Homologous Recombination Deficiency is Detectable from H&E Whole Slide Images in Real World Prostate Needle Core Biopsies

Abbas A Rizvi[1], Kunal Nagpal[1], Isabelle Hu[1], Rohan Joshi[1], Geoffrey Schau[1] , Rachel Baits[1], Yoni Muller[1], Martin C Stumpe[1], and Nike Beaubier[1]

[1]Tempus Labs, Inc., Chicago, IL // **Disclosure:** All authors are employees of Tempus Labs, a for-profit company // **Correspondence:** abbas.rizvi@tempus.com

TEMPUS

INTRODUCTION

Homologous recombination deficiency (HRD) is an important molecular phenotype given the development of targeted treatments for HRD+ tumors. While HRD is routinely assessed in breast and ovarian cancer, prostate cancer patients with alterations in homologous recombination repair (HRR) genes may also benefit from targeted therapy.[1] Here, we applied weakly supervised deep learning to predict HRD status from hematoxylin and eosin (H&E) stained whole-slide images (WSIs) in prostate cancer as a potential screening assay for confirmatory sequencing.

METHODS

Real world prostate cancer tumor biopsy and resection specimens were collected. Each sample included: 1) clinical characteristics, 2) molecular profiles via DNA/RNA sequencing, and 3) digitized WSI data. The ground truth HRD status for each WSI was generated from an analytically validated commercial assay that relies on RNA expression.[2] An attention-based, multiple instance learning network with ResNet-18 backbone was trained to predict HRD status from WSIs. All WSIs (N=2980, HRD+ 8.7%) were randomly split for five-fold cross-validation, with each split using 60% for training (N=1788), 20% for validation (N=596), and 20% for testing (N=596). Data split was stratified by HRD status, scanner, and procedure type. The dataset included biopsies and resections scanned on either Leica GT450 or Philips UFS instruments.

	HRD+, n = 260	**HRD-**, n = 2720
Procedure Type		
Biopsy	30	316
Core needle biopsy	129	1314
Excisional biopsy	2	12
Surgical resection	85	935
Unknown	14	143
Gleason Score		
7	17	436
8	27	408
9	119	1049
10	32	131
Unknown	65	696
Scanner Type		
leica_gt450	198	2130
philips_ufs	62	590

Table 1. Cohort characteristics. Distribution of procedure type, gleason score, and scanner type of the study cohort.

SUMMARY

- An imaging-based model **predicts RNA-based HRD status** and BRCA double-hit mutations **from routine H&E images**.
- This low-cost and rapid detection capability could **help to prioritize tissue for confirmatory molecular testing** and better identify populations that may benefit from existing therapies or clinical trial enrollment eligibility.

RESULTS

Our model robustly predicts RNA-based HRD status across the cross-validation test sets

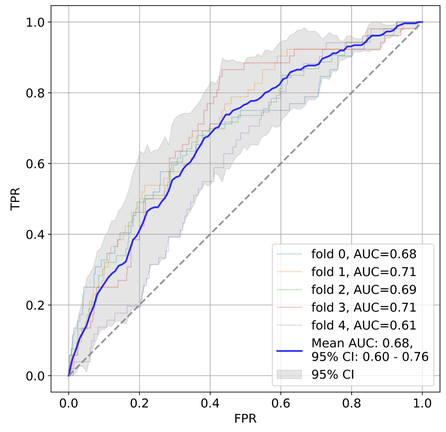

Figure 1. Receiver operating characteristic (ROC) curves for the five cross-validation models (thin, light-colored lines), the mean ROC curve (bold line), and the 95% confidence interval (CI, shaded area) for predicting HRD status. The legend shows the area under the ROC curve (AUC) for each of the curves. The average AUC is 0.68, 95% CI: [0.60, 0.76].

Sensitivity	40%	60%	80%
PPV	16.4%	14.4%	12.1%

Table 2. Positive predictive values (PPV) at various sensitivity levels, which are all above the underlying prevalence of 8.7%

Visualization of high-attention HRD+/HRD- tiles provides insight into features selected by the model

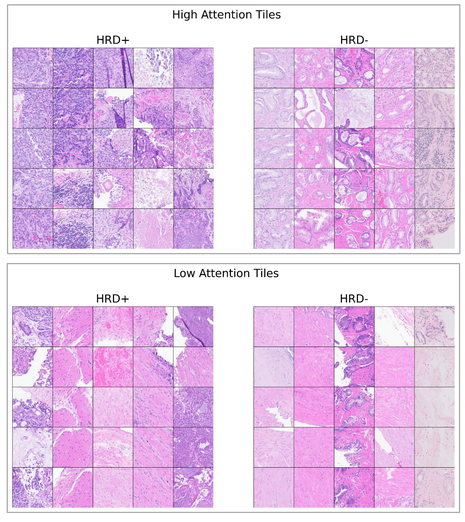

Figure 2. Each column shows tiles that were assigned high (top) and low (bottom) attention scores by our model in a WSI in an HRD positive (left) or negative (right) sample. The selected WSIs received the highest prediction scores in the class corresponding to their labels. These findings suggest that our model relies on dense tumor regions in making its predictions and assigns low attention to stroma and smooth muscle tiles.

Acknowledgements: We thank Tempus Scientific Communications for poster review.

Our model is able to effectively stratify patients with BRCA2 double hit mutations

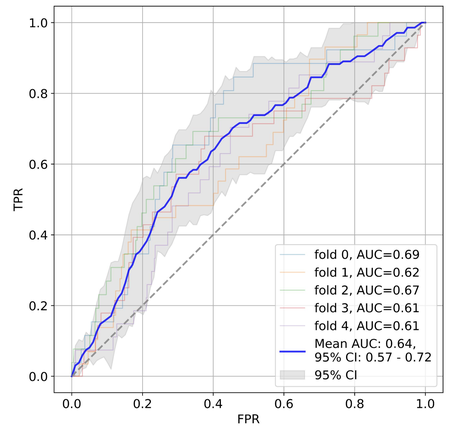

Figure 3. Receiver operating characteristic (ROC) curves for using models trained on HRD labels to predict BRCA2 double hit mutation: five cross-validation models (thin, light-colored lines), the mean ROC curve (bold line), and the 95% confidence interval (CI, shaded area). The legend shows the area under the ROC curve (AUC) for each of the curves. The average AUC is 0.64, 95% CI: [0.57, 0.72].

References:
1. Nizialek E, Antonarakis ES. PARP inhibitors in metastatic prostate cancer: evidence to date. Cancer management and research. 2020;12:8105.
2. Leibowitz BD, et al. Validation of genomic and transcriptomic models of homologous recombination deficiency in a real-world pan-cancer cohort. BMC cancer. 2022 May 28;22(1):587.