# Real-World Utilization of Tissue-Free ctDNA Monitoring In Patients With Breast Cancer

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## BACKGROUND

Leveraging circulating tumor DNA (ctDNA) to assess treatment response and emergence of resistance alterations is coming to the forefront in breast cancer care, particularly for patients receiving endocrine therapy. However, little is known about real-world clinical utilization of ctDNA monitoring. This study describes the real-world clinical use and results of a tissue-free ctDNA monitoring assay in patients with breast cancer.

## MATERIALS AND METHODS

FoundationOneMonitor (F1Monitor), a clinical laboratory developed test, was available on a limited pilot to 93 physicians. The timing and number of tests were determined by the treating physician as medically appropriate. Therapy abstraction was requested but not required. ctDNA was detected and quantified by ctDNA tumor fraction (TF); variants [short variants (SV), copy number (CN), and rearrangements (RE)] were tracked with variant allele frequency (VAF). SV origin was predicted algorithmically and classified as predicted tumor somatic (TS), germline, or clonal hematopoiesis (CH).

TF dynamics were classified as:

- No longer detected: negative following a positive test
- Newly detected: positive following a negative test
- Increase: positive at both timepoints and TF score is higher at the later time point
- Decrease: positive at both timepoints and TF score decreased at later time point
- Persistent negative: negative at both timepoints
- TF dynamics below quantifiable limits: detected at both timepoints, but TF levels are below the limit of detection (LOD95)

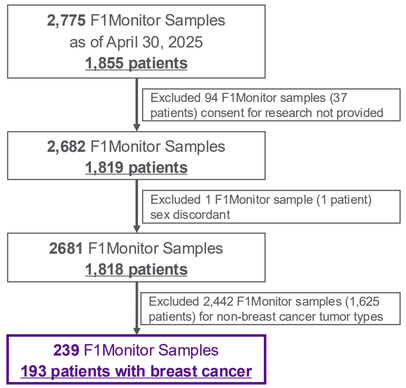



**FIGURE 1: Consort Diagram**

## COHORT CHARACTERISTICS

**TABLE 1:** Cohort characteristics

| Characteristic | Patients with Breast Cancer N = 193[1] |
|---|---|
| **Female** | 189 (97.9%) |
| **Age at Biopsy (1st Sample), years** | 64.0 (52.0, 71.0) |
| **Histology** | |
| Breast carcinoma (NOS) | 160 (82.9%) |
| Breast invasive ductal carcinoma | 24 (12.4%) |
| Breast invasive lobular carcinoma | 8 (4.1%) |
| Breast phyllodes tumor | 1 (0.5%) |
| **Follow-Up Period, days** | 71.0 (43.0, 117.0) |
| **Patients with 2+ tests** | 33 (17.1%) |
| **Therapies Received*** | |
| Hormone Therapy +/- CDK inhibitor | 16 (8.3%) |
| Targeted therapy | 6 (3.1%) |
| Chemotherapy | 6 (3.1%) |
| Antibody Drug Conjugate + Targeted therapy | 4 (2.1%) |
| Antibody Drug Conjugate | 2 (1.0%) |
| Chemotherapy + Immunotherapy | 1 (0.5%) |
| Chemotherapy + Targeted Therapy | 1 (0.5%) |
| PARP inhibitor | 1 (0.5%) |
| Clinical Study Drug | 1 (0.5%) |
| Not Reported | 154 (79.8%) |

* First therapy regimen listed

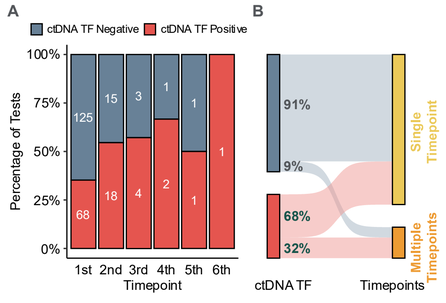
[1] *n (%); Median (Q1, Q3)*

## TESTING CADENCE




**FIGURE 2: Testing cadence for patients with breast cancer.** Test intervals are represented within each arrow. Median days between each testing interval is depicted above. Median cadence of serial testing (3+ tests, 7 patients) was 57 days (IQR: 46.8, 64.5).

## ctDNA TF DETECTION STATUS PER TIMEPOINT



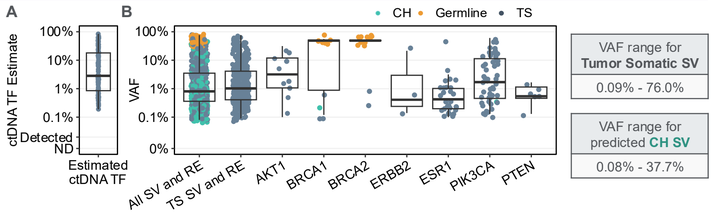




ctDNA TF was positive in any test for 35% (68/193) of patients overall and 41% (16/39) of those known to be on therapy. Patients were more likely to have serial monitoring (2+ tests) if the first test was ctDNA TF positive.

**FIGURE 3: ctDNA TF detection per timepoint. A**) Percentage of tests by ctDNA detection status at each timepoint. **B**) Percentage of patients with a first test result of ctDNA TF positive vs negative with single vs multiple timepoints.

## DISTRIBUTION OF CTDNA TF AND VAF




VAF range for **Tumor Somatic SV**: 0.09% - 76.0%

VAF range for predicted **CH SV**: 0.08% - 37.7%

**FIGURE 4: Distribution of ctDNA TF and VAF estimates. A**) All samples with quantified ctDNA TF estimate. **B**) VAF of all reportable SV and RE, tumor somatic SV and RE, and each NCCN-defined clinically actionable variant. Color indicates predicted variant origin: **Gray**=Tumor Somatic SV and RE, **Teal** = predicted CH, **Gold** = Germline. NCCN = National Comprehensive Cancer Network

## ASSOCIATION BETWEEN CTDNA TF AND VAF

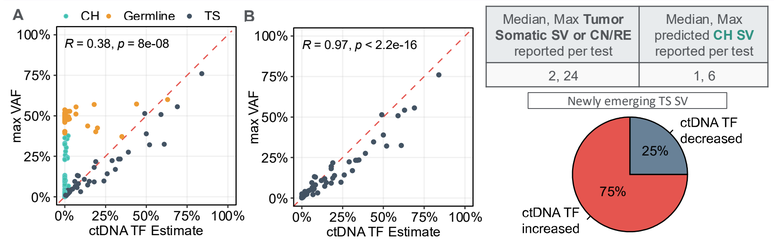



**FIGURE 5. ctDNA TF and maximum VAF by SV origin. A**) All reportable variants, colored by predicted origin. **B**) Predicted tumor somatic variants only. R = Pearson's correlation

| Median, Max **Tumor Somatic SV or CN/RE** reported per test | Median, Max predicted **CH SV** reported per test |
|---|---|
| 2, 24 | 1, 6 |




**FIGURE 6. Percent of tests with ctDNA TF increase vs decrease when new tumor somatic variants emerge.**

## LONGITUDINAL ctDNA TUMOR FRACTION CHANGES

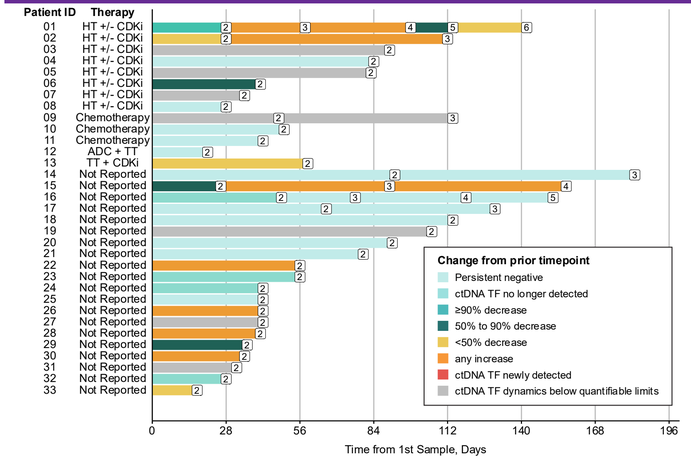



**FIGURE 7. Patient-level longitudinal ctDNA TF changes.** Patients with >1 test are included. Test timepoint is represented in the numbered box. Therapy information included when available. The first therapy listed is represented. HT=hormonal therapy, ADC= antibody-drug conjugate, TT= targeted therapy

ctDNA TF dynamic changes were observed in 55% (18/33) of patients during their course of testing

- Timepoints: 16 (34.8%) persistent negative, 4 (8.7%) TF no longer detected, 1 (2.2%) ≥90% decrease, 4 (8.7%) 50% to 90% decrease, 4 (8.7%) <50% decrease, 9 (19.6%) increase, 8 (17.4%) TF dynamics below quantifiable limits.

## CONCLUSIONS

- In the limited follow up time, physicians chose to monitor patients approximately every 6-8 weeks with a tendency for repeat testing when ctDNA TF was positive in the first test. (Figures 2,3)
- In real-world tissue-free ctDNA-based monitoring in breast cancer, F1Monitor demonstrated high sensitivity in clinical practice, detecting ctDNA TF as low as 0.19% and VAF as low as 0.08% including alterations in clinically actionable genes such as *ESR1* down to 0.1%. (Figure 4)
- ctDNA TF was strongly associated with max VAF of tumor somatic variants determined using algorithmic filtering. (Figure 5)
- ctDNA TF was detected in 41% of patients on known active therapy with observed dynamic changes for 55% of patients with longitudinal testing, supporting potential utility for monitoring treatment response and emerging resistance. (Figures 3, 7, 8)

## DYNAMICS OF CLINICALLY ACTIONABLE VARIANTS

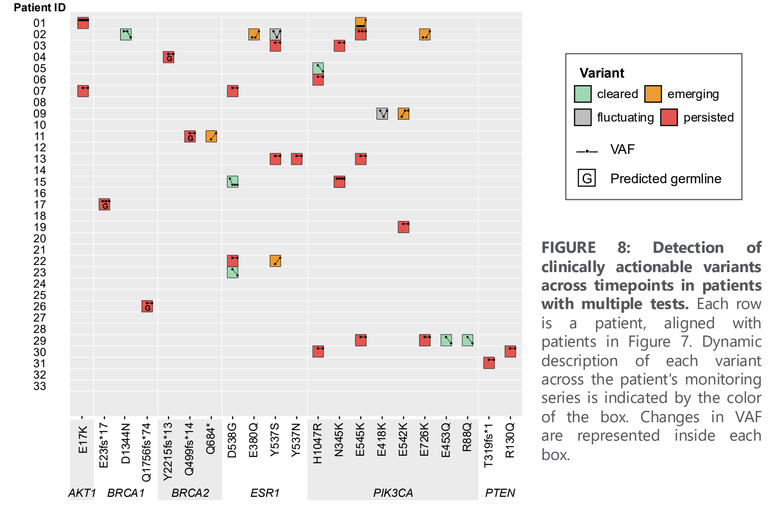



**FIGURE 8: Detection of clinically actionable variants across timepoints in patients with multiple tests.** Each row is a patient, aligned with patients in Figure 7. Dynamic description of each variant across the patient's monitoring series is indicated by the color of the box. Changes in VAF are represented inside each box.

## PATIENT CASE

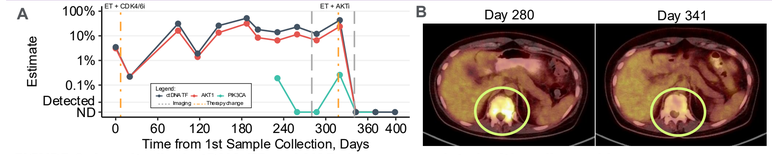



**FIGURE 9. Longitudinal ctDNA TF and VAF changes correlated with radiographic response.** HR+HER2- mBC patient initiated ctDNA monitoring at the start of second line endocrine therapy (ET) +CDK4/6i. The patient had frequent holds on CDK4/6i with unclear response. Clear radiographic PD occurred after 9 months (Day 280). An AKT inhibitor was added to the ET backbone (Day 318). Molecular response by ctDNA TF was in agreement with response by PET CT as shown. **A**) line graph representing ctDNA TF estimate or VAF of detected clinically actionable variant over time. Gray dashed line indicates time of PET CT. Orange dashed line indicates time of therapy change. **B**) PET CT scans taken pre and post addition of AKT inhibitor (at Day 280 and Day 341 from the time of first F1Monitor test).