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The fecal immunochemical test (fit): Selected aspects regarding its effectiveness for colorectal cancer screening in Quebec City

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ABSTRACT

Background and aims: FIT's value has been ascertained across Canada and worldwide, but still needs to be assessed within the province of Quebec. There also remains a gap between formal indications for FIT, and its actual use in clinical practice. This research aims to evaluate some aspects of FIT's effectiveness in our setting, and its application by prescribers.

Methods: We retrospectively identified and reviewed all the colonoscopies conducted for a positive FIT in 2014 at 2 hospitals located in Quebec City.

Results: Five hundred and fifty-nine (559) colonoscopies were reviewed. We obtained PPVs of 6.8% and 46.9% for the detection of CRC and AA, respectively. The PPV for the detection of SCL was higher in men compared to women (OR 1.56, 95%CI 1.11–2.20) and among justified FITs compared to unwarranted ones (OR 1.88, 95%CI 1.34–2.63). The PPV for CRC detection was 25.0% in the presence of unexplained iron deficiency anemia and 6.5% when anemia was absent (p = 0.0058). In 49.9% of cases, the prescription of a FIT was inappropriate.

Conclusion: The FIT holds a better PPV for detecting SCL among men and when it is indicated. Anemia is associated with a higher CRC detection rate. Half of the FITs were not initially indicated.

1. Introduction

Worldwide, colorectal cancer (CCR) is the second and third most diagnosed cancer among women and men, respectively (Torre et al., 2015). It is estimated that in 2008, it was responsible for > 2400 deaths in the province of Quebec (Institut national de santé publique du Québec (INSPQ), 2008). Given this context, several reasons justify CRC screening in an average-risk population. Firstly, survival is related to the stage of the disease (0, I to IV) at the time of diagnosis. Moreover, the natural history of the disease is well known: 80% of CRC cases result from the transformation of an adenoma, which generally grows from grade 1 to grade 5 in about ten years. Polypectomy of advanced adenomas (AA) thus reduces the incidence of CRC (Potvin and Gosselin, 2012; AJCC (American Joint Committee on Cancer), 2010). In fact, colonoscopy is the gold standard for the detection of AA and CRC. However, it is not recommended as a screening tool among the general population because of its high cost, limited accessibility, and associated risk of complications. Currently, one of the endorsed screening tools for average-risk individuals is the immunochemical fecal occult blood test (FIT), followed by a confirmation colonoscopy given a positive result. This strategy allows the selection of individuals who will potentially benefit the most from a colonoscopy, and was also shown to be cost-effective (Sobhani et al., 2011; Wilschut et al., 2011). In Quebec, the guaiac fecal occult blood test (gFOBT) was replaced with the FIT in September of 2013 as part of a newly implemented provincial screening program (PQDCCR). To date, FIT's performance has not been assessed in the province of Quebec. In addition, there seems to remain a discrepancy between the formal indications for a FIT, and its actual use in clinical practice. Thus, this research aims to evaluate some aspects related to the effectiveness of the FIT in our setting and its application by prescribers.

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2. Methods

2.1. The PQDCCR

Quebec's CRC screening program (PQDCCR) was first implemented in 2011 in 8 pilot sites across the province, which includes the Québec University Hospital Center (CHU de Québec). The program is aimed at 50 to 74 year-old, asymptomatic average-risk individuals (Suppl.). Its first phase consisted in the standardization of a colonoscopy prescription, preparation, and reporting. The second phase started in September of 2013. Its purpose was to assess the use of the FIT locally. Primary care physicians request a FIT whenever they consider it is warranted, and refer test-positive patients to either of the designated centers for a confirmation colonoscopy. The third phase, which is pending, should result in the entire target population being mailed an invitation to take part in the screening program.

The technology used for sample laboratory analysis is the OC-Sensor® Diana (Eiken Chemical Co., Ltd.). Of note, the manufacturer recommends a positivity threshold value of 100 ng/mL; however, PQDCCR authorities have set the threshold at 175 ng/mL, based on available evidence regarding the performance and cost-effectiveness of the FIT, which is discussed further in more detail (Potvin and Gosselin, 2012).

2.2. Study population

We included all FIT-positive patients who underwent a confirmation colonoscopy in 2014, at either of the 2 PQDCCR designated centers in Quebec City, i.e. Saint-François d'Assise (HSFA) and Saint-Sacrement (HSS) Hospitals.

We excluded FIT-positive patients who were referred for a colonoscopy which was not performed, for any reason (e.g. refusal), or incomplete because of poor bowel preparation. We also excluded patients who were referred for a positive gFOBT rather than a FIT, whose medical records were unavailable, and whose colonoscopy was performed for another reason than a positive FIT result.

2.3. Data collection

At the CHU de Québec, which is comprised of the HSFA and HSS, all gastrointestinal (GI) endoscopy reports are generated in a standardized manner and electronically stored via Endoworks® (Olympus®) software. In addition, all medical records from the 5 hospitals of the CHU are digitized and merged into a single source. We launched a search in Endoworks® for all reports of colonoscopies performed at HSFA and HSS between January 1st and December 31st 2014 containing the keywords “FIT” or “RSOSi (French equivalent of FIT)”. We then consulted each corresponding medical record to complete data collection. When a record was only partially digitized, we consulted the print version at the Health Records Department.

All colonoscopy reports and medical records were reviewed manually by either one of the two first authors (MC, GL). A data collection tool was created, as well as a database to allow statistical analyses.

2.4. Objectives

The primary objective of the study was to determine the positive predictive value (PPV) of the FIT for the detection of CRC, significant colorectal lesions (SCL), and AA. The secondary objectives were to (i) describe the anatomical site and staging of detected cancers, (ii) identify the false-positive FIT results, (iii) examine the influence of specific variables on the test's PPV, such as age, sex, adequacy of the prescription of a FIT, presence of warning features, and the hospital where the colonoscopy was performed, and (iv) identify the FITs that were unjustified, i.e. that were requested for other than asymptomatic, average-CRC risk patients. Definitions for SCL, AA, and average- CRC risk patients are listed in the Supplementary Material.

2.5. Statistical analyses

Continuous data are presented as means and their corresponding 95% confidence intervals (95% CI), whereas categorical data are shown as frequencies and proportions. PPVs were estimated as the proportion of the true positive tests by the overall number of positive results and are displayed as percentages. The Wald 95% CIs for binomial proportions were estimated using the asymptotic standard error. Fisher's exact tests were used to compare true positive proportions in different subgroups of patients. Univariate and multivariate logistic regression models were arranged to estimate crude and adjusted odd ratios, and to test the association of a true positive test with different factors. Age, sex, adequacy of FIT, and warning features were used to obtain adjusted results with the multivariate analyses. The Hosmer-Lemeshow test was used to test FIT's effectiveness for the logistic regression models. All statistical tests were two-sided, and a p value of < 0.05 was considered statistically significant. The statistical analysis was carried out using SAS Statistical Software v.9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Participants

We identified 253 and 358 colonoscopies performed at HSFA and HSS, respectively, between January 1st and December 31st 2014, for a total of 611 patients. Fifty-two (52) patients were excluded for various reasons (Fig. 1). The demographic and clinical characteristics of 559 retained patients are presented in Table 1.

3.2. Global PPV

Main results are shown in Tables 2, 3A, 3B and 3C. VPPs for the detection of CRC, SCL and AA were 6.8 (CI95% 4.7–8.9), 51.7 (CI95% 47.6–55.9), and 46.9% (CI95% 42.8–51.1), respectively.

Two (2) and 3 patients were excluded from the calculation of PPVs for the detection of SCL and AA, respectively, because described polyps were not retrieved.

3.3. Anatomical site and staging of CRC

Twenty-six (26) CRC were left-sided, and 12 were right-sided. In one case, 2 synchronous cancers were detected; thus, we counted it as one single patient, but reported the characteristics for both lesions. Most cancers (60.5%) were stage I or II CRCs. In one case, the lesion detected was in fact an invasive gallbladder cancer; this was not listed as a CRC in our database.

3.4. False-positive FIT results

We considered the FIT result was falsely positive when the confirmation colonoscopy was strictly normal or when the lesions found were not known to induce occult bleeding (e.g. diverticulosis). Given this definition, 10.6% of false-positive FIT results were identified.

3.5. Influence of selected covariates

Increasing age had a significant positive influence on PPVs for detection of all types of lesions, with ORs of 1.06, 1.03 and 1.02 for CRC, SCL and AA, respectively. Thus, one year of aging resulted in a 6% increase in CRC odds. Statistical significance remained for CRC detection after adjustment for the variables stated earlier. We simultaneously conducted ad hoc subgroup analyses for patients aged < 60 years, and those aged 60 years and over. PPVs were higher in the latter group for CRC (OR 5.09, $p = 0.0077$), and SCL (OR 1.71, $p = 0.0074$). Again,

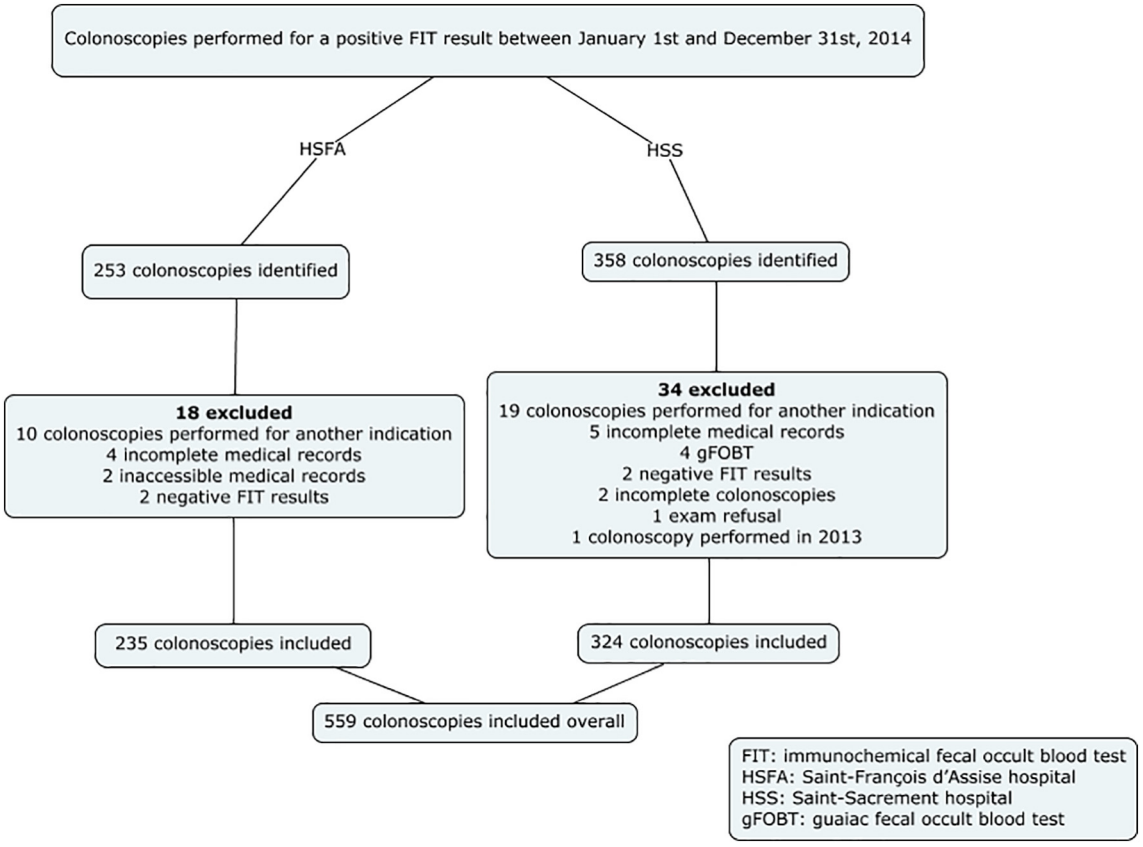

Fig. 1. Study profile.

Table 1
Demographic and clinical characteristics of patients.

Total number of patients	559 (100)
Female sex	224 (40.1)
Mean age at time of colonoscopy, years (CI95%)	64,3 (63.6–65.0)
< 50	10 (1.8)
50–59	159 (28.4)
60–69	235 (42.0)
70–74	93 (16.6)
≥75	62 (11.1)
Family history	
One 1st degree relative with CRC at age < 60	14 (2.5)
One 1st degree relative with AA at age < 60	4 (0.7)
Two 1st degree relatives with CRC and/or AA, any age	12 (2.2)
One 1st and one 2nd degree relatives with CRC, any age	0
Genetic syndrome (such as HNPCC or FAP)	0
No relevant family history or data missing	529 (94.6)
Personal history	
Non-advanced adenomas	9 (1.6)
AA	5 (0.9)
CRC	1 (0.2)
IBD	2 (0.4)
Warning features[a]	
Present	245 (43.8)
Absent or data missing	314 (56.2)

Values are indicated as number of patients (percentage) unless otherwise specified. CI: confidence interval; CRC: colorectal cancer; AA: advanced adenoma; HNPCC: hereditary non-polyposis colorectal cancer; FAP: familial adenomatous polyposis; IBD: inflammatory bowel disease.

[a] Listed in the Supplementary Material.

multivariate analyses led to similar results.

PPVs for CRC detection were 8.1% in men and 4.9% in women. For SCL, they were 56.1 and 45.1%, respectively, and for AA detection, 50.8 and 41.2%, respectively. The difference between men and women was statistically significant for SCL (OR 1.56, p = 0.0106) and AA (OR 1.47, p = 0.0262) detection. These differences remained significant after multivariate analyses were conducted to adjust for previously specified variables.

There was no difference for the detection of CRC among patients whose FIT was indicated and patients for whom it was not (6.8% in both subgroups). A SCL was detected in 59.5% and 43.9% of cases in each group, respectively (OR 1.88, p = 0.0002). Similarly, PPV values for AA detection were 54.8% and 39.0%, respectively (OR 1.90, p = 0.0002). Again, comparable results were obtained after multivariate analyses.

Table 2
Characteristics of CRC detected during confirmation colonoscopy.

	HSS (N = 324)	HSFA (N = 235)	Overall (N = 559)
CRC detected	26[a]	12	38
Anatomical site			
Left colon	18 (69.2)	9 (75.0)	27 (71.1)
Right colon	9 (34.6)	3 (25.0)	12 (31.6)
Stage[b]			
I	11 (42.3)	6 (50.0)	17 (44.7)
II	5 (19.2)	1 (8.3)	6 (15.8)
III	7 (26.9)	4 (33.3)	11 (29.0)
IV	2 (7.7)	1 (8.3)	3 (7.9)
Non-specified	1 (3.9)	0	1 (2.6)
Non-colic neoplasia	1 (N/A)	0	1 (N/A)

Values are indicated as absolute number (percentage). HSS: Saint-Sacrement Hospital; HSFA: Saint-François d'Assise Hospital.

[a] In one patient, two synchronous left and right-sided CRC cancers were detected.

[b] Based on TNM staging system (AJCC (American Joint Committee on Cancer), 2010).

Table 3A
Performance of the FIT for CRC detection, overall and in selected subgroups.

N = 559	PPV	Crude OR (CI95%)	p value
Overall	6.8		
According to sex		1.70 (0.82–3.50)	0.1512
Male	8.1		
Female	4.9		
According to age[a]		1.06 (1.02–1.10)	0.0046
< 50	10.0		
50–59	1.3		
60–69	8.9		
70–74	5.4		
≥75	14.5		
According to warning features		1.04 (0.53–2.03)	0.9148
Absent[b]	6.4		
Present	7.4		
According to adequacy of FIT		1.00 (0.52–1.93)	0.9909
FIT indicated[c]	6.8		
FIT not indicated	6.8		

FIT: fecal immunochemical test; CRC: colorectal cancer; PPV: positive predictive value; OR: odds ratio; CI: confidence interval.
[a] Age was analysed as a continuous variable.
[b] Patients with missing information were listed as asymptomatic.
[c] When information provided was insufficient to determine FIT adequacy, we listed it as indicated.

Table 3B
Performance of the FIT for SCL detection, overall and in selected subgroups.

N = 557	PPV	Crude OR (CI95%)	p value
Overall	51.7		
According to sex		1.56 (1.11–2.20)	0.0106
Male	56.1		
Female	45.1		
According to age[a]		1.03 (1.01–1.05)	0.0013
< 50	30.0		
50–59	42.1		
60–69	56.0		
70–74	50.5		
≥75	65.6		
According to warning features		1.67 (1.17–2.39)	0.0047
Absent[b]	56.4		
Present	45.7		
According to adequacy of FIT		1.88 (1.34–2.63)	0.0002
FIT indicated[c]	59.5		
FIT not indicated	43.9		

FIT: fecal immunochemical test; SCL: significant colorectal lesion; PPV: positive predictive value; OR: odds ratio; CI: confidence interval.
[a] Age was analysed as a continuous variable.
[b] Patients with missing information were listed as asymptomatic.
[c] When information provided was insufficient to determine FIT adequacy, we listed it as indicated.

CRC detection rates were comparable in asymptomatic and in patients presenting at least one warning feature (6.4% and 7.4% respectively). However, the PPV for SCL detection was significantly higher in asymptomatic than in symptomatic patients (56.4% and 45.7% respectively, OR 1.67, p = 0.0047). Similar results were found for AAs (51.9% and 40.6% respectively, OR 1.67, p = 0.0051). Statistical significance could not be reached for SCL and AA after adjustment for prespecified variables. Iron deficiency anemia was the only warning feature associated with a higher PPV for CRC detection. The PPV was 25.0% in patients with anemia and 6.6% in those without anemia (p = 0.0058) (Suppl.).

Three factors were related to a lower detection rate of SCL, AA, or both: a personal history of AA, the presence of diarrhea, and a normal colonoscopy within 10 years prior to actual colonoscopy. Finally, there was no significant difference between the 2 hospitals where colonoscopies were performed regarding lesion detection rates (Suppl.).

Table 3C
Performance of the FIT for AA detection, overall and in selected subgroups.

N = 556	PPV	Crude OR (CI95%)	p value
Overall	46.9		
According to sex		1.47 (1.04–2.07)	0.0272
Male	50.8		
Female	41.2		
According to age[a]		1.02 (1.00–1.04)	0.0446
< 50	20.0		
50–59	41.5		
60–69	49.8		
70–74	41.3		
≥75	54.1		
According to warning features		1.67 (1.17–2.38)	0.0051
Absent[b]	51.9		
Present	40.6		
According to adequacy of FIT		1.90 (1.36–2.66)	0.0002
FIT indicated[c]	54.8		
FIT not indicated	39.0		

FIT: fecal immunochemical test; AA: advanced adenoma; PPV: positive predictive value; OR: odds ratio; CI: confidence interval.
[a] Age was analysed as a continuous variable.
[b] Patients with missing information were listed as asymptomatic.
[c] When information provided was insufficient to determine FIT adequacy, we listed it as indicated.

3.6. Adequacy of the FIT

Only 50.1% of patients in our study were considered average CRC risk individuals, and thus had formal indications for undergoing a FIT. The most common reasons making the FIT unjustified were macroscopic rectal bleeding (61.8%), a normal colonoscopy in the last 10 years without new symptoms (12.9%), and new-onset diarrhea (10.0%) (Suppl.).

4. Discussion

To our knowledge, this is the first FIT performance assessment to be performed in the province of Quebec. It has already been evaluated elsewhere in Canada and worldwide under various screening programs (Major et al., 2013; Jensen et al., 2016; McNamara et al., 2014; Shah et al., 2014; Kapidzic et al., 2014; Hillyer et al., 2014; Redwood et al., 2014; Bujanda et al., 2014; Steele et al., 2013; Chubak et al., 2013; Bujanda et al., 2013; Parente et al., 2013; Parente et al., 2012; Faivre et al., 2012; Crotta et al., 2012; van Roon et al., 2013; Mandelli et al., 2011; Parente et al., 2009; van Rossum et al., 2008; Ciatto et al., 2007). It is difficult to compare our results with those previously published, because study designs are heterogeneous. Factors that may influence test performance, such as the positivity threshold value, sampling technique, analysis device, target population, and outcomes measured, vary widely.

With the data of 5 Canadian provinces from 2009 to 2011, Major et al. obtained PPVs of 50,6% and 4,3% for the detection of adenomas (any type or size) and CRC, respectively (Major et al., 2013). Our PPV for AA detection was lower, but we did not include non-advanced adenomas. On the other hand, our PPV for CRC detection was higher. The unusual 175 ng/mL positivity threshold value set by PQDCCR authorities may have influenced the results. However, other studies using OC-Sensor® technology with the recommended threshold of 100 ng/mL obtained similar or even higher PPVs than ours for CRC detection (Jensen et al., 2016; McNamara et al., 2014; Crotta et al., 2012; van Rossum et al., 2008). The inclusion of patients at higher cancer risk in our study did not seem to influence CRC detection since rates were similar, whether the FIT was warranted or not.

4.1. Influence of selected covariates

Increasing age was positively and independently related to the PPV for CRC detection after adjustment for sex, FIT adequacy, and warning signs. Most societies recommend screening beginning at age 50 (Rex et al., 2009; Davila et al., 2006; Bibbins-Domingo et al., 2016). The rationale underlying these guidelines is the occurrence of 90% of CRCs after this age. Also, only 2 studies have evaluated CRC screening in average-risk persons of 40 to 49 years of age and concluded to a low yield of screening in this age group, which is consistent with current practice (Rundle et al., 2008; Imperiale et al., 2002). The Canadian Task Force on Preventive Health Care recently issued a weak recommendation for screening individuals 50 to 59 years of age (Bacchus et al., 2016). On our part, we found a 5-fold greater risk for CRC detection in patients aged 60 and over, compared to younger patients. This could be of interesting value as part of a future cost-effectiveness evaluation of the PQDCCR. On the other hand, there are no clear recommendations regarding colorectal screening beyond age 74. The Canadian Task Force recommends discontinuing screening after 74 years of age (weak recommendation) (Bacchus et al., 2016), whereas the US Preventive Services Task Force advises that patients over age 85 not be screened and that the decision to screen adults 76 to 85 years be individualized depending on the patient's life expectancy and prior screening history (Bibbins-Domingo et al., 2016). Even though they are not included in the PQDCRR target population, patients 75 years of age and older in our study were assumed to be healthy enough to warrant screening, and their age alone was not a factor for FIT adequacy.

In our study, the FIT had better PPVs for SCL and AA detection in men. Additionally, we observed a similar trend for CRCs, although the difference was not statistically significant. These results are most likely due to a higher prevalence of SCL among men in the general population (Nguyen et al., 2009). A recent prospective study (van Turenhout et al., 2014) suggested using different positivity threshold values, based on sex. Using OC-Sensor® technology and threshold values ranging from 75 to 200 ng/mL, the FIT was shown to be more sensitive and less specific in men than in women for CRC detection, even after adjustment for age and location of lesions. Similarly, even though we did not specifically analyse this possibility, our results raise the question of whether screening could safely start at a later age in women.

PPVs for SCL and AA detection were higher among patients whose FIT was formally indicated. This could be explained by the fact that many benign conditions may lead to positive FIT results as well. For instance, rectal bleeding, which was the most common reason making a FIT inappropriate, was much more often due to hemorrhoids than to a premalignant or malignant lesion.

Unexplained iron-deficiency anemia was the only symptom associated with a more frequent detection of CRC. Anemia is reported in most patients diagnosed with CRC (Majumdar et al., 1999; Rizk and Ryan, 1994), as well as rectal bleeding. However, the latter was not related to a higher neoplastic lesion detection rate in our study. As mentioned earlier, benign anorectal conditions may have accounted for a considerable part of all positive FITs, which once again highlights the test's high sensitivity and low specificity.

Half of prescribed FITs were not initially warranted. This observation reinforces the need for the PQDCCR to make primary care physicians more aware of the specific characteristics of its target population, by providing continuing medical training material.

4.2. Study strengths

Our study has many strengths. First, we included a large number of patients, which made most of our results statistically significant. Also, few patients were excluded from primary analyses. Second, standardized colonoscopy reporting through Endoworks® software improved the quality of the collected data. But most of all, unlike other studies, we examined outcomes related to the adequacy of the FIT prescription, providing a more realistic picture of its use in clinical practice, compared to an ideal setting comprised only of a screening program's target population.

4.3. Study limitations

An inherent limit to our study is its retrospective design. Thus, we cannot provide firm evidence of correlations between assessed variables and the detection rate of colorectal lesions; we can only illustrate certain trends. Similarly, neither could we assess the FIT's uptake (i.e. the proportion of patients who underwent the test after it was prescribed), nor its long-term impact on CRC mortality and other clinical outcomes.

One major limitation of our study is the missing information regarding false-negative results, which prevents calculation of the test's sensitivity. Currently, all FIT samples obtained in the province of Quebec are processed at a single designated center located in Sherbrooke. Thus, identifying all negative results for a given period would be feasible. However, technically, it would be extremely difficult to trace patients who would eventually be diagnosed with a SCL shortly after a negative FIT. Interestingly, the PQDCCR authorities have planned to determine the test's sensitivity as part of their quality assurance assessment (Lévesque and Pelletier, 2013); this will most likely require a randomized controlled setting.

Moreover, we could only provide an estimation of the proportion of warranted FITs because of recurrent missing information about patients' family, personal history and symptoms. We relied solely on the colonoscopists' medical notes and could not access FIT prescribers'. Also, as previously observed (Rex et al., 2009), it was difficult for patients who had a family member who had undergone a polypectomy to tell whether they were benign polyps or advanced adenomas. In those cases, we assumed they were benign when evaluating the relevance of family history. Overall, when clinical information was insufficient to judge on FIT's adequacy, we supposed that it was indicated. For all those reasons, the proportion of indicated FITs was more than likely overestimated, although it remains largely suboptimal. Conversely, in additional subgroup analyses (Suppl.), we excluded patients for which information regarding the examined variable was missing.

The ACG recommends that CRC screening start at 45 years of age in people of African descent (Rex et al., 2009). The retrospective design of our study did not allow us to isolate this subgroup of patients.

Finally, we were unable to verify whether colonoscopy wait times agreed with PQDCCR standards (Direction québécoise de cancérologie du ministère de la Santé et des Services sociaux du Québec, 2014), because a colonoscopy request form was seldom retained in a patient's medical record, Yet, when it was available, we usually observed a wait time of < 60 days, which is the set benchmark for most provinces, including Quebec.

5. Conclusion

FIT's PPV for detecting CRC is higher in our setting than in the rest of Canada, but the clinical significance of this difference remains unclear. The test holds a better PPV for detecting SCL and AA among men, and when it is indicated per PQDCCR recommendations. Unexplained iron deficiency anemia is associated with a higher rate of CRC detection. Half of the positive FITs were not initially indicated. Given the fact that clinical governance has become a major issue in our healthcare system in the last few years, it appears clear that primary care physicians should be made more aware of FIT's appropriate use.

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Appendix A. Supplementary data

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