A Multiomic Liquid Biopsy for the Earlier Detection of Colorectal Cancer

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ABSTRACT

Timely diagnosis and intervention in colorectal cancer are critical to improving patient outcomes and limiting disease progression. Screening of average-risk individuals is essential for detecting tumors at an earlier, more treatable stage. However, adherence to current screening programs remains suboptimal. Liquid biopsies represent a promising alternative to stool-based tests and may play a key role in optimizing colorectal cancer detection and diagnostic pathways. In this study, 957 patients were recruited across various clinical sites in the United States: 48 with colorectal cancer, 157 with advanced precancerous lesions (APL), 331 with nonadvanced lesions, and 421 with a negative colonoscopy diagnosis. Blood was obtained from patients either prior to scheduled colonoscopy or before surgical resection and any anticancer therapies. Streck plasma samples were analyzed by the Dxcover Liquid Biopsy Platform and classified using machine learning algorithms. When colorectal cancer was classified against all other groups, the ROC curve generated an AUC value of 0.95, and test sensitivity and specificity were 90% and 89%, respectively. The diagnostic model accurately predicted 75% of stage I (3/4), 100% of stage II (15/15), 93% of stage III (14/15), and 100% of stage IV (6/6) colorectal cancers. For the advanced colorectal neoplasia model, 29% of APL were detected. A simple blood test with high sensitivity for early-stage colorectal cancer could significantly enhance patient outcomes. With continued development, this liquid biopsy has the potential to make a substantial impact on the early detection of colorectal cancer.

Prevention Relevance: Timely diagnosis and intervention in colorectal cancer are critical to improving patient outcomes. A simple blood test with high sensitivity for early-stage colorectal cancer could significantly enhance patient outcomes. With continued development, this liquid biopsy has the potential to make a substantial impact on the early detection of colorectal cancer.

Introduction

Colorectal cancer is among the most prevalent and lethal cancers globally, with nearly 2 million new cases reported in 2020 (1). However, early detection and intervention can improve the survival rates and quality of life of affected patients. The average 5-year survival rate is approximately 91% for early-stage colorectal cancer but drops dramatically to around 15% at stage IV (1). Although cancer screening programs are essential for detecting early-stage tumors in asymptomatic individuals, current screening methods have notable limitations. Colonoscopy remains the gold standard for colorectal cancer diagnosis; however, its invasive nature and limited resource availability make it unsuitable as a first-line screening tool. Other screening options include flexible sigmoidoscopy, computed tomography (CT) colonography, and less invasive approaches such as stool- or blood-based tests.

The US Food and Drug Administration (FDA) has approved several types of stool-based tests to screen for colorectal cancer: guaiac fecal occult blood test, fecal immunochemical test (FIT), and the Cologuard (Exact Sciences) multitarget stool deoxyribonucleic acid (DNA) test. Perhaps the most developed stool-based test in the colorectal cancer diagnostics field is Cologuard (Exact Sciences), which is a multitarget stool test (2). The Cologuard test aims to detect fecal hemoglobin in stool and utilizes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay (3). The clinical validation of the next-generation Cologuard test (Cologuard Plus) was published in 2024 as part of the BLUE-C trial, demonstrating enhanced performance over the original version, with 95% sensitivity and 94% specificity for colorectal cancer detection (4). Despite these improvements, adherence to stool-based

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screening remains a significant challenge. In a recent study involving more than 10,000 participants, fewer than 25% completed FIT within a 12- to 15-month follow-up period (5). Poor compliance is a major contributor to late-stage diagnoses, with more than half of colorectal cancer cases identified only after the disease has already progressed (6). This underscores the urgent need for alternative screening methods. Blood-based testing is emerging as a preferred option, with many individuals expressing a preference for providing a blood sample over a stool sample (7).

Liquid biopsies hold significant promise as a complement to stool-based tests. Given the discomfort often associated with stool sample collection—which can affect participation rates—a straightforward blood test may offer a more acceptable and convenient alternative for screening. Guardant Health (8) and Freenome (9) are just two examples of companies that have recently undertaken large-scale clinical validation trials to assess the utility of their blood-based technologies. The Shield test (Guardant Health) has now been approved by the FDA in 2024 (10).

A promising liquid biopsy technique for earlier colorectal cancer detection is the clinical use of Fourier transform infrared spectroscopy (11). The Dxcover Liquid Biopsy Platform is a rapid, multiomic test that interrogates a blood plasma (or other derivative) sample with infrared radiation to produce a distinctive signature that represents the whole biomolecular profile of the sample (12). When biological samples are irradiated with infrared light, it causes the molecules within them to vibrate. These vibrations occur at distinct frequencies, which can be visualized as an infrared spectrum. The spectral readout encompasses signals from metabolites, electrolytes, carbohydrates, lipids, proteins, exosomes, and other markers. Peaks within this spectrum are a "fingerprint" of the biomolecules contained within the sample.

Combining information-rich spectral data with machine learning analysis, the technology can be adjusted for higher sensitivity or specificity, depending on clinical objectives and the requirements of different healthcare systems. The field of "-omics" is well established within liquid biopsy research and encompasses areas such as genomics, transcriptomics, proteomics, lipidomics, metabolomics, and, more recently, phenomics. Each "-omic" category is considered to capture distinct biological markers tied to the fundamental characteristics of cancer. Rather than focusing on individual tumor-derived biomarkers, the Dxcover Liquid Biopsy Platform is a "multiomic" technique that encompasses the full range of diagnostic information from both the tumor and the nontumor response, due to the broad range of spectral information detectable from the blood (12). Furthermore, unlike most genetic-based approaches, this method does not require DNA isolation or extraction, offering advantages in both cost and time efficiency as a result of the simplicity of the methodology.

The Dxcover Liquid Biopsy Platform has been developed for use as an early detection cancer test, with the first indication in brain cancer (11). The potential of the blood test for multiple cancer detection was recently reported, in which eight different cancer types were examined with the aim of distinguishing the cancers from asymptomatic and symptomatic noncancer patients (13). Additionally, in a retrospective cohort of patients comprising 100 with colorectal cancers, 92 with adenoma samples removed by surgical resection, and 104 with colonoscopy screening controls diagnosed as noncancer, the test reported 80% colorectal cancer sensitivity and 59% sensitivity for advanced adenoma, at 90% specificity (14). In this article, we further assess the technology, with a focus on colorectal cancer detection. The aim of this discovery study was to determine the diagnostic accuracy of the blood test for early detection of colorectal cancer in an average-risk population. A rapid and cost-effective blood test with high sensitivity for early-stage colorectal cancer could enhance screening strategies, improve patient outcomes, and help reduce the overall burden of colorectal cancer.

Materials and Methods

Study overview

Patients were recruited across various clinical sites in the United States from January 2024 to February 2025. In total, there are 957 patients included in the study: 856 patients were recruited prospectively by Precision for Medicine, a contract research organization (Protocol #PFM064), and 101 were obtained from biobanks (Precision for Medicine; BioIVT). The study was conducted in accordance with ethical guidelines as stipulated in the Declaration of Helsinki, and patients were recruited after approval from the Advarra Institutional Review Board (IRB) and Precision for Medicine Central IRB. Written informed consent was obtained for all patients. The dataset included 48 patients with colorectal cancer, 157 with advanced precancerous lesions (APL), 331 with nonadvanced lesions (NAL), and 421 with a negative colonoscopy diagnosis (**Table 1**).

The patients have been classified into disease groups based on the following criteria:

- Colorectal cancer: Adenocarcinoma of the colorectum, stages I to IV
- APL: Any size of adenoma with high-grade dysplasia/carcinoma *in situ* or with a villous growth pattern (≥25%) and any adenoma or sessile serrated lesion (SSL) or hyperplastic polyps ≥10 mm in size
- NAL: Up to 3 adenomas [including sessile serrated adenomas (SSA), sessile serrated polyps (SSP), and nonadvanced] <10 mm in size
- Negative: No findings on colonoscopy or no adenocarcinomas, adenomas, or other neoplasias, including hyperplastic polyps <10 mm upon histopathology

Detailed classification can be found in Supplementary Table S1.

Table 1. Patient cohort demographics.

Characteristics	Colorectal cancer (*n* = 48)	APL (*n* =157)	NAL (*n* = 331)	Negative (*n* = 421)	Total (*n* = 957)
Age, years					
Mean	64	61	61	58	60
Min–max	42–83	30–80	45–83	42–82	30–83
Sex, *n* (%)					
Female	19 (39.6)	84 (53.5)	172 (52)	242 (57.5)	517 (54)
Male	29 (60.4)	73 (46.5)	159 (48)	179 (42.5)	440 (46)
Race, *n* (%)					
Asian	0 (0)	0 (0)	4 (1.2)	3 (0.7)	7 (0.7)
Black or African American	1 (2.1)	21 (13.4)	40 (12.1)	45 (10.7)	107 (11.2)
White	44 (91.7)	128 (81.5)	283 (85.5)	363 (86.2)	818 (85.5)
Other or unknown	3 (6.3)	8 (5.1)	4 (1.2)	10 (2.3)	25 (2.6)
Ethnicity, *n* (%)					
Hispanic or Latino	2 (4.2)	9 (5.7)	10 (3)	14 (3.3)	35 (3.7)
Non-Hispanic or non-Latino	44 (91.7)	129 (82.2)	308 (93.1)	396 (94.1)	877 (91.6)
Unknown	2 (4.2)	19 (12.1)	13 (3.9)	11 (2.6)	45 (4.7)
Cancer stage, *n* (%)					
I	4 (8.3)	—	—	—	4 (0.4)
II	15 (31.3)	—	—	—	15 (1.6)
III	15 (31.3)	—	—	—	15 (1.6)
IV	6 (12.5)	—	—	—	6 (0.6)
Unknown	8 (16.7)	—	—	—	8 (0.8)

The dataset is age- and sex-matched. The mean age of participants is 60, which falls within the typical age range for average-risk screening (45–85). The inclusion criteria for the prospective recruitment consisted of participants who were aged 45 to 85 years, asymptomatic, at average risk of colorectal cancer, intending to undergo a standard-of-care screening colonoscopy, and willing to consent to a blood draw prior to pre–bowel preparation administration within 90 days of the date of the investigational blood draw. The main exclusion criteria included symptomatic patients, a known diagnosis of inflammatory bowel disease, a prior history of cancer of any type, and currently taking (or having a history of) any antineoplastic or disease-modifying antirheumatic drugs. Of the 856 patients recruited during the prospective collection, there were 102 patients with APL but only two colorectal cancer cases. Therefore, the banked cases (46 with colorectal cancer and 55 with APL) were obtained to supplement the dataset with positives to ensure there were a sufficient number of patients with colorectal cancer for algorithm training. These samples were processed in the same manner as the prospective collection. In both groups, blood was drawn from patients either prior to scheduled colonoscopy or before surgical resection and any anticancer therapies.

Sample processing

Blood samples were collected with venipuncture using Streck plasma BCT (Streck), and plasma was obtained through a double-spin centrifugation process. To separate plasma, the whole blood was centrifuged at 1,600 *g* for 10 minutes at room temperature (18°C–25°C). The upper plasma layer was then removed and transferred to a new conical tube. The plasma aliquot was then centrifuged at 16,000 *g* for 10 minutes. The double-spun plasma was aliquoted and stored at −80°C. The samples were then shipped to the Dxcover laboratory in the UK for analysis.

Patient sample analysis

The procedure for sample analysis is described elsewhere (13). Briefly, plasma aliquots were removed from frozen storage (−80°C) and thawed for up to 30 minutes at room temperature (18°C–25°C) and inverted 3 times to ensure mixing before use. Each patient sample was prepared for analysis by pipetting 3 μL of plasma onto each of the three sample wells of the Dxcover Sample Slide (Dxcover Ltd.). Prepared slides were dehydrated at 35°C for at least 10 minutes to create dried sample films (15). Each dried sample slide was then placed into a Dxcover Autosampler (Dxcover Ltd.) and analyzed by the Dxcover Liquid Biopsy Platform (Dxcover Ltd.). Three spectra (**Fig. 1**) were collected for each sample well, resulting in nine replicates per patient. Analysts were blinded to the true diagnoses during the analysis period. The technology is further discussed in previous publications (16–18).

Data analysis

Machine learning models were developed to build a diagnostic algorithm from the known patient population and enable disease predictions for unknown samples in the test sets. A nested cross-validation (CV) strategy was used to develop the models to reduce sampling bias (Supplementary Fig. S1). In this approach, patients were randomly split into training and test sets with a 70:30 split, repeated 51 times. Model hyperparameters were tuned on the training set (70%)

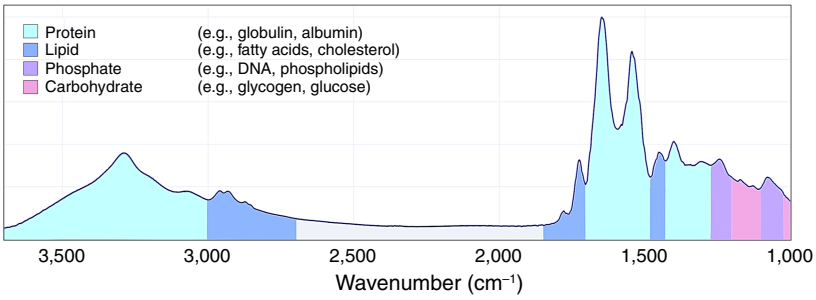

Figure 1.
Example of an infrared spectrum detailing the main blood plasma components. The colors represent the regions of the spectrum that are assigned to specific biomolecular classes: proteins (light blue), lipids (dark blue), phosphates (purple), and carbohydrates (pink).

using fivefold CV, which was used to make predictions for the spectra in the test set (30%). As each patient sample provides nine spectra, the final diagnosis was taken as the consensus prediction (maximum vote) from all nine spectra. Patient samples were reported as positive or negative according to the diagnostic algorithm results. Spectra from individual patients were not allowed to be present in both the training and test sets for a given resample. For each patient, the predictions from all the test sets in which that patient is present were collected, and the majority vote was taken as the overall test set prediction for that patient. From this, an overall detection rate (sensitivity or specificity) was calculated as the ratio of correct predictions to the total number of predictions. Sensitivity will be reported for colorectal cancer (overall and split by stage) and APL. Specificity will be reported for the NAL and negative patients. Mean ROC curves were calculated using bootstrap sampling. Additionally, the statistics were computed in an alternative way to assess differences between machine learning methods. The sensitivity, specificity, and stage-based detection rates were calculated for each resample and then averaged across all resamples. A threshold was selected for the CV from each resample, and sensitivity and specificity were identified from the test set based on the chosen threshold per resample. The sensitivity and specificity for each resample are then subsequently averaged. The results from this approach can be found in Supplementary Table S2.

Results

Colorectal cancer

The detection of colorectal cancer was assessed by initially classifying colorectal cancer against all other groups; this model may be of interest as a risk stratification application for symptomatic patients. The mean ROC curve is illustrated in **Fig. 2**. The AUC value is 0.95 [95% confidence interval (CI), 0.92–0.98], which indicates excellent discriminating ability (19). When specificity was tuned to 90% for the CV, the resulting test set sensitivity and specificity were 90% and 89%, respectively. The diagnostic model accurately predicted 75% (95% CI, 30.1%–95.4%) of stage I (3/4), 100% (95% CI, 79.6%–100%) of stage II (15/15), 93% (95% CI, 70.2%–98.8%) of stage III (14/15), and 100% (95% CI, 61%–100%) of stage IV (6/6) colorectal cancers. There were eight cases of colorectal cancer with unknown stage, of which 63% (95% CI, 30.6%–86.3%; 5/8) had a positive test result.

Advanced colorectal neoplasia

The patients with APL were then grouped with colorectal cancer into the positive class to assess the test performance for advanced colorectal neoplasia, which is the most applicable model for asymptomatic colorectal cancer screening and allows for the determination of APL sensitivity. The detection rates for each category are outlined in **Table 2**, which are based on the test set output after selecting the decision threshold for 90% specificity on the CV set. The overall colorectal cancer sensitivity for this model was 92%, with 95% of stage I and II cancers predicted correctly, and a specificity of 88%. Twenty-nine percent of APLs were detected with this model, and notably, 44% of adenomas with a villous growth pattern were successfully identified. The sensitivity was lower for the group of SSLs and large hyperplastic polyps (22%).

The specificity was 90% for the negative cases in which there were no findings upon colonoscopy and no biopsies were taken. The detection rate of the NAL group varied depending on the size and number of polyps. For the patients with NAL, the detection rate was higher (90%) for those with either smaller (≤5 mm) or a lower number of adenomas (1 or 2) than for the NAL cases with larger polyps (>5 and <10 mm in size; 85%) or a higher number of polyps (≥3 adenomas; 83%). The AUC for this model's ROC curve was 0.7 (95% CI, 0.65–0.74; Supplementary Fig. S2). At the 90% specificity CV threshold, 29% of APL and 92% of colorectal cancers were detected. However, the technology allows for the machine learning models to be tailored toward higher sensitivity (or specificity) depending on clinical priorities. A greater APL sensitivity can be achieved with a reduction in specificity (Supplementary Fig. S3). For example, APL sensitivity is 23% when specificity is tuned to 95% but increases to 40% at 80% specificity.

Discussion

This simple, rapid liquid biopsy holds strong potential as an alternative diagnostic tool for colorectal cancer detection. In the model optimized for colorectal cancer detection, the training set accounted for 90% sensitivity when setting the CV specificity at 90%. Furthermore, when split by stage, the

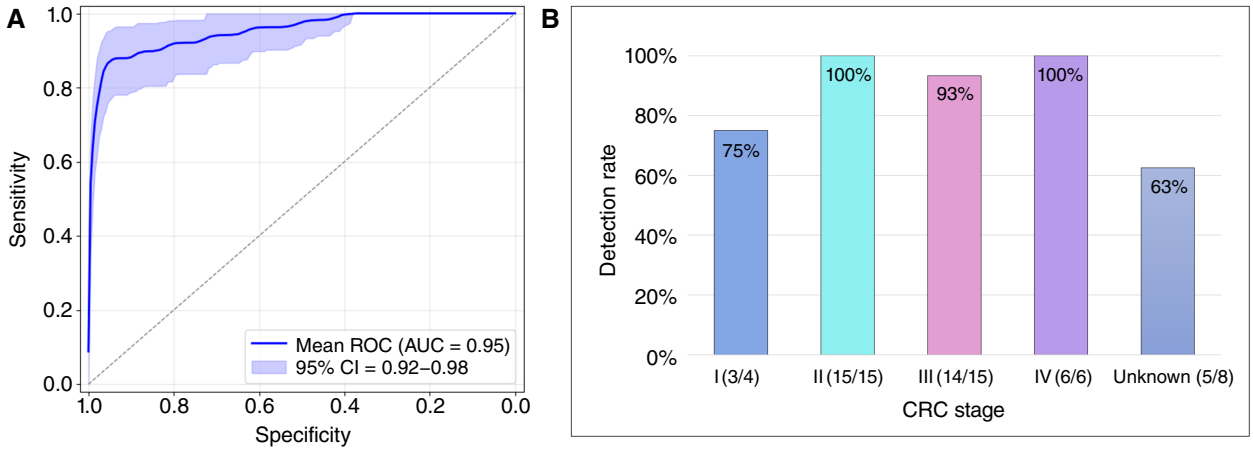

Figure 2.

Mean ROC curve and stage-based detection rates. **A,** The ROC curve, with 95% CIs (shaded), for the classification of colorectal cancer (CRC) against all other groups (APL + NAL + Negative), showing the trade-off between sensitivity and specificity. **B,** The detection rates split by stage when tuned to 90% specificity for the cross validation (CV).

test successfully detected 95% of stage I and II tumors, showing great potential for early-stage detection. The underlying machine learning algorithm used in this discovery study can be tailored to meet the specific needs of different diagnostic pathways and healthcare systems—for instance, prioritizing sensitivity or specificity while maintaining the other at an acceptable level. The results from this discovery study suggest that this test could surpass the current thresholds set by the Centers for Medicare & Medicaid Services; the minimum performance levels set for coverage of colorectal cancer tests are 74% sensitivity and 90% specificity (20).

For the advanced colorectal neoplasia model, 29% of APLs were detected. Although the sensitivity for detecting these precancerous lesions is lower than that for colorectal cancer, it remains a promising result given the known challenges in identifying such conditions with existing screening methods. For example, the Shield test (Guardant Health) was recently

Table 2. Test performance for the assessment of advanced colorectal neoplasia; algorithm tuned to 90% specificity for the CV set with Wilson Score CIs at 95%.

	No. detected/total	Sensitivity or specificity (Wilson score 95% CI), %
Positive findings (sensitivity)		
Colorectal cancer, by stage	44/48	91.7 (80.4–96.7)
I	3/4	75 (30.1–95.4)
II	15/15	100 (79.6–100)
III	13/15	86.7 (62.1–96.3)
IV	6/6	100 (61–100)
Unknown	7/8	87.5 (52.9–97.8)
APL	46/157	29.3 (22.7–36.8)
Adenoma with villous growth pattern (≥25%), any size	10/23	43.5 (25.6–63.2)
Adenoma ≥10 mm in size	29/102	28.4 (20.6–37.8)
SSL ≥10 mm (SSA, SSP, traditional serrated adenoma) and hyperplastic polyps ≥10 mm	7/32	21.9 (11–38.8)
Negative finding (specificity)		
NAL	288/331	87 (83–90.2)
Adenoma(s) including SSA, SSP, nonadvanced, >5 mm in size, <10 mm in size, 1 or 2 adenomas	86/101	85.1 (76.9–90.8)
Adenoma(s) including SSA, SSP, nonadvanced, ≤5 mm in size, ≥3 adenomas	49/59	83.1 (71.5–90.5)
Adenoma(s) including SSA, SSP, nonadvanced, ≤5 mm in size, 1 or 2 adenomas	153/171	89.5 (84–93.2)
Negative	373/421	88.6 (85.2–91.3)
No colorectal neoplasia upon histopathologic review; includes hyperplastic polyps <10 mm	97/115	84.3 (76.6–89.9)
No findings on colonoscopy and no biopsy(ies) taken	276/306	90.2 (86.3–93)

approved by the FDA. In their recent ECLIPSE trial, the test achieved 83% sensitivity for colorectal cancer at a set 90% specificity for any advanced neoplasia. When split by stage, their test was able to detect 81% of colorectal cancer cases for clinical stages I to III but only 55% of stage I cases alone. However, only 13% of advanced adenomas (APLs) were detected in this pivotal clinical trial (21). Freenome also recently reported similar performance to the Shield test, achieving 12.5% APL sensitivity in their clinical validation study (22), which emphasizes the challenge that current blood-based technologies are striving to overcome. As shown in Supplementary Fig. S3, a reduction in specificity can lead to a corresponding increase in APL sensitivity (e.g., 40% APL sensitivity with 80% specificity). Currently, the CMS does not specify sensitivity requirements for adenoma detection in its colorectal cancer screening coverage decisions (23). However, this topic has been widely debated within the field, and it is possible that future CMS guidelines may incorporate criteria for APL sensitivity and the corresponding test specificity (24).

The Dxcover Liquid Biopsy Platform may be utilized in different ways depending on the desired clinical application (**Fig. 3**). For example, it could be placed as an additional gatekeeping test, reducing the number of patients going to further tests for definitive diagnoses, that is, medical imaging. Alternatively, it could be applied as an add-on test, improving the sensitivity of early detection efforts and directing more patients to colonoscopy. Furthermore, the results presented here are based on spectral data alone, yet there may be scope to improve test performance when combined with additional information, such as biomarker data—for example, protein tumor markers—or clinical risk factors.

The Select MDx test for prostate cancer (MDxHealth) is an example of a commercially available liquid biopsy that combines biomarker levels with risk factors (25). Select MDx is directed at symptomatic patients who have an abnormal prostate-specific antigen (PSA) level or an abnormal digital rectal exam. The results from this genomic urine liquid biopsy are used to decide if the patient moves forward with medical imaging followed by biopsy or just has routine PSA follow-up. The Dxcover liquid biopsy could be employed in a similar fashion, in which the spectral output, biomarker data, and clinical risk factors are used in combination. Additionally, collaborations between liquid biopsy technologies could pave the way for a more effective screening tool by examining the combination of various tests that are based on different phenomena. The promise of this liquid biopsy is further highlighted when considering adherence rates across different screening methods, for example, stool-based versus blood-based tests (26).

The findings presented here underscore the potential of this technology to serve as either a screening liquid biopsy or a triage tool to help prioritize patients for colonoscopy, thereby

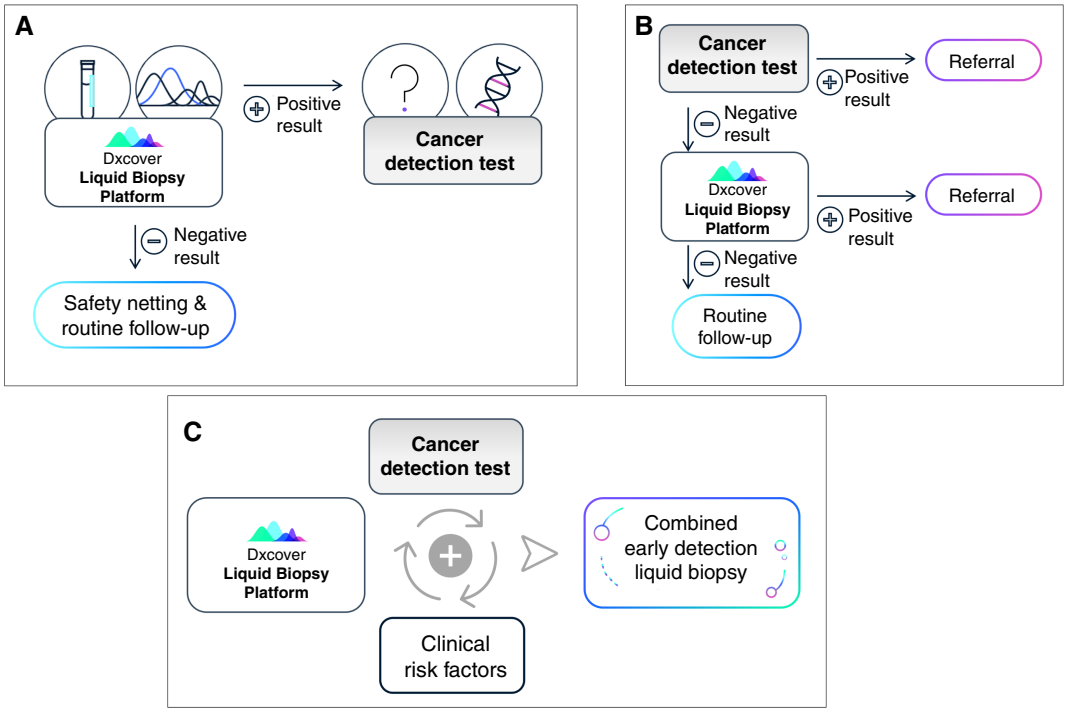

Figure 3.

The Dxcover Liquid Biopsy Platform can be utilized for various clinical uses. The test could be employed as follows: (**A**) an efficient gatekeeper test to triage patients for further confirmatory testing, (**B**) an add-on test to supplement existing pathways and improve detection, and (**C**) a combinatorial pathway consisting of information from various sources to generate super algorithms.

alleviating pressure on overburdened waiting lists. However, it is important to note some limitations of the study. First, we have a mixture of prospective and retrospective cases included in this dataset, which can often lead to bias in algorithm training. The prospective recruitment was supplemented with samples from patients with confirmed colorectal cancer from biobank repositories to ensure there were sufficient positive cases for algorithm training. There can also be limited clinical data available for retrospective cases, for example, those with unknown cancer stage in this study ($n = 8$). Therefore, future studies would benefit from larger prospective trials to eradicate the need for enrichment with retrospective cases. Additionally, all prospective samples and some of the banked samples were collected prior to the patients receiving bowel preparation. In contrast, the bowel preparation status was unknown for most of the banked cases. That said, all patients were treatment-naïve at the time of blood draw, and the blood samples were all processed in the same manner. Further studies are needed to validate this technology, involving larger patient cohorts and exploration of combinatorial diagnostic pathways. A simple blood test with high sensitivity for early-stage colorectal cancer could significantly enhance patient outcomes. With continued development, this liquid biopsy has the potential to make a substantial impact on the early detection of colorectal cancer.

Data Availability

The derived data supporting the findings of this study are available within the article and its supplementary data files.

Authors' Disclosures

J.M. Cameron reports other support from Dxcover Ltd. during the conduct of the study and outside the submitted work. R.G. McHardy reports other support from Dxcover Ltd. during the conduct of the study and outside the submitted work. A. Sala reports employment with Dxcover Ltd. H.J. Butler reports personal fees from Dxcover Ltd. outside the submitted work, a patent for Infra-red spectroscopy system issued, and directorship with Dxcover Ltd. D.S. Palmer reports a patent for Colorectal Cancer Detection (WO2024213878A1) pending and D.S. Palmer is cofounder and chief scientific officer of Dxcover, a company that develops spectroscopic liquid biopsies. P.J. Mitchell reports grants and other support from Dxcover during the conduct of the study. E. Parkin reports grants from Dxcover during the conduct of the study. M.J. Baker reports other support from Dxcover Ltd. during the conduct of the study, other support outside the submitted work, and a patent for CRC pending to Dxcover Ltd. No disclosures were reported by the other authors.

Authors' Contributions

J.M. Cameron: Conceptualization, data curation, supervision, visualization, methodology, writing–original draft, writing–review and editing. **R.G. McHardy:** Data curation, software, formal analysis, validation, visualization, methodology, writing–review and editing. **A. Sala:** Conceptualization, investigation, visualization, methodology, writing–review and editing. **H.J. Butler:** Conceptualization, supervision, methodology, project administration, writing–review and editing. **D.S. Palmer:** Conceptualization, supervision, methodology, project administration, writing–review and editing. **P.J. Mitchell:** Writing–review and editing. **E. Parkin:** Writing–review and editing. **S. Moug:** Writing–review and editing. **M.J. Baker:** Conceptualization, resources, supervision, funding acquisition, visualization, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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