The Era of Liquid Biopsy Biomarkers and Precision Medicine in Gastrointestinal Cancers

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Cancer has emerged as a leading cause of mortality worldwide, claiming over 8 million lives annually. Among all cancers, gastrointestinal (GI) cancers (including colorectal, pancreatic, gastric, esophageal, and liver) account for ~35% of these mortalities. Recent advances in diagnostic and treatment strategies have reduced mortality among patients with GI cancers. Yet, many patients still develop late-stage diseases when treatment options are limited and less effective. Most GI cancers initiate and develop as a result of the accumulation of a series of genomic and epigenomic alterations which lead to the transformation of normal epithelial cells into invasive cancer – a process that can take up to 15-20 years to develop, from the occurrence of the first initiating molecular alteration. These facts highlight a unique window of opportunity for the earlier detection of GI cancers, allowing timely disease interception and improving overall survival outcomes in patients suffering from these fatal malignancies.

In this regard, various types of molecular biomarkers have been explored as potential options for early cancer detection, disease prognosis, and predictive biomarkers that can provide the probability of therapeutic response to specific therapies or disease relapse. While this list of molecular markers continues to grow, in the context of early-detection markers or markers for disease monitoring when the neoplastic tissues have been surgically removed, the majority of the focus has been on the development of non-invasive liquid biopsy markers that can be readily assayed in bodily fluids including blood, urine, and stool. In contrast, most of the prognostic and predictive biomarkers have heavily relied on the analysis of surgically resected tissues in patients before the implementation of adjuvant chemotherapy.

Among various categories of molecular assays, the major categories of analytes involve the analysis of cell-free tumor DNA (ctDNA) for mutational analysis of specific gene(s) and the interrogation of epigenetic DNA methylation patterns, as well as the analysis of various transcriptomic markers including expression of mRNAs and various categories of small non-coding RNAs (ncRNAs) that have been recognized to play a central role in the pathogenesis of

various GI cancers. While there is much interest in developing these cell-free DNA and RNA markers, most of them are still in relatively early stages of development but have intriguing leads and promise for their future development. While the mutational and methylation analysis is quite specific, the challenge remains the need for more sensitivity of these assays due to the limited quantities of ctDNA in the systemic circulation. In contrast, the analysis of cell-free RNAs is quite robust; their tissue-of-origin and specificity remain debatable. More recent data suggests that interrogation of some of these markers within tumor-derived exosomes or extracellular vesicles in blood might offer an adequate balance between appropriate sensitivity and specificity – which is much needed for a given biomarker before its adaption in the clinic. This presentation will provide a summary and an update on where this field currently stands and discuss the enthusiasm and excitement behind developing potential diagnostic, prognostic, and predictive biomarkers for various GI cancers as we usher into the era of precision medicine.