Detection rate for *ESR1* mutations is significantly higher in CTC-derived gDNA than in paired plasma-cfDNA samples as revealed by ddPCR

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Plasma-cfDNA analysis to track *ESR1* mutations is highly beneficial for the identification of tumor molecular dynamics and the improvement of personalized treatments for patients with metastatic breast cancer (MBC). Plasma-cfDNA is established up to now as the most frequent liquid biopsy analyte to evaluate *ESR1* mutational status. CTCs enumeration and molecular characterization analysis provides important clinical information in patients with MBC. In this study, we investigated whether analysis of CTCs and ctDNA provide similar or complementary information for the analysis of *ESR1* mutations. We analyzed both plasma-cfDNA (n=90) and paired CTC-derived gDNA (n=42) from 37 MBC patients for seven *ESR1* mutations. Eight out of 90 (8.9%) plasma-cfDNA samples, tested using the ddPLEX Mutation Detection Assay (Bio-Rad), were found positive for one *ESR1* mutation, while 11/42 (26.2%) CTC-derived gDNA samples were found positive for at least one *ESR1* mutation. Direct comparison of paired samples (n=42) revealed that the mutation rate for *ESR1* mutations was higher in CTC-derived gDNA (11/42, 26.2%) than in plasma-cfDNA samples (6/42, 14.3%), (Concordance: 31/42 (73.81%), $p<0.152$, chi-squared test). Our results, using this highly sensitive ddPLEX assay, reveal a higher percentage of mutations in CTC-derived gDNAs than in paired ctDNA in patients with MBC. CTC-derived gDNA analysis should be further evaluated as an important and complementary tool to ctDNA for identifying patients with *ESR1* mutations and for guiding individualized therapy.