Evaluation of a multi-omics approach to molecular residual disease detection.

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Background & objectives

Background: Tumor-Informed (TI) MRD strategies utilize mutations from the tumor to define a set of patient-specific markers that are tracked in blood as circulating tumor DNA (ctDNA). Whereas tumor-naïve (TN) approaches search for a fixed marker(s) set. Methylated DNA Markers (MDMs) are one such approach to TN cancer detection. We are developing proprietary TN and TI MRD platforms for colorectal cancer (CRC) based on quantification of MDM and plasma proteins and targeted DNA sequencing, respectively.

Objective: We sought to evaluate and characterize the performance of TI and TN assays under development, individually and in combination, in an exploratory cohort of CRC specimens.

Methods

Methods A 20-sample cohort of paired tumor/normal and pre-surgery plasma specimens from stage I (6/20), stage II (7/20), stage III (6/20), and stage IV (1/20) CRC patients and 20 demographically matched non-cancer controls were acquired for our study. The same set of neat and diluted plasma samples were tested with TI and TN assays. Paired tumor/normal exome sequencing identified TI variants for tracking in plasma. Approximately 100 of these variants were sought in plasma using custom enrichment and sequencing assays. MDMs were detected by Target Enrichment Long probe Quantitative Amplified Signal (TELQAS) for 35 MDMs. Proteins were detected by high throughput ELISA. The TN assay employed a cancer detection classifier built from a separate cohort of CRC specimens.

Results

Results: Tumor sequencing of the 20 CRC samples identified between 122 and 7146 (median = 230) somatic mutations per tumor. The combination of features from TI and TN assays achieved 95% accuracy, demonstrating improvement over either assay individually using preliminary cutoffs for "positivity". Indeed, 5 "positive" calls were made for cancer samples for which only one of the two methods met thresholds for ctDNA detection. Comparison of median variant allele fraction from the TI assay with median percent methylation of CRC markers for these CRC samples had a Pearson's correlation of 0.967.

Conclusion

Conclusion: TI and TN assays show high concordance in cancer detection, but also complement each other. Additionally, ctDNA quantifications produced from TI and TN assays are linearly correlated.