Original research

Transition to quantitative faecal immunochemical testing from guaiac faecal occult blood testing in a fully rolled-out population-based national bowel screening programme

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ABSTRACT

Objective Faecal immunochemical tests (FIT) are replacing guaiac faecal occult blood tests (FOBT) in colorectal cancer (CRC) screening. Data from the first year of FIT screening were compared with those from FOBT screening and assumptions based on a pilot evaluation of FIT.

Design Data on uptake, positivity, positive predictive value (PPV) for CRC and higher-risk adenoma from participants in the first year of the FIT-based Scottish Bowel Screening Programme (n=919 665), with a threshold of 80 µg Hb/g faeces, were compared with those from the penultimate year of the FOBT-based programme (n=862 165) and those from the FIT evaluation (n=66 225).

Results Overall, uptake of FIT was 63.9% compared with 56.4% for FOBT. Positivity was 3.1% and 2.2% with FIT and FOBT; increases were seen in both sexes, and across age range and deprivation. More CRC and adenomas were detected by FIT, but the PPV for CRC was less (5.2% with FIT and 6.4% with FOBT). However, for higher-risk adenoma, PPV was greater with FIT (24.3% with FIT and 19.3% with FOBT). In the previous FIT evaluation, uptake was 58.5% with FIT compared with 54.0% with FOBT; positivity was 2.5% with FIT and 2.0% with FOBT.

Conclusion Transition to FIT from FOBT produced higher uptake and positivity with lower PPV for CRC and higher PPV for adenoma. The FIT pilot evaluation underestimated uptake and positivity. Introducing FIT at the same threshold as the evaluation caused a 67.2% increase in colonoscopy demand instead of a predicted 10%.

INTRODUCTION

Screening for colorectal cancer (CRC) using guaiac faecal occult blood tests (gFOBT) has been shown to be effective in reducing disease-specific mortality in four population-based randomised controlled trials (RCT).[1–4] As a result of this evidence, gFOBT screening was rolled out across the four countries of the UK after a demonstration pilot in Scotland and England demonstrated feasibility.[5] However, gFOBT has been superseded by faecal immunochemical tests (FIT) for haemoglobin and this has been adopted as the primary screening test in a number of countries owing to its many advantages.[6] These include specificity for human haemoglobin, ease of use and potential for automated analysis and quantitation of faecal haemoglobin concentration (f-Hb).[7]

In Scotland, a pilot evaluation of FIT as a first-line test was carried out in 2 of the 14 regional National Health Service (NHS) Boards responsible for the protection and the improvement of their population's health and for the delivery of front-line healthcare services.[8] After the submission of a resulting business case, a decision was taken by Scottish Government to replace gFOBT with quantitative FIT as the primary screening test in the Scottish Bowel Screening Programme (SBoSP). Here, we report the performance data from the first year of FIT screening (20 November 2017 to 31 October 2018) and compare it with; (a) the previous performance of gFOBT in the SBoSP (20 November 2015 to 31 October 2016), (b) the performance of FIT at the f-Hb thresholds that mimicked the positivity and the colonoscopy workload generated by FOBT and (c) the assumptions made in the business case based on data from the FIT as a first-line test evaluation (01 July 2010 to 31 December 2010).

METHODS

The methodology used to carry out the UK demonstration pilot of gFOBT was based on the Nottingham RCT,[2] since this study was considered to have most relevance for the UK, and has been reported in detail previously.[9] When FOBT screening was rolled out across Scotland, it deviated from the pilot methodology in that a qualitative FIT was used as a second test in those with a weak positive initial gFOBT[10] following research that demonstrated increased specificity using this approach.[11]

Roll-out of the SBoSP to the whole population started in June 2007 and was completed by December 2009; the detailed methodology employed has been reported previously.[11] In brief, an initial gFOBT (*hema-screen*, Immunostics Inc, Ocean, New Jersey, USA) was sent in the post every 2 years to all males and females aged between 50

Significance of this study

What is already known on this subject?

- Testing for the presence of haemoglobin in faeces is widely used for colorectal cancer (CRC) screening.
- Traditional guaiac faecal occult blood tests (gFOBT) are being replaced with faecal immunochemical tests (FIT) for haemoglobin; quantitative FIT provide estimates of faecal haemoglobin concentration (f-Hb).
- Randomised controlled trials comparing gFOBT and FIT, as well as pilot evaluations of transitioning, show increased uptake with FIT. However, the positivity, and clinical outcomes attained depend on the f-Hb threshold selected.

What are the new findings?

- This is the first study to report the transition to FIT from faecal occult blood tests (FOBT) in a fully rolled-out nationwide screening programme which, due to colonoscopy constraints, uses a high f-Hb threshold (80 µg Hb/g faeces) chosen to approximate to the positivity associated with FOBT.
- Both uptake and positivity of FIT were higher than for FOBT. These increases were seen in both sexes, and across the 50 to 74 year age range and deprivation quintile. The positive predictive value (PPV) for CRC with FIT was lower than for FOBT. For higher-risk adenoma, this was reversed; this was also seen for all adenoma.
- CRC detected increased with decreasing f-Hb threshold, and the PPV also decreased, due to the increases in positivity and numbers of colonoscopies performed. However, despite an increase in the number of adenomas detected with falling f-Hb threshold, the PPV did not change.
- Uptake and positivity in the FIT-based programme were higher than in the evaluation of FIT, despite the same f-Hb threshold being applied.

How might it impact on clinical practice in the foreseeable future?

- Our data support the benefits of transitioning to FIT-based CRC screening programmes from FOBT-based strategies. The major benefits are increased uptake across sex, age and deprivation, and increased detection of colorectal neoplasia, but this has consequences for colonoscopy resources.
- Pilot studies are recommended before introducing screening programmes and transitioning technology. However, although these are informative, variations between pilot and programme are likely to occur and these might have significant consequences for the subsequent programme.

and 74 years registered with a general practitioner (GP). Participants provided six faecal samples (two from each of three individual bowel movements) on to cards with a window for each of the samples and, if five or six of the windows were positive (a 'strong positive' result), an invitation to colonoscopy was issued. If one to four of the windows was positive (a 'weak positive' result), a card-based qualitative immunochromatographic FIT (*hema-screen SPECIFIC*, Immunostics Inc) was sent, and only if this was positive colonoscopy offered. This two-tier reflex gFOBT/FIT screening algorithm, which, for the purposes of this paper will be referred to as FOBT, was used until the SBoSP introduced quantitative FIT instead of FOBT in November 2017.

The evaluation of quantitative FIT as a first-line test was carried out in two NHS Boards (Tayside, and Ayrshire and Arran), and, between 1 July 2010 and 31 December 2010, every eligible person (using the same invitation criteria as the FOBT programme) resident in these two regions was sent a quantitative FIT kit instead of the gFOBT kit, with one specimen collection device, a modified invitation letter and instructions.[8] The FIT used was the OC-Sensor Diana (Eiken Chemical Co, Ltd, Tokyo, Japan) and the threshold chosen to trigger a colonoscopy invitation was 80 µg haemoglobin (Hb) per g faeces (µg Hb/g faeces). This threshold was used throughout the evaluation since evidence from the early work done in The Netherlands[12] suggested that this threshold would give a positivity similar to that of FOBT at the time of planning (2.3%). In addition, the results from the first month of the evaluation indicated that this would give a positivity at least as great as the FOBT strategy then in current use.

The results of this evaluation were used to construct a business case for replacing FOBT with quantitative FIT in the SBoSP and, on acceptance by Scottish Government, a FIT-based programme commenced on 20 November 2017. Because of the tendering process, the FIT used in the SBoSP was HM-JACKarc (Hitachi Chemical Diagnostic Systems Co, Ltd, Tokyo, Japan) rather than OC-Sensor, but the threshold remained at 80 µg Hb/g faeces. The invitation criteria for the FIT programme were the same as those used in the previous FOBT programme, but only a single sample was requested, and a repeat test kit was only issued if the initial kit received in the laboratory was not evaluable.

All samples (gFOBT, qualitative FIT and quantitative FIT) were analysed in the Scottish Bowel Screening Laboratory, which has ISO (International Organization for Standardization) 15189 accreditation. Total quality management is comprehensively practiced, including internal quality control and external quality assessment carried out by the UK National External Quality Assessment Scheme. Data on uptake of screening and test results (including f-Hb from quantitative FIT) were available from the Bowel Screening Scotland system and outcome data were obtained from the Bowel Screening Database held by the Information Services Division of National Services Scotland which is populated by regular mandatory data downloads from the 14 regional NHS Boards.

Data from the FIT-based programme between 20 November 2017 and 31 October 2018 were compared with period 20 November 2015 to 31 October 2016 when FOBT was being used, the penultimate year of the FOBT-based SBoSP. Since the SBoSP runs on a 2-year cycle, the populations screened in two consecutive years differ. For this reason, data from the immediately preceding year would not have been strictly comparable. In addition, the data from the first year of the FIT-based SBoSP were compared with the data from the FIT evaluation to investigate to what extent the evaluation had informed, or confounded, the subsequent performance of the SBoSP in the whole population.

The outcome measures studied were: *uptake* (defined as the percentage of participants with a final definitive screening test result out of those invited), *positivity* (defined as the percentage of participants with a positive screening test result out of those with a final definitive test result), *positive predictive value* (PPV) for neoplasia (defined as the number of individuals with CRC or at least one adenoma as a percentage of the colonoscopies performed) and *neoplasia detection rates* (defined as the number of CRC or adenoma detected in the screened population). Higher-risk (HR) adenoma was defined as at least one adenoma of 1 cm or greater *or* three or more adenomas in the same participant as recommended by the 2001 British Society of Gastroenterology guidance on adenoma surveillance policy.[13] Socioeconomic deprivation was estimated using the Scottish Index of Multiple Deprivation (SIMD), which is derived from postcode of residence and expressed here as quintiles.[14]

Table 1 Demographic characteristics (age (years), sex and socioeconomic deprivation (Scottish Index of Multiple Deprivation; SIMD)) of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) cohorts

	FOBT N (%)	FIT N (%)
Demography		
Total	862 165 (100%)	919 665 (100%)
Age group (years)		
50–54	242 273 (28.1%)	254 581 (27.7%)
55–59	186 161 (21.6%)	181 097 (19.7%)
60–64	173 416 (20.1%)	209 208 (22.7%)
65–69	136 675 (15.9%)	129 759 (14.1%)
70–74	123 640 (14.3%)	145 020 (15.8%)
Sex		
Male	424 207 (49.2%)	454 113 (49.4%)
Female	437 958 (50.8%)	465 552 (50.6%)
SIMD		
1 - most deprived	159 909 (18.5%)	169 266 (18.4%)
2	171 204 (19.9%)	180 739 (19.7%)
3	178 242 (20.7%)	189 291 (20.6%)
4	179 640 (20.8%)	193 321 (21.0%)
5 - least deprived	172 340 (20.0%)	186 194 (20.2%)
Screening history		
First round	92 230 (10.7%)	98 216 (10.7%)
Participated in previous round	457 539 (53.0%)	471 144 (51.2%)
Did not participate in previous round	54 841 (6.4%)	82 276 (8.9%)
Never participated	257 555 (29.9%)	268 029 (29.1%)

The differences between FIT and FOBT were assessed for statistical significance using the χ^2 test. R statistical software V.3.2.3 was used for all calculations. Formal ethical approval was not required because individual participants were not approached, only routinely collected data were utilised and all data were anonymised.

RESULTS

The demographic characteristics of the populations screened by FOBT and FIT are given in table 1.

Uptake

Overall, uptake of FIT in the first year in the SBoSP was 63.9% compared with 56.4% in the penultimate year for FOBT, an absolute difference of 7.4% and a relative difference of 13.2%. This increase was seen in both sexes and across both the age range and the deprivation gradient as estimated by SIMD of the invited population (figure 1, online supplementary table 1). It is noteworthy that the increase was greater in males (53.2% FOBT to 61.6% FIT, p<0.001) than in females (59.6% FOBT to 66.1% FIT, p<0.001) and more pronounced in the 50 to 54 year age groups (47.3% FOBT to 57.5% FIT, p<0.001) and in the areas of greatest socioeconomic deprivation (43.3% FOBT to 51.7% FIT, p<0.001). The relative increase was greatest among those who had never participated before, followed by those who had not participated in the previous round and those invited to their first round of screening. The increase in those who had participated in the previous round was modest by comparison (online supplementary table 1).

Positivity

Positivity was 3.1% in the first year of the FIT-based SBoSP and 2.2% in the penultimate FOBT year, an absolute difference of 0.9% and a relative difference of 42.4%. This increase was again seen in both sexes, and across both the age range and the deprivation gradient (figure 2, online supplementary table 2). The relative difference was smaller in males (2.6% FOBT vs 3.6% FIT, p<0.001) than females (1.8% FOBT vs 2.6% FIT, p<0.001) and, while there was no consistent pattern with age, a larger relative increase was seen in the least deprived (1.5% FOBT vs 2.4% FIT giving a 57% increase, p<0.001) than the most deprived (3.2% FOBT vs 4.3% FIT giving a 32% increase, p<0.001)

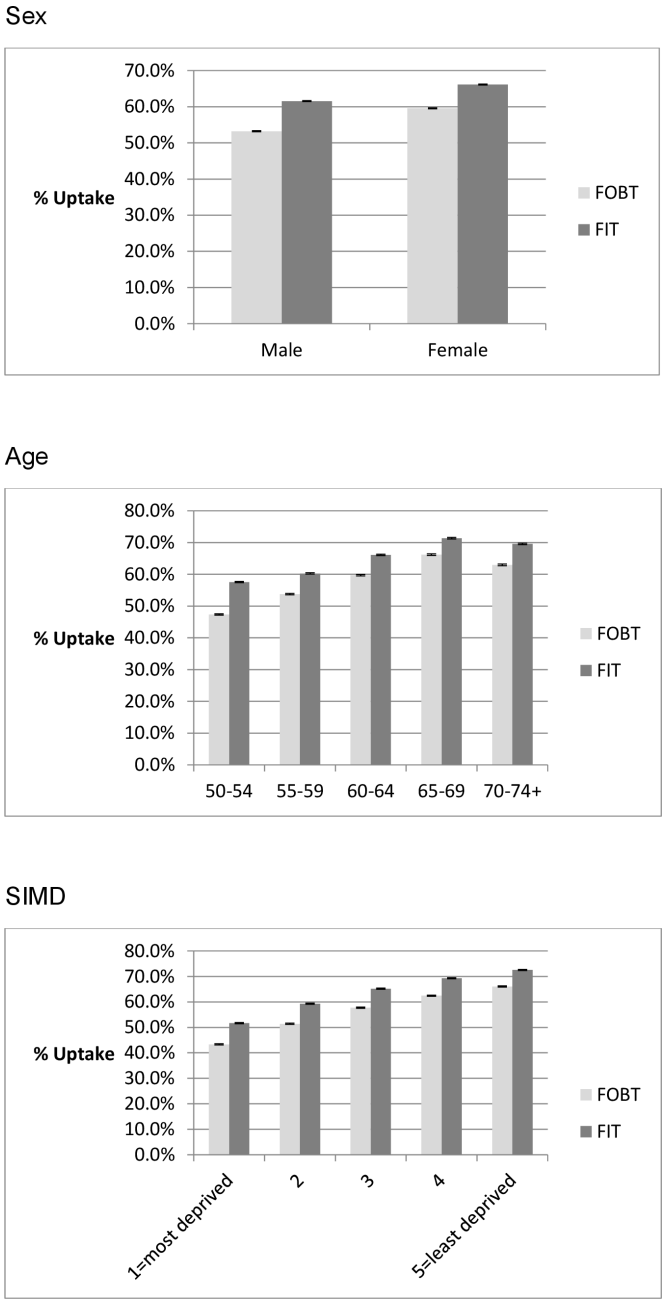


Figure 1 Uptake of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) by sex, age and socioeconomic deprivation (with 95% CI). SIMD, Scottish Index of Multiple Deprivation.

Positive predictive value

The PPV for CRC in the first year of FIT screening was 5.2% compared with 6.4% for the penultimate year of FOBT screening, an absolute difference of −1.2% and a relative difference of

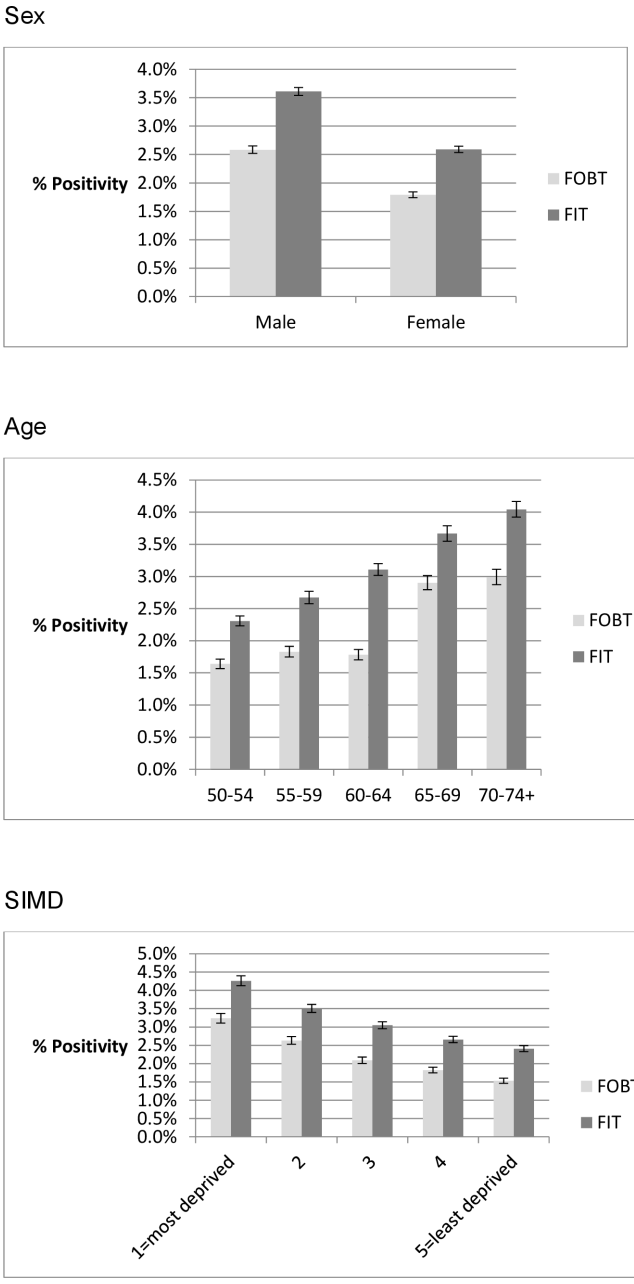


Figure 2 Positivity of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) by sex, age and socioeconomic deprivation (with 95% CI). SIMD, Scottish Index of Multiple Deprivation.

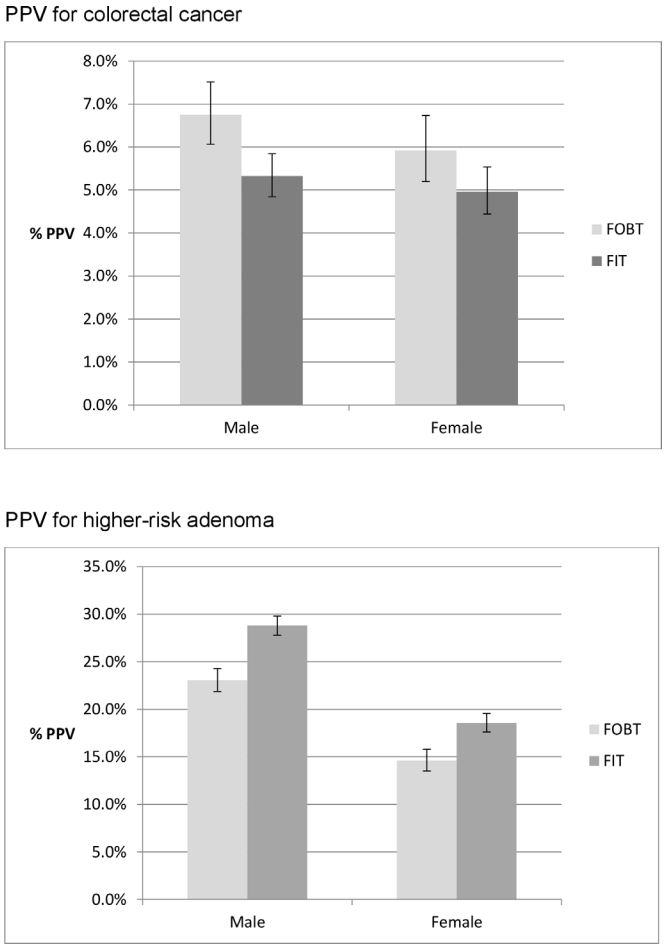


Figure 3 Positive predictive value (PPV) of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) for colorectal cancer and higher-risk adenoma, by sex (with 95% CI).

−19.2%. For HR adenoma, this was reversed with a PPV of 24.3% for FIT and 19.3% for FOBT (absolute difference 5.0%, relative difference 25.6%) and this pattern was also seen for all adenoma, with a PPV of 43.5% for FIT and 35.3% for FOBT (absolute difference 8.2%, relative difference 23.3%),

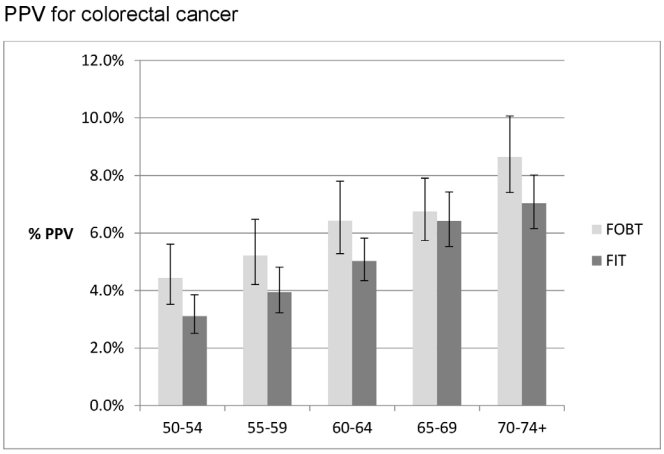
When broken down by sex, the difference between the PPV for CRC with FIT and FOBT was greater for males (6.8% FOBT to 5.3% FIT, p=0.001) than for females (5.9% FOBT to 5.0% FIT, p=0.04) (figure 3, online supplementary table 3). In addition, there was no significant difference in the PPV for CRC between males and females using FIT (5.3% males vs 5.0% females, p=0.34). However, this was not the case for HR adenoma, where PPV was greater for males than females for both FIT and FOBT and the differences between FIT and FOBT were comparable in both sexes (figure 3, online supplementary table 4). This was also true for all adenoma (data not shown).

PPV for both CRC and HR adenoma increased with age with both FIT and FOBT (although there was a slight decrease in PPV for adenoma in the 70 to 74 years age range) and was consistently lower with FIT for CRC and higher with FIT for HR adenoma (figure 4). When examined by deprivation, the PPV for CRC was lower with FIT and FOBT across all quintiles, but this was most pronounced in the least deprived. PPV for CRC steadily increased with decreasing deprivation with both FIT and FOBT (figure 5, online supplementary table 3). PPV for HR adenoma did not vary systematically with deprivation but was consistently higher with FIT (figure 5, online supplementary table 4). The finding for all adenoma was similar to that for HR adenoma for both age and deprivation (data not shown).

Overall, when FIT and FOBT were compared, FIT detected 35.2% more CRC, 110.0% more HR adenoma and 106.2% more adenoma overall, but at the expense of a 72.0% relative increase in the number of positive test results (table 2).

Performance of FIT at different faecal haemoglobin concentration thresholds

Table 3 details the performance of FIT at the chosen threshold of 80 µg Hb/g faeces along with its performance at threshold intervals of 20 µg Hb/g faeces up to 200 µg Hb/g faeces. Choosing a f-Hb threshold of 140 µg Hb/g faeces, to approximate to the



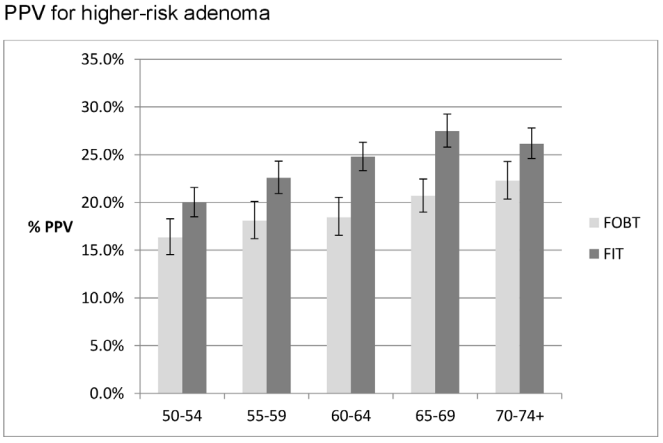
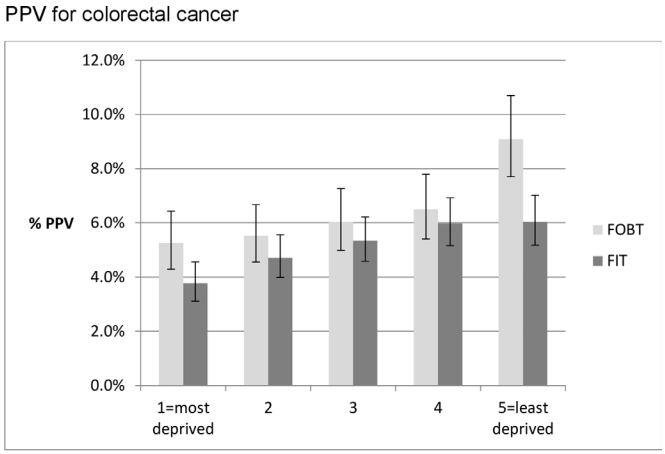


Figure 4 Positive predictive value (PPV) of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) for colorectal cancer and higher-risk adenoma, by age (with 95% CI).



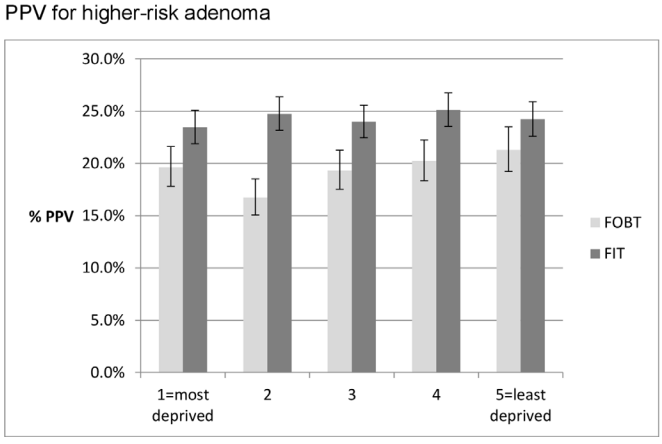


Figure 5 Positive predictive value (PPV) of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) for colorectal cancer and higher-risk adenoma, by Scottish Index of Multiple Deprivation quintile (with 95% CI).

positivity of the penultimate year of FOBT screening, would have detected 72 more CRC and 772 more adenoma than FOBT. Because of the increase in uptake, more colonoscopies were performed for the same positivity with FIT than with FOBT and, if FIT with a f-Hb threshold of 180 µg Hb/g faeces, which generated the same number of positive test results, is compared with FOBT, only 23 more CRC would be detected, but 440 more HR adenoma.

Although the number of CRC detected increased with decreasing f-Hb threshold, the PPV fell, due to the increase in positivity and numbers of colonoscopies performed. However, despite a parallel increase in the number of HR adenoma and all adenoma detected with decreasing f-Hb threshold, the PPV changed very little for HR adenoma and not at all for all adenoma across the measured range of f-Hb thresholds (table 3).

Comparison between evaluation of FIT as a first-line test and FIT in the SBoSP

When the results of the FIT as a first-line test evaluation, carried out from 01 July 2010 to 31 December 2010 in two Scottish NHS Boards,[8] are compared with what transpired in the first year of the FIT-based SBoSP across the whole of Scotland, there are some notable differences as well as similarities (table 4). Uptake of FIT in the evaluation was 58.5%, which compared with 63.9% for the first year of the programme. Positivity in the evaluation was 2.5% compared with 3.1% in the programme.

DISCUSSION

The advantages of FIT over gFOBT include enhanced uptake, specificity for human haemoglobin, automated reading and quantification of haemoglobin in faeces.[7] There is also good evidence that FIT, at least when used at lower thresholds for

Table 2 Comparison of faecal occult blood test (FOBT) and faecal immunochemical test (FIT) at the faecal haemoglobin concentration threshold used in the Scottish Bowel Screening Programme (80 µg Hb/g faeces)

			Difference	
	FIT	FOBT	Absolute	Relative
Number of positive tests	18 067	10 507	7560	72.0%
Colonoscopies performed	13 769	8235	5534	67.2%
Colorectal cancer (CRC) detected	711	526	185	35.2%
Higher-risk adenoma detected	3346	1593	1753	110.0%
All adenoma detected	5993	2906	3087	106.2%
Positivity	3.1%	2.2%	0.9%	42.4%
Positive predictive value (PPV) - CRC	5.2%	6.4%	–1.2%	–19.2%
PPV – higher-risk adenoma	24.3%	19.3%	5.0%	25.6%
PPV – all adenoma	43.5%	35.3%	8.2%	23.3%

Hb, haemoglobin.

Table 3 Performance at different faecal haemoglobin concentration thresholds (µg Hb/g faeces)

	Threshold (µg Hb/g faeces)						
	80	100	120	140	160	180	200
Number screened	587 449	587 449	587 449	587 449	587 449	587 449	587 449
Number of positive test results	18 067	15 369	13 612	12 314	11 279	10 454	9757
Colonoscopies performed	13 769	11 683	10 295	9301	8505	7874	7336
Colorectal cancers (CRC) detected	711	671	629	598	572	549	529
Higher-risk adenoma detected	3346	2892	2595	2365	2180	2033	1886
All adenoma detected	5993	5071	4447	4021	3674	3408	3145
Positivity	3.1%	2.6%	2.3%	2.1%	1.9%	1.8%	1.7%
Positive predictive value (PPV) - CRC	5.2%	5.7%	6.1%	6.4%	6.7%	7.0%	7.2%
PPV – higher-risk adenoma	24.3%	24.8%	25.2%	25.4%	25.6%	25.8%	25.7%
PPV – all adenoma	43.5%	43.4%	43.2%	43.2%	43.2%	43.3%	42.9%

Hb, haemoglobin.

f-Hb than that achieved by FOBT, results in higher neoplasia detection rates.[15 16] Many countries that have recently introduced CRC screening use FIT, but some started with gFOBT and are currently transitioning to FIT.[6] Managing this change is an important and challenging process given the crucial role that the chosen f-Hb threshold plays in determining both workload and the clinical effectiveness of the programme; piloting before introduction of whole-population screening has been considered an essential precaution in the UK.[8 15]

Although the transition to FIT from gFOBT has been recently reported in a regional screening programme,[17] this paper is the first to describe the transition of a national whole-population bowel screening programme to FIT from gFOBT in which the f-Hb threshold was intended to provide approximately the positivity of the previous gFOBT, required for the constraints imposed by colonoscopy capacity. Here, we have compared the performances of FIT and FOBT and examined the value of a pilot evaluation of FIT as a first-line test in predicting changes in performance. By using the penultimate year of FOBT screening as a comparator for the first year of FIT screening, a valid comparison can be made. The invited population increased by 6.7% to 919 665 owing to the addition of 137 415 invitees (mainly in the 50 to 51 year age range) and loss of 79 915 (largely those over the age of 74 years leaving the programme).[18] Thus, the majority of individuals invited to be screened were the same in the two groups.

FIT is associated with higher uptake than gFOBT; in two randomised trials from The Netherlands in screening-naïve populations, FIT was associated with absolute increases in overall uptake of around 12%[16 19] and, in the English demonstration pilot, the increase was 7.1%, very similar to our figure of 7.4%. As in our evaluation of FIT,[20] the increase in uptake was observed in both males and females, and was greater in males, although it remained less than that in females. In addition, uptake increased with age (although with a slight fall from the age of 70 years) with the greatest difference between FIT and FOBT observed in the 50 to 54 year age group, and it increased with decreasing socioeconomic deprivation, the greatest difference seen in the more deprived quintiles. The increase in uptake was greatest among previous non-responders. These findings are important, since they demonstrate that FIT goes some way to addressing the well-established inequalities seen in CRC screening.

As expected, the positivity was greater with FIT than with FOBT. The positivity of 3.1% was broadly in keeping with the English pilot which reported 5.0% for a threshold of 40 µg Hb/g faeces and 2.4% for 100 µg Hb/g faeces.[15] The relative increase was greater in females and in the less deprived quintiles suggesting that the initial gFOBT might detect non-human Hb sources or other relevant dietary components more often in males and more deprived communities. This hypothesis is supported by diet survey data from Scotland which provide convincing evidence that meat and meat product consumption is greater in males than in females[21] and in deprived communities as compared with the more affluent.[22]

The contrast in PPV for colorectal neoplasia between FIT and gFOBT is particularly interesting. As expected, the PPV for CRC was less for FIT than for gFOBT because the marked increase in positivity resulted in a 72.0% relative increase in the number of positive test results with an inevitable increase in the false positive rate. However, whereas the difference in PPV for CRC was greater in males than in females, using FIT the PPV for CRC for males and females was essentially the same. This again might be related to the observed difference between males and females in meat consumption[21] and represents another example of how FIT may reduce inequalities, since the PPV for CRC with gFOBT is higher in males than in females.[23] At the f-Hb threshold of 80 µg Hb/g faeces used in the SBoSP, a reduction in the higher interval cancer rate in females seen with gFOBT[24] is likely since, at lower f-Hb thresholds in The Netherlands, the interval cancer proportion was low in both males and females.[25] The relative difference in PPV for CRC between FIT and gFOBT was high

Table 4 Uptake (%) and positivity (%) in faecal immunochemical test (FIT evaluation) and comparison with other groups

	FIT evaluation (1 July 2010 to 31 Dec 2010)	First year of FIT-based programme (20 Nov 2017 to 31 Oct 2018)	First year of FIT-based programme evaluation NHS boards only (20 Nov 2017 to 31 Oct 2018)	FOBT comparator for the FIT evaluation pilot (01 Jan 2010 to 30 Jun 2008)	FOBT comparator for the first year of the FIT-based programme (20 Nov 2015 to 31 Oct 2016)
Uptake	58.5%	63.9%	64.7%	54.0%	56.4%
Positivity	2.5%	3.1%	3.0%	2.0%	2.2%

FOBT, faecal occult blood test.

in the least deprived quintile of the population, possibly due to dietary issues.[22]

As the f-Hb threshold is lowered to the 80 µg Hb/g faeces used in the SBoSP, the PPV for CRC falls since, although more CRC are detected, the number of colonoscopies that do not detect CRC increases disproportionally, so that the detection rate falls. However, with decreasing f-Hb thresholds, the PPV for adenoma did not change, indicating that the detection rate for adenoma keeps pace with the f-Hb threshold. Interestingly, in the English pilot, a similar observation was made across thresholds from 100 to 180 µg Hb/g faeces.[15] The reason behind this finding is unclear but might involve the possible sources of faecal Hb. CRC is associated with higher f-Hb than adenoma[26] and it is likely that the Hb largely originates from the bleeding surface of the tumour and, a false negative test result will be obtained when a lesion is not bleeding at the time of sampling. However, adenomas are less likely to be visibly bleeding than CRC, and perhaps the relationship between occult colonic bleeding and the detection of adenoma is more subtle than simple bleeding from the lesion. A positive gFOBT result is associated with increased all-cause and non-CRC mortality[27] and one explanation is that occult colonic bleeding reflects systemic inflammation. Since most neoplasia arises in a background of chronic inflammation,[28] it may be that detection of faecal Hb is associated with the detection of adenoma because an inflamed colon has a heightened susceptibility to adenoma formation. This is supported by the evidence that patients with inflammatory bowel disease have significantly increased risk of gastrointestinal malignancies.[29] Thus, at lower f-Hb, sensitivity for adenoma might not be so susceptible to variations in the tendency of the lesion itself to bleed as it is with CRC.

Using the f-Hb threshold data, it is also possible to determine if FIT has inherently better performance characteristics than gFOBT that are independent of uptake and positivity. In table 2, the performance of gFOBT and FIT are shown at the chosen f-Hb threshold of 80 µg Hb/g faeces. However, as documented in table 3, even at a threshold that gave the same number of positive test results as the FOBT algorithm (180 µg Hb/g faeces), FIT had a higher PPV than gFOBT for all neoplasia, particularly adenoma. Thus, the preservation of PPV for adenoma at low f-Hb thresholds and its improved performance over gFOBT, even at similar thresholds, indicates that FIT is likely to be more effective in preventing CRC than gFOBT. Removal of adenomas has been shown conclusively to reduce the incidence of CRC by RCTs of endoscopic screening,[30] and FIT at low f-Hb thresholds will likely have a similar outcome. This is important when modelling cost-effectiveness of screening is done to determine the ideal threshold for a screening programme; interestingly, the UK National Screening Committee indicated that the most cost-effective threshold is likely to be 20 µg Hb/g faeces.[31]

The data from the evaluation of FIT as a first line test carried out in 2010 were used to construct a business case, which estimated a 10% increase in the colonoscopy workload to support a change to a FIT-based programme. However, as summarised in table 4, the evaluation underestimated both the uptake and the positivity, and the effect of introducing the SBoSP at the same threshold as used in the evaluation resulted in a 67.2% increase in colonoscopy demand (table 2). Thus, although the evaluation predicted major trends, the results did not accurately reflect what was found in the rolled-out SBoSP, and the subsequent performance of FIT has resulted in significant challenges for endoscopy workload planning and execution.

It is not clear why the increases in uptake and positivity were smaller in the evaluation than the FIT-based SBoSP, but several explanations are plausible. The evaluation was undertaken in 2010 but, because of the necessity to wait for outcome data and because of logistical delays, almost 7 years elapsed between the completion of the evaluation and commencement of the FIT-based SBoSP. Attitudes may have changed, although there was no indication from the FOBT-based SBoSP that uptake had been increasing significantly.[32] It is likely, however, that the significant publicity accompanying the roll-out of the FIT-based SBoSP had an effect, as would the care adopted with the development of the invitation letters and information accompanying the specimen collection device. The increase in positivity may have been related to differences in the performance between the FIT employed in rolled-out SBoSP (HM-JACKarc) and the evaluation (OC-Sensor), but extensive pre-tendering validation could detect no differences in the analytical performance characteristics: further, it has been shown that outcomes with these two systems are comparable.[33] Another explanation relates to the time between evaluation and roll-out; the background initial gFOBT positivity in 50-year-olds screened in Scotland increased from around 4% to 10% between 2007 and 2017[34] and this may have contributed to the difference.

An alternative explanation for the increases in uptake and positivity would be that the demographic of the population included in the evaluation was not sufficiently representative of the entire population. However, the NHS Boards which carried out the FIT as a first-line test evaluation exhibited increases in uptake and positivity that were in line with the whole of Scotland (table 4). Whatever the reason, the results of an evaluation based on a small proportion of the intended target population carried out several years before implementation of a screening programme should be interpreted with caution. While useful in providing high-level predictive data, such an evaluation cannot obviate the need for careful monitoring of the performance of a newly introduced screening programme and, in a centralised, resource-limited CRC screening programme, changes to the f-Hb threshold to accommodate colonoscopy capacity may become necessary as in The Netherlands[35] and elsewhere.

This study has significant strengths in that it provides data from both a real-life population screening programme and a preliminary evaluation. The main weakness is that the data are necessarily derived from a screening programme in which FIT is used at a f-Hb threshold higher than that used in many other countries. However, the lessons learnt are transferable to any context in which FOBT is being replaced by FIT as a CRC screening test, and the limitations of pilot evaluations are important to appreciate.

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