Clinical performance of Signatera Genome assay for predicting recurrence in patients with breast cancer

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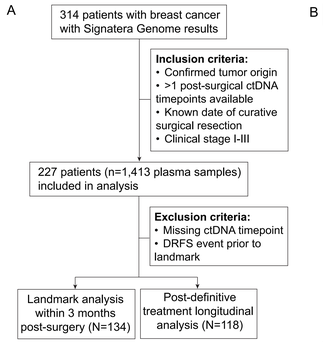
Background

- Circulating tumor DNA (ctDNA) is a clinically validated biomarker in breast cancer for predicting the risk of recurrence, monitoring response to neoadjuvant treatment, and detecting molecular relapse after adjuvant therapy.
- Signatera (Natera, Inc.) is a tumor-informed, multiplex PCR-NGS ctDNA assay that may be developed from a backbone of whole-exome sequencing (WES) or whole-genome sequencing (WGS).
- Early clinical validation of Signatera Genome in a pan-cancer cohort demonstrated improved performance over WES-based Signatera in certain clinical scenarios.
- In this study, we specifically assessed the performance of the Signatera Genome assay in the surveillance setting for breast cancer.

Methods

- A retrospective analysis was performed using clinically annotated residual patient samples from commercial testing with WES-based Signatera.
- Treatment decisions and cadence of ctDNA testing were at the provider's discretion. Blood samples collected longitudinally after surgery were analyzed.
- Signatera Genome assays were designed, consisting of 64 high-quality tumor-specific variants, from matched tumor and normal WGS data, and used to detect ctDNA in the corresponding patients' plasma.
- ctDNA levels were quantified as mean tumor molecules (MTM) per mL of plasma.
- Associations between ctDNA status and dynamics with distant recurrence-free survival (DRFS) and recurrence-free survival (RFS) were evaluated using Cox proportional hazards regression. Firth's penalized likelihood correction was applied when subgroup sizes were fewer than 10 patients and/or when the number of observed events was low.

Figure 1. Patient selection and baseline demographics (N = 227)



B

Characteristic	# Patients (%)
Age in years, median [range]	55 [27-85]
Sex	
Female	226 (99.6%)
Male	1 (0.4%)
Subtype	
Triple negative	139 (61.2%)
HR+/HER2-	86 (37.9%)
HER2+	11 (4.9%)
Stage	
I	50 (22.0%)
II	75 (33.0%)
III	102 (45.0%)
Post-surgery treatment	
Cytotoxic	94 (41.4%)
Non-cytotoxic	60 (26.4%)
None/Unknown	73 (32.2%)
Follow-up in months, median [range]	20 [1.5 54.8]

Figure 1. Patient inclusion and baseline characteristics. A) CONSORT diagram showing patient inclusion in the study and subanalyses. **B)** Patient and tumor characteristics at baseline.

In a cohort of >200 patients with breast cancer (>1400 plasma samples), the Signatera Genome assay demonstrated a clinical sensitivity and specificity of 100% for detecting distant and local relapses

Figure 2. Association of ctDNA status at 3-month landmark timepoint, longitudinal ctDNA status post-definitive treatment, and ctDNA dynamics with distant recurrence-free survival (DRFS)

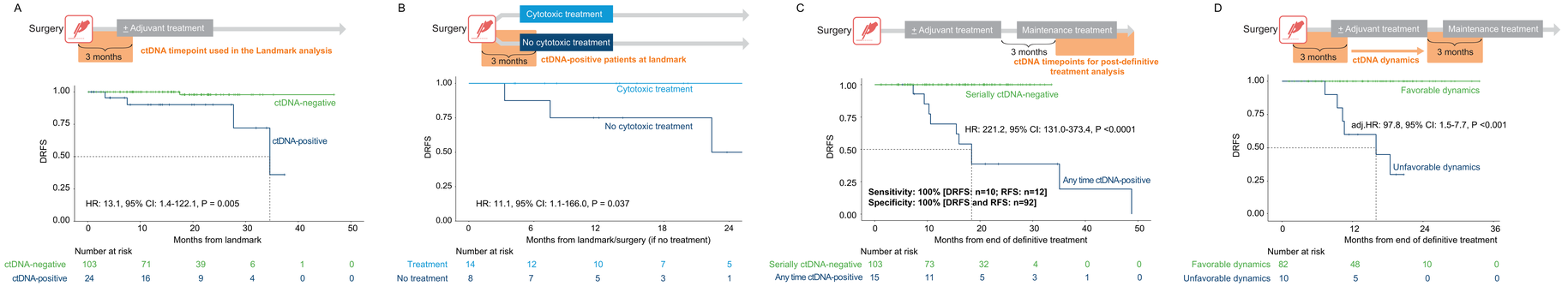


Figure 2. Association of ctDNA status and dynamics with DRFS and predictive value of ctDNA status at landmark. A) The landmark analysis at 3 months post-surgery demonstrated that ctDNA-positive patients experienced significantly inferior DRFS compared with ctDNA-negative patients (HR: 13.1, P=0.005). **B)** ctDNA-positive patients at landmark who received adjuvant treatment containing a cytotoxic agent showed improved DRFS (HR: 11.1, P=0.037) compared with those who did not receive cytotoxic adjuvant treatment. In contrast, ctDNA-negative patients did not receive significant benefit from adjuvant treatment containing a cytotoxic agent (P=1.0; data not shown). Patients with a DRFS event before 3 months of landmark were excluded from analysis **C)** Patients who were serially ctDNA-negative showed markedly improved DRFS compared to those who were ctDNA-positive at any time post-definitive treatment (HR: 221.2, P<0.0001). Of the two anytime ctDNA-positive patients with no evidence of relapse, both experienced early ctDNA clearance during the post-definitive treatment window and remained serially negative with no evidence of relapse at 21 and 34.7 months. **D)** Patients with favorable ctDNA dynamics (serially negative/clearance) demonstrated significantly better outcomes compared to those with unfavorable dynamics (persistently positive/turned positive) (adjusted HR: 97.8, P<0.001). ctDNA dynamics were evaluated from the landmark timepoint to the first ctDNA timepoint taken within 3 months of completion of definitive treatment. Adjusted HR was calculated using Cox regression with Firth's penalized likelihood hazard model. Abbreviations: DRFS, distant, extracranial recurrence-free survival; HR, hazard ratio; CI, confidence interval.

Figure 3. Association of ctDNA status at postsurgical landmark with relapse

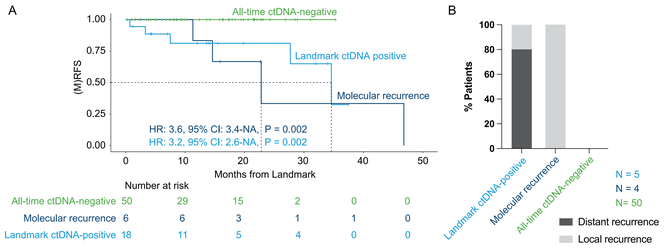


Figure 3. Association of ctDNA status at postsurgical landmark and molecular recurrence with (molecular)RFS. A) Among patients with ctDNA testing within 6 weeks of surgery, significantly inferior survival was observed for patients with molecular recurrence (ctDNA-negative at landmark that turned postive) post-landmark (HR: 3.6, P=0.002) and those who were ctDNA-positive at landmark (HR: 3.2, P=0.002), compared to those who remained serially ctDNA-negative. **B)** Bar plot depicting the location of recurrence. Most (80%) patients with landmark ctDNA positivity later experienced a distant recurrence, whereas all recurrences were local among those with a molecular recurrence. RFS, recurrence-free survival.

Conclusions

- Collectively, our data shows robust clinical performance of the Signatera Genome assay in all subtypes of breast cancer for local and distant recurrence detection following surgery or definitive treatment [DRFS/RFS sensitivity: 100%, specificity 100%].
- Detection and monitoring of molecular residual disease (MRD) in the adjuvant and surveillance settings offer an opportunity for intervention with potential to enroll on treat-on-MRD trials.
- The pivotal prospective SIGNAL-ER 101 trial (NCT07214532) will further establish the clinical utility of Signatera Genome, critically guiding treatment decisions for patients with molecular (non-radiographic) recurrence.

Acknowledgments and Disclosures

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