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Title

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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ABSTRACT

Objectives

The National Health Service Bowel Cancer Screening Programme (NHS BCSP) invites men and women in England between 60 and 74 years of age for colorectal cancer (CRC) screening every two years using a guaiac faecal occult blood test (gFOBT). The aim of this analysis was to estimate the cost-effectiveness of the faecal immunochemical test (FIT) compared with gFOBT for a cohort beginning screening aged 60, and to determine the most appropriate FIT positivity threshold.

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 gained over a 40-year time horizon. Greater health gains and cost savings were achieved as the FIT threshold was decreased, due to savings in cancer management

costs. However, lower thresholds were also associated with more colonoscopies. Parameter uncertainty had limited impact on the conclusions.

Conclusions

This is the first economic analysis of FIT screening in England using data comparing FIT with gFOBT in the NHS BSCP. These results for a cohort starting screening aged 60 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

Strengths of this study include:

- We used data from a recent pilot study, which reached over 50% of the annual screening invitations in England; the first economic analysis to include data on FIT and gFOBT from the English setting.
- This work will help to inform the choice of cut-off threshold for future screening using FIT in the NHS BCSP by providing decision makers with information on predicted resource use, cost and quality of life outcomes.

Limitations of this study include:

- The sensitivity and specificity of gFOBT and FIT were not directly observed in the pilot study population, so we estimated the FIT parameters using the model-estimated prevalence of disease and data for FIT relative to the gFOBT from recent pilot study in England.

We modelled a cohort starting screening at age 60 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].

The National Health Service Bowel Cancer Screening Programme (NHS BCSP) invites men and women between 60 and 74 years of age in England for CRC screening every two 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 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 vs. gFOBT have been performed for the NHS BCSP [9] but reliable data on the test performance of FIT vs. gFOBT in the NHS BCSP had previously not been available.

We used data from the recent large pilot study of FIT vs. 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-effectiveness of screening with FIT compared with gFOBT in the NHS BCSP in England for a cohort beginning screening aged 60, for a range of FIT positivity thresholds. In the NHS BCSP pilot study, a FIT threshold of 180µg Hb/g 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 population-level screening (the current standard test). 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. 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 vs. 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 ICER and incremental net benefit per person invited for screening for a threshold of £20,000 per QALY gained.

To incorporate uncertainty in the results of the model, we carried out probabilistic analyses 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 (e.g. from the BCSP or the 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 in R for each FIT threshold,

based on previously-reported correlations between these parameters [9 12 13]. Further details about the methods and distributional assumptions for the probabilistic analysis are available in the Supplementary Information. The estimated variance-covariance matrices are available as a separate file in Microsoft Excel®.

Model structure

The model structure was developed based on a previously validated model for the NHS Bowel Cancer Screening Programme [9 14]. Here we briefly describe the structural assumptions of the model; full details are given in the Supplementary Information.

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 adenoma (LR), high risk/intermediate risk adenoma (HR/IR), undiagnosed colorectal cancer (CRC) at each Dukes' Stage (A, B, C and D), diagnosed colorectal cancer (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, the HR/IR adenoma group 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 also undergo surveillance colonoscopies.

Model parameters

Natural history

Transition probabilities between underlying disease states are based on parameters from a previously validated model for the NHS Bowel Cancer Screening Programme [9 14]. These are reported in Supplementary Table 1.

Mortality

Age-dependent all-cause mortality estimates were taken from the latest available Office for National Statistics life tables for 2011-13 [16]. All-cause mortality for men and women was averaged for each age-group using a weighting according to the proportion of males/females in the population [17].

Cancer-related mortality by stage at diagnosis was estimated from 5-year survival statistics for England [18]. The available survival data for the first 5 years after diagnosis were extrapolated to the maximum time horizon using a Weibull parametric model. The model parameters for cancer-related mortality is given in the Supplementary Information.

Non-cancer related mortality by age for diagnosed CRC states was estimated using cancer-specific mortality and all-cause mortality described above.

Screening test characteristics

Consistent with the NHSBCSP FIT pilot study, the model is based on FIT using the OC-SENSOR system with DIANA analyser (Eiken Chemical, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using the hema-screen (Immunostics, 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 FIT pilot study [10] and model-estimated prevalence from non-screening disease progression transitions in the model. The assumptions regarding sensitivity and specificity of kits, and further details of the methods used to estimate them, are given in the Supplementary Information. 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 FIT pilot demonstrated an increased uptake with FIT compared with gFOBT in the English setting, and these estimates were used in the model. Uptake in the model is defined in the FIT pilot [10] and in the model as the proportion of people sent a pre-invitation letter who returned a kit (or kits) and reached a definitive result. Screening uptake is applied in the model by 5-year age bands; the parameters are summarised in Supplementary Table 12.

Colonoscopy uptake was taken from the FIT pilot [19]. We assumed that uptake for colonoscopy was equal between arms, and also the same for follow-up following 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 CRC (mean 0.697, SD 0.020) and without CRC (mean 0.795, SD 0.021) from [20]. The mean age for respondents for this health state was 60.9 years, which corresponds well to the age at which screening is started in the BCSP. 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 one year.

Unit costs

Costs were estimated from the perspective of the healthcare system (NHS/BCSP). Supplementary Table 12 summarises the unit costs used in the model. Screening and colonoscopy costs were taken from national NHS [21] 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 colorectal cancer management were taken from a model-based evaluation of colorectal cancer services by Pilgrim et al [22]. No cost was assigned to death. All costs were adjusted to 2013/14 prices using the Health Service Cost Index.

Uncertainty

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.

RESULTS

Based on estimates from the National Office for Statistics, the population aged 60 years in 2014 was 594,213 people [17]. Using the model estimates of prevalence of colorectal cancer at age 60, we estimated the total population invited for screening (those without cancer) to be 586,097.

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 1. Screening costs for a range of FIT thresholds are presented in Supplementary Table 13 and Supplementary Table 14 for the first year of the model, and over a 40 year time horizon respectively.

The total number of screening kits used in the first screening year at age 60 is estimated to be 628,293 for gFOBT screening and 599,986 for FIT screening, after taking into account the need for repeat kits due to unclear results or spoilt test kits. This equates to 28,307 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 £1,380,831greater with FIT in the first year. The average cost of screening kits per person invited for screening is estimated to be £1.58 for gFOBT and £3.93 for FIT.

Long-term colonoscopy resource use

The estimated total number of colonoscopies and associated costs over a 40 year time horizon is given in Table 2 for gFOBT and FIT at the base case threshold of 180µg Hb/g faeces. Supplementary Table 15 gives these results for a range of FIT thresholds.

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 52,200 at initial follow-up (referrals from the screening programme) and 39,705 during surveillance, giving a total of 91,906 over 40 years at a total cost of £18,188,342. For the base case FIT threshold, the estimated number of colonoscopies is 59,073 for initial follow-up and 53,289 for surveillance, giving 112,362 colonoscopies in total over 40 years at a cost of £24,565,996. The estimated additional colonoscopy burden with FIT 180µg Hb/g faeces compared with gFOBT is 20,456 colonoscopies at a cost of £6,377,654, for the cohort over 40 years.

As the FIT threshold is decreased, the number and cost of follow-up and surveillance colonoscopies increases (data presented in Supplementary Table 15). The number (cost) of additional colonoscopies with FIT compared with gFOBT over the 40 year time horizon ranges from 33,036 (£9,413,358) for FIT 150µg Hb/g faeces to 168,017 (£42,137,307) for FIT 40µg Hb/g faeces.

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 (illustrated in Supplementary Figure 6), due to improved detection rates. The increased HR adenoma detection and polypectomy rate for FIT results in a higher proportion 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' B, C, or D CRC is less with FIT than with gFOBT, and the prevalence of Dukes' A CRC is greater (illustrated in Supplementary Figure 7). 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.

Total long-term costs

A summary of the estimated costs over the 40-year time horizon, per person sent an invitation at age 60, is given for a range of FIT thresholds in Table 3.

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.

Colonoscopies over 40 years account for £75.52 (8.2% of total cost) in the gFOBT arm, and £92.76 (10.4% of total cost) for FIT in the base case (180µg Hb/g faeces). As the FIT threshold is decreased, the colonoscopy burden and therefore costs increase, up to £220.09 (26.5% of total cost) for FIT 40µg 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 £831.24 per person invited for screening (90.7% of total cost) for gFOBT and £775.16 (87.0% of total cost) for FIT 180µg Hb/g faeces in the base case. As the FIT threshold is decreased, the lifetime cancer management costs fall, and at the lowest FIT threshold considered, 40µg Hb/g faeces, these costs are £585.92 per person invited for screening (70.6% 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.

Cost-effectiveness

Cost-effectiveness results are presented in Table 4. The mean total cost difference per person ranged from £25 (95% CI: £9 to £42) cheaper for FIT at a 180µg Hb/g faeces threshold to £87 (95% CI: £25 to £155) cheaper for FIT at a 40µg 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 180µg Hb/g faeces threshold to 0.058 (95% CI: 0.051 to 0.064) for FIT at a 40µg Hb/g faeces threshold. These estimates indicate that FIT dominates gFOBT – that is, screening with FIT results in greater total QALYs gained, and lower costs than gFOBT – for all FIT thresholds considered in the 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 dominated gFOBT (more effective and less costly) for all probabilistic simulations.

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 the base case FIT 180µg Hb/g faeces. The results are shown in terms of the ICER in Supplementary Figure 8, and in terms of the incremental net benefit in Supplementary Figure 9. 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 decision (i.e. whether or not FIT is cost-effective), we sought to determine the cost at which FIT would no longer be cost-saving for each threshold.

FIT was found to no longer be cost saving compared to gFOBT when the cancer management costs were reduced to between 50% and 60% of the base case values (dependent on the FIT threshold being considered, data not shown). This corresponds to between £6,735 and £8,081 for CRC A (compared to £13,469 base case cost); £9,266 to £11,119 for CRC B (£18,532 base case); £12,707.78 to £15,249 for CRC C (£25,416 base case); and £13,898 to £16,677 for CRC D (£27,796 base case).

Screening test characteristics

Two published reviews evaluated the sensitivity of the OC-SENSOR test, the same as that considered in this analysis [9 23]. Although neither review provides estimates by FIT threshold, the analyses suggest that the estimates 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. This parameter was varied in increments of +0.05, up to +0.30 above baseline parameter value to test the impact of underestimation of this parameter (data shown in Supplementary Figures 10 and 11).

The results suggest that for all thresholds, if FIT sensitivity has been underestimated in our baseline analysis, this will result in an underestimation of both the total costs and the total QALYs of screening with FIT (as the sensitivity parameter is increased, the total incremental costs and QALYs increase). At a willingness to pay threshold of £20,000 per QALY gained, the results suggest that FIT will remain cost effective (though no longer dominant) compared with gFOBT, even if the true value of FIT sensitivity has been underestimated by as much as 0.30 for any threshold. At these higher estimates, FIT is still associated with positive net benefit, meaning that the QALY gain with FIT is valued at more than the additional cost.

DISCUSSION

Our model results combined with the results of the BCSP pilot study suggest that FIT is dominant (more effective and less costly) vs. gFOBT in an English setting for a single cohort starting screening at age 60. 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, and constraints in 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 analysis suggested that for a single cohort of 586,097 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 234,248 for the lowest threshold considered (FIT 40µg Hb/g faeces). These results

indicate that care should be taken when selecting an appropriate FIT threshold for the healthcare setting. Further analyses following a distribution of ages through screening would enable an estimation of the true burden of colonoscopy over time and on annual colonoscopy numbers in a steady state for the screened population.

A key strength of this analysis is the availability of data on FIT vs. 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 colorectal cancer screening for this setting.

We performed several sensitivity analyses around key parameters as well as presenting the probabilistic simulation for the base case results. The conclusion arising from the mean base case outcomes, that FIT is 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. 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 50-60% lower than our baseline figures (depending on the FIT threshold). It is possible that other cost assumptions – for example, if CRC management costs depended on factors other than CRC stage at diagnosis, such as age - could result in FIT no longer being cost saving compared to gFOBT. However, even under these scenarios, based on our analysis we consider it unlikely that FIT would not be cost-effective compared to gFOBT, due to the health benefits of the expected reduction in CRC prevalence and morbidity.

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 which should be taken into account when interpreting the results. Regarding the model parameters, the sensitivity and specificity of gFOBT and FIT were not directly observed in the pilot study population, so we estimated the FIT parameters using the model-estimated prevalence of disease and data for FIT relative to the gFOBT from recent pilot study in England [10]. 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 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 FIT pilot were observed to be colonoscopy [19], 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. Screening uptake data by age group were available from the FIT pilot [10] so we used these as a proxy for screening history, using an assumption that the pilot patient group was representative of the population.

We have not attempted to model the effects on our results of bowel scope screening, which the NHS BCSP is in the process of rolling out to all men and women in England aged 55 in addition to the existing screening protocol from the age of 60. Neither have we attempted to model changes to the age-range or screening frequency of the existing BCSP in England.

Finally, we modelled a cohort starting screening at age 60 and continuing until death. Further modelling of the entire screened population in England would be required to take into account multiple cohorts starting FIT screening at different ages, as would be the case if FIT were to be introduced in the place of gFOBT across the screening programme.

Conclusions

This is the first analysis to use FIT screening data in England for an economic analysis of FIT, and as such provides the first cost-effectiveness estimates specific to this setting. Our results suggest that FIT is highly cost-effective compared with gFOBT at all thresholds for a cohort aged 60 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.

TABLES

Table 1: Resource use and costs associated with screening kits in the first screening year (population of age 60 years)

	Resource use			Cost (£)		
	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)
Total number of pre-invites sent in first year (excluding repeat kits)	586,097	586,097	0	-	-	-
Number of people returning kit in first year (normal result)	313,832	366,641	52,809	-	-	-
Number of people returning kit in first year (positive result)	5,571	6,752	1,181	-	-	-
Positivity rate	1.74%	1.81%	0.06%	-	-	-
Number of people not returning kit in first year	266,694	212,704	-53,990	-	-	-
Total number of kits returned (normal result)*	336,426	375,329	38,903	677,436	1,910,613	1,233,177
Total number of kits returned (positive result)*	5,972	6,912	940	12,025	35,183	23,158
Total number of kits sent but not returned*	285,895	217,745	-68,150	235,503	359,999	124,496
Total number of kits used in the first year (total screening cost for cohort)	628,293	599,986	-28,307	924,964	2,305,795	1,380,831
TOTAL SCREENING COSTS in the first year per invited person in screening population at age 60 years	-	-	-	1.58	3.93	2.36

* Includes repeat kits

Table 2: Colonoscopy resource use and adverse events for a population of 586,097 people invited for screening, 40 year time horizon

	Resource use			Cost (£)		
	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)
Follow-up						
Colonoscopies without polypectomy	28,261	30,633	2,372	12,730,164	13,855,967	1,125,802
Colonoscopies with polypectomy for HR adenomas	14,993	20,076	5,082	8,322,554	11,218,664	2,896,110
Colonoscopies with polypectomy for LR adenomas	8,946	8,364	-582	4,948,701	4,644,665	-304,037
Deaths at colonoscopy	0	0	0	138	146	8
Total number of follow-up colonoscopies	52,200	59,073	6,873	26,001,558	29,719,442	3,717,884
Major bleeds requiring hospitalisation	21	24	3	7,528	8,565	1,037
Perforation	33	37	4	65,812	73,208	7,396
Surveillance						
Colonoscopies without polypectomy	10,919	14,664	3,745	4,298,683	5,809,896	1,511,213
Colonoscopies with polypectomy for LR adenomas	6,799	9,125	2,325	10,593,015	14,303,872	3,710,857
Colonoscopies with polypectomy for HR adenomas	21,986	29,500	7,514	3,256,781	4,398,375	1,141,594
Deaths at colonoscopy	0	0	0	69	93	24
Total number of surveillance colonoscopies	39,705	53,289	13,584	18,148,548	24,512,236	6,363,688
Major bleeds requiring hospitalisation	16	21	5	5,269	7,117	1,848
Perforation	19	25	6	34,524	46,642	12,118
TOTAL NUMBER OF COLNOSCOPIES	91,906	112,362	20,457	18,188,342	24,565,996	6,377,654

Table 3: Estimated lifetime costs per person sent an invite for screening at age 60, over 40 year time horizon

	gFOBT (£)	FIT 180µg Hb/g faeces (base case) (£)	FIT 150µg Hb/g faeces (£)	FIT 100µg Hb/g faeces (£)	FIT 40µg Hb/g faeces (£)
Kits returned (normal result)	7.27	19.7	19.64	19.51	19.07
Kits returned (positive result)	0.16	0.44	0.48	0.59	0.97
Kits sent but not returned	2.13	3.36	3.36	3.35	3.34
Total screening costs	**9.56**	**23.49**	**23.48**	**23.46**	**23.38**
Follow-up colonoscopy-related costs*	44.36	50.71	56.26	69.92	116.9
Surveillance colonoscopy-related costs*	30.97	41.82	46.99	61.69	102.7
Cost of colonoscopy-related adverse events	0.07	0.09	0.1	0.14	0.23
Total colonoscopy-related costs	**75.52**	**92.76**	**103.5**	**131.92**	**220.09**
CRC A management (% of CRC management costs)	45.76	43.71	42.91	41.2	36.5
CRC B management (% of CRC management costs)	132.23	124.36	121.12	114.71	96.38
CRC C management (% of CRC management costs)	226.69	211.84	205.62	194.2	160.78
CRC D management (% of CRC management costs)	426.57	395.25	381.94	359.49	292.25
Total CRC management costs	**831.24**	**775.16**	**751.59**	**709.59**	**585.92**
Total costs	**916.32**	**891.41**	**878.57**	**864.97**	**829.39**

CRC: colorectal cancer; * also includes the cost of specialist screening practitioner appointments for those not attending colonoscopy

Table 4: Cost-effectiveness per person invited for screening of FIT vs. gFOBT, by FIT threshold

	Incremental total cost (£), mean (95% CI)	Incremental life years, mean (95% CI)	Incremental QALYs, mean (95% CI)	ICER: incremental cost per QALY gained (£)*, mean (95% CI)	Incremental net benefit (£)*, mean (95% CI)
FIT 180µg Hb/g faeces (base case)	-25 (-42, -9)	0.019 (0.016, 0.023)	0.014 (0.012, 0.017)	FIT dominates -1729 (-2784, -683)	313 (0, 0)
FIT 150µg Hb/g faeces	-38 (-61, -16)	0.028 (0.024, 0.032)	0.021 (0.018, 0.024)	FIT dominates -1803 (-2833, -818)	456 (390, 533)
FIT 100µg Hb/g faeces	-51 (-86, -20)	0.038 (0.033, 0.043)	0.029 (0.026, 0.033)	FIT dominates -1757 (-2875, -704)	636 (547, 729)
FIT 40µg Hb/g faeces	-87 (-155, -25)	0.073 (0.065, 0.082)	0.058 (0.051, 0.064)	FIT dominates -1507 (-2694, -443)	1240 (1071, 1409)

Means are deterministic means; all 95% confidence intervals were calculated from the percentiles of each outcome from 1000 probabilistic model runs; * Incremental Cost-Effectiveness Ratio (ICER) = $\Delta C/\Delta E$, where ΔE and ΔC are the incremental QALYs and incremental costs, respectively, of FIT compared to gFOBT; ** INB= $\lambda.\Delta E - \Delta C$, where λ is the willingness to pay threshold = £20,000 per QALY gained.

AUTHOR CONTRIBUTIONS

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.

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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. The views expressed in the paper are those of the authors alone.

SUPPLEMENTARY INFORMATION

Further information on the model structure and parameters, unit costs, derivation of FIT test sensitivity and specificity, PSA distributions, further results 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 also provided in a supplementary Microsoft Excel file.

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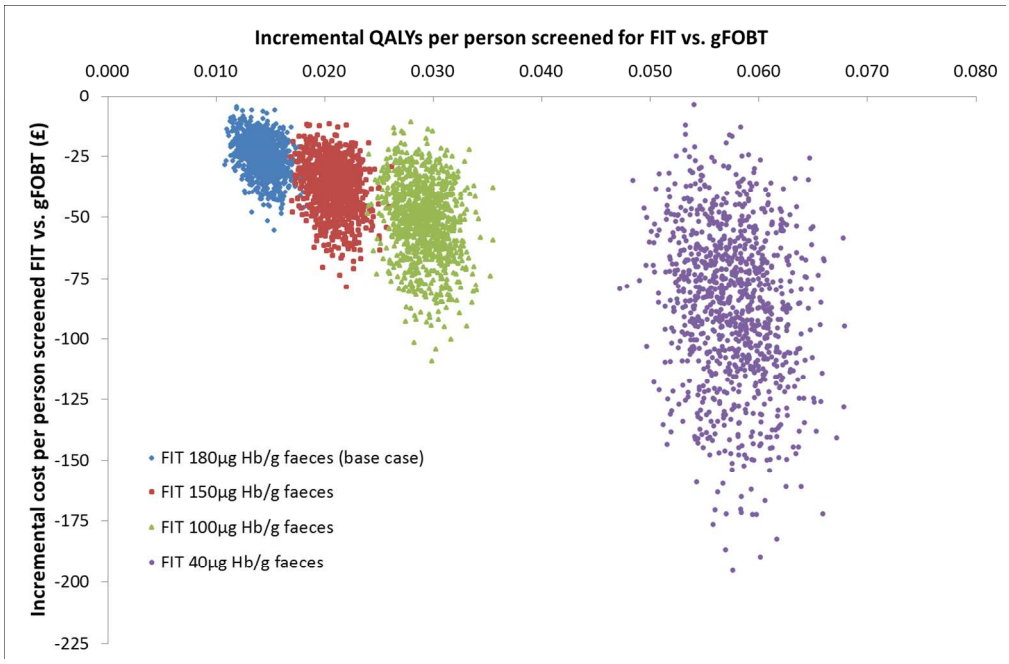

Figure 1: Cost-effectiveness plane illustrating probabilistic sensitivity analysis results for each FIT threshold vs. gFOBT (1000 simulations)

258x168mm (150 x 150 DPI)

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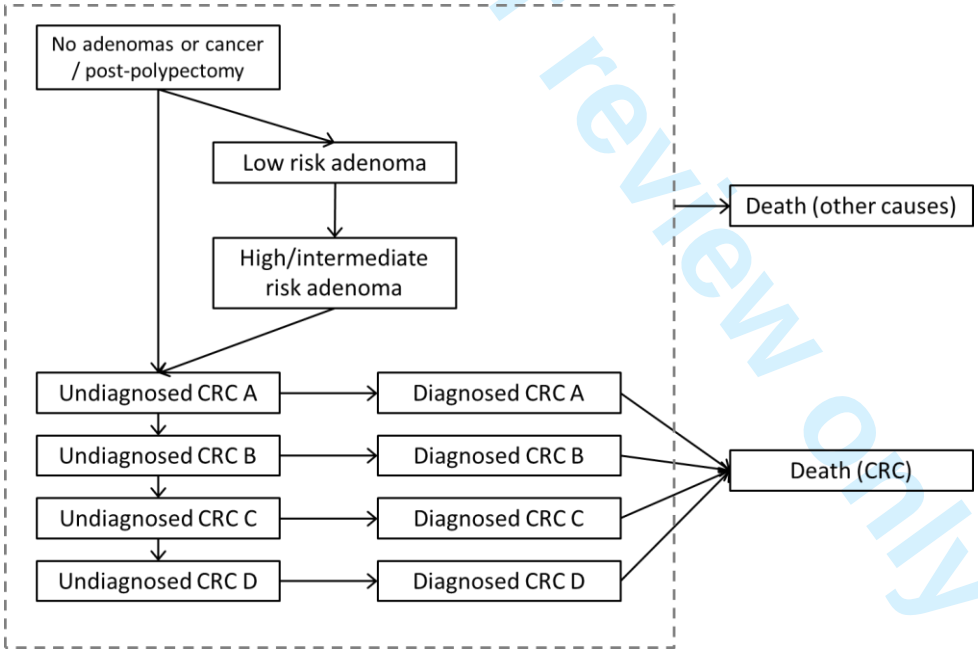
SUPPLEMENTARY INFORMATION

Contents

SECTION 1: MODEL STRUCTURE

The model was constructed using Microsoft Excel® (2010) software. The model structure is based on previously published work for the NHS Bowel Cancer Screening Programme (BCSP) by Whyte et al [1, 2]. Underlying the model is a set of natural history transitions illustrated in Supplementary Figure 1, determining disease progression in a non-screened population. The possible health states are: No adenomas or cancer/no adenomas or cancer post-polypectomy, low risk adenoma (LR), high risk/intermediate risk adenoma (HR/IR), undiagnosed colorectal cancer (CRC) by Dukes' Stage (A,B,C,D), diagnosed colorectal cancer (by Dukes' Stage A,B,C,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 a previously validated model [1, 2] 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 [3], due to the available transition probabilities (see SECTION 2: MODEL PARAMETERS). Transitions between health states occur once in each annual cycle.

Supplementary Figure 1: Diagram of underlying health states and natural history transitions, adapted from [1]

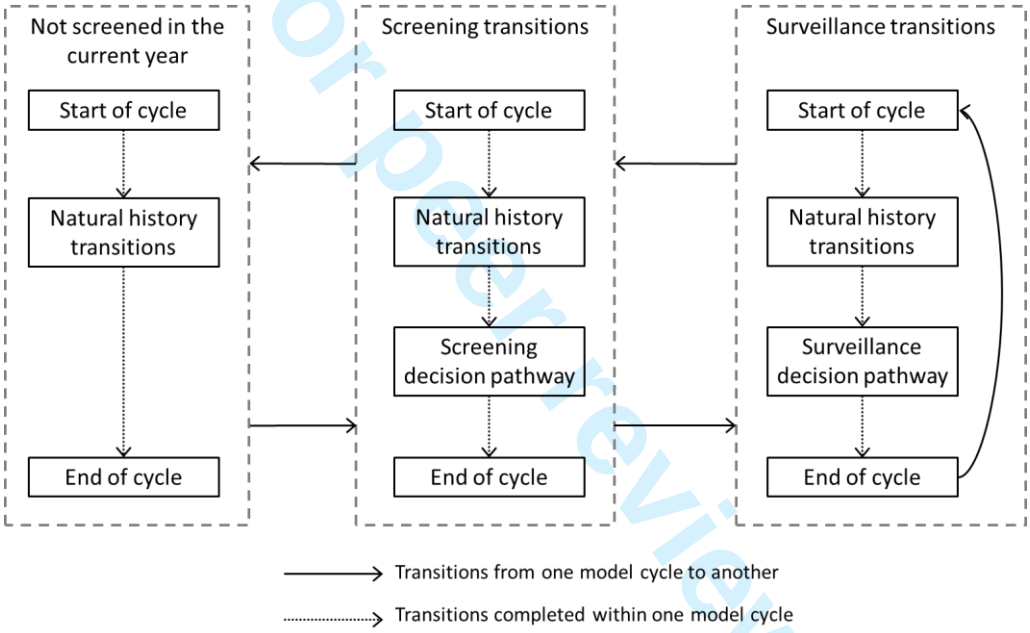


CRC, Colorecal cancer; "CRC A" denotes Dukes' stage A colorectal cancer, and similarly for B,C,D; Death (CRC) denotes death due to colorectal cancer, and similarly for Death (other causes)

To estimate the number of people in the population with polyps and cancers at the start of screening, the model begins with a population at age 30 with no adenomas or cancer. Disease progression without screening is modelled from age 30 to age 60, resulting in a screening eligible population divided between various disease states (simulating the presence of undetected neoplasia), at which stage screening begins.

The screening model is constructed in three parts as illustrated in Supplementary Figure 2: 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. As illustrated in Supplementary Figure 2, subjects in the non-screening component undergo natural history transitions (disease progression). In the screening component, subjects undergo natural history transitions followed by the screening pathway. Subjects who undergo polypectomy at colonoscopy for HR adenomas following screening enter the surveillance component of the model.

Supplementary Figure 2: Overall three part model structure, each lasting for one model cycle (one year)



The modelled surveillance pathways for high risk adenomas are illustrated in Supplementary Figure 3. These align with current guidelines for surveillance after polypectomy for HR adenoma, as updated in 2010 [3]. In the model, the HR/IR adenoma group undergo the same surveillance guidelines; this is a simplifying assumption. Subjects are assumed to undergo a 12-month colonoscopy, followed by a colonoscopy every three years until they have had two consecutive three-yearly procedures with no high risk adenomas detected. At this point we assume that patients re-enter the screening component of the model. Recommendations published in 2010 [3] are that surveillance is stopped at age 75 years. However since people in the model are screened up to age 75 years surveillance transitions are continued until 80 years, so that those with polypectomy for HR adenomas at age 75 also undergo surveillance colonoscopies.

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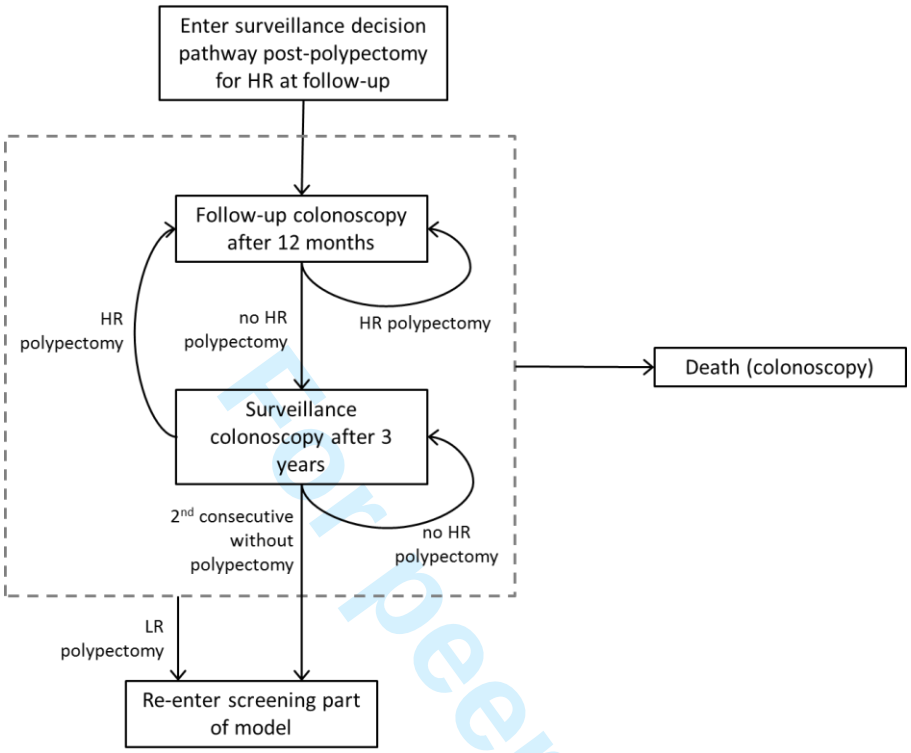
Supplementary Figure 3: Diagram of surveillance decision pathway used in the model



HR: high risk polyp; LR: low risk polyp; "Death (colonoscopy) denotes death due to colonoscopy

SECTION 2: MODEL PARAMETERS

1. Natural history

Transition probabilities between the underlying disease states illustrated in Supplementary Figure 1 were based on a previously validated model for the NHS BCSP, by Whyte et al [1, 2]. These disease progression (or "natural history") parameters are summarised in Supplementary Table 1. Linear interpolation between ages 30, 50, 70 and 100 was used to estimate the age-dependent transition probabilities between Normal, LR, HR/IR, and undiagnosed Dukes' Stage A CRC disease states.

Supplementary Table 1: Disease progression parameters, from [1]

Health state transition model parameter	Transition probability
No adenomas or cancer → LR adenoma age 30	0.021
No adenomas or cancer → LR adenoma age 50	0.020
No adenomas or cancer → LR adenoma age 70	0.045
No adenomas or cancer → LR adenoma age 100	0.011
LR adenoma → HR/IR adenoma age 30	0.009
LR adenoma → HR/IR adenoma age 50	0.008
LR adenoma → HR/IR adenoma age 70	0.008
LR adenoma → HR/IR adenoma age 100	0.004
HR/IR adenoma → undiagnosed Dukes' A CRC age 30	0.029
HR/IR adenoma → undiagnosed Dukes' A CRC age 50	0.025
HR/IR adenoma → undiagnosed Dukes' A CRC age 70	0.054
HR/IR adenoma → undiagnosed Dukes' A CRC age 100	0.115
No adenomas or cancer → undiagnosed Dukes' A CRC	0.000
undiagnosed Dukes' A CRC → undiagnosed Dukes' B CRC	0.508
undiagnosed Dukes' B CRC → undiagnosed Dukes' C CRC	0.692
undiagnosed Dukes' C CRC → undiagnosed Dukes' D CRC	0.708
Symptomatic presentation with Dukes' A CRC (undiagnosed → diagnosed A)	0.044
Symptomatic presentation with Dukes' B CRC (undiagnosed → diagnosed B)	0.176
Symptomatic presentation with Dukes' C CRC (undiagnosed → diagnosed C)	0.369
Symptomatic presentation with Dukes' D CRC (undiagnosed → diagnosed D)	0.735
LR post-polypectomy to LR	0.100
LR post-polypectomy to HR/IR	0.040
Post-polypectomy to LR	0.188
Post-polypectomy to HR/IR	0.568

("1→2" denotes transition from state 1 to state 2); LR: low risk; HR: high risk; IR, intermediate risk; CRC: colorectal cancer; all variables presented by age were converted to piecewise linear distributions for use in the model

2. Screening test characteristics

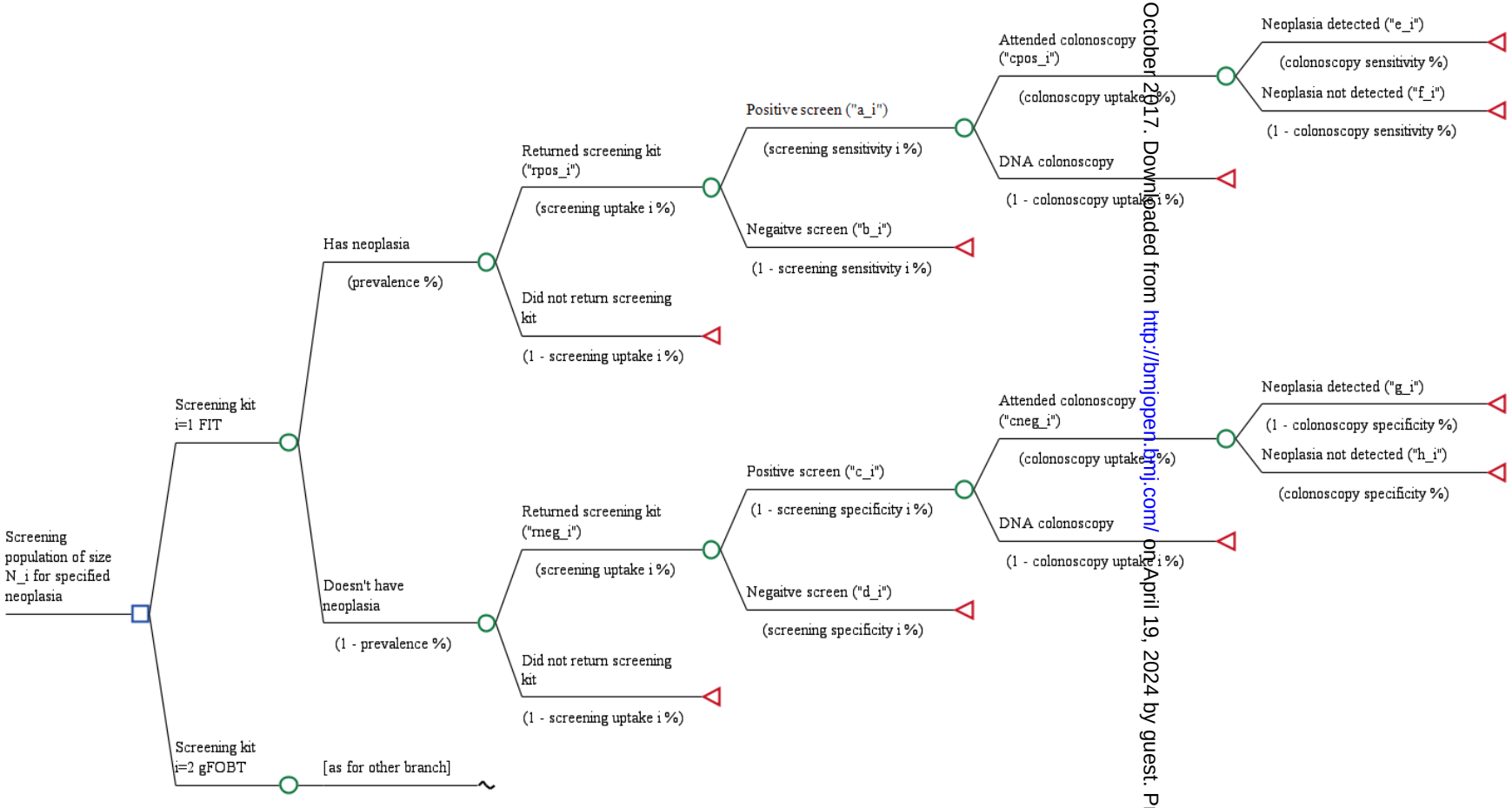
In line with the NHS BCSP pilot study of FIT vs, gFOBT screening, the model is based on FIT using the OC-SENSOR system with DIANA analyser (Eiken Chemical, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using hema-screen (Immunostics, New Jersey, USA, supplied by Alpha Laboratories, Eastleigh UK). More information on the screening kits is available elsewhere [4].

We estimated FIT sensitivity and specificity relative to gFOBT using the detection rates from the FIT pilot study and model-estimated prevalence from non-screening disease progression transitions in the model. The assumptions regarding sensitivity and specificity of kits is given in Supplementary Table 7.

Equations for relative sensitivity and specificity of screening kits

Here we show the assumptions around the calculation of FIT sensitivity and specificity, relative to the gFOBT sensitivity and specificity (see Supplementary Table 7). Supplementary Figure 4, plotted using TreeAge software [5], illustrates the screening and diagnostic test pathway for specified neoplasia (colorectal cancer, low risk, or high risk/intermediate risk adenomas) for a given population. The letter *i* denotes the screening kit (i.e. FIT or gFOBT), and we assume that prevalence of neoplasia, and uptake, sensitivity, and specificity of colonoscopy do not depend on which screening kit is used. All other proportions in the decision tree are different for each screening kit.

Supplementary Figure 4: Illustration of the colorectal cancer screening pathway for specified neoplasia (CRC, LR adenomas, HR adenomas) using screening kit i



Further to the definitions illustrated in Supplementary Figure 4 (a_i to h_i, $rpos_i$, $rneg_i$, $cpos_i$ and $cneg_i$), we define the total number of people screened (i.e. those returning kits) $S_i = rpos_i + rneg_i$, and the total number with a positive screening result $P_i = a_i + c_i$. We also define the total number of people attending colonoscopy $C_i = cpos_i + cneg_i$; and the total number of people with neoplasia detected at colonoscopy $D_i = e_i + g_i$. N_i denotes the number of people invited for screening using kit *i*. Supplementary Table 2 shows the screening outcomes for screening kit *i* using the definitions above.

Supplementary Table 2: Screening outcomes for screening kit i

	Screened positive for the disease	Screened negative for the disease	TOTAL
Has the disease	a_i	b_i	$rpos_i$
Does not have the disease	c_i	d_i	$rneg_i$
TOTAL	P_i	$(b_i + d_i)$	S_i

Calculating relative sensitivity of FIT vs. gFOBT

The sensitivity of a test *i* is defined as

$$sens_i = \frac{true\_positives}{total\_screening\_positive} = \frac{a_i}{a_i + b_i}$$

Then the ratio of FIT vs. gFOBT sensitivity is

$$\frac{sens_{FIT}}{sens_{gFOBT}} = \frac{a_{FIT}}{a_{FIT} + b_{FIT}} \cdot \frac{a_{gFOBT} + b_{gFOBT}}{a_{gFOBT}}$$

Using the decision tree in Supplementary Figure 4, we can see that

$$e_i = a_i \cdot (colonoscopy\_uptake)_i \cdot (colonoscopy\_sensitivity)_i$$

and $$a_i + b_i = N_i \cdot (prevalence)_i \cdot (screening\_uptake)_i$$

Substituting these into the ratio and cancelling out $prevalence$ of neoplasia which appears in both numerator and denominator, we have

$$\frac{sens_{FIT}}{sens_{gFOBT}} = \frac{e_{FIT}}{e_{gFOBT}} \cdot \frac{col\_uptake_{gFOBT} \cdot col\_sens_{gFOBT}}{col\_uptake_{FIT} \cdot col\_sens_{FIT}} \cdot \frac{N_{gFOBT} \cdot screening\_uptake_{gFOBT}}{N_{FIT} \cdot screening\_uptake_{FIT}}$$

Assuming that the sensitivity of colonoscopy is a fixed diagnostic test characteristic,

$$col\_sens_{gFOBT} = col\_sens_{FIT}$$

Therefore

$$\frac{sens_{FIT}}{sens_{gFOBT}} = \frac{e_{FIT}}{e_{gFOBT}} \cdot \frac{col\_uptake_{gFOBT}}{col\_uptake_{FIT}} \cdot \frac{N_{gFOBT} \cdot screening\_uptake_{gFOBT}}{N_{FIT} \cdot screening\_uptake_{FIT}}$$

We assume that the specificity of colonoscopy is zero (no false positives), so that $g_i = 0$ and therefore $D_i = e_i$. Using the definitions of C_i, S_i and P_i above, we have

$$\frac{sens_{FIT}}{sens_{gFOBT}} = \frac{D_{FIT}}{D_{gFOBT}} \left(\cdot \frac{C_{gFOTB}}{P_{gFOBT}} \cdot \frac{P_{FIT}}{C_{FIT}} \right) \cdot \left(\frac{N_{gFOBT}}{N_{FIT}} \right) \cdot \left(\frac{S_{gFOBT}}{N_{gFOBT}} \cdot \frac{N_{FIT}}{S_{FIT}} \right)$$

$$\frac{sens_{FIT}}{sens_{gFOBT}} = \frac{D_{FIT} P_{FIT}}{S_{FIT} C_{FIT}} \div \frac{D_{gFOBT} C_{gFOBT}}{S_{gFOBT} P_{gFOBT}} \quad (1)$$

In this study we have data on D_i (the total number of people with neoplasia detected at colonoscopy), C_i (the total number of people attending colonoscopy), S_i (the total number of people screened (returning kits), and P_i (the total number with a positive screening result).

To illustrate the use of this equation in the model, we take the example of the sensitivity of FIT screening to detect CRC in the base case (FIT 180µg Hb/g faeces). The parameter values are taken from the pilot of FIT vs. gFOBT [4], presented in Supplementary Table 3 and Supplementary Table 4.

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Supplementary Table 3: Screening test data by age-group from the FIT pilot study: source Moss et al [4, 5]

	gFOBT	FIT 180µg Hb/g faeces (base case)	FIT 150µg Hb/g faeces	FIT 100µg Hb/g faeces	FIT 40µg Hb/g faeces
Age 59-64*					
Returned kit	258,875	11,105	11,105	11,105	11,105
Screened positive	4285	152	176	234	505
Positivity rate	1.66%	1.37%	1.58%	2.11%	4.55%
Attended colonoscopy	3665	126	148	197	434
All neoplasia (HR/IR/LR cancer)	1825	78	90	122	247
Normal	743	17	19	24	71
Age 65-69					
Returned kit	248,021	9,668	9,668	9,668	9,668
Screened positive	4064	143	171	240	503
Positivity rate	1.64%	1.48%	1.77%	2.48%	5.20%
Attended colonoscopy	3459	120	146	205	440
All neoplasia (HR/IR/LR cancer)	1782	79	97	137	276
Normal	591	9	11	17	51
Age 70-75**					
Returned kit	161,049	6,394	6,394	6,394	6,394
Screened positive	3226	117	136	182	408
Positivity rate	2.00%	1.83%	2.13%	2.85%	6.38%
Attended colonoscopy	2711	93	106	145	328
All neoplasia (HR/IR/LR cancer)	1488	58	67	92	191
Normal	388	15	15	19	44
All ages (age 59-75)					
Returned kit	667,945	27,167	27,167	27,167	27,167
Screened positive	11,575	412	483	656	1,416
Positivity rate	1.73%	1.52%	1.78%	2.41%	5.21%
Attended colonoscopy	9835	339	400	546	1,202
Tested +ve for LR	1913	63	81	124	298
Tested +ve for HR/IR	2364	116	133	183	351
Tested +ve for Cancer	818	36	40	44	65
All neoplasia (HR/IR/LR cancer)	5095	215	254	351	714
Normal	1722	41	45	60	166

Source: Moss et al [6]. *results for the 59-64 age group were used for the 60-64 age group in the model as a small number of people were invited before their 60th birthday in the pilot and so are included in this age group; **results for the 70-75 age group were used for the 70-74 age group in the model

Supplementary Table 4: Variables for calculation of FIT 180µg Hb/g faeces (base case) sensitivity to detect CRC

Variable	Variable name	gFOBT	FIT180µg Hb/g faeces (base case)
C_i	Number attending colonoscopy	9835	339
P_i	Number screening positive	11575	412
S_i	Number returning kit (all ages)	667945	27167
D_i	Number with CRC detected at colonoscopy	818	36

The sensitivity of gFOBT to detect CRC is assumed to be 0.242 (Supplementary Table 7). Using equation (1) above the sensitivity of FIT 180µg Hb/g faeces to detect CRC is

$$sens_{FIT} = sens_{gFOBT} \cdot \left(\frac{36 \times 412}{27167 \times 339} \right) \div \left(\frac{818 \times 11575}{667945 \times 9835} \right) = 0.242 \times 1.11738 = 0.270$$

Supplementary Table 7 shows the final sensitivity parameters used in the model for CRC, LR and HR adenomas for all FIT thresholds.

Calculating relative specificity of FIT vs. gFOBT

In our model we allow for the assumption that specificity varies by age. We can think of specificity as the probability of correctly identifying those without the condition, for a particular age group. Here we will calculate the specificity of FIT and gFOBT for those aged 50 and aged 70.

A rate over a time period t can be expressed in terms of a probability [7] as

$$rate = \frac{-\ln(1 - probability)}{t} \qquad (2)$$

The specificity of a test *i* for any neoplasia, expressed in terms of a rate for a period of t=1 years is:

$$rate_{spec,i} = \frac{-\ln(1 - spec_i)}{t}$$
$$= -\ln\left(1 - \frac{d_i}{c_i + d_i}\right)$$

Using the decision tree in Supplementary Figure 4, and recalling the definition of S_i as the total number screened (i.e. returning a screening kits), the $prevalence$ of any neoplasia in the population, and $sens_i$ the sensitivity of test *i*, we have

$$d_i = S_i - (a_i + c_i) - b_i \quad \text{and} \quad b_i = S_i \cdot prevalence \cdot (1 - sens_i) \qquad (3)\ (4)$$

Under the simplifying assumption that the prevalence of disease is the same in the screened population, S_i, as in the general population, we have

$$c_i + d_i = S_i \cdot (1 - prev) \qquad (5)$$

Substituting (3) (4) and (5) into the rate equation, and recalling the definition of P_i as the total number with a positive screening result, the specificity of a test *i* at a particular 1-year age group expressed in terms of a rate is

$$rate_{spec,i} = -\ln\left(1 - \frac{S_i - P_i - S_i \cdot prevalence \cdot (1 - sens_i)}{S_i \cdot (1 - prevalence)}\right) \quad (6)$$

The steps of the calculation are as follows:

1. Convert gFOBT specificity estimates (shown in Supplementary Table 3) using equation (2) to specificity rates at age 50 and 70 years

The parameters required for the model are specificity of gFOBT and FIT at age 50 and 70 years. Data were not available from the FIT pilot at age 50 years, so we first performed linear interpolation from the gFOBT estimates from Whyte et al [1] at age 50 and 70, to get estimates for gFOBT at age 62,67 and 72 representing the midpoints of the age categories 60-64, 65-69, and 70-74 to match the pilot data.

2. linear interpolation to obtain gFOBT specificity rates for midpoints of the age bands available in the FIT pilot (age 62,67,and 72 years)
3. Apply ratio of FIT to gFOBT (equation (6)) using the FIT pilot data to obtain specificity rates for FIT at the midpoint of each age group in the pilot data (age 62,67,and 72 years)
4. Use linear extrapolation and interpolation to obtain gFOBT specificity rate at age 50 and 70 years, as required for the model parameters
5. Convert FIT specificity rates into probabilities by rearranging equation (2) to obtain FIT specificity rates at age 50 and 70 years for use in the model.

An example of the calculations made in these steps is given below.

We take the example of the specificity of FIT for any neoplasia at the base case threshold (FIT 180µg Hb/g faeces). The calculation steps and values are shown in Supplementary Table 5, using screening test characteristics from the pilot (Supplementary Table 3) and prevalence of neoplasia as estimated in the model (Supplementary Table 6).

Supplementary Table 5: Illustrative steps of calculation for FIT base case

Process step	**-**	**1**	**2**	**3**	**4**	**5**
Age	**gFOBT specificity [1]**	**Convert from probabilities to rates**	**Linear inter/ extra-polation of gFOBT values**	**Calculate FIT rates using ratio**	**Linear regression of FIT values**	**Convert FIT values from rates to probabilities**
Test	**gFOBT**	**gFOBT**	**gFOBT**	**FIT**	**FIT**	**FIT**
50	0.994	5.116	5.116	-	5.158	0.994
62	-	-	4.214	4.253	-	-
67	-	-	3.838	3.867	-	-
70	0.973	3.612	3.612	-	3.645	0.974
72	-	-	3.462	3.496	-	-

Supplementary Table 6: Estimated prevalence of disease from the natural history (non-screening) model, summed within each age-group

Age-group	LR	HR/IR	CRC	Any neoplasia
60-64	46.59%	4.66%	0.67%	51.92%
65-69	53.46%	5.54%	0.98%	59.98%
70-74	59.90%	6.30%	1.33%	67.53%
All ages	52.99%	5.46%	0.98%	59.43%

A summary of the final model parameters for sensitivity and specificity of screening kits is shown in Supplementary Table 7.

Supplementary Table 7: Sensitivity and specificity of screening kits - model parameters

	gFOBT*	FIT 180µg Hb/g faeces (base case)	FIT 150µg Hb/g faeces	FIT 100µg Hb/g faeces	FIT 40µg Hb/g faeces
Sensitivity - LR	0.009	0.008	0.01	0.015	0.035
Sensitivity - HR/IR	0.124	0.154	0.176	0.241	0.453
Sensitivity - CRC	0.242	0.270	0.299	0.327	0.473
Specificity age 50	0.994	0.994	0.994	0.994	0.995
Specificity age 70	0.973	0.974	0.974	0.974	0.972

*gFOBT parameters were taken from the calibrated parameters in the previous NHS BCSP economic evaluation [1]; FIT parameters were estimated relative to the calibrated gFOBT parameters using data from the FIT pilot study [4].

3. Cancer-related mortality

Cancer-related mortality by stage at diagnosis was estimated from 5-year survival statistics for England [8]. The available survival data for the first 5 years after diagnosis were extrapolated to the maximum time horizon using a Weibull parametric model, fitted using Microsoft Excel® (data shown in Supplementary Figure 5 and Supplementary Table 8).

Murphy J, Halloran S, Gray A. "Cost-effectiveness of the faecal immunochemical test at various positivity thresholds compared with the guaiac faecal occult blood test in England."

Supplementary Figure 5: Weibull extrapolation of 5-year CRC survival data (shown up to 35 years from diagnosis)

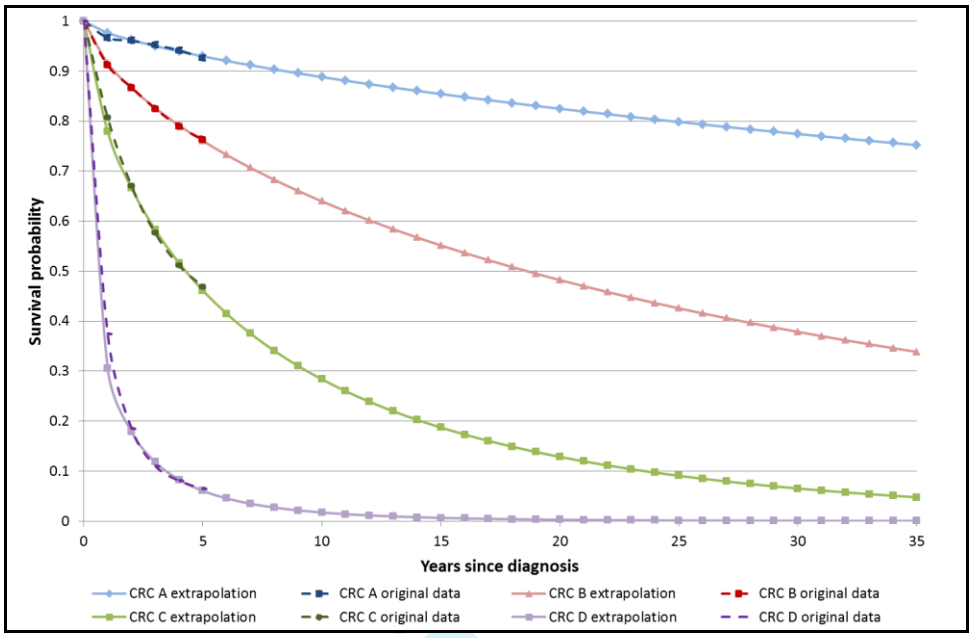


Figure note: CRC A original data: 5-years survival estimates from [8]; CRC A extrapolation: Weibull fit to 5-year estimates extrapolated to a greater number of years since diagnosis than original data

Supplementary Table 8: Fitted survival by CRC stage at diagnosis using Weibull extrapolation of 5-year CRC survival data from [12]

Years since diagnosis	CRC A	CRC B	CRC C	CRC D
0	1	1	1	1
1	0.977	0.916	0.779	0.305
2	0.962	0.866	0.666	0.179
3	0.950	0.826	0.583	0.118
4	0.939	0.791	0.516	0.083
5	0.930	0.760	0.461	0.061
6	0.920	0.732	0.415	0.045
7	0.912	0.707	0.375	0.035
8	0.904	0.683	0.341	0.027
9	0.896	0.660	0.310	0.021
10	0.888	0.640	0.284	0.017
11	0.881	0.620	0.260	0.014
12	0.874	0.601	0.239	0.011
13	0.867	0.584	0.220	0.009
14	0.861	0.567	0.203	0.008
15	0.854	0.551	0.187	0.006
16	0.848	0.536	0.173	0.005
17	0.842	0.522	0.160	0.005
18	0.836	0.508	0.149	0.004
19	0.830	0.495	0.138	0.003
20	0.825	0.482	0.128	0.003
21	0.819	0.470	0.120	0.002
22	0.814	0.458	0.111	0.002
23	0.809	0.447	0.104	0.002
24	0.803	0.436	0.097	0.002
25	0.798	0.426	0.091	0.001
26	0.793	0.416	0.085	0.001
27	0.789	0.406	0.079	0.001
28	0.784	0.396	0.074	0.001
29	0.779	0.387	0.070	0.001
30	0.774	0.379	0.065	0.001
31	0.770	0.370	0.061	0.001
32	0.765	0.362	0.057	0.001
33	0.761	0.354	0.054	0.000
34	0.756	0.346	0.051	0.000
35	0.752	0.338	0.048	0.000
36	0.748	0.331	0.045	0.000
37	0.744	0.324	0.042	0.000
38	0.739	0.317	0.040	0.000
39	0.735	0.311	0.038	0.000
40	0.731	0.304	0.035	0.000
41	0.727	0.298	0.033	0.000
42	0.723	0.292	0.031	0.000
43	0.720	0.286	0.030	0.000
44	0.716	0.280	0.028	0.000
45	0.712	0.274	0.027	0.000
46	0.708	0.269	0.025	0.000
47	0.705	0.263	0.024	0.000
48	0.701	0.258	0.022	0.000
49	0.697	0.253	0.021	0.000
50	0.694	0.248	0.020	0.000
51	0.690	0.243	0.019	0.000
52	0.687	0.239	0.018	0.000
53	0.683	0.234	0.017	0.000
54	0.680	0.230	0.016	0.000
55	0.676	0.225	0.015	0.000
56	0.673	0.221	0.014	0.000
57	0.670	0.217	0.014	0.000
58	0.666	0.213	0.013	0.000
59	0.663	0.209	0.012	0.000
60	0.660	0.205	0.012	0.000
61	0.657	0.201	0.011	0.000
62	0.654	0.197	0.011	0.000
63	0.651	0.194	0.010	0.000
64	0.647	0.190	0.010	0.000
65	0.644	0.187	0.009	0.000
66	0.641	0.183	0.009	0.000
67	0.638	0.180	0.008	0.000
68	0.635	0.177	0.008	0.000
69	0.632	0.174	0.007	0.000
70	0.629	0.171	0.007	0.000
71	0.627	0.168	0.007	0.000

CRC, colorectal cancer

4. Quality of life

Due to a lack of CRC-specific values in the literature we used utility weights for health states with and without any cancer from Ara et al [9]. The mean age for respondents for this health state was 60.9 years, which corresponds well to the age at which screening is started in the BCSP. These values are given in Supplementary Table 9.

Supplementary Table 9: Utility values

Disease state	Mean utility value (SD*)	Source
Cancer health states	0.697 (0.020)	[9]
Cancer-free health states	0.795 (0.021)	[9]

Data are for a sample group of 820 with and 560 without any cancer, with a mean age 60.9 years [9]; * estimated using reported confidence intervals;

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 one year.

5. Unit costs

The unit costs of screening kits (gFOBT and FIT) were taken from a previous costing study at the NHS Bowel BCSP Southern Hub in Guildford [10] and inflated to the 2013/14 cost year using the Health Service Cost Index. Details of these unit costs are shown in Supplementary Table 10.

Supplementary Table 10: Details of cost per screening kit [10], inflated from 2012/13 to 2013/14

Cost item	gFOBT(£, 2013/14)	FIT(£, 2013/14)
Equipment (Post room)		
gFOBT test kit printer	0.02	0.00
Equipment (Laboratory)		
Analyser and Device cost (manufacturer's quoted price per kit)	0.43	2.72
Guillotine	0.00	-
Equipment maintenance cost	0.01	0.01
Test tube racks	-	0.00
Refrigerator for FIT kits and reagents	-	0.00
Postage and Packaging		
Initial kits price per pack (Outsource mail company)	0.08	0.10
Outgoing Postage costs	0.27	0.63
Return kits postage costs (1st class)	0.44	0.50
Outgoing postage from additional kits required (gFOBT 11% FIT 2%)	0.37	0.63
Additional printing costs (pre-printed headed paper/Labels)	0.01	0.28
Instruction leaflets	0.01	-
Pre-printed envelopes (Outsourced Mail)	0.02	-
Pre-printed envelopes (Internal Mail)	0.03	-
Staff Cost (Post room)	0.01	0.01
Staff Cost (Lab)	0.31	0.19
Waste Disposal	0.00	0.00
TOTAL COST PER KIT	**2.01**	**5.09**

Supplementary Table 11 summarises the costs used in the model. Screening and colonoscopy costs were taken from national NHS 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 colorectal cancer management were taken from a model-based evaluation of colorectal cancer services by Pilgrim et al [11]. No cost was assigned to death. All costs were inflated to 2013/14 using the Health Service Cost Index.

Supplementary Table 11: Cost assumptions

Parameter	Value (£, cost year 2013/14)	Source
Screening kits		
Cost of gFOBT screen (non-compliers)	0.82	[10]
Cost of gFOBT screen (returned kit)	2.01	[10]
Cost of FIT screen (non-compliers)	1.65	[10]
Cost of FIT screen (returned kit)	5.09	[10]
Hospital services		
Appointment with Specialist Screening Practitioner	31.50	[12, 13] Mean salary band 6, 45 minute appointment duration
Colonoscopy without polypectomy	545	[14] Day Case (diagnostic)
Colonoscopy with polypectomy	590	[14] Day Case (therapeutic)
Cost of admittance for bleeding (overnight stay on medical ward)	461	[14] Weighted average of all Non-elective inpatient, short stay gastrointestinal bleed groups (FZ38G,H,J,K,L,M,N,P)
Cost of perforation (major surgery)	2,546	[14] Weighted average of all Non-elective inpatient, long stay Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+
Pathology cost for adenoma	80	Standard per-patient lab charge in one centre for routine colonic polyps. Incorporates consultant time for processing, reporting, quality control, audit. (personal communication)
Pathology cost for cancer	80	Standard per-patient lab charge in one centre for routine colonic polyps. Incorporates consultant time for processing, reporting, quality control, audit. (personal communication)
Cancer management		
Lifetime cost - screen-detected Dukes' Stage A	13,469	[1, 11]
Lifetime cost - screen-detected Dukes' Stage B	18,532	[1, 11]
Lifetime cost - screen-detected Dukes' Stage C	25,416	[1, 11]
Lifetime cost - screen-detected Dukes' Stage D	27,796	[1, 11]

6. Incorporating uncertainty around model parameters

The calibrated disease progression parameters shown in Supplementary Table 1 and screening test characteristics shown in Supplementary Table 7 were varied probabilistically using multivariate normal distributions via Cholesky decomposition, following the methods described in Briggs et al [15]. The correlation/covariance matrices for each FIT threshold were estimated in R software [16] due to rounding in the original reported matrix from Whyte et al [1] are provided in a supplementary Microsoft Excel file.

The distributions for the other parameters were estimated following the methods described in Briggs et al [15] and using reported measures of uncertainty, and are shown in Supplementary Table 12.

Supplementary Table 12: Screening and cost parameters and distributions

Parameter	Parameter value	Source	PSA distribution
gFOBT – uptake of those sent a pre-invite			
age 60-64	54.50%	[6]	Beta (258875, 216155)
age 65-69	63.64%	[6]	Beta (248021, 141691)
age 70-74	61.62%	[6]	Beta (161049, 100296)
gFOBT – average number of kits required	1.072	[6]	Gamma (10608382, 0.00)
gFOBT – sensitivity			
LR	0.009	[1]	Cholesky decomposition using correlation matrices
HR/IR	0.124	[1]	Cholesky decomposition using correlation matrices
CRC	0.242	[1]	Cholesky decomposition using correlation matrices
gFOBT specificity			
age 50	0.994	[1]	Cholesky decomposition using correlation matrices
age 70	0.973	[1]	Cholesky decomposition using correlation matrices
FIT – uptake of those sent a pre-invitation letter			
age 60-64	63.71%	[6]	Beta (11105, 6326)
age 65-69	68.88%	[6]	Beta (9668, 4368)
age 70-74	67.57%	[6]	Beta (6394, 3069)
FIT – average number of kits required	1.022	[6]	Gamma (1596858, 0.00)
FIT - sensitivity	see Supplementary Table 7	estimated as in Section3.2 [1, 6]	Cholesky decomposition using correlation matrices
FIT – specificity (at age 50/70)	see Supplementary Table 7	estimated as in Section3.2 [1, 6]	Cholesky decomposition using correlation matrices
Colonoscopy uptake after positive test	86.2%	Southern hub data [17] The proportion of those with a positive test who attended colonoscopy.	Beta (24357, 3901)
Non-attendance after specialist screening practitioner appointment	9.1%	Southern hub data [17]	Beta (2424, 24357)
Sensitivity of colonoscopy for LR adenomas	0.765	[18]	Beta (544, 167)
Sensitivity of colonoscopy for HR adenomas	0.979	[18]	Beta (94, 2)
Sensitivity of colonoscopy for CRC	0.966	[18]	Beta (12057, 430)
Specificity of colonoscopy	1	Assumption	N/A
Colonoscopy perforation rate (without polypectomy)	0.031%	[19]	Beta (19, 61784)
Colonoscopy perforation rate (with polypectomy)	0.091%	[19]	Beta (63, 68965)
Proportion of colonoscopies resulting in hospitalisation for bleeding (transfusion)	0.04%	[19]	Beta (52, 180779)
Proportion of perforations resulting in death	0.85%	NHS BCSP data* [20]	Beta (1, 116)
Proportion of colonoscopies requiring a repeat procedure	9.56%	[6]	Beta (1075, 10182)

*There were 147 recorded perforations between August 2006 and March 2014 of which 117 had complete outcome data, including 1 observed death.

Supplementary Table 12 (contd.): Model parameters and distributions

Parameter	Cost £ (2013/14)	Source	PSA distribution
Cost of screening kits			
Cost of gFOBT screen (non-compliers)	0.82	[10]	Uniform over +/- 10% (£0.74 to £0.91)
Cost of gFOBT screen (returned kit)	2.01	[10]	Uniform over +/- 10% (£1.81 to £2.21)
Cost of FIT screen (non-compliers)	1.65	[10]	Uniform over +/- 10% (£1.49 to £1.82)
Cost of FIT screen (returned kit)	5.09	[10]	Uniform over +/- 10% (£4.58 to £5.60)
Cost of hospital services			
Appointment with Specialist Screening Practitioner	31.50	[12, 13] Mean salary band 6, 45 minute appointment duration assumed	Uniform over +/- 10% (£28.35 to £34.65)
Colonoscopy without polypectomy	545	[14] Day Case (diagnostic)	N/A
Colonoscopy with polypectomy	590	[14] Day Case (therapeutic)	N/A
Cost of admittance for bleeding (overnight stay on medical ward)	461	[14] Weighted average of all Non-elective inpatient, short stay gastrointestinal bleed groups (FZ38G,H,J,K,L,M,N,P)	N/A
Cost of perforation (major surgery)	2,546	[14] Weighted average of all Non-elective inpatient, long stay Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+	N/A
Pathology cost for adenoma	80	Standard per-patient lab charge for routine colonic polyps. Incorporates consultant time for processing, reporting, quality, audit. [12]	Uniform over +/- 10% (£72 to £88)
Pathology cost for cancer	80	Standard per-patient lab charge for routine colonic polyps. Incorporates consultant time for processing, reporting, quality, audit. [12]	Uniform over +/- 10% (£72 to £88)
Cost of cancer management			
Lifetime cost - screen-detected Dukes' stage A	13,469	[11]	Gamma (25, 539) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage B	18,532	[11]	Gamma (25, 741) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage C	25,416	[11]	Gamma (25, 1017) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage D	27,796	[11]	Gamma (25, 1112) 20% SE assumed
Utility values			
CRC health states	0.697 (0.020*)	[9] appendices	Beta(361.73,157.25)
Cancer free health states	0.798 (0.021*)	[9] appendices	Beta(279.34,70.71)

SECTION 3: FURTHER DETAIL ON MODEL RESULTS

Supplementary Table 13 shows detailed model results for the screening resource use and costs for gFOBT and at each FIT threshold, for the first year of the model.

Supplementary Table 13: Screening resource use for a population of 586,097 people invited for screening in first year of the model

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Total number of pre-invites sent in first year (excluding repeat kits)	586,097	-	586,097	-	586,097	-	586,097	-	586,097	-
Number of people returning kit in first year (normal result)	313,832	-	366,641	-	365,864	-	363,868	-	356,593	-
Number of people returning kit in first year (positive result)	5,571	-	6,752	-	7,529	-	9,524	-	16,800	-
Positivity rate	1.74%	-	1.81%	-	2.02%	-	2.55%	-	4.50%	-
Number of people not returning kit in first year	266,694	-	212,704	-	212,704	-	212,704	-	212,704	-
Total number of kits returned (normal result) in first year*	336,426	677,436	375,329	1,910,613	374,534	1,906,565	372,471	1,896,164	365,043	1,858,252
Total number of kits returned (positive result) in first year*	5,972	12,025	6,912	35,183	7,707	39,232	9,750	49,632	17,198	87,545
Total number of kits sent but not returned*	285,895	235,503	217,745	359,999	217,745	359,999	217,745	359,999	217,745	359,999
Total number of kits used in first year*	628,293	924,964	599,986	2,305,795	599,986	2,305,795	599,986	2,305,795	599,986	2,305,795
TOTAL SCREENING COSTS per invited person in screening population at age 60 years	-	1.58	-	3.93	-	3.93	-	3.93	-	3.93

* Includes repeat kits

Supplementary Table 14 shows detailed model results for the screening resource use and costs for gFOBT and at each FIT threshold, over the 40 year time horizon of the model.

Supplementary Table 14: Screening resource use and costs for a population of 586,097 people invited for screening over 40 year time horizon

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Total number of pre-invites sent (excluding repeat kits)	4,260,726	-	4,256,605	-	4,254,560	-	4,249,442	-	4,235,115	-
Number of people returning kits (normal result)	2,469,398	-	2,761,297	-	2,753,525	-	2,734,604	-	2,671,306	-
Number of people returning kits (positive result)	55,282	-	62,560	-	68,969	-	84,482	-	138,269	-
Positivity rate	2.19%	-	2.22%	-	2.44%	-	3.00%	-	4.92%	-
Number of people not returning kit in first year	1,736,046	-	1,432,748	-	1,432,067	-	1,430,356	-	1,425,541	-
Total number of kits returned (normal result)*	2,647,182	4,258,981	2,826,731	11,545,539	2,818,774	11,513,681	2,799,405	11,435,735	2,734,607	11,173,950
Total number of kits returned (positive result)*	59,262	93,306	64,042	256,285	70,603	282,771	86,484	347,189	141,545	570,691
Total number of kits sent but not returned*	1,861,033	1,248,797	1,466,699	1,967,593	1,466,002	1,966,714	1,464,250	1,964,487	1,459,321	1,958,134
Total number of kits used*	4,567,476	5,601,084	4,357,472	13,769,417	4,355,379	13,763,165	4,330,140	13,747,412	4,335,473	13,702,774
TOTAL SCREENING COSTS per invited person in screening population at age 60 years	-	9.56	-	23.49	-	23.48	-	23.46	-	23.38

* Includes repeat kits

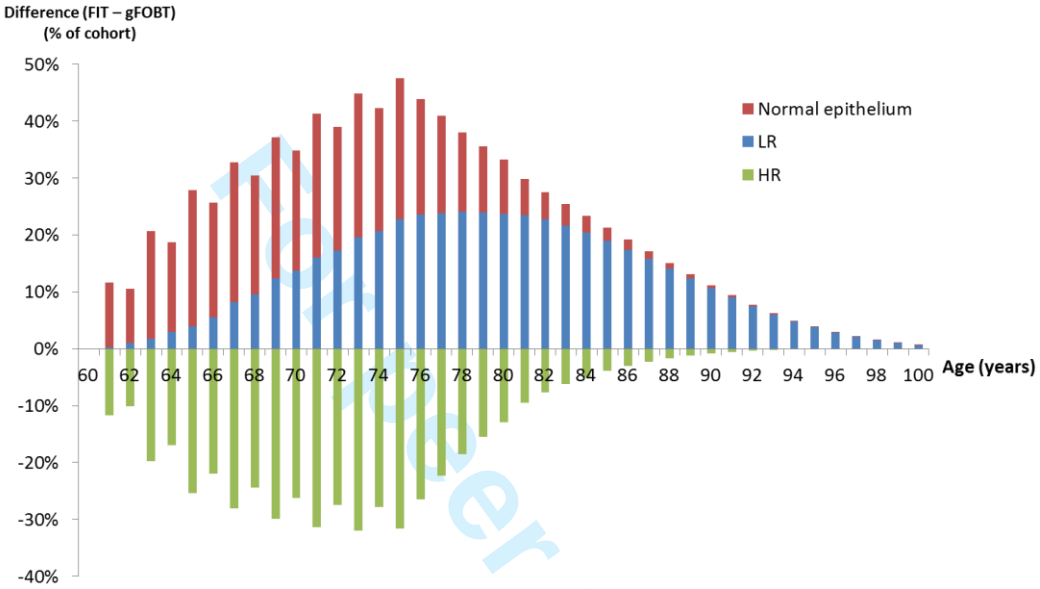
Supplementary Table 15 shows detailed model results for the colonoscopy resource use and costs for gFOBT and at each FIT threshold, over the 40 year time horizon of the model.

Supplementary Table 15: Colonoscopy resource use and adverse events for a population of 586,097 people invited for screening, 40 year time horizon

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Follow-up										
Colonoscopies without polypectomy	28,261	12,730,164	30,633	13,855,967	31,925	14,444,673	34,100	15,443,594	44,220	20,043,962
Colonoscopies with polypectomy for HR adenomas	14,993	8,322,554	20,076	11,218,664	22,526	12,600,980	29,452	16,526,899	48,524	27,451,128
Colonoscopies with polypectomy for LR adenomas	8,946	4,948,701	8,364	4,644,665	10,673	5,927,285	16,221	9,009,392	37,818	21,020,093
Deaths at colonoscopy	0	138	0	146	0	155	0	175	1	249
Total number of follow-up colonoscopies	52,200	26,001,558	59,073	29,719,442	65,125	32,973,094	79,774	40,980,059	130,562	68,515,432
Major bleeds requiring hospitalisation	21	7,528	24	8,565	26	9,450	32	11,603	52	19,073
Perforation	33	65,812	37	73,208	39	78,530	45	90,324	67	134,260
Surveillance										
Colonoscopies without polypectomy	10,919	4,298,683	14,664	5,809,896	16,462	6,528,503	21,555	8,573,325	35,636	14,284,000
Colonoscopies with polypectomy for LR adenomas	6,799	10,593,015	9,125	14,303,872	10,243	16,070,844	13,407	21,095,589	22,147	35,110,021
Colonoscopies with polypectomy for HR adenomas	21,986	3,256,781	29,500	4,398,375	33,113	4,941,843	43,338	6,487,489	71,576	10,799,330
Deaths at colonoscopy	0	69	0	93	0	105	0	138	1	229
Total number of surveillance colonoscopies	39,705	18,148,548	53,289	24,512,236	59,817	27,541,295	78,300	36,156,541	129,360	60,193,581
Major bleeds requiring hospitalisation	16	5,269	21	7,117	24	7,997	31	10,498	52	17,479
Perforation	19	34,524	25	46,642	28	52,408	37	68,810	61	114,589
TOTAL NUMBER OF COLNOSCOPIES	91,906	18,188,342	112,362	24,565,996	124,942	27,601,699	158,074	36,235,849	259,922	60,325,649

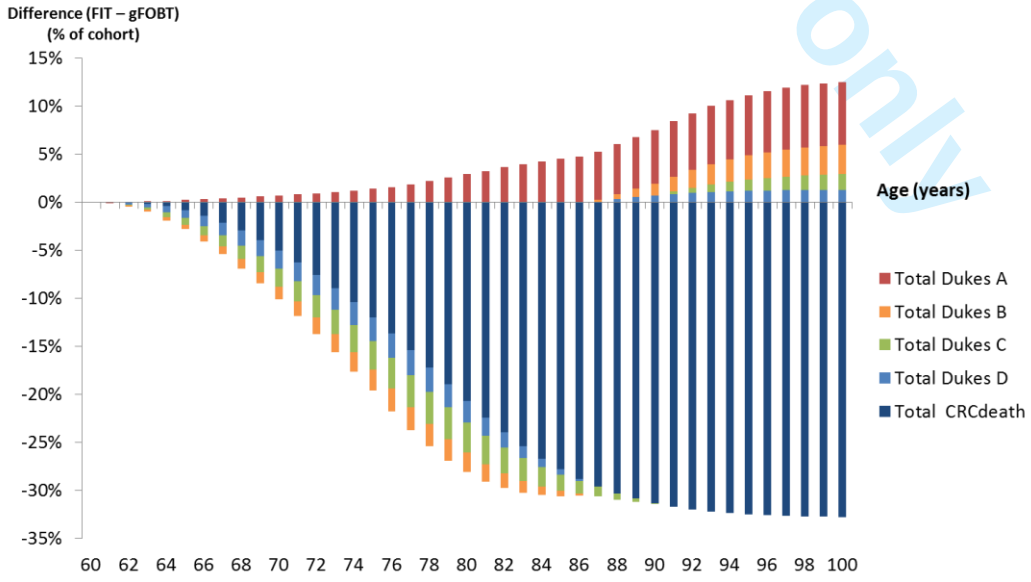
Supplementary Figure 6 shows the model-estimated difference in prevalence of adenomas for FIT at 180µg Hb/g faeces compared with gFOBT in each year of the model after screening begins at age 60 years.

Supplementary Figure 6: Model-estimated difference in non-cancer health state prevalence between FIT and gFOBT, by age



Supplementary Figure 7 shows the model-estimated difference in prevalence of CRC and mortality rate for FIT at 180µg Hb/g faeces compared with gFOBT in each year of the model after screening begins at age 60 years.

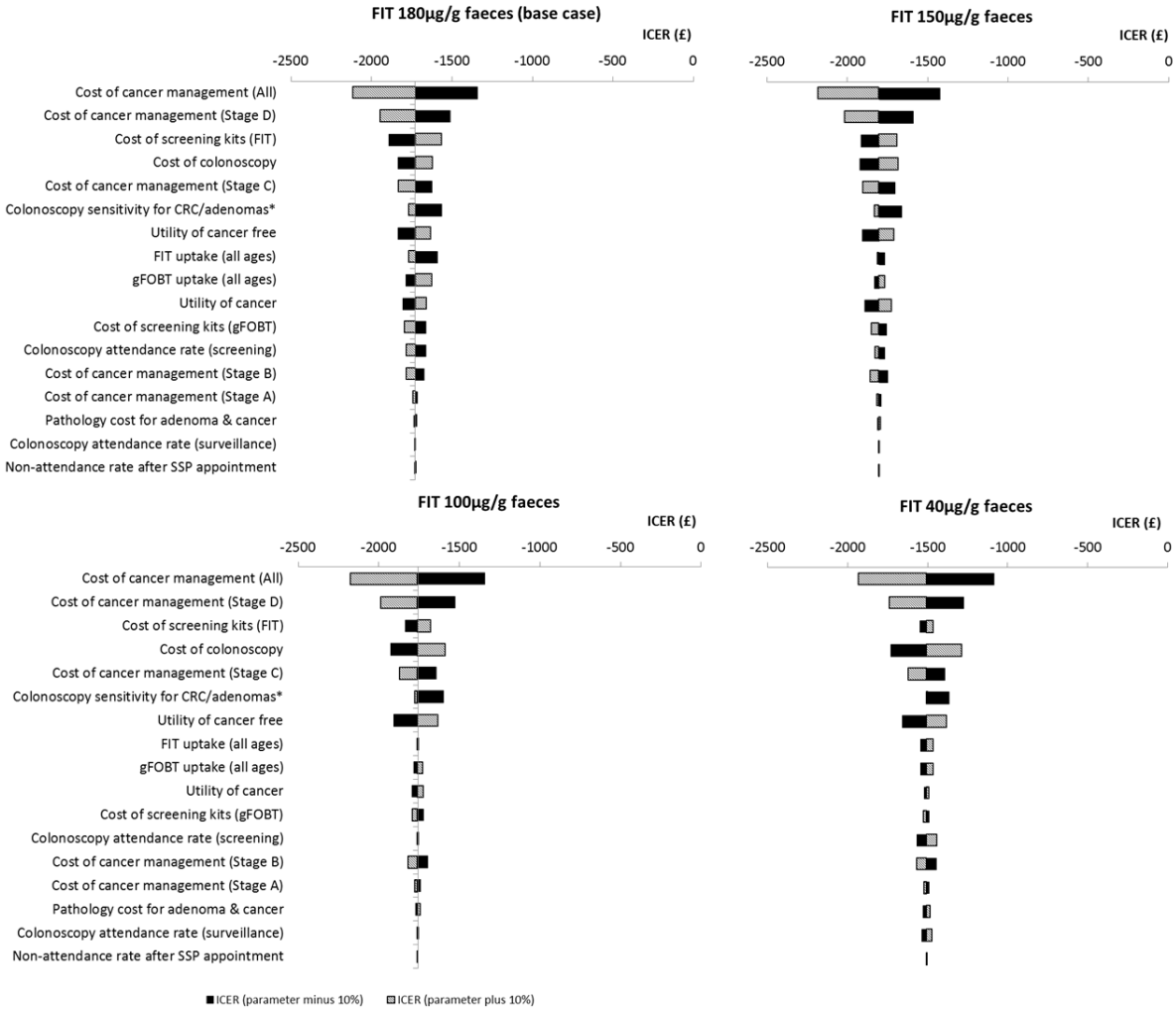
Supplementary Figure 7: Model-estimated difference in colorectal cancer prevalence and mortality between FIT and gFOBT, by age



SECTION 4: SENSITIVITY ANALYSES

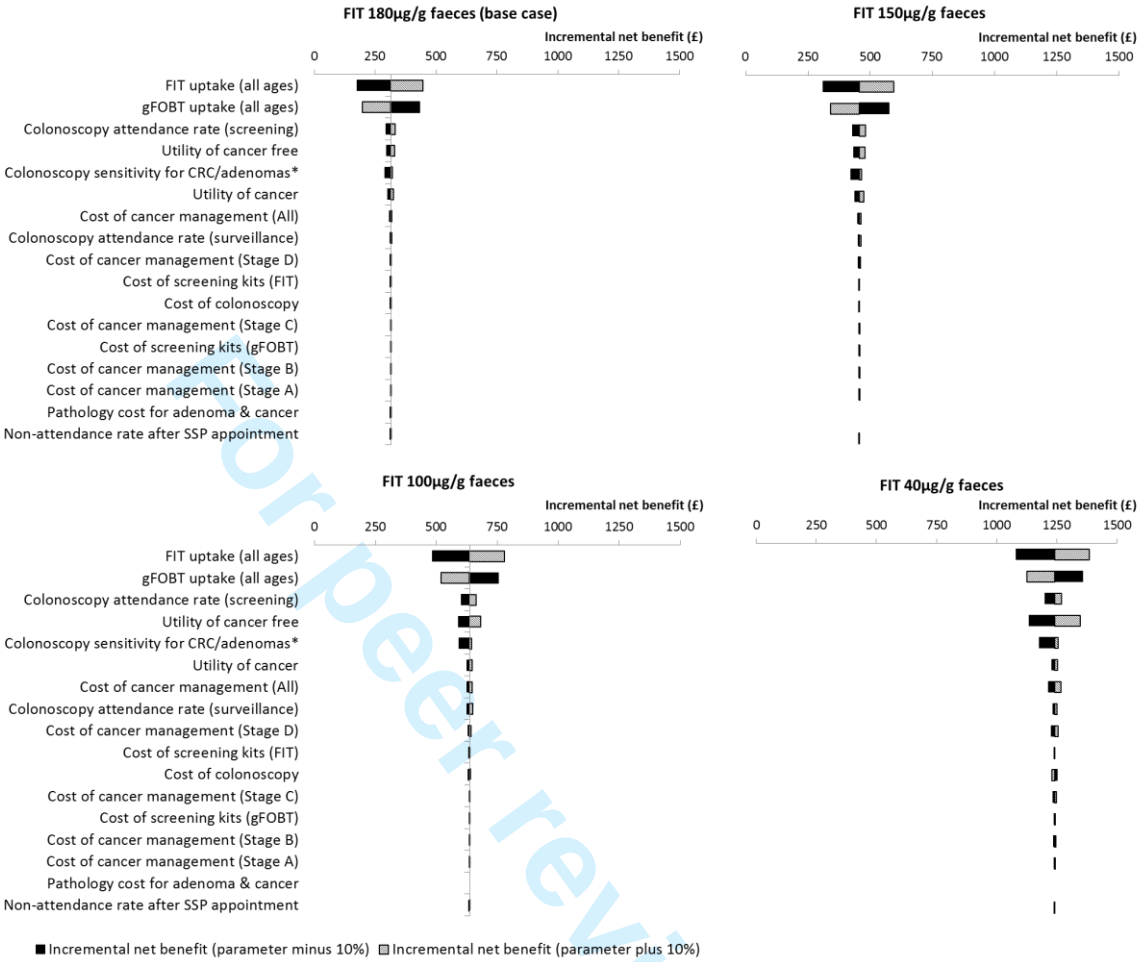
One-way sensitivity analyses were performed around key model parameters by varying the input values by +/- 10% of the base case parameter value for FIT 180µg Hb/g faeces. The results are shown in terms of the incremental cost-effectiveness ratio in Supplementary Figure 8, and in terms of the incremental net benefit in Supplementary Figure 9.

Supplementary Figure 8: One-way sensitivity analyses: incremental cost-effectiveness ratio per person invited for screening



Murphy J, Halloran S, Gray A. "Cost-effectiveness of the faecal immunochemical test at various positivity thresholds compared with the guaiac faecal occult blood test in England."

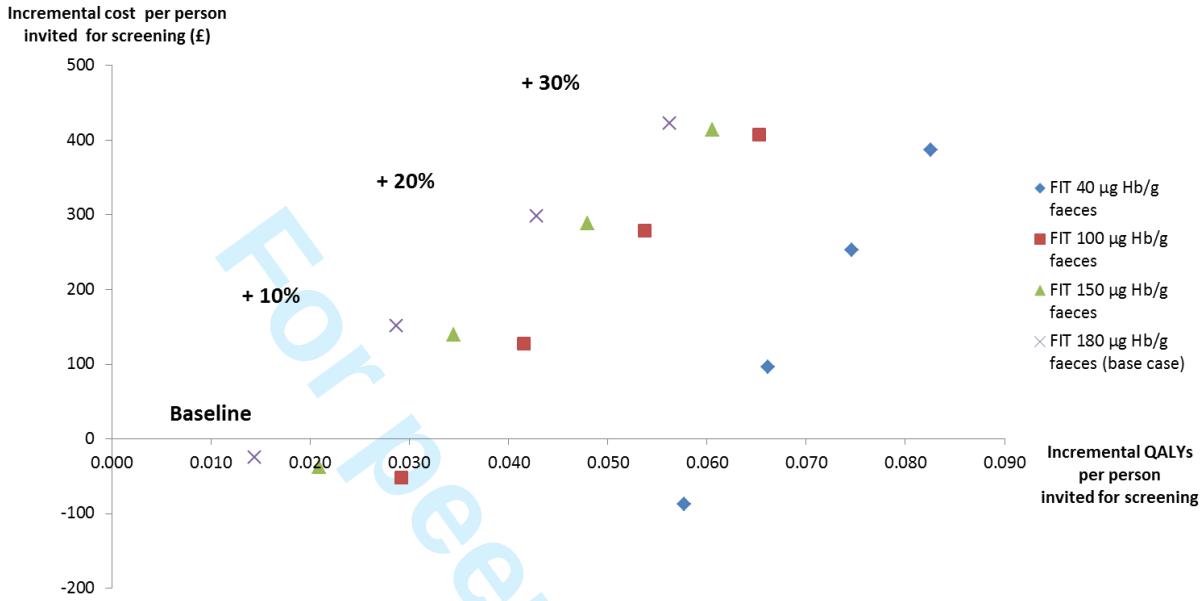
Supplementary Figure 9: One-way sensitivity analyses: incremental net benefit per person invited for screening



* Maximum value limited to 100%; Categories are sorted by ranked difference in INB for the base case (FIT 180µg Hb/g faeces) ; Data are centred on the mean INB for each FIT threshold.

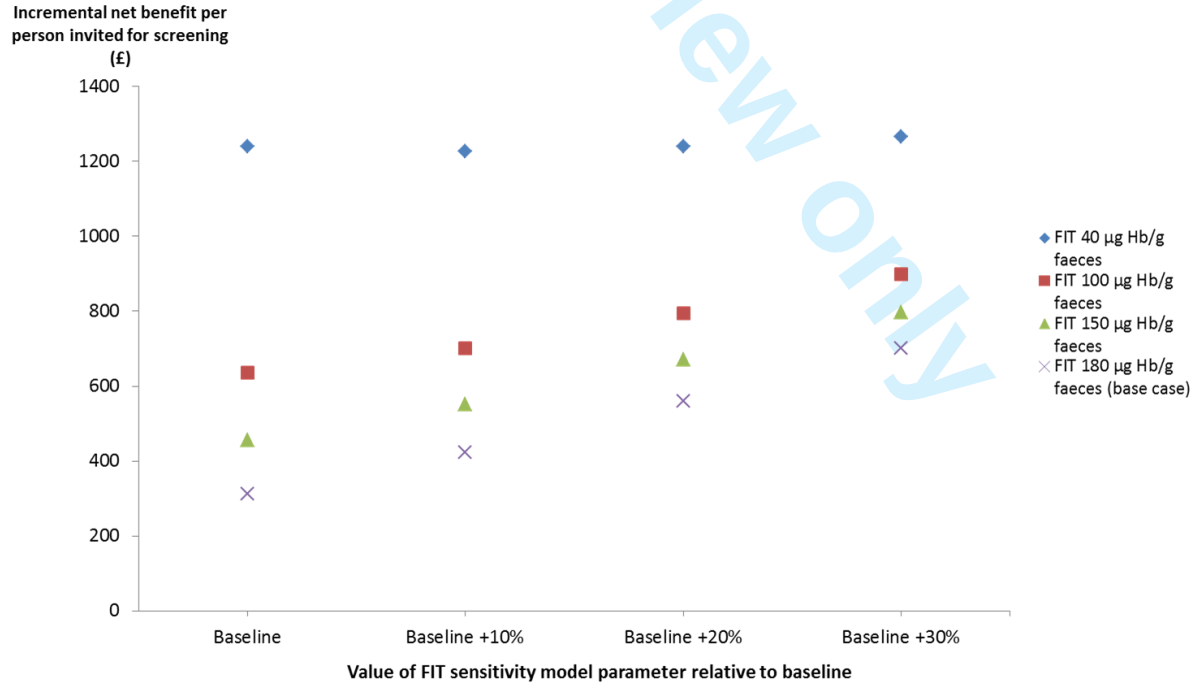
Supplementary Figure 10 shows a one-way sensitivity analyses around the sensitivity of FIT for each FIT threshold, illustrated on the cost-effectiveness plane.

Supplementary Figure 10: : Cost-effectiveness plane showing variation in FIT sensitivity parameter



Supplementary Figure 11 shows a one-way sensitivity analyses around the sensitivity of FIT for each FIT threshold, illustrated in terms of the incremental net benefit.

Supplementary Figure 11: Incremental net benefit changes for variation in FIT sensitivity parameter



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Supplementary tables: correlation matrices for natural history parameters by FIT threshold

Tabs by threshold ("FIT 180" = 180µg Hb/g faeces, etc.)

Variance Covariance matrix estimated in R (FIT 180µg Hb/g faeces)

		A	B
No adenomas or cancer to LR adenomas - age 30	**A**	2.63717E-07	-1.14484E-07
No adenomas or cancer -> LR adenomas - age 50	**B**	-1.14484E-07	2.62217E-07
No adenomas or cancer -> LR adenomas - age 70	**C**	1.89193E-07	-5.6359E-07
No adenomas or cancer -> LR adenomas - age 100	**D**	3.72359E-08	-2.73262E-07
LR adenomas -> high risk adenomas - age 30	**E**	-4.76349E-08	1.48476E-07
LR adenomas -> high risk adenomas - age 50	**F**	-3.92318E-09	-3.2852E-08
LR adenomas -> high risk adenomas - age 70	**G**	2.80723E-08	8.8844E-09
LR adenomas -> HR adenomas - age 100	**H**	1.61545E-07	-1.97976E-08
HR adenomas -> Dukes A CRC - age 30	**I**	1.40502E-07	-5.27076E-07
HR adenomas -> Dukes A CRC - age 50	**J**	1.0823E-07	-1.51449E-07
HR adenomas -> Dukes A CRC - age 70	**K**	3.50864E-07	-2.9177E-07
HR adenomas -> Dukes A CRC - age 100	**L**	2.87453E-07	-8.84909E-07
No adenomas or cancer -> CRC Dukes A	**M**	-1.75534E-10	6.63812E-10
Preclinical CRC: Dukes A -> Dukes B	**N**	1.17757E-05	-4.50986E-06
Preclinical CRC: Dukes B -> Dukes' C	**O**	1.84961E-06	-5.81278E-06
Preclinical CRC: Dukes C -> Stage D	**P**	6.97887E-07	-3.31392E-06
Symptomatic presention with CRC Dukes A	**Q**	6.67736E-07	-1.0546E-07
Symptomatic presention with CRC Dukes B	**R**	-8.74797E-07	-3.27866E-07
Symptomatic presention with CRC Dukes C	**S**	-3.73143E-06	2.54689E-06
Symptomatic presention with CRC Dukes D	**T**	-1.23935E-05	1.14954E-05
gFOBT Sensitivity for LR adenomas	**U**	-1.35777E-08	2.87272E-08
gFOBT Sensitivity for HR adenomas	**V**	4.30162E-08	-3.226E-08
gFOBT Sensitivity for CRC	**Q**	-6.40934E-07	6.66164E-07
gFOBT Specificity age 50	**X**	9.65238E-08	-1.29656E-07
gFOBT Specificity age -70	**Y**	-7.79026E-08	1.62869E-07
FIT Sensitivity for LR adenomas	**Z**	-3.40287E-08	3.15751E-08
FIT Sensitivity for HR adenomas	**AA**	7.48613E-08	-8.13648E-08
FIT Sensitivity for CRC	**AB**	-5.57075E-07	5.52133E-07
FIT Specificity age 50	**AC**	3.51754E-08	-4.84426E-08
FIT Specificity age 70	**AD**	-7.93449E-08	1.67432E-07

CHOLESKY DECOMPOSITION MATRIX (FIT 180µg Hb/g faeces)

		A	B
No adenomas or cancer to LR adenomas - age 30	**A**	0.000513534	0
No adenomas or cancer to LR adenomas - age 50	**B**	-0.000222934	0.000460997
No adenomas or cancer to LR adenomas - age 70	**C**	0.000368415	-0.001044386
No adenomas or cancer to LR adenomas - age 100	**D**	7.25092E-05	-0.000557698
LR adenomas to high risk adenomas - age 30	**E**	-9.2759E-05	0.000277218
LR adenomas to high risk adenomas - age 50	**F**	-7.63959E-06	-7.49575E-05
LR adenomas to high risk adenomas - age 70	**G**	5.4665E-05	4.57077E-05
LR adenomas to HR adenomas - age 100	**H**	0.000314575	0.00010918
HR adenomas to Dukes A CRC - age 30	**I**	0.000273598	-0.001011031
HR adenomas to Dukes A CRC - age 50	**J**	0.000210755	-0.000226605
HR adenomas to Dukes A CRC - age 70	**K**	0.000683235	-0.000302506
HR adenomas to Dukes A CRC - age 100	**L**	0.000559755	-0.001648865
No adenomas or cancer to CRC Dukes A	**M**	-3.41817E-07	1.27465E-06
Preclinical CRC: Dukes A to Dukes B	**N**	0.022930762	0.001306255
Preclinical CRC: Dukes B to Dukes' C	**O**	0.003601725	-0.010867409

Preclinical CRC: Dukes C to Stage D	**P**	0.001358989	-0.006531402
Symptomatic presention with CRC Dukes A	**Q**	0.001300277	0.000400037
Symptomatic presention with CRC Dukes B	**R**	-0.001703485	-0.001535002
Symptomatic presention with CRC Dukes C	**S**	-0.007266179	0.002010885
Symptomatic presention with CRC Dukes D	**T**	-0.024133726	0.013265074
gFOBT Sensitivity for LR adenomas	**U**	-2.64397E-05	4.95294E-05
gFOBT Sensitivity for HR adenomas	**V**	8.3765E-05	-2.94708E-05
gFOBT Sensitivity for CRC	**Q**	-0.001248085	0.00084149
gFOBT Specificity age 50	**X**	0.00018796	-0.000190356
gFOBT Specificity age -70	**Y**	-0.000151699	0.000279938
FIT Sensitivity for LR adenomas	**Z**	-6.62637E-05	3.64485E-05
FIT Sensitivity for HR adenomas	**AA**	0.000145777	-0.000106001
FIT Sensitivity for CRC	**AB**	-0.001084788	0.000673101
FIT Specificity age 50	**AC**	6.84969E-05	-7.19579E-05
FIT Specificity age 70	**AD**	-0.000154508	0.000288478

C	D	E	F	G	H
1.89193E-07	3.72359E-08	-4.76349E-08	-3.92318E-09	2.80723E-08	1.61545E-07
-5.6359E-07	-2.73262E-07	1.48476E-07	-3.2852E-08	8.8844E-09	-1.97976E-08
2.10859E-05	2.89509E-06	-3.52459E-06	1.06527E-06	-9.59474E-07	-2.82781E-06
2.89509E-06	4.39955E-05	9.49985E-07	-1.87435E-07	-1.48867E-08	-8.26983E-07
-3.52459E-06	9.49985E-07	3.19058E-06	-4.42831E-07	4.11467E-07	1.19732E-06
1.06527E-06	-1.87435E-07	-4.42831E-07	2.60819E-07	-1.21834E-07	-3.56136E-07
-9.59474E-07	-1.48867E-08	4.11467E-07	-1.21834E-07	2.6153E-07	4.15802E-07
-2.82781E-06	-8.26983E-07	1.19732E-06	-3.56136E-07	4.15802E-07	3.19008E-06
1.37579E-05	-6.16741E-06	-5.53485E-06	1.65168E-06	-1.4057E-06	-3.56691E-06
1.71236E-06	-3.0047E-07	-5.34554E-07	1.62404E-07	-8.60459E-08	-1.34125E-07
1.91193E-07	6.84028E-07	4.42585E-07	-1.27758E-07	2.6986E-07	1.20711E-06
1.85196E-05	-4.02716E-06	-7.35709E-06	2.14631E-06	-1.92509E-06	-5.42102E-06
-1.62403E-08	8.7697E-09	5.66767E-09	-1.89112E-09	1.43584E-09	3.12007E-09
-0.00012402	-0.000104227	5.0861E-05	-1.57845E-05	2.10459E-05	8.0676E-05
0.000117707	1.7174E-05	-4.06887E-05	1.22859E-05	-1.09648E-05	-3.14413E-05
7.61286E-05	1.3604E-05	-2.6248E-05	8.1098E-06	-7.15049E-06	-2.0449E-05
-1.05952E-05	-8.4515E-06	3.99739E-06	-1.22997E-06	1.52869E-06	5.65783E-06
2.7223E-05	2.8424E-06	-1.10971E-05	3.35283E-06	-3.57153E-06	-1.18624E-05
1.27913E-05	7.69294E-07	-9.32756E-06	2.78356E-06	-4.26419E-06	-1.72038E-05
-4.20295E-05	-1.1675E-05	-6.28827E-07	9.69765E-11	-5.56815E-06	-3.08037E-05
-5.51517E-07	-9.49162E-08	1.89973E-07	-5.65462E-08	5.15963E-08	1.44621E-07
-3.0385E-07	2.04402E-07	1.28543E-07	-5.51937E-08	5.28799E-08	1.73949E-07
-2.81298E-06	-8.12477E-06	-5.94508E-07	1.1837E-07	-2.88243E-07	-1.41413E-06
1.73512E-06	-8.09358E-07	-6.26603E-07	1.86333E-07	-1.25867E-07	-2.07811E-07
-3.2701E-06	2.50101E-07	1.17259E-06	-3.49978E-07	2.90622E-07	7.3568E-07
-1.93365E-07	-5.35143E-08	4.86553E-08	-8.47756E-09	-1.23363E-09	1.78763E-08
1.88605E-07	-2.48872E-06	-3.56409E-07	6.02249E-08	-2.84629E-09	2.01409E-07
-2.40425E-06	-8.26744E-06	-6.47816E-07	1.24672E-07	-2.98466E-07	-1.31633E-06
8.79346E-07	2.64759E-09	-2.4195E-07	6.86503E-08	-5.87973E-08	-6.33926E-08
-5.21317E-06	6.48267E-07	1.73167E-06	-5.20684E-07	4.35832E-07	9.10779E-07

C	D	E	F	G	H
0	0	0	0	0	0
0	0	0	0	0	0
0.004456394	0	0	0	0	0
0.000512954	0.006589088	0	0	0	0
-0.00071827	0.000224576	0.001593354	0	0	0
0.000222109	-5.19976E-05	-0.000157874	0.000422116	0	0
-0.00020911	1.72868E-05	0.000156768	-0.00010873	0.000419557	0
-0.000634969	-7.02969E-05	0.000474433	-0.000315722	0.000365498	0.001487521
0.00282767	-0.00124472	-0.001831751	0.001412	-0.000764971	-0.00016146
0.000313718	-9.15228E-05	-0.000129474	0.000123543	3.26641E-05	7.09754E-05
-8.44749E-05	7.72659E-05	0.000321205	-0.000169914	0.000377798	0.000425458
0.003723028	-0.001046739	-0.002472055	0.0017895	-0.001195536	-0.000639908
-3.31728E-06	1.70084E-06	1.58027E-06	-1.7139E-06	5.69876E-07	-2.67236E-07
-0.029419363	-0.013669706	0.021693115	-0.014837365	0.020981788	0.020862505
0.023568463	-0.000187804	-0.012785164	0.010034697	-0.006287371	-0.003296647

0.015439985	0.000294862	-0.008339312	0.006870198	-0.003928788	-0.001867043
-0.002391266	-0.001076944	0.001588719	-0.001099494	0.001404561	0.001342362
0.005889834	-0.000138313	-0.004122124	0.002981665	-0.002869252	-0.002341472
0.003942282	6.0011E-05	-0.004858229	0.002935932	-0.004897359	-0.00511477
-0.004327355	-4.66666E-05	-0.0060517	0.001926851	-0.010966456	-0.013393725
-0.000109965	-1.36126E-06	5.96926E-05	-4.56232E-05	3.21481E-05	1.55533E-05
-8.20146E-05	3.39898E-05	4.89163E-05	-6.88358E-05	3.99404E-05	2.79596E-05
-0.000330835	-0.001122351	-0.000583129	0.00022499	-0.000458527	-0.000596347
0.000329204	-0.000166641	-0.00017731	0.000150962	-2.74325E-05	6.25036E-05
-0.000655653	0.000114362	0.000366711	-0.000285908	0.000139346	1.97507E-05
-2.93704E-05	-2.02101E-06	7.38224E-06	3.15576E-06	-1.47731E-05	1.2668E-05
5.42879E-06	-0.000388702	-0.000139523	2.35686E-05	6.27324E-05	0.000130387
-0.000292079	-0.001163071	-0.000554572	0.000198246	-0.000482432	-0.000547065
0.000174796	-2.00501E-05	-5.37198E-05	3.65601E-05	-2.37339E-05	5.25713E-05
-0.001089438	0.000209313	0.000507012	-0.000396431	0.000183705	-0.000122356

						Variance Covari
I	J	K	L	M		N
1.40502E-07	1.0823E-07	3.50864E-07	2.87453E-07	-1.75534E-10	A	1.17757E-05
-5.27076E-07	-1.51449E-07	-2.9177E-07	-8.84909E-07	6.63812E-10	B	-4.50986E-06
1.37579E-05	1.71236E-06	1.91193E-07	1.85196E-05	-1.62403E-08	C	-0.00012402
-6.16741E-06	-3.0047E-07	6.84028E-07	-4.02716E-06	8.7697E-09	D	-0.000104227
-5.53485E-06	-5.34554E-07	4.42585E-07	-7.35709E-06	5.66767E-09	E	5.0861E-05
1.65168E-06	1.62404E-07	-1.27758E-07	2.14631E-06	-1.89112E-09	F	-1.57845E-05
-1.4057E-06	-8.60459E-08	2.6986E-07	-1.92509E-06	1.43584E-09	G	2.10459E-05
-3.56691E-06	-1.34125E-07	1.20711E-06	-5.42102E-06	3.12007E-09	H	8.0676E-05
4.74412E-05	2.63554E-06	-1.40704E-07	2.86756E-05	-2.98269E-08	I	-0.000135295
2.63554E-06	1.04618E-06	5.29356E-07	3.14169E-06	-4.0797E-09	J	3.0066E-06
-1.40704E-07	5.29356E-07	4.18037E-06	-7.08438E-07	-1.37326E-09	K	7.4162E-05
2.86756E-05	3.14169E-06	-7.08438E-07	7.52291E-05	-3.34378E-08	L	-0.000217224
-2.98269E-08	-4.0797E-09	-1.37326E-09	-3.34378E-08	1.09585E-10	M	9.85466E-08
-0.000135295	3.0066E-06	7.4162E-05	-0.000217224	9.85466E-08	N	0.009646046
0.000164076	1.98161E-05	1.05711E-06	0.000215597	-1.96904E-07	O	-0.001373246
0.000105952	1.29064E-05	5.59414E-10	0.000137868	-1.2817E-07	P	-0.000923264
-1.16231E-05	-3.16218E-07	4.35766E-06	-1.79222E-05	1.01849E-08	Q	0.000331473
3.93586E-05	2.6966E-06	-7.14319E-06	5.328E-05	-4.22484E-08	R	-0.000603317
1.99868E-05	-3.55389E-06	-2.22679E-05	3.22158E-05	-6.13186E-09	S	-0.001025989
-5.092E-05	-2.44276E-05	-6.8972E-05	-4.58012E-05	1.11546E-07	T	-0.002178253
-7.55508E-07	-8.94477E-08	-6.57046E-09	-9.95576E-07	9.08946E-10	U	6.63947E-06
-6.32576E-07	-3.55977E-09	1.90332E-07	-7.52365E-07	9.75212E-10	V	8.51861E-06
1.75768E-07	-9.92999E-07	-3.75521E-06	-2.21087E-07	2.14331E-09	Q	-7.0153E-05
2.98698E-06	4.45912E-07	3.70419E-07	3.49578E-06	-4.13856E-09	X	-2.50543E-06
-5.00763E-06	-6.29214E-07	-2.10948E-07	-6.17299E-06	6.20976E-09	Y	2.85623E-05
-2.4045E-07	-6.70635E-08	-7.82779E-08	-3.24201E-07	1.19201E-10	Z	1.00523E-06
1.14654E-06	2.17196E-07	2.44649E-07	1.17326E-06	-7.8735E-10	AA	1.94127E-05
3.01675E-07	-9.10093E-07	-3.52811E-06	3.79115E-07	1.71679E-09	AB	-7.32415E-05
1.25418E-06	2.44758E-07	2.47215E-07	1.50029E-06	-1.81694E-09	AC	2.87293E-11
-7.99183E-06	-1.05221E-06	-5.27777E-07	-9.43503E-06	9.72843E-09	AD	2.8489E-05

						CHOLESKY DEC(
I	J	K	L	M		N
0	0	0	0	0	A	0
0	0	0	0	0	B	0
0	0	0	0	0	C	0
0	0	0	0	0	D	0
0	0	0	0	0	E	0
0	0	0	0	0	F	0
0	0	0	0	0	G	0
0	0	0	0	0	H	0
0.00555327	0	0	0	0	I	0
0.000175141	0.000880231	0	0	0	J	0
0.000159825	0.000389027	0.001725188	0	0	K	0
0.001251898	0.00080702	6.59015E-05	0.006623096	0	L	0
-2.02402E-06	-1.98957E-06	-5.615E-07	-8.08347E-07	8.89333E-06	M	0
0.001085996	0.009921904	0.015729081	-0.00369555	-0.00089195	N	0.078348335
0.007616326	0.00612762	0.001914476	0.005122183	-0.003417289	O	-0.002644655

0.004934289	0.004307163	0.001181411	0.003115052	-0.002274981	**P**	-0.001794531
-7.19171E-05	0.000414646	0.000882679	-0.000314745	1.15263E-05	**Q**	0.001132601
0.001280742	-2.16983E-05	-0.001287287	0.001158718	-0.000641373	**R**	-0.001600157
-0.000843045	-0.003543591	-0.005082217	0.000429226	0.000524761	**S**	-0.003429747
-0.007758474	-0.01515053	-0.017149091	-0.001717922	0.003461517	**T**	-0.008621793
-3.38687E-05	-2.40112E-05	-7.90722E-06	-2.28349E-05	1.66862E-05	**U**	1.64186E-05
-3.4071E-05	2.09763E-05	3.33427E-05	-2.62189E-05	5.29909E-05	**V**	5.60456E-06
-0.000166818	-0.000630494	-0.000964949	-1.06825E-05	8.1195E-05	**Q**	-0.000102237
0.000190151	0.000188795	0.000108763	8.72388E-05	-0.000111638	**X**	3.35737E-05
-0.000270394	-0.000219766	-0.000107552	-0.000142749	0.000126794	**Y**	2.76709E-05
-1.89302E-05	-3.67458E-05	-5.00007E-06	-9.51975E-06	-1.80225E-05	**Z**	2.46375E-05
5.05117E-05	9.54837E-05	3.93592E-05	1.78554E-05	7.48242E-05	**AA**	0.000113672
-0.000197349	-0.00062586	-0.000936875	1.92545E-05	7.72563E-05	**AB**	-0.000203319
8.7116E-05	0.000145029	7.80705E-05	3.73449E-05	-4.2035E-05	**AC**	2.34801E-05
-0.000487557	-0.000443802	-0.000255122	-0.000227739	0.000171222	**AD**	-9.52141E-05

iance matrix estimated in R (FIT 180µg Hb/g faeces) contd.

O	P	Q	R	S	T
1.84961E-06	6.97887E-07	6.67736E-07	-8.74797E-07	-3.73143E-06	-1.23935E-05
-5.81278E-06	-3.31392E-06	-1.0546E-07	-3.27866E-07	2.54689E-06	1.14954E-05
0.000117707	7.61286E-05	-1.05952E-05	2.7223E-05	1.27913E-05	-4.20295E-05
1.7174E-05	1.3604E-05	-8.4515E-06	2.8424E-06	7.69294E-07	-1.1675E-05
-4.06887E-05	-2.6248E-05	3.99739E-06	-1.10971E-05	-9.32756E-06	-6.28827E-07
1.22859E-05	8.1098E-06	-1.22997E-06	3.35283E-06	2.78356E-06	9.69765E-11
-1.09648E-05	-7.15049E-06	1.52869E-06	-3.57153E-06	-4.26419E-06	-5.56815E-06
-3.14413E-05	-2.0449E-05	5.65783E-06	-1.18624E-05	-1.72038E-05	-3.08037E-05
0.000164076	0.000105952	-1.16231E-05	3.93586E-05	1.99868E-05	-5.092E-05
1.98161E-05	1.29064E-05	-3.16218E-07	2.6966E-06	-3.55389E-06	-2.44276E-05
1.05711E-06	5.59414E-10	4.35766E-06	-7.14319E-06	-2.22679E-05	-6.8972E-05
0.000215597	0.000137868	-1.79222E-05	5.328E-05	3.22158E-05	-4.58012E-05
-1.96904E-07	-1.2817E-07	1.01849E-08	-4.22484E-08	-6.13186E-09	1.11546E-07
-0.001373246	-0.000923264	0.000331473	-0.000603317	-0.001025989	-0.002178253
0.00268176	0.000867411	-0.000115923	0.000314413	0.000156282	-0.000437537
0.000867411	0.001168524	-7.88755E-05	0.000207543	0.000111097	-0.000276783
-0.000115923	-7.88755E-05	4.74412E-05	-4.42785E-05	-6.55565E-05	-0.000118814
0.000314413	0.000207543	-4.42785E-05	0.000204082	0.000119388	0.000145846
0.000156282	0.000111097	-6.55565E-05	0.000119388	0.000538903	0.000710997
-0.000437537	-0.000276783	-0.000118814	0.000145846	0.000710997	0.004957309
-6.143E-06	-3.92428E-06	5.53453E-07	-1.45763E-06	-7.39938E-07	1.88607E-06
-3.43472E-06	-2.44158E-06	5.62284E-07	-1.45779E-06	-2.01371E-06	-3.95158E-06
-2.51003E-05	-1.65688E-05	-2.63566E-06	6.92435E-06	3.49404E-05	0.000123933
2.06087E-05	1.36039E-05	-5.97366E-07	3.4984E-06	-1.54019E-06	-1.90392E-05
-3.72541E-05	-2.45916E-05	2.58286E-06	-8.19952E-06	-2.48663E-06	1.88596E-05
-1.94486E-06	-1.28516E-06	1.113E-07	-3.64424E-07	6.36378E-08	1.56365E-06
3.2322E-06	1.42209E-06	1.21804E-06	-4.45616E-07	-3.13869E-06	-1.09865E-05
-2.04442E-05	-1.49934E-05	-3.17217E-06	7.20549E-06	3.41101E-05	0.000120453
9.90159E-06	6.8474E-06	-1.88098E-07	1.5607E-06	-1.05725E-06	-1.08981E-05
-6.00852E-05	-4.04882E-05	2.99698E-06	-1.17412E-05	-5.62309E-07	4.08459E-05

ɔMPOSITION MATRIX (FIT 180µg Hb/g faeces) contd.

O	P	Q	R	S	T
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0.039198145	0	0	0	0	0

0.003228899	0.026020244	0	0	0	0
-0.000370879	-0.000392051	0.005345595	0	0	0
0.000947241	0.0008734	-0.001196929	0.010668281	0	0
1.44072E-05	0.000108625	-0.002389653	0.001679808	0.018007947	0
-0.003359901	-0.003455496	-0.00572021	0.003220744	0.009554974	0.054858707
-2.0563E-05	-1.5956E-05	1.25729E-05	-1.16073E-05	9.98897E-07	6.98183E-06
-1.54523E-06	-5.61145E-06	9.2693E-09	-1.11459E-05	-5.02656E-07	-3.46291E-06
-0.000290641	-0.000292438	4.85106E-05	0.000144745	0.000499939	0.000522416
7.07121E-05	7.65108E-05	2.44632E-05	1.20075E-05	-3.61747E-05	-6.22181E-05
-0.000123553	-0.000125719	1.83382E-05	-5.60237E-05	2.88866E-05	8.49167E-05
-4.47521E-06	-7.40134E-06	1.66477E-05	-1.44181E-05	-2.02609E-05	-1.52428E-05
-1.07687E-05	-2.4087E-05	8.26068E-05	-2.6105E-05	-2.60629E-05	-1.02243E-05
-0.000247811	-0.000301549	-6.98368E-05	0.000145993	0.000521496	0.000562821
4.45268E-05	5.52184E-05	2.56937E-05	1.48984E-05	-1.21041E-05	-4.20638E-05
-0.000281774	-0.000297204	-8.32602E-05	-6.27004E-05	0.000125607	0.000230756

U	V	Q	X	Y	Z
-1.35777E-08	4.30162E-08	-6.40934E-07	9.65238E-08	-7.79026E-08	-3.40287E-08
2.87272E-08	-3.226E-08	6.66164E-07	-1.29656E-07	1.62869E-07	3.15751E-08
-5.51517E-07	-3.0385E-07	-2.81298E-06	1.73512E-06	-3.2701E-06	-1.93365E-07
-9.49162E-08	2.04402E-07	-8.12477E-06	-8.09358E-07	2.50101E-07	-5.35143E-08
1.89973E-07	1.28543E-07	-5.94508E-07	-6.26603E-07	1.17259E-06	4.86553E-08
-5.65462E-08	-5.51937E-08	1.1837E-07	1.86333E-07	-3.49978E-07	-8.47756E-09
5.15963E-08	5.28799E-08	-2.88243E-07	-1.25867E-07	2.90622E-07	-1.23363E-09
1.44621E-07	1.73949E-07	-1.41413E-06	-2.07811E-07	7.3568E-07	1.78763E-08
-7.55508E-07	-6.32576E-07	1.75768E-07	2.98698E-06	-5.00763E-06	-2.4045E-07
-8.94477E-08	-3.55977E-09	-9.92999E-07	4.45912E-07	-6.29214E-07	-6.70635E-08
-6.57046E-09	1.90332E-07	-3.75521E-06	3.70419E-07	-2.10948E-07	-7.82779E-08
-9.95576E-07	-7.52365E-07	-2.21087E-07	3.49578E-06	-6.17299E-06	-3.24201E-07
9.08946E-10	9.75212E-10	2.14331E-09	-4.13856E-09	6.20976E-09	1.19201E-10
6.63947E-06	8.51861E-06	-7.0153E-05	-2.50543E-06	2.85623E-05	1.00523E-06
-6.143E-06	-3.43472E-06	-2.51003E-05	2.06087E-05	-3.72541E-05	-1.94486E-06
-3.92428E-06	-2.44158E-06	-1.65688E-05	1.36039E-05	-2.45916E-05	-1.28516E-06
5.53453E-07	5.62284E-07	-2.63566E-06	-5.97366E-07	2.58286E-06	1.113E-07
-1.45763E-06	-1.45779E-06	6.92435E-06	3.4984E-06	-8.19952E-06	-3.64424E-07
-7.39938E-07	-2.01371E-06	3.49404E-05	-1.54019E-06	-2.48663E-06	6.36378E-08
1.88607E-06	-3.95158E-06	0.000123933	-1.90392E-05	1.88596E-05	1.56365E-06
6.60957E-08	1.61728E-08	1.31892E-07	-9.9153E-08	1.77738E-07	2.32012E-08
1.61728E-08	1.04178E-06	-3.65706E-07	-3.53154E-08	1.00031E-07	1.16529E-09
1.31892E-07	-3.65706E-07	2.60338E-05	-6.53393E-07	7.06294E-07	8.45559E-08
-9.9153E-08	-3.53154E-08	-6.53393E-07	1.04355E-06	-7.05894E-07	-5.48437E-08
1.77738E-07	1.00031E-07	7.06294E-07	-7.05894E-07	2.34682E-06	8.50461E-08
2.32012E-08	1.16529E-09	8.45559E-08	-5.48437E-08	8.50461E-08	4.49226E-07
-2.70913E-09	9.36323E-08	1.63663E-07	5.97702E-08	-4.259E-08	-1.23917E-07
8.71404E-08	-2.80998E-07	8.92926E-06	-6.50946E-07	7.45093E-07	3.19125E-07
-4.79062E-08	1.40425E-07	-3.27651E-07	1.69425E-07	-2.81615E-07	-8.94187E-08
2.79837E-07	7.67973E-08	7.33456E-07	-9.06867E-07	1.69432E-06	8.7304E-07

U	V	Q	X	Y	Z
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
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0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0.000200134	0	0	0	0	0
4.53538E-06	0.001005024	0	0	0	0
0.000231531	-0.000109557	0.004391683	0	0	0
-6.6383E-05	2.04313E-06	-1.68691E-05	0.000806629	0	0
0.000105099	6.2372E-06	2.32998E-05	-0.000143651	0.001149522	0
7.01949E-05	5.78211E-06	-1.44387E-05	-1.74047E-05	1.9127E-05	0.000657572
5.78604E-05	8.73293E-05	3.11231E-05	-0.000141976	8.62332E-05	-0.000179919
9.57819E-05	-4.26416E-05	0.000586005	-0.000175749	0.000180924	0.00031138
-4.17011E-05	0.000152421	2.32753E-05	-1.50162E-05	-9.1028E-06	-0.000106008
0.000209657	-7.00733E-05	-0.000104784	6.95724E-05	9.96149E-05	0.001194547

AA	AB	AC	AD
7.48613E-08	-5.57075E-07	3.51754E-08	-7.93449E-08
-8.13648E-08	5.52133E-07	-4.84426E-08	1.67432E-07
1.88605E-07	-2.40425E-06	8.79346E-07	-5.21317E-06
-2.48872E-06	-8.26744E-06	2.64759E-09	6.48267E-07
-3.56409E-07	-6.47816E-07	-2.4195E-07	1.73167E-06
6.02249E-08	1.24672E-07	6.86503E-08	-5.20684E-07
-2.84629E-09	-2.98466E-07	-5.87973E-08	4.35832E-07
2.01409E-07	-1.31633E-06	-6.33926E-08	9.10779E-07
1.14654E-06	3.01675E-07	1.25418E-06	-7.99183E-06
2.17196E-07	-9.10093E-07	2.44758E-07	-1.05221E-06
2.44649E-07	-3.52811E-06	2.47215E-07	-5.27777E-07
1.17326E-06	3.79115E-07	1.50029E-06	-9.43503E-06
-7.8735E-10	1.71679E-09	-1.81694E-09	9.72843E-09
1.94127E-05	-7.32415E-05	2.87293E-11	2.8489E-05
3.2322E-06	-2.04442E-05	9.90159E-06	-6.00852E-05
1.42209E-06	-1.49934E-05	6.8474E-06	-4.04882E-05
1.21804E-06	-3.17217E-06	-1.88098E-07	2.99698E-06
-4.45616E-07	7.20549E-06	1.5607E-06	-1.17412E-05
-3.13869E-06	3.41101E-05	-1.05725E-06	-5.62309E-07
-1.09865E-05	0.000120453	-1.08981E-05	4.08459E-05
-2.70913E-09	8.71404E-08	-4.79062E-08	2.79837E-07
9.36323E-08	-2.80998E-07	1.40425E-07	7.67973E-08
1.63663E-07	8.92926E-06	-3.27651E-07	7.33456E-07
5.97702E-08	-6.50946E-07	1.69425E-07	-9.06867E-07
-4.259E-08	7.45093E-07	-2.81615E-07	1.69432E-06
-1.23917E-07	3.19125E-07	-8.94187E-08	8.7304E-07
3.19123E-06	6.70383E-07	2.33205E-07	-7.86708E-07
6.70383E-07	6.89513E-06	-1.61807E-07	6.05848E-07
2.33205E-07	-1.61807E-07	2.78926E-06	-2.39946E-06
-7.86708E-07	6.05848E-07	-2.39946E-06	7.41402E-06

AA	AB	AC	AD
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
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0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0.001689294	0	0	0
0.000359269	0.000425461	0	0
8.22259E-05	0.000502897	0.001548516	0
-0.000158975	-0.001702212	-0.000589895	5.78753E-05

Variance Covariance matrix estimated in R (FIT 150µg Hb/g faeces)

		A	B
No adenomas or cancer -> LR adenomas - age 30	A	2.66062E-07	-1.16693E-07
No adenomas or cancer -> LR adenomas - age 50	B	-1.16693E-07	2.64245E-07
No adenomas or cancer -> LR adenomas - age 70	C	1.91408E-07	-5.65562E-07
No adenomas or cancer -> LR adenomas - age 100	D	4.21827E-08	-2.77621E-07
LR adenomas -> high risk adenomas - age 30	E	-4.47636E-08	1.45906E-07
LR adenomas -> high risk adenomas - age 50	F	-4.75661E-09	-3.20587E-08
LR adenomas -> high risk adenomas - age 70	G	2.93769E-08	7.64447E-09
LR adenomas -> HR adenomas - age 100	H	1.63977E-07	-2.19758E-08
HR adenomas -> Dukes A CRC - age 30	I	1.40186E-07	-5.2681E-07
HR adenomas -> Dukes A CRC - age 50	J	1.11346E-07	-1.5435E-07
HR adenomas -> Dukes A CRC - age 70	K	3.59467E-07	-2.99458E-07
HR adenomas -> Dukes A CRC - age 100	L	2.87108E-07	-8.84609E-07
No adenomas or cancer -> CRC Dukes A	M	-1.70078E-10	6.58379E-10
Preclinical CRC: Dukes A -> Dukes B	N	1.17758E-05	-4.50991E-06
Preclinical CRC: Dukes B -> Dukes' C	O	1.84976E-06	-5.81292E-06
Preclinical CRC: Dukes C -> Stage D	P	6.9822E-07	-3.31421E-06
Symp->matic presention with CRC Dukes A	Q	6.67858E-07	-1.05565E-07
Symp->matic presention with CRC Dukes B	R	-8.75116E-07	-3.27589E-07
Symp->matic presention with CRC Dukes C	S	-3.7323E-06	2.54765E-06
Symp->matic presention with CRC Dukes D	T	-1.23939E-05	1.14957E-05
gFOBT Sensitivity for LR adenomas	U	-1.40039E-08	2.92266E-08
gFOBT Sensitivity for HR adenomas	V	4.43973E-08	-3.35101E-08
gFOBT Sensitivity for CRC	Q	-6.45772E-07	6.70417E-07
gFOBT Specificity age 50	X	9.93882E-08	-1.32247E-07
gFOBT Specificity age -70	Y	-8.14598E-08	1.66105E-07
FIT Sensitivity for LR adenomas	Z	-4.21964E-08	4.18304E-08
FIT Sensitivity for HR adenomas	AA	8.17364E-08	-8.93305E-08
FIT Sensitivity for CRC	AB	-5.87723E-07	5.84816E-07
FIT Specificity age 50	AC	3.48356E-08	-4.8371E-08
FIT Specificity age 70	AD	-7.58631E-08	1.63997E-07

CHOLESKY DECOMPOSITION MATRIX (FIT 150µg Hb/g faeces)

		A	B
No adenomas or cancer -> LR adenomas - age 30	A	0.000515812	0
No adenomas or cancer -> LR adenomas - age 50	B	-0.000226231	0.000461589
No adenomas or cancer -> LR adenomas - age 70	C	0.000371081	-0.001043377
No adenomas or cancer -> LR adenomas - age 100	D	8.17791E-05	-0.000561365
LR adenomas -> high risk adenomas - age 30	E	-8.67826E-05	0.000273561
LR adenomas -> high risk adenomas - age 50	F	-9.22158E-06	-7.39724E-05
LR adenomas -> high risk adenomas - age 70	G	5.69527E-05	4.44744E-05
LR adenomas -> HR adenomas - age 100	H	0.000317901	0.000108199
HR adenomas -> Dukes A CRC - age 30	I	0.000271778	-0.001008094
HR adenomas -> Dukes A CRC - age 50	J	0.000215865	-0.000228589
HR adenomas -> Dukes A CRC - age 70	K	0.000696895	-0.000307197
HR adenomas -> Dukes A CRC - age 100	L	0.000556613	-0.001643638

No adenomas or cancer -> CRC Dukes A	**M**	-3.29727E-07	1.26473E-06
Preclinical CRC: Dukes A -> Dukes B	**N**	0.022829575	0.001418676
Preclinical CRC: Dukes B -> Dukes' C	**O**	0.003586109	-0.010835668
Preclinical CRC: Dukes C -> Stage D	**P**	0.001353632	-0.006516572
Symptomatic presention with CRC Dukes A	**Q**	0.00129477	0.000405885
Symptomatic presention with CRC Dukes B	**R**	-0.001696577	-0.001541214
Symptomatic presention with CRC Dukes C	**S**	-0.007235771	0.00197296
Symptomatic presention with CRC Dukes D	**T**	-0.02402783	0.013128245
gFOBT Sensitivity for LR adenomas	**U**	-2.71493E-05	5.00112E-05
gFOBT Sensitivity for HR adenomas	**V**	8.60727E-05	-3.04119E-05
gFOBT Sensitivity for CRC	**Q**	-0.001251952	0.000838811
gFOBT Specificity age 50	**X**	0.000192683	-0.000192067
gFOBT Specificity age -70	**Y**	-0.000157925	0.000282452
FIT Sensitivity for LR adenomas	**Z**	-8.18057E-05	5.05285E-05
FIT Sensitivity for HR adenomas	**AA**	0.000158461	-0.000115864
FIT Sensitivity for CRC	**AB**	-0.001139411	0.00070852
FIT Specificity age 50	**AC**	6.75354E-05	-7.16923E-05
FIT Specificity age 70	**AD**	-0.000147075	0.000283205

C	D	E	F	G	H	I
1.91408E-07	4.21827E-08	-4.47636E-08	-4.75661E-09	2.93769E-08	1.63977E-07	1.40186E-07
-5.65562E-07	-2.77621E-07	1.45906E-07	-3.20587E-08	7.64447E-09	-2.19758E-08	-5.2681E-07
2.10878E-05	2.8991E-06	-3.52217E-06	1.06447E-06	-9.58217E-07	-2.82576E-06	1.37577E-05
2.8991E-06	4.40042E-05	9.55269E-07	-1.89242E-07	-1.20695E-08	-8.22501E-07	-6.1679E-06
-3.52217E-06	9.55269E-07	3.19374E-06	-4.43873E-07	4.13093E-07	1.20001E-06	-5.53515E-06
1.06447E-06	-1.89242E-07	-4.43873E-07	2.61114E-07	-1.22296E-07	-3.57019E-07	1.6518E-06
-9.58217E-07	-1.20695E-08	4.13093E-07	-1.22296E-07	2.62253E-07	4.1718E-07	-1.40589E-06
-2.82576E-06	-8.22501E-07	1.20001E-06	-3.57019E-07	4.1718E-07	3.19236E-06	-3.56717E-06
1.37577E-05	-6.1679E-06	-5.53515E-06	1.6518E-06	-1.40589E-06	-3.56717E-06	4.74412E-05
1.71523E-06	-2.9409E-07	-5.30826E-07	1.61291E-07	-8.43056E-08	-1.30966E-07	2.63514E-06
1.98408E-07	6.99791E-07	4.5205E-07	-1.30883E-07	2.74736E-07	1.21513E-06	-1.41613E-07
1.85193E-05	-4.02774E-06	-7.35744E-06	2.14644E-06	-1.92529E-06	-5.42132E-06	2.86756E-05
-1.62377E-08	8.78545E-09	5.67663E-09	-1.89341E-09	1.43911E-09	3.1273E-09	-2.98342E-08
-0.00012402	-0.000104227	5.08611E-05	-1.57845E-05	2.10459E-05	8.06761E-05	-0.000135295
0.000117707	1.71742E-05	-4.06885E-05	1.22858E-05	-1.09647E-05	-3.14411E-05	0.000164076
7.61289E-05	1.36046E-05	-2.62476E-05	8.10968E-06	-7.1503E-06	-2.04487E-05	0.000105952
-1.05951E-05	-8.4513E-06	3.99752E-06	-1.23002E-06	1.52876E-06	5.65793E-06	-1.16231E-05
2.72227E-05	2.84187E-06	-1.10974E-05	3.35295E-06	-3.57171E-06	-1.18626E-05	3.93586E-05
1.27906E-05	7.67771E-07	-9.32849E-06	2.78388E-06	-4.26469E-06	-1.72046E-05	1.99869E-05
-4.20298E-05	-1.16757E-05	-6.29222E-07	2.3249E-10	-5.56836E-06	-3.0804E-05	-5.092E-05
-5.52136E-07	-9.63796E-08	1.89199E-07	-5.6411E-08	5.13809E-08	1.43966E-07	-7.55393E-07
-3.02657E-07	2.07024E-07	1.30104E-07	-5.56928E-08	5.36593E-08	1.75272E-07	-6.32731E-07
-2.81688E-06	-8.13322E-06	-5.99648E-07	1.20139E-07	-2.91001E-07	-1.41849E-06	1.76237E-07
1.73759E-06	-8.0393E-07	-6.23371E-07	1.85297E-07	-1.2425E-07	-2.05071E-07	2.98666E-06
-3.27321E-06	2.43259E-07	1.16853E-06	-3.48695E-07	2.88618E-07	7.3224E-07	-5.00722E-06
-2.51732E-07	-8.11899E-08	5.67676E-08	-1.17264E-08	-2.73766E-10	1.83097E-08	-3.05726E-07
2.1146E-07	-2.84263E-06	-4.10396E-07	6.98607E-08	-5.20797E-09	2.25716E-07	1.30658E-06
-2.63053E-06	-9.07486E-06	-6.84266E-07	1.27788E-07	-3.14118E-07	-1.42698E-06	3.29942E-07
8.79576E-07	3.36044E-09	-2.41728E-07	6.8813E-08	-5.90416E-08	-6.32068E-08	1.25409E-06
-5.20935E-06	6.56447E-07	1.73624E-06	-5.21875E-07	4.37715E-07	9.14676E-07	-7.99204E-06

C	D	E	F	G	H	I
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.004456616	0	0	0	0	0	0
0.000512281	0.006589381	0	0	0	0	0
-0.000719053	0.000225255	0.001594867	0	0	0	0
0.000222301	-5.21891E-05	-0.000158531	0.000422236	0	0	0
-0.00020934	1.75252E-05	0.000157628	-0.00010904	0.00041972	0	0
-0.000635197	-7.01674E-05	0.000474685	-0.000315672	0.000365184	0.001487567	0
0.002828382	-0.00124518	-0.001831847	0.001410564	-0.000762547	-0.000162676	0.005554061
0.000313381	-9.11474E-05	-0.000127716	0.000122453	3.39536E-05	7.03747E-05	0.000175878
-8.54277E-05	7.80214E-05	0.000324519	-0.000172111	0.000380104	0.000424085	0.000160991
0.003724306	-0.001047721	-0.002473891	0.001788582	-0.001193417	-0.000641	0.001253136

-3.31994E-06	1.70322E-06	1.58707E-06	-1.71558E-06	5.70773E-07	-2.67139E-07	-2.02371E-06
-0.029397159	-0.013694508	0.021569728	-0.014752978	0.020871035	0.02091562	0.001019961
0.023576357	-0.000194179	-0.012801526	0.010033987	-0.006280756	-0.00329999	0.007620195
0.015443863	0.000291998	-0.008344466	0.006866567	-0.003920765	-0.001870934	0.004939009
-0.002390167	-0.001078235	0.001581993	-0.001094638	0.001398025	0.001345479	-7.58291E-05
0.005888822	-0.000136782	-0.004111835	0.002972783	-0.002856869	-0.002347473	0.001288058
0.003934409	6.85242E-05	-0.00481704	0.002909289	-0.004863667	-0.005131038	-0.000823115
-0.004356624	-1.65678E-05	-0.005915668	0.001846324	-0.010868448	-0.013441136	-0.007700466
-0.000109922	-1.48327E-06	5.92251E-05	-4.55066E-05	3.19744E-05	1.55318E-05	-3.40208E-05
-8.21987E-05	3.41492E-05	4.95937E-05	-6.92303E-05	4.03545E-05	2.77309E-05	-3.38465E-05
-0.000331442	-0.001121527	-0.000579018	0.000222622	-0.000455517	-0.000597624	-0.000164966
0.000328879	-0.000166326	-0.000175664	0.000149746	-2.59735E-05	6.17316E-05	0.000190958
-0.000655183	0.000113876	0.000364168	-0.000284047	0.000137052	2.09222E-05	-0.000271689
-3.78438E-05	-4.0593E-06	5.98695E-06	9.6376E-07	-1.56095E-05	1.18907E-05	-2.35745E-05
7.12841E-06	-0.000443787	-0.000162934	2.88363E-05	6.91344E-05	0.000149549	5.61495E-05
-0.000329502	-0.001277077	-0.000580758	0.000199468	-0.000509959	-0.000615402	-0.000204998
0.000174956	-2.00375E-05	-5.38843E-05	3.70684E-05	-2.4272E-05	5.3073E-05	8.69277E-05
-0.001090353	0.000210342	0.000510766	-0.000397753	0.000185059	-0.000122774	-0.000486648

Variance Covariance matrix esti

J	K	L	M		N	O
1.11346E-07	3.59467E-07	2.87108E-07	-1.70078E-10	**A**	1.17758E-05	1.84976E-06
-1.5435E-07	-2.99458E-07	-8.84609E-07	6.58379E-10	**B**	-4.50991E-06	-5.81292E-06
1.71523E-06	1.98408E-07	1.85193E-05	-1.62377E-08	**C**	-0.00012402	0.000117707
-2.9409E-07	6.99791E-07	-4.02774E-06	8.78545E-09	**D**	-0.000104227	1.71742E-05
-5.30826E-07	4.5205E-07	-7.35744E-06	5.67663E-09	**E**	5.08611E-05	-4.06885E-05
1.61291E-07	-1.30883E-07	2.14644E-06	-1.89341E-09	**F**	-1.57845E-05	1.22858E-05
-8.43056E-08	2.74736E-07	-1.92529E-06	1.43911E-09	**G**	2.10459E-05	-1.09647E-05
-1.30966E-07	1.21513E-06	-5.42132E-06	3.1273E-09	**H**	8.06761E-05	-3.14411E-05
2.63514E-06	-1.41613E-07	2.86756E-05	-2.98342E-08	**I**	-0.000135295	0.000164076
1.05029E-06	5.40519E-07	3.14125E-06	-4.07301E-09	**J**	3.00668E-06	1.98163E-05
5.40519E-07	4.20863E-06	-7.09506E-07	-1.35021E-09	**K**	7.41622E-05	1.0576E-06
3.14125E-06	-7.09506E-07	7.52291E-05	-3.34459E-08	**L**	-0.000217224	0.000215597
-4.07301E-09	-1.35021E-09	-3.34459E-08	1.09587E-10	**M**	9.85677E-08	-1.96945E-07
3.00668E-06	7.41622E-05	-0.000217224	9.85677E-08	**N**	0.009646046	-0.001373246
1.98163E-05	1.0576E-06	0.000215597	-1.96945E-07	**O**	-0.001373246	0.00268176
1.29068E-05	1.64288E-09	0.000137868	-1.28197E-07	**P**	-0.000923264	0.000867411
-3.16062E-07	4.35802E-06	-1.79222E-05	1.01874E-08	**Q**	0.000331473	-0.000115923
2.69619E-06	-7.14417E-06	5.328E-05	-4.22583E-08	**R**	-0.000603317	0.000314413
-3.55501E-06	-2.22707E-05	3.22159E-05	-6.13563E-09	**S**	-0.001025989	0.000156282
-2.44281E-05	-6.89732E-05	-4.58012E-05	1.11569E-07	**T**	-0.002178253	-0.000437537
-9.00769E-08	-8.91438E-09	-9.95467E-07	9.08898E-10	**U**	6.63946E-06	-6.14305E-06
-1.75735E-09	1.94995E-07	-7.52544E-07	9.79043E-10	**V**	8.51865E-06	-3.43463E-06
-9.99232E-07	-3.77054E-06	-2.20521E-07	2.13009E-09	**Q**	-7.01531E-05	-2.51006E-05
4.49649E-07	3.80077E-07	3.49541E-06	-4.13191E-09	**X**	-2.50537E-06	2.06089E-05
-6.33866E-07	-2.23081E-07	-6.17253E-06	6.20186E-09	**Y**	2.85622E-05	-3.72543E-05
-8.57072E-08	-1.16779E-07	-4.13056E-07	1.76079E-10	**Z**	1.28397E-06	-2.48481E-06
2.42701E-07	2.65534E-07	1.33705E-06	-9.05241E-10	**AA**	2.2114E-05	3.68175E-06
-9.69102E-07	-3.80252E-06	4.14971E-07	1.9669E-09	**AB**	-8.08542E-05	-2.25676E-05
2.44468E-07	2.47947E-07	1.50024E-06	-1.82005E-09	**AC**	3.85941E-11	9.90166E-06
-1.04745E-06	-5.13789E-07	-9.43522E-06	9.73706E-09	**AD**	2.84879E-05	-6.00825E-05

CHOLESKY DECOMPOSITION M/

J	K	L	M		N	O
0	0	0	0	**A**	0	0
0	0	0	0	**B**	0	0
0	0	0	0	**C**	0	0
0	0	0	0	**D**	0	0
0	0	0	0	**E**	0	0
0	0	0	0	**F**	0	0
0	0	0	0	**G**	0	0
0	0	0	0	**H**	0	0
0	0	0	0	**I**	0	0
0.000881239	0	0	0	**J**	0	0
0.000391723	0.00172528	0	0	**K**	0	0
0.000809106	6.66604E-05	0.006623132	0	**L**	0	0

-1.98467E-06	-5.55929E-07	-8.07957E-07	8.89386E-06	**M**	0	0
0.009723281	0.01560919	-0.003712211	-0.000989343	**N**	0.078493031	0
0.006128628	0.001912505	0.005121459	-0.003422155	**O**	-0.002632712	0.039198868
0.004313699	0.001183319	0.003114978	-0.00227582	**P**	-0.001793857	0.003228936
0.000403122	0.000875713	-0.000315691	6.00834E-06	**Q**	0.00114709	-0.000369414
-1.48222E-06	-0.00127567	0.001160291	-0.00063231	**R**	-0.001625478	0.000944551
-0.003482879	-0.00504603	0.000434422	0.000555178	**S**	-0.003512625	5.64063E-06
-0.014966296	-0.017037839	-0.001701531	0.003557783	**T**	-0.008883614	-0.003387636
-2.44324E-05	-8.49141E-06	-2.28495E-05	1.65958E-05	**U**	1.69694E-05	-2.04581E-05
2.15893E-05	3.35403E-05	-2.61762E-05	5.32473E-05	**V**	4.985E-06	-1.60451E-06
-0.000624423	-0.000960554	-1.01076E-05	8.45731E-05	**Q**	-0.000112165	-0.000291789
0.000190761	0.000109473	8.73595E-05	-0.000110956	**X**	3.139E-05	7.04567E-05
-0.000223047	-0.000108987	-0.00014296	0.000125586	**Y**	3.13763E-05	-0.000123125
-4.59834E-05	-1.521E-05	-1.1768E-05	-2.09381E-05	**Z**	3.20808E-05	-4.61015E-06
0.000104668	4.22202E-05	2.00419E-05	8.35014E-05	**AA**	0.000134852	-1.16223E-05
-0.000653903	-0.001015809	2.41571E-05	0.000102214	**AB**	-0.000272943	-0.000278929
0.000144372	7.84825E-05	3.72479E-05	-4.25933E-05	**AC**	2.43725E-05	4.45217E-05
-0.000440525	-0.000252381	-0.000227451	0.000172882	**AD**	-0.000100171	-0.000282368

imated in R (FIT 150μg Hb/g faeces) contd.

P	Q	R	S	T	U	V
6.9822E-07	6.67858E-07	-8.75116E-07	-3.7323E-06	-1.23939E-05	-1.40039E-08	4.43973E-08
-3.31421E-06	-1.05565E-07	-3.27589E-07	2.54765E-06	1.14957E-05	2.92266E-08	-3.35101E-08
7.61289E-05	-1.05951E-05	2.72227E-05	1.27906E-05	-4.20298E-05	-5.52136E-07	-3.02657E-07
1.36046E-05	-8.4513E-06	2.84187E-06	7.67771E-07	-1.16757E-05	-9.63796E-08	2.07024E-07
-2.62476E-05	3.99752E-06	-1.10974E-05	-9.32849E-06	-6.29222E-07	1.89199E-07	1.30104E-07
8.10968E-06	-1.23002E-06	3.35295E-06	2.78388E-06	2.3249E-10	-5.6411E-08	-5.56928E-08
-7.1503E-06	1.52876E-06	-3.57171E-06	-4.26469E-06	-5.56836E-06	5.13809E-08	5.36593E-08
-2.04487E-05	5.65793E-06	-1.18626E-05	-1.72046E-05	-3.0804E-05	1.43966E-07	1.75272E-07
0.000105952	-1.16231E-05	3.93586E-05	1.99869E-05	-5.092E-05	-7.55393E-07	-6.32731E-07
1.29068E-05	-3.16062E-07	2.69619E-06	-3.55501E-06	-2.44281E-05	-9.00769E-08	-1.75735E-09
1.64288E-09	4.35802E-06	-7.14417E-06	-2.22707E-05	-6.89732E-05	-8.91438E-09	1.94995E-07
0.000137868	-1.79222E-05	5.328E-05	3.22159E-05	-4.58012E-05	-9.95467E-07	-7.52544E-07
-1.28197E-07	1.01874E-08	-4.22583E-08	-6.13563E-09	1.11569E-07	9.08898E-10	9.79043E-10
-0.000923264	0.000331473	-0.000603317	-0.001025989	-0.002178253	6.63946E-06	8.51865E-06
0.000867411	-0.000115923	0.000314413	0.000156282	-0.000437537	-6.14305E-06	-3.43463E-06
0.001168524	-7.88755E-05	0.000207543	0.000111097	-0.000276783	-3.92438E-06	-2.44141E-06
-7.88755E-05	4.74412E-05	-4.42785E-05	-6.55565E-05	-0.000118814	5.53412E-07	5.62346E-07
0.000207543	-4.42785E-05	0.000204082	0.000119388	0.000145846	-1.45753E-06	-1.45796E-06
0.000111097	-6.55565E-05	0.000119388	0.000538903	0.000710997	-7.39676E-07	-2.01417E-06
-0.000276783	-0.000118814	0.000145846	0.000710997	0.004957309	1.88618E-06	-3.95178E-06
-3.92438E-06	5.53412E-07	-1.45753E-06	-7.39676E-07	1.88618E-06	6.59883E-08	1.58265E-08
-2.44141E-06	5.62346E-07	-1.45796E-06	-2.01417E-06	-3.95178E-06	1.58265E-08	1.04254E-06
-1.65694E-05	-2.63586E-06	6.92487E-06	3.49419E-05	0.000123933	1.33345E-07	-3.6826E-07
1.36043E-05	-5.97238E-07	3.49806E-06	-1.54115E-06	-1.90396E-05	-9.98745E-08	-3.37322E-08
-2.4592E-05	2.5827E-06	-8.19909E-06	-2.48542E-06	1.88601E-05	1.78601E-07	9.80476E-08
-1.64247E-06	1.41714E-07	-4.64484E-07	8.3681E-08	1.99848E-06	2.43206E-08	-3.80963E-10
1.61947E-06	1.38735E-06	-5.07135E-07	-3.57412E-06	-1.25148E-05	-2.4819E-09	1.04555E-07
-1.65483E-05	-3.50067E-06	7.95119E-06	3.76466E-05	0.00013297	8.94292E-08	-2.95092E-07
6.84749E-06	-1.88069E-07	1.56065E-06	-1.0574E-06	-1.08983E-05	-4.73759E-08	1.40467E-07
-4.0486E-05	2.99706E-06	-1.17413E-05	-5.63739E-07	4.08436E-05	2.7948E-07	7.89902E-08

ATRIX (FIT 150μg Hb/g faeces) contd.

P	Q	R	S	T	U	V
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
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0	0	0	0	0	0	0
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0	0	0	0	0	0	0
0	0	0	0	0	0	0

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0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.026020122	0	0	0	0	0	0
-0.0003917	0.005349606	0	0	0	0	0
0.000872728	-0.001210585	0.01067335	0	0	0	0
0.000106676	-0.002436641	0.001715007	0.018042276	0	0	0
-0.003461423	-0.005871496	0.003336341	0.009763929	0.054945479	0	0
-1.58976E-05	1.28926E-05	-1.18469E-05	4.76355E-07	6.47506E-06	0.000199727	0
-5.61491E-06	-3.93379E-07	-1.08178E-05	1.474E-07	-2.86998E-06	3.79791E-06	0.001005077
-0.000292726	4.23765E-05	0.000149589	0.000508566	0.000528591	0.000229116	-0.000108303
7.6458E-05	2.29874E-05	1.3188E-05	-3.37662E-05	-5.98694E-05	-6.87505E-05	2.45761E-06
-0.000125621	2.06954E-05	-5.78588E-05	2.52179E-05	8.1395E-05	0.000108289	5.6096E-06
-8.38596E-06	2.13836E-05	-1.84582E-05	-2.71497E-05	-2.09926E-05	6.16685E-05	6.07967E-06
-2.72509E-05	9.72892E-05	-3.22001E-05	-3.45881E-05	-1.60564E-05	6.80542E-05	9.86221E-05
-0.000333974	-0.0001076	0.000185334	0.000622508	0.000661873	7.09957E-05	-3.95116E-05
5.51388E-05	2.62202E-05	1.44836E-05	-1.28031E-05	-4.25706E-05	-3.86878E-05	0.000152401
-0.00029738	-8.61321E-05	-6.04268E-05	0.000130034	0.000234228	0.000209803	-6.92356E-05

Q	X	Y	Z	AA	AB	AC
-6.45772E-07	9.93882E-08	-8.14598E-08	-4.21964E-08	8.17364E-08	-5.87723E-07	3.48356E-08
6.70417E-07	-1.32247E-07	1.66105E-07	4.18304E-08	-8.93305E-08	5.84816E-07	-4.8371E-08
-2.81688E-06	1.73759E-06	-3.27321E-06	-2.51732E-07	2.1146E-07	-2.63053E-06	8.79576E-07
-8.13322E-06	-8.0393E-07	2.43259E-07	-8.11899E-08	-2.84263E-06	-9.07486E-06	3.36044E-09
-5.99648E-07	-6.23371E-07	1.16853E-06	5.67676E-08	-4.10396E-07	-6.84266E-07	-2.41728E-07
1.20139E-07	1.85297E-07	-3.48695E-07	-1.17264E-08	6.98607E-08	1.27788E-07	6.8813E-08
-2.91001E-07	-1.2425E-07	2.88618E-07	-2.73766E-10	-5.20797E-09	-3.14118E-07	-5.90416E-08
-1.41849E-06	-2.05071E-07	7.3224E-07	1.83097E-08	2.25716E-07	-1.42698E-06	-6.32068E-08
1.76237E-07	2.98666E-06	-5.00722E-06	-3.05726E-07	1.30658E-06	3.29942E-07	1.25409E-06
-9.99232E-07	4.49649E-07	-6.33866E-07	-8.57072E-08	2.42701E-07	-9.69102E-07	2.44468E-07
-3.77054E-06	3.80077E-07	-2.23081E-07	-1.16779E-07	2.65534E-07	-3.80252E-06	2.47947E-07
-2.20521E-07	3.49541E-06	-6.17253E-06	-4.13056E-07	1.33705E-06	4.14971E-07	1.50024E-06
2.13009E-09	-4.13191E-09	6.20186E-09	1.76079E-10	-9.05241E-10	1.9669E-09	-1.82005E-09
-7.01531E-05	-2.50537E-06	2.85622E-05	1.28397E-06	2.2114E-05	-8.08542E-05	3.85941E-11
-2.51006E-05	2.06089E-05	-3.72543E-05	-2.48481E-06	3.68175E-06	-2.25676E-05	9.90166E-06
-1.65694E-05	1.36043E-05	-2.4592E-05	-1.64247E-06	1.61947E-06	-1.65483E-05	6.84749E-06
-2.63586E-06	-5.97238E-07	2.5827E-06	1.41714E-07	1.38735E-06	-3.50067E-06	-1.88069E-07
6.92487E-06	3.49806E-06	-8.19909E-06	-4.64484E-07	-5.07135E-07	7.95119E-06	1.56065E-06
3.49419E-05	-1.54115E-06	-2.48542E-06	8.3681E-08	-3.57412E-06	3.76466E-05	-1.0574E-06
0.000123933	-1.90396E-05	1.88601E-05	1.99848E-06	-1.25148E-05	0.00013297	-1.08983E-05
1.33345E-07	-9.98745E-08	1.78601E-07	2.43206E-08	-2.4819E-09	8.94292E-08	-4.73759E-08
-3.6826E-07	-3.37322E-08	9.80476E-08	-3.80963E-10	1.04555E-07	-2.95092E-07	1.40467E-07
2.6042E-05	-6.5868E-07	7.12961E-07	1.21143E-07	1.93867E-07	9.80679E-06	-3.28404E-07
-6.5868E-07	1.04683E-06	-7.10003E-07	-7.40273E-08	6.37186E-08	-6.87292E-07	1.69519E-07
7.12961E-07	-7.10003E-07	2.35196E-06	1.12664E-07	-4.30984E-08	7.8333E-07	-2.8165E-07
1.21143E-07	-7.40273E-08	1.12664E-07	5.01416E-07	-1.33018E-07	2.60722E-07	-8.21961E-08
1.93867E-07	6.37186E-08	-4.30984E-08	-1.33018E-07	3.64169E-06	6.93195E-07	2.33305E-07
9.80679E-06	-6.87292E-07	7.8333E-07	2.60722E-07	6.93195E-07	7.93148E-06	-1.59147E-07
-3.28404E-07	1.69519E-07	-2.8165E-07	-8.21961E-08	2.33305E-07	-1.59147E-07	2.78814E-06
7.25362E-07	-9.02268E-07	1.68864E-06	8.68408E-07	-7.9322E-07	6.54343E-07	-2.40059E-06

Q	X	Y	Z	AA	AB	AC
0	0	0	0	0	0	0
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0.004392829	0	0	0	0	0	0
-1.58156E-05	0.00080761	0	0	0	0	0
2.17642E-05	-0.000146441	0.001150736	0	0	0	0
-1.59304E-05	-2.70768E-05	2.75281E-05	0.000691477	0	0	0
3.37193E-05	-0.00016555	0.000101396	-0.000183394	0.001791796	0	0
0.000664164	-0.000159259	0.000167275	0.000155441	0.000316487	0.000320354	0
2.27263E-05	-1.52768E-05	-8.75986E-06	-8.3595E-05	7.41943E-05	0.00072933	0.001457235
-0.00010353	7.34081E-05	9.62268E-05	0.001102669	-0.000136197	-0.001832842	-0.000324149

AD
-7.58631E-08
1.63997E-07
-5.20935E-06
6.56447E-07
1.73624E-06
-5.21875E-07
4.37715E-07
9.14676E-07
-7.99204E-06
-1.04745E-06
-5.13789E-07
-9.43522E-06
9.73706E-09
2.84879E-05
-6.00825E-05
-4.0486E-05
2.99706E-06
-1.17413E-05
-5.63739E-07
4.08436E-05
2.7948E-07
7.89902E-08
7.25362E-07
-9.02268E-07
1.68864E-06
8.68408E-07
-7.9322E-07
6.54343E-07
-2.40059E-06
7.41842E-06

AD
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6.94378E-05

Variance Covariance matrix estimated in R (FIT 100µg Hb/g faeces)

		A	B
No adenomas or cancer -> LR adenomas - age 30	A	2.67102E-07	-1.17794E-07
No adenomas or cancer -> LR adenomas - age 50	B	-1.17794E-07	2.65364E-07
No adenomas or cancer -> LR adenomas - age 70	C	1.93817E-07	-5.67782E-07
No adenomas or cancer -> LR adenomas - age 100	D	4.78531E-08	-2.82809E-07
LR adenomas -> high risk adenomas - age 30	E	-4.25299E-08	1.43789E-07
LR adenomas -> high risk adenomas - age 50	F	-5.0551E-09	-3.17247E-08
LR adenomas -> high risk adenomas - age 70	G	2.99016E-08	7.07298E-09
LR adenomas -> HR adenomas - age 100	H	1.66094E-07	-2.39633E-08
HR adenomas -> Dukes A CRC - age 30	I	1.39804E-07	-5.26467E-07
HR adenomas -> Dukes A CRC - age 50	J	1.13168E-07	-1.56178E-07
HR adenomas -> Dukes A CRC - age 70	K	3.67001E-07	-3.06521E-07
HR adenomas -> Dukes A CRC - age 100	L	2.86712E-07	-8.84249E-07
No adenomas or cancer -> CRC Dukes A	M	-1.71782E-10	6.59492E-10
Preclinical CRC: Dukes A -> Dukes B	N	1.17759E-05	-4.50999E-06
Preclinical CRC: Dukes B -> Dukes' C	O	1.84994E-06	-5.81309E-06
Preclinical CRC: Dukes C -> Stage D	P	6.98611E-07	-3.31457E-06
Symptomatic presention with CRC Dukes A	Q	6.68087E-07	-1.05768E-07
Symptomatic presention with CRC Dukes B	R	-8.75541E-07	-3.27206E-07
Symptomatic presention with CRC Dukes C	S	-3.7334E-06	2.54865E-06
Symptomatic presention with CRC Dukes D	T	-1.23943E-05	1.14961E-05
gFOBT Sensitivity for LR adenomas	U	-1.40361E-08	2.93357E-08
gFOBT Sensitivity for HR adenomas	V	4.538E-08	-3.44555E-08
gFOBT Sensitivity for CRC	Q	-6.51454E-07	6.75603E-07
gFOBT Specificity age 50	X	1.0124E-07	-1.34047E-07
gFOBT Specificity age -70	Y	-8.40019E-08	1.68556E-07
FIT Sensitivity for LR adenomas	Z	-4.46912E-08	4.8504E-08
FIT Sensitivity for HR adenomas	AA	1.13821E-07	-1.23519E-07
FIT Sensitivity for CRC	AB	-6.19147E-07	6.17149E-07
FIT Specificity age 50	AC	3.35011E-08	-4.73026E-08
FIT Specificity age 70	AD	-7.35862E-08	1.6166E-07

CHOLESKY DECOMPOSITION MATRIX (FIT 100µg Hb/g faeces)

		A	B
No adenomas or cancer -> LR adenomas - age 30	A	0.000516819	0
No adenomas or cancer -> LR adenomas - age 50	B	-0.000227921	0.00046197
No adenomas or cancer -> LR adenomas - age 70	C	0.000375019	-0.001044022
No adenomas or cancer -> LR adenomas - age 100	D	9.25916E-05	-0.000566499
LR adenomas -> high risk adenomas - age 30	E	-8.22917E-05	0.000270652
LR adenomas -> high risk adenomas - age 50	F	-9.78117E-06	-7.34982E-05
LR adenomas -> high risk adenomas - age 70	G	5.7857E-05	4.38552E-05
LR adenomas -> HR adenomas - age 100	H	0.000321378	0.000106685
HR adenomas -> Dukes A CRC - age 30	I	0.000270509	-0.001006152
HR adenomas -> Dukes A CRC - age 50	J	0.000218971	-0.000230037
HR adenomas -> Dukes A CRC - age 70	K	0.000710116	-0.000313161
HR adenomas -> Dukes A CRC - age 100	L	0.000554763	-0.00164038

No adenomas or cancer -> CRC Dukes A	**M**	-3.32384E-07	1.26358E-06
Preclinical CRC: Dukes A -> Dukes B	**N**	0.02278528	0.001478994
Preclinical CRC: Dukes B -> Dukes' C	**O**	0.00357948	-0.010817257
Preclinical CRC: Dukes C -> Stage D	**P**	0.001351753	-0.006507956
Symptomatic presention with CRC Dukes A	**Q**	0.001292691	0.000408821
Symptomatic presention with CRC Dukes B	**R**	-0.001694096	-0.001544095
Symptomatic presention with CRC Dukes C	**S**	-0.007223802	0.001952933
Symptomatic presention with CRC Dukes D	**T**	-0.023981942	0.013053101
gFOBT Sensitivity for LR adenomas	**U**	-2.71586E-05	5.01022E-05
gFOBT Sensitivity for HR adenomas	**V**	8.78063E-05	-3.1263E-05
gFOBT Sensitivity for CRC	**Q**	-0.001260507	0.000840546
gFOBT Specificity age 50	**X**	0.000195891	-0.000193516
gFOBT Specificity age -70	**Y**	-0.000162537	0.000284673
FIT Sensitivity for LR adenomas	**Z**	-8.64736E-05	6.23306E-05
FIT Sensitivity for HR adenomas	**AA**	0.000220233	-0.000158718
FIT Sensitivity for CRC	**AB**	-0.001197996	0.000744855
FIT Specificity age 50	**AC**	6.48217E-05	-7.04123E-05
FIT Specificity age 70	**AD**	-0.000142383	0.000279688

C	D	E	F	G	H	I
1.93817E-07	4.78531E-08	-4.25299E-08	-5.0551E-09	2.99016E-08	1.66094E-07	1.39804E-07
-5.67782E-07	-2.82809E-07	1.43789E-07	-3.17247E-08	7.07298E-09	-2.39633E-08	-5.26467E-07
2.1091E-05	2.90651E-06	-3.51874E-06	1.06365E-06	-9.56891E-07	-2.82264E-06	1.37572E-05
2.90651E-06	4.4021E-05	9.63153E-07	-1.91178E-07	-8.93657E-09	-8.15353E-07	-6.16892E-06
-3.51874E-06	9.63153E-07	3.19723E-06	-4.44608E-07	4.14304E-07	1.20321E-06	-5.53565E-06
1.06365E-06	-1.91178E-07	-4.44608E-07	2.61193E-07	-1.2244E-07	-3.57722E-07	1.65193E-06
-9.56891E-07	-8.93657E-09	4.14304E-07	-1.2244E-07	2.62513E-07	4.18333E-07	-1.4061E-06
-2.82264E-06	-8.15353E-07	1.20321E-06	-3.57722E-07	4.18333E-07	3.1953E-06	-3.56762E-06
1.37572E-05	-6.16892E-06	-5.53565E-06	1.65193E-06	-1.4061E-06	-3.56762E-06	4.74413E-05
1.71874E-06	-2.85905E-07	-5.27444E-07	1.6073E-07	-8.33519E-08	-1.27802E-07	2.6346E-06
2.09442E-07	7.25051E-07	4.63416E-07	-1.33391E-07	2.78843E-07	1.22554E-06	-1.43191E-07
1.85188E-05	-4.02888E-06	-7.35798E-06	2.14657E-06	-1.92551E-06	-5.42181E-06	2.86757E-05
-1.62441E-08	8.79872E-09	5.68166E-09	-1.8937E-09	1.43883E-09	3.13112E-09	-2.98525E-08
-0.00012402	-0.000104227	5.08612E-05	-1.57845E-05	2.1046E-05	8.06762E-05	-0.000135295
0.000117707	1.71748E-05	-4.06883E-05	1.22857E-05	-1.09646E-05	-3.14409E-05	0.000164076
7.61294E-05	1.36057E-05	-2.62471E-05	8.10954E-06	-7.15009E-06	-2.04482E-05	0.000105952
-1.05948E-05	-8.45073E-06	3.9978E-06	-1.2301E-06	1.52889E-06	5.65819E-06	-1.16231E-05
2.72222E-05	2.8407E-06	-1.1098E-05	3.3531E-06	-3.57195E-06	-1.18631E-05	3.93587E-05
1.27892E-05	7.64629E-07	-9.32998E-06	2.78426E-06	-4.26529E-06	-1.72059E-05	1.99871E-05
-4.20304E-05	-1.1677E-05	-6.29853E-07	3.90928E-10	-5.56862E-06	-3.08046E-05	-5.09199E-05
-5.52736E-07	-9.78496E-08	1.88736E-07	-5.64299E-08	5.13894E-08	1.43498E-07	-7.55284E-07
-3.01049E-07	2.10735E-07	1.31713E-07	-5.60109E-08	5.41869E-08	1.76759E-07	-6.32968E-07
-2.82422E-06	-8.14985E-06	-6.07483E-07	1.22082E-07	-2.94144E-07	-1.42559E-06	1.77245E-07
1.74074E-06	-7.9663E-07	-6.20245E-07	1.84705E-07	-1.23261E-07	-2.02172E-07	2.98619E-06
-3.27741E-06	2.33559E-07	1.16434E-06	-3.47874E-07	2.87255E-07	7.28361E-07	-5.0066E-06
-3.7678E-07	-1.12291E-07	9.94801E-08	-2.55589E-08	1.12939E-08	3.80347E-08	-4.65703E-07
2.88261E-07	-3.8953E-06	-5.62005E-07	9.47878E-08	-5.89345E-09	3.08558E-07	1.78915E-06
-2.84154E-06	-9.846E-06	-7.10849E-07	1.31955E-07	-3.30762E-07	-1.52678E-06	3.55652E-07
8.7892E-07	2.02717E-09	-2.4279E-07	6.93273E-08	-5.9831E-08	-6.40737E-08	1.25416E-06
-5.20451E-06	6.67543E-07	1.74071E-06	-5.22547E-07	4.38881E-07	9.18888E-07	-7.99263E-06

C	D	E	F	G	H	I
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.004456501	0	0	0	0	0	0
0.000511691	0.00659012	0	0	0	0	0
-0.000719244	0.000226419	0.001596444	0	0	0	0
0.000222279	-5.24493E-05	-0.000158961	0.000422218	0	0	0
-0.000209313	1.78531E-05	0.00015823	-0.000109035	0.000419746	0	0
-0.000635426	-6.97302E-05	0.000475775	-0.000316243	0.000365789	0.001487223	0
0.002828529	-0.001246	-0.001831916	0.00141005	-0.000761706	-0.000161816	0.00555447
0.000313352	-9.05653E-05	-0.000126082	0.000122023	3.46108E-05	7.06551E-05	0.000176347
-8.61241E-05	7.98109E-05	0.000329855	-0.00017455	0.000383123	0.000423134	0.000162638
0.003724478	-0.001049345	-0.002475477	0.001788227	-0.001192808	-0.000640141	0.001253824

-3.32106E-06	1.70629E-06	1.58937E-06	-1.71414E-06	5.68579E-07	-2.65201E-07	-2.02589E-06
-0.029400007	-0.013725894	0.021483968	-0.014738222	0.020840474	0.0208788	0.00098606
0.023577153	-0.000204676	-0.012817201	0.010034685	-0.006281031	-0.003295351	0.007621464
0.015444415	0.000286952	-0.008350517	0.006866403	-0.003919781	-0.001866751	0.004940812
-0.002390394	-0.00107975	0.001577714	-0.001094008	0.001396501	0.001343099	-7.7714E-05
0.00588925	-0.00013515	-0.004104778	0.002970964	-0.002853313	-0.002343288	0.001291875
0.00393518	7.98514E-05	-0.004786091	0.002903285	-0.00485263	-0.005121183	-0.000812246
-0.004355201	2.52785E-05	-0.005809405	0.001826369	-0.010833296	-0.013415143	-0.007667519
-0.000110006	-1.618E-06	5.89971E-05	-4.56344E-05	3.2057E-05	1.5223E-05	-3.40413E-05
-8.22657E-05	3.44438E-05	5.0382E-05	-6.95104E-05	4.07211E-05	2.76728E-05	-3.36241E-05
-0.000330744	-0.001121032	-0.000578016	0.00022351	-0.000456138	-0.000595713	-0.000164772
0.000328788	-0.000165799	-0.000173968	0.000149129	-2.51139E-05	6.18563E-05	0.000191526
-0.000655054	0.000113057	0.000361539	-0.000283114	0.000135723	2.063E-05	-0.000272621
-6.26672E-05	-5.60049E-06	1.98498E-05	-1.19189E-05	-9.27714E-06	6.14895E-06	-2.92055E-05
8.96758E-06	-0.000608516	-0.000223431	3.754E-05	9.65174E-05	0.000202289	7.74712E-05
-0.000362308	-0.001385062	-0.000600093	0.000207191	-0.000542424	-0.000671446	-0.000213362
0.000175272	-2.02649E-05	-5.49643E-05	3.79587E-05	-2.52753E-05	5.37683E-05	8.64182E-05
-0.001090342	0.000211998	0.00051431	-0.000398251	0.000185929	-0.000122303	-0.000485902

Variance Covariance matrix esti

J	K	L	M		N	O
1.13168E-07	3.67001E-07	2.86712E-07	-1.71782E-10	**A**	1.17759E-05	1.84994E-06
-1.56178E-07	-3.06521E-07	-8.84249E-07	6.59492E-10	**B**	-4.50999E-06	-5.81309E-06
1.71874E-06	2.09442E-07	1.85188E-05	-1.62441E-08	**C**	-0.00012402	0.000117707
-2.85905E-07	7.25051E-07	-4.02888E-06	8.79872E-09	**D**	-0.000104227	1.71748E-05
-5.27444E-07	4.63416E-07	-7.35798E-06	5.68166E-09	**E**	5.08612E-05	-4.06883E-05
1.6073E-07	-1.33391E-07	2.14657E-06	-1.8937E-09	**F**	-1.57845E-05	1.22857E-05
-8.33519E-08	2.78843E-07	-1.92551E-06	1.43883E-09	**G**	2.1046E-05	-1.09646E-05
-1.27802E-07	1.22554E-06	-5.42181E-06	3.13112E-09	**H**	8.06762E-05	-3.14409E-05
2.6346E-06	-1.43191E-07	2.86757E-05	-2.98525E-08	**I**	-0.000135295	0.000164076
1.05327E-06	5.51759E-07	3.14068E-06	-4.07614E-09	**J**	3.00679E-06	1.98165E-05
5.51759E-07	4.24548E-06	-7.11236E-07	-1.34376E-09	**K**	7.41625E-05	1.05841E-06
3.14068E-06	-7.11236E-07	7.52292E-05	-3.34663E-08	**L**	-0.000217224	0.000215597
-4.07614E-09	-1.34376E-09	-3.34663E-08	1.0959E-10	**M**	9.8626E-08	-1.97062E-07
3.00679E-06	7.41625E-05	-0.000217224	9.8626E-08	**N**	0.009646046	-0.001373246
1.98165E-05	1.05841E-06	0.000215597	-1.97062E-07	**O**	-0.001373246	0.00268176
1.29074E-05	3.3986E-09	0.000137868	-1.28272E-07	**P**	-0.000923264	0.000867411
-3.15745E-07	4.35893E-06	-1.79223E-05	1.01939E-08	**Q**	0.000331473	-0.000115923
2.69559E-06	-7.14597E-06	5.32801E-05	-4.2284E-08	**R**	-0.000603317	0.000314413
-3.55658E-06	-2.22755E-05	3.22161E-05	-6.14094E-09	**S**	-0.001025989	0.000156282
-2.44287E-05	-6.89752E-05	-4.58011E-05	1.11634E-07	**T**	-0.002178253	-0.000437537
-9.02944E-08	-1.05993E-08	-9.95362E-07	9.11027E-10	**U**	6.63944E-06	-6.1431E-06
-2.39638E-10	2.00268E-07	-7.528E-07	9.80071E-10	**V**	8.5187E-06	-3.43452E-06
-1.00741E-06	-3.79561E-06	-2.1939E-07	2.12301E-09	**Q**	-7.01534E-05	-2.51011E-05
4.52547E-07	3.90357E-07	3.49491E-06	-4.13387E-09	**X**	-2.50527E-06	2.06091E-05
-6.37805E-07	-2.36833E-07	-6.17186E-06	6.20448E-09	**Y**	2.8562E-05	-3.72546E-05
-1.08092E-07	-1.42987E-07	-6.29769E-07	3.51834E-10	**Z**	1.95586E-06	-3.78458E-06
3.33892E-07	3.6171E-07	1.83078E-06	-1.22632E-09	**AA**	3.02754E-05	5.04041E-06
-1.02401E-06	-4.03768E-06	4.4825E-07	2.17063E-09	**AB**	-8.84939E-05	-2.46975E-05
2.42873E-07	2.44949E-07	1.50035E-06	-1.82619E-09	**AC**	2.53225E-11	9.90187E-06
-1.0436E-06	-4.98751E-07	-9.43579E-06	9.74069E-09	**AD**	2.84875E-05	-6.00811E-05

CHOLESKY DECOMPOSITION M/

J	K	L	M		N	O
0	0	0	0	**A**	0	0
0	0	0	0	**B**	0	0
0	0	0	0	**C**	0	0
0	0	0	0	**D**	0	0
0	0	0	0	**E**	0	0
0	0	0	0	**F**	0	0
0	0	0	0	**G**	0	0
0	0	0	0	**H**	0	0
0	0	0	0	**I**	0	0
0.000882008	0	0	0	**J**	0	0
0.000396245	0.001726499	0	0	**K**	0	0
0.000810465	6.78326E-05	0.006623135	0	**L**	0	0

-1.98595E-06	-5.48454E-07	-8.08449E-07	8.89279E-06	**M**	0	0
0.0095962	0.015388354	-0.003719841	-0.001025761	**N**	0.078601228	0
0.006126476	0.00190499	0.005120669	-0.003428841	**O**	-0.002615444	0.039200202
0.00431554	0.00118376	0.003114558	-0.002279858	**P**	-0.001786513	0.00322968
0.000396112	0.000863169	-0.000316092	4.17427E-06	**Q**	0.001157384	-0.000367654
1.14889E-05	-0.001254515	0.001160978	-0.000629587	**R**	-0.001643571	0.000941272
-0.003442229	-0.004977676	0.000436982	0.000567773	**S**	-0.003577324	-5.56785E-06
-0.014838931	-0.016823517	-0.001692958	0.003601713	**T**	-0.009096396	-0.003423997
-2.45724E-05	-9.17729E-06	-2.28349E-05	1.67188E-05	**U**	1.71063E-05	-2.03706E-05
2.22654E-05	3.41004E-05	-2.61427E-05	5.34597E-05	**V**	4.29313E-06	-1.70467E-06
-0.0006226	-0.000953543	-9.94971E-06	8.52621E-05	**Q**	-0.00011793	-0.000293014
0.000192387	0.000111022	8.74163E-05	-0.000110759	**X**	2.98153E-05	7.01359E-05
-0.000225821	-0.000111953	-0.000143069	0.000125149	**Y**	3.42655E-05	-0.000122571
-5.29416E-05	-2.83576E-05	-1.61938E-05	-2.16195E-05	**Z**	2.8859E-05	-7.73434E-06
0.000144204	5.38037E-05	2.76364E-05	0.000115704	**AA**	0.000183904	-1.55255E-05
-0.000679529	-0.001068274	2.84714E-05	0.000122116	**AB**	-0.000347211	-0.000313632
0.000142854	7.79659E-05	3.71026E-05	-4.34539E-05	**AC**	2.65142E-05	4.47105E-05
-0.000437512	-0.000247401	-0.00022726	0.000173875	**AD**	-0.000104969	-0.000283212

imated in R (FIT 100µg Hb/g faeces) contd.

P	Q	R	S	T	U	V
6.98611E-07	6.68087E-07	-8.75541E-07	-3.7334E-06	-1.23943E-05	-1.40361E-08	4.538E-08
-3.31457E-06	-1.05768E-07	-3.27206E-07	2.54865E-06	1.14961E-05	2.93357E-08	-3.44555E-08
7.61294E-05	-1.05948E-05	2.72222E-05	1.27892E-05	-4.20304E-05	-5.52736E-07	-3.01049E-07
1.36057E-05	-8.45073E-06	2.8407E-06	7.64629E-07	-1.1677E-05	-9.78496E-08	2.10735E-07
-2.62471E-05	3.9978E-06	-1.1098E-05	-9.32998E-06	-6.29853E-07	1.88736E-07	1.31713E-07
8.10954E-06	-1.2301E-06	3.3531E-06	2.78426E-06	3.90928E-10	-5.64299E-08	-5.60109E-08
-7.15009E-06	1.52889E-06	-3.57195E-06	-4.26529E-06	-5.56862E-06	5.13894E-08	5.41869E-08
-2.04482E-05	5.65819E-06	-1.18631E-05	-1.72059E-05	-3.08046E-05	1.43498E-07	1.76759E-07
0.000105952	-1.16231E-05	3.93587E-05	1.99871E-05	-5.09199E-05	-7.55284E-07	-6.32968E-07
1.29074E-05	-3.15745E-07	2.69559E-06	-3.55658E-06	-2.44287E-05	-9.02944E-08	-2.39638E-10
3.3986E-09	4.35893E-06	-7.14597E-06	-2.22755E-05	-6.89752E-05	-1.05993E-08	2.00268E-07
0.000137868	-1.79223E-05	5.32801E-05	3.22161E-05	-4.58011E-05	-9.95362E-07	-7.528E-07
-1.28272E-07	1.01939E-08	-4.2284E-08	-6.14094E-09	1.11634E-07	9.11027E-10	9.80071E-10
-0.000923264	0.000331473	-0.000603317	-0.001025989	-0.002178253	6.63944E-06	8.5187E-06
0.000867411	-0.000115923	0.000314413	0.000156282	-0.000437537	-6.1431E-06	-3.43452E-06
0.001168524	-7.88754E-05	0.000207543	0.000111097	-0.000276783	-3.92448E-06	-2.44115E-06
-7.88754E-05	4.74412E-05	-4.42785E-05	-6.55566E-05	-0.000118814	5.53344E-07	5.62483E-07
0.000207543	-4.42785E-05	0.000204082	0.000119388	0.000145846	-1.45741E-06	-1.45822E-06
0.000111097	-6.55566E-05	0.000119388	0.000538904	0.000710997	-7.39383E-07	-2.01488E-06
-0.000276783	-0.000118814	0.000145846	0.000710997	0.004957309	1.8863E-06	-3.95207E-06
-3.92448E-06	5.53344E-07	-1.45741E-06	-7.39383E-07	1.8863E-06	6.58708E-08	1.56449E-08
-2.44115E-06	5.62483E-07	-1.45822E-06	-2.01488E-06	-3.95207E-06	1.56449E-08	1.04328E-06
-1.65706E-05	-2.63642E-06	6.92603E-06	3.4945E-05	0.000123935	1.34836E-07	-3.71954E-07
1.36048E-05	-5.96964E-07	3.49753E-06	-1.54254E-06	-1.90401E-05	-1.00189E-07	-3.23088E-08
-2.45927E-05	2.58233E-06	-8.19839E-06	-2.48358E-06	1.88609E-05	1.79062E-07	9.61312E-08
-2.501E-06	2.15632E-07	-7.07782E-07	1.25976E-07	3.04347E-06	2.76957E-08	6.78416E-09
2.21692E-06	1.89913E-06	-6.93945E-07	-4.8924E-06	-1.71332E-05	-4.74198E-09	1.43318E-07
-1.81061E-05	-3.82833E-06	8.69641E-06	4.11879E-05	0.000145528	9.29953E-08	-3.05451E-07
6.84754E-06	-1.88084E-07	1.56074E-06	-1.05721E-06	-1.08984E-05	-4.67906E-08	1.39904E-07
-4.04845E-05	2.99745E-06	-1.17419E-05	-5.65865E-07	4.08419E-05	2.79284E-07	8.09872E-08

ATRIX (FIT 100µg Hb/g faeces) contd.

P	Q	R	S	T	U	V
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0

0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.026020099	0	0	0	0	0	0
-0.000390641	0.005352363	0	0	0	0	0
0.000870737	-0.001220115	0.010676931	0	0	0	0
0.000100306	-0.002472106	0.001742091	0.018070739	0	0	0
-0.003481563	-0.005989846	0.00342851	0.009943011	0.055022476	0	0
-1.58146E-05	1.29477E-05	-1.18851E-05	3.28329E-07	6.29655E-06	0.000199355	0
-5.65725E-06	-8.26911E-07	-1.04619E-05	8.8302E-07	-2.18535E-06	3.29929E-06	0.001005153
-0.000293516	3.91226E-05	0.000152199	0.000513499	0.000531839	0.000231567	-0.000107385
7.62703E-05	2.19452E-05	1.40272E-05	-3.19008E-05	-5.79754E-05	-6.94408E-05	2.92165E-06
-0.0001253	2.24956E-05	-5.92762E-05	2.21589E-05	7.83605E-05	0.000109436	4.87528E-06
-1.16166E-05	1.93924E-05	-1.7651E-05	-2.22459E-05	-1.5273E-05	5.04342E-05	1.10301E-05
-3.68004E-05	0.000132388	-4.3389E-05	-4.64023E-05	-2.12426E-05	8.60816E-05	0.000134798
-0.000369939	-0.000147191	0.000226454	0.000730146	0.000768103	5.8073E-05	-3.30437E-05
5.51413E-05	2.75305E-05	1.34427E-05	-1.47989E-05	-4.42807E-05	-3.57649E-05	0.000152124
-0.000297849	-8.87914E-05	-5.82833E-05	0.000134475	0.000237894	0.000209477	-6.8283E-05

Q	X	Y	Z	AA	AB	AC
-6.51454E-07	1.0124E-07	-8.40019E-08	-4.46912E-08	1.13821E-07	-6.19147E-07	3.35011E-08
6.75603E-07	-1.34047E-07	1.68556E-07	4.8504E-08	-1.23519E-07	6.17149E-07	-4.73026E-08
-2.82422E-06	1.74074E-06	-3.27741E-06	-3.7678E-07	2.88261E-07	-2.84154E-06	8.7892E-07
-8.14985E-06	-7.9663E-07	2.33559E-07	-1.12291E-07	-3.8953E-06	-9.846E-06	2.02717E-09
-6.07483E-07	-6.20245E-07	1.16434E-06	9.94801E-08	-5.62005E-07	-7.10849E-07	-2.4279E-07
1.22082E-07	1.84705E-07	-3.47874E-07	-2.55589E-08	9.47878E-08	1.31955E-07	6.93273E-08
-2.94144E-07	-1.23261E-07	2.87255E-07	1.12939E-08	-5.89345E-09	-3.30762E-07	-5.9831E-08
-1.42559E-06	-2.02172E-07	7.28361E-07	3.80347E-08	3.08558E-07	-1.52678E-06	-6.40737E-08
1.77245E-07	2.98619E-06	-5.0066E-06	-4.65703E-07	1.78915E-06	3.55652E-07	1.25416E-06
-1.00741E-06	4.52547E-07	-6.37805E-07	-1.08092E-07	3.33892E-07	-1.02401E-06	2.42873E-07
-3.79561E-06	3.90357E-07	-2.36833E-07	-1.42987E-07	3.6171E-07	-4.03768E-06	2.44949E-07
-2.1939E-07	3.49491E-06	-6.17186E-06	-6.29769E-07	1.83078E-06	4.4825E-07	1.50035E-06
2.12301E-09	-4.13387E-09	6.20448E-09	3.51834E-10	-1.22632E-09	2.17063E-09	-1.82619E-09
-7.01534E-05	-2.50527E-06	2.8562E-05	1.95586E-06	3.02754E-05	-8.84939E-05	2.53225E-11
-2.51011E-05	2.06091E-05	-3.72546E-05	-3.78458E-06	5.04041E-06	-2.46975E-05	9.90187E-06
-1.65706E-05	1.36048E-05	-2.45927E-05	-2.501E-06	2.21692E-06	-1.81061E-05	6.84754E-06
-2.63642E-06	-5.96964E-07	2.58233E-06	2.15632E-07	1.89913E-06	-3.82833E-06	-1.88084E-07
6.92603E-06	3.49753E-06	-8.19839E-06	-7.07782E-07	-6.93945E-07	8.69641E-06	1.56074E-06
3.4945E-05	-1.54254E-06	-2.48358E-06	1.25976E-07	-4.8924E-06	4.11879E-05	-1.05721E-06
0.000123935	-1.90401E-05	1.88609E-05	3.04347E-06	-1.71332E-05	0.000145528	-1.08984E-05
1.34836E-07	-1.00189E-07	1.79062E-07	2.76957E-08	-4.74198E-09	9.29953E-08	-4.67906E-08
-3.71954E-07	-3.23088E-08	9.61312E-08	6.78416E-09	1.43318E-07	-3.05451E-07	1.39904E-07
2.60584E-05	-6.65951E-07	7.22618E-07	1.74535E-07	2.69189E-07	1.06476E-05	-3.27164E-07
-6.65951E-07	1.04957E-06	-7.13705E-07	-9.68197E-08	8.78687E-08	-7.18234E-07	1.68326E-07
7.22618E-07	-7.13705E-07	2.35694E-06	1.51889E-07	-5.95573E-08	8.11693E-07	-2.80148E-07
1.74535E-07	-9.68197E-08	1.51889E-07	6.21547E-07	-2.06077E-07	2.6554E-07	-7.3696E-08
2.69189E-07	8.78687E-08	-5.95573E-08	-2.06077E-07	4.98237E-06	7.24008E-07	2.35423E-07
1.06476E-05	-7.18234E-07	8.11693E-07	2.6554E-07	7.24008E-07	9.15004E-06	-1.69027E-07
-3.27164E-07	1.68326E-07	-2.80148E-07	-7.3696E-08	2.35423E-07	-1.69027E-07	2.78742E-06
7.1424E-07	-8.98458E-07	1.68343E-06	8.72872E-07	-7.9632E-07	7.1235E-07	-2.40292E-06

Q	X	Y	Z	AA	AB	AC
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
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0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.004392748	0	0	0	0	0	0
-1.53436E-05	0.000808406	0	0	0	0	0
2.1001E-05	-0.000148844	0.001151857	0	0	0	0
-1.24565E-05	-2.90735E-05	3.01488E-05	0.000770298	0	0	0
4.77349E-05	-0.000226147	0.000138034	-0.000243536	0.00204404	0	0
0.000737755	-0.000138781	0.000147571	8.48999E-05	0.000258277	0.000287296	0
2.18276E-05	-1.66653E-05	-7.41476E-06	-5.30162E-05	5.15987E-05	0.000875455	0.001376929
-0.000102979	7.65052E-05	9.31237E-05	0.000924624	-4.63508E-05	-0.001957758	-0.000108293

AD
-7.35862E-08
1.6166E-07
-5.20451E-06
6.67543E-07
1.74071E-06
-5.22547E-07
4.38881E-07
9.18888E-07
-7.99263E-06
-1.0436E-06
-4.98751E-07
-9.43579E-06
9.74069E-09
2.84875E-05
-6.00811E-05
-4.04845E-05
2.99745E-06
-1.17419E-05
-5.65865E-07
4.08419E-05
2.79284E-07
8.09872E-08
7.1424E-07
-8.98458E-07
1.68343E-06
8.72872E-07
-7.9632E-07
7.1235E-07
-2.40292E-06
7.42315E-06

AD
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8.01311E-05

Variance Covariance matrix estimated in R (FIT 40µg Hb/g faeces)

		A	B	C
No adenomas or cancer to LR adenomas - age 30	A	2.66951E-07	-1.18093E-07	2.039E-07
No adenomas or cancer to LR adenomas - age 50	B	-1.18093E-07	2.66021E-07	-5.77546E-07
No adenomas or cancer to LR adenomas - age 70	C	2.039E-07	-5.77546E-07	2.11259E-05
No adenomas or cancer to LR adenomas - age 100	D	7.71042E-08	-3.10842E-07	3.00064E-06
LR adenomas to high risk adenomas - age 30	E	-3.93517E-08	1.40352E-07	-3.49919E-06
LR adenomas to high risk adenomas - age 50	F	-4.87424E-09	-3.17339E-08	1.06033E-06
LR adenomas to high risk adenomas - age 70	G	2.96749E-08	7.03297E-09	-9.51496E-07
LR adenomas to HR adenomas - age 100	H	1.69596E-07	-2.76406E-08	-2.80371E-06
HR adenomas to Dukes A CRC - age 30	I	1.37561E-07	-5.24338E-07	1.37505E-05
HR adenomas to Dukes A CRC - age 50	J	1.13951E-07	-1.57489E-07	1.7346E-06
HR adenomas to Dukes A CRC - age 70	K	3.80779E-07	-3.20811E-07	2.79628E-07
HR adenomas to Dukes A CRC - age 100	L	2.8457E-07	-8.82202E-07	1.8512E-05
No adenomas or cancer to CRC Dukes A	M	-1.80296E-10	6.66348E-10	-1.6241E-08
Preclinical CRC: Dukes A to Dukes B	N	1.17764E-05	-4.51049E-06	-0.000124019
Preclinical CRC: Dukes B to Dukes' C	O	1.85115E-06	-5.81424E-06	0.000117711
Preclinical CRC: Dukes C to Stage D	P	7.01054E-07	-3.3169E-06	7.6137E-05
Symptomatic presention with CRC Dukes A	Q	6.69273E-07	-1.06893E-07	-1.05913E-05
Symptomatic presention with CRC Dukes B	R	-8.78357E-07	-3.24537E-07	2.72138E-05
Symptomatic presention with CRC Dukes C	S	-3.74058E-06	2.55547E-06	1.27675E-05
Symptomatic presention with CRC Dukes D	T	-1.23974E-05	1.1499E-05	-4.20396E-05
gFOBT Sensitivity for LR adenomas	U	-1.36051E-08	2.90863E-08	-5.55241E-07
gFOBT Sensitivity for HR adenomas	V	4.61309E-08	-3.5393E-08	-2.93444E-07
gFOBT Sensitivity for CRC	Q	-6.79384E-07	7.0239E-07	-2.91459E-06
gFOBT Specificity age 50	X	1.02355E-07	-1.35567E-07	1.7551E-06
gFOBT Specificity age -70	Y	-8.64777E-08	1.71486E-07	-3.29865E-06
FIT Sensitivity for LR adenomas	Z	-5.39643E-08	7.09068E-08	-8.61129E-07
FIT Sensitivity for HR adenomas	AA	2.19754E-07	-2.36321E-07	5.26304E-07
FIT Sensitivity for CRC	AB	-8.28894E-07	8.23075E-07	-3.76023E-06
FIT Specificity age 50	AC	2.86162E-08	-4.284E-08	8.68506E-07
FIT Specificity age 70	AD	-6.53413E-08	1.52995E-07	-5.1539E-06

CHOLESKY DECOMPOSITION MATRIX (FIT 40µg Hb/g faeces)

		A	B	C
No adenomas or cancer to LR adenomas - age 30	A	0.000516673	0	0
No adenomas or cancer to LR adenomas - age 50	B	-0.000228564	0.000462363	0
No adenomas or cancer to LR adenomas - age 70	C	0.00039464	-0.001054032	0.00445636
No adenomas or cancer to LR adenomas - age 100	D	0.000149232	-0.000598519	0.00051856
LR adenomas to high risk adenomas - age 30	E	-7.61636E-05	0.000265902	-0.000715576
LR adenomas to high risk adenomas - age 50	F	-9.4339E-06	-7.32977E-05	0.000221434
LR adenomas to high risk adenomas - age 70	G	5.74346E-05	4.36031E-05	-0.000208287
LR adenomas to HR adenomas - age 100	H	0.000328246	0.000102484	-0.000633976
HR adenomas to Dukes A CRC - age 30	I	0.000266245	-0.001002425	0.002824914
HR adenomas to Dukes A CRC - age 50	J	0.000220548	-0.000231593	0.000314934
HR adenomas to Dukes A CRC - age 70	K	0.000736983	-0.000329531	-8.04585E-05
HR adenomas to Dukes A CRC - age 100	L	0.000550774	-0.001635762	0.0037184

No adenomas or cancer to CRC Dukes A	**M**	-3.48956E-07	1.26868E-06	-3.31347E-06
Preclinical CRC: Dukes A to Dukes B	**N**	0.022792757	0.001512052	-0.029490421
Preclinical CRC: Dukes B to Dukes' C	**O**	0.003582823	-0.010803924	0.023541521
Preclinical CRC: Dukes C to Stage D	**P**	0.001356863	-0.006503064	0.015426735
Symptomatic presention with CRC Dukes A	**Q**	0.001295351	0.000409155	-0.002394602
Symptomatic presention with CRC Dukes B	**R**	-0.001700025	-0.001542299	0.005892495
Symptomatic presention with CRC Dukes C	**S**	-0.007239742	0.001948098	0.003966893
Symptomatic presention with CRC Dukes D	**T**	-0.023994665	0.013008667	-0.004231888
gFOBT Sensitivity for LR adenomas	**U**	-2.63322E-05	4.98908E-05	-0.000110463
gFOBT Sensitivity for HR adenomas	**V**	8.92845E-05	-3.24114E-05	-8.14211E-05
gFOBT Sensitivity for CRC	**Q**	-0.001314921	0.000869115	-0.000332019
gFOBT Specificity age 50	**X**	0.000198104	-0.000195274	0.00033011
gFOBT Specificity age -70	**Y**	-0.000167374	0.000288152	-0.000657236
FIT Sensitivity for LR adenomas	**Z**	-0.000104446	0.000101726	-0.000159926
FIT Sensitivity for HR adenomas	**AA**	0.000425325	-0.00030086	9.27607E-06
FIT Sensitivity for CRC	**AB**	-0.001604291	0.000987087	-0.000468251
FIT Specificity age 50	**AC**	5.53855E-05	-6.52753E-05	0.000174548
FIT Specificity age 70	**AD**	-0.000126466	0.000268381	-0.001081849

D	E	F	G	H	I	J
7.71042E-08	-3.93517E-08	-4.87424E-09	2.96749E-08	1.69596E-07	1.37561E-07	1.13951E-07
-3.10842E-07	1.40352E-07	-3.17339E-08	7.03297E-09	-2.76406E-08	-5.24338E-07	-1.57489E-07
3.00064E-06	-3.49919E-06	1.06033E-06	-9.51496E-07	-2.80371E-06	1.37505E-05	1.7346E-06
4.42739E-05	1.01758E-06	-2.00912E-07	6.81316E-09	-7.62931E-07	-6.18692E-06	-2.40555E-07
1.01758E-06	3.2062E-06	-4.45551E-07	4.15887E-07	1.21224E-06	-5.53967E-06	-5.2162E-07
-2.00912E-07	-4.45551E-07	2.61084E-07	-1.22289E-07	-3.58793E-07	1.65268E-06	1.60634E-07
6.81316E-09	4.15887E-07	-1.22289E-07	2.62307E-07	4.20113E-07	-1.40731E-06	-8.31139E-08
-7.62931E-07	1.21224E-06	-3.58793E-07	4.20113E-07	3.20431E-06	-3.57147E-06	-1.21636E-07
-6.18692E-06	-5.53967E-06	1.65268E-06	-1.40731E-06	-3.57147E-06	4.74426E-05	2.63117E-06
-2.40555E-07	-5.2162E-07	1.60634E-07	-8.31139E-08	-1.21636E-07	2.63117E-06	1.05577E-06
9.18895E-07	4.97516E-07	-1.37657E-07	2.85906E-07	1.25946E-06	-1.57382E-07	5.75608E-07
-4.04697E-06	-7.36192E-06	2.14729E-06	-1.92666E-06	-5.42559E-06	2.86769E-05	3.13738E-06
8.81995E-09	5.67711E-09	-1.89069E-09	1.43398E-09	3.12782E-09	-2.98579E-08	-4.08666E-09
-0.000104223	5.08621E-05	-1.57847E-05	2.10463E-05	8.06771E-05	-0.000135295	3.0076E-06
1.71846E-05	-4.06861E-05	1.22853E-05	-1.09639E-05	-3.14388E-05	0.000164075	1.98184E-05
1.3626E-05	-2.62426E-05	8.10873E-06	-7.14877E-06	-2.04439E-05	0.00010595	1.29112E-05
-8.44124E-06	3.99992E-06	-1.2305E-06	1.52953E-06	5.66022E-06	-1.16238E-05	-3.13933E-07
2.81833E-06	-1.1103E-05	3.35404E-06	-3.57347E-06	-1.18679E-05	3.93603E-05	2.69129E-06
7.06595E-07	-9.34288E-06	2.78667E-06	-4.26918E-06	-1.72183E-05	1.99912E-05	-3.56758E-06
-1.17018E-05	-6.35356E-07	1.41687E-09	-5.57027E-06	-3.08099E-05	-5.09181E-05	-2.44334E-05
-1.05378E-07	1.88264E-07	-5.66214E-08	5.1675E-08	1.42881E-07	-7.54689E-07	-9.0001E-08
2.32228E-07	1.34809E-07	-5.61967E-08	5.45199E-08	1.79957E-07	-6.34577E-07	1.42395E-09
-8.39272E-06	-6.59616E-07	1.31371E-07	-3.09175E-07	-1.47582E-06	1.9454E-07	-1.05076E-06
-7.55864E-07	-6.14647E-07	1.84467E-07	-1.22809E-07	-1.96332E-07	2.98312E-06	4.55312E-07
1.7376E-07	1.15539E-06	-3.47214E-07	2.86105E-07	7.19184E-07	-5.00214E-06	-6.42921E-07
-2.21217E-07	2.84614E-07	-7.90234E-08	5.61617E-08	1.32204E-07	-1.09836E-06	-1.88434E-07
-7.37509E-06	-1.0575E-06	1.75943E-07	-7.54581E-09	5.78308E-07	3.36876E-06	6.33475E-07
-1.32781E-05	-8.58386E-07	1.70223E-07	-4.44413E-07	-2.04083E-06	4.43057E-07	-1.36475E-06
-2.54647E-08	-2.50278E-07	7.10358E-08	-6.25504E-08	-7.10307E-08	1.25635E-06	2.35839E-07
7.75397E-07	1.75654E-06	-5.23967E-07	4.42125E-07	9.36305E-07	-7.98376E-06	-1.02755E-06

D	E	F	G	H	I	J
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.006604882	0	0	0	0	0	0
0.000236063	0.001600601	0	0	0	0	0
-5.42328E-05	-0.000159643	0.000422093	0	0	0	0
2.0038E-05	0.000159247	-0.000108792	0.000419674	0	0	0
-6.38653E-05	0.000481948	-0.000318235	0.000368504	0.001486847	0	0
-0.001255361	-0.001833722	0.001410502	-0.000762213	-0.000155947	0.005554584	0
-8.71162E-05	-0.000123277	0.000122242	3.47649E-05	7.35146E-05	0.000176568	0.000882491
9.89276E-05	0.000350083	-0.000179554	0.000390592	0.00042831	0.000166938	0.000409378
-0.001065334	-0.00248203	0.001789161	-0.001194328	-0.000634706	0.001253874	0.000810565

1.71836E-06	1.58472E-06	-1.70838E-06	5.62093E-07	-2.64402E-07	-2.02949E-06	-1.99461E-06
-0.013842306	0.021467616	-0.014812371	0.020911528	0.020643786	0.000990118	0.009575448
-0.000306451	-0.01288414	0.010047189	-0.006300789	-0.003277901	0.007613979	0.006101501
0.000231897	-0.008388018	0.006876087	-0.003933455	-0.001847907	0.004935729	0.004299382
-0.001082217	0.001581743	-0.001099797	0.001402691	0.001329424	-7.6399E-05	0.000398221
-0.000137275	-0.004106848	0.002978213	-0.002860529	-0.00231614	0.001291837	1.42922E-05
0.000135642	-0.004751777	0.002917653	-0.004862462	-0.005049283	-0.000807755	-0.003418475
0.00028152	-0.005633264	0.001851729	-0.010836787	-0.01320527	-0.007640952	-0.014726037
-2.16593E-06	5.90145E-05	-4.60771E-05	3.24934E-05	1.42333E-05	-3.38716E-05	-2.41668E-05
3.65982E-05	5.20584E-05	-6.96649E-05	4.10883E-05	2.84424E-05	-3.33797E-05	2.30764E-05
-0.001136151	-0.000599929	0.000234071	-0.00046926	-0.000591706	-0.000171518	-0.000641773
-0.000162529	-0.000170591	0.000148964	-2.45094E-05	6.47069E-05	0.000192012	0.000194027
0.000107802	0.000356285	-0.000282907	0.000134829	1.57246E-05	-0.000273499	-0.000228834
-9.35894E-06	8.58303E-05	-5.67285E-05	1.13471E-05	-6.40585E-06	-5.10374E-05	-7.44318E-05
-0.001154213	-0.000416096	6.35562E-05	0.000189149	0.000371765	0.000149115	0.000280141
-0.001847892	-0.000713416	0.000277233	-0.000743536	-0.000890621	-0.000277645	-0.000880838
-2.47259E-05	-6.12044E-05	4.03018E-05	-2.83614E-05	5.33564E-05	8.45559E-05	0.000137161
0.000229513	0.000529315	-0.000400341	0.0001904	-0.000116733	-0.000481509	-0.000425643

Variance Covariance matrix estiamted in R (FIT

K	L	M		N	O	P
3.80779E-07	2.8457E-07	-1.80296E-10	**A**	1.17764E-05	1.85115E-06	7.01054E-07
-3.20811E-07	-8.82202E-07	6.66348E-10	**B**	-4.51049E-06	-5.81424E-06	-3.3169E-06
2.79628E-07	1.8512E-05	-1.6241E-08	**C**	-0.000124019	0.000117711	7.6137E-05
9.18895E-07	-4.04697E-06	8.81995E-09	**D**	-0.000104223	1.71846E-05	1.3626E-05
4.97516E-07	-7.36192E-06	5.67711E-09	**E**	5.08621E-05	-4.06861E-05	-2.62426E-05
-1.37657E-07	2.14729E-06	-1.89069E-09	**F**	-1.57847E-05	1.22853E-05	8.10873E-06
2.85906E-07	-1.92666E-06	1.43398E-09	**G**	2.10463E-05	-1.09639E-05	-7.14877E-06
1.25946E-06	-5.42559E-06	3.12782E-09	**H**	8.06771E-05	-3.14388E-05	-2.04439E-05
-1.57382E-07	2.86769E-05	-2.98579E-08	**I**	-0.000135295	0.000164075	0.00010595
5.75608E-07	3.13738E-06	-4.08666E-09	**J**	3.0076E-06	1.98184E-05	1.29112E-05
4.37293E-06	-7.25221E-07	-1.35491E-09	**K**	7.41659E-05	1.06613E-06	1.91899E-08
-7.25221E-07	7.52305E-05	-3.34717E-08	**L**	-0.000217224	0.000215597	0.000137867
-1.35491E-09	-3.34717E-08	1.0961E-10	**M**	9.86378E-08	-1.97083E-07	-1.28285E-07
7.41659E-05	-0.000217224	9.86378E-08	**N**	0.009646046	-0.001373246	-0.000923264
1.06613E-06	0.000215597	-1.97083E-07	**O**	-0.001373246	0.00268176	0.000867411
1.91899E-08	0.000137867	-1.28285E-07	**P**	-0.000923264	0.000867411	0.001168526
4.36642E-06	-1.79229E-05	1.01961E-08	**Q**	0.000331473	-0.000115923	-7.88747E-05
-7.16367E-06	5.32817E-05	-4.22913E-08	**R**	-0.000603317	0.000314413	0.000207542
-2.23211E-05	3.22202E-05	-6.14771E-09	**S**	-0.00102599	0.00015628	0.000111092
-6.89947E-05	-4.57993E-05	1.11644E-07	**T**	-0.002178253	-0.000437538	-0.000276785
-1.31863E-08	-9.94806E-07	9.14519E-10	**U**	6.6393E-06	-6.14342E-06	-3.92512E-06
2.125E-07	-7.54361E-07	9.76584E-10	**V**	8.51907E-06	-3.43365E-06	-2.43938E-06
-3.98138E-06	-2.0202E-07	2.10433E-09	**Q**	-7.01574E-05	-2.51106E-05	-1.65901E-05
4.128E-07	3.49194E-06	-4.14212E-09	**X**	-2.50455E-06	2.06108E-05	1.36082E-05
-2.7181E-07	-6.16752E-06	6.21402E-09	**Y**	2.8561E-05	-3.72571E-05	-2.45976E-05
-1.90372E-07	-1.48641E-06	9.74587E-10	**Z**	4.60896E-06	-8.917E-06	-5.89105E-06
6.70257E-07	3.44673E-06	-2.27548E-09	**AA**	5.6936E-05	9.47707E-06	4.16494E-06
-5.20666E-06	5.78288E-07	3.08258E-09	**AB**	-0.000128164	-3.57344E-05	-2.6146E-05
2.19744E-07	1.50266E-06	-1.8343E-09	**AC**	-4.12493E-10	9.90322E-06	6.84708E-06
-4.25069E-07	-9.42381E-06	9.71607E-09	**AD**	2.84293E-05	-5.99503E-05	-4.03902E-05

CHOLESKY DECOMPOSITION MATRIX (FIT 40µg

K	L	M		N	O	P
0	0	0	**A**	0	0	0
0	0	0	**B**	0	0	0
0	0	0	**C**	0	0	0
0	0	0	**D**	0	0	0
0	0	0	**E**	0	0	0
0	0	0	**F**	0	0	0
0	0	0	**G**	0	0	0
0	0	0	**H**	0	0	0
0	0	0	**I**	0	0	0
0	0	0	**J**	0	0	0
0.001737432	0	0	**K**	0	0	0
7.00843E-05	0.00662307	0	**L**	0	0	0

-5.34549E-07	-8.09368E-07	8.8934E-06	**M**	0	0	0
0.014730236	-0.003709244	-0.001000412	**N**	0.078707205	0	0
0.001842081	0.005119258	-0.003439373	**O**	-0.002557234	0.039208933	0
0.00115657	0.003113237	-0.002288295	**P**	-0.001749727	0.003238261	0.026022499
0.000830087	-0.00031532	6.69463E-06	**Q**	0.001163557	-0.000363236	-0.000386648
-0.001192009	0.001159912	-0.000632366	**R**	-0.001659844	0.000932027	0.000862731
-0.004750829	0.000434637	0.000565896	**S**	-0.003661948	-4.30662E-05	7.04035E-05
-0.016055423	-0.001697931	0.003611103	**T**	-0.009426724	-0.003556666	-0.003583703
-1.04673E-05	-2.27546E-05	1.70963E-05	**U**	1.65876E-05	-2.02309E-05	-1.56294E-05
3.62647E-05	-2.61546E-05	5.34777E-05	**V**	3.51981E-06	-2.0291E-06	-5.90763E-06
-0.000955485	-1.11048E-05	7.92771E-05	**Q**	-0.000104403	-0.000292658	-0.000294269
0.000116225	8.73418E-05	-0.000110974	**X**	2.8702E-05	6.93184E-05	7.5556E-05
-0.000122385	-0.000142954	0.000125362	**Y**	3.71883E-05	-0.000120961	-0.000123948
-5.45334E-05	-3.40664E-05	-2.86183E-05	**Z**	7.79555E-06	-2.337E-05	-2.73151E-05
9.03514E-05	5.3033E-05	0.000222783	**AA**	0.000336637	-2.84125E-05	-6.76172E-05
-0.001252167	4.21062E-05	0.000193992	**AB**	-0.000655818	-0.000506947	-0.000574359
6.93707E-05	3.68276E-05	-4.53526E-05	**AC**	3.45062E-05	4.6439E-05	5.61549E-05
-0.000218772	-0.000226548	0.000175999	**AD**	-0.000121657	-0.000287679	-0.000300696

40µg Hb/g faeces) contd.

Q	R	S	T	U	V	Q
6.69273E-07	-8.78357E-07	-3.74058E-06	-1.23974E-05	-1.36051E-08	4.61309E-08	-6.79384E-07
-1.06893E-07	-3.24537E-07	2.55547E-06	1.1499E-05	2.90863E-08	-3.5393E-08	7.0239E-07
-1.05913E-05	2.72138E-05	1.27675E-05	-4.20396E-05	-5.55241E-07	-2.93444E-07	-2.91459E-06
-8.44124E-06	2.81833E-06	7.06595E-07	-1.17018E-05	-1.05378E-07	2.32228E-07	-8.39272E-06
3.99992E-06	-1.1103E-05	-9.34288E-06	-6.35356E-07	1.88264E-07	1.34809E-07	-6.59616E-07
-1.2305E-06	3.35404E-06	2.78667E-06	1.41687E-09	-5.66214E-08	-5.61967E-08	1.31371E-07
1.52953E-06	-3.57347E-06	-4.26918E-06	-5.57027E-06	5.1675E-08	5.45199E-08	-3.09175E-07
5.66022E-06	-1.18679E-05	-1.72183E-05	-3.08099E-05	1.42881E-07	1.79957E-07	-1.47582E-06
-1.16238E-05	3.93603E-05	1.99912E-05	-5.09181E-05	-7.54689E-07	-6.34577E-07	1.9454E-07
-3.13933E-07	2.69129E-06	-3.56758E-06	-2.44334E-05	-9.0001E-08	1.42395E-09	-1.05076E-06
4.36642E-06	-7.16367E-06	-2.23211E-05	-6.89947E-05	-1.31863E-08	2.125E-07	-3.98138E-06
-1.79229E-05	5.32817E-05	3.22202E-05	-4.57993E-05	-9.94806E-07	-7.54361E-07	-2.0202E-07
1.01961E-08	-4.22913E-08	-6.14771E-09	1.11644E-07	9.14519E-10	9.76584E-10	2.10433E-09
0.000331473	-0.000603317	-0.00102599	-0.002178253	6.6393E-06	8.51907E-06	-7.01574E-05
-0.000115923	0.000314413	0.00015628	-0.000437538	-6.14342E-06	-3.43365E-06	-2.51106E-05
-7.88747E-05	0.000207542	0.000111092	-0.000276785	-3.92512E-06	-2.43938E-06	-1.65901E-05
4.74416E-05	-4.42793E-05	-6.55588E-05	-0.000118815	5.53029E-07	5.63333E-07	-2.64554E-06
-4.42793E-05	0.000204084	0.000119393	0.000145848	-1.45667E-06	-1.46024E-06	6.94752E-06
-6.55588E-05	0.000119393	0.000538917	0.000711003	-7.37484E-07	-2.02004E-06	3.50007E-05
-0.000118815	0.000145848	0.000711003	0.004957312	1.88711E-06	-3.95428E-06	0.000123958
5.53029E-07	-1.45667E-06	-7.37484E-07	1.88711E-06	6.56156E-08	1.56441E-08	1.42006E-07
5.63333E-07	-1.46024E-06	-2.02004E-06	-3.95428E-06	1.56441E-08	1.04425E-06	-3.92516E-07
-2.64554E-06	6.94752E-06	3.50007E-05	0.000123958	1.42006E-07	-3.92516E-07	2.62917E-05
-5.95345E-07	3.4937E-06	-1.55236E-06	-1.90443E-05	-1.00076E-07	-3.06117E-08	-7.04938E-07
2.57998E-06	-8.19281E-06	-2.46927E-06	1.8867E-05	1.79207E-07	9.32289E-08	7.79846E-07
5.08593E-07	-1.66865E-06	2.92976E-07	7.16991E-06	4.69103E-08	4.24158E-08	3.6745E-07
3.56942E-06	-1.29995E-06	-9.18794E-06	-3.22157E-05	-1.1651E-08	2.70931E-07	5.53221E-07
-5.50717E-06	1.25065E-05	5.94277E-05	0.000210694	1.22306E-07	-3.81349E-07	1.44803E-05
-1.89119E-07	1.56345E-06	-1.05138E-06	-1.08985E-05	-4.53528E-08	1.3676E-07	-3.00759E-07
2.99534E-06	-1.17271E-05	-5.90348E-07	4.07449E-05	2.77118E-07	8.787E-08	6.08007E-07

Hb/g faeces) contd.

Q	R	S	T	U	V	Q
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0

0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.005353159	0	0	0	0	0	0
-0.001226505	0.010681025	0	0	0	0	0
-0.002507855	0.001782036	0.018122448	0	0	0	0
-0.006135218	0.003585014	0.010311111	0.055202068	0	0	0
1.25324E-05	-1.16375E-05	6.37565E-07	6.42319E-06	0.000198616	0	0
-1.19466E-06	-1.00569E-05	1.9321E-06	-1.06811E-06	3.44586E-06	0.001005249	0
4.88891E-05	0.000144874	0.00049852	0.000515518	0.000254113	-0.0001107	0.004388954
2.14367E-05	1.47664E-05	-2.9648E-05	-5.51469E-05	-6.80739E-05	3.43375E-06	-1.79359E-05
2.38723E-05	-6.09531E-05	1.75676E-05	7.30126E-05	0.000107893	3.91583E-06	2.51057E-05
6.71819E-06	-1.11644E-05	6.23389E-06	1.60601E-05	3.88062E-05	3.56302E-05	1.69918E-06
0.000241929	-7.6703E-05	-7.89439E-05	-3.31625E-05	0.00014308	0.000254817	0.000100038
-0.000290652	0.000406074	0.001243715	0.001297317	5.806E-05	-1.65909E-05	0.000986339
3.2064E-05	9.46116E-06	-2.34431E-05	-5.2438E-05	-2.99878E-05	0.000150727	2.21904E-05
-9.70994E-05	-4.9949E-05	0.00015316	0.000255384	0.000204052	-6.51615E-05	-0.000109402

X	Y	Z	AA	AB	AC	AD
1.02355E-07	-8.64777E-08	-5.39643E-08	2.19754E-07	-8.28894E-07	2.86162E-08	-6.53413E-08
-1.35567E-07	1.71486E-07	7.09068E-08	-2.36321E-07	8.23075E-07	-4.284E-08	1.52995E-07
1.7551E-06	-3.29865E-06	-8.61129E-07	5.26304E-07	-3.76023E-06	8.68506E-07	-5.1539E-06
-7.55864E-07	1.7376E-07	-2.21217E-07	-7.37509E-06	-1.32781E-05	-2.54647E-08	7.75397E-07
-6.14647E-07	1.15539E-06	2.84614E-07	-1.0575E-06	-8.58386E-07	-2.50278E-07	1.75654E-06
1.84467E-07	-3.47214E-07	-7.90234E-08	1.75943E-07	1.70223E-07	7.10358E-08	-5.23967E-07
-1.22809E-07	2.86105E-07	5.61617E-08	-7.54581E-09	-4.44413E-07	-6.25504E-08	4.42125E-07
-1.96332E-07	7.19184E-07	1.32204E-07	5.78308E-07	-2.04083E-06	-7.10307E-08	9.36305E-07
2.98312E-06	-5.00214E-06	-1.09836E-06	3.36876E-06	4.43057E-07	1.25635E-06	-7.98376E-06
4.55312E-07	-6.42921E-07	-1.88434E-07	6.33475E-07	-1.36475E-06	2.35839E-07	-1.02755E-06
4.128E-07	-2.7181E-07	-1.90372E-07	6.70257E-07	-5.20666E-06	2.19744E-07	-4.25069E-07
3.49194E-06	-6.16752E-06	-1.48641E-06	3.44673E-06	5.78288E-07	1.50266E-06	-9.42381E-06
-4.14212E-09	6.21402E-09	9.74587E-10	-2.27548E-09	3.08258E-09	-1.8343E-09	9.71607E-09
-2.50455E-06	2.8561E-05	4.60896E-06	5.6936E-05	-0.000128164	-4.12493E-10	2.84293E-05
2.06108E-05	-3.72571E-05	-8.917E-06	9.47707E-06	-3.57344E-05	9.90322E-06	-5.99503E-05
1.36082E-05	-2.45976E-05	-5.89105E-06	4.16494E-06	-2.6146E-05	6.84708E-06	-4.03902E-05
-5.95345E-07	2.57998E-06	5.08593E-07	3.56942E-06	-5.50717E-06	-1.89119E-07	2.99534E-06
3.4937E-06	-8.19281E-06	-1.66865E-06	-1.29995E-06	1.25065E-05	1.56345E-06	-1.17271E-05
-1.55236E-06	-2.46927E-06	2.92976E-07	-9.18794E-06	5.94277E-05	-1.05138E-06	-5.90348E-07
-1.90443E-05	1.8867E-05	7.16991E-06	-3.22157E-05	0.000210694	-1.08985E-05	4.07449E-05
-1.00076E-07	1.79207E-07	4.69103E-08	-1.1651E-08	1.22306E-07	-4.53528E-08	2.77118E-07
-3.06117E-08	9.32289E-08	4.24158E-08	2.70931E-07	-3.81349E-07	1.3676E-07	8.787E-08
-7.04938E-07	7.79846E-07	3.6745E-07	5.53221E-07	1.44803E-05	-3.00759E-07	6.08007E-07
1.05248E-06	-7.18821E-07	-1.73955E-07	1.68909E-07	-9.28488E-07	1.6219E-07	-8.83583E-07
-7.18821E-07	2.36551E-06	2.89441E-07	-1.14657E-07	1.00073E-06	-2.71562E-07	1.65976E-06
-1.73955E-07	2.89441E-07	1.22722E-06	-4.37931E-07	4.80556E-07	-6.1431E-08	8.78973E-07
1.68909E-07	-1.14657E-07	-4.37931E-07	9.36886E-06	8.41405E-07	2.45073E-07	-8.18359E-07
-9.28488E-07	1.00073E-06	4.80556E-07	8.41405E-07	1.71581E-05	-2.92768E-07	1.14725E-06
1.6219E-07	-2.71562E-07	-6.1431E-08	2.45073E-07	-2.92768E-07	2.79026E-06	-2.41193E-06
-8.83583E-07	1.65976E-06	8.78973E-07	-8.18359E-07	1.14725E-06	-2.41193E-06	7.44881E-06

X	Y	Z	AA	AB	AC	AD
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
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0	0	0	0	0	0	0
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0	0	0	0	0	0	0
0	0	0	0	0	0	0
0.000809174	0	0	0	0	0	0
-0.000151721	0.001153505	0	0	0	0	0
-2.57819E-05	3.0026E-05	0.001072514	0	0	0	0
-0.000417919	0.000252183	-0.000308468	0.002575539	0	0	0
-8.89347E-05	8.63469E-05	5.88681E-06	0.000176914	0.000253796	0	0
-2.21799E-05	-1.63259E-06	3.36225E-06	7.2959E-06	0.001051473	0.001251984	0
8.65065E-05	8.14821E-05	0.00046722	9.26215E-05	-0.002110073	0.000231412	0.000103994

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No (page/line numbers from PDF proof)
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page1 line5
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page1 line33
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page2 line44
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page3 line37
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page2-3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page6 line17
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page5 line23
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page3 line40
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page3 line40
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page3 line43
Measurement of	11a	*Single study-based estimates*: Describe fully the design	N/A

effectiveness		features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page 4 line50 – page5 line 55
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	page6 line5
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page6 line17
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page6 line26
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page4 line10 + page21 (Supplementary information Section 1)
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	pages 3-6 (Methods)
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	pages 3-6 (Methods)
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	page24 (Supplementary Information Section 2)
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as	pages 6-9 (Results)

		well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	page8 lines37-53
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	page8 (Sensitivity Analysis) + page45 (Supplementary Information Section 4)
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pages 9-11 (Discussion)
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Submitted online and on page16
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Submitted online and on page16

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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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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Title

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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ABSTRACT

Objectives

Through the National Health Service Bowel Cancer Screening Programme (BCSP), men and women in England aged between 60 and 74 years are invited for colorectal cancer (CRC) screening every two 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 (FIT) compared with gFOBT for a cohort beginning screening aged 60 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 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, 0.017) at the base case threshold of 180µg 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 180µg/g faeces to 421 additional colonoscopies per 1000 people invited for screening for FIT 20µg/g faeces over a 40-year time horizon). Parameter uncertainty had limited impact on the conclusions.

Conclusions

This is the first 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 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

Strengths of this study include:

- 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 FIT and gFOBT from the English setting.
- This work will help to inform the choice of cut-off threshold for future screening using FIT in the NHS BCSP by providing decision makers with information on predicted resource use, cost and quality of life outcomes.

Limitations of this study include:

- 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 the gFOBT from recent pilot study in England.
- We modelled a cohort starting screening at age 60 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 two 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 vs. gFOBT have been performed for the NHS BCSP [9] but reliable data on the test performance of FIT vs. gFOBT in the NHS BCSP had previously not been available.

We used data from a recent large pilot study of FIT vs. 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, at a range of FIT positivity thresholds. In the BCSP FIT pilot study, a FIT threshold of 180µg Hb/g 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 population-level screening (the current standard test). 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. 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 vs. 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 ICER and incremental net benefit per person invited for screening for a threshold of £20,000 per QALY gained.

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.

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 Bowel Cancer Screening Programme [9] [12]. Here we briefly describe the structural assumptions of the model; full details are given in the 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 adenoma (LR), high risk/intermediate risk adenoma (HR/IR), undiagnosed colorectal cancer (CRC) at each Dukes' Stage (A, B, C and D), diagnosed colorectal cancer (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] [12] 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 [13]. 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 [13]. In the model, those with HR and IR adenomas undergo the same surveillance guidelines. The surveillance recommendations published in 2010 [13] 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 also undergo surveillance colonoscopies.

Model parameters

A complete list of model parameters and sources is given in the Supplementary Information, Section 2.

Natural history

Transition probabilities between underlying disease states are based on parameters from a previously validated model for the NHS Bowel Cancer Screening Programme [9] [12].

Mortality

Age-dependent all-cause mortality estimates were taken from Office for National Statistics life tables [14]. 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 [14].

Cancer-related mortality by Dukes' stage at diagnosis was estimated from 5-year survival statistics for England [15]. 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, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using the hema-screen (Immunostics, 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 180µg Hb/g faeces) we used a sensitivity of 0.8% for LR adenomas, 15.4% for advanced ademonas and 27.0% for CRC. Specificity of gFOBT was 99.4% at age 50 and 97.3% at age 70. In the base case, specificity of FIT 180µg Hb/g faeces was 99.8% at age 50 and 97.4% at age 70. Further details of the methods used to estimate sensitivity and specificity are given in the 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 demonstrated an increased uptake with FIT compared with gFOBT in the English setting, and these estimates were used in the model. Uptake in the model 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) and 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 [16]. 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 CRC (mean 0.697, SD 0.020) and without CRC (mean 0.795, SD 0.021) from [17], consistent with previous analyses for the NHS BCSP [9]. The mean age for respondents for this health state 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 one year.

Unit costs

Costs were estimated from the perspective of the healthcare system (NHS/BCSP). Screening and colonoscopy costs were taken from national NHS [18] 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 colorectal cancer management were taken from a model-based evaluation of colorectal cancer services by Pilgrim et al [19]. No cost was assigned to death. All costs were adjusted, where necessary, to 2015/16 prices using the Health Service Cost Index [20].

Uncertainty

To incorporate uncertainty in the results of the model, we carried out probabilistic analyses 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 (e.g. 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 in R for each FIT threshold, based on previously-reported correlations between these parameters [9 21 22]. Further details about the distributional assumptions for the probabilistic analysis are available in the Supplementary Information, Section 2. The estimated variance-covariance matrices are available from the authors upon 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 23]. Although neither review provides estimates by FIT threshold, the analyses suggest that 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 +0.30 above baseline parameter value 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 (LYs) and Quality-Adjusted Life Years (QALYs). The mean total cost difference per person ranged from £25 (95% CI: £12 to £43) cheaper for FIT at a 180µg Hb/g faeces threshold to £84 (95% CI: £24 to £151) cheaper for FIT at a 40µg 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 180µg Hb/g faeces threshold to 0.066 (95% CI: 0.057 to 0.074) for FIT at a 20µg Hb/g faeces threshold. FIT dominates gFOBT – that is, screening with FIT results in greater total QALYs gained, 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.

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 the base case FIT 180µg Hb/g faeces. The results are shown in terms of the ICER and incremental net benefit in the 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 decision concerning whether FIT is cost-effective, we sought to determine the cost at which FIT would no longer be cost-saving for each threshold.

FIT was found to no longer be cost saving compared to 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 £6,884 and £9,637 for CRC A (compared to £13768 base case cost); £9,471 to £13,260 for CRC B (£18,943 base case); £12,989 to £18,185 for CRC C (£25,979 base case); and £14,206 to £19,888 for CRC D (£28,412 base case). In the 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 to gFOBT.

Screening test characteristics

The results of the sensitivity analysis around FIT sensitivity for CRC suggest that for all thresholds, if FIT sensitivity has 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 (data given in Supplementary Information, Section 3).

Budget impact analysis

Based on estimates from the National Office for Statistics, we assumed a population size of 594,418 people aged 60 years in 2015 [24]. Using the model estimates of prevalence of colorectal cancer at age 60, we estimated the total population invited for screening (those without cancer) to be 586,299. We conducted a budget impact analysis fir this population size, and we also present selected key results per 1000 people or per person invited for screening.

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 180µg Hb/g faeces. Screening costs for a range of FIT thresholds are presented in the 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 is estimated to be 628,510 for gFOBT screening and 600,192 for FIT screening, after taking into account the need for repeat kits due to unclear results or spoilt test kits. This equates to 28,317 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 £1,442,738 greater with FIT in the first year. The average cost of screening kits per 1000 people invited for screening is estimated to be £1,648 for gFOBT and £4,109 for FIT at the base case threshold of 180µg Hb/g faeces.

Long-term colonoscopy resource use

The estimated total number of colonoscopies and associated costs over a 40 year time horizon is given in Table 3 for gFOBT and FIT at the base case threshold of 180µg Hb/g faeces. Corresponding results for a range of FIT thresholds are given in 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 52,218 at initial follow-up (referrals from the screening programme) and 39,719 during surveillance, giving a total of 91,937 over 40 years at a total cost of £18,757,263. For the base case FIT threshold, the estimated number of colonoscopies is 57,253 for initial follow-up and 53,308 for surveillance, giving 110,561 colonoscopies in total over 40 years at a cost of £25,334,380. The estimated additional colonoscopy burden with FIT 180µg Hb/g faeces compared with gFOBT is 18,624 colonoscopies at a cost of £6,577,117, 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 31,533 (£9,707,768) for FIT 150µg Hb/g faeces to 246,716 (£58,309,277) for FIT 20µg Hb/g faeces.

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

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 Supplementary Information, Section 4), due to improved detection rates. The increased HR adenoma detection and polypectomy rate for FIT results in a higher proportion 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' B, C, or D CRC is less with FIT than with gFOBT, and the prevalence of Dukes' 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.

Total long-term costs

A summary of the estimated costs over the 40-year time horizon, per person sent an invitation at age 60, 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 (8.3% of total cost) in the gFOBT arm, and £93.59 (10.3% of total cost) for FIT in the base case (180µg Hb/g faeces). As the FIT threshold is decreased, the colonoscopy burden and therefore costs increase, up to £297.58 (34.0% of total cost) for FIT 20µg 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 180µg Hb/g faeces in the base case. As the FIT threshold is decreased, the lifetime cancer management costs fall, and at the lowest FIT threshold considered, 20µg 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.

DISCUSSION

Our model results combined with the results of the BCSP FIT pilot study suggest that FIT is dominant (more effective in terms of total QALYs accrued, and less costly) vs. gFOBT in an English setting for a single cohort starting screening at age 60. 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, and constraints in 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 586,299 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 246,716 for the lowest threshold considered (FIT 20µg Hb/g faeces). These results indicate that care should be taken when selecting an appropriate FIT threshold for the healthcare setting. Further analyses following a distribution of ages through screening would enable an estimation of the burden of colonoscopy over time in a steady state for the screened population.

A key strength of this analysis is the availability of data on FIT vs. 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 colorectal cancer screening for this setting.

We performed several sensitivity analyses around key parameters as well as presenting the probabilistic simulation for the base case results. The conclusion arising from the mean base case outcomes, that FIT is 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 £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 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, such as age - could affect the results. However, even under these scenarios, our analysis suggests it is likely that FIT would still be cost-saving compared to 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 which 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 16]. 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 [16], 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 bowel scope screening, which the NHS BCSP is in the process of rolling out to all men and women in England aged 55 in addition to the existing screening protocol from the age of 60. Neither have we attempted to model possible changes to the age-range or screening frequency of the existing BCSP in England.

Finally, we simulated a cohort starting screening at age 60 and followed in the model until death. Further modelling of the entire screened population in England would be required to take into account multiple cohorts starting FIT screening at different ages, as would be the case if FIT were to be introduced in the place of gFOBT across the screening programme.

Conclusions

This is the first analysis to use FIT screening data in 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 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.

TABLES

Table 1: Cost-effectiveness per person invited for screening of FIT vs. gFOBT, by FIT threshold compared to gFOBT

	Incremental total cost compared to gFOBT, mean(£) (95% CI)	Incremental life years compared to gFOBT, mean (95% CI)	Incremental QALYs compared to gFOBT, mean (95% CI)	ICER: incremental cost per QALY gained compared to gFOBT (£)*	Incremental net benefit compared to gFOBT, mean(£) (95% CI)**
FIT 180µg Hb/g faeces (base case)	-27 (-43, -12)	0.019 (0.016, 0.023)	0.014 (0.012, 0.017)	FIT dominates (p<0.001)	315 (256, 377)
FIT 150µg Hb/g faeces	-40 (-62, -19)	0.028 (0.024, 0.032)	0.021 (0.018, 0.024)	FIT dominates (p=0.001)	458 (388, 531)
FIT 100µg Hb/g faeces	-53 (-86, -23)	0.038 (0.033, 0.043)	0.029 (0.025, 0.033)	FIT dominates (p<0.001)	637 (546, 731)
FIT 40µg Hb/g faeces	-84 (-151, -24)	0.073 (0.065, 0.082)	0.058 (0.051, 0.064)	FIT dominates (p=0.002)	1237 (1072, 1405)
FIT 20µg Hb/g faeces	-62 (-141, 8)	0.082 (0.072, 0.091)	0.066 (0.057, 0.074)	FIT dominates (p=0.050)	1378 (1177, 1582)

Means are deterministic means; all 95% confidence intervals calculated as percentiles of 1000 probabilistic model runs; * Incremental Cost-Effectiveness Ratio (ICER) = $\Delta C/\Delta E$, where ΔE and ΔC are the incremental QALYs and incremental costs, respectively, of FIT compared to gFOBT. p-values calculated as the proportion of the 1000 PSA simulations with positive ICERs; ** INB= $\lambda.\Delta E - \Delta C$, where λ is the willingness to pay threshold = £20,000 per QALY gained.

Table 2: Resource use and costs associated with screening kits in the first screening year for a population of 586,299 people invited for screening aged 60 years

	Resource use			Cost (£)		
	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)
Total number of pre-invites sent in first year (excluding repeat kits)	586,299	586,299	-	-	-	
Number of people returning kit in first year (normal result)	313,940	367,667	53,727	-	-	
Number of people returning kit in first year (positive result)	5,573	5,854	282	-	-	
Positivity rate	1.7%	1.6%	-0.2%	-	-	
Number of people not returning kit in first year	266,786	212,778	-54,009	-	-	
Total number of kits returned (normal result)*	336,542	376,380	39,837	707,808	2,001,168	1,293,360
Total number of kits returned (positive result)*	5,974	5,993	19	12,564	31,864	19,300
Total number of kits sent but not returned*	285,994	217,820	-68,174	246,061	376,138	130,077
Total number of kits used in the first year (total screening cost for cohort)	628,510	600,192	-28,317	966,433	2,409,171	1,442,738
TOTAL SCREENING COSTS in the first year per 1000 people invited for screening at age 60 years	-	-	-	1,648	4,109	2,461

* Includes repeat kits

Table 3: Colonoscopy resource use and adverse events for a population of 586,299 people invited for screening, 40 year time horizon

	Resource use			Cost (£)		
	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)
Follow-up						
Colonoscopies without polypectomy	28,271	28,803	532	13,072,867	13,054,770	-18,096
Colonoscopies with polypectomy for HR adenomas	14,999	20,083	5,084	8,601,586	11,594,795	2,993,209
Colonoscopies with polypectomy for LR adenomas	8,949	8,367	-582	5,114,618	4,800,387	-314,230
Deaths at colonoscopy	0	0	0	143	141	-2
Total number of follow-up colonoscopies	52,218	57,253	5,035	26,789,214	29,450,094	2,660,881
Major bleeds requiring hospitalisation	21	23	2	7,741	8,434	692
Perforation	33	35	2	74,978	78,179	3,201
Surveillance						
Colonoscopies without polypectomy	10,923	14,669	3,746	4,408,649	5,958,520	1,549,871
Colonoscopies with polypectomy for LR adenomas	6,802	9,128	2,326	10,940,253	14,772,752	3,832,499
Colonoscopies with polypectomy for HR adenomas	21,994	29,510	7,516	3,363,538	4,542,553	1,179,015
Deaths at colonoscopy	0	0	0	72	97	25
Total number of surveillance colonoscopies	39,719	53,308	13,589	18,712,511	25,273,922	6,561,411
Major bleeds requiring hospitalisation	16	21	5	5,419	7,319	1,900
Perforation	19	25	6	39,333	53,139	13,806
TOTAL NUMBER OF COLNOSCOPIES	91,937	110,561	18,624	18,757,263	25,334,380	6,577,117
TOTAL NUMBER OF COLNOSCOPIES per 1000 people invited for screening at age 60 years	157	189	32	31,993	43,211	11,218

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

	gFOBT (£)	FIT 180µg Hb/g faeces (base case) (£)	FIT 150µg Hb/g faeces (£)	FIT 100µg Hb/g faeces (£)	FIT 40µg Hb/g faeces (£)	FIT 20µg 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	0.07	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**

CRC: colorectal cancer; * also includes the cost of specialist screening practitioner appointments for those not attending colonoscopy

AUTHOR CONTRIBUTIONS

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.

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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. The views expressed in the paper are those of the authors alone.

SUPPLEMENTARY INFORMATION

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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Cost-effectiveness plane illustrating probabilistic sensitivity analysis results for each FIT threshold vs. gFOBT (1000 simulations)

254x190mm (300 x 300 DPI)

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."

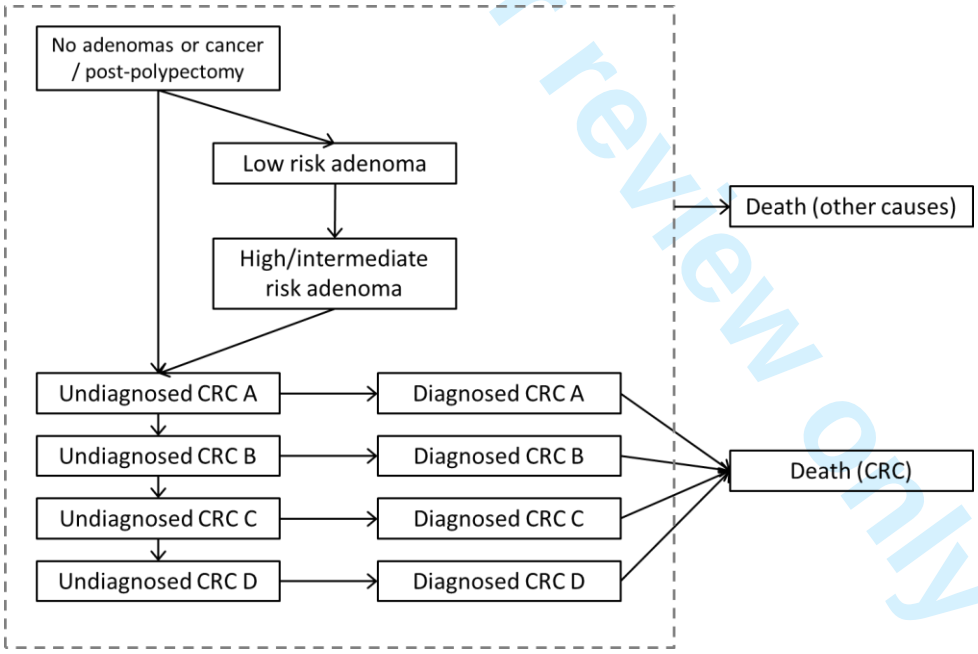
SUPPLEMENTARY INFORMATION

Contents

SECTION 1: MODEL STRUCTURE

The model was constructed using Microsoft Excel® (2010) software. The model structure is based on previously published work for the NHS Bowel Cancer Screening Programme (BCSP) by Whyte et al [1, 2]. Underlying the model is a set of natural history transitions illustrated in Supplementary Figure 1, determining disease progression in a non-screened population. The possible health states are: No adenomas or cancer/no adenomas or cancer post-polypectomy, low risk adenoma (LR), high risk/intermediate risk adenoma (HR/IR), undiagnosed colorectal cancer (CRC) by Dukes' Stage (A,B,C,D), diagnosed colorectal cancer (by Dukes' Stage A,B,C,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 a previously validated model [1, 2] 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 [3], due to the available transition probabilities (see SECTION 2: MODEL PARAMETERS). Transitions between health states occur once in each annual cycle.

Supplementary Figure 1: Diagram of underlying health states and natural history transitions, adapted from [1]

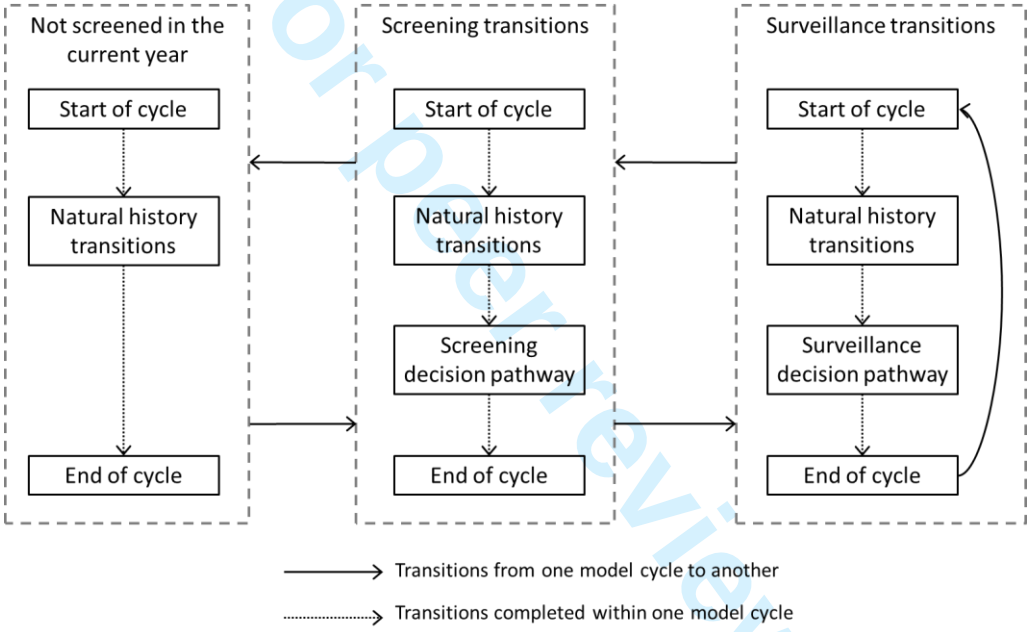


CRC, Colorecal cancer; "CRC A" denotes Dukes' stage A colorectal cancer, and similarly for B,C,D; "Death (CRC)" denotes death due to colorectal cancer, and similarly for Death (other causes)

To estimate the number of people in the population with polyps and cancers at the start of screening, the model begins with a population at age 30 with no adenomas or cancer. Disease progression without screening is modelled from age 30 to age 60, resulting in a screening eligible population divided between various disease states (simulating the presence of undetected neoplasia), at which stage screening begins.

The screening model is constructed in three parts as illustrated in Supplementary Figure 2: 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. As illustrated in Supplementary Figure 2, subjects in the non-screening component undergo natural history transitions (disease progression). In the screening component, subjects undergo natural history transitions followed by the screening pathway. Subjects who undergo polypectomy at colonoscopy for HR adenomas following screening enter the surveillance component of the model.

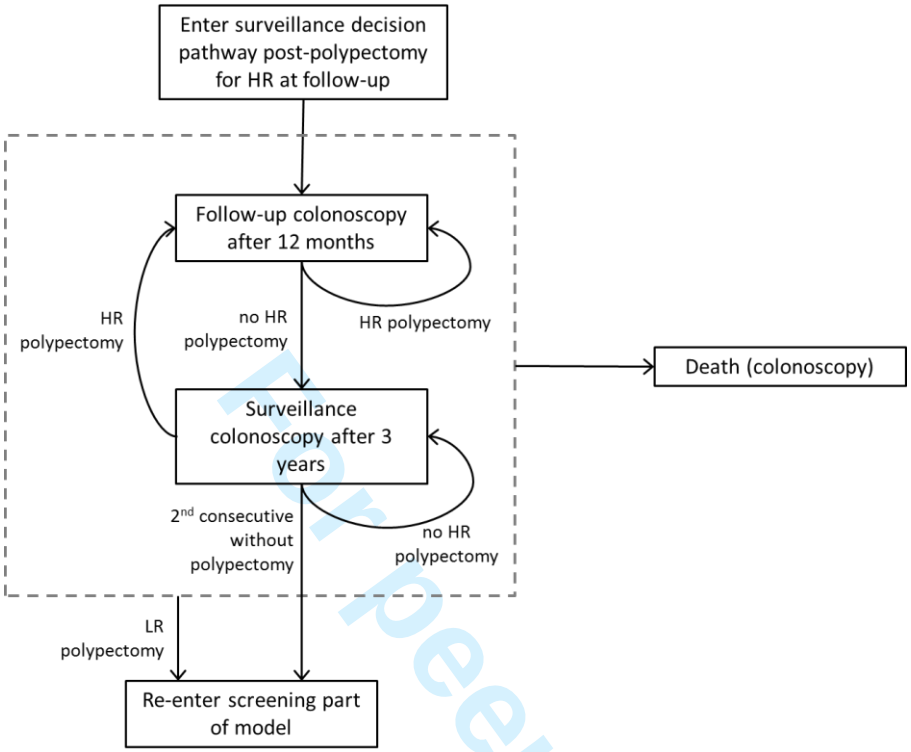
Supplementary Figure 2: Overall three part model structure, each lasting for one model cycle (one year)



The modelled surveillance pathways for high risk adenomas are illustrated in Supplementary Figure 3. These align with current guidelines for surveillance after polypectomy for HR adenoma, as updated in 2010 [3]. In the model, the HR/IR adenoma group undergo the same surveillance guidelines; this is a simplifying assumption. Subjects are assumed to undergo a 12-month colonoscopy, followed by a colonoscopy every three years until they have had two consecutive three-yearly procedures with no high risk adenomas detected. At this point we assume that patients re-enter the screening component of the model. Recommendations published in 2010 [3] are that surveillance is stopped at age 75 years. However since people in the model are screened up to age 75 years surveillance transitions are continued until 80 years, so that those with polypectomy for HR adenomas at age 75 also undergo surveillance colonoscopies.

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."

Supplementary Figure 3: Diagram of surveillance decision pathway used in the model



HR: high risk polyp; LR: low risk polyp; "Death (colonoscopy)" denotes death due to colonoscopy

SECTION 2: MODEL PARAMETERS

1. Natural history

Transition probabilities between the underlying disease states illustrated in Supplementary Figure 1 were based on a previously validated model for the NHS BCSP, by Whyte et al [1, 2]. These disease progression (or "natural history") parameters are summarised in Supplementary Table 1. Linear interpolation between ages 30, 50, 70 and 100 was used to estimate the age-dependent transition probabilities between Normal, LR, HR/IR, and undiagnosed Dukes' Stage A CRC disease states.

Supplementary Table 1: Disease progression parameters, from [1]

Health state transition model parameter	Transition probability	Source
No adenomas or cancer → LR adenoma age 30	0.021	[1]
No adenomas or cancer → LR adenoma age 50	0.020	[1]
No adenomas or cancer → LR adenoma age 70	0.045	[1]
No adenomas or cancer → LR adenoma age 100	0.011	[1]
LR adenoma → HR/IR adenoma age 30	0.009	[1]
LR adenoma → HR/IR adenoma age 50	0.008	[1]
LR adenoma → HR/IR adenoma age 70	0.008	[1]
LR adenoma → HR/IR adenoma age 100	0.004	[1]
HR/IR adenoma → undiagnosed Dukes' A CRC age 30	0.029	[1]
HR/IR adenoma → undiagnosed Dukes' A CRC age 50	0.025	[1]
HR/IR adenoma → undiagnosed Dukes' A CRC age 70	0.054	[1]
HR/IR adenoma → undiagnosed Dukes' A CRC age 100	0.115	[1]
No adenomas or cancer → undiagnosed Dukes' A CRC	0.000	[1]
undiagnosed Dukes' A CRC → undiagnosed Dukes' B CRC	0.508	[1]
undiagnosed Dukes' B CRC → undiagnosed Dukes' C CRC	0.692	[1]
undiagnosed Dukes' C CRC → undiagnosed Dukes' D CRC	0.708	[1]
Symptomatic presentation with Dukes' A CRC (undiagnosed → diagnosed A)	0.044	[1]
Symptomatic presentation with Dukes' B CRC (undiagnosed → diagnosed B)	0.176	[1]
Symptomatic presentation with Dukes' C CRC (undiagnosed → diagnosed C)	0.369	[1]
Symptomatic presentation with Dukes' D CRC (undiagnosed → diagnosed D)	0.735	[1]
LR post-polypectomy to LR	0.100	[1]
LR post-polypectomy to HR/IR	0.040	[1]
Post-polypectomy to LR	0.188	[1]
Post-polypectomy to HR/IR	0.568	[1]

("1→2" denotes transition from state 1 to state 2); LR: low risk; HR: high risk; IR, intermediate risk; CRC: colorectal cancer; all variables presented by age were converted to piecewise linear distributions for use in the model

2. Screening test characteristics

In line with the NHS BCSP pilot study of FIT vs. gFOBT screening, the model is based on FIT using the OC-SENSOR system with DIANA analyser (Eiken Chemical, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using hema-screen (Immunostics, New Jersey, USA, supplied by Alpha Laboratories, Eastleigh UK). More information on the screening kits is available elsewhere [4].

Sensitivity and specificity of FIT and gFOBT were not directly measured in the FIT pilot study moss [4] as no follow-up information was available for on participants with negative screening test results. We therefore estimated the sensitivity and specificity of FIT relative to gFOBT using the detection rates observed in the pilot study [4], and applied these to the sensitivity and specificity of gFOBT from the calibrated parameters in the previous NHS BCSP economic evaluation [1]. We illustrate these calculations below.

Sensitivity

To estimate the sensitivity of FIT, we multiplied the sensitivity of gFOBT in the model by the ratio of the cancer detection rates observed in the BCSP pilot (Supplementary Table 2). Cancer detection rates were calculated separately for each type of neoplasia (CRC, advanced adenomas ("High/Intermediate Risk" in the model), and all other neoplasia ("Low Risk" in the model)) by multiplying the positive predictive value (PPV) of the kit for those attending colonoscopy by the positivity rate from the pilot.

Supplementary Table 2: Detection rates for gFOBT and FIT from the BCSP pilot [4, 5]

	gFOBT	FIT 20	FIT 40	FIT 100	FIT 150	FIT 180
Returned kit	667945	27167	27167	27167	27167	27167
Screened positive	11575	2127	1416	656	483	412
Positivity rate	1.73%	7.83%	5.21%	2.41%	1.78%	1.52%
Attended colonoscopy	9835	1824	1202	546	400	339
Neoplasia detected at colonoscopy:						
LR	1913	471	298	124	81	63
HR/IR (AA)	2364	471	351	183	133	116
Cancer	818	73	65	44	40	36
PPV from colonoscopy results:						
LR	19.5%	25.8%	24.8%	22.7%	20.3%	18.6%
HR/IR (AA)	24.0%	25.8%	29.2%	33.5%	33.3%	34.2%
Cancer	8.3%	4.0%	5.4%	8.1%	10.0%	10.6%
ALL	5095	1015	714	351	254	215
Normal (false positives)	1722	267	166	60	45	41

For example, for gFOBT the PPV for LR adenomas in the pilot was 1913/9835=19.5%, and the positivity rate was 4285/258,875=1.7% [4], giving a detection rate of 19.5% x 1.7% = 0.3%.

Similarly, for the base case FIT threshold of 180µg Hb/g faeces, the detection rate was 18.6% x 1.52% = 0.28%. The ratio of detection rates for LR at this FIT threshold was therefore 0.28% / 0.3% = 0.84. This value was multiplied by the sensitivity of gFOBT from the model (0.90%) to give a sensitivity estimate for FIT (180µg Hb/g faeces) to detect LR adenomas of 0.9% x 0.84 = 0.75%.

Supplementary Table 3 shows the sensitivity estimates for all thresholds.

Supplementary Table 3: Sensitivity estimates used in the model

	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
LR	0.90%	0.75%	0.96%	1.46%	3.45%	5.40%
Advanced adenoma (HR/IR)	12.40%	15.45%	17.60%	24.09%	45.31%	60.19%
CRC	24.20%	27.04%	29.85%	32.67%	47.32%	52.61%

gFOBT parameters were taken from the calibrated parameters in the previous NHS BCSP economic evaluation [1]; FIT parameters were estimated relative to the calibrated gFOBT parameters using data from the FIT pilot study moss [4, 5]

Specificity

To estimate the specificity of FIT, we multiplied the specificity of gFOBT in the model by the ratio of (1-false positive rate) for FIT and gFOBT using data from the BCSP pilot. The false positive rate = FP/(FP+TN), where FP is the number of false positives and TN is the number of true negatives. As the number of true negatives was not directly observed in the pilot (no follow-up diagnosis information was available for participants who returned a negative test), we made an assumption that for the lowest FIT threshold (20µg Hb/g faeces) the number of true negatives in the population was equal to the number of negative kits returned, i.e. there were no false negative screening results.

Supplementary Table 4 shows the screening test data from the pilot, by age group [4, 5].

Supplementary Table 4: Screening test data by age-group from the FIT pilot study: source Moss et al [4, 5]

	gFOBT	FIT 180µg Hb/g faeces (base case)	FIT 150µg Hb/g faeces	FIT 100µg Hb/g faeces	FIT 40µg Hb/g faeces
Age 59-64*					
Returned kit	258,875	11,105	11,105	11,105	11,105
Screened positive	4285	152	176	234	505
Positivity rate	1.66%	1.37%	1.58%	2.11%	4.55%
Attended colonoscopy	3665	126	148	197	434
All neoplasia (HR/IR/LR cancer)	1825	78	90	122	247
Normal	743	17	19	24	71
Age 65-69					
Returned kit	248,021	9,668	9,668	9,668	9,668
Screened positive	4064	143	171	240	503
Positivity rate	1.64%	1.48%	1.77%	2.48%	5.20%
Attended colonoscopy	3459	120	146	205	440
All neoplasia (HR/IR/LR cancer)	1782	79	97	137	276
Normal	591	9	11	17	51
Age 70-75**					
Returned kit	161,049	6,394	6,394	6,394	6,394
Screened positive	3226	117	136	182	408
Positivity rate	2.00%	1.83%	2.13%	2.85%	6.38%
Attended colonoscopy	2711	93	106	145	328
All neoplasia (HR/IR/LR cancer)	1488	58	67	92	191
Normal	388	15	15	19	44
All ages (age 59-75)					
Returned kit	667,945	27,167	27,167	27,167	27,167
Screened positive	11,575	412	483	656	1,416
Positivity rate	1.73%	1.52%	1.78%	2.41%	5.21%
Attended colonoscopy	9835	339	400	546	1,202
Tested +ve for LR	1913	63	81	124	298
Tested +ve for HR/IR	2364	116	133	183	351
Tested +ve for Cancer	818	36	40	44	65
All neoplasia (HR/IR/LR cancer)	5095	215	254	351	714
Normal	1722	41	45	60	166

Source: Moss et al [5]. *results for the 59-64 age group were used for the 60-64 age group in the model as a small number of people were invited before their 60th birthday in the pilot and so are included in this age group; **results for the 70-75 age group were used for the 70-74 age group in the model

For FIT 20µg Hb/g faeces, the number of participants aged 60-64 returning a negative screening kit was 11,105-765 = 10,340. The proportion of the positive screens resulting in no detected neoplasia at colonoscopy (i.e. a false positive screening result) was 110/666=16.5%. 765 participants returned a positive kit in this age group , and therefore the estimated total number of negatives in this age group is 10,340 + 16.5% x 765 = 10,466 (94.2%.of the 11,105 people screened). (Supplementary Table 5)

Using this proportion, the estimated total number of negatives in this age group for those screened with gFOBT is 94.2% x 258,875 = 243,987. Applying the proportions of false positive results at

colonoscopy (above) to the number attending colonoscopy, the false positive rates are calculated as (20.3% * 4287) / 243,987 = 0.36% for gFOBT, and similarly to give 1.21% for FIT. The ratio of 1-false positive rate compared to gFOBT is then 1.21%/0.36% = 0.9915 for FIT 20µg Hb/g faeces for the age group 60-64 years. (Supplementary Table 6)

Equivalent ratios were calculated for the other age groups in the BCSP pilot, namely age 65-59 and age 70-74. We then used linear interpolation/regression to apply the rates to the gFOBT parameters in the model and estimate FIT specificity at age 50 and 70 years. (Supplementary Table 6)

Supplementary Table 5: Calculation of the proportion of negatives in the population by age

FIT 20µg Hb/g faeces	Age group 60-64	65-69	70-74
Number of kits returned	11,105	11,105	11,105
Number of positive screens	765	747	615
Number of the screened population returning a negative kit	11,105 – 765 = 10,340	8,921	5,779
Number attending colonoscopy	666	659	499
Number of false positives at colonoscopy	110	92	65
Proportion of those attending colonoscopy that are false positives (true negative)	110 / 666 = 16.5%	14.0%	13.0%
Estimated total number of negatives in the population	10,340 + (16.5% x 765) = 10,466	9,025	5,859
Estimated proportion of the population that are negative	10,466 / 11,105 = 94.2%	93.4%	91.6%

Supplementary Table 6: Estimating false positive rate and specificity by age group

Age 60-64	gFOBT	FIT 20	FIT 40	FIT 100	FIT 150	FIT 180
Estimated total number of negatives in the population	94.2% x 258,875 = 243,987	10,466	10,466	10,466	10,466	10,466
Proportion of false positives at colonoscopy	743 / 3665 = 20.3%	16.5%	16.4%	12.2%	12.8%	13.5%
Number returning kits	4285	765	505	234	176	152
False positive rate = FP/total number of negatives in population	(20.3% * 4287) / 243,987 = 0.36%	1.21%	0.79%	0.27%	0.22%	0.20%
Ratio of (1-false positive rate) relative to gFOBT	N/A	0.9915	0.9957	1.0008	1.0014	1.0016
Estimated specificity*	0.9814	0.9730	0.9771	0.9822	0.9828	0.9830

A summary of the final model parameters for sensitivity and specificity of screening kits is shown in Supplementary Table 7.

Supplementary Table 7: Sensitivity and specificity of screening kits - model parameters

	gFOBT*	FIT 180µg Hb/g faeces (base case)	FIT 150µg Hb/g faeces	FIT 100µg Hb/g faeces	FIT 40µg Hb/g faeces	FIT 20µg Hb/g faeces
Sensitivity - LR	0.009	0.008	0.010	0.015	0.035	0.054
Sensitivity - HR/IR	0.124	0.154	0.176	0.241	0.453	0.602
Sensitivity - CRC	0.242	0.270	0.299	0.327	0.473	0.526
Specificity age 50	0.994	0.998	0.998	0.997	0.992	0.988
Specificity age 70	0.973	0.974	0.973	0.973	0.968	0.963

*gFOBT parameters were taken from the calibrated parameters in the previous NHS BCSP economic evaluation [1]; FIT parameters were estimated relative to the calibrated gFOBT parameters using data from the FIT pilot study [4].

3. Cancer-related mortality

Cancer-related mortality by stage at diagnosis was estimated from 5-year survival statistics for England [6]. The available survival data for the first 5 years after diagnosis were extrapolated to the maximum time horizon using a Weibull parametric model, fitted using Microsoft Excel® (data shown in Supplementary Figure 4 and Supplementary Table 8).

Supplementary Figure 4: Weibull extrapolation of 5-year CRC survival data (shown up to 35 years from diagnosis)

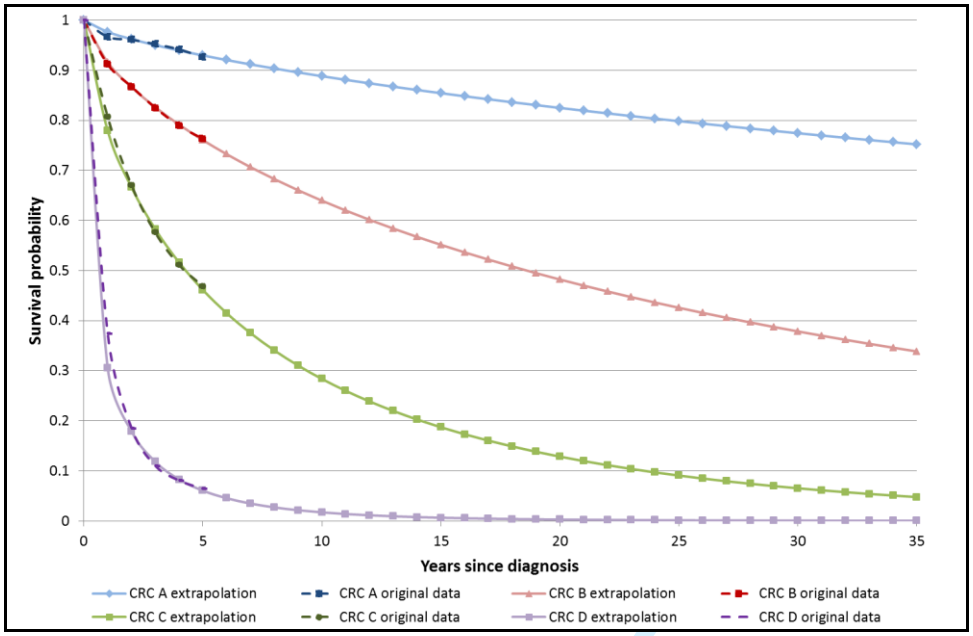


Figure note: CRC A original data: 5-years survival estimates from [6]; CRC A extrapolation: Weibull fit to 5-year estimates extrapolated to a greater number of years since diagnosis than original data

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."

Supplementary Table 8: Fitted survival by CRC stage at diagnosis using Weibull extrapolation of 5-year CRC survival data from [13]

Years since diagnosis	CRC A	CRC B	CRC C	CRC D
0	1	1	1	1
1	0.977	0.916	0.779	0.305
2	0.962	0.866	0.666	0.179
3	0.950	0.826	0.583	0.118
4	0.939	0.791	0.516	0.083
5	0.930	0.760	0.461	0.061
6	0.920	0.732	0.415	0.045
7	0.912	0.707	0.375	0.035
8	0.904	0.683	0.341	0.027
9	0.896	0.660	0.310	0.021
10	0.888	0.640	0.284	0.017
11	0.881	0.620	0.260	0.014
12	0.874	0.601	0.239	0.011
13	0.867	0.584	0.220	0.009
14	0.861	0.567	0.203	0.008
15	0.854	0.551	0.187	0.006
16	0.848	0.536	0.173	0.005
17	0.842	0.522	0.160	0.005
18	0.836	0.508	0.149	0.004
19	0.830	0.495	0.138	0.003
20	0.825	0.482	0.128	0.003
21	0.819	0.470	0.120	0.002
22	0.814	0.458	0.111	0.002
23	0.809	0.447	0.104	0.002
24	0.803	0.436	0.097	0.002
25	0.798	0.426	0.091	0.001
26	0.793	0.416	0.085	0.001
27	0.789	0.406	0.079	0.001
28	0.784	0.396	0.074	0.001
29	0.779	0.387	0.070	0.001
30	0.774	0.379	0.065	0.001
31	0.770	0.370	0.061	0.001
32	0.765	0.362	0.057	0.001
33	0.761	0.354	0.054	0.000
34	0.756	0.346	0.051	0.000
35	0.752	0.338	0.048	0.000
36	0.748	0.331	0.045	0.000
37	0.744	0.324	0.042	0.000
38	0.739	0.317	0.040	0.000
39	0.735	0.311	0.038	0.000
40	0.731	0.304	0.035	0.000
41	0.727	0.298	0.033	0.000
42	0.723	0.292	0.031	0.000
43	0.720	0.286	0.030	0.000
44	0.716	0.280	0.028	0.000
45	0.712	0.274	0.027	0.000
46	0.708	0.269	0.025	0.000
47	0.705	0.263	0.024	0.000
48	0.701	0.258	0.022	0.000
49	0.697	0.253	0.021	0.000
50	0.694	0.248	0.020	0.000
51	0.690	0.243	0.019	0.000
52	0.687	0.239	0.018	0.000
53	0.683	0.234	0.017	0.000
54	0.680	0.230	0.016	0.000
55	0.676	0.225	0.015	0.000
56	0.673	0.221	0.014	0.000
57	0.670	0.217	0.014	0.000
58	0.666	0.213	0.013	0.000
59	0.663	0.209	0.012	0.000
60	0.660	0.205	0.012	0.000
61	0.657	0.201	0.011	0.000
62	0.654	0.197	0.011	0.000
63	0.651	0.194	0.010	0.000
64	0.647	0.190	0.010	0.000
65	0.644	0.187	0.009	0.000
66	0.641	0.183	0.009	0.000
67	0.638	0.180	0.008	0.000
68	0.635	0.177	0.008	0.000
69	0.632	0.174	0.007	0.000
70	0.629	0.171	0.007	0.000
71	0.627	0.168	0.007	0.000

CRC, colorectal cancer

4. Quality of life

Due to a lack of CRC-specific values in the literature we used utility weights for health states with and without any cancer from Ara et al [7]. The mean age for respondents for this health state was 60.9 years, which corresponds well to the age at which screening is started in the BCSP. These values are given in Supplementary Table 9.

Supplementary Table 9: Utility values

Disease state	Mean utility value (SD*)	Source
Cancer health states	0.697 (0.020)	[7]
Cancer-free health states	0.798 (0.021)	[7]

Data are for a sample group of 820 with and 560 without any cancer, with a mean age 60.9 years [7]; * estimated using reported confidence intervals;

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 one year.

5. Unit costs

The unit costs of screening kits (gFOBT and FIT) were taken from a previous costing study at the NHS Bowel BCSP Southern Hub in Guildford [8] and inflated to the 2015/16 cost year using the Health Service Cost Index. Details of these unit costs are shown in Supplementary Table 10.

Supplementary Table 10: Details of cost per screening kit [8], inflated from 2012/13 to 2015/16 costs [9]

Cost item	gFOBT(£, 2015/16)	FIT(£, 2015/16)
Equipment (Post room)		
gFOBT test kit printer	0.02	0.00
Equipment (Laboratory)		
Analyser and Device cost (manufacturer's quoted price per kit)	0.45	2.84
Guillotine	0.00	-
Equipment maintenance cost	0.01	0.01
Test tube racks	-	0.00
Refrigerator for FIT kits and reagents	-	0.00
Postage and Packaging		
Initial kits price per pack (Outsource mail company)	0.08	0.11
Outgoing Postage costs	0.29	0.66
Return kits postage costs (1st class)	0.46	0.53
Outgoing postage from additional kits required (gFOBT 11% FIT 2%)	0.38	0.66
Additional printing costs (pre-printed headed paper/Labels)	0.01	0.30
Instruction leaflets	0.01	-
Pre-printed envelopes (Outsourced Mail)	0.02	-
Pre-printed envelopes (Internal Mail)	0.03	-
Staff Cost (Post room)	0.01	0.01
Staff Cost (Lab)	0.32	0.20
Waste Disposal	0.00	0.01
TOTAL COST PER KIT	2.10	5.32

Supplementary Table 11 summarises the costs used in the model. Screening and colonoscopy costs were taken from national NHS 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 colorectal cancer management were taken from a model-based evaluation of colorectal cancer services by Pilgrim et al [10]. No cost was assigned to death. All costs were inflated to 2015/16 using the Health Service Cost Index [9].

Supplementary Table 11: Cost assumptions

Parameter	Value (£, cost year 2015/16)	Source
Screening kits		
Cost of gFOBT screen (non-compliers)	0.86	[8, 9]
Cost of gFOBT screen (returned kit)	2.10	[8, 9]
Cost of FIT screen (non-compliers)	1.73	[8, 9]
Cost of FIT screen (returned kit)	5.32	[8, 9]
Hospital services		
Appointment with Specialist Screening Practitioner	33.00	[11, 12] Mean salary band 6, 45 minute appointment duration
Colonoscopy without polypectomy	558	[13] Day Case (diagnostic)
Colonoscopy with polypectomy	612	[13] Day Case (therapeutic)
Cost of admittance for bleeding (overnight stay on medical ward)	474	[13] Weighted average of all Non-elective inpatient, short stay gastrointestinal bleed groups (FZ38G,H,J,K,L,M,N,P)
Cost of perforation (major surgery)	2,900	[13] Weighted average of all Non-elective inpatient, long stay Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+
Pathology cost for adenoma	80	Standard per-patient lab charge in one centre for routine colonic polyps. Incorporates consultant time for processing, reporting, quality control, audit. (personal communication)
Pathology cost for cancer	80	Standard per-patient lab charge in one centre for routine colonic polyps. Incorporates consultant time for processing, reporting, quality control, audit. (personal communication)
Cancer management		
Lifetime cost - screen-detected Dukes' Stage A	13,768	[9, 10]
Lifetime cost - screen-detected Dukes' Stage B	18,943	[9, 10]
Lifetime cost - screen-detected Dukes' Stage C	25,979	[9, 10]
Lifetime cost - screen-detected Dukes' Stage D	28,412	[9, 10]

6. Incorporating uncertainty around model parameters

The calibrated disease progression parameters shown in Supplementary Table 1 and screening test characteristics shown in Supplementary Table 7 were varied probabilistically using multivariate normal distributions via Cholesky decomposition, following the methods described in Briggs et al [14]. The correlation/covariance matrices for each FIT threshold were estimated in R software [15] as rounded values were reported by Whyte et al [1] and these are available from the authors upon request.

The distributions for the other parameters were estimated following the methods described in Briggs et al [14] and using reported measures of uncertainty, and are shown in Supplementary Table 12.

Supplementary Table 12: Screening and cost parameters and distributions

Parameter	Parameter value	Source	PSA distribution
gFOBT – uptake of those sent a pre-invite			
age 60-64	54.50%	[5]	Beta (258875, 216155)
age 65-69	63.64%	[5]	Beta (248021, 141691)
age 70-74	61.62%	[5]	Beta (161049, 100296)
gFOBT – average number of kits required	1.072	[5]	Gamma (10608382, 0.00)
gFOBT – sensitivity			
LR	0.009	[1]	Cholesky decomposition using correlation matrices
HR/IR	0.124	[1]	Cholesky decomposition using correlation matrices
CRC	0.242	[1]	Cholesky decomposition using correlation matrices
gFOBT specificity			
age 50	0.994	[1]	Cholesky decomposition using correlation matrices
age 70	0.973	[1]	Cholesky decomposition using correlation matrices
FIT – uptake of those sent a pre-invitation letter			
age 60-64	63.71%	[5]	Beta (11105, 6326)
age 65-69	68.88%	[5]	Beta (9668, 4368)
age 70-74	67.57%	[5]	Beta (6394, 3069)
FIT – average number of kits required	1.024	[5]	Gamma (1596858, 0.00)
FIT - sensitivity	Supplementary Table 7	estimated as in Section 2 [1, 5]	Cholesky decomposition using correlation matrices
FIT – specificity (at age 50/70)	Supplementary Table 7	estimated as in Section 2 [1, 5]	Cholesky decomposition using correlation matrices
Colonoscopy uptake after positive test	86.2%	Southern hub data [16] The proportion of those with a positive test who attended colonoscopy.	Beta (24357, 3901)
Sensitivity of colonoscopy for LR adenomas	0.765	[17]	Beta (544, 167)
Sensitivity of colonoscopy for HR adenomas	0.979	[17]	Beta (94, 2)
Sensitivity of colonoscopy for CRC	0.966	[17]	Beta (12057, 430)
Specificity of colonoscopy	1	Assumption	N/A
Colonoscopy perforation rate (without polypectomy)	0.031%	[18]	Beta (19, 61784)
Colonoscopy perforation rate (with polypectomy)	0.091%	[18]	Beta (63, 68965)
Proportion of colonoscopies resulting in hospitalisation for bleeding (transfusion)	0.04%	[18]	Beta (52, 180779)
Proportion of perforations resulting in death	0.85%	NHS BCSP data* [19]	Beta (1, 116)
Proportion of colonoscopies requiring a repeat procedure	9.55%	[5]	Beta (1075, 10182)

*There were 147 recorded perforations between August 2006 and March 2014 of which 117 had complete outcome data, including 1 observed death.

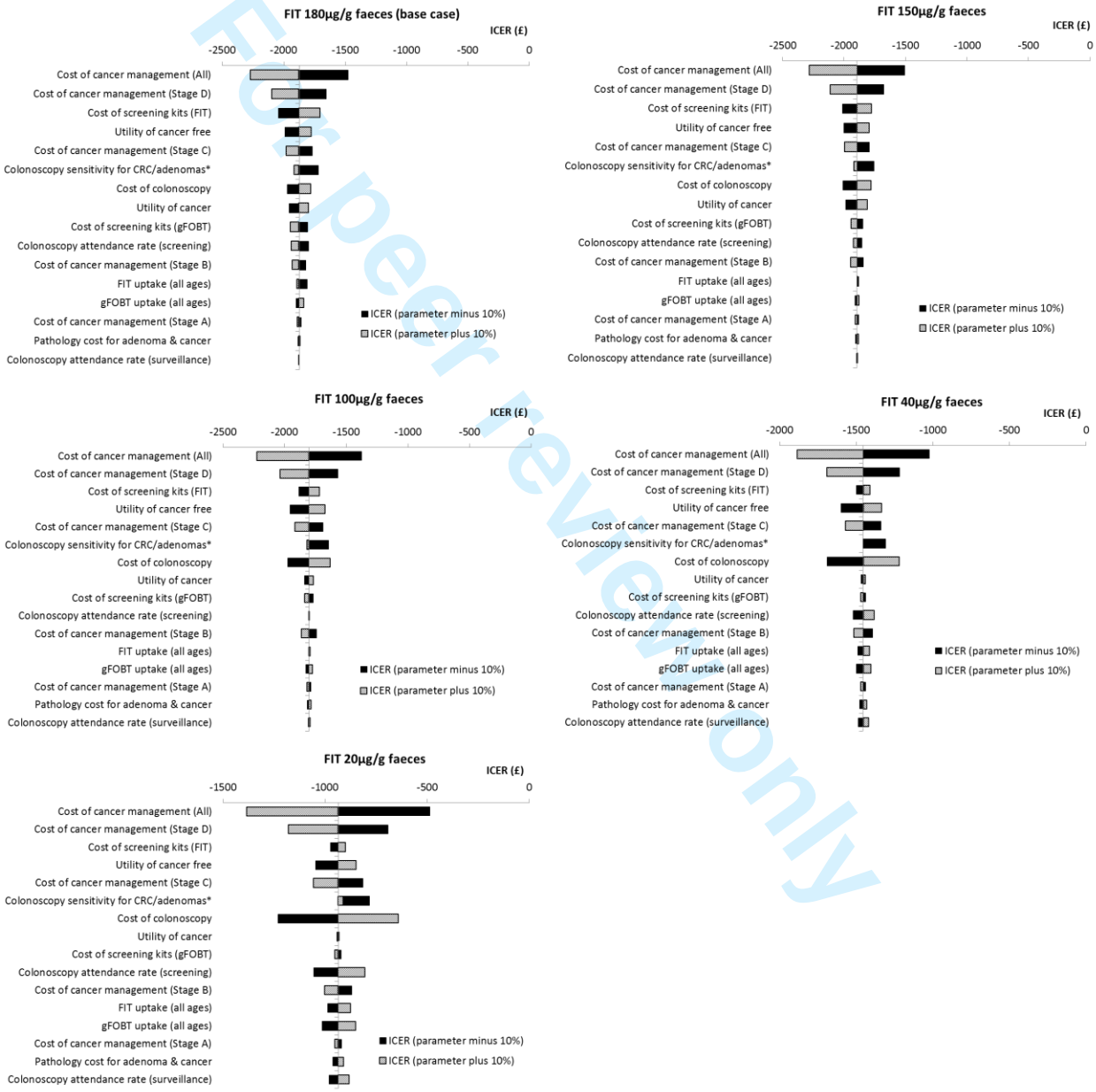
Supplementary Table 12 (contd.): Model parameters and distributions

Parameter	Cost £ (2015/16)	Source	PSA distribution
Cost of screening kits			
Cost of gFOBT screen (non-compliers)	0.86	[8, 9]	Uniform over +/- 10% (£0.74 to £0.91)
Cost of gFOBT screen (returned kit)	2.10	[8, 9]	Uniform over +/- 10% (£1.81 to £2.21)
Cost of FIT screen (non-compliers)	1.73	[8, 9]	Uniform over +/- 10% (£1.49 to £1.82)
Cost of FIT screen (returned kit)	5.32	[8, 9]	Uniform over +/- 10% (£4.58 to £5.60)
Cost of hospital services			
Appointment with Specialist Screening Practitioner	33	[11, 12] Mean salary band 6, 45 minute appointment duration assumed	Uniform over +/- 10% (£28.35 to £34.65)
Colonoscopy without polypectomy	558	[13] Day Case (diagnostic)	N/A
Colonoscopy with polypectomy	612	[13] Day Case (therapeutic)	N/A
Cost of admittance for bleeding (overnight stay on medical ward)	474	[13] Weighted average of all Non-elective inpatient, short stay gastrointestinal bleed groups (FZ38G,H,J,K,L,M,N,P)	N/A
Cost of perforation (major surgery)	2,900	[13] Weighted average of all Non-elective inpatient, long stay Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+	N/A
Pathology cost for adenoma	80	Standard per-patient lab charge for routine colonic polyps. Incorporates consultant time for processing, reporting, quality, audit. [11]	Uniform over +/- 10% (£72 to £88)
Pathology cost for cancer	80	Standard per-patient lab charge for routine colonic polyps. Incorporates consultant time for processing, reporting, quality, audit. [11]	Uniform over +/- 10% (£72 to £88)
Cost of cancer management			
Lifetime cost - screen-detected Dukes' stage A	13,768	[9, 10]	Gamma (25, 539) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage B	18,943	[9, 10]	Gamma (25, 741) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage C	25,979	[9, 10]	Gamma (25, 1017) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage D	28,412	[9, 10]	Gamma (25, 1112) 20% SE assumed
Utility values			
CRC health states	0.697 (0.020)	[7] appendices	Beta(361.73,157.25)
Cancer free health states	0.798 (0.021)	[7] appendices	Beta(279.34,70.71)

SECTION 3: 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 180µg Hb/g faeces. The results are shown in terms of the incremental cost-effectiveness ratio in Supplementary Figure 5, and in terms of the incremental net benefit in Supplementary Figure 6.

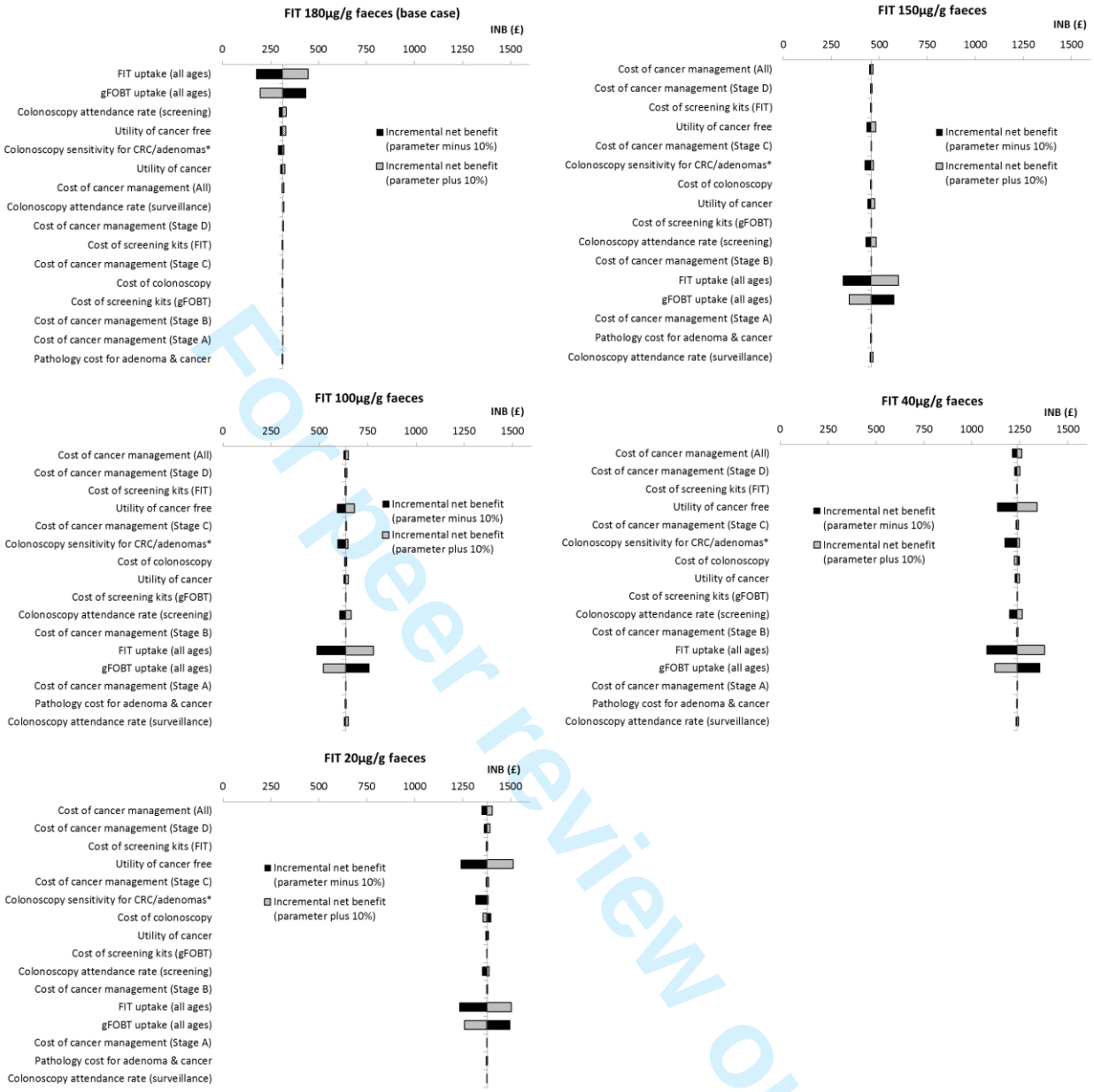
Supplementary Figure 5: One-way sensitivity analyses: incremental cost-effectiveness ratio per person invited for screening



* Maximum value limited to 100%; Categories are sorted by ranked difference in ICER for the base case (FIT 180µg Hb/g faeces) ; Data are centred on the mean ICER for each FIT threshold.

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."

Supplementary Figure 6: One-way sensitivity analyses: incremental net benefit per person invited for screening



* Maximum value limited to 100%; Categories are sorted by ranked difference in INB for the base case (FIT 180µg Hb/g faeces) ; Data are centred on the mean INB for each FIT threshold.

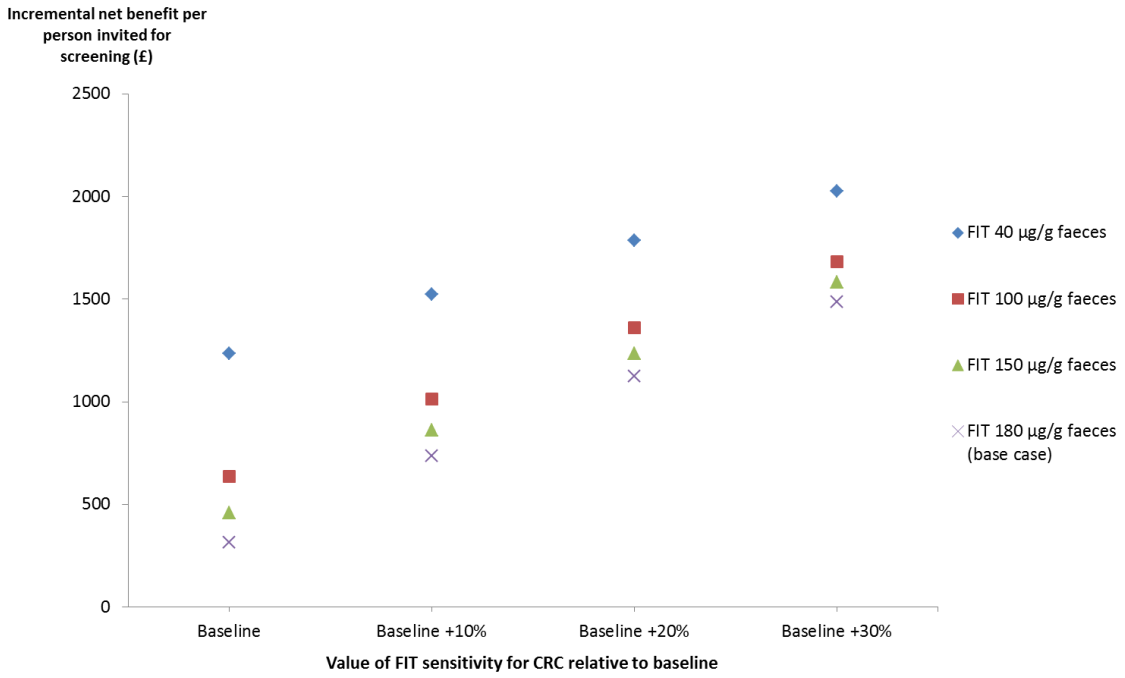
Murphy J, Halloran S, Gray A. "Cost-effectiveness of the faecal immunochemical test at a range of positivity thresholds compared with the guaiac faecal occult blood test in the NHS Bowel Cancer Screening Programme in England."

Table 1 shows a one-way sensitivity analyses around the sensitivity of FIT for CRC at each FIT threshold, illustrated on the cost-effectiveness plane. Supplementary Figure 7 shows the results illustrated in terms of net benefit.

Table 1: Sensitivity analysis results for FIT sensitivity to detect CRC

	Baseline	+10%	+20%	+30%
Incremental cost				
FIT 180 µg/g faeces (base case)	-27	-74	-117	-157
FIT 150 µg/g faeces	-40	-84	-126	-164
FIT 100 µg/g faeces	-53	-94	-133	-168
FIT 40 µg/g faeces	-84	-115	-144	-171
FIT 20 µg/g faeces	-62	-89	-114	-137
Incremental QALYs				
FIT 180 µg/g faeces (base case)	0.014	0.033	0.050	0.066
FIT 150 µg/g faeces	0.021	0.039	0.056	0.071
FIT 100 µg/g faeces	0.029	0.046	0.061	0.076
FIT 40 µg/g faeces	0.058	0.070	0.082	0.093
FIT 20 µg/g faeces	0.066	0.077	0.087	0.096

Supplementary Figure 7: Incremental net benefit changes for variation in FIT sensitivity parameter



SECTION 4: BUDGET IMPACT/COHORT RESULTS

Supplementary Table 13 shows detailed model results for the screening resource use and costs for gFOBT and at each FIT threshold, for the first year of the model.

Supplementary Table 13: Screening resource use for a population of 586,299 people invited for screening in first year of the model

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces		FIT 20µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Total number of pre-invites sent in first year (excluding repeat kits)	586,299	-	586,299	-	586,299	-	586,299	-	586,299	-	586,299	-
Number of people returning kit in first year (normal result)	313,940	-	367,667	-	366,762	-	364,639	-	356,138	-	349,269	-
Number of people returning kit in first year (positive result)	5,573	-	5,854	-	6,759	-	8,882	-	17,384	-	24,252	-
Positivity rate	1.7%	-	1.6%	-	1.8%	-	2.4%	-	4.7%	-	6.5%	-
Number of people not returning kit in first year	266,786	-	212,778	-	212,778	-	212,778	-	212,778	-	212,778	-
Total number of kits returned (normal result) in first year*	336,542	707,808	376,380	2,001,168	375,453	1,996,245	373,280	1,984,688	364,577	1,938,415	357,546	1,901,031
Total number of kits returned (positive result) in first year*	5,974	12,564	5,993	31,864	6,919	36,788	9,093	48,345	17,796	94,618	24,827	132,002
Total number of kits sent but not returned*	285,994	246,061	217,820	376,138	217,820	376,138	217,820	376,138	217,820	376,138	217,820	376,138
Total number of kits used in first year*	628,510	966,433	600,192	2,409,171	600,192	2,409,171	600,192	2,409,171	600,192	2,409,171	600,192	2,409,171
TOTAL SCREENING COSTS per invited person in screening population at age 60 years	-	1.65	0	4.11	0	4.11	0	4.11	0	4.11	0	4.11

* Includes repeat kits

Supplementary Table 14 shows detailed model results for the screening resource use and costs for gFOBT and at each FIT threshold, over the 40 year time horizon of the model.

Supplementary Table 14: Screening resource use and costs for a population of 586,299 people invited for screening over 40 year time horizon

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces		FIT 20µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Total number of pre-invites sent (excluding repeat kits)	4,262,195	-	4,258,073	-	4,256,027	-	4,250,908	-	4,236,576	-	4,228,639	-
Number of people returning kits (normal result)	2,470,249	-	2,764,198	-	2,756,078	-	2,736,344	-	2,668,083	-	2,615,836	-
Number of people returning kits (positive result)	55,301	-	60,633	-	67,389	-	83,715	-	142,461	-	189,458	-
Positivity rate	2.2%	-	2.1%	-	2.4%	-	3.0%	-	5.1%	-	6.8%	-
Number of people not returning kit in first year	1,736,645	-	1,433,242	-	1,432,561	-	1,430,849	-	1,426,032	-	1,423,346	-
Total number of kits returned (normal result)*	2,648,095	4,449,924	2,829,700	12,074,544	2,821,387	12,039,344	2,801,186	11,954,261	2,731,307	11,656,616	2,677,822	11,428,842
Total number of kits returned (positive result)*	59,282	97,489	62,069	256,393	68,986	285,979	85,698	356,928	145,837	614,573	193,947	820,006
Total number of kits sent but not returned*	1,861,674	1,304,784	1,467,205	2,055,806	1,466,507	2,054,887	1,464,755	2,052,561	1,459,824	2,045,923	1,457,074	2,042,173
Total number of kits used*	4,569,051	5,852,197	4,358,974	14,386,743	4,356,880	14,380,211	4,351,640	14,363,751	4,336,968	14,317,112	4,328,843	14,291,021
TOTAL SCREENING COSTS per invited person in screening population at age 60 years	-	9.98		24.54		24.53		24.50		24.42		24.37

* Includes repeat kits

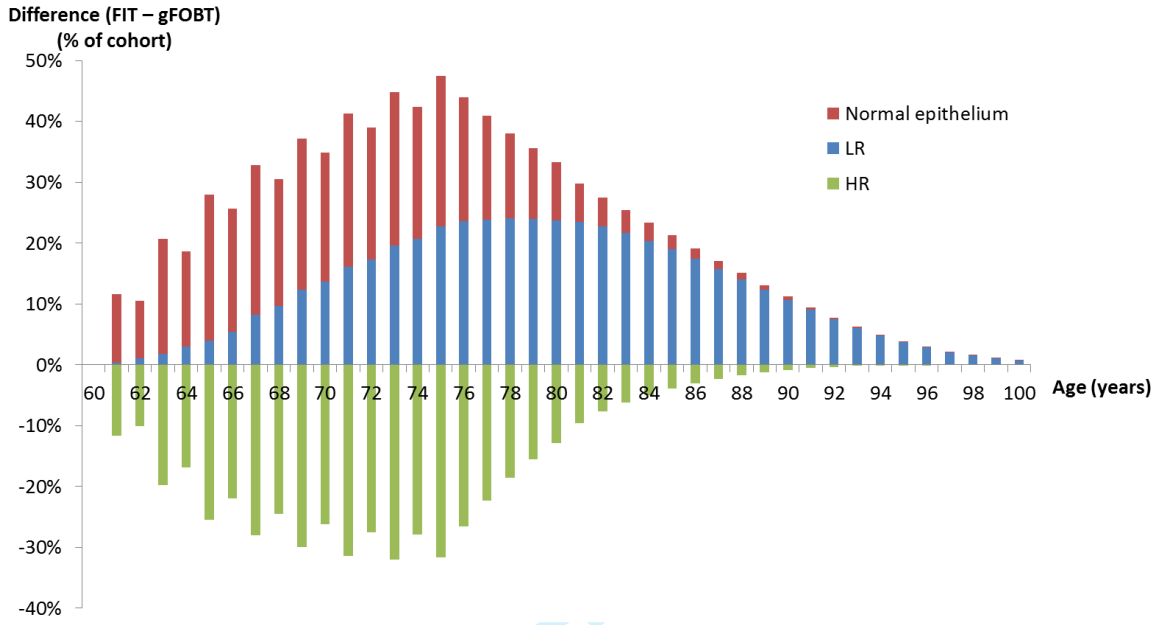
Supplementary Table 15 shows detailed model results for the colonoscopy resource use and costs for gFOBT and at each FIT threshold, over the 40 year time horizon of the model.

Supplementary Table 15: Colonoscopy resource use and adverse events for a population of 586,299 people invited for screening, 40 year time horizon

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces		FIT 20µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Follow-up												
Colonoscopies without polypectomy	28,271	13,072,867	28,803	13,054,770	30,422	13,856,678	33,360	15,258,274	48,149	22,471,009	60,557	28,444,169
Colonoscopies with polypectomy for HR adenomas	14,999	8,601,586	20,083	11,594,795	22,534	13,023,456	29,462	17,081,000	48,540	28,371,488	59,869	35,116,525
Colonoscopies with polypectomy for LR adenomas	8,949	5,114,618	8,367	4,800,387	10,677	6,126,010	16,226	9,311,452	37,831	21,724,838	58,471	33,608,325
Deaths at colonoscopy	0	143	0	141	0	153	0	17	1	275	1	352
Total number of follow-up colonoscopies	52,218	26,789,214	57,253	29,450,094	63,633	33,006,297	79,049	41,650,90	134,521	72,567,611	178,898	97,169,370
Major bleeds requiring hospitalisation	21	7,741	23	8,434	25	9,407	32	11,74	54	20,215	72	26,973
Perforation	33	74,978	35	78,179	38	85,121	44	100,22	70	161,360	92	210,759
Surveillance												
Colonoscopies without polypectomy	10,923	4,408,649	14,669	5,958,520	16,468	6,695,510	21,562	8,792,64	35,648	14,649,402	44,021	18,153,000
Colonoscopies with polypectomy for LR adenomas	6,802	10,940,253	9,128	14,772,752	10,246	16,597,644	13,412	21,787,10	22,155	36,260,924	27,350	44,913,610
Colonoscopies with polypectomy for HR adenomas	21,994	3,363,538	29,510	4,542,553	33,124	5,103,836	43,353	6,700,14	71,601	11,153,330	88,384	13,815,629
Deaths at colonoscopy	0	72	0	97	0	109	0	14	1	238	1	295
Total number of surveillance colonoscopies	39,719	18,712,511	53,308	25,273,922	59,838	28,397,099	78,327	37,280,03	129,405	62,063,895	159,755	76,882,533
Major bleeds requiring hospitalisation	16	5,419	21	7,319	24	8,224	31	10,79	52	17,974	64	22,266
Perforation	19	39,333	25	53,139	28	59,708	37	78,39	61	130,550	76	161,741
TOTAL NUMBER OF COLNOSCOPIES	91,937	18,757,263	110,561	25,334,380	123,471	28,465,031	157,376	37,369,22	263,925	62,212,419	338,653	77,066,540
Additional colonoscopies and cost compared to gFOBT (per 1000)	-	-	32	11,218	54	16,558	112	31,74	293	74,118	421	99,453

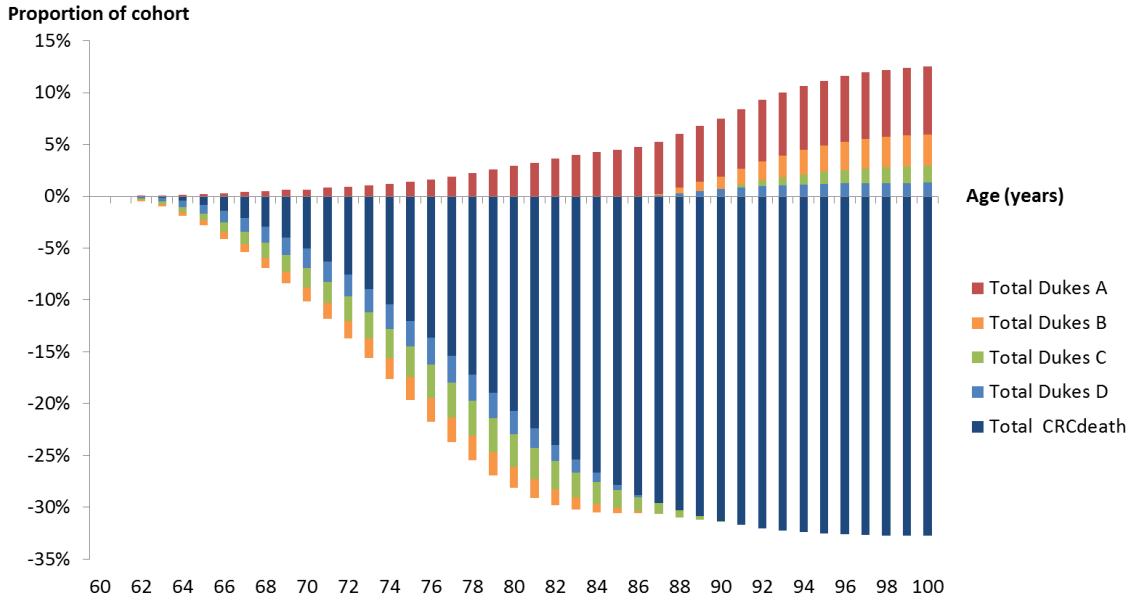
Supplementary Figure 8 shows the model-estimated difference in prevalence of adenomas for FIT at 180µg Hb/g faeces compared with gFOBT in each year of the model after screening begins at age 60 years.

Supplementary Figure 8: Model-estimated difference in non-cancer health state prevalence between FIT and gFOBT, by age



Supplementary Figure 9 shows the model-estimated difference in prevalence of CRC and mortality rate for FIT at 180µg Hb/g faeces compared with gFOBT in each year of the model after screening begins at age 60 years.

Supplementary Figure 9: Model-estimated difference in colorectal cancer prevalence and mortality between FIT and gFOBT, by age



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CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No (page/line numbers from PDF proof)
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page2 line50
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page3 line45
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page2-3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page6 line37
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page3 line41
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page3 line50
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page3 line40
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page3 line49
Measurement of	11a	*Single study-based estimates*: Describe fully the design	N/A

effectiveness		features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page5 – page6
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	page6 line25
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page6
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page6 line35
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page4 line25 + Supplementary information Section 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	pages 3-7 (Methods)
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	pages 3-7 (Methods)
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Supplementary Information Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	pages 7-10 (Results)

		applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	page 7-8 (Sensitivity analyses)
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	page 7-8 (Sensitivity analyses) + Supplementary Information Section 4
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pages 10-12 (Discussion)
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Submitted online and on page17
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Submitted online and on page17

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

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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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Public health, Oncology, Diagnostics, Health policy
Keywords:	Screening, Colorectal cancer, Economic evaluation, Decision modelling, Cost-effectiveness, Cost-utility

Title

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

Authors

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Abstract 299

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ABSTRACT

Objectives

Through the National Health Service Bowel Cancer Screening Programme (BCSP), men and women in England aged between 60 and 74 years are invited for colorectal cancer (CRC) screening every two 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 (FIT) compared with gFOBT for a cohort beginning screening aged 60 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 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, 0.017) at the base case threshold of 180µg 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 180µg Hb/g faeces to 421 additional colonoscopies per 1000 people invited for screening for FIT 20µg Hb /g faeces over a 40-year time horizon). Parameter uncertainty had limited impact on the conclusions.

Conclusions

This is the first 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 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

Strengths of this study include:

- 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 FIT and gFOBT from the English setting.
- This work will help to inform the choice of cut-off threshold for future screening using FIT in the NHS BCSP by providing decision makers with information on predicted resource use, cost and quality of life outcomes.

Limitations of this study include:

- 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 the gFOBT from recent pilot study in England.
- We modelled a cohort starting screening at age 60 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 two 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 vs. gFOBT have been performed for the NHS BCSP [9] but reliable data on the test performance of FIT vs. gFOBT in the NHS BCSP had previously not been available.

We used data from a recent large pilot study of FIT vs. 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, at a range of FIT positivity thresholds. In the BCSP FIT pilot study, a FIT threshold of 180µg Hb/g 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 population-level screening (the current standard test). 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. 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 vs. 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 ICER and incremental net benefit per person invited for screening for a 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 colorectal cancer at age 60, 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 [13], we estimated the annual budget impact of FIT compared to gFOBT at the population level.

We estimated the age distribution for the population in England using ONS data for mid-2015 [12]. We then multiplied the model-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 Bowel Cancer Screening Programme [9 14]. Here we briefly describe the structural assumptions of the model; full details are given in the 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 adenoma (LR), high risk/intermediate risk adenoma (HR/IR), undiagnosed colorectal cancer (CRC) at each Dukes' Stage (A, B, C and D), diagnosed colorectal cancer (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 also undergo surveillance colonoscopies.

Model parameters

A complete list of model parameters and sources is given in the Supplementary Information, Section 2.

Natural history

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

Mortality

Age-dependent all-cause mortality estimates were taken from Office for National Statistics 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, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using the hema-screen (Immunostics, 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 180µg 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 and 97.3% at age 70. In the base case, specificity of FIT 180µg Hb/g faeces was 99.8% at age 50 and 97.4% at age 70. Further details of the methods used to estimate sensitivity and specificity are given in the 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 demonstrated an increased uptake with FIT compared with gFOBT in the English setting, and these estimates were used in the model. Uptake in the model 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) and 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 CRC (mean 0.697, SD 0.020) and without CRC (mean 0.795, SD 0.021) from [19], consistent with previous analyses for the NHS BCSP [9]. The mean age for respondents for this health state 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 one year.

Unit costs

Costs were estimated from the perspective of the healthcare system (NHS/BCSP). Screening and colonoscopy costs were taken from national 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 colorectal cancer management were taken from a model-based evaluation of colorectal

cancer services by Pilgrim et al [21]. No cost was assigned to death. All costs were adjusted, where necessary, to 2015/16 prices using the Health Service Cost Index [22].

Uncertainty

To incorporate uncertainty in the results of the model, we carried out probabilistic analyses 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 (e.g. 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 in R for each FIT threshold, 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 Supplementary Information, Section 2. The estimated variance-covariance matrices are available from the authors upon 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 analyses suggest that 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 +0.30 above baseline parameter value 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 (LYs) and Quality-Adjusted Life Years (QALYs). The mean total cost difference per person ranged from £25 (95% CI: £12 to £43) cheaper for FIT at a 180µg Hb/g faeces threshold to £84 (95% CI: £24 to £151) cheaper for FIT at a 40µg 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 180µg Hb/g faeces threshold to 0.066 (95% CI: 0.057 to 0.074) for FIT at a 20µg Hb/g faeces threshold. FIT dominates gFOBT – that is, screening with FIT results in greater total QALYs gained, 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.

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 the base case FIT 180µg Hb/g faeces. The results are shown in terms of the ICER and incremental net benefit in the 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 decision concerning whether FIT is cost-effective, we sought to determine the cost at which FIT would no longer be cost-saving for each threshold.

FIT was found to no longer be cost saving compared to 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 £6,884 and £9,637 for CRC A (compared to £13768 base case cost); £9,471 to £13,260 for CRC B (£18,943 base case); £12,989 to £18,185 for CRC C (£25,979 base case); and £14,206 to £19,888 for CRC D (£28,412 base case). In the 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 to gFOBT.

Screening test characteristics

The results of the sensitivity analysis around FIT sensitivity for CRC suggest that for all thresholds, if FIT sensitivity has 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 (data given in 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 180µg Hb/g faeces. Screening costs for a range of FIT thresholds are presented in the 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 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 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 £1,648 for gFOBT and £4,109 for FIT at the base case threshold of 180µg Hb/g faeces.

Long-term colonoscopy resource use

The estimated total number of colonoscopies and associated costs for the population (582,218 starting screening aged 60) over a 40 year time horizon is given in Table 3 for gFOBT and FIT at the base case threshold of 180µg Hb/g faeces. Corresponding results for a range of FIT thresholds are given in 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 180µg 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 150µg Hb/g faeces to 244,999 (£57,903,423) for FIT 20µg Hb/g faeces.

Per 1000 people invited for screening, the number (cost) of additional colonoscopies with FIT ranges from 32 (£11,218) for FIT 180µg Hb/g faeces to 421 (£99,453) for FIT 20µg 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, 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 (8.3% of total cost) in the gFOBT arm, and £93.59 (10.3% of total cost) for FIT in the base case (180µg Hb/g faeces). As the FIT threshold is decreased, the colonoscopy burden and therefore costs increase, up to £297.58 (34.0% of total cost) for FIT 20µg 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 180µg Hb/g faeces in the base case. As the FIT threshold is decreased, the lifetime cancer management costs fall, and at the lowest FIT threshold considered, 20µg 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 Supplementary Information, Section 4. The cost projections suggest that in a "steady state" scenario (i.e. 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 to 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 Supplementary Information, Section 4), due to improved detection rates. The increased HR adenoma detection and polypectomy rate for FIT results in a higher proportion 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' B, C, or D CRC is lower with FIT than with gFOBT, and the prevalence of Dukes' 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 in terms of total QALYs accrued, and less costly) vs. gFOBT in an English setting for a single cohort starting screening at age 60. 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, and constraints in 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 20µg Hb/g faeces). These results indicate that care should be taken when selecting an appropriate FIT threshold for the healthcare setting.

A key strength of this analysis is the availability of data on FIT vs. 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 colorectal cancer 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 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 simulation for the base case results in order to explore the effect of varying the model parameters on the results.

The conclusion arising from the sensitivity analyses around the mean base case outcomes, 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 £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 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, such as age - could affect the results. However, even under these scenarios, our analysis suggests it is likely that FIT would still be cost-saving compared to 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 which 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 flexi-scope), which the NHS BCSP is in the process of rolling out to all men and women in England aged 55 in addition to the existing screening protocol from the age of 60. The results of a UK trial with 17 years of follow-up data [28] suggest that flexible sigmoidoscopy screening at age 55 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 to 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 to 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 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 analysis to use FIT screening data in 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 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.

TABLES

Table 1: Cost-effectiveness per person invited for screening of FIT vs. gFOBT, by FIT threshold compared to gFOBT

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

Means are deterministic means; all 95% confidence intervals calculated as percentiles of 1000 probabilistic model runs; * Incremental Cost-Effectiveness Ratio (ICER) = $\Delta C/\Delta E$, where ΔE and ΔC are the incremental QALYs and incremental costs, respectively, of FIT compared to gFOBT. p-values calculated as the proportion of the 1000 PSA simulations with positive ICERs; ** INB= $\lambda.\Delta E - \Delta C$, where λ is the willingness to pay threshold = £20,000 per QALY gained.

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 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)
Total number of pre-invites 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)	5,534	5,814	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)*	5,932	5,951	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	-	-	-	1,648	4,109	2,461

* Includes repeat kits

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 180µg Hb/g faeces (base case)	Difference (FIT – gFOBT)	gFOBT	FIT 180µg 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	5,049	8,541,716	11,514,091	2,972,375
Colonoscopies with polypectomy for LR adenomas	8,886	8,309	-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	5,000	26,602,751	29,245,111	2,642,360
Major bleeds requiring hospitalisation	21	23	2	7,688	8,375	687
Perforation	33	35	2	74,456	77,635	3,178
Surveillance						
Colonoscopies without polypectomy	10,847	14,567	3,720	4,377,963	5,917,047	1,539,084
Colonoscopies with polypectomy for LR adenomas	6,754	9,064	2,310	10,864,104	14,669,928	3,805,823
Colonoscopies with polypectomy for HR adenomas	21,841	29,305	7,464	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	5,381	7,268	1,887
Perforation	19	25	6	39,059	52,769	13,710
TOTAL NUMBER OF COLNOSCOPIES	91,297	109,791	18,494	18,626,705	25,158,043	6,531,337
TOTAL NUMBER OF COLNOSCOPIES per 1000 people invited for screening at age 60 years	157	189	32	31,993	43,211	11,218

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

	gFOBT (£)	FIT 180µg Hb/g faeces (base case) (£)	FIT 150µg Hb/g faeces (£)	FIT 100µg Hb/g faeces (£)	FIT 40µg Hb/g faeces (£)	FIT 20µg 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**

CRC: colorectal cancer; * also includes the cost of specialist screening practitioner appointments for those not attending colonoscopy

AUTHOR CONTRIBUTIONS

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.

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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. The views expressed in the paper are those of the authors alone.

SUPPLEMENTARY INFORMATION

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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FIGURE LEGENDS

Figure 1: Cost-effectiveness plane illustrating probabilistic sensitivity analysis results for each FIT threshold vs. gFOBT (1000 simulations)

Cost-effectiveness plane illustrating probabilistic sensitivity analysis results for each FIT threshold vs. gFOBT (1000 simulations)

254x190mm (300 x 300 DPI)

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."

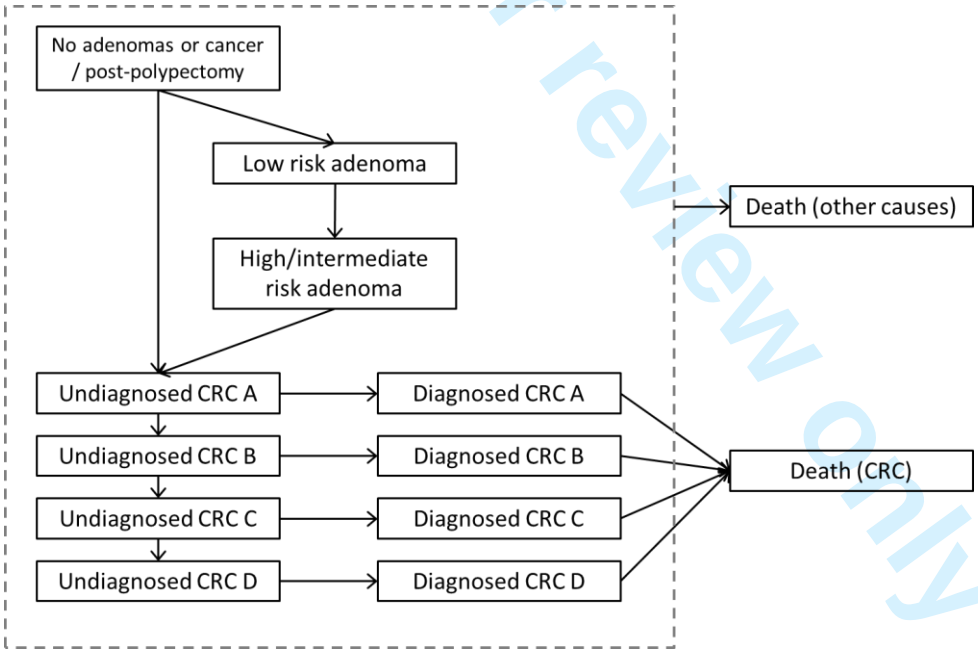
SUPPLEMENTARY INFORMATION

Contents

SECTION 1: MODEL STRUCTURE

The model was constructed using Microsoft Excel® (2010) software. The model structure is based on previously published work for the NHS Bowel Cancer Screening Programme (BCSP) by Whyte et al [1, 2]. Underlying the model is a set of natural history transitions illustrated in Supplementary Figure 1, determining disease progression in a non-screened population. The possible health states are: No adenomas or cancer/no adenomas or cancer post-polypectomy, low risk adenoma (LR), high risk/intermediate risk adenoma (HR/IR), undiagnosed colorectal cancer (CRC) by Dukes' Stage (A,B,C,D), diagnosed colorectal cancer (by Dukes' Stage A,B,C,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 a previously validated model [1, 2] 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 [3], due to the available transition probabilities (see SECTION 2: MODEL PARAMETERS). Transitions between health states occur once in each annual cycle.

Supplementary Figure 1: Diagram of underlying health states and natural history transitions, adapted from [1]

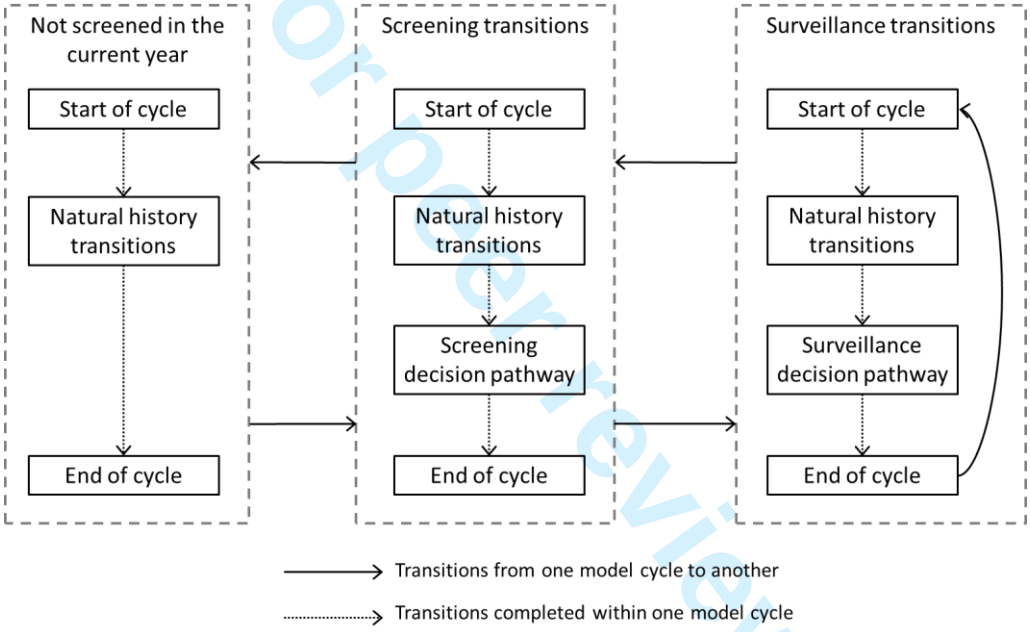


CRC, Colorecal cancer; "CRC A" denotes Dukes' stage A colorectal cancer, and similarly for B,C,D; "Death (CRC)" denotes death due to colorectal cancer, and similarly for Death (other causes)

To estimate the number of people in the population with polyps and cancers at the start of screening, the model begins with a population at age 30 with no adenomas or cancer. Disease progression without screening is modelled from age 30 to age 60, resulting in a screening eligible population divided between various disease states (simulating the presence of undetected neoplasia), at which stage screening begins.

The screening model is constructed in three parts as illustrated in Supplementary Figure 2: 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. As illustrated in Supplementary Figure 2, subjects in the non-screening component undergo natural history transitions (disease progression). In the screening component, subjects undergo natural history transitions followed by the screening pathway. Subjects who undergo polypectomy at colonoscopy for HR adenomas following screening enter the surveillance component of the model.

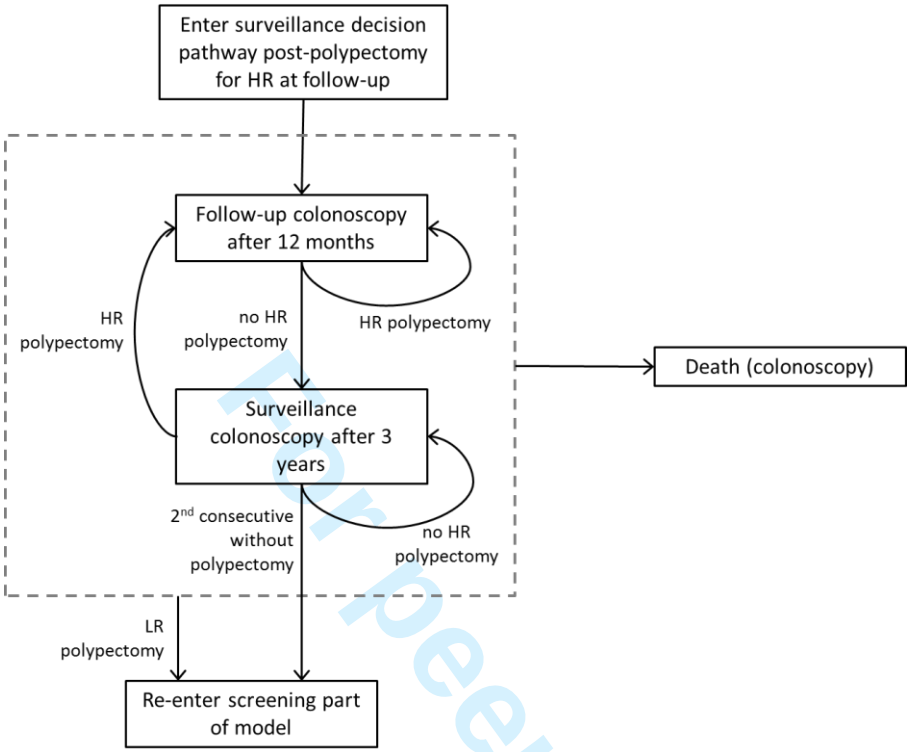
Supplementary Figure 2: Overall three part model structure, each lasting for one model cycle (one year)



The modelled surveillance pathways for high risk adenomas are illustrated in Supplementary Figure 3. These align with current guidelines for surveillance after polypectomy for HR adenoma, as updated in 2010 [3]. In the model, the HR/IR adenoma group undergo the same surveillance guidelines; this is a simplifying assumption. Subjects are assumed to undergo a 12-month colonoscopy, followed by a colonoscopy every three years until they have had two consecutive three-yearly procedures with no high risk adenomas detected. At this point we assume that patients re-enter the screening component of the model. Recommendations published in 2010 [3] are that surveillance is stopped at age 75 years. However since people in the model are screened up to age 75 years surveillance transitions are continued until 80 years, so that those with polypectomy for HR adenomas at age 75 also undergo surveillance colonoscopies.

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."

Supplementary Figure 3: Diagram of surveillance decision pathway used in the model



HR: high risk polyp; LR: low risk polyp; "Death (colonoscopy)" denotes death due to colonoscopy

SECTION 2: MODEL PARAMETERS

1. Natural history

Transition probabilities between the underlying disease states illustrated in Supplementary Figure 1 were based on a previously validated model for the NHS BCSP, by Whyte et al [1, 2]. These disease progression (or "natural history") parameters are summarised in Supplementary Table 1. Linear interpolation between ages 30, 50, 70 and 100 was used to estimate the age-dependent transition probabilities between Normal, LR, HR/IR, and undiagnosed Dukes' Stage A CRC disease states.

Supplementary Table 1: Disease progression parameters*

Health state transition model parameter	Transition probability
No adenomas or cancer → LR adenoma age 30	0.021
No adenomas or cancer → LR adenoma age 50	0.020
No adenomas or cancer → LR adenoma age 70	0.045
No adenomas or cancer → LR adenoma age 100	0.011
LR adenoma → HR/IR adenoma age 30	0.009
LR adenoma → HR/IR adenoma age 50	0.008
LR adenoma → HR/IR adenoma age 70	0.008
LR adenoma → HR/IR adenoma age 100	0.004
HR/IR adenoma → undiagnosed Dukes' A CRC age 30	0.029
HR/IR adenoma → undiagnosed Dukes' A CRC age 50	0.025
HR/IR adenoma → undiagnosed Dukes' A CRC age 70	0.054
HR/IR adenoma → undiagnosed Dukes' A CRC age 100	0.115
No adenomas or cancer → undiagnosed Dukes' A CRC	0.000
undiagnosed Dukes' A CRC → undiagnosed Dukes' B CRC	0.508
undiagnosed Dukes' B CRC → undiagnosed Dukes' C CRC	0.692
undiagnosed Dukes' C CRC → undiagnosed Dukes' D CRC	0.708
Symptomatic presentation with Dukes' A CRC (undiagnosed → diagnosed A)	0.044
Symptomatic presentation with Dukes' B CRC (undiagnosed → diagnosed B)	0.176
Symptomatic presentation with Dukes' C CRC (undiagnosed → diagnosed C)	0.369
Symptomatic presentation with Dukes' D CRC (undiagnosed → diagnosed D)	0.735
LR post-polypectomy to LR	0.100
LR post-polypectomy to HR/IR	0.040
Post-polypectomy to LR	0.188
Post-polypectomy to HR/IR	0.568

All parameters are taken from the calibrated model parameters reported in [1]; ("1→2" denotes transition from state 1 to state 2); LR: low risk; HR: high risk; IR, intermediate risk; CRC: colorectal cancer; all variables presented by age were converted to piecewise linear distributions for use in the model

2. Screening test characteristics

In line with the NHS BCSP pilot study of FIT vs. gFOBT screening, the model is based on FIT using the OC-SENSOR system with DIANA analyser (Eiken Chemical, Japan, supplied by Mast Diagnostics, Bootle, UK) and gFOBT using hema-screen (Immunostics, New Jersey, USA, supplied by Alpha Laboratories, Eastleigh UK). More information on the screening kits is available elsewhere [4].

Sensitivity and specificity of FIT and gFOBT were not directly measured in the FIT pilot study moss [4] as no follow-up information was available for on participants with negative screening test results. We therefore estimated the sensitivity and specificity of FIT relative to gFOBT using the detection rates observed in the pilot study [4], and applied these to the sensitivity and specificity of gFOBT from the calibrated parameters in the previous NHS BCSP economic evaluation [1]. We illustrate these calculations below.

Sensitivity

To estimate the sensitivity of FIT, we multiplied the sensitivity of gFOBT in the model by the ratio of the cancer detection rates observed in the BCSP pilot (Supplementary Table 2). Cancer detection rates were calculated separately for each type of neoplasia (CRC, advanced adenomas ("High/Intermediate Risk" in the model), and all other neoplasia ("Low Risk" in the model)) by multiplying the positive predictive value (PPV) of the kit for those attending colonoscopy by the positivity rate from the pilot.

Supplementary Table 2: Detection rates for gFOBT and FIT from the BCSP pilot [4, 5]

	gFOBT	FIT 20	FIT 40	FIT 100	FIT 150	FIT 180
Returned kit	667945	27167	27167	27167	27167	27167
Screened positive	11575	2127	1416	656	483	412
Positivity rate	1.73%	7.83%	5.21%	2.41%	1.78%	1.52%
Attended colonoscopy	9835	1824	1202	546	400	339
Neoplasia detected at colonoscopy:						
LR	1913	471	298	124	81	63
HR/IR (AA)	2364	471	351	183	133	116
Cancer	818	73	65	44	40	36
PPV from colonoscopy results:						
LR	19.5%	25.8%	24.8%	22.7%	20.3%	18.6%
HR/IR (AA)	24.0%	25.8%	29.2%	33.5%	33.3%	34.2%
Cancer	8.3%	4.0%	5.4%	8.1%	10.0%	10.6%
ALL	5095	1015	714	351	254	215
Normal (false positives)	1722	267	166	60	45	41

For example, for gFOBT the PPV for LR adenomas in the pilot was 1913/9835=19.5%, and the positivity rate was 4285/258,875=1.7% [4], giving a detection rate of 19.5% x 1.7% = 0.3%.

Similarly, for the base case FIT threshold of 180µg Hb/g faeces, the detection rate was 18.6% x 1.52% = 0.28%. The ratio of detection rates for LR at this FIT threshold was therefore 0.28% / 0.3% = 0.84. This value was multiplied by the sensitivity of gFOBT from the model (0.90%) to give a sensitivity estimate for FIT (180µg Hb/g faeces) to detect LR adenomas of 0.9% x 0.84 = 0.75%.

Supplementary Table 3 shows the sensitivity estimates for all thresholds.

Supplementary Table 3: Sensitivity estimates used in the model

	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
LR	0.90%	0.75%	0.96%	1.46%	3.45%	5.40%
Advanced adenoma (HR/IR)	12.40%	15.45%	17.60%	24.09%	45.31%	60.19%
CRC	24.20%	27.04%	29.85%	32.67%	47.32%	52.61%

gFOBT parameters were taken from the calibrated parameters in the previous NHS BCSP economic evaluation [1]; FIT parameters were estimated relative to the calibrated gFOBT parameters using data from the FIT pilot study moss [4, 5]

Specificity

To estimate the specificity of FIT, we multiplied the specificity of gFOBT in the model by the ratio of (1-false positive rate) for FIT and gFOBT using data from the BCSP pilot. The false positive rate = FP/(FP+TN), where FP is the number of false positives and TN is the number of true negatives. As the number of true negatives was not directly observed in the pilot (no follow-up diagnosis information was available for participants who returned a negative test), we made an assumption that for the lowest FIT threshold (20µg Hb/g faeces) the number of true negatives in the population was equal to the number of negative kits returned, i.e. there were no false negative screening results.

Supplementary Table 4 shows the screening test data from the pilot, by age group [4, 5].

Supplementary Table 4: Screening test data by age-group from the FIT pilot study: source Moss et al [4, 5]

	gFOBT	FIT 180µg Hb/g faeces (base case)	FIT 150µg Hb/g faeces	FIT 100µg Hb/g faeces	FIT 40µg Hb/g faeces
Age 59-64*					
Returned kit	258,875	11,105	11,105	11,105	11,105
Screened positive	4285	152	176	234	505
Positivity rate	1.66%	1.37%	1.58%	2.11%	4.55%
Attended colonoscopy	3665	126	148	197	434
All neoplasia (HR/IR/LR cancer)	1825	78	90	122	247
Normal	743	17	19	24	71
Age 65-69					
Returned kit	248,021	9,668	9,668	9,668	9,668
Screened positive	4064	143	171	240	503
Positivity rate	1.64%	1.48%	1.77%	2.48%	5.20%
Attended colonoscopy	3459	120	146	205	440
All neoplasia (HR/IR/LR cancer)	1782	79	97	137	276
Normal	591	9	11	17	51
Age 70-75**					
Returned kit	161,049	6,394	6,394	6,394	6,394
Screened positive	3226	117	136	182	408
Positivity rate	2.00%	1.83%	2.13%	2.85%	6.38%
Attended colonoscopy	2711	93	106	145	328
All neoplasia (HR/IR/LR cancer)	1488	58	67	92	191
Normal	388	15	15	19	44
All ages (age 59-75)					
Returned kit	667,945	27,167	27,167	27,167	27,167
Screened positive	11,575	412	483	656	1,416
Positivity rate	1.73%	1.52%	1.78%	2.41%	5.21%
Attended colonoscopy	9835	339	400	546	1,202
Tested +ve for LR	1913	63	81	124	298
Tested +ve for HR/IR	2364	116	133	183	351
Tested +ve for Cancer	818	36	40	44	65
All neoplasia (HR/IR/LR cancer)	5095	215	254	351	714
Normal	1722	41	45	60	166

Source: Moss et al [4, 5]. *results for the 59-64 age group were used for the 60-64 age group in the model as a small number of people were invited before their 60th birthday in the pilot and so are included in this age group; **results for the 70-75 age group were used for the 70-74 age group in the model

For FIT 20µg Hb/g faeces, the number of participants aged 60-64 returning a negative screening kit was 11,105-765 = 10,340. The proportion of the positive screens resulting in no detected neoplasia at colonoscopy (i.e. a false positive screening result) was 110/666=16.5%. 765 participants returned a positive kit in this age group , and therefore the estimated total number of negatives in this age group is 10,340 + 16.5% x 765 = 10,466 (94.2%.of the 11,105 people screened). (Supplementary Table 5)

Using this proportion, the estimated total number of negatives in this age group for those screened with gFOBT is 94.2% x 258,875 = 243,987. Applying the proportions of false positive results at

colonoscopy (above) to the number attending colonoscopy, the false positive rates are calculated as (20.3% * 4287) / 243,987 = 0.36% for gFOBT, and similarly to give 1.21% for FIT. The ratio of 1-false positive rate compared to gFOBT is then 1.21%/0.36% = 0.9915 for FIT 20µg Hb/g faeces for the age group 60-64 years. (Supplementary Table 6)

Equivalent ratios were calculated for the other age groups in the BCSP pilot, namely age 65-59 and age 70-74. We then used linear interpolation/regression to apply the rates to the gFOBT parameters in the model and estimate FIT specificity at age 50 and 70 years. (Supplementary Table 6)

Supplementary Table 5: Calculation of the proportion of negatives in the population by age

FIT 20µg Hb/g faeces	Age group 60-64	65-69	70-74
Number of kits returned	11,105	11,105	11,105
Number of positive screens	765	747	615
Number of the screened population returning a negative kit	11,105 – 765 = 10,340	8,921	5,779
Number attending colonoscopy	666	659	499
Number of false positives at colonoscopy	110	92	65
Proportion of those attending colonoscopy that are false positives (true negative)	110 / 666 = 16.5%	14.0%	13.0%
Estimated total number of negatives in the population	10,340 + (16.5% x 765) = 10,466	9,025	5,859
Estimated proportion of the population that are negative	10,466 / 11,105 = 94.2%	93.4%	91.6%

Supplementary Table 6: Estimating false positive rate and specificity by age group

Age 60-64	gFOBT	FIT 20	FIT 40	FIT 100	FIT 150	FIT 180
Estimated total number of negatives in the population	94.2% x 258,875 = 243,987	10,466	10,466	10,466	10,466	10,466
Proportion of false positives at colonoscopy	743 / 3665 = 20.3%	16.5%	16.4%	12.2%	12.8%	13.5%
Number returning kits	4285	765	505	234	176	152
False positive rate = FP/total number of negatives in population	(20.3% * 4287) / 243,987 = 0.36%	1.21%	0.79%	0.27%	0.22%	0.20%
Ratio of (1-false positive rate) relative to gFOBT	N/A	0.9915	0.9957	1.0008	1.0014	1.0016
Estimated specificity*	0.9814	0.9730	0.9771	0.9822	0.9828	0.9830

A summary of the final model parameters for sensitivity and specificity of screening kits is shown in Supplementary Table 7.

Supplementary Table 7: Sensitivity and specificity of screening kits - model parameters

	gFOBT*	FIT 180µg Hb/g faeces (base case)	FIT 150µg Hb/g faeces	FIT 100µg Hb/g faeces	FIT 40µg Hb/g faeces	FIT 20µg Hb/g faeces
Sensitivity - LR	0.009	0.008	0.010	0.015	0.035	0.054
Sensitivity - HR/IR	0.124	0.154	0.176	0.241	0.453	0.602
Sensitivity - CRC	0.242	0.270	0.299	0.327	0.473	0.526
Specificity age 50	0.994	0.998	0.998	0.997	0.992	0.988
Specificity age 70	0.973	0.974	0.973	0.973	0.968	0.963

*gFOBT parameters were taken from the calibrated parameters in the previous NHS BCSP economic evaluation [1]; FIT parameters were estimated relative to the calibrated gFOBT parameters using data from the FIT pilot study [4].

3. Cancer-related mortality

Cancer-related mortality by stage at diagnosis was estimated from 5-year survival statistics for England [6]. The available survival data for the first 5 years after diagnosis were extrapolated to the maximum time horizon using a Weibull parametric model, fitted using Microsoft Excel® (data shown in Supplementary Figure 4 and Supplementary Table 8).

Supplementary Figure 4: Weibull extrapolation of 5-year CRC survival data (shown up to 35 years from diagnosis)

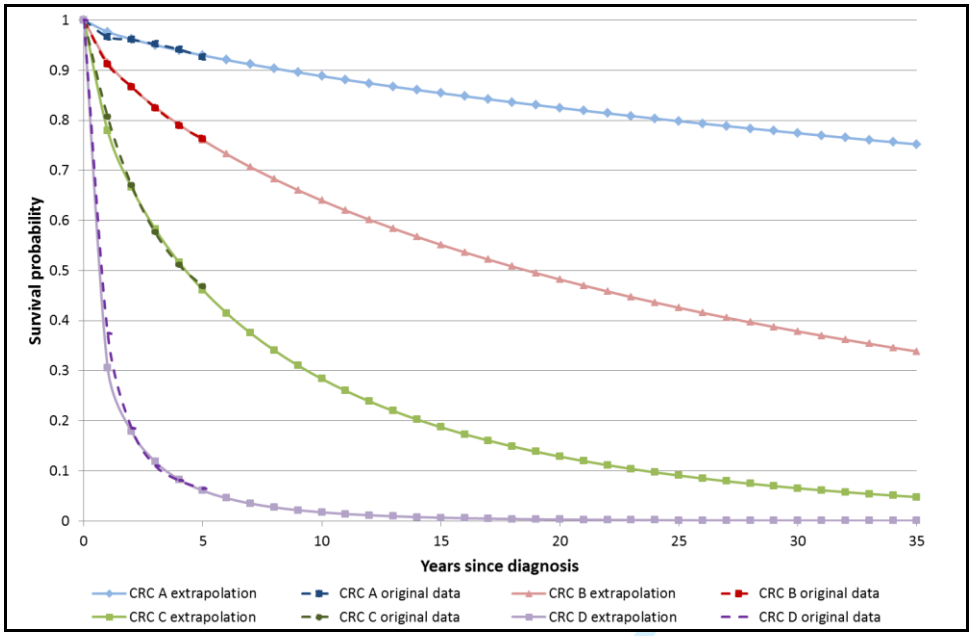


Figure note: CRC A original data: 5-years survival estimates from [6]; CRC A extrapolation: Weibull fit to 5-year estimates extrapolated to a greater number of years since diagnosis than original data

Supplementary Table 8: Fitted survival by CRC stage at diagnosis using Weibull extrapolation of 5-year CRC survival data from [13]

Years since diagnosis	CRC A	CRC B	CRC C	CRC D
0	1	1	1	1
1	0.977	0.916	0.779	0.305
2	0.962	0.866	0.666	0.179
3	0.950	0.826	0.583	0.118
4	0.939	0.791	0.516	0.083
5	0.930	0.760	0.461	0.061
6	0.920	0.732	0.415	0.045
7	0.912	0.707	0.375	0.035
8	0.904	0.683	0.341	0.027
9	0.896	0.660	0.310	0.021
10	0.888	0.640	0.284	0.017
11	0.881	0.620	0.260	0.014
12	0.874	0.601	0.239	0.011
13	0.867	0.584	0.220	0.009
14	0.861	0.567	0.203	0.008
15	0.854	0.551	0.187	0.006
16	0.848	0.536	0.173	0.005
17	0.842	0.522	0.160	0.005
18	0.836	0.508	0.149	0.004
19	0.830	0.495	0.138	0.003
20	0.825	0.482	0.128	0.003
21	0.819	0.470	0.120	0.002
22	0.814	0.458	0.111	0.002
23	0.809	0.447	0.104	0.002
24	0.803	0.436	0.097	0.002
25	0.798	0.426	0.091	0.001
26	0.793	0.416	0.085	0.001
27	0.789	0.406	0.079	0.001
28	0.784	0.396	0.074	0.001
29	0.779	0.387	0.070	0.001
30	0.774	0.379	0.065	0.001
31	0.770	0.370	0.061	0.001
32	0.765	0.362	0.057	0.001
33	0.761	0.354	0.054	0.000
34	0.756	0.346	0.051	0.000
35	0.752	0.338	0.048	0.000
36	0.748	0.331	0.045	0.000
37	0.744	0.324	0.042	0.000
38	0.739	0.317	0.040	0.000
39	0.735	0.311	0.038	0.000
40	0.731	0.304	0.035	0.000
41	0.727	0.298	0.033	0.000
42	0.723	0.292	0.031	0.000
43	0.720	0.286	0.030	0.000
44	0.716	0.280	0.028	0.000
45	0.712	0.274	0.027	0.000
46	0.708	0.269	0.025	0.000
47	0.705	0.263	0.024	0.000
48	0.701	0.258	0.022	0.000
49	0.697	0.253	0.021	0.000
50	0.694	0.248	0.020	0.000
51	0.690	0.243	0.019	0.000
52	0.687	0.239	0.018	0.000
53	0.683	0.234	0.017	0.000
54	0.680	0.230	0.016	0.000
55	0.676	0.225	0.015	0.000
56	0.673	0.221	0.014	0.000
57	0.670	0.217	0.014	0.000
58	0.666	0.213	0.013	0.000
59	0.663	0.209	0.012	0.000
60	0.660	0.205	0.012	0.000
61	0.657	0.201	0.011	0.000
62	0.654	0.197	0.011	0.000
63	0.651	0.194	0.010	0.000
64	0.647	0.190	0.010	0.000
65	0.644	0.187	0.009	0.000
66	0.641	0.183	0.009	0.000
67	0.638	0.180	0.008	0.000
68	0.635	0.177	0.008	0.000
69	0.632	0.174	0.007	0.000
70	0.629	0.171	0.007	0.000
71	0.627	0.168	0.007	0.000

CRC, colorectal cancer

4. Quality of life

Due to a lack of CRC-specific values in the literature we used utility weights for health states with and without any cancer from Ara et al [7]. The mean age for respondents for this health state was 60.9 years, which corresponds well to the age at which screening is started in the BCSP. These values are given in Supplementary Table 9.

Supplementary Table 9: Utility values

Disease state	Mean utility value (SD*)	Source
Cancer health states	0.697 (0.020)	[7]
Cancer-free health states	0.798 (0.021)	[7]

Data are for a sample group of 820 with and 560 without any cancer, with a mean age 60.9 years [7]; * estimated using reported confidence intervals;

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 one year.

5. Unit costs

The unit costs of screening kits (gFOBT and FIT) were taken from a previous costing study at the NHS Bowel BCSP Southern Hub in Guildford [8] and inflated to the 2015/16 cost year using the Health Service Cost Index. Details of these unit costs are shown in Supplementary Table 10.

Supplementary Table 10: Details of cost per screening kit [8], inflated from 2012/13 to 2015/16 costs [9]

Cost item	gFOBT(£, 2015/16)	FIT(£, 2015/16)
Equipment (Post room)		
gFOBT test kit printer	0.02	0.00
Equipment (Laboratory)		
Analyser and Device cost (manufacturer's quoted price per kit)	0.45	2.84
Guillotine	0.00	-
Equipment maintenance cost	0.01	0.01
Test tube racks	-	0.00
Refrigerator for FIT kits and reagents	-	0.00
Postage and Packaging		
Initial kits price per pack (Outsource mail company)	0.08	0.11
Outgoing Postage costs	0.29	0.66
Return kits postage costs (1st class)	0.46	0.53
Outgoing postage from additional kits required (gFOBT 11% FIT 2%)	0.38	0.66
Additional printing costs (pre-printed headed paper/Labels)	0.01	0.30
Instruction leaflets	0.01	-
Pre-printed envelopes (Outsourced Mail)	0.02	-
Pre-printed envelopes (Internal Mail)	0.03	-
Staff Cost (Post room)	0.01	0.01
Staff Cost (Lab)	0.32	0.20
Waste Disposal	0.00	0.01
TOTAL COST PER KIT	2.10	5.32

Supplementary Table 11 summarises the costs used in the model. Screening and colonoscopy costs were taken from national NHS 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 colorectal cancer management were taken from a model-based evaluation of colorectal cancer services by Pilgrim et al [10]. No cost was assigned to death. All costs were inflated to 2015/16 using the Health Service Cost Index [9].

Supplementary Table 11: Cost assumptions

Parameter	Value (£, cost year 2015/16)	Source
Screening kits		
Cost of gFOBT screen (non-compliers)	0.86	[8, 9]
Cost of gFOBT screen (returned kit)	2.10	[8, 9]
Cost of FIT screen (non-compliers)	1.73	[8, 9]
Cost of FIT screen (returned kit)	5.32	[8, 9]
Hospital services		
Appointment with Specialist Screening Practitioner	33.00	[11, 12] Mean salary band 6, 45 minute appointment duration
Colonoscopy without polypectomy	558	[13] Day Case (diagnostic)
Colonoscopy with polypectomy	612	[13] Day Case (therapeutic)
Cost of admittance for bleeding (overnight stay on medical ward)	474	[13] Weighted average of all Non-elective inpatient, short stay gastrointestinal bleed groups (FZ38G,H,J,K,L,M,N,P)
Cost of perforation (major surgery)	2,900	[13] Weighted average of all Non-elective inpatient, long stay Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+
Pathology cost for adenoma	80	Standard per-patient lab charge in one centre for routine colonic polyps. Incorporates consultant time for processing, reporting, quality control, audit. (personal communication)
Pathology cost for cancer	80	Standard per-patient lab charge in one centre for routine colonic polyps. Incorporates consultant time for processing, reporting, quality control, audit. (personal communication)
Cancer management		
Lifetime cost - screen-detected Dukes' Stage A	13,768	[9, 10]
Lifetime cost - screen-detected Dukes' Stage B	18,943	[9, 10]
Lifetime cost - screen-detected Dukes' Stage C	25,979	[9, 10]
Lifetime cost - screen-detected Dukes' Stage D	28,412	[9, 10]

6. Incorporating uncertainty around model parameters

The calibrated disease progression parameters shown in Supplementary Table 1 and screening test characteristics shown in Supplementary Table 7 were varied probabilistically using multivariate normal distributions via Cholesky decomposition, following the methods described in Briggs et al [14]. The correlation/covariance matrices for each FIT threshold were estimated in R software [15] as rounded values were reported by Whyte et al [1] and these are available from the authors upon request.

The distributions for the other parameters were estimated following the methods described in Briggs et al [14] and using reported measures of uncertainty, and are shown in Supplementary Table 12.

Supplementary Table 12: Screening and cost parameters and distributions

Parameter	Parameter value	Source	PSA distribution
gFOBT – uptake of those sent a pre-invite			
age 60-64	54.50%	[5]	Beta (258875, 216155)
age 65-69	63.64%	[5]	Beta (248021, 141691)
age 70-74	61.62%	[5]	Beta (161049, 100296)
gFOBT – average number of kits required	1.072	[5]	Gamma (10608382, 0.00)
gFOBT – sensitivity			
LR	0.009	[1]	Cholesky decomposition using correlation matrices
HR/IR	0.124	[1]	Cholesky decomposition using correlation matrices
CRC	0.242	[1]	Cholesky decomposition using correlation matrices
gFOBT specificity			
age 50	0.994	[1]	Cholesky decomposition using correlation matrices
age 70	0.973	[1]	Cholesky decomposition using correlation matrices
FIT – uptake of those sent a pre-invitation letter			
age 60-64	63.71%	[5]	Beta (11105, 6326)
age 65-69	68.88%	[5]	Beta (9668, 4368)
age 70-74	67.57%	[5]	Beta (6394, 3069)
FIT – average number of kits required	1.024	[5]	Gamma (1596858, 0.00)
FIT - sensitivity	Supplementary Table 7	estimated as in Section 2 [1, 5]	Cholesky decomposition using correlation matrices
FIT – specificity (at age 50/70)	Supplementary Table 7	estimated as in Section 2 [1, 5]	Cholesky decomposition using correlation matrices
Colonoscopy uptake after positive test	86.2%	Southern hub data [16] The proportion of those with a positive test who attended colonoscopy.	Beta (24357, 3901)
Sensitivity of colonoscopy for LR adenomas	0.765	[17]	Beta (544, 167)
Sensitivity of colonoscopy for HR adenomas	0.979	[17]	Beta (94, 2)
Sensitivity of colonoscopy for CRC	0.966	[17]	Beta (12057, 430)
Specificity of colonoscopy	1	Assumption	N/A
Colonoscopy perforation rate (without polypectomy)	0.031%	[18]	Beta (19, 61784)
Colonoscopy perforation rate (with polypectomy)	0.091%	[18]	Beta (63, 68965)
Proportion of colonoscopies resulting in hospitalisation for bleeding (transfusion)	0.04%	[18]	Beta (52, 180779)
Proportion of perforations resulting in death	0.85%	NHS BCSP data* [19]	Beta (1, 116)
Proportion of colonoscopies requiring a repeat procedure	9.55%	[5]	Beta (1075, 10182)

*There were 147 recorded perforations between August 2006 and March 2014 of which 117 had complete outcome data, including 1 observed death.

Supplementary Table 12 (contd.): Model parameters and distributions

Parameter	Cost £ (2015/16)	Source	PSA distribution
Cost of screening kits			
Cost of gFOBT screen (non-compliers)	0.86	[8, 9]	Uniform over +/- 10% (£0.74 to £0.91)
Cost of gFOBT screen (returned kit)	2.10	[8, 9]	Uniform over +/- 10% (£1.81 to £2.21)
Cost of FIT screen (non-compliers)	1.73	[8, 9]	Uniform over +/- 10% (£1.49 to £1.82)
Cost of FIT screen (returned kit)	5.32	[8, 9]	Uniform over +/- 10% (£4.58 to £5.60)
Cost of hospital services			
Appointment with Specialist Screening Practitioner	33	[11, 12] Mean salary band 6, 45 minute appointment duration assumed	Uniform over +/- 10% (£28.35 to £34.65)
Colonoscopy without polypectomy	558	[13] Day Case (diagnostic)	N/A
Colonoscopy with polypectomy	612	[13] Day Case (therapeutic)	N/A
Cost of admittance for bleeding (overnight stay on medical ward)	474	[13] Weighted average of all Non-elective inpatient, short stay gastrointestinal bleed groups (FZ38G,H,J,K,L,M,N,P)	N/A
Cost of perforation (major surgery)	2,900	[13] Weighted average of all Non-elective inpatient, long stay Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 3+	N/A
Pathology cost for adenoma	80	Standard per-patient lab charge for routine colonic polyps. Incorporates consultant time for processing, reporting, quality, audit. [11]	Uniform over +/- 10% (£72 to £88)
Pathology cost for cancer	80	Standard per-patient lab charge for routine colonic polyps. Incorporates consultant time for processing, reporting, quality, audit. [11]	Uniform over +/- 10% (£72 to £88)
Cost of cancer management			
Lifetime cost - screen-detected Dukes' stage A	13,768	[9, 10]	Gamma (25, 539) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage B	18,943	[9, 10]	Gamma (25, 741) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage C	25,979	[9, 10]	Gamma (25, 1017) 20% SE assumed
Lifetime cost - screen-detected Dukes' stage D	28,412	[9, 10]	Gamma (25, 1112) 20% SE assumed
Utility values			
CRC health states	0.697 (0.020)	[7] appendices	Beta(361.73,157.25)
Cancer free health states	0.798 (0.021)	[7] appendices	Beta(279.34,70.71)

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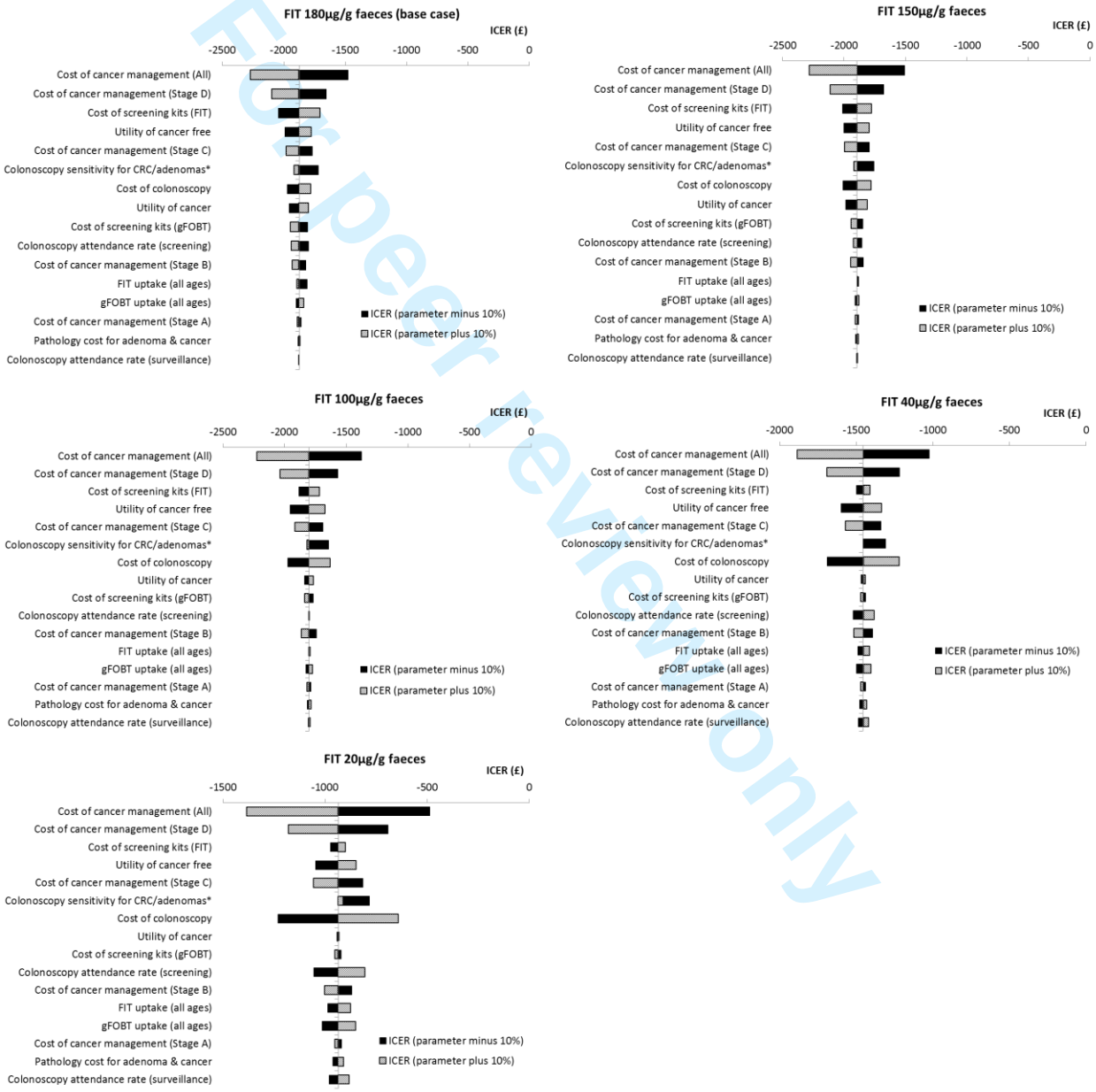
SECTION 3: SENSITIVITY ANALYSES

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 180µg Hb/g faeces. The results are shown in terms of the incremental cost-effectiveness ratio in Supplementary Figure 5, and in terms of the incremental net benefit in Supplementary Figure 6.

Supplementary Figure 5: One-way sensitivity analyses: incremental cost-effectiveness ratio per person invited for screening



* Maximum value limited to 100%; Categories are sorted by ranked difference in ICER for the base case (FIT 180µg Hb/g faeces) ; Data are centred on the mean ICER for each FIT threshold.

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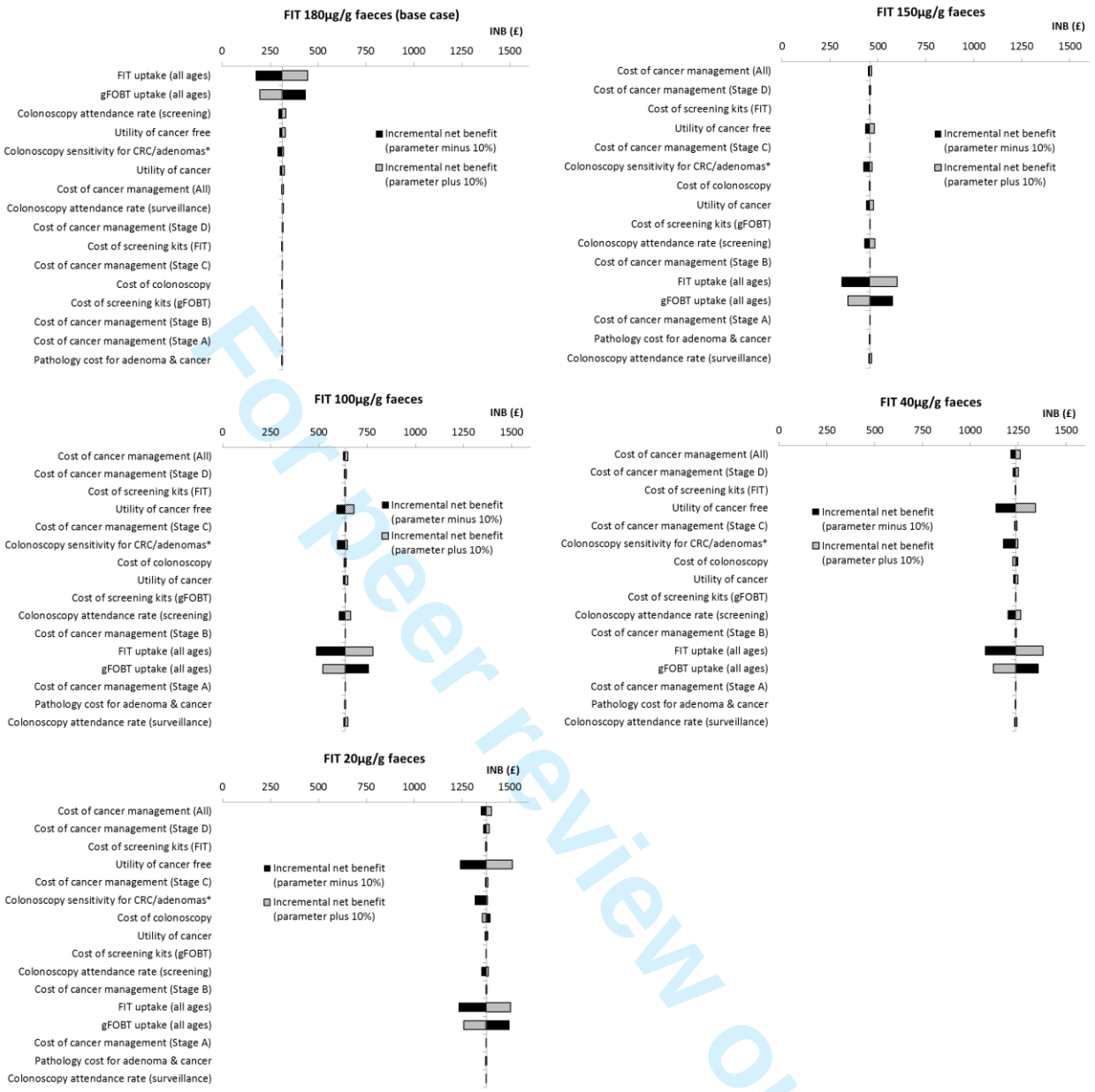
Supplementary Figure 6: One-way sensitivity analyses: incremental net benefit per person invited for screening



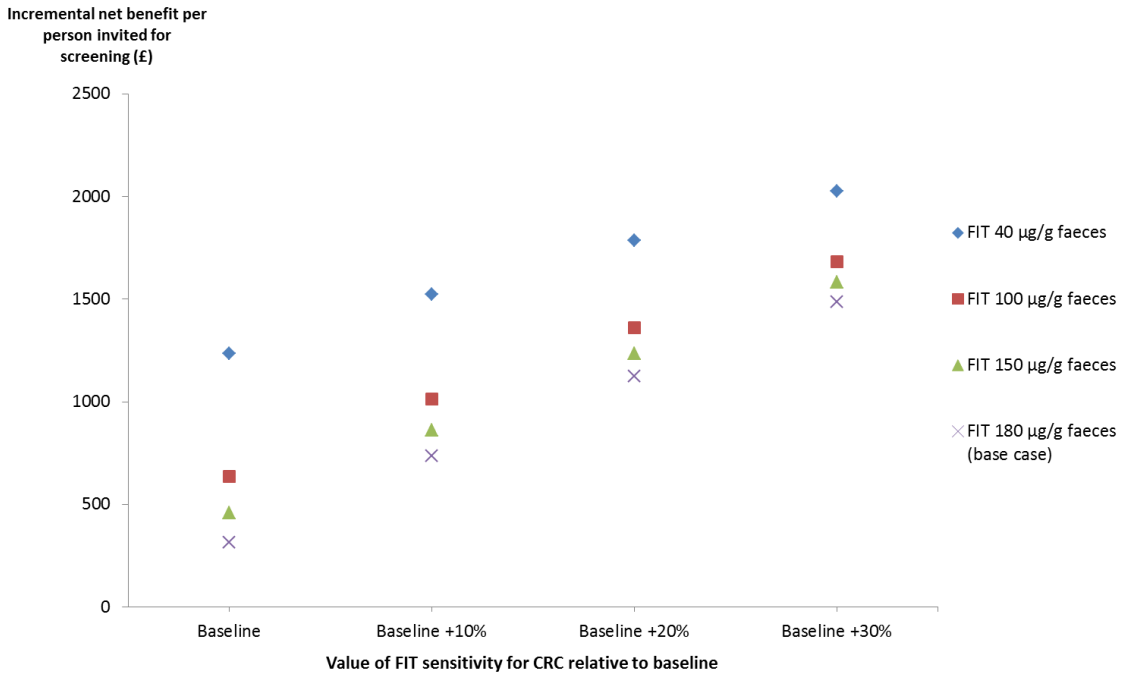
* Maximum value limited to 100%; Categories are sorted by ranked difference in INB for the base case (FIT 180µg Hb/g faeces) ; Data are centred on the mean INB for each FIT threshold.

Supplementary Table 13 shows a one-way sensitivity analyses around the sensitivity of FIT for CRC at each FIT threshold, illustrated on the cost-effectiveness plane. Supplementary Figure 7 shows the results illustrated in terms of net benefit.

Supplementary Table 13: Sensitivity analysis results for FIT sensitivity to detect CRC

	Baseline	+10%	+20%	+30%
Incremental cost				
FIT 180 µg Hb/g faeces (base case)	-27	-74	-117	-157
FIT 150 µg Hb/g faeces	-40	-84	-126	-164
FIT 100 µg Hb/g faeces	-53	-94	-133	-168
FIT 40 µg Hb/g faeces	-84	-115	-144	-171
FIT 20 µg Hb/g faeces	-62	-89	-114	-137
Incremental QALYs				
FIT 180 µg Hb/g faeces (base case)	0.014	0.033	0.050	0.066
FIT 150 µg Hb/g faeces	0.021	0.039	0.056	0.071
FIT 100 µg Hb/g faeces	0.029	0.046	0.061	0.076
FIT 40 µg Hb/g faeces	0.058	0.070	0.082	0.093
FIT 20 µg Hb/g faeces	0.066	0.077	0.087	0.096

Supplementary Figure 7: Incremental net benefit changes for variation in FIT sensitivity parameter



Model validation

We compared the model-esitmated screening results to data from the BCSP Southern Hub [20] on the proportion of successfully completed screening episodes that resulted in a diagnosis of CRC, adenomas, or negative results, by age group. We took data from the Hub's 2013-14 report as this is before the introduction of any FIT screening (introduced as part of the pilot study), and therefore the results were comparable with the gFOBT arm of the model. Supplementary Table 14 shows the data from the BCSP and Supplementary Table 15 shows the esitmates from the model. 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.

Supplementary Table 14: Screening outcomes by age-group - all England, 2013-14

Age group	60-64	65-69	70-74
CRC	7%	8%	10%
High & Intermediate risk adenoma	23%	23%	26%
Low-risk adenoma	18%	20%	20%
No adenomas or cancer detected/no result	52%	49%	44%

Data from BCSP Southern Hub Annual report, Figure 26[20]

Supplementary Table 15: Screening outcomes by age-group – estimates from the model

Age group	60-64	65-69	70-74
CRC	9%	9%	10%
High & Intermediate risk adenoma	30%	29%	27%
Low-risk adenoma	18%	17%	17%
No adenomas or cancer detected	43%	44%	46%

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SECTION 4: ADDITIONAL MODEL RESULTS

1. Budget Impact Results

Supplementary Table 16 shows detailed model results for the screening resource use and costs for gFOBT and at each FIT threshold, for the first year of the model.

Supplementary Table 16: Screening resource use for a population of 582,218 people invited for screening in first year of the model

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces		FIT 20µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Total number of pre-invites sent in first year (excluding repeat kits)	582,218	-	582,218	-	582,218	-	582,218	-	582,218	-	582,218	-
Number of people returning kit in first year (normal result)	311,755	-	365,108	-	364,210	-	362,101	-	353,659	-	346,838	-
Number of people returning kit in first year (positive result)	5,534	-	5,814	-	6,712	-	8,820	-	17,263	-	24,083	-
Positivity rate	1.7%	-	1.6%	-	1.8%	-	2.4%	-	4.7%	-	6.5%	-
Number of people not returning kit in first year	264,929	-	211,297	-	211,297	-	211,297	-	211,297	-	211,297	-
Total number of kits returned (normal result) in first year*	334,200	702,881	373,760	1,987,239	372,840	1,982,350	370,682	1,970,874	362,039	1,924,923	355,057	1,887,799
Total number of kits returned (positive result) in first year*	5,932	12,477	5,951	31,643	6,871	36,532	9,029	48,008	17,672	93,959	24,654	131,083
Total number of kits sent but not returned*	284,003	244,349	216,304	373,520	216,304	373,520	216,304	373,520	216,304	373,520	216,304	373,520
Total number of kits used in first year*	624,135	959,707	596,015	2,392,403	596,015	2,392,403	596,015	2,392,403	596,015	2,392,403	596,015	2,392,403
TOTAL SCREENING COSTS per invited person in screening population at age 60 years	-	1.65	-	4.11	-	4.11	-	4.11	-	4.11	-	4.11

* Includes repeat kits

Supplementary Table 17 shows detailed model results for the screening resource use and costs for gFOBT and at each FIT threshold, over the 40 year time horizon of the model.

Supplementary Table 17: Screening resource use and costs for a population of 582,218 people invited for screening over 40 year time horizon

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces		FIT 20µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Total number of pre-invites sent (excluding repeat kits)	4,232,528	-	4,228,435	-	4,226,404	-	4,221,320	-	4,207,087	-	4,199,206	-
Number of people returning kits (normal result)	2,453,056	-	2,744,958	-	2,736,895	-	2,717,298	-	2,649,512	-	2,597,628	-
Number of people returning kits (positive result)	54,916	-	60,211	-	66,920	-	83,132	-	141,469	-	188,139	-
Positivity rate	2.2%	-	2.1%	-	2.4%	-	3.0%	-	5.1%	-	6.8%	-
Number of people not returning kit in first year	1,724,557	-	1,423,266	-	1,422,589	-	1,420,890	-	1,416,106	-	1,413,439	-
Total number of kits returned (normal result)*	2,629,663	4,418,951	2,810,004	11,990,501	2,801,750	11,955,546	2,781,689	11,871,055	2,712,296	11,575,482	2,659,183	11,349,293
Total number of kits returned (positive result)*	58,869	96,811	61,637	254,608	68,505	283,989	85,102	354,444	144,822	610,295	192,597	814,299
Total number of kits sent but not returned*	1,848,716	1,295,702	1,456,993	2,041,497	1,456,300	2,040,585	1,454,560	2,038,275	1,449,663	2,031,682	1,446,932	2,027,959
Total number of kits used*	4,537,248	5,811,464	4,328,634	14,286,605	4,326,555	14,280,119	4,321,351	14,263,774	4,306,781	14,217,459	4,298,713	14,191,551
TOTAL SCREENING COSTS per invited person in screening population at age 60 years	-	9.98		24.54		24.53		24.50		24.42		24.37

* Includes repeat kits

Supplementary Table 18 shows detailed model results for the colonoscopy resource use and costs for gFOBT and at each FIT threshold, over the 40 year time horizon of the model.

Supplementary Table 18: Colonoscopy resource use and adverse events for a population of 582,218 people invited for screening, 40 year time horizon

	gFOBT		FIT 180µg Hb/g faeces (base case)		FIT 150µg Hb/g faeces		FIT 100µg Hb/g faeces		FIT 40µg Hb/g faeces		FIT 20µg Hb/g faeces	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
Follow-up												
Colonoscopies without polypectomy	28,074	12,981,875	28,603	12,963,904	30,210	13,760,230	33,128	15,152,071	47,814	22,314,603	60,135	28,246,187
Colonoscopies with polypectomy for HR adenomas	14,894	8,541,716	19,943	11,514,091	22,377	12,932,808	29,257	16,962,116	48,202	28,174,012	59,453	34,872,101
Colonoscopies with polypectomy for LR adenomas	8,886	5,079,018	8,309	4,766,975	10,602	6,083,371	16,113	9,246,641	37,568	21,573,625	58,064	33,374,398
Deaths at colonoscopy	0	142	0	140	0	152	0	175	1	273	1	349
Total number of follow-up colonoscopies	51,855	26,602,751	56,855	29,245,111	63,190	32,776,561	78,498	41,360,996	133,584	72,062,513	177,653	96,493,035
Major bleeds requiring hospitalisation	21	7,688	23	8,375	25	9,341	31	11,659	53	20,075	71	26,785
Perforation	33	74,456	35	77,635	38	84,528	44	99,532	70	160,237	91	209,292
Surveillance												
Colonoscopies without polypectomy	10,847	4,377,963	14,567	5,917,047	16,353	6,648,907	21,412	8,731,447	35,400	14,547,437	43,715	18,026,648
Colonoscopies with polypectomy for LR adenomas	6,754	10,864,104	9,064	14,669,928	10,175	16,482,119	13,318	21,635,454	22,001	36,008,535	27,160	44,600,994
Colonoscopies with polypectomy for HR adenomas	21,841	3,340,127	29,305	4,510,935	32,893	5,068,311	43,051	6,653,513	71,103	11,075,699	87,769	13,719,467
Deaths at colonoscopy	0	71	0	96	0	108	0	142	1	236	1	293
Total number of surveillance colonoscopies	39,442	18,582,265	52,937	25,098,006	59,421	28,199,445	77,782	37,020,556	128,504	61,631,907	158,644	76,347,402
Major bleeds requiring hospitalisation	16	5,381	21	7,268	24	8,166	31	10,721	51	17,849	63	22,111
Perforation	19	39,059	25	52,769	28	59,292	37	77,848	61	129,641	75	160,615
TOTAL NUMBER OF COLNOSCOPIES	91,297	18,626,705	109,791	25,158,043	122,611	28,266,903	156,280	37,109,119	262,088	61,779,397	336,296	76,530,128
Additional colonoscopies and cost compared to gFOBT (per 1000)	-	-	32	11,218	54	16,558	112	31,747	293	74,118	421	99,453

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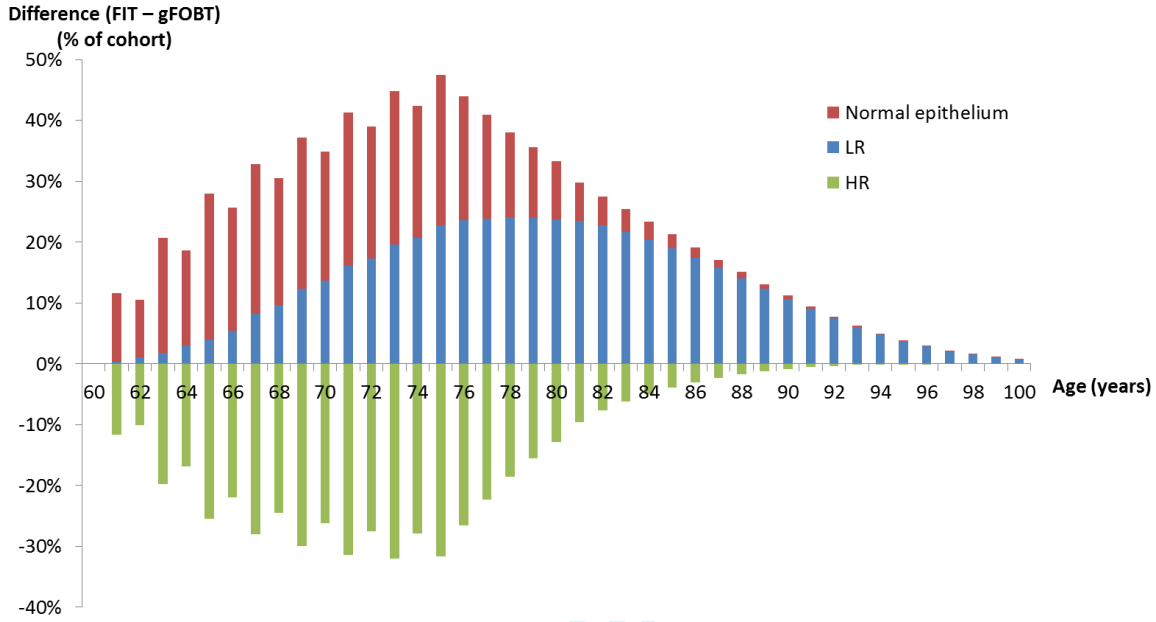
2. Health state distribution (prevalence)

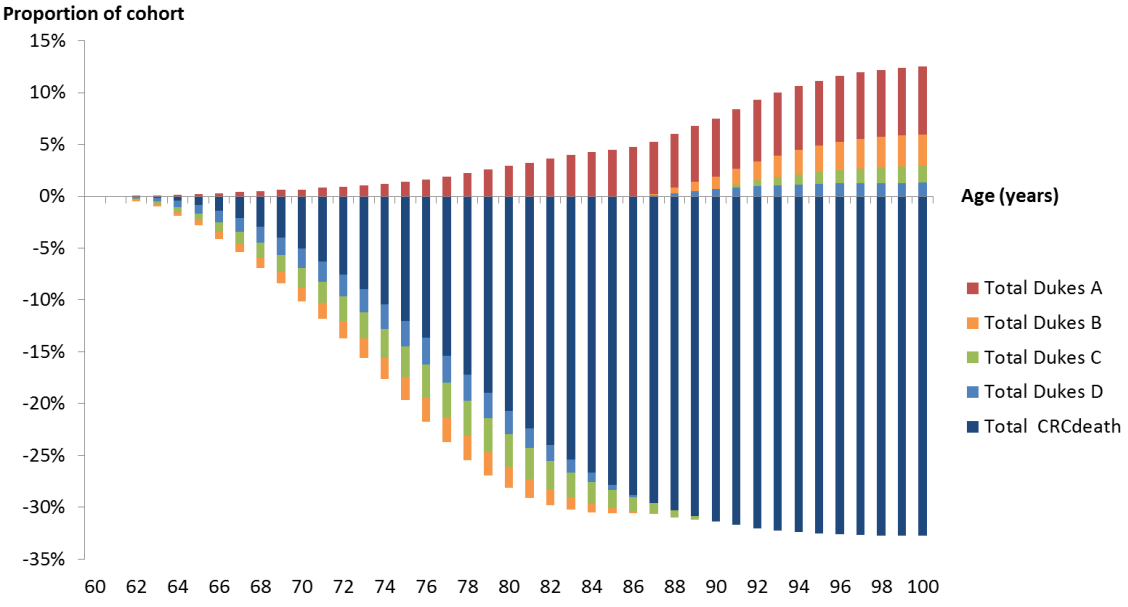
Supplementary Figure 8 shows the model-estimated difference in prevalence of adenomas for FIT at 180µg Hb/g faeces compared with gFOBT in each year of the model after screening begins at age 60 years.

Supplementary Figure 8: Model-estimated difference in non-cancer health state prevalence between FIT and gFOBT, by age



Supplementary Figure 9 shows the model-estimated difference in prevalence of CRC and mortality rate for FIT at 180µg Hb/g faeces compared with gFOBT in each year of the model after screening begins at age 60 years.

Supplementary Figure 9: Model-estimated difference in colorectal cancer prevalence and mortality between FIT and gFOBT, by age



3. Estimated cross-sectional population-level costs

The estimated annual budget impact of FIT compared to gFOBT for a cross-section of the population aged between 60 and 100 years is shown in Supplementary Table 19. The estimated cost saving of FIT compared to gFOBT in a steady state (i.e. comparing populations screened only with FIT or gFOBT from 60 years of age) is approximately £26 million per year.

Supplementary Table 19: Estimated population-level budget impact for one year at steady state

	Estimated population costs per year (£millions)		
	gFOBT	**FIT (180µg Hb/g faeces)**	**Difference (FIT-gFOBT)**
Screening-related costs	7.2	17.8	10.6
Colonoscopy/diagnosis-related costs	58.5	70.5	12.0
CRC management costs	725.2	676.7	-48.5
TOTAL ESTIMATED COSTS	791.0	765.0	-26.0

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CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No (page/line numbers from PDF proof)
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page2 line50
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page3 line45
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page2-3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page6 line50
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page3 line41
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page3 line50
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page3 line50
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page3 line52
Measurement of	11a	*Single study-based estimates*: Describe fully the design	N/A

effectiveness		features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page5 – page6
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	page6 line38
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page6
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page6 line50
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page4 line40 + Supplementary information Section 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	pages 3-7 (Methods)
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	pages 3-7 (Methods)
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Supplementary Information Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	pages 7-10 (Results)

		applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	page 8 (Sensitivity analyses)
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	page 8 (Sensitivity analyses) + Supplementary Information Section 4
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pages 11-13 (Discussion)
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Submitted online and on page18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Submitted online and on page18

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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