583P A Rapid Blood Test for the Earlier Detection of Colorectal Cancer

James M. Cameron[1], Georgios Antoniou[1], Paul M. Brennan[2], Ewan Gray[1], Sharon King[3], Rose G. McHardy[1,4], Susan Moug[5], **Jennifer Nobes**[3,6], David S. Palmer[1,4], Alexandra Sala[1], Judith Strachan[6], Craig Mowat[3,7], and Matthew J. Baker[1,8]

[1]Dxcover Ltd, Suite RC534, Royal College Building, 204 George Street, Glasgow, G1 1XW, UK; [2]Translational Neurosurgery, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, EH4 2XU, UK; [3]School of Medicine, University of Dundee, Dundee, DD1 9SY, UK; [4]Department of Pure and Applied Chemistry, Thomas Graham Building, 295 Cathedral Street, University of Strathclyde, Glasgow, G1 1XL, UK; [5]Royal Alexandra Hospital, NHS Greater Glasgow and Clyde and Golden Jubilee National Hospital, Glasgow, PA2 9PN, UK; [6]Department of Blood Sciences, Ninewells Hospital and Medical School, NHS Tayside, Dundee, DD2 1SG, UK; [7]Department of Gastroenterology, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK; [8]School of Medicine, Faculty of Clinical and Biomedical Sciences, University of Central Lancashire, Preston, PR1 2HE, UK.

MADRID 2023 ESMO congress
MADRID SPAIN
20-24 OCTOBER 2023

CONSIDERATIONS

- **Detecting colorectal cancer (CRC) in early stages of the disease reduces mortality** (Figure 1).
- Screening for CRC is still recommended for average-risk adults aged 45-75, even though **early onset of CRC is rising**.[2,3,4]
- **Most CRCs develop from adenomas**, among which advanced adenomas (AA) are considered to be the clinically relevant precursors of CRC.[5]
- **Current screening methodologies** (i.e., Fecal Immunochemical Test; FIT) **cannot reliably identify AAs**, highlighting the need for alternative strategies.
- Tumor derived signals are more abundant in late-stage cancer; for reliable detection of pre-cancer and early-stage cancer, **screening tests must also be sensitive to signals from non-tumor sources** (Figure 2).

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

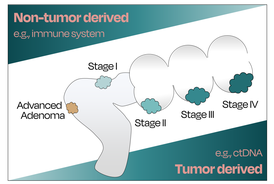

Figure 2. Trends of tumor and non-tumor derived information with CRC stages

SAMPLES AND TECHNOLOGY

- This discovery cohort contained **296 patients**: 100 colorectal cancers with histopathological confirmed diagnosis, 99 'advanced' and 'non-advanced' adenomas, and 97 non-cancers with non-malignant conditions (Figure 3).
- The adenomas 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.[6]
- Patient serum samples were analyzed using a **Colorectal Cancer Liquid Biopsy** (Dxcover Ltd., Glasgow, UK) that combines ATR-FTIR spectroscopy with machine learning algorithms to predict the presence of disease.[7]
- **The test only needs 9 µL of blood serum**, deposited onto a manufactured Sample Slide (Dxcover Ltd., Glasgow., UK) and dried for at least 10 minutes before spectroscopic collection.
- The test consists of **infrared light interacting with the sample** and initiating molecular vibrations; this generates a distinctive signature that represents the whole biomolecular profile of the blood serum sample (Figure 4).
- A nested cross-validation 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.

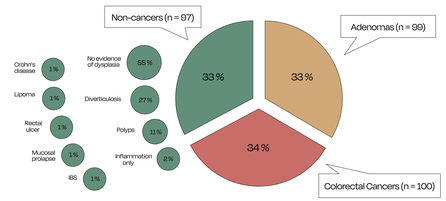

Figure 3. CREATE (ColoREctal Cancer & Adenoma Test Evaluation) feasibility study patient cohort (n = 296)

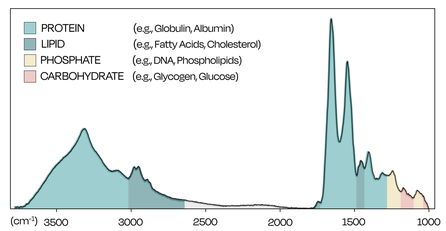

Figure 4. Infrared spectrum detailing the main blood serum components

LIQUID BIOPSY 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, this Liquid Biopsy is an excellent candidate for a CRC screening tool (Figure 5, 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 5, right).
- The CRC v NC model had an AUC of 0.93 (Figure 6, left). At 90% specificity, the overall CRC sensitivity was 80%, and by CRC stage: 83% (I), 73% (II), 76% (III), and 100% (IV).
- **Feature Importance analysis** identified the **Amide II region**, one of the proteinaceous spectral regions, as the spectral region found to be most significant for the classification, differentiating CRC, Adenoma and Non-cancer samples.
- **The 3 classes neatly separate at 1527 cm^{-1}**, where the mean intensity (absorbance; A) plot of the peak shows a split between the classes (Figure 6), with [mean A] = 0.334 (CRC); 0.337 (Adenomas); 0.340 (Non-cancers).

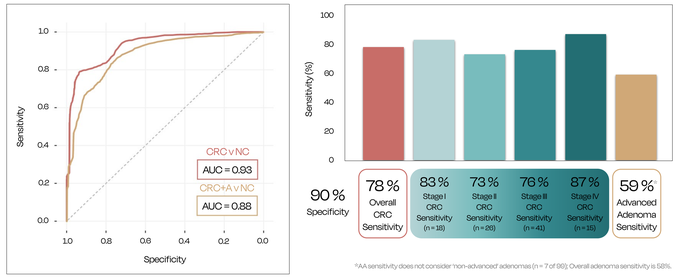

Figure 5. Models ROC curves (left) and CRC+A v NC Model Sensitivity values at 90% Specificity (right)

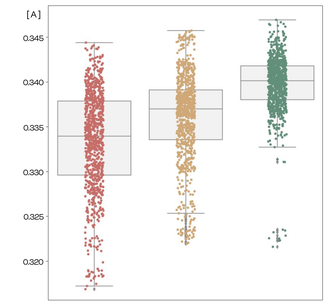

Figure 6. Absorbance (A) differentiation at 1527 cm^{-1}

FIT + LIQUID BIOPSY COMBINATION COULD INCREASE COLORECTAL CANCERS AND ADVANCED ADENOMAS SENSITIVITIES

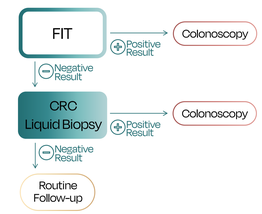

Figure 7. Add-on FIT + CRC blood serum Liquid Biopsy Combination

- CRC diagnosis relies on confirmation by colonoscopy. A 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 7).
- If the 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 8, left).

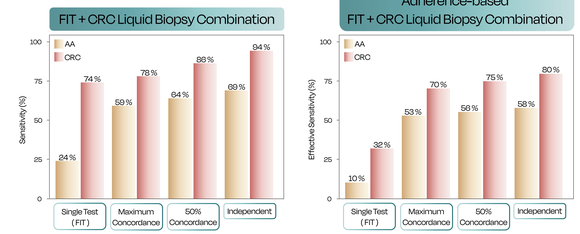

Figure 8. CRC and AA sensitivities (left) and adherence-based 'effective' sensitivities (right) of FIT combined with CRC blood serum Liquid Biopsy

- When considering adherence, **only 43% of average risk adults comply with stool-based screening**.[8,9] Hence, the 'effective sensitivity' of FIT alone is only 32% for CRC and 10% for AA (Figure 8, right).
- However, **blood-based screening has 90% adherence**.[9] Therefore, there is an even greater improvement in effective sensitivity when accounting for diverse adherence (Figure 8, right).
- FIT testing has addressable shortcomings, and **the emergence of new technologies is essential to support CRC screening**.

REFERENCES

1. Siegel R.L. *et al*, CA. Cancer J. Clin., 2023. DOI: 10.3322/caac.21763
2. NICE Bowel Screening. Available from: https://cks.nice.org.uk/topics/bowel-screening [Accessed September 2023]
3. USPSTF Screening for Colorectal Cancer. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening [Accessed September 2023]
4. Zhao J. *et al*, BMJ Oncol., 2023. DOI: 10.1136/bmjonc-2023-000049
5. Brenner H. *et al*, Gut, 2007. DOI: 10.1136/gut.2007.122739
6. Imperiale T.F. *et al*, N. Engl. J. Med., 2014. DOI: 10.1056/NEJMoa1311194
7. Cameron J.M. *et al*, Neuro-oncol. Adv., 2022. DOI: 10.1093/noajnl/vdac024
8. Fendrick A.M. *et al*, Cancer Prev. Res. (Phila.), 2021. DOI: 10.1158/1940-6207.CAPR-21-0075
9. Guardant Health presentation at the annual JP Morgan conference (January 2023).

ACKNOWLEDGEMENTS

The CREATE (ColoREctal Cancer & Adenoma Test Evaluation) feasibility study was sponsored by Dxcover Ltd. (Glasgow, UK). The authors would like to thank the sponsor for funding, and all the staff who took part in the study at NHS Tayside, and Ninewells Hospital and Medical School (Dundee, UK) for their contributions to patient recruitment. The authors would also like to thank the patients for their involvement in this study, as well as their families and caregivers.

j.nobes@dundee.ac.uk // matthew.baker@dxcover.com

DOI: The presenter has no conflicts of interests to declare.