Incorporating faecal haemoglobin measurement using the faecal immunochemical test (FIT) in the referral, triage, and prioritisation pathway for patients with colorectal symptoms

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ABSTRACT

Incorporating faecal haemoglobin (FHb) measurement using the faecal immunochemical test (FIT) in the investigation pathway for patients with colorectal symptoms may improve access to colonoscopy for those at greatest risk of significant disease.

AIM: To derive a colorectal symptom pathway incorporating standard clinical and FIT data to guide referral, triage, and prioritisation of cases in New Zealand.

METHOD: Diagnostic accuracy of FIT to rule out colorectal cancer (CRC) was determined by meta-analysis. Thereafter, the risk of CRC after FIT was estimated for common clinical presentations by Bayesian methodology, using a specifically collated retrospective cohort of symptomatic cases. A symptom/FIT pathway was developed iteratively following multi-disciplinary engagement.

RESULTS: Eighteen studies were included in meta-analysis. The sensitivity and specificity for CRC were 89.0% (95%CI 87.0–90.9%) and 80.1% (95%CI 77.7–82.4%) respectively, at a FHb threshold of >10mcg haemoglobin per gram stool, and 95.7% (95%CI 93.2–97.7%) and 60.5% (95%CI 53.8–67.0%) respectively, at the limit of detection. The final pathway was 97% sensitive for CRC, compared with 90% for the current direct access criteria, and requires 47% fewer colonoscopies. Estimated prevalence of CRC among those declined investigation was 0.23%.

CONCLUSION: Incorporating FIT in the new patient symptomatic pathway as presented appears feasible, safe, and allows for resources to be targeted to those at greatest risk of disease. Further work is needed to ensure equity for Māori if this pathway were introduced nationally.

Waiting times for colonoscopies are long and risk harm due to the delayed diagnosis of serious gastrointestinal diseases, including colorectal cancer (CRC). We have reported that the New Zealand Ministry of Health, now Manatū Hauora, referral criteria for direct access outpatient colonoscopy or computed tomography colonography (CTC),[1] hereafter the direct access criteria, have a low specificity for CRC.[2] This low specificity, together with high colorectal symptom burden in the general population contributes to high referral rates and low yield from investigation. Improving access to colorectal investigations for New Zealanders who have significant bowel disease is an immediate priority for gastroenterology and surgical services and should be undertaken to increase the detection of significant diseases, reduce time to diagnosis, and reduce the number of investigations performed with no significant finding.

Data indicates that incorporating faecal haemoglobin (FHb) measurement by using the faecal immunochemical test (FIT) into the new patient investigation pathway may help to satisfy these goals.[3,4] FIT has been extensively investigated in symptomatic populations and has been successfully incorporated into new patient symptomatic pathways,[5] and used to re-prioritise cases waiting for colonoscopy following pandemic related delays.[6] Indeed, the British Society of Gastroenterology (BSG) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) recommend the implementation of FIT as a diagnostic tool for all patients with symptoms or signs of a suspected CRC diagnosis, other than those with an anal or rectal mass or anal ulceration.[7] Identifying

combined FIT/symptom thresholds to direct referral and investigation of cases requires both a reliable estimate of the prior risk of disease for common clinical presentations, and knowledge of the diagnostic accuracy of FIT at the proposed FHb thresholds, neither of which is known absolutely.

We aimed to derive a colorectal symptom pathway incorporating standard referral (direct access criteria), and FIT data, to guide referral, triage, and prioritisation of cases.

Methods

An overview of the study design is shown in Figure 1.

Diagnostic accuracy of a single rule out FIT for colorectal cancer

Search strategy and exclusions are summarised in Figure 2. Studies were included if they reported the diagnostic accuracy of a single rule out FIT (at threshold >10mcg/g or at a threshold of >4mcg/g or lower) for colorectal cancer in a cohort of patients with unexplained colorectal symptoms. Studies reported as full papers, with a complete, patient level dataset (sufficient to allow sensitivity and specificity to be calculated), were considered for inclusion, including those reporting outcomes based on either clinical follow-up (>6 months) or colonic investigation. A quality assessment tool for diagnostic accuracy studies (QUADAS-2) was used to facilitate the assessment of study quality. Studies from the same population were allowed when referral dates did not overlap. Studies were excluded if they did not meet inclusion criteria and furthermore if they included surveillance cases, or where the mode of investigation or follow-up period was deemed insufficient to diagnose incident colorectal cancer. Database search, literature review, quality assessment, decision to include or exclude, and data extraction was made by one author (James Falvey). Patient level data was manually extracted from each included study and grouped according to FIT threshold for meta-analysis. FHb thresholds for analysis were at >10mcg haemoglobin per gram of stool (mcg/g), and at the limit of detection of the test (LoD) (any threshold <4mcg/g). Meta analyses were undertaken using a random effects model due to heterogeneity in study design, and performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). The pragmatic approach to the LoD was taken to avoid overestimating sensitivity for CRC, reflect variation in assay sensitivity, and to remain consistent with prior methodology.[8]

The prior risk of CRC according to the direct access criteria has been reported previously (2018 dataset).[2] Briefly, a retrospective cohort study was performed which collected referral, demographic and outcome data for all first primary care referrals for direct access colorectal investigations made to Canterbury district health board (now Te Whatu Ora – Waitaha Canterbury) using a dedicated electronic referral form (eform) in the year 2018. The eform includes a free text section for clinical history and tick boxes that allow the case history to be summarised with respect to the direct access criteria. General practitioners have access to additional guidance regarding the investigation and referral of cases through an online resource (Community HealthPathways). Faecal occult blood (FOB) testing is not included in the direct access criteria or included as a required field in the eform. Cases were followed for a median of 33 months. One hundred and twenty-eight CRC cases were detected among 3,200 referrals. For the purposes of this study, referrals for patients with suspected Inflammatory bowel disease (IBD) were not included (2 CRC among 214 referrals for suspected IBD [0.9%]).

Likelihood ratios (LR) derived from summary accuracy data were used to calculate disease prevalence for clinical groups following FIT and were unadjusted. Simple proportions were converted to odds (and vice versa) as required and are presented as percentages or number needed to investigate (NNI) or decline (NND) to detect or miss one CRC. Detection of high-risk adenoma is estimated based on the prevalence of advanced polyps in the 2018 dataset, and using LRs derived from published data for advanced adenomas.[9] FIT positivity rates at each threshold were calculated as follows: $n=([C–c_bP]/[c_a–c_b])/P$, where n is the proportion of cases with a test result at or above the threshold, C is the total number of cases of CRC in a population (P), and c_a and c_b are the prevalence of CRC for cases with test results above and below the threshold, respectively. To determine the investigative resource requirements of the pathway, the secondary care decision aid has been followed with additional assumptions for categories requiring triagers' discretion as follows:

- iron deficiency anaemia (IDA) 80% colonoscopy and 20% CTC.

- rectal bleeding (RB) 40–49 years/detectable FHb <10mcg/g, 50% colonoscopy and 50% CTC.
- RB <39 years/FHb >10mcg/g, 100% colonoscopy.
- altered bowel habit (ABH) >50 years/ detectable FHb <10mcg/g, 50% colonoscopy and 50% CTC.
- other presentations FHb >10mcg/g, 100% colonoscopy, detectable FHb <10mcg/g, 50% CTC and 50% decline.

Modelling does not make allowance for any change in primary care referral practice, or the effect of expanding access criteria in the proposed pathway (to younger patients with rectal bleeding, or due to lowering age thresholds for Māori and Pacific people). The proportion of cases meeting criteria for colonoscopy, but who in usual clinical practice would be offered an alternative mode of investigation due to age-related frailty or the presence of significant comorbidity has not been estimated for either the current proposal or the direct access criteria, or the ACPGBI/BSG guideline for urgent colonoscopy. Outcome estimates of sensitivity, specificity, NNI, and NND were determined for each of these criteria. The upper 95% CI of negative likelihood ratios (NLR) derived from summary data were used to determine the worst-case missed cancer rates for rule out thresholds. Ninety-five percent CI were calculated by the binomial exact method.

CRC incidence by novel symptom criteria was determined from the 2018 dataset by mapping the direct access criteria to the novel criteria. Symptom thresholds for referral are unchanged from the direct access criteria (e.g., altered bowel habit [ABH] refers to looser and/or more frequent stools, and unexplained rectal bleeding [RB] refers to cases where benign anal causes have been treated or excluded).

Results

Meta-analysis

Eighteen studies were included in meta-analysis. The study characteristics, quality assessment, and diagnostic accuracy of included studies are shown in Table 1. One study was excluded as it did not report FIT accuracy data at a threshold consistent with our analysis.[25] Of those studies excluded on methodological or other grounds despite apparently meeting inclusion criteria, one provided insufficient information regarding the reference standard and had too short a period of clinical follow-up,[26] one was deemed at high risk of bias in both case selection and case follow-up,[27] four had incomplete investigation or follow-up of cases (usually FIT negative),[28–31] one did not contain patient level data,[32] and one was excluded due to multiple samples counted as a single positive if any gave an above threshold result.[33] Forrest plots for the primary analyses are shown in Figure 3. Summary sensitivity and specificity of FIT at FHb threshold >10mcg/g were 89.0% (95%CI 87.0–90.9%)(I^2 33.14%) and 80.1% (95%CI 77.7–82.4%)(I^2 98.2%) respectively, and at the LoD were 95.7% (95%CI 93.2–97.7%)(I^2 58.84%) and 60.5% (95%CI 53.8–67.0%)(I^2 99.4%), respectively. Correspondingly, the NLR of FIT for CRC at thresholds of >10mcg/g and at LoD were 0.14 (95%CI 0.12–0.16) and 0.07 (95%CI 0.04–0.11), respectively. There was significant heterogeneity between studies. The source of this was investigated by subgroup analysis according to the following study characteristics: cohort date (pre vs not pre-2017), retrospective vs prospective data collection, recruitment location (primary or secondary care), analyser (HM-jack arc, OC-sensor, other/unknown), colorectal cancer prevalence (>3% vs <3%), and reference standard (colonoscopy only,[9,10,12,15,16] any colonic investigation,[3,11,14,17,19,24] follow-up[4,13,18,20–23]) (see Table 1 for study characteristics). Significant heterogeneity was still identified within the subgroups for both sensitivity and specificity, and the estimates between subgroups did not differ significantly; however, the limited sample size limits the robustness with which these effects can be explored. Outliers were sought with respect to study design, prevalence, sensitivity, and specificity; however, exclusion of individual studies did not significantly influence results.

Canterbury colorectal symptom pathway

The proposed pathway is summarised in Figure 4. For Symptom/FHb categories where the risk of CRC is low, triagers will use discretion in determining the most appropriate outcome (e.g., CTC, flexible sigmoidoscopy, outpatient review, or a further period of observation in primary care) based on age, case presentation, co-morbidity, and local resource availability. The outcome in the secondary care decision aid (Figure 4b) for such categories is denoted ‘triagers discretion’, and for simplicity in modelling, it is assumed that all cases will undergo either colonoscopy or

CTC (see methods). Estimated CRC prevalence by clinical category, age, and FHb threshold are shown in Table 2. Pathway sensitivity and specificity are shown in Table 3, along with those for the direct access criteria, and those of the ACPGBI/BSG guidance for urgent colonoscopy. Within the limits of the analysis, the sensitivity for advanced polyps is estimated to fall from 84.2% for the direct access criteria to 70.4% for the Canterbury pathway.

Discussion

Our study demonstrates how incorporating FIT in the investigation, referral, and prioritisation of patients with colorectal symptoms may both improve sensitivity for colorectal cancer, while simultaneously reducing the number of investigations performed. Indeed, including FHb measurement to guide patient care was previously an established strategy in New Zealand. In Canterbury, between 2010–2017, a qualitative FIT was incorporated in the colorectal symptom assessment and referral pathway and provided the strongest single predictor for colorectal cancer diagnosis, above anaemia and rectal bleeding.[34] Thereafter, while Canterbury moved away from FHb and adopted the direct access criteria (based on the 2005 NICE guideline, CG27), the United Kingdom sought to increase sensitivity for CRC (NICE NG12) by incorporating a rule-in guaiac based FOB (gFOB) for primary care patients with low risk symptoms (CRC risk of <3%).[35] In the UK the low specificity of gFOB led to increased demand for colorectal investigation and a higher NNI to detect one cancer,[36] and this was addressed by replacing gFOB with FIT >10mcg/g (NICE DG30) in 2017.[33] The discriminatory value of a quantitative FIT for CRC, and its validity beyond population screening and low risk symptoms to high risk scenarios such as rectal bleeding have subsequently been confirmed.[11,12,37,38] This reflects a broader concept, that the discriminating power of FIT for CRC is determinate (notwithstanding variation in tumour size, location, biology, and stool sampling method), while its clinical utility varies by FHb threshold and the pre-test probability of disease.

A major strength of this study is that our conclusions are based on actual cancer rates in our referral population, and a current estimate of FIT accuracy. Furthermore, because we are primarily concerned with optimising the clinical pathway sensitivity and understanding the risk of declining investigation, we have estimated the worst-case scenario miss rates for each clinical presentation using the upper 95th CI of the NLR calculated from our summary sensitivity and specificity, which encompass the least favourable estimate of the diagnostic accuracy of rule out FIT found in contemporary meta-analysis.[8,39,40] Table 4 shows that this is important because there was significant heterogeneity between studies included in meta-analysis, and this impacts on the accuracy with which the diagnostic accuracy of FIT can be estimated.

We estimate the missed cancer rate for the Canterbury pathway to be 2.9%, compared with 9.5% for the direct access criteria (Table 3). In our proposal, cases meeting symptom threshold who have FHb >10mcg/g undergo investigation with colonoscopy. However, because almost 10% of CRC are missed at this threshold, we further recommend that all cases with detectable FHb <10mcg/g be referred and investigated appropriately given case characteristics and resource availability. Although the CRC rate of those with detectable FHb<10mcg/g is just 1.47%, we see benefit in a pathway that provides definitive care at the first contact, reducing the risk of frequent repeat testing (and associated false positive tests) and the inequity that is likely to result from such an approach. A higher rule out threshold of >10mcg/g would reduce colonoscopy volumes further; however, the pathway as it stands has the potential to lower demand for colonoscopy by 47%. More restrictive criteria may not only delay diagnosis for some cases of colorectal cancer, but also reduce sensitivity of the pathway for other significant colorectal disease.[9,41–43]

Simplifying the clinical categories when compared with the direct access criteria is justified on several grounds. Foremost, the distinction between urgent and non-urgent categories in the direct access criteria appears arbitrary with some non-urgent categories having greater risk of CRC than others afforded urgent investigation.[2] Thereafter, as New Zealand data have repeatedly shown that CRC risk falls in the order IDA>RB>ABH,[2,34,44] and because FIT discriminates CRC risk with greater power than any of these,[12] it follows that all cases be stratified by FIT, and usability of the resulting criteria is enhanced by simplifying the clinical component.

We see benefit in amending the access criteria in several other ways. Lowering age thresholds for investigating Māori and Pacific people by 10

Figure 1: Overview of study design.

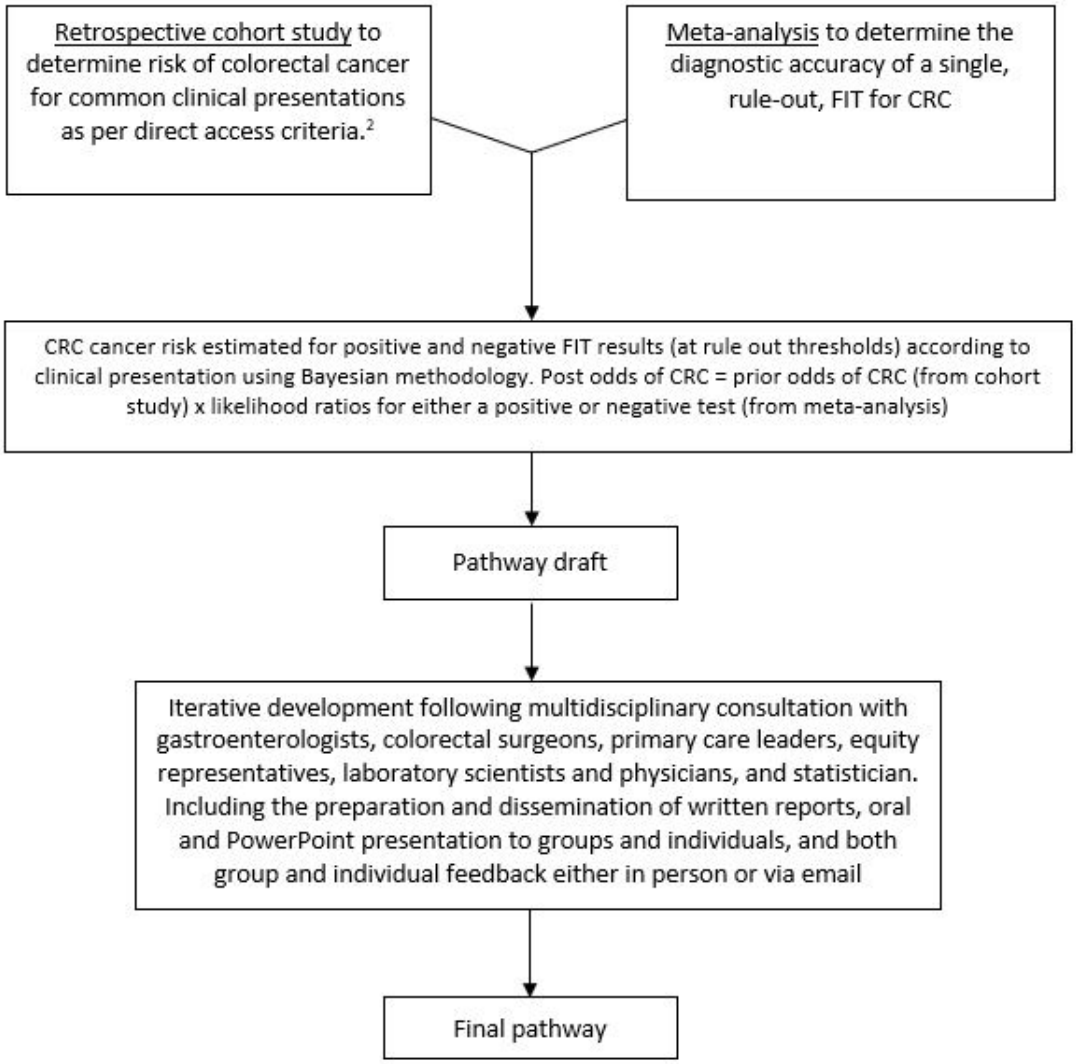


Figure 2: Meta-analysis search strategy and review process.

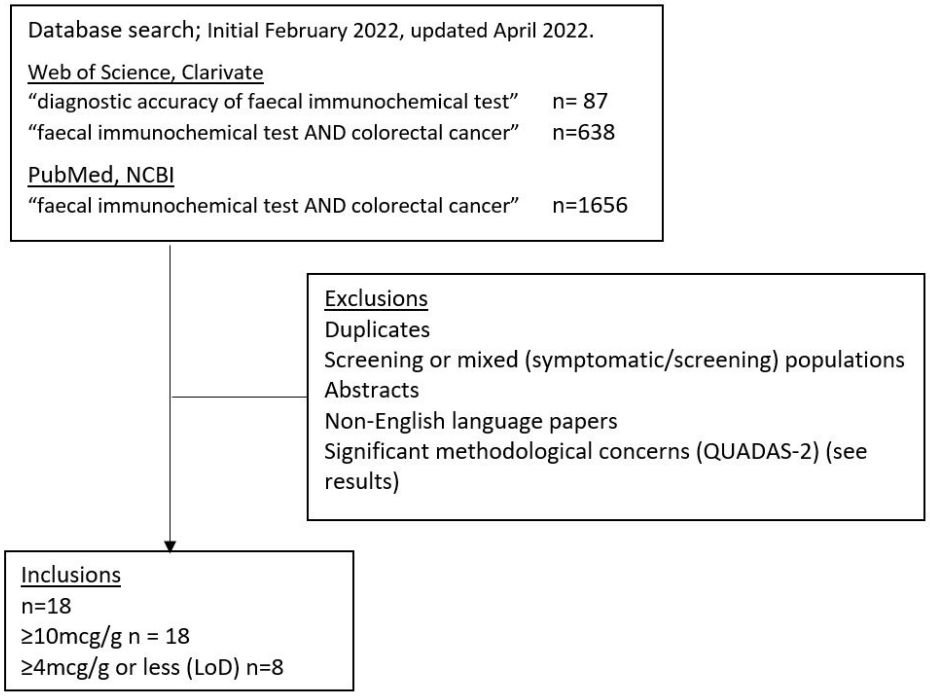


Table 1: Studies included in meta-analysis.

Study	Description *(Including retrospective vs prospective design, primary or secondary care recruitment, cohort date, laboratory analyser, and location)*	n	CRC prevalence %	FU interval months	QUADAS-2							Threshold mcg/g	Sensitivity	Specificity
					Risk of bias			Applicability concerns			Flow and timing			
					Selection	Index test	Reference standard	Selection	Index test	Reference standard				
McDonald et al.[3]	Consecutive referrals from primary care for investigation of lower GI tract completing FIT and endoscopy. Secondary care prospective cohort. 2010–2012. OC-Sensor. Tayside, Scotland.	280	2.14	NA	Low	Unclear	Low	Low	Low	Low	Low	10	1.00	0.94
Rodriguez-Alonso et al.[10]	Symptomatic outpatients referred for and completing diagnostic colonoscopy. Secondary care prospective cohort. 2011–2012. OC-Sensor. Barcelona, Spain.	1003	2.99	NA	Low	Low	Low	Low	Low	Low	Low	0	1.00	0.43
												10	0.97	0.80
Mowat et al. 2016[11]	All adults referred for investigation of bowel symptoms. 2013–2014. Secondary care prospective cohort study. OC-Sensor. Tayside, Scotland	750	3.73	NA	Low	Unclear	Low	Low	Low	Low	High	2	1.00	0.43
												10	0.89	0.79

Table 1 (continued): Studies included in meta-analysis.

Study	Description *(Including retrospective vs prospective design, primary or secondary care recruitment, cohort date, laboratory analyser, and location)*	n	CRC prevalence %	FU interval months	QUADAS-2							Threshold mcg/g	Sensitivity	Specificity
					Risk of bias			Applicability concerns			Flow and timing			
					Selection	Index test	Reference standard	Selection	Index test	Reference standard				
Herrero et al.[12]	Consecutive symptomatic patients referred for colonoscopy. Prospective secondary care cross-sectional study. 2012–2013. OC-Sensor. Ourense, Spain.	1572	13.6	NA	Low	Low	Low	Low	Low	Low	Low	10	0.93	0.63
Mowat et al. 2019[13]	New onset symptomatic patients in primary care as per NICE NG12. Primary care prospective cohort. 2015–2018. HM-JACKarc. Tay-side, Scotland	5372	1.82	24-36	Low	Low	Low	Low	Low	Low	Low	10	0.88	0.79
Khan et al.[14]	Patients with bowel symptoms referred under 2 week wait colorectal cancer pathway, and completing investigations. Secondary care prospective. 2017–2018. HM-JACKarc. East Sussex, England.	928	5.06	NA	Unclear	Un-clear	Low	Low	Low	Low	Low	10	0.85	0.84

Table 1 (continued): Studies included in meta-analysis.

Study	Description *(Including retrospective vs prospective design, primary or secondary care recruitment, cohort date, laboratory analyser, and location)*	n	CRC prevalence %	FU interval months	QUADAS-2							Threshold mcg/g	Sensitivity	Specificity
					Risk of bias			Applicability concerns			Flow and timing			
					Selection	Index test	Reference standard	Selection	Index test	Reference standard				
Navarro et al.[15]	Secondary care prospective observational study of patients referred with symptoms and accepted for colonoscopy. 2016–2018. SENTiFIT. Zaragoza, Spain.	727	4.95	NA	Low	Low	Low	Low	Low	Low	Low	10	0.94	0.75
Tsapournas et al.[16]	Patients referred for colonoscopy with colorectal symptoms. Secondary care prospective cohort. 2013–2017. QuikRead go. Sweden.	242	5.37	NA	Unclear	Low	Low	Low	Low	Low	Low	10	0.92	0.77
d'Souza et al.[9]	Patients referred and accepted for investigation by colonoscopy under the NICE NG12 2-week wait rules. Prospective multi-centre secondary care cohort. 2017–2019. HM-JACKarc. England.	9822	3.35	NA	Unclear	Low	Unclear	Low	Low	Low	Low	2	0.97	0.65
												10	0.91	0.84

Table 1 (continued): Studies included in meta-analysis.

Study	Description *(Including retrospective vs prospective design, primary or secondary care recruitment, cohort date, laboratory analyser, and location)*	n	CRC prevalence %	FU interval months	QUADAS-2							Threshold mcg/g	Sensitivity	Specificity
					Risk of bias			Applicability concerns			Flow and timing			
					Selection	Index test	Reference standard	Selection	Index test	Reference standard				
Mowat et al. 2021[4]	FIT requested in primary care to guide referral for any colorectal symptom. Retrospective, primary care, cohort. 2015–2016. HM-JACK-arc. Tayside, Scotland.	5381	1.95	24–36	Low	Low	Unclear	Low	Low	Unclear	Low	2	0.97	0.49
												10	0.87	0.79
Turvill et al. [17]	Patients referred according to NICE NG12 2-week wait. Multicentre. Prospective, secondary care cohort. HM-JACKarc. 2018–2019. Yorkshire/Humber, England.	5040	3.00	NA	High	Un-clear	Low	Low	Low	Low	Low	2	0.93	0.61
												10	0.87	0.81
J Bailey et al. 2021[18]	Patients referred for investigation of colorectal symptoms; excluding rectal bleeding and rectal mass. Result incorporated into referral pathway. Retrospective audit. Primary care. 2017–2019. OC-sensor. Nottingham, England.	13032	1.77	2–25	Low	Low	Low	Low	Low	Low	High	4	0.97	0.70
												10	0.92	0.82

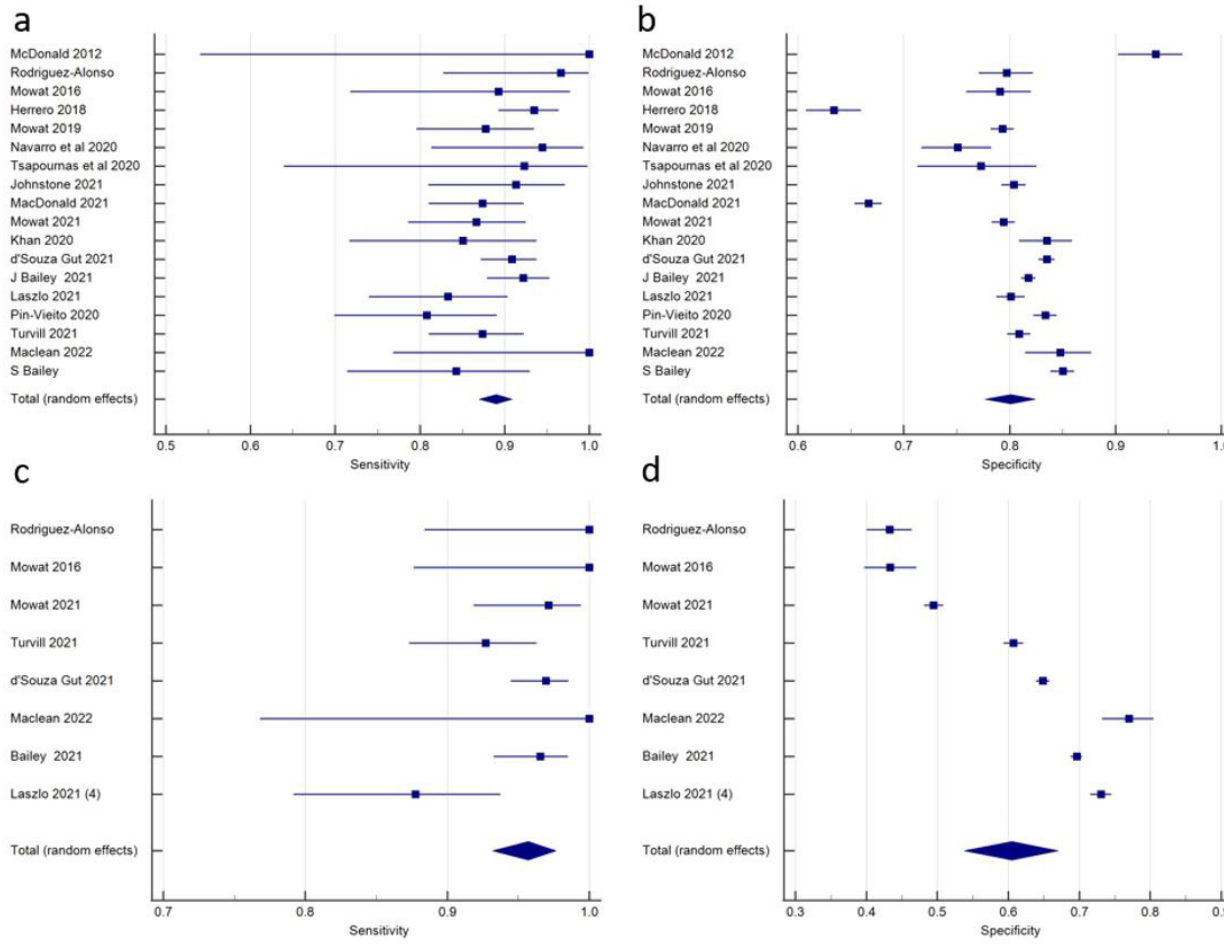
Table 1 (continued): Studies included in meta-analysis.

Study	Description *(Including retrospective vs prospective design, primary or secondary care recruitment, cohort date, laboratory analyser, and location)*	n	CRC prevalence %	FU interval months	QUADAS-2							Threshold mcg/g	Sensitivity	Specificity
					Risk of bias			Applicability concerns			Flow and timing			
					Selection	Index test	Reference standard	Selection	Index test	Reference standard				
Laszlo et al.[19]	Prospective, secondary care, multicentre observational study. All patients referred with abdominal symptoms for suspected CRC and those meeting NG12. 2017–2019. OC-Sensor. England.	3589	2.51	NA	Unclear	Un-clear	Low	Low	Low	Low	Low	4	0.88	0.73
												10	0.83	0.80
Johnstone et al.[20]	Retrospective observational study of all patients with FIT submitted from primary care. 2018–2019. Greater Glasgow and Clyde, Scotland.	4737	1.22	22–28	Low	Low	Low	Low	Low	Low	Low	10	0.91	0.80
MacDonald et al.[21]	Prospective, observational. Consecutive referrals of symptomatic colorectal patients from primary care. 2016–2019. HM-JACKarc. Lanarkshire, Scotland.	5250	2.88	24	Low	Low	Low	Low	Low	Low	Low	10	0.87	0.67

Table 1 (continued): Studies included in meta-analysis.

Study	Description *(Including retrospective vs prospective design, primary or secondary care recruitment, cohort date, laboratory analyser, and location)*	n	CRC prevalence %	FU interval months	QUADAS-2							Threshold mcg/g	Sensitivity	Specificity
					Risk of bias			Applicability concerns			Flow and timing			
					Selection	Index test	Reference standard	Selection	Index test	Reference standard				
Pin-Vieito et al.[22]	Population based retrospective cohort of patients with lower GI symptoms referred from primary care. San Sebastian cohort only. 2012–2016. OC-Sensor. Spain.	4543	1.61	24	Unclear	Low	Low	Unclear	Unclear	Low	Low	10	0.81	0.83
S Bailey et al.[23]	Patients with low-risk symptoms meeting NICE NG12/DG30. Retrospective, observational study of primary care based FIT. 2018. HM-JACKarc. Southwest England.	3890	1.31	12	Low	Low	Low	Low	Low	Low	Low	10	0.84	0.85
Maclean et al.[24]	Symptomatic patients referred under NICE NG12 completing investigation. Prospective, secondary care-based cohort. 2019–2020. SENTiFIT. Surrey, England.	553	2.53	NA	Unclear	Unclear	Low	Unclear	Low	Low	Low	3	1.00	0.77
												10	1.00	0.85

Figure 3: Forrest plots of studies reporting the diagnostic accuracy of a single rule out FIT for CRC.



a and b: sensitivity and specificity at >10mcg/g respectively.
c and d: sensitivity and specificity at LoD respectively.

Figure 4: Canterbury colorectal symptom pathway. a: Patient flow diagram. b: Secondary care decision aid.

a

Primary care

Initial assessment	
Rectal mass found	Refer
Above investigation threshold†	Request FIT
Below investigation threshold†	Continue management in Primary care

→

FIT interpretation	
FHb Detectable (exception‡)	Refer
FHb Undetectable	Continue investigation and symptom management in primary care

→

Secondary care

Triage
Refer to decision matrix below

† As per MOH direct access criteria + unexplained rectal bleeding in young cases at risk of CRC (see methods).
‡FHb threshold ≥10µg/g for rectal bleeding aged ≤39 years (≤29 Maori/Pacific) & IDA in menstruating females.
Referrals for cases on clinical grounds outside criteria require FIT for prioritisation, and are unlikely to be investigated unless FIT ≥10µg/g.

b

	Imaging abnormality	Mass palpable or visible on rectal examination	Iron deficiency anaemia with or without rectal bleeding (IDA) <55 female require menstrual history. Exclude CD and urinary losses.	
			FHb result	Outcome
Any age	Triage according to acuity of finding	Triage according to acuity of finding	≥150µg/g Detectable <150µg/g Undetectable	Urgent colonoscopy (2) Colonoscopy (14) Triagers discretion (141, 90)

Age dependent. Thresholds 10 year younger for Maori/Pacific People		Rectal bleeding† with or without change in bowel habit (RB) †Benign anal causes treated or excluded.		Altered bowel habit (ABH) looser and or more frequent		Other clinical presentations
		FHb result	Outcome	FHb result	Outcome	
	≥ 50	≥150µg/g ≥10 to <150µg/g Detectable <10µg/g Undetectable	Urgent colonoscopy (2) Colonoscopy (14) Colonoscopy (48) Decline (237, 151)	≥150µg/g ≥10 to <150µg/g Detectable <10µg/g Undetectable	Urgent colonoscopy (4) Colonoscopy (31) Triagers discretion (105) Decline (528, 336)	
	40 to 49	≥150µg/g ≥10 to <150µg/g Detectable <10µg/g Undetectable	Urgent colonoscopy (3) Colonoscopy (27) Triagers discretion (91) Decline (458, 292)	Exclude coeliac disease and follow local suspected IBD pathway where appropriate. Consider referral if symptomatic and high risk for colorectal cancer e.g. Family history category 2 or 3 and FIT detectable Other referrals of symptomatic patients with FHb <10µg/g not considered except in rare situations		
	≤39	≥10µg/g <10µg/g	Triagers discretion (33) Decline (1022, 895)			

Numbers in parenthesis are NNI for accepted categories and NND for declined categories. For declined categories, two numbers are presented; the NND based on the summary NLR, and the NND at the upper 95%CI of NLR (worst-case scenario).

Table 2: Colorectal cancer prevalence, and number needed to investigate or decline according to symptom and FHb threshold.

Category	2018 Canterbury dataset*		Calculated case number by FHb threshold or range									
			>150 mcg/g		10–150 mcg/g		<10 mcg/g		<LoD		LoD–10 mcg/g	
	n (% of total)	CRC (%)	n	CRC (%) NNI	n	CRC (%) NNI	n	CRC (%) NNI (WC)	n	CRC (%) NNI (WC)	n	CRC (%) NNI
IDA + RB	389 (13.4)	36 (9.25)	44.55	25.49 (57.21) 1.75	57.52	6.47 (11.25) 9	286.93	4.04 (1.41) 71 (62)	214.82	1.52 (0.71) 141 (90)	72.10	2.52 (3.49) 29
RB + ABH >50years	684 (23.6)	39 (5.70)	62.44	27.61 (44.22) 2.26	100.29	7.01(6.99) 14	521.27	4.38 (0.84) 119 (104)	391.39	1.65 (0.42) 237 (151)	129.88	2.73 (2.10) 48
RB + ABH 40–49 years	66 (2.3)	2 (3.03)	4.87	1.42 (29.06) 3.44	9.61	0.36 (3.74) 27	51.51	0.22 (0.44) 230 (201)	38.76	0.08 (0.22) 458 (292)	12.76	0.14 (1.10) 91
RB + ABH <39 years	144 (5.0)	1 (0.69)	8.43	0.71 (8.40) 11.91	20.86	0.18 (0.86) 116	114.71	0.11 (0.10) 1022 (895)	86.45	0.04 (0.05) 2044 (1301)	28.26	0.07 (0.25) 404
ABH >50 years	1061 (36.6)	28 (2.64)	75.61	19.82 (26.22) 3.81	154.42	5.03 (3.26) 31	830.97	3.14 (0.38) 265 (232)	625.38	1.18 (0.19) 528 (336)	205.59	1.96 (0.95) 105
Other criteria	554 (19.1)	11 (1.99)	37.11	7.79 (20.99) 4.77	80.50	1.98 (2.46) 41	436.39	1.23 (0.28) 354 (310)	328.58	0.47 (0.14) 706 (450)	107.81	0.77 (0.71) 140
All*	2898 (100)	117 (4.04)	233.01	82.84 (35.55) 2.81	423.21	21.04 (4.97) 20	2241.78	13.13 (0.59) 171 (150)	1685.38	4.95 (0.29) 341 (217)	556.40	8.18 (1.47) 68

*excluding 88 cases (9 CRC) referred with a rectal mass, and 214 cases (2 CRC) referred for concern regarding inflammatory bowel disease.
IDA: iron deficiency anaemia
RB: rectal bleeding
ABH: altered bowel habit
CRC: colorectal cancer
NNI: number needed to investigate to detect one cancer
WC: NND at upper 95% CI of the NLR (worst case scenario)

Table 3: Overall sensitivity, specificity, and resource implications of proposed pathway.

Criteria	Colonoscopy per 1,000 referrals	Expected CTC per 1,000 referrals	Sensitivity for CRC (95% CI)	Specificity for CRC (95% CI)	NNI	NND
MOH direct access criteria	775		90.5 (84.0–95.0)	24.0 (22.4–25.6)	21	56
Urgent referral for colonoscopy ACPGBI/BSG 2022[7]	250		89.6 (82.1–93.8)	77.9 (76.4–79.4)	7	171
Canterbury pathway	407*	81	97.1 (92.1–99.1)	54.2 (52.3–56.0)	12	426

*includes 10% conversion from CTC to colonoscopy.
NNI: number needed to investigate.
NND: number needed to decline.
CTC: computed tomography colonography.
CRC: colorectal cancer.
ACPGBI/BSG: Association of coloproctology of Great Britain and Ireland/British Society of Gastroenterology.

Table 4: Negative likelihood ratios for rule out thresholds of FIT calculated from contemporary meta-analyses.

	Current study (95% CI)	Saw et al. 2022[39] *>2mcg/g	Booth et al. 2022[40]	Pin-Vieito et al. 2022[8]
>10mcg/g	0.14 (0.12–0.16)	0.14	0.12	0.15
LoD	0.07 (0.04–0.11)	*0.05	0.08	0.09

years reflects disease risk and survival outcomes for these peoples,[45,46]and aims to align the rate of investigation of these peoples with the higher rate of investigation of NZ Europeans found in the 2018 dataset.[2] The change also aligns the colorectal pathway with the Canterbury upper gastrointestinal pathway, which has lower age thresholds for at risk populations, and is consistent with the recent extension of age criteria for Māori and Pacific people in the National Bowel Screening Program (NBSP). Meanwhile, recommending FHb measurement for patients below the age of 50 years who have unexplained RB addresses concern regarding the increasing incidence of CRC in the young,[47] and brings order to the current *ad hoc* approach for this patient group, the higher rule out threshold (>10mcg/g) being justified by the low prior risk.

Primary sector engagement indicates a strong preference for FHb testing in primary care supported by comprehensive education and online resources (in Canterbury via Community HealthPathways) for both test interpretation and to guide primary care-based management of colorectal symptoms. FIT request and interpretation in primary care has several benefits: promoting decision making by a single physician aware of the entire patient history, optimising sample return through explanation of the investigative process and the immediate provision of standardised collection device and requisition form for all faecal tests, and allowing follow-up in primary care for cases not returning samples using community-based staff. Furthermore, FHb testing in primary care avoids unnecessary case referral, saving time in primary and secondary care, and facilitating rapid clinical decision making.

There are few data regarding accuracy of FIT for most non-malignant colorectal conditions other than IBD and high-risk adenomas. FIT has good diagnostic accuracy for colonic IBD,[42] and is likely to have utility in the diagnosis of other bleeding pathologies such as drug induced, ischaemic, or diverticular colitis, colonic angiodysplastic bleeding and ulcerative conditions such as stercoral ulceration or rectal ulcer syndrome. However, there is no expectation that FIT would be useful in the diagnosis of microscopic colitis or other non-bleeding pathologies, and FIT is unreliable in the diagnosis of proximal gastrointestinal bleeding and small bowel Crohn's disease.[48,49] To ensure that a FIT based colorectal investigation pathway does not compromise the diagnosis of either malignant, or non-malignant colorectal disease, we have started with the lowest rule out threshold and propose to develop the pathway iteratively in response to prospective data.

FIT is currently being used in Canterbury to re-prioritise cases awaiting non-urgent new patient colonoscopy, and outcome data from the project will be reported in due course. Subsequently, the safe implementation of a pathway for new patients is dependent on robust primary sector engagement, education, and strong governance. Several future scenarios are conceivable. Future data may show that FIT has greater accuracy than estimated in the present study. In that situation, it would be appropriate to adopt a higher rule out threshold, retaining excellent sensitivity for CRC with lower rates of investigation. The current modelling assumes no change in GP referral practice; however, it is likely that GPs will have a lower threshold for investigating with FIT than they currently have for referring for invasive investigation. To maintain a high yield from invasive investigation in this situation, it may be necessary to increase the FIT threshold at which cases are accepted. Effort should be made to avoid this scenario, and the extreme case of surrogate screening, by emphasising the importance of symptom threshold for testing, as the higher the rule out FIT threshold is set, the less reassurance an individual symptomatic patient will receive from a 'negative' test. Reassuringly, where data are available, FIT testing rates have been shown to stabilise over time, suggesting that surrogate screening is unlikely to be widespread.[13,33]

Comparison of the current proposal with the new UK guideline is pertinent. Neither pathway recommends FIT in cases with anorectal lesions, and both recommend FIT in primary care. Thereafter, the pathways diverge with the ACPGBI/BSG recommending urgent referral for symptomatic cases with FHb >10mcg/g, while the Canterbury pathway follows a graduated approach, both to urgency and mode of investigation dependent on FHb concentration and case presentation. The ACPGBI/BSG delegates decisions regarding referral of cases with FHb<10mcg to the discretion of the referring doctor, while the Canterbury pathway anticipates accepting cases for non-urgent investigation when the FHb is detectable above the LoD. Referral of cases below this threshold, made due to enduring concern, would be judged on their merit. To

derive future iterations of the pathway, and ultimately a national solution for FIT in symptomatic cases, the merits of resource distribution between various facets of colonoscopy activity must be considered, including for symptomatic, screening, and surveillance cases. According to our dataset, the number needed to investigate to detect one CRC in the current direct access criteria is 21 (90.5% sensitive), compared with 12 for the current proposal (97% sensitive), 14 in the NBSP (assuming 7% CRC detection at colonoscopy), and 6 in the latest UK guideline (sensitivity 90%). Further discussion on this point is important but beyond the current work.

Much is beyond the scope of this study. We have neither performed economic analysis, nor detailed the complex processes required to ensure patient engagement and equity of outcome for population groups. Neither have we sought to resolve all clinical scenarios. For example, given the increasing risk of CRC with age, is there an upper age threshold beyond which all cases should be investigated irrespective of FHb result? How long should a persistently symptomatic patient be observed and managed in primary care before repeat FHb testing, and how should a repeat FIT result be interpreted? Neither have we fully addressed the investigation of colorectal symptoms in younger cases where IBD is the more common diagnosis, nor how to approach a case at risk of both CRC and IBD.

Improving access to colonoscopy for patients at risk of serious disease is an immediate concern for New Zealand. Formally incorporating FHb measurement into the assessment, referral, and prioritisation of colorectal symptoms appears achievable and should enable a high sensitivity for colorectal cancer, while also reducing the number of colonoscopies performed with no significant finding. This will expedite the investigation of those at higher risk, as colonoscopies can be undertaken more rapidly in this group. Robust primary and secondary sector education, community collaboration, development of strategies to ensure equity, research, prospective data gathering, analysis and feedback, are all essential for the initial and future success of the pathway.

CONFLICTS OF INTEREST
Nil.

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REFERENCES
1. Manatū Hauora – Ministry of Health [Internet]. Referral Criteria for Direct Access Outpatient Colonoscopy or Computed Tomography Colonography; 2019 [cited 2022 Sep 1]. Available from: https://www.health.govt.nz/publication/referral-criteria-direct-access-outpatient-colonoscopy-or-computed-tomography-colonography.
2. John RA, Wang H, Sylevych V, Falvey JD. Improving early detection of colorectal cancer in Aotearoa New Zealand: how do the direct access criteria perform? N Z Med J. 2022 Oct 28;135(1564):31-40.
3. McDonald PJ, Digby J, Innes C, Strachan JA, Carey FA, Steele RJ et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. Colorectal Dis. 2013 Mar;15(3):e151-9. doi: 10.1111/codi.12087.
4. Mowat C, Digby J, Strachan JA, McCann RK, Carey FA, Fraser CG et al. Faecal haemoglobin concentration thresholds for reassurance and urgent investigation for colorectal cancer based on a faecal immunochemical test in symptomatic patients in primary care. Ann Clin Biochem. 2021 May;58(3):211-219. doi: 10.1177/0004563220985547.
5. NICE National Institute for Health and Care Excellence [Internet]. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care.; 2017 July 26 [cited 2022 Sep 1]. Available from: https://www.nice.org.uk/guidance/dg30
6. Maclean W, Limb C, Mackenzie P, Whyte MB, Benton SC, Rockall T et al. Adoption of faecal immunochemical testing for 2-week-wait colorectal patients during the COVID-19 pandemic: an observational cohort study reporting a new service at a regional centre. Colorectal Dis. 2021 Jul;23(7):1622-1629. doi: 10.1111/codi.15408.
7. Monahan KJ, Davies MM, Abulafi M, Banerjea A, Nicholson B, Arasaradnam R et al. Faecal immunochemical testing (FIT) in patients with signs or symptoms of suspected colorectal cancer (CRC): a joint guideline from the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the British Society of Gastroenterology (BSG). Gut. 2022;71(10):1939–62.
8. Pin-Vieito N, Tejido-Sandoval C, De Vicente-Bielza N, et al. Faecal immunochemical tests safely enhance rational use of resources during the assessment of suspected symptomatic colorectal cancer in primary care: Systematic review and meta-analysis. Gut. 2022;71(5):1939-1962.
9. D'souza N, Georgiou Delisle T, Chen M, Benton S, Abulafi M; NICE FIT Steering Group. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. Gut. 2021 Jun;70(6):1130-1138. doi: 10.1136/gutjnl-2020-321956.
10. Rodríguez-Alonso L, Rodríguez-Moranta F, Ruiz-Cerulla A, Lobatón T, Arajol C, Binefa G et al. An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical faecal occult blood test. Dig Liver Dis. 2015 Sep;47(9):797-804. doi:

10.1016/j.dld.2015.05.004.
11. Mowat C, Digby J, Strachan JA, Wilson R, Carey FA, Fraser CG et al. Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. Gut. 2016 Sep;65(9):1463-9. doi: 10.1136/gutjnl-2015-309579.
12. Herrero JM, Vega P, Salve M, Bujanda L, Cubiella J. Symptom or faecal immunochemical test based referral criteria for colorectal cancer detection in symptomatic patients: a diagnostic tests study. BMC Gastroenterol. 2018 Oct 25;18(1):155. doi: 10.1186/s12876-018-0887-7.
13. Mowat C, Digby J, Strachan JA, McCann R, Hall C, Heather D et al. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. BMJ Open Gastroenterol. 2019 May 4;6(1):e000293. doi: 10.1136/bmjgast-2019-000293.
14. Khan AA, Klimovskij M, Harshen R. Accuracy of faecal immunochemical testing in patients with symptomatic colorectal cancer. BJS Open. 2020 Sep 18;4(6):1180-8. doi: 10.1002/bjs5.50346.
15. Navarro M, Hijos G, Sostres C, Lué A, Puente-Lanzarote JJ, Carrera-Lasfuentes P et al. Reducing the Cut-Off Value of the Fecal Immunochemical Test for Symptomatic Patients Does Not Improve Diagnostic Performance. Front Med (Lausanne). 2020 Sep 2;7:410 doi: 10.3389/fmed.2020.00410.
16. Tsapournas G, Hellström PM, Cao Y, Olsson LI. Diagnostic accuracy of a quantitative faecal immunochemical test vs. symptoms suspected for colorectal cancer in patients referred for colonoscopy. Scand J Gastroenterol. 2020 Feb;55(2):184-192. doi: 10.1080/00365521.2019.1708965.
17. Turvill JL, Turnock D, Cottingham D, Haritakis M, Jeffery L, Girdwood A et al. The Fast Track FIT study: diagnostic accuracy of faecal immunochemical test for haemoglobin in patients with suspected colorectal cancer. Br J Gen Pract. 2021 Jul 29;71(709):e643-e651. doi: 10.3399/BJGP.2020.1098.
18. Bailey JA, Weller J, Chapman CJ, Ford A, Hardy K, Oliver S et al. Faecal immunochemical testing and blood tests for prioritization of urgent colorectal cancer referrals in symptomatic patients: a 2-year evaluation. BJS Open. 2021 Mar 5;5(2):zraa056. doi: 10.1093/bjsopen/zraa056.
19. Laszlo HE, Seward E, Ayling RM, Lake J, Malhi A, Stephens C et al. Faecal immunochemical test for patients with 'high-risk' bowel symptoms: a large prospective cohort study and updated literature review. Br J Cancer. 2022 Mar;126(5):736-743. doi: 10.1038/s41416-021-01653-x.
20. Johnstone MS, Burton P, Kourounis G, Winter J, Crighton E, Mansouri D et al. Combining the quantitative faecal immunochemical test and full blood count reliably rules out colorectal cancer in a symptomatic patient referral pathway. Int J Colorectal Dis. 2022 Feb;37(2):457-466. doi: 10.1007/s00384-021-04079-2.
21. MacDonald S, MacDonald L, Godwin J, Macdonald A, Thornton M et al. The diagnostic accuracy of the faecal immunohistochemical test in identifying significant bowel disease in a symptomatic population. Colorectal Dis. 2022 Mar;24(3):257-263. doi: 10.1111/codi.15994.
22. Pin-Vieito N, García Nimo L, Bujanda L, Román Alonso B, Gutierrez-Stampa MÁ, Aguilar-Gama V et al. Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study. United European Gastroenterol J. 2021 Mar;9(2):256-267. doi: 10.1177/2050640620949714.
23. Bailey SER, Abel GA, Atkins A, Byford R, Davies SJ, Mays J et al. Diagnostic performance of a faecal immunochemical test for patients with low-risk symptoms of colorectal cancer in primary care: an evaluation in the South West of England. Br J Cancer. 2021 Mar;124(7):1231-1236. doi: 10.1038/s41416-020-01221-9.
24. MacLean W, Zahoor Z, O'Driscoll S, Piggott C, Whyte MB, Rockall T et al. Comparison of the QuikRead go®point-of-care faecal immunochemical test for haemoglobin with the FOB Gold Wide® laboratory analyser to diagnose colorectal cancer in symptomatic patients. Clin Chem Lab Med. 2021 Oct 25;60(1):101-108. doi: 10.1515/cclm-2021-0655.
25. Widlak MM, Thomas CL, Thomas MG, Tomkins C, Smith S, O'Connell N et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther. 2017 Jan;45(2):354-363. doi: 10.1111/apt.13865.
26. Chapman C, Bunce J, Oliver S, Ng O, Tangri A, Rogers R et al. Service evaluation of faecal immunochemical testing and anaemia for risk stratification in the 2-week-wait pathway for colorectal cancer. BJS open. 2019 Jan 28;3(3):395-402. doi: 10.1002/bjs5.50131.
27. Farrugia A, Widlak M, Evans C, Smith SC, Arasaradnam R et al. Faecal immunochemical testing (FIT) in symptomatic patients: what are we missing? Frontline Gastroenterol. 2020 Jan;11(1):28-33. doi: 10.1136/flgastro-2018-101174.
28. Juul JS, Hornung N, Andersen B, Laurberg S,

Olesen F, Vedsted P et al. The value of using the faecal immunochemical test in general practice on patients presenting with non-alarm symptoms of colorectal cancer. Br J Cancer. 2018 Aug;119(4):471-479. doi: 10.1038/s41416-018-0178-7.
29. Ayling RM, Machesney M. Service evaluation of faecal immunochemical testing introduced for use in North East London for patients at low risk of colorectal cancer. J Clin Pathol. 2021 Mar;74(3):163-166. doi: 10.1136/jclinpath-2020-206632.
30. Clackett W, Barclay ST, Stanley AJ, Cahill A. The Value of Quantitative Faecal Immunochemical Testing as a Prioritisation Tool for the Endoscopic Investigation of Patients With Iron Deficiency. Front Med (Lausanne). 2021 Jul 22;8:700753. doi: 10.3389/fmed.2021.700753.
31. Turvill J, Mellen S, Jeffery L, Bevan S, Keding A, Turnock D et al. Diagnostic accuracy of one or two faecal haemoglobin and calprotectin measurements in patients with suspected colorectal cancer. Scand J Gastroenterol. 2018 Dec;53(12):1526-1534. doi: 10.1080/00365521.2018.1539761.
32. D'Souza N, Hicks G, Benton SC, Abulafi M. The diagnostic accuracy of the faecal immunochemical test for colorectal cancer in risk-stratified symptomatic patients. Ann R Coll Surg Engl. 2020 Mar;102(3):174-179. doi: 10.1308/rcsann.2019.0144.
33. Nicholson BD, James T, East JE, Grimshaw D, Paddon M, Justice S et al. Experience of adopting faecal immunochemical testing to meet the NICE colorectal cancer referral criteria for low-risk symptomatic primary care patients in Oxfordshire, UK. Frontline Gastroenterol. 2019 Oct;10(4):347-355. doi: 10.1136/flgastro-2018-101052.
34. Sanders AD, Stevenson C, Pearson J, Burt M, McGeoch G, Hudson B et al. A novel pathway for investigation of colorectal symptoms with colonoscopy or computed tomography colonography. N Z Med J. 2013 Sep 13;126(1382):45-57.
35. NICE National Institute for Health and Care Excellence [Internet]. NICE guideline; 2015 June 23 [cited 2022 Sep 1]. Suspected cancer: recognition and referral Available from: https://www.nice.org.uk/guidance/ng12.
36. Christopher J, Flint TR, Ahmed H, Dhir N, Li R, Macfarland K et al. Straight-to-test for the two-week-wait colorectal cancer pathway under the updated NICE guidelines reduces time to cancer diagnosis and treatment. Ann R Coll Surg Engl. 2019 May;101(5):333-339. doi: 10.1308/rcsann.2019.0022.
37. Digby J, Strachan JA, McCann R, Steele RJ, Fraser CG, Mowat C et al. Measurement of faecal haemoglobin with a faecal immunochemical test can assist in defining which patients attending primary care with rectal bleeding require urgent referral. Ann Clin Biochem. 2020 Jul;57(4):325-327. doi: 10.1177/0004563220935622.
38. Högberg C, Gunnarsson U, Cronberg O, Thulesius H, Lilja M, Jansson S et al. Qualitative faecal immunochemical tests (FITs) for diagnosing colorectal cancer in patients with histories of rectal bleeding in primary care: a cohort study. Int J Colorectal Dis. 2020 Nov;35(11):2035-2040. doi: 10.1007/s00384-020-03672-1.
39. Saw KS, Liu C, Xu W, Varghese C, Parry S, Bissett I. Faecal immunochemical test to triage patients with possible colorectal cancer symptoms: meta-analysis. Br J Surg. 2022 Feb 1;109(2):182-190.
40. Booth R, Carten R, D'Souza N, Westwood M, Kleijnen J, Abulafi M. Role of the faecal immunochemical test in patients with risk-stratified suspected colorectal cancer symptoms: A systematic review and meta-analysis to inform the ACPGBI/BSG guidelines. Lancet Reg Health Eur. 2022 Oct 3;23:100518. doi: 10.1016/j.lanepe.2022.100518.
41. Takashima S, Kato J, Hiraoka S, Nakarai A, Takei D, Inokuchi T et al. Evaluation of Mucosal Healing in Ulcerative Colitis by Fecal Calprotectin Vs. Fecal Immunochemical Test. Am J Gastroenterol. 2015 Jun;110(6):873-80. doi: 10.1038/ajg.2015.66.
42. Mooiweer E, Fidder HH, Siersema PD, Laheij RJ, Oldenburg B. Fecal hemoglobin and calprotectin are equally effective in identifying patients with inflammatory bowel disease with active endoscopic inflammation. Inflamm Bowel Dis. 2014 Feb;20(2):307-14. doi: 10.1097/01.MIB.0000438428.30800.a6.
43. Mowat C, Digby J, Cleary S, Gray L, Datt P, Goudie DR et al. Faecal haemoglobin concentration in adenoma, before and after polypectomy, approaches the ideal tumour marker. Ann Clin Biochem. 2022 Jul;59(4):272-276. doi: 10.1177/00045632221080897.
44. Hirsz M, Hunt L, Mayo M, Chepulis L. Symptoms associated with colorectal cancer in patients referred to secondary care. N Z Med J. 2022 May 6;135(1554):137-139.
45. McLeod M, Harris R, Paine SJ, Crengle S, Cormack D, Scott N et al. Bowel cancer screening age range extension for Māori: what is all the fuss about? N Z Med J. 2021 May 21;134(1535):71-77.
46. Sharples KJ, Firth MJ, Hinder VA, Hill AG, Jeffery M, Sarfati D et al. The New Zealand PIPER Project: colorectal cancer survival according to rurality, ethnicity and socioeconomic depreivation-results from a retrospective cohort study. N Z Med J. 2018 Jun 8;131(1476):24-39.

47. Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K et al. Rising incidence of early-onset colorectal cancer - a call to action. Nat Rev Clin Oncol. 2021 Apr;18(4):230-243. doi: 10.1038/s41571-020-00445-1.
48. Inokuchi T, Kato J, Hiraoka S, Takashima S, Nakarai A, Takei D et al. Fecal Immunochemical Test Versus Fecal Calprotectin for Prediction of Mucosal Healing in Crohn's Disease. Inflamm Bowel Dis. 2016 May;22(5):1078-85. doi: 10.1097/MIB.0000000000000728.
49. Pin-Vieito N, Iglesias MJ, Remedios D, Rodríguez-Alonso L, Rodriguez-Moranta F, Álvarez-Sánchez V et al. Retrospective cohort study: Risk of gastrointestinal cancer in a symptomatic cohort after a complete colonoscopy: Role of faecal immunochemical test. World J Gastroenterol. 2020 Jan 7;26(1):70-85. doi: 10.3748/wjg.v26.i1.70.