Original research

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

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ABSTRACT

Objective Implementation of faecal immunochemical tests (FIT) as a triage test in primary healthcare may improve the efficiency of referrals without missing cases of colorectal cancer (CRC). We aim to summarise the performance characteristics of FITs for CRC in symptomatic patients presenting to primary healthcare.

Design We performed a systematic literature review of Medline and EMBASE databases from May 2018 to November 2020. Previous related systematic searches were also adapted to this aim and completed with reference screening. We identified studies performed on adult patients consulting for abdominal symptoms in primary care which reported data such that the FIT diagnostic performance parameters for CRC could be obtained. Bivariate models were used to synthesise available evidence. Meta-regression analysis was performed to evaluate the causes of heterogeneity.

Results Twenty-three studies (69 536 participants) were included (CRC prevalence 0.3%–6.2%). Six studies (n=34 691) assessed FIT as rule in test (threshold of ≥150 µg Hb/g faeces) showing a sensitivity of 64.1% (95% CI 57.8% to 69.9%) and a specificity of 95.0% (95% CI 91.2% to 97.2%). A threshold of 10 µg/g (15 studies; n=48 872) resulted in a sensitivity of 87.2% (95% CI 81.0% to 91.6%) and a specificity of 84.4% (95% CI 79.4% to 88.3%) for CRC. At a 20 µg Hb/g faeces threshold (five studies; n=24 187) less than one additional CRC would be missed per 1000 patients investigated compared with 10 µg Hb/g faeces threshold (CRC prevalence 2%).

Conclusion FIT is the test of choice to evaluate patients with new-onset lower gastrointestinal symptoms in primary healthcare.

Significance of this study

What is already known on this subject?

- Colorectal cancer (CRC) detection in symptomatic patients is a challenge for healthcare systems given the low specificity of symptoms. This results in overuse of colonoscopy resources and delay in diagnosis.
- Faecal immunochemical test (FIT) may be effective in the stratification of CRC risk in patients with abdominal symptoms seen in primary healthcare.

What are the new findings?

- A 150 µg Hb/g of faeces threshold identifies more than half of CRC with high specificity.
- In low CRC prevalent populations, CRC risk in patients with faecal haemoglobin <10 µg/g of faeces equals the risk of colonoscopy severe complications and the CRC risk in asymptomatic subjects.

How might it impact on clinical practice in the foreseeable future?

- The evaluation of patients consulting with new-onset lower gastrointestinal symptoms in primary healthcare with FITs enables rational use of the available resources.
- In the near future, we will have to address two questions: how to detect FIT negative CRC and whether FIT evaluation in symptomatic patients improves CRC prognosis.

INTRODUCTION

A significant percentage of colorectal cancers (CRCs) are diagnosed in symptomatic patients, after the implementation of CRC screening programmes.[1] Unfortunately, most symptoms are non-specific at presentation as they are shared among non-malignant conditions and different types of cancer, which produces additional difficulties and delay in diagnosis.[2] Moreover, concordance between patient-reported and doctor-reported symptoms is low,[3] and most patients with abdominal symptoms do not have significant colorectal disease.[4]

In the last few years, evidence has proven that faecal immunochemical tests for haemoglobin (FIT) may be effective in evaluating patients with abdominal symptoms to identify patients at low risk of CRC.[5] Furthermore, the amount of faecal haemoglobin (f-Hb) detected has been shown to be related to severity of disease,[6] and constitutes a better CRC risk predictor than demographic (age and sex), clinical (presence of symptoms) and family history or lifestyle factors.[7]

For these reasons, the National Institute for Health and Care Excellence recommended (DG30) in 2017 the use of FIT to guide referral for suspected CRC in patients without rectal bleeding who complain with certain unaccounted for low-risk symptoms.[8] Furthermore, implementation of FIT as a triage test in primary care with appropriate safety netting may improve the efficiency of referrals without missing cases of relevant bowel disease. This is even more important nowadays, in regions with additional capacity issues due to the COVID-19 pandemic.[9]

Notwithstanding the above, a recent systematic review revealed that few countries recommend FIT in primary healthcare as an adjunct to clinical assessment.[10] There is limited evidence of the use of FITs in this setting as most studies supporting DG30 recommendation were performed in secondary care.[5] This could increase the concerns of general practitioners to use FITs to aid their decision-making process when dealing with a patient with symptoms suggesting CRC. Several studies have recently been published evaluating FIT in symptomatic patients seen in primary healthcare. We, therefore, aim to perform a systematic review to assess the diagnostic accuracy of FIT for CRC detection in patients presenting with recent onset gastrointestinal symptoms in primary healthcare, with special interest on the clinical effectiveness for triaging referrals in this setting.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to conduct and report this systematic review.[11]

Data sources and searches

MEDLINE (via PubMed) and EMBASE (via Ovid) databases were searched from May 2018 to November 2020 without restrictions on language or publication status. Published search strategies in related systematic reviews were consulted and updated.[5 12] The reference lists of all relevant articles extracted were also reviewed to identify additional potentially interesting articles following an iterative process. Furthermore, we also included all studies identified by previous systematic reviews that satisfied the inclusion criteria of this research (online supplemental appendix 1).

Study selection

Three authors (CT-S, NPV and CS-G) independently screened titles and abstracts and assessed full text articles of studies considered relevant. We included any cohort study which met all the following criteria: (1) adult subjects (older than 18 years) consulting for abdominal symptoms in primary healthcare, (2) FIT diagnostic performance parameters for CRC and/or significant colonic lesions (SCL) available and (3) thresholds used to determine a positive result expressed as micrograms of haemoglobin per gram of faeces (µg Hb/g). We included in this systematic review studies that reported colon evaluation (either by endoscopic or imaging techniques) or or longitudinal follow-up of controls with medical records or cancer registry and a minimum monitoring time of 3 months as reference standard. A previous study showed that the different follow-up periods (3, 6, 12 months) did not affect FIT diagnostic performance for CRC detection.[13]

We excluded studies if two by two tables with absolute numbers of true positive, true negative, false positive and false negative (FN) test results could not be constructed. Case–control studies, conference abstracts, studies with hospital inpatients and those including screening, or mixed (with and without symptoms) population were also excluded. Those studies conducted on symptomatic patients who were recruited in colonoscopy units, were only included if authors explicitly state that they were performed on patients referred solely from primary healthcare facilities.

Outcome assessment

Our primary and secondary outcomes were FIT diagnostic performance estimates to detect CRC and SCL respectively, at a cut-off value of limit of detection (LoD), 10 µg Hb/g faeces, 20 µg Hb/g faeces and 150 µg Hb/g faeces.

Data extraction

Two reviewers (CT-S and NPV) extracted data and extractions were verified by a second reviewer (CS-G). Any disagreement was consulted with a third reviewer (NPV/JC). In addition to test performance outcome measures, information on study details (author, year of publication, aim and setting, period of recruitment and type of cohort), participant characteristics (inclusion and exclusion criteria, demographic characteristics, symptoms, acceptability defined as the proportion of participants who returned a FIT sample), target reported (prevalence of CRC and SCL as well as the definition used), FITs characteristics (brand, analyser used, f-Hb concentration used as threshold) and reference standard used (bowel examination and follow-up length when applicable) were considered relevant.

Quality assessment

The potential risks of bias were evaluated for each study included using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2).[14] An inverted funnel scatterplot was used to detect publication bias.

Statistical analysis

To avoid threshold effect, studies were classified by f-Hb threshold for a positive test result. Threshold effect is a specific cause of heterogeneity in meta-analyses of diagnostic test accuracy. It occurs when different criteria (cut-off values or thresholds) are used between studies to assess whether a test result is positive or negative. We calculated pooled estimates of sensitivity, specificity and likelihood ratios using a bivariate random-effects model when at least four studies with similar characteristics were available.[15] When necessary, a hierarchical summary receiver operating characteristic (ROC) curve presenting summary estimates of sensitivities and specificities along with their corresponding 95% CI and prediction region was also generated for each subgroup of studies.[16] If this approach was not possible, a random-effects model was applied following DerSimonian's method and summary sensitivity and specificity estimates were reported by plotting a summary ROC curve using DerSimonian and Lair's model.[17] We evaluated the diagnostic yield of FIT according to the CRC prevalence and the post-test probabilities of CRC assessed through Fagan nomograms. We calculated the number of necessary colonoscopies to find one CRC (number necessary to scope, NNS), and the number of missed CRC per 1000 patients with an f-Hb value below a chosen threshold.

The percentage of total variation across studies attributable to heterogeneity rather than chance was assessed statistically using the inconsistency index I^2, and values greater than 50% represent substantial heterogeneity.[18] Threshold effect was assessed through Spearman's rank correlation ($p<0.1$ was considered to be statistically significant).

FIT brand, the location where the patient was recruited (colonoscopy unit or primary health facility) or the reference standard

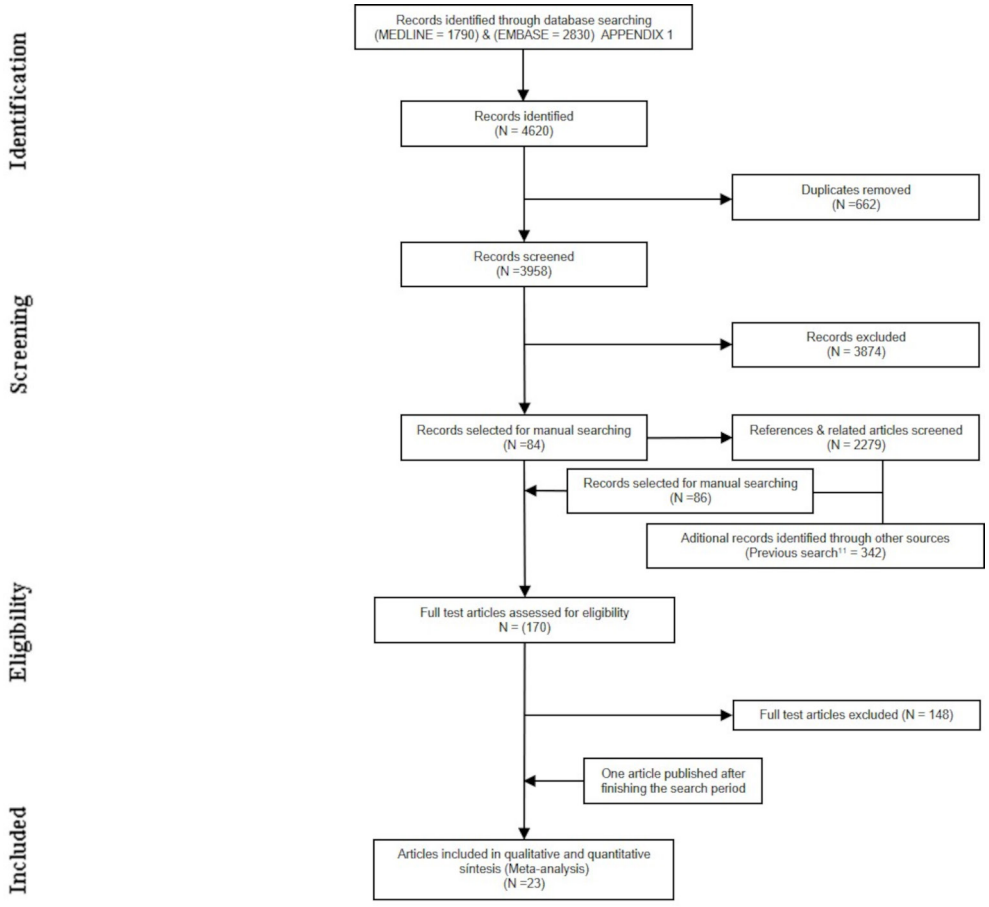

Figure 1 Summary of evidence search and selection.

used to follow-up on patients with negative FIT results, are variables which may affect the assessment of FIT accuracy. Thus, when the number of studies allowed, we performed a bivariate random-effects meta-regression to evaluate the impact of these variables on our results. Visual inspection of ROC space was used to enable identification of those studies with major differences from each subgroup based on threshold and sensitivity analysis was performed after removing keynote outliers when those differences can be accounted for through bias. We used Stata V.14.0 (StataCorp), and MetaDisc software for statistical analyses.[19]

Patient and public involvement

We consulted a European association of CRC patients and their relatives during the development of the study protocol (https://europacolonespana.org) to assess the general public acceptability as well as any concern about using FITs as a triage tool for symptomatic patients with suspected CRC in primary care. Feedback was used to select the most relevant information collected in this systematic review from a general public point of view. These data will be included in a friendly designed poster to be shown in primary care centres, patient association websites and disseminated through press releases.

RESULTS

Study selection

The literature search in MEDLINE and EMBASE identified 4620 potentially relevant articles, of which 170 full-text articles were evaluated and 22 articles met the inclusion criteria (figure 1 and online supplemental appendix 2). The reasons for excluding the articles were as follow: secondary literature (41), studies mixing symptomatic and asymptomatic subjects (76), research performed outside primary healthcare (97), uncertainty with the index test (53), the reference standard (21) or the outcome definition (13). These were supplemented by one article from a manual search published 1 month from the search date, providing a total of 23 studies included in this systematic review (table 1 and online supplemental table 1).[13 20–41] Furthermore, additional information of the same patients evaluated in the studies of Khan *et al*,[38] and Chapman *et al*,[31] is respectively reported in another two secondary published studies.[42 43] Partial information reported in the studies of Högberg *et al*,[40] and McSorley *et al*,[37] can also be found in other studies included in this review,[29 34] and this has been considered in the quantitative synthesis.

Study characteristics

The total number of participants was 69 536. Sample sizes ranged from 178 to 15 789. Median age ranged from 58 to 72 years and the proportion of women from 49.0% to 64.6%. CRC and SCL prevalence ranged from 0.3% to 6.2% and 2.6% to 31.0%, respectively. Twelve studies provided information on the FIT's accuracy for SCL detection. SCL definition varied widely between the different studies. Most authors defined it as the sum of CRC plus high risk and/or advanced adenoma plus Inflammatory bowel disease,[13 21–24 27 29–32 35 36] although diverticulitis, significant diverticular disease or complicated diverticular disease were also included in three studies.[22 26 31] With respect to

Table 1 Characteristics of the studies included in the meta-analysis

										Symptoms											Reference standard*		
				Age	Sex	CRC		SCL		AbPa		ReBl		ChBoHa		WeLo		Anaemia			Performed BI		
Author, year	Country	Type	n	Median	% Fem	N	%	N	%	N	%	N	%	N	%	N	%	N	%	FIT brand	N	%	Censor date/ follow-up time†
Recruited in primary care																							
Högberg, 2010[20]	SWE	Pro	303	ND	ND	1	0.3	9	3.0	250	82.5	47	15.5	70	23.1	ND	ND	51	16.8	AFB	ND	54.0	31/05/08
Mowat, 2015[21]	UK (Sco)		755	64	54.7	28	3.7	103	13.6	83	11.0	258	34.2	323	42.8	7	0.9	67	8.9	OC-S	755	100.0‡	NA
Elias, 2016[22]	NL		810	61	54.9	37	4.6	141	17.4	ND	80.7	ND	43.6	ND	65.5	ND	19.2	ND	5.5	COS	810	100.0‡	3 months
Högberg, 2016[23]	Sweden		373	63	64.6	8	2.1	26	6.8	207	58.0	92	25.3	161	45.7	46	13.5	62	21.0	AFB	185	49.6	2 years
Juul, 2018[24]	Denmark		3462	ND	56.1	54	1.6	153	4.4	1579	45.6	0	0.0	1867	53.9	ND	ND	424	12.3	OC-S	834	24.1	3 months
Ayling, 2020[35]	UK (Eng)		894	60	55.7	8	0.9	23	2.6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	OC-S	217	24.3	31/01/20
Mowat, 2019[29]	UK (Sco)		5372	65	56.4	103	1.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	1926	35.9	01/11/18
Keenan, 2019[30]	NZ		185	59	50.8	2	1.0	7	3.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Ngaio	67	36.2	1 year
Chapman, 2019[31]	UK (Eng)		810	ND	55.7	40	4.9	108	13.3	ND	ND	0	0.0	ND	58.2	ND	ND	288	37.8	OC-S	ND	ND	22/09/17
Pin-Vieito, 2020[33]	ES[P]	Ret	5623	61	53.4	80	1.4	ND	ND	1008	ND	ND	ND	ND	ND	ND	ND	ND	ND	OC-S	ND	ND	2 years
Nicholson, 2018[13]	UK (Eng)		238	58	57.0	7	2.9	20	8.4	45	18.9	23	9.7	59	24.8	4	1.7	62	26.1	HM-J	75	31.5	21–23 months
Högberg, 2020[34]	SWE		5683	64	59.9	107	1.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	AFB	ND	ND	2 years
Nicholson, 2020[27]	UK (Eng)		9896	60	58.6	105	1.1	682	6.9	ND	25.2	ND	19.7	ND	50.6	ND	ND	ND	28.2	HM-J	ND	ND	6–36 months
McSorley, 2020[37]	UK (Sco)		4841	66	52.7	266	5.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	4841	100.0‡	NA
Bailey, 2020[39]	UK (Eng)		5733	67.4§	56.0	106	1.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	OC-S	ND	ND	31/12/18
Högberg, 2020[40]	SWE		15789	65	60.9	304	1.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Mix¶	ND	ND	2 years
Recruited in colonoscopy unit																							
Widlak, 2018[25]	UK (Eng)	Pro	562	68	49.0	35	6.2	173	31.0	164	29.0	232	41.0	369	66.0	87	15.0	121	22.0	HM-J	562	100.0	NA
Turvill, 2018[26]	UK (Eng)		515	69	50.0	27	5.0	76	15.0	134	26.0	187	36.0	409	79.0	ND	14.0	ND	18.0	HM-J	515	100.0	NA
D'Souza, 2019[32]	UK (Eng)		298	60.6§	51.4	12	4.0	27	9.1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	298	100.0	NA
D'Souza, 2020[36]	UK (Eng)		9822	65	54.9	329	3.3	1177	12.0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	9822	100.0	NA
Khan, 2020[38]	UK (Eng)		928	72	59.5	47	5.1	ND	ND	69	7.4	94	10.1	609	65.6	70	7.5	189	20.4	HM-J	928	100.0	NA
Laszlo, 2020[41]	UK (Eng)		3596	67	53.1	90	2.5	444	12.3	427	11.9	970	27.0	1835	51.0	312	8.7	684	19.0	OC-S	3596	100.0	NA
Ayling, 2019[28]	UK (Eng)	Ret	178	71	51.2	7	3.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	178	100	OC-S	178	100.0	NA

*The studies performed on patients recruited in primary care facilities used follow-up by means of review of clinical records and cross-databases as reference standard. However, a variable fraction of the cohort performed different bowel imaging investigations, mainly colonoscopy, CT colonography, plain CT and/or sigmoidoscopy.
†Follow-up end date or monitoring time.
‡Colonoscopy was performed as reference standard in 100% of patients.
§Mean age.
¶This study used various FIT: Actim Faecal Blood in Örebro, Analyz FOB in Kronoberg, Västerbotten and Västernorrland, Chemtrue FOB Test in Jämtland Härjedalen and Diaquick FOB also in Kronoberg.
AbPa, abdominal pain; AFB, Actim Faecal Blood; BI, bowel image; ChBoHa, change of bowel habit; COS, clearview one step; CRC, colorectal cancer; Fem, female; FIT, faecal immunochemical tests; HM-J, HM-JACKarc; NA, not applicable; ND, no data; Ngaio, Ngaio Diagnostics; NL, Netherlands; NZ, New Zealand; OC-S, OC-Sensor; Pro, prospective; ReBl, Rectal bleeding; Ret, retrospective; SCL, significant colonic lesion; SWE, Sweden; WeLo, weight loss.;

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Hogberg 2010	☺	☺	☹	☺	?	☺	☺
Mowat 2015	☹	☺	☺	☺	?	☺	☺
Elias 2016	☹	☹	☺	☺	?	☺	☺
Hogberg 2016	☺	☺	?	☺	?	☺	☺
Juul 2018	☺	☺	☹	☺	☺	☺	☺
Widlak 2018	☹	☺	☺	☺	?	☺	☺
Turvill 2018	☹	☺	☺	☺	?	☺	☺
Nicholson 2018	☺	☹	☹	?	?	☹	☺
Ayling 2019	☹	☹	☺	?	?	☺	☺
Mowat 2019	☺	☺	?	☺	☺	☺	☺
Keenan 2019	?	☺	☹	☺	?	☺	☺
Chapman 2019	☺	☺	☹	☺	☺	☺	☺
D'Souza 2019	☹	☺	☺	☺	?	☺	☺
Pin-Vieito 2020	☺	☺	?	?	☺	☺	☺
Hogberg 2020	?	☺	?	?	☺	☺	☺
Ayling 2020	☺	☺	☹	☺	☺	☺	☺
Nicholson 2020	☺	☹	☹	?	☺	☹	☺
D'Souza 2020	☹	☺	☺	☺	?	☺	☺
McSorley 2020	☹	☺	☺	?	☺	☺	☺
Khan 2020	☹	☺	☺	☺	☺	☹	☺
Bailey 2020	☺	☺	☹	?	☺	☺	☺
Hogberg Nov 2020	?	☺	?	?	☺	☺	☺
Lazlo 2020	☹	☺	☺	☺	?	☺	☺

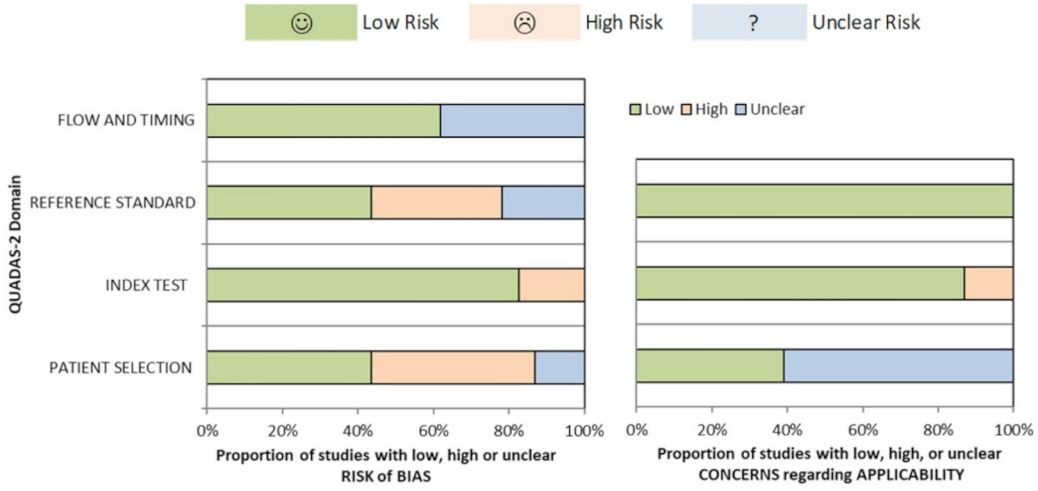

Figure 2 Quality Assessment of Diagnostic Accuracy Studies (QUADAS).

the reference standard for CRC and/or SCL, colonoscopy was performed as reference standard in 100% of patients recruited in colonoscopy units and in a variable percentage in patients recruited in primary healthcare. In this subgroup of studies, the CRC diagnosis was based either on different bowl imaging investigations (colonoscopy, CT colonography, plain CT and/or sigmoidoscopy) or in follow-up with a variable length of time (3 to 36 months). Full details of these studies are shown in table 1 and online supplemental table 1).

Quality assessment

Overall results of the quality assessment from the 23 articles are reported in figure 2 by means of the QUADAS-2 instrument. Eight studies were retrospective in design.[13 27 28 33 34 37 39 40] Of the 13 articles using longitudinal follow-up as reference standard, eight articles were at high risk of bias because they used heterogenous monitoring periods less than 2 years.[13 20 24 27 30 31 35 39] Ten articles had a high risk of selection bias, as their cohorts had either been recruited in colonoscopy units or comprised solely of patients referred to colonoscopy, thus having an increased risk of CRC.[21 22 25 26 28 32 36–38 41] Two studies included frozen stool samples,[22 28] and another two, which assessed the accuracy of a quantitative FIT (HM-JACKarc), evaluated more than one sample for each patient and considered a positive result if any of those samples had a positive outcome.[13 27] One study collected the stool sample for FIT through a digital rectal examination.[38] A

number of studies had 'patient selection' applicability concerns. In many cases, a low proportion of patients who were either invited or agreed to participate in the study were included in the analysis.[21 22 25 26 36 41] Other studies also had a very low number of patients.[13 20 23 28 30 32]

Overall accuracy of FIT based on positivity threshold to detect CRC

The LoD value depended on the FIT brand used and ranged from 2 µg Hb/g faeces to 7 µg Hb/g faeces.The overall pooled sensitivity and specificity of FITs for CRC for studies which used the LoD as threshold (11 studies; n=41 338 patients) were 93.4% (95% CI 88.0% to 96.4%) and 76.9% (95% CI 67.7% to 84.0%), respectively. Sensitivity for CRC decreased from 87.2% (95% CI 81.0% to 91.6%) for studies with a threshold of ≥10 µg Hb/g faeces (15 studies; n=48 872 patients) to 84.1% (95% CI 78.6% to 88.4%) for studies with a threshold ≥20 µg Hb/g faeces (five studies; n=24 187 patients), and specificity increased from 84.4% (95% CI 79.4% to 88.3%) to 86.6% (95% CI 75.6% to 93.1%). Furthermore, six studies (n=34 691 patients) evaluated the diagnostic accuracy of FIT with a threshold of ≥150 µg Hb/g faeces showing a sensitivity and specificity of 64.1% (95% CI 57.8% to 69.9%) and 95.0% (95% CI 91.2% to 97.2%), respectively (table 2). Online supplemental appendix 3 shows pooled sensitivity and specificity for FIT studies based on a cut-off value (online supplemental file).

Evaluation of heterogeneity

We found substantial heterogeneity between studies when calculating the summary performance estimates of FITs for CRC using the bivariate model (table 2 and online supplemental appendix 3). The type of reference standard used (colonoscopy or follow-up), the place of recruitment (primary care facility or colonoscopy unit) and CRC prevalence (CRC <3% or CRC ≥3%) were significant predictors of heterogeneity for both sensitivity and specificity. Moreover, FIT brand (OC-Sensor or HM-JACKarc) was also a significant predictor of heterogeneity for specificity (figure 3). However, the magnitude of change for the pooled summary estimates and their confidence intervals in each subgroup was small (online supplemental table 2). Online supplemental figure 1 shows ROC space plots. When we removed keynote outliers in the sensitivity analysis the magnitude of change between the summary estimates and their confidence intervals in each subgroup based on a cut-off value was again small. However, pooled sensitivity estimates were more homogeneous. Instead, pooled specificity estimates remained with high heterogeneity (table 2).

Threshold effect was unsurprisingly detected in the subgroup of studies using cut-off values at LoD due to the differences in the threshold defined by each brand. Moreover, a threshold effect was also found in the subgroup of studies at a cut-off value of ≥150 µg Hb/g faeces. In addition to explicit threshold effect, implicit threshold effect may arise due to several biases (ie, different spectrum of patients) which may determine differences in sensitivity and specificity between studies. Once outliers were removed, heterogeneity related to implicit threshold effect in this subgroup was also controlled (table 2).

Diagnostic yield for CRC

Figure 4 shows the expected NNS and the number of missed CRC per 1000 patients according to the CRC prevalence expected in primary care (1%–5%). The post-test probabilities of CRC were assessed through Fagan nomograms (online supplemental figure 2). As an example, the number of missed CRC per 1000 patients if a patient has a 'negative' FIT result in population with a CRC prevalence of 2% is expected to increase from four to five when using the threshold of 20 µg Hb/g faeces instead of 10 µg Hb/g faeces. On the other hand, at the same CRC prevalence, the NNS is expected to decrease from ten to four if the 150 µg Hb/g faeces threshold is used instead of 10 µg Hb/g faeces.

Overall accuracy of FIT based on positivity threshold to detect SCL

The overall pooled sensitivity and specificity of FITs for SCL for studies which used the LoD as threshold (seven studies; n=22 624 patients) were 70.4% (95% CI 68.4% to 72.3%) and 78.4% (95% CI 77.8% to 78.9%), respectively. If we consider all SCLs as target instead of solely CRC, FIT sensitivity decreased from 87.2% (95% CI 81.0% to 91.6%) for studies with a threshold of≥10 µg Hb/g faeces (fifteen studies; n=48 872 patients) to 69.1% (95% CI 60.5% to 76.5%) at the same threshold (seven studies; n=20 407 patients), and specificity increased from 84.4% (95% CI 79.4% to 88.3%) to 87.2% (95% CI 83.4% to 90.2%). Furthermore, three studies (n=20 528 patients) assessed the diagnostic accuracy of FIT with a threshold of ≥150 µg Hb/g faeces showing a sensitivity and specificity of 35.9% (95% CI 33.8% to 38.1%) and 97.5% (95% CI 97.3% to 97.8%), respectively (table 2). SCL prevalence ranged widely between 4.4% and 13.6% anticipating high heterogeneity when assessing summary sensitivity and specificity FIT estimates for SCL detection, which combined with reduced number of studies restricted the possibility of subgroup analysis (table 2 and online supplemental appendix 3).

Publication bias

Online supplemental figure 3 shows various funnel plots where each study is represented by one point on the plot drawn based on the natural logarithm of its diagnostic OR (dOR) (x axis) and the value of its standard error (y axis). The existence of a symmetric figure around an axis traced by the pooled dOR value suggests the absence of publication bias.

DISCUSSION

Statement of principal findings

Our results confirm that FITs are the test of choice to evaluate patients with new-onset lower gastrointestinal symptoms in primary healthcare. The high sensitivity for CRC shown at the 10 µg Hb/g faeces threshold means that any result below has a negative predictive value for CRC greater than 99.6%–99.9% at CRC prevalence most commonly reported in primary healthcare. The risk of CRC detection in patients with a negative FIT equals the risk of colonoscopy-associated side effects and the CRC prevalence in asymptomatic adults aged 50–69.[44 45] Moreover, the minor differences between sensitivities for CRC shown at 10 µg Hb/g faeces and 20 µg Hb/g faeces thresholds mean that if we choose the higher threshold, less than one additional CRC would be missed per 1000 patients investigated. Finally, pooled estimates of sensitivity for CRC suggest that more than 60% of CRC would be identified at a f-Hb threshold of 150 µg Hb/g faeces. This threshold has recently been proposed in several large studies as a rule in criteria for urgent evaluation.[13 31 36 37 39 41] Furthermore, the NNS range is between 2 and 7 for a CRC prevalence between 1% and 3% at this threshold, which constitutes an appropriate criterion for colonoscopy prioritisation.

Strengths and weaknesses

This is the first systematic review and meta-analysis evaluating the diagnostic performance of FIT in symptomatic patients

Table 2 Diagnostic accuracy parameters based on quantitative FIT threshold concentration to detect CRC and significant colonic lesion

Target	Studies (n)	Sensitivity*	I^2†	Specificity*	I^2†	Positive LR‡	I^2†	Negative LR‡	I^2†	Diagnostic OR‡	I^2†	P value§	AUC
>LoD µg Hb/g faeces													
CRC	11	93.4 (88.0 to 96.4)	83.6	76.9 (67.7 to 84.0)	99.6	4.03 (2.91 to 5.60)	99.2	0.09 (0.05 to 0.15)	81.2	46.64 (28.08 to 77.49)	100.0	<0.01	0.93 (0.90 to 0.95)
SCL¶	7	70.4 (68.4 to 72.3)	95.3	78.4 (77.8 to 78.9)	99.7	3.31 (2.31 to 4.77)	98.5	0.36 (0.28 to 0.46)	87.1	9.33 (7.26 to 11.99)	70.2	<0.01	0.81 (0.79 to 0.82)
≥10 µg Hb/g faeces													
CRC	15	87.2 (81.0 to 91.6)	92.4	84.4 (79.4 to 88.3)	99.7	5.57 (4.28 to 7.26)	99.6	0.15 (0.10 to 0.22)	97.2	36.77 (23.51 to 57.51)	100.0	0.16	0.92 (0.90 to 0.94)
CRC**	13	88.9 (85.8 to 91.4)	37.0	84.0 (81.4 to 86.3)	97.4	5.54 (4.71 to 6.53)	93.5	0.13 (0.10 to 0.17)	43.6	41.91 (28.85 to 60.87)	99.7	0.58	0.93 (0.91 to 0.95)
SCL	8	69.1 (60.5 to 76.5)	93.6	87.2 (83.4 to 90.2)	98.2	5.38 (4.39 to 6.59)	88.0	0.35 (0.23 to 0.45)	90.6	15.18 (11.41 to 20.19)	100.0	0.33	0.82 (0.79 to 0.85)
≥20 µg Hb/g faeces													
CRC	5	84.1 (78.6 to 88.4)	94.4	86.6 (75.6 to 93.1)	99.9	6.29 (3.46 to 11.47)	99.8	0.18 (0.14 to 0.23)	95.1	34.37 (19.99 to 59.10)	100.0	0.51	0.90 (0.87 to 0.92)
CRC**	4	81.8 (76.4 to 86.1)	00.0	90.3 (86.5 to 93.2)	98.8	8.44 (5.85 to 12.18)	96.0	0.20 (0.15 to 0.27)	00.0	41.81 (23.41 to 76.67)	98.8	0.80	0.89 (0.86 to 0.91)
SCL¶	2	47.0 (43.3 to 50.8)	0.0	94.1 (93.6 to 94.6)	0.0	8.00 (7.15 to 8.96)	0.0	0.56 (0.52 to 0.60)	0.0	14.22 (11.98 to 16.87)	0.0	NA	NA
≥150 µg Hb/g faeces													
CRC	6	64.1 (57.8 to 69.9)	87.1	95.0 (91.2 to 97.2)	99.7	12.70 (7.65 to 21.10)	99.0	0.38 (0.33 to 0.44)	89.2	33.56 (21.32 to 52.82)	98.1	0.02	0.82 (0.78 to 0.85)
CRC**	5	62.9 (55.5 to 69.6)	72.9	96.2 (94.6 to 97.3)	97.9	16.58 (12.36 to 22.23)	88.5	0.39 (0.32 to 0.46)	72.9	42.95 (32.33 to 57.04)	98.9	0.10	0.88 (0.85 to 0.91)
SCL¶	3	35.9 (33.8 to 38.1)	94.7	97.5 (97.3 to 97.8)	95.7	13.05 (10.3 to 16.55)	70.2	0.67 (0.57 to 0.78)	94.6	20.48 (17.03 to 24.63)	35.5	0.67	0.83 (0.62 to 1.00)

*Values are expressed as percentages and its 95% CI.
†Values are expressed as percentages.
‡Values are expressed as absolute numbers and its 95% CI.
§Significance of the threshold effect using the Spearman rank correlation (p<0.1 is considered statistically significant).
¶Diagnostic accuracy parameters were estimated with DerSimonian method.
**Sensitivity analysis: diagnostic accuracy parameters for CRC detection after removing keynote outliers.
AUC, area under the curve; CRC, colorectal cancer; FIT, faecal immunochemical test for haemoglobin; LoD, limit of detection; LR, likelihood ratio; NA, not applicable; SCL, significant colonic lesion.

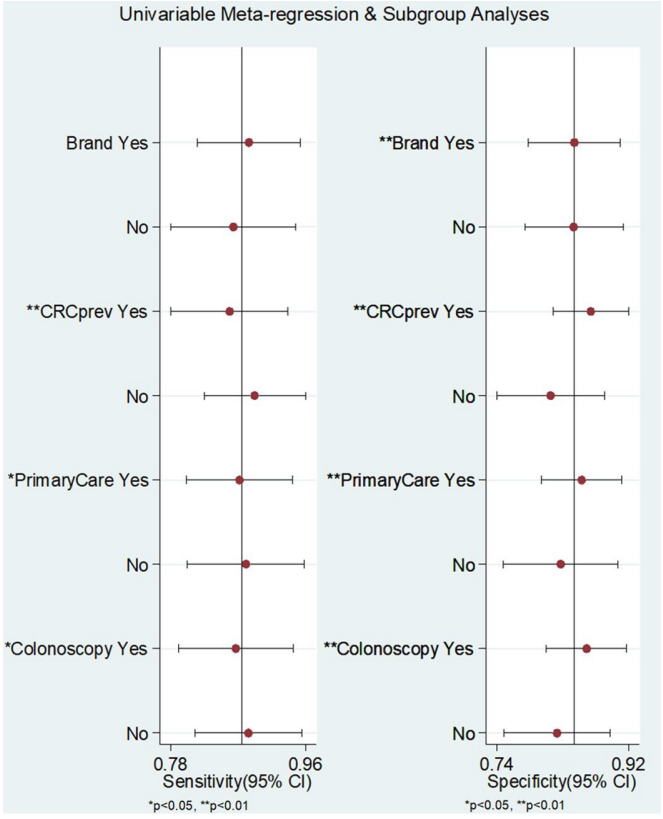

Figure 3 Forest plot of multiple univariable meta-regression and subgroup analyses. Meta-regression to assess the effect of covarying factors on summary measures of performance: 'Brand', yes: OC-sensor versus no: HM-JACKarc; 'CRCprev', yes: CRC prevalence <3% vs no: CRC prevalence ≥3%; 'primary care', yes: recruitment performed in primary care facilities versus No: recruitment performed in colonoscopy units; 'colonoscopy', yes: follow-up performed as reference standard versus no: colonoscopy performed as reference standard.

in primary healthcare. The high number of patients included and consistency in relation to previously published systematic reviews in various settings reinforce the validity of these findings.[5 46] However, studies included in this systematic review are not free from bias, which could affect our results. On the one hand, verification bias arises in diagnostic and prognostic studies when the reference test may have been performed preferably in those patients with 'positive' index tests, as occurs in those studies performed on patients recruited in primary care facilities. Besides, we have found a large heterogeneity in the reference standard used, the length of follow-up in case bowel imaging was not performed and, finally, in the definition of SCL across the studies included. This finding highlights the need of common definition both for a reference standard for CRC diagnosis and for SCL.

Conversely, those studies performed on patients recruited in colonoscopy units are at risk of clinical spectrum bias, because they could lack representation of the whole clinical spectrum of CRC in the study population. Instead of presenting vague symptoms, patients from those studies are more likely to have developed specific symptoms related to advanced stages, and therefore higher f-Hb concentration.[6] In both cases, sensitivity could be overestimated. Furthermore, the low ratio between eligible patients and those included in the final analysis may bring risks of representativeness in a number of studies. Although this could also involve selection bias, it would be necessary to compare the characteristics between both subgroups to know in which way the evaluation of FIT diagnostic performance estimates could be affected.

However, these biases may not have a significant impact on the results of this meta-analysis. As stated previously in the methods section of this manuscript, all patients who did not undergo colonoscopy as a reference standard were monitored and any CRC causing symptoms would worsen in the following months leading to diagnosis even if the FIT test proved to be a FN.[13] IWe are aware that a short follow-up period could overestimate FIT sensitivity for CRC as long as patients with a positive result would perform a confirmation test. However, in the heterogeneity analysis the magnitude of change for the pooled summary estimates related to the reference standard used was small (online supplemental table 2), suggesting that the reference test had little effect on the diagnostic performance. Furthermore, despite the high risk of selection bias, the patients included in this meta-analysis should be representative of the population consulting in primary care whose clinical situation constitutes a cause of concern for their physician, which is the clinical spectrum where FIT should prove useful.

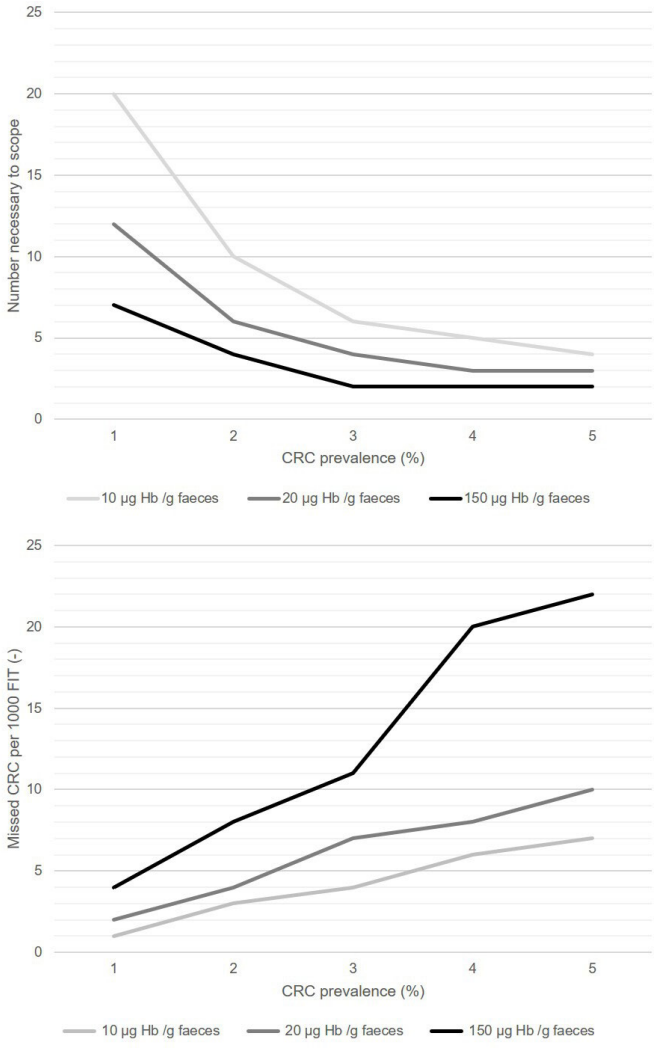

Figure 4 Number of patients necessary to scope to find one CRC and number of missed CRC per 1000 patients. Figures are calculated according to the post-test probabilities of CRC assessed by means of Fagan nomograms for different thresholds and CRC prevalence. CRC, colorectal cancer; FIT, faecal immunochemical tests.

As expected, this meta-analysis showed high heterogeneity when calculating pooled estimates of specificity. This is because f-Hb can be detected in a number of benign and malignant conditions other than CRC.[47] The major variability in the prevalence of some of these conditions (ie, non-steroidal anti-inflammatory drugs enteropathy), together with the absence of randomised or consecutive sampling in most studies included in this review determine the presence of heterogeneity. Instead, those conditions which could account for the presence of f-Hb over the detection limit should only affect FIT sensitivity to detect CRC by serendipity.[48] Thus, after removing those studies with higher selection bias, pooled estimates of sensitivity revealed low heterogeneity.

Strengths and weaknesses in relation to other studies

This systematic review could not detect information to compare the accuracy of quantitative and qualitative tests. Several studies offered information on the precision of different brands of qualitative tests, but different cut-off points were used and there are not enough studies to perform an analysis by the different subgroups. However, it is interesting to highlight that several qualitative FIT brands with diverse cut-off values were indirectly compared in the study of Högberg *et al*,[40] which shows that sensitivity to detect CRC was always higher than 80% despite cut-off values ranging between 2 µg Hb/g faeces and 50 µg Hb/g faeces. This information, combined with sensitivity evaluated at a cut-off value of 150 µg Hb/g faeces, and the minor differences between pooled estimates of sensitivity and specificity assessed at 10 µg Hb/g faeces and 20 µg Hb/g faeces for any demographic subgroup,[33] strongly suggest that f-Hb should be evaluated for any patient who has been requested a colonoscopy for symptom evaluation to effectively handle the colonoscopy waiting list, as priority. We specifically evaluated the 150 µg Hb/g faeces threshold because several studies have evaluated recently this cut-off due to its reduced number of positive results, high specificity and positive predictive value.[13 31 36 37 39 41] The likelihood of cancer increases with increasing f-Hb concentrations, and consequently, FIT could be used to rule-in cancer or prioritise patients for investigation.[36]

This systematic review cannot recommend any specific quantitative FIT assay either. Although the meta-regression analysis suggests statistically significant differences between OC-Sensor and HM-JACKarc at a cut-off value of 10 µg Hb/g faeces, these are clinically irrelevant and could be partially justified by the different methodology used in the design of their respective studies. Moreover, to the best of our knowledge only one study in this setting directly compared both FIT brands on the same patients,[43] and although large variations were found between the different devices, the correlation of the f-Hb results between both was gradually higher as the threshold was increased; 91.7% at a cut-off value of 10 µg Hb/g faeces. Thus, considering that approximately 90% of CRC may be detected above that threshold, it is unlikely that further information will show clinically significant differences between both FIT assays.

The small number of studies conducted in primary care, together with heterogeneity makes it difficult to evaluate publication bias. However, it is unlikely that the most important conclusions of this review will be refuted by additional data. At the time of writing this manuscript, another two studies reporting information are available and their results are in line with this work's conclusions.[49 50]

Unanswered questions and future research

Three relevant questions remain to be answered and are critical in the implementation of FIT in primary healthcare. The first is related to the 'FIT negative CRCs'. It is relevant to know what the factors are that account for a negative result, either related to the patient or to the CRC, to reduce the FN results. The information available is limited to description of the characteristics of the 47 CRC with a negative result in five studies.[13 29 37 41 42] On the other hand, if FIT-based strategies are implemented, it is necessary to establish a safety netting strategy to avoid delays in CRC diagnosis that could worsen the prognosis. A re-evaluation of the symptoms and referral to secondary healthcare in case they persist could be a reasonable option until we have further evidence.[51] We have additional potential options: CRC prediction models and the combination of noninvasive biomarkers including the microbiota, but these options are complex and not validated in primary healthcare.[52–55]

The second question is related to the effect of FIT on CRC prognosis. The main objective of any diagnostic strategy is to improve the prognosis of the disease detected. The information regarding CRC prognosis detected after a positive FIT in symptomatic subjects in primary healthcare is still limited. We have evidence from two retrospective studies that suggest that CRC survival is improved in cancers detected through an FIT-based strategy when compared with a clinical evaluation strategy.[1 56] The reason for these findings is not clear but could be related either to a reduction in diagnostic delay or, on the contrary, to an opportunistic CRC screening. A specifically designed study is, however, required to answer this relevant question.

Another relevant implication is the effect of a screening programme in the evaluation of patients with symptoms in primary care. On one hand, including FIT in primary care can facilitate opportunistic screening, increasing inequities in the health system and reducing its efficiency.[57] On the other hand, the establishment of a population-based CRC screening programme reduces the risk of CRC among the population that adheres to it. This point raises the hypothesis that the diagnostic approach in patients with recent onset gastrointestinal symptoms could be different if they are invited and adherent to a population-based CRC screening programme.[58]

CONCLUSION

In this systematic review and meta-analysis, we confirmed that implementation of FIT as a triage test in primary care may improve the efficiency of referrals. Thus, FIT is the test of choice to evaluate patients with new-onset lower gastrointestinal symptoms in this setting. Use of this test as 'rule in' at a cut-off value of 150 µg Hb/g faeces identifies more than half of CRCs using few resources while an f-Hb concentration below 20 µg Hb/g faeces rules out more than 85% of CCR at the expected prevalence in this setting (1%–3%). However, appropriate safety netting is still necessary.

Contributors NPV and JC conceived and designed the research. NPV, CT-S, NdV-B and CS-G performed data acquisition. NPV analysed and interpretated data. NPV and JC drafted the article or made critical revisions related to important intellectual content of the manuscript. All the authors gave their final approval of the version of the article to be published.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. Data obtained from the systematic review and meta-analysis are included in the article and online supplemental material.

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SUPPLEMENTARY MATERIAL

Appendix 1. Search strategy

We avoided the routine use of any study design terms or methodology search filters. A previously published filter designed to simplify the identification of FIT-related studies in MEDLINE based on the last name of first and corresponding authors of “FIT in symptomatic patients” related studies was also used to complete our data sources.

MEDLINE (Pubmed) May 1, 2018 to November 10, 2020

1. immunochem* [tiab] or immuno-chem* [tiab] or immunohistochem* [tiab] or immuno-histochem* [tiab] or immunol* [tiab] or immunochromatographic [tiab] or immuno-chromatographic [tiab] or immunoassay [tiab] or "immuno assay" [tiab] (76214)

2. fecal [tiab] or faecal [tiab] or feces [tiab] or faeces [tiab] or stool* [tiab] (23882)

3. ifobt or "faecal haemoglobin" or "fecal hemoglobin" or fobt or (FIT and hemoglobin) or (FIT and haemoglobin) (475)

4. occult blood or occult hemoglobin or occult haemoglobin (1252)

5. OC-Sensor or "OC Sensor" or HM-JACKarc or "HM JACKarc" or "FOB Gold" or HM-JACK or HM JACK or Ridascreen or jack-arc or jackarc or FOBgold (64)

6. ("Atef SH" [au]) OR ("Bachir NM" [au]) OR ("Barber MD" [au]) OR ("Boereboom CL" [au]) OR ("Calogero A" [au]) OR ("Ferraris R" [au]) OR ("Hata K" [au]) OR ("Adelstein BA" [au]) OR ("Ahlquist DA" [au]) OR ("Ahmed S" [au]) OR ("Akbari A" [au]) OR ("Allameh Z" [au]) OR ("Allard J" [au]) OR ("Allison JE" [au]) OR ("Alvarez-Urturi C" [au]) OR ("Annibale B" [au]) OR ("Armitage N" [au]) OR ("Ashraf I" [au]) OR ("Astin M" [au]) OR ("Auge JM" [au]) OR ("Azlie S" [au]) OR ("Ballal MS" [au]) OR ("Ballantyne GH" [au]) OR ("Bampton PA" [au]) OR ("Barrett P" [au]) OR ("Barrison IG" [au]) OR ("Bassett ML" [au]) OR ("Bates T" [au]) OR ("Bernardini S" [au]) OR ("Bessa X" [au]) OR ("Bhargava A" [au]) OR ("Bini EJ" [au]) OR ("Bjerregaard NC" [au]) OR ("Bjornsson ES" [au]) OR ("Bosch LJ" [au]) OR ("Brault J" [au]) OR ("Brenner H" [au]) OR ("Brodersen J" [au]) OR ("Burch JA" [au]) OR ("Cade D" [au]) OR ("Cai QC" [au]) OR ("Capurso G" [au]) OR ("Carlsson L" [au]) OR ("Carroll M" [au]) OR ("Castells A" [au]) OR ("Castiglione G" [au]) OR ("Celestino A" [au]) OR ("Chang HJ" [au]) OR ("Chen HH" [au]) OR ("Chen LS" [au]) OR ("Chiang TH" [au]) OR ("Chiu HM" [au]) OR ("Church JM" [au]) OR ("Ciatto S" [au]) OR ("Cilona A" [au]) OR ("Clarke N" [au]) OR ("Collins JF" [au]) OR ("Corley DA" [au]) OR ("Corte C" [au]) OR ("Crotta S" [au]) OR ("Cubiella J" [au]) OR ("Dancourt V" [au]) OR ("Daveson AJ" [au]) OR ("de Vet HC" [au]) OR ("Dent OF" [au]) OR ("Diaz-Ondina M" [au]) OR ("Dilshad AT" [au]) OR ("Doi Y" [au]) OR ("Dominitz JA" [au]) OR ("Dutta AK" [au]) OR ("Eckardt VF" [au]) OR ("Elsafi SH" [au]) OR ("Eskeland SL" [au]) OR ("Ewald N" [au]) OR ("Faivre J" [au]) OR ("Falkson CB" [au]) OR ("Farkouh M" [au]) OR ("Farrands PA" [au]) OR ("Fauzi A" [au]) OR ("Favre H" [au]) OR ("Fenocchi E" [au]) OR ("Fisher DA" [au]) OR ("Flashman K" [au]) OR ("Fletcher RH" [au]) OR ("Fraser CG" [au]) OR ("Freedman A" [au]) OR ("Freitas BR" [au]) OR ("Friedman A" [au]) OR ("Fu R" [au]) OR ("Gandhi S" [au]) OR ("Garman KS" [au]) OR ("Gibson P" [au]) OR ("Gillberg A" [au]) OR ("Godber IM" [au]) OR ("Gopalswamy N" [au]) OR ("Goulston KJ" [au]) OR ("Greenberg PD" [au]) OR ("Guardiola J" [au]) OR ("Guittet L" [au]) OR ("Haddy RI" [au]) OR ("Hamilton W" [au])

OR ("Han DS" [au]) OR ("Harmston C" [au]) OR ("Harrison AJ" [au]) OR ("Hatch QM" [au]) OR ("Haug U" [au]) OR ("Hazazi R" [au]) OR ("Heresbach D" [au]) OR ("Herrero J" [au]) OR ("Hewett DG" [au]) OR ("Hewitson P" [au]) OR ("Hill AG" [au]) OR ("Hippisley-cox J" [au]) OR ("Hirai HW" [au]) OR ("Hirayama Y" [au]) OR ("Hirobe K" [au]) OR ("Hoepffner N" [au]) OR ("Hogberg C" [au]) OR ("Hol L" [au]) OR ("Holden DJ" [au]) OR ("Holloway RH" [au]) OR ("Hope RL" [au]) OR ("Howden CW" [au]) OR ("Hreinsson JP" [au]) OR ("HU H-" [au]) OR ("Huang G" [au]) OR ("Hundt S" [au]) OR ("Hunt RH" [au]) OR ("Imperiale TF" [au]) OR ("Ioannidis JP" [au]) OR ("Ioannou GN" [au]) OR ("Ip S" [au]) OR ("Iwase N" [au]) OR ("Jamil S" [au]) OR ("Jeanson A" [au]) OR ("Jellema P" [au]) OR ("Jimbo M" [au]) OR ("Jin P" [au]) OR ("Kadakia SC" [au]) OR ("Kalimutho M" [au]) OR ("Kalra L" [au]) OR ("Kato J" [au]) OR ("Kaul A" [au]) OR ("Kemppainen M" [au]) OR ("Kepczyk MT" [au]) OR ("Khakimov N" [au]) OR ("Khasanova G" [au]) OR ("kim BC" [au]) OR ("Klewandrowski K" [au]) OR ("Ko CW" [au]) OR ("Koga Y" [au]) OR ("Kok L" [au]) OR ("Kolligs F" [au]) OR ("Konrad C" [au]) OR ("Koo JH" [au]) OR ("Kovarova JT" [au]) OR ("Kozlowski T" [au]) OR ("Krivec S" [au]) OR ("Kubisch H" [au]) OR ("Lanoy G" [au]) OR ("Lansdorp-Vogelaar I" [au]) OR ("Launois R" [au]) OR ("Lawson N" [au]) OR ("Lee FI" [au]) OR ("Lee JK" [au]) OR ("Lee TJ" [au]) OR ("Lee YC" [au]) OR ("Leicester RJ" [au]) OR ("Leis VM" [au]) OR ("Letsou G" [au]) OR ("Levi Z" [au]) OR ("Levy BT" [au]) OR ("Li R" [au]) OR ("Li ZC" [au]) OR ("Lieberman DA" [au]) OR ("Macrae FA" [au]) OR ("Mansouri D" [au]) OR ("Mansson J" [au]) OR ("Manus B" [au]) OR ("Marshall JK" [au]) OR ("Marshall TP" [au]) OR ("Matsumura Y" [au]) OR ("Maw A" [au]) OR ("McDonald CA" [au]) OR ("McDonald PJ" [au]) OR ("McDonald R" [au]) OR ("McDonald RL" [au]) OR ("Meijer GA" [au]) OR ("Mesquita MA" [au]) OR ("Miyoshi H" [au]) OR ("Moran A" [au]) OR ("Morikawa T" [au]) OR ("Morini S" [au]) OR ("Mowat C" [au]) OR ("Murakami R" [au]) OR ("Murphy J" [au]) OR ("Nagaoka S" [au]) OR ("Nakama H" [au]) OR ("Narula N" [au]) OR ("Niedermaier T" [au]) OR ("Niv Y" [au]) OR ("Olsson L" [au]) OR ("Oono Y" [au]) OR ("Oort FA" [au]) OR ("Ostrow JD" [au]) OR ("Ou C-" [au]) OR ("Parente FR" [au]) OR ("Park DD" [au]) OR ("Park JG" [au]) OR ("Park Y" [au]) OR ("Paz-Valiñas L" [au]) OR ("Peacock O" [au]) OR ("Petty MT" [au]) OR ("Pfeifer RM" [au]) OR ("Piperno A" [au]) OR ("Pochapin MB" [au]) OR ("Pongprasobchai S" [au]) OR ("Pye G" [au]) OR ("Quintero E" [au]) OR ("Rae AJ" [au]) OR ("Rai S" [au]) OR ("Rajasekhar PT" [au]) OR ("Ransohoff DF" [au]) OR ("Rao J" [au]) OR ("Rao SK" [au]) OR ("Rees CJ" [au]) OR ("Rentier B" [au]) OR ("Riboe DG" [au]) OR ("Rigas B" [au]) OR ("Ritchie MC" [au]) OR ("Robertson R" [au]) OR ("Robinson MH" [au]) OR ("Rockey DC" [au]) OR ("Rodriguez-Alonso L" [au]) OR ("Rodriguez-Moranta F" [au]) OR ("Rosman AS" [au]) OR ("Rozen P" [au]) OR ("Rubeca T" [au]) OR ("Saccomanno S" [au]) OR ("Saito H" [au]) OR ("Saldanha JD" [au]) OR ("Saquib N" [au]) OR ("Saratzis A" [au]) OR ("Scales CD" [au]) OR ("Schwartz S" [au]) OR ("Scriven AJ" [au]) OR ("Segal WN" [au]) OR ("Selinger RR" [au]) OR ("Selvachandran SN" [au]) OR ("Sequist TD" [au]) OR ("Shah R" [au]) OR ("Sharma VK" [au]) OR ("Shashideep S" [au]) OR ("Shastri YM" [au]) OR ("Shaw AG" [au]) OR ("Sheng J" [au]) OR ("Sieg A" [au]) OR ("Singh H" [au]) OR ("Singhal S" [au]) OR ("Skaife P" [au]) OR ("Smith A" [au]) OR ("Sohn DK" [au]) OR ("Songster CL" [au]) OR ("Sontag SJ" [au]) OR ("St John DJ" [au]) OR ("Stapley S" [au]) OR ("Steele RJ" [au]) OR ("Stegeman I" [au]) OR ("Stein J" [au]) OR ("Stelling HP" [au]) OR ("Stockbrugger RW" [au]) OR ("Stray N" [au]) OR ("Stubbs RS" [au]) OR ("Subramanian S" [au]) OR ("Sung JJ" [au]) OR ("Symonds EL" [au]) OR ("Tan V" [au]) OR ("Tannous B" [au]) OR ("Tao S" [au]) OR ("Tarpay Ad" [au]) OR ("Tate JJ" [au]) OR ("Thompson M" [au]) OR ("Tsoi KK" [au]) OR ("van Turenhout ST" [au]) OR ("Vega P" [au]) OR ("Weller D" [au]) OR ("Whitlock EP" [au]) OR ("Wu MS" [au]) OR ("Yansong J" [au]) OR ("Young GP" [au]) OR ("Zullo A" [au]) OR ("Terhaar sive Droste JS" [au]) OR

("Thomas WM" [au]) OR ("Thompson MR" [au]) OR ("Thomson AD" [au]) OR ("Tibble J" [au]) OR ("Tonus C" [au]) OR ("Trickett JP" [au]) OR ("Donaldson DR" [au]) OR ("Trojan J" [au]) OR ("Turunen MJ" [au]) OR ("Adlercreutz H" [au]) OR ("van Rijn AF" [au]) OR ("van Rossum LG" [au]) OR ("Vandvik P" [au]) OR ("van Roon AH" [au]) OR ("Vart G" [au]) OR ("Vasilyev S" [au]) OR ("Syrjanen K" [au]) OR ("Vaughan-Shaw PG" [au]) OR ("Wheeler JM" [au]) OR ("Vilkin A" [au]) OR ("Vironen J" [au]) OR ("Kellokumpu I" [au]) OR ("Wanebo HJ" [au]) OR ("de Wijkerslooth TR" [au]) OR ("Williams JA" [au]) OR ("Winawer SJ" [au]) OR ("Wong WM" [au]) OR ("Wong BC" [au]) OR ("Wong CK" [au]) OR ("Sadowski DC" [au]) OR ("Dube C" [au]) OR ("Wong MC" [au]) OR ("Woo HY" [au]) OR ("Park H" [au]) OR ("Wu D" [au]) OR ("Li JN" [au]) OR ("Guoxiang L" [au]) OR ("Jufang S" [au]) OR ("Yoshinaga M" [au]) OR ("Zhu MM" [au]) OR ("Widlak MM" [au]) OR ("Arasaradnam R" [au]) OR ("Ran ZH" [au]) OR ("Wen-xian Z" [au]) (32922)

7. #1 AND #2 (1416)

8. #1 AND #6 (1254)

9. #2 AND #6 (568)

10. #3 OR #4 OR #5 OR #7 OR #8 OR #9 (3943)

11. #10 NOT DNA [ti] NOT MicroRNA [ti] NOT (COVID [tiab] OR SARS* [tiab] OR coronavirus [tiab]) NOT #10 filter "review" "editorial" "guideline" (3552)

12. colon* OR gastrointestinal OR colorectal OR bowel OR intestinal OR gut (193824)

13. #11 AND #12 (1790)

Embase (Ovid) May 1, 2018 to November 10, 2020

1. (immunochem# or immuno-chem# or immunohistochem# or immuno-histochem# or immunol# or immunochromatographic or immuno-chromatographic or immunoassay or "immuno assay").mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (40118)

2. (fecal or faecal or feces or faeces or stool#).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (81005)

3. (ifobt or "faecal haemoglobin" or "fecal hemoglobin" or fobt or (FIT and hemoglobin) or (FIT and haemoglobin)).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (4670)

4. (occult blood or occult hemoglobin or occult haemoglobin).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (4721)

5. OC-Sensor or "OC Sensor" or HM-JACKarc or "HM JACKarc" or "FOB Gold" or HM-JACK or HM JACK or Ridascreen or jack-arc or jackarc or FOBgold limit to yr="2018 -Current"; original articles (390)

6. (colon# or gastrointestinal or colorectal or bowel or intestinal or gut).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (521912)

7. #1 AND #2 (1652)

8. #7 OR #3 (6267)

9. #8 OR #4 OR #5 (10050)

10. #9 AND #6 (5496)

11. #10 NOT (DNA OR MicroRNA OR COVID OR SARS# OR coronavirus .m_titl limit to yr="2018 -Current"; original articles) (5374)

12. Remove duplicates from #11 (3987)

13. #12 limit to human and embase (2830)

Appendix 2. RATIONAL FOR EXCLUSION OF 148 STUDIES

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Ahmed S, Leslie A, Thaha MA, Carey FA, Steele RJ. Lower gastrointestinal symptoms are not predictive of colorectal neoplasia in a faecal occult blood screen-positive population. *Br J Surg*. 2005;92(4):478-481. doi:10.1002/bjs.4879	Yes	No	Yes	Yes	Yes	Yes	Screening setting. No data about FIT accuracy.
Almilaji O, Smith C, Surgenor S, et al. Refinement and validation of the IDIOM score for predicting the risk of gastrointestinal cancer in iron deficiency anaemia. *BMJ Open Gastroenterol*. 2020;7(1):e000403. doi:10.1136/bmjgast-2020-000403	Yes	No	No	Yes	Yes	No	To refine and validate a model for predicting the risk of GI cancer in iron deficiency anaemia and to develop an app to facilitate use in clinical practice.
Arasaradnam RP, Bhala N, Evans C, et al. Faecal immunochemical testing in the COVID-19 era: balancing risk and costs [published correction appears in Lancet Gastroenterol Hepatol. 2020 Jun 19;:]. *Lancet Gastroenterol Hepatol*. 2020;5(8):717-719. doi:10.1016/S2468-1253(20)30185-0	No	NA	NA	NA	NA	NA	Comment
Auge JM, Fraser CG, Rodriguez C, et al. Clinical utility of one versus two faecal immunochemical test samples in the detection of advanced colorectal neoplasia in symptomatic patients. Clin Chem Lab Med. 2016;54(1):125-132. doi:10.1515/cclm-2015-0388	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Auge JM, Rodriguez C, Espanyol O, et al. An evaluation of the SENTiFIT 270 analyser for quantitation of faecal haemoglobin in the investigation of patients with suspected colorectal cancer. Clin Chem Lab Med. 2018;56(4):625-633. doi:10.1515/cclm-2017-0605	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Bailey SE, van Melle MA, Nicholson BD. Faecal immunochemical (rule-in) testing in general practice. *Br J Gen Pract*. 2019;69(681):178. doi:10.3399/bjgp19X702173	No	NA	NA	NA	NA	NA	Letter
Bampton PA, Holloway RH. A prospective study of the gastroenterological causes of iron deficiency anaemia in a general hospital. *Aust N Z J Med*. 1996;26(6):793-799. doi:10.1111/j.1445-5994.1996.tb00627.x	Yes	Yes	No	No	Yes	Yes	Secondary care. No data about FIT accuracy
Benton SC, Fraser CG. Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration - can a repeat test be used? [published online ahead of print, 2020 Oct 27]. *Ann Clin Biochem*. 2020;4563220967569. doi:10.1177/0004563220967569	No	NA	NA	NA	NA	NA	Editorial

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Bjerregaard NC, Tøttrup A, Sørensen HT, Laurberg S. Evaluation of the Danish national strategy for selective use of colonoscopy in symptomatic outpatients without known risk factors for colorectal cancer. *Scand J Gastroenterol*. 2007;42(2):228-236. doi:10.1080/00365520600815662	Yes	Yes	No	No	yes	Yes	Secondary care; Haemoccult Sensa. Unknown cut-off
Bjerregaard NC, Tøttrup A, Sørensen HT, Laurberg S. Detection of colorectal cancer in symptomatic outpatients without visible rectal bleeding: Validity of the fecal occult blood test. *Clin Epidemiol*. 2009;1:119-124. Published 2009 Aug 9. doi:10.2147/clep.s7097	Yes	Yes	No	No	yes	Yes	Secondary care; Haemoccult Sensa. Unknown cut-off
Borges LV, Mattar R, Silva JMKD, Silva ALWD, Carrilho FJ, Hashimoto CL. FECAL OCCULT BLOOD: A COMPARISON OF CHEMICAL AND IMMUNOCHEMICAL TESTS. Arq Gastroenterol. 2018;55(2):128-132. doi:10.1590/S0004-2803.201800000-22	Yes	Yes	No	Yes	Yes	Yes	Secondary care. Patients older than 14 years of both genders who had indications for colonoscopy and who attended at the Clinics Hospital of the University of São Paulo Medical School.
Bretthauer M, Kalager M, Weinberg DS. From Colorectal Cancer Screening Guidelines to Headlines: Beware!. *Ann Intern Med*. 2019;170(10):734. doi:10.7326/L19-0086	No	NA	NA	NA	NA	NA	Letter
Byun UH, Anderson N, Upton A, Frankish P. Faecal immunochemical tests for occult blood testing should not be used outside of bowel screening: an audit of a large general practice. *J Prim Health Care*. 2019;11(3):259-264. doi:10.1071/HC18068	Yes	Yes	Yes	Unclear	Unclear	Yes	Unknown FIT & Unclear number of samples & Unclear indication in a percentage of patients.
Chandrapalan S, Arasaradnam RP. The role of fecal markers in the investigation of patients with chronic diarrhea. *Pol Arch Intern Med*. 2019;129(6):408-413. doi:10.20452/pamw.14787	No	NA	NA	NA	NA	NA	Review
Chang WY, Chiu HM. Bringing fecal immunochemical test into play in symptomatic population: Exploring the feasibility of fecal immunochemical test-symptom combined approach. *J Gastroenterol Hepatol*. 2020;35(6):911-912. doi:10.1111/jgh.15100	No	NA	NA	NA	NA	NA	Editorial
Chapman C, Thomas C, Morling J, et al. Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham. Colorectal Dis. 2020;22(6):679-688. doi:10.1111/codi.14944	Yes	Yes	Yes	Yes	Yes	Yes	Data were completed in Bailey`s study
Chapman C, Banerjea A, Ng Oet al. PTU-076 The 'getting fit' project in Nottingham: a comparison of haemoglobin levels as measured by OC sensor and HM jack in two week wait referrals. Gut 2017; 66(Suppl 2): A88–A89.	No	Yes	Yes	Yes	Yes	Yes	Poster; Repeated data

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Chapman CJ, Banerjea A, Humes DJ, et al. Choice of faecal immunochemical test matters: comparison of OC-Sensor and HM-JACKarc, in the assessment of patients at high risk of colorectal cancer [published online ahead of print, 2020 Oct 29]. Clin Chem Lab Med. 2020;cclm-2020-1170. doi:10.1515/cclm-2020-1170	No	Yes	Yes	Yes	Yes	Yes	Same data of another study. Compares OC-Sensor and HM-JACKarc
Chen CH, Yan SL, Yang TH, et al. The Relationship between the Methylated Septin-9 DNA Blood Test and Stool Occult Blood Test for Diagnosing Colorectal Cancer in Taiwanese People. *J Clin Lab Anal*. 2017;31(1):e22013. doi:10.1002/jcla.22013	Yes	No	No	Yes	Yes	Yes	No data about FIT accuracy. Secondary care
Chen M-Y, Chang H-C, Chong L-W, et al. Relatively low risk and nonaggressive stage of colorectal cancer in individuals with negative baseline fecal immunochemical test results: A cohort study. Adv Dig Med. 2020;1–8. https://doi.org/10.1002/aid2.13169	Yes	No	No	Yes	Yes	Yes	Screening setting
Chen KC, Chung CS, Hsu WF, et al. Identification of risk factors for neoplastic colonic polyps in young adults with bloody stool in comparison with those without symptom. *J Gastroenterol Hepatol*. 2018;33(7):1335-1340. doi:10.1111/jgh.14070	Yes	No	No	No	Yes	Yes	Secondary care. No data about FIT accuracy
Christopher J, Flint TR, Ahmed H, 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;101(5):333-339. doi:10.1308/rcsann.2019.0022	Yes	Yes	Yes	No	No	No	No data about FIT accuracy
Chuter C, Keding A, Holmes H, Turnock D, Turvill J. Getting the best out of faecal immunochemical tests and faecal calprotectin. *Frontline Gastroenterol*. 2019;11(5):414-416. Published 2019 Dec 24. doi:10.1136/flgastro-2019-101381	No	Yes	No	Yes	Yes	Yes	Letter; Repeated data
Cilona A, Zullo A, Hassan C, Ridola L, Annese M. Is faecal-immunochemical test useful in patients with iron deficiency anaemia and without overt bleeding?. Dig Liver Dis. 2011;43(12):1022-1024. doi:10.1016/j.dld.2011.08.002	Yes	Yes	Unclear	Unclear	Yes	Yes	Consecutive patients with iron deficiency anaemia and without either overt bleeding or thalassaemia minor referred to our Endoscopic Units for diagnostic work-up. No FIT brand
Clark SK. Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham, Chapman et al. Colorectal Dis. 2020 Jun;22(6):608-608. doi: 10.1111/codi.15101	No	NA	NA	NA	NA	NA	Editorial

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Cross AJ, Wooldrage K, Robbins EC, et al. Whole-colon investigation vs. flexible sigmoidoscopy for suspected colorectal cancer based on presenting symptoms and signs: a multicentre cohort study. *Br J Cancer*. 2019;120(2):154-164. doi:10.1038/s41416-018-0335-z	Yes	No	No	No	Yes	Yes	No data about FIT accuracy
Cubiella J, Salve M, Díaz-Ondina M, et al. Diagnostic accuracy of the faecal immunochemical test for colorectal cancer in symptomatic patients: comparison with NICE and SIGN referral criteria. Colorectal Dis. 2014;16(8):O273-O282. doi:10.1111/codi.12569	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Cubiella J, Vega P, Salve M, et al. Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients. BMC Med. 2016;14(1):128. Published 2016 Aug 31. doi:10.1186/s12916-016-0668-5	Yes	Yes	No	Yes	Yes	Yes	Secondary and primary care
Cunin L, Khan AA, Ibrahim M, Lango A, Klimovskij M, Harshen R. FIT negative cancers: A right-sided problem? Implications for screening and whether iron deficiency anaemia has a role to play [published online ahead of print, 2020 Mar 18]. *Surgeon*. 2020;S1479-666X(20)30035-4. doi:10.1016/j.surge.2020.02.003	No	Yes	yes	yes	Yes	Yes	Same data than Khan´s study
de Klerk CM, Woudstra AJ, Fransen MP, Bossuyt PM, Dekker E. Invitees do not adequately act on alarm symptoms in colorectal cancer screening with fecal immunochemical tests. *Eur J Gastroenterol Hepatol*. 2019;31(1):141-142. doi:10.1097/MEG.0000000000001275	Yes	No	No	Yes	No	No	No data about FIT accuracy. Abstract
de Klerk CM, van der Vlugt M, Bossuyt PM, Dekker E. A large proportion of fecal immunochemical test-positive participants in colorectal cancer screening is symptomatic. *United European Gastroenterol J*. 2018;6(3):471-479. doi:10.1177/2050640617733922	Yes	No	No	Yes	No	No	No data about FIT accuracy
Digby J, Strachan JA, Mowat C, Steele RJC, Fraser CG. Appraisal of the faecal haemoglobin, age and sex test (FAST) score in assessment of patients with lower bowel symptoms: an observational study. *BMC Gastroenterol*. 2019;19(1):213. Published 2019 Dec 11. doi:10.1186/s12876-019-1135-5	No	Yes	Yes	Yes	Yes	Yes	Same data than Mowat´s study
Digby J, Strachan JA, McCann R, Steele RJ, Fraser CG, Mowat C. 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;57(4):325-327. doi:10.1177/0004563220935622	No	Yes	Yes	Yes	Yes	Yes	Repeated data

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Digby J, Steele RJ, Strachan JA, et al. Do other variables add value to assessment of the risk of colorectal disease using faecal immunochemical tests for haemoglobin?. *Ann Clin Biochem*. 2019;56(4):472-479. doi:10.1177/0004563219839423	No	Yes	Yes	Yes	Yes	Yes	Same data than Mowat´s study
Digby J, Mowat C, Steele R*, et al* OC-020 Validation of the utility of a faecal immunochemical testfor haemoglobin (fit) in patients presenting to primary care with new bowel symptoms *Gut* 2017;**66:**A10-A11.	No	Yes	Yes	Yes	Yes	Yes	Poster; Repeated data
Digby J, Cleary S, Gray L, et al. Faecal haemoglobin can define risk of colorectal neoplasia at surveillance colonoscopy in patients at increased risk of colorectal cancer. United European Gastroenterol J. 2020;8(5):559-566. doi:10.1177/2050640620913674	Yes	No	Yes	Yes	Yes	Yes	Surveillance
Dillon R, Croner LJ, Bucci J, et al. Analytical validation of a novel multiplex test for detection of advanced adenoma and colorectal cancer in symptomatic patients. *J Pharm Biomed Anal*. 2018;154:85-94. doi:10.1016/j.jpba.2018.02.038	Yes	No	No	No	No	Yes	No data about FIT accuracy
D'Souza N, Brzezicki A, Abulafi M. Faecal immunochemical testing in general practice. *Br J Gen Pract*. 2019;69(679):60-61. doi:10.3399/bjgp19X700853	No	NA	NA	NA	NA	NA	Editorial
Falkson CB, Bates T. Faecal occult blood screening for patients with gastrointestinal symptoms. *Br J Surg*. 1993;80(10):1326. doi:10.1002/bjs.1800801036	Yes	Yes	No	No	Unclear	Yes	Secondary care; Haemoccult; no follow up
Farrands PA, O'Regan D, Taylor I. An assessment of occult blood testing to determine which patients with large bowel symptoms require urgent investigation. *Br J Surg*. 1985;72(10):835-837. doi:10.1002/bjs.1800721020	Yes	Yes	No	No	Unclear	Yes	Secondary care; Haemoccult; no follow up
Farrugia A, Widlak M, Evans C, Smith SC, Arasaradnam R. Faecal immunochemical testing (FIT) in symptomatic patients: what are we missing?. Frontline Gastroenterol. 2020;11(1):28-33. doi:10.1136/flgastro-2018-101174	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Farrugia A, Widlak MM, Smith S, Waugh N, Arasaradnam RP. Letter: faecal immunochemical testing for adults with symptoms of colorectal cancer-ready for prime time?. *Aliment Pharmacol Ther*. 2020;52(8):1419. doi:10.1111/apt.16068	No	NA	NA	NA	NA	NA	Letter
Fernández-Bañares F, Clèries R, Boadas J, et al. Prediction of advanced colonic neoplasm in symptomatic patients: a scoring system to prioritize colonoscopy (COLONOFIT study). *BMC Cancer*. 2019;19(1):734. Published 2019 Jul 25. doi:10.1186/s12885-019-5926-4	Yes	Yes	Yes	No	Yes	Yes	to derive a predictive score of advanced colonic neoplasia in symptomatic patients in fast-track programs. No data about FIT accuracy.

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Fraser CG. Faecal immunochemical tests (FIT) in the assessment of patients presenting with lower bowel symptoms: Concepts and challenges. *Surgeon*. 2018;16(5):302-308. doi:10.1016/j.surge.2018.01.004	No	NA	NA	NA	NA	NA	Review
Fraser CG. Faecal immunochemical tests for haemoglobin (FIT) in the assessment of patients with lower abdominal symptoms: current controversies. *Gastroenterol Hepatol*. 2019;42(4):263-270. doi:10.1016/j.gastrohep.2018.09.007	No	NA	NA	NA	NA	NA	Review
Godber IM, Todd LM, Fraser CG, MacDonald LR, Younes HB. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. *Clin Chem Lab Med*. 2016;54(4):595-602. doi:10.1515/cclm-2015-0617	Yes	No	Yes	Yes	Yes	Yes	Mixed population; symptomatic & follow up
Gopalswamy N, Stelling HP, Markert RJ, Maimon HN, Wahlen SD, Haddy RI. A comparative study of eight fecal occult blood tests and HemoQuant in patients in whom colonoscopy is indicated. *Arch Fam Med*. 1994;3(12):1043-1048. doi:10.1001/archfami.3.12.1043	Yes	No	Unclear	No	Yes	Yes	Mixed population; Unknown cut-off
Greenberg PD, Bertario L, Gnauck R, et al. A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol*. 2000;95(5):1331-1338. doi:10.1111/j.1572-0241.2000.02032.x	Yes	No	No	No	Yes	Yes	Secondary care; Mixed population; Unknown cut-off
Guimarães DP, Fregnani JH, Reis RM, et al. Comparison of a New-generation Fecal Immunochemical Test (FIT) With Guaiac Fecal Occult Blood Test (gFOBT) in Detecting Colorectal Neoplasia Among Colonoscopy-referral Patients. Anticancer Res. 2019;39(1):261-269. doi:10.21873/anticanres.13106	Yes	No	No	Yes	Yes	Yes	Mixed population
Gutiérrez-Stampa MA, Aguilar Gama V, Bujanda L. Utilidad del test de sangre oculta en heces para el diagnóstico del cáncer colorrectal en la práctica clínica en atención primaria [Utility of faecal occult blood test for the diagnosis of colorectal cancer in clinical practice in primary care]. *Aten Primaria*. 2020;52(4):286-287. doi:10.1016/j.aprim.2019.07.009	No	Yes	Yes	Yes	Yes	Yes	Letter; Repeated data
Gutierrez-Stampa MA, Aguilar V, Sarasqueta C, Cubiella J, Portillo I, Bujanda L. Impact of the faecal immunochemical test on colorectal cancer survival. *BMC Cancer*. 2020;20(1):616. Published 2020 Jul 1. doi:10.1186/s12885-020-07074-y	Yes	No	Yes	Yes	Yes	Yes	No data about FIT accuracy

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Hamarneh Z, Symonds EL, Kholmurodova F, Cock C. Older age, symptoms, or anemia: Which factors increase colorectal cancer risk with a positive fecal immunochemical test?. *J Gastroenterol Hepatol*. 2020;35(6):1002-1008. doi:10.1111/jgh.14888	Yes	No	No	Yes	Yes	Yes	This study aimed to examine factors that may increase neoplasia risk associated with a positive FIT, specifically age, gastrointestinal symptoms, or IDA. Only FIT positive patients.
Hazazi R, Rozen P, Leshno M, et al. Can patients at high risk for significant colorectal neoplasms and having normal quantitative faecal occult blood test postpone elective colonoscopy?. *Aliment Pharmacol Ther*. 2010;31(4):523-533. doi:10.1111/j.1365-2036.2009.04202.x	Yes	No	No	Yes	Yes	Yes	Screening setting
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;18(1):155. Published 2018 Oct 25. doi:10.1186/s12876-018-0887-7	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Hippisley-Cox J, Coupland C. Identifying patients with suspected colorectal cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract*. 2012;62(594):e29-e37. doi:10.3399/bjgp12X616346	Yes	Yes	Yes	No	Yes	Yes	No data about FIT accuracy
Hirata I, Hoshimoto M, Saito O, et al. Usefulness of fecal lactoferrin and hemoglobin in diagnosis of colorectal diseases. World J Gastroenterol. 2007;13(10):1569-1574. doi:10.3748/wjg.v13.i10.1569	Yes	Yes	Unclear	No	Yes	Yes	Secondary care. Patients scheduled to undergo colorectal endoscopy.
Hoepffner N, Shastri YM, Hanisch E, et al. Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study. Aliment Pharmacol Ther. 2006;23(1):145-154. doi:10.1111/j.1365-2036.2006.02702.x	Yes	No	No	Yes	Yes	Yes	Mixed population
Högberg C, Karling P, Rutegård J, Lilja M. Patient-reported and doctor-reported symptoms when faecal immunochemical tests are requested in primary care in the diagnosis of colorectal cancer and inflammatory bowel disease: a prospective study. *BMC Fam Pract*. 2020;21(1):129. Published 2020 Jul 1. doi:10.1186/s12875-020-01194-x	No	Yes	Yes	Yes	Yes	Yes	Same data than another Hogberg´s study included in the review
Högberg C, Karling P, Rutegård J, Lilja M, Ljung T. Immunochemical faecal occult blood tests in primary care and the risk of delay in the diagnosis of colorectal cancer. *Scand J Prim Health Care*. 2013;31(4):209-214. doi:10.3109/02813432.2013.850205	Yes	No	No	Yes	Yes	Yes	Only CRC patients

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Högberg C, Samuelsson E, Lilja M, Fhärm E. Could it be colorectal cancer? General practitioners' use of the faecal occult blood test and decision making--a qualitative study. *BMC Fam Pract*. 2015;16:153. Published 2015 Oct 26. doi:10.1186/s12875-015-0371-1	Yes	No	Yes	No	No	No	Semi-structured individual interviews were conducted with eleven purposely selected GPs and registrars in Region Jämtland Härjedalen, Sweden, and subjected to qualitative content analysis. No data about FIT accuracy.
Högberg C, Söderström L, Lilja M. Faecal immunochemical tests for the diagnosis of symptomatic colorectal cancer in primary care: the benefit of more than one sample. *Scand J Prim Health Care*. 2017;35(4):369-372. doi:10.1080/02813432.2017.1397255	Yes	No	No	Yes	Yes	Yes	Only CRC patients
Holden CA, Frank O, Caruso J, et al. From participation to diagnostic assessment: a systematic scoping review of the role of the primary healthcare sector in the National Bowel Cancer Screening Program. *Aust J Prim Health*. 2020;26(3):191-206. doi:10.1071/PY19181	Yes	No	No	Yes	Yes	Yes	Screening setting
Imperiale TF, Gruber RN, Stump TE, Emmett TW, Monahan PO. Performance Characteristics of Fecal Immunochemical Tests for Colorectal Cancer and Advanced Adenomatous Polyps: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2019;170(5):319-329. doi:10.7326/M18-2390	No	NA	NA	NA	NA	NA	Review
James T, Nicholson BD, Marr Rm, et al. Faecal immunochemical testing (FIT): Sources of analytical variation based on three years of routine testing in the context of DG30. medRxiv 2020.04.15.20066191; doi:10.1101/2020.04.15.20066191	Yes	No	Yes	Yes	No	No	Data obtained from independent verification studies and clinical testing of the HM-JACKarc FIT method were analysed to derive analytical performance characteristics. No data about FIT accuracy
Jeanson A, Jamart J, Maisin JM, et al. Assessment of the new immunological test Hemoblot for detecting occult blood in faeces. *Eur J Cancer Prev*. 1994;3(5):407-412. doi:10.1097/00008469-199409000-00004	Yes	Yes	No	No	Yes	Yes	Secondary care; Mixed population; Unknown cut-off
Jellema P, van der Windt DA, Bruinvels DJ, et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. *BMJ*. 2010;340:c1269. Published 2010 Mar 31. doi:10.1136/bmj.c1269	No	NA	NA	NA	NA	NA	Review
Juul J, Vedsted P, Bro F. Development of an Intervention for Implementing Immunochemical Faecal Occult Blood Test in General Practice. *Quality in Primary Care* 2016; 24 (6): 289-292	Yes	No	No	No	No	No	No data about FIT accuracy

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Juul JS, Bro F, Hornung N, et al. Implementation of immunochemical faecal occult blood test in general practice: a study protocol using a cluster-randomised stepped-wedge design. *BMC Cancer*. 2016;16:445. Published 2016 Jul 11. doi:10.1186/s12885-016-2477-9	Yes	No	No	No	No	No	No data about FIT accuracy
Kalimutho M, Del Vecchio Blanco G, Cretella M, et al. A simplified, non-invasive fecal-based DNA integrity assay and iFOBT for colorectal cancer detection. *Int J Colorectal Dis*. 2011;26(5):583-592. doi:10.1007/s00384-010-1128-x	Yes	No	No	Yes	Yes	Yes	The purpose of the endoscopy was for screening and to investigate symptoms
Kalra L, Hamlyn AN. Comparative evaluation of investigations for colorectal carcinoma in symptomatic patients. *Postgrad Med J*. 1988;64(755):666-668. doi:10.1136/pgmj.64.755.666	Yes	Yes	No	No	Yes	Yes	Haemoccult. No data about FIT specificity
Kamarudin M. Low-risk bowel cancer symptoms: is it time for FIT?. *Br J Gen Pract*. 2019;69(684):356-357. doi:10.3399/bjgp19X704501	No	NA	NA	NA	NA	NA	Review
Karl J, Wild N, Tacke M, et al. Improved diagnosis of colorectal cancer using a combination of fecal occult blood and novel fecal protein markers. Clin Gastroenterol Hepatol. 2008;6(10):1122-1128. doi:10.1016/j.cgh.2008.04.021	Yes	No	No	Yes	Yes	Yes	Screening setting
Katsoula A, Paschos P, Haidich AB, Tsapas A, Giouleme O. Diagnostic Accuracy of Fecal Immunochemical Test in Patients at Increased Risk for Colorectal Cancer: A Meta-analysis. *JAMA Intern Med*. 2017;177(8):1110-1118. doi:10.1001/jamainternmed.2017.2309	No	NA	NA	NA	NA	NA	Review
Kaul A, Shah A, Magill FH, Hawkins SA, Skaife P. Immunological faecal occult blood testing: a discriminatory test to identify colorectal cancer in symptomatic patients. Int J Surg. 2013;11(4):329-331. doi:10.1016/j.ijsu.2013.02.013	Yes	Yes	Unclear	Yes	Yes	Yes	all consecutive consenting patients attending the rapid access colorectal service were prospectively studied.
Kemppainen M, Häkkinen I, Räihä I, Pomoell R, Sourander L. Finding colorectal tumours with an immunological faecal occult blood test in symptomatic primary health care patients. *Age Ageing*. 1994;23(5):365-370. doi:10.1093/ageing/23.5.365	Yes	Yes	Yes	No	Yes	Yes	Guaiac plus FIT. Unknown cut-off
Kim NH, Lee MY, Park JH, et al. A Combination of Fecal Immunochemical Test Results and Iron Deficiency Anemia for Detection of Advanced Colorectal Neoplasia in Asymptomatic Men. *Yonsei Med J*. 2017;58(5):910-917. doi:10.3349/ymj.2017.58.5.910	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population
Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. Am J Med. 2003;115(2):111-114. doi:10.1016/s0002-9343(03)00294-8	Yes	No	Yes	Yes	Yes	Yes	Mixed population

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Kok L, Elias SG, Witteman BJ, et al. Diagnostic accuracy of point-of-care fecal calprotectin and immunochemical occult blood tests for diagnosis of organic bowel disease in primary care: the Cost-Effectiveness of a Decision Rule for Abdominal Complaints in Primary Care (CEDAR) study. *Clin Chem*. 2012;58(6):989-998. doi:10.1373/clinchem.2011.177980	No	Yes	Yes	Yes	Yes	Yes	Repeated data
Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. *BMJ Open*. 2013;3(10):e003989. Published 2013 Oct 30. doi:10.1136/bmjopen-2013-003989	Yes	No	Yes	Yes	Yes	Yes	Mixed population
Lee MW, Pourmorady JS, Laine L. Use of Fecal Occult Blood Testing as a Diagnostic Tool for Clinical Indications: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2020;115(5):662-670. doi:10.14309/ajg.0000000000000495	No	NA	NA	NA	NA	NA	Review
Leicester RJ, Lightfoot A, Millar J, Colin-Jones DG, Hunt RH. Accuracy and value of the Hemoccult test in symptomatic patients. *Br Med J (Clin Res Ed)*. 1983;286(6366):673-674. doi:10.1136/bmj.286.6366.673	Yes	Yes	No	No	Unclear	Yes	Secondary care; Haemoccult; no follow up
Li S, Wang H, Hu J, et al. New immunochemical fecal occult blood test with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: results of a prospective multicenter study in Chinese patients. *Int J Cancer*. 2006;118(12):3078-3083. doi:10.1002/ijc.21774	Yes	No	No	No	yes	Yes	Secondary care; Mixed population; Unknown cut-off
Li W, Zhao LZ, Ma DW, et al. Predicting the risk for colorectal cancer with personal characteristics and fecal immunochemical test. *Medicine (Baltimore)*. 2018;97(18):e0529. doi:10.1097/MD.0000000000010529	Yes	No	No	No	Yes	Yes	A risk prediction model for CRC based on a series of symptoms and signs related to enteric diseases in combination with a FIT. No data about FIT accuracy
Loktionov A, Soubieres A, Bandaletova T, et al. Biomarker measurement in non-invasively sampled colorectal mucus as a novel approach to colorectal cancer detection: screening and triage implications. *Br J Cancer*. 2020;123(2):252-260. doi:10.1038/s41416-020-0893-8	Yes	Yes	No	No	Yes	Yes	No data about FIT accuracy
Loveday C, Sud A, Jones ME, et al. Prioritisation by FIT to mitigate the impact of delays in the 2-week wait colorectal cancer referral pathway during the COVID-19 pandemic: a UK modelling study [published online ahead of print, 2020 Aug 27]. *Gut*. 2020;gutjnl-2020-321650. doi:10.1136/gutjnl-2020-321650	Yes	Yes	Yes	Yes	Yes	Yes	Data about FIT accuracy from D´Souza´s study

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Lué A, Hijos G, Sostres C, et al. The combination of quantitative faecal occult blood test and faecal calprotectin is a cost-effective strategy to avoid colonoscopies in symptomatic patients without relevant pathology. Therap Adv Gastroenterol. 2020;13:1756284820920786. Published 2020 May 18. doi:10.1177/1756284820920786	Yes	Yes	No	Yes	Yes	Yes	Secondary and primary care
Maclean W, Limb C, Mackenzie P, Whyte MB, Benton SC, Rockall T, Jourdan I. 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. 2020 Oct 17. doi: 10.1111/codi.15408. Epub ahead of print. PMID: 33068489.	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Maclean W, Singh R, Mackenzie P, et al. The two-week rule colorectal cancer pathway: an update on recent practice, the unsustainable burden on diagnostics and the role of faecal immunochemical testing. *Ann R Coll Surg Engl*. 2020;102(4):308-311. doi:10.1308/rcsann.2020.0019	Yes	Yes	Yes	No	No	No	No data about FIT accuracy
Mashlab S, Large P, Laing W, et al. Anaemia as a risk stratification tool for symptomatic patients referred via the two-week wait pathway for colorectal cancer. *Ann R Coll Surg Engl*. 2018;100(5):350-356. doi:10.1308/rcsann.2018.0030	Yes	Yes	Yes	No	Yes	Yes	No data about FIT accuracy
Masood U, Dhamoon AS, Murthy U. Influence of Varying Quantitative Fecal Immunochemical Test Positivity Thresholds on Colorectal Cancer Detection. Ann Intern Med. 2019;170(10):736. doi:10.7326/L19-0094	No	No	No	No	No	No	Commentary
Mattar R, Marques SB, Minata MK, Silva-Etto JMKD, Sakai P, DE Moura EGH. DIAGNOSTIC ACCURACY OF ONE SAMPLE OR TWO SAMPLES QUANTITATIVE FECAL IMMUNOCHEMICAL TESTS FOR INTESTINAL NEOPLASIA DETECTION. Arq Gastroenterol. 2020;57(3):316-322. doi:10.1590/S0004-2803.202000000-58	Yes	Yes	Unclear	Yes	Yes	Yes	Referred to colonoscopy. Setting not detailed
McDonald PJ, Digby J, Innes C, et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. Colorectal Dis. 2013;15(3):e151-e159. doi:10.1111/codi.12087	Yes	No	Yes	Yes	Yes	Yes	Primary care; Mixed population
McKinney R, Chapman C, Morling J, Weller J, Tangri A, Simpson JA, et al. Keeping FIT: early clinical outcomes of a novel two week wait pathway for colorectal cancer using faecal immunochemical testing. Colorectal Dis 2019;21(2):10. conference Abstract	No	Yes	Yes	Yes	Yes	Yes	Poster; Repeated data
Miyoshi H, Oka M, Sugi K, et al. Accuracy of Detection of colorectal neoplasia using an immunochemical occult blood test in symptomatic referred patients: comparison of retrospective and prospective studies. *Internal Medicine*. 2000; 39: 701-706.	Yes	No	No	No	Yes	Yes	Referred population; Unknown cut-off

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Mozdiak E, Weldeselassie Y, McFarlane M, et al. Systematic review with meta-analysis of over 90 000 patients. Does fast-track review diagnose colorectal cancer earlier?. *Aliment Pharmacol Ther*. 2019;50(4):348-372. doi:10.1111/apt.15378	No	NA	NA	NA	NA	NA	Review
Nakama H, Zhang B, Fattah AS, Zhang X. Colorectal cancer in iron deficiency anemia with a positive result on immunochemical fecal occult blood. *Int J Colorectal Dis*. 2000;15(5-6):271-274. doi:10.1007/s003840000255	Yes	Yes	Yes	No	Yes	Yes	Subgroup of asymptomatic with anaemia. Unknown cut-off
Nakama H, Kayano T, Katsuura T, et al. Comparison of predictive value for colorectal cancer in subjects with and without rectal bleeding. *Hepatogastroenterology*. 1999;46(27):1730-1732.	Yes	No	No	No	No	Yes	Not a symptomatic population
Nakama H, Zhang B, Abdul Fattah AS, Kamijo N, Fukazawa K. Relationships between a sign of rectal bleeding and the results of an immunochemical occult blood test, and colorectal cancer. *Eur J Cancer Prev*. 2000;9(5):325-328. doi:10.1097/00008469-200010000-00006	Yes	No	No	No	No	Yes	Not a symptomatic population
Narula N, Ulic D, Al-Dabbagh R, et al. Fecal occult blood testing as a diagnostic test in symptomatic patients is not useful: a retrospective chart review. Can J Gastroenterol Hepatol. 2014;28(8):421-426. doi:10.1155/2014/189652	Yes	No	Yes	No	Yes	Yes	Mixed population;gFOBT
Navarro M, Hijos G, Sostres C, et al. Reducing the Cut-Off Value of the Fecal Immunochemical Test for Symptomatic Patients Does Not Improve Diagnostic Performance. Front Med (Lausanne). 2020;7:410. Published 2020 Sep 2. doi:10.3389/fmed.2020.00410	Yes	Yes	Unclear	Yes	Yes	Yes	Referred to colonoscopy. Setting not detailed
Navarro M, Hijos G, Ramirez T, Omella I, Carrera-Lasfuentes P, Lanas Á. Fecal Hemoglobin Concentration, a Good Predictor of Risk of Advanced Colorectal Neoplasia in Symptomatic and Asymptomatic Patients. Front Med (Lausanne). 2019;6:91. Published 2019 May 3. doi:10.3389/fmed.2019.00091	Yes	No	Yes	Yes	Yes	Yes	Mixed population
Nicholson BD, East JE, Oke J, Roberts NW, James T, Shine B. Letter: extending FIT from DG30 to NG12 patients. Letter: faecal immunochemical testing for adults with symptoms of colorectal cancer - ready for prime time? Authors' reply: a unified approach to safety netting negative FITs is required. *Aliment Pharmacol Ther*. 2020;52(8):1420-1421. doi:10.1111/apt.16082	No	NA	NA	NA	NA	NA	Letter
Niedermaier T, Balavarca Y, Brenner H. Stage-Specific Sensitivity of Fecal Immunochemical Tests for Detecting Colorectal Cancer: Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2020;115(1):56-69. doi:10.14309/ajg.0000000000000465	No	NA	NA	NA	NA	NA	Letter

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Niv Y, Sperber AD. Sensitivity, specificity, and predictive value of fecal occult blood testing (Hemoccult II) for colorectal neoplasia in symptomatic patients: a prospective study with total colonoscopy. *Am J Gastroenterol*. 1995;90(11):1974-1977.	Yes	Yes	No	No	yes	Yes	Secondary care; Haemoccult II; no follow up
Oono Y, Iriguchi Y, Doi Y, et al. A retrospective study of immunochemical fecal occult blood testing for colorectal cancer detection. *Clin Chim Acta*. 2010;411(11-12):802-805. doi:10.1016/j.cca.2010.02.057	Yes	Yes	Unclear	Yes	Yes	Yes	patients thought to be symptomatic for a range of colorectal disorders following either point-of-care rapid test or physician examination were referred to the Tokyo Metropolitan Cancer Detection Center and scheduled for colonoscopy;
Oort FA, Terhaar Sive Droste JS, Van Der Hulst RW, et al. Colonoscopy-controlled intra-individual comparisons to screen relevant neoplasia: faecal immunochemical test vs. guaiac-based faecal occult blood test. *Aliment Pharmacol Ther*. 2010;31(3):432-439. doi:10.1111/j.1365-2036.2009.04184.x	Yes	No	No	Yes	Yes	Yes	Mixed population
Oort FA, van Turenhout ST, Coupé VM, et al. Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study. *BMC Cancer*. 2011;11:434. Published 2011 Oct 10. doi:10.1186/1471-2407-11-434	Yes	No	No	Yes	Yes	Yes	Mixed population
Ou CH, Kuo FC, Hsu WH, et al. Comparison of the performance of guaiac-based and two immunochemical fecal occult blood tests for identifying advanced colorectal neoplasia in Taiwan. J Dig Dis. 2013;14(9):474-483. doi:10.1111/1751-2980.12077	Yes	No	No	Yes	Yes	Yes	Mixed population
Parente F, Marino B, Ilardo A, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. *Eur J Gastroenterol Hepatol*. 2012;24(10):1145-1152. doi:10.1097/MEG.0b013e328355cc79	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Park CH, Jung YS, Kim NH, Park JH, Park DI, Sohn CI. Usefulness of risk stratification models for colorectal cancer based on fecal hemoglobin concentration and clinical risk factors. Gastrointest Endosc. 2019;89(6):1204-1211.e1. doi:10.1016/j.gie.2019.02.023	Yes	No	No	Yes	Yes	Yes	Screening setting

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Peabody J, Saldivar JS, Swagel E, Fugaro S, Paculdo D, Tran M. Primary care variability in patients at higher risk for colorectal cancer: evaluation of screening and preventive care practices. *Curr Med Res Opin*. 2018;34(5):851-856. doi:10.1080/03007995.2017.1417244	Yes	No	No	No	No	No	to evaluate physician practice variation in patients with a higher risk of CRC. To identify the physician characteristics and the types of patients that were associated with missed screening opportunities. No data about FIT accuracy.
Peacock O, Watts ES, Hanna N, Kerr K, Goddard AF, Lund JN. Inappropriate use of the faecal occult blood test outside of the National Health Service colorectal cancer screening programme. *Eur J Gastroenterol Hepatol*. 2012;24(11):1270-1275. doi:10.1097/MEG.0b013e328357cd9e	Yes	No	No	No	Unclear	Yes	Mixed population; Haemoccult
Pye G, Marks CG, Martin S, Marks V, Jackson J, Hardcastle JD. An evaluation of Fecatwin/Feca EIA; a faecal occult blood test for detecting colonic neoplasia. *Eur J Surg Oncol*. 1989;15(5):446-448.	Yes	Yes	No	No	Yes	Yes	Secondary care; Guaiac plus FIT. Unknown cut-off
Pye G, Jackson J, Thomas WM, Hardcastle JD. Comparison of Coloscreen Self-Test and Haemoccult faecal occult blood tests in the detection of colorectal cancer in symptomatic patients. *Br J Surg*. 1990;77(6):630-631. doi:10.1002/bjs.1800770612	Yes	Yes	No	No	Yes	Yes	Secondary care; Unknown cut-off
Quyn AJ, Steele RJ, Digby J, et al. Application of NICE guideline NG12 to the initial assessment of patients with lower gastrointestinal symptoms: not FIT for purpose?. *Ann Clin Biochem*. 2018;55(1):69-76. doi:10.1177/0004563217707981	No	No	No	Yes	Yes	Yes	Mixed population;
Rodríguez-Alonso L, Rodríguez-Moranta F, Ruiz-Cerulla A, 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;47(9):797-804. doi:10.1016/j.dld.2015.05.004	Yes	Yes	No	Yes	Yes	Yes	Referrals originated from general practitioners and community gastroenterologists, as well as from the hospital environment.
Rodriguez-Alonso L, Rodriguez-Moranta F, Ruiz-Cerulla A, et al. The use of faecal immunochemical testing in the decision-making process for the endoscopic investigation of iron deficiency anaemia. *Clin Chem Lab Med*. 2020;58(2):232-239. doi:10.1515/cclm-2019-0203	No	Yes	No	Yes	Yes	Yes	Mixed (Tertiary care & Primary care)
Rodriguez-Alonso L, Rodriguez-Moranta F, Arajol C, et al. Proton pump inhibitors reduce the accuracy of faecal immunochemical test for detecting advanced colorectal neoplasia in symptomatic patients. *PLoS One*. 2018;13(8):e0203359. Published 2018 Aug 31. doi:10.1371/journal.pone.0203359	No	Yes	No	Yes	Yes	Yes	Mixed (Tertiary care & Primary care)

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Rozen P, Comaneshter D, Levi Z, et al. Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Cancer*. 2010;116(9):2115-2125. doi:10.1002/cncr.25012	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Senore C, Haug U. Faecal immunochemical tests have the potential for correctly ruling out colorectal cancer in symptomatic patients. *BMJ Evid Based Med*. 2018;23(3):113-114. doi:10.1136/bmjebm-2018-110901	No	NA	NA	NA	NA	NA	Comment
Shastri YM, Loitsch S, Hoepffner N, et al. Comparison of an established simple office-based immunological FOBT with fecal tumor pyruvate kinase type M2 (M2-PK) for colorectal cancer screening: prospective multicenter study. *Am J Gastroenterol*. 2008;103(6):1496-1504. doi:10.1111/j.1572-0241.2008.01824.x	Yes	No	No	No	Yes	Yes	Mixed population. Unknown cut-off
Sieg A, Scheida M, John MR, et al. Validity of new immunological human fecal hemoglobin and albumin tests in detecting colorectal neoplasms--an endoscopy-controlled study. *Z Gastroenterol*. 1998;36(6):485-490.	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Sieg A, Thoms C, Lüthgens K, John MR, Schmidt-Gayk H. Detection of colorectal neoplasms by the highly sensitive hemoglobin-haptoglobin complex in feces. *Int J Colorectal Dis*. 1999;14(6):267-271. doi:10.1007/s003840050226	Yes	Yes	Yes	No	Yes	Yes	No relevant index test
Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. *Cancer*. 2006;107(9):2152-2159. doi:10.1002/cncr.22230	Yes	No	No	No	Yes	Yes	Mixed population. Unknown cut-off
Singhal S, Verma A, Anand K. Colonoscopy for colorectal cancer screening above age 75: outcomes in symptomatic african american and Hispanic adults. *J Gastrointest Cancer*. 2011;42(4):212-216. doi:10.1007/s12029-010-9190-8	Yes	Yes	Yes	No	Yes	Yes	To evaluate the outcome of colonoscopies in symptomatic adults ≥75 years of age. No data about FIT accuracy
Sokoro A, Singh H. Fecal Occult Blood Test for Evaluation of Symptoms or for Diagnostic Testing. *Am J Gastroenterol*. 2020;115(5):679-680. doi:10.14309/ajg.0000000000000560	No	NA	NA	NA	NA	NA	Editorial
Stonestreet J, Chandrapalan S, Woolley D, Uthman U, Arasaradnam RP. Systematic review and meta-analysis : diagnostic accuracy of faecal immunochemical testing for haemoglobin (FIT) in detecting colorectal cancer for both symptomatic and screening population. *Acta Gastroenterol Belg*. 2019;82(2):291-299.	No	NA	NA	NA	NA	NA	Review

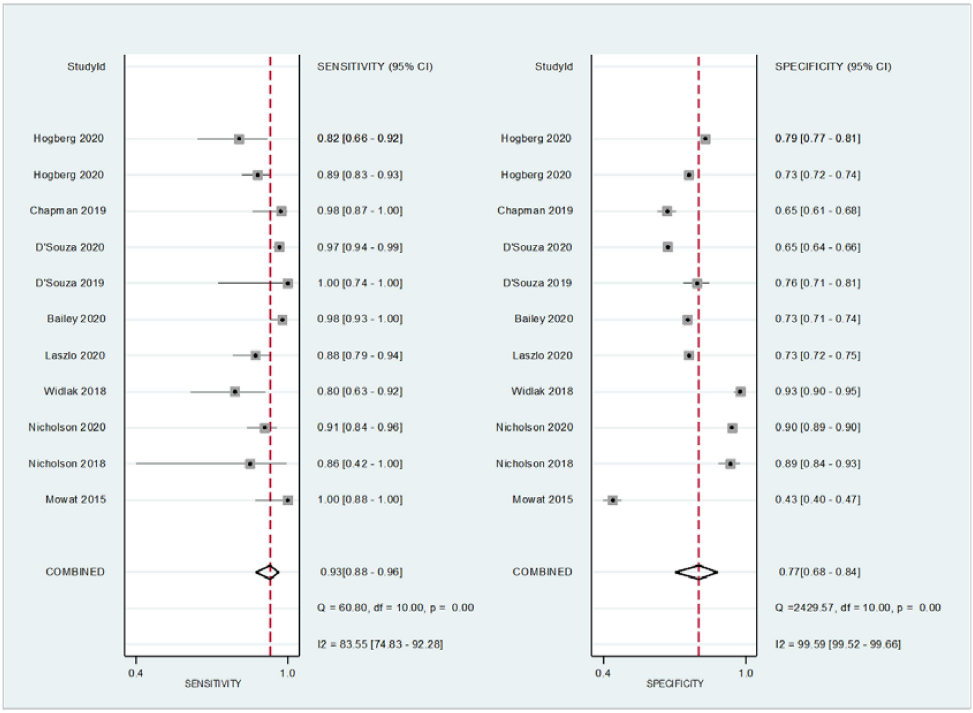
Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Steele RJ, McDonald PJ, Digby J, et al. Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity. *United European Gastroenterol J*. 2013;1(3):198-205. doi:10.1177/2050640613489281	Yes	No	No	Yes	Yes	Yes	Screening setting
St John DJ, Young GP, Alexeyeff MA, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. *Gastroenterology*. 1993;104(6):1661-1668. doi:10.1016/0016-5085(93)90643-q	Yes	No	No	No	Yes	Yes	Mixed population; Case-control
Symonds EL, Pedersen SK, Baker RT, et al. A Blood Test for Methylated BCAT1 and IKZF1 vs. a Fecal Immunochemical Test for Detection of Colorectal Neoplasia. *Clin Transl Gastroenterol*. 2016;7(1):e137. Published 2016 Jan 14. doi:10.1038/ctg.2015.67	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Szilagyi A, Xue X. Evaluation of a fecal immunochemistry test prior to colonoscopy for outpatients with various indications. Clin Exp Gastroenterol. 2017;10:285-292. Published 2017 Nov 10. doi:10.2147/CEG.S147928	Yes	No	Yes	Yes	Yes	Yes	Mixed population
Tate JJ, Northway J, Royle GT, Taylor I. Faecal occult blood testing in symptomatic patients: comparison of three tests. *Br J Surg*. 1990;77(5):523-526. doi:10.1002/bjs.1800770516	Yes	Yes	Yes	No	No	Yes	Guaiac plus FIT. Unknown cut-off. Double-contrast barium enema examination
Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. *Cancer Epidemiol Biomarkers Prev*. 2011;20(2):272-280. doi:10.1158/1055-9965.EPI-10-0848	No	Yes	No	Yes	Yes	Yes	Secondary care
Thomas WM, Hardcastle JD, Jackson J, Pye G. Chemical and immunological testing for faecel occult blood: a comparison of two tests in symptomatic patients. *Br J Cancer*. 1992;65(4):618-620. doi:10.1038/bjc.1992.125	Yes	Yes	Yes	No	Yes	Yes	No relevant index test; Unknown cut-off
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;55(2):184-192. doi:10.1080/00365521.2019.1708965	Yes	Yes	No	Yes	Yes	Yes	Referred from primary care or local hospitals
van de Veerdonk W, Hoeck S, Peeters M, Van Hal G. Towards risk-stratified colorectal cancer screening. Adding risk factors to the fecal immunochemical test: Evidence, evolution and expectations. *Prev Med*. 2019;126:105746. doi:10.1016/j.ypmed.2019.06.004	No	NA	NA	NA	NA	NA	Review

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
van Melle M, Yep Manzano SIS, Wilson H, Hamilton W, Walter FM, Bailey SER. Faecal immunochemical test to triage patients with abdominal symptoms for suspected colorectal cancer in primary care: review of international use and guidelines. *Fam Pract*. 2020;37(5):606-615. doi:10.1093/fampra/cmaa043	No	NA	NA	NA	NA	NA	Review
van Turenhout ST, Oort FA, van der Hulst RW, et al. Prospective cross-sectional study on faecal immunochemical tests: sex specific cut-off values to obtain equal sensitivity for colorectal cancer?. *BMC Gastroenterol*. 2014;14:217. Published 2014 Dec 21. doi:10.1186/s12876-014-0217-7	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Vasilyev S, Smirnova E, Popov D, et al. A New-Generation Fecal Immunochemical Test (FIT) Is Superior to Quaiac-based Test in Detecting Colorectal Neoplasia Among Colonoscopy Referral Patients. *Anticancer Res*. 2015;35(5):2873-2880.	Yes	No	No	No	Yes	Yes	Secondary care; Mixed population; Unclear indication for colonoscopy
Vironen J, Kellokumpu S, Andersson LC, Kellokumpu I. Comparison of a peanut agglutinin test and an immunochemical faecal occult blood test in detecting colorectal neoplasia in symptomatic patients. *Scand J Clin Lab Invest*. 2004;64(2):140-145. doi:10.1080/00365510410004876	Yes	Yes	No	No	Yes	Yes	Secondary care; Unclear indication for colonoscopy; Unknown cut-off
von Wagner C, Verstraete W, Hirst Y, Nicholson BD, Stoffel ST, Laszlo H. Public preferences for using quantitative faecal immunochemical test versus colonoscopy as diagnostic test for colorectal cancer: evidence from an online survey. *BJGP Open*. 2020;4(1):bjgpopen20X101007. Published 2020 May 1. doi:10.3399/bjgpopen20X101007	Yes	No	No	No	No	No	To elicit public preferences for FIT versus colonoscopy (CC) and its delivery in primary care. No data about FIT accuracy
von Wagner C, Stoffel S, Freeman M, et al. Attitudes towards faecal immunochemical testing in patients at increased risk of colorectal cancer: an online survey of GPs in England. *Br J Gen Pract*. 2018;68(676):e757-e764. doi:10.3399/bjgp18X699413	Yes	No	No	No	No	No	to investigate general practitioneers attitudes and willingness to use a FIT over an urgent 2-week wait (2WW) referral. No data about FIT accuracy
Von Wagner C, Stoffel ST, Freeman M, et al. General practitioners' awareness of the recommendations for faecal immunochemical tests (FITs) for suspected lower gastrointestinal cancers: a national survey. *BMJ Open*. 2019;9(4):e025737. Published 2019 Apr 11. doi:10.1136/bmjopen-2018-025737	Yes	No	No	No	No	No	Cross-sectional online survey of GPs hosted by an English panel of Primary health care professionals. No data about FIT accuracy
Yoshinaga M, Motomura S, Takeda H, Yanagisawa Z, Ikeda K. Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. *Am J Gastroenterol*. 1995;90(7):1076-1079.	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population

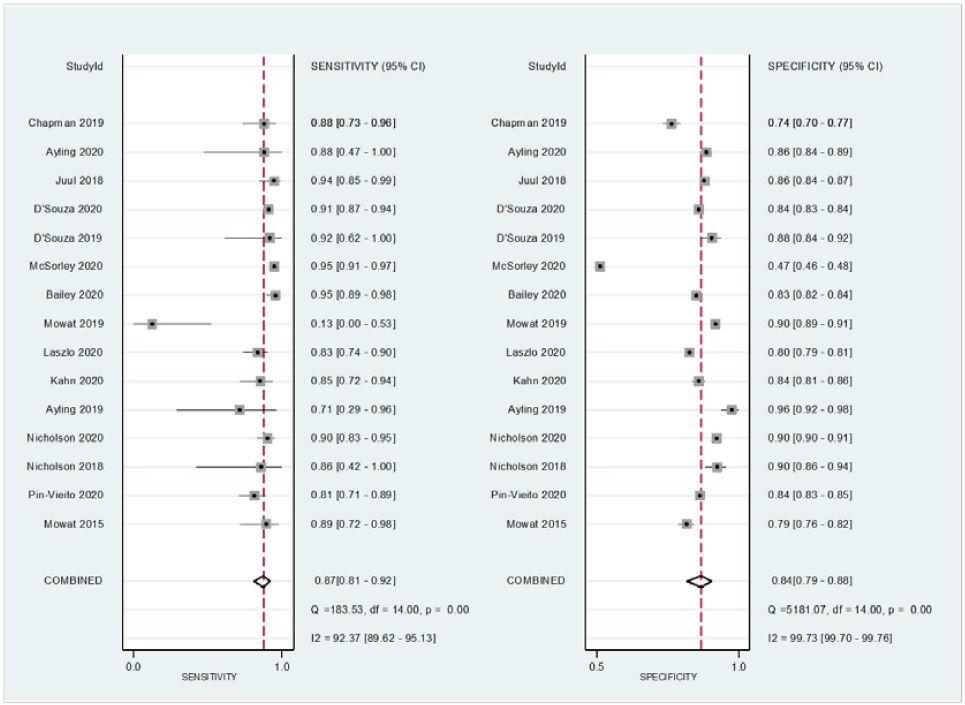
Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Widlak MM, Thomas CL, Thomas MG, et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther. 2017;45(2):354-363. doi:10.1111/apt.13865	Yes	Yes	No	Yes	Yes	Yes	All the referrals were seen in colorectal and dedicated gastroenterology clinics at University Hospitals Coventry and Warwickshire National Health Service Trust.
Wong WM, Lam SK, Cheung KL, et al. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. *Cancer*. 2003;97(10):2420-2424. doi:10.1002/cncr.11369	Yes	No	No	No	Yes	Yes	Mixed population
Woo HY, Mok RS, Park YN, et al. A prospective study of a new immunochemical fecal occult blood test in Korean patients referred for colonoscopy. Clin Biochem. 2005;38(4):395-399. doi:10.1016/j.clinbiochem.2005.01.003	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Young GP, St John DJ, Cole SR, et al. Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin. *J Med Screen*. 2003;10(3):123-128. doi:10.1177/096914130301000305	Yes	Yes	No	No	Yes	Yes	Secondary care; Mixed population; Unknown cut-off
Wu D, Luo HQ, Zhou WX, Qian JM, Li JN. The performance of three-sample qualitative immunochemical fecal test to detect colorectal adenoma and cancer in gastrointestinal outpatients: an observational study. PLoS One. 2014;9(9):e106648. Published 2014 Sep 8. doi:10.1371/journal.pone.0106648	Yes	No	No	No	Yes	Yes	Secondary care; Mixed patients

Appendix 3. Forest plot showing pooled sensitivity and specificity for faecal immunochemical tests for the detection of colorectal cancer and significant colonic lesion based on cut-off value.

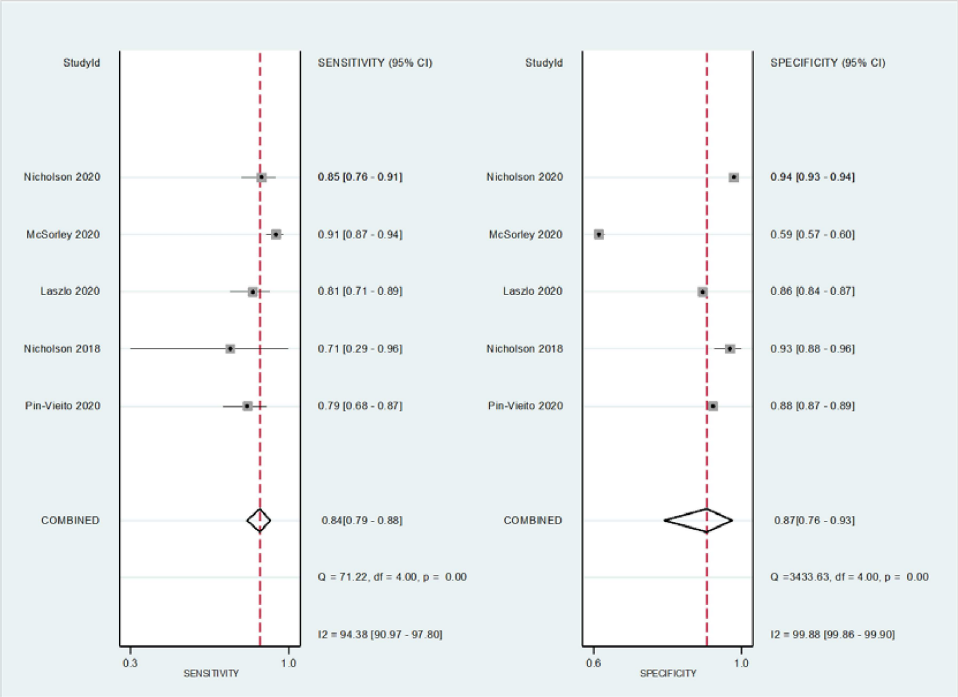
A) Cut-off value above the limit of detection (colorectal cancer)



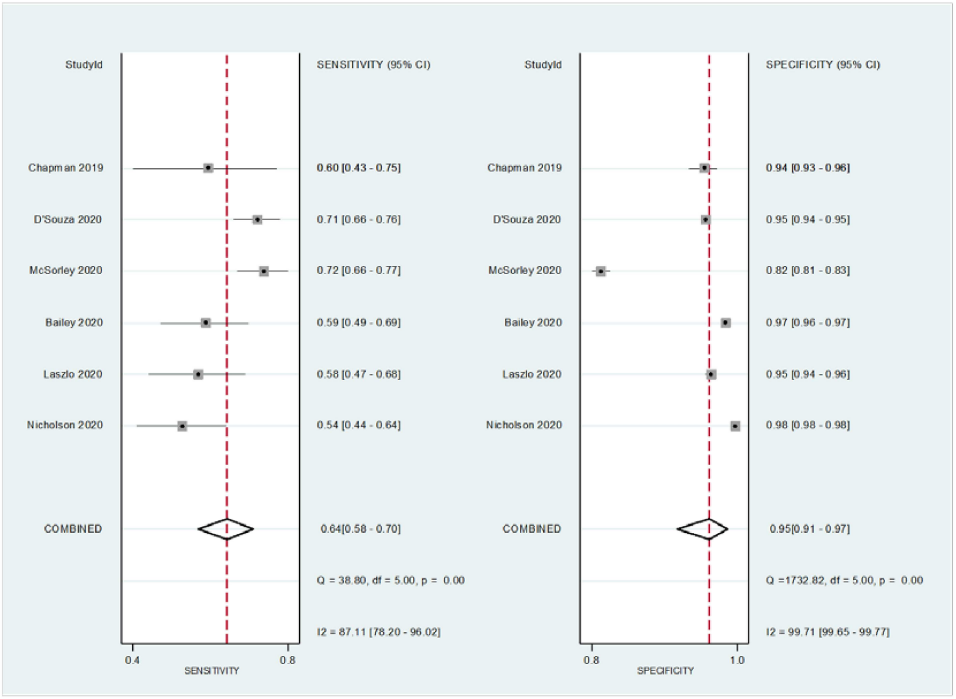
B) Cut-off value at 10 µg Hb/g faeces (colorectal cancer)



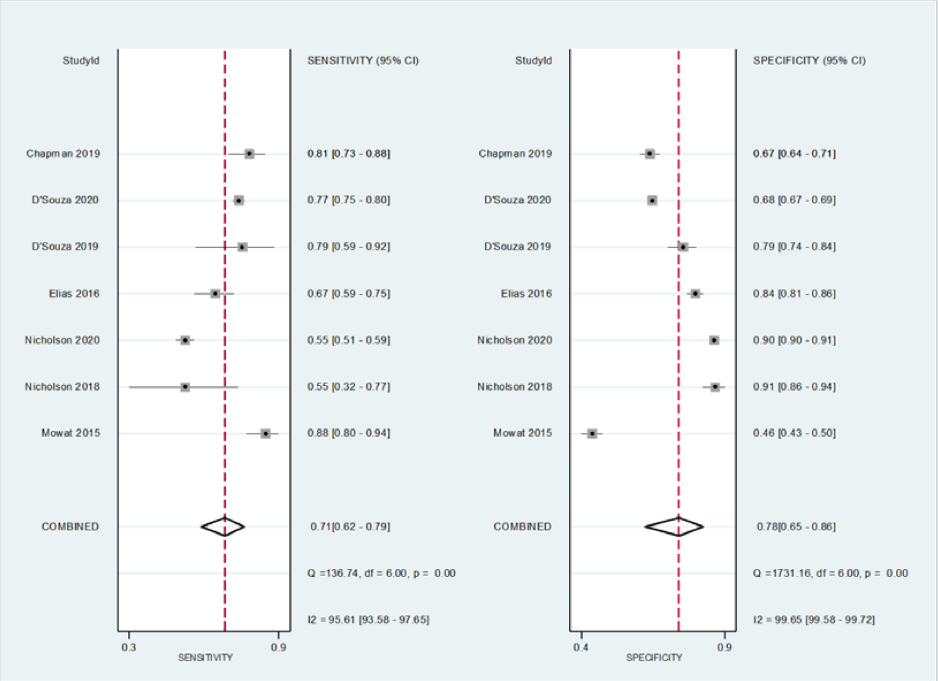
C) Cut-off value at 20 µg Hb/g faeces (colorectal cancer)



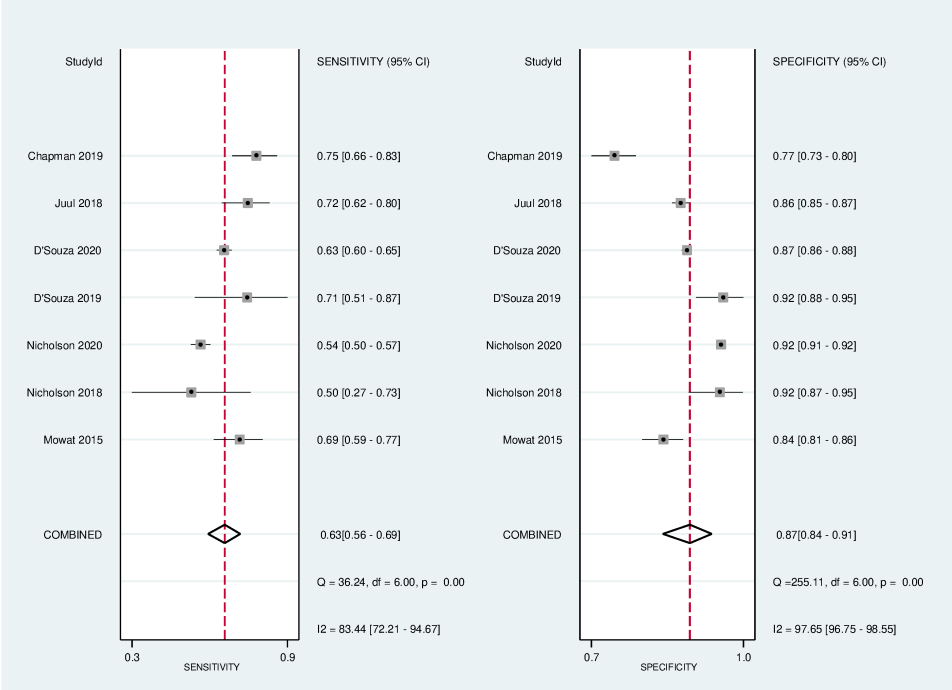
D) Cut-off value at 150 µg Hb/g faeces (colorectal cancer)



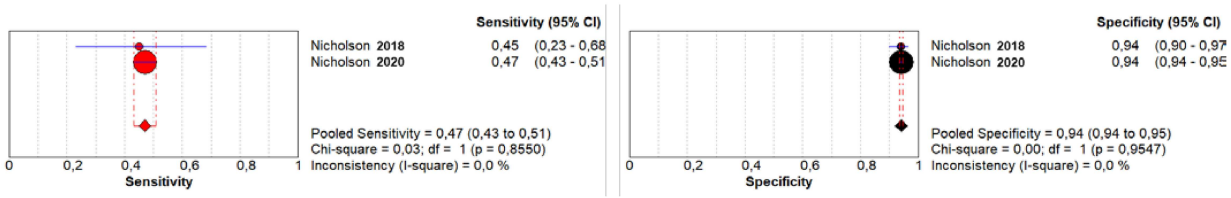
E) Cut-off value above the limit of detection (Significant colonic lesion)



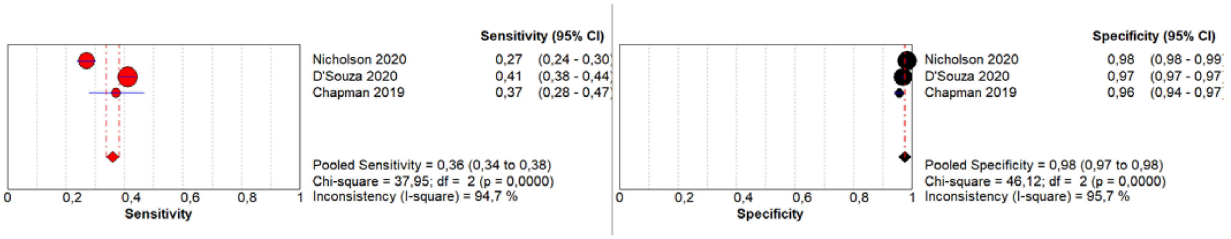
F) Cut-off value at 10 µg Hb/g faeces (significant colonic lesion)



G) Cut-off value at 20 µg Hb/g faeces (significant colonic lesion). DerSimonian method.



H) Cut-off value at 150 µg Hb/g faeces (significant colonic lesion). DerSimonian method.



Supplementary table 1: Characteristics of the studies included in the systematic review.

Author & Objective	Design & Setting	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Hogberg, 2010 **Aim**: to gain better knowledge about the use and outcome of an immunochemical faecal haemoglobin method in Swedish primary care, and how these tests contribute to the diagnosis of colorectal cancer.	Prospective cohort study. Setting: Primary care, Jämtland (Sweden). Period of recruitment: 1 December 2005 – 31 December 2007. The FIT was regarded positive when one or more of three samples showed a positive result.	All patients aged 18 years and over were eligible for the study when a a general practitioner ordered a FIT during the period of study.	Not reported. A total of 11 patients did not submit the tests, and 2 patients moved outside the county council during the observation period and were excluded.	Enrolled: 316 patients, of these 303 (95.9%) were included in the analysis. Three FIT samples were provided by 226 (75%) of the patients. 58 patients (19%) had positive samples. Symptoms: 250 (82.5%) abdominal pain, 70 (23.1%) change in bowel habit, 47 (15.5%) rectal bleeding, 51 (16.8%) anaemia. In 17 of the 58 who left a positive F-Hb test no examination of either the colon or rectum was performed. 1 (0.3%) CRC was found.	***Index test:*** Point of care qualitative FIT (Actim Faecal Blood; Oy Medix Biochemica Ab, Finland). 1 sample from each of 3 consecutive stools. Cut-off value for a positive result: 50 ng hb/ml of faecal solution (25–50 lg hb/g faeces according to the manufacturer). ***Reference standard:*** 54% performed bowel imaging. Medical records of the Care Administration System Development & Cancer Registry were reviewed. Follow up: 5–31 (mean 18) months.
Mowat, 2015 ***Aim:*** to study the diagnostic accuracies of faecal haemoglobin and faecal calprotectin, in a cohort of patients presenting to primary care with bowel symptoms. Other target: High risk adenoma; Significant colonic lesion;	Prospective cohort study. Setting: Primary care, NHS Tayside, Scotland (UK). Referrals are triaged by consultant gastroenterologists; 75% are brought straight to investigation and the remainder were seen in outpatient clinics. The percentage of referrals from GPs marked as 'urgent' or 'urgent suspected cancer' consistently runs at 35–40%.	All adult patients referred to secondary care for investigation of bowel symptoms from October 2013 to March 2014. (if patients had more than one symptom, they were attributed only one in order of decreasing importance: rectal bleeding, anaemia, diarrhea, altered bowel habit, abdominal pain and weight loss)	Not reported. 12 patients were excluded (seven in whom neither faecal sample was suitable for analysis, four who returned samples outside the study period and one patient with known inflammatory bowel disease.)	2189 patients were referred for investigation. 1032 (47.1%) referrals were either 'urgent' or 'urgent suspected cancer' and 1043 (34.5%) patients returned faecal samples; 1031 patients (47.1%) formed the study cohort. A total of 755 patients (54.7% women, median age 64 years) returned faecal samples and completed bowel investigations and were included in the analysis. Prevalence CRC: 3.7%. Prevalence SCL (CRC + HRA + IBD) 10.0%. 100% Symptomatic (Weight loss 7 (0.9%); Pain 83 (11.0%); rectal bleeding 258 (34.2%), anemia 67 (8.9%); change in bowel habit 323 (42.8%); diarrhea 127 (16.8%)).	***Index test:*** OC-Sensor (Eiken Chemical Co., Tokyo, Japan). Any faecal haemoglobin sample that was reported by the analytical system as a positive numerical result greater than zero mg/g was considered as a 'detectable faecal haemoglobin'. Cut-offs: detectable faecal haemoglobin and 10 µg hemoglobin/ g feces. ***Reference standard:*** colonoscopy up to the caecum or obstructing carcinoma plus histopathology.
Elias, 2016 ***Aim:*** to develop a diagnostic model for significant colonic disease (CRC + IBD + diverticulitis + advanced adenoma) with routine clinical information, extended with faecal calprotectin and/or FIT results.	This paper reports data from the CEDAR (Cost-effectiveness of a Decision Rule for Abdominal Complaints in Primary Care) study: A prospective cross-sectional diagnostic study in	Patients consulting their general prectitioners for persistent lower-abdomen complaints in the period of study. Patients were eligible if they were at high risk of organic bowel disease	Patients < 18 years, unable to give informed consent, previously diagnosed with organic bowel disease or positive on the triple faeces test, used for the detection of intestinal parasites, not	Eligible patients: 1495. Of these, 843 were enrolled and 810 (54.2%) were included in the analysis. The median age of participants was 61 years 54.9% were female. Organic bowel disease was present in 141	***Index test:*** A qualitative point of care test: Clearview One Step Fecal Occult Blood Test Device, (Inverness Medical Innovations). The lower detection limit as stated by the manufacturer was 6 µg hemoglobin/ g feces.

In 2012 (subgroup data) Kok´s article aimed to quantify the diagnostic accuracy of 3 biomarker tests (Quantum Blue® calprotectin quantitative lateral flow assay, EK-CAL calprotectin ELISA and Clearview One Step immunochemical faecal occult blood test device) for the inclusion or exclusion of organic bowel disease in patients with persistent (i.e., ≥2 weeks) lower-abdomen complaints in primary care. Other analysis: accuracy of combined faecal calprotectin & FIT	266 general practices in 2 regions of the Netherlands: central (Gelderse Vallei) and south (Oostelijke Mijnstreek). Period of recruitment: from July 2009 through January 2012. When patient referral outpaced study resources, every nth case was screened to keep study participants representativeness.	(lower-abdomen complaints present for ≥ 2 weeks plus ≥ 1 of the following: rectal bleeding, altered defecation pattern, abdominal pain, fever, diarrhea, weight loss, sudden onset in the elderly, or palpable abdominal or rectal mass). Recruitment was at the general practitioner´s office (19.9%) or after scheduling at the endoscopy department (80.1%).	requiring endoscopy. In some patients, endoscopy was scheduled in <1 week so they could not become part of the study. Patients not reached or who refused participation also were not included.	patients (17.4%), the majority of whom had neoplastic disease (37 carcinoma and 49 adenomas), followed by IBD (37) and diverticulitis (18). Sixteen patients had advanced adenomas. Symptoms: 80.7% abdominal pain; 43.6% rectal bleeding; 65.5% change in bowel habit; 29.1% Diarrhoea; 57.9% constipation; 19.2% weight loss; 5.5% anaemia.	***Reference standard:*** endoscopy (i.e., colonoscopy or sigmoidoscopy). Furthermore, all patients for whom there was an inconclusive diagnostic reference procedure were followed for 3 months to establish a definite diagnosis.
Hogberg, 2016 ***Aim:*** to assess the value of a point of care FIT and a quantitative faecal calprotectin test in detecting CRC, HRAs and IBD in primary care. *Secondary aim:* to assess the value of combining these tests with tests for haemoglobin concentration, iron saturation and serum ferritin. Another target: significant colonic lesion (CRC + HRA + IBD)	Prospective cohort study. Setting: Primary care, four health care centres which provide care for approximately 29.000 (23%) inhabitants of the Jämtland Härjedalen region of Sweden. There is no CRC screening program.	All patients aged 20 years and over were eligible for the study when a physician ordered a FIT and/or a faecal calprotectin test during the period of 30 January 2013–31 May 2014. Nurses invited consecutive patients to participate in the study. The sample size was calculated, based on the hypothesis that there would be a significant difference in sensitivity between the faecal calprotectin test and the FIT for detecting CRC and high-risk adenomas.	Not reported.	In total, 510 patients were eligible for the study, 391 agreed to participate and 384 returned both tests. Of these, five died of other conditions before endoscopy, and six moved away from the area during the 2-year follow-up, thus, 373 (73.1%) patients (median age 63.0 years, 64.6% women) were included in the final analysis. All patients were symptomatic. 92 (25.3%) of patients consulted with rectal bleeding, 207 (58%) abdominal pain, 161 (45.7%) change in bowel habit,156 (44.7%) diarrhoea, 98 (28.2%) constipation, 46 (13.5%) weight loss, 62 (21.0%) anaemia. CRC, HRA and SCL were diagnosed in 8 (2.1%), 8 (2.1%) and 26 (6.8%) patients respectively.	***Index test:*** Point of care qualitative FIT (Actim Faecal Blood; Oy Medix Biochemica Ab, Finland). One sample from each of three consecutive stools. The cut-off value for a positive result was set at 50 ng haemoglobin/ml of faecal solution, which corresponded to 25–50 lg haemoglobin/g faeces according to the manufacturer. The FIT was regarded positive when one or more of three samples showed a positive result. ***Reference standard:*** colonoscopy and/or follow up (2 years) through medical records.
Juul, 2018 ***Aim:*** to investigate in a large-scale study the value of using FIT in general practice on patients presenting with non-alarm symptoms of CRC.	Prospective cohort study based on the establishment of access to the FIT for general practitioners in the Central Denmark Region.	All individuals aged ≥30 years who presented in general practice with non-alarm symptoms of CRC (change in bowel habits, abdominal pain, unexplained anaemia, and unspecific	Individuals aged ≥40 years with alarm symptoms: rectal bleeding, change in bowel habits >4 weeks, abdominal pain and iron deficiency anaemia. Or symptoms which could be eligible for	During the study period, 3745 FITs were requested, and 3462 (92.5%) FITs were included in the analyses. Of these, 540 (15.6%) were positive. Diagnostic investigation was performed in 416 (77.0%) of individuals with a	***Index test:*** OC Sensor DIANA (Eiken Chemical Company, Ltd, Japan). The measuring range was 7–200 µg Hb/g faeces (stated as <7 µg Hb/g faeces for faecal haemoglobin concentrations below the detection limit). Only one FIT per individual

Another target: significant bowel disease (CRC + IBD + HRA)	The study took place from 1 September 2015 to 30 August 2016.	symptoms e.g., fatigue or weight loss). Furthermore, FIT was recommended as part of the diagnostic work up of irritable bowel syndrome.	urgent referral in the cancer patient pathway for CRC. Invalid FIT (2.4%) and duplicated (5.1%) were also excluded.	positive FIT and 418 (14.3%) with a negative FIT. Among all individuals with a positive FIT, 51 (9.4%) were diagnosed with CRC, 11 with IBD and 62 with HRA. Less than three (<0.1%) CRCs and 26 (0.9%) cases of SBD (20 IBDs and 6 HRAs) were found among individuals with a negative test. Symptoms: 1579 (45.6%) abdominal pain, 1867 (53.9%) change in bowel habit, 424 (12.3%) anaemia.	was included (Defined either the latest performed FIT or the FIT requested immediately before the referral to diagnostic investigation). Cut-off: 10 µg hemoglobin/ g faeces. ***Reference standard:*** follow up during 3 months from the day of FIT request through Danish registers.
Widlak, 2018 ***Aim:*** to assess the diagnostic accuracy of FIT, faecal calprotectin and urinary volatile organic compounds in patients with lower GI symptoms. Other results: Diagnostic performance of FIT in combination with faecal calprotectin and urinary volatile compounds for CRC, high-risk adenoma and all adenomas.	Single-centre, prospective, blinded study. Patients referred from primary care to tertiary care with suspected CRC. Unknown recruitment period.	Patients with lower GI symptoms with suspected CRC.	Under the age of 18, pregnant, did not meet the referral criteria for urgent review for lower gastrointestinal symptoms or had incomplete colonic examinations were excluded. 834 patients were excluded for a combination of reasons including "physical frailty, illness, language barriers, etc."	Invited: 1850 patients. Of these, 562 (30.4%) patients with matching urine and stool samples were included for statistical analysis. 49% female; Median age 68 (range 29-89). Symptoms: Altered bowel habit 369 (66%), Weight loss 87 (15%), Rectal bleeding 232 (41%), Anaemia 121 (22%), Iron-deficiency anaemia 91 (16%), Abdominal pain 164 (29%). Of these, 35 were diagnosed with CRC (6.2%)	***Index test:*** HM-JACKarc (Kyowa Medex). The lowest detection limit of this assay for FIT is 3 µg /g faeces. EIA Calprotectin iluoroimmunoassay -automated Thermo Fisher Immuno-Cap 250 analyser (Thermo Fisher Scientific, Waltham, Massachusetts, USA). A commercial gas analysis instrument [Lonestar (FAIMS), Owlstone, Cambridge, UK] was used to analyse VOCs emanating from the urine samples. ***Reference standard:*** endoscopic or radiological colonic cross-sectional imaging.
Turvill, 2018 ***Aim:*** To assess the diagnostic accuracy of FIT and faecal calprotectin for CRC, significant adenomatous polyps (10 mm or multiple 5 sub-centimetre polyps or with high-grade dysplasia) and organic enteric disease (which required secondary care management: IBD, microscopic colitis, radiation proctopathy and significant diverticular disease).	Prospective Cohort study. Patients referred from primary care. Period of recruitment: February 2016 to March 2017. UK; England (York)	Patients who were referred through the 'two-week wait' pathway, fulfilling alarm criteria for suspected CRC (NICE NG12 Sections 1.3.1–1.3.3).	Patients under the age of 18, unbeing able to give informed consent to participate in the research study or who did not return one or both faecal samples before investigation.	Invited: 1491; Enrolled 700; Analysed: 515 (34.5%). 50% Female. Median age 69 years (IQR 61–76). 18% had a family history of CRC and 30% were taking NSAID, antiplatelet therapy or anticoagulants. 93% of the referrals were judged to strictly fulfil criteria for a 'two-week wait' suspected CRC referral. 79% of the patients had a change in	***Index test:*** HM-JACKarc (Kyowa-Medex Co., Ltd, supplied by Alpha Laboratories Ltd, Eastleigh SO50 4NU, UK). The manufacturer's quoted limit of quantitation of 7 µg Hb/g faeces was used in this study; Limit of detection was determined as 2 µg Hb/g faeces. Cut-off: 12 µg hemoglobin/ g faeces.

To determine whether repeat or combined biomarker testing improves diagnostic accuracy for CRC or clinically significant disease. Other analysis: Diagnostic accuracy of a single FIT for CRC in subgroups of NICE NG12 symptom complexes and demographics.				bowel habit, 36% rectal bleeding, 26% abdominal pain, 18% iron-deficiency anaemia, 14% weight loss, 4% abdominal mass and 1% rectal mass.	Monoclonal Enzyme-Linked Immuno-Sorbent Assay (EK-CAL Calprotectin ELISA, Buhlmann) ***Reference standard:*** full colonoscopy or CT colonography or a lesser investigation (such as CT abdomen/pelvis with contrast plus flexible sigmoidoscopy)
Ayling, 2019 **Aim:** to study FIT in patients with anaemia attending a gastroenterology clinic in Plymouth and to look at an artificial intelligence learning algorithm (ColonFlagTM) in these patients, together with a cohort who had undergone colonoscopy for iron deficiency anaemia in London.	One of this cohort of the study is used. Retrospective cohort analysis. Patients recruited in a Gastroenterology Clinic at Plymouth, between March 2014 and March 2017, who had been referred from Primary Care.	Patients seen in the Gastroenterology Clinic, referred from Primary Care with a low haemoglobin concentration, ostensibly secondary to iron deficiency, on a 2-week wait cancer pathway	Not reported	Plymouth cohort was compound by 428 patients. The median age was 71 and 51.2% were female. Of these, FIT was performed in 178 patients (41.6%). Seven (3.9%) and 13 (7.3%) were diagnosed with CRC and HRA respectively.	***Index test:*** OC Sensor (Eiken Chemical Co, Tokyo, Japan). Cut-off: 10 µg hemoglobin/ g faeces. ***Reference standard:*** colonoscopy.
Nicholson, 2018 ***Aim:*** To compare the diagnostic performance of guaiac faecal occult blood testing with FIT. Another target: significant colonic lesion (CRC+IBD+polyp > 10 mm)	Retrospective cohort study. Data & Setting: Consecutive samples sent to the laboratory from primary care in the period January to March 2016 for investigation of faecal occult blood in Oxfordshire, UK (population of approximately 660,000)	Patients with lower gastrointestinal symptoms. Where more than one sample result was available for any individual patient, any positive result within those samples tested was considered a positive outcome on the basis that a single positive would trigger referral. Where multiple samples on a single patient were collected, these were on sequential days, which precluded assessment of changes in FOB test results with disease progression.	Not reported	Faecal occult blood testing by both FIT and guaiac faecal occult blood was undertaken on 332 samples from 238 patients, (median age 58 years (range 19–93); 57% women). Symptoms: change in bowel habit 59 (24.8%), abdominal pain /discomfort 45 (18.9%), blood in stools 23 (9.7%), rectal bleeding 9 (3.5%) and weight loss 4 (1.7%), anaemia 62 (26.1%) absent / uninterpretable clinical info (n=46). Significant colorectal disease was detected in 20 patients, 7 of which had CRC.	***Index test:*** HM-KACKarc (Kyowa Medex, Tokyo, Japan). The method had a calibration range of 7 to 450 µg Hb/g faeces. Various cut-off used: 7; 10; 20 and 50 µg haemoglobin /g faeces. ***Reference standard:*** clinical and diagnostic databases were searched for between 21 and 23 months following the faecal occult blood testing for all patients.
Mowat, 2019 ***Aim:*** to determine the impact of introducing quantitative FIT into routine practice within	Single-centre prospective cohort study. Period of study: the first calendar year beginning December 2015.	Patients who consulted primary care with lower GI symptoms.	Not reported but 152 samples (2.7%) were unsuitable for analysis (most commonly due to faecal contamination) in whom 40	A total of 5422 patients submitted a total of 5660 FIT samples to the laboratory. 5372 (99.1%) were included in the final analysis. The median age of patients was 65	***Index test:*** HM-JACKarc (Kyowa Medex) with an analytical working range of 7–400 µg Hb/g faeces. Results with f-Hb ≥10 µg/g were defined as positive.

primary care on the outcome of patients presenting with new bowel symptoms. Another target: significant colonic lesion (CRC+IBD+polyp > 10 mm) collected from Digby´s study. *Other results:* Cases of colorectal cancer presenting in patients with f-Hb <10 µg/g but who had been referred from primary care on clinical judgement.	NHS Tayside, Scotland (UK). (population of around 400,000 with approximately 4000 referrals from primary care to secondary care for assessment of bowel symptoms per year).	This population has no access to guaiac faecal occult blood tests (out with the National Bowel Cancer Screening Programme). These patients may be referred to either the direct-to-test colorectal service or to gastroenterology.	patients did not complete a repeat test. Ten patients had known IBD. In total, 50 patients were excluded from further analysis.	years (range: 2–99, IQR: 51–75) and 56.4% were female.	***Reference standard:*** 2848 patients were referred to secondary care and colonoscopy was performed in 2141 (39.9%) patients and was complete in 1447 (26.9%) patients. Other patients were assessed with CT colonography, sigmoidum endoscopy or barium enema) & All patients were followed through post hoc anonymised record linkage with the Scottish Cancer Registry to identify all incident cases of CRC.
Keenan, 2019 ***Aim:*** to compare the accuracy of faecal M2-PK and FIT in detecting pre-cancerous bowel lesions and CRC in patients who present in primary care with bowel symptoms. Another target: significant colonic lesion (CRC+Adenoma > 9 mm)	Prospective cohort study. Setting: Primary care. New Zealand. Unknown period of recruitment.	One of the cohorts of the study was used: this included patients who presented to their general practitioners with bowel problems and were subsequently referred for a faecal immunochemical test to detect the presence of faecal haemoglobin.	Not reported Four patients were subsequently excluded from the general practitioner derived cohort, because bacterial pathogens were detected in their samples.	Enrolled: 189. Analyzed: 185 (97.9%). 50.8% female; Median age (interquartile range): 59 (51–70). 7 were found to have evidence of Significant colonic lesions that included CRC (n=2), adenomas greater than 1 cm in size (n=5).	***Index test:*** A qualitative (one-step membrane cassette) immunoassay (Ngaio Diagnostics Ltd, Nelson, New Zealand). This assay detects human haemoglobin above 50µg of f-Hb per gram of faeces. ***Reference standard:*** Clinical follow-up on the patients in the GP cohort was monitored for a minimum of 12 months after stool collection.
Chapman, 2019 ***Aim:*** to evaluate anaemia and faecal haemoglobin levels as risk stratification tools in a '2 week wait' pathway, and to assess FIT within an operational urgent colorectal cancer pathway in England. Anaemia was defined as a haemoglobin level below 120 g/l in women and 130 g/l in men. Data about FIT as "Rule in" tool. Another target: significant colonic lesion (CRC+IBD+HRA + complicated diverticular disease)	Prospective cohort study. Recruitment of patients in primary care setting between 6 September 2016 and 31 August 2017. (Nottingham, England, UK)	All patients referred under the 2 week-wait pathway from primary care for suspected colorectal cancer in the period of study were included.	Patients referred with rectal bleeding were excluded from FIT stratification. Patients who should be evaluated through other pathways (not 2ww).	During the study period, 1891 referrals were vetted by the straight-to-test team and 1106 referrals were deemed suitable for FIT and were sent kits, 895 OC-Sensor™ kits were returned (80.9%), three patients had incomplete data and one kit was unanalysable. Finally, 810 (73.2%) were analysed. The median age of those referred was 71.7 (62.6–79.3) years. 55.7% were female. 40 CCR were diagnosed (4.9%). Symptoms: 58.2% change in bowel habit, 288 (37.8%) anaemia.	***Index test:*** OC-Sensor™; Eiken Chemical Company, Tokyo, Japan. Various cut-off used: LoD; 10; and 150 µg haemoglobin /g faeces. 4 µgHb/g faeces was the limit of reliable detectability on the analyser platform. ***Reference standard:*** all outcomes were censored on 22 September 2017. Patient data including clinical outcomes for all 2WW referrals were recorded on a NUhCLEUS software system.
D'Souza, 2019	Prospective cohort study.	All symptomatic patients undergoing colonoscopy	Colonoscopy was performed for surveillance in 86 patients who were excluded.	800 patients accepted and 384 completed colonoscopy and FIT (48%). 298 were analyzed. Mean	***Index test:*** HM-JACKarc (Kyowa Medex/Alpha Labs). Various cut-off used: LoD; and 10 µg haemoglobin

Aim: to determine the diagnostic accuracy of FIT to rule out colorectal cancer in symptomatic patients, including low risk patients meeting the NICE criteria (DG30). Another target: significant colonic lesion (CRC+IBD+HRA)	Setting: Patients from primary care referred for colonoscopy at Croydon University Hospital between November 2016 and October 2017.	who were referred through a 2WW pathway.		age 60.6 years (range 20–90); 198 (51.4%) women. 160 NG12 & 138 DG30 criteria. 33% Iron deficiency anaemia or change in bowel habit > 60y; 18% change in bowel habit < 60 y; 16% rectal bleeding > 50y.	/g faeces. The analytical working range was 2–8000 µg Hb/g faeces (µg/g). The limit of detection of the assay is 2 µg/g and the limit of quantification was 10 µg/g. ***Reference standard:*** colonoscopy.
Pin-Vieito, 2020 ***Aim:*** To assess the diagnostic accuracy of FIT in daily clinical practice in primary health care for CRC diagnosis. To evaluate the performance of FIT when threshold is increased from 10 µg Hb/g faeces to 20 µg Hb/g faeces	Population-based retrospective cohort study. Setting: Primary care (real life data). Two areas of northern Spain between 2012 and 2016.	Asymptomatic and Symptomatic patients aged ≥18 years who consulted their general practitioners who requested a FIT as part of their medical treatment	Hospitalization; Secondary care patients; Regional screening program; < 18 years old; Patients with a history of CRC in the 2 years prior to FIT determination.	Included: n=38,675; Age: (median) 65.2 years; Sex: 54.0% women. Prevalence CRC: 1.7%; Information regarding FIT indication and CRC location was only available for San Sebastián (5623 symptomatic patients).	***Index test:*** OC-Sensor (Eiken Chemical, Tokyo, Japan). cut-off of 10 and 20 µg haemoglobin /g faeces. ***Reference standard:*** Spanish Health System's Hospital Discharge Records Database (CRC diagnosis)
Hogberg, 2020 ***Aim:*** to evaluate the usefulness of FITs requested by primary care physicians for patients with and without histories of rectal bleeding, in the diagnosis of CRC.	Retrospective cohort study. Setting: patients recruited in primary care from 1 January to 31 December 2015 in the region of Örebro in Sweden (population 290,890 on 1 November 2015).	Patients aged ≥ 18 with FIT results requested by primary care physicians in the period of study. Samples registered within 14 days of each other were considered as belonging to the same FIT. The date of the FIT was set as the date of the first faecal sample. If more than one FIT had been provided during the year, the first FIT was registered only. The FIT was considered as positive if one or more of the samples tested positive.	Not reported	5683 patients (Median age 64 years, 59.9% women, 107 (1.9%) CRC) provided FITs with 1-8 samples. Three sample FITs were provided by 4232 patients (60.7% women, median age 62 years, 79 (1.9%) CRC). Information about rectal bleeding was available for 2404 patients, of which 2027 (84.3%; 62.0% women, median age 58 years, 59 (2.9%) CRC) provided three-sample FITs. In total, rectal bleeding was registered for 606 (29.9%) of the 2027 patients with three-sample FITs who had 26 (4.3%) CRCs.	***Index test:*** Actim Fecal Blood (Oy Medix Biochemica AB, Finland). Cutoff: 50 ng haemoglobin/ml of faecal solution corresponding to 25–50 µg haemoglobin/g faeces. ***Reference standard:*** patients with CRC within 2 years after their FIT date were identified from the Swedish Cancer Register.
Ayling, 2020 ***Aim:*** to audit a new FIT service for primary care for use in symptomatic patients at low risk of CRC, focusing on the indication for request and referral for diagnostic tests as recommended in NICE guidance.	Prospective cohort study. Setting: Primary care. Period: between 1 April and 30 September 2019. Newham, Tower Hamlets and Waltham Forest (combined population of about 950,000 years and 128 Primary Care practices).	All patients with samples that were analysed between 1 April and 30 September 2019 were included.	Not recorded 309 samples (25.7%) were not able to be analysed; 17 samples were unlabelled, 37 were grossly overfilled with contamination of the collection device, 227 were in screw top pots rather than specimen collection devices and 13 requests had no accompanying sample.	Enrolled: 1203, of these, FIT analysis was performed in 894 (74.3%) patients (median age 60 years, range 23-98; 55.7% women), 209 (23.4%) patients were younger than 50 years of age. Eight (0.9%) CRC were diagnosed.	***Index test:*** OC-Sensor (Eiken Chemical, Tokyo, Japan) cut-off of 10 µg haemoglobin /g faeces. The lower limit of quantification was 4 µg/g. The upper analytical limit was 200 µg/g and samples with a concentration above this were reported as >200 µg/g. ***Reference standard:*** CRC and other diagnoses were determined by reviewing clinical notes and

					endoscopy, histology and radiology report.
Nicholson, 2020 ***Aim:*** to assess the diagnostic performance of FIT to detect serious bowel disease based on age-group, gender and FIT threshold. Another info: to describe FIT negative cases of colorectal cancer and the effect of adjusting the period of follow-up on diagnostic accuracy measures for colorectal cancer using FIT ≥10 µg Hb/g faeces	Retrospective cohort study. Setting: primary care. Oxfordshire (population of approximately 660 000), England,UK. Period of study from March 2017 to March 2020.	Consecutive FIT samples sent to Oxford University Hospitals Trust clinical biochemistry laboratory from primary care for adults (≥18 years old) during the period study. *Where more than one sample result was available for any individual patient, any positive result within those samples tested was considered a positive outcome on the basis that a single positive would trigger referral.*	Not described. *"Although 'high-risk' symptoms qualifying for urgent colonoscopy were noted in the clinical details, such as weight loss or anaemia, it can be assumed that GPs assessed these cases to be lower risk and not to qualify for fast-track referral and that GPs required additional information to guide their management."*	A total of 14,487 consecutive FITs were conducted for 12,509 patients, of these 9896 (79.1%) patients had at least 6 months of follow-up. The median age was 60 years and 58.6% were women. Patients commonly presented with combinations of clinical features: change in bowel habit (50.6%), anaemia (28.2%), abdominal pain (25.2%), blood in stools (19.7%) and iron deficiency (12.2%). CRC and Significant colorectal disease was detected in 105 (1.1%) and 682 (6.9%) of patients, 373 (3.8%) large >10 mm or high-grade dysplastic polyps and 204 (2.1%) had bowel inflammation.	***Index test:*** HM-JACKarc (Hitachi Chemical Diagnostics Systems Co., Ltd). The method had a calibration range of 7-450 µg Hb/g faeces and immunoassay reproducibility, assessed across 12 months was between 4.5% and 8.7% when expressed as a percentage coefficient of variation. Multiple cut-offs used (7, 10, 20, 50, 100, 120 and 150 µg haemoglobin / g faeces ***Reference standard:*** clinical and diagnostic databases were searched for evidence of cellular pathology for up to 36 months following the FIT test for all patients.
D'Souza, 2020 ***Aim:*** To assess whether FIT could be used to select patients with suspected colorectal cancer symptoms for urgent investigation. The primary outcome measure was to identify a suitable faecal haemoglobin cut-off that would maximise sensitivity for CRC. The secondary outcome measures were to establish the diagnostic accuracy of FIT for CRC and other serious bowel disease at different faecal haemoglobin cut-offs, and investigate the impact of other variables, such as age, sex, ethnicity and deprivation.	Multicentre, double-blinded diagnostic accuracy study using patients referred from primary care to 50 National Health Service (NHS) hospitals across England between October 2017 and December 2019.	Patients referred from primary care with symptoms of suspected CRC meeting NICE referral criteria under the 2WW pathway and who were triaged by secondary care clinicians to investigation by colonoscopy. Patients referred urgently on a 2WW pathway without meeting NICE criteria due to clinical concerns were classified as 'others' and included in the analysis.	Patients were not included if they did not return a suitable for analysis FIT sample or did not have a complete colonoscopy unless due to CRC or withdrew consent. Patients due to undergo colonoscopy within 3 days of identification were not invited to participate in the study, as there would not have been sufficient time to return a sample. FIT samples that were performed after the colonoscopy were not included in the study.	Invited: 21,126 patients; Complete FIT and colonoscopy outcomes were available for 9,822 (46.5%) patients (median age 65.0 years, 54.9% women). Ethnic groups: white (75.9%), other (11.2%) and Asian (6.3%). The median deprivation index score was 6.0. High-risk symptoms meeting NG12 criteria (73.2%), low-risk symptoms meeting DG30 criteria (21.4%) or other symptoms warranting urgent referral (6.4%). CRC and SBD (CRC, HRA or IBD) was detected in 3.3% and 11.9% of patients.	***Index test:*** HM-JACKarc (Hitachi Chemical Diagnostics Systems, Tokyo, Japan, supplied by Alpha Labs, Eastleigh, Hants, UK). The analytical working range is 7–400 µg/g. The limit of detection (LoD) of the assay is 2 µg/g and the limit of quantitation is 7 µg/g. Cut-off LoD, 10 and 150 µg Hb/g faeces. ***Reference standard:*** colonoscopy.
Mc Sorley, 2020 ***Aim:*** to examine the yield of CRC in patients who 1) underwent colonoscopy across three Scottish NHS Boards after referral from	Retrospective audit of data from three cohorts. Some data were prospectively collected as part of Mowat´s study published in 2019.	Patients who had undergone colonoscopy because of a primary care referral with lower GI symptoms (including rectal	Patients without a FIT result, who had undergone colonoscopy without submitting a previous FIT, had not undergone	A total of 4841 patients were included. Of these, 266 (5.5%) were diagnosed with CRC. NHS Tayside included 1447 patients (with a median age of 66, 52.7%	***Index test:*** HM-JACKarc (HM-JACKarc, Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo, Japan). Limit of detection (LoD) of 2 µg/g, a limit of quantification (LoQ)

primary care with lower gastrointestinal symptoms and 2) had submitted a FIT at the time of referral.	Primary care setting. Three Scottish NHS Boards: The period of data collection was between December 2015 and December 2016 (12 months) in Tayside, June 2018 and December 2019 (18 months) in Fife and September 2018 and January 2019 (5 months) in Greater Glasgow and Clyde.	bleeding) and had an associated FIT result were included. All categories of urgency of referral were included.	colonoscopy following a FIT, or had been investigated by other methods such as CT colonography were not included in the analysis.	women, of whom 92 (6.4%) were diagnosed with CRC). NHS Fife included 2082 patients (median age 65; 54.0% women, of whom 125 (6.0%) were diagnosed with CRC). NHS Greater Glasgow and Clyde included 1312 patients (median age 60, 56.4% women, of whom 49 (3.7%) were diagnosed with CRC).	of 7 µg/g and an upper measurement limit of 400 µg/g. Multiple cut-offs used (10, 20, 50, 100, 150, 200, 250, 300, 350 and 400 µg haemoglobin / g faeces ***Reference standard:*** colonoscopy
Khan, 2020 ***Aim:*** to assess the diagnostic accuracy of FIT for CRC in symptomatic patients referred by local primary care physicians via the 2-week-wait pathway. Secondary aims were to assess the diagnostic accuracy of FIT in detecting high-risk polyps and to evaluate the impact on FIT results of using digital rectal examination to obtain stool samples. Other results: Cases of colorectal cancer presenting in patients with f-Hb <10 µg/g reported on Cunin´s study.	Single-centre prospective and blinded study undertaken at East Sussex Healthcare NHS Trust, England, UK. The period of study was from August 2017 to August 2018.	Patients with bowel symptoms, referred via the 2-week-wait CCR pathway.	72 patients were excluded. 45 (63%) were deemed unfit for further investigation, 17 (24%) declined further investigation, nine (13%) had not completed investigation at the time of analysis, and one (1%) had no stool for analysis on digital rectal examination.	Enrolled 1000 patients, of these, 928 (92.8%) patients (59.5% female; median age 72) were included in the final analysis. Change in bowel habit 609 (65.6%), Anaemia 189 (20.4%), Intermittent rectal bleeding 94 (10.1%), Weight loss 70 (7.5%), Abdominal pain 69 (7.4%), Abdominal mass 29 (3.1%), Rectal mass 21 (2.3%), FOB test-positive 2 (0.2%).	***Index test:*** HM-JACKarc (Kyowa Medex and Alpha Laboratories, Eastleigh, UK). Minimum and maximum reported values were 0·0 and > 450 µg Hb/g faeces respectively. Cut-off 10 µg Hb/g faeces. ***Reference standard:*** Definitive diagnostic investigations performed depending on the patient's fitness status and willingness. Colonoscopy (68.4%); Colon TC (16.9%); Sigmoidoscopy + Plain CT (14.7%)
Bailey, 2020 ***Aim:*** to evaluate the impact of general practitioner access to FIT and Rapid Colorectal Cancer Diagnosis. Retrospective audit of FIT results, CRC outcomes and resource utilization before and after introduction of FIT in Primary Care. Another info: objective criteria to define different cut-offs based on clinical data. Rule in criteria.	Retrospective Cohort study. Setting: primary care, Nottingham, England, UK. Period of study from November 2017 – December 2018	All patients that were subject of a FIT request between 7th November 2017 and 31st December 2018.	Requests mentioning rectal bleeding were rejected (4.0%). Duplicate requests (1.4%) and patient who did not return their kit within 14 days (9.6%) and kits not suitable for analysis (0.5%).	6747 general practitioner FIT test requests yielded 5733 (89.8%) FIT results, (56% female, mean age 67.4 years) of which 4082 (71.2%) were <4.0 mg Hb/g faeces, 579 (10.1%) were 4.0-9.9 mg Hb/g faeces, 836 (14.6%) were 10.0-149.9 mg Hb/g faeces, and 236 (4.1%) were >150.0 mg Hb/g faeces.	***Index test:*** OC-Sensor™; Eiken Chemical Company, Tokyo, Japan. Multiple cut-offs used (4, 10 and 150 µg haemoglobin / g faeces ***Reference standard:*** Various datasets were used to evaluate diagnoses of CRC previously recorded with a censor date of 31st December 2018. NUH Trust data, electronic patient records and NUhCLEUS data were used for cross-checking and data validation.
Hogberg, Nov 2020	Population-based cohort study using electronic health	Patients aged ≥18 years, for whom FITs had been requested and test results	Not reported	15789 patients with three FIT samples (60.9% female; median age 65 years); 304 (1.9%) were	***Index test:*** Actim Fecal Blood (Oy Medix Biochemica AB, Finland) in Örebro; cut-off: 25–50 µg/g faeces.

Aim: To evaluate the usefulness of qualitative FITs requested for symptomatic patients in primary care, alone and combined with findings of anaemia and thrombocytosis, in the diagnosis of CRC. Another information: calculated the accuracy of FIT using one and two years as follow up period	records and data from the Swedish Cancer Register. Five Swedish regions (Jämtland Härjedalen, Kronoberg, Västerbotten, Västernorrland and Örebro; Period of study from 1 January 2015 to 31 December 2015.	had been registered in primary care in the study period.		diagnosed with CRC within 2 years.	Analyz FOB (LumiraDx AB, Sweden) in Kronoberg, Västerbotten, and Västernorrland; cut-off level: 2 µg/g faeces. Chemtrue FOB Test (Chemtron Biotech Co Ltd, China) in Jämtland Härjedalen; 40 ng/ml faecal solution (µg/g not available). Diaquick FOB (Dialab GmbH, Austria) in Kronoberg; cut-off 5 µg/g faeces. ***Reference standard:*** Swedish Cancer Register
Laszlo, 2020 ***Aim:*** To evaluate the ability of quantitative FIT to rule out colorectal cancer for patients who present to primary care with 'high risk' symptoms defined by national guidelines for urgent referral for suspected cancer (NICE NG12). Another reported data: clinical features and location of tumour in the 15 patients diagnosed with colorectal adenocarcinoma who had f-Hb <10 µg/g.	Prospective multi-centre observational study (24 hospitals in England and 59 general practices in London) between April 2017 and March 2019.	Adult patients with abdominal symptoms that merited an urgent referral to the NG12 CRC pathway referred from primary care.	Patients < 16 years and people were unable to understand instructions. Patient characteristics were similar between the 3596 patients who were included in the analyses and the 1055 who were excluded because their cancer outcome was unknown by the study team.	Recruited: 4676 patients; Included: 3596 (76.9%) patients (Median age 67 years; 53% were female) Of these, 78% had colonoscopy. CRC: 90 (2.5%), 7 (0.2%) had other cancers; 99% were recruited in secondary care. Symptoms: Change of bowel habit 1835 (51%), rectal bleeding 970 (27%), anaemia 684 (19%), abdominal pain 427 (11.9%) and weight loss 312 (8.7%).	***Index test:*** OC-Sensor™; Eiken Chemical Company, Tokyo, Japan. LoD 4 µg/g. Upper analytical limit 200 µg/g. Multiple cut-offs used (4, 6, 10, 20, 50, 80, 100, 120, 150 and 200 µg haemoglobin / g faeces ***Reference standard:*** patient examination reports (colonoscopy 77.7%, colono TC 18.3%, sigmoidoscopy 7.5%, CT 0.1%, other/missing 0.4%) were verified by researchers.

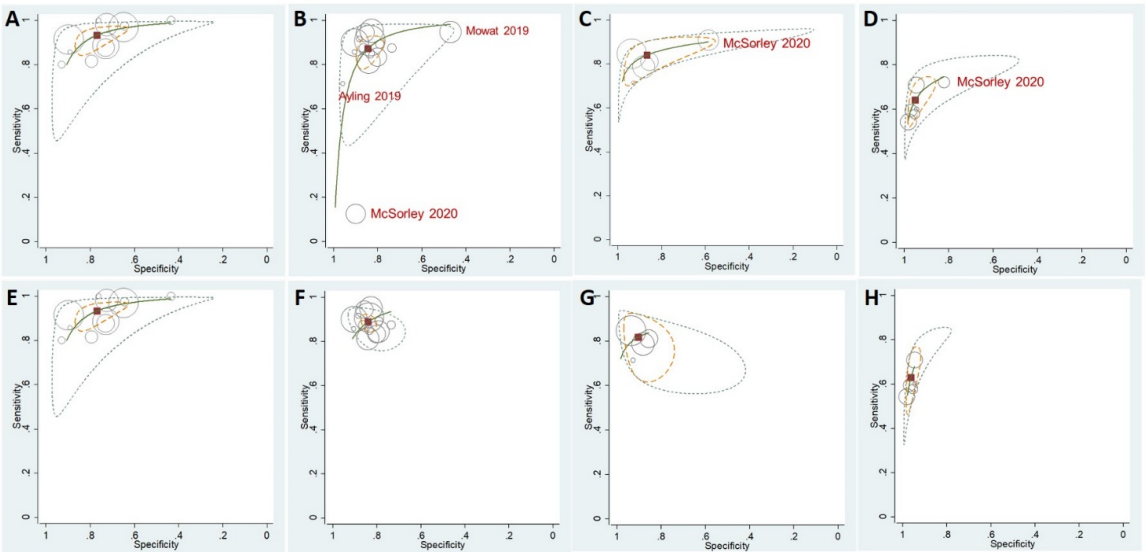
Supplementary Table 2. Results of bivariate meta-regression with covariates at the 10µg Hb/ g of feces

Covariate	Studies (n)	Sensitivity (95% CI)	*P* Value	Specificity (95% CI)	*P* Value
FIT Brand					
• **OC-Sensor**	8	0.88 (0.81 – 0.95)	0.07	0.84 (0.78 – 0.90)	0.00
• **HM-JACKarc**	7	0.86 (0.78 – 0.94)		0.84 (0.78 – 0.91)	
CRC prevalence					
• **< 3% CRC**	8	0.86 (0.78 – 0.93)	0.01	0.87 (0.82 – 0.92)	0.01
• **≥ 3% CRC**	7	0.89 (0.82 – 0.96)		0.81 (0.74 – 0.88)	
Recruitment					
• **PCF**	9	0.87 (0.80 – 0.94)	0.03	0.85 (0.80 – 0.91)	0.01
• **CU**	6	0.88 (0.80 – 0.95)		0.83 (0.75 – 0.90)	
Reference Standard					
• **Follow-up**	8	0.86 (0.79 – 0.94)	0.02	0.86 (0.81 – 0.91)	0.01
• **Colonoscopy**	7	0.88 (0.81 – 0.95)		0.82 (0.75 – 0.89)	

CRC, colorectal cancer; CU, colonoscopy unit; PCF, primary care facility

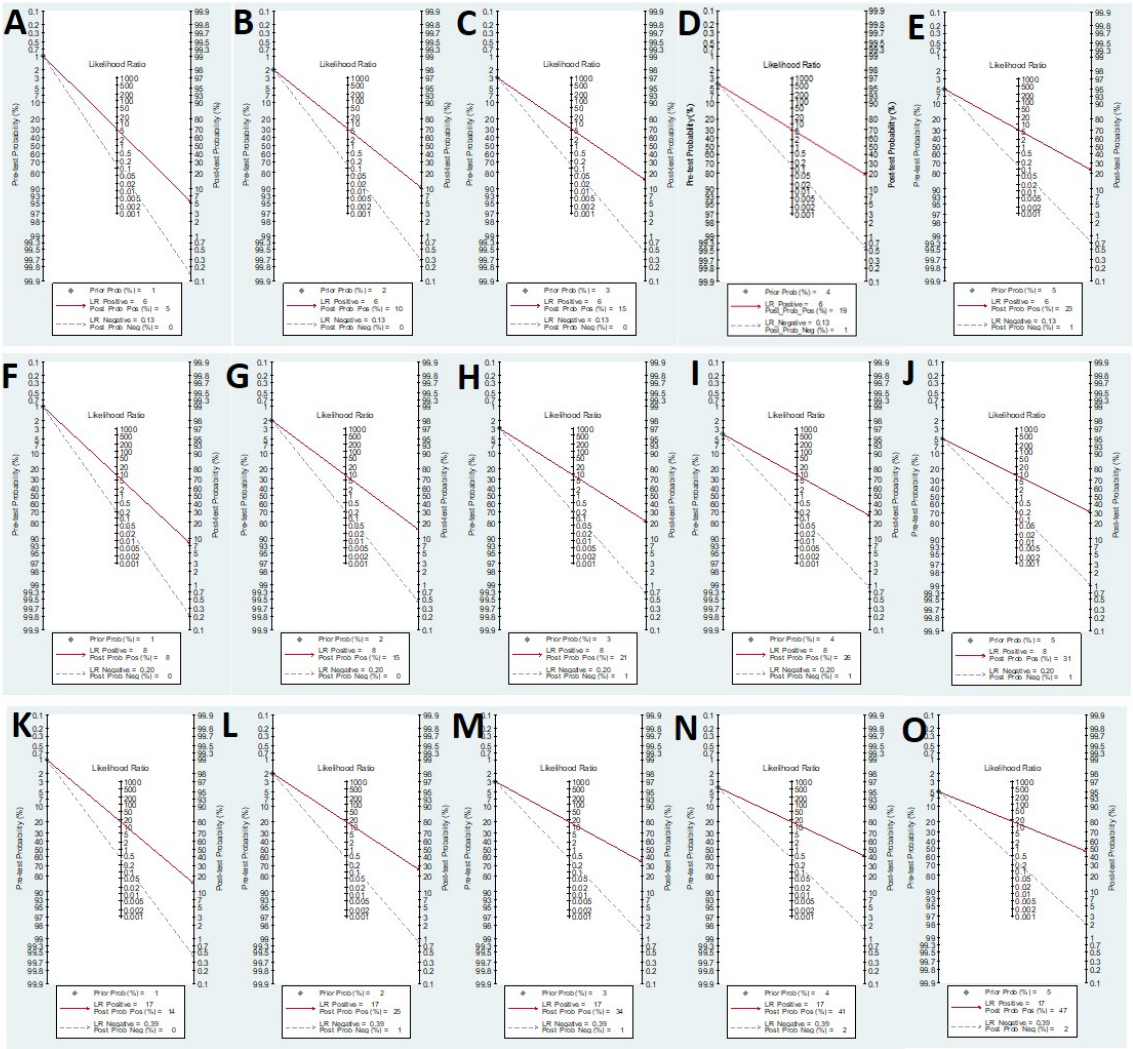
SUPPLEMENTARY FIGURE LEGENDS AND FOOTNOTES

Supplementary Figure 1. Hierarchical summary receiver-operating characteristic curves for colorectal cancer detection by cut-off value using all available studies (*top*) and after removing outliers (*bottom*).



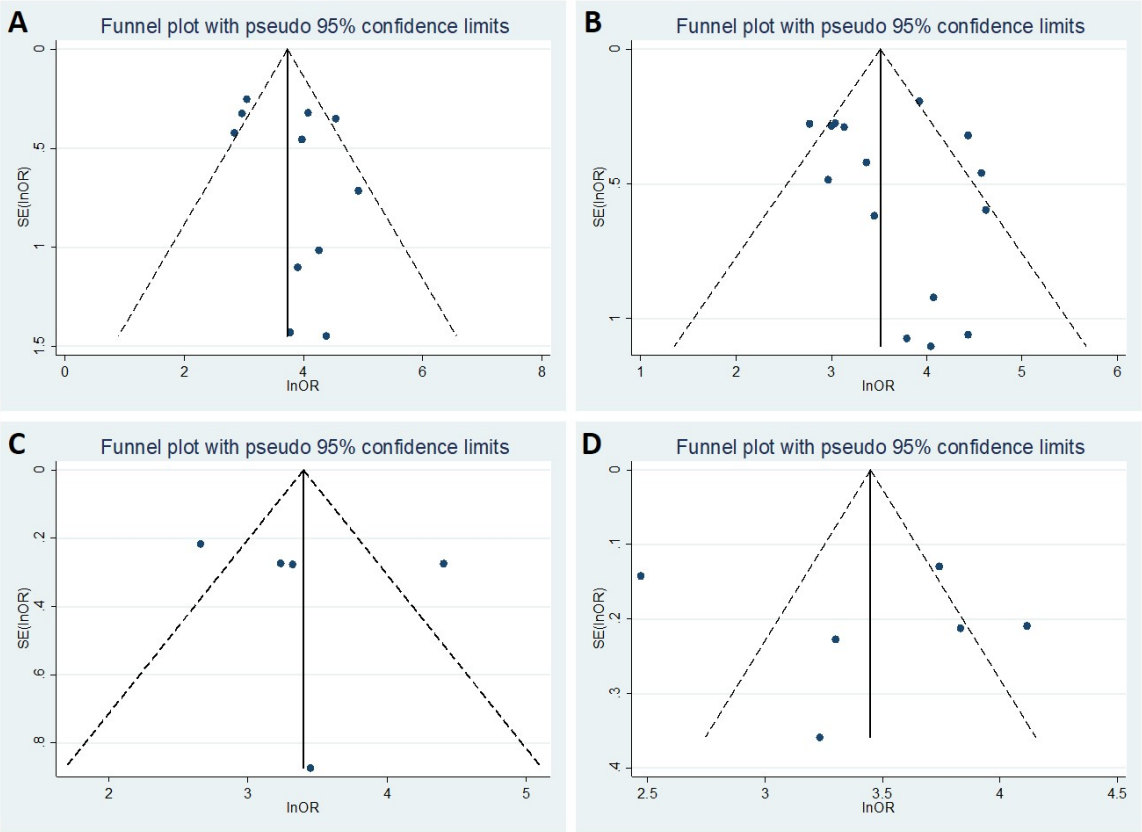
(A & E) cut-off value at limit of detection; (B & F) cut-off value at 10 µg Hb/g faeces; (C & G) cut-off value at 20 µg Hb/g faeces; (D & H) cut-off value at 150 µg Hb/g faeces.

Supplementary Figure 2. Fagan nomograms used to calculate post-test probabilities based on different scenarios defined by colorectal cancer prevalence and faecal immunochemical test cut-off value.



A-E: These scenarios are defined by colorectal cancer prevalence of 1%,2%,3%,4% and 5% respectively and faecal immunochemical test for haemoglobin accuracy at 10 µg Hb/g faeces; H-J: These scenarios are defined by colorectal cancer prevalence of 1%,2%,3%,4% and 5% respectively and faecal immunochemical test for haemoglobin accuracy at 20 µg Hb/g faeces; K-O These scenarios are defined by colorectal cancer prevalence of 1%,2%,3%,4% and 5% respectively and faecal immunochemical test for haemoglobin accuracy at 150 µg Hb/g faeces

Supplementary Figure 3. Funnel scatterplot to evaluate publication bias for studies using different cut-off values to detect colorectal cancer.



Symmetry suggests absence of publication bias. OR diagnostic odds ratio. (A) cut-off value at limit of detection; (B) cut-off value at 10 µg Hb/g faeces; (C) cut-off value at 20 µg Hb/g faeces; (D) cut-off value at 150 µg Hb/g faeces.

Text S1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 & Appendix1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 Figure 1 Appendix 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 Appendix 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 -10 & Table 1 & Supplementary table 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	10 & Figure 2 &
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 & Appendix 3 & Supplementary Table 2 & Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2 & Supplementary Table 2 & Figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA