Improving Cancer Recurrence Detection using ctDNA Measures in Colorectal, Breast, and Non-small Cell Lung Cancers

Code: MT6

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INTRODUCTION:

- Solid tumor cancer recurrence is associated with poor morbidity and mortality.[1,2,3] Early detection of recurrence provides the best opportunity for treatment intervention to improve patient outcomes.
- Detecting molecular residual disease (MRD) in solid tumors using circulating tumor DNA (ctDNA) is an emerging practice to assess the effect of surgery and systemic therapies, and to monitor for impending recurrence.
- A systematic literature review (SLR) was conducted to identify studies reporting outcomes of patients diagnosed with non-metastatic solid tumors on whom ctDNA testing was performed after surgical resection. Data with respect to the prediction of recurrent disease were captured. Studies identified for colorectal (CRC), breast (BC), and non-small lung cancer (NSCLC) are reported herein.

OBJECTIVE:

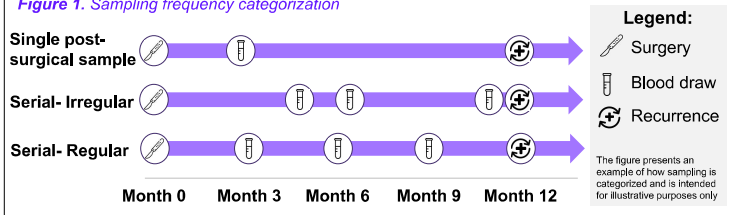
To synthesize evidence of a subset of studies from the broader SLR reporting the clinical validity of ctDNA to detect MRD and/or disease recurrence for individuals with non-metastatic CRC, BC, or NSCLC to answer the following questions:

1. Can MRD as measured by ctDNA after surgical resection predict recurrence?
2. Can serial ctDNA measurements be utilized to predict recurrence during follow-up?
3. Can ctDNA be utilized to detect recurrence following surgical resection sooner than radiographic imaging?

METHODOLOGY

- The SLR search was executed in PubMed and Embase from 01/01/2018 to 11/01/2023 to identify studies detecting MRD via ctDNA in adult patients with solid tumors after surgical resection.
- The SLR was conducted per the University of York's Centre for Review and Dissemination guidelines[4] and reported per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[5]
- Studies providing sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for recurrence, and clinical lead times for CRC, BC, and NSCLC are reported.
- Data were grouped by sampling frequency as 'singular post-surgical sample' or 'serial sampling' (>1 sample). 'Serial sampling' was further stratified by either irregular or regular sampling intervals based on study methodology (**Figure 1**). Descriptive data are described herein; no statistical analyses were performed.

Figure 1. Sampling frequency categorization



Sampling was categorized as 'longitudinal' if >1 sample was captured at irregular time points prior to recurrence, or as 'surveillance' if multiple samples were obtained, taken at regular or predetermined time points (e.g., every 3-6 months).

REFERENCES:

1) Balboa-Barreiro et al. *Digestive and Liver Disease*. Vol: 56; Issue 7 (2024). 2) Courtney et al. *Ir J Med Sci*. Vol: 191; Issue 6 (2022). 3) Uramoto et al. *Transl Lung Cancer Res*. Vol: 3; Issue 4 (2014). 4) University of York CRD. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (2009). 5) PRISMA 2020. *BMJ*. Vol: 372 Issue: 71 (2021).

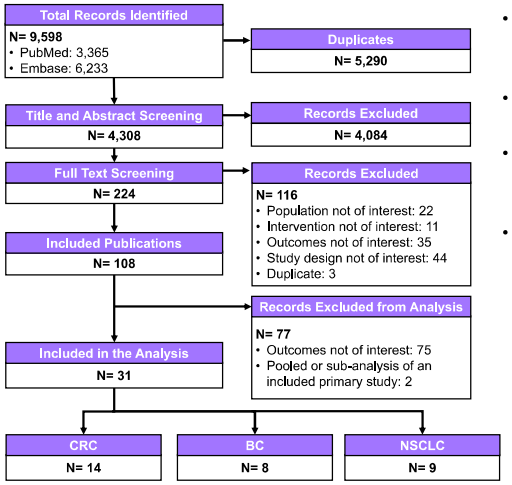
CONFERENCE AND DISCLOSURES:

Presented at the ISPOR Conference 13-15 May 2025; Montreal, Quebec, Canada.

This study was sponsored by Exact Sciences and conducted in partnership with MAPLE HEALTH GROUP

RESULTS:

Figure 2. PRISMA flow diagram



- A total of 4,308 unique records were screened by title and abstract; 224 were screened as full texts; 31 included studies reported the outcomes of interest in CRC, BC and NSCLC (**Figure 2**).
- Most patients were stage II/III; median follow-up time ranged from 11.0–61.2 months. There was notable heterogeneity related to sample timing and frequency, length of follow-up time, and ctDNA assay methodology.
- ctDNA detected recurrence earlier than radiological imaging (RI) for all studies reporting lead time (= date of RI recurrence – date of ctDNA positive status) (**Table 1**).
- Studies using serial (irregular or regular) sampling had generally higher, and less variable, sensitivity and specificity compared to single sample studies across all three cancer types. Conversely, specificity did not vary considerably with sampling frequency/regularity (**Table 2**).
- Increasing the frequency/regularity of ctDNA sampling generally increased both PPV and NPV across the three cancer types (**Table 3**).

Table 1. Median and mean lead time reported across all studies regardless of sampling frequency

	Lead Time	
	Median (Range %)	**Mean (Range %)**
CRC (n=9 studies)	1.0–11.5 months (6 studies, n=88)	2.6–8.7 months (3 studies, n=36)
BC (n=6 studies)[a]	1.6–12.4 months (4 studies, n=66)	8.0 months (1 study, n=5)
NSCLC (n=6 studies)	3.4–10.0 months (5 studies, n=>159)[b]	4.6 months (1 study, n=11)

a One study reported a lead time range of 7–13 months, without reporting a mean or median. b One study did not report a sample size for lead time

Table 2. Sensitivity and specificity of ctDNA to capture MRD following surgery (Single post-surgical sample) and to predict disease recurrence (Longitudinal & Surveillance)

	Single Post-Surgical Sample		Longitudinal Sampling		Surveillance Sampling	
	Sensitivity (Range %)	**Specificity (Range %)**	**Sensitivity (Range %)**	**Specificity (Range %)**	**Sensitivity (Range %)**	**Specificity (Range %)**
CRC (n=12 studies)	27.0%–67.0% (5 studies, n=746)	87.0%–100% (5 studies, n=746)	55.0%–74.0% (4 studies, n=669)	80.1%–100% (2 studies, n=498)	66.7%–100% (5 studies, n=452)	84.0%–100% (5 studies, n=394)
BC (n=3 studies)	79.0% (1 study, n=142)	--	--	--	85.7%–89.0% (2 studies, n=132)	97.4%–100% (2 studies, n=132)
NSCLC (n=6 studies)	26.1%–57.9% (5 studies, n=652)	87.0%–97.8% (3 studies, n=408)	45.5%–86.4% (3 studies, n=309)	90.4%–92.3% (2 studies, n=265)	73.2%–87.2% (2 studies, n=224)	81.6% (1 study, n=177)

Table 3. PPV and NPV of ctDNA to capture MRD following surgery (Single post-surgical sample) and to predict disease recurrence (Longitudinal & Surveillance)

	Single Post-Surgical Sample		Longitudinal Sampling		Surveillance Sampling	
	PPV (Range %)	**NPV (Range %)**	**PPV (Range %)**	**NPV (Range %)**	**PPV (Range %)**	**NPV (Range %)**
CRC (n=5 studies)	44.0%–100% (4 studies, n=424)	75.5%–91.0% (4 studies, n=424)	90.9% (1 study, n=72)	82.0% (1 study, n=72)	60.0%–100% (2 studies, n=79)	92.6%–100% (2 studies, n=79)
BC (n=3 studies)	--	--	85.7% (1 study, n=24)	82.3% (1 study, n=24)	75.0%–100% (2 studies, n=132)	94.0%–98.7% (2 studies, n=132)
NSCLC (n=8 studies)	53.6%–93.0% (4 studies, n=516)	68.0%–89.0% (5 studies, n=552)	69.6% (1 study, n=110)	88.7%–96.6% (2 studies, n=265)	20.0%–89.1% (2 studies, n=129)	88.4%–96.8% (3 studies, n=306)

CONCLUSIONS:

- ctDNA detected recurrence sooner than radiographic imaging across all three solid tumor types. Current evidence consistently shows high specificity for using ctDNA to predict the presence of MRD or molecular recurrence regardless of solid tumor type. Sensitivity is highly variable when singular ctDNA samples are utilized, and less variable when measured serially.
- Until 11/01/2023, there was a notable lack of papers reporting validity measures for ctDNA in breast cancer, and for NPV and PPV outcomes in general.
- Methodological factors associated with ctDNA measurement and pre-analytical specimen handling, as well as key patient (e.g., liver function) and tumor (e.g., histology, staging) characteristics that can influence the detection of ctDNA, likely contributed to the variability of the data captured in this SLR. Establishing consistently accurate ctDNA assays will be needed to optimize this technology
- Consistency in sampling frequency, sampling definitions, and reporting, with sufficient follow-up for recurrence, will improve our understanding of the reliability of ctDNA for detecting MRD and/or recurrence of disease after solid tumor resection– important factors that should be considered when interpreting test validity data.