**Development and validation of novel genomic classifiers for prediction of adverse pathology after prostatectomy**

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**Objectives:** To develop and validate novel molecular biomarker signatures to predict adverse pathology (AP) after radical prostatectomy (RP).

**Methods:** We developed two classifiers specifically aimed at predicting 1) high-grade disease and 2) AP using CAPRA-S as an endpoint. For the development of the Grade Group (GG) classifier, we queried the expression profiles of 967 high-risk prostate cancer (PCa) patients who underwent RP from the genomic resource information database (GRID™) using primary pattern 4 or higher as the endpoint. For the development of the high-grade disease (HGD) classifier, we used the expression profiles of 425 high-risk PCa patients who underwent RP at Mayo Clinic to predict a CAPRA-S score ≥7 vs ≤4. Validation cohorts consisted of two sets: 1) RP cohort consisting of 2,092 consecutive RP specimens from 285 centers that were part of the Decipher GRID program from 2015-2016 and 2) Biopsy (Bx) cohort consisting of 107 biopsy specimens from 4 academic institutions. The GG classifier was trained using a deep neural network model with 3 hidden layers consisting of 79 genes using the "h2o" package in R v3.1. The HGD classifier was based on an elastic net algorithm consisting of 109 genes. Both of these models generate scores from 0 to 1 with higher scores indicating greater risk of disease. To validate the classifiers, we defined the AP endpoint as having either pT3b or higher **or** lymph node invasion. Discrimination performance of the classifiers was evaluated via the c-index and logistic regression.

**Results:** On the RP validation cohort, the GG and HGD classifiers had c-indices of 0.68 (0.65-0.71) and 0.71 (95% confidence interval [CI] 0.69-0.74) for prediction of AP endpoint, respectively. On the Bx cohort, the GG and HGD classifiers had c-indices of 0.80 (95% CI 0.70-0.90) and 0.82 (95% CI 0.71-0.92), respectively, for the prediction of AP. On multivariable analysis using the Bx validation cohort, adjusting for CAPRA, the HGD classifier had an odds ratio of 1.57 (95% CI 1.18-2.26) compared to 1.63 (95% CI 1.14-3.15) for the GG classifier, per 10% increase in score for AP prediction.

**Conclusions:** GG and HGD classifiers were both predictive of adverse pathology on RP using two validation cohorts of Bx and RP specimens with high accuracy. This independent genomic profiling of tumors at diagnosis may help optimize treatment selection for physicians and patients and ultimately lead to improved oncologic outcome.

**Conflict of Interest:** HA, NE, QW, ZH, VC, KY, ED are employees of GenomeDx Biosciences. FA, AER, and EAK have consulted for GenomeDx Biosciences. EAK has consulted for Genomic Health, Inc. RD has research funded by GenomeDx Biosciences.

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