Research Article

Cancer Prevention Research

A National Bowel Cancer Screening Programme using FIT: Achievements and Challenges

Diarmuid O'Donoghue[1], Kieran Sheahan[2], Padraic MacMathuna[2], Richard B. Stephens[2], Helen Fenlon[2], Martina Morrin[2], Jenny Mooney[1], Lorraine E. Fahy[1], Therese Mooney[1], and Alan Smith[1]

Abstract

Colorectal cancer accounts for 11% of all cancer-related deaths in Ireland. With the aim of diagnosing these cancers at an earlier stage, and detecting premalignant lesions, the National Screening Service (NSS) offered a fecal immunochemical test (FIT) to all individuals aged 60 to 69. All individuals in the age range were contacted by post and invited to participate in the programme. Those with a positive FIT result were offered a colonoscopy in an internationally accredited unit. From an eligible population of 488,628, 196,238 individuals participated giving an uptake of 40.2%. Commencing at a FIT threshold of 20 μg Hg/g feces, the positivity rate was 8.6%, which overwhelmed colonoscopy capacity and, thus, the threshold was increased to 45 μg, resulting in an overall 5% positivity rate. A total of 520 individuals had cancer detected (68.3% stage I or II), of which 104 were removed endoscopically (pT1s). Adenomas were present in 54.2% of all colonoscopies, 17.4% deemed high risk. Despite a lower uptake, males were twice as likely to have colorectal cancers as females and had a 59% increased rate of high-risk adenomas diagnosed. Challenges facing the programme include increasing participation, especially among males, and increasing colonoscopy capacity. The ability to alter the sensitivity of FIT to match colonoscopy capacity is a valuable option for such a programme as it ensures that the maximum public health benefit can be achieved within available resources.

Introduction

Colorectal cancer is the second commonest cancer in males and females in Ireland and accounts for 11% of all cancer-related deaths (1). Screening by means of a guaiac fecal occult blood (gFOBT) has been shown to reduce mortality in randomized controlled trials (2, 3). The National Screening Service (NSS) began a nationwide colorectal cancer screening programme (BowelScreen) in 2013 using the fecal immunochemical test (FIT). The FIT quantitatively measures only human blood and is easier to use than the gFOBT (4). This report of the first round of screening highlights the achievements and challenges facing the nationwide screening programme.

[1]BowelScreen, The National Screening Service, Dublin, Ireland. [2]Clinical Advisory Group. The National Screening Service, Dublin, Ireland.

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Corresponding Author: Diarmuid O'Donoghue, National Screening Service, 200 Parnell Street, Dublin DO1 A3Y8, Ireland. Phone: 3538-7254-4319; E-mail: bowelscreen.q&a@screeningservice.ie

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Materials and Methods

Individuals aged 60–69 years were invited with the intention of expanding to 55–74 years age group when colonoscopy capacity allowed. Eligible individuals were identified from the NSS database populated by information from the Department of Social Protection (DSP). Individuals were invited by post to indicate whether they wished to participate and, if agreeable, they were sent a FIT kit (OC-Sensor) along with an explanatory leaflet including instructions on how to complete the test and outlining the benefits and risks of participating in the programme. All FIT kits were returned by free post to a central laboratory and results were communicated within 10 working days to individuals and their general practitioners (GP). All invitees were informed that their personal data would be shared with their family doctors and, where relevant, with the colonoscopy units and the National Cancer Registry. (Supplementary Data).

Individuals with a negative FIT were invited to undergo a repeat FIT in 2 years. Those with a positive result were offered a colonoscopy in one of 14 UK Joint Advisory Group (JAG)-approved colonoscopy screening units sited throughout the country. In the event of an incomplete colonoscopy, other than for poor bowel prep, CT

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Table 1. Invitation, outcomes, and acceptance of diagnostic testing against programme KPIs

		KPI
Number of clients invited	488,628	
Number of FIT returns	196,238	
% Uptake (M/F)	40.2 (36.4/44.1)	>50
Positive FIT rate[a]	5%	
Number referred for colonoscopy	9,788	
Number deemed suitable and attending for colonoscopy	8,062 (82.4%)	>85%
Colonoscopy appt. offered <4 weeks	63.6%	>90%
% Complete colonoscopy	95.6	>90
% FIT positive sent for CTC	2.8	<10

[a]Overall rate.

colonoscopy (CTC) was offered in five regional centers according to European Society of Gastrointestinal and Abdominal Radiology practice guidelines. Clients who were considered medically unfit for colonoscopy were also considered for CTC.

Patients who had adenomas removed were followed up in line with European Guidelines (5). Those with high-risk adenomas ($\geq$5 small adenomas or $\geq$1 adenoma $\geq$20 mm) were offered a surveillance colonoscopy at 1 year, those with intermediate risk adenomas (3 or 4 small adenomas), a colonoscopy in 3 years, whereas those with low-risk adenomas or a normal colonoscopy were offered a repeat FIT in 2 years. Sessile serrated lesions (SSLs), regardless of size, were counted as adenomas in assessing risk categories.

All pathology arising from these colonoscopies was examined in one of the eight designated Cancer Centers in Ireland restricted to 24 BowelScreen histopathologists. Anyone requiring surgery, cancer and noncancer, were offered treatment in these same Cancer Centers. This approach ensured the application of standard pathologic criteria.

BowelScreen collaborated with international experts to develop a comprehensive set of quality assurance guidelines covering every aspect of the programme (6). These guidelines incorporated a number of key performance indicators (KPI), some of which are shown in Tables 1 and 2.

Statistical analysis

Rates and their corresponding 95% confidence intervals (CI) for the range of colonoscopy findings were estimated. Rates were compared using rate ratios. For gender comparisons, females were the baseline group; for comparing rates for the different FIT thresholds, 45 μg was the baseline group. Differences in uptake were compared using two-proportion z-tests. P values <0.05 were considered significant. All analyses were performed with SAS (version 9.4, SAS).

Results

The eligible and invited population was 488,628. Uptake during the first round of screening was 40.2% (Table 1; females 44.1%: males 36.4%). Ninety-nine percent of clients received their result within 2 weeks of the sample being received in the laboratory (KPI 4 weeks). The FIT threshold for positivity for the first 14 months of the programme was set at 20 μg Hb/g feces. This resulted in a positivity rate of 8.6%, which overwhelmed colonoscopy capacity and screening sensitivity, was, therefore, reduced to 45 μg Hb/g feces. This threshold reduced the positivity rate to 4.1% that resulted in an overall positivity rate of 5% for all screened over the course of round 1. Of these, 82.4% attended for colonoscopy at one of the colonoscopy screening units, 63% attending within 4 weeks and 83.7% within 6 weeks.

The findings at colonoscopy are shown in Table 2. Colorectal cancer was identified in 520 individuals giving a detection rate of 2.65 per 1,000 screened by FIT. The positive predictive value (PPV) for detecting colorectal cancer for a positive FIT in the first 14 months (FIT threshold 20 μg/g) was 4.75% [confidence interval (CI), 3.91–5.75] as against 5.01% (CI, 4.34–5.78) after adjustment (FIT threshold 45 μg/g). The cancer detection rate was 2.1 times higher in men compared with women for those with a positive FIT, whereas for those undergoing colonoscopy, the rate was 29% higher in men than women. This gender difference was also seen

Table 2. Pathology findings in FIT positive persons: Gender comparisons

				Rate ratio	
Colonoscopy findings	**All persons**	**Male**	**Female**	**(95% CI)**	**P[a]**
CRCs detected (n)	520	341	179		
CRC rate/1,000 screened (95% CI)	2.65 (2.4–2.9)	3.7 (3.3–4.1)	1.7 (1.5–2.0)	2.12 (1.77–2.54)	$P < 0.0001$
CRC rate/100 colonoscopies (95% CI)	6.5 (5.9–7.03)	7.1 (6.4–7.9)	5.5 (4.7–6.3)	1.29 (1.08–1.55)	0.0048
Adenomas removed (n)	12,983	9,376	3,607		
ADR (%)[b] (95% CI)	54.2 (52.6–55.8)	60.4 (58.2–62.6)	45.3 (43.1–47.7)	1.33 (1.25–1.42)	$P < 0.0001$
High-risk adenomas (%)[c] (95% CI)	17.4 (16.2–18.7)	19.9 (18.4–21.6)	12.6 (10.9–14.5)	1.59 (1.35–1.87)	$P < 0.0001$
(AP)[d] (%) (95% CI)	16.1 (15.2–17.0)	19.3 (18.4–20.7)	11.3 (10.2–12.5)	1.72 (1.52–1.94)	$P < 0.0001$
Intermediate-risk adenomas (%)[c] (95% CI)	34.0 (32.3–35.7)	34.4 (32.3–36.6)	33.2 (30.4–36.2)	1.04 (0.93–1.15)	0.5177
SSLs (n)	676	409	267		

Abbreviation: CRC, colorectal cancer.
[a]Testing for significance at 5% level.
[b]KPI: >40%.
[c]=% of colon-bearing adenomas.
[d]AP = CRC + high-risk adenomas.

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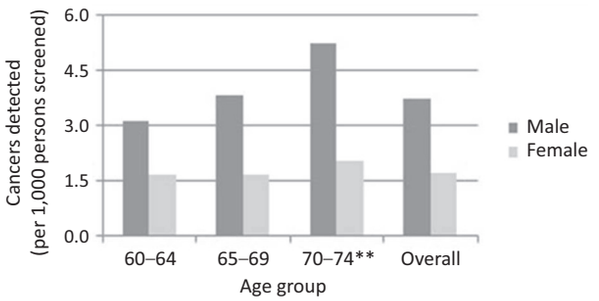

Figure 1.
Cancer detection rate (per 1,000 screened) by gender and age. Some patients were >70 years when received FIT kit or underwent surgery.

across the age spectrum (Fig. 1). The adenoma detection rate (ADR) was 54.2% and here again a similar pattern was seen where males had a 33% higher risk of both adenomas and advanced pathology (AP; colorectal cancer + high-risk adenomas) than females. For high-risk adenomas alone, males had a 59% higher risk than females.

A total of 676 SSLs were removed from 474 colons, 64% of which were located proximal to the splenic flexure. The dysplasia rate was 6.7%, predominantly low grade. A total of 362 of the 474 individuals (78%) had one or more synchronous adenomas. A Mann–Whitney test showed there was no significant difference in FIT concentrations for those colons with and without accompanying adenomas ($U = 9068.5$; $P = 0.3025$).

The staging of the cancers is shown in Table 3. Sixty-eight percent had early disease (stages I and II). A total of 104 patients had pT1 polyp cancers removed by endoscopic resection, 60 of whom had "completion surgery." Of these, 5 had evidence of nodal disease and 1 additional patient had residual disease in the bowel wall (pT2). Eighty-six of these 104 patients (83%) had their polyp cancers located in the rectum or sigmoid colon.

The effect of changing the sensitivity of the FIT threshold after 14 months is shown in Table 4. The FIT-positive rate was 81% higher when the threshold was 20 μg compared with 45 μg Hb/g feces. Likewise, the colorectal cancer detection rate per 1,000 colonoscopies was 67% higher with the 20 μg cutoff and when combined with high-risk adenomas, this rose to 81%. These increased rates were evident for both males and females. The overall ADR was similar at both thresholds.

Table 3. Staging of BowelScreen cancers

CRC Staging	*N* (%)	M/F Ratio
I	237 (45.7%)	1.86
II	117 (22.6%)	1.72
III	141 (27.2%)	2.0
IV	23 (4.4%)	1.88

NOTE: 2 unclassified.
Abbreviation: CRC, colorectal cancer.

Table 4. FIT-Positive rate, adenoma detection rate, cancer detection rate, and advanced pathology rate for different FIT levels[1]

	All persons				Male				Female			
			Rate ratio[a]				Rate ratio				Rate ratio	
Colonoscopy findings	**20 μg**	**45 μg**	**(95% CI)**	***P***	**20 μg**	**45 μg**	**(95% CI)**	***P***	**20 μg**	**45 μg**	**(95% CI)**	***P***
FIT positive (%)	8.2	4.5	1.81	<0.0001	9.8	5.6	1.74	<0.0001	6.7	3.6	1.87	<0.0001
(95% CI)	(7.9–8.6)	(4.4–4.6)	(1.73–1.90)		(9.2–10.4)	(5.5–5.8)	(1.63–1.85)		(6.3–7.1)	(3.4–3.7)	(1.74–2.02)	
Colorectal cancer per 1,000	3.8	2.3	1.67	<0.0001	5.1	3.2	1.62	0.0006	2.5	1.5	1.66	0.0096
(95% CI)	(3.1–4.7)	(2.1–2.5)	(1.33–2.09)		(4.0–6.6)	(2.8–3.6)	(1.23–2.14)		(1.8–3.6)	(1.3–1.8)	(1.13–2.44)	
AP[b] rate per 1,000	10.2	5.6	1.81	<0.0001	15.0	8.6	1.75	<0.0001	5.5	3.0	1.80	<0.0001
(95% CI)	(9.0–11.5)	(5.3–6.0)	(1.58–2.08)		(13.0–17.3)	(7.9–9.2)	(1.30–1.76)		(4.3–6.9)	(2.7–3.4)	(1.38–2.34)	
ADR (%)	53.9	55.0	0.98	0.6016	59.3	60.7	0.98	0.6071	45.7	46.7	0.98	0.7504
(95% CI)	(50.4–57.6)	(53.2–56.9)	(0.91–1.06)		(54.6–64.3)	(58.3–63.3)	(0.89–1.07)		(40.8–51.3)	(44.1–49.4)	(0.86–1.11)	

NOTE: The figures in bold represent the pathology findings at the different FIT sensitivities.
Abbreviations: CRC, colorectal cancer.
[a]20 μg Hb/g faeces, old threshold; 45 μg, new threshold. Rate ratio compares old threshold with new threshold.
[b]AP = colorectal cancers + high-risk adenomas.

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Discussion

Screening for colorectal cancer is carried out nationally or regionally in 20 of the 28 member states of the European Union (EU), the majority of which use the FIT (7), which is now regarded as superior to the gFOBT in screening programmes (8). The ability to adjust the sensitivity of the test proved of considerable value in our programme when the initial threshold of 20 μg Hb/g feces gave a positivity of 8.6% with a referral rate for the colonoscopy beyond our capacity. A recent Dutch study reported similar difficulties and also reduced the sensitivity in a similar manner (9). Like the Dutch study, this reduction in FIT sensitivity did not change the PPV for the detection of cancers for FIT-positive individuals.

The low uptake (40.2%) was disappointing and requires addressing in future rounds. The uptake among the male population reflects the experience of other screening programmes (10, 11) and needs tackling, given the much higher incidence of both cancers and high-risk adenomas in our screened population. Some of this disparity may be explained by the lower sensitivity of FIT in detecting lesions in females than men (12). Interestingly, a study from Flanders and colleagues showed that directly mailing a FIT kit to people resulted in a much higher participation rate (13).

The failure to meet the KPI for colonoscopy waiting times within 4 weeks reflects the pressure on colonoscopy services in Ireland and although it may not have a significant effect on the staging of the cancers, (14) it undoubtedly adds to patients' anxieties.

The majority of cancers found in this prevalent round of FIT screening were at an early stage (Table 3). The percentage of pT1 cancers treated by endoscopic resection is similar to that recently reported by a national Slovenian FIT screening study (15). These pT1 cancers were discussed at multidisciplinary team meetings. The decision to follow-up clinically or proceed to surgery was largely based on whether or not these cancers had adverse pathologic features such as a positive resection margin or evidence of lymphovascular invasion. The finding of nodal disease in 5 of 60 "pT1" resections undergoing "completion" surgery, and 1 additional patient with residual disease in the bowel wall (pT2), highlights the difficulty facing the clinicians following endoscopic resection of a malignant polyp. This 10% rate of "residual disease" postpolypectomy of pT1 cancer is broadly that to be anticipated. Richards and colleagues advise segmental resection in cases of incomplete resection or evidence of lymphovascular invasion (16). The presence of tumor budding may in the future be an additional indicator of potential nodal involvement in these early cancers (17).

The PPV for colorectal cancer detection for those submitting a FIT is broadly similar to another reported FIT programme (15) and not greatly different from the earlier guaiac-based programmes, especially given the differing age cohorts (Table 5; refs. 18, 19). This same table shows that a positive guaiac test is more likely to predict a cancer than a positive FIT (at a sensitivity of 45 μg Hb/g feces) but less likely to predict an adenoma. These findings suggest that, at this sensitivity, the FIT is a better test for the detection of neoplasia. Comparisons of guaiac and FIT-based programmes are limited by differing age cohorts and varying definitions of high-risk adenomas. The pilot FIT study in England by Moss and colleagues using a sensitivity similar to our study (40 μg/g) reported a PPV for high-risk adenomas of 33% (20). The higher percentage of pT1 colorectal cancers in the FIT-based programmes may be due to this greater sensitivity of FIT, but also may reflect improved endoscopic techniques over the years.

Despite a lower participation rate compared with females, males were almost twice as likely to have colorectal cancer diagnosed at every age group (Fig. 1). This was also true for every stage of cancer (Table 3). These findings raise the question as to whether these individuals were truly asymptomatic at the time of screening. However, the same ratio is seen for ADRs when presumably individuals were truly asymptomatic (Table 2). BowelScreen is currently evaluating ways of improving male uptake. Interestingly, Moss and colleagues report that males offered a FIT rather than a guaiac-based FOBT had an improved acceptance rate compared with females (20).

The detection and removal of high-risk adenomas is an important part of a screening programme and is expected to play a role in cancer prevention (21). Lowering the sensitivity of the FIT threshold reduced the detection of colorectal cancer and advanced adenomas (AP) though it did not impact on the overall ADR rates (Table 4). As the vast majority of adenoma-bearing colons were either low or intermediate risk, it is likely that many of these lesions were detected by careful colonoscopic evaluation rather than by active bleeding.

SSLs and TSAs are now recognized as significant alternative pathways to the development of colorectal cancer (22). This is one of the first screening programmes to record

Table 5. Results of FIT and guaiac-based national programmes

	Test	Age	Colorectal cancer rate/all FOBT returns	Colorectal cancer/ FOBT+	Colorectal cancer/ colonoscopy	Stage I and II colorectal cancers	ADR	Polyp colorectal cancer
BowelScreen	FIT (45 μg/g)	60–69	2.6/1,000	5.15%	6.5%	68%	54.8%	20.1%
Slovenia (15)	FIT	50–69	2.8/1,000	5.6%	6.2%	70%	51.3%	22.8%
BNCSP (18)	Guaiac	60–69	1.7/1,000	8.4%	10.0%	71%	42.9%	10.1%
Scottish (19)	Guaiac	50–69	2.1/1,000	12.0%		69.5%	36.5%	17.8%

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these lesions. As screening for occult blood is unlikely to identify SSLs (23), it is more likely that these lesions were detected by careful endoscopic technique, rather than by the primary screening kit. The use of DNA stool analysis is superior to FIT in identifying SSLs but, at present, is cumbersome and expensive (24).

The finding of the majority of the SSLs in the proximal colon fits with recognition that most postcolonoscopy colorectal cancers occur in the right colon and that SSLs with dysplasia may be the precursor lesions (25). There was no gender difference between colons bearing only SSLs.

In summary, this study shows the feasibility and impact of a FIT-based nationwide bowel cancer screening programme. The use of the FIT test allows adjustment of the threshold and optimization of the programme. Too sensitive a FIT can potentially overwhelm colonoscopy capacity and ultimately reduce the population health impact on a national screening programme. With a 5% overall positive rate in the first round of screening, 40% of individuals undergoing colonoscopy had negative or nonsignificant findings. The number of negative colonoscopies will invariably rise as sensitivity increases. It is reassuring to note that using microsimulation modeling techniques, FIT at lower sensitivity levels is still more effective in terms of health outcomes and cost compared with gFOBT at all colonoscopy capacity levels (26, 27).

A comparison between the older guaiac and the newer FIT-based programmes appears to show similar PPVs for cancer detection per 1,000 individuals screened. Similarly, both methodologies detect the majority of cancers at an early stage. The FIT-based programmes appear to be much more sensitive in detecting adenomas and as a result, the authors are confident that these programmes will have a greater population health impact in terms of bowel cancer prevention and survival. It will be of interest to observe the rate of high-risk adenomas in the other EU FIT-based programmes when they are reported.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D. O'Donoghue, P. MacMathuna, R.B. Stephens, T. Mooney

Development of methodology: K. Sheahan, P. MacMathuna, R.B. Stephens, T. Mooney

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. O'Donoghue, K. Sheahan, P. MacMathuna, R.B. Stephens, H. Fenlon, M. Morrin, T. Mooney

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.B. Stephens, L. Fahy, T. Mooney, A. Smith

Writing, review, and/or revision of the manuscript: D. O'Donoghue, K. Sheahan, P. MacMathuna, R.B. Stephens, H. Fenlon, M. Morrin, T. Mooney, A. Smith

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Sheahan, R.B. Stephens, H. Fenlon, J. Mooney, T. Mooney, A. Smith

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International peer review committee:

Dr David Burling, St Mark's Hospital, London; Professor Stephen Halloran, University of Surrey, Guilford; Professor Philip Quirke, St James's Hospital, Leeds; Professor Robert Steele, University of Dundee; Dr Roland Valori, Gloucestershire Royal Hospital; Dr Lawrence von Karsa, IARC, Lyon, France.

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