

## **Deciphering Signatures of Broken DNA Repair Pathways in Long-range Cancer Whole Genome Sequences**

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Abstract: DNA repair pathway defects (homologous recombination, mismatch repair) play a key role in the oncogenesis of many malignancies and may also serve as a biomarker to select anti-cancer therapies. Recent advances in whole genome sequencing (WGS) analysis have made it possible to identify tumor with defective DNA repair by examining the pattern/signature of passenger mutation patterns in tumor DNA. These results suggest that the number of patients harboring actionable DNA repair phenotypes is significantly larger than what can be assessed through the genotyping of specific loci. In this project, we propose to expand the catalogue of mutational signatures associated with specific DNA repair defects through the application of a novel microfluidic-based “linked-read” WGS technology (10X Chromium) that enables the detection of long-range patterns of mutation (also referred to as “phase”) in cancer samples. We will use this technology to profile 40 breast, ovarian, pancreatic, and head and neck cancers arising from patients with known defects in homologous recombination and interstrand- crosslink repair. The work will involve development of innovative computational methodologies to phase complex somatic variants and characterize recurrent mutational patterns associated with specific DNA repair defects. The results will be validated in isogenic cell line models of genome instability and correlated with *in vitro* sensitivity to chemical and radiologic DNA damaging agents. The proposed research has the potential for wide impact on the basic understanding of the mutational signatures associated with DNA repair defects and genomically-informed management of patients with both sporadic and inherited forms of cancer.