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MINIREVIEWS

Faecal immunochemical test outside colorectal cancer screening?

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Abstract

Faecal immunochemical tests (FITs) are the most widely colorectal cancer (CRC) diagnostic biomarker available. Many population screening programmes are based on this biomarker, with the goal of reducing CRC mortality. Moreover, in recent years, a large amount of evidence has been produced on the use of FIT to detect CRC in patients with abdominal symptoms in primary healthcare as well as in surveillance after adenoma resection. The aim of this review is to highlight the available evidence on these two topics. We will summarize the evidence on diagnostic yield in symptomatic patients with CRC and significant colonic lesion and the different options to use this (thresholds, brands, number of determinations, prediction models and combinations). We will include recommendations on FIT strategies in primary healthcare proposed by regulatory bodies and scientific societies and their potential effects on healthcare resources and CRC prognosis. Finally, we will show information regarding FIT-based surveillance as an alternative to endoscopic surveillance after high-risk polyp resection. To conclude, due to the coronavirus disease 2019 pandemic, FIT-based strategies have become extremely relevant since they enable a reduction of colonoscopy demand and access to the healthcare system by selecting individuals with the highest risk of CRC.

Key Words: Adenoma; Colorectal cancer; Diagnostic performance; Faecal biomarkers; Faecal haemoglobin; Faecal immunochemical test; Primary healthcare

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biomarker used widely in CRC screening programmes. In recent years, a large body of evidence has appeared that enables recommending its use in different scenarios. For the evaluation of symptomatic patients in primary healthcare, FIT improves use of available endoscopic resources, avoiding unnecessary colonoscopies, predicts the risk of CRC and may have an impact on prognosis. Furthermore, although endoscopic surveillance after adenoma resection is widely extended, there are relevant doubts over its efficiency in the context of high-quality baseline colonoscopies and a FIT-based surveillance strategy could be an alternative.

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INTRODUCTION

Colorectal cancer (CRC) is a relevant health problem in the Western world. In 2018, almost half a million new cases were diagnosed in Europe and 250000 patients died due to CRC[1]. Health authorities have devised two main strategies to reduce the impact of CRC: screening in average- and high-risk populations and early detection in symptomatic patients[2-4].

All preventive and diagnostic strategies are based either on invasive or non-invasive techniques. Colonoscopy is the cornerstone of all techniques, due to its diagnostic yield, the capacity of histological sampling, and especially, its ability to perform therapeutic procedures. However, colonoscopy is time and resource consuming, there is limited capacity with potential waiting lists and it is associated with side effects. Among the non-invasive techniques either imaging techniques or several diagnostic biomarkers have been evaluated[5].

Faecal occult blood tests (FOBTs) are the most widely CRC diagnostic biomarker available. FOBTs detect either blood or blood products (such as globin) in faeces with different methods. There are two main types of FOBTs: Chemical (cFOBT) or immunological (faecal immunochemical test, FIT). cFOBTs demonstrated its effect on reducing CRC mortality in CRC screening in large-scale randomized controlled trials[5]. However, they have been gradually replaced by semiquantitative FITs due to their advantages. FITs are based on the reaction of monoclonal or polyclonal antibodies specific for human faecal haemoglobin (f-Hb), albumin, or other faecal blood components. Thus, they do not require any dietary or pharmacological restriction, as long as they do not react with blood from the upper digestive tract or with any food component. The greatest advantage is determined by its ability to detect and quantify f-Hb concentrations 7 to 15 times lower than those detected by chemical tests. This significantly improves CRC and advanced adenoma detection sensitivity. Moreover, FITs enable reliable and accurate automated analyses, which prevents subjective interpretation[6]. For this reason, most CRC mass screening programmes have opted for FIT. Moreover, there is a large amount of evidence on the diagnostic accuracy of FITs for CRC and adenoma detection in asymptomatic patients[7].

In recent years, a large amount of evidence has been produced on the use of FITs to detect CRC in patients with abdominal symptoms[8-10] as well as in the surveillance of high-risk subjects (surveillance after adenoma resection)[11,12]. Furthermore, due to the coronavirus disease 2019 (COVID-19) pandemic, FIT has become extremely relevant due to the limited endoscopic resources available and access to healthcare systems[13]. The aim of this review is, therefore, to update the evidence and recommendations available on use of FIT outside the scope of CRC screening. This topic is structured into the following sections: Evidence on FIT in the evaluation of symptomatic patients; risk prediction models for CRC incorporating FIT in symptomatic patients; a combination of FIT with other non-invasive biomarkers in patients with abdominal symptoms; recommendations on the use of FIT in primary healthcare; effect of FIT on CRC prognosis; and FIT for surveillance after adenoma resection.

EVIDENCE ON FIT IN THE EVALUATION OF SYMPTOMATIC PATIENTS

Despite the implementation of CRC screening programmes, most CRC cases are still diagnosed after symptomatic presentation[14]. A large number of studies have been performed on the effectiveness of FIT for triaging referrals; also in symptomatic patients, which have been summarized in a number of recent systematic reviews[8-10, 15]. The first systematic review assessing the value of immunochemical-based FOBTs as first-line investigation in symptomatic patients was completed in 2008[15]. This review included nine studies evaluating several FIT assays using different methods and reported that FIT had better diagnostic performance than cFOBTs. However, the studies included had a small sample size and a high degree of clinical heterogeneity (*i.e.* different populations, use of quantitative and qualitative FITs), which limits the conclusions of the meta-analysis.

This work was supplemented by another systematic review[10], conducted to inform the development of a new National Institute for Health and Care Excellence (NICE) diagnostics guidance (DG) 30[16]. This review included nine studies, which provided data about clinical evaluations of three quantitative FIT assays and showed that when the FIT result is based on a single sample with a cut-off point of 10 μg Hb/g of faeces, the sensitivity for detecting CRC was 92.1% (95% confidence interval [CI]: 86.9-95.3) and 100% (95%CI: 71.5-100) for OC-Sensor (Eiken Chemical Co. Ltd., Tokyo, Japan) and HM-JACKarc (Kyowa-Medex Co. Ltd., Tokyo, Japan) FIT assays, respectively, indicating that both could be useful to rule out CRC. In that review, specificity was estimated to be 85.8% (95%CI: 78.3-91) and 76.6% (95%CI: 72.6-80.3) for OC-Sensor and HM-JACKarc FIT assays, respectively. The systematic review also included results from a study evaluating the diagnostic accuracy of the FOB Gold (Sentinel Diagnostics, Milan, Italy) FIT assay to detect a significant colonic lesion (SCL) using a f-Hb cut-off of 9 μg Hb/g faeces, defined as bleeding, cancer or polyp (sensitivity 45.2%; specificity 92.3%). As a result of this evidence,[10] NICE recommended use of the OC Sensor®, HMJACKarc®, and FOB Gold® FIT assays in primary healthcare to assess people who have accounted low risk symptoms (without rectal bleeding) who do not meet the criteria for a suspected cancer pathway referral, using a threshold of 10 μg Hb/g faeces[16,17]. However, important clinical concerns have been raised related to this recommendation[18].

Applicability of quantitative FITs in the assessment of patients with abdominal symptoms in primary healthcare

The systematic review supporting DG 30 only included one study performed in a primary healthcare setting[19], and none of the reviewed studies assessed FIT accuracy in real practice. Hence, the assessment of FIT accuracy to detect CRC in a cohort of symptomatic patients recruited from primary healthcare could lead to different results when compared to another comprised by symptomatic patients referred to secondary healthcare[8]. This could happen for reasons unrelated to CRC prevalence[20]. In this sense, high-risk symptoms (*i.e.* rectal bleeding) are shared between CRC and other benign conditions (*i.e.* anorectal disease, diverticular disease, colorectal polyps, inflammatory bowel disease or non-steroidal anti-inflammatory drug related enteropathy) which are more prevalent, thus reducing FIT specificity to detect CRC[21].

A subsequent meta-analysis was aimed at solving these problems[8]. The authors performed subgroup analyses according to the characteristics of the studies (100% symptomatic cohorts/mixed cohorts of symptomatic/asymptomatic subjects) and CRC prevalence. In this respect, the pooled estimates of sensitivity for studies comprised solely by symptomatic patients and studies made up of mixed cohorts was 94.1% (95%CI: 90.0-96.6) and 85.5% (95%CI: 76.5-91.4), respectively. Conversely, there were no statistically significant differences between the pooled sensitivity of studies with CRC prevalence < 2.5% (84.9%, 95%CI: 73.4-92.0) and ≥ 2.5% (91.7%, 95%CI: 83.3-96.1).

Since then, many studies assessing the diagnostic accuracy of FIT have been performed in primary healthcare. However, some have limitations, mainly due to their retrospective nature[9] or the criteria used for CRC diagnosis. Several studies have not used colonoscopy or a sufficient follow-up time (at least 2 years) to detect incident CRC. These two criteria have been used as "reference tests" in the systematic reviews available to select high-quality studies[8,10,15,22]. Furthermore, they have been confirmed in a different meta-analysis which detected similar diagnostic accuracy among the studies that used these criteria[7]. This evidence has been summarized in a recently published meta-analysis that has evaluated the diagnostic accuracy of FIT in patients presenting lower abdominal symptoms in primary healthcare. The results

confirmed previous findings. Twenty-three studies (69536 participants) were included with a CRC prevalence ranging between 0.3% and 6.2%. Six studies (n = 34691) evaluated FIT as rule in test (threshold of ≥ 150 μg Hb/g faeces) showing moderate sensitivity (64.1%, 95%CI: 57.8-69.9) and high specificity (95.0%, 95%CI: 91.2-97.2). A threshold of 10 μg/g (15 studies; n = 48872) resulted in sensitivity and specificity of 87.2% (95%CI: 81.0-91.6) and 84.4% (95%CI: 79.4-88.3) for CRC, respectively[9].

In this meta-analysis, the number needed to scope to detect a CRC as well as the number of missed CRC per 1000 patients according to expected CRC prevalence in primary care was calculated. The number of missed CRC per 1000 patients if a patient has a 'negative' FIT result in a population with a CRC prevalence of 2% is expected to increase from four to five when using the threshold of 20 μg Hb/g faeces instead of 10 μg Hb/g faeces. However, at the same CRC prevalence, the number needed to scope is expected to decrease from 10 to 4 if the 150 μg Hb/g faeces threshold is used instead of 10 μg Hb/g faeces[9].

Accuracy of FIT in detecting SCL and gastrointestinal cancer in patients with abdominal symptoms

As previously discussed, abdominal symptoms are non-specific and shared among benign and malignant diseases. Thus, the aim of a physician is not only to rule out CRC as long as other benign conditions may also present with the same symptoms and may benefit from diagnosis. In this sense, a previous meta-analysis revealed that FIT may not be sensitive enough to rule out all SCL[8]. Unfortunately, there is a high degree of heterogeneity among the studies evaluated due to the FIT brands used, the threshold selected, and especially, the differences in SCL definitions. The definitions used vary among inflammatory bowel disease, cancer, or high-risk adenoma; plus any type of colitis; plus any advanced adenoma, polyposis, complicated diverticular disease, colonic ulcer and bleeding angiodysplasia or even any colonic lesion detection regardless of its importance[8]. In a recently published meta-analysis, the overall pooled sensitivity and specificity of FITs for SCL for studies that used the limit of detection as a threshold (seven studies; n = 22624 patients) was 70.4% (95%CI: 68.4-72.3) and 78.4% (95%CI: 77.8-78.9), respectively. At the ≥ 10 μg Hb/g faeces threshold (seven studies; n = 20407 patients), the sensitivity and specificity were 69.1% (95%CI: 60.5-76.5) and 87.2% (95%CI: 83.4-90.2), respectively. Furthermore, three studies (n = 20528 patients) evaluated the diagnostic accuracy of FIT with a threshold of ≥ 150 μg Hb/g faeces showing sensitivity and specificity of 35.9% (95%CI: 33.8-38.1) and 97.5% (95%CI: 97.3-97.8), respectively[9].

Gastrointestinal (GI) symptoms are non-specific and could be related to different GI diseases. A relevant question is whether symptomatic patients with a completely normal colonoscopy after a positive FIT require further evaluation. In a recently published study, the risk of GI cancer detection (upper GI cancer and CRC) after a complete colonoscopy without CRC was evaluated according to the FIT result (threshold 10 μg Hb/g faeces). During a mean time of 45.5 ± 20.0 mo, GI cancer was detected in 57 (2.1%) patients: upper GI cancer in 35 (1.3%) and CRC in 14 (0.5%). FIT-positive subjects revealed a higher CRC risk (hazard ratio [HR] 3.8, 95%CI: 1.2-11.9] with no differences in GI (HR 1.5, 95%CI: 0.8-2.7) or upper GI cancer risk (HR 1.0, 95%CI: 0.5-2.2). Upper GI cancer was detected in 22 (0.8%) patients during the first year. Two variables were independently associated: anaemia (odds ratio [OR] 5.6, 95%CI: 2.2-13.9) and age ≥ 70 years (OR 2.7, 95%CI: 1.1-7.0)[23].

Does one sample with a cut-off point of 10 μg Hb/g of faeces fit everybody?

NICE recommends a single f-Hb cut-off of 10 μg Hb/g faeces to be used in the evaluation of symptomatic patients at all ages regardless of sex. However, using FIT with the same cut-off for asymptomatic populations has been associated with a higher accuracy for advanced adenoma detection in males[24]. However, a recently published meta-analysis on the diagnostic accuracy for CRC detection in asymptomatic patients did not show any differences between males and females[7]. These variations may be related to the differences in advanced adenoma prevalence and location as well as colonic transit.

One key question is what threshold is used to determine a positive result in the evaluation of symptomatic patients. Most studies have evaluated the 10 μg Hb/g of faeces threshold to triage symptomatic patients as this cut-off approximates to the quantitation limit documented by the manufacturers of most FIT analytical systems[8, 10]. Nonetheless, a recent study showed that using a cut-off point of 20 μg Hb/g of faeces could reduce the number of colonoscopy examinations without missing more than 1 CRC per 1000 patients evaluated belonging to the low-risk group defined by

NICE DG 30[9]. Moreover, other thresholds have also been proposed: limit of determination, and recently, 150 μg Hb/g of faeces[25]. Thus, while patients with a concentration below the limit of determination had a risk of detecting a CRC less than 0.2%; in patients with a Hb greater than 150 μg/g of faeces the risk of detecting a CRC was greater than 31.1%.

In fact, the choice of threshold is a trade-off among the number of patients required to be referred to colonoscopy, the number of missing CRC, and CRC prevalence. In our meta-analysis, we calculated the number needed to scope to detect a CRC as well as the number of missed CRC per 1000 patients according to expected CRC prevalence in primary care. The number of missed CRC per 1000 patients if a patient has a 'negative' FIT result in a population with a CRC prevalence of 2% is expected to increase from four to five when using the threshold of 20 μg Hb/g faeces instead of 10 μg Hb/g faeces. However, at the same CRC prevalence, the number needed to scope is expected to decrease from 10 to 4 if the 150 μg Hb/g faeces threshold is used instead of 10 μg Hb/g faeces[9]. With respect to colonoscopy, we must take into account not only the resources required to evaluate patients and waiting lists but also the risks associated with colonoscopy. In a recently published meta-analysis, they were estimated at 5.8 perforations per 10000 colonoscopies (95%CI: 5.7-6.0) and 2.4 cases of relevant bleeding per 1000 colonoscopies (95%CI: 2.4-2.5)[26]. In this sense, it also seems reasonable to use a higher cut-off than that recommended by NICE, if there is well-planned safety netting to evaluate symptomatic patients with a negative result if symptoms persist. Furthermore, results could also be closely monitored locally to enable the rapid adjustment of cut-offs to optimize each area's resources[27]. However, because f-Hb correlates directly with the severity of colorectal lesions, raising the f-Hb cut-off will lead to losing a higher number of SCLs. However, those are less urgent for diagnosis and could easily be subsequently rescued in an environment whose colonoscopy resources are preserved through the appropriate use of FIT as a first line triage test.

There is the option of using more than one FIT determination. Two studies included in a previous meta-analysis[8,10] examined the utility of one *vs* two faecal samples for detecting advanced neoplasia (CRC plus advanced adenoma). The diagnostic yield of the two samples using a cut-off of 20 μg Hb/g faeces was attained with only one sample using a cut-off of 10 μg Hb/g faeces. This highlights the need for further investigation to verify the efficiency of using different strategies to triage not only advanced adenoma but also any SCL, if the use of a higher cut-off than that recommended by NICE (10 μg Hb/g faeces) is conditioned to a "safety netting", which requires more than one FIT sample.

RISK PREDICTION MODELS FOR CRC INCORPORATING FIT IN SYMPTOMATIC PATIENTS

A number of predictive models have been developed to improve clinical judgement in patients with abdominal symptoms, and some have included quantitative FITs[28]. In recent years, two prediction models (COLONPREDICT and the FAST score) have been developed and were externally validated, not only to identify people at higher risk of CRC but also to define a subgroup whose CRC risk is so low that we can ensure that no further evaluation is required[29,30]. For that purpose, both prediction models defined two cut-offs. The first (COLONPREDICT< 3.50 and FAST score < 2.12 respectively) was evaluated to identify a low-risk population with a negative predictive value (NPV) of having CRC higher than 99%. In this subgroup, no further evaluation should be recommended as the risk of performing a colonoscopy is similar to the risk of severe complications associated with this exploration[26]. A second cut-off (COLONPREDICT ≥ 5.60, FAST score ≥ 4.50) was calculated to define a high-risk subgroup in which at least 90% of CRC would be detected.

Despite COLONPREDICT, the model has shown a high diagnostic performance, with an area under the curve (AUC) of 0.92 in both derivation and validation cohorts, it has been criticized as too complex for routine primary healthcare practice due to considering too many clinical (age, sex, acetylsalicylic acid treatment, previous colonoscopy, rectal mass, benign anorectal lesion, rectal bleeding and change in bowel habit) and laboratory (serum carcinoembryonic antigen, faecal and blood haemoglobin) variables[29]. Conversely, the FAST score combines only three variables (f-Hb, sex and age). In addition to being easier, this model has also shown high accuracy to predict the individual risk of CRC and SCL in symptomatic patients (AUC = 0.88)[30]. To date, none of these prediction models have been validated in primary

healthcare.

A similar risk score was developed by Rodríguez-Alonso *et al*[31] for advanced neoplasia detection. A score between 0 and 11 is calculated for each patient according to three variables (sex, age, and FIT), and a risk score ≥ 5 is considered the optimal cut-off point for colonoscopy referral. More recently, the COLONOFIT score aims to assess the risk of advanced neoplasia (CRC plus advanced adenoma) in symptomatic patients with indication of a fast-track colonoscopy[32]. This model is based on age, colonoscopy (in the previous 5 years), tobacco use, and variables related to FIT (maximum f-Hb value and number of samples with FIT > 4 μg Hb/g faeces). A COLONOFIT score > 10 points enables diagnosis of 98% of CRC (NPV = 99.7%) and 77% of advanced adenomas, and has been shown to classify patients 3% to 4% better than the FAST score in this study. However, COLONFIT needs the submission of three FIT samples, which could reduce adherence and compromise its successful implementation in primary healthcare.

COMBINATION OF FIT WITH OTHER NON-INVASIVE BIOMARKERS IN PATIENTS WITH ABDOMINAL SYMPTOMS

Although many biomarkers have been evaluated for the detection of CRC in a screening setting[33], they have shown little applicability in clinical practice. A few studies have explored the possibility of improving the diagnostic performance of FIT in combination with other non-invasive biomarkers, mainly faecal calprotectin, M2-piruvate kinase and volatile organic compounds, in symptomatic patients[19,34-36]. In general, adding a second biomarker either improves sensitivity reducing specificity and increasing the number of patients referred to colonoscopy, or by contrast, increases specificity reducing sensitivity and the number of patients with a positive result. Only one study has evaluated the concomitant analysis of FIT and faecal calprotectin. This has shown mixed results, presumably due to heterogeneity of both targets, FIT assays, and cut-offs used. Mowat *et al*[19] reported the diagnostic accuracy of FIT (OC-Sensor®) and faecal calprotectin to detect SCL (CRC plus higher risk adenoma plus inflammatory bowel disease) using different cut-offs. The sensitivity of one sample of the OC-Sensor to detect CRC and SCL was 89.3% and 68.6% respectively (cut-off 10 μg Hb/g faeces). Furthermore, when using the limit of haemoglobin detection as a cut-off, the sensitivity to detect CRC and SCL improved by 100% and 88.2%, respectively. Finally, when adding the measurement of faecal calprotectin, the sensitivity to detect SCL increased by 91.2% and 96.1% using the 200 μg Hb/g faeces and 50 μg Hb/g faeces cut-offs, respectively[19].

RECOMMENDATIONS ON USE OF FIT IN PRIMARY HEALTHCARE

Not many international clinical guidelines have opted for the potential advantages of introducing FIT in daily clinical practice. The available literature was reviewed by van Melle *et al*[37], which identified a limited number of countries with clinical guidelines that explicitly recommended use of FIT in symptomatic patients: Australia[38], Spain [5], United Kingdom[16,17] and Denmark (limited to specialized healthcare). We searched most guidelines mentioned by van Melle *et al*[37], in addition to others such as the Italian[39], Colombian[40] and English versions of the Chinese guideline[41]. However, only the 2019 update of the Scottish guideline[42] raised the possibility of including FIT, after completion of several pilot studies currently being developed in Scotland (Table 1).

As previously noted, the NICE recommended that FIT be performed in primary healthcare in symptomatic patients with a positive predictive value below 3%[16,17] after performing a systematic review[10]. Specifically, in the National Institute for Health and Care Excellence guideline, 12 FIT is recommended in patients without rectal bleeding aged under 60 with altered bowel habits or iron deficiency anaemia, patients without rectal bleeding aged over 50 with abdominal pain or weight loss (in which the combination of both symptoms would have been a fast-track criterion); and patients older than 60 with anaemia[17]. Patients with a positive FIT should be referred through the fast-track pathway for further evaluation. In the DG 30, FIT is recommended in any symptomatic patient that does not meet any of the fast-track criteria[18]. The Australian guideline[38] includes the indications of the NICE guidelines to recommend FIT in patients aged under 60 without overt bleeding with a

Table 1 Clinical guidelines and recommendations on colorectal cancer diagnosis that include the use of faecal immunochemical test in primary healthcare

Guideline	Year	Criteria to use FIT
NICE DG 30 United Kingdom [16]	2017	People without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE's guideline on suspected cancer
Australia[38]	2018	In people with symptoms other than overt rectal bleeding, FIT can be used as part of the diagnostic assessment in primary healthcare. It is of particular use in the following circumstances to support diagnostic assessment and notify the urgency of colonoscopy: people over 50 yr with either unexplained weight loss or abdominal pain; and people under 60 yr with either altered bowel habit or anaemia
Spain[5]	2018	Patients with lower gastrointestinal symptoms of recent onset who do not meet criteria for referral without delay to a specialist service due to high suspicion of CRC (rectal or abdominal mass, rectal bleeding or iron-deficiency anaemia) should undergo a FIT
NICE NG12 United Kingdom [17]	2021	Offer FIT to assess for CRC in adults without rectal bleeding who: Are aged 50 and over with unexplained abdominal pain or weight loss, or are aged under 60 with changes in their bowel habit, or iron-deficiency anaemia, or are aged 60 and over and have anaemia even in the absence of iron deficiency

CRC: Colorectal cancer; DG: Diagnostics guidance; FIT: Faecal immunochemical test; NG: National Institute for Health and Care Excellence guideline; NICE: National Institute for Health and Care Excellence.

change in bowel habit or anaemia; and in those over 50 with abdominal pain or weight loss. Based on the article published by Mowat *et al*[19], the recommendation justified performing FIT to rule out SCL.

The Spanish guideline on CRC diagnosis and prevention[5] is based on the NICE DG 30 (including the 10 μg Hb/g of faeces cut-off) and the systematic review performed by Westwood *et al*[10]. FIT is recommended for the evaluation of any patient with lower GI symptoms if they do not meet the criteria for urgent referral to colonoscopy (tumour or mass on examination or imaging tests, rectal bleeding associated with CRC or iron deficiency anaemia). Therefore, this guide includes non-suspicious rectal bleeding as a FIT application criterion. In the event of a positive result, the guide recommends requesting a colonoscopy and in case of negative result, to monitor symptoms and refer the patient to a specialized level if symptoms persist.

On the other hand, guidelines that do not recommend FIT in primary healthcare generally propose referral to specialized healthcare for all high-risk symptoms and only recommend observation in patients with low-risk symptoms such as loss of appetite, constipation or mucus in the faeces[37]. The specialist will probably finally request the colonoscopy and decide priority himself. The New Zealand guide, updated in 2014[43], explicitly advises against its use, due to the lack of evidence in its favour and compares it with carcinoembryonic antigen. The Ontario clinical guidelines[44] withdrew the recommendations that included cFOBTs in 2017, to avoid a possible conflict with its screening programme. In 2019, this exclusion was extended to FITs. Other clinical guidelines only contemplate cFOBTs[45].

EFFECT OF A FIT-BASED STRATEGY ON RESOURCES

As we have seen, the guidelines that recommend FIT in primary healthcare are intended to identify a subgroup of patients at high risk of CRC detection despite presenting mild symptoms. Otherwise, these patients would not have been included in the fast-track colonoscopy. However, a negative FIT result in these patients would reduce the number of colonoscopies performed with no relevant findings[10]. This strategy may avoid colonoscopy-related risks in subjects with a low CRC risk and facilitate better prioritization on colonoscopy waiting lists. In this sense, an estimation performed based on the results obtained in the Pin-Vieito study[8] with a 3% CRC estimated prevalence and 10 μg Hb/g and 20 μg Hb/g of faeces cut-off (cohorts 100% symptomatic) highlights that FIT will avoid approximately 2/3 of the colonoscopy with two missed CRC out of 1000 patients evaluated (Figure 1). If we take the SCL into consideration with 12% and 10 μg Hb/g of faeces cut-off, the positive predictive value would be 24.8%, and the number of undetected SCL would be 24 out of 1000 subjects, mainly advanced adenomas.

Due to the COVID-19 pandemic, the risk stratification of subjects with GI symptoms has become of the utmost relevance. A modelling study has recently been published.

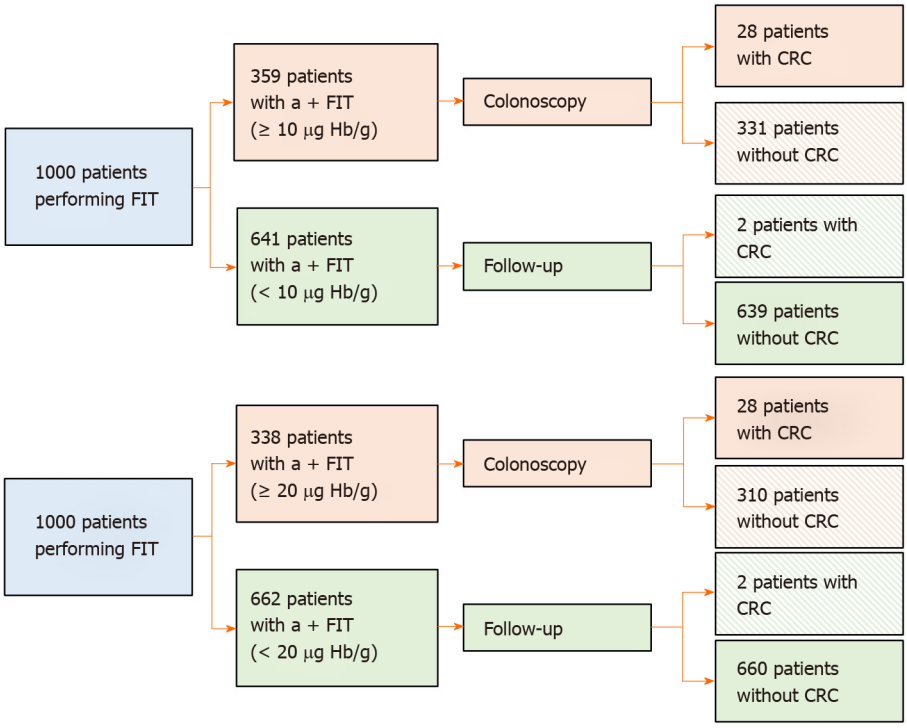

Figure 1 Estimation of the number of patients who need to be referred for colonoscopy, and the diagnostic yield for colorectal cancer in the 10 and 20 μg Hb/g of faeces thresholds[8]. CRC: Colorectal cancer; FIT: Faecal immunochemical test.

This model evaluated the effect of delays for colonoscopy on CRC mortality due to lack of endoscopic capacity and prioritization of colonoscopy in patients with a f-Hb ≥ 10 μg Hb/g of faeces. A delay higher than 6 mo would lead to 2250 attributable deaths and loss of 32799 life-years. In contrast, using FIT to stratify only 18% of symptomatic patients would be referred to colonoscopy; 89% of these deaths would be avoided and the requirements for colonoscopy would be reduced by > 80%[13]. This information has been confirmed in a recently published retrospective study in primary healthcare with a sample size of 14487 consecutive patients who underwent a FIT due to low-risk symptoms without fast-track criteria[46]. Using a ≥ 10 μg Hb/g faeces threshold, 10% of adults would be investigated to detect 91% of cancers with a number needed to scope of ten to detect one cancer and three to detect a SCL. Only 12 CRCs (< 2/1000 subjects) would be missed in the subjects evaluated. This proportion is similar to the colonoscopy-associated side effects[26] and CRC prevalence in asymptomatic adults aged 50-69[47].

A relevant topic is the strategy in subjects with a negative FIT result. Unfortunately, the information is limited. Hypothetically, symptoms in patients with CRC and a negative FIT will persist or even worsen, so they would require additional medical healthcare. In the Spanish guidelines, follow-up and request for colonoscopy are recommended if symptoms persist[5]. The results of the study performed by Nicholson *et al*[46] support this strategy because seven out of the 12 FIT-negative CRC were detected within 1 mo after FIT. A better understanding of the characteristics of patients with false negative results and their clinical course, is key to guide the most effective diagnostic tests to perform during follow-up.

Westwood *et al*[10] published a cost-effectiveness analysis to inform NICE about the use of FIT in symptomatic patients. For the effectiveness analysis, a meta-analysis was performed and for the cost analysis, a model based on quality-of-life-adjusted life years (QALYs) was devised. Researchers compared three strategies: triage with FIT, triage with cFOBT and no triage (direct referral to colonoscopy). The cost of a colonoscopy and the FIT was estimated at £372 and £4.53, respectively. The differences in QALYs between the three strategies were minimal. The triage strategy using FIT demonstrated a higher cost, but also higher efficacy and cost-effectiveness than cFOBT. It would only be surpassed in cost-effectiveness by placing the cut-off point at the detection threshold of 2 μg/g of Hb in faeces. The FIT also demonstrated greater cost-effectiveness compared to no triage, with an incremental cost of £258.09 per patient. Taking into account the lost QALYs due to FIT false-negatives, saving of £2578.543 per lost QALY was calculated using triage with FIT.

EFFECT OF FIT ON CRC PROGNOSIS

The main objective of any diagnostic strategy is to improve the prognosis of the disease detected. We have evidence that FIT-based CRC screening improves CRC prognosis through early detection[48]. However, the information regarding CRC prognosis detected after a positive FIT in symptomatic subjects is still limited. In this sense, a Polish retrospective analysis of 535 CRC detected in symptomatic subjects evaluated the effect of the pathway to CRC diagnosis on prognosis. CRC detected after a positive FIT (HemCheck-1) result revealed better prognosis than CRC detected on the basis of clinical evaluation (40 ± 47 mo *vs* 25 ± 38 mo; $P < 0.001$)[49].

In a recently published Spanish population-based study[14], a significantly longer 3-year survival was observed in patients with CRC diagnosed after a positive FIT in comparison with CRC detected after a negative result or without a FIT (HR 1.50; 95%CI: 1.22-1.84). These differences in prognosis were related to an earlier CRC stage at diagnosis in the positive FIT group. The reason for these findings is unclear; it is hypothesized that requesting a FIT could reduce diagnostic delay. However, there is a risk of bias, since in one-third of the positives the reason for the FIT request could not be confirmed and they could be related to opportunistic CRC screening.

Although these two retrospective studies have limitations and risk of bias (ignorance of comorbidities, circumstances of the CRC diagnosis, indications for FIT, single-centre, *etc.*), they support the hypothesis that evaluation of symptomatic patients with FIT could modify CRC prognosis. The causes of these differences are not clear and may include diagnostic delay, severity of the onset symptoms and characteristics of the general practitioner. Prospective studies need to be performed that evaluate the effect of a FIT-based diagnostic strategy on CRC prognosis to fully identify the strengths and weaknesses and thus find their ideal place in clinical practice guidelines.

FIT IN SURVEILLANCE AFTER ADENOMA RESECTION

Colorectal polyps are precursor lesions for CRC. Therefore, their removal during colonoscopy reduces CRC risk[5]. These patients have an increased risk of developing more polyps and eventually CRC over the years, so adopting surveillance strategies is recommended[5]. In recent years, mainly motivated by the implementation of the CRC populations screening programmes, there has been an increase in the number of patients with resected colorectal polyps that require surveillance. This has meant that colonoscopies have also undergone a major increase, which require large amounts of resources and highlights the currently overloaded endoscopy services[50,51]. However, we must keep in mind that colonoscopy is an invasive and expensive procedure, with a risk of adverse events, associated both with the procedure itself and with the sedation necessary for it to be performed correctly[26]. For these reasons, it seems reasonable that surveillance colonoscopy for patients after polyp removal should be targeted at those most likely to benefit[51].

The aim of surveillance after colorectal polyp resection is to reduce CRC incidence [51]. In order to make decisions on surveillance, there are two questions that need to be answered: what is the long term (10 years) risk of CRC without surveillance, and does endoscopic surveillance reduce CRC risk compared with no surveillance/participation in a CRC screening programme?

Until recently, the information available was limited and referred to the short-term risk of advanced adenoma detection, an intermediate lesion[52]. Several long-term studies with CRC incidence as the main endpoint have recently been published (Table 2)[53-58]. They reveal that subjects with low-risk lesions (mainly 1-2 non-advanced adenomas or serrated lesions) have a long-term CRC risk similar to the control group (general population or subjects with normal colonoscopy). In contrast, CRC risk is increased in subjects with high-risk lesions (mainly advanced adenomas/serrated lesions and/or multiple adenomas). Taking into account these results, the available practice guidelines recommend in the low-risk group a surveillance strategy equivalent to that recommended in the general population: participation in a CRC screening programme[2,5,59-61].

However, the evidence regarding the benefits of endoscopic surveillance in high-risk lesions is limited to cohort studies. In the study published by Cottet *et al*[62] in 2012, the standardized incidence ratio was 1.10 (95%CI: 0.62-1.82) and 4.26 (95%CI: 2.89-6.04) in those patients with and without colonoscopy follow-up, respectively. In a recently published study including 6239 patients with high-risk lesions, endoscopic

Table 2 Colorectal cancer risk in patients with high risk adenomas or low risk adenomas

Ref.	Patients	Follow-up in yr	Comparison group	High risk lesions	Low risk lesions
Løberg *et al*[53], 2014	40826	7.7	General population	SIR 1.62 (95%CI: 1.50-1.75)	SIR 0.98 (95%CI: 0.89-1.08)
Click *et al*[56], 2018	15935	12.9	No adenoma group	RR 2.7 (95%CI: 1.9-3.7)	RR 1.2 (95%CI: 0.8-1.7)
Lee *et al*[54], 2020	64422	8.1	No adenoma group	HR 2.61 (95%CI: 1.87-3.63)	HR 1.29 (95%CI: 0.89-1.88)
Wieszczy *et al*[55], 2020	236089	7.1	General population	SIR 0.65 (95%CI: 0.51-0.82)	SIR 0.35 (95%CI: 0.26-0.45)
He *et al*[58], 2020	122899	10	No adenoma group	HR 4.07 (95%CI: 2.89-5.72)	HR 1.21 (95%CI: 0.68-2.16)
Cross *et al*[57], 2021	21318	10.1	General population	SIR 1.30 (95%CI: 1.03-1.62)	SIR 0.75 (95%CI: 0.63- 0.88)

HR: Hazard ratio; RR: Rate ratio; SIR: Standardized incidence ratio.

surveillance was associated with a reduction in CRC risk (HR 0.71, 95%CI: 0.49-1.03 for 1 visit; 0.44, 0.28-0.70 for ≥ 2 visits)[57]. Atkin *et al*[63] also showed in a study including 12000 patients with high-risk lesions (1-2 adenomas ≥ 10 mm or 3-4 adenomas < 10 mm), that performing at least one endoscopic surveillance reduces the incidence of CRC (HR 0.57, 95%CI: 0.40-0.80). However, this risk reduction was limited to a subgroup of patients: low-quality colonoscopy, large (≥ 20 mm), high-grade dysplasia and proximal adenomas. In this respect, available guidelines recommend performing baseline colonoscopy with full exploration of the colonic mucosa and resection of all polyps detected[2,5,59-61]. CRC detection during surveillance depends not only on the characteristics of the polyps but also on the endoscopist's technical ability. A recently published Polish study revealed that long-term risk of CRC is increased (HR 2.69, 95%CI: 1.62-4.47) if baseline colonoscopy is performed by low-performing endoscopists (adenoma detection rate < 20%)[64].

One limitation of FIT is its limited diagnostic accuracy for adenomas at a single determination. In asymptomatic subjects, at a single determination FIT detects 31% and 21% of advanced adenomas at the 10 μg Hb/g and 20 μg Hb/g of faeces thresholds, respectively, with specificity higher than 90%[7]. There are several characteristics of the adenomas associated with a positive FIT: number, location, morphology and size[5]. However, the strength of a FIT-based CRC screening is that it is based on periodic (annual or biennial) determination. Furthermore, the threshold used can be tailored according to colonoscopy capacity and long-term objective. The evidence available on a FIT-based surveillance is limited. A prospective British study published in 2019 investigated whether faecal FIT could reduce the surveillance burden on patients and endoscopy services. The study population was patients with intermediate risk of CRC after polyp removal (1-2 adenomas ≥ 10 mm or 3-4 adenomas < 10 mm). Subjects were offered an annual FIT and all subjects underwent a 3-year scheduled colonoscopy. The number of patients that required work-up colonoscopy using the 10 μg Hb/g threshold was 28.8%. The 3-year programme sensitivity for CRC and advanced adenoma was 72.4% and 56.6% with a specificity of 71.1% and 73.7%, respectively. Incremental cost-effectiveness of colonoscopy *vs* FIT surveillance was £7354 per additional advanced adenoma detected and £180778 per additional CRC detected[11].

Similar results were obtained in a diagnostic accuracy study that evaluated FIT (2 μg Hb/g) in a cohort of high-risk patients who underwent endoscopic surveillance. A total of 593 patients were included, including 41 (6.9%) with advanced neoplasia (4 CRC, 37 higher-risk adenoma). Of the 238 patients (40.1%) who had detectable FIT, 31 (13.0%) had advanced neoplasia (2 CRC, 29 higher-risk adenoma) compared with 10 (2.8%) with undetectable FIT (2 CRC, 8 higher-risk adenoma). A detectable FIT gave NPV of 99.4% for CRC and 97.2% for CRC plus higher-risk adenoma. According to these results, a FIT determination can provide an objective estimate of the risk of advanced neoplasia, and could enable tailored scheduling of colonoscopy[65].

In the absence of results from randomized clinical trials evaluating a FIT-based surveillance strategy, we have information from a simulation study[66]. This study evaluated the additional benefit in terms of cost-effectiveness of adding colonoscopy surveillance to a CRC screening programme. Based on the information obtained from the Dutch CRC screening programme, FIT screening without colonoscopy surveillance after adenoma removal reduces CRC mortality by 50.4% compared with no screening or surveillance. Adding colonoscopy surveillance after adenoma resection to FIT screening would reduce mortality by an additional 1.7% to 52.1% but would increase

lifetime colonoscopy demand by 62% at an additional cost of €68000, for an increase of 0.9 life-year. Despite the reduction in mortality provided by endoscopic surveillance compared to FIT follow-up, this study concludes that it is not a cost-effective strategy based on the incremental cost-effectiveness ratios, which exceeds the Dutch willingness-to-pay threshold of €36602 per life-year gained and also substantially increases colonoscopy demand[66].

CONCLUSION

In conclusion, we have enough evidence to recommend use of FIT to triage symptomatic patients in primary healthcare. FIT improves use of available endoscopic resources, avoids unnecessary colonoscopies, accurately predicts the risk of CRC and may have an impact on CRC prognosis. On the other hand, although endoscopic surveillance after adenoma resection is widely extended, there are relevant doubts about its efficiency in the context of high-quality baseline colonoscopies. Moreover, in terms of evaluating the effect on CRC incidence, endoscopic surveillance should be compared with participation in a CRC screening programme. In this sense, we require a randomized controlled trial comparing endoscopic with FIT-based surveillance after high-risk polyp resection.

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