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Analytical validation of a novel circulating tumor DNA detection platform for targeted and immunotherapy selection

Short Title:
Novel ctDNA detection platform

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Abstract:
Introduction Comprehensive genomic profiling of solid tumors using circulating tumor DNA (ctDNA) has enabled the detection of all NCCN guideline-recommended somatic genomic classes of alterations from a single, non-invasive blood draw. However, current ctDNA tests still face two major challenges: the inability to reliably identify somatic variants at low mutant allele fraction (MAF), and inconsistency in how the tests have been validated. This study shows how the Single Molecule Sequencing (SMSEQ) platform addresses these challenges. The platform integrates innovative ctDNA extraction methodology, highly optimized library preparation and an error-based variant-calling algorithm to drastically improve sensitivity and specificity. The platform analyzes 5 classes of somatic variants: single nucleotide variants (SNVs), insertions and deletions (Indels), copy number variants (CNVs), fusions and microsatellite instability (MSI). **Methods** We analyzed a 73 gene panel covering NCCN recommended actionable variants for solid tumors in 60 reference ctDNA samples with known variants to establish the limit of detection, sensitivity, specificity, accuracy and reproducibility of the SMSEQ platform. For clinical validation, we tested 36 patients with metastatic colorectal cancer (mCRC) and 34 healthy controls from the Chang Gung Memorial Hospital, and 227 patients diagnosed with solid tumor from Taiwan. Circulating DNA was extracted from plasma followed by library preparation using a highly optimized NGS workflow. Somatic variants in ctDNA are identified using locus-specific modeling to separate tumor variants from normal errors. **Results** Validation according to recently published ACMG/AMP guidelines shows that the SMSEQ platform allows calling of variants with >99.999% analytical specificity for SNVs, Indels and fusions; and >99% analytical specificity for CNVs and MSI. The platform successfully detected variants at low MAF: 0.1% for SNVs and Indels, <1% for fusions, 5 copies for CNVs, and 1% for MSI. Somatic variants were identified in 35 of 36 mCRC patient samples (97.2%). No false positives were observed within the targeted region for all 34 healthy controls tested. In paired samples, the SMSEQ platform showed 89.7% concordance with tissue biopsy. Observed gene mutation profiles from ctDNA were consistent with published tissue biopsy data: the most frequently mutated genes were *TP53, APC,* and *KRAS*; KRAS and BRAF variants were mutually exclusive. In addition to mCRC patients, we tested 227 patients diagnosed with various solid tumors from Taiwan. Actionable variants were detected in 170/227 (75%) patients. **Conclusion** The CellMax 73-gene liquid biopsy test detects 5 NCCN-guideline recommended variant classes: MSI for immunotherapy and SNVS, Indels, CNVs, and fusions for targeted therapy selection at low variant allele fraction/copy number at high sensitivity and specificity.
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Author Disclosure Information:

P. Gupta: ; CellMax Life. **J. Lucas:** ; CellMax Life. **A. Atkins:** ; CellMax Life. **W. Tsai:** None. **T. Marfatia:** ; CellMax Life. **S. Chang:** ; CellMax Life. **O. Segurado:** ; CellMax Life. **R. Mei:** ; CellMax Life.
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