Review Article

Liquid biopsies for colorectal cancer: a narrative review of ongoing clinical trials and the current use of this technology at a comprehensive cancer center

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Objective: In this review, we summarize ongoing clinical trials involving liquid biopsies (LB) for colorectal cancer (CRC), outlining the current landscape and the future implementation of this technology. We also describe the current use of LB in CRC treatment at our institution, the Mayo Clinic Enterprise.

Background: The use of LB in CRC treatment merits close attention. Their role is being evaluated in the screening, non-intervention, intervention, and surveillance settings through many active trials. This, coupled with the technique's rapid integration into clinical practice, creates constant evolution of care.

Methods: Review of ClinicalTrials.gov was performed identifying relevant and active trials involving LB for CRC. "Colorectal cancer" plus other terms including "liquid biopsies" and "ctDNA" were used as search terms, identifying 35 active trials.

Conclusions: LB use for the CRC is actively being investigated and requires close attention. Based on current evidence, Mayo Clinic Enterprise currently uses LB in the non-interventional, interventional and surveillance setting, but not for screening. Results of these trials may further establish the use of LB in the management of CRC.

Keywords: Liquid biopsy; colorectal cancer (CRC); clinical trial

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Introduction

In 1948, Mandel and Metais first described obtaining circulating tumor DNA (ctDNA) from the bloodstream (1). As the technology matured, ctDNA was found to correlate with disease burden. Later, following advances in prenatal testing, the use of tumor specific ctDNA to identify gene mutations was developed. Targeted and untargeted approaches allow for the identification of individual genes or genome wide analysis, respectively (2). Next-generation

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based high-throughput sequencing substantially reduced costs. At the same time, it generates large amounts of data with unspecified clinical utility. Machine learning and artificial intelligence offer an apparent solution because they have the capacity to analyze a large volume of individual data points provided by a single liquid biopsy (3). As ctDNA allows for mutational analysis in a minimally invasive way, without the need for resection or excision, it can be used to improve early diagnosis, prognosis, therapy monitoring (4). Tumor-uninformed testing includes NGS with probe set to evaluate the standard set of genes and report out variants. Additional sensitivity can be achieved by using methylation signatures (5,6). Conversely, tumor-informed testing involves sequencing to identify specific mutations present in an individual tumor and then testing only for specified previously identified mutations. This affords the ability to identify rare mutations per million base pairs, however new mutations are more difficult to identify compared to tumor-non informed testing (6).

With the rise of and continued move towards personalized medicine, the thirst for the implementation and routine use of these technologies in the clinical setting continues to grow. Data proving benefit of obtaining real-time tumor-specific information throughout the colorectal cancer (CRC) treatment process is not yet available. Therefore, the frequency with which ctDNA meaningfully impacts care remains largely unproven (7,8). Although, up to now, no test based on liquid biopsy is approved for monitoring the response during treatment, several studies have been demonstrated the promising role of ctDNA in monitoring of treatment response, leading to early detection of progressive disease. Accordingly, ctDNA can improve both specificity and sensitivity of monitoring response. Most studies assessing this role have focused on CRC, melanoma, breast cancer, and non-small cell lung cancer (9-12).

As there are different mechanisms by which different tumors release various amount of ctDNA into the blood, most studies have been focused on patients with metastatic cancers (13). Understanding the strengths and limitations of this technology, as well as how and when to implement it, is currently being examined in multiple ongoing trials. In this review, we focus specifically on the active clinical trials that show promise to continue pushing the forefront of ctDNA and its utility in the management of CRC. We divide the intended and desired clinical utility of ctDNA into four settings: screening, non-interventional (prognostication), interventional (treatment decision-making), and surveillance. Each of these settings can be further divided into multiple independent clinical applications. In the screening setting, ctDNA is under investigation as a tool for early detection of colorectal malignant and precancerous lesions. ctDNA is accepted as a method of detecting persistent micro-metastatic disease following definitive treatment, referred to as minimal residual disease (MRD) in some disease states but remains unproven in others. In the non-interventional setting, MRD shows promise as a tool for prognostication, while ctDNA allows identification of mutated genes such as *KRAS*, *NRAS*, *BRAF*, *APC*, when tumor tissue is not available. To evaluate MRD, ctDNA can be obtained from both plasma or urine. However, detecting ctDNA in urine less sensitive and less specific than plasma because of significantly lower levels. Thus, ctDNA may detect the micro metastasis or MRD earlier than image-based diagnosis. In the interventional setting, MRD is being evaluated to guide the use of adjuvant chemotherapy (ACT). Additionally, during active treatment ctDNA may aid in detecting therapy resistance, adjusting treatment and de-escalation. In the surveillance setting, ctDNA is being evaluated as a method of detecting recurrence. Taken together, this technique has the potential to impact care throughout the diagnosis and treatment of CRC (11,12,14,15). The purpose of this review is to outline the currently ongoing active clinical trials investigating liquid biopsies (LB) for CRC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-470/rc).

Methods

For the identification of trials that would be discussed in this review, ClinicalTrials.gov was used. "Colorectal cancer" was used as the search term under "Condition or disease" "liquid biopsies" and "ctDNA" were used as the search terms for "Other terms". This identified 35 trials; 7 trials were excluded either due to premature termination secondary to inadequate accrual, uncertain status, or lack of relevance with current review. This resulted in 28 trials meeting criteria for inclusion.

Results

Current clinical trials of LB in CRC

LB for screening

The following trials in *Table 1* explore the use of ctDNA

Table 1 Active trails regarding LB for screening

Study	Country	Type/ technique	Summary/ intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT02665299	USA	ctDNA	LB as a screening tool in asymptomatic patients	Peripheral blood draw before colonoscopy Patient contacted yearly for up to 5 years to learn whether they have been found to have a dx of colon cancer	206	Correlations between plasma ctDNA and colonoscopy	Rate of CRC
NCT03688906 AI-EMERG	USA	ctDNA, cfRNA, protein (Freenome test)	LB for screening (CRC) in average risk patients and comparison to patients with CRC	Blood and stool samples collected in 3 groups: Group A: patients aged 50–84 with CRC cancer or strong clinical suspicion Group B: patients aged 50–84 undergoing screening colonoscopy Group C: patients aged 18 or older with a diagnosis of CRC cancer or strong clinical suspicion	3,275	Clinical annotation of LB in patients with diagnosis of CRC or advanced adenoma	n/a
NCT04369053 PREEMT (CRC)	USA	ctDNA, cfRNA, proteins (Freenome test)	LB for screening and detection of (CRC) in average risk patients who will undergo colonoscopy	Detection of CRC by collecting blood samples from average-risk participants who will undergo a routine screening colonoscopy	25,000	Sensitivity and specificity of Freenome test for (CRC) detection	n/a
NCT04136002 ECLIPSE	USA	ctDNA (LUNAR-2)	LB for screening and detection of CRC in average risk	Blood draw prior to the patient undergoing the standard of care colonoscopy and retrospectively compare the performance characteristics of the LUNAR-2 test with the findings of the index colonoscopy	10,000	Sensitivity and specificity for (CRC) detection	PPV, NPV, sensitivity and specific of adenoma detection

LB, liquid biopsies; ctDNA, circulating tumor DNA; CRC, colorectal cancer.

for CRC screening. With recent studies demonstrating promising levels of sensitivity and specificity for detecting cancerous lesions, large multisite population-based trials are currently enrolling patients. One major limitation is the inability to achieve adequate sensitivity for detecting precancerous lesions such as small adenomas. The benefit of LB for screening will likely be in high risk populations and in combination with other tools to calculate risk and determine timing for endoscopic evaluation. While LB will play a role as an addition to standard screening practices, it will likely not serve as a replacement.

Non-interventional LB (i.e., prognostication)

Eleven trials (*Table 2*) evaluate the pathophysiology and biochemical characteristics of ctDNA throughout CRC treatment: including surgery, chemotherapy, radiation therapy and immunotherapy. Understanding how and when to collect samples, and correlating them to different stages in treatment allows determination of their prognostic value. These trials highlight the importance of establishing institutional protocols for collecting and storing specimens as well as for multi-institutional data comparison.

Interventional LB

Ten trials (*Table 3*) are aimed at identifying LB as tool for guiding therapy and for triggering modifications in treatment. The growing understanding of MRD and its implications position LB to make a significant impact on adjuvant therapy. Patients receiving care at Mayo Clinic benefit from information gained with post-resection LB. Interventional LB trials constitute a growing proportion of trials, a trend that will continue as non-interventional LB

Table 2 Active trails regarding non-interventional LB

Study	Country	Type/ technique	Summary/intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT03776591	Norway	ctDNA	Compare surgical technique of open D33 *vs.* Lap CME for right sided CRC	Patients ≤85 years with tumor localized in the right colon included. Blood samples for analysis of ctDNA/CTCs collected preoperatively, 3–10th postoperative day, at 3 months, and at each check the next five years at six months intervals. Sample times correlated to surveillance CEA and CT	218	Complications	Prognostic significance of ctDNA
NCT04726800 CITCCA	Norway, Sweden	ctDNA	Feasibility of profiling ctDNA in stage I–III CRC	Blood draw before surgery (baseline), after surgery at 4–6 weeks, 3-, 6-, 12- and 24 months postoperatively to measure ctDNA in plasma	300	Rate of post-op ctDNA+, rate of ctDNA+ conversion to ctDNA-negative following surgery	n/a
NCT04108481 iRE-C	USA	ctDNA	Feasibility and safety of Y90 with immunotherapy in MCRC MSS	Analyze changes in the expression profile and in levels of ctDNA in blood pre- and post- treatment with Y90-radioembolization	18	Maximum tolerated Y90 dose in combination with immunotherapy	ctDNA levels pre- and post-treatment, adverse events, response rate
NCT03284684 Periop ctDNA	France	ctDNA	Determine kinetics of perioperative ctDNA testing in CRC, breast and prostate	Analyze the kinetics of perioperative circulating DNA in breast, prostate, and colon cancer	30	ctDNA concentration, ctDNA integrity, ctDNA proportion	Plasma concentration of *KDRA*, *ACTB*
NCT03546569 CISMO	Denmark	ctDNA	Determine ctDNA levels following colonic stenting in malignant obstruction in CRC	Base line blood samples to determine the level of ctDNA, cfDNA, and CTC are drawn prior to SEMS placement	20	ctDNA levels in relation to colonic stenting	Immune response, metastatic ability of cancer cells
NCT04354064	USA	ctDNA	Describe ctDNA levels in solid tumors undergoing treatment	Not provided	3,362	Freedom from progression	Post treatment ctDNA detection, DFS, OS
NCT04491929	Denmark	ctDNA	Describe tumor specific mutations using ctDNA in patients undergoing Y90 for refractory MCRC	Total cell free DNA level will be quantified in all samples. The samples will be analyzed for tumor specific mutations such as the *KRAS*, *BRAF* and *NRAS* oncogenes	30	Feasibility	Response rate, PFS, OS
NCT03841799 COLON-IM	France	ctDNA	Describe local tissue microenvironment of patients with CRC	Blood and stool samples at surgery, at month 3 post surgery and at month 6 post surgery	80	Characterize local microenvironment	Describe ctDNA, lymphocyte infiltrate, cytokine environment

Table 2 (*continued*)

Table 2 (*continued*)

Study	Country	Type/ technique	Summary/intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT03975491 EXACT	USA	ctDNA	Evaluate relationship between exercise and recurrence in post treatment CRC	Exercise intervention consists of moderate-intensity (50–70% age-predicted maximum heart rate) treadmill walking. Examine the effect of 12 week aerobic exercise on systemic inflammation, CRP, IL-6, insulin resistance quantified using an oral glucose tolerance test, and ctDNA.	60	Levels of CRP, IL-6	Proportion of ctDNA, TNF, insulin resistance
NCT03702309 LIBERATE	Canada	ctDNA, cfRNA	Develop LB protocol	Peripheral blood samples collected serially for DNA extraction for 5 years.	2,500	Collection and annotation of biospecimens	n/a
NCT04853017 AMPLIFY-201	USA	ctDNA	Phase 1/2 safety and efficacy of adjuvant immunotherapy for NRAS mutated solid tumors with MRD	Post-surgical LB will guide a molecular adjuvant treatment as follows: (I) ctDNA+ patients will receive CAPOX for 3 months; (II) ctDNA– patients will receive CAPE for 6 months but will be retested after 1 cycle, and if found ctDNA+ will be switched to CAPOX treatment	159	Maximum tolerated dose, safety, relapse compared to observation	ctDNA clearance rate, relapse free survival, OS

LB, liquid biopsies; ctDNA, circulating tumor DNA; CRC, colorectal cancer; SEMS, self-expanding metal stent; MRD, minimal residual disease; CAPE, capecitabine.

trials increase our understanding of the specific relationships between malignancy and ctDNA.

LB for surveillance

These four trials (*Table 4*) depict a future role of LB in the setting of surveillance and early identification of recurrence or relapse. The consistent use over the last half century of carcinoembryonic antigen (CEA) and the acknowledged limitations of this blood test exemplify the persistent interest in blood tests with the ability identify disease prior to radiologic visualization. Tumor informed tests, using patient/tumor specific sequencing, currently play a role in surveillance at Mayo Clinic and other institutions.

The current Mayo Clinic practice (16)

As there are limited publications on the actual clinical use, liquid biopsy-based technologies are far from reaching their full potential. Centers across North America, including our own, have begun integrating ctDNA to clinical practice to aid in the care of patients with CRCs. We report our institutional practice with LB as it pertains to the screening, non-interventional (prognostication), interventional (treatment decision-making), and surveillance settings. Our current standards of practice are based on interpretation of published (not ongoing) studies and are not intended to be institutional evidence-based recommendations (16).

- In the screening setting (*Table 1*), Mayo Clinic does not use LB as part of routine care.
- In the non-interventional setting (*Table 2*), LB is performed for patients with stage IV disease. This has potential benefits, including establishment of baseline ctDNA characteristics that may be compared to levels following treatment, correlation of ctDNA with the primary tumor characteristics, and obtaining material for analysis if tissue biopsy is not feasible.
- In the interventional setting (*Table 3*), LB-guided therapy alteration is occurring at Mayo Clinic.
- For patients with stage IV disease who are receiving systemic treatment, LB is used when

Table 3 Active trials regarding interventional LB

Study	Country	Type/technique	Summary/ intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT04259944 PEGASUS	Italy	ctDNA (LUNAR1)	LB to guide the post-treatment therapy in high-risk CRC (chemo *vs.* targeted *vs.* observation)	Not provided	140	Positive cases following interventional LB	DFS, OS, ctDNA seroconversion
NCT04089631 CIRCULATE	Germany	ctDNA	LB to guide the post-treatment therapy in stage II CRC (chemo *vs.* observation)	4 to 8 weeks after resection, the patient is randomized: ctDNA+ patients are randomized (2:1) in "chemotherapy" (with capecitabine) or "follow-up", ctDNA– patients are randomized (1:4) in "follow-up" or "off study" (follow-up will be organized within the routine clinical practice)	4,812	DFS in ctDNA pos	OS, DFS in ctDNA neg
NCT04068103 COBRA	USA	ctDNA (LUNAR-1)	LB to guide the post-treatment therapy in patients with stage IIa CRC (chemo *vs.* observation)	Patients are randomized to 1 of 2 arms: Arm I (blood stored and tested for ctDNA later): patients undergo active surveillance Arm II (blood tested for ctDNA at baseline): patients are assigned to 1 of 2 groups Group I (ctDNA detected): patients will undergo chemotherapy Group II (ctDNA not detected): patients undergo active surveillance After completion of study treatment, patients are followed up at 12 months and then every 6 months for 2 years	1,408	Rate ctDNA clearance, RFS in ctDNA+	ctDNA prevalence following resection
NCT04120701	France	ctDNA	LB to guide the post-treatment therapy in stage II CRC (chemo *vs.* observation)	Not provided	1,980	DFS in ctDNA+	n/a
NCT04264702 BESPOKE	USA	ctDNA (SIGNATERA™)	LB to guide post-treatment therapy in stage II/III CRC	Blood sample from patients who have undergone surgery for stage I to IV CRC are drawn. Patients will be followed for up to two years with periodic whole blood collection	1,000	Impact of ctDNA on adjuvant therapy, ctDNA detected recurrence	Molecular residual disease, rate of metastatic resection

Table 3 (*continued*)

Table 3 (*continued*)

Study	Country	Type/technique	Summary/ intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT03803553	USA	CtDNA (LUNAR-1)	LB to guide post-treatment therapy in MCRC (chemo *vs.* targeted *vs.* immune *vs.* observation)	Patients with stage III CRC following resection assigned into 1 of 3 groups based on ctDNA results: ctDNA+: FOLFIRI ctDNA+: active surveillance ctDNA–: active surveillance	500	DFS for ctDNA+ receiving additional treatment compared to ctDNA+ who are observed, ctDNA clearance rate	OS, DFS
NCT02997241 CCTDRP	China	ctDNA	Determine relationship between change in gene copies and recurrence	Phase I component: predict recurrence through Oncocare™ Phase II component: patients placed into four groups on the basis of genetic risk judged by Oncocare™ and clinical risk judged by clinical routine method	500	Rate of treatment of chemo based on standard of care *vs.* with ctDNA	
NCT04775862	Saudi Arabia	ctDNA	LB to evaluate RAS status and guide rechallenge with anti-EGFR in advanced CRC	*RAS* wild type and left sided primary disease receive standard chemotherapy with an anti *EGFR* mAb. Upon progression of disease, second line systemic chemotherapy ± anti-*VEGF* antibody will be given as per standard of care. With progression, patients will be enrolled into the study as per inclusion criteria, and a cfDNA blood test will be drawn, and *RAS* status will be examined. If *RAS* is wildtype, then the investigator will decide whether to re-challenge with an anti EGFR antibody, or give standard of care third line chemotherapy	60	Response rate, PFS	Rate of RAS wt after progressions using ctDNA
NCT03436563	USA	ctDNA	Evaluate immunotherapy for MSI-H unresectable MCRC and ctDNA+ patients	Patients receive M7824 IV over 1 hour on days 1 and 15. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity or for six doses in patients with detectable ctDNA following resection of all known liver metastases	74	Response rate, clearance of ctDNA	PFS, OS, DFS, adverse events

Table 3 (*continued*)

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Study	Country	Type/technique	Summary/ intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT03765736 COLOMATE	USA	ctDNA	LB to identify genetic mutations in MCRC or unresectable CRC	Screens patients with colon or rectal cancer that has spread to other places in the body (metastatic) or cannot be removed by surgery (unresectable) for genetic mutations via blood samples for recommendation to a molecularly assigned therapy	500	Proportion of patients with actionable genomic profile	n/a
NCT04670588	USA	ctDNA	Determine the feasibility of tumor response assessment by ctDNA in patients with locally advanced rectal cancer undergoing total neoadjuvant therapy	Peripheral blood sample obtained 4 weeks before neoadjuvant therapy. For patients with 16 and 8 week therapy respectively, 3 and 2 blood samples for ctDNA are obtained. Tumor response rate assessed by ctDNA will be compared with the response rate assessed by the standard method to explore if a significant correlation exists between these two response assessment methods	30	Mean serum ctDNA concentration	Response based on serum ctDNA level, and standard clinical assessments

LB, liquid biopsies; ctDNA, circulating tumor DNA; CRC, colorectal cancer.

disease resistance is identified radiologically and there is concern for mutation. For example, LB potentially guides discontinuation of an *EGFR* inhibitor when a new *KRAS*/*RAS* mutation is identified on ctDNA.

- ❖ Post-surgical LB to evaluate MRD following resection is selectively used to identify patients who have a higher risk of recurrence. This information can occasionally help guide adjuvant therapy discussions; however, we would caution against its routine use in clinical practice until prospective trials show a benefit from early detection and treatment.

In our view, ctDNA should not be used as a decision point for de-escalation of ACT until fully studied in prospective trials given the relatively poor sensitivities for these tests (generally less than 50% sensitive for single time point). LB is provided by independent companies (e.g., Natera Inc., San Carlos, CA, USA) and is selectively used for surveillance with sequential LBs at progressive intervals in combination with traditional biochemical tests (i.e., serum CEA levels). The tests used are primarily tumor non-informed (i.e., Guardant360) at initiation and during treatment while tumor informed (i.e., Natera) are used for detecting recurrence (16).

Discussion

These active LB trials reveal the broad investigation of the many possible uses of LB as well as its pathophysiology. By breaking down the setting of LB use in current ongoing clinical trials, we can better understand the focus and desired integration of this technology. Of the 29 clinical trials, four are evaluating LBs in the screening setting, eleven are looking at non-interventional LB use, ten are focused on interventional LB, and four in the surveillance setting. Multiple recent in-depth reviews (2,16-20). have extensively outlined the potential impacts of LBs on clinical practice and the theoretical benefits of early detection, improved prognostication, ACT escalation, ACT de-escalation, LB guided ACT adjustments, and earlier identification of recurrence. Moreover, it can be used as a

Table 4 Active trails regarding LB for surveillance

Study	Country	Type/ technique	Summary/intervention	Study protocol	Accrual target	Primary outcome	Secondary outcome
NCT03883802 NeoFox	Spain	ctDNA	Tolerability and effect of Foxy-5 in neo-adjuvant setting for CRC	The level of ctDNA in plasma as a surrogate for disease recurrence in patients with *Wnt-5a* low colon cancer treated with Foxy-5.	100	Adverse events, ctDNA as marker for disease free period	OS, DFS, RFI
NCT04084249 IMPROVE-IT2	Denmark	ctDNA	LB to guided post-treatment surveillance	Patients with stage III or high-risk stage II assigned into two groups Experimental: ctDNA guided surveillance No intervention: standard Danish follow-up program	254	Fraction of patient with recurrence receiving curative intent treatment	OS, time to clinical recurrence
NCT03484195	China	ctDNA	Evaluate the efficacy of NAC FOLFOXIRI in locally advanced colon CA	Patients with locally advanced colon cancer treated with 4 cycles of neoadjuvant chemotherapy followed by surgical resection. PET-CT scanning performed before and after the neoadjuvant chemotherapy to assess SUV max changes. The ctDNA in peripheral blood before and after each cycle of neoadjuvant chemotherapy will be detected	30	Rate of tumor downstaging	Relationship between ctDNA and survival, DFS, OS
NCT04046445 KISIMA-01	USA	ctDNA	Phase Ib for ATP128 alone or with BI 754091 for stage IV CRC MSS anti PD-1 non-responders	Patients with CRC stage IV assigned in one of the following groups: Cohort 1a: 6 patients with stage IV CRC Cohort 1b: 6 patients with stage IV MSS/MMRp CRC with progression Cohort 2a: 5 patients with stage IV MSS/MMRp CRC with progression Cohort 2b: 15 patients with stage IV MSS/MMRp with liver-limited CRC Cohort 2c: 19 patients with stage IV MSS/MMRp CRC with progression	32	Safety and tolerability	Detect early signal of relapse by ctDNA
NCT03615170	China	ctDNA	Application of ctDNA test in the diagnosis and treatment of patients with advanced rectal cancer	Not provided	200	Disease free survival	n/a

LB, liquid biopsies; ctDNA, circulating tumor DNA; CRC, colorectal cancer.

reliable biomarker for treatment response monitoring (21). However, the standardization of protocols and assays across institutions, has not kept up with the strong desire to include ctDNA within clinical trials or clinical care.

The National Cancer Institute's recent publication and recommendation to address implementation barriers for the use of ctDNA in CRC merits attention (8). This NCI paper accepts ctDNA as a viable marker for MRD. For patients without tumor tissue available, recommendations state ctDNA provides reliable tumor material for analysis. They endorse next-generation sequencing-based multigene assays as the superior technique as opposed to the PCR-based assays. Noting the variability of the ctDNA assays and pre-analytical variables, the NCI stresses the importance of standardization of practices. Proactive collaboration in creating high-quality databases that allow for subsequent pooled analysis is essential for establishing clinical utility. Overall, the NCI task force simply recommends the continued evaluation of these technologies with emphasis on collaborative initiatives (8).

Though the current NCI recommendations do not entirely guide LB use, their conclusions for achieving cohesive and reproducible results are actionable. Certain settings for LB use, such as surveillance, have lower barriers for entrance into clinical practice (22,23). There are a few active LB trials that are promising across each setting. In the screening setting, AL EMERGE Trial in CRC (NCT03688906) evaluated 3,275 asymptomatic patients. Dr. Putcha *et al.* (24) reported 94% sensitivity and specificity rate in screening for stage I/II CRC. The follow-up trial, PREEMT CRC (NCT04369053) is actively recruiting patients with a goal of 25,000. In the non-interventional LB setting, CITCCA (Scandinavia), is one of the larger trials with a goal of 300 patients evaluating perioperative ctDNA and its role in prognostication. In the interventional LB setting, the CIRCULATE trial out of Germany randomized 4,812 patients with stage II CRC with ctDNA+ to ACT or follow-up. In the surveillance setting, the IMPROVE-IT2 trial out of Denmark randomizes CRC patients to ctDNA surveillance or standard Danish follow-up. One of the more valuable trials that is directly in line with NCI recommendations comes from Canada. Though it is not immediately impactful, the LIBERATE trial aims to establish an institution wide LB protocol.

Reimbursement plays an important role in the clinical adoption of these technologies as the evidence regarding their utility unfolds. As the evidence continues to emerge, reimbursement will likely impact the clinical adoption of these technologies. The cost, though continually dropping, must be factored into decision-making as the potential for sequential LB in numerous cancers could significantly impact the cost of cancer care. A recent JNCCN review described the specifics of ctDNA reimbursement from Medicare and more than 200 commercial payers between 2015 and 2019 (25,26). The variation in insurance policy structures, indications for testing, coverage by test type, and the documentation required for approval of testing creates an exceedingly confusing landscape for all parties involved. While ctDNA coverage has expanded from a previously near-exclusive use in NSCLC to pan-cancer use, its coverage remains significantly (27) limited. Solid tumor analysis for non-specified gene (i.e., Grardant360) was covered in 4 policies (14%) of private payers and in 4 Medicare policies. Although sequential LB throughout treatment provides more accurate and more actionable data, most payers cover one-time tests for treatment selection. Only 11% of the few payers covering any LB testing, cover sequential ctDNA testing for disease and treatment monitoring (25-27).

Conclusions

The desire to implement and benefit from LB across CRC care continues to grow. Technological innovations, including next-generation sequencing and pooled algorithmic automated analysis, combined with sequential data extraction has led to highly sensitive and specific tests. The intended use of LB throughout the diagnosis, treatment, and surveillance of CRC is actively under investigation. There is broad acceptance that ctDNA can detect MRD and these technologies are selectively being integrated into practice. Mayo Clinic currently uses ctDNA to adjust treatment in stage IV disease, to identify the low-risk stage II patients that may benefit from ACT, and selectively for surveillance. However, the lack of standardization in LB protocols—preanalytical processing, storage, and analytical methods—has prevented acceptable cross study verification. Because of this, NCI recommendations are still broad-based and call for continued collaborative evaluation of LB use. The collaboration of national databases, such as BloodPAC in North America and the European Liquid Biopsy, will be key to further the safe, effective, and clinically useful implementation of LB technologies.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-470/rc

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