Faecal Immunochemical Tests For Patients With Symptoms Suggestive Of Colorectal Cancer: A Systematic Review And Multiple-Threshold Meta-Analysis

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Introduction

Faecal immunochemical tests (FITs) detect haemoglobin (Hb) in stool samples, which may be a sign of colorectal cancer (CRC). FITs were recommended in England by the National Institute for Health and Care Excellence (NICE) for use in primary care for patients with low-risk symptoms and signs of CRC (Table 1). However, long waiting lists for colonoscopies were delaying diagnoses. NICE wanted to know if FIT tests could be used in patients with medium and high-risk symptoms to guide referral to secondary care. We conducted a systematic review to identify and synthesise diagnostic test accuracy studies of FIT in primary care patients.

Table 1: NICE's National Guideline 12 (NG12) referral criteria (pre 2023 update)

Low risk symptoms	Medium risk symptoms	High risk symptoms
• aged 50 years and over with unexplained abdominal pain or weight loss, or • aged under 60 with changes in their bowel habit or iron-deficiency anaemia, or • aged 60 and over with anaemia even in the absence of iron deficiency	• under 50 with rectal bleeding and ≥ 1 of: unexplained abdominal pain, change in bowel habit, weight loss or iron deficiency anaemia.	• aged 40+ years with unexplained weight loss and abdominal pain or • aged 50+ with unexplained rectal bleeding or • aged 60+ with iron-deficiency anaemia or changes in their bowel habit, or • tests show occult blood in their faeces.
Give FIT test, if faecal Hb >10µg/g, refer to secondary care	**Consider referral to secondary care**	**Refer to secondary care with an urgent 2 week wait (2WW) referral**

Methods

In December 2022 we searched 10 sources, including Medline, Embase and Cochrane to update an existing review.[1] We checked reference lists and contacted experts to identify any missed studies. We included studies according to the criteria in Table 2. We extracted data and a second reviewer checked the data. The synthesis was conducted using a modelling approach described in Jones *et al.*,[2] where data at multiple thresholds per study are pooled to produce summary sensitivity and specificity curves at all possible thresholds. We selected clinically relevant thresholds to report and convert into referrals and missed diagnoses.

Tests could be used singly (single FIT), or in duplicate (dual FIT), where patient were asked during their initial consultation to do two tests on separate bowel motions. A positive test would be interpreted as either test positive to maximise sensitivity, but this may adversely affect specificity.

Table 2: Review inclusion criteria

Element	Inclusion criteria
Population	People presenting to, or referred from, primary care with symptoms or signs indicating a risk of CRC as per NG12
Intervention	HM-JACKarc; FOB Gold; OC-Sensor; NS Prime; IDK TurbiFIT; IDK Haemoglobin ELISA; IDK Hb/Hp complex ELISA; QuikRead go. Tests used singly (single FIT) or planned use in duplicate (dual FIT).
Reference standard	Colonoscopy or Computed tomography colonography (CTC); Index-test-dependent differential reference standard e.g., imaging for FIT+ and records follow-up for FIT- patients
Outcomes	Test accuracy metrics (sensitivity, specificity, True positive (TP), true negative (TN), false positive (FP), false negative (FN))
Study design	Comparative or non-comparative diagnostic test accuracy studies that avoided a case-control design; English language, or non-English language if sufficient data could be extracted

Results

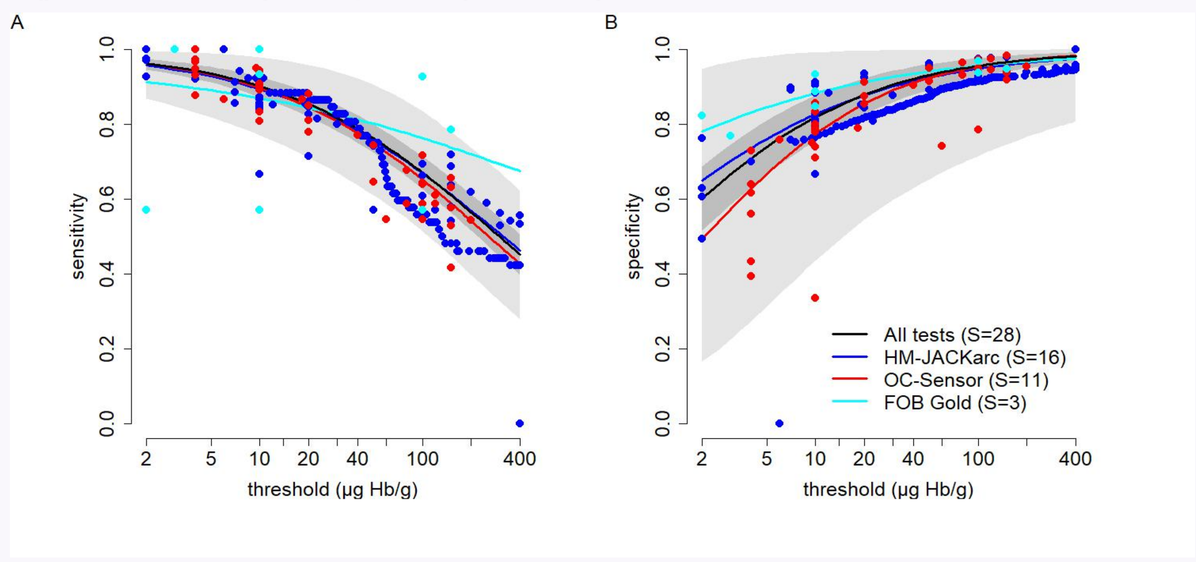
From 2,058 records, we selected 37 studies (46 publications, some contributed only to subgroup and sensitivity analyses). Tests with <2 included studies were not synthesised. For some tests, there were no (IDK TurbiFIT) or only one study (QuikRead go; NS-Prime; IDK Hb, IDK Hb/Hp).

For **single FIT**, the numbers of studies per test that entered the synthesis are indicated in Table 3, along with summary estimates of sensitivity and specificity. Figure 1 shows the synthesised summary curves.

Table 3: Sensitivity and specificity at key thresholds (95% Credible Interval).

Threshold (µg/g)	HM-JACKarc (16 studies)		OC-Sensor (11 studies)		FOB Gold (3 studies)	
	Sens	**Spec**	**Sens**	**Spec**	**Sens**	**Spec**
2	95.9 (92.7, 97.9)	65.1 (55.6, 74.8)	NR	NR	91.4 (71.6, 99.6)	78.1 (70, 86)
4	93.8 (89.8, 96.5)	73.7 (65.1, 82.2)	94.2 (91.2, 96.7)	62.7 (47.4, 77.2)	89.8 (69.8, 99.2)	83.2 (75.6, 90.2)
7	91.4 (86.8, 94.8)	79.6 (71.7, 87.1)	91.8 (88.2, 94.9)	72.3 (58.1, 84.8)	88.2 (68.4, 98.7)	86.5 (79.5, 92.8)
10	89.5 (84.6, 93.4)	82.8 (75.2, 89.6)	89.8 (85.9, 93.3)	77.6 (64.3, 88.6)	87 (67.3, 98.3)	88.4 (81.7, 94.2)
20	84.7 (79.1, 89.6)	87.9 (81.1, 93.4)	84.7 (80.3, 89)	85.6 (74.5, 93.6)	84.5 (65.1, 97.1)	91.3 (85.4, 96.2)
150	61.3 (53.7, 68.9)	96 (91.9, 98.4)	58.9 (53.4, 64.7)	96.7 (91.6, 99.1)	73.9 (53.8, 91.2)	96.4 (92.6, 98.9)

Figure 1: Sensitivity and specificity summary curves



For **dual FIT,** three studies reported data at 10µg/g. Sensitivity was higher compared to single FIT, but specificity was lower.

Table 4: Dual FIT data at a threshold of 10µg/g

	Dual FIT, either test positive			Single FIT		
Test, number of studies	**CRC n/N (%)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**CRC n/N (%)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
HM-JACKarc, n=1 study	88/2637 (3.34)	97 (90 - 99)	71 (69 - 73)	135/3426 (3.94)	93 (88-97)	78 (77-79)
OC-Sensor, n=1 study	317/28,622 (1.11)	98 (96 - 99)	66 (66 - 67)	NA	NR	NR
QuikRead go, n=1 study	13/242 (5.37)	100 (NR)	71 (66–77)	13/242 (5.37)	92 (78 - 100)	77 (72 - 83)

Discussion

Using the HM-JACKarc synthesis data as an example, Table 5 converts sensitivity and specificity into referrals (positive tests (FIT +)) and missed diagnoses (FN) for 1000 patients. Numbers needed to scope (NNS) indicate how many referrals would be needed to identify one case of CRC. Even at the lowest threshold (2µg/g), CRC cases would be missed, but referrals and NNS would be around double those at a threshold of 10µg/g. Using HM-JACKarc data for dual FIT, one case of CRC would still likely be missed per 1000 patients tested, but the NNS increases compared to single FIT, especially if CRC prevalence is low.

Table 5 Referrals, missed diagnoses and numbers needed to scope for 1000 patients

Threshold (µg/g)	FIT + (referral)	FIT – (no referral)	TP	FN (missed diagnoses)	NNS	FIT +	FIT -	TP	FN	NNS
CRC Prevalence	1%					3%				
2	355	645	10	0.4	37	367	633	29	1	13
10	179	821	9	1	20	194	806	27	3	7
20	128	872	8	2	15	143	857	25	5	6
150	46	954	6	4	7	57	943	18	12	3
Dual FIT (10)	297	703	10	0.3	31	310	690	29	1	11

Conclusions

If using a single FIT to guide referral, a threshold of 10µg/g for medium/high-risk patients would align with the threshold used for low-risk patients and would reduce referrals compared to NG12 guidelines. Use of two tests (dual FIT) would increase the NNS and costs but decrease missed diagnoses. However, some cases would likely still be missed. For either single or dual FIT, safeguards (e.g., advice to return, repeat FIT) should be in place for patients with ongoing or worsening symptoms to identify missed diagnoses.

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