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Methylated ctDNA as a biomarker for detecting previously undetectable clinically significant somatic mutations.

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Background: Treatment selection liquid biopsies can be re-run upon clinical progression to identify the new clinically significant somatic mutations that might be contributing to resistance to therapy or that can help guide the selection of an alternative therapy. However, there are not currently any biomarkers or tests that suggest an increased likelihood for the detection of new, i.e. previously undetected, clinically significant somatic mutations in a subsequent treatment selection liquid biopsy assay.

Methods: We explored whether a methylation-based liquid biopsy could indicate when new clinically significant alterations are more likely to be detected in a treatment selection liquid biopsy. As part of a retrospective study of metastatic lung cancer patients (N = 75 new treatment starts), both a treatment selection assay and a therapy monitoring methylation assay were performed on plasma collected pre-treatment for a subset of patients that underwent at least two separate treatment regimens. By quantifying the number of methylated ctDNA molecules at > 500 genomic locations, the methylation assay assessed the total burden of methylated ctDNA (represented as tumor methylation score), as well as the percent of methylated molecules originating from newly methylated genomic loci, representing a change in the methylation profile. **Results:** When the methylation assay detected at least a 2x increase in the tumor methylation score, indicating a significant increase in the fraction of ctDNA present in the patient's blood, new clinically significant somatic mutations (including actionable ERBB2 alterations) were found 83% of the time. This appeared to be more frequent than among patients without an increase in tumor methylation score, where new clinically significant somatic mutations were found 33% of the time. Importantly, when the increase in the methylation score was coupled with a significant change in the methylation profile, new clinically significant mutations were identified in 100% of patients. **Conclusions:** The preliminary data suggests that an overall increase in methylated ctDNA, in combination with a significant change in methylation profile, is correlated with detecting new, previously undetected clinically significant somatic mutations in a treatment selection assay. Leveraging this methylated ctDNA assay may inform clinicians as to when to run another treatment selection assay, thereby potentially identifying the appearance of clinically significant somatic mutations which could influence clinical decision making and affect patient clinical outcomes. Research Sponsor: BillionToOne, Inc.