BMJ Open

Cost-effectiveness of the faecal immunochemical test at a range of positivity thresholds compared with the guaiac faecal occult blood test in the NHS Bowel Cancer Screening Programme in England

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To cite: Murphy J, Halloran S, Gray A. Cost-effectiveness of the faecal immunochemical test at a range of positivity thresholds compared with the guaiac faecal occult blood test in the NHS Bowel Cancer Screening Programme in England. *BMJ Open* 2017;**7**:e017186. doi:10.1136/bmjopen-2017-017186

► Prepublication history and additional material for this paper are available online. To view please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-017186).

Received 6 April 2017
Revised 9 August 2017
Accepted 22 August 2017

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ABSTRACT

Objectives Through the National Health Service (NHS) Bowel Cancer Screening Programme (BCSP), men and women in England aged between 60 and 74 years are invited for colorectal cancer (CRC) screening every 2 years using the guaiac faecal occult blood test (gFOBT). The aim of this analysis was to estimate the cost–utility of the faecal immunochemical test for haemoglobin (FIT) compared with gFOBT for a cohort beginning screening aged 60 years at a range of FIT positivity thresholds.

Design We constructed a cohort-based Markov state transition model of CRC disease progression and screening. Screening uptake, detection, adverse event, mortality and cost data were taken from BCSP data and national sources, including a recent large pilot study of FIT screening in the BCSP.

Results Our results suggest that FIT is cost-effective compared with gFOBT at all thresholds, resulting in cost savings and quality-adjusted life years (QALYs) gained over a lifetime time horizon. FIT was cost-saving ($p<0.001$) and resulted in QALY gains of 0.014 (95% CI 0.012 to 0.017) at the base case threshold of 180 µg Hb/g faeces. Greater health gains and cost savings were achieved as the FIT threshold was decreased due to savings in cancer management costs. However, at lower thresholds, FIT was also associated with more colonoscopies (increasing from 32 additional colonoscopies per 1000 people invited for screening for FIT 180 µg Hb/g faeces to 421 additional colonoscopies per 1000 people invited for screening for FIT 20 µg Hb/g faeces over a 40-year time horizon). Parameter uncertainty had limited impact on the conclusions.

Conclusions This is the first published economic analysis of FIT screening in England using data directly comparing FIT with gFOBT in the NHS BSCP. These results for a cohort starting screening aged 60 years suggest that FIT is highly cost-effective at all thresholds considered. Further modelling is needed to estimate economic outcomes for screening across all age cohorts simultaneously.

Strengths and limitations of this study

- We used data from a recent pilot study, which reached over 50% of the annual screening invitations in England to produce the first economic analysis to include data on faecal immunochemical test (FIT) and guaiac faecal occult blood test (gFOBT) from the English setting.
- This work will help to inform the choice of cut-off threshold for future screening using FIT in the National Health Service Bowel Cancer Screening Programme (NHS BCSP) by providing decision makers with information on predicted resource use, cost and quality of life outcomes.
- The sensitivity and specificity of gFOBT and FIT were not directly observed in the BCSP pilot study population, so we estimated the FIT parameters using screening data for FIT relative to gFOBT.
- We modelled a cohort starting screening at age 60 years and continuing until death. Further modelling would be required to take into account multiple cohorts starting FIT screening at different ages.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer in the UK, with 41 300 new cases diagnosed (12% of all new cases of cancer) in 2014.[1] It is the second most common cause of cancer death in the UK, with 15 903 CRC-related deaths (10% of all deaths due to cancer) in 2014.[1]

Through the National Health Service Bowel Cancer Screening Programme (NHS BCSP), men and women between 60 and 74 years of age in England are invited for CRC screening every 2 years using the guaiac faecal occult blood test (gFOBT). The faecal immunochemical test for haemoglobin (FIT) has been shown to have higher uptake and improved clinical outcomes compared with gFOBT in international settings[2 3] and also has the advantage over gFOBT that the

faecal haemoglobin concentration cut-off for test positivity can be adjusted according to colonoscopy resources and the required programme sensitivity.[4] Other national screening programmes, such as those in the Netherlands and Ireland,[5–7] already use FIT for CRC screening.

In order to select the most appropriate test and, in the case of FIT, the positivity cut-off, health economic analysis can provide information on the longer term health and economic consequences of choosing one test over another.[7 8] Economic analyses of FIT versus gFOBT have been performed for the NHS BCSP,[9] but reliable data on the test performance of FIT versus gFOBT in the NHS BCSP had previously not been available.

We used data from a recent large pilot study of FIT versus gFOBT screening in two of the five NHS BCSP hubs,[10] which reached over 50% of the annual screening invitations in England, to model CRC screening in England. The objective was to estimate the cost–utility of screening with FIT compared with gFOBT in the NHS BCSP in England for a cohort beginning screening aged 60 years, at a range of FIT positivity thresholds. In the BCSP FIT pilot study, a FIT threshold of 180 µg Hb/g faeces was found to have a similar positivity rate to gFOBT, thereby minimising the impact on colonoscopy services. We use this threshold as the base case and also discuss what effect lowering this threshold would have on the cost-effectiveness outcomes.

METHODS

Overview

We constructed a cohort-based Markov state transition model to estimate the difference in costs and health outcomes between FIT (at various positivity thresholds) and gFOBT (the current standard test) for population-level screening. The population considered in the model was the cohort of screening-eligible individuals in England invited to participate in the programme at age 60 years, screened from age 60–74 years and continuing in the model to death or age 100 years. As recommended in the UK setting,[11] costs and quality of life outcomes were discounted at 3.5% per year from age 60 years to the end of the time horizon at age 100 years. The incremental cost of FIT versus gFOBT (cost of FIT screening minus cost of gFOBT screening), life years and quality-adjusted life years (QALYs) were calculated per person invited for screening, along with the incremental cost-effectiveness ratio (ICER) and incremental net benefit per person invited for screening for a willingness to pay threshold of £20 000 per QALY gained.

Budget impact analysis

We also report a budget impact analysis for a cohort of individuals invited for screening at age 60 years, including resource use and costs for the first year of screening and for a lifetime time horizon.

Based on estimates from the National Office for Statistics, we assumed a population size of 590 280 people aged 60 years in 2015.[12] Using the model estimates of prevalence of CRC at age 60 years, we estimated the total size of the cohort invited for screening in the first year (those without cancer) to be 582 218. We conducted a budget impact analysis for the cohort, and we also present selected key results per 1000 people or per person invited for screening.

Estimated cross-sectional population-level costs

Using a similar method to that described by Ladabaum *et al*,[13] we estimated the annual budget impact of FIT compared with gFOBT at the population level.

We estimated the age distribution for the population in England using Office for National Statistics (ONS) data for mid-2015.[12] We then multiplied the estimated cost for each age group in the model by the population distribution from the ONS data to give an estimated total cost for each age group. We used undiscounted costs as the estimate is for a single year across a cross-section of the population, rather than several years with the same cohort (as for the main results).[13] Summing the costs across all age groups gave an estimate of the total annual cost for gFOBT and FIT for a cross-section of the population between 60 and 100 years of age.

Therefore, the cost estimates approximate those of a 'steady state' scenario, where the population in each arm of the model has only ever received screening with either FIT or gFOBT.

Model structure

The model was constructed using Microsoft Excel (2010) software. The model structure was developed based on a previously validated model for the NHS BCSP.[9 14] Here we briefly describe the structural assumptions of the model; full details are given in the online supplementary information, section 1.

Underlying the model is a set of natural history transitions determining disease progression between health states in a non-screened population. The possible health states are: no adenomas or cancer, no adenomas or cancer post-polypectomy, low-risk (LR) adenoma, high-risk (HR)/intermediate-risk (IR) adenoma, undiagnosed CRC (by Dukes' stage A, B, C and D), diagnosed CRC (by Dukes' stage A, B, C and D), death due to CRC and death due to other causes (non-CRC mortality or perforation during colonoscopy). We use the same structural assumption as the previously validated model[9 14] that the health state 'high risk adenoma' encompasses people with adenomas requiring surveillance, including both 'intermediate' and 'high' risk adenomas as defined in surveillance screening guidelines.[15] Transitions between health states occur once in each annual cycle.

The screening model comprises a screening year, non-screening year and surveillance pathway. All subjects in the cohort start in the non-screening part of the model and transition between screening and non-screening in each yearly cycle to simulate biennial screening.

The surveillance pathway for HR adenomas aligns with current guidelines for surveillance after polypectomy for HR adenoma, as updated in 2010.[15] In the model, those with HR and IR adenomas undergo the same surveillance guidelines. The surveillance recommendations published in 2010[15] recommend that surveillance is stopped at age 75 years. However, since people in the model are screened up to age 75 years, we used a maximum age for surveillance of 80 years, so that those with polypectomy for HR adenomas at age 75 years also undergo surveillance colonoscopies.

Model parameters

A complete list of model parameters and sources is given in the online supplementary information, section 2.

Natural history

Transition probabilities between underlying disease states are based on parameters from a previously validated model for the NHS BCSP.[9 14]

Mortality

Age-dependent all-cause mortality estimates were taken from ONS life tables.[16] All-cause mortality for men and women was calculated for each age group using a weighted average according to the proportion of males/females in the population.[16]

Cancer-related mortality by Dukes' stage at diagnosis was estimated from 5-year survival statistics for England.[17] The available survival data for the first 5 years after diagnosis were extrapolated to the maximum time horizon using a Weibull parametric model.

Non-cancer-related mortality by age for diagnosed CRC states was estimated by adjusting all-cause mortality to account for cancer-specific mortality.

Screening test characteristics

Consistent with the BCSP FIT pilot study, the model is based on FIT using the OC-Sensor system with DIANA analyser (Eiken Chemical, Tokyo, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using the hemascreen (Immunostics, Ocean Township, New Jersey, USA, supplied by Alpha Laboratories, Eastleigh, UK). More information on the screening kits is available elsewhere.[10]

We estimated FIT sensitivity and specificity relative to gFOBT using the detection rates from the BCSP FIT pilot study.[10] For gFOBT we used a gFOBT sensitivity of 0.9% for LR adenomas, 12.4% for advanced adenomas and 24.2% for CRC. For FIT in the base case (FIT 180 µg Hb/g faeces), we used a sensitivity of 0.8% for LR adenomas, 15.4% for advanced adenomas and 27.0% for CRC. Specificity of gFOBT was 99.4% at age 50 years and 97.3% at age 70 years. In the base case, specificity of FIT 180 µg Hb/g faeces was 99.8% at age 50 years and 97.4% at age 70 years. Further details of the methods used to estimate sensitivity and specificity are given in the online supplementary information, section 2. Univariate sensitivity analyses were performed around the test characteristics to assess the impact of uncertainty on the results.

Uptake of screening and colonoscopy

The results of the BCSP FIT pilot study[18] demonstrated an increased uptake with FIT compared with gFOBT in the English setting, and these estimates were used in the model. Uptake is defined in the BCSP FIT pilot study and in the model as the proportion of people sent a pre-invitation letter who returned a kit (or kits) which reached a definitive result. Screening uptake is applied in the model by 5-year age bands, and the assumption within the model is that a random proportion of the population is screened in each year, as it was not possible to track individual screening history.

Colonoscopy uptake was taken from the BCSP FIT pilot study.[18] We assumed that uptake for colonoscopy was equal between arms and also the same for follow-up after screening as for surveillance. To test the latter assumption, we included the uptake rate for follow-up and surveillance colonoscopy separately in univariate sensitivity analyses.

Quality of life

Due to a lack of CRC-specific values in the literature, we used utility weights for health states with cancer (mean 0.697, SD 0.020) and without cancer (mean 0.795, SD 0.021) from Ara and Brazier,[19] consistent with previous analyses for the NHS BCSP.[9] The mean age of respondents in the study was 60.9 years, which corresponds well to the age at which screening is started in the model. We assumed that screening tests, diagnostic procedures (colonoscopy) and polypectomy were not associated with a significant utility decrement due to their short duration relative to the model cycle length of 1 year.

Unit costs

Costs were estimated from the perspective of the healthcare system (NHS/BCSP). Screening and colonoscopy costs were taken from NHS[20] or BCSP sources. We used a simplifying assumption that all diagnostic tests were colonoscopies but varied the sensitivity, specificity and cost of the diagnostic test in the sensitivity analyses to test the impact of this assumption on the results. Costs of CRC management were taken from a model-based evaluation of CRC services by Pilgrim *et al*.[21] No cost was assigned to death. All costs were adjusted, where necessary, to 2015/2016 prices using the Health Service Cost Index.[22]

Uncertainty

To incorporate uncertainty in the results of the model, we carried out probabilistic analysis for each FIT threshold by sampling 1000 sets of model input values drawn at random from appropriate statistical distributions. Parameters based on large data sets or national data (eg, from the BCSP or the BCSP FIT pilot study) were not varied probabilistically as they were assumed to be representative of the true screened population. Correlations between the natural history and screening parameters were modelled using Cholesky decomposition matrices, which were estimated using R software for each FIT threshold,

Table 1 Cost-effectiveness per person invited for screening of FIT versus gFOBT by FIT threshold compared with gFOBT

	Incremental total cost compared with gFOBT, mean (£) (95% CI)	Incremental life years compared with gFOBT, mean (95% CI)	Incremental QALYs compared with gFOBT, mean (95% CI)	ICER: incremental cost per QALY gained compared with gFOBT (£)*	Incremental net benefit compared with gFOBT, mean (£) (95% CI)**
FIT 180 µg Hb/g faeces (base case)	–27 (–43 to -12)	0.019 (0.016 to 0.023)	0.014 (0.012 to 0.017)	FIT dominates (p<0.001)	315 (256 to 377)
FIT 150 µg Hb/g faeces	–40 (–62 to -19)	0.028 (0.024 to 0.032)	0.021 (0.018 to 0.024)	FIT dominates (p<0.001)	458 (388 to 531)
FIT 100 µg Hb/g faeces	–53 (–86 to -23)	0.038 (0.033 to 0.043)	0.029 (0.025 to 0.033)	FIT dominates (p<0.001)	637 (546 to 731)
FIT 40 µg Hb/g faeces	–84 (–151 to -24)	0.073 (0.065 to 0.082)	0.058 (0.051 to 0.064)	FIT dominates (p<0.005)	1237 (1072 to 1405)
FIT 20 µg Hb/g faeces	–62 (–141 to 8)	0.082 (0.072 to 0.091)	0.066 (0.057 to 0.074)	FIT dominates (p<0.050)	1378 (1177 to 1582)

Means are deterministic means; all 95% CIs calculated as percentiles of 1000 probabilistic model runs.
*Incremental cost-effectiveness ratio (ICER)=ΔC/ΔE, where ΔE and ΔC are the incremental QALYs and incremental costs, respectively, of FIT compared with gFOBT. p -values calculated as the proportion of the 1000 PSA simulations with positive ICERs.
**INB= λ.ΔE – ΔC, where λ is the willingness to pay threshold=£20 000 per QALY gained.
FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; QALY, quality-adjusted life years.

based on previously reported correlations between these parameters.[9 23 24] Further details about the distributional assumptions for the probabilistic analysis are available in the online supplementary information, section 2. The estimated variance–covariance matrices are available from the authors on request.

In addition to the probabilistic analysis, which incorporates uncertainty around all parameters simultaneously, we also conducted univariate sensitivity analyses. These explore the impact on the results of uncertainty around individual parameters of interest, including utility weights, screening uptake, colonoscopy attendance rates and the cost of screening kits, colonoscopy and cancer management.

Two published reviews evaluated the sensitivity of the OC-Sensor test, the same as that considered in this analysis.[9 25] Although neither review provides estimates by FIT threshold, the estimates for sensitivity to detect CRC used in this analysis may be considered low compared with those in the literature. Therefore, we performed a separate sensitivity analysis around the sensitivity of FIT for CRC. This parameter was varied in increments of +0.1, up to +0.3 above baseline to test the impact of potentially underestimating of this parameter.

RESULTS

Cost–utility analysis

Cost-effectiveness results are presented in table 1 in terms of both life years and QALYs. The mean total cost difference per person ranged from £25 (95% CI £12 to £43) cheaper for FIT at a 180 µg Hb/g faeces threshold to £62 (95% CI £8 to £141) cheaper for FIT at a 20 µg Hb/g faeces threshold. The mean QALYs gained with FIT ranged from 0.014 (95% CI 0.012 to 0.017) for FIT at a 180 µg Hb/g faeces threshold to 0.066 (95% CI 0.057 to 0.074) for FIT at a 20 µg Hb/g faeces threshold. FIT dominates gFOBT—that is, screening with FIT results in greater total QALYs and lower costs than gFOBT—for all FIT thresholds considered in the analysis.

Sensitivity analyses

Probabilistic sensitivity analysis

The results of the probabilistic analysis for each FIT threshold are illustrated on a cost-effectiveness plane in figure 1. For all thresholds, FIT dominates gFOBT in at least 95% of the 1000 probabilistic simulations.

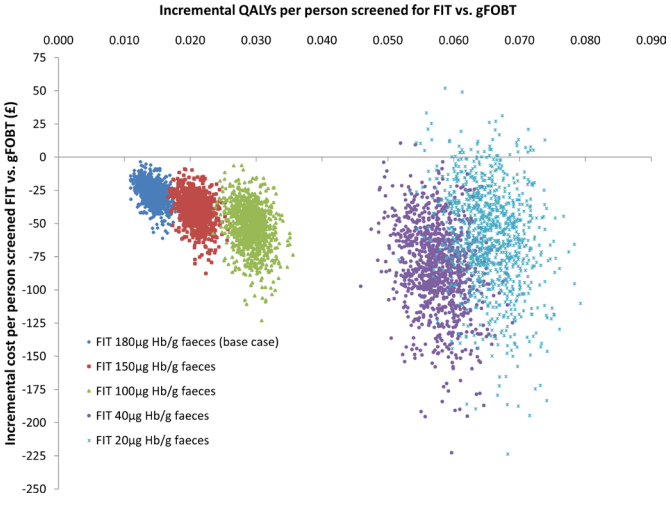

Figure 1 Cost-effectiveness plane illustrating probabilistic sensitivity analysis results for each FIT threshold versus gFOBT (1000 simulations). FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test.

One-way sensitivity analyses

One-way sensitivity analyses were performed around key model parameters by varying the input values by ±10% of the base case parameter value for FIT 180 µg Hb/g faeces. The results are shown in terms of the ICER and incremental net benefit in the online supplementary information, section 3 . For all thresholds, the conclusion that FIT dominates gFOBT was not affected by variation in any single key model parameter; however, for all FIT thresholds, the cancer management costs were identified as key drivers of changes in the ICER. We therefore conducted further sensitivity analysis around these costs.

Cancer management costs

In order to assess the impact of CRC management costs on the findings, we sought to determine the cost at which FIT would no longer be cost saving for each FIT threshold.

FIT was found to no longer be cost saving compared with gFOBT when the cancer management costs were reduced to between 50% and 70% of the base case values (depending on the FIT threshold being considered, data not shown). This corresponds to cancer management costs of between £6884 and £9637 for CRC A (compared with £13 768 base case cost), £9471–£13 260 for CRC B (£18 943 base case), £12 989–£18 185 for CRC C (£25 979 base case) and £14 206–£19 888 for CRC D (£28 412 base case). For FIT 180 µg Hb/g faeces, a reduction in cancer management costs of 50% would be required before FIT is no longer cost saving compared with gFOBT.

Screening test characteristics

The results of the sensitivity analysis around FIT sensitivity for CRC suggest that, for all thresholds, if FIT sensitivity had been underestimated in our baseline analysis this would result in an underestimation of both the total cost saving and the total QALY gain of screening with FIT. At all higher estimates of sensitivity, FIT is associated with a positive net benefit (see online supplementary information, section 3).

Budget impact analysis

Screening costs in the first year of screening

Screening resource use and costs for the cohort in the first year of screening are given in table 2 for gFOBT and FIT at the base case threshold of 180 µg Hb/g faeces. Screening costs for a range of FIT thresholds are presented in the online supplementary information, section 4 for the first year of the model and over a 40-year time horizon.

The total number of screening kits used in the first screening year at age 60 years is estimated to be 624 135 for gFOBT screening and 596 015 for FIT screening, after taking into account the need for repeat kits due to unclear

Table 2 Resource use and costs associated with screening kits in the first screening year for a population of 582 218 people invited for screening aged 60 years

	Resource use			Cost (£)		
	gFOBT	FIT 180 µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180 µg Hb/g faeces (base case)	Difference (FIT – gFOBT)
Total number of preinvites sent in first year (excluding repeat kits)	582 218	582 218	–	–	–	-
Number of people returning kit in first year (normal result)	311 755	365 108	53 353	–	–	-
Number of people returning kit in first year (positive result)	5534	5814	280	–	–	-
Positivity rate (%)	1.7	1.6	–0.18	–	–	-
Number of people not returning kit in first year	264 929	211 297	–53 633	–	–	-
Total number of kits returned (normal result)*	334 200	373 760	39 560	702 881	1 987 239	1 284 358
Total number of kits returned (positive result)*	5932	5951	19	12 477	31 643	19 166
Total number of kits sent but not returned*	284 003	216 304	–67 699	244 349	373 520	129 172
Total number of kits used in the first year (total screening cost for cohort)	**624 135**	**596 015**	**–28 120**	**959 707**	**2 392 403**	**1 432 696**
Total screening costs in the first year per 1000 people invited for screening at age 60 years	**–**	**–**	**–**	**1648**	**4109**	**2461**

*Includes repeat kits.
FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test.

Table 3 Colonoscopy resource use and adverse events for a population of 582 218 people invited for screening, 40-year time horizon

	Resource use			Cost (£)		
	gFOBT	FIT 180 µg Hb/g faeces (base case)	Difference (FIT - gFOBT)	gFOBT	FIT 180 µg Hb/g faeces (base case)	Difference (FIT - gFOBT)
Follow-up						
Colonoscopies without polypectomy	28 074	28 603	529	12 981 875	12 963 904	–17 970
Colonoscopies with polypectomy for HR adenomas	14 894	19 943	5049	8 541 716	11 514 091	2 972 375
Colonoscopies with polypectomy for LR adenomas	8886	8309	–578	5 079 018	4 766 975	–312 043
Deaths at colonoscopy	0	0	0	142	140	–2
Total number of follow-up colonoscopies	51 855	56 855	5000	26 602 751	29 245 111	2 642 360
Major bleeds requiring hospitalisation	21	23	2	7688	8375	687
Perforation	33	35	2	74 456	77 635	3178
Surveillance						
Colonoscopies without polypectomy	10 847	14 567	3720	4 377 963	5 917 047	1 539 084
Colonoscopies with polypectomy for LR adenomas	6754	9064	2310	10 864 104	14 669 928	3 805 823
Colonoscopies with polypectomy for HR adenomas	21 841	29 305	7464	3 340 127	4 510 935	1 170 809
Deaths at colonoscopy	0	0	0	71	96	25
Total number of surveillance colonoscopies	39 442	52 937	13 494	18 582 265	25 098 006	6 515 741
Major bleeds requiring hospitalisation	16	21	5	5381	7268	1887
Perforation	19	25	6	39 059	52 769	13 710
Total number of colonoscopies	**91 297**	**109 791**	**18 494**	**18 626 705**	**25 158 043**	**6 531 337**
Total number of colonoscopies per 1000 people invited for screening at age 60 years	**157**	**189**	**32**	**31 993**	**43 211**	**11 218**

FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; HR, high risk; LR, low risk.

results or spoilt test kits. This equates to 28 120 fewer kits used for FIT screening than for gFOBT screening. However, due to higher unit costs and uptake for FIT, the total cost of screening kits is estimated to be £1 432 696 greater with FIT in the first year. The average cost of screening kits per 1000 people invited for screening is estimated to be £1648 for gFOBT and £4109 for FIT at the base case threshold of 180 µg Hb/g faeces.

Long-term colonoscopy resource use

The estimated total number of colonoscopies and associated costs for the cohort over a 40-year time horizon is given in table 3 for gFOBT and FIT at the base case threshold of 180 µg Hb/g faeces. Corresponding results for a range of FIT thresholds are given in the online supplementary information, section 4.

The number of colonoscopies performed was higher for FIT than for gFOBT for all FIT thresholds, resulting in higher colonoscopy costs. The estimated number of colonoscopies required with gFOBT screening is 51 855 at initial follow-up (referrals from the screening programme) and 39 442 during surveillance, giving a total of 91 297 over 40 years at a total cost of £18 626 705. For the base case FIT threshold, the estimated number of colonoscopies is 56 855 for initial follow-up and 52 937 for surveillance, giving 109 791 colonoscopies in total over 40 years at a cost of £25 158 043. The estimated additional colonoscopy burden with FIT 180 µg Hb/g faeces compared with gFOBT is 18 494 colonoscopies at a cost of £6 531 337, for the cohort over 40 years.

As the FIT threshold is decreased, the number and cost of follow-up and surveillance colonoscopies increases. The number (cost) of additional colonoscopies with FIT compared with gFOBT over the 40 year time horizon ranges from 31 314 (£9 640 198) for FIT 150 µg Hb/g faeces to 2 44 999 (£57 903 423) for FIT 20 µg Hb/g faeces.

Per 1000 people invited for screening, the number (cost) of additional colonoscopies with FIT ranges from 32 (£11 218) for FIT 180 µg Hb/g faeces to 421 (£99 453) for FIT 20 µg Hb/g faeces.

Total long-term costs

A summary of the estimated costs over the 40-year time horizon, per person sent an invitation at age 60 years, is given for a range of FIT thresholds in table 4.

The costs of screening over the 40-year time horizon of the model (from age 60 to 100 years) are estimated to be higher for FIT (at any threshold) than for gFOBT; however, this constitutes a small proportion of the total cost (between 1% and 3% across the FIT thresholds).

Colonoscopies over 40 years account for £77.83 per person invited for screening (8.3% of total cost) in the gFOBT arm and £93.59 (10.3% of total cost) for FIT in the base case (180 µg Hb/g faeces). As the FIT threshold is decreased, the colonoscopy burden and therefore costs increase, up to £297.58 per person invited for screening (34.0% of total cost) for FIT 20 µg Hb/g faeces.

The largest component of total costs, lifetime cancer management costs, are estimated to be lower for FIT than for gFOBT, accounting for £849.59 per person invited for screening (90.6% of total cost) for gFOBT and £792.27 (87.0% of total cost) for FIT 180 µg Hb/g faeces in the base case. As the FIT threshold is decreased, the lifetime cancer management costs fall, and forFIT 20 µg Hb/g faeces, these costs are £553.82 per person invited for screening (63.2% of total cost).

Overall, the total cost over 40 years is predicted to be lower for FIT at any threshold than for gFOBT, and this difference increases as the FIT threshold is decreased.

Cross-sectional population-level costs

The estimated annual costs for a cross-section of the population aged between 60 and 100 years are shown in the online supplementary information, section 4. The cost projections suggest that in a 'steady state' scenario (ie, comparing populations that have only ever received either FIT or gFOBT screening), a population screened with FIT would have £10.6 million higher screening costs, £12 million higher colonoscopy costs and £48.5 million lower cancer management costs, resulting in a total estimated cost saving of £26 million per year compared with a population screened with gFOBT.

Long-term disease prevalence and mortality

The model predicts that with FIT screening a lower proportion of the cohort will have high-risk polyps for all years from the start of screening (data shown in the online supplementary information, section 4) due to improved detection rates. The increased HR adenoma detection and polypectomy rate for FIT results in a higher proportion of the cohort at younger ages with no adenomas or cancer.

From the start of screening until age 87 years, the model predicts that the prevalence of Dukes' stage B, C or D CRC is lower with FIT than with gFOBT, and the prevalence of Dukes' stage A CRC is greater. From age 88 years onwards, the proportion of people with CRC of any stage is greater in the FIT arm, attributable to improved survival with FIT screening.

Discussion

Our model results combined with the results of the BCSP FIT pilot study suggest that FIT is dominant (more effective and less costly) versus gFOBT in an English setting for a single cohort starting screening at age 60 years. In the long term, the higher costs of colonoscopy with FIT are outweighed by savings in cancer management costs for all thresholds. At lower thresholds, the net savings are greatest, but the impact on colonoscopy volumes is also greatest. Therefore, constraints on colonoscopy capacity in the short-term may prohibit using lower FIT thresholds despite the predicted health benefits and cost savings in the long term. Our results suggest that for a single cohort of 582 218 people aged 60 years invited for screening, the additional colonoscopy demand over the 40-year time horizon of the model could be as large as 245 000 for the lowest threshold considered (FIT 20 µg Hb/g faeces). These results indicate that care should be taken when selecting an appropriate FIT threshold.

A key strength of this analysis is the availability of screening data for FIT versus gFOBT from the recent pilot study in the BCSP in England,[10] the first time these data have been used in an economic analysis of CRC screening for this setting.

Our model was based on a previous model for the English BCSP setting,[9] for which external validation results are available elsewhere.[26] We performed additional validation checks using data from the BCSP Southern Hub[27] on the proportion of successfully completed screening episodes that resulted in a diagnosis of CRC, adenomas or negative results (data presented in the online supplementary information). The results show good agreement for most age groups, though at younger age groups, the model may be overestimating the proportion of HR adenomas detected and underestimating the proportion with no neoplasia detected. We performed several sensitivity analyses around key parameters, including sensitivity of the screening tests, as well as a probabilistic simulations in order to explore the effect of uncertainty around the model parameters on the results.

The conclusion using the point estimates (that FIT is either cost-saving or highly cost-effective compared with gFOBT for all thresholds) was not affected by parameter uncertainty. There were no probabilistic simulations or univariate sensitivity analyses under which FIT was not found to be cost-effective compared with gFOBT at the

Table 4 Estimated lifetime costs per person sent an invite for screening at age 60 years, over 40-year time horizon

	gFOBT (£)	FIT 180 µg Hb/g faeces (base case) (£)	FIT 150 µg Hb/g faeces (£)	FIT 100 µg Hb/g faeces (£)	FIT 40 µg Hb/g faeces (£)	FIT 20 µg Hb/g faeces (£)
Kits returned (normal result)	7.59	20.59	20.53	20.39	19.88	19.49
Kits returned (positive result)	0.17	0.44	0.49	0.61	1.05	1.40
Kits sent but not returned	2.23	3.51	3.50	3.50	3.49	3.48
Total screening costs	**9.98**	**24.54**	**24.53**	**24.50**	**24.42**	**24.37**
Follow-up colonoscopy-related costs*	45.69	50.23	56.30	71.04	123.77	165.73
Surveillance colonoscopy-related costs*	31.92	43.11	48.43	63.59	105.86	131.13
Cost of colonoscopy-related adverse events	0.08	0.10	0.12	0.15	0.25	0.31
Total colonoscopy-related costs	**77.83**	**93.59**	**105.01**	**134.97**	**230.19**	**297.58**
CRC A management (% of CRC management costs)	46.77	44.67	43.86	42.11	37.31	35.53
CRC B management (% of CRC management costs)	135.15	127.10	123.79	117.24	98.51	91.39
CRC C management (% of CRC management costs)	231.69	216.52	210.16	198.49	164.33	151.88
CRC D management (% of CRC management costs)	435.99	403.99	390.37	367.43	298.71	275.01
Total CRC management costs	**849.59**	**792.27**	**768.18**	**725.26**	**598.85**	**553.82**
Total costs	**937.40**	**910.40**	**897.72**	**884.73**	**853.47**	**875.78**

*Also includes the cost of specialist screening practitioner appointments for those not attending colonoscopy.
CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test.

£20 000 willingness to pay threshold. When we considered the cost of CRC management in more detail, we estimated that FIT would no longer be cost-saving if these management costs were 50%–70% lower than our baseline figures (depending on the FIT threshold); however, we consider it unlikely that the true CRC management costs are significantly lower than those used in this analysis. It is possible that other cost assumptions—for example, if CRC management costs depended on factors other than CRC stage at diagnosis—could affect the results. However, even under these scenarios, our analysis suggests it is likely that FIT would still be cost-saving compared with gFOBT.

Our analysis suggests that obtaining further information (for example, by running further large-scale studies comparing FIT and gFOBT) in order to resolve parameter uncertainty for this particular model would have limited value.

Limitations

There are some limitations of the analysis that should be taken into account when interpreting the results. Regarding the model parameters, the sensitivity and specificity of gFOBT and FIT were not directly measured in the BCSP FIT pilot study, so we estimated the FIT parameters using screening test data for FIT relative to the gFOBT from the study.[10 18] We also used utility weights that were not CRC-specific due to the limited number of appropriate studies in the literature. However, the model results were robust to uncertainty in these parameters.

Regarding the model structure, male/female cohorts and the location (proximal/distal colon) of occurrences of neoplasia were not modelled separately due to lack of data on disease progression. This is in line with previous analyses for the BCSP,[9] but these remain key areas of the model that could be improved when more data become available.

It is also possible to model short-term decrements in utility following screening tests or procedures; however, we do not think including small utility decrements over short time periods such as this would have any meaningful effect on the results over the 40-year time horizon of the model.

It is assumed in the model that the diagnostic procedure used after a positive screening test (or on presentation with symptoms in primary care) is a colonoscopy. Data from the BCSP suggest that a range of diagnostic procedures are used, both at first and repeat test, including CT colonography and flexible sigmoidoscopy. However, since approximately 90% of the diagnostic procedures in the BCSP FIT pilot study were observed to be colonoscopy,[18] the modelling assumptions are reflective of practice in the majority of cases.

A key property of Markov state transition models is that transition probabilities between states cannot be dependent on patient history, and therefore we were not able to track subjects in the model by screening episode. As a result, the model assumes that a random proportion of the population is screened in each year, rather than considering screening history. In our model screening uptake varies with age, in line with data by age group available from the BCSP FIT pilot study,[10] but this cross-sectional information may not represent the experience of a cohort moving through the programme.

We have not attempted to model the effects on our results of flexible sigmoidoscopy screening (also known as bowel scope or flexiscope), which the NHS BCSP is in the process of rolling out to all men and women in England aged 55 years in addition to the existing screening protocol from the age of 60 years. The results of a UK trial with 17 years of follow-up data[28] suggest that flexible sigmoidoscopy screening at age 55 years results in significant reductions in long-term incidence of CRC and CRC-related mortality. The addition of flexible sigmoidoscopy screening to the existing UK screening protocol will result in differences in the detection rates of gFOBT and FIT screening compared with the data that were available for this analysis. However, the precise impact of flexible sigmoidoscopy screening has not yet been quantified, and the intention of this analysis was to compare FIT with gFOBT based on the existing setup of the screening programme. Neither have we attempted to model possible changes to the age range or screening frequency in the existing BCSP in England.

Finally, we simulated a cohort starting screening at age 60 years and followed in the model until death. Although we have estimated the annual cost for a steady state, further modelling would be required to simulate a roll-out with multiple cohorts starting FIT screening at different ages, as would likely be the case if FIT were to be introduced in the place of gFOBT across the screening programme.

Conclusions

This is the first published analysis to use FIT screening data from England for an economic analysis of FIT. Our results suggest that FIT is highly cost-effective compared with gFOBT at all thresholds for a cohort aged 60 years at first screen in England. In our analysis, greater long-term cost savings were achieved as the FIT threshold was decreased, but this was also associated with an increase in colonoscopy resource requirements.

Acknowledgements The authors would like to thank Sue Moss and Christopher Mathews (Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London) for providing data from the Bowel Cancer Screening Programme pilot study of FIT versus gFOBT and giving feedback on the draft manuscript; Katy Reed (NHS Bowel Cancer Screening Southern Programme Hub) for providing screening kit cost estimates; and Helen Seaman (NHS Bowel Cancer Screening Southern Programme Hub) for providing feedback on the draft manuscript.

Contributors JM conducted the analysis and drafted the manuscript. SH advised on the analysis and contributed to the manuscript. AG conceived the study, advised on the analysis and contributed to the manuscript. All authors approved the final version of the manuscript.

Funding This work was supported by a research grant from the UK National Screening Committee (Public Health England) and was conducted independently. The views expressed in the paper are those of the authors alone.

Competing interests AG reports grants from Public Health England during the conduct of the study and is a member of the United Kingdom National Screening Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Further information on the model structure, parameters and sensitivity analyses are available in the supplementary information. Correlation matrices used for Cholesky decomposition to model the uncertainty around the natural history parameters are available from the authors upon request.

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