Original article

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Reappraisal of the options for colorectal cancer screening in England

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Abstract

Aim The aim was to use newly available data to estimate the cost effectiveness and endoscopy requirements of screening options for colorectal cancer (CRC) to inform screening policy in England.

Methods A state transition model simulated the life experience of a cohort of individuals in the general population of England with normal colon/rectal epithelium through to the development of adenomas and CRC and subsequent death. CRC natural history model parameters and screening test characteristics were estimated simultaneously by a process of model calibration. This process was fitted to observed data on CRC incidence in the absence of screening, data from existing screening programmes, and data from the UK flexible sigmoidoscopy (FS) screening trial. The costs, effects and resource impact were evaluated for a range of screening options involving the guaiac or immunochemical faecal occult blood test (gFOBT/iFOBT) and FS.

Results The model suggests that screening strategies involving FS or iFOBT may produce additional benefits compared with the current policy of biennial gFOBT for 60–74-year-olds. The age at which a single FS screen results in the greatest quality-adjusted life year gain was 55, with similar gains for ages between 52 and 58. Strategies which combined FS and iFOBT showed further benefits and improved economic outcomes.

Conclusions Strategies which combine different screening modalities may provide greater clinical and economic benefits. The collection of comprehensive screening data using a uniform format will enable comparative analysis across screening programmes in different countries, will improve our understanding of the disease and will allow identification of optimal screening modalities.

Keywords Colorectal cancer, screening, economic model, faecal occult blood test, flexible sigmoidoscopy

What is new in this paper?

The optimal age for the greatest quality-adjusted life year gain using a one-off flexible sigmoidoscopy screen is age 55. Combining flexible sigmoidoscopy with the immunochemical faecal occult blood test increases clinical and economic benefits over the use of a single screening modality. A better understanding of the natural history of colorectal cancer is achieved with estimates of disease onset and progression parameters derived from recent large data sets from screening programmes in England, Italy and Germany, using a calibration method which describes parameter uncertainty.

Introduction

Colorectal cancer (CRC) is the third most common form of cancer in the UK. In 2008, 39 991 new cases were diagnosed and there were 16 259 CRC-related deaths [1]. The aim of population-based screening for CRC is to reduce incidence and mortality through both prevention of CRC (by the removal of adenomas) and earlier diagnosis of CRC.

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In 2004 Tappenden *et al.* [2,3] produced a report to the English Bowel Cancer Screening Working Group that estimated the clinical and economic impact of options for CRC screening. This study used a mathematical model to compare screening options using the guaiac faecal occult blood test (gFOBT), flexible sigmoidoscopy (FS) or a combination of the two. The report concluded that screening using gFOBT and/or FS was potentially cost effective. The report informed the Department of Health's policy on bowel cancer screening in England, and the National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) commenced rollout in England in 2006. Initially biennial screening with

gFOBT was offered to persons aged 60–69 years and then in 2009 the programme was extended to include the 70–74 age groups.

New data on several CRC screening modalities has now been published. In 2010 a large UK-based randomized trial of FS for individuals aged 55–64 years reported CRC incidence and mortality reductions in the 11-year period following an FS screen [4]. Substantial data from the first two rounds of the England gFOBT screening programme were available [5]. Further data on the immunochemical FOBT (iFOBT) were made available from the Italian screening programme [6]. In 2010 a large data set from a colonoscopy screening programme in Germany was published [7]. The availability of these new highly relevant primary data provided the motivation for the study described here, a reappraisal of the options for CRC screening.

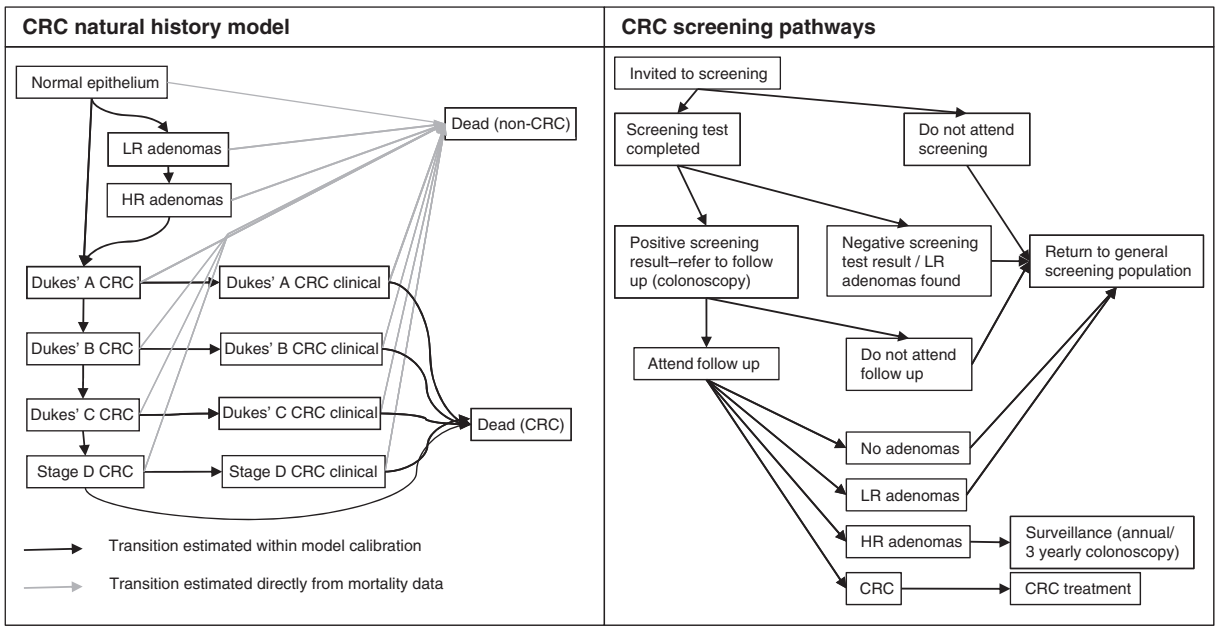
This study used the new data together with an improved 'calibration' method to update our understanding of CRC natural history. Our estimates of CRC natural history model parameters and screening test characteristics are used to reappraise the options for CRC screening in England [8]. The aim was to estimate the effectiveness, cost effectiveness and resource requirements of a range of screening strategies involving gFOBT, iFOBT and FS. The study was undertaken on behalf of the NHS Cancer Screening Programme to help inform future CRC screening policy in England.

Method

Model overview

The model consists of two components (illustrated in Fig. 1): the first describes the natural history of CRC by representing the development of adenomas and their progression to CRC, and the second describes the screening interventions and surveillance. 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 colon epithelium through to the development of adenomas and CRC and subsequent death. The model structure is an adaptation of the original CRC model developed by Tappenden *et al.* [3].

Total costs and quality-adjusted life years (QALYs) accrued by the cohort from ages 50 to 100 were calculated for each screening option. The model takes the perspective of the NHS and a discount rate of 3.5% per annum was applied to costs and QALYs from age 50, in line with current National Institute for Health and Clinical Excellence recommendations [9]. Estimates of expected costs, QALYs, resource use, CRC incidence reduction and CRC mortality reduction were produced for a range of possible screening strategies. The net monetary benefit (NMB) of each screening strategy was calculated using a willingness to pay threshold of £20 000 per QALY. In health economic terms, a screening strategy associated with a greater NMB is preferred. Incremental



CRC = colorectal cancer, LR = low risk, HR = high risk

Figure 1 Diagram of colorectal cancer (CRC) natural history model structure and screening pathways.

cost effectiveness ratios were evaluated compared with a strategy of no screening. Screening strategies involving gFOBT, iFOBT and FS or a combination of screening modalities were considered.

CRC natural history model structure

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; and an individual's progression from low risk to high risk adenomas. The choice of modelling approach was determined by the data available on different screening modalities and by previous experience in CRC modelling [3,10]. Data are available from the current gFOBT screening programme in England describing the number of persons found to have low, intermediate or high risk adenomas or CRC using the British Society of Gastroenterologists (BSG) colonoscopic surveillance guidelines for adenoma risk levels [11,12]. For the purpose of this model we define the 'high risk adenomas' health state to consist of persons requiring surveillance under the BSG guidelines (i.e. those classified as intermediate or high risk), and those persons with adenomas who do not require surveillance comprise the 'low risk adenomas' health state. The model consists of the following health states: normal epithelium, low risk adenomas, high risk adenomas, preclinical CRC Stages A–D, clinical CRC Stages A–D, and dead. The health states and transitions included within the CRC natural history model are shown in Fig. 1.

The natural history of CRC can be modelled using a patient-level or a cohort model [8,10]. In this instance, a cohort model was used and this choice is associated with both advantages and limitations. A patient-level model may have greater flexibility in modelling disease natural history and management but will generally require more parameters and distributional assumptions than a cohort model. For example, there is considerable uncertainty surrounding several CRC natural history model parameters, such as adenoma growth rates. A cohort model requires information on the average rate at which an adenoma would develop into a CRC, but a patient-level model would also require knowledge of the between-patient variation in this rate.

We define a sequence of annual transition probabilities between the health states relating to CRC developing though the adenoma–carcinoma sequence, as most CRCs are believed to develop though this sequence [13]. In addition, we define a transition probability from normal epithelium to Dukes A CRC to allow for the possibility that a proportion of cancers do not arise from adenomas (*de novo* cancers). For each cancer stage we allow diagnosis through symptomatic presentation or chance detection, and this transition corresponds to moving from a preclinical to a clinical CRC health state. There is evidence to suggest that the adenoma growth rate varies with age [14]. The probabilities associated with the transition to low risk adenomas, the transition from low to high risk adenomas and the transition from high risk adenomas to Dukes A CRC were allowed to vary by age using a piecewise linear model (with parameter values being the transition probabilities at ages 30, 50, 70 and100). Transitions between the preclinical CRC states and from preclinical to clinical CRC were assumed to be independent of age. All persons may die of non-CRC causes, and this is modelled using age-specific mortality rates [15]. 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. It was also assumed that 'preclinical Stage D CRC' may be fatal. Survival rates for clinical CRC Stages A–D and preclinical Stage D CRC are assumed to be dependent on the CRC stage at diagnosis and patient age and were modelled using a mixed model [16].

Screening and surveillance model

The screening and surveillance pathways represented by the model are described in Fig. 1. The screening and surveillance part of the model describes the detection of adenomas and CRC at screening, and the surveillance of individuals in whom high risk adenomas are detected.

Existing screening studies were used to inform the following parameters: uptake rates for screening; compliance with follow-up; compliance with surveillance; screening re-test rates; follow-up repeat test rates; rates of bleeding, perforation and death following endoscopy. Details and sources of parameter values are provided in Table 1.

The numbers of adenomas and CRC detected at screening are determined by the underlying prevalence of adenomas and CRC and the screening test sensitivity. The sensitivity of a test to a particular condition is defined as the probability that an individual with that condition will receive a positive test result. The sensitivity and specificity of gFOBT, iFOBT and FS were estimated within the model calibration process (described later). Test sensitivities for low risk adenomas, high risk adenomas and CRC were assumed to be constant by age. The test characteristics of iFOBT are dependent on the test threshold used. Data on iFOBT are taken from the Italian screening programme which uses a threshold of 100 ng haemoglobin/ml of buffer (20 μg haemoglobin/g faeces) with an OC-Sensor single test device (Eiken, Japan); hence the iFOBT base case

Table 1 Model parameter values.

Parameter name	Mean	Distribution used in PSA and 95% CI	Source
Harm/complications parameters			
COL (without polypectomy) perforation rate	0.0%	N/A	FS UK screening trial data, Atkin *et al.*, [25]]
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	0.0%	N/A	FS UK screening trial data, Atkin *et al.* [25]
FS (with polypectomy) perforation rate	0.01%	Beta (1, 9, 498) (0.00–0.00)	FS UK screening trial data, Atkin *et al.* [25]
FS probability of death following perforation	6.5%	Beta (2, 29) (0.01–0.17)	Gatto *et al.*, (2003)
FS probability of hospitalization for bleeding	0.03%	Beta (12, 40, 609) (0.00–0.00)	FS UK screening trial data, Atkin *et al.* [25]
COL probability of hospitalization for bleeding	0.3%	Beta (7, 2, 040) (0.00–0.01)	FS UK screening trial data, Atkin *et al.* [25]
Repeat rates			
gFOBT mean number of tests completed	1.08	N/A	Assumption 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.* [6]
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.* [25]
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.* [25]
COL surveillance compliance	0.83	N/A	NHS BCSP data
FS screening compliance	0.85	N/A	Assumed same as for FOBT, Atkin *et al.* [4]
Health-related quality of life parameters			
Utility value cancer free	0.80	Beta (279, 71) (0.75–0.84)	Ara and Brazier [22]
Utility value CRC	0.70	Beta (361, 157) (0.66–0.74)	Ara and Brazier [22]
Resource Use parameters			
Cost of gFOBT screen (non-compliers)	£2.03	Uniform (1.83, 2.23)	Southern Hub screening costings model
Cost of gFOBT screen (normal result)	£3.36	Uniform (3.03, 3.70)	Southern Hub screening costings model
Cost of gFOBT screen (positive result)	£11.94	Uniform (10.74, 13.13)	Southern Hub screening costings model
Cost of iFOBT screen (non-compliers)	£6.43	Uniform (5.79, 7.07)	Southern Hub screening costings model
Cost of iFOBT screen (normal result)	£7.37	Uniform (6.63, 8.11)	Southern Hub screening costings model
Cost of iFOBT screen (positive result)	£16.20	Uniform (14.58, 17.82)	Southern Hub screening costings model

Table 1 (Continued).

Parameter name	Mean	Distribution used in PSA and 95% CI	Source
Cost of FS screen excluding FS exam (non-compliers)	£5.02	Uniform (4.52, 5.53)	Southern Hub screening costings model
Cost of FS screen excluding FS exam (not referred to COL)	£6.01	Uniform (5.41, 6.61)	Southern Hub screening costings model
Cost of FS screen excluding FS exam (referred to COL)	£14.84	Uniform (13.36, 16.32)	Southern Hub screening costings model
Cost of FS (without polypectomy)	£186	Uniform (167, 205)	NHS reference costs, screening centre estimates
Cost of FS (with polypectomy)	£195	Uniform (176, 215)	NHS reference costs, screening centre estimates
Proportion of LR adenomas being referred for COL following FS	3%	Uniform (0.02, 0.05)	FS trial data
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)	£2164	Gamma (117, 18) (1790–2573)	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)
Test characteristics			
gFOBT sensitivity for LR adenomas	0.01	Correlated parameter set (0.009–0.010)	Model calibration
gFOBT sensitivity for HR adenomas	0.12	Correlated parameter set (0.121–0.125)	Model calibration
gFOBT sensitivity for CRC	0.24	Correlated parameter set (0.233–0.253)	Model calibration
gFOBT specificity age 50	0.99	Correlated parameter set (0.991–0.995)	Model calibration
gFOBT specificity age 70	0.97	Correlated parameter set (0.972–0.978)	Model calibration
FS sensitivity for LR adenomas	0.22	Correlated parameter set (0.212–0.229)	Model calibration
FS sensitivity for HR adenomas	0.71	Correlated parameter set (0.685–0.742)	Model calibration
FS sensitivity for CRC	0.62	Correlated parameter set (0.612–0.741)	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 (0.043–0.047)	Model calibration
iFOBT sensitivity for HR adenomas	0.32	Correlated parameter set (0.315–0.332)	Model calibration
iFOBT sensitivity for CRC	0.63	Correlated parameter set (0.606–0.646)	Model calibration
iFOBT specificity age 50	0.98	Correlated parameter set (0.971–0.978)	Model calibration
iFOBT specificity age 70	0.93	Correlated parameter set (0.919–0.937)	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

Table 1 (Continued).

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 (0.020–0.022)	Model calibration
Normal epithelium to LR adenomas – age 50	0.020	Correlated parameter set (0.019–0.021)	Model calibration
Normal epithelium to LR adenomas – age 70	0.045	Correlated parameter set (0.029–0.047)	Model calibration
Normal epithelium to LR adenomas – age 100	0.011	Correlated parameter set (0.005–0.031)	Model calibration
LR adenomas to HR adenomas – age 30	0.009	Correlated parameter set (0.007–0.014)	Model calibration
LR adenomas to HR adenomas – age 50	0.008	Correlated parameter set (0.006–0.008)	Model calibration
LR adenomas to HR adenomas – age 70	0.008	Correlated parameter set (0.008–0.010)	Model calibration
LR adenomas to HR adenomas – age 100	0.004	Correlated parameter set (0.003–0.010)	Model calibration
HR adenomas to Dukes A CRC – age 30	0.029	Correlated parameter set (0.004–0.031)	Model calibration
HR adenomas to Dukes A CRC – age 50	0.025	Correlated parameter set (0.022–0.026)	Model calibration
HR adenomas to Dukes A CRC – age 70	0.054	Correlated parameter set (0.050–0.058)	Model calibration
HR adenomas to Dukes A CRC – age 100	0.115	Correlated parameter set (0.084–0.118)	Model calibration
Normal epithelium to CRC Dukes A	0.000	Correlated parameter set (0.000–0.000)	Model calibration
Preclinical CRC: Dukes A to Dukes B	0.508	Correlated parameter set (0.501–0.886)	Model calibration
Preclinical CRC: Dukes B to Dukes C	0.692	Correlated parameter set (0.499–0.702)	Model calibration
Preclinical CRC: Dukes C to Stage D	0.708	Correlated parameter set (0.594–0.728)	Model calibration
Symptomatic presentation with CRC Dukes A	0.044	Correlated parameter set (0.043–0.070)	Model calibration
Symptomatic presentation with CRC Dukes B	0.176	Correlated parameter set (0.124–0.180)	Model calibration
Symptomatic presentation with CRC Dukes C	0.369	Correlated parameter set (0.303–0.394)	Model calibration
Symptomatic presentation with CRC Dukes D	0.735	Correlated parameter set (0.647–0.923)	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 advanced adenomas classified as HR adenomas	0.746	N/A	FS trial data
Proportion of HR adenomas requiring annual surveillance	0.290	N/A	NHS BCSP data
LR polypectomy, transition probability to LR adenomas	0.100	N/A	England BCSP data Martinez *et al.* [18]
LR polypectomy, transition probability to HR adenomas	0.040	N/A	England BCSP data, Martinez *et al.*, (2010)
IR polypectomy, transition probability to LR adenomas	0.163	N/A	England BCSP data, Martinez *et al.*, (2012)
IR polypectomy, transition probability to HR adenomas	0.091	N/A	England BCSP data, Martinez *et al.*, (2013)
HR polypectomy, transition probability to LR adenomas	0.188	N/A	England BCSP data, Martinez *et al.*, (2015)
HR polypectomy, transition probability to HR adenomas	0.568	N/A	England BCSP data, Martinez *et al.*, (2016)

PSA, probabilistic sensitivity analysis; COL, colonoscopy; FS, flexible sigmoidoscopy; FOBT, faecal occult blood test; LR, low risk; HR, high risk; IR, intermediate risk; NHS, National Health Service; BCSP, Bowel Cancer Screening Programme.

test characteristic estimates reflect this threshold. Data on detection rates for different thresholds were used to estimate iFOBT test characteristic values for 150 and 200 ng/ml thresholds [17].

Persons with a positive screening test result may or may not have adenomas/CRC, i.e. true and false positive. The number of false positive screening test results is related to the underlying prevalence of adenomas/CRC and the screening test specificity. Specificity was defined to be the probability of a negative result in a person with no adenomas or CRC. A lower FOBT specificity for older ages may be expected due to a higher prevalence of other colonic conditions. The specificity of gFOBT and iFOBT was assumed to vary (linearly) by age. Colonoscopy and FS were both assumed to have perfect specificity due to the visual nature of the investigation.

Individuals in whom adenomas were found are assumed to receive polypectomy and were subsequently assigned a higher risk of adenoma recurrence [18]. The modelling reflects the BSG guidelines for colonoscopic surveillance currently used in the English BCSP in which individuals receive annual, 3-yearly or no surveillance colonoscopies depending on their risk level [11,12].

Following CRC diagnosis, either through screening or symptomatic presentation, people move to one of the clinical CRC health states and survival and treatment costs are determined by CRC stage at diagnosis.

Model calibration

The CRC natural history model parameters (transition probabilities for adenoma/CRC growth and transition probabilities for symptomatic presentation with CRC) and the screening test characteristics cannot be empirically observed so a process of calibration was used to estimate these values. This calibration process fitted natural history model parameters and screening test characteristics to observed data given the model structure. The observed data consisted of CRC incidence by age and stage in the absence of screening and several CRC screening data sets which are detailed in Table 2. A systematic review was performed to identify colonoscopy studies [19]. In addition to the large study by Brenner *et al.* [7] a study by Chung *et al.* [26] was included to incorporate data on low risk adenomas (not reported by Brenner *et al.*) and data for persons aged < 60.

For a given set of values for CRC natural history parameters and screening test characteristics, a model can be run with this 'parameter set' which produces predictions of CRC incidence in the absence of screening and also 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 of the squared

Table 2 Screening data used within the model calibration.

Screening test	Country	Time period screening undertaken	Number of participants undergoing screening	Age range of participants	Data reported from initial screen (prevalent screening round)	Source
gFOBT	England	2006–2010	2 889 925	59–74	False positive rate; LR adenomas, HR adenomas and CRC detection rates	England BCSP data [23]
iFOBT	Italy	2006–2010	591 152	50–69	False positive rate; non-advanced/advanced adenomas and CRC detection rates	Italian iFOBT data [24]
FS	England	2005–2008	40 621	55–65	LR adenomas, HR adenomas and CRC detection rates	Atkin *et al.* [25]
Colonoscopy	Germany	2003–2007	2 185 153	55–75	Advanced adenomas and CRC detection rates	Brenner *et al.* [7]
Colonoscopy	Germany	2003–2004	840 149	50–80+	Advanced adenoma detection rate	Brenner *et al.* [14]
Colonoscopy	Korea	2003–2007	5254	30–59	Non-advanced adenomas, advanced adenomas and CRC detection rates	Chung *et al.* [26]

FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; LR, low risk; HR, high risk; CRC, colorectal cancer.
False positive rate is the number of persons with an FOBT result in whom no adenomas or CRC are detected at follow-up.

error (SSE) was calculated by comparing the observed number of observations with 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 produce a model that fits well to the observed data sets (determined by consideration of total SSE).

The model calibration uses methods described by Whyte *et al.* applying the Metropolis–Hastings algorithm to generate multiple sets of parameters [8,20]. The parameter sets generated form the posterior distribution, which is compatible with the observed data and accurately represents parameter uncertainty. This approach embeds the problem in the framework of Bayesian inference and produces correlated parameter sets that represent the joint uncertainty in these parameters. The model calibration was run several times using different sets (randomly generated) of initial parameter values to ensure that the best-fitting parameter set was obtained. Samples of the parameter sets from each of these runs were combined and these were used in the probabilistic sensitivity analysis (PSA).

Details of the maximum clinical incidence reduction which illustrates model differences in the dwell time of preclinical disease are provided within the supporting information.

Resources, costs and health outcome valuation

Health outcomes were measured in QALYs gained; this reflects both the time spent in a particular state of health and the health-related quality of life (HRQoL) associated with the time spent in that state.

A recent *Health Technology Assessment* of chemoprevention for CRC undertook a systematic review to identify HRQoL literature relevant to CRC-specific health states [21]. The evidence available on utility values for CRC was very limited. Only three studies report utilities based upon public preferences, the sample sizes were small, and two of the studies focus only on patients undergoing treatment. No relationship between HRQoL and cancer stage, treatment, phase of disease or time since diagnosis was identified in the available studies.

Because of the limitations in HRQoL CRC-specific data, EQ-5D values from the Health Survey for England for persons with and without cancer were used in the model [22]. These data are limited by the fact that the Health Survey for England does not include persons in hospital or in nursing homes. No data on the utility decrement associated with undergoing a screening test were available; however, the short time period involved suggests that any decrement would be very small and thus was assumed to be negligible here.

The model incorporates costs associated with the treatment of CRC, with CRC screening and with surveillance (screening tests, follow-up endoscopy, treatment of adverse events etc.). Evidence on costs and resource requirements was taken from published sources, including routine data returns, and from personal communications with a range of expert sources: NHS Cancer Screening Programmes, bowel cancer screening hubs, and the FS trial team. Detailed screening costs were estimated using a cost model for the BCSP Southern Hub and includes staff costs, consumables, capital purchases and overheads. There is likely to be some variation in costs between hubs, but the scale of these variations is uncertain.

Details of the costs and utility values used in the model and the sources of the estimates are provided in Table 1. A detailed description of the HRQoL data, and the screening pathways and resource use assumptions underlying the cost estimates, is available within the full report [19].

Results

Model calibration results

The calibration process produced a model with a good fit to all of the observed data sets. A comparison of the model predictions using the best-fitting parameter set to the observed data used within the calibration process is presented in Figs 2 and 3.

The model was validated by comparing model predictions to screening data which had not been used in the

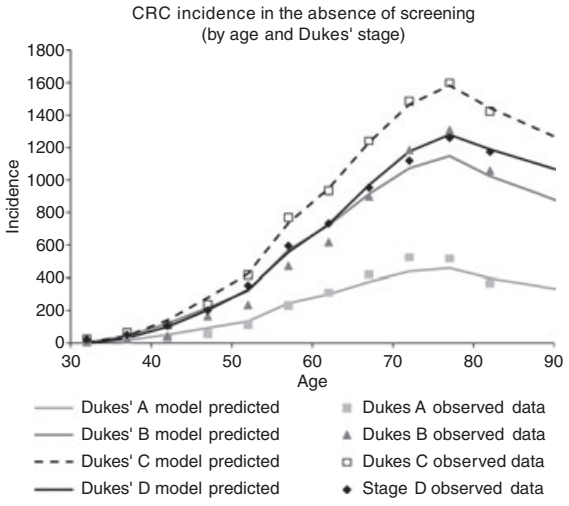


Figure 2 Results of model calibration: model predictions compared with observed data for colorectal cancer (CRC) incidence in the absence of screening. Observed CRC incidence data are from the National Cancer Data Repository [16].

calibration process. The FS trial reports reductions in CRC incidence and mortality of 33% [hazard ratio (HR) 0.67, 95% CI 0.60–0.76] and 43% (HR 0.57, 95% CI 0.45–0.72) respectively in the follow-up period (median 11.2 years) [4]. 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 an FS screen at ages 55–64. Hence model predictions are similar to those seen in the trial and the hazard ratios are well within the confidence intervals reported by the trial.

The Italian iFOBT screening programme data did not specifically detail results of second screens and so was not used within the validation process. Data on detection and positivity rates at second gFOBT screens were available from the English BCSP [23]. These data showed an increase in false positive rates at the second screen compared with the first screen (0.7%–1.2% for 65-year-olds). One might expect a very slightly higher false positive rate at the second screen due to a lower prevalence of adenomas/CRC. The scale of the increase seen in the data was therefore surprising and suggests that this data set may be biased. This discrepancy meant that the gFOBT second round data were unsuitable for model validation.

Central estimates of cost effectiveness and resource use

All screening strategies evaluated had an incremental cost effectiveness ratio of < £20 000 compared with a strategy of no screening. An analysis was performed comparing one-off FS screening for a range of ages from 50 to 70. FS screening at age 55 was associated with the greatest QALY gain; however, the QALY gains are very similar

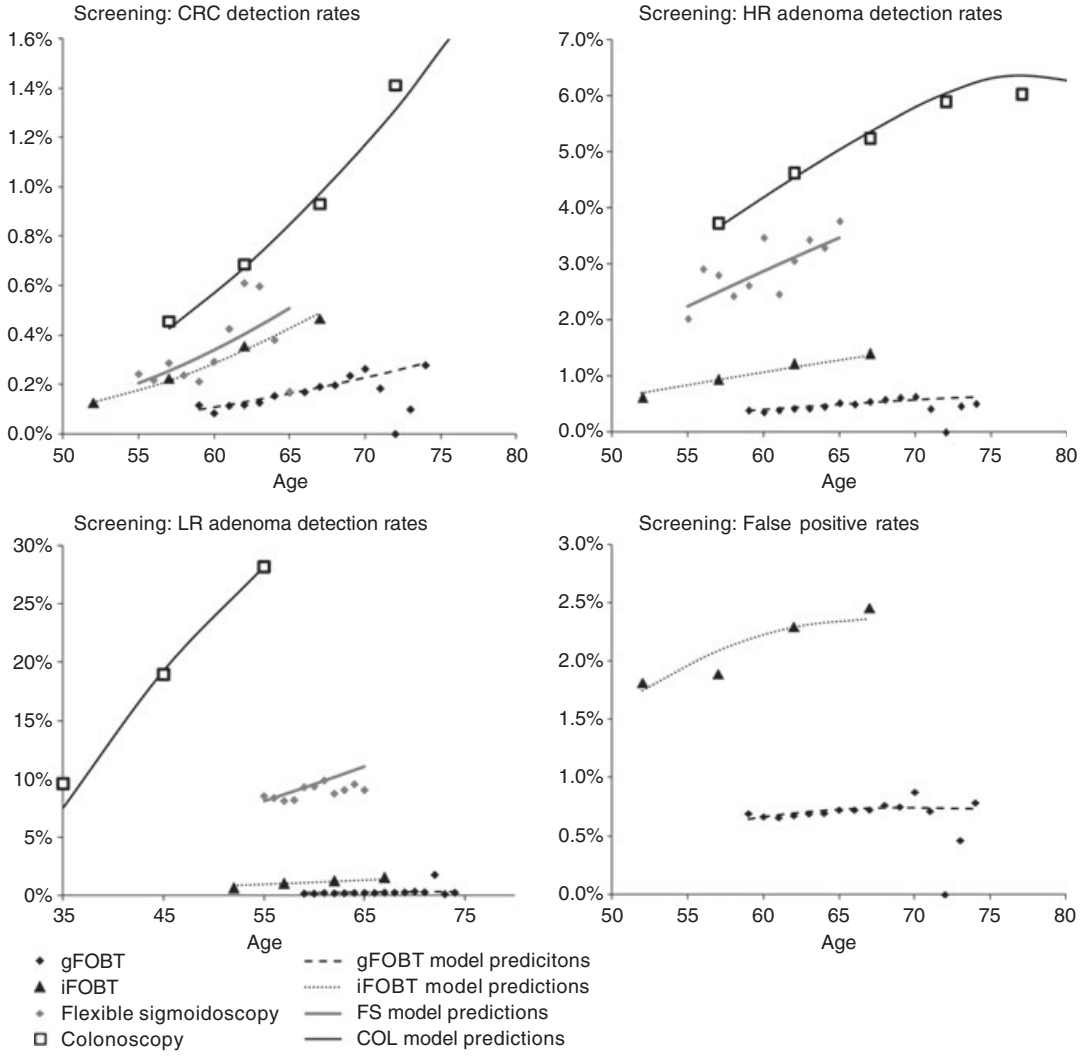


Figure 3 Results of model calibration: model predictions compared with observed data for detection rates at gFOBT, iFOBT, flexible sigmoidoscopy and colonoscopy screen. Table 2 provides sources of the observed screening data presented here.

between ages 52 and 58. The greatest reduction in CRC incidence and mortality is seen when a one-off FS screen is offered at age 64.

A range of screening options was considered for gFOBT, iFOBT and FS, and the results of several different screening strategies are presented in Tables 3 and 4. The total cost to the NHS is reported and this encompasses any screening costs incurred and any reduction in CRC treatments as a result of screening. The resource use estimates reflect the lifetime resource use for a cohort of 649 400 50-year-olds (the population in England in 2010). Tables 3–5 present marginal analyses compared with the current screening programme. Marginal analyses are presented because the choice of screening strategy will also be determined by the feasibility of resource implications.

The strategies of biennial screening with gFOBT or iFOBT were cost saving compared with no screening. A strategy of biennial screening with iFOBT dominates, i.e. is less costly and more effective than, biennial screening with gFOBT. However, iFOBT also results in approximately three times the number of colonoscopies.

A strategy of 'biennial iFOBT 60–74' is expected to be cost saving and result in QALY gains compared with the current screening programme of 'biennial gFOBT 60–74'. However, the strategy with the greatest NMB was 'FS at age 55, followed by biennial iFOBT screening for ages 56–74', irrespective of whether the comparator was the current screening programme or no screening. This strategy was associated with the greatest NMB and the greatest reduction in CRC incidence, CRC mortality and CRC treatment costs. The strategy was also associated with the greatest endoscopy requirements of all the screening strategies considered, requiring approximately nine times as many endoscopic procedures as the current programme.

Uncertainty analysis

One-way sensitivity analyses were undertaken to consider several scenarios for alternative model parameters (e.g. alternative endoscopy costs and screening uptake rates). For clarity the results are presented for just five screening strategies. The results of the one-way sensitivity analyses are presented on a marginal cost effectiveness plane, which displays the differences in expected costs and QALYs compared with the current screening policy of 'biennial gFOBT 60–74' (Fig. 4). These analyses demonstrate that the results are highly sensitive to several model parameters, such as uptake, endoscopy costs and iFOBT threshold. However, in all of these analyses the screening strategy with the highest NMB remained unchanged.

Table 3 Screening strategies involving faecal occult blood test and flexible sigmoidoscopy – summary results.

	Total per person			Marginals compared with gFOBT at 60–74 years (biennial)				Reduction in (%)		
Screening strategy	Cost	LYs	QALYs	Cost	LYs saved	QALYs saved	NMB	CRC incidence	CRC mortality	CRC treatment costs
No screening	£593	19.352	15.4075					0	0	0
gFOBT at 60–69 years (biennial)	£566	19.367	15.4196					7	10	8
gFOBT at 60–74 years (biennial)	£558	19.371	15.4229	–	–	–	–	9	15	12
iFOBT at 60, 65, 70 years	£556	19.374	15.4254	–£2	0.003	0.003	£52	10	15	12
iFOBT at 60–69 years (biennial)	£541	19.384	15.4337	–£17	0.013	0.011	£235	14	21	17
iFOBT at 60–74 years (biennial)	£530	19.391	15.4391	–£28	0.020	0.016	£352	19	28	23
FS age 55	£622	19.377	15.4289	£65	0.006	0.006	£57	9	11	10
FS age 55, 65	£638	19.391	15.4405	£80	0.020	0.018	£272	18	22	19
FS age 55, gFOBT 66–74 (biennial)	£606	19.385	15.4355	£48	0.014	0.013	£204	14	19	16
FS age 55, iFOBT 66–74 (biennial)	£590	19.395	15.4433	£33	0.024	0.020	£377	20	28	24
FSIG age 55, iFOBT 60, 65,70	£599	19.393	15.4416	£41	0.022	0.019	£335	17	22	19
FS age 55, iFOBT 60–74 (biennial)	£581	19.406	15.4525	£23	0.035	0.030	£569	25	33	28
FS age 55, iFOBT 56–74 (biennial)	£582	19.412	15.4573	£25	0.041	0.034	£665	26	35	30

LY, life year; QALY, quality-adjusted life year; NMB, net monetary benefit; CRC, colorectal cancer; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy.

Costs and health benefits discounted at 3.5% per annum from age 50. NMB = (increase in quality-adjusted life years) × willingness to pay + (increase in costs), where willingness to pay = £20 000.

Table 4 Screening strategies involving faecal occult blood test and flexible sigmoidoscopy-summary results (part 2).

	Endoscopy requirements			Harm	Number needed to screen	
Screening strategy	Flexible sigmoidoscopy	Colonoscopy (screening)	Colonoscopy (surveillance)	Deaths due to perforation	To prevent one case of CRC	To save one life
No screening	–	–	–	–		
gFOBT at 60–69 years (biennial)	–	24 216	15 154	2.8	570	595
gFOBT at 60–74 years (biennial)	–	38 430	21 057	4.4	617	621
iFOBT at 60, 65, 70 years	–	48 530	22 982	5.6	224	230
iFOBT at 60–69 years (biennial)	–	76 528	32 778	8.3	256	279
iFOBT at 60–74 years (biennial)	–	119 302	43 054	12.5	291	314
FS age 55	343 341	9 376	19 097	2.5	87	115
FS age 55, 65	660 120	19 975	37 610	5.2	88	114
FS age 55, gFOBT 66–74 (biennial)	343 341	33 300	30 104	5.1	301	351
FS age 55, iFOBT 66–74 (biennial)	343 341	85 082	43 581	10.5	208	237
FSIG age 55, iFOBT 60, 65,70	343 341	54 761	36 337	7.3	180	213
FS age 55, iFOBT 60–74 (biennial)	343 341	124 369	53 032	13.7	261	307
FS age 55, iFOBT 56–74 (biennial)	343 341	147 156	56 480	15.2	303	359

FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; CRC, colorectal cancer.
Model predictions correspond to a cohort of 649 400 50-year-olds (the number in England in 2010).

Table 5 Endoscopy resource use requirement estimates from the probabilistic sensitivity analysis.

	Endoscopy resource use requirements (mean and 95% percentiles from PSA)		
Screening strategy	Flexible sigmoidoscopy	Colonoscopy (screening)	Colonoscopy (surveillance)
No screening	–	–	–
gFOBT at 60–74 (biennial)	–	38 242 (32 746, 43 758)	21 030 (18 047, 23 987)
iFOBT at 60–74 (biennial)	–	117 681 (100 445, 135 065)	43 254 (36 883, 49 554)
FS age 55	340 871 (292 719, 390 657)	9 280 (7 506, 10 946)	18 688 (14 838, 22 147)
FS age 55, gFOBT 66–74 (biennial)	340 871 (292 719, 390 657)	33 075 (28 547, 37 895)	29 822 (24 889, 34 643)
FS age 55, iFOBT 56–74 (biennial)	340 871 (292 719, 390 657)	145 112 (124 135, 166 320)	56 451 (48 435, 64 360)

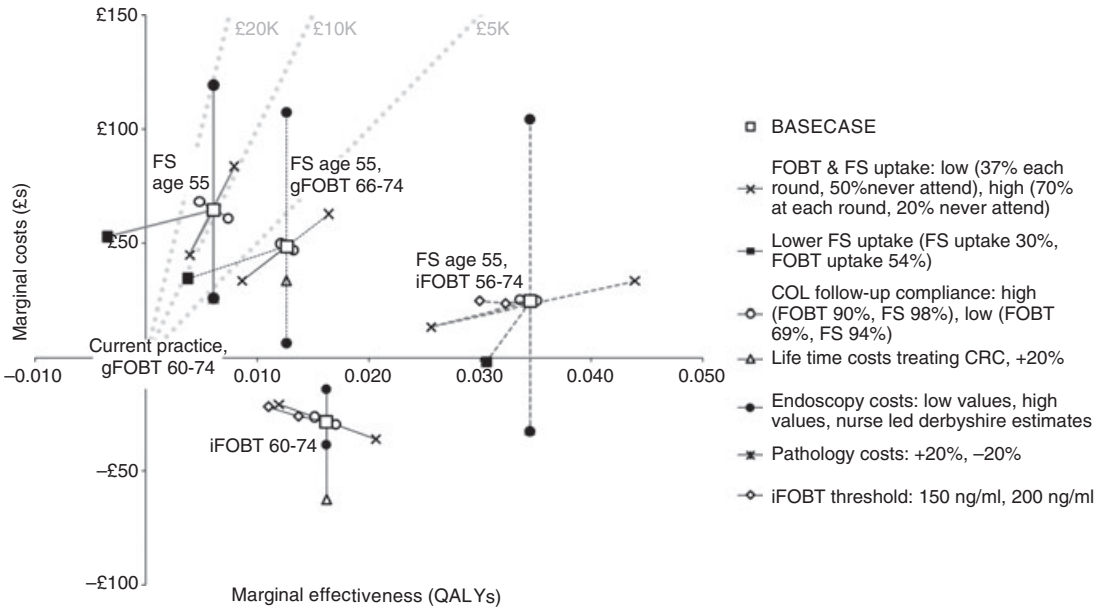
PSA, probabilistic sensitivity analysis; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy.
Model predictions correspond to a cohort of 649 400 50-year-olds (the number in England in 2010).

Figure 4 demonstrates that the model results are highly sensitive to endoscopy costs. For example, the long vertical line in the strategy of 'FS at age 55' indicates that the overall marginal cost per person invited for screening is £65 in the base case; however, given the uncertainty in endoscopy costs, the value may range between £20 and £120.

Figure 4 shows that screening with biennial iFOBT using the higher thresholds of 150 and 200 ng haemoglobin/ml buffer (OC-Sensor device) is associated with lower QALY gains but little difference in costs. At an OC-Sensor threshold of 200 ng/ml, 'biennial iFOBT 60–74' was associated with slightly greater benefits than one-off FS at age 55 and slightly fewer benefits than 'FS age 55, biennial gFOBT 66–74'. Castiglione *et al.* [17] reported that increasing the OC-Sensor iFOBT threshold from 100 to 200 ng/ml reduced the positivity rates from 4.2% to 2.4%; hence the threshold used will have a direct impact on endoscopy requirements.

An analysis was performed to evaluate the benefit of NHS spending to increase screening uptake, e.g. through increasing screening awareness. An increase in uptake from 54% to 70% results in an increase in marginal QALYs of 0.004 and a decrease in marginal costs of £8 for the strategy 'biennial gFOBT ages 60–74'. Based on a willingness-to-pay threshold of £20 000 per QALY, it would therefore be cost effective to spend up to £88 per person (over their lifetime) on measures which will increase the uptake from 54% to 70% (i.e. approximately £5 per 1% increase in uptake).

The PSA examined uncertainty surrounding expected costs and QALYs. The distributions used within the PSA



COL, colonoscopy; FS, flexible sigmoidoscopy; iFOBT, immunochemical faecal occult blood test; gFOBT, guaiac faecal occult blood test; CRC, colorectal cancer; QALYs, quality adjusted life years

Figure 4 Results of scenario analyses, marginal costs and effects compared with the current screening policy. The marginal cost effectiveness plane displays the differences in expected costs and QALYs compared with the current screening policy (gFOBT 60–74). The dotted grey lines radiating from the origin segment the cost effectiveness plane by the willingness-to-pay thresholds indicated. Four different screening strategies are presented, compared with current screening which is at the origin. For each screening strategy the base case estimate of cost effectiveness is represented by a white square. The effect of various scenarios and parameter values are described by the lines radiating from the base case.

for the model parameters are described in Table 1. Figure 5 presents the results of the PSA using a cost effectiveness plane scatter plot, which shows the distribution of marginal costs and QALYs compared with the current screening policy. Figure 5 shows that the PSA results for the different strategies do not overlap which indicates that when uncertainty is taken into account the model still predicts a difference in expected costs and QALYs between the screening strategies. At a willingness-to-pay threshold of £4000 or above, the strategy of 'FS at age 55, biennial iFOBT 56–74' had a 100% probability producing the greatest NMB. Table 5 presents the endoscopy requirements results from the PSA.

The analysis presented here captures uncertainty in model parameter values but does not investigate uncertainty in relation to structural assumptions in the model which will be discussed in the limitations section.

Discussion

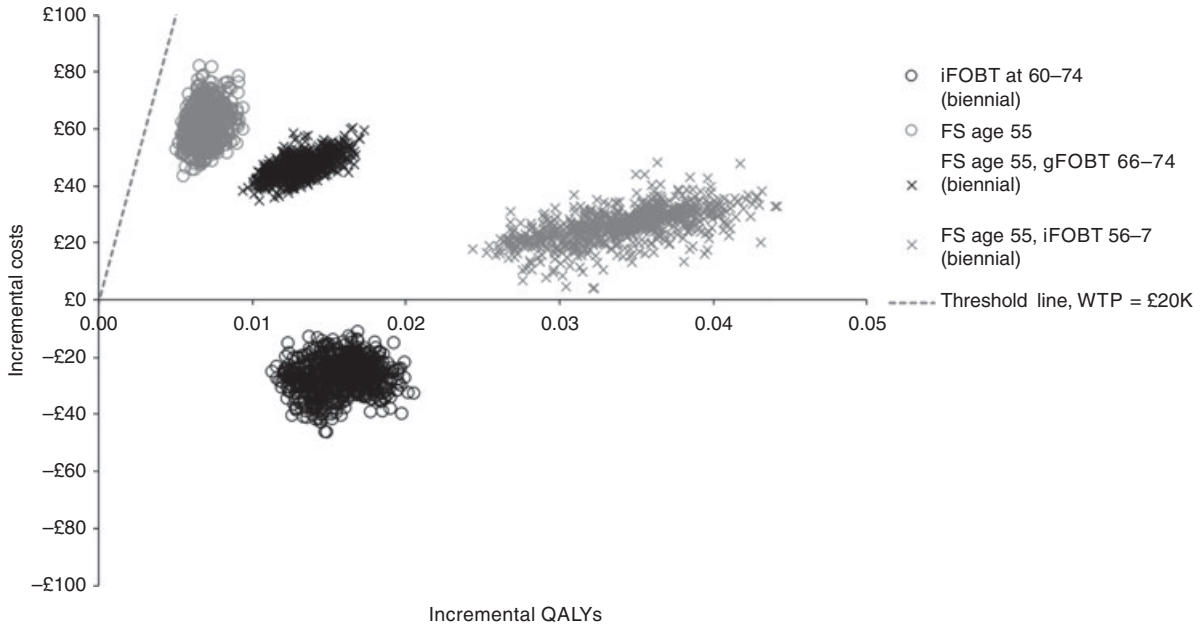
Summary of health economics results

The model suggests that screening strategies involving FS or iFOBT may produce additional benefits compared with the current policy of 'biennial gFOBT for ages 60–74'. The age at which one-off FS screening results in the greatest QALY gain was 55, with similar gains between ages 52 and 58. Strategies combining FS with iFOBT were associated with further benefits and improved economic outcomes. However, the resource use results suggested that there are considerable differences between the strategies considered in terms of endoscopy requirements. The results are highly sensitive to several model parameters, such as uptake rates, endoscopy costs and iFOBT threshold.

Model limitations

As with any health economics model, our analysis incorporates both structural and parametric assumptions which influence the predictions of cost and effectiveness of the screening strategies. It is important that these cost effectiveness results are interpreted in the light of the uncertainties within the existing evidence base.

The original options appraisal by Tappenden *et al.* [3] identified the calibrated natural history model parameters as an important area of uncertainty. This analysis obtained estimates of CRC natural history model parameters and screening test characteristics using an improved method



FS, flexible sigmoidoscopy; iFOBT, immunochemical faecal occult blood test; gFOBT, guaiac faecal occult blood test; QALYs, quality adjusted life years

Figure 5 Marginal cost effectiveness plane (compared with the current screening strategy of 'biennial gFOBT age 60–74'), discounted.

and a range of screening data [3]. It is thought that the improved calibration method used and the wider range of screening data incorporated will have resulted in more robust parameter estimates.

The endoscopy costs used in this model are associated with considerable uncertainty, and the sensitivity analyses demonstrated that the expected costs are very sensitive to these values. The results indicate a higher marginal cost of the FS screening strategies than was predicted by the original options appraisal; this difference is due to a higher estimate of the cost of FS.

The model predictions have an excellent fit to data from the first round of both gFOBT and iFOBT screening and the FS trial data. The model was also shown to fit well to the FS trial 11-year follow-up data on incidence and mortality reductions. Suitable data from the iFOBT second screen were not available.

The model used the common assumption that FOBT characteristics do not vary by screening round (although specificity was allowed to vary by age) but the gFOBT second round data were inconsistent with this assumption. The gFOBT second screen data hence draw attention to possible limitations in our understanding of the relative effectiveness of gFOBT in different screening rounds/patient subgroups and highlight the need for further research. If significantly higher false positive rates are in fact seen at a second/repeat screen then the results presented here may overestimate the benefit of screening strategies involving repeated FOBT screens. Further data from subsequent screening rounds will help determine the validity of this assumption and reduce uncertainty.

Data on adenoma prevalence by both age and location (proximal/distal) were not available. This made accurate modelling of the variation in screening test sensitivity between the proximal and distal colon impossible, hence introducing uncertainty into the modelling. Even with this limitation the modelling approach employed here will accurately represent the benefit associated with screening strategies involving just one screen, such as FS.

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

This analysis combined data from several countries. Adenoma and CRC prevalence may vary by country, but the extent of this variation is unknown. The value of using data from more than one country is that it allows the use of large data sets from several screening modalities. The definitions used to classify persons with adenomas varied by country, with the English screening data reporting low/intermediate/high risk adenomas according to BSG guidelines, and the Italian and German

screening data reporting 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 data set, so it introduces uncertainty into the modelling. Overall, the benefit of including large data sets on different screening modalities was considered to outweigh the uncertainty associated with using data sets from different countries.

Further research

The areas of uncertainty mentioned here generally correspond to data requirements. Collecting and reporting detailed, complete and comprehensive observational data from existing screening programmes should be considered a high priority for the future. The variation in positivity rates and detection rates by age, shown in Fig. 3, highlights the importance of reporting screening outcome data by age. Data from existing screening programmes often consist of far larger data sets than are available from trials. For example, the gFOBT screening programme data used here contain almost 3 million screening episodes. This has a distinct advantage when looking at, for example, detection rates for CRC at screening since even age-specific sample sizes remain useful for the screening programme data. Collecting and reporting data in a format which allows easy comparison across screening programmes in different countries would markedly improve our understanding of the disease and would support the optimization of CRC treatment and prevention strategies through improved modelling.

Conclusions

The analysis of a range of screening strategies, compared with the current CRC screening policy in England (biennial gFOBT 60–74), suggests that a change to this policy would produce additional clinical benefits and be cost effective. Screening strategies involving more than one screening modality should be considered as these have the potential to provide additional benefits whilst greater patient choice may also increase uptake. The additional endoscopy resources required by such new strategies may influence adoption by the screening programme.

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Contributorship statement

Sophie Whyte undertook acquisition of data, modelling and analysis, drafting of the manuscript. Jim Chilcott advised on modelling, revision of the manuscript. Neelam Kalita undertook the systematic review of adenoma detection rates from colonoscopy screening and autopsy studies. Stephen Halloran advised on screening pathways, revision of the manuscript. Wendy Atkin provided data, advised on screening pathways. Claire Nickerson, Eva Morris, Matthew Day, Ariadni Aravani provided data.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Maximum clinical incidence reduction.

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