Clinical validation of the Northstar Response: A novel quantitative methylation ctDNA monitoring assay for advanced GI cancer treatment response.

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Background: Circulating tumor DNA (ctDNA) is a promising tool for monitoring treatment response but is challenged by pan-cancer quantification and consistent outcome correlations. Northstar Response (NSR) quantifies >500 cancer specific methylated loci, offering a reflection of disease burden and clinical response. **Methods:** We present a prospective observational study to evaluate the clinical utility of NSR. Patients with advanced GI cancers had serial ctDNA assessed at baseline and during systemic treatment with correlations to radiographic or clinical response. Tumor methylation scores (TMS) were expressed as Log10 values and a mixed-effects model evaluated clinical assessment correlations. **Results:** 73 patients with locally advanced or metastatic GI cancers were analyzed. Among these, 35 (47.9%) had at least four ctDNA assays and all had radiographic or clinical response assessments. The median age was 66 years (± 8.5), with most being male (67.1%) and White (74.0%). Table 1 shows the case distribution. Baseline TMS had significant variation (p=0.023), but was measurable across all tumor types. CRC exhibited the highest mean TMS-log10 while biliary and pancreatic cancers had the lowest. Cases with both primary and metastatic lesions had a higher mean TMS-log10 than cases with either primary tumors alone or metastatic lesions alone (3.4 vs. 3.0). Compared to stable and responsive disease, TMS changes correlated with progressive disease, with a coefficient of 0.48 at the third collection time point (p=0.05). However, 23/73 (32%) cases were without an on-treatment TMS timepoint (OTT) due to rapid progression (average time to death of 24 vs. 103 days for patients with OTT). In exploratory modeling of TMS relative to RECIST-like treatment response for those with OTT, NSR evaluations were associated with response assessments (p<0.04, Fisher's Exact Test). **Conclusions:** TMS was consistently measurable but varied across tumor types and correlated with disease burden. TMS changes appeared associated with response assessments when accounting for rapid progressors. Additional analyses are ongoing and will be presented. Research Sponsor: BillionToOne, Inc.; University of Florida Health Cancer Center; P30CA247796.

Baseline study cohort characteristics.

Characteristic	HCC N = 25 (34%)	BTC N = 12 (16%)	EGA N = 12 (16%)	CRC N = 11 (15%)	PDAC N = 8 (11%)	Other GI N = 5 (7%)	p-value
Age Median (25% to 75%)	67 (63 - 76)	68.5 (62.3 – 75.5)	73.5 (62.5 – 75.3)	54 (39.5 – 60)	67.5 (55.5 – 76.3)	60 (57 – 63)	0.008
Baseline TMS Log10 Median (25% - 75%)	3.2 (2.3 – 3.9)	2.5 (2.1 – 3.4)	3.2 (2.2 – 3.8)	4.4 (3.5 – 5)	2.5 (1.9 – 3.3)	4 (3.4 – 5.2)	0.023
Primary tumor present	12 (48%)	8 (66.7%)	12 (100%)	6 (54.5%)	7 (87.5%)	4 (80%)	0.015
First line therapy vs. not	23 (92%)	5 (41.7%)	5 (41.7%)	6 (54.5%)	3 (37.5%)	5 (100%)	0.001
Progressive disease	16 (64%)	4 (33.3%)	9 (75%)	5 (45.5%)	3 (37.5%)	4 (80%)	0.2
Death	13 (52%)	3 (25%)	9 (75%)	7 (63.6%)	3 (37.5%)	2 (40%)	0.2

Kruskal-Wallis rank sum test; Fisher's exact test.