SUCCESS

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Circulating tumor DNA (ctDNA) as a strong prognostic biomarker of minimal residual disease (MRD) using a tissue-free, epigenomic assay in early-stage breast cancer

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Background

ctDNA may serve as an early biomarker of recurrence and could facilitate identification of patients with asymptomatic distant metastasis who might benefit from early treatment intervention. Here, we utilized a tissue-free, epigenomic assay for the detection of ctDNA in patients with early-stage breast cancer.

Methods

Whole blood samples were collected in EDTA tubes from patients with stage I-III breast cancer who were enrolled in the SUCCESS-A phase 3 clinical trial (NCT02181101) between 2005 and 2007. All patients received adjuvant chemotherapy +/- endocrine therapy and/or anti-HER2 therapy. Samples were collected approximately two years after completion of adjuvant chemotherapy, and plasma samples selected for analysis were from patients without evidence of disease recurrence prior to sample collection. Plasma was isolated according to the manufacturer's protocol and stored at -80°C. Plasma samples were analyzed for the presence of ctDNA using Guardant Reveal which evaluates the epigenomic signals associated with cancer versus normal DNA for the detection of ctDNA. An analytically validated bioinformatics pipeline was used for the detection of breast cancer ctDNA. Guardant Reveal additionally reports a methylation-based tumor fraction (TF) in ctDNA detected samples (see Figure 1). Samples were analyzed blinded to the clinical data. The prognostic significance of ctDNA was evaluated by analyzing distant recurrence-free interval (D-RFI), recurrence-free interval (RFI), and overall survival (OS) from the time of sample collection. Median survival times were estimated using the Kaplan-Meier method and hazard ratios were calculated based on univariable cox regression models.

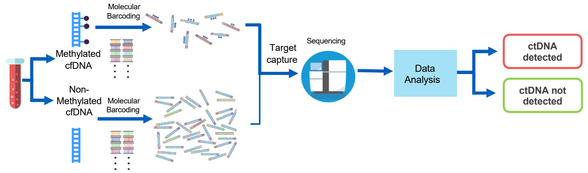


Figure 1: Guardant Reveal Assay Workflow

A "ctDNA detected" result is defined by the de novo identification of tumor-specific contribution to methylation profile exceeding predefined thresholds.

Results

A total of 313 samples from 313 patients were evaluable for analysis. Samples were collected at a median of 28 months (range, 15-40 months) post-adjuvant chemotherapy, and patients had a median clinical follow-up of 66 months (range, 31-96 months) from surgery. Table 1 shows baseline patient characteristics. There was a total of 45 disease recurrences: 38 (12.1%) patients had distant metastatic recurrence, and 7 (2.2%) patients had local recurrence or contralateral breast cancer (Table 1).

In the overall cohort, the ctDNA positivity rate at approximately 2 years post-adjuvant chemotherapy completion was 5.8% (18/313). Of the 18 ctDNA detected samples, 94% (17/18) were from patients with a subsequent metastatic recurrence (Figure 2). One patient had ctDNA detected but no recurrence - this patient remained alive and showed no evidence of disease recurrence up to 34 months following the sample collection.

Patients with ctDNA detected compared to those without ctDNA detection had a worse D-RFI (Hazard Ratio [HR] 33.3, 95% Confidence Interval [CI] 4.12-268, P<0.001; Figure 3A), RFI (HR 26.1, 95% CI 3.68-185, P<0.001; Figure 3B), and OS (HR 27.3, 95% CI 1.15-647, P<0.001; Figure 3C).

Table 1: Patient characteristics

	N (%)
Total N	313 (100%)
Age (years)	
<65	258 (82.4%)
≥65	55 (17.6%)
Subtype	
HR+/HER2-	176 (56.2%)
HER2+	71 (22.7%)
TNBC	61 (19.5%)
Other/unknown	5 (1.6%)
Pathological T stage	
pT1	123 (39.3%)
pT2	184 (58.8%)
pT3	3 (1.0%)
pT4	2 (0.6%)
Unknown	1 (0.3%)
Pathological N stage	
Node-negative	108 (34.5%)
Node-positive	203 (64.9%)
Unknown	2 (0.6%)
Tumor grade	
G1	12 (3.8%)
G2	161 (51.4%)
G3	140 (44.7%)
Recurrence	
Distant	38 (12.1%)
Local	7 (2.2%)
None	268 (85.6%)

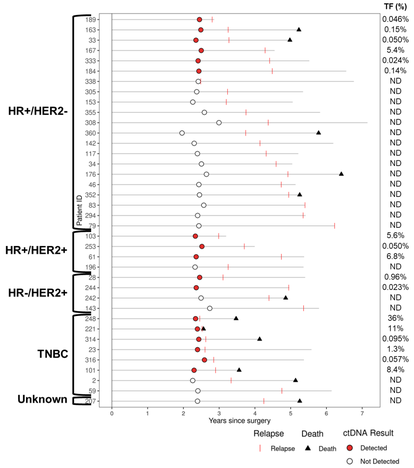


Figure 2. Swimmer plot of all patients with distant metastatic recurrence (n = 38)

The tumor fraction (TF) for ctDNA-positive samples is annotated. ND = ctDNA not detected

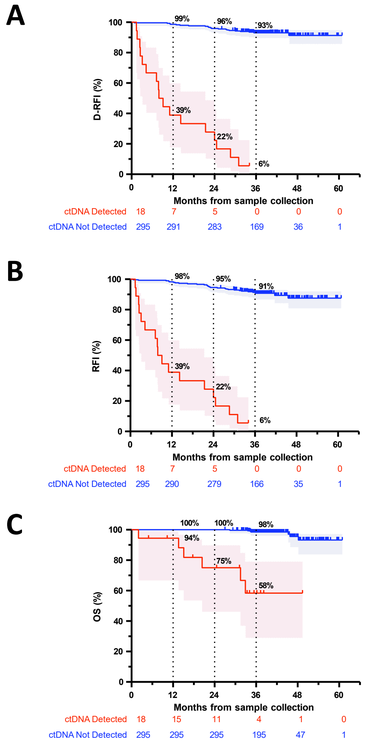


Figure 3: Prognostic Significance of ctDNA

Detection of ctDNA was associated with worse (A) distant recurrence-free survival, (B) recurrence-free survival, and (C) overall survival. 95% confidence intervals are shaded.

Since longitudinal sampling was not available for this study, we estimated the sensitivity for distant recurrence using six-month extension intervals ranging from six months to three years (Figure 4). The overall sensitivity for metastatic recurrence increased as the time interval between the blood sample and disease recurrence decreased (chi-square test for trend P = 0.010).

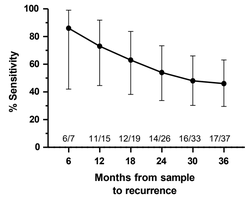


Figure 4. Sensitivity of ctDNA in detecting metastatic recurrence.

Sensitivity for metastatic recurrence by samples collected within defined timing from recurrence (Chi-square test for trend P = 0.010).

Key Findings

- Approximately 6% of patients (18/313) with early breast cancer had ctDNA detected 2 years after completing adjuvant chemotherapy. Detection of ctDNA was associated with over 33-fold increased risk for distant recurrence and over 27-fold increased risk for death (Figure 3).
- Of the 18 ctDNA detected samples, 94% (17/18) were from patients with a subsequent metastatic recurrence.

Conclusion

Tissue-free detection of ctDNA two years after adjuvant chemotherapy was highly prognostic in an early-stage breast cancer cohort. Thus, ctDNA testing can be used to stratify early-stage breast cancer patients at high risk for recurrence during follow-up who may benefit from early interventions.

Acknowledgments

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