Deep Learning AI Predicts HRD and Platinum Response from Histologic Slides

Erik N. Bergstrom Ph.D.[1-3], Ammal Abbasi B.S.[1-3], Marcos Díaz-Gay Ph.D.[1-3], Loïck Galland Ph.D.[4-7], Sylvain Ladoire M.D.[4-7], Scott M. Lippman M.D.[1*], Ludmil B. Alexandrov Ph.D.[1-3*, **]

Affiliations

[1]Moores Cancer Center, UC San Diego, La Jolla, CA, 92037, USA; [2]Department of Cellular and Molecular Medicine, UC San Diego, La Jolla, CA, 92093, USA; [3]Department of Bioengineering, UC San Diego, La Jolla, CA, 92093, USA; [4]Department of Medical Oncology, Centre Georges-François Leclerc, Dijon, France; [5]Platform of Transfer in Biological Oncology, Centre Georges-François Leclerc, Dijon, France;[6]University of Burgundy-Franche Comté, France; [7]Centre de Recherche INSERM LNC-UMR1231, Dijon, France

*Drs. Lippman and Alexandrov contributed equally to this article; **Correspondence to Dr. Alexandrov

ABSTRACT

Background: Cancers with homologous recombination deficiency (HRD) can benefit from platinum salts and PARP inhibitors. Standard diagnostic tests, including FDA-approved companion diagnostics, for detecting HRD require molecular profiling, which is not universally available with global testing rates lowest among minority, rural, and other underserved populations.

Methods: We trained DeepHRD, a deep-learning platform for predicting HRD from hematoxylin and eosin (H&E)-stained histopathological slides, using primary breast (*n*=1,008) and ovarian (*n*=459) cancers from The Cancer Genome Atlas (TCGA). DeepHRD was compared to four standard HRD molecular tests using breast (*n*=349) and ovarian (*n*=141) cancers from multiple external and independent datasets, including clinical cohorts with platinum complete response, progression-free survival (PFS) and overall survival (OS) endpoints.

Results: DeepHRD detected HRD from held-out H&E-stained breast cancer slides in TCGA with an AUC of 0.81 ([0.77-0.85]; 95% confidence interval). This performance was confirmed in two independent primary breast cancer cohorts (AUC=0.76; [0.71-0.82]). In an external platinum-treated metastatic breast cancer cohort, samples detected as HRD had a higher complete response (AUC=0.76; [0.54-0.93]) with 3.7-fold increase in median PFS (14.4 versus 3.9 months; p-value=0.0019) and hazard ratio (HR) of 0.45 (p=0.0047) after correcting for PAM50 molecular subtype and age at diagnosis. This deep-learning classifier outperformed four genomic HRD tests used in the clinic, including standard HRD score, *BRCA1/2*, 26-HR gene panel and single-base substitution signature 3 (SBS3). Multiresolution spatial mapping identified morphological features utilized by DeepHRD for detecting HRD, notably enriched for neoplastic and necrotic tissues, and a higher macrophage density. Through transfer learning to high-grade serous-ovarian cancer, DeepHRD-positive samples exhibited better overall survival after TCGA first-line (HR=0.46; p=0.030) and an external neoadjuvant (HR=0.49; p=0.015) platinum-treated cohorts.

Conclusion: In summary, DeepHRD exhibits consistent hazard ratios ranging from 0.45 to 0.49 across the three clinical cohorts and captures 1.8- to 3.1-fold more HRD-positive breast and ovarian cancer patients. DeepHRD-positive breast cancer patients that received platinum exhibited better complete response and PFS. Similarly, DeepHRD-positive platinum-treated ovarian cancer patients had a better OS. DeepHRD's ability to detect HRD from digital H&E slides provides an important precision oncology tool that can be utilized in resource-constrained and underserved areas where genomic testing is generally not existent.