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Cost-effectiveness of fecal calprotectin used in primary care in the diagnosis of inflammatory bowel disease

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is a chronic, autoimmune, gastrointestinal disorder. Canada has one of the highest prevalence and incidence rates of IBD in the world. Diagnosis is challenging due to the similarity of symptoms to functional gastrointestinal disorders. Fecal calprotectin (FC) is a biomarker for active mucosal inflammation and has proven effective in the diagnosis of IBD. Our study objective was to assess the cost-effectiveness of adding a FC test compared with standard practice (blood test) in primary care among adult patients presenting with gastrointestinal symptoms.

Design: We constructed a decision analytic tree with a one-year time horizon. The cut-off level of 100μg/g was used for FC testing. Probabilistic analyses were conducted for the base case and all scenarios.

Setting: Canadian health sector perspective.

Population: A hypothetical cohort of adult patients presenting with gastrointestinal symptoms in the primary care setting

Interventions: FC test compared with blood test

Main outcome measures: Costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER) of FC test expressed as cost per QALY gained compared with blood test, and time to IBD diagnosis.

Results: FC testing costs more ($295.1 vs. $273.9) than standard practice but yielded little higher QALY (0.751 vs. 0.750). The ICER of FC test was $20,323 per QALY. Probabilistic analysis demonstrated that at a willingness-to-pay threshold of $50,000 per QALY, there was 81.3% probability of FC test being cost-effective. The use of FC test in primary care reduced the

time to IBD diagnosis by 40.0 days (95% Confidence Interval: 16.3-65.3 days), compared with blood testing alone.

Conclusions: Screening adult patients in primary care by FC test at the cut-off level of 100µg/g is cost-effective in Canada.

ARTICLE SUMMARY

Strengths and limitations of this study

- This paper presents a cost-effectiveness analysis (CEA) comparing a fecal calprotectin test to blood test in diagnosis of inflammatory bowel disease (IBD) in the primary care setting.
- This was the first CEA of FC test in the Canadian context and one of few CEAs of FC test in the primary care setting in literature.
- We also compared the average time to IBD diagnosis between using FC test and blood test in primary care and estimated the reduced time to IBD diagnosis by using FC test.
- The analysis was from the Canadian health sector perspective and did not consider costs (e.g., productivity losses) from a societal perspective.

INTRODUCTION

Inflammatory bowel disease (IBD), of which the two main subtypes are Crohn's Disease (CD) and ulcerative colitis (UC), is characterized by mucosal inflammation and ulceration of the gastrointestinal tract. During the course of the disease, patients often present with symptoms such as diarrhea, abdominal pain, and fatigue, which significantly impact the quality of life of IBD patients.[1] Canada has one of the highest reported prevalence and incidence rates of IBD in the world.[2] The prevalence of IBD in Canada was estimated at 0.67% [129,000 individuals with CD and 104,000 with UC] in 2012, with approximately 10,200 incidents occurring annually.[3] The corresponding economic costs of IBD were estimated at $2.8 billion.[3]

In order to distinguish IBD from functional gut disorders that often share similar symptoms, the conventional diagnostic pathway in primary care includes initial blood tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are used to determine whether patients should be referred to gastroenterologists for further investigation including imaging studies and/or endoscopy.[4] However, these blood tests lack accuracy. They may not only delay IBD diagnosis in the case of false negatives, but also lead to unnecessary endoscopies in the case of false positives.[5,6] Due to limited resources, endoscopy is not readily accessible in many areas of Canada and unnecessary endoscopies can have further impacts on health care resources and costs.

Recently, the detection of fecal calprotectin (FC), the most extensively studied fecal marker of IBD, has been shown to be an accurate and useful screening tool for identifying patients who need further investigation through endoscopy.[5–8] The majority of studies that assessed the

accuracy of FC testing to date have been in the secondary care setting.[5–7] A recent prospective primary care cohort study conducted in the United Kingdom (UK) demonstrated that FC testing using the cut-off of 100 µg/g accurately distinguishes IBD from functional gut disorder in primary care and reduces secondary care referrals as well as diagnostic health care costs.[9] Waugh *et al*. have also shown that FC testing is cost-effective for distinguishing between IBD and non-IBD in adults in primary care in the UK.[6,10] The National Institute for Health and Care Excellence (NICE) in the UK therefore recommends FC testing as an option to help clinicians distinguish between IBD and non-IBD in adults with recent onset of gastrointestinal symptoms.[10] In Canada, however, FC tests are currently only covered by provincial health plans in Alberta and Quebec, as well as some extended health insurance plans.[11] There is still no cost-effectiveness evidence within primary care in Canada. The objective of this study, therefore, is to determine the cost-effectiveness of FC testing in the diagnosis of adult cases of IBD in primary care from the Canadian health care sector perspective.

MATERIALS AND METHODS

Decision model

A decision analytic model was built to estimate the cost-effectiveness of using FC test as compared to the current practice using blood test, in the screening for IBD in the primary care setting. The patient population in the model was a hypothetical cohort of adult patients aged 19 to 64 years old, presenting with gastrointestinal symptoms suggestive of IBD in a primary care setting. No patients were involved in this study. A decision tree was developed in Microsoft Excel where the hypothetical cohort of adult patients underwent certain pathways. The

associated cost and effectiveness of each pathway was captured in the model and the expected cost and effectiveness was estimated.

Effectiveness was measured using quality-adjusted life years (QALYs). The time horizon for the cost-effectiveness analysis was one year as this was a reasonable length of time for a patient to reach a confirmed diagnosis of either IBD or non-IBD. Due to the brief time horizon, discounting was not applied to either costs or benefits in this analysis. Time to IBD diagnosis was also estimated from the model. The analysis perspective was the Canadian health sector.

The clinical pathways of patients presenting with gastrointestinal symptoms in primary care were established from published literature[6,12–14] as well as input by two gastroenterologists from St. Paul's Hospital, Vancouver. Established clinical pathways were consistent with the best-practice clinical care pathway for management of irritable bowel syndrome (IBS) in primary care as outlined by the Canadian Association of Gastroenterology[15] and local primary care guidelines on the use of FC by the NICE, UK.[16]

Figure 1 illustrates the current practice using the standard blood test whereas Figure 2 depicts the proposed strategy of adding FC test as a diagnostic support tool for general practitioners (GPs). Under the current practice (Figure 1), based on results of the blood investigation (ESR and CRP), a GP will make a decision on whether to refer patients to specialist care or not. Patients with abnormal blood results will be referred to gastroenterology for specialist assessment. The specialist may then order an endoscopy as necessary to confirm IBD diagnosis or follow-up with patients unlikely to have IBD and monitor their symptoms accordingly. If symptoms are still

persistent after 3 months (assumed and same as Waugh *et al*.[6]), an endoscopy may be ordered at the specialist follow-up visit to confirm diagnosis of IBD. Under the proposed strategy of adding FC test (Figure 2), patients with positive results of FC test will be referred to specialist care and an endoscopy will be ordered for them at the specialist visit to confirm diagnosis of IBD.

Patients with normal blood results or negative FC test results will be followed-up by the GP and receive lifestyle and dietary advice with appropriate medication to treat symptoms for 3 months (assumed) (Figure 3). Those with symptoms inadequately controlled will receive more intensive management (different medication) from their GP for another 4 weeks (assumed). If symptoms are still persistent, further assessment by a gastroenterologist and endoscopy will be performed.

Model parameters

The model parameters (Table 1) were obtained from literature or based on assumptions. The parameters include sensitivity and specificity for FC testing at the 100 µg/g cut-off and ≥15mm/h for ESR and ≥5mg/l for CPR blood testing; prevalence of IBD in primary care; the ratio of UC and CD; non-IBD patients with negative test results; costs; utilities; and waiting time.

Sensitivity and specificity

The 100 µg/g cut-off was proposed for FC testing in this analysis. As mentioned above, the majority of studies measuring FC testing accuracy were conducted in the secondary care setting. As such, we used the sensitivity and specificity of FC testing at the 100 µg/g cut-off from the recent UK study conducted with the prospective primary cohort.[9] For blood testing, we chose the cut-offs of ≥15mm/h for ESR and ≥5mg/l for CRP. Three studies using these

ESR and CRP cut-offs were identified from a published systematic review.[5] Following this, a meta-analysis was conducted to synthesize the logit-transformation of sensitivity and specificity.

Prevalence of IBD in primary care

Very few studies have estimated the prevalence of IBD in primary care,[6,9,17–19] with most estimates originating from UK studies. To be consistent with the sensitivity and specificity estimates used in our model, we used the prevalence of IBD (=6.8%) in primary care from the same study.[9] Among IBD cases, 45% were UC and 55% were CD.[3]

Non-IBD patients with negative test results

Previous studies estimated a 50% or 60% probability of non-IBD patients still having persistent symptoms after the initial management by GPs, estimates were based on expert opinion.[12–14] In our study, we applied the 47% probability used in the cost-effectiveness analysis conducted by Waugh *et al*.[6] We also assumed that 15% of these who have persistent symptoms after initial management by GP (based on expert advice) would subsequently experience uncontrolled symptoms after further intensive management by GPs, be referred to a specialist, and undergo endoscopy.

Costs

Only the diagnosis related costs, including the costs for diagnostic testing (FC, endoscopy, and pathology) and physician and gastroenterologist visits, were considered. All costs were reported in 2017 Canadian dollars. Cost data were obtained from the British Columbia

Ministry of Health Medical Services Commission Payment Schedule (July 1, 2017 version)[20] which is comparable with other provinces in Canada; literature review for colonoscopy cost in Canada adjusted to 2017 cost using total health care implicit price index;[21] and literature review and a local gastroenterology clinic for FC testing cost.[6,14] Costs of managing complications associated with colonoscopy such as bleeding and perforation were not considered in this analysis due to the unavailability of data.

Utilities

Our utility estimates for IBS were taken from a study conducted among 257 patients in the United States (US) using EuroQol-5D.[22] The utilities of 0.78 for IBS patients with adequate relief of symptoms or 0.73 for those with persistent symptoms were applied to non-IBD patients in our analysis.[22] A weighted IBS utility of 0.76 was calculated based on the proportion (47% assumed above) of non-IBD patients with persistent symptoms and the remaining 53% with adequately controlled symptoms. In our model, patients with adequately controlled symptoms started with a weighted utility of 0.76 until the time of diagnosis, wherein a weighted utility of 0.78 (utility for adequately controlled) was applied for the rest of the one-year time horizon. Patients with persistent symptoms started with 0.73 (utility for persistent symptoms) until the time of diagnosis followed by 0.78 if symptoms were eventually controlled or 0.76 if they had to undergo endoscopy.

Similar to Waugh *et al*.[6], our utility estimates of IBD were taken from a study conducted among 225 CD patients and 219 UC patients in Germany using the EuroQol-5D.[23] This study had a reasonably large sample size and reported utility estimates for active disease compared with

remission for both UC and CD. The utility estimates of 0.71 for active UC and 0.61 for active CD were chosen to represent the utility of IBD patients when they visited GP for the first time. We assumed that their utilities would then decrease by a certain amount every month due to disease progression until diagnosis was made, at which point the utility value at the time of diagnosis would be maintained throughout the rest of the one-year time horizon. Following the method of Waugh *et al*. by taking the utility difference between active disease and remission and dividing it by twelve, we derived a monthly utility decrement of 0.0167 for UC and 0.023 for CD.[6]

Waiting time

The median time an IBD patient was first referred to specialist until consultation by a specialist was 72 days (95% confidence interval (CI) 52-121) and the median time from the first specialist consultation to endoscopy was 44 days (95% CI: 27-100) in Canada.[24] The median time for non-IBD patients from the first referral to specialist consultation was 126 days (95% CI: 103-141).[24] Other wait times were assumed to be fixed according to the guidelines.

Analyses

All costs were reported in 2017 Canadian dollars. We performed probabilistic analyses to estimate means and 95% CI of total costs, QALYs, and incremental cost-effectiveness ratios (ICERs) to reflect the underlying parameter uncertainty. Additionally, the time to the diagnosis of IBD among IBD patients was calculated. A total of 5,000 Monte Carlo simulations were generated from the parameter probability distributions. The base-case results were presented as the cost-effectiveness acceptability curve, which demonstrates the probability of the FC testing

strategy being cost-effective compared to the standard care across a range of willingness-to-pay thresholds. To explore the sensitivity of results to specific parameter uncertainty, alternative assumptions and sources of data, we conducted a series of scenario analyses.

RESULTS

Base case

For the base case, the probabilistic analysis based on 5,000 Monte Carlo simulations showed that the FC testing strategy was about $21 more expensive than the standard practice using blood test ($295.12 vs. $273.93) but yielded a slightly higher QALY (0.751 vs. 0.750, respectively) (Table 2). Thus, the ICER was $20,323.35 per QALY gained. The time to diagnosis for IBD patients was 39.96 days (95% CI: 16.34-65.29) shorter under the FC testing strategy (192.39 days (95% CI: 143.10-239.74) than standard practice (232.36 days (95% CI: 186.02-277.92)). There was an 81.3% probability that the FC testing strategy was cost-effective at the willingness-to-pay threshold of $50,000/QALY (Figure 4).

Scenario analyses

We conducted a series of scenario analyses (Table 2). 1) IBD prevalence was varied from 5% to 20% in 5% increments. 2) FC testing accuracy was changed using alternative data source. The meta-analysis results of sensitivity and specificity at the cut-off of 50 μg/g (conducted and used by Waugh *et al*.[6]) were used in the model. The estimated mean for both sensitivity and specificity were higher than the inputs we applied in the base case. 3) We increased the proportion of patients with abnormal blood test for whom an endoscopy was ordered in the initial gastroenterologist consultation from 83% to 100%. 4) We changed the proportion of non-IBD

patients with symptoms after further intensive management by GPs that needed further investigation by specialist and endoscopy from 5% (same as Waugh *et al*.[6] and Whitehead *et al*.[12]) to 25% with 5% increments. 5) Different FC test costs and an increase or decrease in other costs by 20% were implemented. 6) We changed the source of utility decrement estimates from Stark *et al*.[23] to that of Gregor *et al*.[25]and Poole *et al*.[26] 7) Time taken to the first follow-up by GP and time taken to follow-up by a specialist were changed from 1 month to 4 months with 1-month increments.

Our analyses showed that the cost-effectiveness of FC testing strategy was sensitive to the prevalence of IBD among the patients presenting with gastrointestinal symptoms in primary care, the FC cost, and the value of utility decrements. When the prevalence increased to 20%, the probability of FC testing strategy being cost-effective would increase to 96.7% at the threshold of $50,000/QALY. The price threshold at which FC testing strategy became cost-effective was $70. At $70, the probability of FC testing being cost-effective was 47.4% at the willingness-to-pay threshold of $50,000/QALY. When applying a much lower utility monthly decrement especially for CD (from 0.023 to 0.006 for CD and from 0.017 to 0.014 for UC), the probability of FC testing strategy was 68.6% at the threshold of $50,000/QALY.

DISCUSSION

Based on cost-effectiveness models built in previous studies,[6,12–14] current practice guidelines in Canada,[15] and clinical expertise from gastroenterologists, we constructed a decision analytic model to evaluate the cost-effectiveness of adding FC testing to current practice compared with the current practice of blood test only in the diagnosis of adult IBD patients in the Canadian

primary care setting. To our knowledge, this is the first cost-effectiveness analysis of FC testing in primary care in Canada. Our base-case analysis suggested that the FC test was cost-effective. Probabilistic analysis showed that at a willingness-to-pay threshold of $50,000 per QALY, there was an 81.3% chance of the FC testing strategy being cost-effective. Scenario analysis demonstrated that the cost-effectiveness was most sensitive towards prevalence of IBD, monthly utility decrement of IBD, and cost of FC test.

A 6.8% prevalence of IBD was applied in our base case analysis. This estimate was based on a prospective UK primary care cohort,[9] the prevalence was very similar to the one used in the cost-effectiveness analysis conducted by Waugh *et al*.[6] Unfortunately, Canadian estimates were not found in published literature. Thus, we conducted scenario analysis by varying the prevalence from 5% to 20%. Although the cost-effectiveness of the FC testing strategy was highly sensitive to the prevalence of IBD in the adult patient population presented in the primary care setting, our study has shown it is still cost-effective when the prevalence is as low as 5%.

The ICER of the FC testing strategy compared with blood testing increased when the monthly utility decrement for IBD was lower. This finding is consistent with the assumption made in the calculation of QALYs for IBD patients. A delay in diagnosis would cause patients to reach a lower utility value before diagnosis. Therefore, a higher utility decrement for IBD increased the difference in QALYs gained between the two strategies and caused a decrease in ICER and vice versa.

We used the current FC test cost, $40, in our base case, which was consistent with the cost used in previous cost-effectiveness analyses conducted in the UK and US.[6,14] When the cost of FC testing was under $70, the FC testing strategy had the potential to be cost-effective. The wider implementation of FC testing across Canada may drive the cost down. Laboratory-based FC testing has been shown to be cost-effective when conducted in batches.[6,10]

One of the strengths of our study is that we used the FC testing accuracy in primary care [9] instead of the secondary care setting. The test accuracy in the secondary care setting was found to be higher than that of primary care setting. According to the most recent meta-analysis conducted by Waugh *et al*.,[6] all of studies included were for secondary setting and the synthesized sensitivity (0.93) and specificity (0.94) of FC testing at the 50µg/g cut-off were both higher than the estimates (0.86 and 0.90) for the 100µg/g cut-off we used for the primary care setting.

Additionally, we estimated the benefit of using FC testing in primary care in terms of reducing the time to IBD diagnosis (by about 40 days). The average times to IBD diagnosis among IBD patients were 192.4 days with FC testing and 232.4 days for standard practice. The time to diagnosis under the standard practice was reasonably consistent with a Canadian study that reported the mean time to diagnosis for CD and UC to be 255.5 and 202.3 days, respectively.[27] Delayed diagnosis is a common problem in IBD. A study involving 1,591 IBD patients from the Swiss IBD cohort reported a diagnostic delay of 9 and 4 months for CD and UC.[28] The delay was due to similarities in symptoms among patients with mild IBD and those with IBS. A literature review on natural history studies of CD reported that at time of diagnosis, one third of patients

already had intestinal complications such as ileitis, colitis, or ileocolitis.[29] In UC, an early diagnosis and identification of patients with a high risk of developing complicated disease, is crucial for choosing appropriate treatment and prevention of colectomies.[30] The FC testing strategy has the potential to speed up diagnosis and reduce the wait time for a specialist and endoscopy by avoiding the unnecessary referrals.

Our study has several limitations. First, there was a lack of data for certain parameter inputs of the model. For example, costs and utility decrements of complications associated with colonoscopy such as bleeding and perforation could not be identified and were therefore not considered in this analysis. In Canada, the pooled rates of colonoscopy-related bleeding, perforation, and mortality were 1.64/1000, 0.85/1000, and 0.074/1000, respectively.[31] While the rates of complications associated with colonoscopy may be low, the impact on the overall costs and outcomes may be significant if the time horizon of the analysis was longer, especially when deaths occur. As the number of colonoscopies were expected to be reduced by FC testing, we took a more conservative approach by not considering the impact of the complications associated with colonoscopies. Data on the utility decrement of IBD due to delayed diagnosis was also unavailable. Therefore, we adopted the approach used in Waugh *et al*.,[6] assuming the annual utility decrement of IBD due to delayed diagnosis as the difference between active disease and remission of UC. While our CEA was limited to costs from a health sector perspective, considering costs from a societal perspective, e.g., productivity losses due to colposcopy, would further make FC testing more cost effective.

Secondly, some modelling assumptions we made may have simplified actual clinical practice. For instance, the modelling assumed that patients with FC levels above 100µg/g have positive test results and patients with FC levels below 100µg/g have negative test results. Subsequently, every patient who tests positive is referred to secondary care and will receive endoscopy. The modelling does not consider indeterminate results of FC testing and assumes that FC testing is only carried out once and is not repeated in the diagnosis pathway. In actual practice, patients whose initial FC test results were found to be within an indeterminate range, for example between 100µg/g to 250µg/g, may be subjected to a second FC test and only be referred to a specialist if the result of the second FC test still yielded a result above 100µg/g. Literature showed that over 10% of patients had results which fell in this 'grey zone'.[16] Retesting patients with indeterminate results will essentially increase the cost of the FC testing strategy. However, the impact of retesting on the overall costs will depend on the proportion of patients who fall back to FC levels below 100µg/g and would not need to be referred unnecessarily, avoiding the costs of specialist consultations and colonoscopies.

Additionally, our modelling assumed 100% patient uptake for every diagnostic test, blood test, FC test, and endoscopy. Given the invasive nature and set of complications associated with colonoscopies, patients may refuse this diagnostic test. The FC test may also not be widely accepted, with a variable uptake rate between primary and secondary care. Some patients might decline to produce a sample of feces for their GP, but may possibly be willing to do so for a gastroenterologist if the alternative is colonoscopy. Recently, a home-based FC kit has been made available, allowing patients to measure the concentration of FC directly using a rapid

immunochromatographic assay captured by a smartphone's camera. The availability of this kit may increase the uptake and patient adherence of FC testing.[32]

Future research can be conducted to estimate the cost-effectiveness of FC test for distinguishing between IBD and non-IBD in the paediatrics population when the important model parameters are available. Furthermore, there has also been growing interest in the use of FC test in a few areas of IBD management. For example, FC test might be used to monitor disease progression, predict relapse and monitor response to treatment.[33] As such, an economic model which links the diagnostic outcomes of this analysis to the management of IBD in terms of treatment and monitoring can be considered in the future.

In conclusion, using FC at the 100µg/g cut-off in primary care in the diagnosis of IBD can be a cost-effective strategy and can speed up IBD diagnosis in adults who present with gastrointestinal symptoms in Canada.

Author Statement:

WZ and GR designed the study. All authors contributed to the cost-effectiveness model: CHW initiated the model, MC, TM and GR contributed their expertise in the model building and parameter determination, and WZ modified and finalized the model. WZ and CHW drafted the manuscript and all authors significantly contributed to and reviewed the final manuscript. All authors agree to be accountable for all aspects of the work.

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Competing interests: None declared.

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Data sharing statement: There is no additional unpublished data from the study.

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Table 1. Model input parameters

Parameter	Estimate	Distribution	Distribution parameters	Data source
IBD prevalence, %	6.8	Beta	Alpha = 50 Beta = 689	Walker et al.[9]
UC proportion, %	44.6	Fixed		Rocchi et al.[3]
Test accuracy				
Sensitivity				
Blood test	0.649	Normal, logit transformation	Logit estimate = 0.613 Logit SE = 0.199	Meta-analysis based on Jellema et al.[5]
FC test, at 100µg/g cut-off	0.860	Beta	Alpha = 43 Beta = 7	Walker et al.[9]
Specificity				
Blood test	0.866	Normal, logit transformation	Logit estimate = 1.867 Logit SE = 0.196	Meta-analysis based on Jellema et al.[5]
FC test, at 100µg/g cut-off	0.901	Beta	Alpha = 621 Beta = 68	Walker et al.[9]
Model probabilities, %				
Proportion of patients with abnormal blood test with endoscopy ordered in the initial gastroenterologist consultation	88.3	Beta	Alpha = 7.520 Beta = 0.993	Expert opinion
Proportion of non-IBD patients with persistent symptoms after the initial management by GPs	47.0	Log-normal	95% CI: 33-57	Waugh et al.[6]
Proportion of non-IBD patients with symptoms after further intensive management by GPs that need further investigation by specialist and endoscopy	15.0	Fixed		Expert opinion
Cost estimates ($)				
Colonoscopy, with biopsy	427.70	Fixed		Sharara et al.[34]
Surgical pathology	85.52	Fixed		BC MSC payment schedule[20]
FC test	40.00	Fixed		Local clinic cost, Waugh et al.[6] and Yang et al.[14]
Initial GP visit	68.64	Fixed		BC MSC payment schedule[20]
Follow-up GP visit	30.92	Fixed		BC MSC payment schedule[20]
Initial gastroenterologist consultation	160.25	Fixed		BC MSC payment

Parameter	Estimate	Distribution	Distribution parameters	Data source
				schedule[20]
Follow-up gastroenterologist consultation	97.39	Fixed		BC MSC payment schedule[20]
Utilities				
IBD				
Active UC	0.71	Beta	Alpha = 3.802 Beta = 1.553	Stark et al.[23]
Active CD	0.61	Beta	Alpha = 1.116 Beta = 0.713	Stark et al.[23]
Monthly utility decrement for UC	0.017	Beta	Alpha = 1.601 Beta = 94.443	Stark et al.[23]
Monthly utility decrement for CD	0.023	Beta	Alpha = 1.647 Beta = 68.958	Stark et al.[23]
Non-IBD				
a) With adequately controlled symptoms	0.78	Beta	Alpha = 5.367 Beta = 1.514	Spiegel et al.[22]
b) With persistent symptoms	0.73		Calculated from a/c	Spiegel et al.[22]
c) Fixed ratio for utility of adequately controlled over persistent symptoms		Fixed	1.068	
Weighted IBS utility	0.76		Calculated from a), b) and Proportion of non-IBD patients with persistent symptoms above	
Wait time				
Time taken to undergo blood test and/or FC test after presenting with symptoms in primary care	7 days	Fixed		Expert opinion
Time taken to obtain results of blood test and FC test	7 days	Fixed		Expert opinion
Time taken to follow-up by GP first time	3 months	Fixed		Expert opinion
Time taken to follow-up by GP second time	4 weeks	Fixed		Expert opinion
Time taken to a specialist consultation for IBD patients	86.50	Normal	SE=17.602	Leddin et al.[24]
Time taken to a specialist consultation for non-IBD patients	122.00	Normal	SE=9.694	Leddin et al.[24]
Time taken to endoscopy after seeing a specialist	63.50	Normal	SE=18.622	Leddin et al.[24]
Time taken to follow-up by a specialist	3 months	Fixed		Expert opinion

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; FC: fecal calprotectin; GP: general practitioner; IBS: irritable bowel

Parameter	Estimate	Distribution	Distribution parameters	Data source
syndrome; SE: standard error; MSC: Medical Services Commission				

Table 2. Results of base-case analysis

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
Base-case	295.12 (274.49,317.53)	0.751 (0.431,0.939)	273.93 (245.40,306.05)	0.750 (0.430,0.938)	21.19 (-7.50,46.57)	0.001 (0.0003,0.002)	20,323.35	81.3%
Scenario Analysis								
IBD prevalence, %								
5	286.17 (268.43,306.09)	0.757 (0.427,0.943)	264.65 (238.41,294.96)	0.756 (0.426,0.942)	21.52 (-7.75,46.72)	0.001 (0.0002,0.002)	24,440.81	75.5%
10	312.60 (295.98,331.11)	0.743 (0.434,0.928)	291.21 (267.12,319.28)	0.742 (0.433,0.927)	21.39 (-5.67,45.80)	0.001 (0.0004,0.003)	15,594.08	89.3%
15	339.26 (323.00,357.86)	0.740 (0.448,0.916)	318.14 (294.04,345.63)	0.738 (0.447,0.915)	21.12 (-5.02,43.94)	0.002 (0.0004,0.005)	11,515.23	93.8%
20	365.81 (350.40,383.68)	0.728 (0.442,0.907)	344.93 (322.74,371.08)	0.725 (0.440,0.904)	20.88 (-3.94,41.96)	0.002 (0.0006,0.006)	8,843.74	96.7%
FC test accuracy at 50 µg/g cut-off (Waugh et al.[6])								
Sensitivity=0.93 (CI: 0.83-0.97) Specificity=0.94 (CI 0.73-0.99)	285.81 (240.29,392.06)	0.753 (0.424,0.939)	274.25 (246.24,306.17)	0.752 (0.423,0.938)	11.55 (-38.38,120.29)	0.001 (-0.0006,0.003)	8,535.62	82.1%
Proportion of patients with abnormal blood test with endoscopy ordered in the initial gastroenterologist consultation, %								
100	295.38 (274.60,317.32)	0.751 (0.430,0.938)	276.23 (248.77,307.54)	0.750 (0.429,0.937)	19.15 (-10.31,44.69)	0.001 (0.0002,0.002)	22,007.50	76.9%
Proportion of non-IBD patients with symptoms after further intensive management by GPs that need investigation by specialist and endoscopy, %								
5	268.69 (251.37,286.92)	0.754 (0.444,0.940)	248.96 (222.27,278.72)	0.753 (0.444,0.939)	19.73 (-10.67,46.48)	0.001 (0.0003,0.003)	17,988.04	83.5%
10	281.84 (263.26,301.20)	0.754 (0.447,0.938)	261.12 (234.23,290.74)	0.753 (0.446,0.937)	20.72 (-8.35,46.16)	0.001 (0.0002,0.002)	19,504.34	82.4%
20	308.68 (286.39,332.03)	0.751 (0.426,0.938)	286.82 (257.72,318.88)	0.750 (0.426,0.938)	21.85 (-5.70,45.83)	0.001 (0.0002,0.002)	21,405.41	81.2%
25	322.23 (297.17,350.17)	0.749 (0.423,0.937)	300.26 (268.29,334.99)	0.748 (0.422,0.936)	21.97 (-5.25,45.94)	0.001 (0.0003,0.002)	22,040.22	79.5%
Cost of FC, $								
50	305.42 (284.54,327.76)	0.751 (0.428,0.941)	274.12 (246.34,305.69)	0.750 (0.428,0.940)	31.29 (2.93,55.78)	0.001 (0.0003,0.002)	29,789.72	71.7%
60	315.60	0.751	274.19	0.750	41.40	0.001	39,243.50	59.8%

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
	(295.76,337.54)	(0.430,0.936)	(246.49,305.45)	(0.430,0.936)	(13.49,66.07)	(0.0002,0.002)		
70	325.29	0.753	274.15	0.751	51.14	0.001	48,712.48	47.4%
	(305.29,347.98)	(0.428,0.938)	(246.63,305.86)	(0.427,0.936)	(22.70,75.99)	(0.0002,0.002)		
All cost estimates except FC test cost, $								
+20%	346.68	0.752	329.42	0.751	17.26 (-16.39,48.03)	0.001	16,191.86	83.4%
	(321.97,372.92)	(0.430,0.940)	(295.89,367.82)	(0.429,0.939)		(0.0003,0.002)		
-20%	244.18	0.752	219.14	0.751	25.04	0.001	23,509.13	79.8%
	(227.92,262.28)	(0.433,0.936)	(196.94,244.50)	(0.432,0.935)	(2.13,44.91)	(0.0003,0.003)		
Utility decrement								
CD = 0.006 (Gregor et al.[25]) UC = 0.014 (Poole et al.[26])	295.11 (274.59,316.66)	0.755 (0.427,0.941)	274.24 (246.79,304.96)	0.755 (0.427,0.940)	20.87 (-6.50,45.47)	0.001 (0.0002,0.001)	30,136.89	68.6%
Time taken to follow-up by GP first time								
1 month	294.97	0.756	274.09	0.755	20.89 (-8.13,46.10)	0.001	18,830.57	81.9%
	(274.80,316.36)	(0.422,0.945)	(245.92,306.40)	(0.421,0.944)		(0.0002,0.002)		
2 months	295.36	0.758	274.07	0.757	21.29 (-7.90,45.83)	0.001	19,650.08	81.7%
	(274.91,317.69)	(0.437,0.943)	(246.25,306.46)	(0.436,0.942)		(0.0002,0.002)		
4 months	295.28	0.749	274.03	0.748	21.25 (-6.75,45.57)	0.001	21,451.73	80.8%
	(275.08,317.76)	(0.442,0.940)	(245.76,304.35)	(0.441,0.939)		(0.0002,0.002)		
Time taken to follow-up by a specialist								
1 month	295.47	0.747	274.37	0.746	21.10 (-7.54,46.45)	0.001	23,213.73	76.1%
	(275.10,317.87)	(0.425,0.937)	(246.13,305.91)	(0.424,0.936)		(0.0002,0.002)		
2 months	295.35	0.757	274.19	0.756	21.16 (-7.75,45.96)	0.001	21,587.69	79.6%
	(275.19,318.36)	(0.435,0.939)	(247.23,305.55)	(0.434,0.937)		(0.0002,0.002)		
4 months	295.49	0.751	274.42	0.750	21.07 (-7.51,46.49)	0.001	18,991.77	83.4%
	(274.69,317.09)	(0.430,0.940)	(246.23,305.94)	(0.429,0.939)		(0.0003,0.003)		

95% confidence intervals (CI) in brackets
IBD: inflammatory bowel disease; FC: fecal calprotectin; GP: general practitioner; CD: Crohn's disease; UC: ulcerative colitis; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio
*at $50,000/QALY threshold

Figure 1. Overview of the model structure for standard practice using blood test

IBD: inflammatory bowel disease; GP: general practitioner

Figure 2. Overview of the model structure for fecal calprotectin testing strategy

FC: fecal calprotectin IBD: inflammatory bowel disease; GP: general practitioner

Figure 3. Overview of the decision branch for normal blood test or negative fecal calprotectin test results

FC: fecal calprotectin IBD: inflammatory bowel disease; GP: general practitioner

Figure 4. Cost-effectiveness acceptability curve

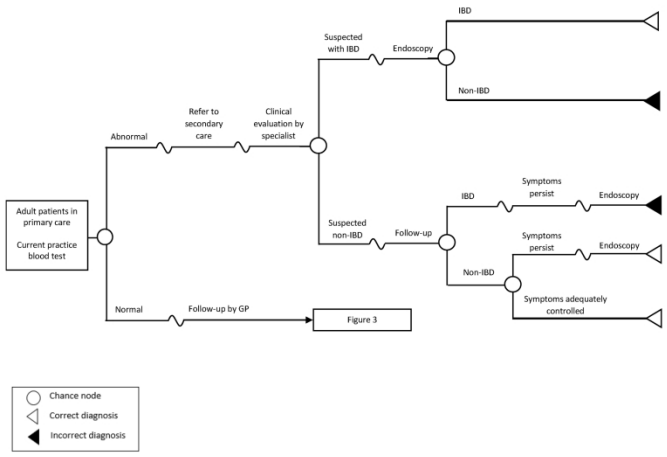

Figure 1

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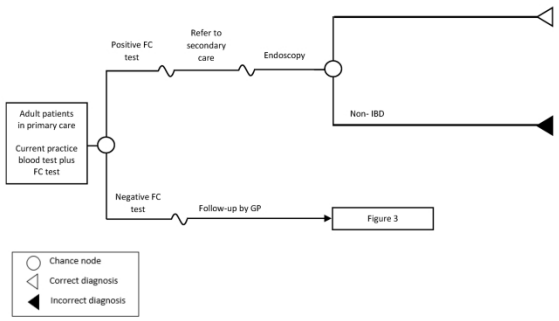

Figure 2

279x361mm (300 x 300 DPI)

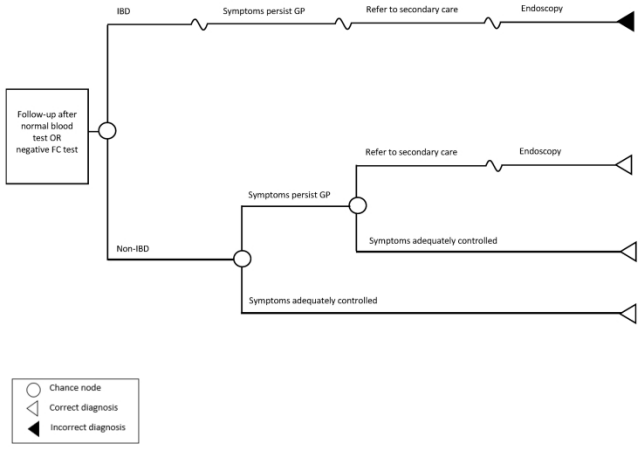

Figure 3

279x361mm (300 x 300 DPI)

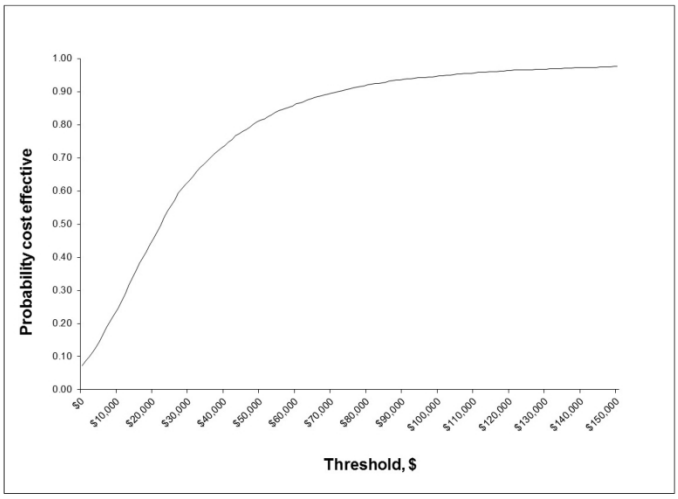

Figure 4

279x361mm (300 x 300 DPI)

Reporting checklist for economic evaluation of health interventions

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Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	P1
Abstract	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	P2-P3
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	P5-P6
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Last paragraph on P6

Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P6
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	P6
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	P6
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2nd paragraph on P7
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	N/A, 2nd paragraph on P7
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	P7-P8
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	P8
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	P8-9
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	P10-P11
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	N/A
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate	P9-P10

		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P9-P10
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	P6-8 and Figures 1-3
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	P6-11
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P11-P12
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	P12 and Table 2
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological	N/A

		assumptions (such as discount rate, study perspective).	
	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P12-P13
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P13-18
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	P19
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	P19

BMJ Open

Cost-effectiveness of fecal calprotectin used in primary care in the diagnosis of inflammatory bowel disease

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Primary Subject Heading:	Health economics
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Keywords:	Fecal calprotectin, Inflammatory bowel disease < GASTROENTEROLOGY, cost-effectiveness

Cost-effectiveness of fecal calprotectin used in primary care in the diagnosis of inflammatory bowel disease

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Keywords: Fecal calprotectin; inflammatory bowel disease; cost-effectiveness

ABSTRACT

Objective: Inflammatory bowel disease (IBD) is a chronic, autoimmune, gastrointestinal disorder. Canada has one of the highest prevalence and incidence rates of IBD in the world. Diagnosis is challenging due to the similarity of symptoms to functional gastrointestinal disorders. Fecal calprotectin (FC) is a biomarker for active mucosal inflammation and has proven effective in the diagnosis of IBD. Our study objective was to assess the cost-effectiveness of adding a FC test compared with standard practice (blood test) in primary care among adult patients presenting with gastrointestinal symptoms.

Design: We constructed a decision analytic tree with a one-year time horizon. The cut-off level of 100µg/g was used for FC testing. Probabilistic analyses were conducted for the base case and all scenarios.

Setting: Canadian health sector perspective.

Population: A hypothetical cohort of adult patients presenting with gastrointestinal symptoms in the primary care setting

Interventions: FC test compared with blood test

Main outcome measures: Costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER) of FC test expressed as cost per QALY gained compared with blood test, and time to IBD diagnosis.

Results: FC testing is expected to cost more ($295.1 vs. $273.9) than standard practice but yield little higher QALY (0.751 vs. 0.750). The ICER of FC test was $20,323 per QALY. Probabilistic analysis demonstrated that at a willingness-to-pay threshold of $50,000 per QALY, there was 81.3% probability of FC test being cost-effective. The use of FC test in primary care reduced the

time to IBD diagnosis by 40.0 days (95% Confidence Interval: 16.3-65.3 days), compared with blood testing alone.

Conclusions: Based on this analysis of short-term outcomes, screening adult patients in primary care using FC test at a cut-off level of 100µg/g is expected to be cost-effective in Canada.

ARTICLE SUMMARY

Strengths and limitations of this study

- This paper presents a cost-effectiveness analysis (CEA) comparing a fecal calprotectin test to blood test in diagnosis of inflammatory bowel disease (IBD) in the primary care setting.
- This was the first CEA of FC test in the Canadian context and one of few CEAs of FC test in the primary care setting in literature.
- We also compared the average time to IBD diagnosis between using FC test and blood test in primary care and estimated the reduced time to IBD diagnosis by using FC test.
- The analysis was from the Canadian health sector perspective and did not consider costs (e.g., productivity losses) from a societal perspective.
- The main limitation was the short-term time horizon of the analysis and thus there is outstanding uncertainty over the long-term impact of FC testing in this setting.

INTRODUCTION

Inflammatory bowel disease (IBD), of which the two main subtypes are Crohn's Disease (CD) and ulcerative colitis (UC), is characterized by mucosal inflammation and ulceration of the gastrointestinal tract. During the course of the disease, patients often present with symptoms such as diarrhea, abdominal pain, and fatigue, which significantly impact the quality of life of IBD patients.[1] Canada has one of the highest reported prevalence and incidence rates of IBD in the world.[2] The prevalence of IBD in Canada was estimated at 0.67% [129,000 individuals with CD and 104,000 with UC] in 2012, with approximately 10,200 incidents occurring annually.[3] The corresponding annual economic costs of IBD were estimated at $2.8 billion.[3]

IBD shares similar presenting symptoms with functional gut disorders. One of the most common function gut disorders is difficult to distinguish from IBD is Irritable Bowel Syndrome (IBS), which affects around 11% of the population in Canada and globally. IBS usually requires symptomatic management in primary care and causes no serious consequences permanent damage. However, IBD have serious complications and may lead to surgical resections of the bowel and therefore requires specialist care management. In order to distinguish IBD from functional gut disorders, the conventional diagnostic pathway in primary care includes initial blood tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are used to determine whether patients should be referred to gastroenterologists for further investigation including imaging studies and/or endoscopy.[4] However, these blood tests lack accuracy. They may not only delay IBD diagnosis in the case of false negatives, but also lead to unnecessary endoscopies in the case of false positives.[5,6] Due to limited resources, endoscopy is

not readily accessible in many areas of Canada and unnecessary endoscopies can have further impacts on health care resources and costs.

Recently, the detection of fecal calprotectin (FC), the most extensively studied fecal marker of IBD, has been shown to be an accurate and useful screening tool for identifying patients who need further investigation through endoscopy.[5–8] The majority of studies that assessed the accuracy of FC testing to date have been in the secondary care setting.[5–7] A recent prospective primary care cohort study conducted in the United Kingdom (UK) demonstrated that FC testing using the cut-off of 100µg/g accurately distinguishes IBD from functional gut disorder in primary care and reduces secondary care referrals as well as diagnostic health care costs.[9] Waugh *et al*. have also shown that FC testing is cost-effective for distinguishing between IBD and non-IBD in adults in primary care in the UK.[6,10] The National Institute for Health and Care Excellence (NICE) in the UK therefore recommends FC testing as an option to help clinicians distinguish between IBD and non-IBD in adults with recent onset of gastrointestinal symptoms.[10] A consensus document has subsequently been published to support the implementation of NICE recommendation.[11] More recently, Turvill et al. have also demonstrated repeating FC testing among those with first FC testing ≥100µg/g in primary care is cost-saving compared with CRP/ESR testing or a single FC testing at cut-off of 50µg/g.[12]

In Canada, however, FC tests are currently only covered by provincial health plans in Alberta and Quebec, as well as some extended health insurance plans.[13] There is still no cost-effectiveness evidence within primary care in Canada. The objective of this study, therefore, is to

determine the cost-effectiveness of FC testing in the diagnosis of adult cases of IBD in primary care from the Canadian health care sector perspective.

MATERIALS AND METHODS

Comparison groups

A higher 100µg/g cut-off in primary care has been advocated and demonstrated to increase the positive predictive power of the test and counter the high false positive rate observed at the lower 50µg/g cut-off.[9,11,12,14] Therefore, we chose the 100µg/g cut-off for FC testing in primary care setting. Ideally, we would have the current primary care practice as our control group. However, there was not good data sources for the sensitivity and specificity of the primary care practice. Waugh et al.[6] used a very high sensitivity (=1) and specificity (=0.788) for the primary care practice. Turvill et al. considered it unlikely that general practitioners (GPs) were more accurate at referring patients based on symptomatology than based on ESR/CRP testing alone.[12] Thus, we chose CRP/ESR as the comparison group, which is consistent with previous CEAs by Whitehead and Hutton[15] and Turvill et al.[12]. This implies that patients with a normal CRP/ESR would not be referred initially but if they have ongoing symptoms, they would subsequently be referred.

Decision model

A decision analytic model was built to estimate the cost-effectiveness of using FC test as compared to the current practice using blood test, in the screening for IBD in the primary care setting. The patient population in the model was a hypothetical cohort of adult patients aged 19 to 64 years old, who present with gastrointestinal symptoms suggestive of IBD in a primary care setting but are not suspected of having cancer that needs for urgent referral. A decision tree was

developed in Microsoft Excel where the hypothetical cohort of adult patients underwent certain pathways. The associated cost and effectiveness of each pathway was captured in the model and the expected cost and effectiveness was estimated.

Effectiveness was measured using quality-adjusted life years (QALYs). The time horizon for the cost-effectiveness analysis was one year as this was a reasonable length of time for a patient to reach a confirmed diagnosis of either IBD or non-IBD. We did not consider the longer time horizon mainly due to the limited direct data and evidence to enable us to estimate the long term impact and the possibility of adding more uncertainties and assumptions in terms of management/treatment pathway for IBD and non-IBD. Due to the brief time horizon, discounting was not applied to either costs or benefits in this analysis. Time to IBD diagnosis was also estimated from the model. The analysis perspective was the Canadian health sector.

The clinical pathways of patients presenting with gastrointestinal symptoms in primary care were established from published literature[6,12,15–17] as well as input by two gastroenterologists from St. Paul's Hospital, Vancouver. Established clinical pathways were consistent with the best-practice clinical care pathway for management of IBS in primary care as outlined by the Canadian Association of Gastroenterology[18] and local primary care guidelines on the use of FC in UK.[11,14]

Figure 1 illustrates the current practice using the standard blood test whereas Figure 2 depicts the proposed strategy of adding FC test as a diagnostic support tool for general practitioners (GPs). Under the current practice (Figure 1), based on results of the blood investigation (ESR and CRP), a GP will make a decision on whether to refer patients to specialist care or not. Patients with

abnormal blood results will be referred to gastroenterology for specialist assessment. The specialist may then order an endoscopy as necessary to confirm IBD diagnosis or follow-up with patients unlikely to have IBD and monitor their symptoms accordingly. If symptoms are still persistent after 3 months (assumed and same as Waugh *et al*.[6]), an endoscopy may be ordered at the specialist follow-up visit to confirm diagnosis of IBD. Under the proposed strategy of adding FC test (Figure 2), patients with positive results of FC test will be referred to specialist care and an endoscopy will be ordered for them at the specialist visit to confirm diagnosis of IBD.

Patients with normal blood results or negative FC test results will be followed-up by the GP and receive lifestyle and dietary advice with appropriate medication to treat symptoms for 3 months (assumed) (Figure 3). Those with symptoms inadequately controlled will receive more intensive management (different medication) from their GP for another 4 weeks (assumed). If symptoms are still persistent, further assessment by a gastroenterologist and endoscopy will be performed.

Model parameters

The model parameters (Table 1) were obtained from literature or based on assumptions. The parameters include sensitivity and specificity for FC testing at the 100µg/g cut-off and ≥15mm/h for ESR and ≥5mg/l for CRP blood testing; prevalence of IBD in primary care; the ratio of UC and CD; non-IBD patients with negative test results; costs; utilities; and waiting time.

Sensitivity and specificity

As mentioned above, the majority of studies measuring FC testing accuracy were conducted in the secondary care setting. As such, we used the sensitivity and specificity of FC testing at the

100μg/g cut-off from the recent UK study conducted with the prospective primary cohort.[9] For blood testing, we chose the cut-offs of ≥15mm/h for ESR and ≥5mg/l for CRP. Three studies using these ESR and CRP cut-offs were identified from a published systematic review.[5,19–21] Following this, a meta-analysis was conducted to synthesize the logit-transformation of sensitivity and specificity and the details can be found in the Supplementary file.

Prevalence of IBD in primary care

Very few studies have estimated the prevalence of IBD in primary care,[6,9,22–24] with most estimates originating from UK studies. To be consistent with the sensitivity and specificity estimates used in our model, we used the prevalence of IBD (=6.8%) in primary care from the same study.[9] Among IBD cases, 45% were UC and 55% were CD.[3]

Non-IBD patients with negative test results

Previous studies estimated a 50% or 60% probability of non-IBD patients still having persistent symptoms after the initial management by GPs, estimates were based on expert opinion.[15–17] In our study, we applied the 47% probability used in the cost-effectiveness analysis conducted by Waugh *et al*.[6] We also assumed that 15% of these who have persistent symptoms after initial management by GP (based on expert advice) would subsequently experience uncontrolled symptoms after further intensive management by GPs, be referred to a specialist, and undergo endoscopy.

Costs

Only the diagnosis related costs, including the costs for diagnostic testing (FC, endoscopy, and pathology) and physician and gastroenterologist visits, were considered. All costs were reported in 2017 Canadian dollars. Cost data were obtained from the British Columbia Ministry of Health Medical Services Commission Payment Schedule (July 1, 2017 version)[25] which is comparable with other provinces in Canada; literature review for colonoscopy cost in Canada[26] adjusted to 2017 cost using total health care implicit price index;[27] and literature review and a local gastroenterology clinic for FC testing cost.[6,17] Costs of managing complications associated with colonoscopy such as bleeding and perforation were not considered in this analysis due to the unavailability of data.

Utilities

Our utility estimates for IBS were taken from a study conducted among 257 patients in the United States (US) using EuroQol-5D.[28] The utilities of 0.78 for IBS patients with adequate relief of symptoms or 0.73 for those with persistent symptoms were applied to non-IBD patients in our analysis.[28] A weighted IBS utility of 0.76 was calculated based on the proportion (47% assumed above) of non-IBD patients with persistent symptoms and the remaining 53% with adequately controlled symptoms. In our model, patients with adequately controlled symptoms started with a weighted utility of 0.76 until the time of diagnosis, wherein a weighted utility of 0.78 (utility for adequately controlled) was applied for the rest of the one-year time horizon. Patients with persistent symptoms started with 0.73 (utility for persistent symptoms) until the time of diagnosis followed by 0.78 if symptoms were eventually controlled or 0.76 if they had to undergo endoscopy.

Similar to Waugh *et al*.[6], our utility estimates of IBD were taken from a study conducted among 225 CD patients and 219 UC patients in Germany using the EuroQol-5D.[29] This study had a reasonably large sample size and reported utility estimates for active disease compared with remission for both UC and CD. The utility estimates of 0.71 for active UC and 0.61 for active CD were chosen to represent the utility of IBD patients when they visited GP for the first time. We assumed that their utilities would then decrease by a certain amount every month due to disease progression until diagnosis was made, at which point the utility value at the time of diagnosis would be maintained throughout the rest of the one-year time horizon. Following the method of Waugh *et al*. by taking the utility difference between active disease and remission and dividing it by twelve, we derived a monthly utility decrement of 0.0167 for UC and 0.023 for CD.[6]

Waiting time

The median time an IBD patient was first referred to specialist until consultation by a specialist was 72 days (95% confidence interval (CI) 52-121) and the median time from the first specialist consultation to endoscopy was 44 days (95% CI: 27-100) in Canada.[30] The median time for non-IBD patients from the first referral to specialist consultation was 126 days (95% CI: 103-141).[30] Other wait times were assumed to be fixed according to the guidelines.

Analyses

All costs were reported in 2017 Canadian dollars. We performed probabilistic analyses to estimate means and 95% CI of total costs, QALYs, and incremental cost-effectiveness ratios (ICERs) to reflect the underlying parameter uncertainty. Additionally, the time to the diagnosis

of IBD among IBD patients was calculated. A total of 5,000 Monte Carlo simulations were generated from the parameter probability distributions. The base-case results were presented in a cost-effectiveness plane (Supplementary file) and as the cost-effectiveness acceptability curve, which demonstrates the probability of the FC testing strategy being cost-effective compared to the standard care across a range of willingness-to-pay thresholds.

To explore the sensitivity of results to specific parameter uncertainty, alternative assumptions and sources of data, we also conducted a series of scenario analyses. 1) IBD prevalence was varied from 5% to 20% in 5% increments. 2) FC testing accuracy was changed using an alternative data source. The sensitivity and specificity for repeating FC testing among the first FC testing ≥100μg/g in Turvill et al.[12] were used in the model. 3) The sensitivity and specificity of the primary care practice in Waugh et al.[6] was used. 5) We increased the proportion of patients with abnormal blood test for whom an endoscopy was ordered in the initial gastroenterologist consultation from 83% to 100%. 6) We changed the proportion of non-IBD patients with symptoms after further intensive management by GPs that needed further investigation by specialist and endoscopy from 5% (same as Waugh *et al*.[6] and Whitehead and Hutton.[15]) to 30% with 5% increments. 7) Different FC test costs and an increase or decrease in other costs by 20% were implemented. 8) We changed the source of utility decrement estimates from Stark *et al*.[29] to that of Gregor *et al*.[31]and Poole *et al*.[32] 9) Time taken to the first follow-up by GP and time taken to follow-up by a specialist were changed from 1 month to 4 months with 1-month increments. 10) We applied our model to a patient population without gastrointestinal alarm symptoms described by Walker et al.[9]

Patient and public involvement

Patients and/or public were not involved in our study. A hypothetical cohort of adult patients has been simulated.

RESULTS

Base case

For the base case, the probabilistic analysis based on 5,000 Monte Carlo simulations showed that the FC testing strategy was about $21 more expensive on average than the standard practice using blood test ($295.12 vs. $273.93) but yielded a slightly higher QALY (0.751 vs. 0.750, respectively) (Table 2). Thus, the ICER was $20,323.35 per QALY gained. The time to diagnosis for IBD patients was 39.96 days (95% CI: 16.34-65.29) shorter under the FC testing strategy (192.39 days (95% CI: 143.10-239.74) than standard practice (232.36 days (95% CI: 186.02-277.92)). There was an 81.3% probability that the FC testing strategy was cost-effective at the willingness-to-pay threshold of $50,000/QALY (Figure 4).

Scenario analyses

Our analyses showed that the cost-effectiveness of FC testing strategy was sensitive to the prevalence of IBD among the patients presenting with gastrointestinal symptoms in primary care, the FC cost, and the value of utility decrements (Table 2). When the prevalence increased to 20%, the probability of FC testing strategy being cost-effective would increase to 96.7% at the threshold of $50,000/QALY. The price threshold at which FC testing strategy became cost-effective was $70. At $70, the probability of FC testing being cost-effective was 47.4% at the willingness-to-pay threshold of $50,000/QALY. When applying a much lower utility monthly

decrement especially for CD (from 0.023 to 0.006 for CD and from 0.017 to 0.014 for UC), the probability of FC testing strategy was 68.6% at the threshold of $50,000/QALY.

DISCUSSION

Based on cost-effectiveness models built in previous studies,[6,15–17] current practice guidelines in Canada,[18] and clinical expertise from gastroenterologists, we constructed a decision analytic model to evaluate the cost-effectiveness of adding FC testing to current practice compared with the current practice of blood test only in the diagnosis of adult IBD patients in the Canadian primary care setting. To our knowledge, this is the first cost-effectiveness analysis of FC testing in primary care in Canada. Our base-case analysis suggested that the FC test was cost-effective. Probabilistic analysis showed that at a willingness-to-pay threshold of $50,000 per QALY, there was an 81.3% chance of the FC testing strategy being cost-effective. Scenario analysis demonstrated that the cost-effectiveness was most sensitive towards prevalence of IBD, monthly utility decrement of IBD, and cost of FC test.

A 6.8% prevalence of IBD was applied in our base case analysis. This estimate was based on a prospective UK primary care cohort of patients aged between 18 and 46 years old.[9] The prevalence was very similar to the one used in the cost-effectiveness analysis conducted by Waugh *et al*.[6] Among our model population (aged 19-64 years old), the prevalence would be likely to be higher. Unfortunately, Canadian estimates were not found in published literature. Thus, we conducted scenario analysis by varying the prevalence from 5% to 20%. Although the cost-effectiveness of the FC testing strategy was highly sensitive to the prevalence of IBD in the

adult patient population presented in the primary care setting, our study has shown it is still cost-effective when the prevalence is as low as 5%.

The ICER of the FC testing strategy compared with blood testing increased when the monthly utility decrement for IBD was lower. This finding is consistent with the assumption made in the calculation of QALYs for IBD patients. A delay in diagnosis would cause patients to reach a lower utility value before diagnosis. Therefore, a higher utility decrement for IBD increased the difference in QALYs gained between the two strategies and caused a decrease in ICER and vice versa.

We used the current FC test cost, $40, in our base case, which was consistent with the cost used in previous cost-effectiveness analyses conducted in the UK and US.[6,17] When the cost of FC testing was under $70, the FC testing strategy had the potential to be cost-effective. The wider implementation of FC testing across Canada may drive the cost down. Laboratory-based FC testing has been shown to be cost-effective when conducted in batches.[6,10]

One of the strengths of our study is that we used the FC testing accuracy in primary care [9] instead of the secondary care setting. The test accuracy in the secondary care setting was found to be higher than that of primary care setting. According to the most recent meta-analysis conducted by Waugh *et al*.,[6] all of studies included were for secondary setting and the synthesized sensitivity (0.93) and specificity (0.94) of FC testing at the 50µg/g cut-off were both higher than the estimates (0.86 and 0.90) for the 100µg/g cut-off we used for the primary care

setting. However, the sensitivity and specificity values of CRP/ESR in our study were derived from secondary care sources[19–21] and thus might differ in primary care setting.

Additionally, we estimated the benefit of using FC testing in primary care in terms of reducing the time to IBD diagnosis (by about 40 days). The average times to IBD diagnosis among IBD patients were 192.4 days with FC testing and 232.4 days for standard practice. The time to diagnosis under the standard practice was reasonably consistent with a Canadian study that reported the mean time to diagnosis for CD and UC to be 255.5 and 202.3 days, respectively.[33] Delayed diagnosis is a common problem in IBD. A study involving 1,591 IBD patients from the Swiss IBD cohort reported a diagnostic delay of 9 and 4 months for CD and UC.[34] The delay was due to similarities in symptoms among patients with mild IBD and those with IBS. A literature review on natural history studies of CD reported that at time of diagnosis, one third of patients already had intestinal complications such as ileitis, colitis, or ileocolitis.[35] In UC, an early diagnosis and identification of patients with a high risk of developing complicated disease, is crucial for choosing appropriate treatment and prevention of colectomies.[36] The FC testing strategy has the potential to speed up diagnosis and reduce the wait time for a specialist and endoscopy by avoiding the unnecessary referrals.

Our study has several limitations. Firstly, there was a lack of data for certain parameter inputs of the model. For example, costs and utility decrements of complications associated with colonoscopy such as bleeding and perforation could not be identified and were therefore not considered in this analysis. In Canada, the pooled rates of colonoscopy-related bleeding, perforation, and mortality were 1.64/1000, 0.85/1000, and 0.074/1000, respectively.[37] While the

rates of complications associated with colonoscopy may be low, the impact on the overall costs and outcomes may be significant if the time horizon of the analysis was longer, especially when deaths occur. As the number of colonoscopies were expected to be reduced by FC testing, we took a more conservative approach by not considering the impact of the complications associated with colonoscopies. Data on the utility decrement of IBD due to delayed diagnosis was also unavailable. Therefore, we adopted the approach used in Waugh *et al*.,[6] assuming the annual utility decrement of IBD due to delayed diagnosis as the difference between active disease and remission of UC. While our CEA was limited to costs from a health sector perspective, considering costs from a societal perspective, e.g., productivity losses due to colonoscopy, would further make FC testing more cost effective.

Secondly, we did not consider a longer time horizon. In long term, because of the early diagnosis, we expect FC to generate more benefits, e.g., avoiding mortality/risk resulting from reduced unnecessary colonoscopies or bowel perforations/surgeries. Therefore, our study provides a relatively conservative cost-effectiveness results. Adopting a long-term horizon would produce more favourable results for FC and hence our finding that FC is cost-effective should hold in the long-run.

Thirdly, some modelling assumptions we made may have simplified actual clinical practice. For instance, the modelling assumed that patients with FC levels above 100μg/g have positive test results and patients with FC levels below 100μg/g have negative test results. Subsequently, every patient who tests positive is referred to secondary care and will receive endoscopy. The modelling does not consider indeterminate results of FC testing and assumes that FC testing is

only carried out once and is not repeated in the diagnosis pathway. In actual practice, patients whose initial FC test results were found to be within an indeterminate range, for example between 100µg/g to 250µg/g, may be subjected to a second FC test and only be referred to a specialist if the result of the second FC test still yielded a result above 100µg/g. Literature showed that over 10% of patients had results which fell in this 'grey zone'.[16] Retesting patients with indeterminate results will essentially increase the cost of the FC testing strategy. However, the impact of retesting on the overall costs will depend on the proportion of patients who fall back to FC levels below 100µg/g and would not need to be referred unnecessarily, avoiding the costs of specialist consultations and colonoscopies. Turvill et al. recently compared such retesting FC strategy for the first FC test ≥100µg/g with using CRP/ESR testing without FC testing in a UK primary care setting.[12] They found retesting FC strategy to be cost-saving, due to saving 100-150 unnecessary colonoscopies and 140-190 gastroenterology outpatient appointments, with the trade-off being 4 incorrectly diagnosed IBD patients. The utility of the second FC test is that it can cut out a high proportion of false positive test results, resulting in overall cost-savings. The future research should focus on these kinds of confirmatory testing strategies.

Additionally, our modelling assumed 100% patient uptake for every diagnostic test, blood test, FC test, and endoscopy. Given the invasive nature and set of complications associated with colonoscopies, patients may refuse this diagnostic test. The FC test may also not be widely accepted, with a variable uptake rate between primary and secondary care. Some patients might decline to produce a sample of feces for their GP, but may possibly be willing to do so for a gastroenterologist if the alternative is colonoscopy. Recently, a home-based FC kit has been

made available, allowing patients to measure the concentration of FC directly using a rapid immunochromatographic assay captured by a smartphone's camera. The availability of this kit may increase the uptake and patient adherence of FC testing.[38]

It is worth noticing that FC test accuracy might differ by populations with different age or in different settings. We used test sensitivity and specificity values from Walker et al.,[9] which focused on young adults between 18 and 46 years old in UK and might not be applicable to our model population aged 19-64 years old. In addition, different FC tests produced by different manufacturers and using different platforms, can produce significantly different test results (i.e. between-method bias).[6] This means that the sensitivity and specificity values adopted in our study (based on Walker et al.[9] using a specific ELISA test), may not hold for different laboratories with different pre-analytical and analytical operating procedures and/or using different test kits/methods. This is potentially a significant issue for home-based FC kits since the benefits of increased uptake of testing may be negated by issues with test imprecision and bias.

Future research can be conducted to estimate the cost-effectiveness of FC test for distinguishing between IBD and non-IBD in the paediatrics population when the important model parameters are available. Furthermore, there has also been growing interest in the use of FC test in a few areas of IBD management. For example, FC test might be used to monitor disease progression, predict relapse and monitor response to treatment.[39] As such, an economic model which links the diagnostic outcomes of this analysis to the management of IBD in terms of treatment and monitoring can be considered in the future.

In conclusion, using FC at the 100µg/g cut-off in primary care in the diagnosis of IBD can be a cost-effective strategy and can speed up IBD diagnosis in adults who present with gastrointestinal symptoms in Canada.

Author Statement:

WZ and GR designed the study. All authors contributed to the cost-effectiveness model: CHW initiated the model, MC, TM and GR contributed their expertise in the model building and parameter determination, and WZ modified and finalized the model. WZ and CHW drafted the manuscript and all authors significantly contributed to and reviewed the final manuscript. All authors agree to be accountable for all aspects of the work.

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Data sharing statement: There is no additional unpublished data from the study.

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Table 1. Model input parameters

Parameter	Estimate	Distribution	Distribution parameters	Data source
IBD prevalence, %	6.8	Beta	Alpha = 50 Beta = 689	Walker et al.[9]
UC proportion, %	44.6	Fixed		Rocchi et al.[3]
Test accuracy				
Sensitivity				
Blood test	0.649	Normal, logit transformation	Logit estimate = 0.613 Logit SE = 0.199	Meta-analysis based on a systematic review of three studies[5,19–21]
FC test, at 100µg/g cut-off	0.860	Beta	Alpha = 43 Beta = 7	Walker et al.[9]
Specificity				
Blood test	0.866	Normal, logit transformation	Logit estimate = 1.867 Logit SE = 0.196	Meta-analysis based on a systematic review of three studies[5,19–21]
FC test, at 100µg/g cut-off	0.901	Beta	Alpha = 621 Beta = 68	Walker et al.[9]
Model probabilities, %				
Proportion of patients with abnormal blood test with endoscopy ordered in the initial gastroenterologist consultation	88.3	Beta	Alpha = 7.520 Beta = 0.993	Expert opinion
Proportion of non-IBD patients with persistent symptoms after the initial management by GPs	47.0	Log-normal	95% CI: 33-57	Waugh et al.[6]
Proportion of non-IBD patients with symptoms after further intensive management by GPs that need further investigation by specialist and endoscopy	15.0	Fixed		Expert opinion
Cost estimates ($)				
FC test	40.00	Fixed		Local clinic cost, Waugh et al.[6] and Yang et al.[17]
Initial GP visit	68.64	Fixed		BC MSC payment schedule[25]
Follow-up GP visit	30.92	Fixed		BC MSC payment schedule[25]
Initial gastroenterologist consultation	160.25	Fixed		BC MSC payment schedule[25]

Parameter	Estimate	Distribution	Distribution parameters	Data source
Follow-up gastroenterologist consultation	97.39	Fixed		BC MSC payment schedule[25]
Surgical pathology	85.52	Fixed		BC MSC payment schedule[25]
Colonoscopy, with biopsy	427.70	Fixed		Sharara et al.[26]
Utilities				
Non-IBD				
a) With adequately controlled symptoms	0.78	Beta	Alpha = 5.367 Beta = 1.514	Spiegel et al.[28]
b) With persistent symptoms	0.73		Calculated from a/c	Spiegel et al.[28]
c) Fixed ratio for utility of adequately controlled over persistent symptoms		Fixed	1.068	
Weighted IBS utility	0.76		Calculated from a), b) and Proportion of non-IBD patients with persistent symptoms above	
IBD				
Active UC	0.71	Beta	Alpha = 3.802 Beta = 1.553	Stark et al.[29]
Active CD	0.61	Beta	Alpha = 1.116 Beta = 0.713	Stark et al.[29]
Monthly utility decrement for UC	0.017	Beta	Alpha = 1.601 Beta = 94.443	Stark et al.[29]
Monthly utility decrement for CD	0.023	Beta	Alpha = 1.647 Beta = 68.958	Stark et al.[29]
Wait time				
Time taken to undergo blood test and/or FC test after presenting with symptoms in primary care	7 days	Fixed		Expert opinion
Time taken to obtain results of blood test and FC test	7 days	Fixed		Expert opinion
Time taken to follow-up by GP first time	3 months	Fixed		Expert opinion
Time taken to follow-up by GP second time	4 weeks	Fixed		Expert opinion
Time taken to a specialist consultation for IBD patients	86.50	Normal	SE=17.602	Leddin et al.[30]
Time taken to a specialist consultation for non-IBD patients	122.00	Normal	SE=9.694	Leddin et al.[30]
Time taken to endoscopy after seeing a specialist	63.50	Normal	SE=18.622	Leddin et al.[30]

Parameter	Estimate	Distribution	Distribution parameters	Data source
Time taken to follow-up by a specialist	3 months	Fixed		Expert opinion

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; FC: fecal calprotectin; GP: general practitioner; IBS: irritable bowel syndrome; SE: standard error; MSC: Medical Services Commission

Table 2. Results of base-case analysis and scenario analyses

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
Base-case	295.12 (274.49,317.53)	0.751 (0.431,0.939)	273.93 (245.40,306.05)	0.750 (0.430,0.938)	21.19 (-7.50,46.57)	0.001 (0.0003,0.002)	20,323.35	81.3%
Scenario Analyses								
IBD prevalence, %								
5	286.17 (268.43,306.09)	0.757 (0.427,0.943)	264.65 (238.41,294.96)	0.756 (0.426,0.942)	21.52 (-7.75,46.72)	0.001 (0.0002,0.002)	24,440.81	75.5%
10	312.60 (295.98,331.11)	0.743 (0.434,0.928)	291.21 (267.12,319.28)	0.742 (0.433,0.927)	21.39 (-5.67,45.80)	0.001 (0.0004,0.003)	15,594.08	89.3%
15	339.26 (323.00,357.86)	0.740 (0.448,0.916)	318.14 (294.04,345.63)	0.738 (0.447,0.915)	21.12 (-5.02,43.94)	0.002 (0.0004,0.005)	11,515.23	93.8%
20	365.81 (350.40,383.68)	0.728 (0.442,0.907)	344.93 (322.74,371.08)	0.725 (0.440,0.904)	20.88 (-3.94,41.96)	0.002 (0.0006,0.006)	8,843.74	96.7%
FC test accuracy (Turvill et al.[12])								
Sensitivity=0.94 (95% CI: 0.85-0.98) Specificity=0.92 (95% CI 0.90-0.94)	285.36 (265.56,306.98)	0.755 (0.431,0.939)	274.16 (245.10,306.04)	0.754 (0.430,0.937)	11.21 (-16.20,35.83)	0.001 (0.0005,0.003)	8,012.69	96.5%
Primary care practice accuracy (Waugh et al.[6])								
Sensitivity=1 (7/7) Specificity=0.79 (82/104)	295.55 (275.41,317.36)	0.753 (0.446,0.938)	312.85 (270.56,359.49)	0.752 (0.445,0.937)	-17.30 (-62.90,22.76)	0.001 (-0.0001,0.002)	N/A	93.6%
Proportion of patients with abnormal blood test with endoscopy ordered in the initial gastroenterologist consultation, %								
100	295.38 (274.60,317.32)	0.751 (0.430,0.938)	276.23 (248.77,307.54)	0.750 (0.429,0.937)	19.15 (-10.31,44.69)	0.001 (0.0002,0.002)	22,007.50	76.9%
Proportion of non-IBD patients with symptoms after further intensive management by GPs that need investigation by specialist and endoscopy, %								
5	268.69 (251.37,286.92)	0.754 (0.444,0.940)	248.96 (222.27,278.72)	0.753 (0.444,0.939)	19.73 (-10.67,46.48)	0.001 (0.0003,0.003)	17,988.04	83.5%
10	281.84 (263.26,301.20)	0.754 (0.447,0.938)	261.12 (234.23,290.74)	0.753 (0.446,0.937)	20.72 (-8.35,46.16)	0.001 (0.0002,0.002)	19,504.34	82.4%
20	308.68 (286.39,332.03)	0.751 (0.426,0.938)	286.82 (257.72,318.88)	0.750 (0.426,0.938)	21.85 (-5.70,45.83)	0.001 (0.0002,0.002)	21,405.41	81.2%
25	322.23 (297.17,350.17)	0.749 (0.423,0.937)	300.26 (268.29,334.99)	0.748 (0.422,0.936)	21.97 (-5.25,45.94)	0.001 (0.0003,0.002)	22,040.22	79.5%

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
30	335.85 (308.40,366.80)	0.750 (0.432,0.934)	313.02 (280.31,348.54)	0.749 (0.431,0.933)	22.84 (-3.46,45.44)	0.001 (0.0002,0.002)	23,221.90	78.8%
Cost of FC, $								
20	275.24 (254.13,297.02)	0.755 (0.446,0.940)	273.98 (246.12,304.75)	0.754 (0.445,0.939)	1.26 (-27.32,25.62)	0.001 (0.0002,0.002)	1,206.34	94.9%
30	285.21 (264.91,307.09)	0.753 (0.436,0.940)	274.13 (246.69,306.58)	0.752 (0.435,0.939)	11.08 (-17.29,36.28)	0.001 (0.0003,0.002)	10,567.51	89.8%
50	305.42 (284.54,327.76)	0.751 (0.428,0.941)	274.12 (246.34,305.69)	0.750 (0.428,0.940)	31.29 (2.93,55.78)	0.001 (0.0003,0.002)	29,789.72	71.7%
60	315.60 (295.76,337.54)	0.751 (0.430,0.936)	274.19 (246.49,305.45)	0.750 (0.430,0.936)	41.40 (13.49,66.07)	0.001 (0.0002,0.002)	39,243.50	59.8%
70	325.29 (305.29,347.98)	0.753 (0.428,0.938)	274.15 (246.63,305.86)	0.751 (0.427,0.936)	51.14 (22.70,75.99)	0.001 (0.0002,0.002)	48,712.48	47.4%
All cost estimates except FC test cost, $								
+20%	346.68 (321.97,372.92)	0.752 (0.430,0.940)	329.42 (295.89,367.82)	0.751 (0.429,0.939)	17.26 (-16.39,48.03)	0.001 (0.0003,0.002)	16,191.86	83.4%
-20%	244.18 (227.92,262.28)	0.752 (0.433,0.936)	219.14 (196.94,244.50)	0.751 (0.432,0.935)	25.04 (2.13,44.91)	0.001 (0.0003,0.003)	23,509.13	79.8%
Utility decrement								
CD = 0.006 (Gregor et al.[31]) UC = 0.014 (Poole et al.[32])	295.11 (274.59,316.66)	0.755 (0.427,0.941)	274.24 (246.79,304.96)	0.755 (0.427,0.940)	20.87 (-6.50,45.47)	0.001 (0.0002,0.001)	30,136.89	68.6%
Time taken to follow-up by GP first time								
1 month	294.97 (274.80,316.36)	0.756 (0.422,0.945)	274.09 (245.92,306.40)	0.755 (0.421,0.944)	20.89 (-8.13,46.10)	0.001 (0.0002,0.002)	18,830.57	81.9%
2 months	295.36 (274.91,317.69)	0.758 (0.437,0.943)	274.07 (246.25,306.46)	0.757 (0.436,0.942)	21.29 (-7.90,45.83)	0.001 (0.0002,0.002)	19,650.08	81.7%
4 months	295.28 (275.08,317.76)	0.749 (0.442,0.940)	274.03 (245.76,304.35)	0.748 (0.441,0.939)	21.25 (-6.75,45.57)	0.001 (0.0002,0.002)	21,451.73	80.8%
Time taken to follow-up by a specialist								
1 month	295.47 (275.10,317.87)	0.747 (0.425,0.937)	274.37 (246.13,305.91)	0.746 (0.424,0.936)	21.10 (-7.54,46.45)	0.001 (0.0002,0.002)	23,213.73	76.1%
2 months	295.35 (275.19,318.36)	0.757 (0.435,0.939)	274.19 (247.23,305.55)	0.756 (0.434,0.937)	21.16 (-7.75,45.96)	0.001 (0.0002,0.002)	21,587.69	79.6%
4 months	295.49 (274.69,317.09)	0.751 (0.430,0.940)	274.42 (246.23,305.94)	0.750 (0.429,0.939)	21.07 (-7.51,46.49)	0.001 (0.0003,0.003)	18,991.77	83.4%
Patient population without gastrointestinal alarm symptoms (Walker et al.[9])								

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
Prevalence = 4% (18/447) Sensitivity = 0.84 (15/18) Specificity = 0.91 (390/429)	276.29 (253.94,299.86)	0.760 (0.429,0.948)	258.90 (230.11,291.19)	0.760 (0.429,0.947)	17.40 (-13.70,44.78)	0.001 (0.0002,0.002)	21,608.85	75.6%

95% confidence intervals (CI) in brackets
IBD: inflammatory bowel disease; FC: fecal calprotectin; GP: general practitioner; CD: Crohn's disease; UC: ulcerative colitis; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio
*at $50,000/QALY threshold

Figure 1. Overview of the model structure for standard practice using blood test

IBD: inflammatory bowel disease; GP: general practitioner

Figure 2. Overview of the model structure for fecal calprotectin testing strategy

FC: fecal calprotectin IBD: inflammatory bowel disease; GP: general practitioner

Figure 3. Overview of the decision branch for normal blood test or negative fecal calprotectin test results

FC: fecal calprotectin IBD: inflammatory bowel disease; GP: general practitioner

Figure 4. Cost-effectiveness acceptability curve

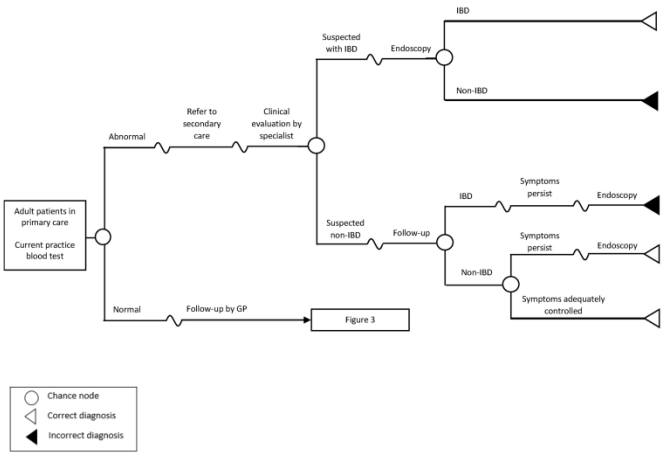


Figure 1

279x361mm (300 x 300 DPI)

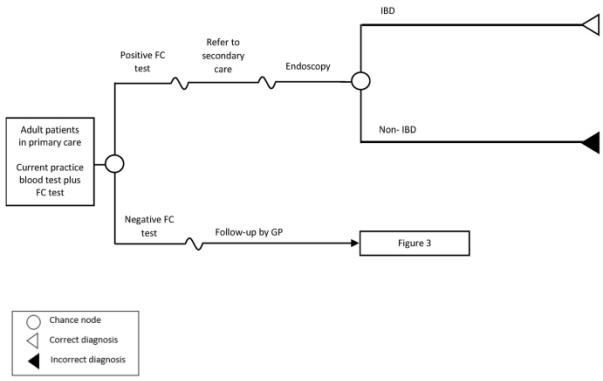


Figure 2

215x279mm (300 x 300 DPI)

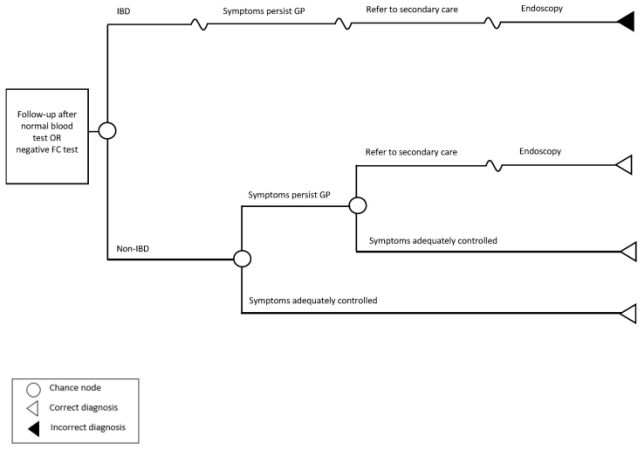


Figure 3

279x361mm (300 x 300 DPI)

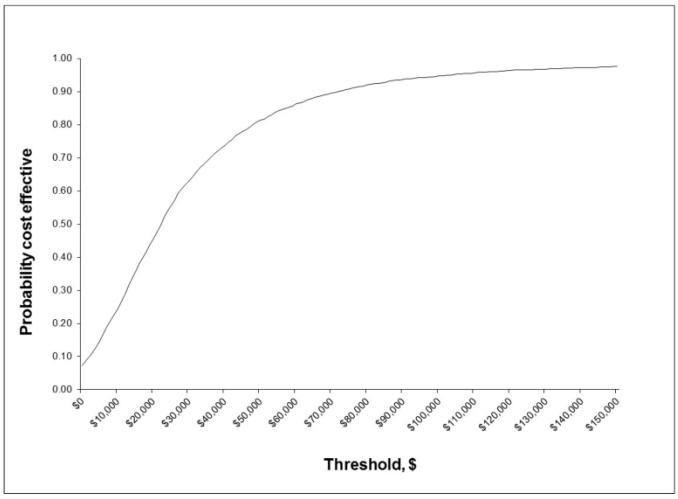


Figure 4

279x361mm (300 x 300 DPI)

Supplementary File

Meta-analysis for sensitivity and specificity of blood test

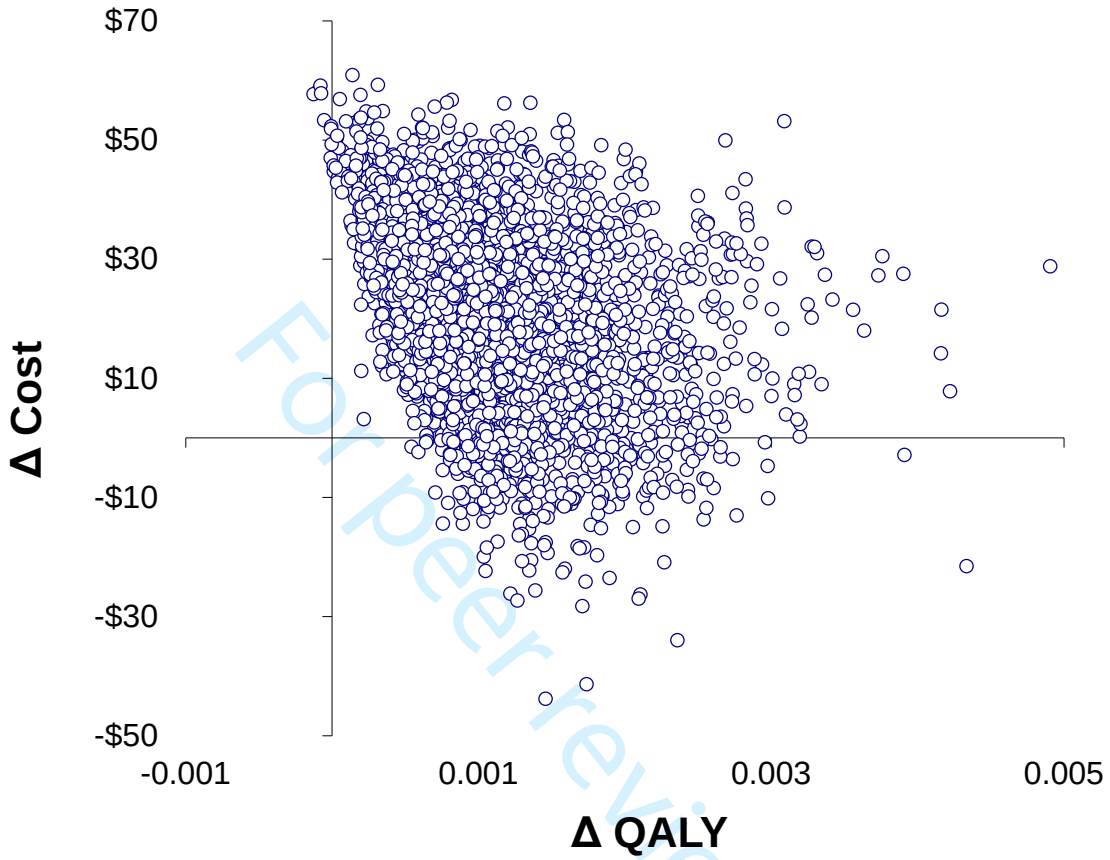
Jellema et al. conducted a high quality systematic review that summarized the evidence on the performance of different diagnostic tests including the blood tests (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) in patients with abdominal symptoms.[1] They identified four studies that investigated the diagnostic performance of CRP or ESR with different diagnostic cut-off points. The gastroenterologists (Drs. Rosenfeld and Chavannes) in our study selected the studies and the cut-off points that are most relevant to the clinical practice.

Table 1. Diagnostic performance of studies with test cut-offs of CRP ≥5mg/l and ESR ≥15mm/h

Study	True Positives	False Positives	True Negatives	False Negatives
Kaiser *et al*, 2007[2]	29	5	19	21
Poullis *et al*, 2002[3]	11	16	143	9
Shine *et al*, 1985[4]	32	9	32	9
The numbers were directly obtained from Jellema et al.[1]				

Subsequently, we have attempted to model these data using a bivariate analysis to take account of the correlation between the sensitivity and specificity based on Reitsma et al.[5] (model specification shown on page 988). However, the estimated covariance matrix was not full rank and might be unreliable, possibly due to our small sample size (only 3 studies). Therefore, we estimated the sensitivity and specificity independently (i.e., without accounting for the correlation between the sensitivity and specificity). The logit estimates for sensitivity and specificity were 0.613 (SE=0.199) and 1.867 (0.196), respectively.

Cost-effectiveness plane for our base case



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diarrhoea-predominant functional bowel disorders. *Eur J Gastroenterol Hepatol*. 2002;14:409–412.

4. Shine B, Berghouse L, Jones JE, et al. C-reactive protein as an aid in the differentiation of functional and inflammatory bowel disorders. *Clin. Chim. Acta*. 1985;148:105–109.
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Reporting checklist for economic evaluation of health interventions

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Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the CHEERS reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	P1

Abstract	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	P2-P3
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	P5-P7
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Last paragraph on P7
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P7
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	P7
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	P7
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2nd paragraph on P8
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	N/A, 2nd paragraph on P8

Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	P7-P8
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	P9-P10
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	P9-P10 and supplementary file
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	P11-P12
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	N/A
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states.	P11

		Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P11
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	P7-P9 and Figures 1-3
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	P7-P13
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P12-P13

Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	P14 and Table 2
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P13-P15
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of	N/A

		patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P15-P20
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	P22
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	P22

BMJ Open

Cost-effectiveness of fecal calprotectin used in primary care in the diagnosis of inflammatory bowel disease

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	General practice / Family practice, Gastroenterology and hepatology, Public health
Keywords:	Fecal calprotectin, Inflammatory bowel disease < GASTROENTEROLOGY, cost-effectiveness

Cost-effectiveness of fecal calprotectin used in primary care in the diagnosis of inflammatory bowel disease

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Keywords: Fecal calprotectin; inflammatory bowel disease; cost-effectiveness

ABSTRACT

Objective: Inflammatory bowel disease (IBD) is a chronic, autoimmune, gastrointestinal disorder. Canada has one of the highest prevalence and incidence rates of IBD in the world. Diagnosis is challenging due to the similarity of symptoms to functional gastrointestinal disorders. Fecal calprotectin (FC) is a biomarker for active mucosal inflammation and has proven effective in the diagnosis of IBD. Our study objective was to assess the cost-effectiveness of adding a FC test compared with standard practice (blood test) in primary care among adult patients presenting with gastrointestinal symptoms.

Design: We constructed a decision analytic tree with a one-year time horizon. The cut-off level of 100μg/g was used for FC testing. Probabilistic analyses were conducted for the base case and all scenarios.

Setting: Canadian health sector perspective.

Population: A hypothetical cohort of adult patients presenting with gastrointestinal symptoms in the primary care setting

Interventions: FC test compared with blood test

Main outcome measures: Costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER) of FC test expressed as cost per QALY gained compared with blood test, and time to IBD diagnosis.

Results: FC testing is expected to cost more ($295.1 vs. $273.9) than standard practice but yield little higher QALY (0.751 vs. 0.750). The ICER of FC test was $20,323 per QALY. Probabilistic analysis demonstrated that at a willingness-to-pay threshold of $50,000 per QALY, there was 81.3% probability of FC test being cost-effective. The use of FC test in primary care reduced the

time to IBD diagnosis by 40.0 days (95% Confidence Interval: 16.3-65.3 days), compared with blood testing alone.

Conclusions: Based on this analysis of short-term outcomes, screening adult patients in primary care using FC test at a cut-off level of 100µg/g is expected to be cost-effective in Canada.

ARTICLE SUMMARY

Strengths and limitations of this study

- This paper presents a cost-effectiveness analysis (CEA) comparing a fecal calprotectin test to blood test in diagnosis of inflammatory bowel disease (IBD) in the primary care setting.
- This was the first CEA of FC test in the Canadian context and one of few CEAs of FC test in the primary care setting in literature.
- We also compared the average time to IBD diagnosis between using FC test and blood test in primary care and estimated the reduced time to IBD diagnosis by using FC test.
- The analysis was from the Canadian health sector perspective and did not consider costs (e.g., productivity losses) from a societal perspective.
- The main limitation was the short-term time horizon of the analysis and thus there is outstanding uncertainty over the long-term impact of FC testing in this setting.

INTRODUCTION

Inflammatory bowel disease (IBD), of which the two main subtypes are Crohn's Disease (CD) and ulcerative colitis (UC), is characterized by mucosal inflammation and ulceration of the gastrointestinal tract. During the course of the disease, patients often present with symptoms such as diarrhea, abdominal pain, and fatigue, which significantly impact the quality of life of IBD patients.[1] Canada has one of the highest reported prevalence and incidence rates of IBD in the world.[2] The prevalence of IBD in Canada was estimated at 0.67% [129,000 individuals with CD and 104,000 with UC] in 2012, with approximately 10,200 incidents occurring annually.[3] The corresponding annual economic costs of IBD were estimated at $2.8 billion.[3]

IBD shares similar presenting symptoms with functional gut disorders. One of the most common function gut disorders that is difficult to distinguish from IBD is Irritable Bowel Syndrome (IBS), which affects around 11% of the population in Canada and globally.[4] While IBS can be safely managed within primary care setting, the risk of serious complications associated with IBD (such as bowel obstruction and toxic megacolon) necessitates specialist care management. In order to distinguish IBD from functional gut disorders, the conventional diagnostic pathway in primary care includes initial blood tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are used to determine whether patients should be referred to gastroenterologists for further investigation including imaging studies and/or endoscopy.[5] However, these blood tests lack accuracy. They may not only delay IBD diagnosis in the case of false negatives, but also lead to unnecessary endoscopies in the case of false positives.[6,7] Due to limited resources, endoscopy is not readily accessible in many areas of Canada and unnecessary endoscopies can have further impacts on health care resources and costs.

Recently, the detection of fecal calprotectin (FC), the most extensively studied fecal marker of IBD, has been shown to be an accurate and useful screening tool for identifying patients who need further investigation through endoscopy.[6–9] The majority of studies that assessed the accuracy of FC testing to date have been in the secondary care setting.[6–8] Based predominantly on secondary care data using the standard cut-off of 50µg/g, Waugh *et al* have shown that FC testing is cost-effective for distinguishing between IBD and non-IBD in adults in primary care in the United Kingdom (UK).[7,10] The National Institute for Health and Care Excellence (NICE) in the UK therefore recommends FC testing as an option to help clinicians distinguish between IBD and non-IBD in adults with recent onset of gastrointestinal symptoms.[10] A recent prospective primary care cohort study conducted in the UK demonstrated that FC testing using the cut-off of 100µg/g accurately distinguishes IBD from functional gut disorder in primary care and reduces secondary care referrals as well as diagnostic health care costs.[11] More recently, Turvill *et al* have also demonstrated that repeating FC testing among those with a first FC test ≥100µg/g in primary care is cost-saving compared with CRP/ESR testing or single FC testing using the standard cut-off of 50µg/g.[12] NICE has subsequently endorsed this repeated testing algorithm, using the higher 100µg/g cut-off, within a recent consensus document.[13]

In Canada, however, FC tests are currently only covered by provincial health plans in Alberta and Quebec, as well as some extended health insurance plans.[14] There is still no cost-effectiveness evidence within primary care in Canada. The objective of this study, therefore, is to determine the cost-effectiveness of FC testing in the diagnosis of adult cases of IBD in primary care from the Canadian health care sector perspective.

MATERIALS AND METHODS

Comparison groups

A higher 100µg/g cut-off in primary care has been advocated and demonstrated to increase the positive predictive power of the test and counter the high false positive rate observed at the lower 50µg/g cut-off.[11–13,15] Therefore, we chose the 100µg/g cut-off for FC testing in primary care setting as the intervention for our analysis. Referrals based on standard care CRP/ESR testing in primary care were used as the comparator. This assumes that patients with a normal CRP/ESR would not be referred initially but would subsequently be referred if they have ongoing symptoms. This is a simplification of real-world practice – clinicians are known, for example, to refer patients with normal CRP/ESR to secondary care. Nevertheless, there is currently a lack of reliable data on the accuracy of real-world primary care referral practices in the literature particularly in Canada. Thus, we based the comparator on CRP/ESR testing, in line with previous cost-effectiveness analyses.[12,16]An alternative estimate of primary care referral accuracy was based on the study of Waugh *et al*,[7] which estimated a high sensitivity (=1) and specificity (=0.788). Since the reliability of these estimates has been previously questioned,[12] they were used as a scenario analysis only.

Decision model

A decision analytic model was built to estimate the cost-effectiveness of using FC test as compared to the current practice using blood test, in the screening for IBD in the primary care setting. The patient population in the model was a hypothetical cohort of adult patients aged 19 to 64 years old, who present with gastrointestinal symptoms suggestive of IBD in a primary care

setting but are not suspected of having cancer (which requires urgent specialist referral). A decision tree was developed in Microsoft Excel where the hypothetical cohort of adult patients underwent certain pathways. The associated cost and effectiveness of each pathway was captured in the model and the expected cost and effectiveness was estimated.

Effectiveness was measured using quality-adjusted life years (QALYs). The time horizon for the cost-effectiveness analysis was one year as this was a reasonable length of time for a patient to reach a confirmed diagnosis of either IBD or non-IBD. Due to the brief time horizon, discounting was not applied to either costs or benefits in this analysis. Time to IBD diagnosis was also estimated from the model. The analysis perspective was the Canadian health sector.

The clinical pathways of patients presenting with gastrointestinal symptoms in primary care were established from published literature[7,12,16–18] as well as input by two gastroenterologists from St. Paul's Hospital, Vancouver. Established clinical pathways were consistent with the best-practice clinical care pathway for management of IBS in primary care as outlined by the Canadian Association of Gastroenterology[19] and local primary care guidelines on the use of FC in the UK.[13,15]

Figure 1 illustrates the current practice using the standard blood test whereas Figure 2 depicts the proposed strategy of adding FC test as a diagnostic support tool for general practitioners (GPs). Under the current practice (Figure 1), based on results of the blood investigation (ESR and CRP), a GP will make a decision on whether to refer patients to specialist care or not. Patients with abnormal blood results will be referred to gastroenterology for specialist assessment. The

specialist may then order an endoscopy as necessary to confirm IBD diagnosis or follow-up with patients unlikely to have IBD and monitor their symptoms accordingly. If symptoms are still persistent after 3 months (assumed and same as Waugh *et al*[7]), an endoscopy may be ordered at the specialist follow-up visit to confirm diagnosis of IBD. Under the FC testing strategy (Figure 2), patients with positive FC test results will be referred to specialist care and an endoscopy will be ordered for them at the specialist visit to confirm diagnosis of IBD.

Patients with normal blood results or negative FC test results will be followed-up by the GP and receive lifestyle and dietary advice with appropriate medication to treat symptoms for 3 months (assumed) (Figure 3). Those with symptoms inadequately controlled will receive more intensive management (different medication) from their GP for another 4 weeks (assumed). If symptoms are still persistent, further assessment by a gastroenterologist and endoscopy will be performed.

Model parameters

The model parameters (Table 1) were obtained from literature or based on assumptions. The parameters include sensitivity and specificity for FC testing at the 100µg/g cut-off and ≥15mm/h for ESR and ≥5mg/l for CRP blood testing; prevalence of IBD in primary care; the ratio of UC and CD; non-IBD patients with negative test results; costs; utilities; and waiting time.

Sensitivity and specificity

As mentioned above, the majority of studies measuring FC testing accuracy were conducted in the secondary care setting. As such, we used the sensitivity and specificity of FC testing at the 100µg/g cut-off from the recent UK study conducted with the prospective primary cohort.[11]

For blood testing, we chose the cut-offs of ≥15mm/h for ESR and ≥5mg/l for CRP. Three studies using these ESR and CRP cut-offs were identified from a published systematic review.[6,20–22] Following this, a meta-analysis was conducted to synthesize the logit-transformation of sensitivity and specificity and the details can be found in the Supplementary file.

Prevalence of IBD in primary care

Very few studies have estimated the prevalence of IBD in primary care,[7,11,23–25] with most estimates originating from UK studies. To be consistent with the sensitivity and specificity estimates used in our model, we used the prevalence of IBD (=6.8%) in primary care from the same study.[11] Among IBD cases, 45% were UC and 55% were CD.[3]

Non-IBD patients with negative test results

Based on expert opinions, previous studies estimated that the probability of non-IBD patients still having persistent symptoms after the initial management by GPs was 50% or 60%.[16–18] In our study, we applied the 47% probability used in the cost-effectiveness analysis conducted by Waugh *et al*.[7] We also assumed that 15% of these who have persistent symptoms after initial management by GP (based on expert advice) would subsequently experience uncontrolled symptoms after further intensive management by GPs, be referred to a specialist, and undergo endoscopy.

Costs

Only the diagnosis related costs, including the costs for diagnostic testing (FC, endoscopy, and pathology) and physician and gastroenterologist visits, were considered. All costs were reported in 2017 Canadian dollars. Cost data were obtained from the British Columbia Ministry of Health Medical Services Commission Payment Schedule (July 1, 2017 version)[26] which is comparable with other provinces in Canada; literature review for colonoscopy cost in Canada[27] adjusted to 2017 cost using total health care implicit price index;[28] and literature review and a local gastroenterology clinic for FC testing cost.[7,18] Costs of managing complications associated with colonoscopy such as bleeding and perforation were not considered in this analysis due to the unavailability of data.

Utilities

Our utility estimates for IBS were taken from a study conducted among 257 patients in the United States (US) using EuroQol-5D.[29] The utilities of 0.78 for IBS patients with adequate relief of symptoms or 0.73 for those with persistent symptoms were applied to non-IBD patients in our analysis.[29] A weighted IBS utility of 0.76 was calculated based on the proportion (47% assumed above) of non-IBD patients with persistent symptoms and the remaining 53% with adequately controlled symptoms. In our model, patients with adequately controlled symptoms started with a weighted utility of 0.76 until the time of diagnosis, wherein a weighted utility of 0.78 (utility for adequately controlled) was applied for the rest of the one-year time horizon. Patients with persistent symptoms started with 0.73 (utility for persistent symptoms) until the time of diagnosis followed by 0.78 if symptoms were eventually controlled or 0.76 if they had to undergo endoscopy.

Similar to Waugh *et al*,[7] our utility estimates of IBD were taken from a study conducted among 225 CD patients and 219 UC patients in Germany using the EuroQol-5D.[30] This study had a reasonably large sample size and reported utility estimates for active disease compared with remission for both UC and CD. The utility estimates of 0.71 for active UC and 0.61 for active CD were chosen to represent the utility of IBD patients when they visited GP for the first time. We assumed that their utilities would then decrease by a certain amount every month due to disease progression until diagnosis was made, at which point the utility value at the time of diagnosis would be maintained throughout the rest of the one-year time horizon. Following the method of Waugh *et al* by taking the utility difference between active disease and remission and dividing it by twelve, we derived a monthly utility decrement of 0.0167 for UC and 0.023 for CD.[7]

Waiting time

The median time an IBD patient was first referred to specialist until consultation by a specialist was 72 days (95% confidence interval (CI) 52-121) and the median time from the first specialist consultation to endoscopy was 44 days (95% CI: 27-100) in Canada.[31] The median time for non-IBD patients from the first referral to specialist consultation was 126 days (95% CI: 103-141).[31] Other wait times were assumed to be fixed according to the guidelines.

Analyses

We performed probabilistic analyses to estimate means and 95% CI of total costs, QALYs, and incremental cost-effectiveness ratios (ICERs) to reflect the underlying parameter uncertainty. Additionally, the time to the diagnosis of IBD among IBD patients was calculated. A total of

5,000 Monte Carlo simulations were generated from the parameter probability distributions. The base-case results were presented in a cost-effectiveness plane (Supplementary file) and as the cost-effectiveness acceptability curve, which demonstrates the probability of the FC testing strategy being cost-effective compared to the standard care across a range of willingness-to-pay thresholds.

To explore the sensitivity of results to specific parameter uncertainty, alternative assumptions and sources of data, we also conducted a series of scenario analyses. 1) IBD prevalence was varied from 5% to 20% in 5% increments. 2) FC testing accuracy was changed using an alternative data source. The sensitivity and specificity for repeating FC testing among the first FC testing ≥100μg/g in Turvill *et al*[12] were used in the model. 3) The sensitivity and specificity of the primary care practice in Waugh *et al*[7] was used. 4) We increased the proportion of patients with abnormal blood test for whom an endoscopy was ordered in the initial gastroenterologist consultation from 83% to 100%. 5) We changed the proportion of non-IBD patients with symptoms after further intensive management by GPs that needed further investigation by specialist and endoscopy from 5% (same as Waugh *et al*[7] and Whitehead and Hutton.[16]) to 30% with 5% increments. 6) Different FC test costs and an increase or decrease in other costs by 20% were implemented. 7) We changed the source of utility decrement estimates from Stark *et al*[30] to that of Gregor *et al*[32]and Poole *et al*.[33] 8) Time taken to the first follow-up by GP and time taken to follow-up by a specialist were changed from 1 month to 4 months with 1-month increments. 9) We applied our model to a patient population without gastrointestinal alarm symptoms described by Walker *et al*.[11]

Patient and public involvement

Patients and/or public were not involved in our study. A hypothetical cohort of adult patients has been simulated.

RESULTS

Base case

For the base case, the probabilistic analysis based on 5,000 Monte Carlo simulations showed that the FC testing strategy was about $21 more expensive on average than the standard practice using blood test ($295.12 vs. $273.93) but yielded a slightly higher QALY (0.751 vs. 0.750, respectively) (Table 2). Thus, the ICER was $20,323.35 per QALY gained. The time to diagnosis for IBD patients was 39.96 days (95% CI: 16.34-65.29) shorter under the FC testing strategy (192.39 days (95% CI: 143.10-239.74) than standard practice (232.36 days (95% CI: 186.02-277.92)). There was an 81.3% probability that the FC testing strategy was cost-effective at the willingness-to-pay threshold of $50,000/QALY (Figure 4).

Scenario analyses

Our analyses showed that the cost-effectiveness of FC testing strategy was sensitive to the prevalence of IBD among the patients presenting with gastrointestinal symptoms in primary care, the FC cost, and the value of utility decrements (Table 2). When the prevalence was increased to 20%, the probability of the FC testing strategy being cost-effective would increase to 96.7% at the threshold of $50,000/QALY. The probability of FC testing being cost effective became 96.5% when using the sensitivity and specificity estimates for repeating FC testing strategy in Turvill *et al*. The maximum price at which the FC testing strategy would still be cost-effective

was about $70. At $70, the probability of FC testing being cost-effective was 47.4% at the willingness-to-pay threshold of $50,000/QALY. When applying a much lower utility monthly decrement especially for CD (from 0.023 to 0.006 for CD and from 0.017 to 0.014 for UC), the probability of FC testing strategy was 68.6% at the threshold of $50,000/QALY.

DISCUSSION

Based on cost-effectiveness models built in previous studies,[7,16–18] current practice guidelines in Canada,[19] and clinical expertise from gastroenterologists, we constructed a decision analytic model to evaluate the cost-effectiveness of adding FC testing to current practice compared with the current practice of blood test only in the diagnosis of adult IBD patients in the Canadian primary care setting. To our knowledge, this is the first cost-effectiveness analysis of FC testing in primary care in Canada. Our base-case analysis suggested that the FC test was cost-effective. Probabilistic analysis showed that at a willingness-to-pay threshold of $50,000 per QALY, there was an 81.3% chance of the FC testing strategy being cost-effective. Scenario analysis demonstrated that the cost-effectiveness was most sensitive towards prevalence of IBD, monthly utility decrement of IBD, and cost of FC test.

A 6.8% prevalence of IBD was applied in our base case analysis. This estimate was based on a prospective UK primary care cohort of patients aged between 18 and 46 years old.[11] The prevalence was very similar to the one used in the cost-effectiveness analysis conducted by Waugh *et al*.[7] Among our model population (aged 19-64 years old), the prevalence would likely be higher. Unfortunately, Canadian estimates were not found in published literature. Thus, we conducted scenario analysis by varying the prevalence from 5% to 20%. Although the cost-

effectiveness of the FC testing strategy was highly sensitive to the prevalence of IBD in the adult patient population presented in the primary care setting, our study has shown it is still cost-effective when the prevalence is as low as 5%.

The ICER of the FC testing strategy compared with blood testing increased when the monthly utility decrement for IBD was lower. This finding is consistent with the assumption made in the calculation of QALYs for IBD patients. A delay in diagnosis would cause patients to reach a lower utility value before diagnosis. Therefore, a higher utility decrement for IBD increased the difference in QALYs gained between the two strategies and caused a decrease in ICER and vice versa.

We used the current FC test cost, $40, in our base case, which was consistent with the cost used in previous cost-effectiveness analyses conducted in the UK and US.[7,18] When the cost of FC testing was under $70, the FC testing strategy had the potential to be cost-effective. The wider implementation of FC testing across Canada may drive the cost down. Laboratory-based FC testing has been shown to be cost-effective when conducted in batches.[7,10]

One of the strengths of our study is that we used the FC testing accuracy in primary care[11] instead of the secondary care setting. The test accuracy in the secondary care setting was found to be higher than that of primary care setting. According to the most recent meta-analysis conducted by Waugh *et al*,[7] all of studies included were for secondary setting and the synthesized sensitivity (0.93) and specificity (0.94) of FC testing at the 50μg/g cut-off were both higher than the estimates (0.86 and 0.90) for the 100μg/g cut-off we used for the primary care

setting. However, the sensitivity and specificity values of CRP/ESR in our study were derived from secondary care sources[20–22] and thus might differ in primary care setting.

Additionally, we estimated the benefit of using FC testing in primary care in terms of reducing the time to IBD diagnosis (by about 40 days). The average times to IBD diagnosis among IBD patients were 192.4 days with FC testing and 232.4 days for standard practice. The time to diagnosis under the standard practice was reasonably consistent with a Canadian study that reported the mean time to diagnosis for CD and UC to be 255.5 and 202.3 days, respectively.[34] Delayed diagnosis is a common problem in IBD. A study involving 1,591 IBD patients from the Swiss IBD cohort reported a diagnostic delay of 9 and 4 months for CD and UC.[35] The delay was due to similarities in symptoms among patients with mild IBD and those with IBS. A literature review on natural history studies of CD reported that at time of diagnosis, one third of patients already had intestinal complications such as ileitis, colitis, or ileocolitis.[36] In UC, an early diagnosis and identification of patients with a high risk of developing complicated disease, is crucial for choosing appropriate treatment and prevention of colectomies.[37] The FC testing strategy has the potential to speed up diagnosis and reduce the wait time for a specialist and endoscopy by avoiding the unnecessary referrals.

Our study has several limitations. Firstly, there was a lack of data for certain parameter inputs of the model. For example, costs and utility decrements of complications associated with colonoscopy such as bleeding and perforation could not be identified and were therefore not considered in this analysis. In Canada, the pooled rates of colonoscopy-related bleeding, perforation, and mortality were 1.64/1000, 0.85/1000, and 0.074/1000, respectively.[38] While the

rates of complications associated with colonoscopy may be low, the impact on the overall costs and outcomes may be significant if the time horizon of the analysis was longer, especially when deaths occur. As the number of colonoscopies were expected to be reduced by FC testing, we took a more conservative approach by not considering the impact of the complications associated with colonoscopies. Data on the utility decrement of IBD due to delayed diagnosis was also unavailable. Therefore, we adopted the approach used in Waugh *et al*,[7] assuming the annual utility decrement of IBD due to delayed diagnosis as the difference between active disease and remission of UC. While our CEA was limited to costs from a health sector perspective, considering costs from a societal perspective, e.g., productivity losses due to colonoscopy, would further make FC testing more cost effective.

Secondly, we did not consider a longer time horizon. In long term, because of the earlier diagnosis, we expect FC to generate more benefits, e.g., by avoiding mortality/risk resulting from reduced unnecessary colonoscopies or bowel perforations/surgeries. Therefore, we expect our study to provide a relatively conservative cost-effectiveness estimate for FC. Nevertheless, further research on the long-term impact of early diagnosis of IBD and IBS is needed to validate this claim. Adopting a long-term horizon would likely produce more favourable results for FC and hence our finding that FC is cost-effective should hold in the long-run.

Thirdly, the model assumed that FC would be used as a single test applying a fixed cut-off of 100μg/g. Alternative two-stage testing strategies may also be used. Turvill *et al*, for example, recently evaluated such a retesting FC strategy, using a cut-off of 100μg/g and conducting a repeat FC testing for patients with an initial test above this cut-off.[12] They found this retesting

FC strategy to be cost-saving in a UK primary care setting, due to saving 100-150 unnecessary colonoscopies and 140-190 gastroenterology outpatient appointments compared to CRP/ESR testing alone. The utility of the second FC test is that it can cut out a high proportion of false positive test results, resulting in overall cost-savings. The results of our scenario analysis using the sensitivity and specificity estimates from Turvill *et al* indicate a higher cost-effectiveness of FC using the retesting strategy (a 96.5% probability of being cost-effective compared to CRP/ESR testing alone) versus the single testing base-case strategy (81.3%). The future research should focus on these kinds of confirmatory testing strategies.

Additionally, our modelling assumed 100% patient uptake for every diagnostic test, blood test, FC test, and endoscopy. Given the invasive nature and set of complications associated with colonoscopies, patients may refuse this diagnostic test. The FC test may also not be widely accepted, with a variable uptake rate between primary and secondary care. Some patients might decline to produce a sample of feces for their GP, but may possibly be willing to do so for a gastroenterologist if the alternative is colonoscopy. Recently, a home-based FC kit has been made available, allowing patients to measure the concentration of FC directly using a rapid immunochromatographic assay captured by a smartphone's camera. The availability of this kit may increase the uptake and patient adherence of FC testing.[39]

It is worth noting that FC test accuracy might differ by populations with different age or in different settings. We used test sensitivity and specificity values from Walker *et al*,[11] which focused on young adults between 18 and 46 years old in the UK and might not be applicable to our model population aged 19-64 years old. In addition, different FC tests produced by different

manufacturers and using different platforms, can produce significantly different test results (i.e. between-method bias).[7] This means that the sensitivity and specificity values adopted in our study (based on Walker *et al*[11] using a specific ELISA test), may not hold for different laboratories with different pre-analytical and analytical operating procedures and/or using different test kits/methods. This is potentially a significant issue for home-based FC kits since the benefits of increased uptake of testing may be negated by issues with test imprecision and bias.

Future research can be conducted to estimate the cost-effectiveness of FC test for distinguishing between IBD and non-IBD in the paediatrics population when the important model parameters are available. Furthermore, there has also been growing interest in the use of FC test in a few areas of IBD management. For example, FC test might be used to monitor disease progression, predict relapse and monitor response to treatment.[40] As such, an economic model which links the diagnostic outcomes of this analysis to the management of IBD in terms of treatment and monitoring can be considered in the future.

In conclusion, using FC at the 100µg/g cut-off in primary care in the diagnosis of IBD can be a cost-effective strategy and can speed up IBD diagnosis in adults who present with gastrointestinal symptoms in Canada.

Author Statement:

WZ and GR designed the study. All authors contributed to the cost-effectiveness model: CHW initiated the model, MC, TM and GR contributed their expertise in the model building and parameter determination, and WZ modified and finalized the model. WZ and CHW drafted the manuscript and all authors significantly contributed to and reviewed the final manuscript. All authors agree to be accountable for all aspects of the work.

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Data sharing statement: There is no additional unpublished data from the study.

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Table 1. Model input parameters

Parameter	Estimate	Distribution	Distribution parameters	Data source
IBD prevalence, %	6.8	Beta	Alpha = 50 Beta = 689	Walker et al.[11]
UC proportion, %	44.6	Fixed		Rocchi et al.[3]
Test accuracy				
Sensitivity				
Blood test	0.649	Normal, logit transformation	Logit estimate = 0.613 Logit SE = 0.199	Meta-analysis based on a systematic review of three studies[6,20–22]
FC test, at 100µg/g cut-off	0.860	Beta	Alpha = 43 Beta = 7	Walker et al.[11]
Specificity				
Blood test	0.866	Normal, logit transformation	Logit estimate = 1.867 Logit SE = 0.196	Meta-analysis based on a systematic review of three studies[6,20–22]
FC test, at 100µg/g cut-off	0.901	Beta	Alpha = 621 Beta = 68	Walker et al.[11]
Model probabilities, %				
Proportion of patients with abnormal blood test with endoscopy ordered in the initial gastroenterologist consultation	88.3	Beta	Alpha = 7.520 Beta = 0.993	Expert opinion
Proportion of non-IBD patients with persistent symptoms after the initial management by GPs	47.0	Log-normal	95% CI: 33-57	Waugh et al.[7]
Proportion of non-IBD patients with symptoms after further intensive management by GPs that need further investigation by specialist and endoscopy	15.0	Fixed		Expert opinion
Cost estimates ($)				
FC test	40.00	Fixed		Local clinic cost, Waugh et al.[7] and Yang et al.[18]
Initial GP visit	68.64	Fixed		BC MSC payment schedule[26]
Follow-up GP visit	30.92	Fixed		BC MSC payment schedule[26]
Initial gastroenterologist consultation	160.25	Fixed		BC MSC payment schedule[26]

Parameter	Estimate	Distribution	Distribution parameters	Data source
Follow-up gastroenterologist consultation	97.39	Fixed		BC MSC payment schedule[26]
Surgical pathology	85.52	Fixed		BC MSC payment schedule[26]
Colonoscopy, with biopsy	427.70	Fixed		Sharara et al.[27]
Utilities				
Non-IBD				
a) With adequately controlled symptoms	0.78	Beta	Alpha = 5.367 Beta = 1.514	Spiegel et al.[29]
b) With persistent symptoms	0.73		Calculated from a/c	Spiegel et al.[29]
c) Fixed ratio for utility of adequately controlled over persistent symptoms		Fixed	1.068	
Weighted IBS utility	0.76		Calculated from a), b) and Proportion of non-IBD patients with persistent symptoms above	
IBD				
Active UC	0.71	Beta	Alpha = 3.802 Beta = 1.553	Stark et al.[30]
Active CD	0.61	Beta	Alpha = 1.116 Beta = 0.713	Stark et al.[30]
Monthly utility decrement for UC	0.017	Beta	Alpha = 1.601 Beta = 94.443	Stark et al.[30]
Monthly utility decrement for CD	0.023	Beta	Alpha = 1.647 Beta = 68.958	Stark et al.[30]
Wait time				
Time taken to undergo blood test and/or FC test after presenting with symptoms in primary care	7 days	Fixed		Expert opinion
Time taken to obtain results of blood test and FC test	7 days	Fixed		Expert opinion
Time taken to follow-up by GP first time	3 months	Fixed		Expert opinion
Time taken to follow-up by GP second time	4 weeks	Fixed		Expert opinion
Time taken to a specialist consultation for IBD patients	86.50	Normal	SE=17.602	Leddin et al.[31]
Time taken to a specialist consultation for non-IBD patients	122.00	Normal	SE=9.694	Leddin et al.[31]
Time taken to endoscopy after seeing a specialist	63.50	Normal	SE=18.622	Leddin et al.[31]

Parameter	Estimate	Distribution	Distribution parameters	Data source
Time taken to follow-up by a specialist	3 months	Fixed		Expert opinion

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; FC: fecal calprotectin; GP: general practitioner; IBS: irritable bowel syndrome; SE: standard error; MSC: Medical Services Commission

Table 2. Results of base-case analysis and scenario analyses

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
Base-case	295.12 (274.49,317.53)	0.751 (0.431,0.939)	273.93 (245.40,306.05)	0.750 (0.430,0.938)	21.19 (-7.50,46.57)	0.001 (0.0003,0.002)	20,323.35	81.3%
Scenario Analyses								
IBD prevalence, %								
5	286.17 (268.43,306.09)	0.757 (0.427,0.943)	264.65 (238.41,294.96)	0.756 (0.426,0.942)	21.52 (-7.75,46.72)	0.001 (0.0002,0.002)	24,440.81	75.5%
10	312.60 (295.98,331.11)	0.743 (0.434,0.928)	291.21 (267.12,319.28)	0.742 (0.433,0.927)	21.39 (-5.67,45.80)	0.001 (0.0004,0.003)	15,594.08	89.3%
15	339.26 (323.00,357.86)	0.740 (0.448,0.916)	318.14 (294.04,345.63)	0.738 (0.447,0.915)	21.12 (-5.02,43.94)	0.002 (0.0004,0.005)	11,515.23	93.8%
20	365.81 (350.40,383.68)	0.728 (0.442,0.907)	344.93 (322.74,371.08)	0.725 (0.440,0.904)	20.88 (-3.94,41.96)	0.002 (0.0006,0.006)	8,843.74	96.7%
FC test accuracy (Turvill et al.[12])								
Sensitivity=0.94 (95% CI: 0.85-0.98) Specificity=0.92 (95% CI 0.90-0.94)	285.36 (265.56,306.98)	0.755 (0.431,0.939)	274.16 (245.10,306.04)	0.754 (0.430,0.937)	11.21 (-16.20,35.83)	0.001 (0.0005,0.003)	8,012.69	96.5%
Primary care practice accuracy (Waugh et al.[7])								
Sensitivity=1 (7/7) Specificity=0.79 (82/104)	295.55 (275.41,317.36)	0.753 (0.446,0.938)	312.85 (270.56,359.49)	0.752 (0.445,0.937)	-17.30 (-62.90,22.76)	0.001 (-0.0001,0.002)	N/A	93.6%
Proportion of patients with abnormal blood test with endoscopy ordered in the initial gastroenterologist consultation, %								
100	295.38 (274.60,317.32)	0.751 (0.430,0.938)	276.23 (248.77,307.54)	0.750 (0.429,0.937)	19.15 (-10.31,44.69)	0.001 (0.0002,0.002)	22,007.50	76.9%
Proportion of non-IBD patients with symptoms after further intensive management by GPs that need investigation by specialist and endoscopy, %								
5	268.69 (251.37,286.92)	0.754 (0.444,0.940)	248.96 (222.27,278.72)	0.753 (0.444,0.939)	19.73 (-10.67,46.48)	0.001 (0.0003,0.003)	17,988.04	83.5%
10	281.84 (263.26,301.20)	0.754 (0.447,0.938)	261.12 (234.23,290.74)	0.753 (0.446,0.937)	20.72 (-8.35,46.16)	0.001 (0.0002,0.002)	19,504.34	82.4%
20	308.68 (286.39,332.03)	0.751 (0.426,0.938)	286.82 (257.72,318.88)	0.750 (0.426,0.938)	21.85 (-5.70,45.83)	0.001 (0.0002,0.002)	21,405.41	81.2%
25	322.23 (297.17,350.17)	0.749 (0.423,0.937)	300.26 (268.29,334.99)	0.748 (0.422,0.936)	21.97 (-5.25,45.94)	0.001 (0.0003,0.002)	22,040.22	79.5%

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
30	335.85 (308.40,366.80)	0.750 (0.432,0.934)	313.02 (280.31,348.54)	0.749 (0.431,0.933)	22.84 (-3.46,45.44)	0.001 (0.0002,0.002)	23,221.90	78.8%
Cost of FC, $								
20	275.24 (254.13,297.02)	0.755 (0.446,0.940)	273.98 (246.12,304.75)	0.754 (0.445,0.939)	1.26 (-27.32,25.62)	0.001 (0.0002,0.002)	1,206.34	94.9%
30	285.21 (264.91,307.09)	0.753 (0.436,0.940)	274.13 (246.69,306.58)	0.752 (0.435,0.939)	11.08 (-17.29,36.28)	0.001 (0.0003,0.002)	10,567.51	89.8%
50	305.42 (284.54,327.76)	0.751 (0.428,0.941)	274.12 (246.34,305.69)	0.750 (0.428,0.940)	31.29 (2.93,55.78)	0.001 (0.0003,0.002)	29,789.72	71.7%
60	315.60 (295.76,337.54)	0.751 (0.430,0.936)	274.19 (246.49,305.45)	0.750 (0.430,0.936)	41.40 (13.49,66.07)	0.001 (0.0002,0.002)	39,243.50	59.8%
70	325.29 (305.29,347.98)	0.753 (0.428,0.938)	274.15 (246.63,305.86)	0.751 (0.427,0.936)	51.14 (22.70,75.99)	0.001 (0.0002,0.002)	48,712.48	47.4%
All cost estimates except FC test cost, $								
+20%	346.68 (321.97,372.92)	0.752 (0.430,0.940)	329.42 (295.89,367.82)	0.751 (0.429,0.939)	17.26 (-16.39,48.03)	0.001 (0.0003,0.002)	16,191.86	83.4%
-20%	244.18 (227.92,262.28)	0.752 (0.433,0.936)	219.14 (196.94,244.50)	0.751 (0.432,0.935)	25.04 (2.13,44.91)	0.001 (0.0003,0.003)	23,509.13	79.8%
Utility decrement								
CD = 0.006 (Gregor et al.[32]) UC = 0.014 (Poole et al.[33])	295.11 (274.59,316.66)	0.755 (0.427,0.941)	274.24 (246.79,304.96)	0.755 (0.427,0.940)	20.87 (-6.50,45.47)	0.001 (0.0002,0.001)	30,136.89	68.6%
Time taken to follow-up by GP first time								
1 month	294.97 (274.80,316.36)	0.756 (0.422,0.945)	274.09 (245.92,306.40)	0.755 (0.421,0.944)	20.89 (-8.13,46.10)	0.001 (0.0002,0.002)	18,830.57	81.9%
2 months	295.36 (274.91,317.69)	0.758 (0.437,0.943)	274.07 (246.25,306.46)	0.757 (0.436,0.942)	21.29 (-7.90,45.83)	0.001 (0.0002,0.002)	19,650.08	81.7%
4 months	295.28 (275.08,317.76)	0.749 (0.442,0.940)	274.03 (245.76,304.35)	0.748 (0.441,0.939)	21.25 (-6.75,45.57)	0.001 (0.0002,0.002)	21,451.73	80.8%
Time taken to follow-up by a specialist								
1 month	295.47 (275.10,317.87)	0.747 (0.425,0.937)	274.37 (246.13,305.91)	0.746 (0.424,0.936)	21.10 (-7.54,46.45)	0.001 (0.0002,0.002)	23,213.73	76.1%
2 months	295.35 (275.19,318.36)	0.757 (0.435,0.939)	274.19 (247.23,305.55)	0.756 (0.434,0.937)	21.16 (-7.75,45.96)	0.001 (0.0002,0.002)	21,587.69	79.6%
4 months	295.49 (274.69,317.09)	0.751 (0.430,0.940)	274.42 (246.23,305.94)	0.750 (0.429,0.939)	21.07 (-7.51,46.49)	0.001 (0.0003,0.003)	18,991.77	83.4%
Patient population without gastrointestinal alarm symptoms (Walker et al.[11])								

Scenario	FC testing strategy		Standard practice (blood test)		Incremental Cost	Incremental QALY	ICER ($/QALY)	Probability of FC being cost-effective*
	Cost, $	QALY	Cost, $	QALY				
Prevalence = 4% (18/447) Sensitivity = 0.84 (15/18) Specificity = 0.91 (390/429)	276.29 (253.94,299.86)	0.760 (0.429,0.948)	258.90 (230.11,291.19)	0.760 (0.429,0.947)	17.40 (-13.70,44.78)	0.001 (0.0002,0.002)	21,608.85	75.6%

95% confidence intervals (CI) in brackets

IBD: inflammatory bowel disease; FC: fecal calprotectin; GP: general practitioner; CD: Crohn's disease; UC: ulcerative colitis; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

*at $50,000/QALY threshold

Figure 1. Overview of the model structure for standard practice using blood test

IBD: inflammatory bowel disease; GP: general practitioner

Figure 2. Overview of the model structure for fecal calprotectin testing strategy

FC: fecal calprotectin IBD: inflammatory bowel disease; GP: general practitioner

Figure 3. Overview of the decision branch for normal blood test or negative fecal calprotectin test results

FC: fecal calprotectin IBD: inflammatory bowel disease; GP: general practitioner

Figure 4. Cost-effectiveness acceptability curve

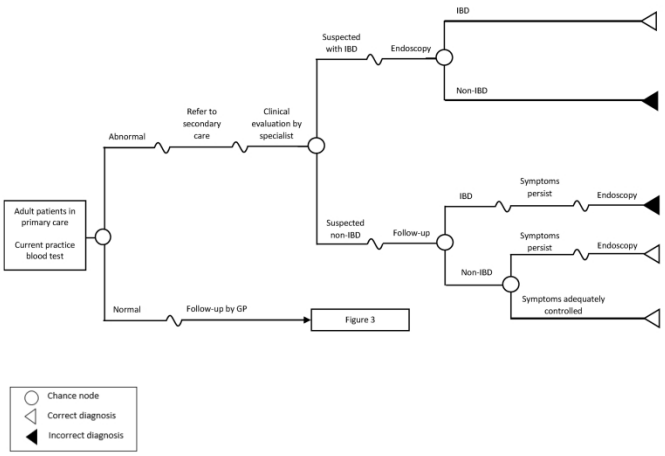


Figure 1

279x361mm (300 x 300 DPI)

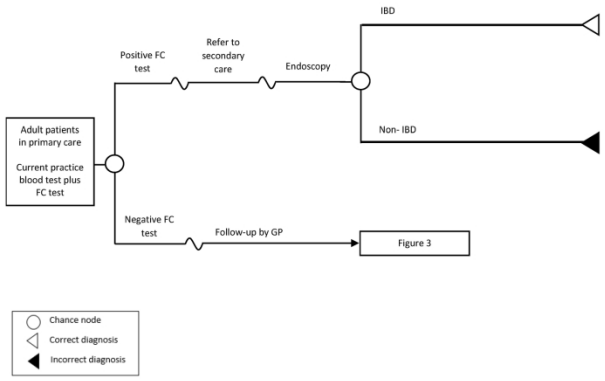


Figure 2

215x279mm (300 x 300 DPI)

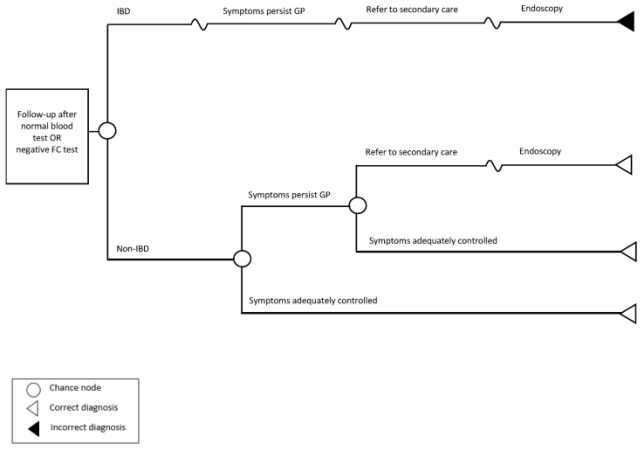


Figure 3

279x361mm (300 x 300 DPI)

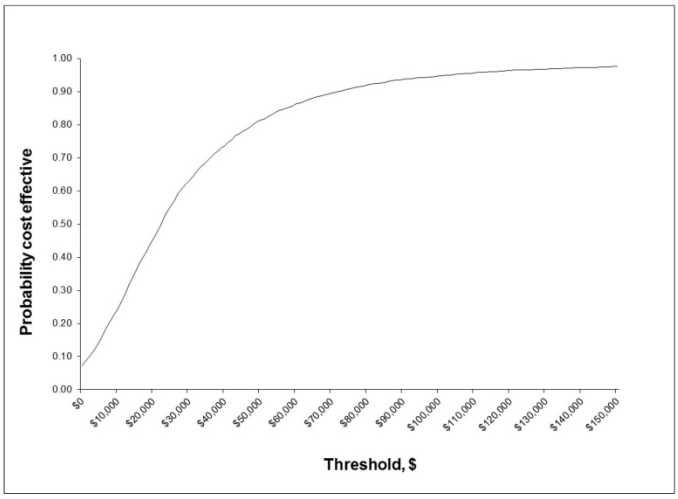


Figure 4

279x361mm (300 x 300 DPI)

Supplementary File

Meta-analysis for sensitivity and specificity of blood test

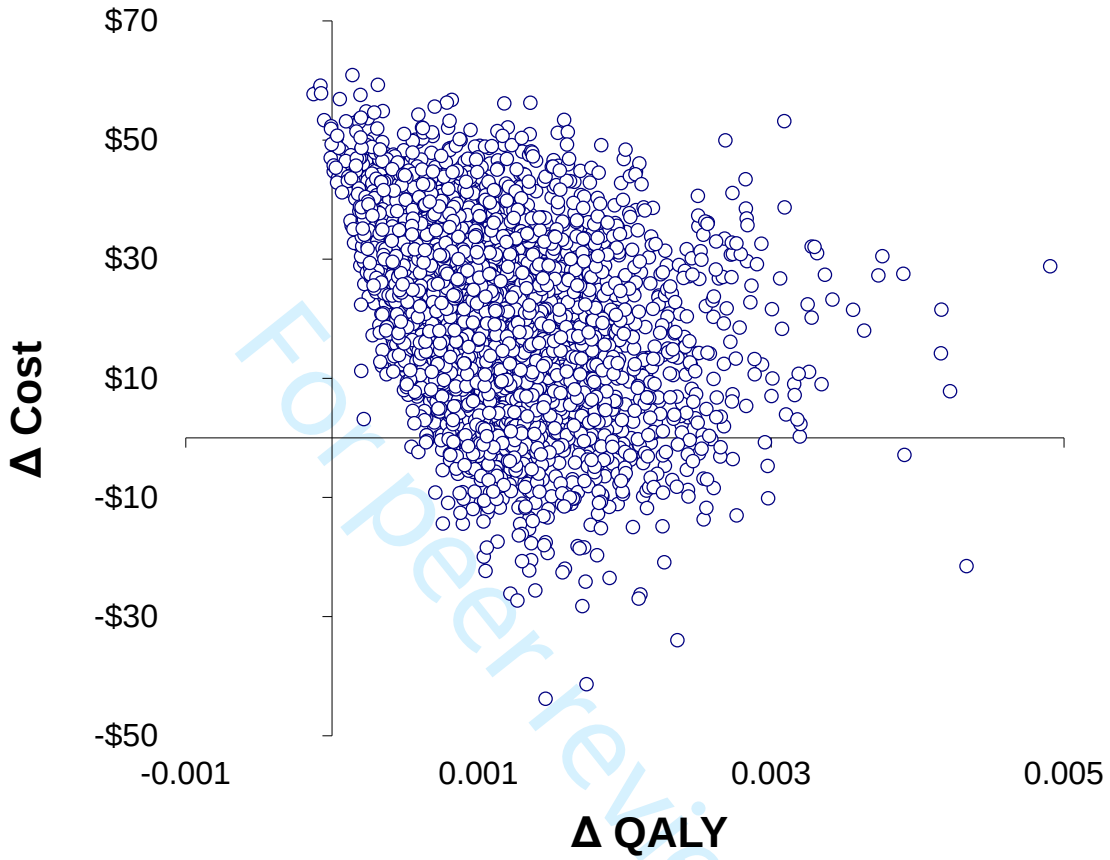
Jellema et al. conducted a high quality systematic review that summarized the evidence on the performance of different diagnostic tests including the blood tests (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) in patients with abdominal symptoms.[1] They identified four studies that investigated the diagnostic performance of CRP or ESR with different diagnostic cut-off points. The gastroenterologists (Drs. Rosenfeld and Chavannes) in our study selected the studies and the cut-off points that are most relevant to the clinical practice.

Table 1. Diagnostic performance of studies with test cut-offs of CRP ≥5mg/l and ESR ≥15mm/h

Study	True Positives	False Positives	True Negatives	False Negatives
Kaiser *et al*, 2007[2]	29	5	19	21
Poullis *et al*, 2002[3]	11	16	143	9
Shine *et al*, 1985[4]	32	9	32	9
The numbers were directly obtained from Jellema et al.[1]				

Subsequently, we have attempted to model these data using a bivariate analysis to take account of the correlation between the sensitivity and specificity based on Reitsma et al.[5] (model specification shown on page 988). However, the estimated covariance matrix was not full rank and might be unreliable, possibly due to our small sample size (only 3 studies). Therefore, we estimated the sensitivity and specificity independently (i.e., without accounting for the correlation between the sensitivity and specificity). The logit estimates for sensitivity and specificity were 0.613 (SE=0.199) and 1.867 (0.196), respectively.

Cost-effectiveness plane for our base case



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1. Jellema P, Windt D a. WM van der, Schellevis FG, et al. Systematic review: accuracy of symptom-based criteria for diagnosis of irritable bowel syndrome in primary care. *Aliment. Pharmacol. Ther.* 2009;30:695–706.
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diarrhoea-predominant functional bowel disorders. *Eur J Gastroenterol Hepatol*. 2002;14:409–412.

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Reporting checklist for economic evaluation of health interventions

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Based on the CHEERS guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CHEERS reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	P1
Abstract	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	P2-P3
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	P5-P6

Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Last paragraph on P7
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P6-P7
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	P6
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	P7
Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2nd paragraph on P8
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	N/A, 2nd paragraph on P8
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	P7-P8
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	P9-P10
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	P9-P10 and supplementary file
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	P11-P12
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit	N/A

		cost. Describe any adjustments made to approximate to opportunity costs	
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P11
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P11
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	P7-P9 and Figures 1-3
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	P7-P13
Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P12-P13
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1

Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	P14 and Table 2
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P13-P15
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P15-P20
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	P21
Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	P21