CLINICAL TRIAL AND REAL-WORLD EVIDENCE OF ctDNA MONITORING TO PREDICT RECURRENCE IN PATIENTS WITH RESECTED COLORECTAL CANCER

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A new study published in ESMO Real World Data and Digital Oncology demonstrated that:

- ✓ Post-operative ctDNA was a strong **independent prognostic biomarker.**
- ✓ **Performance** of ctDNA was comparable between clinical trial and real-world cohorts.
- ✓ ctDNA was **more sensitive and specific** than CEA to detect recurrence.
- ✓ High frequency of co-mutations in **TP53, APC and KRAS** was observed in relapsed patients.

## Background and Solutions for Minimal Residual Disease (MRD) Detection

● Current Limitations

- **Limited sensitivity and specificity** characterize conventional methods like ultrasound, CT scans, physical exams, and CEA blood tests, making early detection of MRD challenging
- **Lacks clinical validation and adoption,** ctDNA monitoring in cancer management is limited in developing countries.

● The ctDNA Solutions

- **ctDNA is a promising biomarker** for detecting and quantifying MRD, with strong prognostic value for cancer recurrence.
- Analysis from clinical trials and real-world data shows ctDNA as an **independent and strong prognostic biomarker for predicting CRC recurrence**, aiding personalized intervention and surveillance.

Introducing K-TRACK™ – A Personalized ctDNA Analysis Workflow
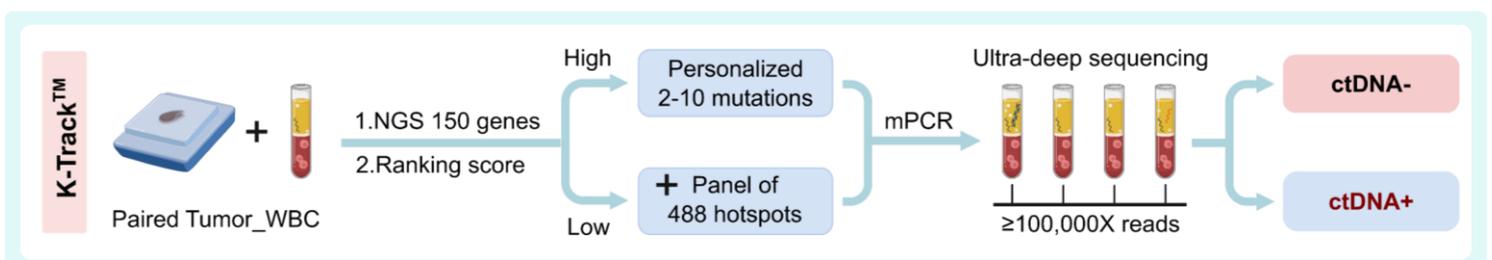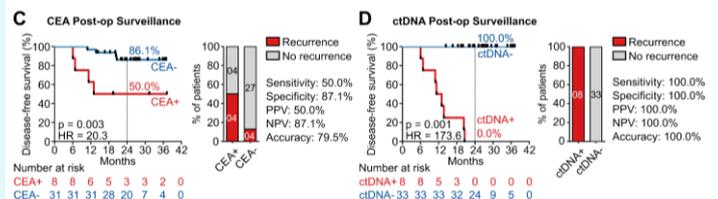
K-TRACK™ Performance in Clinical Trials

80.0% sensitivity
at the post-op landmark

(2-4 weeks post-surgery) was observed. ctDNA was detected in 19.4% of patients and was associated with a significantly shorter DFS, while CEA status could not predict DFS. ctDNA detection increased the risk of recurrence by 30.3 times
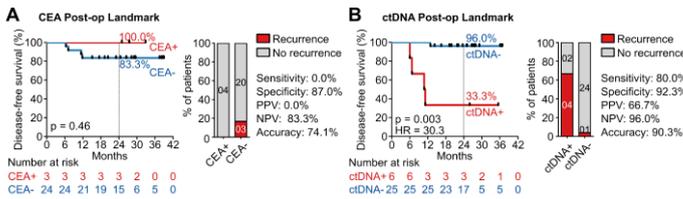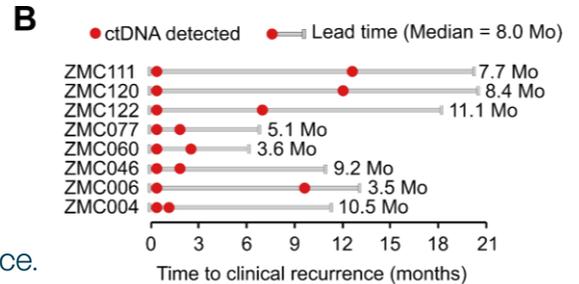
100.0% sensitivity
at post-op surveillance

was observed. ctDNA continued to show the strongest prognostic value, with a hazard ratio of 173.6 for predicting recurrence. ctDNA detection increased the risk of recurrence by 173.6 times

A — CEA Post-op Landmark: CEA+ 100.0%, CEA- 83.3%, p = 0.46. Sensitivity: 0.0%, Specificity: 87.0%, PPV: 0.0%, NPV: 83.3%, Accuracy: 74.1%. Number at risk: CEA+ 3 3 3 3 2 0 0; CEA- 24 24 21 19 15 6 5 0

B — ctDNA Post-op Landmark: ctDNA- 96.0%, ctDNA+ 33.3%, p = 0.003, HR = 30.3. Sensitivity: 80.0%, Specificity: 92.3%, PPV: 66.7%, NPV: 96.0%, Accuracy: 90.3%. Number at risk: ctDNA+ 6 3 3 3 2 1 0; ctDNA- 25 25 25 23 17 5 5 0

C — CEA Post-op Surveillance: CEA- 86.1%, CEA+ 50.0%, p = 0.003, HR = 20.3. Sensitivity: 50.0%, Specificity: 87.1%, PPV: 50.0%, NPV: 87.1%, Accuracy: 79.5%. Number at risk: CEA+ 8 8 6 5 3 3 2 0; CEA- 31 31 31 28 20 7 4 0

D — ctDNA Post-op Surveillance: ctDNA- 100.0%, ctDNA+ 0.0%, p = 0.001, HR = 173.6. Sensitivity: 100.0%, Specificity: 100.0%, PPV: 100.0%, NPV: 100.0%, Accuracy: 100.0%. Number at risk: ctDNA+ 8 8 5 3 0 0 0 0; ctDNA- 33 33 33 32 24 9 5 0

8 months
Lead Time for Recurrence Detection

The study reported a median lead time of 8 months between ctDNA detection and the clinical diagnosis of recurrence.
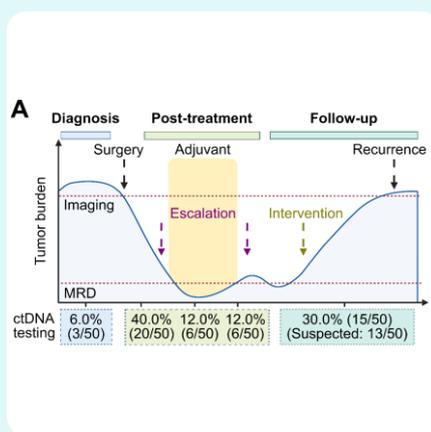
This early detection window offers a critical opportunity for intervention before traditional imaging would detect a recurrence.

B — ctDNA detected ● — Lead time (Median = 8.0 Mo):
ZMC111 — 7.7 Mo
ZMC120 — 8.4 Mo
ZMC122 — 11.1 Mo
ZMC077 — 5.1 Mo
ZMC060 — 3.6 Mo
ZMC046 — 9.2 Mo
ZMC006 — 3.5 Mo
ZMC004 — 10.5 Mo
Time to clinical recurrence (months)

K-TRACK™ Performance in Real-world Practice

Infrequent Surveillance Testing:
In real-world practice, regular ctDNA surveillance was not routinely performed. Most patients were tested only once or twice post-surgery, particularly around **landmark time points** (immediately after surgery or after adjuvant therapy). This highlights potential missed opportunities for early detection of recurrence and treatment modification.
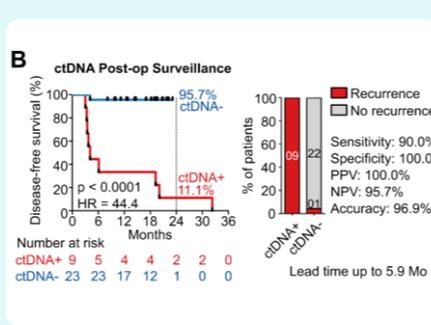

A — Diagnosis / Post-treatment / Follow-up; Surgery, Adjuvant, Recurrence; Tumor burden; Imaging; Escalation; Intervention; MRD.
ctDNA testing: 6.0% (3/50), 40.0% (20/50), 12.0% (6/50), 12.0% (6/50), 30.0% (15/50) (Suspected: 13/50)

ctDNA detection identified 87.5% of recurrences before clinical diagnosis
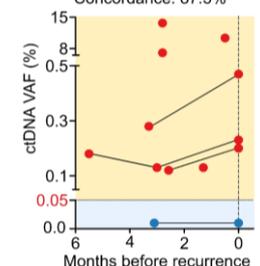
This early detection provides oncologists with a crucial tool for timely intervention, potentially improving patient outcomes by catching recurrence earlier than imaging methods.

90.0% sensitivity and 100.0% specificity for detecting recurrence

This underscores ctDNA's reliability as a Prognostic biomarker for identifying patients at high risk of recurrence. Lead time up to 5.9 months


B — ctDNA Post-op Surveillance: ctDNA- 95.7%, ctDNA+ 11.1%, p < 0.0001, HR = 44.4. Sensitivity: 90.0%, Specificity: 100.0%, PPV: 100.0%, NPV: 95.7%, Accuracy: 96.9%. Number at risk: ctDNA+ 9 5 4 4 2 2 0; ctDNA- 23 23 17 12 1 0 0. Lead time up to 5.9 Mo

C — Suspected cases (n=8), Concordance: 87.5%. ctDNA VAF (%); Months before recurrence.

Mutational Insights

Common mutations detected in ctDNA among relapsed patients were in the TP53, APC, and KRAS genes

These mutations, detected in both clinical trials and real-world practice, could help stratify patients for targeted therapies and further personalize treatment approaches
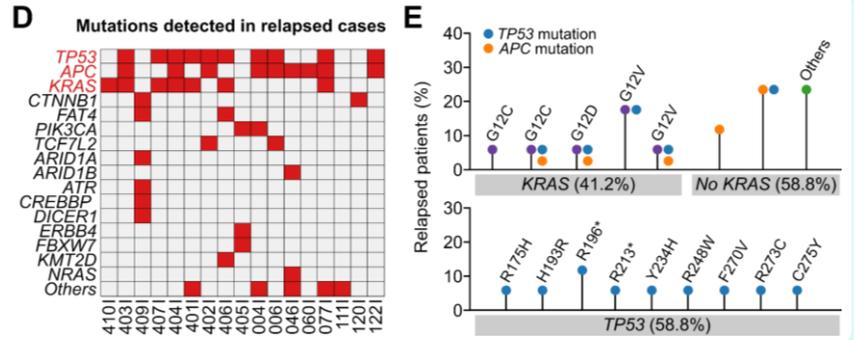
Comparison to Conventional Markers

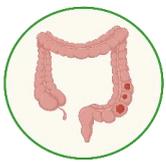Before surgery, ctDNA detection was 91.2%, compared to 42.9% for CEA.

ctDNA detection was far more effective than carcinoembryonic antigen (CEA), the traditional blood marker for CRC.
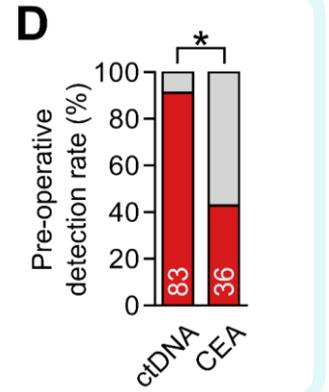
CASE STUDY - SILENT SIGNALS:
ctDNA's Early Warning of Recurrence in Colorectal Cancer

Patient Information

Case ZMC111
62 years old – Female
Sigmoid colon adenocarcinoma, Grade 2, stage III/IV pT4N0Mx

A 62-year-old woman with **stage III/IV sigmoid colon adenocarcinoma** underwent surgery and XELOX chemotherapy. Her **CEA and ctDNA levels normalized post-surgery**, indicating remission. However, at the **12-month follow-up, ctDNA reappeared at 0.10%, despite normal CEA and no symptoms**. A CT scan at **20 months revealed metastasis**, showing that ctDNA monitoring provided an early, non-invasive alert of **recurrence 7.7 months before imaging detected** it.

Pre-Operative	Therapy Treatment		Monitoring		Recurrence
	Surgery	Adjuvant Therapy	6.5 months	12 months	20 months
CEA + 8.1 ng/ml	Curative-intent	XELOX	CEA -	CEA -	Inferior mesenteric lymph node metastasis detected via CT scan
ctDNA + 0.22%			ctDNA -	ctDNA + 0.1%	

Recurrence Detection
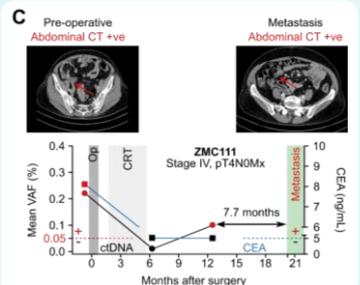
Longitudinal ctDNA monitoring can serve as an early, non-invasive indicator of cancer recurrence, detecting it significantly earlier than traditional imaging methods