Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report [1]

Multi gene blood-based methylation tests for the screening of colorectal cancer

What is a Topic Exploration Report?

Topic Exploration Reports are not health technology assessments. These reports provide a high-level briefing on new topics submitted to Health Technology Wales and are not based on exhaustive or systematic literature searches. Instead, they rely on a focussed scan of key resources.

What evidence is used in a Topic Exploration Report?

Priority is given to summarising the most relevant or useful evidence, rather than covering all possible evidence. Information reported is typically based on abstracts and study authors' own conclusions, rather than detailed scrutiny of full texts.

What are the aims of a Topic Exploration Report?

Topic Exploration Reports offer an overview of the available evidence on a topic and aim to highlight any uncertainties or gaps in the evidence. These reports outline the quantity and type of evidence found, but no critical appraisal or formal evidence synthesis is conducted.

How should a Topic Exploration Report be used?

Topic Exploration Reports can be used to indicate what evidence may be available for a topic, and do not provide definitive guidance on how a technology should be used. The evidence presented within the reports should be interpreted with caution.

[1] Cyfieithu dogfennau HTW wedi'u cyhoeddi o'r Saesneg i'r Gymraeg
Translation of published technical HTW documents from English into Welsh

Topic exploration report number	TER636
Topic	Multi-gene blood-based methylation tests for the screening of colorectal cancer
Summary of findings	Multi-gene blood-based methylation tests detect abnormal DNA methylation patterns from several cancer related genes circulating in the blood. Colon AiQ is an example of a multi-gene methylation test that uses a blood test for the detection of colorectal cancer and uses artificial intelligence to interpret results. Currently, quantitative faecal immunochemical testing (FIT) and a colonoscopy is used to identify colorectal cancer. The test could help clinicians identify and prioritise people with suspected cancer for further investigation and could be used in the screening of people at higher risk of colorectal cancer or people on surveillance pathways following previous adenomas. A similar topic exploration report, one NICE guideline on the recognition and referral of suspected cancer, one diagnostic guidance report, one clinical guidance, and four non-randomised studies were identified. In summary, multi-gene methylation tests report sensitivity values of 73.9% to 89% and specificity values of 90% to 97%. One study found that ColonAiQ can identify cancers missed by FIT. One longitudinal study reported that circulating tumour DNA (ctDNA) positive participants showed higher recurrence risk and shorter recurrence-free survival after treatment. It is uncertain where multi-gene blood-based methylation tests are best placed in the care pathway. There is lack of evidence of what difference the current findings would make to patient management decisions and other outcomes such as resource use, waiting times and burden on colonoscopy waiting lists. We did not identify any full-text papers that evaluated the cost-effectiveness of multi gene blood-based methylation tests when compared with the standard care pathway.

Introduction and aims

Colorectal cancer includes the colon and rectum which form part of the large bowel. Colorectal cancer is the fourth most common cancer in Wales (Bowel Cancer UK 2024), and more than 2,000 people diagnosed every year (Welsh Government 2024). It can be treatable, curable and survival chances increase significantly when it is caught early enough (Bowel Cancer UK 2024). However, five out of seven health boards in Wales currently breach waiting times for diagnostic tests (Bowel Cancer UK 2024) and a late diagnosis can negatively affect survival rates. The increasing demand for endoscopy and a lack of capacity in hospitals is the root cause of long waiting times for appointments (Bowel Cancer UK 2024). Between 2017 and 2019, there were 429 more colorectal cancer cases on average each year compared to trends from 2002 to 2004 in Wales (a 22% increase) (Public Health Wales 2024). PHW state that if trends continue, they estimate there could be 2,832 colorectal cancer cases each year by 2035 (a projected 9% increase from 2025 to 2035) (Public Health Wales 2024).

Currently, people who present with symptoms of colorectal cancer are offered a faecal immunochemical test (FIT) and if positive or have high-risk symptoms, a colonoscopy is offered under the NHS cancer pathway. Colon AiQ by Singlera Genomics is a novel non-invasive blood muti-gene methylation test, incorporating artificial intelligence (AI). It uses qPCR (quantitative polymerase chain reaction analysis) to identify methylation profiles of five colorectal cancer biomarkers/DNA regions. Information from the manufacturer states that the groups of people who would benefit most from the test include those considered high risk (such as those with a family history of colorectal cancer or genetic predispositions), symptomatic patients, those with a positive FIT test to stratify risk, people who do not engage with traditional screening, the general population as part of wider screening and surveillance of those who have undergone treatment to monitor recurrence. Potential benefits from use of ColonAiQ include improvements in patient prioritisation, reduction in unnecessary procedures, and more effective use of NHS Wales colonoscopy capacity.

Colon AiQ has received CE marking in Europe as an in-vitro diagnostic (IVD) medical device and is MHRA registered for use in the UK.

Health Technology Wales researchers searched for evidence on multi gene blood-based methylation tests (including Colon AiQ) for colorectal cancer. Single-gene tests were considered out of scope for this TER.

Evidence overview

Previous work by HTW

A similar topic was the subject of a previous HTW topic exploration report TER584. The topic explored CanSense, a Raman spectroscopy blood test combined with machine learning to identify colorectal cancer after a FIT. The test detects biochemical changes in blood spectra rather than muti-gene methylation testing.

Guidance

A NICE guideline on the recognition and referral of suspected cancer [NG12] recommends FIT testing using HM-JACKarc or OC-Sensor to guide referral for suspected colorectal cancer in symptomatic adults [recommendation 1.3.1] (NICE 2015). Adults with a FIT test of 10 micrograms of haemoglobin per gram of faeces or more should be referred using a suspected cancer pathway referral [recommendation 1.3.2] (NICE 2015). Recommendations from this section of the guideline are from diagnostic guidance [DG56] on the quantitative faecal immunochemical testing to guide colorectal cancer pathway referral in primary care (NICE 2023).

Evidence overview

Healthcare Improvement Scotland published a national clinical guideline on the diagnosis and management of colorectal cancer, revised in 2016 (SIGN 2011). Colonoscopy is recommended as a method of diagnosing colorectal cancer. CT colonography is also recommended as an alternative. The guideline makes no reference to multi-gene blood-based methylation testing (SIGN 2011).

Non-randomised studies

Two non-randomised studies were identified that evaluated ColonAiQ.

Wang et al. (2024) conducted a cross-sectional study in China to evaluate the screening performance of a blood-based multi-gene DNA methylation test (ColonAiQ) in an average-risk population aged 40 to 74 years. A total of 105,285 participants were prospectively enrolled between January 2021 and December 2022. The study found that people with colorectal cancer had higher ColonAiQ scores and showed more positive cancer-associated DNA methylation regions than healthy participants. The test's positive predictive value was 1.92% for colorectal cancer and 13.44% for advanced adenoma.

A multicentre, prospective longitudinal cohort study was conducted between December 2019 and February 2022 (Mo et al. 2023). A total of 350 participants with stage I–III colorectal cancer were enrolled from two hospitals, and blood samples were collected before and after surgery, throughout and following adjuvant chemotherapy, and then every three months for up to two years. The study reports on how circulating tumour DNA (ctDNA) with six DNA methylation markers measured with the ColonAiQ assay could provide early detection of recurrence. At one month post procedure of 299 participants evaluated, participants who were ctDNA-positive were 17.5 times more likely to relapse than participants who were ctDNA-negative (hazard ratio [HR], 17.5; 95% CI, 8.9 to 34.4; P <0.001). The integration of ctDNA and carcinoembryonic antigen tests showed risk stratification for recurrence with an HR of 19.0 (95% CI, 8.9 to 40.7; P <0.001). After adjuvant chemotherapy, participants who were ctDNA-positive had a significantly shorter recurrence-free survival than the participants who were ctDNA-negative (HR, 13.8; 95% CI, 5.9 to 32.1; P <0.001).

The following two studies evaluated the use of other multi-gene tests or detection kits for colorectal cancer. It is unclear to what extent they target the same biomarkers as ColonAiQ or use the same methodology.

Liu et al. (2024) published a diagnostic biomarker study on the performance evaluation of a multi-gene methylation detection kit for colorectal cancer in 88 people. A total of 47 of these participants were diagnosed with stage I to IV colorectal cancer, 24 people with no abnormal colonoscopy findings, three patients with colon polyps, and 14 healthy individuals. Based on findings in the abstract, the kit's sensitivity, specificity and accuracy were 89.36%, 97.56% and 93.18%, respectively.

Young et al. (2021) retrospectively evaluated a panel of tumour specific differentially methylated DNA regions in IRF4, IKZF1 and BCAT1 biomarkers for blood-based detection of colorectal cancer. Specimens were from plasma biobanks established from studies undertaken at sites in Australia, the Netherlands and Denmark. The sensitivity value for combined PCR signals for all targeted differentially methylated regions was reported as 73.9% (95% CI 67.1 to 79.7) and a specificity of 90.1% for neoplasia (95% CI 87.9 to 92.0, p<0.01).

Ongoing studies

Evidence overview

Information from the topic proposer states that an ongoing validation study of approximately 1,500 participants is underway about ColonAiQ based in the Netherlands. Outcome measures will include receiver operating characteristic (ROC), Area Under the Curve (AUC), sensitivity, specificity, negative predictive value and positive predictive value. The estimated completion date is in the summer of 2026.

Areas of uncertainty

Information from the topic proposer suggests that ColonAiQ can support key patient groups across both primary and secondary care. This may include use in those considered high risk (such as those with a family history of colorectal cancer or genetic predispositions), symptomatic patients, those with a positive FIT to stratify risk, people who do not engage with traditional screening, the general population as part of wider screening and surveillance of those who have undergone treatment to monitor recurrence. It is uncertain where the technology would be placed in the care pathway for maximum benefit within NHS Wales.

There is variation in the interventions evaluated in the studies identified in terms of biomarker composition and intended use.

There is lack of evidence of what difference this intervention would make to patient management decisions and outcomes such as resource use, waiting times and burden on colonoscopy waiting lists as these outcomes were not evaluated in the identified studies. We did not identify any published full-text studies that evaluated the cost-effectiveness of multi gene blood-based methylation test when compared with standard procedures.

There is a lack of clinical evidence in people with symptoms or in screening of higher risk populations.

Further details on the artificial intelligence component of the technology would be useful. The topic proposer states that ColonAiQ does not use generative artificial intelligence to generate new data or to adapt or modify models in real time. ColonAiQ does incorporate trained neural network-based calling models that are locked down for use in production.

If this topic were to proceed to a fuller appraisal, consideration would need to be given to any potential narrowing of the multi-gene tests included based on biomarkers, and the most appropriate comparator, such as colonoscopy.

Literature search results

Previous work by HTW
HTW (2025) CanSense - Raman spectroscopy blood test combined with machine learning to identify colorectal cancer (CRC). Health Technology Wales. Available at: https://healthtechnology.wales/reports-guidance/raman-spectroscopy-blood-tests/
Health technology assessments and guidance
NICE. (2015). Suspected cancer: recognition and referral. NG12. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer#colorectal-cancer [Accessed 11 December 2025]. NICE. (2023). Quantitative faecal immunochemical testing to guide colorectal cancer pathway referral in primary care. Diagnostics guidance [DG56]. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/dg56/ [Accessed 11 December 2025]. SIGN. (2011). Diagnosis and management of colorectal cancer. A national clinical guideline. Healthcare Improvement Scotland. Available at: https://www.sign.ac.uk/our-guidelines/diagnosis-and-management-of-colorectal-cancer/ [Accessed 11 December 2025].
Individual studies
Liu W, Luo H, Xiao L, et al. (2024). Performance Evaluation of the Multi-gene Methylation Detection Kit for Colorectal Cancer. Altern Ther Health Med. 30(6): 222-8. Available at: https://pubmed.ncbi.nlm.nih.gov/37944961/ Young GP, Symonds EL, Nielsen HJ, et al. (2021). Evaluation of a panel of tumor-specific differentially-methylated DNA regions in IRF4, IKZF1 and BCAT1 for blood-based detection of colorectal cancer. Clin Epigenetics. 13(1): 14. doi: 10.1186/s13148-020-00999-y Available at: https://pubmed.ncbi.nlm.nih.gov/33478584/
Ongoing research
No additional ongoing research was identified with an estimated completion date within the next 6-12 months.
References from topic proposer
Mo S, Ye L, Wang D, et al. (2023). Early Detection of Molecular Residual Disease and Risk Stratification for Stage I to III Colorectal Cancer via Circulating Tumor DNA Methylation. JAMA Oncol. 9(6): 770-8. doi: 10.1001/jamaoncol.2023.0425. Available at: https://pubmed.ncbi.nlm.nih.gov/37079312/ Wang B, Zhang Y, Liu J, et al. (2024). Colorectal cancer screening using a multi-locus blood-based assay targeting circulating tumor DNA methylation: a cross-sectional study in an average-risk population. BMC Med. 22(1): 560. doi: 10.1186/s12916-024-03777-2. Available at: https://link.springer.com/article/10.1186/s12916-024-03777-2
Background references
Bowel Cancer UK. 2024). A Spotlight on Bowel Cancer in Wales. Available at: https://www.bowelcanceruk.org.uk/news-and-blogs/research-blog/a-spotlight-on-bowel-cancer-in-wales/ [Accessed 11 December 2025 2025]. Public Health Wales. (2024). Bowel Screening Wales Annual Statistical Report 2022-23. Programme Reports. Available at: https://phw.nhs.wales/services-and-teams/screening/bowel-screening/programme-reports/bowel-screening-wales-annual-statistical-report-2022-23/#:~:text=Coverage%20and%20uptake%20rates%20were%20also%20higher%20in%20those%20living,adenoma%20detection%20rate%20was%2056.7%25. [Accessed 11 December 2025]. Welsh Government. (2024). Bowel screening age lowered to 50 in Wales. Welsh Government. Available at: https://www.gov.wales/bowel-screening-age-lowered-50-wales.

Date of search	11 December 2025
Concepts used	Methylation test; ColonAiQ; Multi gene blood-based methylation test; Colorectal cancer.

Proposed research question and evidence selection criteria (if selected)

Proposed Research question	**What is the clinical and cost-effectiveness of using a multi-gene blood-based methylation test to identify colorectal cancer?**

	Inclusion criteria	Exclusion criteria
Population	People with symptoms of colorectal cancer (for diagnosis and triage) or people at higher risk of colorectal cancer (screening)	General population (generic screening)
Intervention	Multi-gene blood-based methylation tests (in isolation or alongside FIT)	Single gene testing FIT only testing
Comparison/ Comparators	Colonoscopy FIT (if used instead of FIT)	
Outcome measures	Diagnostic accuracy Uptake of screening Referrals to secondary care Diagnosis rates for colorectal cancer Patient waiting times Patient experience Health related QoL Resource use Economic outcomes	

Proposed speciality	**Cancer**