High-throughput computational assessment of clinically relevant prostate cancer genetic phenotypes using AI analysis of H&E whole slide images

Oakley, J[1]. Goldfinger MH[1], Millar EKA[2], Rothrock B, Lee MCH[1], Wang YK[1], van Eck A[1], Trlifaj Tydlitatova L.[1], Burza M[1], Kunz J[1], Sue J[1], Stefanelli J[1], Retamero J[1],Hamilton P[1], Fuchs TJ[1], Klimstra D[1]

1. Paige AI., 11 Times Sq, New York, NY 10036, USA 2. Department of Anatomical Pathology, NSW Health Pathology, St George Hospital, Sydney, Australia

Background:

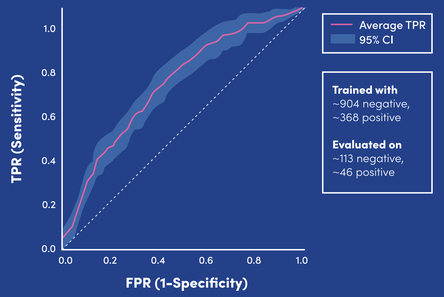
Prostate cancer is the second most diagnosed cancer and the fifth leading cause of cancer death among men worldwide, with global rates projected to rise over the next thirty years. Prostate cancer is driven by a range of molecular alterations including loss of heterozygosity, hypermethylation, activating and inactivating mutation of key genes, chromosomal loss or gain, and gene amplification. These alterations are commonly assessed for clinical uses ranging from prognostic to therapeutic response prediction using single or multi-gene assays, which often take weeks and come at high cost. Previous studies using machine learning methods have identified histologic phenotypes of single genomic alterations using the H&E image alone, with variable performance. We demonstrate that a deep learning model can be trained to identify genomic features hidden in scanned H&E whole slide images of prostate cancer biopsies.

Methods:

This model is trained to classify alterations defined by the MSK Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay for abnormalities in 16 genes *(AR, RB1, TP53, PTEN, JAK1, ELOC, APC, CTNNB1, CDK12, KMT2C, KMT2D, ZFHX3, FOXA1, BRCA2, SPOP, PIK3CA)* with published clinical relevance in prostate cancer. The algorithm operates by first identifying localized image tiles containing cancer using an FDA approved detection algorithm (Paige Prostate). These tiles are then processed by a convolutional neural network to extract 512-dimensional feature embeddings that are further aggregated into a slide-level classification for each genomic marker. 8-fold cross validation was used, where the whole dataset was split into 8 folds with a 6:1:1 ratio between the train, tune, and test sets, respectively.

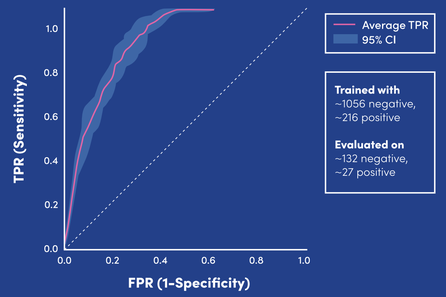
TP53 (mutation)

AUC: 0.69 [0.64-0.74]



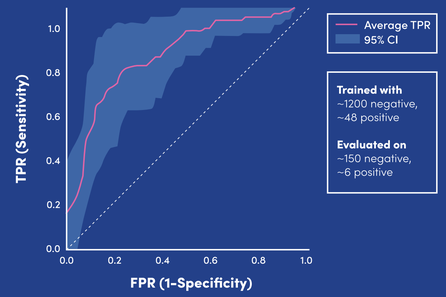
AR (amplification)

AUC: 0.86 [0.83-0.89]



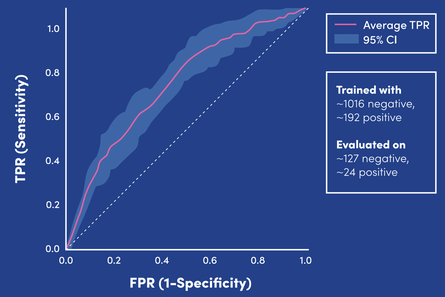
RB1 (deletion)

AUC: 0.81 [0.69-0.93]



PTEN (deletion + loss)

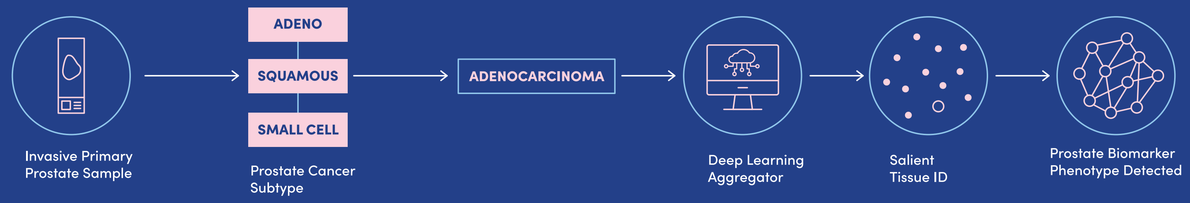
AUC: 0.68 [0.62-0.74]



Results:

We demonstrate the ability of this model to rapidly screen for a discriminating morphologic signal in multiple clinically significant genes. Of the 16 genes screened digitally, results were seen with particularly strong signal for detection of *AR amplification*, *TP53 mutation*, and *RB1* and *PTEN deletion*, with AUCs of 0.86 [95% confidence interval (CI): 0.83-0.89], 0.69 [95% CI: 0.64-0.74], 0.81 [95% CI: 0.69-0.93], 0.68 [95% CI: 0.62-0.74] respectively. The potential signals in the other 12 genes warrant further investigation with alternate approaches.

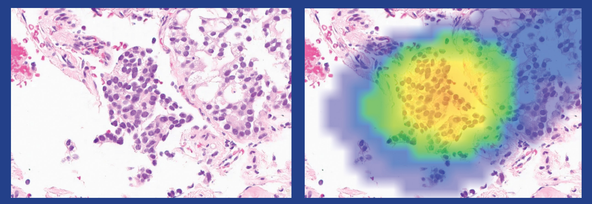
Prostate Biomarker Model Development



Results of Screening for Key Genomic Alterations

Gene	AUC [CI]	N	Mutation Type
JAK1	AUC: 0.74 [0.58-0.90]	Trained: 1290 negative, 48 positive Evaluated: 150 negative, 6 positive	Deletion and SNV
ELOC	AUC: 0. 69 [0.63 -0.75]	Trained: 1104 negative, 48 positive Evaluated: 138 negative, 6 positive	Amplification
APC	AUC: 0.66 [0.52-0.80]	Trained: 1208 negative, 72 positive Evaluated: 151 negative, 9 positive	Mutation
CTNNB1	AUC: 0.65 [0.53-0.78]	Trained: 1200 negative, 56 positive Evaluated: 152 negative, 7 positive	Mutation
CDK12	AUC: 0.58 [0.50-0.64]	Trained: 1200 negative, 56 positive Evaluated: 150 negative, 7 positive	Mutation
KMT2C	AUC: 0.59 [0.49-0.69]	Trained: 1200 negative, 48 positive Evaluated: 150 negative, 6 positive	Mutation
KMT2D	AUC: 56 [0.44-0.69]	Trained: 1200 negative, 80 positive Evaluated: 150 negative, 10 positive	SNV and deletion
ZFHX3	AUC: 0.60 [0.51-0.69]	Trained: 1120 negative, 40 positive Evaluated: 140 negative, 5 positive	Mutation
FOXA1	AUC: 0.59 [0.51-0.67]	Trained: 112 negative, 104 positive Evaluated: 139 negative, 13 positive	Mutation and deep deletion
BRCA2	AUC: 0.59 [0.46-0.62]	Trained: 1200 negative, 48 positive Evaluated: 150 negative, 6 positive	Mutation and loss
SPOP	AUC: 0.55 [0.49-0.61]	Trained: 1136 negative, 136 positive Evaluated: 142 negative, 17 positive	Mutation
PIK3CA	AUC: 0.53 [0.34-0.72]	Trained: 1200 negative, 40 positive Evaluated: 150 negative, 5 positive	Mutation and amplification

Detection of AR Amplification Signal Localized to Tumor Cells



Conclusion:

This study demonstrates a method for rapid screening for association of tumor morphology on H&E with clinically relevant gene abnormalities, enabling the potential for multiplex screening of cases for abnormalities, either for direct clinical predictions or cost- and time-efficient triage to definitive molecular testing for patient care stratification.

Paige