6506 Early Colorectal Cancer Detection with a Spectroscopic Liquid Biopsy

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INTRODUCTION

- **Detecting colorectal cancer (CRC) in early stages of the disease reduces mortality** by enabling the removal of pre-cancerous lesions and earlier treatments (Figure 1).
- Screening for CRC is recommended for average-risk adults aged 50-75 to detect CRC before it progresses.[2,3]
- **Most CRCs develop from adenomas**, among which advanced adenomas (AA) are considered to be the clinically relevant precursors of CRC.[4]
- Although, **current screening methodologies cannot reliably identify AAs**, highlighting the need for alternative strategies.
- Tumor derived signals are more abundant in late-stage cancer, whilst the non-tumor derived response dominates at pre-cancerous and early stages of the disease (Figure 2).
- For reliable detection of pre-cancer and early-stage cancer, screening tests must also be sensitive to signals from non-tumor sources.
- The **Dxcover® Colorectal Cancer Liquid Biopsy** is a spectroscopic test that interrogates a blood sample with infrared light, initiating molecular vibrations, and generates a distinctive signature that represents the whole biomolecular profile of the sample (Figure 3).

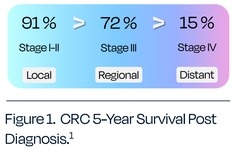


Figure 1. CRC 5-Year Survival Post Diagnosis.[1]

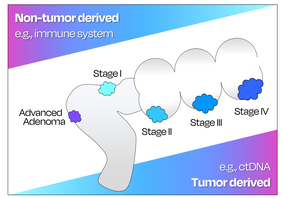


Figure 2. Availability of tumor derived information is directly related to disease progression.

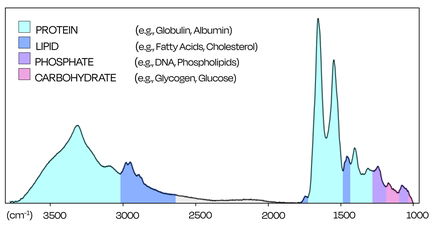
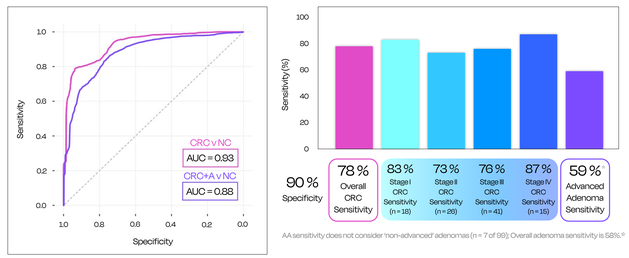


Figure 3. Infrared spectrum detailing the main blood serum components.

BLOOD TEST DETECTS 78% OF COLORECTAL CANCERS AND 59% OF ADVANCED ADENOMAS AT 90% SPECIFICITY

- **The CRC+A v NC model represents the most applicable classifier for a screening test** to identify both CRC and adenoma patients for rapid referral to colonoscopy; with an area under the curve (AUC) of 0.88, the Dxcover Liquid Biopsy is an excellent candidate for a CRC screening tool (Figure 4, left).
- From the CRC+A v NC model, at 90% specificity, **the overall CRC sensitivity was 78%**. The test successfully detected 83% of stage I, 73% of stage II, 76% of stage III and 87% of stage IV CRC. Furthermore, **59% of AA patients were predicted correctly** (Figure 4, right).
- The CRC v NC model had an AUC of 0.93 (Figure 4, left). At 90% specificity, the overall CRC sensitivity was 80%, and by CRC stage: 83% (I), 73% (II), 76% (III), and 100% (IV).



AA sensitivity does not consider 'non-advanced' adenomas (n = 7 of 99); Overall adenoma sensitivity is 58%.[6]

Figure 4. ROC curves (left) and sensitivity values at 90% specificity (right) from the CRC+A v NC model.

COMBINED PATHWAY COULD INCREASE CRC AND AA SENSITIVITIES

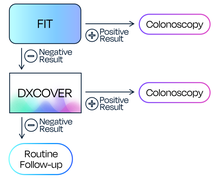


Figure 5. Combination of Dxcover test with FIT.

- CRC diagnosis relies on confirmation by colonoscopy. The Dxcover Liquid Biopsy may be utilized in different ways in the preceding diagnostic pathway. It could be placed as **an additional gate-keeping test**, reducing the number of patients going to colonoscopy; alternatively, it can be applied as **an add-on test**, improving sensitivity of early detection efforts and directing more patients to colonoscopy (Figure 5).
- If the Dxcover Liquid Biopsy is used as an add-on to FIT testing, patients would be referred for rapid colonoscopy if either test has a positive result. When the tests are maximally concordant, the combined sensitivity is simply the maximum of the two tests; all cases that would be detected by the less sensitive test are also detected by the more sensitive. When the tests are fully independent, the results are concordant only as often as we would expect due to chance alone (Figure 6, left).
- When considering adherence, **only 43% of average risk adults comply with stool-based screening**.[5,6] Hence, the 'effective sensitivity' of FIT alone is only 32% for CRC and 10% for AA (Figure 6, right).
- However, **blood-based screening has 90% adherence**.[6] Therefore, there is an even greater improvement in effective sensitivity when accounting for diverse adherence (Figure 6, right).
- FIT testing has addressable shortcomings, and **the emergence of new technologies is essential to support CRC screening.**

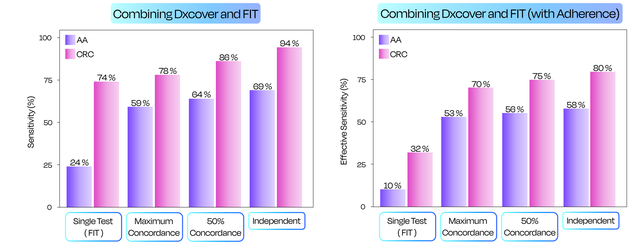


Figure 6. CRC and AA sensitivities (left) and effective sensitivities (right) of FIT combined with Dxcover® Colorectal Cancer Liquid Biopsy.

PATIENT COHORT AND METHODS

- This discovery cohort was comprised of **296 patients**, including 100 colorectal cancer, 99 adenoma, and 97 non-cancer samples (Figure 7).
- All cancer samples were collected from patients with a histopathological confirmed CRC diagnosis. Non-cancer samples comprised a variety of non-malignant conditions (Figure 7).
- The adenoma samples were categorized as 'advanced' (n = 92) if they were classed as: (i) carcinoma in situ/high-grade dysplasia/villous growth pattern (any size); or (ii) adenomas/serrated lesions > 10 mm in size. Adenomas were classed as 'non-advanced' (n = 7) if they were < 10 mm in size.[7]
- Patient blood serum samples were analyzed using the Dxcover® Liquid Biopsy Platform (Figure 8); it utilizes infrared spectroscopy combined with machine learning algorithms to predict the presence of disease.[8]
- A nested cross-validation (CV) strategy was used to develop the machine learning models. Patients were randomly split into training and test sets with a 70:30 split; this was repeated 51 times and results were then averaged. Spectra from individual patients were not allowed to be present in both the training and test sets for a given resample.

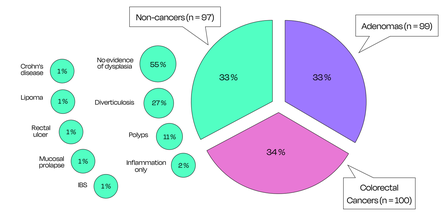


Figure 7. Full patient cohort (n = 296).

Figure 8. Dxcover® Sample Slide (left) and Dxcover® Platform (right).

DROP. DRY. DETECT.™

- We **DROP** 3µL of human blood serum onto three wells of a Dxcover® Sample Slide, leaving well 0 blank for background collection.
- After that, we **DRY** the slide in less than 10 minutes before inserting it in the Dxcover® Liquid Biopsy Platform for spectral collection.
- We then **DETECT** the presence of cancer; the spectra are fed into a trained classification algorithm for disease prediction.

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