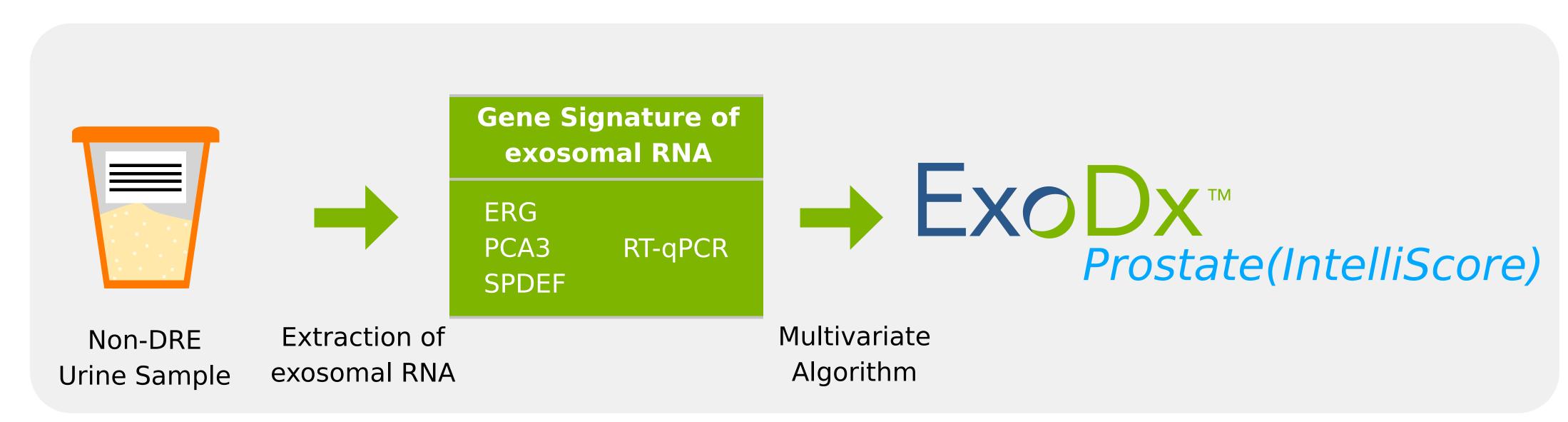
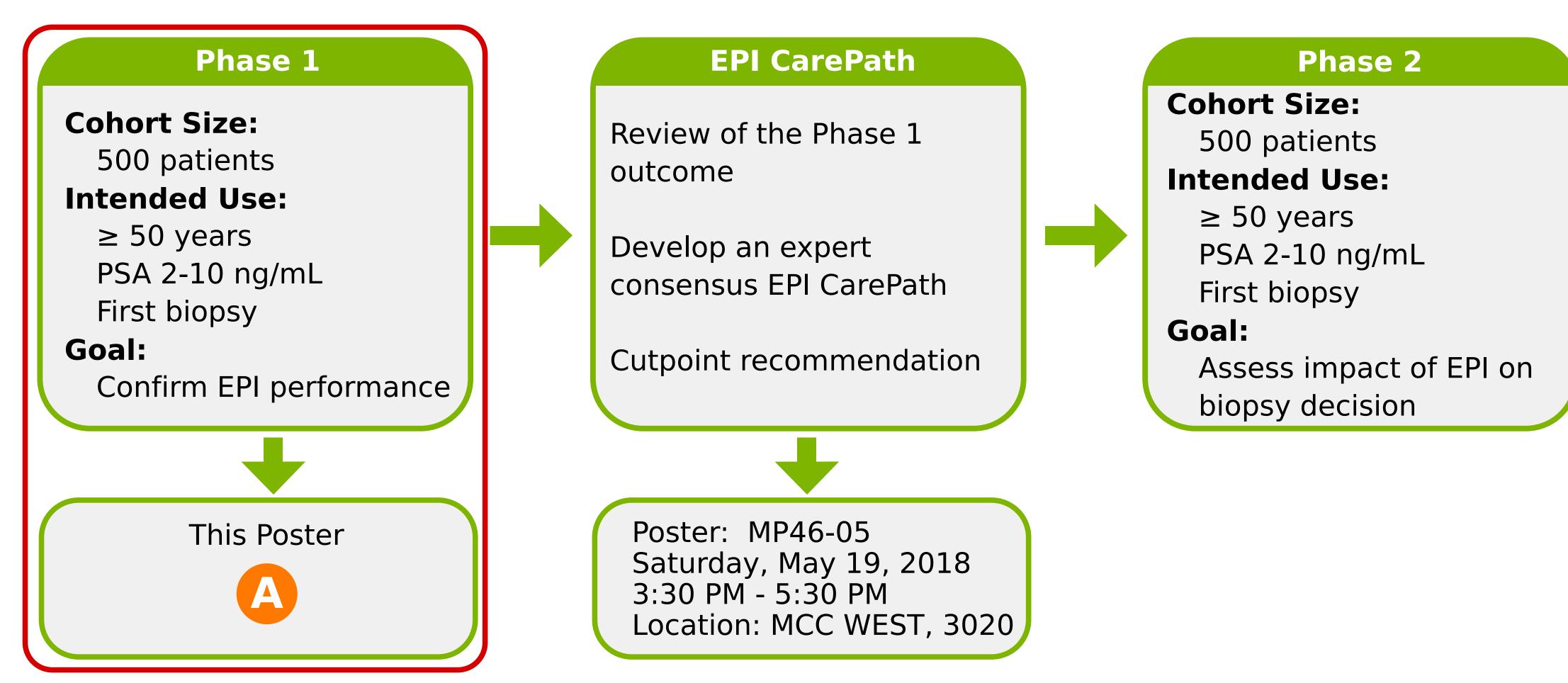


Figure 1: Schematic overview of the ExoDx™ Prostate(IntelliScore) (EPI) assay.

### **Methods:**

This second independent validation study was designed as a two cohort, adaptive clinical implementation and utility study. In Phase 1 EPI test results were compared to biopsy outcomes for eligible subjects: ≥50 years, PSA 2-10 ng/mL, scheduled for initial prostate needle biopsy. Here we report on the test performance in Phase 1 using the area under the receiver operating characteristic curve (AUC), negative predictive value (NPV), sensitivity, and specificity for discriminating ≥GG2 from GG1 and benign disease on initial biopsy. Results are compared to a previously published validation study [2]. After completion of Phase 1, a CarePath was developed for utilizing the EPI test in Phase 2, where the biopsy decision is uncertain (Figure 2). The CarePath is described in a separate poster. The outcome of Phase 2 will be reported separately.

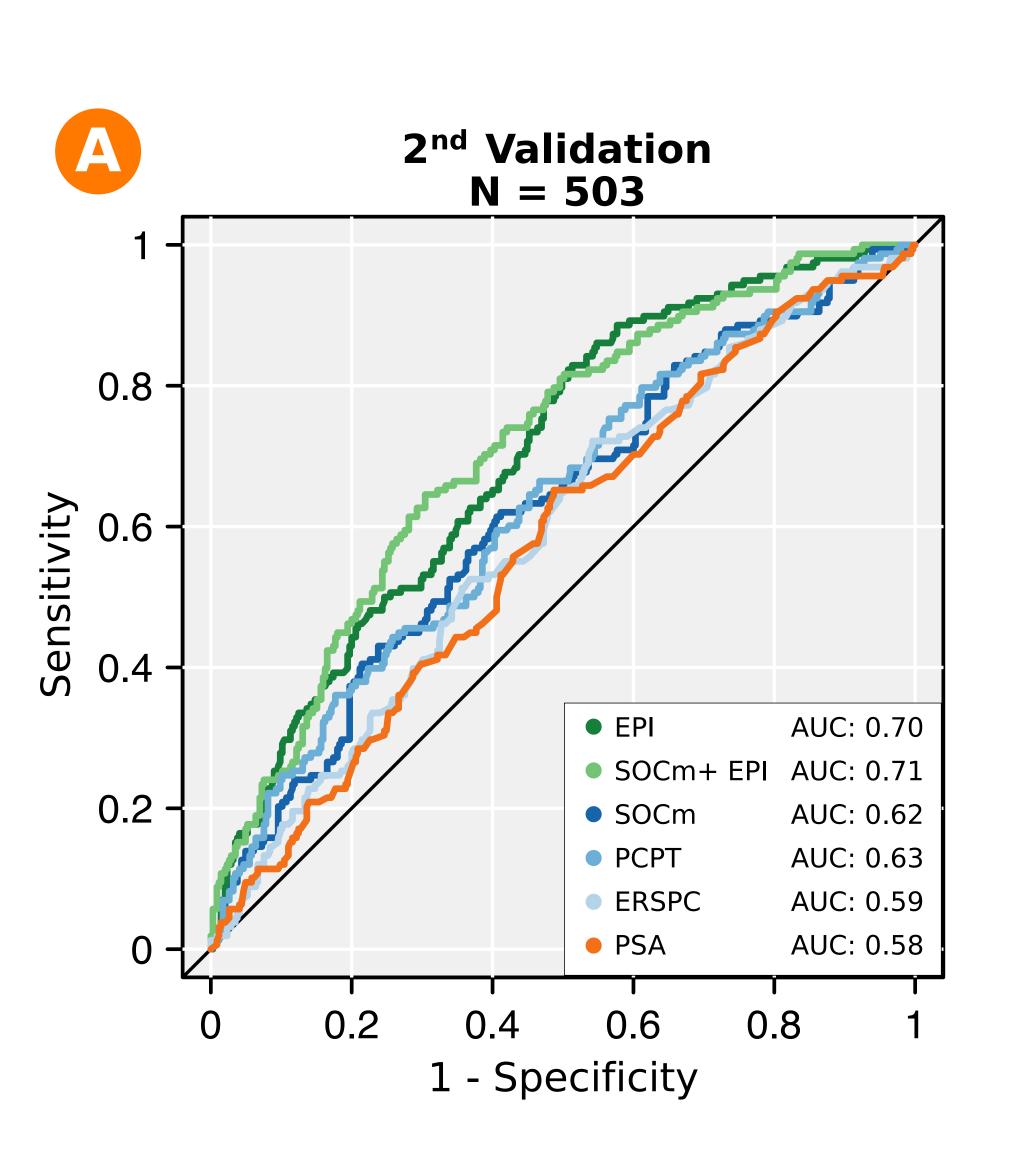


**Figure 2**: Schematic overview of the adaptive, prospective clincial trial design. After completion of Phase 1, a panel of clinicians and risk modeling experts convened at a Consensus Conference to review the performance of the EPI test and compare with previous validation study results using both the validated and alternative cut-points of 15.6 and 20, respectively, for patient stratification.

# **Results:**

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Phase 1 cohort consists of N=503 patients with median age 64 years, median PSA 5.4 ng/mL, 14% African American, 70% Caucasian, 53% positive biopsy rate (22% GG1, 17% GG2 and 14% >GG3). EPI shows an AUC of 0.70 superior to SOCm AUC of 0.62 and PSA AUC of 0.58 for discriminating ≥GG2 PCa from benign and GG1 PCa (Figure 3 △). Comparison to the original validation cohort (N=519 patients, EPI AUC 0.71) demonstrated good agreement (Figure 3 ③). Using the previously validated cut-point of 15.6 (or alternative 20) (Figure 4) would avoid 26% (or 40%) of unnecessary prostate biopsies and 20% (or 31%) of total biopsies, with an NPV of 89% for both cut-points, and miss only 7% (or 11%) of ≥GG3, respectively (Table 1).



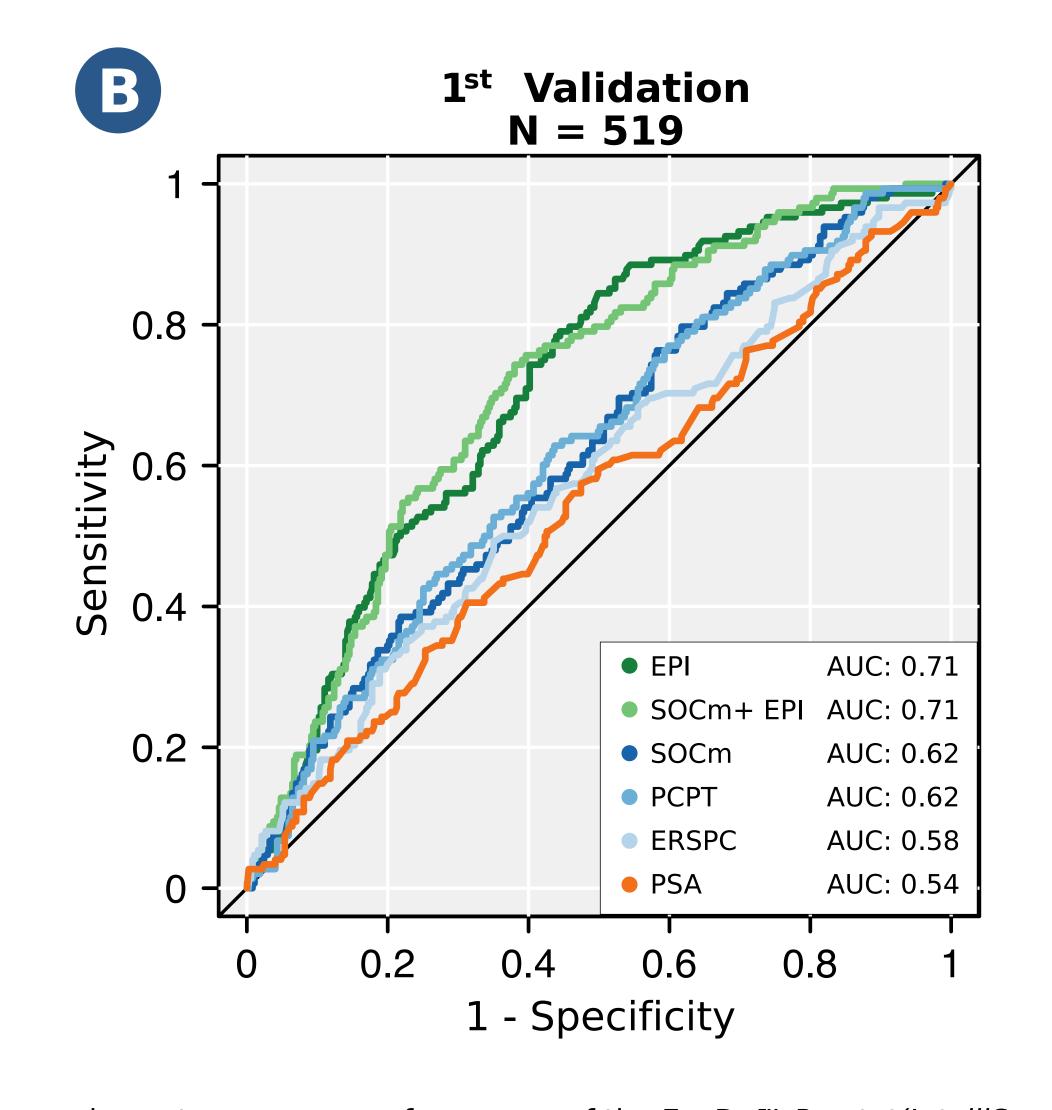
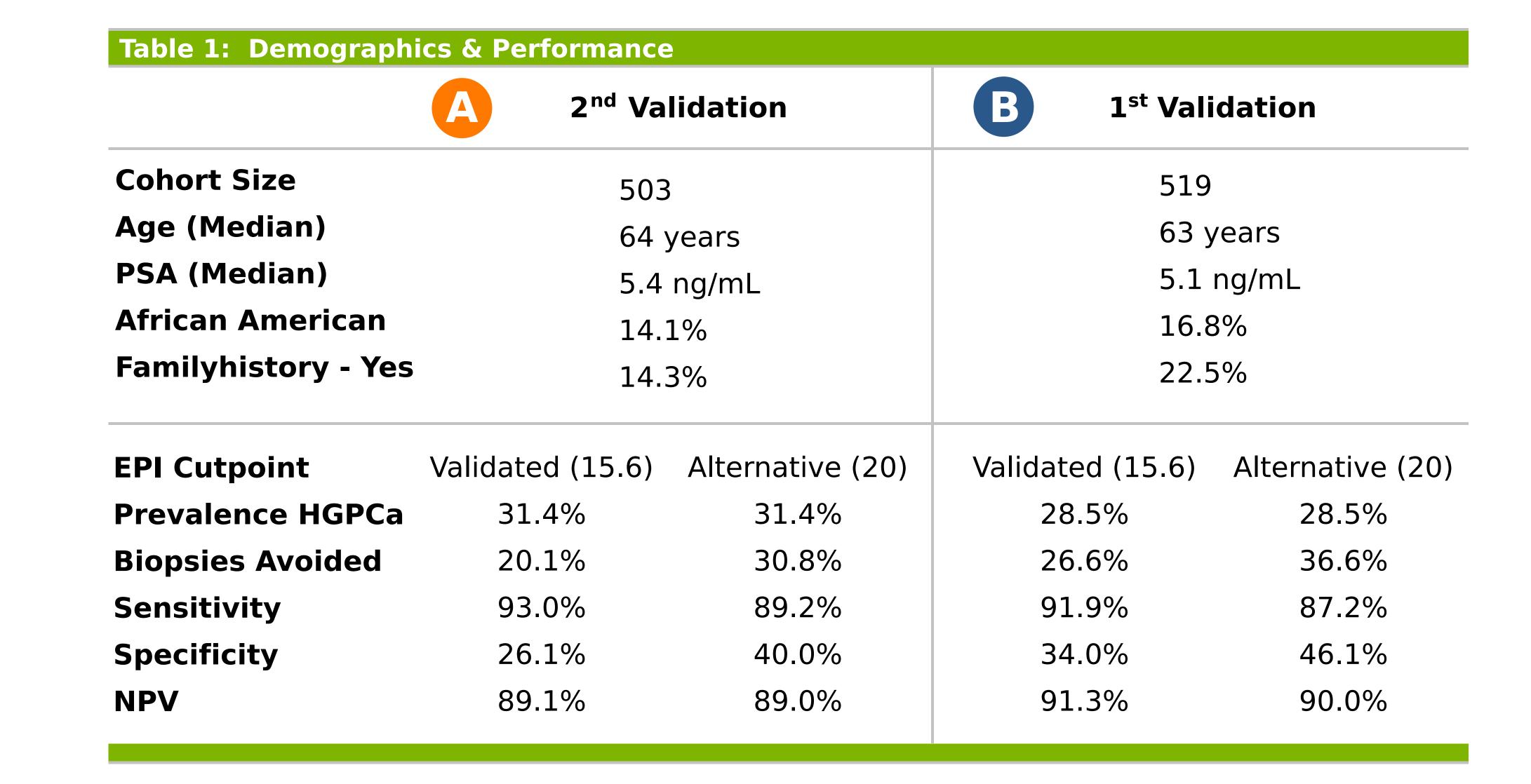
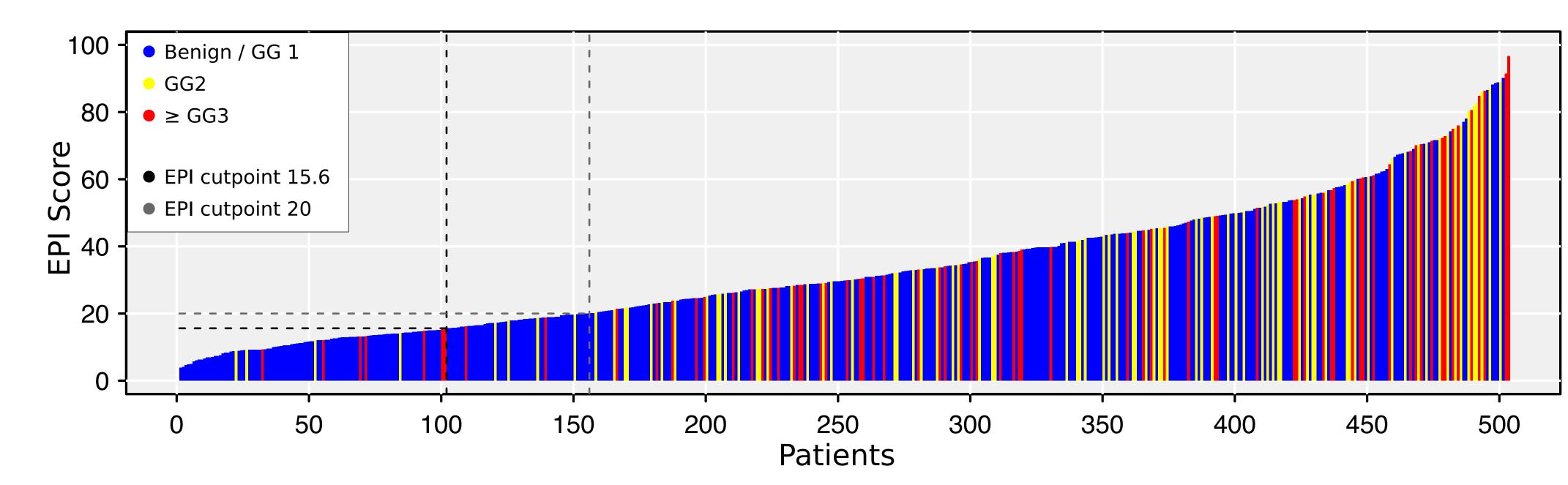


Figure 3: Area Under Receiver Operating Characteristic (AUC) curves are shown to compare performances of the ExoDx™ *Prostat(IntelliScore)* (EPI) in the 2<sup>nd</sup> validation cohort (N=503) and the 1<sup>st</sup> validation cohort (N=519) with the standard of care model (SOCm, e.g. PSA, age, race and family history), PCPT / ERSPC risk calculators and PSA alone.





**Figure 4**: Waterfall plot of EPI scores in relation to prostate biopsy outcomes across cohort (A) (N=503). EPI scores are shown on y-axis, patients on x-axis and the Grade Group biopsy results is shown color-coded (Figure legend and Table 2). Validated (15.6, black) and alternative (20, gray) cutpoints for patient stratification are shown as dashed lines.

| Table 2: Histological Definition of New Grading System |        |         |         |         |                     |     |
|--|--------|---------|---------|---------|---------------------|-----|
| Grade Group (GG)                                       | Benign | 1       | 2       | 3       | 4                   | 5   |
| Gleason Score (GS)                                     | Benign | 6 (3+3) | 7 (3+4) | 7 (4+3) | 8 (4+4) (5+3) (3+5) | ≥ 9 |

### **Conclusion:**

EPI is a non-invasive, easy to use, world's first exosome based 3-gene expression urine assay, which:

- has been validated in >1000 patients with PSA 2-10ng/mL
- discriminates high-grade (≥GG2) from low-grade (GG1) PCa and benign disease
- accurately identifies patients with higher grade disease
- reduces the total number of unnecessary biopsies

## References:

[1] McKiernan J, Donovan MJ, Margolis A, Partin A, Carter B, Brown G, Torkler P, Noerholm M, Skog J, Shore N, Andriole G, Etzioni R, Thompson I, Carroll P (2018) A prospective adaptive utility trial to validate performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer in patients with PSA 2-10 ng/mL at initial biopsy. *European Urology*, Manuscript submitted

[2] 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.

[3] 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.

