Supplementary Figure 1A.

The ctDNA panel (Guardant360™) utilized here employs digital sequencing to detect mutations in 73 genes. Whole gene sequencing is performed in 19 cancer genes, critical exons coverage in 54 genes and amplifications (18 genes), fusions (6 genes) and indels (23 genes).

Supplementary Figure 1B

Digital Sequencing-based ctDNA assay workflow.(**a**) cfDNA is extracted from stabilized peripheral whole blood, (**b**) labeled with oligonucleotide barcodes at high efficiency, and (**c**) up to 30ng is used for library preparation. (**d**) Sequencing libraries are enriched using hybrid capture and sequenced to an average depth of ~15,000x. (**e**) Individual unique input molecules are then bioinformatically reconstructed using barcode and sequence data to suppress analytical error modes. (**f**) Somatic variants are deconvoluted from germline and reported by clinical priority with both treatment and clinical trial annotations.

Supplementary figures 2A and 2B

Copy number plots from two pre-treatment HERACLES A samples. X axis represents chromosome (chr) number across the Guardant360 genomic footprint. Y axis represents observed copy number in plasma. Colored dots represent probe-specific copy number signals at each chromosomal position and light green horizontal line represents the sample-specific normalized diploid copy number. The 18 reported gene amplifications are labelled, including *ERBB2* on chromosome 17. The sample represented in panel 2A is suggestive of chromosome 17 aneuploidy, as all 5’ probe specific signals adjacent to and including *ERBB2* are increased (*ERBB2* observed pCN = 52.8). In contrast, panel 2B shows clear focal amplification of *ERBB2* only (*ERBB2* observed pCN = 7.7).

Supplementary figure 3

Correlation between pCN and tumor fraction in plasma where z=((2\*(1-x))+(y\*x)), and x is set from 0 to 100% as tumor fraction. Centiles of *ERBB2* pCN in the Guardant Health database were as follows: copy number <2.4 (<50th percentile), >2.4 but < 4 (50th-90th percentile), and >4.0 (≥90th percentile).

Supplementary figure 4

*ERBB2* pCN (pCN), RAS/RAF status and maximum mutant allele fraction (Max MAF) in 4,294 plasma samples from mCRC patients in the Guardant Health historical database. An observed pCN cutoff of 2.4 (>50th %ile) allowed for exclusion of 84% of all *KRAS, NRAS*, and *BRAF* driver mutations in the historical cohort. Dark blue dots - *ERBB2* amplified and clonal RAS/RAF mutation positive; Light blue dots *ERBB2* amplified and sub-clonal RAS/RAF mutation positive; Red dots – *ERBB2* amplified and RAS/RAF mutation not detected.