MSIPredict: Highly Sensitive Detection of Tumor Derived Cell-free DNA for Cancer Interception in Lynch Syndrome

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Abstract: Lynch syndrome (LS) is a common pan-cancer genetic predisposition syndrome with 80% lifetime risk of cancer, yet effective early-detection screening modalities outside of colonoscopy are not available. A hallmark of LS-associated malignancies is the presence of microsatellite instability (MSI) in tumors related to the underlying DNA mismatch repair defect. Independent but complementary methodologies for reliably detecting MSI in tumors, using ultra-deep targeted and low-pass whole genome next-generation sequencing technologies, have been well-established by study Co-PIs at MSKCC (Berger) and the Broad Institute (Getz). More recently, novel technologies for detecting tumor-derived cell-free DNA (cfDNA) have been developed to track cancer cfDNA for response to cancer treatment, including an innovative, MSK-developed clinically-approved assay.

Here, we will integrate these existing state-of-the-art, orthogonal computational approaches and develop MSIPredict, a highly sensitive/specific MSI-cfDNA assay for the detection of early-stage MSI tumors in LS patients that utilizes deep-targeted and ultra-low-pass whole genome sequencing for MSI detection. We will then use established, clinically well-annotated MSK and WCM LS-patient registries, matched controls and clinical standard-of-care precision medicine LS patient MSI tumor sequencing to delineate MSIPredict sensitivity/specificity in plasma, stool and urine, thereby providing the first steps towards developing a non-invasive, LS pan-cancer surveillance assay for this high cancer-risk patient population.