Figure 1: Overview of study design.

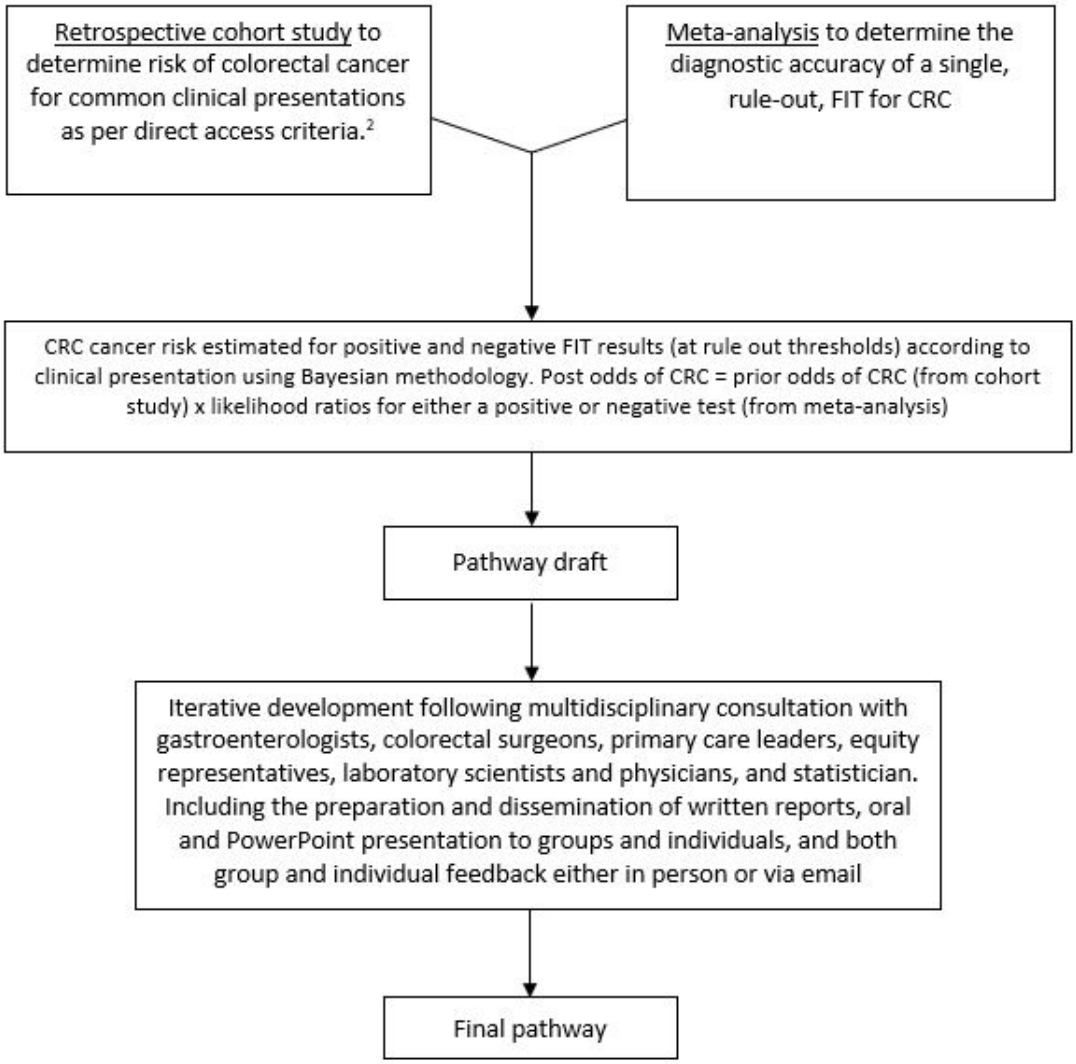


Figure 2: Meta-analysis search strategy and review process.

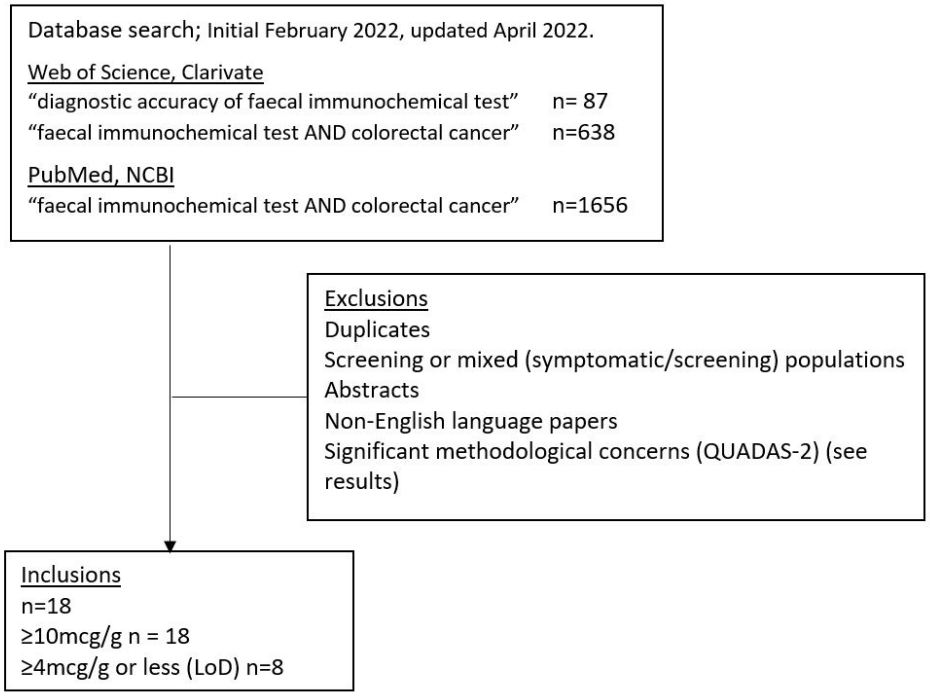


Table 1: Studies included in meta-analysis.

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

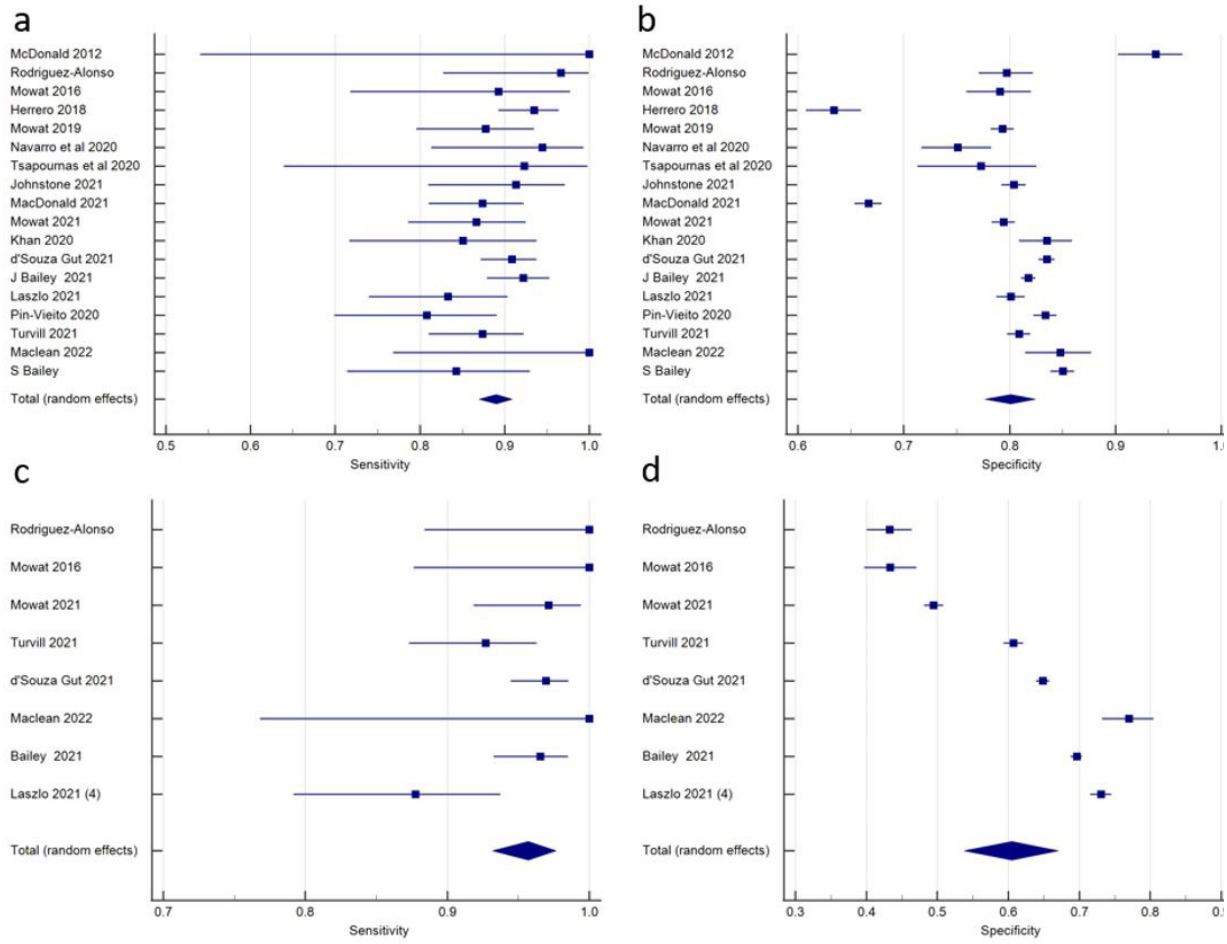
Table 1 (continued): Studies included in meta-analysis.

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

Any age	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
	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