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Comparing Effectiveness of Colonoscopy versus Fecal Immunochemical Testing in Screening for Colorectal Cancer

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Abstract:

Introduction: Colorectal cancer (CRC) is deadly neoplasm that takes many lives in the United States and is a leading cause of cancer worldwide. If CRC is detected early through screening, there is a higher chance of remission which makes screening an important tool in CRC prevention. Currently, colonoscopy is the gold standard, but due to the undesirable preparation needed for a colonoscopy, patient compliance is low. Giving patients a screening option that requires less preparation may help to increase the compliance for CRC screening. Fecal Immunological testing has been shown to have higher compliance rates among patients as compared to colonoscopy.

Objective: The purpose of this paper is to evaluate three research studies to compare the effectiveness of FIT to the gold standard colonoscopy.

Methods: Utilized PubMed database with several MeSH terms: colorectal neoplasms, diagnosis, and colonoscopy to find the three articles outlined in this paper.

Results: All three studies demonstrated that FIT had comparable effectiveness in detecting colorectal cancer but was insufficient in detecting advanced adenomas in comparison to colonoscopy. A high compliance rate was noted among the FIT group versus colonoscopy, as well.

Conclusions: We recommend that colonoscopy remain the gold standard to be conducted every 10 years with a yearly FIT to attempt to detect rapidly growing neoplasms. Further research should be conducted in which all participants complete a FIT and undergo a colonoscopy.

Keywords: Colorectal-cancer, screening, fecal immunochemical testing

Introduction:

There are 150,000 new cases of colorectal cancer (CRC) diagnosed per year in the U.S.[1] In 2015, CRC resulted in the loss of approximately 9 million lives.[2] Currently, the gold standard for screening for CRC is a colonoscopy every 5-10 years, depending on family history. Patient compliance is difficult due to the strict dietary regimens and bowel preparation required for a successful colonoscopy. Colonoscopy preparation includes: low fiber diet within several days of procedure, clear liquid diet the day before, NPO 2 hours prior to procedure, and bowel preparation.[3] Different surgeons use different bowel preparation methods which usually consist of consuming a gallon of water mixed with a laxative solution[4]. The goal is to have clear bowel eliminations which often requires a whole day. Newer alternatives have been recently researched as other screening options compared to colonoscopy. One of these tests being fecal immunochemical testing (FIT), which requires no dietary changes and only 1 stool sample versus an endoscopic procedure. While new cancer treatments are constantly being researched each year, the number of new cases have increased 33% from 2005 to 2015.[1] Deaths due to CRC have decreased in the past several years, to 100,000 deaths per year in the US[2]. New screening techniques could lead to fewer deaths in the future.

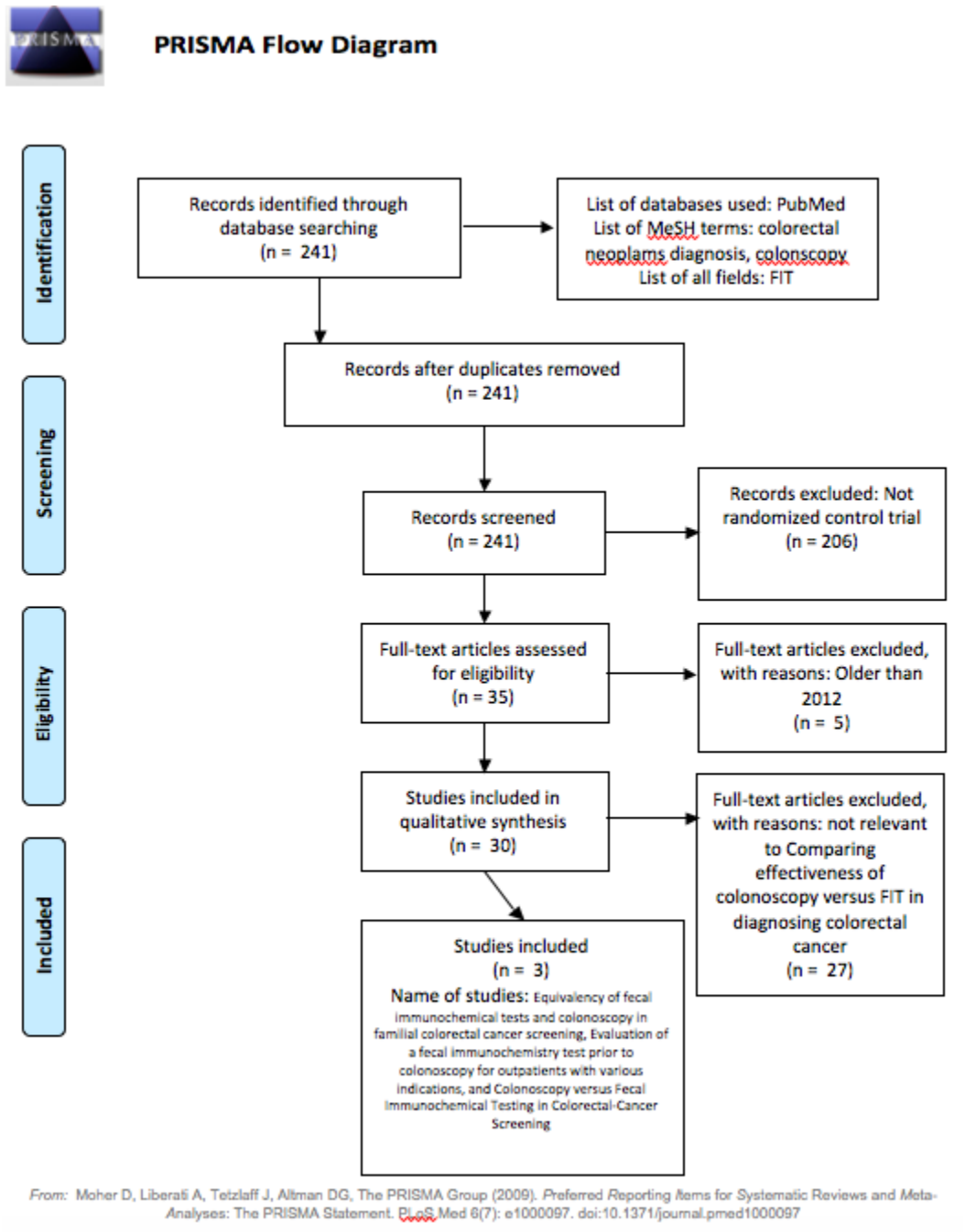
Fecal immunochemical testing examines stool for hidden blood that may be related to fragile blood vessels caused by cancer.[2] It detects the globulin portion of hemoglobin, which is usually broken down by enzymes in the upper GI tract making it more specific to lower GI bleeding.[5] Although the effort required for the FIT test is minimal, if it comes back as positive for blood, the current recommendation is to undergo a colonoscopy as the FIT test cannot be used to diagnose colorectal cancer.[6] The recommendation is for patients to complete the FIT test annually.[2] FIT testing for patients who are uninsured is a much more affordable option than the gold standard colonoscopy. The average colonoscopy cost is around $3,000 without insurance[7] as compared to FIT testing which is, on average, $22 without insurance.[8] Compliance for CRC screening is so critical because CRC is treatable if it is detected early.[9] FIT is a way to ensure that more people are being screened as new studies have shown higher compliance and participation rates as compared to colonoscopy.[10] This paper will evaluate 3 different articles comparing the effectiveness of FIT versus colonoscopy in screening for CRC.

Clinical Question: *In asymptomatic men and women over 18 years old, is the FIT test as effective in diagnosing colon cancer as compared to the gold standard, colonoscopy?*

Methods:

Using Pubmed database, the MeSH terms “colorectal neoplasms, diagnosis, colonoscopy” as well as the all fields term “FIT” was used to perform an initial search. The original article yield was 241, and no duplicates were found. Any study that was not a randomized control trial or was older than 2012 was excluded which brought the new yield to 30. The last articles were examined for their ability to compare the effectiveness of colonoscopy versus FIT in diagnosing CRC. Final yield of studies that met inclusion and exclusion criteria was 3. The Prisma Flow diagram (Figure 1) depicts the methods used to find these articles.

Figure 1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Results:

Study #1

Equivalency of Fecal Immunochemical Tests and Colonoscopy in Familial Colorectal Cancer Screening[11]

***Objective*:** To compare efficacy of colonoscopy and FIT testing in identifying advanced neoplasms in individuals with a first degree relative family history of CRC.

Design:

This was a prospective study from 2006 to 2010 in which 1,488 asymptomatic males and females older than 40 years (or 10 years younger the soonest case of CRC in first degree relatives) were recruited from the University Hospital of Canary Islands area. Refer to Table 1 for inclusion and exclusion criteria.

Table 1.

Inclusion Criteria:	Exclusion Criteria:
1st degree relative with history of CRC	History of CRC screening
>40 years or 10 years younger than youngest family member when diagnosed with CRC	Hereditary CRC syndrome - high risk group
	History of colorectal neoplasm or inflammatory bowel disease
	Symptoms of CRC - rectal bleeding, weight loss, night sweats, anemia, etc.
	Fatal illness with less than 5 years of life expectancy

Study participants were randomly assigned, 744 per group, to receive 1 colonoscopy or 3 FIT (1 per year for three years) over a 36 month period. FIT participants were given 1 OC-Sensor kit each year and were instructed to return each sample within 5 days after collecting the sample. The samples were to be kept at 4℃. A positive result was defined as a sample with ≥ 10 μg (hemoglobin)/g(feces). If a result was positive, participants underwent a colonoscopy within 6 weeks. All colonoscopies were conducted by 4 endoscopists who perform at least 200 similar procedures each year and were blinded. Patients were to undergo colonic cleansing for proper visualization of the colon which was photographically documented. Procedures with clean segments where the cecum was reached were described as complete procedures. Advanced neoplasms include invasive lesions which contain malignant cells through the muscularis mucosa or advanced adenomas (high-grade dysplasia, intramucosal carcinomas,

tubulovillous/villious, or ≥10 cm). Lesions were removed and staged in accordance with the American Joint Committee on Cancer. All participants were followed up with for 3 years after the study to observe for false-negatives. Statistical analysis was performed with a 95% confidence interval (CI) for comparison of advanced neoplasia detection.

Results:

The first FIT screening successfully detected 23 of 29, or 79.1%, of advanced neoplasms after being confirmed on colonoscopy. Colonoscopy screening detected 48 advanced neoplasms in the colonoscopy group (and the 29 in the FIT group). Overall, the difference between the two tests in identifying advanced neoplasms was not statistically significant if stratified by number of relatives with CRC, age, sex, index-case age, kinship of first degree relative with CRC. Compliance rate was higher among the FIT group versus colonoscopy by approximately 5-20%. During 36 month follow-up, 16 advanced adenomas were identified in participants with 1 or 2 negative FIT during the study. 41 total cases were detected between the study and follow-up in which FIT failed to detect 39% of total cases of advanced adenomas but all cases of CRC. Overall detection rates were recorded in table 2 for CRC and different adenoma subtypes.

Table 2. Overall detection rates of Colonoscopy and FIT

	Colonoscopy		FIT				
Colorectal lesion	Subjects, n	Rate, %	Subjects, n	Rate, %	OR[a]	95% CI	*P* value
Intention-to-treat analysis	782		784				
Nonadvanced adenomas	148	18.9	52	6.6	3.49	2.49–4.91	<.001
Advanced adenoma[b]	39	5.0	28	3.6	1.48	0.89–2.44	.12
Colorectal cancer	5	0.6	5	0.6	1.23	0.34–4.42	.75
Advanced neoplasia[c]	44	5.6	33	4.2	1.41	0.88–2.26	.14
Any neoplasia	192	24.6	85	10.8	2.92	2.19–3.89	<.001
Per-protocol analysis	747		709				
Nonadvanced adenomas	148	19.8	38	5.4	4.71	3.22–6.89	<.001
Advanced adenoma[b]	38	5.1	24	3.4	1.58	0.93–2.67	.09
Colorectal cancer	5	0.7	4	0.6	1.64	0.42–6.41	.48
Advanced neoplasia[c]	43	5.8	28	3.9	1.56	0.95–2.56	.08
Any neoplasia	191	25.6	66	9.3	3.72	2.73–5.10	<.001

NOTE. In the intention-to-treat analysis, the detection rate was calculated as the number of subjects with true-positive results divided by the number of subjects who were eligible to undergo testing. In the per-protocol analysis, the detection rate was calculated as the number of positive results divided by the number of subjects who actually underwent screening according to the assigned group. Subjects were classified according to the most advanced lesion.
[a]ORs were adjusted according to age, sex, age (younger than 60 years or 60 years or older) of the index case at diagnosis of CRC, having siblings with CRC or more than one first-degree relative with CRC.
[b]Advanced adenoma was defined as an adenoma measuring ≥10 mm in diameter, with villous architecture, high-grade dysplasia, or intramucosal carcinoma.
[c]Advanced neoplasia was defined as advanced adenoma or cancer.

Critique:

This study had several strengths. First, it was the first study to conduct a randomized control trial comparing the screening ability of FIT and colonoscopy in familial CRC. A large sample size was used of 1,488 participants (after exclusions) which were randomly assigned, and the study was blinded. Lastly, a 3 year follow-up was conducted to evaluate for false positives, and the number of participants lost to follow up was less than 5%.
Within the FIT group, the number of FIT conducted throughout the 3 year period was variable, but this was compensated for by follow-up colonoscopies no matter how many FIT were

completed. If all participants completed all 3 yearly tests, more adenomas may have been detected. The study also only used participants with a first degree family history of CRC which limits the extrapolation of the results to familial CRC and not the general population.

Study #2:
Evaluation of fecal immunochemistry test prior to colonoscopy for outpatients with carious indications[12]

Objective: To compare the ability of pre-colonoscopy FIT to predict colonoscopy findings.

Design:

This study was designed as a retrospective chart review of outpatients from the Jewish General Hospital in Montreal from 2015-2016. Charts were reviewed by 2 separate reviewers, once by an independent observer and once by one of the authors of this study. Exclusion criteria included emergent/urgent colonoscopies. Patients were given proper instructions, per gastroenterology clinic, on how to prepare for their colonoscopies the day before the procedure and the morning of with either 4 liters of Peglyte® or powdered magnesium sulfate. Quality of colonic preparation was recorded along with the results of the colonoscopy. Masses were defined as adenomas, villous adenoma, tubulovillous (TVA), serrated adenomas (SSA), or advanced adenomas. Advanced adenomas were defined as polyps larger than 10 mm, villous, presence of high-grade dysplasia (HGD), or invasive adenocarcinoma. Participants were stratified based on the absence or presence of symptoms related to CRC: rectal bleeding, iron deficiency, change in bowel habits, diarrhea, weight loss, or abdominal pain. Patients who underwent a colonoscopy were requested to complete a FIT test, which was provided by the hospital. Instructions on how to obtain a proper sample were included in the kit. A positive result was defined as 35 µg hemoglobin/g of stool. Results were further reviewed for false positive and false negative FIT results. Statistical analysis was calculated with a 95% CI, odds ratios, and a p value ≤ to 0.05 was considered to be statistically significant.

Results:

After exclusion of 64 patients, 325 patients remained in the study. In 86% of these patients, adenomas were found on colonoscopy. Within the FIT negative group, the colonoscopy results revealed no invasive cancers or adenomas with high grade dysplasia. However, colonoscopy picked up 28 cases of adenomas in the FIT negative group. Table 2 below shows the specific types of adenomas found. Statistical significance was found (p=0.0016) between the FIT positive and FIT negative groups when comparing advanced adenomas and adenocarcinoma detection. However, no statistical significance was found between the FIT-not done and FIT-done groups when looking at advanced adenomas and invasive cancer. The overall adenoma detection rate of the FIT had a sensitivity of 30% and specificity of 82.7%. For advanced neoplasms, the FIT test had a sensitivity of 63.6% and specificity of 82.7%.

Table 2 Summary of colonoscopy findings in all patients and in the different groups[a]

Category	Total	All patients, N=325			FIT-done patients, N=144		
		FIT-not done	FIT-done	*p*-value	FIT negative	FIT positive	*p*-value
Number of patients	325	181	144		114	30	
Advanced adenomas or invasive adenocarcinoma	20 (6.2)	9 (5.0) 2/9 TVA	11 (7.6)	0.3204	4 (3.5)[b] 1/4 TVA	7 (23.3) 1/7 TVA	0.0016
Overall adenomas	86 (26.5)	46 (25.4)	40 (27.8)	0.6314	28 (24.5)	12 (40.0)	0.0930
CA or TA HGD	7 (2.2)	5 (2.8)[c]	2 (1.4)[c]		0	2 (6.7)[c]	
TA ≥2 cm or 1 cm	13 (4.0)	4 (2.2)	9 (6.3)		4 (3.5)	5 (16.7)	
TA <1cm	66 (20.0)	37 (20.1)	29 (20.1)		24 (21.0)	5 (16.7)	
HP	7 (2.2)	7 (3.9)	0		0	0	
SSA	4 (0.9)	4 (2.2)	0		0	0	

Notes: [a]The definition of advanced adenomas is based on Corley et al[14] and that of TA, TVA, HGD, CA is based on Kleihues and Sobin.[11] HP and SSA are listed to emphasize that these are not part of the definition of adenoma detection rate reference.[12] [b]There were no cases of adenoma with HDG or invasive CA in FIT-negative group. [c]There were three invasive adenocarcinomas and two adenomas with HDG in FIT-not done group. Both were invasive CAs in FIT-done (Fit+) group. Data presented as n (%).
Abbreviation: CA, invasive adenocarcinoma; FIT, fecal immunochemistry test; HGD, high-grade dysplasia; HP, hyperplastic polyps; SSA, sessile serrated adenomas (SSA); TA, tubular adenoma; TVA, tubulovillous adenoma.

Critique:

A strength of this article was the inclusion of false negative data in which there was a negative FIT test but a positive colonoscopy. Secondly, the results of the study proved the author's original hypothesis that FIT is a good screening tool for CRC and indications for invasive diagnostic tools like a colonoscopy. This study is limited by its small sample size (n=325), which prevented the results from being statistically significant due to lack of statistical power. Furthermore, it was unable to evaluate the true screening ability of FIT in CRC in this patient population because not all the participants were asymptomatic. Consequently, since the design was a retrospective review, further evaluation should be done in a randomized control trial to confirm the results.

Study #3:

Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening[13]

Objective: Compare the efficiency of FIT and colonoscopy in the reduction in colorectal cancer death rates over a ten year timeframe.

Design:

This study is designed as a randomized control trial to compare FIT with colonoscopy. It took place from November 2008 to June 2011 in 15 tertiary care hospitals in Spanish regions (Aragón, Basque Country, Canarias, Catalonia, Galicia, Madrid, Murcia, and Valencia). After filling out a questionnaire and using exclusion and inclusion criteria, 57,404 men and women ages 50 to 69 were enrolled in this study. Exclusion criteria included: being symptomatic, history of CRC, Irritable bowel disease (IBD), or adenoma, a family history of CRC, previous colectomy, and a severe coexisting illness. Temporary exclusion criteria included fecal occult blood testing within the past two years or colonoscopy/sigmoidoscopy within the past 5 years or required further workup because of current symptoms. Once an adequate time had passed (time frame not specified by article) and testing came back negative for patients with symptoms, these subjects were able to participate. Community Health Registries were used and then divided up by household, age, and sex. A computer-generated algorithm randomly assigned households to either the one-time colonoscopy or a biennial FIT. Invitations went out to explain the study and invite the subject to participate. After agreeing to take part in the study, they were asked to fill out a questionnaire.

All participants in the colonoscopy intervention underwent a colonoscopy by an experienced endoscopist and had to perform the usual bowel cleansing beforehand. Specific criteria for polyps, adenomas, invasive cancer, and advanced neoplasm were made. The FIT participants had no diet restrictions before the stool sample was taken. If a participant had a level of more than 75 ng per milliliter of hemoglobin in their stool, they were offered a colonoscopy.
The analysis was done using both intention-to-treat and as-screened analyses. A P value of 0.025 was used to determine statistical significance. There will be a ten-year follow up in 2021.

Results:

After being randomly assigned and after exclusions, 26,703 subjects were in the colonoscopy group and 26,599 in the FIT group. Participants in the colonoscopy group had a lower participation rate, as more underwent FIT instead of doing their assigned colonoscopy. There was a 24.6% participation rate for the colonoscopy and 34.2% participation rate in the FIT group. Results were compared by looking at the diagnostic yield of each screening method. Table 2 below stratifies the data by location and type of lesion found and uses odds ratios with confidence intervals for comparison. Colonoscopy was shown to be a better diagnostic tool for advanced and non-advanced adenomas that were located either distal or proximal to the splenic flexure. The odds ratio of colonoscopy to FIT for advanced adenomas is 4.32 with a confidence interval of 3.69 to 5.07. The odds ratio of colonoscopy to FIT for non-advanced adenomas is 25.98 with a 95% confidence interval of 21.27 to 31.74. No statistically significant difference was seen between FIT and colonoscopy with diagnosis of proximal or distal CRC.

Colorectal Lesion	Colonoscopy (N=26,703)		FIT (N=26,599)		Odds Ratio (95% CI)†	P Value
	Subjects	Rate	Subjects	Rate		
	no.	%	*no.*	%		
Cancer						
Proximal	6	<0.1	11	<0.1	0.56 (0.21–1.53)	0.26
Distal	25	0.1	23	0.1	1.22 (0.69–2.16)	0.49
Advanced adenoma‡						
Proximal	199	0.7	51	0.2	4.06 (2.98–5.53)	<0.001
Distal	365	1.4	206	0.8	1.82 (1.53–2.16)	<0.001
Advanced neoplasia§						
Proximal	205	0.8	62	0.2	3.44 (2.58–4.57)	<0.001
Distal	390	1.5	229	0.9	1.76 (1.49–2.08)	<0.001
Nonadvanced adenoma						
Proximal	608	2.3	62	0.2	10.06 (7.74–13.08)	<0.001
Distal	677	2.5	85	0.3	8.21 (6.55–10.29)	<0.001
Any neoplasia						
Proximal	813	3.0	124	0.5	6.84 (5.65–8.27)	<0.001
Distal	1067	4.0	314	1.2	3.58 (3.15–4.07)	<0.001

* The diagnostic yield was calculated as the number of subjects with true positive results divided by the number of subjects who were eligible to undergo testing. Subjects were classified according to the most advanced lesion that was proximal or distal to the splenic flexure. The total number of subjects with proximal and distal lesions may exceed the total number of subjects because subjects could have lesions in both locations.
† Odds ratios were adjusted for age, sex, and participating center.
‡ Advanced adenoma was defined as an adenoma measuring 10 mm or more in diameter, with villous architecture (>25%), high-grade dysplasia, or intramucosal carcinoma.
§ Advanced neoplasia was defined as either advanced adenoma or cancer.

Table 3: Stratified diagnostic yield data by type and location of lesion.

Critique:

This study had a good mix of strengths and weaknesses. To begin, the population size was rather large, regardless of the fact that many subjects did not end up participating in CRC screening. In addition, the results were compared by location (proximal vs. distal) in order to show more specifically how each screening method performed. A weakness of the article was that there was no false negative or false positive data included. While participants who had an abnormal FIT test were offered colonoscopy, the colonoscopy participation rate is 86%. It is unclear whether there were false positives (positive FIT and negative colonoscopy). In addition, false negatives (negative FIT, positive colonoscopy) were not mentioned because negative FIT subjects were not offered a colonoscopy. False negative and false positive data would be important in determining the efficacy of FIT compared to colonoscopy. A downside of this study for our purposes is that the ten-year data will not be available until 2021 so the results are all preliminary, but they do have more research that will be available in the future.

Table 4. Overview of Results

	Quintero et al. 2014	Szilagyi et al.	Quintero et al. 2012
Sample Size:	1,566	325	15,670
Demographics:	Residents of the Canary Islands	Jewish General Hospital in Montreal patients	8 regions of Spain
Study Type:	Randomized control trial	Retrospective cohort	Randomized control trail
Results:	FIT detected all CRC, but missed 16/41 adenomas	FIT missed 5 advanced adenomas and some multiple adenoma cases. Similar detection rates of CRC between FIT and colonoscopy.	Low compliance rates among colonoscopy group. FIT missed several adenomas in proximal and distal colon. No difference in CRC detection.

Discussion:

There is a high mortality rate due to CRC worldwide, but if caught early, there is a greater likelihood of remission. There is a need for non-invasive screening techniques for CRC due to the low compliance of the current invasive gold standard, colonoscopy. FIT testing is a non-invasive screening tool that showed higher compliance rates and similar screening effectiveness for CRC in all 3 studies focused on in this paper. Study results and demographics are compared below in table 4.

Quintero et al. 2014 demonstrated that there was no statistically significant difference in CRC detection rates between FIT and colonoscopy. FIT detected all CRC and advanced neoplasms that were later confirmed with a colonoscopy; however, there was less false negative data than desired due to the lack of compliance with colonoscopy. Szilagyi et al. had similar results and conclusions, however the results were not statistically significant due to inadequate statistical power. The negative predictive value for FIT testing was 96.5% for advanced polyps, proving that FIT is a useful tool for determining if a colonoscopy is necessary. Quintero et al. 2012 yielded much lower participation rates among those assigned to the colonoscopy group versus the FIT group. There was no statistically significant difference between the CRC detection abilities of FIT and colonoscopy, but FIT was inferior to colonoscopy in detecting adenomas in the distal and proximal colon. All 3 studies demonstrated that colonoscopy was superior to FIT in overall detection rate of adenomas. Due to higher compliance rates and the high detection ability of FIT, it would be beneficial to be used more frequently as a screening tool for those unwilling to comply with colonoscopy or as an adjuvant between colonoscopies.

A strength of our review is that the selected studies answer our clinical question that FIT is a useful adjuvant screening tool to the gold standard. In addition, all of the studies had similar results showing that there is no significant difference (2 of which showed no statistically significant difference) between colonoscopy and FIT in detecting CRC, but FIT is inferior to colonoscopy in detecting adenomas. Lastly, two of our studies were randomized control studies that had large sample sizes. A limiting factor of our review is that Szilagyi et al. is a retrospective study with a smaller sample size (n = 325). Furthermore, Szilagyi et al. used symptomatic patients as well as asymptomatic patients which did not demonstrate the true screening ability of FIT for the symptomatic participants. Finally, participation rates for colonoscopy were lower than the FIT test, which limited the data on false negatives and positives.

Conclusion:

Clinical Question: *In asymptomatic men and women over 18 years old, is the FIT test as effective in diagnosing colon cancer as compared to the gold standard, colonoscopy?*

Overall, the FIT test had equal efficacy in diagnosing colorectal cancer as colonoscopy, which was seen in all studies. However, colonoscopy was superior in detecting advanced adenomas and should remain the gold standard for screening. Our recommendation based on the results of these studies would still be a colonoscopy every 10 years with annual FIT test to pick up the more rapidly growing CRC.[11] Rapidly growing CRC could be detected later if they form in between the recommended colonoscopy screening times. For patients resistant to having a colonoscopy, FIT would be a reasonable alternative since it has a similar efficacy to detecting CRC as colonoscopy. Any patient with a positive FIT test should be recommended to get a colonoscopy.

Currently, there is not enough data to support FIT as a replacement to the gold standard in CRC screening. Further studies should be done with large populations in asymptomatic patients who are screened with both colonoscopy and FIT in order to ensure false negative and false positive data. In addition, further studies should be done in the United States in order to more accurately extrapolate the data to the US population since diets and incidence rates are different around the world. Death rates would be an additional factor to look at in the future to see if the FIT screening is useful in decreasing the amount of CRC deaths. Quintero et al. 2012 will have results in 2021 discussing how FIT and colonoscopy compare in reducing death rates from CRC.

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