

Potential Modifiers and Different Cut-offs in Diagnostic Accuracy of Fecal Immunochemical Test in Detecting Advanced Colon Neoplasia: A Diagnostic Test Accuracy Meta-analysis

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Background:

Fecal immunoglobulin test (FIT) has been advocated as the first line of screening for colorectal cancer (CRC) in several jurisdictions. Most studies have focused on CRC as the outcome of interest. Our goal was to quantify the diagnostic accuracy of different thresholds of FIT as compared with colonoscopy for detection of advanced colonic neoplasia and potential modifiers using proper Cochrane methodology.

Abstract

Methods:

A comprehensive electronic search was performed for studies on FIT using colonoscopy as the reference standard to detect advanced neoplasia. Cochrane methodology was used to perform a diagnostic test accuracy (DTA) metaanalysis. Diagnostic accuracy of different cut-offs of FIT, including 25, 50, 75, 100, 150, and 200 ng/mL, were calculated separately. Meta-regression analysis was also performed to detect potential *a priori* modifiers, including age, location of the tumor, and time from FIT to colonoscopy.

Results:

Twenty-four studies were included with no evidence of publication bias. The sensitivity of FIT did not decrease with lowering the cut-off, although specificity increased in higher cut-offs. Commonly used cut-offs of 50 ng/mL, 75 ng/mL, and 100 ng/mL for FIT provided sensitivity of 39%, 36%, 27% and specificity of 92%, 94%, 96%, respectively. Diagnostic accuracy of FIT did not significantly differ in proximal versus distal lesions or in individuals below or over the age of 50 years. The results remained robust in a meta-regression of the location of the study, time from FIT to colonoscopy, and methodological quality.

Conclusion:

The sensitivity of FIT might have been overestimated in previous studies focusing on CRC, and it seems to be independent of age, location of neoplasia, or cut-offs, contrary to some previous studies. Lowering the cut-off will reduce the diagnostic odds ratio (DOR) by increasing specificity but without any effect on sensitivity.

Keywords:

Colon cancer screening, Fecal immunoglobulin test, Colonoscopy, Meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, and colonoscopy is one of the most accurate and commonly performed screening and preventive methods for CRC.¹ Apart from colonoscopy, fecal immunoglobulin test (FIT) has recently gained popularity, but colonoscopy remains the reference standard to detect CRC and colorectal precancerous polyps and is therefore used in most diagnostic accuracy studies.^{2,3} Despite its widespread use, the utility of colonoscopy is hindered by a sub-optimal participation rate due to the semi-invasive nature of the procedure, risk of potential complications, and higher costs.^{4,5} In contrast to colonoscopy, FIT is less expensive, noninvasive, and does not require bowel preparation, resulting in improved participation.⁶⁻⁸ In addition, FIT has shown a promising 30% diagnostic accuracy for CRC or advanced adenoma (diameter > 1cm or villous/ advanced dysplasia).9 However, FIT has been proved to miss a significant portion of early stage I or distal cancers and precancerous polyps, which could be easily removed in colonoscopy.¹⁰ In 2017, the United States Multi-Society Task Force on Colorectal Cancer recommended colonoscopy every 10 years or annual FIT as first-tier options for screening the average-risk persons for colorectal neoplasia.9 A few groups to date have attempted to perform diagnostic test accuracy (DTA) meta-analysis assessing various cut-offs of FIT using colonoscopy as the reference standard, but the effect of factors such as age, location of the tumor, and the time gap between the FIT and colonoscopy has not yet been defined.¹⁰⁻¹² Most studies have focused on colon cancer and not advanced neoplasia. The advantage of finding advanced adenomas as compared with cancer is a potentially better outcome and avoiding surgical resection and possibly chemotherapy or radiation. Individual studies have shown a lower sensitivity of FIT for proximal and compared to distal lesions and increased sensitivity but decreased specificity by decreasing the cut-off.^{13,14} In this study, we aimed to investigate the role of cut-offs in the accuracy of FIT in detecting advanced neoplasia, including cancer and advanced adenomas, as well as factors that might affect this accuracy, including the location of the tumor and the age of patients.

Materials and Methods

Registration

The study protocol was registered (CRD42020177526) with the international prospective register of systematic reviews (PROSPERO).

Study Selection

We included all studies assessing the diagnostic accuracy of FIT using colonoscopy as the reference standard. Studies with insufficient data, abstracts, pediatric studies, duplicate publications, lack of DTA data, and studies with no reference standards were excluded. No restriction was applied in terms of language, location, or quality of the studies. Two authors (MY and PM) independently screened references and selected studies for inclusion. A third author (YY) assisted with decision-making if there was a conflict.

Search Methods for Identification of Studies

Two individual investigators completed а comprehensive literature search using MEDLINE (Ovid), EMBASE (Ovid), Web of Science, Cochrane Library, and Google Scholar databases up to August 2020. The following search terms were used: colorectal or rectal - neoplasm, cancer, adenocarcinoma, malignancy or tumor, fecal immunochemistry test, FIT, diagnostic accuracy, sensitivity, and specificity. MeSH terms as well as free text words and variations of root words, were searched. No restriction was applied in terms of language and publication year during the literature search. Recursive searching and cross-referencing were carried out by using a "similar articles" function. References of articles identified after the initial search were manually reviewed.

Data Extraction and Management

Two authors (MY and PM) independently extracted data from each included study. A third author (YY) was involved in the event of a conflict. True positive, true negative, false negative, and false positive values were determined for FIT and/or colonoscopy when applicable. All reporting units were converted to ng/ mL for consistency.

Assessment of Methodological Quality

Study quality and risk of bias were assessed by two

independent reviewers (MY and PM) using the Cochrane tool for assessment of the risk of bias according to the recommendation by the Cochrane Collaboration.¹⁵ There are two main categories: risk of bias and applicability. Each category has its own set of assessment domains. Studies without "high risk of bias" in all domains were considered to have low risk of bias. The quality of the body of evidence was assessed by two independent reviewers (MY and PM) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.^{15,16}

Outcome Measures

The main outcome of interest was the DTA of FIT in detecting advanced neoplasia, defined as advanced adenoma or cancer in different cut-offs. Secondary objectives were to identify the diagnostic accuracy of FIT in proximal versus distal lesions as well as in individuals under 50 as compared with those over 50 years old.

Statistical Analysis and Data Synthesis

We reported pooled sensitivities and specificities, diagnostic odds ratio (DOR) and area under the curve (AUC), 95% confidence intervals where appropriate, alongside positive and negative likelihood ratio forest plots and receiver operating characteristic (ROC) curves. We used RevMan version 5.4 to create forest plots and risk of bias graphs. We computed the pooled diagnostic accuracy (sensitivity, specificity, DOR) using the midas command in STATA version 16.0 using a bivariate mixed-effects regression framework. Model fit was assessed by examining goodness of fit, bivariate normality, and outlier effects using the modchk command. Publication bias was evaluated using Deek's funnel plot test (pubbias command). The proportion of heterogeneity likely due to cutoff effects was computed since the univariate tests for heterogeneity do not account for heterogeneity explained by positivity cut-off effects. Given that there were different thresholds in our variation, we visually inspected the degree to which the observed study results lied close to the summary ROC curve as depicted graphically.15

We conducted sensitivity analyses using univariable meta-regression approaches and the *reg* command.

A random effect model was used in DTA meta.¹⁰ GRADEpro guideline development tool by McMaster University was used to assess the level of evidence.

Results

Literature Search

A total of 24 out of a total of 1722 records were included in the DTA meta-analysis. These studies were published between 2005 and 2018. Eleven studies were from Asia and 13 from the rest of the world. All studies defined advanced neoplasia as the total number of advanced adenoma and cancer. Figure 1 depicts the PRISMA flowchart for the detail of study selection, and Table 1 shows the characteristics of included studies. The risk of bias using the Cochrane tool in included studies is represented in Figures 2 and 3.

Cut-off Effect on Diagnostic Accuracy of FIT

Table 2 depicts the detail of the analysis of diagnostic accuracy of different cut-offs of FIT by considering colonoscopy as the reference standard. Diagnostic accuracy and specificity numerically increased by increasing the cut-off for FIT positivity, but the sensitivity did not follow any pattern (Table 2). Figure 4 depicts the SROC across different thresholds of FIT. The Forest plot for sensitivity and specificity of FIT across different cut-offs is presented in Figure 5.

Test for Publication Bias

There was no prominent visual asymmetry in the Deek's funnel plot for DORs, and the Deek's Funnel plot asymmetry test showed no significant publication bias (P=0.31).

Subgroup and Sensitivity Analyses for Diagnostic Accuracy of FIT

Effect of Location of Neoplasia in Diagnostic Accuracy of FIT

The sensitivity and specificity of FIT were 31% (26-36%) and 95% (94-96%), respectively, for distal lesions and 20% (13-27%) and 95% (94-96%), respectively, for proximal lesions. The joint model did not show a significant difference in diagnostic accuracy of FIT in detecting proximal versus distal lesions (P=0.16) in three studies, including 47688 patients reporting extractable information for this analysis.



Figure 1. PRISMA study flow diagram for inclusion of eligible studies

Effect of Age on Diagnostic Accuracy of FIT

The sensitivity and specificity of FIT were 18% (3-33%) and 97% (96-98%), respectively in those older than 50 as compared to 10% (1-19) and 98% (97-99%), respectively, for those under 50. The joint model did not show a significant difference in diagnostic accuracy of FIT in patients over and under 50 (P=0.47) in four studies, including 36,755 patients reporting extractable information for this analysis.

Meta-regression Analysis

Meta-regression analysis did not show any significant predictability for the location of the study (Asian versus non-Asian, P=0.06), the inclusion of patients with unclear or high risk (P=0.14), time gap from FIT to colonoscopy (P=0.09) and risk of bias (high or unclear as compared to low) criteria in diagnostic accuracy of FIT (P=0.82)

Heterogeneity

The visual assessment showed a low to moderate amount of heterogeneity in SROC. Further analysis showed that studies avoiding inappropriate exclusion, as compared to those which did not, showed a numerically higher diagnostic accuracy in all cut-offs of FIT.

Assessment of Quality of Body of Evidence

The quality of evidence was evaluated as low to moderate due to imprecision and indirectness.

Discussion

In this study, we showed that higher cut-offs of FIT increased specificity and positive likelihood ratio while sensitivity and negative likelihood ratio did not show a predictable pattern. Furthermore, we demonstrated

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Study	Design	Year of publication	Country of origin	Study population	Study objective	Time between FIT and colonoscopy (days)	Bowel preparation	Age range	Sample size	Number of adenoma	Number of advanced neoplasia	Advanced non- cancerous neoplasia	Cancer
Ou ³²	Multicenter cross-sectional	2013	Taiwan	Average risk	Optimal FIT cut-off	Unclear	Not available	Median: 59.5	669	133	37	34	3
Park ³³	Multicenter cross-sectional	2010	South Korea	Average-risk	Accuracy of FOBT vs. FIT	7	Not available	50-75	770	Not available	72	59	13
Parra-Blanco ³⁴	Randomized sampling	2010	Spain	Average risk	Accuracy of FOBT vs. FIT	Unclear	Not available	50-79	1756	Not available	63	49	14
Rozen ³⁵	Multicenter cross-sectional	2009	Israel	Average and non-average	Accuracy of FOBT vs. FIT	Unclear	Not available	50-75	330	Not available	32	26	6
Shapiro ³⁶	Multicenter cross-sectional RCT	2018	NSA	Average-risk	Accuracy of FOBT vs FIT	100	Not available	50-75	1095	Not available	55	53	2
Siripongpreeda ³⁷	⁷ Unicenter cross-sectional	2016	Thailand	Average risk	Accuracy of FIT	Unclear	Pico-Salax	50-65	1404	277	116	98	18
Sohn ³⁸	Unicenter cross-sectional	2005	South Korea	Average risk versus CRC	Accuracy of FIT	Unclear	Not available	15-78	3794	613	79	67	12
Terhaar ³⁹	Multicenter cross-sectional	2011	The Netherlands	Average and non-average risk	Accuracy of FIT	1	Not available	40-89	2145	Not available	315	236	79
Wong ⁴⁰	Multicenter cross-sectional	2012	Canada	Average risk, including FH	Accuracy of FOBT versus FIT	10	Polyethylene glycol 4L	40-75	1075	252	69	67	2

that the sensitivity and specificity of FIT for advanced neoplasia were not significantly affected by age or location of the lesion, and they might be lower than presented in previous studies, given that most studies used CRC as the outcome of interest.

To our knowledge, there are a few ongoing RCTs comparing screening colonoscopy and FIT in longitudinal observational studies.41-43 The interim result of one study on 26703 individuals who were invited to have a screening colonoscopy and 26599 to have biennial FIT showed that participation was higher in the FIT arm (34.2% vs. 24.6%).⁴¹ Advanced neoplasia detection was higher in individuals randomized to colonoscopy (1.9% vs. 0.9%). Another US study compared participation with a no-cost FIT and no-cost screening colonoscopy in an uninsured US population and showed higher participation with FIT (40.7% versus 24.6%) with no difference in cancer detection (0.4%)vs. 0.4%) although advanced neoplasia detection was higher with colonoscopy (1.3%) as compared to FIT (0.8%).⁴⁴ One should note that diagnosis of advanced adenoma has potential advantages to the diagnosis of CRC in avoiding the need for an extensive colorectal resection and/or chemoradiation therapy.

Recommendations on using FIT as the first option for screening for CRC for the average-risk population are mainly based on financial advantage and ease of access rather than robust diagnostic accuracy. Most of the guidelines have quoted sensitivity of around 60% for FIT as compared to 27-48% in the analysis of different cut-offs of FIT in our study.⁴⁵ This warrants a new cost-effectiveness analysis to see if the policies need to be revised.

Currently, most people undergo colonoscopy as the screening method of choice in the United States.⁴⁶ Different estimates of sensitivity and specificity of FIT up to 0.79 and 0.94, respectively have been reported.⁴⁷ Based on these values, many jurisdictions employed FIT as the preferred screening method as its cost was significantly lower than colonoscopy, however, later studies showed lower values.¹¹ Therefore, FIT may not be a screening tool as desirable as it was previously assumed.

In our study, we did not find a significant difference in diagnostic accuracy of FIT above and under the age of 50. Previous studies reported a higher detection rate for



Figure 2. Cochrane risk of bias assessment of each included study



Figure 3. Cochrane risk of bias assessment presented as a percentage across all studies

Table 2. Di	agnostic	test accuracy of F	IT for most used o	cut-off			
Cut-off	Number of studies	Sensitivity	Specificity	Area under curve	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio
25 ng/mL	6	0.48 (0.37-0.59)	0.84 (0.73-0.91)	0.69 (0.65-0.73)	3.0 (2.1-4.3)	0.62 (0.54-0.71)	5 (4-7)
50 ng/mL	17	0.35 (0.30-0.42)	0.93 (0.91-0.94)	0.78 (0.74-0.81)	4.8 (3.8-6.0)	0.70 (0.64-0.76)	7 (5-9)
75 ng/mL	10	0.36 (0.29-0.43)	0.94 (0.92-0.96)	0.79 (0.75-0.82)	5.9 (4.5-7.8)	0.69 (0.62-0.76)	9 (6-12)
100 ng/mL	15	0.27 (0.20-0.34)	0.96 (0.95-0.97)	0.85 (0.82-0.88)	7.1 (6.0-8.5)	0.76 (0.70-0.83)	9 (8-12)
150 ng/mL	9	0.29 (0.21-0.39)	0.96 (0.96-0.97)	0.92 (0.89-0.94)	7.9 (6.7-9.4)	0.72 (0.65-0.82)	10.9 (8.3-14.2)
200 ng/mL	5	0.37 (0.30-0.46)	0.96 (0.95-0.97)	0.87 (0.84-0.90)	10.0 (7.8-12.9)	0.65 (0.58- 0.73)	15 (12-21)

1 0.9 0.8 0.7 0.6 Ainti 20.5 28 0.4 0.3 0.2 0.1 0 0.9 0.2 0.1 0.8 0.3 0.7 0.6 0.5 Specificity 0.4 Legend ● FIT25 FIT50 FIT75 ● FIT100 ● FIT150 ● FIT200

Figure 4. Summary receiver operating characteristic curve (SROC) of diagnostic accuracy of colonoscopy and different cutoffs of FIT

advanced adenoma or cancer in older individuals,⁴⁸ but one should note that the detection rate is independent of the diagnostic accuracy and is more a representation of prevalence, which is expectedly higher in the older individuals.

Our study showed that commonly used cut-offs of 50, 100, and 150 ng/mL for FIT provide very modest sensitivity for detecting advanced neoplasia of under 39%, 27%, and 29%, respectively, when providing an

acceptable specificity, albeit still not as accurate as colonoscopy. A cost-effective analysis using this data will shed some light on whether using FIT is within the acceptable framework in each jurisdiction. Our results are also in accordance with the findings of a recent study which showed that reducing the cut-off of FIT will not improve the accuracy of the test.⁴⁵ This will also answer an important question on this topic since each jurisdiction chooses its own cut-off. Based

Study	т	P FP	FN	TN Sen	sitivity (95	% CI) Spe	ecificity (95% CI)	Sensitivity (95% CI) Specificity (9	5% CI)
Aniwan 2017	93	519	37 €	670 Q	.72 [0.63, (0.79] (.56 [0.53, 0.59]	- -	,
Hundt 2009	- 56	213	79 11	129 0	.42 [0.34, (0.51] (.84 [0.82, 0.86]		
Khalid-de Bakker 2011	11	15	27 2	286 0).29 [0.15, (0.46] (0.95 [0.92, 0.97]	_ _	. *
Omata 2011 Ou 2013	21	63	35 / 16 /	/61 U).51 (U.39, 4)57 (N 39 (0.63] (1731 ().77 [U.74, U.60]) 89 [0 86 0 91]		- e -
Wong 2012	33	124	36 6	382 0	.48 [0.36, (0.60] (.88 [0.85, 0.90]		
FITSO								0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6	0.8 1
Study		FP F	P FN	1 TN	Sensitivit	y (95% Cl) Specificity (95% CI)	Sensitivity (95% CI) Specificity (9	5% CI)
Chang 2017	11	0 111	3 229	4746	0.32 [0	.24, 0.41	1 0.81 [0.80, 0.92]		- C.
Chen 2014	5	6 17	3 198	5669	0.22 [0	.17, 0.28	0.97 [0.97, 0.97]	+	
Chiu 2016		6 43	7 108	3278	0.38 [0	.31, 0.46	0.86 [0.87, 0.89]	-	•
Hernandez 2014 Hundt 2009	3	14 3 13 4	3 63	649	0.35[0	18 0 34	0.95 [0.93, 0.97]		- 21
Khalid-de Bakker 2011		6 3	2 10	281	0.38 [0	.15, 0.65	0.90 [0.86, 0.93]		
Lies 2016	4	8 16	1 163	2389	0.23 0	.17, 0.29	0.94 [0.93, 0.95]	+	
Morikawa 2005	19	7 103	3 530	20045	0.27 [0	.24, 0.30	0.95 [0.95, 0.95]	• •	- 1 -1
Omata 2011 Oprt 2011	5	10 10 10 11	2 40	604 844	0.35 [0	.24, 0.47	1 0.87 (0.85, 0.89) 1 0.88 (0.86, 0.90)		- 24
Park 2010	3	8 7	1 34	627	0.53 [0	.41, 0.65	0.90 [0.87, 0.92]		
Parrablanco 2010	3	6 1	7 25	322	0.60 [0	.47, 0.72	0.95 [0.92, 0.97]		
Rozen 2009 Sistemania 2016	1	7 1	6 15 5 05	280	0.53 [0	.35, 0.71	0.94 [0.91, 0.96]		- 1
Terhaar 2010	17	0 18	5 93 5 0	1646	i 0.14 [0	.98, 0.22	0.90 [0.95, 0.97]		- e -
Wijkerslooth 2012	4	5 8	0 74	1057	0.38 [0	.29, 0.47	0.93 [0.91, 0.94]	····	
FIT75								0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6	0.8 1
Churchen =	'n					-	G-1 (0.52) CP	Constatutes (Orac on a life to the	F0/ 61
Study I	Р 6 (FP FP 37 17	1 10	Sensit	111111 (95% (21015 05	al OR	FICITY (95% CI)	Sensitivity (95% CI) Specificity (9	5% CI)
Hernandez 2014 3	2 2	29 64	653	0.3	2 [0.15, 0.5 3 [0.24, 0.4	4) 0.8 31 0.9	6 (0.94, 0.97)		· •
Omata 2011 1	6 i	81 59	933	0.2	3 [0.13, 0.3	4] 0.9	2 [0.90, 0.94]		
Oort 2011 5	7 1	91 67	866	i 0.4	6 [0.37, 0.5	5] 0.9	0 [0.88, 0.92]		
Park 2010 2 Rozen 2009 1	4 ; 6 ·	57 40 13 14	6 661 285	L 0.3) E 0.5/	3 [0.23, 0.4 0 10 32 0 6	5] 0.9 81 0.0	5 [0.93, 0.96] 6 [0.93, 0.98]		
Shapiro 2018	8 2	20 49	874	0.1	5 [0.07, 0.2	6] 0.9	6 [0.97, 0.99]		
Terhaar 2010 16	4 14	43 151	1687	0.5	2 [0.46, 0.5	6] 0.9	2 [0.91, 0.93]	-	
Wijkerskooth 2012 3 Wong 2012 2	94 61	45 BL 68 43) 1092 936	2 0.3	3 (V.24, V.4 8 (0.26, 0.5	2] U.9 0] 0.9	6 [0.95, 0.97] 3 [0.92, 0.95]		
EIT100	•				• [••] •-•	•, •	- []]	0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6	0.8 1
FILTO0									
Study	ТР	FP	FN	TN S	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017	ТР 31 71	FP 76 1113	FN 106 268	TN 5 1266 4746	Sensitivity (0.23 [0.1 0.21 [0.1	(95% CI) 6, 0.31] 7. 0.26]	Specificity (95% CI) 0.94 [0.93, 0.96] 0.61 [0.60, 0.62]	Sensitivity (95% CI) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009	ТР 31 71 0	FP 76 1113 0	FN 106 268 0	TN 5 1266 4746 0	Sensitivity (0.23 [0.1 0.21 [0.1 Not e:	(95% CI) 6, 0.31] 7, 0.26] stimable	Specificity (95% CI) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable	Sensitivity (95% Cl) Specificity (9 -	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014	TP 31 71 0 31	FP 76 1113 0 24	FN 106 268 0 66	TN 5 1266 4746 0 658	Sensitivity (0.23 [0.1 0.21 [0.1 Not e: 0.32 [0.2	(95% Cl) 6, 0.31] 7, 0.26] stimable 3, 0.42]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98]	Sensitivity (95% Cl) Specificity (9 	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016	TP 31 71 0 31 226 93	FP 76 1113 0 24 468 816	FN 106 268 0 66 594 371	TN 5 1266 4746 0 658 8699 25136	Sensitivity (0.23 [0.1 0.21 [0.1 Not e: 0.32 [0.2 0.28 [0.2 0.20 [0.1]	(95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.97, 0.97]	Sensitivity (95% Cl) Specificity (9 	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018	TP 31 71 31 226 93 30	FP 76 1113 0 24 468 816 87	FN 106 268 0 66 594 371 181	TN 5 1266 4746 0 658 8699 25136 2463	Sensitivity (0.23 [0.1 0.21 [0.1 Not e: 0.32 [0.2 0.28 [0.2 0.20 [0.1 0.14 [0.1	(95% Cl) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.97, 0.97] 0.97 [0.96, 0.97]	Sensitivity (95% Cl) Specificity (9 	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011	TP 31 71 228 93 30 16	FP 76 1113 0 24 468 816 87 61	FN 106 268 0 66 594 371 181 55	TN 1266 4746 0 658 8699 25136 2463 953	Sensitivity (0.23 [0.1 0.21 [0.1 0.32 [0.2 0.28 [0.2 0.20 [0.1 0.14 [0.1 0.23 [0.1	(95% Cl) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95]	Sensitivity (95% Cl) Specificity (9 	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Omt 2011 Back 2010	TP 31 71 228 93 30 16 56	FP 76 1113 0 24 468 816 87 61 72	FN 106 268 0 66 594 371 181 55 68 49	TN 5 1266 4746 658 8699 25136 2463 953 885 664	Sensitivity (0.23 [0.1 0.21 [0.1 0.32 [0.2 0.28 [0.2 0.20 [0.1 0.14 [0.1 0.23 [0.1 0.23 [0.2 0.20 [0.2	(95% Cl) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.94 0.92]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Oort 2011 Park 2010 Rozen 2009	TP 31 71 228 93 30 16 56 23 15	FP 76 1113 0 24 468 816 87 61 72 34 8	FN 106 268 0 66 594 371 181 55 68 49 17	TN 2 1266 4746 0 658 8699 25136 2463 953 885 664 290	Sensitivity (0.23 [0.1 0.21 [0.1 Note: 0.32 [0.2 0.20 [0.1 0.14 [0.1 0.23 [0.1 0.45 [0.3 0.32 [0.2 0.47 [0.2	(95% Cl) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 6, 0.54] 9, 0.65]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.97 [0.95, 0.99]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2016 Omata 2011 Oort 2011 Park 2010 Rozen 2009 Siripongpreeda 2016	TP 31 71 228 93 30 16 56 23 15 60	FP 76 1113 0 24 468 816 87 61 72 34 8 24	FN 106 268 0 66 594 371 55 68 49 17 371	TN 3 1266 4746 0 658 8699 25136 2463 953 885 664 290 1672	Sensitivity (0.23 [0.1 0.21 [0.1 Not e: 0.28 [0.2 0.28 [0.2 0.20 [0.1 0.14 [0.1 0.23 [0.1 0.45 [0.3 0.32 [0.2 0.47 [0.2 0.14 [0.1	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.46] 9, 0.65] 1, 0.18]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.99 [0.98, 0.99]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Oort 2011 Park 2010 Rozen 2009 Siripongpreeda 2016 Sohn 2005	TP 31 71 228 93 30 16 56 23 15 60	FP 76 1113 468 816 87 61 72 34 8 24 38	FN 106 268 0 66 594 371 181 55 68 49 17 371 546	TN 2 1266 4746 0 658 8699 25136 2463 953 885 664 290 1672 3128	Sensitivity (0.23 [0.1 0.21 [0.1 Note: 0.32 [0.2 0.28 [0.2 0.20 [0.1 0.14 [0.1 0.45 [0.3 0.32 [0.2 0.47 [0.2 0.47 [0.2 0.14 [0.1 0.16 [0.0 0.6 5 5 5 5	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.44] 9, 0.65] 1, 0.16] 8, 0.13]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.97, 0.97] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.97 [0.96, 0.99] 0.99 [0.98, 0.99] 0.99 [0.98, 0.99]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2016 Omata 2011 Oont 2011 Park 2010 Rozen 2009 Siripongpreeda 2016 Sohn 2005 Terhaar 2010 Wilkersboth 2012	TP 31 71 226 93 30 16 56 23 15 60 61 159 37	FP 76 1113 0 24 468 816 87 61 72 34 8 24 38 119 34	FN 106 268 66 594 371 55 68 49 17 371 546 156 82	TN 2 1266 4746 0 658 8699 25136 2463 953 885 664 290 1672 3128 1711 1103	Sensitivity (0.23 [0.1: 0.21 [0.1] Note: 0.32 [0.2 0.28 [0.2 0.28 [0.2 0.28 [0.2 0.23 [0.1] 0.32 [0.2 0.32 [0.2 0.47 [0.2 0.47 [0.2 0.47 [0.2 0.40 [0.1] 0.14 [0.1] 0.14 [0.1] 0.14 [0.1] 0.14 [0.1] 0.14 [0.1] 0.14 [0.1]	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.44] 9, 0.65] 1, 0.18] 6, 0.13] 5, 0.56] 3, 0.40]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.97, 0.97] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.95 [0.93, 0.97] 0.95 [0.93, 0.97] 0.99 [0.96, 0.99] 0.99 [0.96, 0.99] 0.93 [0.92, 0.95] 0.97 [0.96, 0.95] 0.93 [0.92, 0.95] 0.93 [0.92, 0.95] 0.94 [0.96, 0.95] 0.95 [0.96, 0.	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Oort 2011 Park 2010 Rozen 2009 Sirlpongpreeda 2016 Sohn 2005 Terhaar 2010 Wijkerskooth 2012 Wong 2012	TP 31 71 228 93 30 16 56 60 61 159 37 22	FP 76 1113 0 24 468 816 816 61 72 34 8 24 38 24 38 119 34 46	FN 106 268 0 594 371 55 68 49 17 371 546 156 82 47	TN 5 1266 4746 0 658 8699 25136 2463 953 885 2463 953 885 2463 953 864 290 1672 3128 1711 1103 960	Sensitivity (0.23 (0.1 0.21 (0.1 Note: 0.32 (0.2 0.28 (0.2 0.20 (0.1) 0.28 (0.2 0.20 (0.1) 0.45 (0.3 0.45 (0.3 0.45 (0.3 0.45 (0.3 0.45 (0.1) 0.45 (0.1) 0.45 (0.1) 0.14 (0.1)	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.44] 9, 0.65] 1, 0.16] 8, 0.13] 5, 0.56] 3, 0.40] 1, 0.44]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.97, 0.97] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.99 [0.96, 0.99] 0.99 [0.96, 0.99] 0.99 [0.96, 0.99] 0.93 [0.92, 0.95] 0.97 [0.96, 0.98]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Oort 2011 Park 2010 Rozen 2009 Siripongpreeda 2016 Sohn 2005 Terhaar 2010 Wijkersboth 2012 Wong 2012 FIT150	TP 31 71 226 93 30 16 56 61 159 37 22	FP 76 1113 0 24 468 816 87 61 72 34 8 24 38 24 38 119 34 46	FN 106 268 0 66 594 371 55 68 49 371 546 156 82 47	TN 2 1266 4746 058 8699 25136 2463 953 885 664 290 1672 3128 1711 1103 960	Sensitivity (0.23 [0.1 Note: 0.32 [0.2 0.28 [0.2 0.28 [0.2 0.20 [0.1 0.42 [0.1 0.42 [0.1 0.42 [0.1 0.42 [0.1 0.42 [0.1 0.47 [0.2 0.47 [0.1 0.47 [0.2 0.47 [0.2 0.47 [0.1 0.47 [0.1 0.47 [0.1 0.47 [0.2 0.47 [0.1 0.47 [0.1] [0.2 0.47 [0.2] [0.1 0.47 [0.1] [0.2 0.47 [0.2] [0.2] [0.2 0.47 [0.2] [0.2] [0.2 0.47 [0.2]	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.44] 9, 0.65] 1, 0.18] 6, 0.13] 5, 0.56] 3, 0.40] 1, 0.44]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.97 [0.96, 0.99] 0.99 [0.96, 0.99] 0.99 [0.96, 0.99] 0.97 [0.96, 0.98] 0.95 [0.94, 0.97]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Oort 2011 Park 2010 Rozen 2009 Siripongpreeda 2016 Sohn 2005 Terhaar 2010 Wijkerskooth 2012 Wong 2012 FIT150	TP 31 71 228 93 30 16 56 23 15 60 61 159 37 22	FP 76 1113 0 24 466 816 87 61 72 34 8 24 38 119 34 46	FN 106 268 0 594 371 55 68 49 17 371 546 156 82 47	TN 2 1266 4746 0 658 8699 25136 2463 953 885 685 685 685 1672 3128 1711 1103 960	Sensitivity (0.23 (0.1 0.21 (0.1 Note: 0.32 (0.2 0.28 (0.2 0.28 (0.2 0.20 (0.1 0.4 (0.1) 0.4 (0.1) 0.4 (0.1) 0.32 (0.2 0.47 (0.2 0.47 (0.2 0.47 (0.2 0.47 (0.2 0.47 (0.2 0.32 (0.2 0.32 (0.2 0.32 (0.2) 0.50 (0.4)	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.44] 9, 0.65] 1, 0.18] 8, 0.13] 5, 0.56] 3, 0.40] 1, 0.44]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.94 [0.92, 0.95] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.99 [0.98, 0.99] 0.99 [0.98, 0.99] 0.93 [0.92, 0.95] 0.97 [0.96, 0.98] 0.93 [0.92, 0.95] 0.95 [0.94, 0.97]	Sensitivity (95% Cl) Specificity (9	5% CI)
Study Aniwan 2017 Chang 2017 Graser 2009 Hernandez 2014 Imperiale 2014 Kim 2016 Liles 2018 Omata 2011 Oort 2011 Park 2010 Rozen 2009 Siripongpreeda 2016 Sohn 2005 Terhaar 2010 Wijkerslooth 2012 Wong 2012 FIT150 Study TF Aniwan 2017 24	TP 31 71 228 93 30 16 56 61 159 37 22 FP 64	FP 76 1113 0 24 468 816 87 61 72 34 8 24 38 119 34 46 FN 113	FN 106 268 0 66 594 371 181 55 68 49 171 546 156 82 47 TN 1278	TN 2 1266 4746 0 658 8699 25136 2463 953 885 685 685 685 685 1672 3128 1711 1103 960 Sensitiv 0.18	Sensitivity (0.23 [0.1 0.21 [0.1 Note: 0.32 [0.2 0.28 [0.2 0.28 [0.2 0.28 [0.2 0.20 [0.1 0.4 [0.1 0.4 [0.1 0.14 [0.1 0.32 [0.2 0.47 [0.2 0.47 [0.2 0.47 [0.2 0.47 [0.2 0.32 [0.2 0.32 [0.2 0.50 [0.4 0.50 [0.4 0.5 0.50 [0.4 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	95% CI) 6, 0.31] 7, 0.26] stimable 3, 0.42] 5, 0.31] 6, 0.24] 0, 0.20] 3, 0.34] 6, 0.54] 1, 0.44] 9, 0.65] 1, 0.18] 5, 0.56] 3, 0.40] 1, 0.44]	Specificity (95% Cl) 0.94 [0.93, 0.96] 0.81 [0.80, 0.82] Not estimable 0.96 [0.95, 0.98] 0.95 [0.94, 0.95] 0.97 [0.96, 0.97] 0.97 [0.96, 0.97] 0.92 [0.91, 0.94] 0.95 [0.93, 0.97] 0.97 [0.96, 0.99] 0.99 [0.96, 0.99] 0.99 [0.96, 0.99] 0.99 [0.96, 0.99] 0.95 [0.94, 0.97] ity (95% Cl) 0.94, 0.96]	Sensitivity (95% CI) Specificity (9	5% CI) 0.8 1 5% CI)
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Figure 5. Forest plot for diagnostic accuracy of FIT at various cut-offs

on this data, it might be reasonable to increase the cutoff to achieve higher specificity without sacrificing sensitivity. Previous studies have shown that the diagnostic accuracy of FIT may not simply follow the common sense. For instance, one might expect higher sensitivity of FIT in more advanced stages of CRC; however, Niedermaier et al showed that the sensitivity of FIT is unrelated to the stage of cancer and may even decrease in higher stages, likely due to anemia caused by the tumor. They also showed that although sensitivity is decreasing by rising the cut-off in T1 tumors, such a relation was not true for higherstage tumors.¹⁰ This might support the overall lack of relationship between the cut-off and sensitivity of FIT in our study. Future studies may focus on the different diagnostic accuracy of FIT in different stages of a polyp or cancer and identify pitfalls where further optimization might be required.

One of the limitations of this study was the crosssectional method in all included studies. Most authorities recommend biennial FIT screening as compared to one in ten years frequency of colonoscopy. One might expect higher overall diagnostic accuracy for FIT in 10 years as compared to what is shown in our study based on one test. Once again, it should be noted that the lesions which are missed in the initial test as false negative and are found in the subsequent screening will likely be of higher grade and require a more advanced therapeutic modality. Moreover, there is no evidence that adding more tests in upcoming years will necessarily increase diagnostic accuracy, given the absence of long-term studies and the fact that the number of false positives and false negative results will also increase over time. As an example, if we consider the sensitivity and specificity of 0.35 and 0.93, respectively, for FIT50 achieved in our study, 24% of the average risk population screened by FIT, including all true and false positives, will require a colonoscopy in the first year. All other individuals with true and false negative results will have a FIT test in 2 years, and if the diagnostic accuracy of FIT50 remains the same, another 22% (previous false negatives and new true and false positives) will require colonoscopy. In this example, a total of 46% of the initial population required a colonoscopy just in 2 years, and this will incrementally increase up to 10 years. Therefore,

it should be noted that FIT is only cost-effective and ethically permitted if provided a certain level of diagnostic accuracy, and therefore more accurate modeling and prediction will shed more light on this aspect of the applicability of FIT.

One of the *a priori* sources of heterogeneity in our study was the variety of FIT tests across different trials, geographical and ethnic disparity, different demographics of included cases, and variation in methodology. A meta-regression analysis did not show any significant impact by location of the study, patient's risk of developing CRC, time gap from FIT to colonoscopy, and the quality of methodology, and the results remained robust after excluding the role of these potential factors. Furthermore, the possibility of publication bias was ruled out by using a proper statistical method. Lastly, our study was limited by the limited sample size due to the cost and complexity associated with performing a DTA study using additional reference standards to colonoscopy alone.

We found that the accuracy of FIT was not different in detecting proximal versus distal lesions. This has been a controversial topic, and although some studies showed less sensitivity for more proximal lesions, others failed to show so.^{13,14} The study by Kim et al also showed that lowering the cut-off of FIT did not change the accuracy for proximal lesions.¹³ One major reason might be that some studies looked at the sensitivity as compared to overall diagnostic accuracy.

Although screening colonoscopy has the potential to be a cost-effective form of CRC screening, although it requires a large number of precipitants, non-invasive screening strategies can also be cost-effective.46 Studies on FIT which used almost similar sensitivity to our results, have shown colonoscopy to be more cost-effective than FIT in screening for CRCs.47 However, another study assuming a sensitivity of 35% for FIT did show similar cost-effectiveness for the two strategies.⁴⁹ Another study reached the same conclusion using a sensitivity of 42% for detection of advanced adenoma for FIT.50 Therefore, it seems that the relative cost-effectiveness of two tests can be changed based on which number is quoted, and this may have led to different jurisdictions recommending different screening modalities.

Some investigators have described better compliance

with FIT as an advantage as compared to colonoscopy, although this remains controversial. A recent large randomized controlled trial in the United States comparing FIT versus colonoscopy outreach invited 2400 individuals aged 50-64 years in each group to attend the screening program, and they showed that 38.4% of the target population completed screening in the colonoscopy outreach group as compared to 28.0% in the FIT outreach group (P < 0.001).⁵¹

On the other hand, multiple studies have shown higher sensitivity of FIT for CRC and much lower sensitivity for the detection of advanced adenoma.⁴¹⁻⁴³ One should consider major comorbidities and mortality due to late or even early diagnosis of CRC as compared to adenoma since an adenoma is usually treated by an endoscopic resection without the need for surgical intervention and/or chemotherapy or radiation and basically replaces a preventive measure by a therapeutic measure. Also, it is likely less complicated to remove a small polyp at an earlier age rather than waiting till a polyp is advanced enough to be detected by FIT and likely requires more advanced endoscopic techniques such as endoscopic mucosal resection and endoscopic submucosal dissection or a full thickness resection such as hemicolectomy. So far, no study has compared the long-term effectiveness of FIT and colonoscopy by considering all these factors.

In conclusion, this study provided a more realistic estimation of the sensitivity and specificity of FIT as a screening modality to be used in new cost-effectiveness analyses to determine if current guidelines and policies by associations and health jurisdictions need to be revised accordingly.

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Author Contributions

Mohammad Yaghoobi: Conceptualization, data curation, formal analysis, supervision, verifying the underlying data Parsa Mehraban Far: Data curation, verified the underlying data Lawrence Mbuagbaw: Formal analysis, supervision, verified the underlying data

Yuhong Yuan: Review and editing

David Armstrong: Review and editing, supervision Lehana Thabane: Review and editing, formal analysis Paul Moayyedi: Supervision, review, and editing.

Conflict of Interest

The authors declare no conflict of interest related to this work.

Ethical Approval

There is nothing to be declared.

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