University of Sheffield



Re-appraisal of the options for colorectal cancer screening FULL REPORT

Report for the NHS Bowel Cancer Screening Programme

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1 Introduction and aims

Colorectal cancer (CRC) is the third most common form of cancer in the UK; 36,600 new cases were diagnosed in 2007 and there were 16,259 CRC-related deaths in 2008.(1) The aim of population-based screening for CRC is to reduce mortality through both prevention (by the removal of adenomas) and earlier diagnosis of CRC.

In 2004, Tappenden et al. produced a report to the English Bowel Cancer Screening Working Group which appraised the options for colorectal cancer screening evaluating cost-effectiveness, cost-utility and resource impact. (2, 3) This study used a mathematical model to compare screening options using the guaiac faecal occult blood test (gFOBT) or flexible sigmoidoscopy (FS) for different age groups. The report concluded that screening using FOBT and/or FS is potentially a cost-effective strategy for the early detection of colorectal cancer. This report informed the Department of Health's policy on bowel cancer screening in England. The Bowel Cancer Screening Programme (BCSP) commenced rollout in England in 2006 offering biennial screening with gFOBT to persons aged 60 – 69 years, and in 2009, rollout to include the 70-74 age group commenced.

Since the original options appraisal, the ScHARR CRC screening model has been updated considerably. The model now uses a Bayesian approach with the Metropolis Hastings algorithm to jointly estimate the CRC natural history state transition parameters and gFOBT test characteristics.(4) This approach generates parameter estimates using the ScHARR CRC natural history and screening model, together with several data sources including CRC incidence in the absence of screening and data from the first round of screening.

Since the original options appraisal, significant new data has become available:

- Data from the first two rounds of the England BCSP is available, including approximately 1.9 million gFOBT screening participants.
- A large randomised UK trial of flexible sigmoidoscopy (FS) for ages 55 to 64 years reported findings at baseline FS in 2000 and 10 year CRC incidence and mortality in 2010. (5, 6)
- Further data is now available on the sensitivity and specificity of the immunochemical FOBTs, which are thought to be more sensitive than guaiac FOBTs.

This study reappraises the options for CRC screening in England using these new data sources. Data from the gFOBT BCSP and the FS trial is used to estimate the characteristics of FS and gFOBT (including test characteristics, complication rates, and uptake). A systematic review and meta-analysis of iFOBT test characteristics is undertaken, and data from the Italian iFOBT screening programme is used to inform the model.

A sensitivity analysis was performed to determine the optimal age for once-only FS screening.
The following screening strategies were evaluated:

- Biennial guaiac FOBT for ages 60-74
- Biennial immunochemical FOBT for ages 60-74 (with several different iFOBT thresholds)
- FS once at optimal age/age 55
- FS once at optimal age/age 55, then biennial FOBT (guaiac/immuno) for ages 60-74
- FS once at optimal age/age 55, biennial FOBT (guaiac/immuno) for ages 60-74 for those not receiving FS

For each of the screening options the following key outputs were calculated and presented:

- Cost effectiveness (incremental cost per QALY gained)
- Number of cases of cancer avoided
- Endoscopy resource use requirements
- Number of cancer deaths avoided and number of deaths caused by screening

2 Description of screening interventions

2.1 Screening tests: guaiac faecal occult blood test (gFOBT)

Description of test

The faecal occult blood test (FOBT) detects non-visible blood in the faeces associated with colorectal cancer (CRC) and adenomas. The FOBT has been shown to be clinically and economically effective when used for CRC screening, and it was first used in the National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) in England in 2006. (2, 7) However, it is not a perfect test; there will be some false positive and false negative results because blood and blood breakdown products may have causes other than CRC/adenomas, some CRC/adenomas will not bleed, and not all blood will be detected. The gFOBT is relatively cheap, straightforward to use, and not associated with any significant complications. Several different types and brands of test are available. The test can be rehydrated before processing, which has been shown to increase sensitivity.

Pathways in gFOBT screening

In the English BCSP, participants are sent an invitation letter and then a second letter including a screening test kit to be completed at home. An un-rehydrated gFOBT called a HemaScreen is used. The NHS BCSP does not require persons undergoing FOBT to partake in any dietary restrictions. The test requires 6 stool samples (2 from each of three separate bowel motions). The test kit is returned by mail and is processed in a laboratory to determine if the card samples are positive or negative for blood. In the English BCSP, persons with weak positive results are asked to complete up to two repeat tests. Figures 1 and 2 describe the referral algorithm and the screening pathways used in the NHS BCSP. Anyone with an abnormal result (positive result in figure) will be offered a colonoscopy.

Figure 2.1.1: gFOBT referral algorithm used in NHS BCSP

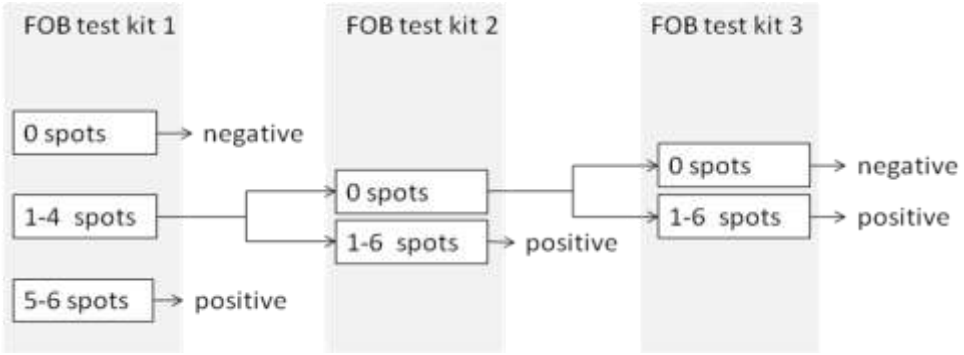
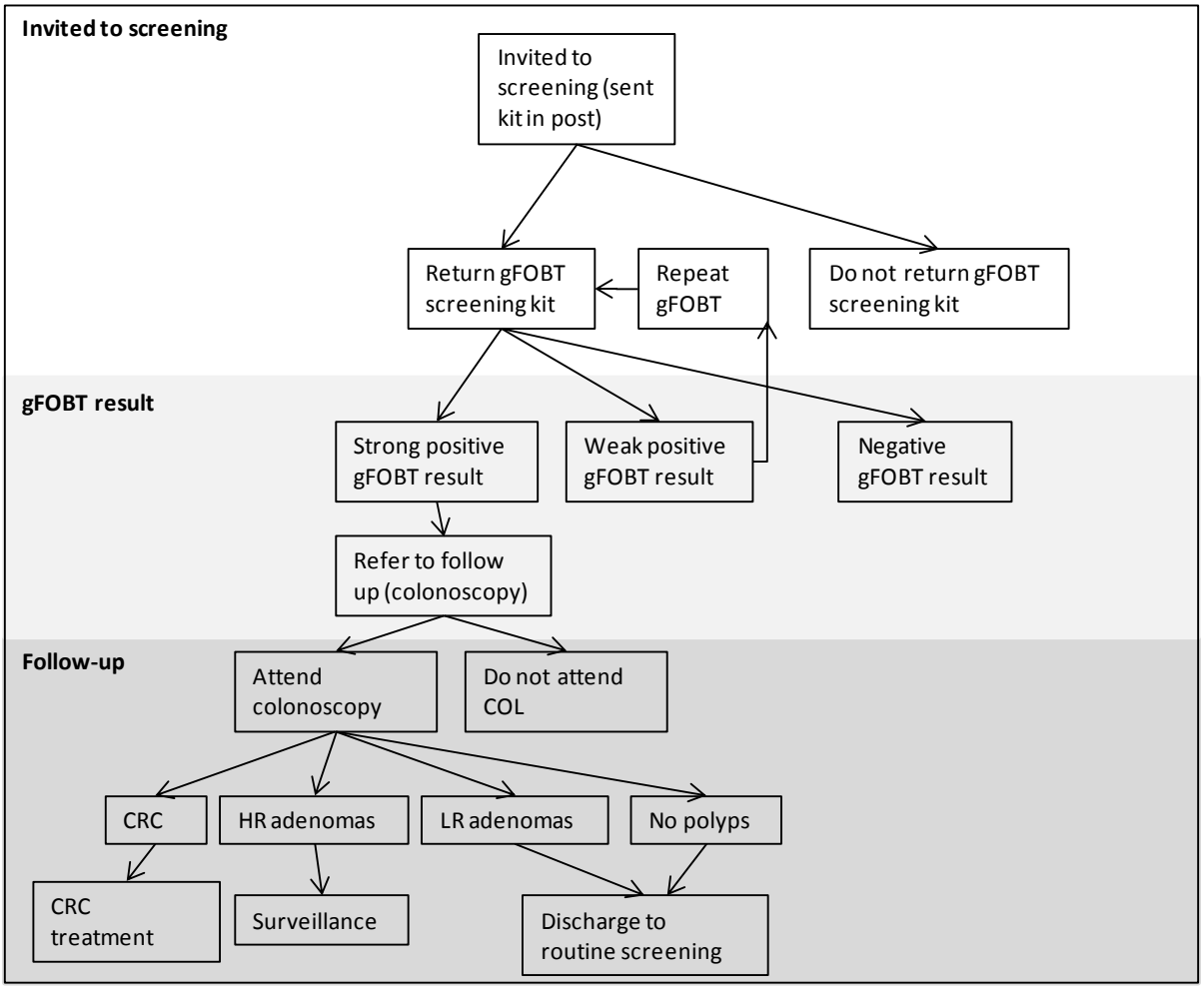


Figure 2.1.2: England gFOBT screening pathways



2.2 Screening tests: immunochemical faecal occult blood test (iFOBT)

In 2001, a class of occult blood tests called Faecal Immunochemical Tests was introduced. These tests detect the globin in faeces rather than haem. By detecting globin, the tests are both more sensitive and specific for lower gastrointestinal bleeding. The iFOBT is associated with a much lower retest rate compared to the gFOBT.

The iFOBT Evaluation Report produced by the Centre for Evidence-based Purchasing concluded that the OC-Sensor/DIANA analyser was the most suitable system for the English BCSP. Hence this analysis will focus on the OC-Sensor test. The patient pathways for iFOBT screening are assumed to be the same as for gFOBT screening.

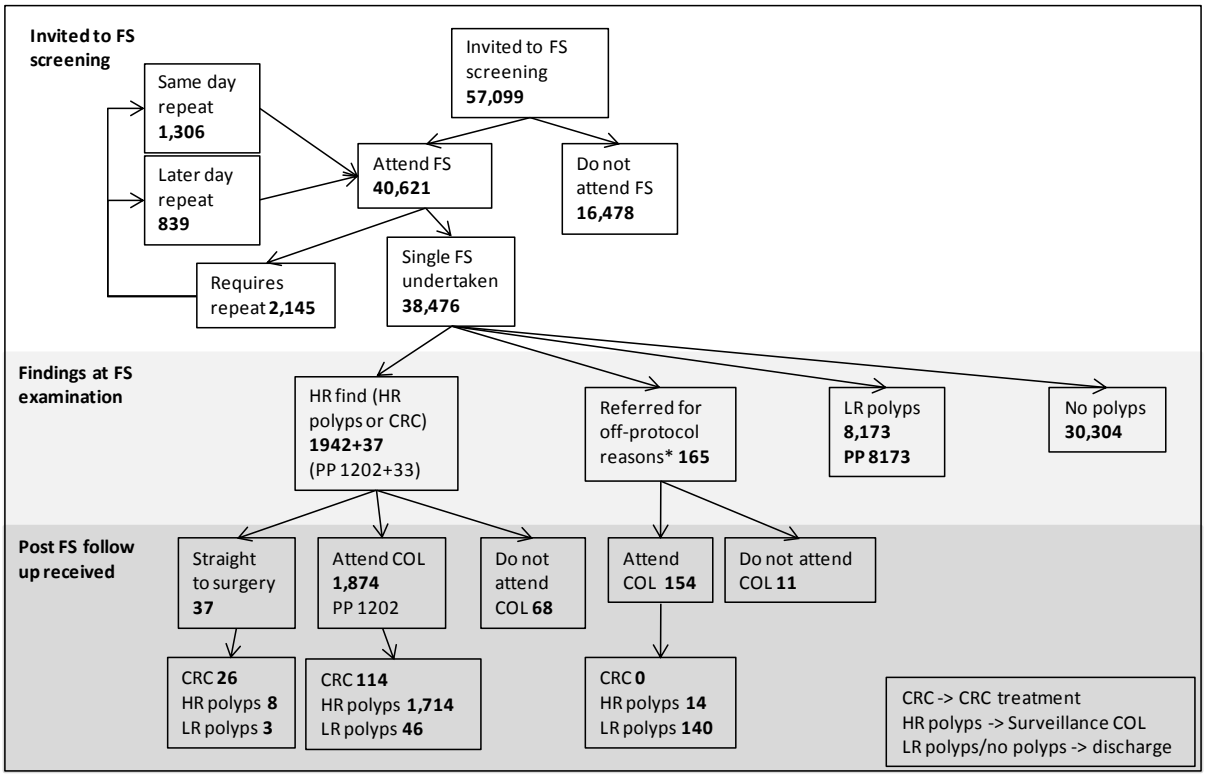
2.3 Screening tests: flexible sigmoidoscopy (FS)

Description of test

Flexible sigmoidoscopy is a procedure used to visualise the sigmoid colon and rectum. Two-thirds of CRC and adenomas are located in the rectum and sigmoid colon, which can be examined by flexible sigmoidoscopy (FS). During a FS procedure, biopsies from abnormal-looking tissues are also taken in order to test for signs of disease.

Where possible, the implementation and pathways for a FS screening programme were taken from the methods used in the FS trial or from the pathways discussed at a Bowel Cancer Screening Committee (BCSC) workshop held in September 2010.(8) Figure 2.3.1 describes the screening pathways used within the UK FS trial.

Figure 2.3.1: Flexible sigmoidoscopy screening pathways (including data from UK FS trial)



The FS workshop held in September 2010 made the following recommendations regarding the FS screening pathway:

- pre-invitation letter sent to subject
- scannable health questionnaire sent to subject
- letter with FS appointment time (subject suitable for screening)
- appointment confirmed via automated telephone service (with access to real person if required)
- bowel preparation medical and consent form sent to subjects who have confirmed appointment
- contact SSP - individuals with uncertain fitness for FS
- failure because of poor bowel preparation: repeat procedure on same day
- post-procedure information and discharge and patient feedback: apply current BCSP arrangements
- FS endoscopist stop the procedure and refer for colonoscopy when examining intermediate/high risk groups as defined in BCSP guidelines (3 or more small adenomas or one adenoma >1cm/ 5 or more small adenomas or 3 adenomas with one >1cm)
- surveillance: current BCSP arrangements should be extended to cover FS

It is suggested that the assumptions and cost estimates used here could be updated when further details of FS screening implementation are decided.

The referral to follow-up diagnostic colonoscopy after FS is modelled to reflect the FS trial referral criteria rather than the BCSP guidelines which were suggested at the workshop. Table 2.3.1 shows that the FS trial referral criteria include an additional criterion, so are effectively a lower threshold for referral than the BSG guidelines. The NHS BCSP would like to consider the implications of the use of the BSG guidelines for referral from FS to colonoscopy. This would result in a lower sensitivity and higher specificity than seen in the FS trial. The number of important lesions which would be missed by FS if the BSG guidelines were used instead of the 'BSG+' guidelines is being investigated by Wendy Atkin.

Table 2.3.1: Comparison of BSG surveillance guidelines and FS trial referral criteria

British Society of Gastroenterology(BSG) guidelines for surveillance colonoscopy after removal of colorectal adenomatous polyps (9, 10)	FS trial criteria for referral to colonoscopy 'BSG+' (11)
• Low risk: Patients with only 1–2, small (<1 cm) adenomas. • Intermediate risk: Patients with 3–4 small adenomas or at least one >1 cm • High risk: >5 adenomas OR >3 adenomas at least one of which is >1 cm. • Receive surveillance colonoscopy: >= 3 adenomas or at least one >1 cm	Any of the following: • Number >=3 • size >=1 cm • histology: tubulovillous or villous • dysplasia: severe or malignant • 20 or more hyperplastic polyps above the distal rectum

2.4 Description of screening strategies under evaluation

The following screening strategies will be evaluated:

- Biennial guaiac FOBT for ages 60-74
- Biennial immunochemical FOBT for ages 60-74 (with several different iFOBT thresholds)
- FS once at optimal age/age 55
- FS once at optimal age/age 55, then biennial FOBT (guaiac/immuno) for ages 60-74
- FS once at optimal age/age 55, biennial FOBT (guaiac/immuno) for ages 60-74 for those not receiving FS

3 Methods

3.1 Colorectal cancer natural history model structure

Evidence suggests that most CRC develops from adenomas in the lining of the bowel which is known as the adenoma-carcinoma sequence.(12) Various approaches can be taken to model the development of adenomas and CRC. These include modelling: the growth of individual adenomas; the number/size/type/location of adenomas; an individual's progression from non-advanced to advanced adenomas; an individual's progression from low-risk to high-risk adenomas.

The natural history of CRC can be modelled using a patient-level or a cohort model.(13) (14) A patient-level simulation gives greater flexibility in modelling disease natural history and management, allowing, for instance, easier implementation of surveillance colonoscopy (as a patient's pathways will depend on their past surveillance results). A patient-level modelling approach will generally require more parameters and distributional assumptions than a cohort model. For example, a cohort modelling approach requires information on the average rate at which an adenoma would develop into a colorectal cancer, but a patient-level modelling approach would also require knowledge of the between-patient variation in this rate.

There is considerable uncertainty surrounding several of the natural history parameters such as adenoma growth rates. A cohort modelling approach was used in preference to a patient-level model in this instance to reduce the number of assumptions required and to ensure that there was sufficient data available to inform the model parameters. This choice was based on previous experience with both methods in modelling colorectal cancer. A state transition model was used to simulate the life experience of a cohort of 30 year old individuals in the general population of England with normal epithelium through to the development of adenomas and colorectal cancer and subsequent death.

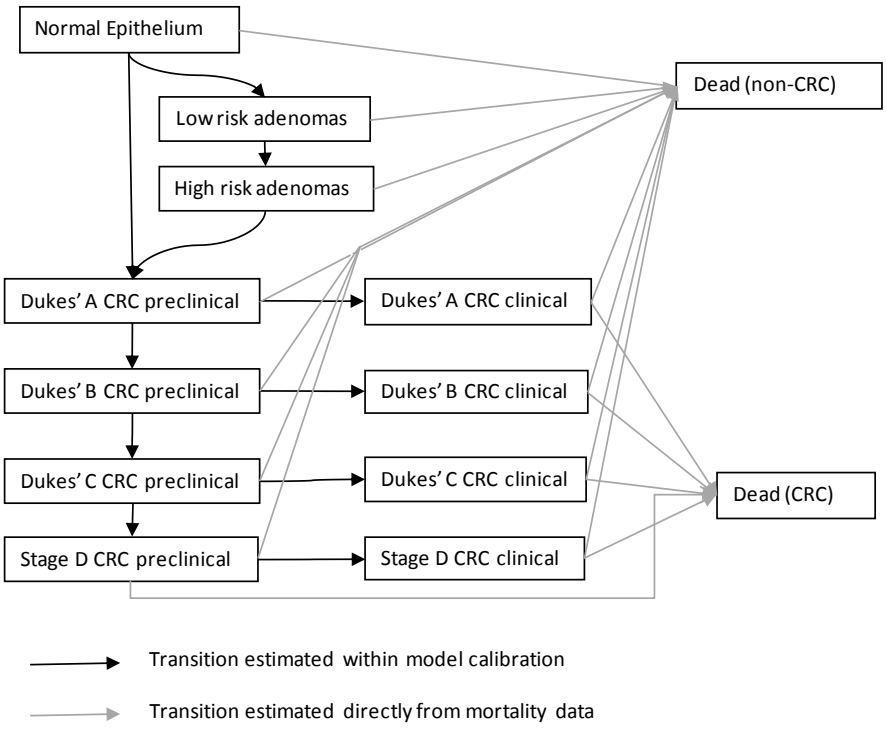
3.1.1 Definition of health states

Health states were defined according to an individual's true underlying histological state. CRC was divided into eight health states which describe the Dukes' stages A-D and whether or not the CRC has been clinically diagnosed: preclinical/clinical.

Individuals with adenomas can be classified in many different ways to reflect the size, type, number and location of adenomas present, but it is important that the choice of adenoma health states reflects the data available to inform the model. The current gFOBT screening programme in England records detection rates for "low-risk" and "intermediate/high-risk" adenomas as defined by the current British Society of Gastroenterology (BSG) guidelines for endoscopic surveillance following adenoma removal.(9) Detection rates from the FS screening trial which use this classification into "low-risk" and "intermediate/high-risk" adenomas were also obtained. The modelling uses this classification of adenomas to define two health states to describe individuals with adenomas. The "high risk adenomas" health state includes persons with at least 3 small adenomas or at least one adenoma of size >1cm (this includes the BSG intermediate and high risk surveillance categories). The "low-risk adenomas" health state includes persons with 1-2 small (<1cm) adenomas. These health states correspond to those used to determine an individual's surveillance strategy, so this approach eases the modelling of surveillance.

The model health states are: normal epithelium, low risk adenomas, high risk adenomas, preclinical CRC Dukes' stages A-D, clinical CRC Dukes' stages A-D, and dead. The health states and transitions included within the natural history model are shown in Figure 3.1.1.

Figure 3.1.1: Diagram of model structure



3.1.2 Transition between health states

The transitions between health states are presented in Figure 1. We define a sequence of annual transition probabilities between these states relating to CRC developing through the adenoma–carcinoma sequence, as this is thought to be the natural history of most CRC. In addition, we define a transition probability from normal epithelium to Dukes' A CRC to allow for the hypothesis that a proportion of cancers do not arise from adenomas (*de novo* cancers). For each cancer state we define the probability of being diagnosed through symptomatic presentation or chance detection, and this transition corresponds to moving from a preclinical to a clinical health state.

There is evidence to suggest that adenoma growth rate varies with age. Brenner et al examined the results of 840,149 screening colonoscopies and found that the age gradient is much stronger for CRC incidence than for advanced adenoma prevalence, hence projected annual transition rates from advanced adenomas to CRC strongly increase with age. (15) The probability of developing a low risk adenoma, the transition probability from low to high risk adenoma, and the transition probability from high risk adenoma to Dukes' stage A CRC were allowed to vary by age using a piecewise linear model whose parameter values were the transition probabilities at ages 30, 50,70,100.

Transitions between the preclinical CRC states and from preclinical to clinical CRC are assumed to be independent of age. All persons may die of non-CRC causes, and this is modelled using age-specific mortality rates. Once a person is diagnosed with CRC, the transitions between Dukes' stages are no longer modelled and a stage-specific CRC relative survival rate is applied. In addition, preclinical stage D CRC may be fatal. Survival rates for clinical CRC stages A-D and preclinical stage D CRC is assumed to be dependent on the CRC stage at diagnosis and patient age.

3.1.3 Location of adenomas and cancer

Adenomas and CRC may develop in various locations within the colon and rectum. Little data was identified describing CRC/adenoma prevalence by location and age. A study by Yamaji et al analysed the records of a colonoscopic follow-up study on 2900 subjects after polypectomy. They describe the

change in adenoma location by age: “Although there may be individual predilection for right-side or left-side location of colorectal adenomas, aging tends to increase the number of adenomas in the right-side colon, while only modestly affecting those in the left-side colon.”(16) We observed that the proportion of persons who only had adenomas in the proximal colon did not vary significantly by age; see Table 3.1.1.

Table 3.1.1: Location of adenomas by age as reported by Yamaji et al 2007

Age group	Adenomas located only in the left side colon and rectum	Adenomas located in both the left side and the right-side colon	Adenomas located only in the right-side colon
<40	59%	12%	30%
40-49	56%	15%	29%
50-59	43%	24%	34%
>=60	37%	34%	29%

Table 3.1.2 shows incidence of cancer in the proximal and distal colon by age for newly diagnosed cases in England in 2007. Of diagnosed cases of CRC with known location, 62% are located in the distal colon and 38% in the proximal colon. Distal and proximal CRC may be associated with different likelihoods of displaying symptoms and receiving a diagnosis. Hence the difference in incidence between the proximal and distal colon is unlikely to accurately reflect the difference in prevalence between the distal and proximal colon.

Table 3.1.2: CRC by age and location, registrations of newly diagnosed cases 2007

	Incidence Rates per 100,000 population						CRC with known location	
Age range	Proximal Colon (C18.0-C18.6)		Distal Colon (C18.7,C18.8,C19,C20)		Unknown location (C18.9)		Proximal	Distal
30-34	1.2	41%	1.4	51%	0.2	8%	45%	55%
35-39	2.1	39%	2.9	53%	0.4	8%	42%	58%
40-44	3.6	36%	5.6	56%	0.8	8%	39%	61%
45-49	5.5	29%	12.2	64%	1.4	7%	31%	69%
50-54	10.2	27%	25.6	67%	2.6	7%	29%	71%
55-59	18.2	27%	44.7	66%	5.3	8%	29%	71%
60-64	36.5	31%	70.8	61%	9.0	8%	34%	66%
65-69	57.9	31%	112.0	61%	15.1	8%	34%	66%
70-74	79.0	33%	143.4	59%	20.0	8%	36%	64%
75-79	115.8	37%	166.8	54%	28.8	9%	41%	59%
80-84	149.9	40%	181.1	49%	40.8	11%	45%	55%
85 and ove	140.4	39%	165.6	46%	55.4	15%	46%	54%
All ages	20.7	34%	33.7	56%	5.7	10%	38%	62%

3.1.4 Screening test sensitivity by location

The sensitivity of a screening test may vary between the distal and the proximal colon. This gives two important considerations for the modelling of screening. Firstly, as CRC/adenoma location distributions vary by age, it follows that the overall sensitivity of a screening test may vary by age. Secondly, a screening test with significantly different proximal and distal sensitivity will impact the location distribution for remaining undetected CRC and adenomas. This in turn will impact on the detection rates seen at subsequent screens. Hence, adenoma/CRC location distribution and screening test sensitivity by location may be important considerations when modelling combined or repeated screening strategies.

The extent to which the CRC sensitivity of a screening test varies between the distal/proximal colon can be estimated by comparing the location distribution of screen detected CRC with that of prevalent CRC. As no data on the location distribution of prevalent CRC was available, data on the location distribution of CRC incidence was used. The use of incidence as a proxy for prevalence will introduce errors, as symptoms and diagnosis rates will vary by location. Hence this calculation is simply a crude estimate for illustrative purposes. Location specific sensitivities for CRC are estimated in Table 3.1.3.

Table 3.1.3: Screening test CRC detection by location

	Screen detected CRC		Age group	Proportion of CRC incidence in	Sensitivity to CRC		
Screening	Distal	Proximal	screened	distal colon for age group	Overall	Distal*	Proximal*
gFOBT BCSP data	72%	28%	60-69	66%	0.24	0.26	0.20
FS trial data	90%	10%	55-64	69%	0.62	0.81	0.20

*Formulae used in calculation: overall sensitivity = proportion distal * distal sensitivity + proportion proximal * proximal sensitivity

In the England gFOBT screening programme, 72% of CRC detected (with a known location) was found in the distal colon, compared to 66% of CRC incidence which is distal for this age group. Using this data we estimate that gFOBT has very similar sensitivity in the distal and proximal colon.

Flexible sigmoidoscopy examines the distal colon only; however, a participant may be referred to colonoscopy following FS and colonoscopy may find lesions in both the proximal and distal colon. In the UK flexible sigmoidoscopy trial, 90% of all CRC detected at screening was found in the distal colon, compared to 69% of CRC incidence which is distal for this age group. This implies a significant difference between distal and proximal sensitivity which corresponds with the nature of the test. A FS CRC sensitivity of 20% for the proximal colon implies that 20% of proximal CRC was associated with a distal adenoma which required referral to colonoscopy.

Sensitivity at repeat screens

The estimated location specific test sensitivities were used to examine the degree to which the overall sensitivity to CRC may vary between a first and a repeat screen. An initial distal:proximal CRC split of 70:30 was assumed, and calculation details are presented in Table 3.1.4. This calculation estimated the maximum possible change in overall sensitivity, as it assumes that the CRC location distribution does not change in the time after the first screen to before the repeat screen. The gFOBT overall sensitivity to CRC did not vary significantly by first/repeat screen; however, FS overall sensitivity to CRC may be reduced to as little at 0.42 for a repeat screen. Hence modelling varying FS sensitivity by first/repeat screen is important for a strategy involving two or more FS screens. This estimate of minimum FS overall sensitivity to CRC for a repeat FS screen is used within a sensitivity analysis.

Table 3.1.4: Estimated overall sensitivity at first/repeat screen incorporating location-specific sensitivities

		CRC location distribution		Sensitivity to CRC		
		Distal	Proximal	Distal	Proximal	Overall
gFOBT	First screen	0.70	0.30	0.26	0.20	0.24
	Repeat screen	0.68	0.32	0.26	0.20	0.24
FS	First screen	0.70	0.30	0.81	0.20	0.63
	Repeat screen	0.36	0.64	0.81	0.20	0.42

Data on detection rates in the distal/proximal colon for iFOBT is not available, so no conclusions can be reached on the sensitivity in the proximal and distal locations.

Location-specific sensitivity to adenomas

Data on the location of adenomas is very complex to report. The definition used for high risk adenomas (or advanced adenomas) refers to the whole colon. An individual will often have

adenomas in both the proximal and distal colon, and it may be the combination of these that determines the risk level.

Yamaji et al found that the proportion of persons who only had adenomas in the proximal colon did not vary significantly by age; see Table 3.1.1. (16) Hence, even though the sensitivity of FS varies significantly between the proximal and the distal colon, this suggests that the overall sensitivity of FS may not significantly vary by age.

Data from gFOBT screening showed a significantly lower HR adenoma detection rate at the repeat screen. This may suggest that the location specific variation in gFOBT HR adenoma sensitivity is significant. However, data on HR adenoma prevalence by location is not available, so this remains an area requiring further research.

Further data on the location of CRC and adenomas detected at screening would allow more accurate modelling of location specific test characteristics in the future. In particular, data on location of screen detected CRC in iFOBT and colonoscopy screening would be valuable.

3.1.5 Gender- and location-specific natural history model

Future work could use different natural history model parameters for male and female and the distal and proximal colon. This would make the model structure more accurate, but such a model would require significantly more data to avoid adding additional unobservable input parameters. Screening data reporting detection rates for males and females separately and detailing the most advanced adenoma present in the proximal and distal colon would be required. The current model has a classification into four health states: normal epithelium, LR/HR adenomas and CRC stages A-D. However, when the most advanced lesion in both the proximal and distal colon is taken into consideration, this would require a large number of health states.

3.1.6 Metachronous adenomas – adenoma recurrence rates post-polypectomy

The model uses data on the risk of recurrence of adenomas in persons who have had adenomas removed by polypectomy and are undergoing surveillance. To ensure consistency between the model parameters, it is important that the post-polypectomy transition probabilities used align with the other natural history transition probabilities in the model. We assume that persons who are undergoing surveillance post-polypectomy are at higher risk of developing adenomas than persons with a normal epithelium. We also assume that polypectomy reduces the risk of developing CRC. Hence we place restrictions on the post-polypectomy transition probabilities as described in Table 3.1.5.

Table 3.1.5: Restrictions on transition probabilities post-polypectomy

Restrictions on transition probabilities post polypectomy
Post polypectomy(LR) to LR adenoma **>** Normal epithelium to LR adenoma
Post polypectomy(HR) to LR adenoma **>** Normal epithelium to LR adenoma
Post polypectomy(LR) to HR adenoma **<** LR adenoma to HR adenoma **>** Normal epithelium to HR adenoma
Post polypectomy(HR) to HR adenoma **>** Normal epithelium to HR adenoma
Post polypectomy(LR) to CRC **<** LR adenoma to CRC **>** Normal epithelium to CRC
Post polypectomy(HR) to CRC **<** HR adenoma to CRC **>** Normal epithelium to CRC
Post polypectomy(LR) to LR adenoma< Post polypectomy(HR) to LR adenoma
Post polypectomy(LR) to HR adenoma< Post polypectomy(HR) to HR adenoma
Post polypectomy(LR) to CRC adenoma< Post polypectomy(HR) to CRC adenoma

Data on the surveillance results from the England gFOBT BCSP details over 4000 surveillance colonoscopies. Unfortunately, data which details the results of 1 and 3 year (IR/HR) surveillance separately is not currently available, so some assumptions had to be made.

Table 3.1.6: Detection rates at surveillance in the England gFOBT screening programme

	Detection rates at surveillance		Estimated annual reccurrence rate *	
Find	Surveillance undertaken in 2008 assumed to be 1-year surveillance)	Surveillance (undertaken in 2010 assumed to be mainly 3-year surveillance)	Persons undergoing 3-yearly surveillance	Persons undergoing 1-year surveillance
CRC	1.3%	0.3%	0.1%	1.3%
HR adenomas	55.7%	24.4%	9.1%	56.8%
LR adenomas	14.5%	31.9%	16.3%	18.8%

*Estimated annual recurrence rates were calculated by adjusting for the number of years until surveillance and colonoscopy miss rates.

There is currently no data available of recurrence rates for persons with LR adenomas who do not receive surveillance in the English BCSP.

Martinez et al report a pooled analysis of individual data from 8 prospective studies comprising 9167 men and women aged 22 to 80 with previously resected colorectal adenomas to quantify their risk of developing subsequent advanced adenoma or cancer, as well as identify factors associated with the development of advanced colorectal neoplasms during surveillance.(17) Risk of new neoplasia at follow-up evaluation is estimated according to baseline adenoma characteristics. Data from the Martinez study was converted into annual transition probabilities assuming a follow-up period of 4 years; see Table 3.1.7. It should be noted that the definitions of low and high risk used in the Martinez study differs slightly from the definitions used in the BSG surveillance guidelines; however, the Martinez study was still deemed to be the best available data source.

Table 3.1.7: Data from Martinez et al 2009

	Risk of new neoplasia at follow-up evaluation (median duration of follow up 47.2 months)			Annual transition probabilities (assuming a follow-up of 4 years)		
Adenoma history*	Non advanced adenoma	Advanced adenoma**	Colorectal cancer	Non advanced adenoma	Advanced adenoma	Colorectal cancer
Low-risk	0.345 (0.331,0.358)	0.069 (0.062,0.076)	0.005 (0.003,0.007)	10.0%	1.8%	0.1%
High-risk	0.353 (0.339,0.367)	0.155 (0.145,0.166)	0.008 (0.005,0.01)	10.3%	4.1%	0.2%

*The low-risk group includes patients with 1–2 small (<1 cm), tubular adenoma(s) with low-grade dysplasia.

**Advanced adenoma are defined as those with a diameter 10mm or larger, having greater than 25% villous

The model uses recurrence rates from the English BCSP for persons with HR adenomas and data from Martinez et al for persons with LR adenomas. This data on recurrence rates post-polypectomy has several limitations. The transition probabilities reported are not age-dependent; however, the transition probabilities used in the model are age-dependent. The study populations do not reflect the English screening population, are quite small in size, do not use the BSG surveillance guidelines to categorise adenomas, and report highly varying recurrence rates. It is very important that detailed data on outcomes at surveillance in the English gFOBT screening programme is collected and available for future modelling work to improve the accuracy of decision support for the screening programmes.

3.1.7 Classification of adenomas

Adenomas can be categorised in the following ways: by size: <5mm, 5-10mm, 10-20mm, 20+mm and by type: tubulovillous/villous (>25% villous features), advanced/non-advanced, high grade dysplasia. In addition, persons can be classified by number of adenomas present or by BSG surveillance guidelines risk level: low/intermediate/high.

The majority of the colonoscopy studies identified in the systematic review classify adenomas as advanced or non-advanced. As the definition of “advanced adenoma” includes tubulovillous or villous adenomas, it will include some individuals who would be classified as low-risk according the BSG guidelines. There will also be some individuals with 3-4 small adenomas who are classified as intermediate risk according the BSG guidelines but who do not have advanced adenoma. Out of persons found to have an advanced adenoma in the FS trial, 74% were classified as intermediate or high risk according to the BSG guidelines. Hence it was assumed that 74% of persons with advanced adenoma had high-risk adenomas.

Table 3.1.8: Classification of persons with adenomas

	BSG surveillence guidelines			Definition used in Brenner et al.	Model health states	
	low risk	intermediate risk	high risk	Advanced adenoma	low risk adenomas	high risk adenomas
1-2 small (<10mm) adenomas	X				X	
3-4 small (<10mm) adenomas		X				X
large (<=10mm) adenoma		X		X		X
5+ small (<10mm) adenomas			X			X
3+ adenomas at least one of which is >=10mm			X			X
high grade dysplasia				X		X
1-2 small (<10mm) tubulovillous or villous adenoma	X			X	X	
3-4 small (<10mm) tubulovillous or villous adenoma		X		X		X
5+ small (<10mm) tubulovillous or villous adenoma			X	X		X

Data from the gFOBT screening programme in England reports detection rates of low/intermediate/high-risk adenomas (according the the BSG guidelines), and this classification is used to determine an individual’s surveillance. Data from iFOBT screening in Italy and colonoscopy screening in Germany reports detection rates for “advanced adenomas”. There is great value to be had in using all of these data sources, as they provide valuable information regarding the different screening modalities. The differences in the reporting of adenoma detection rates are problematic and

introduce great uncertainty into the modelling. An internationally consistent way of reporting adenoma findings from screening programmes and trials should be a priority for the future.

3.1.8 Adenoma and CRC prevalence in an asymptomatic population

Data on the prevalence of CRC and adenomas by age in a screening population (asymptomatic) was required to inform the CRC natural history model. Such data are available from autopsy studies and can also be estimated from colonoscopy screening studies. A systematic review of data from colonoscopy studies in an asymptomatic population and autopsy studies was undertaken. Studies which report adenoma detection/prevalence rates by age were identified. Full details of the systematic review are included in Appendix 1.

Colonoscopy studies provide data on adenoma prevalence but as colonoscopy is not a perfect test some adenomas (in particular small adenomas) may be missed. Adenoma prevalence estimates from colonoscopy screening studies may also be biased as they consist of a population who attend screening which is likely to differ slightly to the general population. The systematic review identified eight colonoscopy studies which are described in Table 3.1.9; the largest of which described the results of over 2 million colonoscopies from the German screening programme. (18) For the model calibration data the study by Brenner et al was selected due to the large sample sizes, broad age range, and the expected similarity between the German and English screening populations. To incorporate some data on LR adenomas (not reported by Brenner et al) and some information for persons aged under 60, data from Chung et al 2010 was also included. (19) Further discussion on the international variation in CRC and adenoma prevalence is included in a later section of this report. Figures 3.1.2 and 3.1.3 present data on advanced adenoma prevalence by age from colonoscopy studies identified by the systematic review.

Table 3.1.9: Summary of colonoscopy study characteristics

Study	Data Collected (Time-Interval)	Country of study	Sample Size	Age Range	Included within study definition of advanced adenoma: adenoma >=1cm in size/diameter	adenoma containing villous features />= 25% villous features	adenoma with high grade dysplasia	adenoma with malignant features	adenoma with carcinoma in situ
Rundle et al (2008)	2004 - 2006	United States	905	40-59	Y	Y	Y		
Lin et al (2006)	2002 - 2005	United States	1244	>= 50	Y	Y			
Strull et al (2006)	1996 - 2003	Israel	1177	40-80	Y	Y	Y		
Soon et al (2005)	2002 - 2004	United States Taiwan	3403 1456	40-70 40-70	Y	Y	Y	Y	
Yamaji et al (2004)	1988 - 2002	Japan	4084	all ages	Y		Y		Y
Chung et al (2010)	2004 - 2007	Korea	5254	30-59	Y	Y	Y		
Brenner et al (2007)	2003 - 2004	Germany	840,149	50-80+	Y	Y	Y		
Brenner et al (2010)	2003 - 2007	Germany	2,185,153	50-75	Y	Y	Y		
Choe et al (2007)	1998 - 2004	Korea	5086	>=20	Y	Y	Y		Y

Figure 3.1.2: Advanced adenoma detection rates in colonoscopy studies identified by systematic review

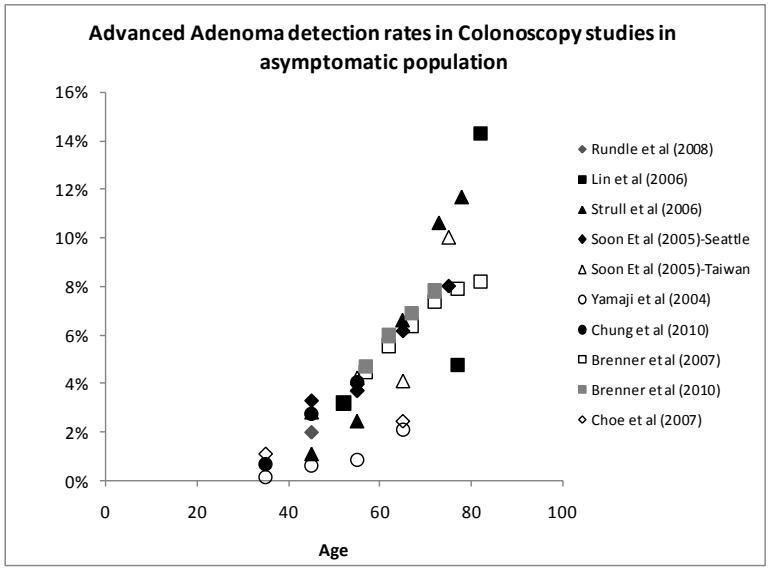
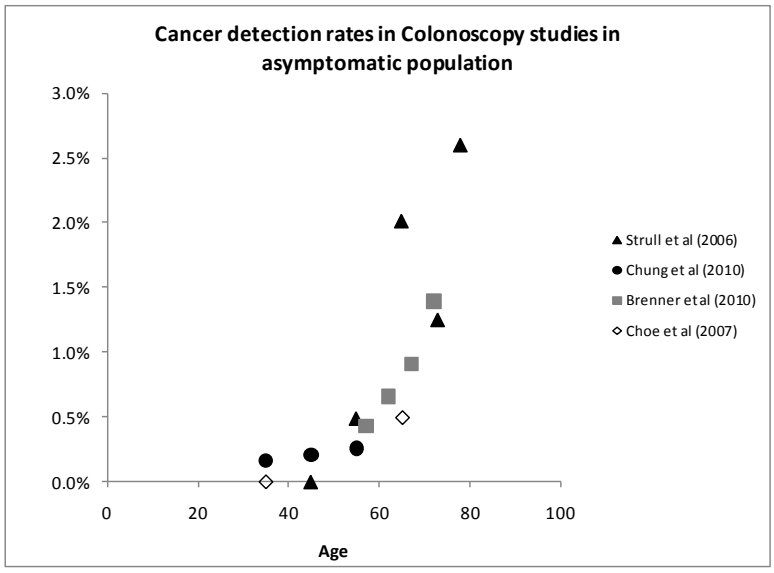


Figure 3.1.3: Advanced adenoma detection rates in colonoscopy studies identified by systematic review

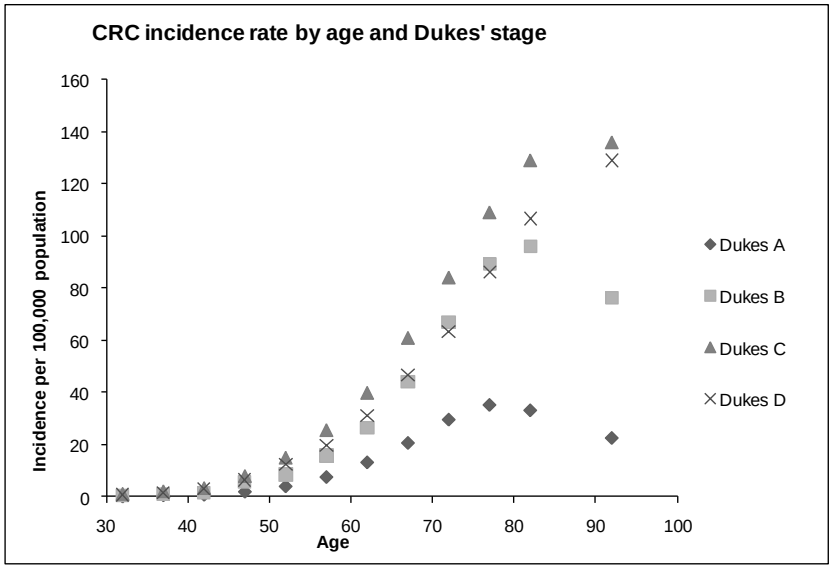


Autopsy studies allow a complete and thorough examination of the colon and rectum; however, data from autopsy studies may be biased, as autopsied individuals represent a biased sample of deaths. In addition, autopsy studies do not always include an equal cross-section of ages. The systematic review identified X autopsy studies. Due to the large amount of heterogeneity in the autopsy studies and the small sample sizes when compared to colonoscopy studies, the autopsy study data was not used within the model calibration.

3.1.9 Colorectal cancer incidence in the absence of screening by age and stage

Data on CRC incidence in the absence of screening categorised by age and Dukes' stage at diagnosis was taken from England cancer registry data for Oxford, Northern and Yorkshire, and Eastern regions from 2004 – 2006.(20)

Figure 3.1.4: CRC incidence rates in the absence of screening by age and Duke' stage



3.1.10 Screening programme data

Observed data from existing screening programmes and screening trials was used within the calibration of the model. The screening detection rates are essential to estimate the sensitivities of the screening tests while the false positive rates inform screening test specificity. Note that we define the false positive rate to be the proportion of persons undergoing colonoscopy following FOBT in whom no CRC or adenomas were found at colonoscopy. The change in screening positivity and detection rates by age provide important information for the natural history model, i.e. the change in underlying adenoma and CRC prevalence by age.

Table 3.1.9 provides a summary of the screening data used within the model calibration. The current gFOBT BCSP in England reported numbers of persons with positive gFOBT result and the detection rates of low and high risk adenomas and CRC at screening.(21) Data from the FS trial consisted of detection rates of CRC, low/high risk adenomas and non-advanced/advanced adenomas at screening.(5) As UK data is only available for the gFOBT and FS, screening test data from Italy was used for iFOBT screening.

The population of the FS trial differed slightly from a screening population, as all persons had indicated that they were interested in attending screening in the questionnaire. The screening data used in the calibration relates to persons who attended screening. Screening attenders in the FS trial may be slightly healthier than those undergoing gFOBT screening, hence they may have slightly lower detection rates at FS screening leading to a slightly lower estimate of FS sensitivity, thus biasing the result slightly in the favour of FOBT. This slight difference between the screening populations is not expected to significantly bias the model results. In fact, an analysis demonstrated that the FS trial control population had lower mortality rates than Norwegian control but incidence was the same.

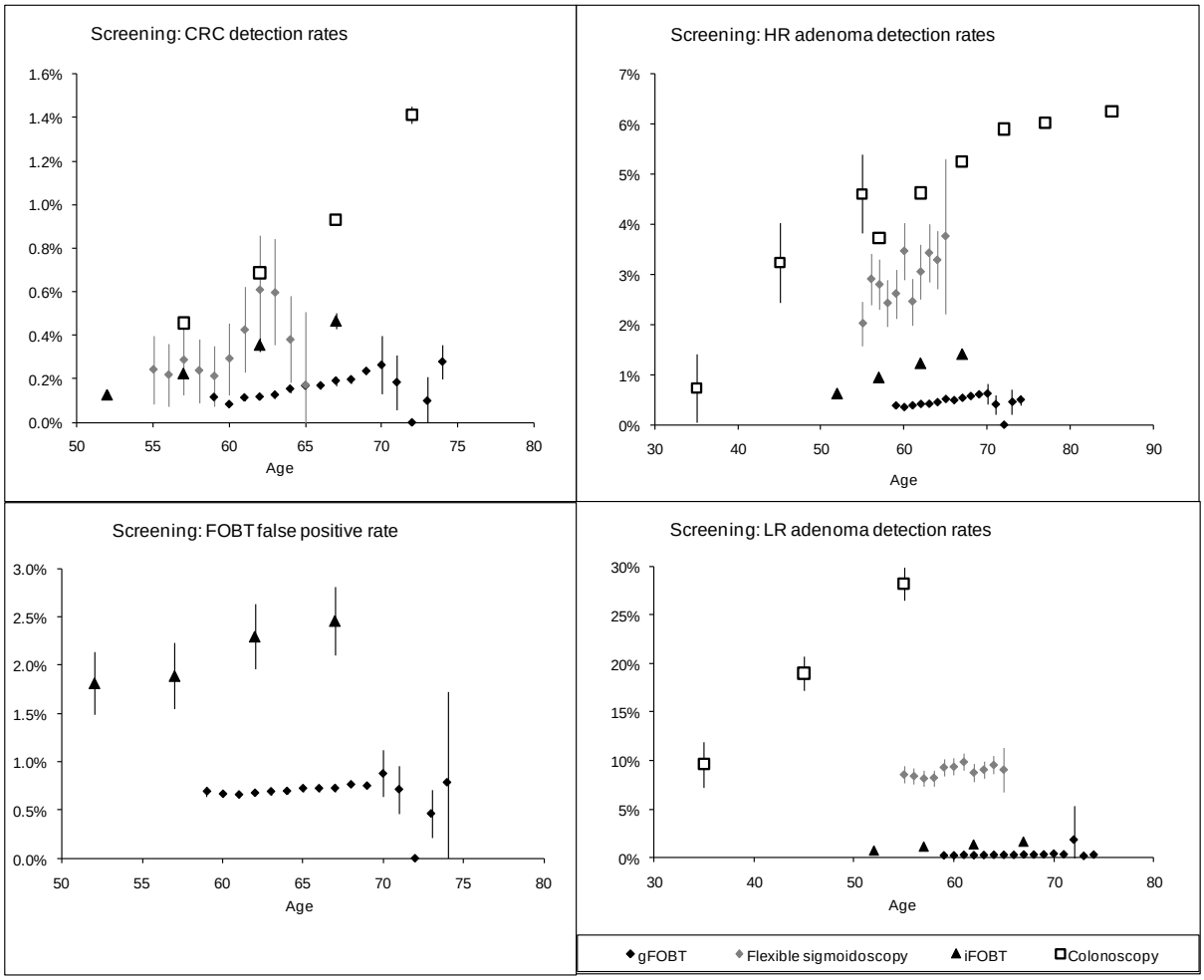
Colonscopy screening is not considered in this evaluation; however, data from screening colonoscopies is of particular use for calibrating the model because of the accuracy of colonoscopy. As mentioned earlier, colonoscopy screening data was used in preference to autopsy study data as the sample sizes are much larger.

Figures X to Y present the screening data which was used within the calibration process. The higher detection rates seen at FS screening indicate that FS is much more sensitive than gFOBT.

Table 3.1.9: Screening data used within model calibration

Screening test	Source	Country	Time period screening undertaken	Number of particpants undergoing screening	Age range of participants	Data reported
gFOBT	England BCSP	England	2006-2010	2,889,925	59-74	false positive rate; detection rates for LR adenomas, HR adenomas and CRC
iFOBT	Zorzi et al	Italy	2006-2010	591,152	50-69	false positive rate; detection rates for non-advanced adenomas, advanced adenomas and CRC
FS	Atkin et al	England	2005-2008	40,621	55-65	detection rates for LR adenomas, HR adenomas and CRC
Colonoscopy	Brenner et al	Germany	2003-2007	2,185,153	55-75	detection rates for advanced adenomas and CRC
Colonoscopy	Brenner et al	Germany	2003-2004	840,149	50-80+	detection rates for advanced adenomas
Colonoscopy	Chung et al		2003-2007	5,254	30-59	detection rates non-advanced adenomas, advanced adenomas and CRC

Figure 3.1.5: CRC and adenoma detection rates at screening and FOBT false positive rates with 95% confidence intervals presented as vertical lines



3.1.11 International variation in CRC and adenoma prevalence

There exists data describing the international differences in the incidence of CRC, however, there is little evidence describing the difference in the prevalence of CRC and adenomas. Soon et al undertook a study in which a cohort of patients in both Taiwan and Seattle received colonoscopy. They concluded that “compared to Westerners, Chinese patients have a slightly lower prevalence of

colon neoplasia (but not advanced neoplasia), more distal distribution of neoplasia, and higher likelihood of concomitant proximal advanced neoplasia and distal neoplasia." (22)

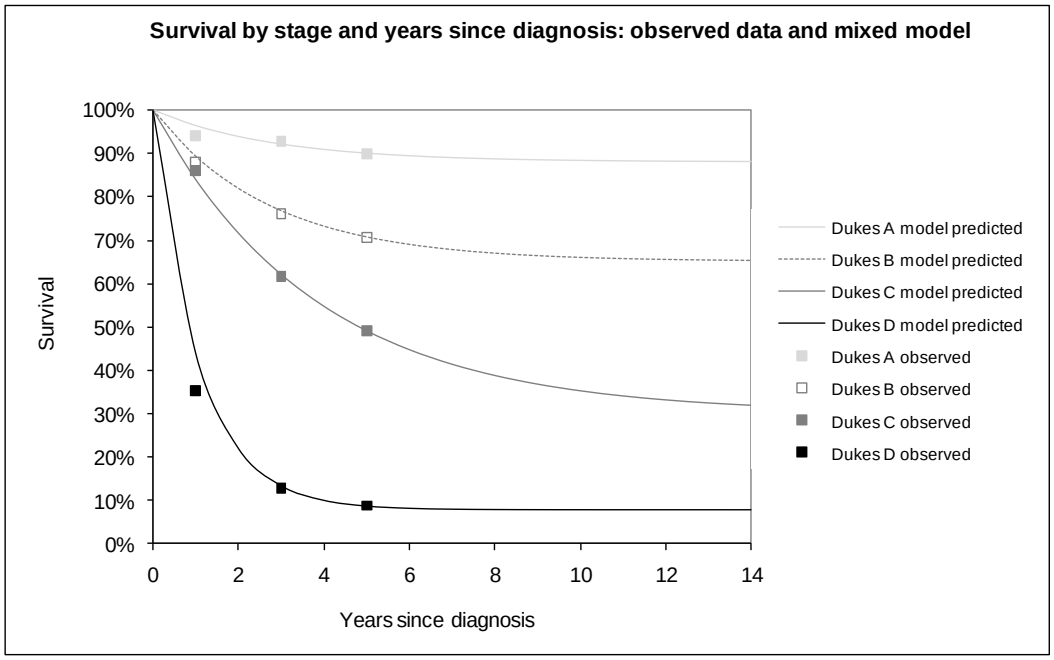
Differences in adenoma and CRC prevalence between England, Germany and Italy may exist; however, the extent of these differences is unknown. The value of using data from more than one country is that it allows the use of large datasets from several different screening modalities. The benefit of including data on different screening modalities was considered to outweigh the uncertainty introduced by using datasets from different countries.

3.1.12 Mortality rates

CRC 1, 3 and 5 years relative survival by stage at diagnosis were taken from England cancer registry data of diagnoses between 1997 and 2001.(20) As a significant proportion of patients survive colorectal cancer (5 year relative survival is over 90% for Dukes A), it is not appropriate to use a constant mortality rate (exponential model). For each Dukes' stage a mixed model was used for CRC mortality which assumes that a certain proportion of patients will be cancer survivors.

Other-cause mortality was taken from ONS life tables based on data for the years 2007-2009 with CRC death removed.(23)

Figure 3.1.6: CRC survival by stage and time from diagnosis



3.2 Natural history model calibration method

Model calibration used the methods described by Whyte et al, and figures describing the method are included in Appendix 2.(4) For a given parameter set, the model can be run to produce predictions of CRC incidence, adenoma prevalence and screening outcomes. The aim of the calibration is to obtain parameter sets whose predictions are close to the observed data. For each data set, the sum squared error (SSE) was calculated by comparing the observed number of observations to the predicted number of observations for each age. The total SSE is a measure of how well the model fits to all the observed data sets. The aim of the calibration is to obtain multiple parameter sets which each produces a model that has a good fit to the observed data sets (determined by consideration of total SSE).

The Metropolis Hastings (MH) algorithm was used for the calibration process to generate multiple sets of parameters.(24) These parameter sets form the posterior distribution which is compatible with the observed data, accurately representing parameter uncertainty. This approach embeds the problem in the framework of Bayesian inference and produces correlated parameter sets which can be used for probabilistic sensitivity analyses (PSA). Correct representation of the joint uncertainty in these parameters is particularly important because of the potential for correlation between several of these parameters.

The model calibration was run eight times using different sets (randomly generated) of initial parameter values to ensure that the best fitting parameter set was obtained. Each run consisted of 50,000 iterations of the MH algorithm and could be run overnight on a standard PC. A sample of 250 parameter sets from after convergence from four of the runs were combined to form 1000 parameters sets to be used to run the PSA.

A large number of parameters was being estimated within the calibration process, which can lead to low acceptance rates and slow convergence. Hence an approach was implemented in which there was a random 30% probability that a given parameter was varied on each run, and this increased acceptance rates and time to convergence.

3.3 Model calibration results

Figures 3.3.1-3.3.2 show the model predictions compared to the observed data for the best fitting parameter set resulting from the calibration process. The model obtained a good fit to the observed data on CRC incidence in the absence of screening and to the data on gFOBT, iFOBT and FS screening.

The best fitting parameter set and 95% percentiles are presented in Table 3.3.1. The 95% percentiles demonstrate that there are varying degrees of uncertainty surrounding the different parameter values. For example, there is considerable uncertainty surrounding the FS CRC sensitivity value, as the sample sizes are quite small for the CRC detection rates at FS screening. We note that although the CRC sensitivity estimates for FS and iFOBT were similar, FS has higher detection rates because it is associated with a higher rate of compliance with follow-up colonoscopy.

The correlation matrix for all the parameters estimated within the calibration process is included in Appendix 2, and this demonstrates the importance of including between-parameter correlation within the modelling.

Figure 3.3.1: Model predictions compared to observed data for CRC incidence in the absence of screening

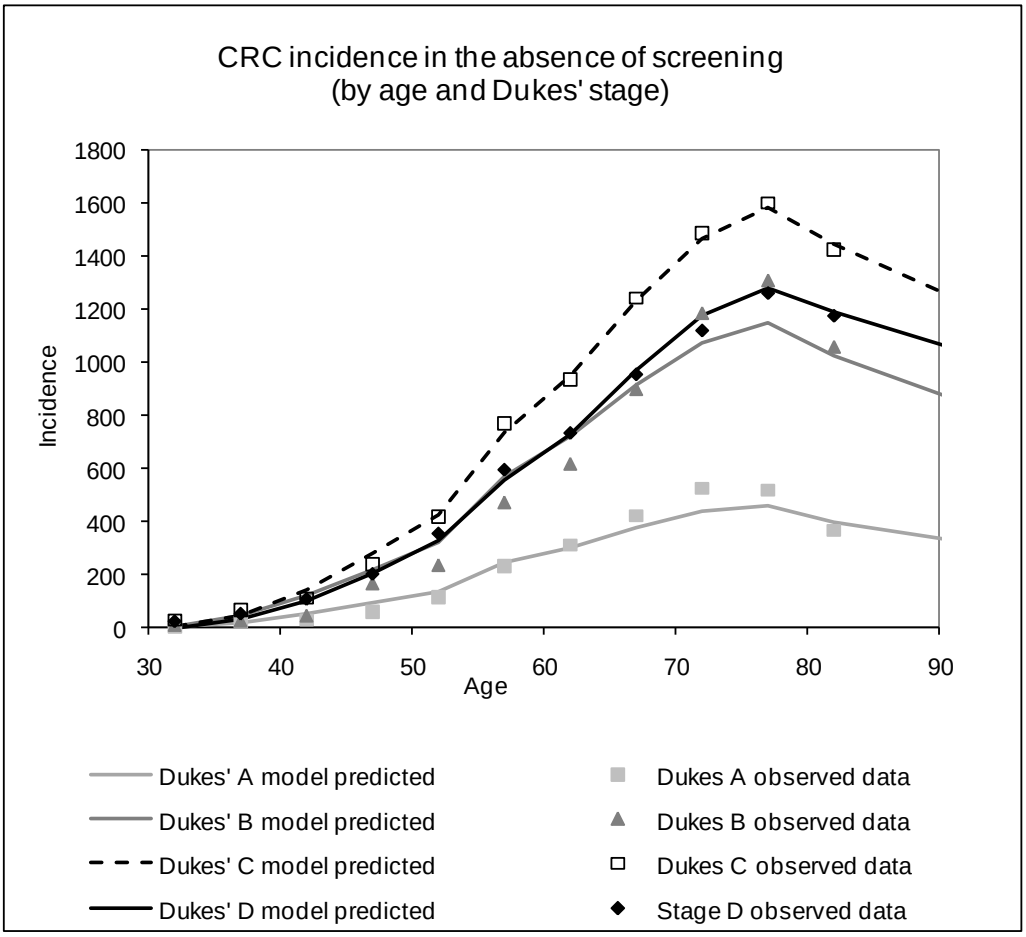


Figure 3.3.2: Model predictions compared to observed data for detection rates at gFOBT, iFOBT, flexible sigmoidoscopy and colonoscopy screen

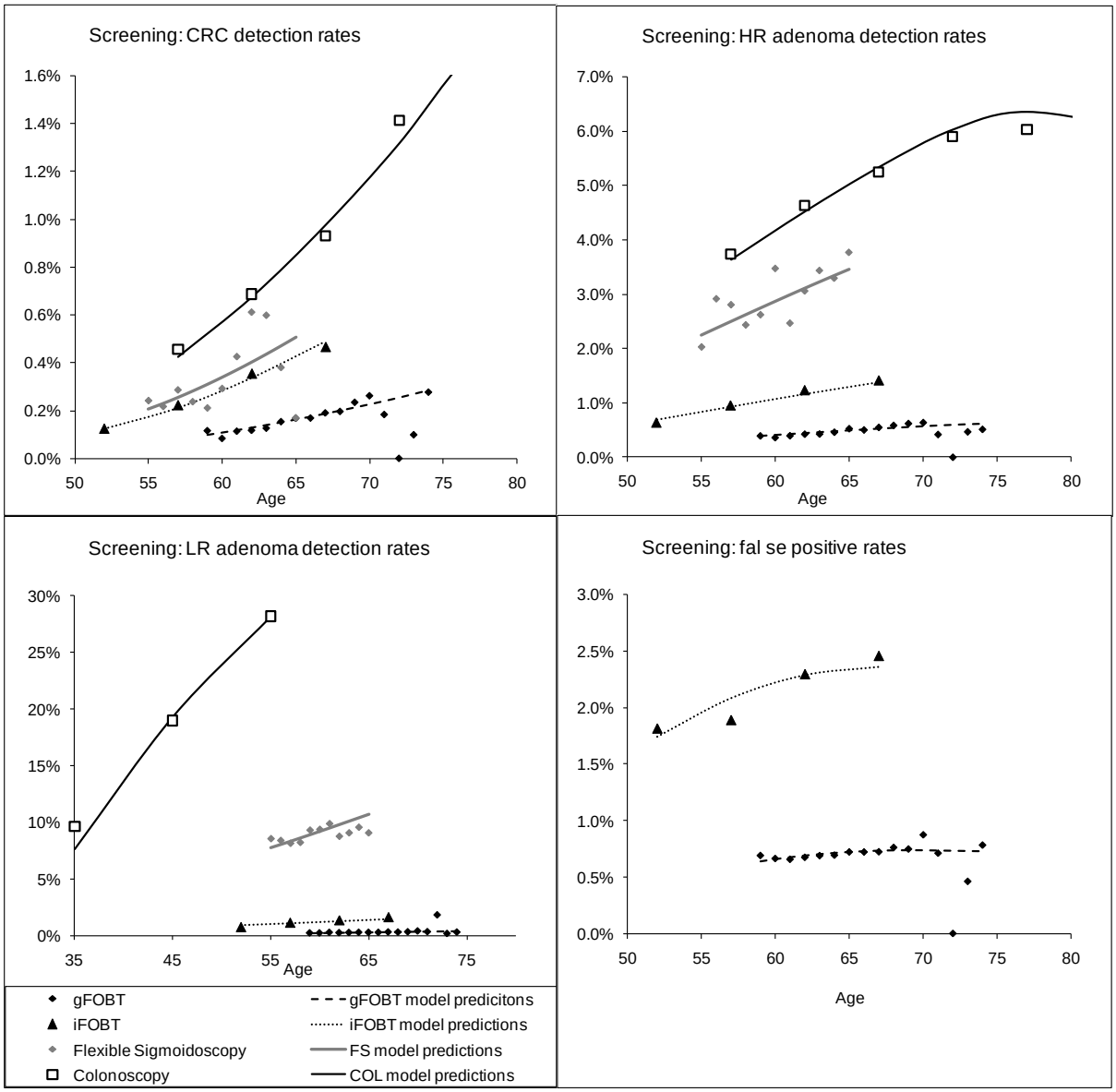


Table 3.3.1: Model calibration results: best fitting parameter set and 95% percentiles

Parameter	Maximum a posteriori estimate, (95% percentiles)
Annual transition probabilities	
Normal epithelium to LR adenomas - age 30	0.021 (0.020, 0.022)
Normal epithelium to LR adenomas - age 50	0.020 (0.019, 0.021)
Normal epithelium to LR adenomas - age 70	0.045 (0.029, 0.047)
Normal epithelium to LR adenomas - age 100	0.011 (0.005, 0.031)
LR adenomas to high risk adenomas - age 30	0.009 (0.007, 0.014)
LR adenomas to high risk adenomas - age 50	0.008 (0.006, 0.008)
LR adenomas to high risk adenomas - age 70	0.008 (0.008, 0.010)
LR adenomas to HR adenomas - age 100	0.004 (0.003, 0.010)
HR adenomas to Dukes A CRC - age 30	0.029 (0.004, 0.031)
HR adenomas to Dukes A CRC - age 50	0.025 (0.022, 0.026)
HR adenomas to Dukes A CRC - age 70	0.054 (0.050, 0.058)
HR adenomas to Dukes A CRC - age 100	0.115 (0.084, 0.118)
Normal epithelium to CRC Dukes A	0.00004 (0.00003, 0.00008)
Preclinical CRC: Dukes A to Dukes B	0.51 (0.50, 0.89)
Preclinical CRC: Dukes B to Dukes' C	0.69 (0.50, 0.70)
Preclinical CRC: Dukes C to Stage D	0.71 (0.59, 0.73)
Symptomatic presention with CRC Dukes A	0.04 (0.04, 0.07)
Symptomatic presention with CRC Dukes B	0.18 (0.12, 0.18)
Symptomatic presention with CRC Dukes C	0.37 (0.30, 0.39)
Symptomatic presention with CRC Dukes D	0.74 (0.65, 0.92)
Screening test characteristics	
gFOBT Sensitivity for LR adenomas	0.009 (0.009, 0.010)
gFOBT Sensitivity for HR adenomas	0.124 (0.121, 0.125)
gFOBT Sensitivity for CRC	0.242 (0.233, 0.253)
gFOBT Specificity age 50	0.994 (0.991, 0.995)
gFOBT Specificity age 70	0.973 (0.972, 0.978)
FS Sensitivity for LR adenomas	0.219 (0.212, 0.229)
FS Sensitivity for HR adenomas	0.710 (0.685, 0.742)
FS Sensitivity for CRC	0.617 (0.612, 0.741)
iFOBT Sensitivity for LR adenomas	0.045 (0.043, 0.047)
iFOBT Sensitivity for HR adenomas	0.322 (0.315, 0.332)
iFOBT Sensitivity for CRC	0.629 (0.606, 0.646)
iFOBT Specificity age 50	0.975 (0.971, 0.977)
iFOBT Specificity age 70	0.925 (0.920, 0.937)

3.4 Model validation

The model was validated by comparing model predictions to screening data which was not used in the calibration process. This data consisted of results from repeat screens in the FOBT screening programmes and changes in incidence and mortality in the 11 year period following FS screening.

Model predictions of changes to CRC incidence and mortality following a FS screen were compared to those seen in the FS trial. The FS trial reports that in persons attending screening, CRC incidence was reduced by 33% (HR 0·67, 95% CI 0·60–0·76) and CRC mortality by 43% (HR 0·57, 95% CI 0·45–0·72) in the follow-up period (median 11.2 years).(6) Considering a follow-up period of 11 years, the model predicts that CRC incidence will be reduced by 29% (HR=0.71) and mortality by 34% (HR=0.66) for persons receiving a FS screen at ages 55-64. These hazard ratios are within the confidence intervals reported by the FS trial.

Data from persons undergoing repeat screens with iFOBT in Italy provides details of positivity and detection rates and is presented in Figure 3.4.1.(25) The data demonstrates a significant decrease in positivity and detection rates at the repeat screen with a more marked difference in the older ages. In this data set, “repeat screens” includes persons undergoing their second or third screen. As specific data on the second iFOBT screen was not available, this data was not suitable for validation.

Figure 3.4.1: Positivity and detection rates and initial and repeat iFOBT screen in the Italian screening programme

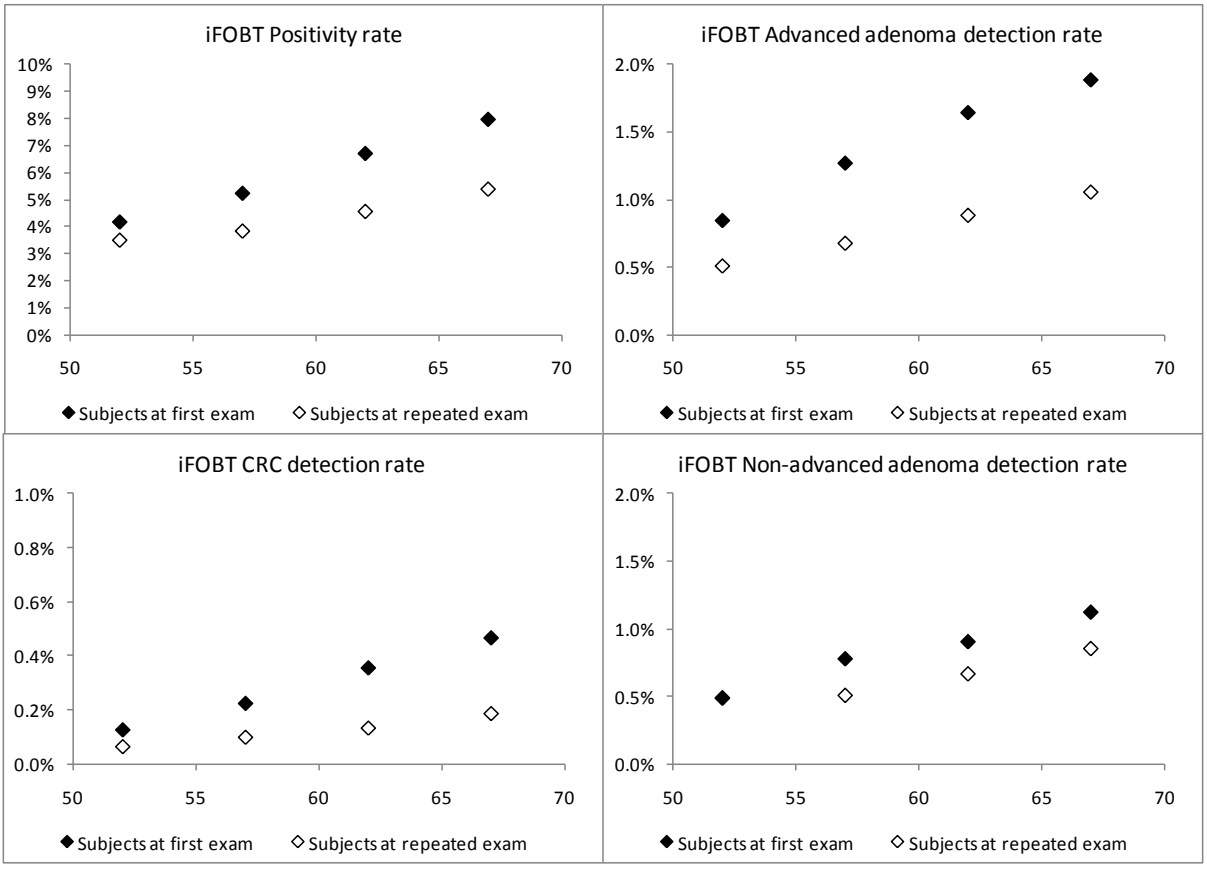


Figure 3.4.2 presents data on persons undergoing a second gFOBT in the NHS BCSP that was used for model validation. The comparison between gFOBT second screen data and the model prediction is presented in Figure 3.4.3. This demonstrates that the model produces a good fit to CRC detection rate for the second screen data. Surprisingly, the data shows a small increase in the LR adenoma detection rate between the first and second screens. It is suspected that this may be due to

improvements in colonoscopy quality between the first and repeat screens. The data shows a marked decrease in HR adenoma detection rates which is much larger than the decrease predicted by the model. There is also a much higher false positive rate seen at the second screen; however, the model predicts that specificity will not vary by number of screens.

The difference between the gFOBT second screen data and the model predictions suggests that: (1) the second screen data is in some way biased, or (2) gFOBT sensitivity and specificity vary by first/repeat screen which is not represented by our model structure. Possible sources of bias effecting the gFOBT first/second screen data are not well understood. Lower detection rates and higher false positive rates at a second/repeat screen would result in a strategy of repeated gFOBT being significantly less effective than is predicted by this model. This issue results in significant uncertainty surrounding the efficacy of the use of gFOBT for repeated screens.

Figure 3.4.2: Positivity and detection rates at initial and second gFOBT screens in the NHS BCSP (showing 95% CIs)

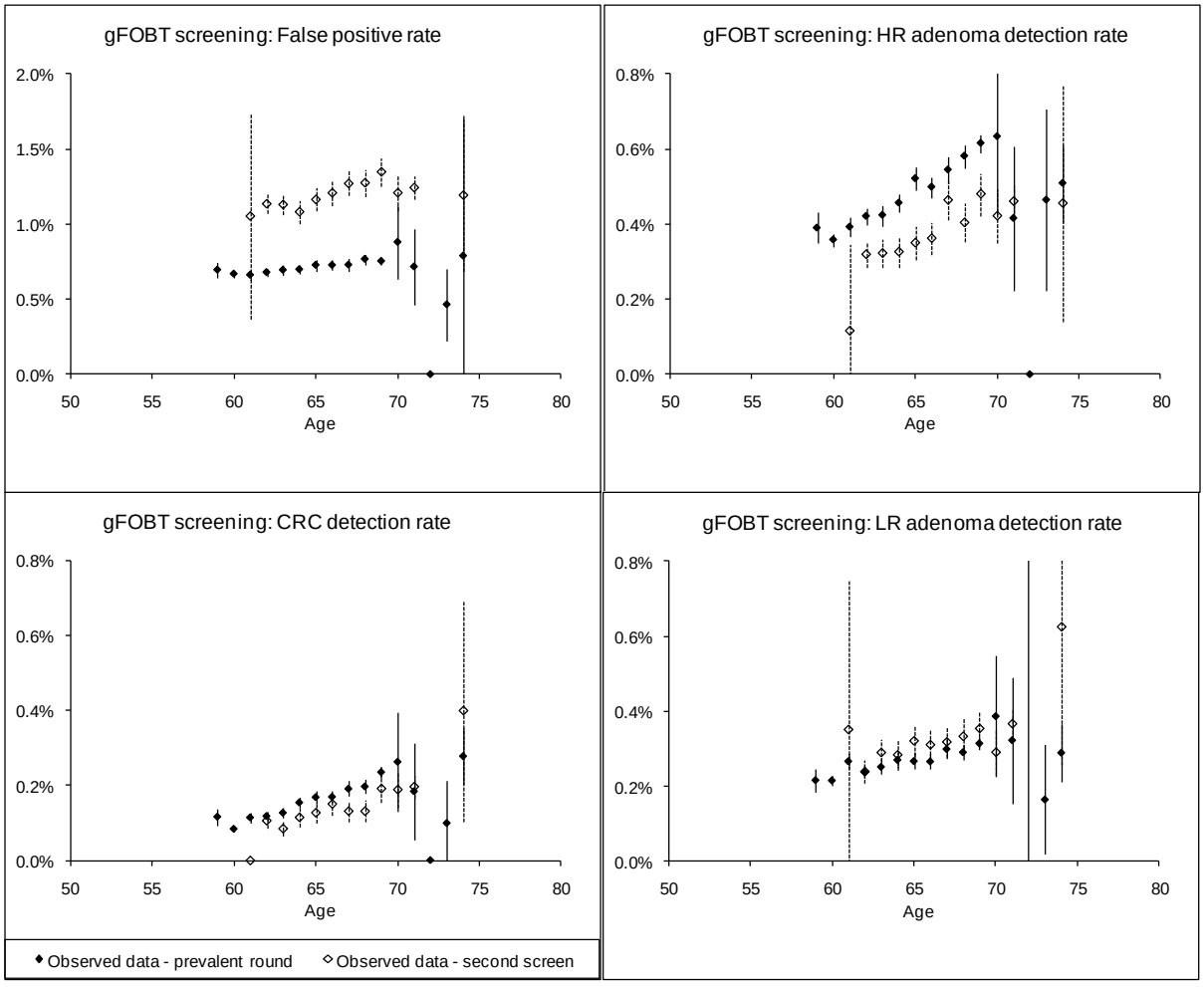
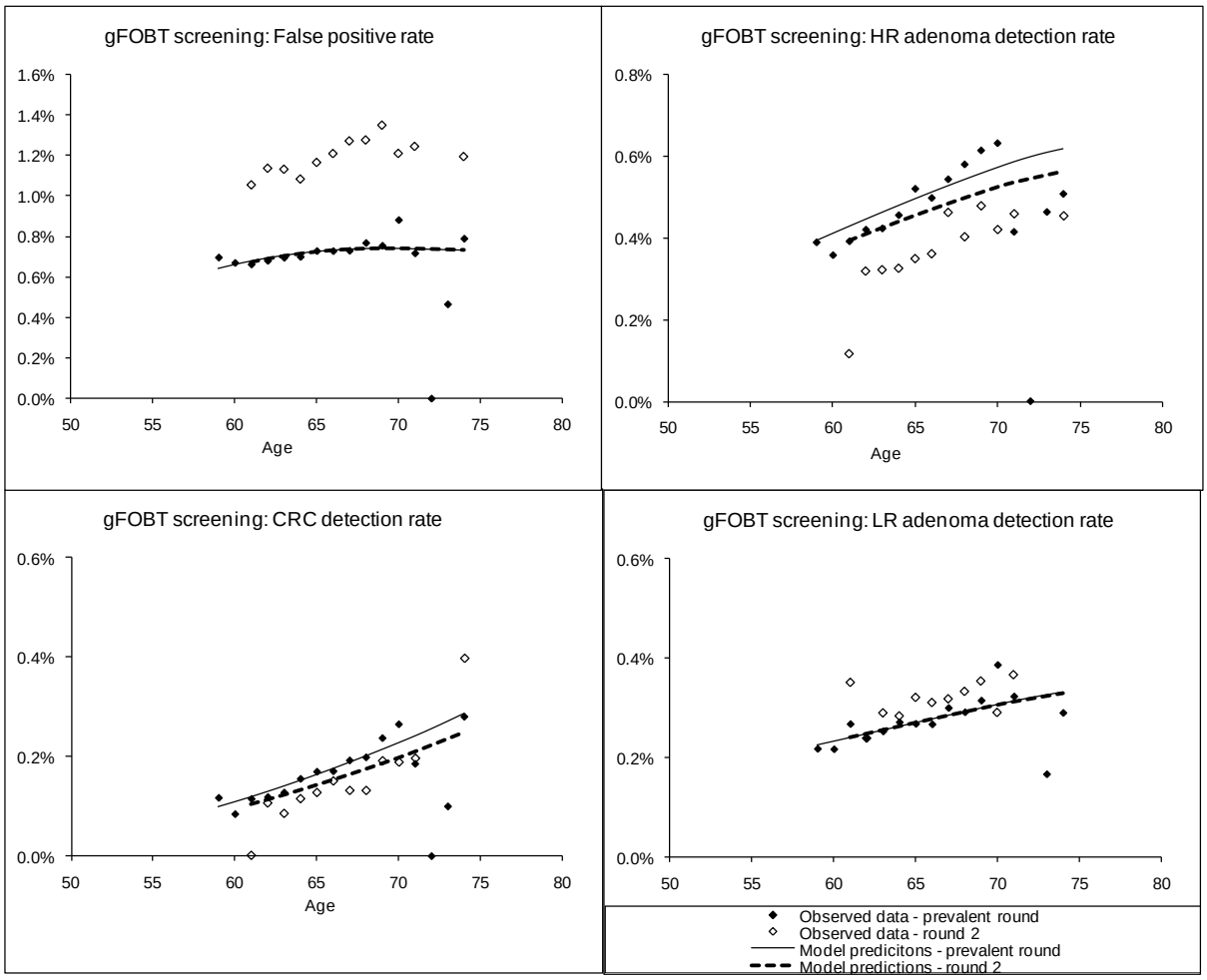


Figure 3.4.3: Model predictions compared to observed data for second gFOBT screens in the NHS BCSP



3.5 Model parameter values

3.5.1 Modelling assumptions

The modelling approach and data sources follow the NICE guidelines for technology appraisal. (26) Costs and QALYs will be discounted by 3.5%. To allow a fair comparison between screening interventions which commence at different ages, discounting will start at age 50, which is earlier than the age at which screening intervention is first offered. A willingness-to-pay threshold of £20,000 is used.

3.5.2 Cost of screening programme

The costs associated with the various components of a screening programme were estimated using a cost model for the Southern screening hub. There is likely to be some variation in costs between hubs, but the scale of these variations is uncertain. The Southern hub cost model includes estimates of staff costs, consumables, capital purchases and overheads.

Details of the costs used, data sources and assumptions made are provided in Table 3.5.1.
The cost of letters sent out includes cost of consumables, fulfilment (packing), postage, staff costs, capital costs and overheads. The costs associated with the following letters involved in the gFOBT screening process were estimated: invitation letter (subject), kit letter and leaflets (subject), reminder letter (subject), retests (subject), normal FOBT letter (subject and GP), non-attendance letters(GP) and positive FOBT letters (subject and GP). The other components of screening programme costs estimated were: return postage for test kits, dealing with kits returned “not known at this address”, helpline, laboratory for processing test kits, booking appointments for subjects with positive FOBT.
In order to estimate the costs associated with an iFOBT or FS screening programme, several assumptions were made.

The cost of sending out an iFOBT kit was assumed to include the cost of posting a packet weighing less than 100g second class with Royal Mail; the cost of packaging and fulfilment (estimated by Stephen Halloran); and staff costs and overheads at the same rate as was incurred for sending out the gFOBT kit. The return postage costs for an iFOBT kit were assumed to be the cost of posting a packet weighing less than 100g first class with Royal Mail. Estimates of iFOBT processing costs include predicted laboratory staff requirements for the Southern hub; the cost of instrument rental is assumed to be £0, and the cost of instrument maintenance is assumed to be £100,000 per annum for five instruments. The number of letters sent out for iFOBT screening was assumed to be the same as for gFOBT screening. The proportion of persons phoning the helpline was assumed to be the same as for gFOBT.

FS screening was assumed to involve the following steps: pre-invitation letter sent to subject, scannable health questionnaire sent to subject, letter with FS appointment time (sent to subject suitable for screening), appointment confirmed via automated telephone service, consent form sent to subject, bowel preparation sent to subject, individuals with uncertain fitness for FS contact SSP. There may be NHS IT issues with the immediate implementation of the “scannable health questionnaire and appointment confirmed via automated telephone service”, but it is assumed that in the long term this approach would be used. Each of the letters sent was assumed to cost the same as the gFOBT invitation letter. The BNF price for a Fleet enema was assumed, and postage of the enema was assumed to be the cost of posting a packet weighing less than 100g second class with Royal Mail, signed for. However, as a bulk purchase of enemas would be required, it is likely that a price lower than the BNF price could be achieved in practice. Fulfillment and overhead costs for sending out of enemas were assumed to be the same as for sending out FOBT kits. The proportion of persons phoning the helpline with queries relating to FS screening was assumed to be 40% higher than for that seen with FOBT screening.

Table 3.5.1: Screening Costs

	Cost		Source
Test costs, return test postage, test processing costs			
gFOBT kit (includes device, spatula, envelope, and reagents)	£	0.46	National contract cost
gFOBT kit consumables, fulfillment, postage	£	0.38	Southern hub cost estimates: postage 0.192, fulfillment 0.072, consumables 0.059, staff costs and overheads 0.05
gFOBT return postage	£	0.35	Royal mail business reply plus
gFOBT processing costs (per test)	£	0.78	Southern hub cost estimates
iFOBT kit	£	2.50	Stephen Halloran (note: Northern Italy currently pay 1 euro, a lower cost is considered in a SA)
iFOBT kit postage	£	2.74	Postage 2nd class packet<100g £1.17, packaging costs of £0.25, fulfillment of £0.10, staff costs and overheads 0.05
iFOBT return postage	£	1.17	Royal mail 1st class packet <100g £1.39
iFOBT processing costs (per test)	£	0.64	Southern hub cost estimates
Bowel preparation for FS	£	0.57	BNF cost for Fleet® Ready-to-use Enema (Casen-Fleet) Enema £0.57 133-mL pack (delivers 118 mL dose) with standard tube
Bowel prep for FS postage, packaging and fulfillment	£	2.32	Postage 2nd class packet<100g £1.17+ for signed for £0.75, packaging £0.25, fulfillment £0.10, staff costs and overheads 0.05
Repeat test costs			
gFOBT Retest costs (kit and processing)	£	3.19	Additional cost of hub sending out retests via royal mail is £1.22
gFOBT Retest rate		0.08	Southern hub data and gFOBT pilot data
gFOBT Retest costs per screening completer	£	0.25	Calculated from above
iFOBT Retest costs (kit and processing)	£	9.49	Additional cost of hub sending out retests via royal mail is assumed to be 2x£1.22 due to additional packaging and storage costs
iFOBT Retest rate		0.03	Retesting will be required if test is not returned within 7/10 days, approximately 97% of gFOBTs are returned within 7 days, 95% within 5 days
iFOBT Retest costs per screening completer	£	0.28	Calculated from above
FS repeat test rate			
Letter costs (including consumables, fulfillment, postage, staff costs, overheads…)			
Invitation letter	£	0.34	Southern hub cost estimates
Reminder letter	£	0.34	Southern hub cost estimates
Reminder letter cost per invitee	£	0.17	Calculated from above
Non-attender letter to GP	£	0.14	Southern hub cost estimates
Normal result letter to subject and GP	£	0.45	Southern hub cost estimates
Positive result letter to subject and GP	£	3.74	Southern hub cost estimates
Helpline costs			
Helpline costs per call	£	2.83	Southern hub cost estimates
gFOBT Proportion of those invited calling helpline		0.19	Southern hub cost estimates
gFOBT Helpline costs per screening invitee	£	0.53	Calculated from above
iFOBT Proportion of those invited calling helpline		0.19	Assume helpline call frequency same for gFOBT and iFOBT
iFOBT Helpline costs per screening invitee	£	0.53	Calculated from above
FS Proportion of those invited calling helpline		0.40	Estimate by Stephen Halloran (to include persons with uncertain fitness for FS talking to a SSP)
FS Helpline costs per screening invitee	£	1.13	Calculated from above
Appointments for follow up for positives	£	5.53	Southern hub cost estimates
Endoscopy costs			
Flexible Sigmoidoscopy Examination Alone	£	186	NHS reference costs 2003 (inflated)
Flexible Sigmoidoscopy with Biopsy or Therapy	£	195	NHS reference costs 2003 (inflated)
Colonoscopy Examination Alone	£	205	NHS reference costs 2003 (inflated)
Colonoscopy with Biopsy or Therapy	£	237	NHS reference costs 2003 (inflated)
Cost of pathology	£	27	

A summary of costs of screening (excluding the costs of follow up colonoscopy) are provided in table 3.5.2.

Table 3.5.2: Costs of screening - summary

Summary screening costs	Cost	
gFOBT screening		
Non attender	£ 2.03	
Normal test result	£ 3.36	
Positive test result	£ 11.94	
iFOBT screening		
Non attender	£ 6.43	
Normal	£ 7.37	
Positive	£ 16.20	
Flexible Sigmoidoscopy screening		
Non attender	£ 5.02	
Normal	£ 6.01	Note this cost excludes the cost of flexible sigmoidoscopy
Positive	£ 14.84	Note this cost excludes the cost of flexible sigmoidoscopy

3.5.3 Cost of colonoscopy and flexible sigmoidoscopy

An appointment with a specialised screening practitioner (SSP) nurse is required before a patient receives a follow up colonoscopy. Based on clinical opinion we assume that this will incur 30 minutes nurse time for referral to colonoscopy from FOBT and 15 minutes nurse time for referral to COL from FS screen. For FS the appointment may either take place immediately following their exam before they leave the clinic, or be arranged by telephone once pathology results are in. The cost of SSP nurse time is assumed to be the cost of a specialist nurse (community) of £36 per hour taken from the Unit costs of health and social care 2009. (27)

Evidence on the cost of colonoscopy and flexible sigmoidoscopy is available in the 2003 and 2005 NHS reference costs (more recent NHS reference costs unfortunately do not include costs which relate specifically to these procedures) and in a paper by Whynes et al. (28-30) The reference costs were inflated to 2008/2009 values using inflation indices reported in the Unit costs of health and social care 2009. (27) In addition an estimate of costs has been provided by Derbyshire Screening Centre and these costs include staff, procedure and pathology costs. (31) A cost estimate for colonoscopy (including specialised screening practitioner, imaging and pathology costs) was provided by Chesterfield Royal Hospital NHS Foundation Trust.(32)

Table 3.5.3: Endoscopy costs

Procedure	Published cost	Source	Inflated to 2008/2009
Colonoscopy	£347	2005 Reference Costs	£401
Colonoscopy with Biopsy or Therapy	£198	2003 Reference costs *	£237
Colonoscopy Examination Alone	£172	2003 Reference costs *	£205
Colonoscopy, incl. pathology	£245	Derbyshire BCSP	£245
Colonoscopy including SSP, imaging, pathology	£550	Chesterfield Royal Hospital	£550
Flexible Sigmoidoscopy	£275	2005 Reference Costs	£318
Flexible Sigmoidoscopy with Biopsy or Therapy	£164	2003 Reference costs *	£195
Flexible Sigmoidoscopy Examination Alone	£156	2003 Reference costs *	£186
Flexible Sigmoidoscopy	£56	Whynes 2003	£80
Flexible Sigmoidoscopy, nurse led, incl pathology	£101	Derbyshire BCSP	£101

*Average of procedures with surgical and medical gastroenterology HRG labels

The cost of FS will vary considerably depending on whether it is nurse-led or consultant-led. The proportion of FS procedures which are likely to be nurse-led in a screening programme situation is unknown.

The ratio of the cost of a FS procedure to a colonoscopy procedure is unknown. In a third sensitivity analysis, a greater difference between the cost of FS and colonoscopy is considered based on the costs estimates from the Derbyshire screening programme. This analysis is consistent with the suggestion that the number of procedures completed per session is 10-12 for flexible sigmoidoscopy compared to 4-6 per session for colonoscopy. (5)

The 2003 values have been used in the base case analysis as they distinguish between procedures with and without polypectomy. The differences between the 2003 and 2005 reference cost values and the estimate from Whynes et al demonstrate that there is considerable uncertainty surrounding endoscopy costs. Sensitivity analyses on the endoscopy costs were undertaken. The first sensitivity analysis uses the values reported in 2003 multiplied by a factor of 1.7 to reflect the values in the 2005 reference costs, whilst still distinguishing between with/without polypectomy. The second sensitivity analysis will consider lower values for endoscopy costs (50% of base case cost estimates) to reflect the fact that costs in a population screening situation may be lower than those reported in the NHS reference costs. A third one-way sensitivity analysis reflects the likely reduced cost of nurse-led flexible sigmoidoscopy with values derived from the Derbyshire screening centre estimates.

Table 3.5.4: Endoscopy costs used in model

Procedure	Base case estimate	Low values for SA	High values for SA	Values for 3rd SA
Colonoscopy with Biopsy or Therapy	£237	£118	£402	£269
Colonoscopy Examination Alone	£205	£103	£349	£245
Flexible Sigmoidoscopy with Biopsy or Therapy	£195	£98	£332	£111
Flexible Sigmoidoscopy Examination Alone	£186	£93	£316	£101

Polypectomy will always involve a biopsy. Unfortunately it is unclear whether the NHS reference costs for endoscopy include the pathology costs associated with biopsy. For the purposes of this analysis we assume that pathology cost will be incurred on top of the procedure costs. The Derbyshire screening programme estimates average pathology costs of £50 for FS and £72 for colonoscopy. The NHS reference cost for histopathology is £26 and this cost has been used in the model for both cancer and adenoma. The mean number of adenomas requiring pathology was assumed to be 1.9 based on data reported from the National Polyp Study by Winawer et al.(33) Wendy Atkin is proposing the introduction of a “National/regional pathology processing centre” which would aim to reduce pathology costs while at the same time increasing standardisation. To reflect this possibility a one-way sensitivity analysis on pathology costs (+/- 20%) was performed.

3.5.4 Complications following endoscopy

Colonoscopy and flexible sigmoidoscopy procedures are associated with a small risk of bleeding or perforation; and perforation may lead to death. Incidence of bleeding, hospitalisation for bleeding and perforation following flexible sigmoidoscopy and colonoscopy procedures with and without perforation are taken from the flexible sigmoidoscopy trial. There were no perforations following colonoscopy or flexible sigmoidoscopy without perforation, so the perforation rate was assumed to be 0%. Data on perforation rates for colonoscopy following a positive FOBT was also taken for the FS trial, as data from the BCSP was suspected to be inaccurate due to incomplete reporting.

Gatto et al report that the incidence of death subsequent to a perforation within 14 days of a procedure was 4 out of 77 colonoscopic perforations (5.2%) and 2 out of 31 sigmoidoscopic perforations (6.5%). This study refers to a Medicare population, so the cases may be older and in worse health than the proposed English screening population; however, no alternative reference was

identified. Gatto et al also reported that the risk of perforation from FS increased in association with increasing age, but this association has not been modelled here.(34)

Table 3.5.5: Number of persons with bleeding, hospitalisation for bleeding and perforations in the FS trial

Procedure	Number	Bleeding		Hospitalisation for bleeding		Perforation	
FS with polypectomy	9499	29	0.31%	8	0.08%	1	0.011%
FS without polypectomy	31122	48	0.15%	4	0.01%	0	-
FS	40621	77	0.19%	12	0.03%	1	0.002%
COL with polypectomy	1431	9	0.63%	6	0.42%	4	0.280%
COL without polypectomy	616	0	-	1	0.16%	0	-
COL	2047	9	0.44%	7	0.34%	4	0.195%

Endoscopy complication rates are available for other countries. Rabeneck et al report a hospitalisation for bleeding rate of 0.14% and a perforation rate of 0.06% from over 90,000 colonoscopies undertaken in Canada.(35) Although the data from the FS trial is a much smaller dataset, we have chosen to use it here as it is specific to the UK setting.

3.5.5 Cost of treating screening complications

The cost of treating a perforation due to flexible sigmoidoscopy or colonoscopy was assumed to be £2164 (Major therapeutic open or endoscopic procedures, 19 years and over with major colon cancer major surgery).(36) The cost of treating hospitalised bleeding following flexible sigmoidoscopy or colonoscopy was assumed to be £262 (Very major procedure for gastrointestinal bleed). (36)

The cost of treating a gastrointestinal bleed ranges from £350 to £407 (Non-Elective inpatient short stay HRG data HRGFZ38D, FZ38E, FZ38F) depending on length of stay and complication, hence a cost of £380 is assumed here.

3.5.6 Colonoscopy test characteristics

A systematic review of studies of tandem colonoscopies was undertaken by Van Rijn et al. (37) For adenomas of size <10mm 167 out of 711 were missed, and for adenomas of size >10mm 2 out of 96 were missed. A study by Bressler et al estimated that out of 12496 cases of CRC, 430 were missed at colonoscopy (2%).(38) Based on these studies, sensitivity to low risk adenomas was assumed to be 77%, sensitivity to high risk adenomas or CRC 98%, and specificity was assumed to be 100%.

3.5.7 Screening test characteristics

A systematic review of the diagnostic accuracy of FOBTs identified thirty-three studies that evaluated guaiac FOBTs.(39, 40) Sensitivities for the detection of all neoplasms ranged from 6.2% (specificity 98.0%) to 83.3% (specificity 98.4%) for guaiac FOBTs. Specificity ranged from 65.0% (sensitivity 44.1%) to 99.0% (sensitivity 19.3%) for guaiac FOBTs. The wide range in sensitivity values may be attributed to a number of factors including: study design, study populations, whether the test was rehydrated, test processing, and the choice of reference standard and test threshold. The substantial between-study heterogeneity makes performing a meta-analysis difficult.

A systematic review and meta-analysis was undertaken to obtain estimates for the test characteristics of immunochemical faecal occult blood tests (iFOBT). More specifically, this assessment updates and extends the systematic review conducted by Burch et al.,(39) which included studies up to November 2004. As the iFOBT Evaluation Report produced by the Centre for Evidence-based Purchasing concluded that the OC-Sensor/DIANA analyser was the most suitable system for the English BCSP,

the review was limited to the OC-Sensor test. Full details of the search strategy and studies found are provided in Appendix 3.

Several limitations of the results of the meta-analysis were identified:

- Very poor reporting of the cut-off threshold used by the studies
- The test characteristic estimates produced were surrounded by considerable uncertainty
- Differences in test characteristic estimates between a trial and a screening setting

This led to concerns over using the results of the meta-analysis within the modelling. Hence data from the existing Italian iFOBT screening programme was incorporated within the model calibration process to provide estimates of the sensitivity and specificity of iFOBT.

In this study, sensitivity and specificity of the FS and FOBT screening tests will be estimated within the model calibration process. This approach combines observational data from screening with a natural history and screening model to estimate test characteristics.(41) FOBTs may identify conditions other than CRC and adenomas, and such conditions are likely to be more prevalent in an older population. Hence it follows that the number of persons with a positive FOBT result without CRC/adenomas increases with age, and this was observed in the data sets. In the modelling a specificity value which varied by age (linearly) was used.

3.5.8 Test completion rates

The bowel cancer screening pilot 2nd round evaluation reports that 5% of initial FOBTs have 1-4 positive spots (weak positive) so require repeat testing per the NHS BCSP referral algorithm.(7) The evaluation of the 2nd round of the screening pilot reported that 66,264 gFOBTs were completed in phase 1, 2,972 in phase 2 and 2,236 in phase 3, hence the mean number of tests completed per person was 1.08.

Repeat testing will be required for iFOBT kits which are not returned within a certain period. The period of time in which a test must be returned is unclear, but we assume that a test must be returned within 7/10 days. Approximately 97% of gFOBTs are returned within 7 days and 95% within 5 days, hence the retest rate for iFOBT was assumed to be 3%. The Italian screening programme reported that 0.6% of persons had an inadequate test (due to incorrect sampling by the subject). (42)

The FS screening trial reported that out of 40621 examinations undertaken, 2145 (5%) required repeating, and out of these1306 (3%) were repeated on the same day and 839 (2%) were repeated on a later day. It was assumed that FS examinations repeated on the same day incurred no additional costs, and that if the examination was repeated on a later day then the cost of an additional FS examination would be incurred.

Out of a total of 32,213 follow up colonoscopies undertaken from Aug 2006 to Aug 2008 in the NHS BCSP, in 1,481 (4.6%) the caecum was not reached, which could be due to pathology encountered, inadequate bowel preparation or patient discomfort. One can assume that majority of the 1,481 will have required a subsequent test which would usually be undertaken on a later day.(43) Persons requiring a subsequent test will receive a colonoscopy, a CT colonoscopy or a barium enema. Data from the NHS BCSP reports that out of 78,311 colonoscopy examinations, 5453 people (7%) who return within an episode to have another procedure which could be to remove more adenomas, to complete an incomplete test, or to check an adenoma removal site. Hence a repeat colonoscopy rate of 7% is assumed here.

A summary of the repeat test rates used in the model is included within Table 3.5.6.

Table 3.5.6: Repeat test rates

Test	Rate	Source
gFOBT mean number of tests completed	1.08	Bowel cancer screening pilot 2nd round evaluation, Table 5.2
iFOBT mean number of tests completed	1.01	Asumption based on number of gFOBTs returned within 7 days, and data from Italian screening programme Zorzi et al 2009
FS Probability test repeated on a later day	0.02	FS UK screening trial data, Atkin et al 2002
COL repeat test rate	0.07	Data from gFOBT BCSP

3.5.9 Lifetime costs of treating CRC

A report entitled “The Costs and Benefits of Bowel Cancer Services” quantified the activities, costs and outcomes, associated with the treatment of bowel cancer.(44) Costs for treating CRC, which are dependent on cancer stage at diagnosis, were taken from this report and inflated to give values for 2010 using the inflation indices reported in the Unit costs of health and social care 2009.(27) It was assumed that the cost of treating a screen-detected case of CRC was the same as the cost of treating a symptomatic case detected at the same stage. These costs are presented in Table 3.5.7.

Table 3.5.7: Lifetime costs of treating CRC

Parameter name	Mean	Distribution used in PSA and 95% CI	Source
Lifetime cost of treatment - Dukes' A CRC	£ 12,455	Gamma(100,125) (10,134-15,012)	Pilgrim et al 2008
Lifetime cost of treatment - Dukes' B CRC	£ 17,137	Gamma(100,171) (13,943-20,655)	Pilgrim et al 2008
Lifetime cost of treatment - Dukes' C CRC	£ 23,502	Gamma(100,235) (19,122-28,327)	Pilgrim et al 2008
Lifetime cost of treatment - Stage D CRC	£ 25,703	Gamma(100,257) (20,913-30,980)	Pilgrim et al 2008

A sensitivity analysis was performed on cost of treating CRC. With the increased use of expensive chemotherapy treatments, it is believed that the cost of treating CRC which was used in the model could be an underestimate, and in addition the cost of treating CRC is likely to increase significantly in future years. To reflect the possible increased costs, a sensitivity analysis was performed using these treatment costs +20%.

3.5.10 Uptake of gFOBT in the English BCSP

Uptake is defined as the proportion of individuals who attend a screening round (referred to as attenders or responders). Data on uptake is available for the first two rounds of the BCSP in England and this is shown in Table 3.5.8. Data from the NHS BCSP found that a small proportion of persons opted out from screening for clinical reasons or informed dissent after receiving an invitation. The current estimates of opt-out rates do not include persons who opt out after receiving a test kit. Data from the NHS BCSP on the total number of persons opting out was not available at the time of writing.

Figure 3.5.1: Uptake of gFOBT screening in rounds one and two of the England BCSP

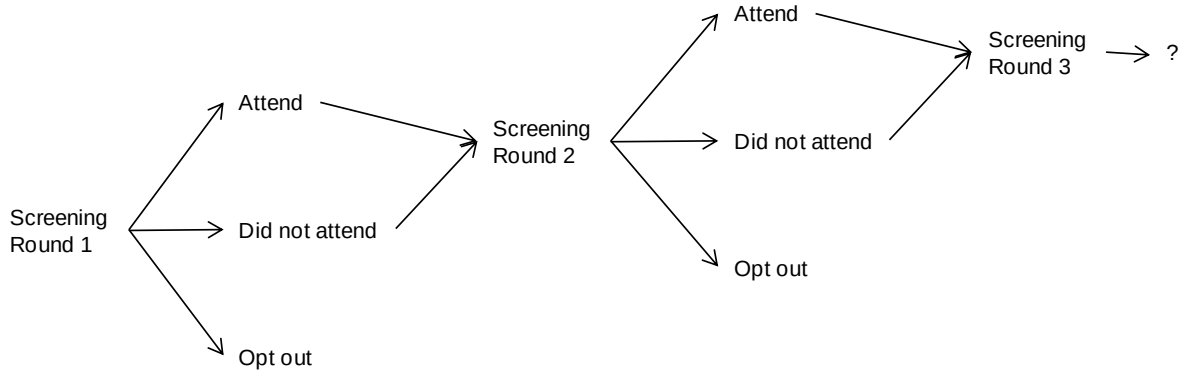


Table 3.5.8: Uptake of gFOBT screening in rounds one and two of the England BCSP

	Screening round 1		Screening round 2		Screening round 2, did not attend round 1		Screening round 2, attended round 1	
Invited	6,074,725		1,070,246		396,056		674,190	
Opted out from screening for clinical reasons or dissent	2,181	0.04%	317	0.03%	199	0.05%	117	0.02%
Invited and then sent test kit	6,072,544	100%	1,069,929	100%	395,857	7%	674,073	63%
Attended screening	3,195,533	53%	659,730	62%	77,794	20%	581,936	86%
Did not attend screening	2,877,011	47%	410,199	38%	318,063	80%	92,137	14%

The overall uptake data from screening round 2 is misleading, as the persons invited for round 2 include a particularly high number of persons who attended round 1. Adjusting to account for this bias, the uptake for round 2 is estimated to be 55%, which is similar to that seen in round 1. A study of gFOBT screening in France reported participation rates of 52.8% for the first screening round and between 53.8% and 58.3% in rounds 2-6. (45) Based on these two data sources, a constant uptake rate is assumed in this analysis.

When modelling just one round of screening, varying the uptake rate has little effect on cost effectiveness. This is because costs for non-attenders are very low, so an increase in uptake would lead to a proportional increase in both costs incurred and QALYs gained. In reality, however, the situation is more complex. For example, if we consider two scenarios both associated with 50% uptake: all persons attend 50% of screening rounds; and 50% of persons attend all screening rounds; we see that it is likely that these two scenarios will be associated with differing QALY gains.

The modelling approach taken here partitions the population into subgroups according to their preference for screening: “sometimes attend” and “never attend”. The proportion of persons who sometimes attend and the attendance rate for this group was chosen so that the number of persons attending 0,1,or 2 of the first two rounds matches that seen in the current gFOBT screening programme. The model parameters and the fit of the model to attendance rates in rounds one and two are presented in Table 3.5.9.

Table 3.5.9: Model for gFOBT uptake rates

Subgroup of screening population	Proportion of persons in subgroup	Attendance rate of subgroup
Never attend	0.37	0%
Sometimes attend	0.63	85%
Attendance rate for each round	54%	

Screening attendance	gFOBT screening programme data	Model
Attended rounds 1 and 2	0.45	0.45
Attended round 1 only	0.07	0.08
Attended round 2 only	0.09	0.08
Did not attend round 1 or 2	0.38	0.38

Uptake varies by gender, with higher uptake seen in men than in women. Uptake only varies slightly by age: women's uptake starts to fall off from about 65 years old whereas men's steadily increases. The modelling approach does not allow uptake to vary by age or gender. This simplification could be considered a limitation of the modelling approach. Further analysis of uptake data would allow a more sophisticated model of uptake to be considered in the future.

3.5.11 Uptake rates for flexible sigmoidoscopy and iFOBT

A pilot study in which FS screening was delivered as if it was a screening programme found that 45% attended, 5% accepted but were unable to attend within the time-frame of the study, 5% accepted but failed to attend, 7% declined, 27% did not respond, and 11% were ineligible or the invitation was returned unopened. Among those eligible to be screened, uptake was 51%. The programme was offered in two London Boroughs; one socioeconomically deprived and both ethnically diverse. There were no gender differences in uptake, but rates were substantially higher in affluent (63%) than deprived areas (38%). (46)

The study makes a comparison with FOBT uptake: “Despite FS requiring bowel preparation, a visit to the hospital, and a more invasive test, uptake rates for the two tests seem surprisingly similar. Data from the London Screening Hub show FOBT kit return rates of 47% in Harrow and 40% in Brent, which are very close to the raw uptake rates of 53% and 39% in these boroughs in the FS pilot. Differences by deprivation were also similar. This suggests that the barriers to CRC screening are likely to lie not in the specifics of the test but in the public’s lack of awareness of the high incidence of CRC or the potential value of screening. This is encouraging for ultimately achieving uptake rates comparable to those in the established cancer screening programmes.”

Based on this study we will use the same uptake rates for FS as has been seen in the current gFOBT BCSP. We will also assume that uptake for iFOBT is the same as for gFOBT. The Italian screening programme reports an average uptake rate of 47% for iFOBT and 27% for FS; however, these data related to different regions.(42) Based on this data, we will undertake a sensitivity analysis in which a lower uptake rate of 30% is assumed for FS.

3.5.12 Deprivation

Socioeconomic status (SES) affects CRC incidence and mortality rates. The SES gradient for CRC incidence is small. The National Cancer Intelligence Network reported a difference in age-standardised incidence rates between the least and most deprived groups of 2.5 (41.2-43.8 per 100,000). (47) As the incidence rate is slightly higher for the most deprived groups, the benefits associated with screening these groups will be slightly higher. To accurately model the benefits of

screening for groups with different SES levels, data would be required on the relationship between SES and adenoma growth rates. Such data is not available.

Uptake rates are known to vary by SES. The evaluation of the second round of the English bowel cancer screening pilot reported that uptake fell with increasing level of deprivation, from 61.2% to 37.2% in IMD quintiles 1 to 5 respectively.(7) A sensitivity analysis in which a lower uptake rate is used to reflect one of the most deprived areas was undertaken. This demonstrates the comparative benefits of screening in the most deprived areas compared to the base case which represents England.

3.5.13 Compliance with follow-up colonoscopy and surveillance colonoscopy

Data from the NHS BCSP reports colonoscopy compliance rates of 79.1% for follow-up colonoscopy and 82.4% for persons invited for surveillance colonoscopy. (21)

3.5.14 Utility values

A utility value is a preference weight reflecting the relative value that individuals place on different health states. Here we use a different utility value for persons with CRC and for persons without CRC.

A recent HTA of chemoprevention for colorectal cancer undertook a systematic review to identify relevant HRQoL literature. (48) The studies identified did not demonstrate a clear relationship between HRQoL and stage of cancer, treatment, phase of disease, or time since diagnosis.

NICE recommends that utilities should be based upon public preferences (e.g. EQ-5D values) and valued by patients; three studies report such data. (26) A study by Ramsey et al, which was undertaken using 173 long-term survivors of bowel cancer (mean age 70), elicited preferences using the Health Utilities Index Mark 3 (HUI3) reported a mean utility score of 0.85 (SD=0.15). (49) The FOCUS trial included patients with metastatic bowel cancer undergoing chemotherapy and reported an EQ-5D value of 0.76 (0.72-0.80). (50) The MABEL study included patients with metastatic bowel cancer who had failed on at least one prior line of chemotherapy and reported a health utility EQ-5D value of 0.73. (51)

The data available on utility values for CRC is very limited. The sample sizes are small, and two of the studies focus only on patients undergoing treatment. Some of the utility values reported are higher than the general population utility value for a person aged 75 of 0.75. (52) This inconsistency means that it is not possible to use age-adjusted utility values, and it is difficult to determine a without-CRC utility value to use.

An analysis of EQ-5D data from the health survey for England reports a value of 0.697 (95% CI 0.657-0.736) for persons with cancer and 0.798 (95% CI 0.755-0.839) for persons without cancer. (53) This data is limited by the fact that the health survey for England does not include persons in hospital or in nursing homes. Due to the problems mentioned with the CRC-specific data, this data will be used in the model here.

There may be a small utility decrement associated with undergoing a screening test; however, such a decrement is likely to only last a short period of time. There is no data available for utility values during a screening test, so no utility decrement due to screening test was included within the modelling.

The uncertainty in the utility value data suggests that intermediate outcome measures such as cost per case avoided may be more reliable measures.

4 Results

4.1 Optimal age for FS screening

Data comparing the model results for one-off FS screening for a range of ages from 50 to 70 is presented in Table 4.1.1. FS screening at age 55 is associated with the greatest gain in QALYs; however, the QALY gains are very similar for screening ages of 52-58. The greatest reduction in CRC incidence and mortality is seen for screening at age 64.

Table 4.1.1: One-off FS screening at different ages – summary results

Summary health and resource outcomes

Screening Strategy	Reduction in CRC incidence (%)	Reduction in CRC mortality (%)	Reduction in CRC treatment costs (%)	Number of flexible sigmoidoscopies undertaken	Number of colonoscopies (screening)	Number of colonoscopies (surveillance)	Number of deaths due to perforation	Number needed to screen to prevent one case of CRC	Number needed to screen to save one life
No screening	0.0%	0.0%	0.0%	-	-	-	-		
FS age 50	6.9%	8.4%	7.3%	334,143	6,561	13,557	1.8	118	155
FS age 52	7.9%	9.6%	8.3%	331,899	7,506	15,507	2.0	103	136
FS age 54	8.8%	10.7%	9.3%	329,229	8,466	17,352	2.3	92	121
FS age 55	9.2%	11.2%	9.8%	327,681	8,948	18,226	2.4	87	115
FS age 56	9.6%	11.7%	10.2%	325,985	9,428	19,044	2.5	84	109
FS age 57	9.9%	12.1%	10.6%	324,158	9,903	19,853	2.6	80	105
FS age 58	10.2%	12.5%	11.0%	322,217	10,373	20,592	2.8	77	101
FS age 59	10.5%	12.9%	11.3%	320,094	10,833	21,233	2.9	75	97
FS age 60	10.7%	13.2%	11.6%	317,776	11,281	21,889	3.0	73	94
FS age 62	11.1%	13.6%	12.0%	312,566	12,132	22,774	3.1	70	90
FS age 64	11.2%	13.8%	12.2%	306,374	12,903	23,473	3.3	67	87
FS age 66	11.1%	13.8%	12.2%	299,051	13,570	23,571	3.4	67	85
FS age 68	10.7%	13.4%	11.9%	290,497	14,111	22,424	3.4	67	85
FS age 70	10.1%	12.7%	11.4%	280,429	14,494	21,598	3.4	68	86

*Model predictions correspond to a cohort of 618,900 50 year olds (the number in England in 2007)

Cost effectiveness: Discounted*

Screening strategy	Total cost per person	Total life years per person	Total QALYs per person	Incrementals compared to no screening			
				Cost per person	LYs saved	QALYs saved	Net Monetary Benefit (WTP=£20K)
No screening	£593	19.352	15.4075	-	-	-	-
FS age 50	£650	19.376	15.4276	£57	0.0236	0.0202	£346
FS age 52	£638	19.377	15.4285	£45	0.0246	0.0210	£376
FS age 54	£627	19.377	15.4289	£34	0.0250	0.0214	£394
FS age 55	£622	19.377	15.4289	£30	0.0251	0.0214	£399
FS age 56	£618	19.377	15.4288	£25	0.0250	0.0213	£401
FS age 57	£614	19.377	15.4285	£21	0.0247	0.0211	£400
FS age 58	£610	19.376	15.4282	£18	0.0243	0.0207	£396
FS age 59	£607	19.376	15.4277	£14	0.0237	0.0202	£390
FS age 60	£604	19.375	15.4271	£12	0.0231	0.0196	£381
FS age 62	£600	19.373	15.4256	£7	0.0214	0.0182	£357
FS age 64	£596	19.371	15.4239	£4	0.0194	0.0164	£325
FS age 66	£594	19.369	15.4220	£2	0.0171	0.0145	£288
FS age 68	£593	19.367	15.4199	£0	0.0147	0.0124	£248
FS age 70	£593	19.364	15.4178	£1	0.0123	0.0104	£207

*Costs and health benefits discounted at 3.5% per annum from age 50

4.2 Comparison of different screening options

Several screening options were considered involving gFOBT, iFOBT and FS and the results of 12 different screening strategies are presented in Table 4.2.1 and Figures 4.2.1-4.2.3.

The strategies of biennial screening with gFOBT or iFOBT were cost-saving when compared to “no screening”. A strategy of biennial screening with iFOBT dominates (i.e. is less costly and more effective than) biennial screening with gFOBT. However, it is also associated with approximately three times the number of colonoscopies.

The most cost effective strategy was FS at age 55 followed by biennial iFOBT screening for ages 56-74 irrespective of whether the comparator was the current screening programme of biennial gFOBT 60-74 or no screening. This strategy was associated with the greatest net monetary benefit and also

the greatest reduction in CRC incidence, CRC mortality and CRC treatment costs. This strategy was also associated with the greatest endoscopy requirements of all the screening strategies considered requiring six times as many screening colonoscopies as the current programme.

Table 4.2.1: Screening strategies involving FOBT and FS – summary results

Screening Strategy	Reduction in CRC incidence (%)	Reduction in CRC mortality (%)	Reduction in CRC treatment costs (%)	Number of flexible sigmoidoscopies undertaken	Number of colonoscopies (screening)	Number of colonoscopies (surveillance)	Number of deaths due to perforation	Number needed to screen to prevent one case of CRC	Number needed to screen to save one life
No screening	0.0%	0.0%	0.0%	-	-	-	-		
gFOBT at 60-69 (biennial)	6.5%	9.9%	8.0%	-	23,111	14,463	2.7	570	595
gFOBT at 60-74yrs (biennial)	9.2%	14.5%	11.6%	-	36,678	20,097	4.2	617	621
iFOBT at 60, 65, 70 yrs	9.8%	15.2%	12.1%	-	46,316	21,934	5.4	224	230
iFOBT at 60-69 (biennial)	14.4%	21.0%	17.2%	-	73,037	31,283	7.9	256	279
iFOBT at 60-74yrs (biennial)	19.3%	28.5%	23.4%	-	113,861	41,090	11.9	291	314
FS age 55	9.2%	11.2%	9.8%	327,681	8,948	18,226	2.4	87	115
FS age 55, 65	17.7%	21.5%	19.0%	630,012	19,064	35,895	5.0	88	114
FS age 55, gFOBT 66-74 (biennial)	14.0%	19.1%	16.1%	327,681	31,781	28,731	4.9	301	351
FS age 55, iFOBT 66-74 (biennial)	20.1%	28.1%	23.6%	327,681	81,201	41,593	10.0	208	237
FSIG age 55, iFOBT 60, 65,70	16.6%	22.4%	18.8%	327,681	52,263	34,680	6.9	180	213
FS age 55, iFOBT 60-74 (biennial)	24.7%	33.4%	28.4%	327,681	118,697	50,613	13.0	261	307
FS age 55, iFOBT 56-74 (biennial)	26.4%	35.4%	30.2%	327,681	140,444	53,904	14.5	303	359

Screening strategy	Total cost per person	Total life years per person	Total QALYs per person	Incrementals compared to no screening				Incrementals compared to gFOBT at 60-74yrs (biennial)			
				Cost per person	LYs saved	QALYs saved	Net Monetary Benefit (WTP=£20K)	Incremental cost per person	Incremental LYs saved	Incremental QALYs saved	Net Monetary Benefit (WTP=£20K)
No screening	£593	19.352	15.4075	-	-	-	-	£0	-	-	
gFOBT at 60-69 (biennial)	£566	19.367	15.4196	-£26	0.0150	0.0122	£270				
gFOBT at 60-74yrs (biennial)	£558	19.371	15.4229	-£35	0.0192	0.0154	£343	-	-	-	-
iFOBT at 60, 65, 70 yrs	£556	19.374	15.4254	-£37	0.0222	0.0179	£395	-£2	0.003	0.003	£52
iFOBT at 60-69 (biennial)	£541	19.384	15.4337	-£52	0.0323	0.0263	£577	-£17	0.013	0.011	£235
iFOBT at 60-74yrs (biennial)	£530	19.391	15.4391	-£63	0.0389	0.0316	£695	-£28	0.020	0.016	£352
FS age 55	£622	19.377	15.4289	£30	0.0251	0.0214	£399	£65	0.006	0.006	£57
FS age 55, 65	£638	19.391	15.4405	£45	0.0387	0.0330	£615	£80	0.020	0.018	£272
FS age 55, gFOBT 66-74 (biennial)	£606	19.385	15.4355	£13	0.0334	0.0280	£547	£48	0.014	0.013	£204
FS age 55, iFOBT 66-74 (biennial)	£590	19.395	15.4433	-£2	0.0431	0.0359	£720	£33	0.024	0.020	£377
FSIG age 55, iFOBT 60, 65,70	£599	19.393	15.4416	£6	0.0408	0.0342	£677	£41	0.022	0.019	£335
FS age 55, iFOBT 60-74 (biennial)	£581	19.406	15.4525	-£12	0.0540	0.0450	£912	£23	0.035	0.030	£569
FS age 55, iFOBT 56-74 (biennial)	£582	19.412	15.4573	-£11	0.0597	0.0498	£1,007	£25	0.041	0.034	£665

Figure 4.2.1: Cost effectiveness plane, discounted

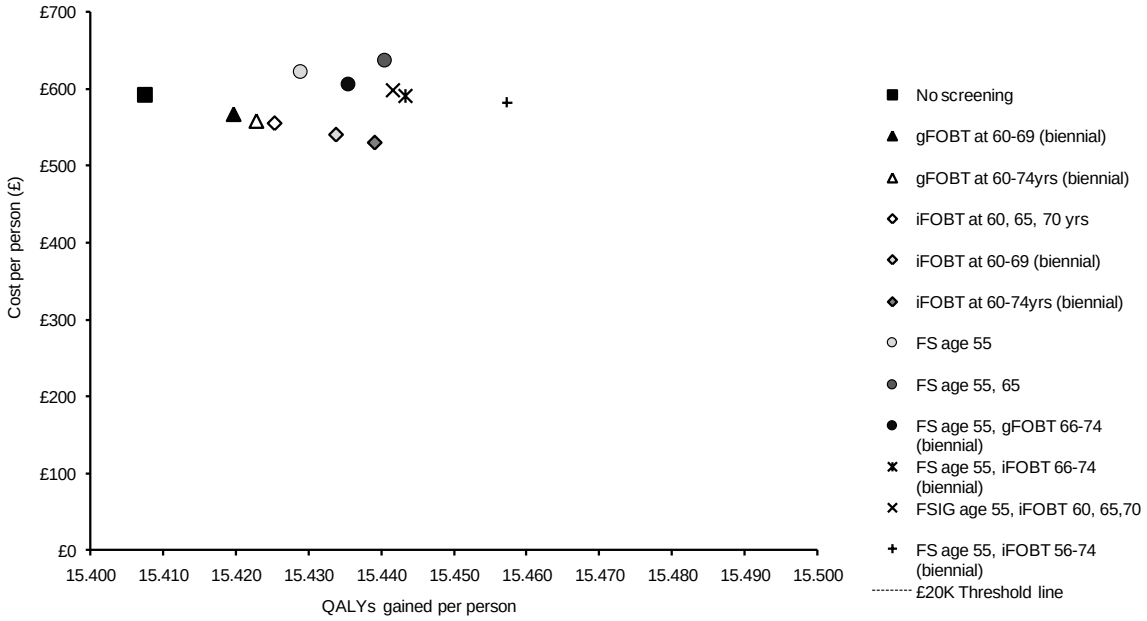


Figure 4.2.2: Incremental cost effectiveness plane (compared to no screening), discounted

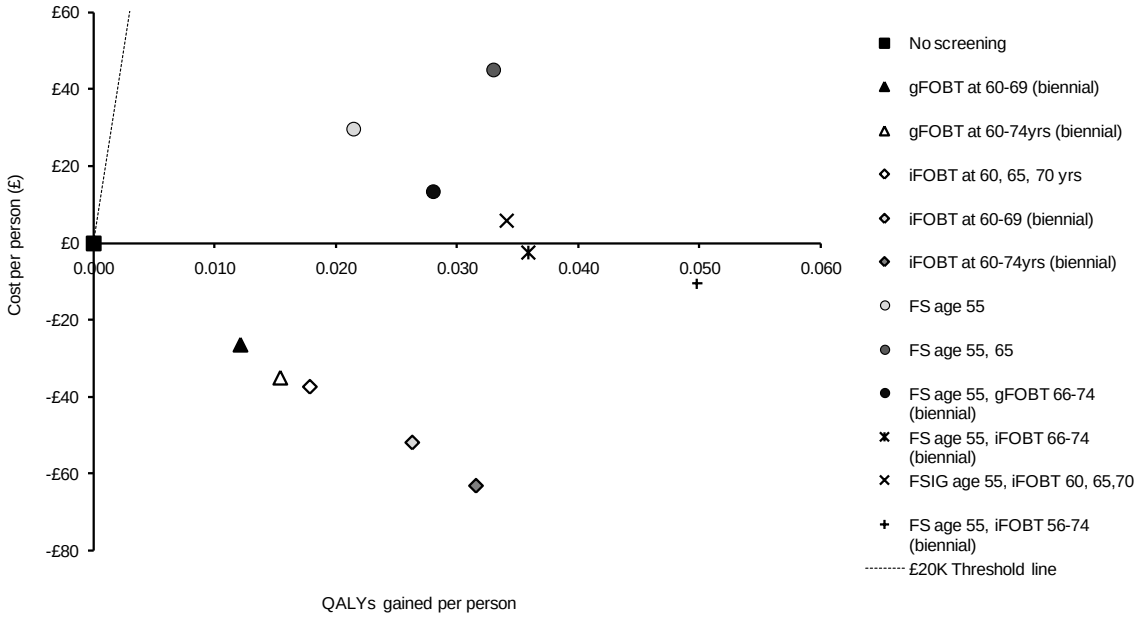
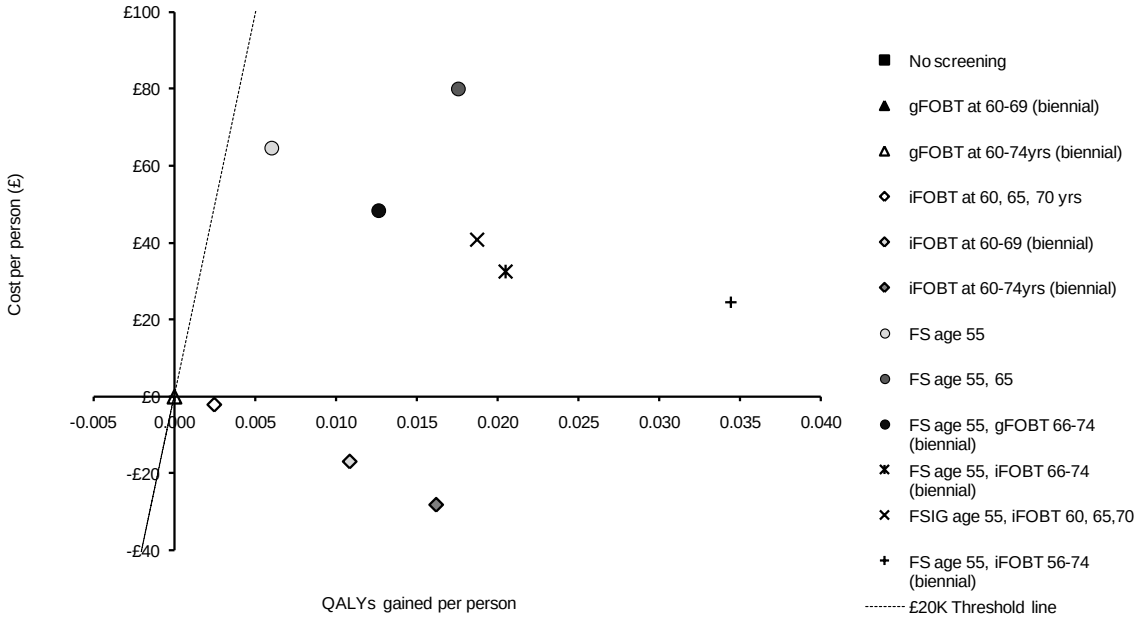


Figure 4.2.3: Incremental cost effectiveness plane (compared to biennial gFOBT 60-74), discounted



Economics of increasing screening awareness

An analysis was performed to evaluate the economics of spending to increase screening awareness, which can increase uptake. An increase in uptake from 54% to 70% results in an increase in incremental QALYs of 0.004 and a decrease in incremental costs of £8 for the strategy gFOBT 60-74 (biennial). Based on a willingness to pay threshold of £20,000, for an age cohort, it is cost effective to spend up to £88 per each person in the cohort (over the cohort's lifetime) on measures which will increase the uptake from 54% to 70%.

4.3 Sensitivity analysis

One-way sensitivity analyses

A series of one-way sensitivity analyses were undertaken to investigate the impact on the model results of varying individual model parameters. The parameters considered were those for which there was thought to be considerable uncertainty surrounding estimates. A description of the reasons for the selection is included within the relevant parts of the model parameters section of this report. The results of the one-way sensitivity analyses undertaken are presented in Table 4.3.1 including incremental compared to the current programme of 'gFOBT biennial 60-74'.

Several sensitivity analyses were performed in relation to the costs used within the model. There is considerable uncertainty surrounding the cost of endoscopy, so three different analyses were performed in relation to these costs. The analysis undertaken using high estimates for endoscopy costs resulted in slightly increased costs for FOBT but significantly increased costs for the screening strategies involving FS. For example, the ICER for one-off FS at age 55 compared to the current screening almost doubled from £11K to £20K.

An analysis was performed in which the cost of treating CRC was increased by 20% to reflect the possible costs associated with increased use of expensive chemotherapy regimens. This analysis resulted in an increase in total costs for all screening strategies. Under this analysis the strategy of

'FS age 55, iFOBT 56-74 biennial' is cost saving compared to the current screening strategy. The model results were not sensitive to changes to the pathology costs of +/- 20%.

Three sensitivity analyses were performed on uptake rates. For FOBT and FS screening, a lower uptake of 37% (with 50% of persons never attending) was considered to reflect the lowest quintile of the IMD deprivation. Secondly, an uptake of 70% (with 20% never attending) was considered to reflect higher uptake following increased promotion of the BCSP. A lower uptake results in lower screening costs (as the costs of a person not attending screening are low) and also a smaller gain in QALYs, but the effect on the ICER is not significant. The effect on the QALYs of a higher/lower uptake rate is significant. An uptake rate of 37% compared to 54% results in 0.004 fewer QALYs per person. It follows that a higher uptake rate will be associated with significantly higher reductions in both incidence and mortality.

Lastly, a sensitivity analysis was performed in which the uptake of FS was assumed to be 30%, to reflect the data from Italy which showed considerably lower uptake rates for FS compared to iFOBT. With this low uptake rate for FS, the QALY gains associated with one-off FS at age 55 are considerably less than those associated with the current strategy of gFOBT 60-74 biennial screening. However, even with this lower uptake rate for FS, the strategy of FS age 55 followed by biennial iFOBT 56-74 is the most cost effective.

Table 4.3.1: Results of one-way sensitivity analyses (incremental costs and QALYs are compared to a strategy of no screening)

	No screening		**gFOBT at 60-74yrs (biennial)**		**iFOBT at 60-74yrs (biennial)**				
One-way sensitivity analyses	Total per person (discounted) QALYs	Costs	Total per person (discounted) QALYs	Costs	Total per person (discounted) QALYs	Costs	Incr. compared to current QALYs	Costs	ICER
BASECASE	15.407	£593	15.423	£558	15.439	530	0.016	-£28	-£1,737
Low FOBT & FS uptake (37% each round, 50% never attend)	15.407	£593	15.418	£569	15.430	548	0.012	-£21	-£1,727
High FOBT & FS uptake (70% at each round, 20% never	15.407	£593	15.427	£547	15.448	512	0.021	-£36	-£1,737
Lower FS uptake (FS uptake 30%, FOBT uptake 54%)	15.407	£593	15.423	£558	15.439	530	0.016	-£28	-£1,737
High COL follow-up compliance (FOBT 90%, FS	15.407	£593	15.425	£553	15.442	524	0.017	-£29	-£1,729
Low COL follow-up compliance (FOBT 69%, FS 94%)	15.407	£593	15.421	£563	15.436	537	0.015	-£26	-£1,727
Life time costs treating CRC, +20%	15.407	£853	15.423	£783	15.439	721	0.016	-£62	-£3,841
Endoscopy costs - low values	15.407	£593	15.423	£552	15.439	514	0.016	-£38	-£2,361
Endoscopy costs - high values	15.407	£593	15.423	£566	15.439	552	0.016	-£14	-£863
Endoscopy costs - nurse led Derbyshire estimates	15.407	£593	15.423	£560	15.439	535	0.016	-£25	-£1,539
Pathology costs +20%	15.407	£593	15.423	£558	15.439	530	0.016	-£28	-£1,715
Pathology costs -20%	15.407	£593	15.423	£557	15.439	529	0.016	-£29	-£1,759

One-way sensitivity analyses	FS age 55					FS age 55, gFOBT 66-74 (biennial)					FS age 55, iFOBT 56-74 (biennial)				
	Total per person (discounted)		Incr. compared to current			Total per person (discounted)		Incr. compared to current			Total per person (discounted)		Incr. compared to current		
	QALYs	Costs	QALYs	Costs	ICER	QALYs	Costs	QALYs	Costs	ICER	QALYs	Costs	QALYs	Costs	ICER
BASECASE	15.429	622	0.006	£65	£10,659	15.435	606	0.013	£48	£3,824	15.457	582	0.034	£25	£712
Low FOBT & FS uptake (37% each round, 50% never attend)	15.422	613	0.004	£45	£11,342	15.427	602	0.009	£33	£3,838	15.444	582	0.026	£13	£521
High FOBT & FS uptake (70% at each round, 20% never attend)	15.435	631	0.008	£84	£10,522	15.444	610	0.016	£63	£3,821	15.471	581	0.044	£33	£756
Lower FS uptake (FS uptake 30%, FOBT uptake 54%)	15.419	610	-0.003	£53	-£15,165	15.427	592	0.004	£34	£9,130	15.453	556	0.031	-£2	-£67
High COL follow-up compliance (FOBT 90%, FS 98%)	15.429	621	0.005	£68	£14,223	15.437	603	0.012	£50	£4,100	15.460	578	0.035	£25	£703
Low COL follow-up compliance (FOBT 69%, FS 94%)	15.428	623	0.007	£61	£8,213	15.434	610	0.013	£47	£3,550	15.455	588	0.034	£25	£746
Life time costs treating CRC, +20%	15.429	851	0.006	£68	£11,195	15.435	816	0.013	£33	£2,631	15.457	751	0.034	-£32	-£924
Endoscopy costs - low values	15.429	578	0.006	£26	£4,231	15.435	559	0.013	£6	£505	15.457	520	0.034	-£32	-£940
Endoscopy costs - high values	15.429	685	0.006	£119	£19,674	15.435	673	0.013	£107	£8,479	15.457	670	0.034	£104	£3,027
Endoscopy costs - nurse led Derbyshire estimates	15.429	586	0.006	£27	£4,418	15.435	571	0.013	£11	£907	15.457	552	0.034	-£7	-£217
Pathology costs +20%	15.429	623	0.006	£65	£10,709	15.435	607	0.013	£49	£3,856	15.457	584	0.034	£25	£737
Pathology costs -20%	15.429	622	0.006	£64	£10,609	15.435	605	0.013	£48	£3,792	15.457	581	0.034	£24	£686

Probabilistic sensitivity analysis (PSA)

A probabilistic sensitivity analysis was undertaken in which parameter values are all simultaneously sampled from the distributions, reflecting their uncertainty. The parameter values varied in the PSA and the distributions used are described in Appendix 4. The correlated parameter sets generated by the Metropolis-Hasting calibration were used to reflect the uncertainty in the natural history parameters and screening test characteristics estimated in the calibration process. This approach correctly represents the joint uncertainty in these parameters, which is particularly important because of the potential for correlation between several of these parameters.

The results of the PSA are presented in a cost-effectiveness scatter plot and a cost-effectiveness acceptability curve; see Figures 4.3.1 and 4.3.2. At a willingness to pay of £10,000, “FS at age 55, biennial iFOBT 66-74” had a 75% chance of being the most cost effective strategy. At a willingness to pay threshold of £15,000 or above, the strategy of “FS at age 55, biennial iFOBT 56-74” had a 100% probability of being the most cost effective strategy.

Figure 4.3.1: PSA incremental cost-effectiveness plane scatter plot compared to no screening

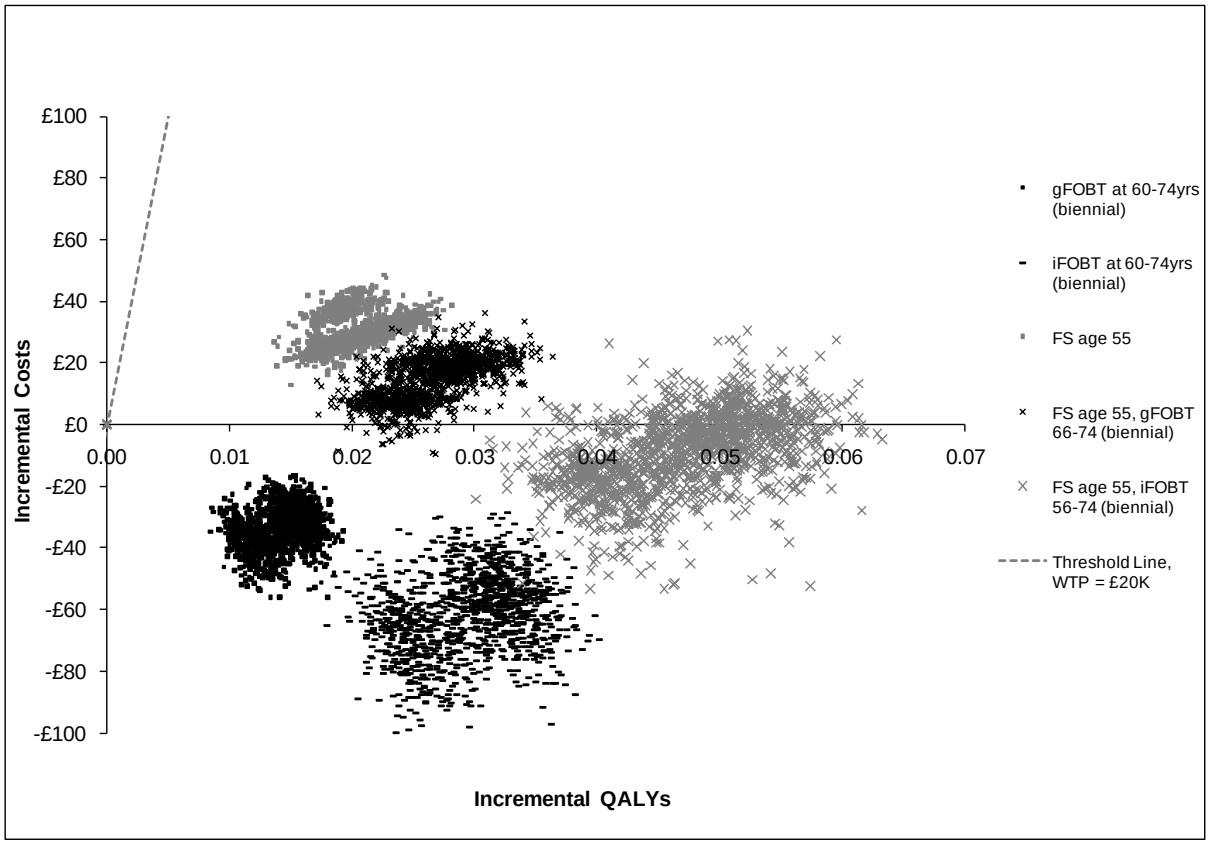
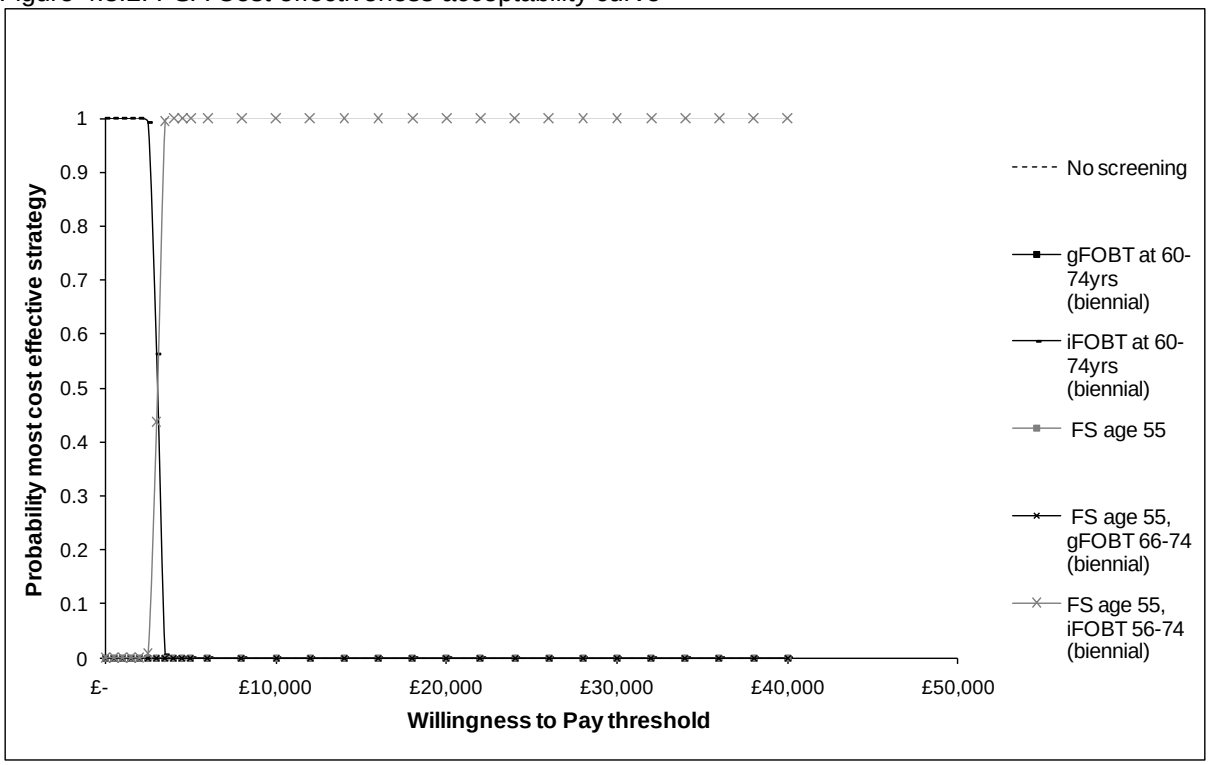


Figure 4.3.2: PSA Cost effectiveness acceptability curve



5 Conclusions

All screening strategies evaluated were cost-effective when compared to no screening using a willingness to pay threshold of £20K per QALY. The strategies of biennial screening with gFOBT or iFOBT were cost-saving when compared to “no screening”. A strategy of biennial screening with iFOBT dominates (i.e. is less costly and more effective than) biennial screening with gFOBT; however, it is also associated with approximately three times the number of colonoscopies. For a strategy of one-off FS screening, the optimal effectiveness (QALYS) is achieved with a one-off FS screen at age in the range 55-60.

The most cost effective strategy was FS at age 55 followed by biennial iFOBT screening for ages 56-74, irrespective of whether the comparator was the current screening programme of biennial gFOBT 60-74 or no screening. This strategy was associated with the greatest net monetary benefit and also the greatest reduction in CRC incidence, CRC mortality and CRC treatment costs.

Sensitivity analyses demonstrated that the results were highly sensitive to several model parameters such as uptake and endoscopy costs. However, in all of these analyses the most cost-effective screening strategy remained unchanged.

The probabilistic sensitivity analysis examined uncertainty surrounding expected costs and QALYs. At a willingness to pay threshold of £4,000 or above, the strategy of “FS at age 55, biennial iFOBT 56-74” had a 100% probability of being the most cost-effective strategy.

The analysis demonstrated that it may be cost-effective to spend considerable resources on increasing screening awareness.

Areas of uncertainty

The definitions used to classify persons with adenomas varied between the English screening data (FS and gFOBT) which classify persons as low/intermediate/high risk according to BSG guidelines and the German colonoscopy study which reported numbers of persons with advanced adenomas. In order to include both data sources within the modelling, an adjustment had to be made to estimate the proportion of advanced adenomas which would be classified as high risk. This adjustment was crude as it was based on a small dataset, so it introduces uncertainty into the modelling.

The model predictions fit the data from the first round of gFOBT screening and the FS trial data very well. The model predicts a small decrease in HR adenoma detection rates at the second gFOBT screen; however, the data from the second screen showed a much higher decrease in HR adenoma detection rates. The second screen data was associated with a much higher false positive rate than seen at the first screen; however, the model predicts that the false positive rates will not vary significantly between the first and second screen.

The difference between the gFOBT second screen data and the model predictions suggests that either: (1) the second screen data is in some way biased, or (2) gFOBT sensitivity and specificity vary by first/repeat screen which is not represented by our model structure. Possible sources of bias affecting the gFOBT first/second screen data are not well understood. Lower detection rates and higher false positive rates at a second/repeat screen would result in a strategy of repeated gFOBT being significantly less effective than is predicted by this model. This issue results in significant uncertainty surrounding the efficacy of the use of gFOBT for repeated screens.

Data on transition rates post-polypectomy was very limited, hence there is considerable uncertainty surrounding the modelling of surveillance. The model predictions for screening effectiveness were shown to be highly sensitive to this data. When detailed data on the outcomes at surveillance in the English gFOBT screening programme becomes available, this can be used to improve the accuracy of this area of the modelling.

There is considerable uncertainty surrounding the comparative sensitivity of the screening tests in the distal and proximal colon. Due to data limitations, accurate modelling of the differing sensitivity between the proximal and distal colon was not possible.

This analysis combined data from three different countries (England, Germany and Italy). Differences in adenoma and CRC prevalence between England, Germany and Italy may exist; however, the extent of these differences is unknown. The value of using data from more than one country is that it allows the use of large datasets from several different screening modalities. The benefit of including data on different screening modalities was considered to outweigh the uncertainty introduced by using datasets from different countries.

6 Discussion/future priorities

Cancer screening is an area where mathematical modelling is of great use. If data from several countries is considered, this provides large datasets for different screening modalities. As demonstrated here, modelling allows data from screening programmes of three different modalities to be used to produce predictions for a large range of screening options including various age ranges, screening intervals and screening strategies which combine more than one modality.

This analysis was limited not by the need to run further screening trials, but by the availability of data from existing screening programmes. Collecting and reporting detailed, complete and comprehensive observational data from existing screening programmes should be a high priority for the future.

Summary of currently available screening programme reporting:

- The Italian screening programme produces an annual survey “Screening for colorectal cancer in Italy” 2004-2008.(42) Positivity and CRC/adenoma detection rates are reported by age and gender. Data is grouped into five-year age bands, and proximal and distal findings are not reported separately.
- England produced a report of the first and second rounds of the Bowel cancer screening pilot but no report on rollout of entire screening programme.(7) Data on advanced adenomas/tubulovillous adenomas has been collected but is not available. Data on finds at surveillance is not yet available separated according to the patient’s classified risk level following screening.
- Brenner has produced several interesting papers which provide insight into the natural history of CRC using the results of survey of screening colonoscopies in Germany. (15, 18) No paper has been identified that reports a complete summary of screening findings for the German programme.
- Scotland produces a report of key performance indicators. (54)

Reporting and availability of complete information from existing screening programmes is essential to enable accurate modelling and to increase the understanding of the natural history of CRC. Information of use includes linked data on patient characteristics (age, sex, racial background, socioeconomic status), number of screens attended, screening and surveillance outcomes: attendance, adenomas detected (location, size, number, type, advanced/non-advanced), CRC

detected (stage and location). The sharing of such complete information may require a departure from the traditional constraints of presenting results in small two-dimensional tables in journal articles.

7 Appendices

7.1 Appendix 1: Adenoma prevalence by age in an average risk population: A systematic review of adenoma detection rates from colonoscopy screening and autopsy studies – available in separate file.

7.2 Appendix 2: Calibration method and results

Figures A2.1 and A2.2 illustrate the calibration method used. A full description of the calibration method is included in the paper by Whyte et al. (13)

Figure A2.1: CRC model calibration method

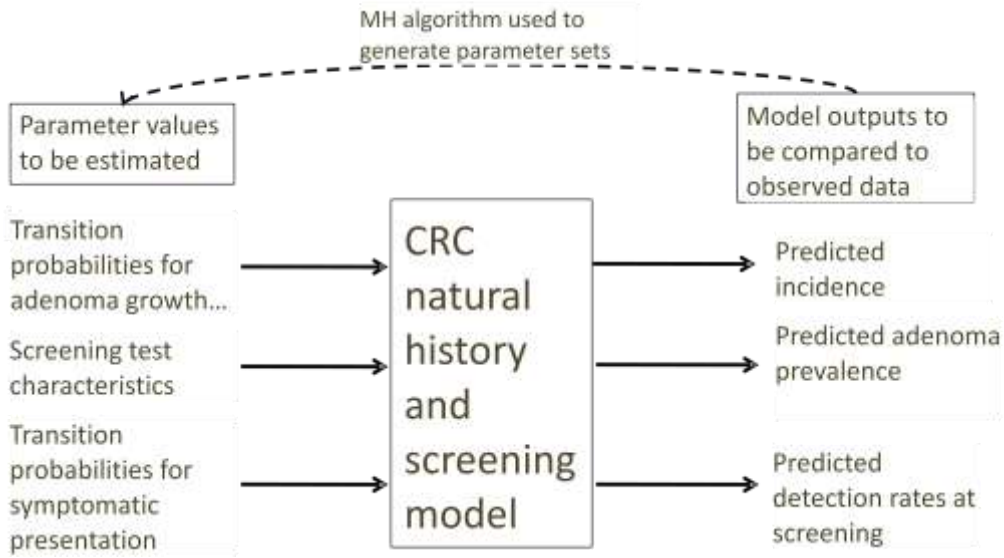


Figure A2.2: Metropolis-Hastings algorithm illustrated for a 2-dimensional parameter space
The aim is to find values for the two parameters which minimise the difference between the model predictions and the observed data; this is the lowest point region on the surface.

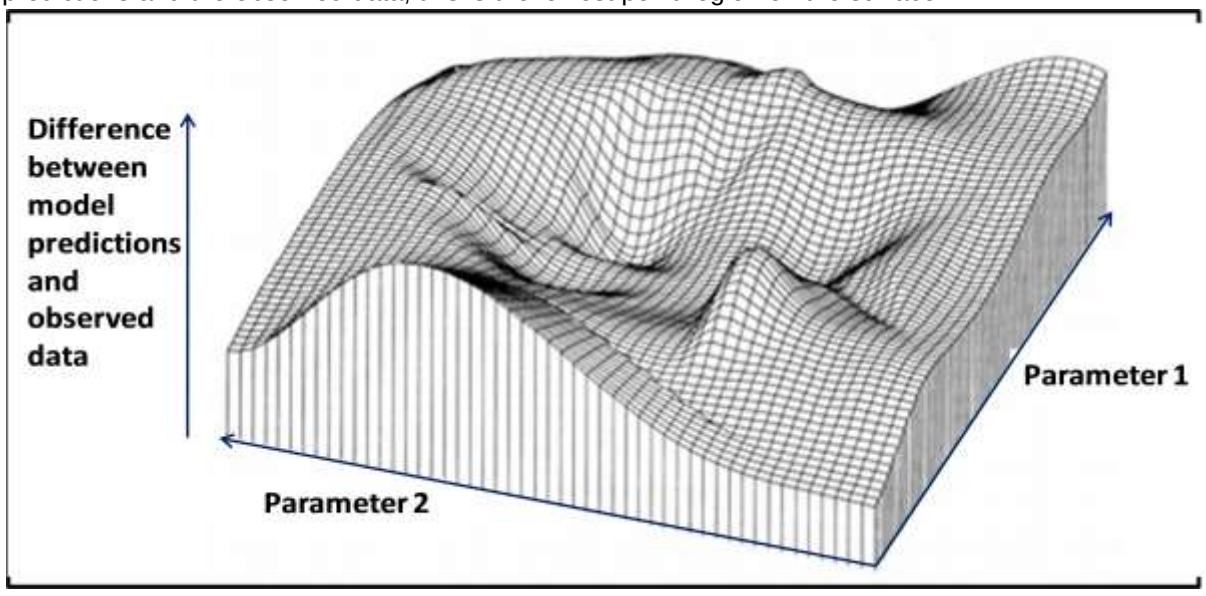


Figure A2.3 Correlation matrix for parameters estimated within model calibration process

	Normal epithelium to LR adenomas - age 30	Normal epithelium to LR adenomas - age 50	Normal epithelium to LR adenomas - age 70	Normal epithelium to LR adenomas - age 100	LR adenomas to high risk adenomas - age 30	LR adenomas to high risk adenomas - age 50	LR adenomas to high risk adenomas - age 70	LR adenomas to HR adenomas - age 100	HR adenomas to Dukes A CRC - age 30	HR adenomas to Dukes A CRC - age 50	HR adenomas to Dukes A CRC - age 70	HR adenomas to Dukes A CRC - age 100	Normal epithelium to CRC Dukes A	Preclinical CRC: Dukes A to Dukes B	Preclinical CRC: Dukes B to Dukes' C	Preclinical CRC: Dukes C to Stage D	Symptomatic presention with CRC Dukes A	Symptomatic presention with CRC Dukes B	Symptomatic presention with CRC Dukes C	Symptomatic presention with CRC Dukes D	gFOBT Sensitivity for LR adenomas	gFOBT Sensitivity for HR adenomas	gFOBT Sensitivity for CRC	gFOBT Specificity age 50	gFOBT Specificity age 70	FS Sensitivity for LR adenomas	FS Sensitivity for HR adenomas	FS Sensitivity for CRC	iFOBT Sensitivity for LR adenomas	iFOBT Sensitivity for HR adenomas	iFOBT Sensitivity for CRC	iFOBT Specificity age 50	iFOBT Specificity age 70
Normal epithelium to LR adenomas - age 30	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Normal epithelium to LR adenomas - age 50	-0.86	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Normal epithelium to LR adenomas - age 70	0.16	-0.48	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Normal epithelium to LR adenomas - age 100	0.02	-0.16	0.19	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LR adenomas to high risk adenomas - age 30	-0.11	0.33	-0.86	0.16	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LR adenomas to high risk adenomas - age 50	-0.02	-0.26	0.91	-0.11	-0.97	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LR adenomas to high risk adenomas - age 70	0.20	0.08	-0.82	-0.01	0.90	-0.93	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LR adenomas to HR adenomas - age 100	0.35	-0.04	-0.69	-0.14	0.75	-0.78	0.91	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HR adenomas to Dukes A CRC - age 30	0.08	-0.30	0.87	-0.27	-0.90	0.94	-0.80	-0.58	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HR adenomas to Dukes A CRC - age 50	0.40	-0.57	0.73	-0.09	-0.59	0.63	-0.34	-0.15	0.75	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HR adenomas to Dukes A CRC - age 70	0.66	-0.55	0.04	0.10	0.24	-0.24	0.51	0.66	-0.02	0.50	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HR adenomas to Dukes A CRC - age 100	0.13	-0.40	0.93	-0.14	-0.95	0.97	-0.87	-0.70	0.96	0.71	-0.08	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Normal epithelium to CRC Dukes A	-0.07	0.25	-0.67	0.25	0.60	-0.70	0.53	0.33	-0.82	-0.76	-0.13	-0.73	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Preclinical CRC: Dukes A to Dukes B	0.47	-0.18	-0.55	-0.32	0.58	-0.63	0.84	0.92	-0.40	0.06	0.74	-0.51	0.19	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Preclinical CRC: Dukes B to Dukes' C	0.14	-0.44	0.99	0.10	-0.88	0.93	-0.83	-0.68	0.92	0.75	0.02	0.96	-0.72	-0.54	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Preclinical CRC: Dukes C to Stage D	0.08	-0.38	0.97	0.12	-0.86	0.93	-0.82	-0.67	0.90	0.74	0.00	0.93	-0.71	-0.55	0.98	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptomatic presention with CRC Dukes A	0.38	-0.06	-0.67	-0.37	0.65	-0.70	0.87	0.92	-0.49	-0.09	0.62	-0.60	0.28	0.98	-0.65	-0.67	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptomatic presention with CRC Dukes B	-0.24	-0.09	0.83	0.06	-0.87	0.92	-0.98	-0.93	0.80	0.37	-0.49	0.86	-0.56	-0.86	0.85	0.85	-0.90	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptomatic presention with CRC Dukes C	-0.63	0.43	0.24	0.01	-0.45	0.47	-0.72	-0.83	0.25	-0.30	-0.94	0.32	-0.05	-0.90	0.26	0.28	-0.82	0.72	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptomatic presention with CRC Dukes D	-0.69	0.64	-0.26	-0.05	-0.01	0.00	-0.31	-0.49	-0.21	-0.68	-0.96	-0.15	0.30	-0.63	-0.24	-0.23	-0.49	0.29	0.87	1.00	-	-	-	-	-	-	-	-	-	-	-	-
gFOBT Sensitivity for LR adenomas	-0.18	0.42	-0.94	-0.11	0.84	-0.88	0.81	0.64	-0.86	-0.67	-0.01	-0.90	0.68	0.53	-0.93	-0.90	0.63	-0.80	-0.25	0.21	1.00	-	-	-	-	-	-	-	-	-	-	-
gFOBT Sensitivity for HR adenomas	0.16	-0.12	-0.13	0.06	0.14	-0.21	0.20	0.19	-0.18	-0.01	0.18	-0.17	0.18	0.17	-0.13	-0.14	0.16	-0.20	-0.17	-0.11	0.13	1.00	-	-	-	-	-	-	-	-	-	-
gFOBT Sensitivity for CRC	-0.49	0.51	-0.24	-0.48	-0.13	0.09	-0.22	-0.31	0.01	-0.38	-0.72	-0.01	0.08	-0.28	-0.19	-0.19	-0.15	0.19	0.59	0.69	0.20	-0.14	1.00	-	-	-	-	-	-	-	-	-
gFOBT Specificity age 50	0.36	-0.49	0.74	-0.24	-0.69	0.72	-0.49	-0.23	0.85	0.85	0.35	0.79	-0.77	-0.05	0.78	0.78	-0.17	0.48	-0.13	-0.53	-0.75	-0.07	-0.25	1.00	-	-	-	-	-	-	-	-
gFOBT Specificity age 70	-0.19	0.41	-0.93	0.05	0.86	-0.90	0.75	0.54	-0.95	-0.80	-0.13	-0.93	0.77	0.38	-0.94	-0.94	0.49	-0.75	-0.14	0.35	0.90	0.13	0.18	-0.90	1.00	-	-	-	-	-	-	-
FS Sensitivity for LR adenomas	-0.26	0.44	-0.69	-0.24	0.63	-0.61	0.61	0.55	-0.54	-0.44	0.07	-0.65	0.36	0.48	-0.68	-0.67	0.56	-0.60	-0.25	0.09	0.64	-0.00	0.16	-0.47	0.59	1.00	-	-	-	-	-	-
FS Sensitivity for HR adenomas	0.10	0.07	-0.62	0.15	0.62	-0.68	0.63	0.50	-0.73	-0.44	0.15	-0.67	0.62	0.43	-0.68	-0.68	0.48	-0.67	-0.34	0.01	0.61	0.20	-0.06	-0.52	0.65	0.42	1.00	-	-	-	-	-
FS Sensitivity for CRC	0.27	-0.02	-0.45	-0.05	0.56	-0.57	0.68	0.69	-0.42	0.01	0.56	-0.49	0.20	0.72	-0.47	-0.44	0.71	-0.71	-0.68	-0.46	0.39	0.18	-0.26	-0.07	0.31	0.39	0.52	1.00	-	-	-	-
iFOBT Sensitivity for LR adenomas	-0.20	0.29	-0.46	-0.05	0.44	-0.42	0.32	0.22	-0.41	-0.42	-0.14	-0.44	0.24	0.12	-0.44	-0.44	0.19	-0.30	0.03	0.26	0.43	0.13	0.14	-0.39	0.44	0.36	0.24	0.18	1.00	-	-	-
iFOBT Sensitivity for HR adenomas	0.15	-0.16	0.04	-0.36	-0.19	0.11	-0.00	0.11	0.16	0.21	0.12	0.13	-0.07	0.19	0.06	0.04	0.17	-0.03	-0.13	-0.15	-0.02	0.09	0.03	0.06	-0.03	0.11	-0.06	-0.08	-0.10	1.00	-	-
iFOBT Sensitivity for CRC	-0.52	0.51	-0.24	-0.57	-0.17	0.12	-0.28	-0.34	0.02	-0.42	-0.80	0.02	0.07	-0.34	-0.18	-0.20	-0.21	0.23	0.67	0.78	0.18	-0.13	0.80	-0.30	0.23	0.16	-0.07	-0.39	0.15	0.21	1.00	-
iFOBT Specificity age 50	0.07	-0.10	0.21	-0.00	-0.15	0.15	-0.13	-0.04	0.20	0.26	0.13	0.19	-0.19	-0.00	0.21	0.22	-0.03	0.12	-0.05	-0.17	-0.20	0.15	-0.07	0.18	-0.20	-0.10	-0.06	0.18	-0.05	0.17	-0.13	1.00
iFOBT Specificity age 70	-0.07	0.14	-0.47	0.04	0.40	-0.42	0.35	0.21	-0.48	-0.43	-0.11	-0.45	0.38	0.12	-0.48	-0.49	0.18	-0.34	-0.01	0.24	0.46	0.03	0.06	-0.37	0.46	0.23	0.35	-0.03	0.25	-0.21	0.15	-0.65

* Pairs of parameters with correlation of magnitude greater than 0.8 are shaded in grey

7.3 Appendix 3 Systematic review and Bayesian meta-analysis of the sensitivity and specificity of immunochemical FOBT

A systematic review and meta-analysis was undertaken to obtain estimates for the test characteristics of immunochemical faecal occult blood tests (iFOBT). More specifically, this assessment updates and extends the systematic review conducted by Burch et al.,(39) which included studies up to November 2004. As the iFOBT Evaulation Report produced by the Centre for Evidence-based Purchasing concluded that the OC-Sensor / DIANA analyser was the most suitable system for the English BCSP, the review was limited to the OC-Sensor test. Full details of the search strategy and studies found are provided in the separate appendix file.

Summary of results from individual studies

Sensitivity and specificity of iFOBT for the detection of all neoplasms ranged from 5.4%(55) to 19.8%(56) and 91.6%(57) to 98.5%(55) respectively, when data was derived from cohort studies. Case-control studies generally reported higher sensitivities, ranging from 38.9%(58) to 68.9%(59) and specificity ranging from 93.9%(60) to 98.3%.(61) A higher sensitivity for the detection of CRC was observed ranging from 23.7%(62) to 91.0%(63) and specificity ranged from 77.1%(64) to 98.9%.(65) For all adenomas, the sensitivity ranged from 4.4%(55) to 91.0%(66) and specificity ranged from 42.8%(66) to 98.5%.(55) Only one study(67) reported sensitivity and specificity values for adenomas of 1cm or larger. Twelve studies did not report the haemoglobin threshold; however, the five studies which did report the haemoglobin threshold ranged from 30 ng/ml to 200 ng/ml.(64) A study by Chen(64) assessed the optimal cut-off of iFOBT by using cost-effectiveness analysis and concluded that 110 ng/ml as the optimal cut-off of iFOBT for CRC screening.

Bayesian meta-analysis of the sensitivity and specificity of immunochemical FOBT (iFOBT)

The data for all neoplasms, colorectal cancer and adenomas were analysed separately using a Bayesian bivariate random effects model based on the model presented by Reitsma et al.(68) The advantage of the Bayesian approach compared to the Classical approach is that it allows for uncertainty in the between-study standard deviation. The model allows for correlation between sensitivity and specificity on the logit scale. Posterior results are presented for sensitivity, specificity in Table A3.1. Summary statistics are presented from the joint posterior distribution including: mean, SD, median, 2.5%-ile and 95%-ile.

Samples from the joint posterior distribution were used within the probabilistic sensitivity analysis of the decision analytic model to preserve the properties of the joint posterior distribution.

Table A3.1: Posterior Results of Bayesian meta-analysis of the sensitivity and specificity of iFOBT

Parameter	Mean (SD)	2.5%-ile, median, 97.5%-ile
Sensitivity (adenomas)	0.27 (0.204)	0, 0.23, 0.75
Sensitivity (CRC)	0.59 (0.219)	0.061, 0.64, 0.9
Specificity (CRC and adenomas)	0.95 (0.013)	0.92, 0.95, 0.97

7.4 Appendix 4: Table of model inputs

Parameter name	Mean	Distribution used in PSA and 95% CI	Source
Test Characteristics			
gFOBT Sensitivity for LR adenomas	0.01	Correlated parameter set from calibration	Model calibration
gFOBT Sensitivity for CRC	0.24	Correlated parameter set from calibration	Model calibration
gFOBT Specificity age 50	0.994	Correlated parameter set from calibration	Model calibration
gFOBT Specificity age 70	0.973	Correlated parameter set from calibration	Model calibration
FS Sensitivity for LR adenomas	0.22	Correlated parameter set from calibration	Model calibration
FS Sensitivity for HR adenomas	0.71	Correlated parameter set from calibration	Model calibration
FS Sensitivity for CRC	0.62	Correlated parameter set from calibration	Model calibration
FS Specificity	1.00	N/A	Assumption due to nature of the test
iFOBT Sensitivity for LR adenomas	0.05	Correlated parameter set from calibration	Model calibration
iFOBT Sensitivity for CRC	0.629	Correlated parameter set from calibration	Model calibration
iFOBT Specificity age 50	0.975	Correlated parameter set from calibration	Model calibration
iFOBT Specificity age 70	0.93	Correlated parameter set from calibration	Model calibration
COL Sensitivity for LR adenomas	0.77	Beta(544,167) (0.73-0.80)	Van Rijn et al 2006
COL Sensitivity for HR adenomas	0.98	Beta(94,2) (0.94-1.00)	Van Rijn et al 2006
COL Sensitivity for CRC	0.98	Beta(94,2) (0.94-1.00)	Bressler et al 2007
COL Specificity	1.00	N/A	Assumption due to nature of the test
Harm/complications parameters			
COL (without polypectomy) perforation rate	-		
COL (with polypectomy) perforation rate	0.3%	Beta(4,1,427) (0.00-0.01)	Bowel cancer screening pilot 2nd round evaluation, Table 5.2
COL Probability of death following perforation	5.2%	Beta(4,73) (0.01-0.11)	Gatto et al 2003
FS (without polypectomy) perforation rate	-		
FS (with polypectomy) perforation rate	0.01%	Beta(1,9,498) (0.00-0.00)	FS UK screening trial data, Atkin et al 2002
FS Probability of death following perforation	6.5%	Beta(2,29) (0.01-0.17)	Gatto et al 2003
FS probability of hospitalisation for bleeding	0.03%	Beta(12,40,609) (0.00-0.00)	FS UK screening trial data, Atkin et al 2002
COL probability of hospitalisation for bleeding	0.3%	Beta(7,2,040) (0.00-0.01)	FS UK screening trial data, Atkin et al 2002
Repeat rates			
gFOBT mean number of tests completed	1.08	N/A	Asumption based on number of gFOBTs returned within 7 days
iFOBT mean number of tests completed	1.01	N/A	NHS BCSP data, Italian iFOBT screening programme Zorzi et al 2009
FS Probability test repeated on a later day	0.02	Beta(839,39,782) (0.02-0.02)	FS UK screening trial data, Atkin et al 2002
COL repeat test rate	0.07	Beta(5,453,72,858) (0.07-0.07)	NHS BCSP data
Screening participation parameters			
FOBT participation for each screening round	0.54	Beta(1,080,920) (0.52-0.56)	NHS BCSP data
Proportion completing at least one FOBT screening round	0.63	Beta(63,37) (0.53-0.72)	NHS BCSP data
FOBT participation for a round for those who comply with at least one FOBT test	0.85	N/A	NHS BCSP data
COL follow-up compliance FOBT screening	0.79	Beta(46,288,12,242) (0.79-0.79)	NHS BCSP data
COL follow-up compliance FS screening	0.96	Beta(2,047,79) (0.95-0.97)	FS UK screening trial data, Atkin et al 2002
COL surveilance compliance	0.83	N/A	NHS BCSP data
FS screening compliance	0.54	N/A	Assumed same as for FOBT, Atkin et al 2010
Health-related quality of life parameters			
Utility value cancer free	0.80	Beta(279,71) (0.75-0.84)	Ara et al 2010
Utility value CRC	0.70	Beta(361,157) (0.66-0.74)	Ara et al 2010

Parameter name	Mean	Distribution used in PSA and 95% CI	Source
Resource Use parameters			
Cost of gFOBT screen (non-compliers)	£ 2.03	Uniform(2,2)	Southern hub screening costings model
Cost of gFOBT screen (normal result)	£ 3.36	Uniform(3,4)	Southern hub screening costings model
Cost of gFOBT screen (positive result)	£ 11.94	Uniform(11,13)	Southern hub screening costings model
Cost of iFOBT screen (non-compliers)	£ 6.43	Uniform(6,7)	Southern hub screening costings model
Cost of iFOBT screen (normal result)	£ 7.37	Uniform(7,8)	Southern hub screening costings model
Cost of iFOBT screen (positive result)	£ 16.20	Uniform(15,18)	Southern hub screening costings model
Cost of FS screen excl. FS exam (non-compliers)	£ 5.02	Uniform(5,6)	Southern hub screening costings model
Cost of FS screen excl. FS exam (not referred to COL)	£ 6.01	Uniform(5,7)	Southern hub screening costings model
Cost of FS screen excl. FS exam (referred to COL)	£ 14.84	Uniform(13,16)	Southern hub screening costings model
Cost of FS (without polypectomy)	£ 186	Uniform(167,205)	Southern hub screening costings model, NHS reference costs and screening centre estimates
Cost of FS (with polypectomy)	£ 195	Uniform(176,215)	Southern hub screening costings model, NHS reference costs and screening centre estimates
Cost of COL (without polypectomy)	£ 205	Uniform(185,226)	NHS reference costs and screening centre estimates
Cost of COL (with polypectomy)	£ 237	Uniform(213,261)	NHS reference costs and screening centre estimates
Cost of treating bowel perforation (major surgery)	£ 2,164	Gamma(117,18) (1,790-2,573)	NHS reference costs
Cost of admittance for bleeding (overnight stay on medical ward)	£ 278	Gamma(193,1) (240-319)	NHS reference costs
Pathology cost for adenoma	£ 26	Gamma(81,0) (21-33)	NHS reference costs 08/09, histopathology
Pathology cost for cancer	£ 26	Gamma(81,0) (21-33)	NHS reference costs 08/09, histopathology
Lifetime cost - screen-detected Dukes' A	£ 12,455	Gamma(100,125) (10,134-15,012)	Pilgrim et al 2008
Lifetime cost - screen-detected Dukes' B	£ 17,137	Gamma(100,171) (13,943-20,655)	Pilgrim et al 2008
Lifetime cost - screen-detected Dukes' C	£ 23,502	Gamma(100,235) (19,122-28,327)	Pilgrim et al 2008
Lifetime cost - screen-detected Stage D	£ 25,703	Gamma(100,257) (20,913-30,980)	Pilgrim et al 2008

Parameter name	Mean	Distribution used in PSA and 95% CI	Source
Natural history parameters			
Normal epithelium to LR adenomas - age 30	0.021	Correlated parameter set from calibration	Model calibration
LR adenomas to high risk adenomas - age 30	0.009	Correlated parameter set from calibration	Model calibration
LR adenomas to high risk adenomas - age 50	0.008	Correlated parameter set from calibration	Model calibration
LR adenomas to high risk adenomas - age 70	0.008	Correlated parameter set from calibration	Model calibration
LR adenomas to HR adenomas - age 100	0.004	Correlated parameter set from calibration	Model calibration
HR adenomas to Dukes A CRC - age 30	0.029	Correlated parameter set from calibration	Model calibration
HR adenomas to Dukes A CRC - age 50	0.025	Correlated parameter set from calibration	Model calibration
HR adenomas to Dukes A CRC - age 70	0.054	Correlated parameter set from calibration	Model calibration
HR adenomas to Dukes A CRC - age 100	0.115	Correlated parameter set from calibration	Model calibration
Normal epithelium to CRC Dukes A	0.000	Correlated parameter set from calibration	Model calibration
Preclinical CRC: Dukes A to Dukes B	0.508	Correlated parameter set from calibration	Model calibration
Preclinical CRC: Dukes B to Dukes' C	0.692	Correlated parameter set from calibration	Model calibration
Preclinical CRC: Dukes C to Stage D	0.708	Correlated parameter set from calibration	Model calibration
Symptomatic presention with CRC Dukes A	0.044	Correlated parameter set from calibration	Model calibration
Symptomatic presention with CRC Dukes B	0.176	Correlated parameter set from calibration	Model calibration
Symptomatic presention with CRC Dukes C	0.369	Correlated parameter set from calibration	Model calibration
Symptomatic presention with CRC Dukes D	0.735	Correlated parameter set from calibration	Model calibration
Proportion of cancer incidence classified as proximal	0.380	N/A	Cancer Registrations 2007, England
Average number of adenomas present in patient with at least one adenoma	1.900	N/A	Winawer et al 1993
Proportion of HR pp requiring annual surveillence	0.290	N/A	NHS BCSP data
LR polypectomy, tran prob LR	0.100	N/A	English BCSP, Martinez et al 2009
LR polypectomy, tran prob HR	0.040	N/A	English BCSP, Martinez et al 2009
IR polypectomy, tran prob LR	0.163	N/A	English BCSP, Martinez et al 2009
IR polypectomy, tran prob HR	0.091	N/A	English BCSP, Martinez et al 2009
HR polypectomy, tran prob LR	0.188	N/A	English BCSP, Martinez et al 2009
HR polypectomy, tran prob HR	0.568	N/A	English BCSP, Martinez et al 2009

FS= flexible sigmoidoscopy, COL=colonoscopy, FOBT=faecal occult blood test, LR=low risk, HR=high risk

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