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Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity

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Abstract

Introduction: Because of their many advantages, faecal immunochemical tests (FIT) are superseding traditional guaiac-based faecal occult blood tests in bowel screening programmes.

Methods: A quantitative FIT was adopted for use in two evaluation National Health Service (NHS) Boards in Scotland using a cut-off faecal haemoglobin concentration chosen to give a positivity rate equivalent to that achieved in the Scottish Bowel Screening Programme. Uptake and clinical outcomes were compared with results obtained contemporaneously in two other similar NHS Boards and before and after the evaluation in the two evaluation NHS Boards.

Results: During the evaluation, uptake was 58.5%. This was higher than in the same NHS Boards both before and after the evaluation, higher than in the other two NHS Boards and higher than the 53.7% achieved overall in Scotland. The overall positivity rate was higher in men than in women and increased with age in both genders. Positive predictive values for cancer (4.8%), high-risk adenoma (23.3%), all adenoma (38.2%) and all neoplasia (43.0%) in the two test NHS Boards were similar in all groups.

Conclusions: In summary, this evaluation of the FIT supports the introduction of FIT as a first-line test, even when colonoscopy capacity is limited.

Keywords

Colorectal cancer, faecal immunochemical test, faecal occult blood test, positive predictive value, screening

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Introduction

Colorectal cancer remains a significant health problem, but there is good evidence that screening the asymptomatic population can reduce both mortality and incidence.[1] Traditional guaiac-based faecal occult blood tests (gFOBT) have been shown to reduce mortality in randomised controlled trials,[2] and these results have been mirrored in practice in the bowel screening programmes that have been established after successful pilots in Scotland,[3] England[4] and elsewhere. However, although gFOBT have advantages for use in structured screening programmes, they also have major disadvantages,[5] in particular the cut-off concentration between gFOBT negative and positive results is set by the methodology adopted by the manufacturer. Thus, the

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positivity rate and the clinical characteristics cannot be adjusted by the end-user, unless an algorithm is used based on the different results from the six sample windows,[6,7] an approach that is used in the UK, but that makes the programme organisation and execution complex. Moreover, the other problems related to sample collection, handling and analysis mean that gFOBT are now widely considered to be obsolete for use in screening programmes.[8]

Newer faecal immunochemical tests for haemoglobin (FIT) have many advantages over gFOBT; only one sample is generally collected, the available collection devices encourage uptake and the test is more specific for lower gastrointestinal bleeding. FIT are recommended in current guidelines[1] and there are many studies that document clinical outcomes which show that FIT are superior to gFOBT, particularly for adenoma detection.[9] Quantitative FIT measure the haemoglobin concentration and allow the cut-off to be set to give characteristics, such as positivity rate, deemed appropriate by programme organisers. Most studies on FIT have been performed using methods with a haemoglobin cut-off concentration that is lower than that of traditional gFOBT, resulting in a higher positivity rate and greater sensitivity, albeit with lower specificity. However, increasing the cut-off concentration reduces the positivity rate thereby lowering sensitivity but with the benefit of higher specificity.

Countries starting bowel screening programmes or pilots are choosing FIT and a number in which gFOBT are currently used are investigating replacement with FIT. A vital consideration for service planning and delivery is the ability to meet colonoscopy demand generated by screening and surveillance at a time when colonoscopy capacity is under increasing pressure. Thus, high cut-off concentrations may need to be used and the clinical outcomes at these high concentrations are as yet unknown. Therefore, we evaluated the use of FIT as a first-line test in two National Health Service (NHS) Board areas in Scotland within a fully rolled-out national screening programme that uses a gFOBT/FIT two-tier reflex screening algorithm.[6] We compared uptake and clinical outcomes with those obtained in the two evaluation NHS Boards before and after the evaluation, and contemporaneously in another two similar (control) NHS Boards.

This report follows standards for reporting of diagnostic accuracy as far as possible.[10]

Methods

Currently, the population eligible for invitation to participate in the Scottish Bowel Screening Programme (SBoSP) are all men and women aged 50–74 years and registered with a general practitioner (GP) practice. About 850,000 invitations are sent each year. The general NHS in Scotland is managed by 14 NHS Boards covering different geographical regions. All individuals in two of these NHS Boards—NHS Tayside and NHS Ayrshire & Arran—eligible to participate in the SBoSP during the evaluation period (1 July 2010–12 January 2011) were sent an invitation pack different to that used for the other 12 NHS Boards. This pack contained the usual SBoSP invitation letter and booklet on bowel cancer, and a thin card wallet with printed written and pictorial instructions for specimen collection: the wallet contained a single faecal specimen collection device (Eiken Chemical Co., Tokyo, Japan), a small zip-lock plastic bag with integral absorbent material and a foil mailing pouch for device return. The collection device is designed to collect c. 10 mg freshly passed faeces, using a serrated probe integral to the device cap into 2.0 ml of buffer in the device. Invitees were treated as per the usual practices of the SBoSP.

Ethics approval to collect data additional to that generated in the SBoSP was granted by NHS Tayside Ethics Committee and West of Scotland Research Ethics Service. The work was approved by the SBoSP Board and had Caldicott Guardian approval from both NHS Tayside and NHS Ayrshire & Arran.

Each participant had received an adhesive identification label integral to the invitation letter; this was attached by the participant to the outside of the zip-lock bag. The label documented the name of the participant, the Community Health Index (CHI) number, which is a unique 10-digit identifier used ubiquitously in NHS Scotland to access healthcare, and a unique 10-digit kit number from the Bowel Screening Scotland information technology (IT) system (BoSS). The participant wrote the date of faecal collection on the label and stuck this on the zip-lock bag. The information for specimen collection emphasised the need to post the device back to the Scottish Bowel Screening Centre Laboratory immediately. The foil mailing pouches, with completed collection devices in the zip-lock bags, were returned through the UK Royal Mail system via the First Class service and free of charge.

On return to the Scottish Bowel Screening Centre Laboratory, the foil mailing pouches were opened and the label on the zip-lock bag replicated using in-house software. The secondary label generated was then fixed to the specimen collection device and the receipt of a sample captured electronically by BoSS, which gave confirmation of the name, CHI number and kit number via scanning of the barcode. Specimens that were received >10 days from the date of collection were termed 'expired' and not tested further: this decision was based on in-house validation studies done early during the commissioning of the analysers

(the decrease in faecal haemoglobin concentration at 10 days was approximately 30% at 20°C) and has subsequently been validated by others.[11] Of the returned samples, 93.3% were tested on the day of receipt; where this did not happen samples were stored at 4°C until analysis.

The returned samples were analysed for faecal haemoglobin concentration using OC-Sensor Diana automated immunoturbidimetric analysers (Eiken Chemical Co., supplied by MAST Diagnostics, Bootle, UK). Analyses were carried out in the Scottish Bowel Screening Centre Laboratory by trained staff whose main job is to perform faecal test analyses. The laboratory has a comprehensive total quality management system and is accredited to ISO 15189-based standards by Clinical Pathology Accreditation (UK) Ltd. The analytical strategy and performance achieved have been detailed previously.[12]

The cut-off faecal haemoglobin concentration of 80 μg haemoglobin/g faeces (equivalent to 400 ng haemoglobin/ml buffer) was selected to give approximately the 2.4% positivity rate found in the SBoSP.[13] All participants with a faecal haemoglobin concentration of <80 μg haemoglobin/g faeces were considered negative and sent a letter explaining this and the need to be watchful for symptoms of bowel disease. Those who sent an untestable device were sent another FIT kit pack and 86.9% returned a satisfactory device suitable for analysis. All participants with faecal concentration >80 μg haemoglobin/g faeces were considered positive and a letter was sent informing them of this, their GP was notified and the individual was referred to the appropriate geographical NHS Board for colonoscopy.

Uptake was defined as the percentage of people with a screening test result out of those invited. This relates only to persons who successfully completed a screening test, i.e. an outright positive or negative result. Uptake was recorded in six calendar-month periods during the evaluation, and before and after the use of FIT in the two NHS Boards participating in the evaluation and also in two similar, in terms of population and stage of bowel screening, NHS Boards for which contemporaneous clinical outcome data were also collected, these being surrogate controls. Data on gender and age were determined from the CHI number. Number, size and location of colorectal cancers and adenomas were recorded. Assignment to outcome groups was as recommended by the British Society of Gastroenterology (BSG),[14] but in accordance with the protocol for patient follow-up used in the SBoSP in that the high-risk adenoma (HRA) group was based on combining the intermediate and high-risk groups identified by the BSG.

Colonoscopy outcomes and any subsequent pathology in the participants with positive results from the FIT were downloaded from the appropriate NHS Tayside and NHS Ayrshire & Arran clinical IT systems for colonoscopy and pathology (group 1). Data on clinical outcomes for NHS Fife and NHS Forth Valley were provided by the Information Services, Division NHS National Services Scotland (group 2). Data on clinical outcomes for an identical period of time, at the same time of year, before the evaluation (1 July 2009–12 January 2010) were collected as described above for NHS Tayside and NHS Ayrshire & Arran (group 3). Data on clinical outcomes for an identical period of time, immediately after the evaluation, (13 January 2011–27 July 2011) were similarly collected for NHS Tayside and NHS Ayrshire & Arran (group 4). At these times, a gFOBT/FIT two-tier reflex screening algorithm, which has been described in detail elsewhere,[6] was used in the SBoSP.

Chi-squared tests were used to assess the significance of differences in uptake during the FIT evaluation period compared with uptake in the other time periods combined and weighted. MedCalc (MedCalc Software, Mariakerke, Belgium) statistical software was used for all calculations. Probability of $p<0.05$ was considered significant. Positive Predictive Values (PPV) were also compared for the Groups for each clinical outcome.

Results

For the group offered the FIT sample collection device 66,225 kits were sent out; 40,125 (60.6%) were returned. Uptake, defined as the invitees (66,225) who completed their cycle with a positive or negative test result (38,720), was 58.5%.

Uptake before and after the use of FIT in the four NHS Boards for three periods of six calendar months are shown in Table 1. The *p*-values demonstrate that the uptake was significantly higher during the FIT evaluation period, in both NHS Tayside and NHS Ayrshire & Arran, than during the time periods before and after.

There were 943 participants with a positive test result in group 1: 453 (48.0%) from participants in NHS Tayside, who had been involved in three pilot studies and who were in the second round of screening; and 490 (52.0%) from participants in NHS Ayrshire & Arran, who were in their first round of screening, which began on 1 September 2007. For group 2, there were 736 positive results: 383 (52.0%) from NHS Fife, which also had been involved in three pilot studies and was in the second round of screening, and 353 (48.0%) from participants in NHS Forth Valley, in which screening began on 1 December 2007, giving another group of participants in the first incidence round. For group 3, there were 732 positive results: 374 (51.1%) from NHS Tayside, which was in the second round of screening,

Table 1. Identification of groups used for analysis of clinical outcomes showing time periods, National Health Service (NHS) Boards and screening algorithms in use [faecal immunochemical test (FIT) evaluation group in bold]

Group	NHS Board	Date of invitation	Screening algorithm
Group 1	NHS Tayside, NHS Ayrshire & Arran	1 July 2010–12 January 2011	FIT algorithm
Group 2	NHS Fife, NHS Forth Valley	1 July 2010–12 January 2011	gFOBT/FIT two-tier reflex algorithm
Group 3	NHS Tayside, NHS Ayrshire & Arran	1 July 2009–12 January 2010	gFOBT/FIT two-tier reflex algorithm
Group 4	NHS Tayside, NHS Ayrshire & Arran	13 January 2011–27 July 2011	gFOBT/FIT two-tier reflex algorithm

gFOBT, guaiac-based faecal occult blood tests.

Table 2. Uptake (%) in four National Health Service Boards for three 6-month periods (faecal immunochemical test evaluation group in bold evaluation group in bold)

	Tayside	Ayrshire & Arran	Fife	Forth Valley
1 July–31 December 2009				
Invited	37,275	31,713	30,685	21,972
Accepted (%)	20,764 (55.7)	16,491 (52.0)	16,311 (53.2)	11,640 (53.0)
1 July–31 December 2010				
Invited	**32,195**	**30,570**	29,397	22,881
Accepted (%)	**19,600 (60.9)**	**17,742 (58.0)**	15,425 (52.5)	11,626 (50.8)
1 July–31 December 2011				
Invited	37,153	32,450	30,938	22,898
Accepted (%)	20,274 (54.6)	16,790 (51.7)	16,044 (51.9)	11,848 (51.7)
p-value	<0.0001	<0.0001	0.102	0.036

and 358 (48.9%) participants from NHS Ayrshire & Arran, who were in their final 2 months of prevalence screening and 4 months in their first incidence round For group 4, there were 626 positive results: 280 (44.7%) from participants in NHS Tayside in the second/third round of screening and 346 (55.3%) from participants in NHS Ayrshire & Arran in the first incidence round. The prevalent screening round encompasses 100% of individuals who have never undertaken screening (Table 2). Incident rounds are the subsequent screening rounds; a small number, 50-year-olds and others new to screening will be in a prevalent screening round.

The number and percentages of participants with a positive test by 5-year age group are shown in Table 3 for groups 1, 3 and 4; similar data for group 2 were unavailable. As expected, the proportion of participants receiving a positive result increased with increasing age and was higher in men than in women.

The clinical outcomes found in the participants with positive test results are shown in Table 4. This demonstrates that the performance of the FIT (group 1) was essentially the same as in the three other groups. Of note is the positive predictive value (PPV) for cancer was lower for group 1 participants (4.8%) than group 3 participants (7.7%) ($p = 0.0291$); the reasons for this are obscure at the present time.

Discussion

The uptake of the FIT (58.5%) was greater than that achieved throughout the three pilot screening rounds undertaken in Scotland, which used gFOBT only.[6] The SBoSP **statistics,** in the form of key performance indicators for Scotland overall and each of the 14 NHS Boards, includes uptake and clinical outcomes of screened individuals. The most recent data available are for the period 1 November 2008–31 October 2010, in which uptake was 53.7% in Scotland.[15] As shown in Table 2, the uptake in the two NHS Boards that participated in the FIT as a first-line test evaluation rose by 5.2% and 6.0% during the use of FIT, but then fell to similar values to those previously seen when the gFOBT/FIT algorithm was reinstituted. The two NHS Boards in which FIT was not used had small changes in uptake over time, but did not have the important rise in participation seen with use of the quantitative FIT. It is not surprising that uptake with a FIT sample collection device, which requires a single sample, is higher than that in screening programmes that use gFOBT as an initial test, as gFOBT require two samples from each of three faeces and, in the UK, only those with five or six windows positive are referred directly for colonoscopy whereas those with 1–4 windows positive are required to undertake

Table 3. Number (percentage) of participants with a positive result by gender and age (faecal immunochemical test evaluation group in bold)

	Group 1	Group 2	Group 3	Group 4
Total	**943**	736	732	626
Men	**532 (56.4)**	401 (54.5)	443 (60.5)	376 (60.1)
Women	**411 (45.6)**	335 (45.5)	289 (39.5)	250 (39.9)
50–54 years	**151 (16.0)**	–	99 (13.5)	88 (14.1)
55–59 years	**189 (20.0)**	–	139 (19.0)	129 (20.6)
60–64 years	**173 (18.3)**	–	131 (17.9)	129 (20.6)
65–69 years	**206 (21.8)**	–	168 (23.0)	136 (21.7)
70–74 years	**224 (23.6)**	–	195 (26.6)	144 (23.0)

–, data were unavailable from Information Services, NHS National Services Scotland.

another test. This finding is similar to the results found in other studies comparing uptake with gFOBT and FIT.[7,12] Our findings provide support for the widely held view that more user-friendly faecal collection devices encourage participation in screening programmes.

As shown in Table 3, and as expected from previous findings in all bowel screening pilots and programmes using faecal tests, men accounted for a higher percentage of positive results than women in all four groups. The percentages of positive results in each 5-year age group for groups 1, 3 and 4 are shown in Table 3. In the three groups, the highest proportion of positive results was in the 70–74 years of age quintile and, in general, positivity increased with age in both sexes. We have shown that, using gFOBT for screening, substantial interval cancer rates occur and these increase with screening round; although interval cancers are associated with a better prognosis than cancers arising in a non-screened population, gFOBT appears to preferentially detect cancers in men at the expense of cancers in women.[15] We plan to investigate the number and characteristics of the interval cancers that occur in the 2 years following a faecal haemoglobin concentration result of <80 μg haemoglobin/g faeces. It is also known that faecal haemoglobin concentration is affected by sex and age,[12] and we have discussed the potential consequences of these relationships in detail previously.[6,16,17] It may be that different cut-off faecal haemoglobin concentrations or different screening intervals should be applied for the different sexes and ages; this is controversial, however, and further study is required.

As this evaluation was done in the context of a fully rolled-out operational screening programme, those participants who had results below the chosen cut-off of 80 μg haemoglobin/g faeces were not investigated further. This is in contrast to the two randomised controlled trials performed in the Netherlands[18–21] and in some other studies.[22,23] Such studies have shown that, at the lower cut-off haemoglobin concentrations used, positivity rates for FIT were higher than for gFOBT. Moreover, when reported, sensitivity was higher for FIT than gFOBT, although the specificity was lower. Thus, the gain in disease detected was offset by the number of false-positive results. Moreover, it has been well documented that the sensitivity increases and the specificity decreases as the cut-off concentration is lowered: the gain is mainly in adenoma detection.[19,21,24]

The PPV of the screening strategy is a vital characteristic of any programme. PPV has been shown to increase as positivity rate decreases because the cut-off haemoglobin concentration rises.[22,24] The results in Table 4 demonstrate that there is very little difference between the four groups and the PPVs found with the FIT were similar to those achieved with the gFOBT/FIT two-tier reflex screening algorithm. This finding was not unexpected as the cut-off concentration that we selected was chosen to give the same positivity rate for both approaches. If the benefits of FIT for detection of adenomas in particular[9] are to be achieved, then a lower cut-off haemoglobin concentration would be required, a greater colonoscopy resource would have to be available and the programme would have to be prepared to deal with lower specificity with a greater number of false-positive results, as shown by the decrease in PPV that occurs as cut-off haemoglobin concentration is lowered.[9,20]

The comparison of PPV between the four groups comes with some caveats. Although NHS Tayside and NHS Fife had both been in the screening pilot and were in the second round of programme screening, during the evaluation NHS Ayrshire & Arran were in their first incidence round of programme screening, as was NHS Forth Valley. Upon further examination, for those in Ayrshire & Arran, the PPV was found to be statistically significantly higher ($p < 0.05$) for the two months in prevalence screening than the four months of incidence screening for cancer + HRA (50.0% and 31.4%), HRA (41.7% and 23.5%), and total neoplasia (60.4% and 53.6%). Those invited within the prevalence round accounted for 20.6% of the NHS Ayrshire & Arran participants in group 3, but had 35% of the cancers and 34.2% of the HRA detected. We have shown that the clinical outcomes with a quantitative FIT using a high cut-off faecal haemoglobin concentration are similar to those gained with gFOBT and gFOBT/FIT approaches.

The germane question then is whether FIT should be adopted by those with mature screening programmes. Overall, the planning and delivery of the evaluation were both very smooth with no major problems

Table 4. Clinical outcomes in participants with a positive test result

	Group 1						Group 2					
	Total		Men		Women		Total		Men		Women	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Participants with positive result	943		532		411		736		401		335	
No investigations/incomplete investigations/outcome unknown/excluded	129	13.7	73	13.7	56	13.6	130	17.7	65	16.2	65	19.4
Investigations completed	814	86.7	459	86.6	355	86.8	606	82.3	336	83.8	270	80.6
Clinical outcomes	*n*	PPV	*n*	PPV	*n*	PPV	*n*	PPV	*n*	PPV	*n*	PPV
Cancer	39	4.8	23	5.0	16	4.5	33	5.4	19	5.7	14	5.2
High-risk adenoma (HRA)	190	23.3	127	27.7	63	17.7	115	19.0	80	23.8	35	13.0
Cancer + HRA	229	28.1	150	32.7	79	22.3	148	24.4	99	29.5	49	18.1
All adenoma	311	38.2	205	44.7	106	29.9	217	35.8	139	41.4	78	28.9
Total neoplasia (cancer + all adenoma)	350	43.0	228	49.7	122	34.4	250	41.3	158	47.0	92	34.1
Hyperplastic polyps	64	7.9	40	8.7	24	6.8	–	–	–	–	–	–
Normal/Other pathology (IBD, DD, angiodysplasia, haemorrhoids, etc.,)	400	49.1	191	41.6	209	58.9	–	–	–	–	–	–
	Group 3						Group 4					
	Total		Males		Females		Total		Males		Females	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Participants with positive result	732		443		289		626		376		250	
No investigations/incomplete investigations/outcome unknown/excluded	80	10.9	45	10.2	35	12.1	84	13.4	58	15.4	26	10.4
Investigations completed	652	89.8	398	90.5	254	88.8	542	86.6	318	84.6	224	89.6
Clinical outcomes	*n*	PPV	*n*	PPV	*n*	PPV	*n*	PPV	*n*	PPV	*n*	PPV
Cancer	50	7.7	35	8.8	15	5.9	38	7.0	26	8.2	12	5.4
High-risk adenoma (HRA)	157	24.1	114	28.6	43	16.9	120	22.1	88	27.7	32	14.3
Cancer + HRA	207	31.7	149	37.4	58	22.8	158	29.2	114	35.8	44	19.6
All adenoma	252	38.7	181	45.5	71	28.0	190	35.1	130	40.9	60	26.8
Total neoplasia (cancer + all adenoma)	302	46.3	216	54.3	86	33.9	228	42.1	156	49.1	72	32.1
Hyperplastic polyps	58	8.9	40	10.1	18	7.1	32	5.9	19	6.0	13	5.8
Normal/other pathology (IBD, DD, angiodysplasia, haemorrhoids, etc.)	292	44.8	142	35.7	160	63.0	284	52.4	143	45.0	141	62.9

IBD, inflammatory bowel disease; DD, diverticular disease; PPV, positive predictive value; –, data were unavailable from Information Services, NHS National Services Scotland

experienced by participants or the SBoSP. The analytical reproducibility was good. Automated FIT analyses eliminated observer variation, a major concern with gFOBT and qualitative FIT.[6] No analytical batch required repeat testing owing to technical issues. There were no problems with consistency and quality of reagents: fluctuations in the positivity rate that have been observed with different batches of gFOBT and qualitative FIT kits[25] were not evident. Uptake was higher than with the current screening algorithm and, for the first time, to our knowledge, we have shown that uptake returns to usual when the initial invitations using FIT were performed with gFOBT. More than 99% of results were reported within 3 days of receipt of samples in the laboratory and most participants received an unequivocal result in less than 2 weeks from sample collection. Importantly, the quantitative nature of the analyses allows considerable flexibility and permits modification of the cut-off faecal haemoglobin concentration used, perhaps to allow for colonoscopy capacity, sex and age. In summary, the increased uptake, clinical outcomes and good analytical

reproducibility of the FIT all support the introduction of FIT as a first-line test, even when colonoscopy capacity is limited.

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Conflict of interest

CGF undertakes consultancy with Immunostics Inc., Ocean, NJ, USA, and Mode Diagnostics, Glasgow, UK. The other authors do not have any potential conflicts of interest to declare.

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