A197 · Timing the onset of homologous recombination deficiency before breast cancer diagnosis

Presenter: Michail Andreopoulos — Department of Biomedical Informatics, Harvard Medical School

Authors: Michail Andreopoulos, Muchun Niu, Yang Zhang, Vinayak V. Viswanadham, Doga C. Gulhan, Hu Jin, Felipe Batalini, Gerburg Wulf, Chenghang Zong, Peter J. Park, Dominik Glodzik

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Mutations in BRCA1 and BRCA2 genes, whether inherited or somatically acquired, cause homologous recombination deficiency (HRD) in tumor cells. The timing of HRD onset in the emerging tumor lineage is unknown. Here, we present HRDTimer, an algorithm to infer the onset of HRD-driven mutagenesis prior to cancer diagnosis. We estimate that HRD arises at 34% of SBS1-based molecular time — corresponding to a median of 8.3 years (IQR 7.1–10.4) prior to diagnosis in triple-negative breast cancers, and 15.0 years (IQR 12.0–20.6) in ER-positive breast cancers. Bulk sequencing reveals accelerated SBS1 accumulation following neoplastic transformation compared to normal tissue, influencing the estimated age of HRD onset. Single-cell duplex sequencing confirms SBS1 acceleration in tumors and further shows that non-tumor cells largely lack the HRD signature, indicating that HRD is rare in pre-malignant cells, even in BRCA1/2 mutation carriers. Together, our analysis pinpoints the onset of HRD before diagnosis, defining a window for detection and potential interception.