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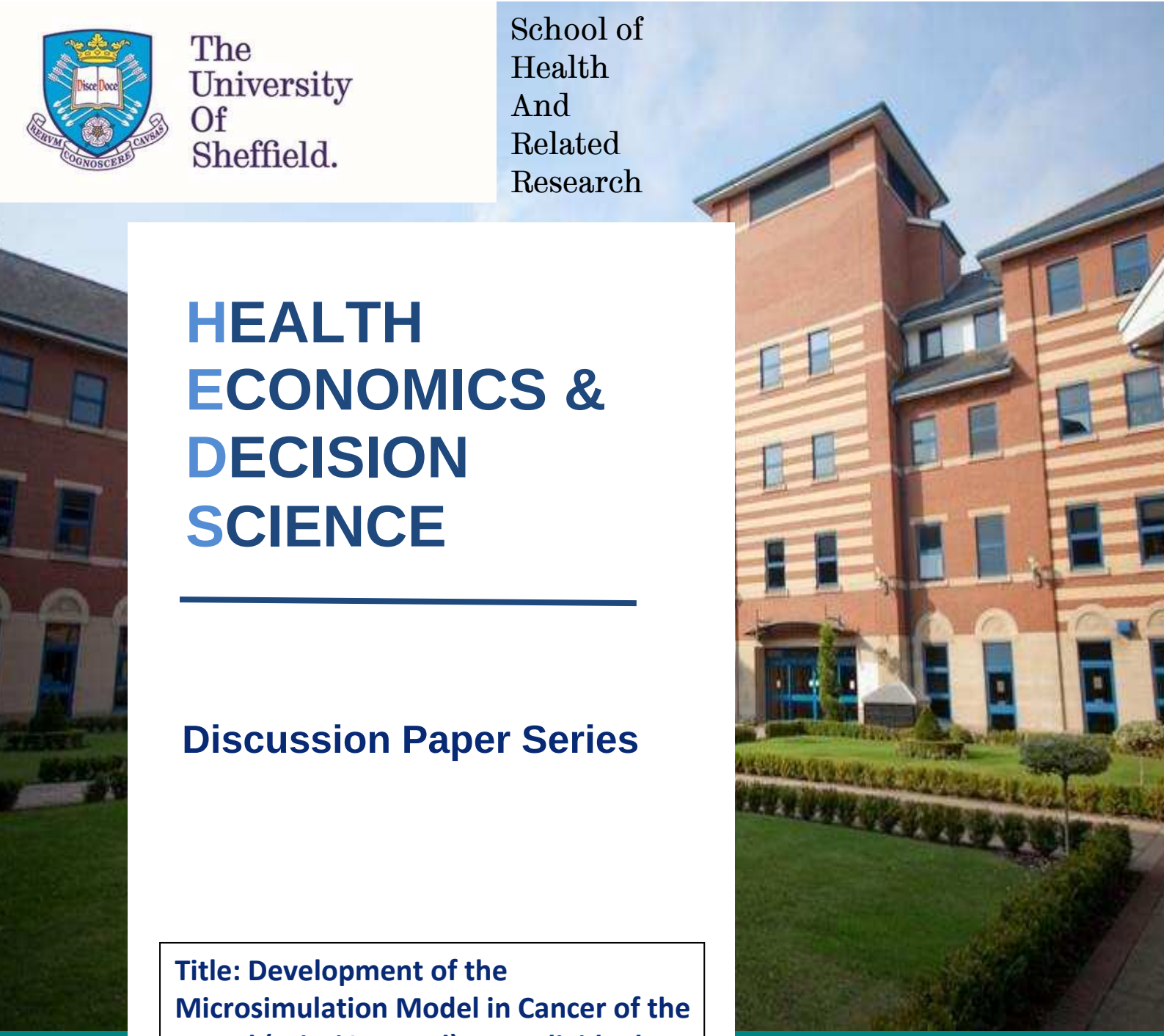

HEALTH ECONOMICS & DECISION SCIENCE

Discussion Paper Series

Title: Development of the Microsimulation Model in Cancer of the Bowel (MiMiC-Bowel), an Individual Patient Simulation Model for Investigation of the Cost-effectiveness of Personalised Screening and Surveillance Strategies.

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Development of the Microsimulation Model in Cancer of the Bowel (MiMiC-Bowel), an Individual Patient Simulation Model for Investigation of the Cost-effectiveness of Personalised Screening and Surveillance Strategies.

Technical Document

Chloe Thomas, Olena Mandrik & Sophie Whyte

Date: April 2020

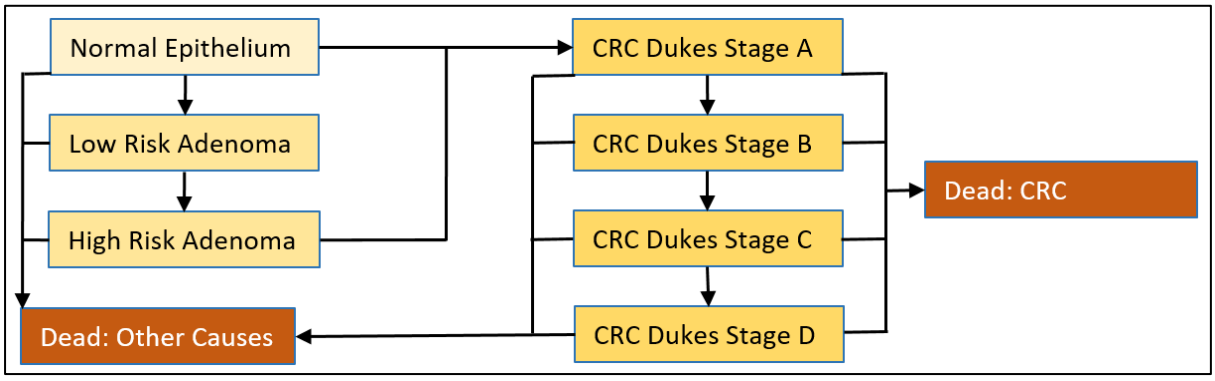
Contents

Model Structure

Microsimulation Model in Cancer of the Bowel (MiMiC-Bowel) is an individual patient simulation model built in the R programming language, which has been designed to enable comparison of the effectiveness, cost-effectiveness and resource use of different personalised screening and surveillance strategies for colorectal cancer (CRC). The model simulates the life course of patients representing the population of England, who each have a set of individual characteristics which determines their cancer risk and response to screening and surveillance. The model has a lifetime horizon and takes an NHS perspective.

Underpinning the model is a CRC natural history module with nine mutually exclusive health states: Normal Epithelium; Low Risk Adenoma; High Risk Adenoma; CRC Dukes Stage A; CRC Dukes Stage B; CRC Dukes Stage C; CRC Dukes Stage D; CRC Death; Other Cause Death. In each time cycle of the model (set to one year as default) individuals have the probability of transitioning between health states as shown in Figure 1. Only one transition is possible within each time cycle. Low and high-risk adenoma health states are defined using the British Society of Gastroenterology (BSG) guidelines for endoscopic surveillance following adenoma removal [1]. The high-risk adenoma health state includes persons with at least 3 small adenomas or at least one adenoma of size >1cm. The low-risk adenoma health state includes persons with 1-2 small (<1cm) adenomas. This means that the model does not simulate progression of individual adenomas, instead taking the perspective of an individual's overall risk without having to define their exact status in terms of number, size and type of adenomas. Most CRC develops through adenomas; however, there is thought to be some development of CRC through serrated pathways, which is also reflected in the model structure by transition from normal epithelium directly to CRC.

Figure 1: Structure of the CRC natural history model health states



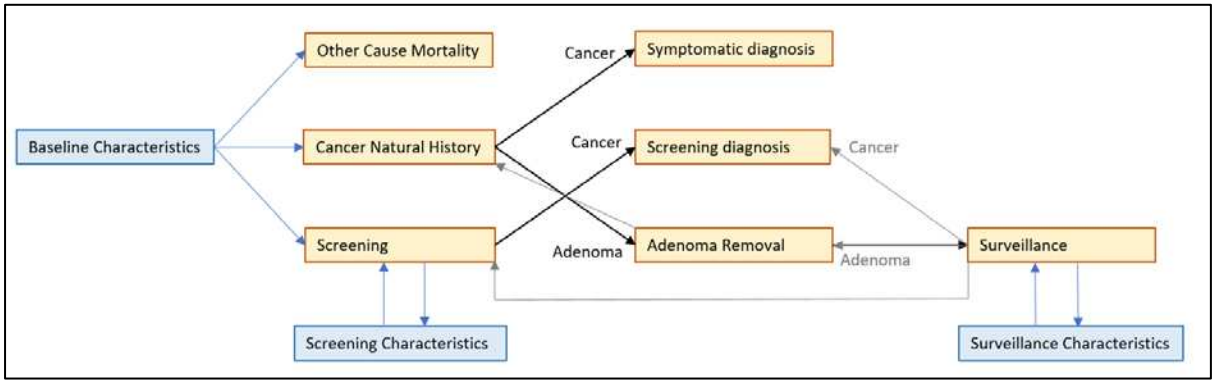
Once an individual develops CRC, they have a probability of progressing to the next stage. At each stage there is a probability that the individual will be diagnosed either through screening,

surveillance or via symptomatic/chance presentation. Diagnosed CRC is not represented as a separate set of mutually exclusive health states in the model, but is flagged separately. This means it is possible for an individual to both progress to the next health state and be diagnosed within a single model cycle. However, it is assumed that CRC stops progressing after diagnosis. After CRC diagnosis individuals are also no longer eligible for the modelled screening and surveillance pathways, instead following a disease pathway which includes treatment costs, utility reductions and reduced survival compared to the general population.

The model has two absorbing states. Whilst all individuals have a probability of dying from other causes, only those with CRC can die from CRC. It is possible to die from CRC Stage D in the model without prior diagnosis. In this case it is assumed that individuals are diagnosed within the same time cycle (i.e. just before or after death). It is also possible that individuals can die from CRC Stage D but are never diagnosed. It is assumed that this probability increases with age. In this case it is assumed that their death would be recorded as due to other causes, and therefore this is modelled through transition to other cause mortality.

The screening, surveillance and symptomatic diagnosis modules of the model sit on top of the natural history model and feed into it (see Figure 2). Two types of screening are modelled; flexible sigmoidoscopy (FS) and Faecal Immunochemical Test (FIT), together with further investigation using colonoscopy or computerised tomography colonography (CTC). Whilst the screening and surveillance pathways are hard coded (see Screening and Surveillance sections for details), the model allows flexible specification of eligibility criteria, enabling a large number of different screening strategies, including personalised strategies, to be easily modelled.

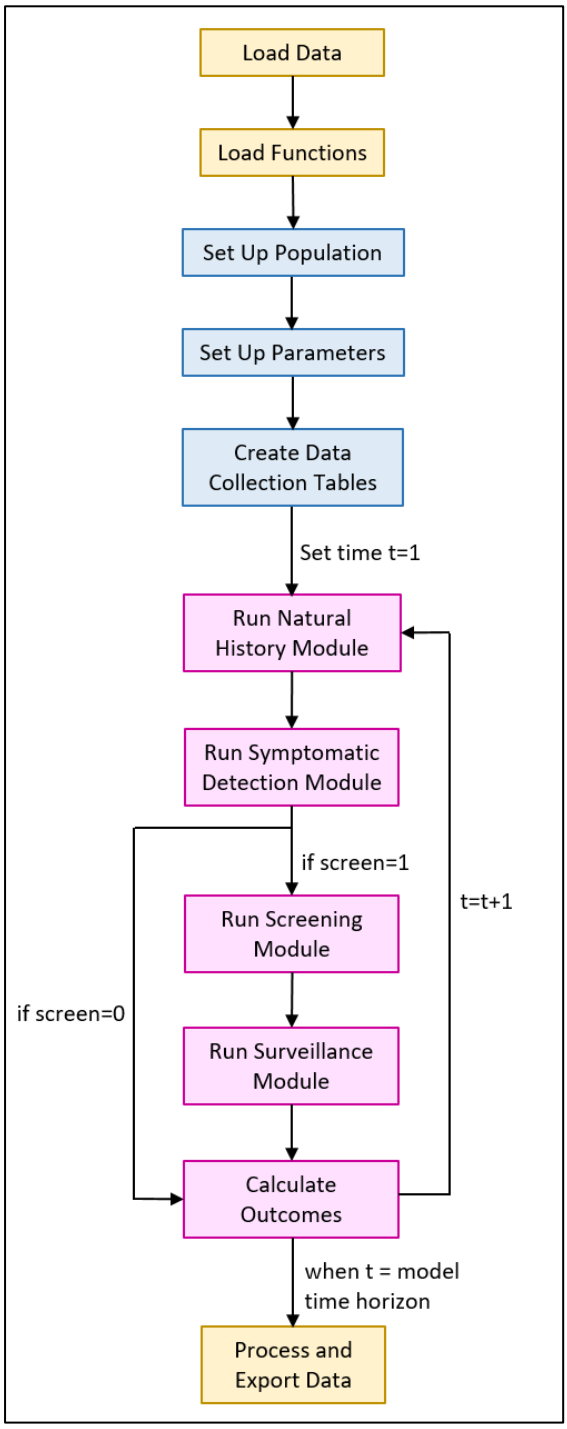
Figure 2: Model structure diagram showing how information feeds across the different model modules



Following model setup, the model simulation progresses by first evaluating the natural history transitions that happen in that cycle (Figure 3). The next step is to decide who is diagnosed with CRC symptomatically, then if screening is selected, the screening and surveillance modules of the model

are run. Finally, model outcomes are gathered. The process is repeated each cycle until the model time horizon is reached. In each model cycle, each individual may accumulate costs (from resource use related to screening and cancer treatment) and utility decrements (due to age, screening harms and cancer diagnosis). Costs, QALYs and other outcomes such as resource use and cancer cases are aggregated; half cycle correction and discounting is applied to costs, QALYs and life years, and incremental results are estimated.

Figure 3: Model process diagram showing the order that events happen in the model



The model can be run in various different modes including Deterministic, PSA, Calibration and Testing modes. These enable users to choose between different types of inputs and outputs reflecting the different model functions. Deterministic, Calibration and Testing modes all use mean parameter values in every model loop, whilst the PSA mode enables a user-defined number of random samples to be taken from each parameter distribution and used sequentially in model loops. Users can also separately decide the number of model loops that they wish to run.

In terms of outputs, the Deterministic mode produces a single results table saving only outputs aggregated over the entire population, which maximises model speed and efficiency. In addition to this, the PSA mode produces a table of key results for each PSA loop. The Calibration mode only produces results that are relevant to calculating CRC and adenoma incidence and mortality, whilst the Testing mode produces a wide range of outputs including individual health state transitions, individual screening history and individual costs and utilities to enable thorough testing of model function.

Model Population

Baseline Phenotypic Characteristics

The model baseline population is composed of individuals from the Health Survey for England (HSE) 2014 [2], an annual survey which is designed to provide a snapshot of the nation's health. Individuals aged under 30 were excluded from the model as it was assumed that no individuals aged under 30 would have yet developed adenomas or CRC. This resulted in a sample of 6,787 individuals. The 2014 sample was chosen as this was the most recent that included estimates of health-related quality of life using EuroQol - 5 Dimensions (EQ-5D) [3]. Other individual phenotypic attributes extracted from HSE 2014 for use in the model included age, sex, ethnicity, indices of multiple deprivation (IMD) quintile (a measurement of socioeconomic deprivation), smoking status, body mass index (BMI), physical activity (measured in weekly metabolic equivalents [METS]), alcohol consumption (measured in weekly units) and the individual survey weights. The survey weights have been calculated by the HSE to enable adjustment of the sample so that it matches national population estimates of age, sex and regional distribution, correcting for non-response, and thereby making the sample more representative of the English population. Given that the model is used to estimate resource use in the English population, it was essential that the survey weights were included in model outcomes. Table 1 summarises the individual characteristics extracted from HSE 2014.

Table 1: Summary of individual characteristics extracted from HSE 2014 [2], their coding in the model and the numbers with missing data.

Characteristic (Unit)	**HSE 2014 Survey Code**	**How Coded in the Model**	**Number with Missing Data**
Age (Years)	Age90	Continuous integer	0
Sex	Sex	Binary; 1 = Male, 0 = Female.	0
Ethnicity	origin2	Numeric; 1 = white; 2 = black; 3 = Asian; 4 = mixed; 5 = other	27
IMD Quintile	qimd	Numeric: 1 = least deprived; 5 = most deprived.	0
BMI (kg/m^2)	BMIval	Continuous variable	953
Smoking Status	cigsta3	Split into two binary variables: Current Smoker (1 = yes; 0 = no); Former Smoker (1 = yes; 0 = no).	20
Alcohol Intake (Weekly Units)	totalwu	Continuous variable.	92

Physical Activity (Weekly METS)	TotmModWk TotmVigWk	Single continuous variable calculated by combining minutes of moderate activity (4 METS per minute) and vigorous activity (8 METS per minute).	1070 996
EQ-5D	Mobility Selfcare UsualAct Pain Anxiety	EQ-5D score calculated from responses to each question using UK value sets generated through time trade-off valuation [3].	751 772 758 755 767
weighting	wt_int	Continuous variable.	0
HSE = Health Survey for England; IMD = Indices of Multiple Deprivation; BMI = Body Mass Index; EQ-5D = EuroQol 5 dimensions.			

Missing Data for Phenotypic Characteristics

Values were missing for some of the variables in some individuals. For some of the variables with small numbers of missing data it was assumed that those with missing data belonged to the largest group. Therefore, it was assumed that those missing ethnicity data were white and those missing smoking data were never regular smokers. It was also assumed that individuals with missing physical activity data for either moderate or vigorous activity did not do any moderate or vigorous activity. Individuals with missing data for both of these categories were assumed to be inactive.

For those missing data about alcohol consumption, data from an additional HSE variable called 'dnevr' was used, representing whether an individual had always been a non-drinker. Those who had answered either that they had never been a drinker, or had previously been a drinker but stopped were assumed to drink zero units per week. All others with missing consumption data were assumed to drink the average weekly number of units drank by other alcohol drinkers in HSE 2014, which was 12.77.

A large number of individuals were missing data about one or more of the EQ-5D dimensions, meaning that their EQ-5D could not be calculated. To estimate these values, EQ-5D for all other individuals was calculated and a linear regression was performed using age, sex and IMD quintile as explanatory variables to predict EQ-5D (Table 2), given that all individuals had data for these three variables. All three coefficients were very highly significant (P = <0.0001) and adjusted R2 was 0.37 indicating that 37% of the differences between individuals could be explained by these three variables. EQ-5D was then imputed for individuals with missing data using these variables.

Table 2: Linear regression coefficients used to calculate missing EQ-5D values

Coefficients	**Mean**	**Standard Error**
Intercept	1.1041305	0.0172774
Age	-0.0036214	0.0002317
Sex	0.0335711	0.0081017
IMD Quintile	-0.0282924	0.0028597

A similar approach was used to estimate BMI in those with missing data about BMI (Table 3). In this case the only significant variable was IMD quintile. Sex was not significant and its removal improved the model. Age was significant but its removal reduced the predictive ability of the model so this was left in. Adjusted R-squared was only 0.06. However, the F statistic was highly significant indicating that the model was better at predicting BMI than just using the intercept (i.e. mean BMI value) alone. BMI was then imputed for individuals with missing data using these variables.

Table 3: Linear regression coefficients used to calculate missing BMI values

Coefficients	**Mean**	**Standard Error**
Intercept	26.761749	0.381804
Age	0.005334	0.005242
IMD Quintile	0.288154	0.065263

Modelling Changes in Phenotypic Characteristics by Age

Several of the characteristics included in the baseline modelled population will change as a person ages. These include EQ-5D, BMI, alcohol consumption, physical activity levels and smoking status. Accurate modelling of individual level changes in these factors is extremely complex, but a simple set of methods was sought in order to be able to approximate changing risk and health benefits over time.

Continuous Risk Factors (BMI, Alcohol Consumption and Physical Activity)

A percentile method was used to model trajectories of continuous risk factors by age. Plots showing the mean BMI, physical activity (measured in weekly METS) and alcohol consumption (measured in weekly units) for each decile of the HSE 2014 population indicate that there are clear trends that it would be important to reflect in risk modelling (Figure 4, Figure 5 and Figure 6). Note that these population trends are unlikely to correlate exactly with individual level trajectories for two reasons. Firstly, unhealthy people (e.g. those with very high BMI, high alcohol consumption and low physical

activity) are likely to die earlier which will shift all deciles down/up slightly compared to individual level trajectories. Secondly, population trends also include birth cohort differences due to social changes over time. This may have particular impact for the alcohol consumption trends as it is known that alcohol consumption has been falling amongst young people in recent years [4].

Figure 4: Mean BMI for each decile of the HSE 2014 population [2]

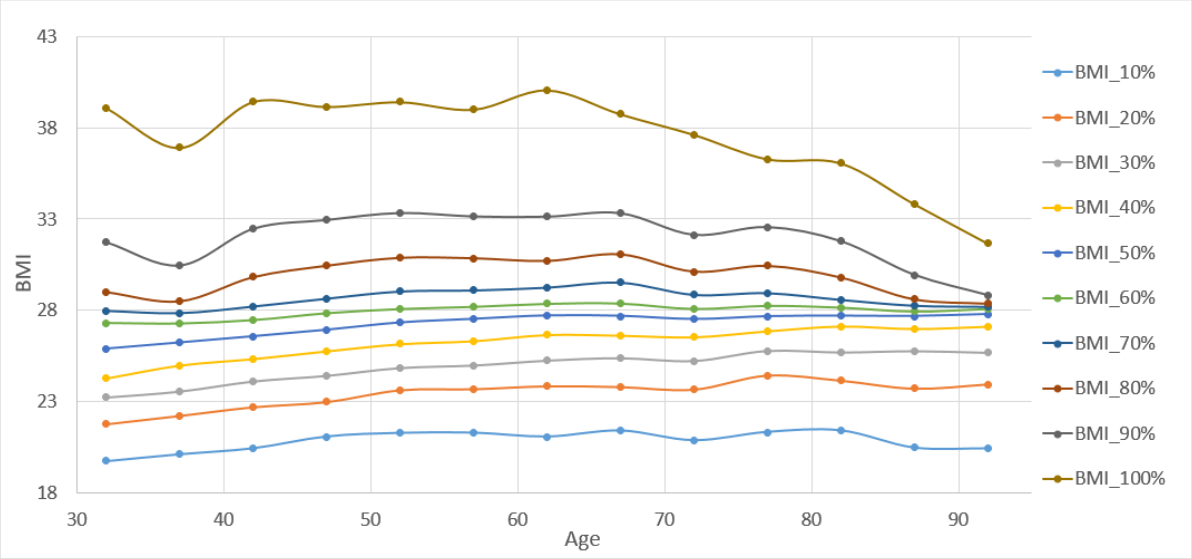


Figure 5: Mean Physical Activity METS per week for each decile of the HSE 2014 population [2]

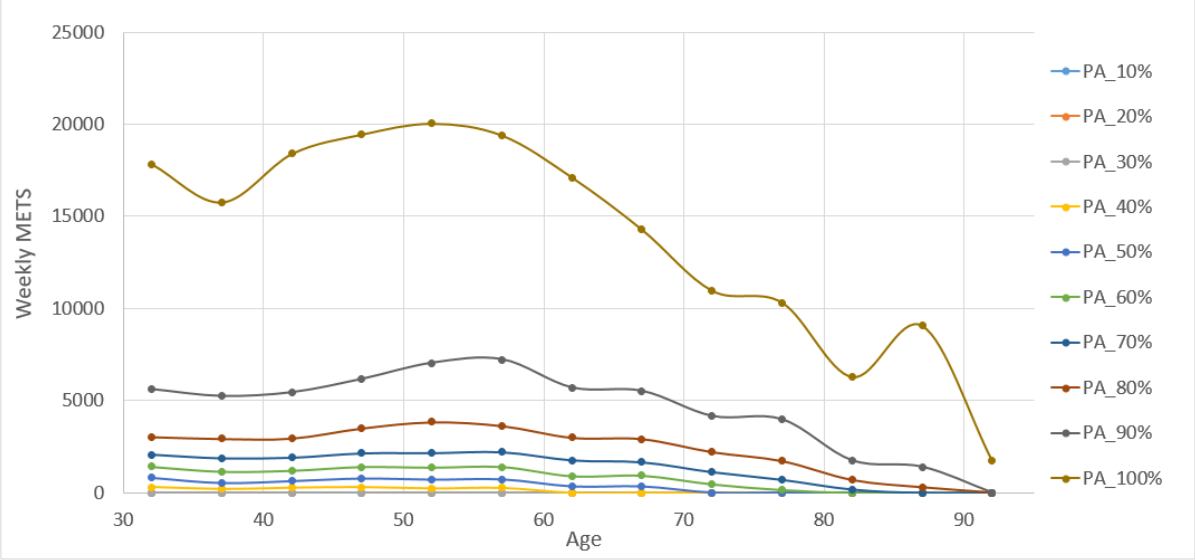
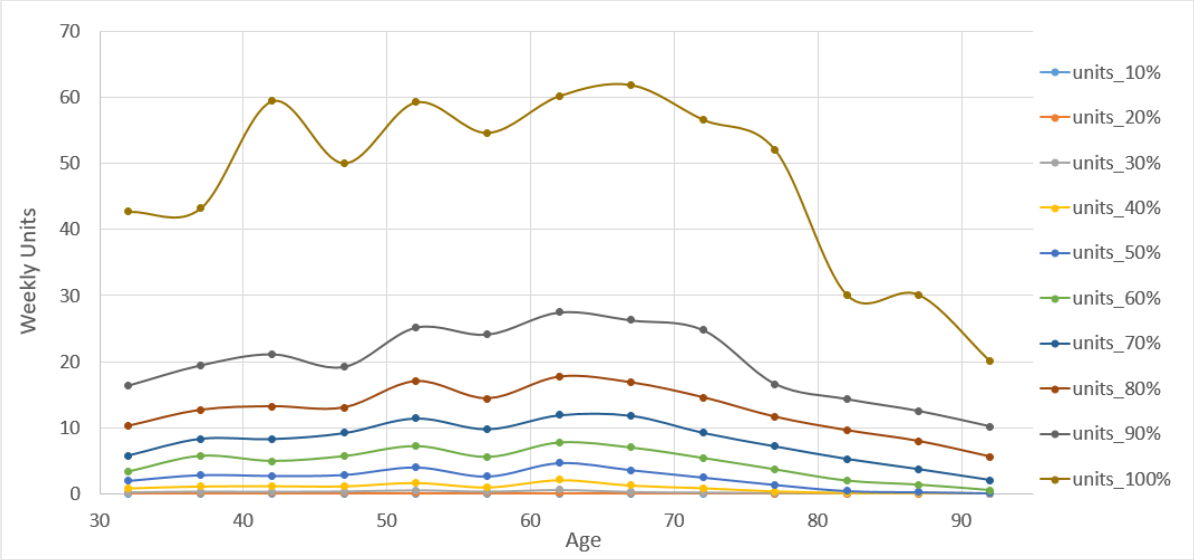


Figure 6: Mean alcohol units per week for each decile of the HSE 2014 population [2]



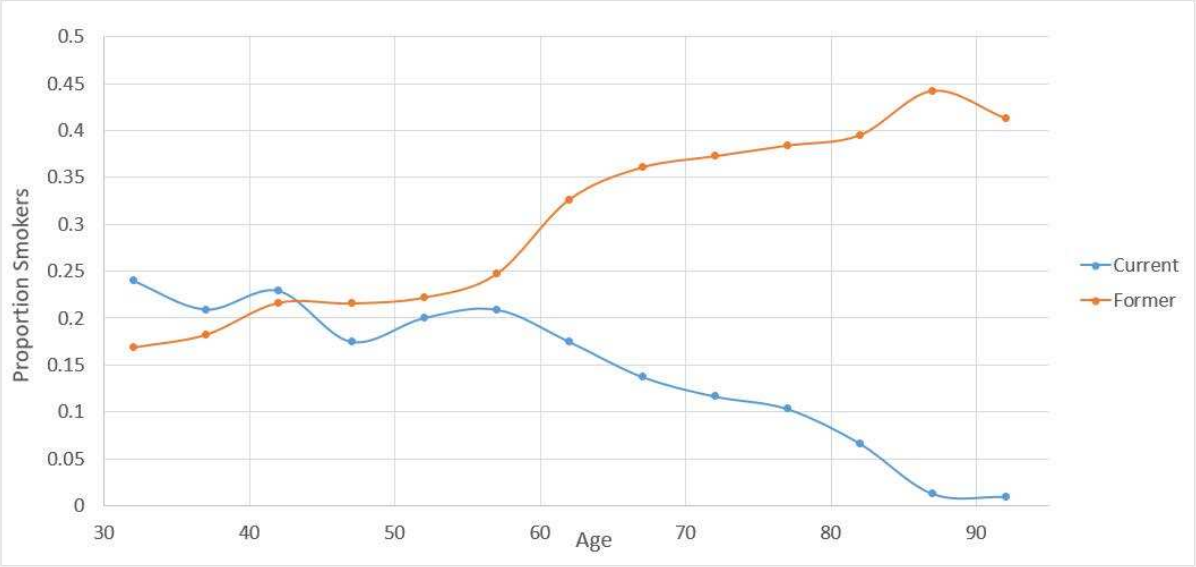
The percentile method was implemented in the model by assigning each person to the relevant decile for BMI, physical activity and alcohol units based on the surveyed values for these measurements at their surveyed age. BMI, physical activity and alcohol units for each individual were then altered to follow the trajectory corresponding to the relevant decile and current age of the individual in the model. Using deciles rather than smaller percentiles does mean that some individual level variation is removed from the model (i.e. everyone follows one of 10 predefined trajectories); however, this was constrained by the relatively small sample size of HSE 2014, to reduce the amount of noise in the trajectories.

Smoking

Data from HSE 2014 indicates that the number of current smokers reduces by age, whilst the number of former smokers increases, indicating that there is a general trend for smoking cessation from the age of 30. It would therefore be reasonable to assume that no individuals who were surveyed as non-smokers in HSE 2014 would start smoking after the age of 30.

Modelling a change in a binary factor is complex, particularly in a multi-age model, but is likely to have little impact on the performance of risk models given that the difference in relative risk of CRC between current and former smokers is small (see the Modelling Individual Cancer Risk section). The trend for current smokers to become past smokers as they age was therefore not implemented in this version of the model; however, it may be incorporated into future model versions.

Figure 7: The proportion of current and former smokers by age in the HSE 2014 population [2]



EQ-5D

EQ-5D decreases with age, therefore age decrements were applied to each individual's baseline EQ-5D score reflecting their current age in the model, compared with their baseline age. It was assumed that age-related decrements were constant over time. The size of this decrement was calculated using data from a study that pooled several years of HSE data to estimate general population values of EQ-5D by age [5]. Annual age decrement was calculated as the difference between EQ-5D score at ages 80-84 and 30-34, divided by 50, which resulted in a change of -0.00432 (95% CI: -0.00460; -0.00404) for each additional year of age. This process was used both to reduce EQ-5D as individuals age beyond their surveyed age, and to increase EQ-5D in the cohort version of the model where individuals all start at age 30, which may be considerably younger than their surveyed age. EQ-5D at younger ages was constrained to a maximum of 1.

Genetic Characteristics

HSE 2014 does not contain any information about genetic characteristics. Huyghe and others (2019)[6] described identification of over 40 new genetic risk variants for CRC, using data from genome-wide small nucleotide polymorphism (SNP) genotyping of over 125,000 different individuals. When combined with previously reported risk variants, this resulted in 120 CRC risk loci with estimated per allele log odds ratios.

Information about the frequency of each risk allele in the English population was obtained from UK Biobank [7], which also provided information about the correlation between risk alleles on each chromosome. Each individual from HSE 2014 was randomly assigned a continuous dosage of each

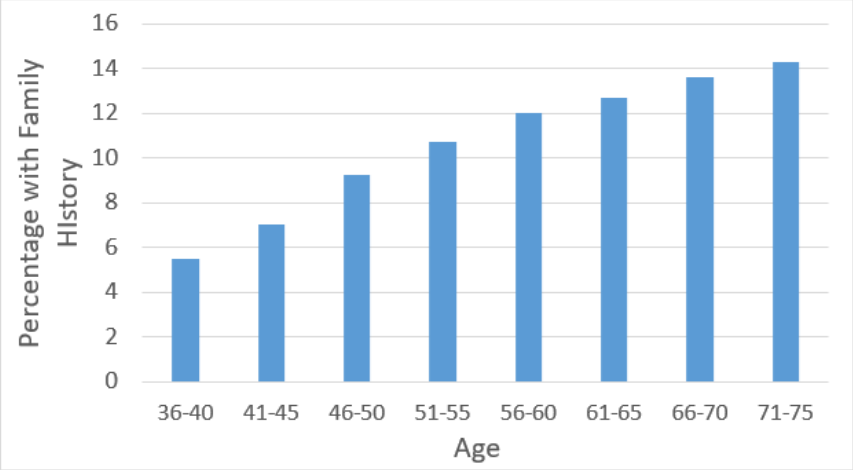
risk allele between zero and two (corresponding to zero, one or two copies of the risk allele at a locus, and equivalent to the output from a genetic imputation algorithm), taking into account the correlations between risk alleles on the same chromosome, but assuming independence between risk alleles on different chromosomes and between genetic and phenotypic characteristics. This is because no data was available on correlation between genetic and phenotypic characteristics.

Family History

HSE 2014 does not contain any information about family history of CRC, which is a risk factor for CRC and included in many risk models. Family history of CRC can be defined in different ways, but for the purposes of this model was defined as having one or more first-degree relatives who had been previously diagnosed with CRC. Information about family history of CRC was obtained from UK Biobank [7]. Family history is correlated with age (Figure 8); however, it would be incorrect to model individual risk levels changing over time due to changes in family history, when in fact it is the knowledge about familial risk that changes, not the risk itself. Instead, two different family history variables were modelled corresponding to true family history and known family history, with true family history used to influence modelled natural history of CRC and known family history used to calculate CRC risk in risk models. For both of these family history at a given age was estimated through fitting a linear model to all data points between the 36-40 and 56-60 age groups from the UK Biobank data (intercept = -0.07266 [95% CI: -0.083 to -0.0616] and age coefficient = 0.00337 [95% CI: 0.0035 to 0.0032]).

True family history was assigned randomly to 12.9% of individuals, corresponding to the proportion estimated to have a family history aged 60. Age 60 was chosen to represent the average age at which the familial relative risk for CRC used in the model had been calculated (see Modelling Individual Cancer Risk section). Known family history was assigned to a subset of those individuals with true family history, corresponding to the age at which a risk model might be used to estimate CRC risk (ranging between age 30 and 60, depending upon model user input). Individuals were randomly assigned to having family history as no evidence was available to correlate family history with other characteristics already included in the model.

Figure 8: Graph showing increase in family history of CRC with age, from UK Biobank [7]



Single-Aged Cohort versus Multi-Aged Cohort

The model was set up to enable a single-aged cohort to be modelled, in order to answer cost-effectiveness questions. A starting age of 30 was chosen, as it could be assumed that all individuals aged 30 would be in the normal epithelium health state (in reality a very small percentage may have adenomas or CRC, but these individuals are likely to represent those with rare monogenic conditions predisposing them to CRC). The cohort was created by artificially setting the ages of all individuals from HSE 2014 to 30. At the same time, adjustments were made to individual BMI, alcohol consumption, physical activity and EQ-5D to reflect the change in age, based on the methods described above. Summary statistics for this population are shown in Table 4. The cohort was modelled over their lifetime to provide estimates of cost-effectiveness for fully rolled out screening strategies.

For resource use questions, it is essential that the baseline population should represent the current population of England, i.e. a multi-aged cohort. In theory, this can be approximated using the HSE 2014 population with survey weights (Table 4). Because baseline individuals start at a range of different ages, it would be necessary to simulate a starting health state for each individual, rather than assuming all individuals were in normal epithelium. This functionality has not yet been added to the model, but will be available in future model versions.

Table 4: Summary statistics for the model population at baseline, for multi-aged and single-aged cohorts. All characteristics come from HSE 2014 [2] apart from probability of family history, which comes from UK Biobank [7].

Characteristic	**Mean (HSE 2014)**	**Standard Deviation**	**Weighted Mean at Multi-Aged Cohort Model Start**	**Weighted Mean at Single-Aged Cohort Model Start (Age 30)**
Age (years)	55.2	15.5	53.9	30
BMI (kg/m^2)	28.0	4.9	27.9	27.0
Alcohol Consumption in Drinkers (units/wk)	12.8	21.2	12.9	10.0
Physical Activity in the Active (METS/wk)	4621.8	6685.9	4560.4	5230.6
EQ-5D Score	0.841	0.227	0.847	0.950
	Number in HSE 2014	**Percentage in HSE 2014**	**Weighted Percentage (Multi-Aged Cohort)**	**Weighted Percentage Single-Aged Cohort)**
Male	3011	44.4%	48.3%	48.3%
Ethnicity: White	6105	90.0%	88.6%	88.6%
Ethnicity: Asian	395	5.8%	6.8%	6.8%
Ethnicity: Black	164	2.4%	2.6%	2.6%
IMD1	1546	22.8%	22.3%	22.3%
IMD2	1424	21.0%	20.9%	20.9%
IMD3	1346	19.8%	19.7%	19.7%
IMD4	1289	19.0%	19.7%	19.7%
IMD5	1182	17.4%	17.4%	17.4%
Current Smoker	1134	16.7%	17.4%	17.4%
Former Smoker	1909	28.1%	27.7%	27.7%
Non drinker	1158	17.1%	17.2%	17.2%
Non active	2888	42.6%	41.4%	41.4%
Family History Age 30	NA	NA	2.8%	2.8%
Family History Age 35	NA	NA	4.5%	4.5%
Family History Age 40	NA	NA	6.2%	6.2%

Family History Age 45	NA	NA	7.9%	7.9%
Family History Age 50	NA	NA	9.6%	9.6%
Family History Age 55	NA	NA	11.3%	11.3%
Family History Age 60 (known family history)	NA	NA	12.9%	12.9%

CRC Natural History

Calibration of unobservable parameters

The natural history module of the model relies upon transitions between the 9 health states as shown in Figure 1, in addition to parameters for symptomatic/chance diagnosis. Transition probabilities cannot be directly observed, so are usually obtained through calibration against target data that can be observed.

The model calibration fitted to several observed data sets: low-risk adenoma prevalence, high-risk adenoma prevalence, undiagnosed CRC, and CRC incidence. The calibration also applied two dependent data sets: diagnosed CRC by stage at diagnosis and undiagnosed CRC by stage. Because of data unavailability, only CRC incidence data were retrieved from English sources [8]. The prevalence of low- and high risk adenoma and undiagnosed CRC in the population was estimated from the detection rates of lesions by single colonoscopy screening reported in the large population German study reported by Brenner (2013, 2014)[9-11] adjusted by colonoscopy sensitivity and relative prevalence of advanced versus high risk adenomas[12-14].

Transition between precancerous health states: Normal epithelium->Low risk adenoma; Low risk adenoma->high risk adenoma; high risk adenoma-> CRC_Dukes' A; Normal Epithelium-> CRC_Dukes' A (estimated separately for males and females to represent differing CRC incidence).

CRC stage progression: CRC Dukes' A -> CRC Dukes' B; CRC Dukes' B -> CRC Dukes' C; CRC Dukes' C -> CRC Dukes' D

CRC symptomatic diagnosis: CRC Dukes' A -> CRC Dukes' A diagnosed; CRC Dukes' B -> CRC Dukes' B diagnosed, CRC Dukes' C -> CRC Dukes' C diagnosed; CRC Dukes' D -> CRC Dukes' D diagnosed

The main assumptions of the calibration process were the following:

- Pre-cancer transitions and transitions to CRC are assumed to be sex and age-specific, while transitions between CRC stages and symptomatic presentation rates are assumed to be age and sex independent due to a lack of data to confirm otherwise.

- 15% of CRC cases among men and 15% of CRC cases among women are assumed to develop through the serrated neoplastic pathway, this rate was reported in the British Society of Gastroenterology position statement [15].

- The first cases of CRC in England in 2005[16] were among 15-19 years old, so it was assumed that the transition probability from normal epithelium to CRC stage A at age 15 is equal to zero and

that it linearly increases to a maximum value at age 100 years. The transition rate at age 100 was determined within the first stage of the calibration process.

- The annual probability that an individual is diagnosed increases with more advanced cancer stage. The probability of diagnosis at stages CRC A and B was assumed to be lower in older people who are more likely to have other comorbid conditions, so an age-related linear decrement in the probability of diagnosis was applied to individuals aged over 75.

Calibration process

The calibration used the Metropolis–Hastings algorithm to estimate the posterior probability distributions of model parameters. The starting parameter set was manually calibrated to receive an approximate fit to all independent data targets. For each data set, a measure of model fit was calculated as the sum squared error (SSE) between the model predictions (scaled to the same population size as the target data set) and the observed data. The objective function which we aim to minimise includes the total SSE from each of the target data sets. The SSE for each target data sets was adjusted by dividing by variance. A parameter epsilon was used to determine the maximum step size for each iteration of the algorithm. The epsilon value was set to 10% of the parameters values. As the algorithm converges on the solution parameter set it is efficient to reduce the maximum step size. This tuning was achieved by using an epsilon multiplier, which was initially set to one and subsequently decreased by 20% if during the last 25 calibration cycles two or less parameter sets were accepted. The probability of accepting a proposal set which increases the objective function by more than 5 is less than 10%.

Calibration outcomes

The calibration approach applied, allowed a good fit to each of the four main data sets (Figure 9 to Figure 14).

Figure 9: Prevalence of low-risk adenoma predicted by the model and target data

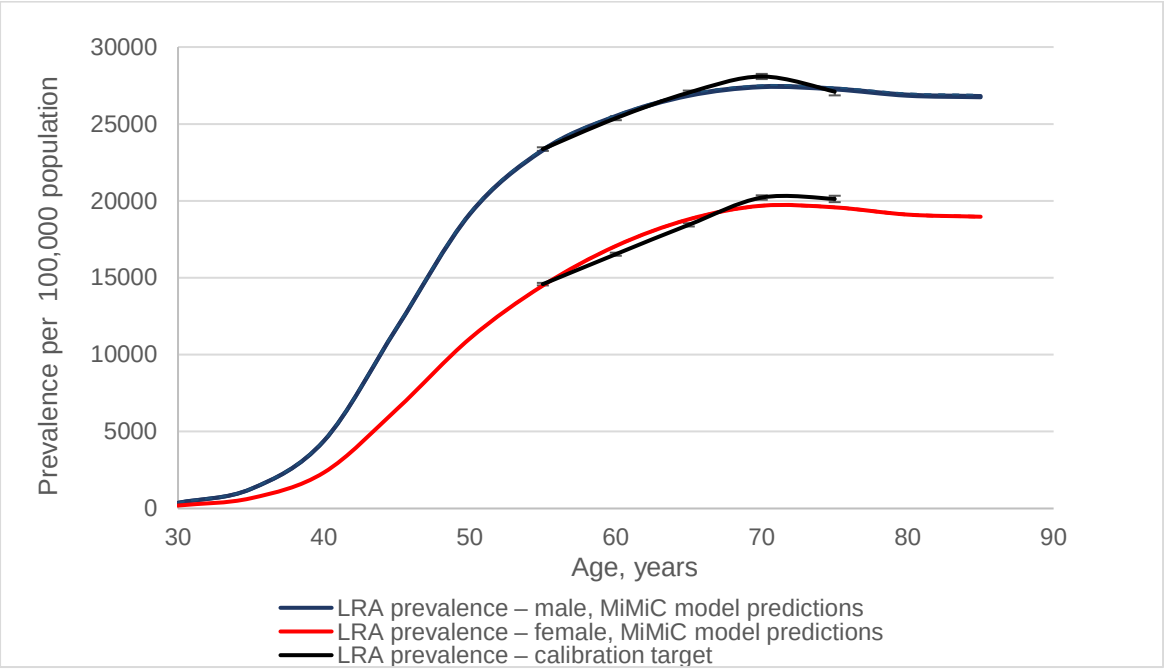


Figure 10: Prevalence of high-risk adenoma predicted by the model and target data

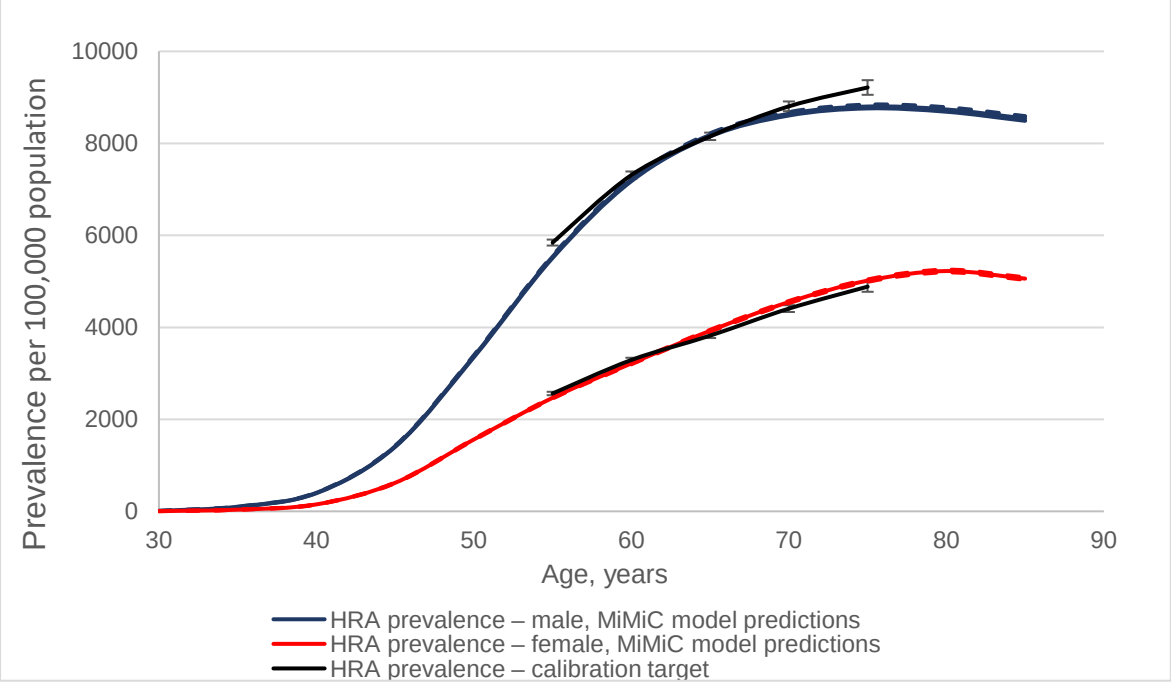


Figure 11: Prevalence of CRC predicted by the model and target data

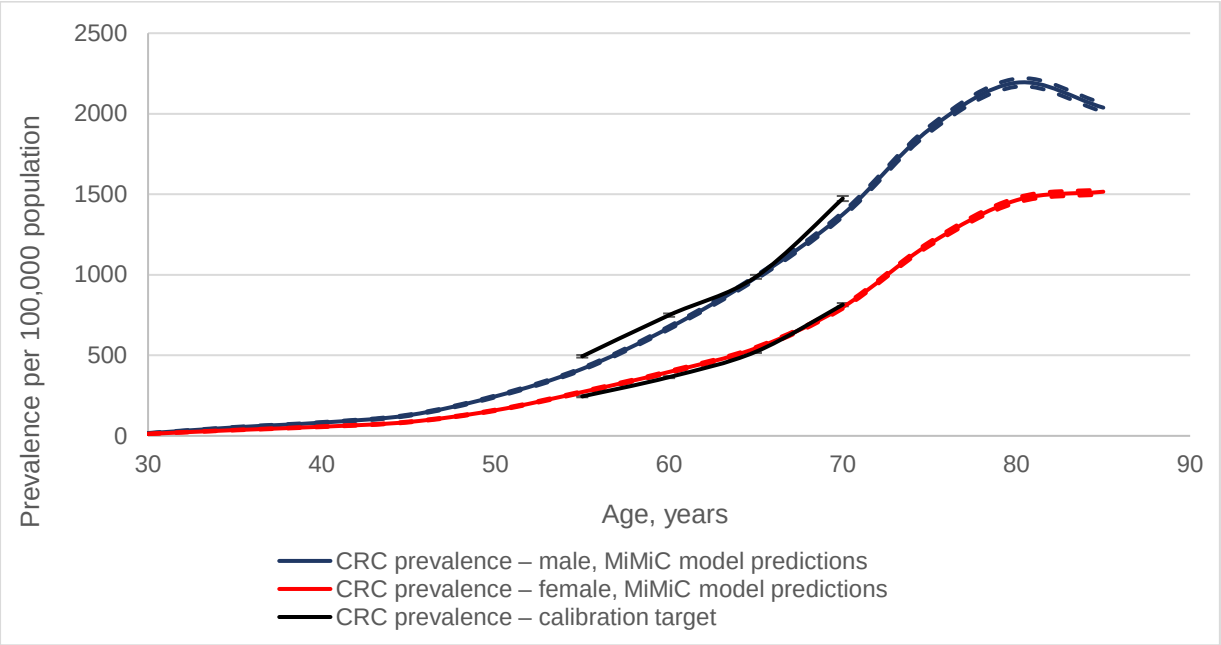


Figure 12: Incidence of CRC predicted by the model and target data

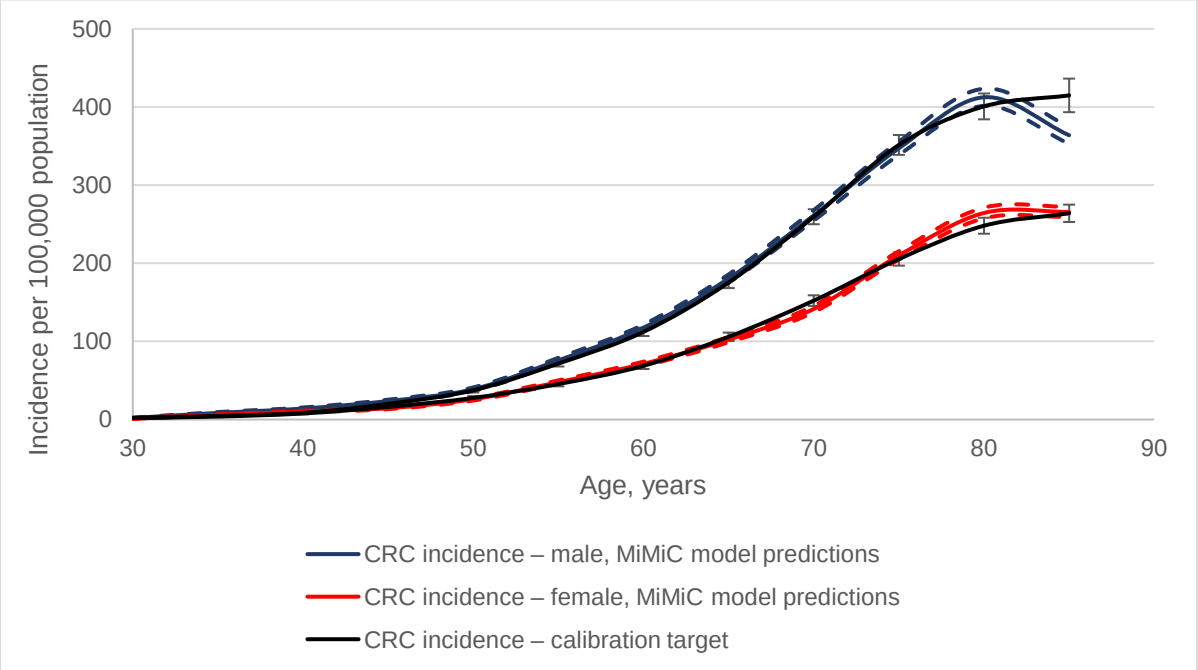


Figure 13: Incidence of CRC by stage among males predicted by the model and target data

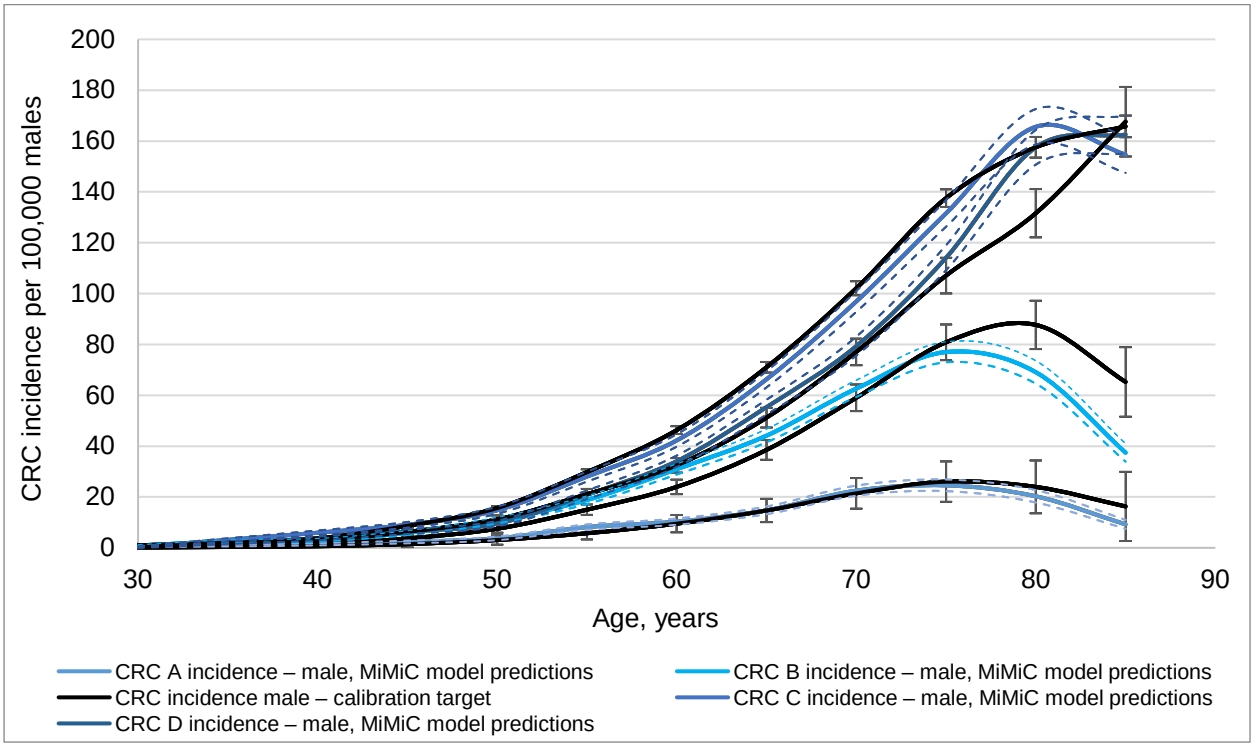
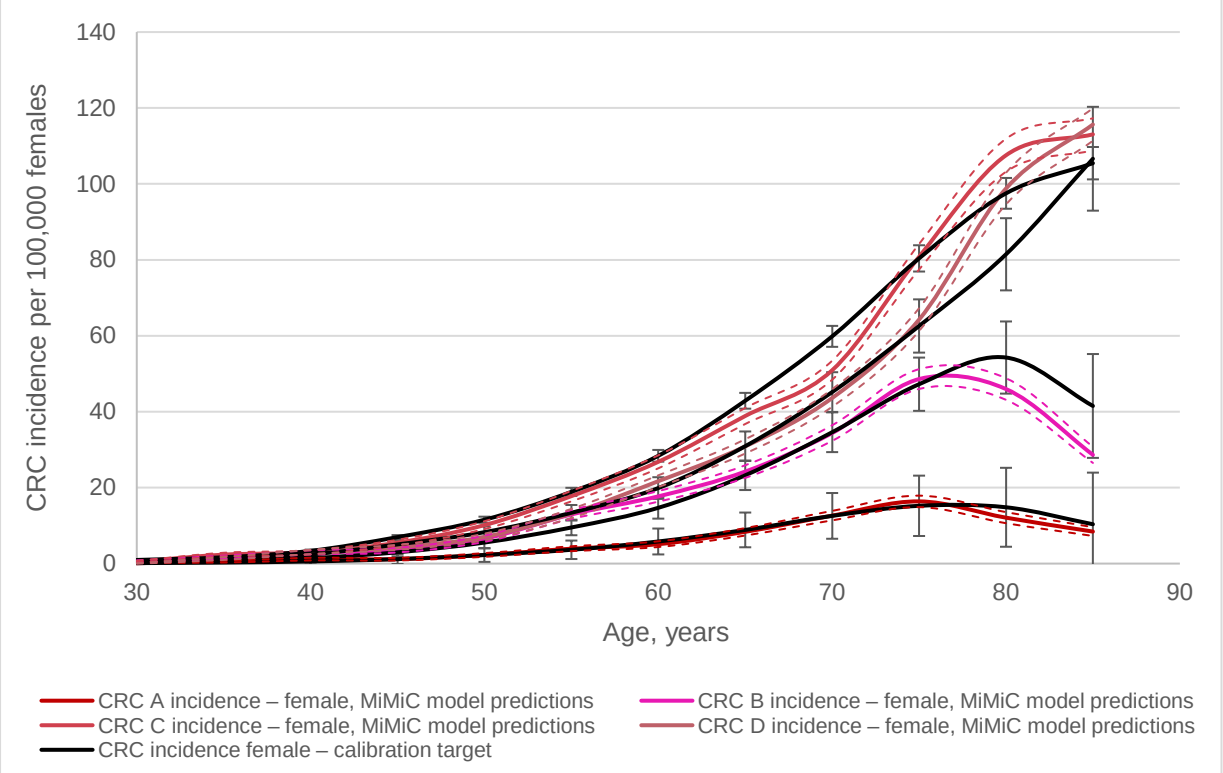


Figure 14: Incidence of CRC by stage among females predicted by the model and target data



The calibrated values of the parameters are reported in Table 5.

Table 5: Calibrated parameter values

Parameter	**Calibrated Mean Value**
Transition probability from normal epithelium to low-risk adenoma, male, age 37	0.0020
Transition probability from normal epithelium to low-risk adenoma, male, age 47	0.0268
Transition probability from normal epithelium to low-risk adenoma, male, age 57	0.0149
Transition probability from normal epithelium to low-risk adenoma, male, age 67	0.0082
Transition probability from normal epithelium to low-risk adenoma, male, age 77	0.0044
Transition probability from normal epithelium to low-risk adenoma, male, age 87	0.0032
Transition probability from low-risk adenoma to high-risk adenoma, male, age 37	0.0282
Transition probability from low-risk adenoma to high-risk adenoma, male, age 47	0.0313
Transition probability from low-risk adenoma to high-risk adenoma, male, age 57	0.0206
Transition probability from low-risk adenoma to high-risk adenoma, male, age 67	0.0121
Transition probability from low-risk adenoma to high-risk adenoma, male, age 77	0.0155
Transition probability from low-risk adenoma to high-risk adenoma, male, age 87	0.0093
Transition probability from high-risk adenoma to colorectal cancer, male, age 37	0.0092
Transition probability from high-risk adenoma to colorectal cancer, male, age 47	0.0163
Transition probability from high-risk adenoma to colorectal cancer, male, age 57	0.0181
Transition probability from high-risk adenoma to colorectal cancer, male, age 67	0.0284
Transition probability from high-risk adenoma to colorectal cancer, male, age 77	0.0502
Transition probability from high-risk adenoma to colorectal cancer, male, age 87	0.0352
Transition probability from normal epithelium to low-risk adenoma, female, age 37	0.0012
Transition probability from normal epithelium to low-risk adenoma, female, age 47	0.0162
Transition probability from normal epithelium to low-risk adenoma, female, age 57	0.0115
Transition probability from normal epithelium to low-risk adenoma, female, age 67	0.0083
Transition probability from normal epithelium to low-risk adenoma, female, age 77	0.0040
Transition probability from normal epithelium to low-risk adenoma, female, age 87	0.0030
Transition probability from low-risk adenoma to high-risk adenoma, female, age 37	0.0175
Transition probability from low-risk adenoma to high-risk adenoma, female, age 47	0.0285
Transition probability from low-risk adenoma to high-risk adenoma, female, age 57	0.0145
Transition probability from low-risk adenoma to high-risk adenoma, female, age 67	0.0144
Transition probability from low-risk adenoma to high-risk adenoma, female, age 77	0.0199
Transition probability from low-risk adenoma to high-risk adenoma, female, age 87	0.0114
Transition probability from high-risk adenoma to colorectal cancer, female, age 37	0.0047
Transition probability from high-risk adenoma to colorectal cancer, female, age 47	0.0208
Transition probability from high-risk adenoma to colorectal cancer, female, age 57	0.0272
Transition probability from high-risk adenoma to colorectal cancer, female, age 67	0.0359

Transition probability from high-risk adenoma to colorectal cancer, female, age 77	0.0650
Transition probability from high-risk adenoma to colorectal cancer, female, age 87	0.0531
Transition probability from normal epithelium to colorectal cancer	0.0006
Annual decrement in symptomatic cancer A,B presentation among people older than 75 years	0.0361
Probability of death undiagnosed at stage D	0.0400
Transition probability from colorectal cancer stage A to stage B	0.2932
Transition probability from colorectal cancer stage B to stage C	0.5539
Transition probability from colorectal cancer stage C to stage D	0.3500
Probability of being symptomatic, colorectal cancer stage A	0.0203
Probability of being symptomatic, colorectal cancer stage B	0.1429
Probability of being symptomatic, colorectal cancer stage C	0.2741
Probability of being symptomatic, colorectal cancer stage D	0.2500

Modelling Individual Cancer Risk

Modelling Individual Cancer Risk for Natural History Transitions

Individualised cancer risk, based on phenotypic and genetic risk factors beyond that conferred by age and sex, was incorporated into the model through modification of the first transitions from normal epithelium to low risk adenoma (representing the adenoma-carcinoma pathway) and from normal epithelium to CRC Stage A (representing the serrated pathway). This approach was used for two reasons. Firstly, modification of a single transition probability rather than all three transitions leading to CRC through the adenoma-carcinoma pathway simplified the process of incorporating individual cancer risk considerably. Secondly, the evidence from Brenner et al (2013/2014 indicates that male/female differences in transition probabilities are only significant for the first transition [9 10], suggesting that differences in CRC risk are implemented through differences in adenoma risk. It appeared to be a reasonable assumption that this could be extended to differences in risk due to other characteristics. There is no information about how phenotypic and genetic risks impact on the serrated pathway compared with the adenoma-carcinoma pathway. However, it seems biologically plausible that the same risk factors could apply to both pathways, so it was assumed in the model that risk factors acted equally on both transitions.

Modelling genetic risk for natural history transitions

It was assumed that an individual's true genetic risk of CRC was represented by all the risk alleles known about to date; i.e. the 120 alleles described in Huyghe et al (2019) [6]. Genetic risk for each individual was calculated as the sum of the per allele log odds ratio estimates for each of the 120 genetic risk loci multiplied by the dosage for each of the simulated risk alleles.

$$prs = \sum(allele.freq * allele.logOR)$$

Where prs = individual genetic risk score, allele.freq = dosage for each of the simulated risk alleles, allele.logOR = per allele log odds ratio estimate for each of the simulated risk alleles.

Individual genetic risk was then standardised by subtracting the population weighted mean genetic risk score and dividing by the weighted risk score standard deviation as follows:

$$stprs = (prs - wtdmean(prs)) / wtdsd(prs)$$

Where stprs = individual standardised genetic risk score, prs = individual genetic risk score, wtdmean(prs) = weighted population mean of the genetic risk score and wtdsd(prs) = weighted population standard deviation of the genetic risk score.

This was then converted into an individual relative risk using the following equation:

Individual RR = exp (wtdsd(prs) * stprs)

where stprs = individual standardised genetic risk score and wtdsd(prs) = weighted population standard deviation of the (non-standardised) genetic risk score.

Modelling phenotypic risk for natural history transitions

Relative risks for CRC relating to a range of different environmental risk factors were obtained from a recent study by Brown et al (2014) [17] calculating the fraction of cancer attributable to modifiable risk factors in the UK (Table 6). Risk factors for CRC included smoking, alcohol consumption, (lack of) physical activity, red meat consumption, (lack of) fibre consumption and BMI. The study looked at some other risk factors (e.g. air pollution, occupation, infections, radiation and oral contraceptives), but no data was found relating to these for CRC. Modifiable risk factors incorporated in the model were those for which information was available in HSE 2014 [2]; i.e. smoking, alcohol consumption, physical activity and BMI. Neither fibre nor red meat consumption were detailed in HSE 2014 and no simple method was available for imputing these from other HSE 2014 characteristics, so these were not included in the modelled CRC risk estimates.

In addition to these modifiable phenotypic risk factors, family history of CRC and ethnicity were also included in phenotypic risk. Individuals having one or more first-degree relatives previously diagnosed with CRC have been found to have a risk of CRC that is around 2.2 fold greater than those without family history [18]. Family history is likely to occur through a mixture of shared genetics and shared environment. The proportion of familial relative risk already accounted for by the Huyghe et al (2019) genetic risk factors described above was estimated in that study as 11.9% [6]. To avoid double counting, familial risk was adjusted to remove this genetic component, resulting in a relative risk of 2.003. No evidence was available to inform the proportion of familial risk arising from each of the modifiable risk factors already incorporated in the model, so no further adjustments to familial risk were made.

Ethnic differences in CRC incidence in England are very large, with most minority ethnic groups having a much lower risk of CRC than the white population. It is thought that this is likely to be partially due to differences in diet between white and non-white populations, but may also be partially genetic. Differences in risk by ethnic groups (white, black, south Asian and other) were taken from QCancer research [19], which is based on English primary care data. Data for each ethnic group used in the model was combined using a weighted average as follows: black = black African and Caribbean; Asian = Indian and Pakistani and Bangladeshi and other Asian; Other = Chinese and Other.

In order to ensure that the overall risk in the modelled population remained unchanged (i.e. product of all relative risks equals 1), it was necessary to adjust relative risks for each risk factor using the following equation:

Individual RR = Unit RR (from Table 6) ^ (Individual Value - Population Average Value)

Where individual value is the HSE 2014 data entry for that individual, by unit stated in Table 6, and population average value is the mean, weighted value in the HSE 2014 sample.

For binary characterisics (e.g. current smoker), the individual value was considered to be 1 for an individual possessing that characteristics, and 0 for an individual not possessing that characteristics, with the population mean value representing the proportion of current smokers in the population. Individual relative risks for each phenotypic risk factor were multiplied together to produce a personalised risk of CRC due to phenotypic risk factors. This was then multiplied by each person's individual genotypic risk to produce an overall personalised relative risk of CRC for each modelled individual. For each individual, a personalised probability of transition from normal epithelium to low risk adenoma, or from normal epithelium to CRC stage A was calculated by multiplying their personalised relative risk by the relevant calibrated age and sex specific transition probability.

Calibration of relative risks for natural history transitions

Relative risks described above represent the lifetime relative risk of CRC. However, application of the relative risks at the level of the transitions from normal epithelium to low risk adenoma and normal epithelium to CRC stage A does not translate into equivalent relative risk of CRC, so values had to be adjusted through calibration.

A simple iterative process was chosen which incorporated the following steps:

1. The model was run for 200 sets of individuals in HSE 2014 population using a starting set of relative risks to calculate personalised transitions from normal epithelium to low risk adenomas, and normal epithelium to CRC stage A for each individual. Initially this starting set was based on the published relative risks described in Table 6 and the default individualised genetic relative risks calculated from the Huyghe et al (2019) paper [6].
2. Following model running, the weighted incidence of CRC in individuals with and without each characteristic was calculated and a modelled relative risk of CRC calculated. For genetic risk, the modelled relative risk was calculated as the weighted incidence in individuals with a Huyghe relative risk of above one divided by the weighted incidence in individuals with a Huyghe relative risk of below 1 (i.e. high genetic risk vs low genetic risk).

3. Modelled relative risk was compared against the target (published) relative risk for each characteristic. Multipliers were calculated as target relative risk/modelled relative risk.
4. Multipliers were applied to the starting set used for the last set of model runs, to create a new starting set of relative risks for each characteristic.

This process was repeated multiple times until values converged. Convergence occurred within 10 iterations for all relative risks. Lower and upper confidence intervals were estimated to be in proportion with target lower and upper confidence intervals for phenotypic risks, and were calculated directly for genetic risk from the standard deviation of the population distribution of risk. To simplify the calibration process, it was assumed that all risk factors were fixed over an individual's lifetime, for modifiable risk factors taking the original value given in or imputed from the HSE 2014 (i.e. no changes in BMI, alcohol units or physical activity). Table 6 shows both the published and calibrated relative risks.

Table 6: Published and calibrated relative risks of CRC for phenotypic risk factors included in the model. Published RRs taken from Brown et al. (2014) [17] (all risk factors apart from ethnicity, family history and genetic risk) from Hippisley-Cox et al (2015)[19] (ethnicity), from Lowery et al. (2016) [18] (family history), and calculated from Huyghe et al (2019) [6] (genetic RRs).

Risk Factor	**Description**	**Sex**	**Target (published)**			**Calibrated**		
			Mean	***Lower CI***	***Upper CI***	**Mean**	***Lower CI***	***Upper CI***
Smoking	Current vs Never	Male	1.22	1.07	1.39	1.38	1.12	1.72
		Female	1.22	1.07	1.39	1.38	1.12	1.72
	Former vs Never	Male	1.14	1.05	1.25	1.19	1.06	1.35
		Female	1.14	1.05	1.25	1.19	1.06	1.35
Overweight & Obesity	Overweight vs Healthy	Male	1.17	1.12	1.22	1.29	1.20	1.38
		Female	1.07	1.01	1.14	1.11	1.02	1.23
	Obese vs Healthy	Male	1.38	1.32	1.44	1.74	1.62	1.88
		Female	1.17	1.06	1.30	1.33	1.11	1.61
Alcohol (8g per unit)	Light (<12.5g per day) vs Never	Male	1	0.94	1.05	0.85	0.79	0.90
		Female	1	0.94	1.05	0.85	0.79	0.90
	Moderate (12.5-50g per day) vs Never	Male	1.17	1.09	1.25	1.03	1.02	1.05
		Female	1.17	1.09	1.25	1.03	1.02	1.05
	Heavy (50g+ per day) vs Never	Male	1.33	1.14	1.56	1.16	1.07	1.26
		Female	1.33	1.14	1.56	1.16	1.07	1.26
		Male	0.903	0.851	0.952	0.84	0.75	0.92

Physical Activity (METS)	>600 METS vs <600 mins per week	Female	0.903	0.851	0.952	0.84	0.75	0.92
Ethnicity	Black vs White	Male	0.73	0.56	0.97	0.57	0.34	0.95
		Female	0.70	0.52	0.96	0.65	0.45	0.95
	South Asian vs White	Male	0.55	0.40	0.76	0.41	0.26	0.67
		Female	0.51	0.34	0.77	0.42	0.25	0.72
	Other vs White	Male	0.64	0.46	0.89	0.43	0.23	0.80
		Female	0.75	0.55	1.04	0.70	0.47	1.04
Family History (first degree relative with CRC, adjusted to remove genetic risk)	Family history vs no family history	Male	2.003	1.47	2.48	3.05	1.86	4.31
		Female	2.003	1.47	2.48	3.05	1.86	4.31
Genetic risk calculated from data in Huyghes et al. 2019 paper	High genetic risk (RR > 1) vs low genetic risk (RR < 1)	Both	1.071	NA	NA	1.730	NA	NA
NA = Not Applicable (constant)								

Modelling Individual Cancer Risk for Risk Prediction

A variety of different risk prediction scores were incorporated into the model to enable screening strategies based on risk stratification to be assessed. This included the Ma model for prediction of CRC risk based on phenotypic factors only [20], the Jeon model for prediction of CRC risk based on genetic factors only [21], and the Dunlop model for prediction of CRC risk based on genetic and phenotypic factors [22].

Genetic risk is fixed, whilst phenotypic risk changes over the course of a person's life. As a consequence of this, genetic risk scores were calculated just once in the model at population setup. Calculation of relative risk for the Jeon score was done in a similar way to that for the Huyghe genetic risk, using information about allele frequency from UK Biobank [7], and the odds ratio per risk allele from the Jeon paper [21]. The Jeon score uses information about 57 SNPs.

The Dunlop model uses a points-based scoring system to calculate absolute risk based on 10 SNPs, age, sex and family history, based on Scottish data [22]. The genetic component of the risk score was calculated just once in the model at population setup, whilst calculation of the final risk score, including phenotypic risk, was performed annually within the model to reflect changes in age over

time. Average risk for each age group was given in the Dunlop paper, so the absolute risk score given by the Dunlop model was converted to a relative risk by dividing the score by the age-specific absolute risk, and then adjusted to ensure that average risk over the whole weighted population was 1.

The Ma model is a Cox proportional hazards model for calculation of 10-year absolute CRC risk, which includes coefficients for age, BMI, physical activity, alcohol consumption and smoking status [20]. Alcohol consumption categories differ slightly from those used in the model; occasional consumption was assumed to equate to light consumption as defined in Brown et al. (2018) (<87.5g per week) [17]. Calculation of the Ma risk score was performed annually within the model to reflect changes in population characteristics over time, using the following equation:

10-Year Absolute Risk = (1 – baseline survival function ^ exp(∑(β * (value – mean value))))

Where value = individual value for each characteristic, mean value = population mean as given in Ma paper, β = β coefficient for that characteristic, baseline survival function = 10 year baseline survival function.

Table 7: Ma model for 10-year absolute CRC risk-prediction [20]

Risk Factor	B Coefficient	Hazard Ratio (Mean)	Hazard Ratio (Lower 95% CI)	Hazard Ratio (Upper 95% CI)
Age (Year)	0.080	1.08	1.07	1.10
BMI (kg/m^2)	0.047	1.05	1.02	1.08
Physical Activity (MET hours per day)	-0.019	0.98	0.97	0.99
Alcohol Consumption: Never	-0.163	0.85	0.56	1.28
Alcohol Consumption: Occasional	0	1	NA	NA
Alcohol Consumption: Regular <300g/week	0.358	1.43	0.98	2.09
Alcohol Consumption: Regular >=300g/week	0.659	1.93	1.32	2.83
Smoking Status: Never	0	1	NA	NA
Smoking Status: Former	0.071	1.07	0.83	1.39
Smoking Status: Current	0.238	1.27	1.01	1.60

Baseline survival function at 10 years	0.9882	NA	NA	NA

The Ma risk score is based on a population of Japanese men, in whom the absolute risk of CRC is considerably higher than in the UK population (Table 8) [16 20]. The absolute risk score given by the Ma model was therefore converted to a relative risk by dividing the score by the absolute risk in a Japanese male population of the same age as the modelled individuals, and then adjusted to ensure that average risk over the whole weighted population was 1.

An additional genetic plus phenotypic risk score was implemented in the model through combining the Ma and Jeon risk scores [20 21]. This was achieved by simply multiplying together the individual relative risks obtained by each score separately.

Following calculation of a CRC relative risk using any of the risk scores described above, it was necessary to convert this into an age at first FIT screen. The approach used was to base screening start age for all individuals on the age at which they were calculated to reach a user-defined 10-year absolute risk level, assuming that all risk factors apart from age and sex would remain constant. Absolute risk was obtained from CRC incidence rates per 100,000 population by age and sex from CRUK [16], and converted to 10-year absolute risk using the following equation.

10-Year Absolute Risk = 1 - exp(-10 * rate / 100000)

Screening start age was calculated as the age at which absolute risk was equal to user-defined risk divided by the individual relative risk score.

Table 8: 10-year absolute CRC risk in Japanese and UK populations, from Ma et al (2010) [20] and derived from CRUK [16] respectively.

Age Group	Japanese Population	UK Population (Male)	UK Population (Female)
40-44	0.5%	0.13%	0.12%
45-49	0.9%	0.23%	0.21%
50-54	1.4%	0.47%	0.38%
55-59	1.9%	0.84%	0.61%
60-64	2.7%	1.51%	0.91%
65-69	3.0%	1.98%	1.19%

Survival and Mortality

CRC Mortality

Individuals can either die from CRC or from other causes. Survival following CRC diagnosis is known to vary by age, sex, socioeconomic deprivation, diagnostic route, cancer stage, cancer location and time since diagnosis, and has also seen significant improvements in recent years, some of which may reflect an increase in diagnosis through screening, which has improved survival compared to symptomatic diagnosis [23-27]. However, detailed and up-to-date information about CRC survival, taking all these variables into account, is not currently available for England. Instead, available information from a variety of sources was combined to produce an estimate of survival for the first ten years following CRC diagnosis by age, sex and stage. It was assumed that anyone surviving for ten years post-diagnosis was cured and would have no further risk of death from CRC.

One and five year net CRC survival data by age group, sex and stage is available from the Office for National Statistics (ONS) based on data from adults diagnosed between 2013 and 2017 in England [28] (Table 9).

Table 9: Net one and five year survival by age group, sex and stage for 2013-2017 from ONS [28].

Sex	Age	1 Year					5 Years				
		Stage A	Stage B	Stage C	Stage D	All	Stage A	Stage B	Stage C	Stage D	All
Male	15 to 44	99%	98%	94%	60%	87%	98%	86%	70%	19%	66%
	45 to 54	99%	99%	95%	60%	85%	96%	89%	73%	15%	62%
	55 to 64	99%	97%	95%	57%	86%	96%	88%	73%	14%	66%
	65 to 74	98%	95%	92%	48%	82%	94%	85%	69%	13%	63%
	75 to 79	95%	89%	82%	31%	68%	80%	76%	51%	5%	46%
	All ages	97%	93%	90%	44%	78%	90%	82%	64%	10%	57%
Female	15 to 44	100%	99%	97%	61%	88%	98%	92%	79%	17%	70%
	45 to 54	100%	98%	96%	61%	87%	98%	89%	77%	17%	66%
	55 to 64	99%	98%	96%	55%	86%	96%	90%	77%	15%	67%
	65 to 74	99%	95%	91%	44%	81%	97%	86%	70%	12%	64%
	75 to 79	96%	88%	76%	24%	62%	85%	77%	49%	5%	44%
	All ages	98%	92%	86%	39%	74%	92%	83%	64%	10%	55%

Whilst this data was sufficient to inform one and five year survival, a method was required to estimate survival for years two to four and six to ten post diagnosis. Data about net CRC survival for every year up to ten years after diagnosis from 2010/11 is available from CRUK [29] (Table 10). This is presented by sex, but not by age or stage, and is fairly similar to the ONS values for year one and five survival over all ages and stages. Therefore, it was assumed that the ratio between average five-year survival and other year survival would remain constant. Ratios of five-year survival to all subsequent years were derived using the following equation.

$$Ratio_{(stage,\ age,\ year\ x/year\ 5)} = 1 - ((1 - Ratio_{(stage,\ age,\ year\ 5/\ year\ 1)}) / (1 - Ratio_{(year\ 5/year\ 1)}) * (1 - Ratio_{(year\ x/year\ 5)}))$$

These ratios were then applied to the five-year survival by age, stage and sex to obtain survival for all other years by age, stage and sex (Figure 15).

Table 10: Net survival up to ten years after diagnosis for 2010/11 from CRUK [29]. Note that nine and ten-year survival in women is slightly higher than eight-year survival, so it was assumed in the calculations above that survival was identical in years eight to ten, to avoid negative mortality.

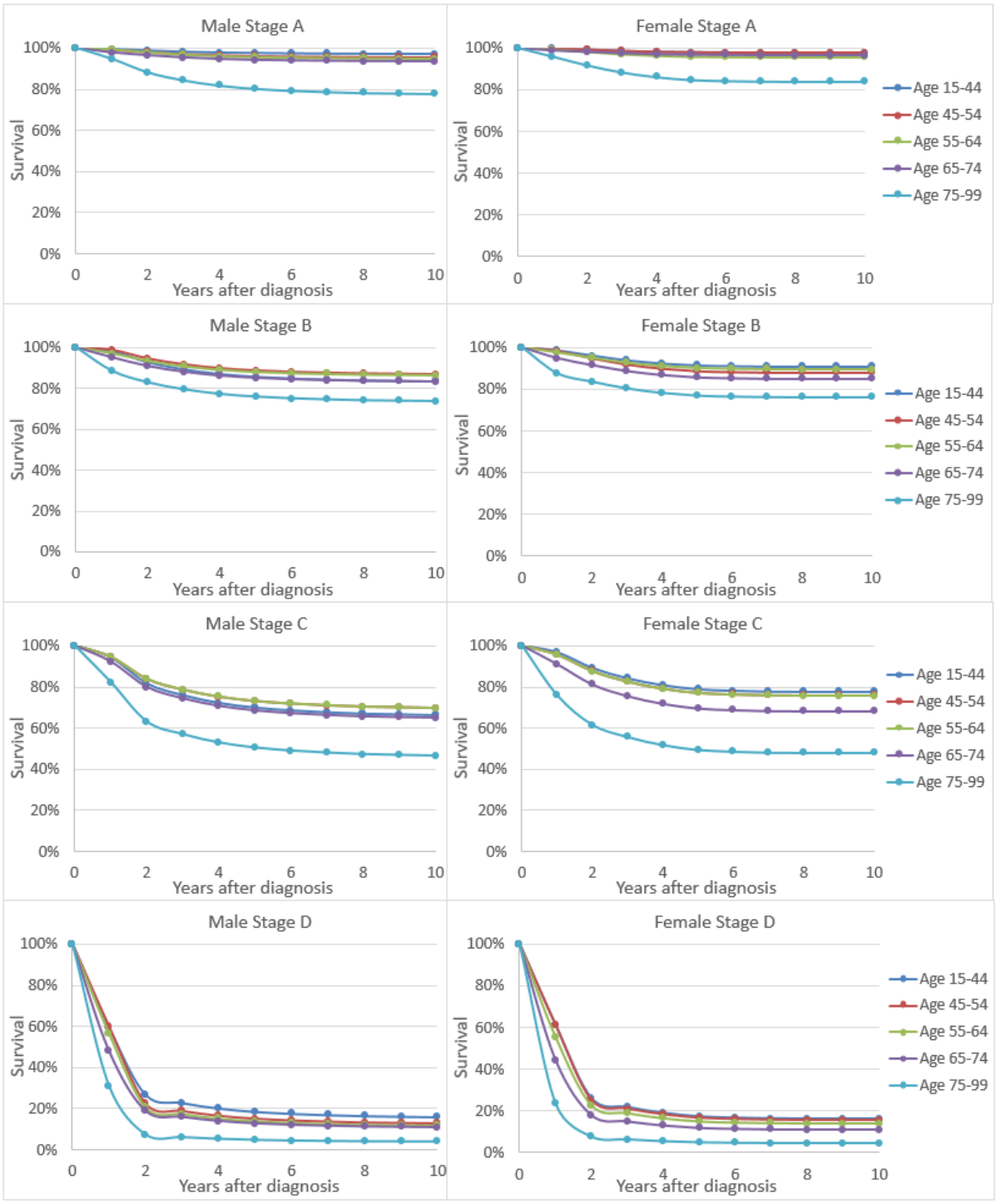
Years after Diagnosis	**Men**	**Women**
0	100.0%	100.0%
1	77.4%	73.9%
2	69.5%	66.3%
3	64.5%	61.9%
4	61.2%	59.5%
5	59.2%	58.2%
6	58.0%	57.5%
7	57.2%	57.1%
8	56.6%	57.0%
9	56.3%	57.1%
10	56.0%	57.2%

Probability of dying due to CRC was calculated from the survival data as follows:

$$CRC\_mort_{(age,\ sex,\ stage,\ year)} = 1 – (CRC\_surv_{(age,\ sex,\ stage,\ year)} / CRC\_surv_{(age,\ sex,\ stage,\ year-1)})$$

It was assumed that the probability of dying from CRC beyond ten years post diagnosis was 0. A multiplier was incorporated into the modelling of CRC mortality to enable model users to globally increase or decrease CRC mortality over all ages, sexes, stages and years since diagnosis.

Figure 15: Imputed CRC survival by age, sex and stage.



Some assumptions had to be made around classification of mortality in undiagnosed individuals with CRC. In practice, mortality from CRC will only be registered as such if diagnosis of CRC has occurred – either prior to death, or following death during a post-mortem. This means that individuals who die from CRC that never get diagnosed will be registered as dying from other causes, and therefore the death certificate data used in the model will reflect this under-diagnosis. This led to two logical alternatives that could be implemented in the model – either individuals who die when undiagnosed

are assumed to die from other causes, or they die from CRC but are automatically diagnosed with CRC within the same model cycle. A combination of these two approaches was chosen, depending upon CRC stage, to reflect the available evidence that a small proportion of diagnoses are noted through death certificates only [30]. For stages A-C, undiagnosed individuals were assumed to have a 0% probability of dying from CRC in any given model cycle. For stage D, undiagnosed individuals were assumed to have the same probability of dying from CRC as those who are in the first year of diagnosis. Of those with undiagnosed stage D that died from CRC, a proportion were assumed to be diagnosed within the year of death, with the rest remaining undiagnosed. The proportion dying from CRC but remaining undiagnosed was obtained through calibration and was assumed to be zero for those aged under 75, then to increase linearly with age above 75.

Other Cause Mortality

All-cause mortality by age and sex was obtained from English life tables for 2016-2018 [31]. This includes mortality from CRC and mortality from other causes. Death registration summary statistics for England and Wales (2018) [32] were used to determine the proportion of all registered deaths that were due to CRC. It was assumed that CRC deaths included deaths due to ICD code C18: Malignant neoplasm of colon and ICD codes C19-21: Malignant neoplasm of rectosigmoid junction, rectum and anus. Anal cancer is not included in CRC, but it was not possible to separate this out from rectal cancer in death registration data. Other cause mortality was then calculated by subtracting CRC mortality from all-cause mortality using the following equation:

$$Oth\_Cause\_Mort_{(age,\ sex)} = All\_Cause\_Mort_{(age,\ sex)} * (1 - (N\_CRC\_Deaths_{(age,\ sex)} / N\_All\_Deaths_{(age,\ sex)}))$$

Screening

As default the model can simulate the two different screening modalities that are currently used in England; Faecal Immunochemical Testing (FIT) and Flexible Sigmoidoscopy (FS). The screening pathways modelled reflect the pathways currently used in England; however, specification of eligibility criteria is flexible to enable a range of different screening strategies to be easily modelled.

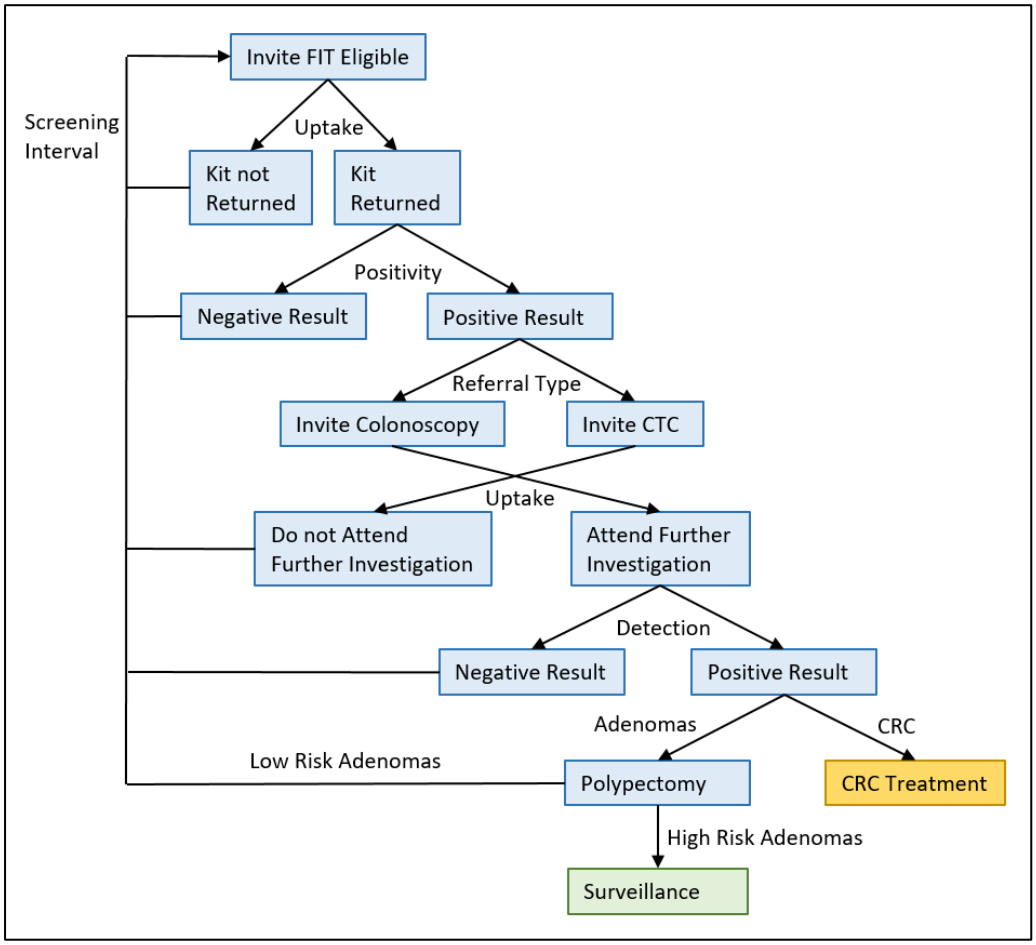
FIT Screening

FIT Eligibility

The modelled FIT screening pathway is shown in Figure 16. Eligible individuals are invited to FIT screening. The default eligibility criteria reflect the current eligibility in England and are specified as follows:

- No history of CRC diagnosis
- Not undergoing surveillance
- Age 60, 62, 64, 66, 68, 70, 70 or 74.

Figure 16: FIT screening pathway and follow-up investigations



FIT Uptake

Response to FIT screening varies depending upon individual characteristics. The English FIT pilot results included a multivariate analysis of adequate uptake which provided odds ratios for uptake by screening modality (gFOBT or FIT), age group, sex, screening episode, deprivation (IMD quintiles) and region [33]. This indicates that uptake is lower in males, older age groups, more highly socioeconomically deprived groups and in screening non-responders. Model coefficients were calculated by taking the log of each odds ratio. Uptake in the reference group (gFOBT, male, age 59-64, IMD1 [least deprived], first screening round, Midlands and North West Hub) was 53.6% (personal communication from Christopher Mathews). This information was used to calculate an intercept for the model using the formula: intercept = -LN((1/x)-1) where x = baseline proportion uptake with gFOBT. The intercept was then adjusted to represent country-wide FIT screening by adding the coefficient for FIT screening and half the coefficient for the Southern Hub region. Odds ratios and model coefficients are shown in Table 11.

Table 11: Odds Ratios from Moss et al (2017) [33] and calculated model coefficients used to predict FIT uptake

Variable	**Odds Ratio (95% CI)**	**Coefficients (95% CI)**
Intercept	NA	0.710 (0.627 to 0.802)
Age 65-69	0.89 (0.88; 0.9)	-0.117 (-0.128 to -0.105)
Age 70+	0.79 (0.78; 0.8)	-0.119 (-0.121 to -0.118)
Sex Female	1.15 (1.14; 1.16)	0.140 (0.131 to 0.148)
Prevalent non-responder	0.16 (0.156; 0.161)	-1.833 (-1.858 to -1.826)
Incident	6.55 (6.45; 6.54)	1.879 (1.864 to 1.878)
IMD2	0.93 (0.91; 0.94)	-0.073 (-0.094 to -0.062)
IMD3	0.86 (0.85; 0.88)	-0.151 (-0.163 to -0.128)
IMD4	0.75 (0.73; 0.76)	-0.288 (-0.315 to -0.274)
IMD5 (most deprived)	0.55 (0.54; 0.55)	-0.598 (-0.616 to -0.598)

Given that the model will be used to assess the impact of screening at ages below 60, data from the Scottish Bowel Screening Programme 2017-18 was used to inform FIT uptake between ages 50 and 60 [34]. FIT uptake in Scotland is 66% in people aged 60-64, but only 60% in people aged 55-59 and 58% in people aged 50-54. This data was converted into log odds coefficients to be used in the regression in the same way as the other coefficients. It was assumed that individuals aged under 50 would have the same uptake as those aged between 50 and 54.

Table 12: Odds Ratios derived from the Scottish Bowel Screening Programme uptake data[34] and calculated model coefficients used to predict FIT uptake

Variable	Odds Ratio (95% CI)	Coefficients (95% CI)
Age 50-54	0.694 (0.694; 0.695)	-0.365 (-0.366 to -0.364)
Age 55-59	0.778 (0.777; 0.778)	-0.252 (-0.252 to -0.251)

There is also evidence that uptake of screening may be lower in some ethnic minority groups. Whilst no evidence about this could be found specifically for FIT screening in England, there was evidence from gFOBT screening in England that people of Asian ethnicity have considerably lower uptake, even after adjusting for deprivation [35]. No evidence could be found to inform uptake in other ethnic minority groups.

Table 13: Odds ratios and calculated model coefficients for uptake of FIT in people of Asian ethnicity compared to non-Asian people [35].

Variable	Odds Ratio (95% CI)	Coefficients (95% CI)
Asian ethnicity	0.390 (0.353; 0.434)	-0.941 (-1.041 to -0.834)

In the FIT pilot, individuals that did not send their FIT screening kit back were sent reminder letters. Amongst those that did return kits, around 2% required an additional kit to be sent before an adequate sample was received. These processes were not explicitly modelled, but were included in costings.

FIT Sensitivity and False Positives

Sensitivity of the FIT test is likely to depend upon a range of factors including FIT threshold, sex, age, screening round and test manufacturer. Published estimates of FIT sensitivity and specificity do exist and have been summarised in a meta-analysis by Lee et al (2014) [36]. This calculated a mean sensitivity of 79% and specificity of 94% for CRC, but the included studies comprised a range of different FIT cut-off points, kit manufacturers, number of samples taken and study populations. These studies have estimated sensitivity through one of two methods, both of which are flawed. Some studies have compared FIT performance against a reference colonoscopy. However; colonoscopy sensitivity is not perfect, particularly for low risk adenomas, and depends upon colonoscopy quality. Other studies have calculated sensitivity based on the number of interval cancers occurring in the two years following the original test. However; this method will miss pre-existing cancers that take more than two years to manifest symptomatically, or include cancers that have developed de novo since screening, which could either over or underestimate sensitivity.

Furthermore, this method cannot inform sensitivity to adenomas. The differences between the population of the included studies and the screening population of England are substantial; many of the studies were carried out in Asian populations who are much younger than the English screening population, and the underlying CRC prevalence in the study populations is much higher than that estimated by the model. Given that the aim of the model was to make decisions around the current BCSP (using FIT screening from spring 2019), it was necessary that estimates of sensitivity were compatible with detection rates found in large scale UK studies, rather than using direct estimates from small, unrepresentative trials.

The method used to calculate sensitivity was similar to that described previously for the ScHARR Bowel Cancer Screening cohort model [37]. Following calibration of natural history transition probabilities, it was possible to use the model to estimate the underlying prevalence of LR adenomas, HR adenomas and CRC in the population for each age and sex, in the absence of screening. This was combined with published data about detection rates to estimate sensitivity for FIT, as sensitivity is calculated as detection rate divided by prevalence. Note that false positive rate, rather than specificity, is used in the model to calculate the risk of false positives in people with normal epithelium, so calculations of specificity were not directly required.

Data about detection rates was available from a range of sources; however, only one English data source was available – the UK FIT Pilot [33]. Data from individuals screened for the first time (prevalent round) in the UK FIT pilot was the most appropriate source to use to inform first round screening sensitivities given that it used the same population, test kit and test protocol as are now being used in the English BCSP. During the pilot, 3,933 individuals aged 60 were screened using FIT for the first time. The UK prevalent round FIT pilot data had some limitations. Firstly, the published data did not include information about detection rates for LR adenomas or about false positives. Secondly, all individuals were aged 60 at the prevalent screen, so no information about sensitivity at other ages could be gathered. Thirdly, the number of individuals diagnosed with CRC as a result of screening was low in the prevalent round (only 6 with FIT20), reducing the accuracy of estimates of CRC sensitivity. To investigate the accuracy of the sensitivity estimates and to investigate trends by age, sex, screening round and FIT threshold, a comparison of FIT pilot detection with data from other countries was carried out (see Appendix C for details). A series of steps were then undertaken to process the data in order to incorporate additional information from other data sources:

1. Detection rates for CRC and HR adenoma at five different FIT thresholds were calculated from the data for prevalent first time screenees from the UK FIT pilot (Table 14) [33]. Note that detection rates for CRC are based on very small numbers, and evidence from our

international comparisons indicated that CRC detection rate was likely to be underestimated by UK FIT pilot data (and underestimated in our previous model).

Table 14: Detection rates from prevalent first time screenees from the UK FIT pilot [33]

	FIT20	**FIT40**	**FIT100**	**FIT150**	**FIT180**
Detection Rate CRC	0.0015	0.0015	0.0008	0.0008	0.0008
Detection Rate HR Adenoma	0.0150	0.0114	0.0071	0.0053	0.0051

2. An Office for Data Release request was made to the FIT pilot study which enabled unpublished data about detection rates for CRC, HR adenomas, LR adenomas and false positives to be obtained for the age 59-64 age group (all screenees, N = 11,105). This was compared against the prevalent round data and was found to be similar for HR adenomas, but higher for CRC detection. The CRC detection rate was therefore re-estimated as a fixed proportion of the HR adenoma detection rate for each FIT threshold, to match the proportions from the ODR request data (Table 15). LR adenoma detection rates were calculated as a proportion of HR adenoma detection rates in the same way. False positive rates were estimated by calculating the numbers of individuals with LR adenoma, HR adenoma, CRC and therefore false positive results expected in the prevalent round using the new detection rates. Confidence intervals for each value were estimated based on the numbers of individuals in the prevalent round (not shown).

Table 15: Estimated detection rates following adjustment using data from all screenees in FIT pilot.

	FIT20	**FIT40**	**FIT100**	**FIT150**	**FIT180**
Estimated Detection Rate CRC	0.0020	0.0019	0.0017	0.0016	0.0016
Detection Rate HR Adenoma	0.0150	0.0114	0.0071	0.0053	0.0051
Estimated Detection Rate LR Adenoma	0.0163	0.0100	0.0048	0.0033	0.0028
Estimated False Positive Rate	0.0216	0.0112	0.0040	0.0035	0.0017

3. Published data about CRC and HR adenoma detection rates by sex are available from the FIT pilot for all screenees by FIT threshold [33]. Separate estimates for male and female detection rates were calculated by assuming the same ratio male to female for each FIT threshold and disease state. Given the lack of published data about LR adenomas, they were assumed to follow the same male to female ratio as HR adenomas. The male to female ratio for false positives was estimated without taking LR adenomas into account.
4. Sensitivity at the first screen was then calculated directly using the following formula:

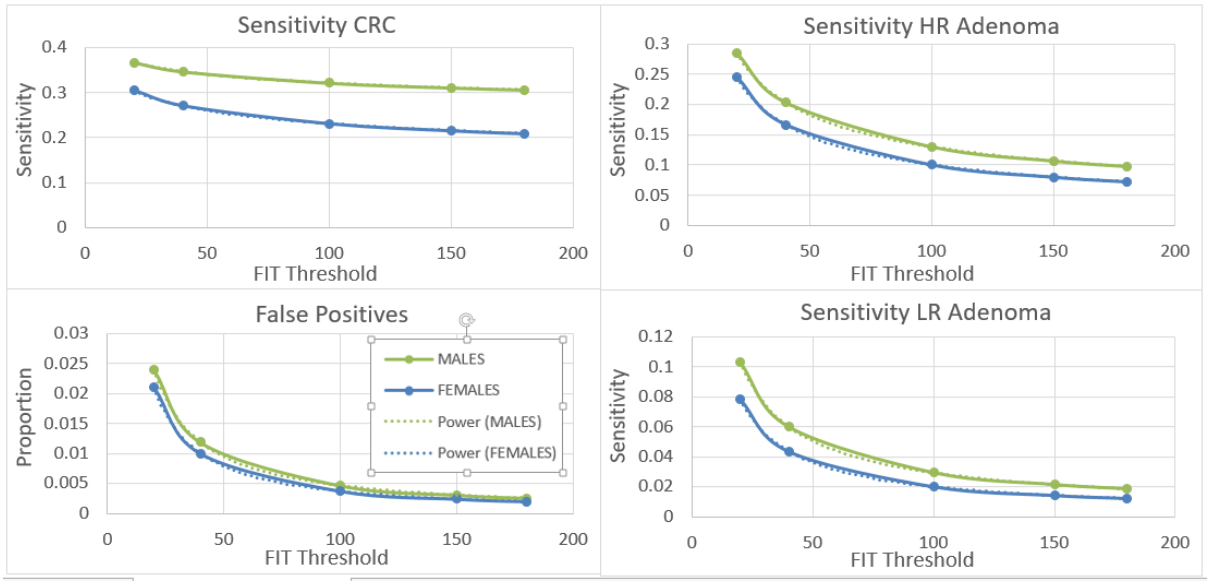
Sensitivity (disease state, sex, FIT threshold) = Detection Rate (disease state, sex, FIT threshold) / Underlying Prevalence (disease state, sex)

5. Detection rates by FIT threshold were found previously to follow a power curve distribution following the formula y = a*x^b; where a is the intercept, b is a parameter and x is the FIT threshold [37]. Sensitivity and false positive rates were also found to fit a power curve with the same FIT threshold parameter but different intercept from the detection rate curves. Power curves were fitted in R and the intercept of those curves obtained in order to enable sensitivity and false positive rates to be estimated for any FIT threshold (Table 16 & Figure 17).

Table 16: Power curve parameters to calculate sensitivity and false positive rate by FIT threshold, sex and underlying disease state, together with calculated sensitivity at a threshold of FIT20 for age 60.

	Intercept (95% CI]	**FIT_Param (95% CI)**	**FIT20 Sensitivity**
Male Sensitivity to CRC	0.526 (0.270; 0.867)	-0.083 (-0.145; -0.054)	0.410 (0.175; 0.738)
Male Sensitivity to HR Adenoma	1.071 (1.047; 1.096)	-0.487 (-0.591; -0.413)	0.249 (0.184; 0.328)
Male Sensitivity to LR Adenoma	0.841 (0.706; 1.207)	-0.784 (-0.981; -0.654)	0.080 (0.037; 0.170)
Male False Positive Rate	0.510 (0.361; 0.975)	-1.02 (-1.293; -0.847)	0.024 (0.008; 0.077)
Female Sensitivity to CRC	0.353 (0.176; 0.582	-0.171 (-0.232; -0.142)	0.211 (0.088; 0.380)
Female Sensitivity to HR Adenoma	1.205 (1.177; 1.233)	-0.555 (-0.659; -0.481)	0.229 (0.169; 0.301)
Female Sensitivity to LR Adenoma	0.630 (0.529; 0.905)	-0.852 (-1.05; -0.723)	0.049 (0.023; 0.104)
Female False Positive Rate	0.538 (0.382; 1.029)	-1.082 (-1.335; -0.909)	0.021 (0.007; 0.068)

Figure 17: Curves indicating how FIT sensitivity and proportion of false positives varies by FIT threshold in males (green) and females (blue). Fitted power curves are shown by the dotted lines.



6. The next step was to incorporate age and screening round into the sensitivity and false positive estimates. Our review of international data identified a Veneto study based on screening of over 123,000 individuals in Italy as the best source of data about these effects [38]. This study estimated the independent effects of age and screening round on detection rates using multivariable analysis. We also calculated similar age effects using an independent data source from the first round of the Dutch screening programme [39], and calculated an equivalent age effect for false positive rate, not included in the Veneto study. The Veneto data indicates that detection rates increase exponentially with age; however, prevalence also increases by age, so the age effect multipliers were converted into sensitivities using modelled prevalence. This analysis indicated that age had no significant impact on sensitivity of FIT to CRC, but that it did increase sensitivity to HR and LR adenomas. To account for changing prevalence by age, the false positive rate was first converted into specificity for two different ages using the following equation:

$$\text{Specificity (age, sex)} = \frac{(1 - \text{False Positive Rate (age)})}{\text{Underlying Prevalence (age, sex)}}$$

The false positive rates were then estimated assuming identical underlying prevalence and the age effect multipliers recalculated (Table 17).

Table 17: Age effect multipliers (age parameters) applied exponentially per year of age over 60

	For detection rates from Veneto study [38] – prevalence not considered (95% CI)	**Calculated for sensitivity taking prevalence by sex into account (95% CI)**	
		Male	**Female**
CRC Detection/Sensitivity	1.077 (1.062; 1.093)	0.999 (0.985; 1.014)	1.008 (0.993; 1.023)
HR Adenoma Detection/Sensitivity	1.049 (1.042; 1.055)	1.027 (1.021; 1.034)	1.014 (1.007; 1.020)
LR Adenoma Detection/Sensitivity	1.041 (1.032; 1.049)	1.034 (1.026; 1.043)	1.026 (1.018; 1.035)
False Positive Rate	1.048 (1.045; 1.051)	1.056 (1.040; 1.071)	1.056 (1.040; 1.072)

7. A reduction in detection rates and false positives is seen in subsequent screening rounds, but prevalence is lower too, due to the impact of the first screen [38]. The effect of a second screening round on sensitivity and false positive rates was calculated in a similar way to the age parameters, taking into account the underlying prevalence two years after a round of screening carried out using the screening sensitivities calculated in steps 1-6 above. This indicates that sensitivity does diminish in subsequent screening rounds. Once calculated and included in the modelling, the additional impact of a third screening round could also be calculated, although this was found to only be significant for CRC sensitivity and false positives. Note that these screening round multipliers have been calculated for a screening interval of two years; however, in the model we assume that they hold for subsequent screening rounds no matter how large the interval between an individual's previous and subsequent screen.

Table 18: Screening round multipliers (compared to previous round)

	Round 2 (95% CI)		**Round 3 (95% CI)**	
	Male	**Female**	**Male**	**Female**
Sensitivity to CRC	0.991 (0.825; 1.177)	1.016 (0.847; 1.207)	0.845 (0.676; 1.081)	0.863 (0.690; 1.104)
Sensitivity to HR Adenoma	0.827 (0.763; 0.909)	0.829 (0.764; 0.910)	NS	NS
Sensitivity to LR Adenoma	0.823 (0736; 0.909)	0.801 (0.717; 0.885)	NS	NS

False Positive Rate	0.604 (0.595; 0.613)	0.634 (0.624; 0.644)	0.517 (0.499; 0.526)	0.550 (0.531; 0.560)

The estimated parameters enabled a personalised probability of a positive result at FIT screening to be calculated for each modelled individual based upon their age, sex, underlying disease state, screening history and selected FIT threshold, using the following equations:

Prevalent Screening Round

$Probability_{(D, S, Age, FIT\_Thresh)} = Intercept_{(D, S)} * (FIT\_Thresh \wedge Param_{(D, S)}) * (Age\_Param \wedge (Age - 60))$

Subsequent Screening Rounds

$Probability\_Scr2_{(D, S, Age, FIT\_Thresh)} = Probability\_Scr1_{(D, S, Age, FIT\_Thresh)} * Round2\_Effect$

$Probability\_Scr3+_{(D, S, Age, FIT\_Thresh)} = Probability\_Scr2_{(D, S, Age, FIT\_Thresh)} * Round3\_Effect$

where D = Disease State and S = Sex.

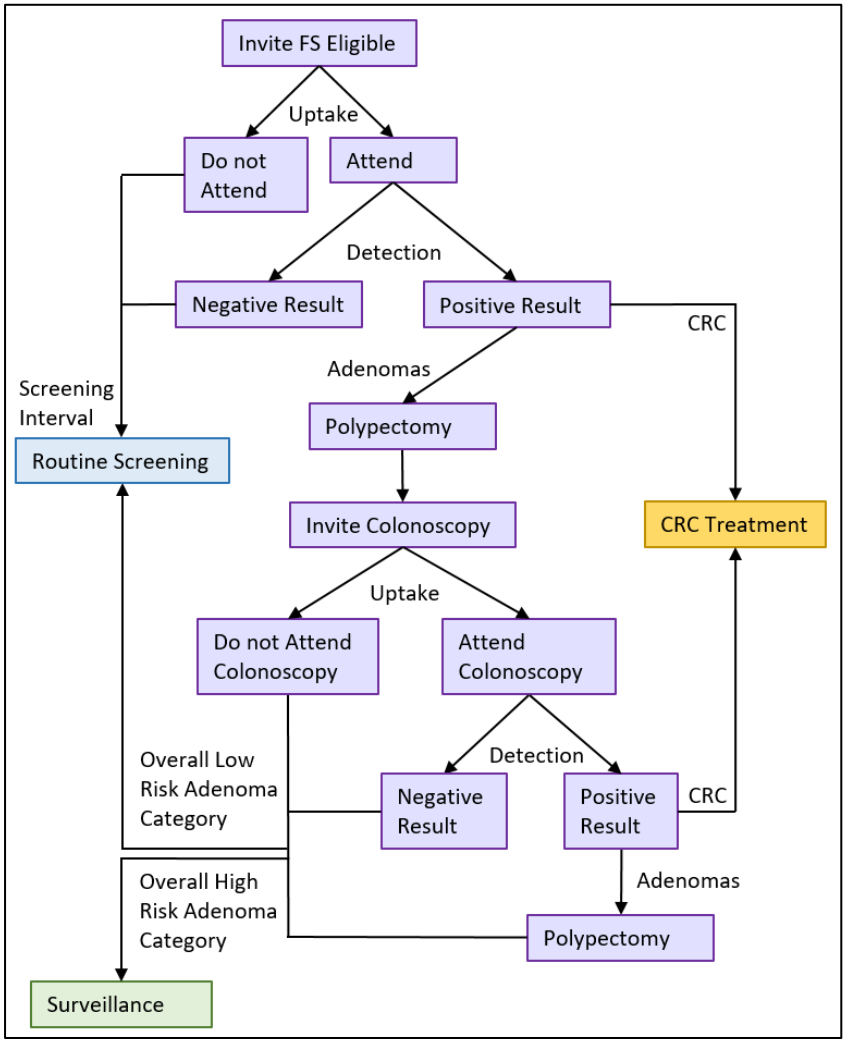
FS Screening

FS Eligibility

The modelled FS screening pathway is shown in Figure 18. All eligible individuals are invited to FS screening. The default eligibility criteria reflect the current eligibility in England and are specified as follows:

- No history of CRC diagnosis
- Not undergoing surveillance
- Age 55.

Figure 18: FS screening pathway and follow-up investigations



FS Uptake

FS uptake in the BCSP is currently 44% [40]; however, it varies depending upon individual characteristics. A multivariate analysis of BCSP data by McGregor et al. (2016) [41] provided odds ratios for uptake by sex and socioeconomic deprivation (IMD quintiles). The multivariate analysis also

included area-based ethnic diversity quintiles, locality and type of appointment offered as variables. However, with the exception of some of the local areas, these were not significant predictors and in any case could not be included in the model as they did not relate to the HSE 2014 baseline characteristics. Whilst the sample used for analysis is less up-to-date than current estimates, the overall uptake was very similar (43% rather than 44%) suggesting that uptake has not changed considerably over time. Model coefficients were calculated by taking the log of each odds ratio.

Uptake in the reference group (female & IMD5 [most deprived]) was unknown, but was estimated from the reported data as 31.5%, assuming that the proportion female in the IMD5 group was the same as the proportion female in the total population. This information was used to calculate an intercept for the model using the formula: intercept = -LN((1/x)-1) where x = reference group uptake with FS. Odds ratios and model coefficients are shown in Table 19.

Table 19: Odds Ratios from McGregor et al (2016) [41] and calculated model coefficients used to predict FS uptake

Variable	**Odds Ratio (95% CI)**	**Coefficients (95% CI)**
Intercept	NA	-0.778 (-0.870 to -0.689)
Sex Male	1.15 (1.09; 1.21)	0.139 (0.083 to 0.194)
IMD1 (least deprived)	2.05 (1.85; 2.27)	0.716 (0.614 to 0.818)
IMD2	1.77 (1.60; 1.95)	0.569 (0.471 to 0.666)
IMD3	1.44 (1.32; 1.58)	0.367 (0.274 to 0.460)
IMD4	1.20 (1.09; 1.31)	0.181 (0.090 to 0.272)

Currently, FS screening in the BCSP only relates to a single age group: age 55; however, uptake is also likely to vary by age. The UK Flexible Sigmoidoscopy Screening Trial (UKFSST) trialled FS in a range of ages from 55 to 65 [42]. Uptake was much higher than is currently found in the BCSP (73% at age 55), but tended to be slightly lower in older ages, corresponding to -2.7% per year of age above 55 (Figure 19). Normalising this to the average 44% uptake in the BCSP resulted in an average reduction of 0.163% (95% CI 0.108% to 0.223%) per year of age above 55 (Table 20). It was assumed that uptake would reduce linearly for ages above 65 and increase linearly for ages under 55.

Figure 19: Trends in FS uptake by age from the UKFSST [42]

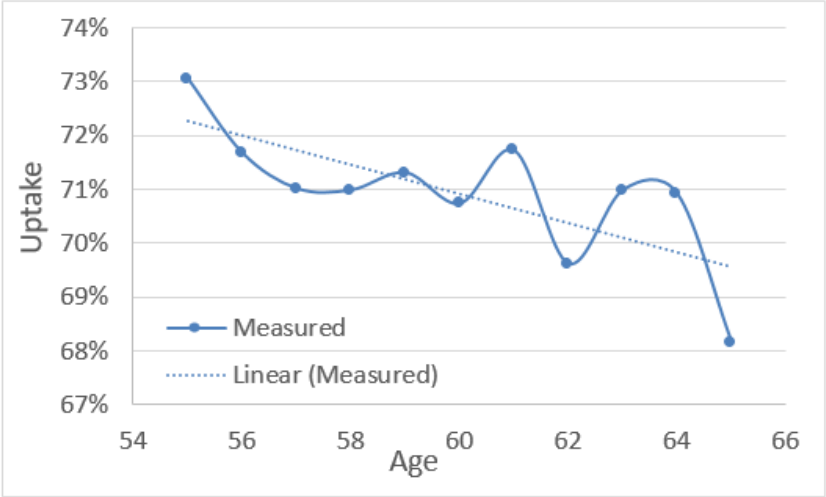


Table 20: Odds ratios (normalised to BCSP mean uptake) and calculated model coefficients for uptake of FS in people per year of age greater than 55.

Variable	**Odds Ratio (95% CI)**	**Coefficients (95% CI)**
Asian ethnicity	0.994 (0.994; 0.994)	-0.0056 (-0.0055 to -0.0057)

A study based on the UKFSST was also used to inform uptake by ethnicity, which was found to be considerably lower in people of Asian ethnicity than those of from either white or black ethnic groups [43]. Again, results were normalised to BCSP uptake and model coefficients were calculated as log odds ratios.

Table 21: Odds ratios (normalised to BCSP mean uptake) and calculated model coefficients for uptake of FS in people of Asian ethnicity compared to white people.

Variable	**Odds Ratio (95% CI)**	**Coefficients (95% CI)**
Asian ethnicity	0.681 (0.510; 0.876)	-0.385 (-0.673 to -0.132)

Sensitivity and False Positives

It is assumed that specificity of FS is 100% due to the nature of the test and therefore that the probability of false positives is zero. Sensitivity of FS to CRC, HR adenomas and LR adenomas is likely to vary by personal characteristics including age, sex and whether previously screened. Whilst published estimates of FS sensitivity using colonoscopy as a reference do exist, there are problems with these similar to those described above for FIT screening. Furthermore, given that individual adenomas are not modelled, the estimates of sensitivity need to include the overall outcomes of the test including detection of disease at any follow-up investigations that occur as a result of a positive

FS result. It was therefore particularly important that sensitivity estimates were derived from UK large-scale screening data. A similar process to that described for estimating FIT sensitivity, based on dividing detection rates by modelled prevalence, was therefore carried out to estimate FS sensitivity.

Data about detection rates of CRC and HR adenoma following FS in over 34,000 people are available from the BCSP [40]. Unfortunately, the data about LR adenoma detection is incomplete. Separate data is available for men and women; however, as FS is only given at age 55, no information can be obtained through the BCSP about detection at other ages. Data about detection rates of all three disease states is available from the UKFSST for a total of over 40,000 patients aged 55 to 65, and by sex [42]. For both these data sources, no patients have been previously screened, so no information is available about detection rates following previous screening. A graph of detection rates by age and sex is shown in Figure 20 to Figure 22. This indicates that slightly lower detection rates were found for CRC and HR adenomas in 55 year olds in the BCSP compared with the UKFSST. There is a lot of uncertainty around the CRC detection results due to small numbers (only about 10 for each age group in the UKFSST, and 58 in the BCSP). It was decided to use the BCSP data where available due to the larger numbers and the representation of a screening rather than a trial population, and use UKFSST results to inform the age trend and the LR adenoma results (for the latter it was assumed that there was no reduction in detection rate compared to the UKFSST). It is unclear whether the trends in detection rates by age are linear or exponential; however, given that an exponential trend seemed to fit FIT detection by age, this curve format was also used for FS detection by age.

Figure 20: Trends in CRC detection rates following FS screening by age based on data from the UKFSST [42]

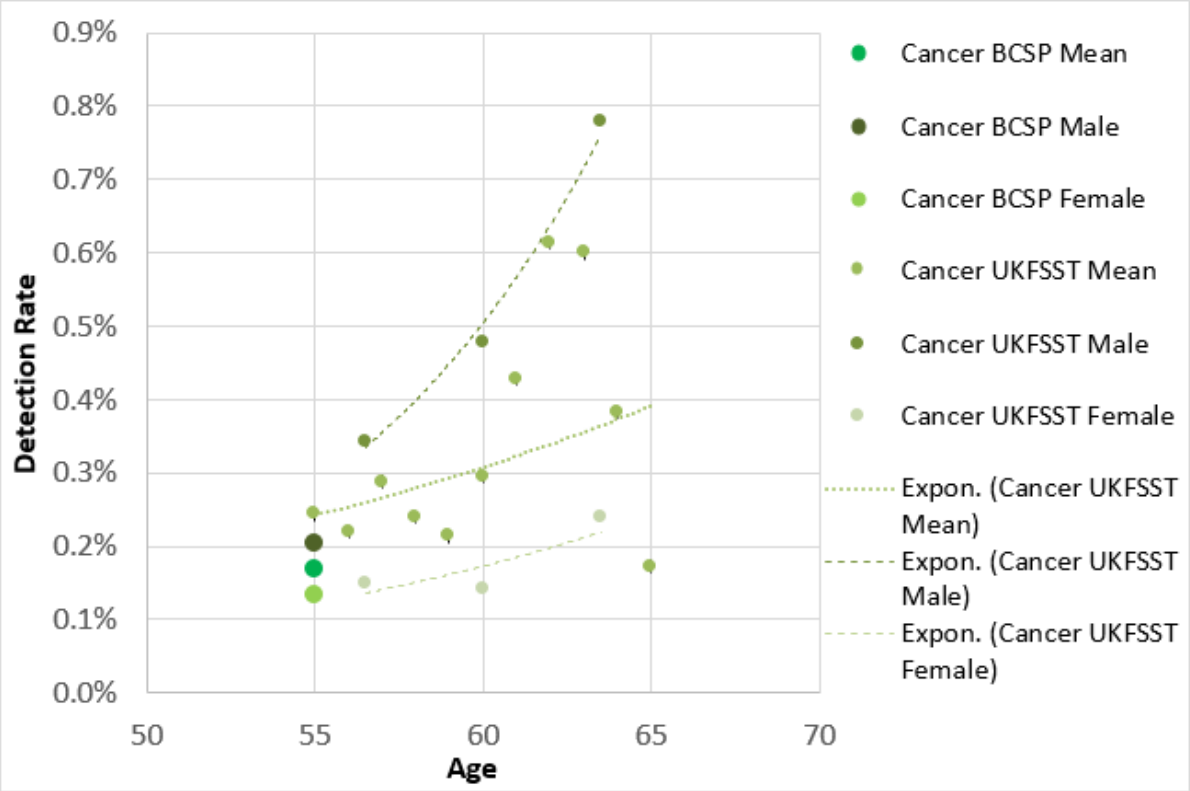


Figure 21: Trends in high risk adenoma detection rates following FS screening by age based on data from the UKFSST [42]

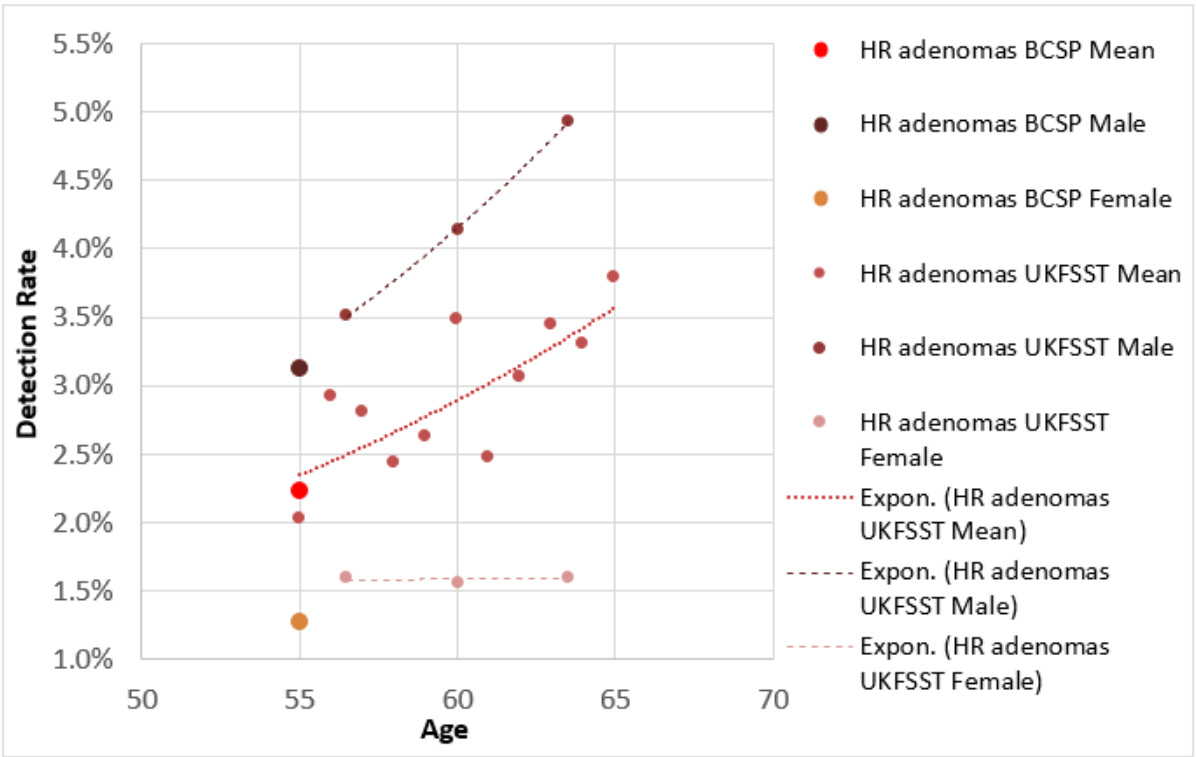
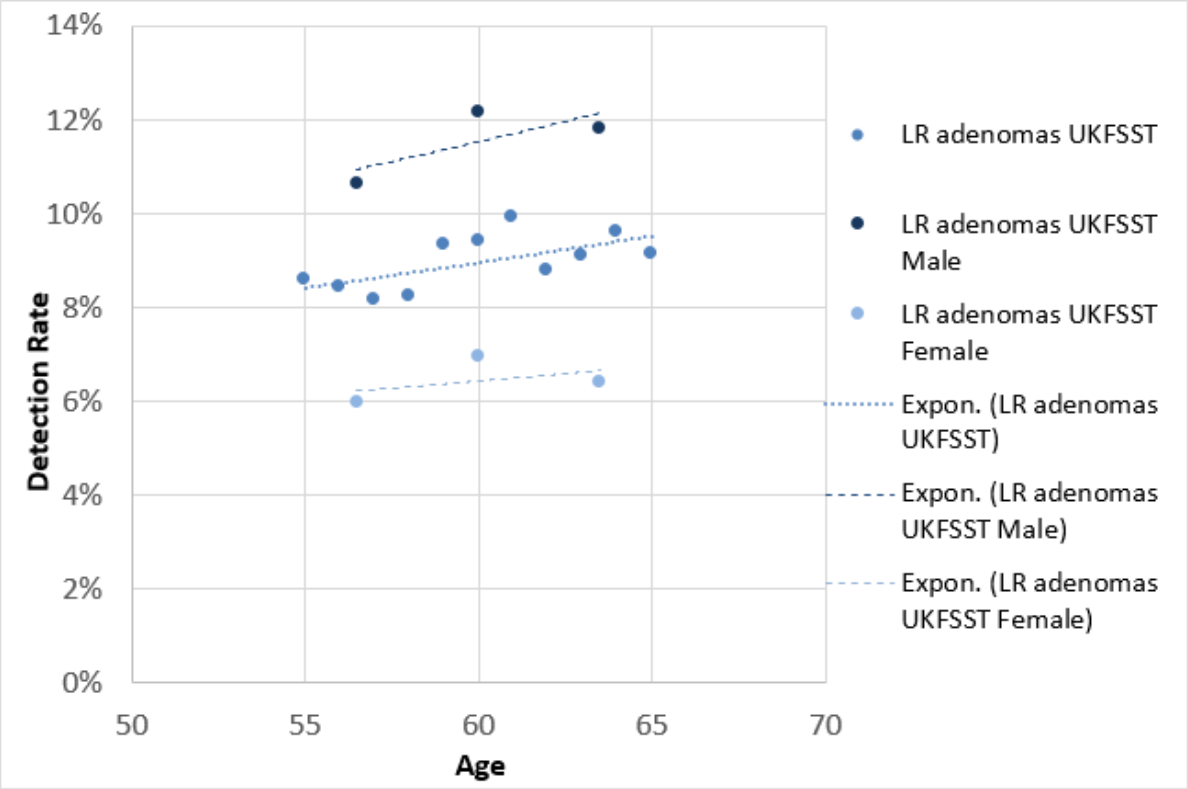


Figure 22: Trends in low risk adenoma detection rates following FS screening by age based on data from the UKFSST [42]



Sensitivity estimates were first performed for age 55, then the impact of the age effect on sensitivity calculated through comparison with sensitivity estimated aged 60. The parameters enabled a personalised probability of a positive result at FS screening to be calculated for each modelled individual based upon their age, sex and underlying disease state using the following equation:

$$Probability_{(Disease\ State,\ Sex,\ Age)} = Sensitivity\_Age55_{(Disease\ State,\ Sex)} * (Age\_Param\ ^{\wedge}\ (Age - 55))$$

Table 22: Parameters used to calculate FS sensitivity by age, sex and disease state

	Sensitivity_ Age55 (95% CI)	**Age_Param (95% CI)**
Male Sensitivity to CRC	0.438 (0.295; 0.581)	1.034 (0.969; 1.140)
Male Sensitivity to HR Adenoma	0.486 (0.447; 0.526)	0.988 (0.972; 1.005)
Male Sensitivity to LR Adenoma	0.394 (0.369; 0.418)	0.999 (0.988; 1.011)
Female Sensitivity to CRC	0.366 (0.213; 0.519)	0.947 (0.927; 0.969)
Female Sensitivity to HR Adenoma	0.380 (0.329; 0.431)	0.947 (0.927; 0.969)
Female Sensitivity to LR Adenoma	0.321 (0.294; 0.348)	0.978 (0.964; 0.994)

Further Investigation with Colonoscopy and CTC

All individuals testing positive with FIT or FS go on to be invited to further investigations. It is assumed that criteria for further investigation would be the same for FIT as currently for gFOBT in the BCSP. For FS, the data from the BCSP is unclear about the eligibility criteria for further investigation; in the UKFSST no-one with LR adenoma was investigated further [42] whilst a proportion of those with LR adenoma or other abnormalities also appear to be invited in the BCSP and it is unclear why. The total number of people requiring further investigation in the BCSP 2014/15 was 1,544 [40]; slightly higher than the sum total found to have CRC, HR, or LR adenomas (1,377), and therefore it was assumed in the model that all individuals found to have adenomas of any risk level would get further investigation.

CTC Referral

It is assumed in the model that all FS positives are suitable for colonoscopy, whereas a proportion of FIT positives are not suitable and are instead referred to CTC. The proportion referred to CTC through the BCSP increases with age as shown in (Table 23) [40]. It was assumed that the rate of referral for patients aged under 60 would be the same as for the 60-61 age group, whilst for patients aged over 74 it would be the same as for the 72-74 age group.

Table 23: The proportion of patients referred to CTC rather than colonoscopy after a FIT positive result, from BCSP data (2014/15) [40]

Age Group	**Proportion Referred to CTC (95% CI)**
Age 60-61	3.2% (2.8% to 3.5%)
Age 62-63	3.7% (3.3% to 4.1%)
Age 64-65	4.5% (4.1% to 4.9%)
Age 66-67	4.4% (4.0% to 4.8%)
Age 68-69	4.7% (4.3% to 5.2%)
Age 70-71	5.3% (4.8% to 5.9%)
Age 72-74	6.1% (5.5% to 6.7%)

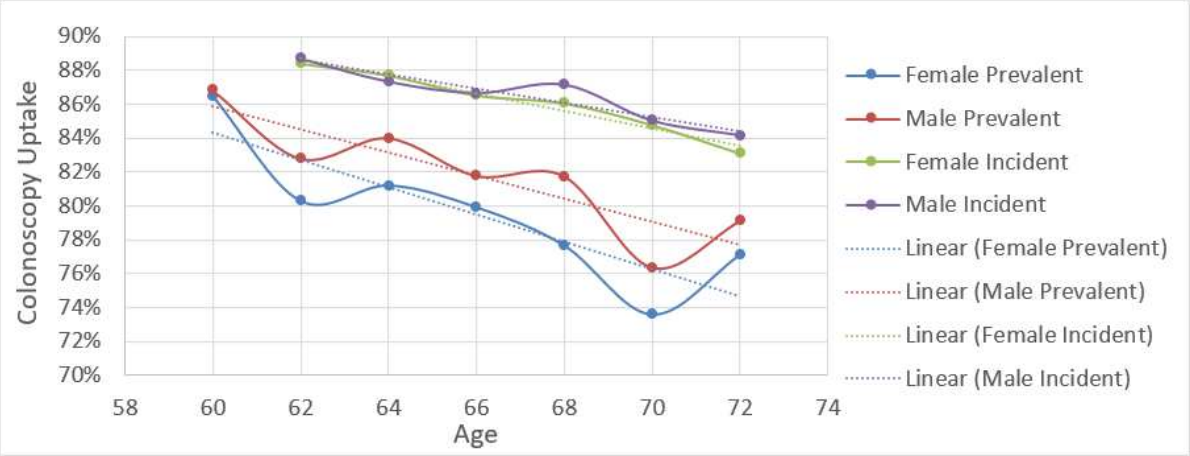
Uptake

Data about uptake rates for CTC and colonoscopy following either FIT or FS were obtained from a variety of sources. The only UK source of uptake data in FIT positives comes from the UK FIT pilot [33]. This reported that overall uptake of adequate further investigations (CTC plus colonoscopy) was 85.7% in FIT positives compared with 85.0% in gFOBT positives. Given the similarity between overall uptake in gFOBT and FIT positives, it was therefore thought reasonable to use BCSP data to inform

uptake rather than FIT pilot data, given that BCSP data is based on larger numbers and reports uptake by age, sex, screening round and modality (CTC vs colonoscopy).

BCSP data from over 200,000 gFOBT positive 2011 to 2015 was used to inform uptake of colonoscopy following FIT [33]. Similar to FIT pilot estimates, overall uptake was 85%, but the data also indicated that uptake varies by age, sex and screening round (Figure 23). Uptake tends to be lower in older people, and is considerably lower in the prevalent (first) screening round than in incident (subsequent) screening rounds. There is also a significant difference between the sexes for the prevalent round, with males taking up colonoscopy more than females; in incident screening rounds there is no significant difference between male and female uptake.

Figure 23: Colonoscopy uptake in FIT positive patients by age, sex and screening round from BCSP data [33]



Whilst this BCSP data excerpt did not include information about other personal characteristics, there is some evidence that colonoscopy uptake in the BCSP varies by deprivation and ethnicity. A study by Morris et al (2012) [44] of 24,000 gFOBT positive individuals within the BCSP included a multivariate analysis which found that there was significantly lower uptake of colonoscopy in the most deprived quintile of the population. However; this trend did not appear to continue in less deprived quintiles. Other independent variables included in the model were age and sex (grouped into under and over 65 for each sex), percentage of the population who were non-white, population density and self-assessed health. The only other significant variables were proportion non-white and the age over 65 * female variable. However, the fact that three of the variables could not be incorporated into MiMic-Bowel (as they were based on populations rather than individuals), and the low significance of most of the variables (probably due to the relatively low sample size), meant that the BCSP data was preferred for use in the model.

To calculate model coefficients for colonoscopy uptake in FIT positives from the BCSP data, linear trend lines were fitted to each curve in Excel and intercept and slope calculated. The coefficients used to predict colonoscopy uptake are shown in Table 24.

Table 24: Calculated model coefficients used to predict colonoscopy uptake in FIT positives

Variable	**Coefficients (95% CI)**
Intercept	1.169 (1.167 to 1.171)
Prevalent Screen	0.099 (0.071 to 0.128)
Age	-0.00453 (-0.00463 to -0.00449
Age * Prevalent Screen	-0.00227 (-0.00277 to -0.00171)
Female Sex * Prevalent Screen	0.056 (0.049 to 0.062)
Age * Female Sex * Prevalent Screen	-0.0012 (-0.0014 to -0.0011)

CTC usage in the BCSP was reported in a publication by Plumb et al. (2013) [45], which indicated that 99.2% of those referred to CTC took it up. No information was provided about differences by age, gender or screening round, so a fixed uptake rate was used for all individuals.

BCSP data was not used to inform uptake of follow-up colonoscopy in FS positives, as the number of colonoscopies attended was not recorded in this excerpt. Instead, information from the UKFSST was used, which indicated that 96.25% of FS positives referred to colonoscopy took it up [42]. No information about differences in colonoscopy uptake by personal characteristics were reported. The much higher uptake rate compared with gFOBT positives is likely to be due to colonoscopy being a similar process to FS and patients having already been identified to have abnormality and therefore being more motivated to follow it up further. However, it cannot be excluded that this could be an overestimate of actual uptake in the BCSP, given the trial conditions and the slightly different eligibility criteria for further investigation used.

Inadequates

Not all further investigations lead to an adequate result. It was assumed that 7% of colonoscopies had to be repeated (taken from NHS BCSP data [40]), and that a further investigation (assumed to be a single colonoscopy) was required in 35% of CTC patients [45]. No evidence was found to inform differences in inadequacy rates by personal characteristics.

Sensitivity and Specificity

It was assumed that colonoscopy specificity for adenomas and CRC is 1. Colonoscopy sensitivity however is not perfect. Sensitivity of colonoscopy to CRC was estimated from a population-based

study which used an interval cancer approach to determine the underlying true incidence of CRC, assuming that sojourn time was three years [46]. Estimated sensitivity to CRC was 96.6%, which was used directly in the model. There are inaccuracies with using the interval cancer method, which may underestimate or overestimate sensitivity depending upon the accuracy of estimated sojourn time, local detection rates and the rate of de novo development of cancer within the interval period. It is also possible that this is an underestimate of sensitivity in the BCSP, as colonoscopy quality is known to be particularly high in England due to the long and well-regulated training procedure and has also improved over time. However, this was the best data available for CRC sensitivity. No evidence was found to inform differences in sensitivity by personal characteristics.

A 2006 meta-analysis investigated colonoscopy sensitivity for adenomas, measured by tandem same-day colonoscopy [13]. This incorporated data from six studies with 465 patients in total. Estimated miss rates were 2.1% for polyps larger than 1cm in diameter and 23.5% for polyps under 1cm in diameter. This data was used in the model to calculate sensitivity (1 – miss rate) for LR adenomas (Table 25). HR adenomas are defined both through size and number of lesions, and the calculated value for sensitivity of 97.9% based on adenoma size alone is actually higher than that used in the model for CRC sensitivity, so was not thought to be valid for representing HR adenoma sensitivity in the model. Instead, an alternative estimate was found from a 2013 study comparing the diagnostic accuracy of CTC and colonoscopy[14]. Colonoscopy sensitivity was estimated at 92.5% for HR adenomas based on the proportion of adenomas that were not detected with initial colonoscopy but were found through CTC and later confirmed through a second colonoscopy where the colonoscopist was able to view the CTC images.

Sensitivity of CTC to CRC and HR adenomas was calculated from the SIGGAR1 study which included a multicentre, randomised trial comparing CTC with colonoscopy in patients with symptoms suggestive of CRC [47]. It was reported that the relative risk for detection of CRC using CTC rather than colonoscopy was 0.98, whilst the relative risk for detection of HR adenomas using CTC was 0.82, although neither of these two values were significant. In the absence of further data it was assumed that the relative risk of detection of low risk adenomas was the same as that of high risk adenomas. These relative risks were multiplied by colonoscopy sensitivity for each disease type to obtain values for sensitivity of CTC. Sensitivity estimates used in the model are shown in Table 25. CTC specificity came from a separate study

A systematic review of the effectiveness, diagnostic accuracy and harms of CRC screening was recently carried out to inform the US Preventive Services Task Force [48]. The review included seven studies, none from the UK, which estimated the sensitivity and specificity of CTC screening. The

weighted mean specificity was calculated as 88% for adenomas ≥ 6mm, or 91% for adenomas ≥ 10mm. CTC specificity in the model was assumed to be 88% for all disease types.

Table 25: Values used in the model for sensitivity and specificity of colonoscopy and CTC

Parameter	**Value (95% CI)**
Colonoscopy Sensitivity to CRC	0.966 (0.962 to 0.969)
Colonoscopy Sensitivity to HR adenoma	0.925 (0.894 to 0.952)
Colonoscopy Sensitivity to LR adenoma	0.765 (0.733 to 0.796)
Colonoscopy Specificity	1
CTC Sensitivity to CRC	0.946 (0.606 to 1.472)
CTC Sensitivity to HR adenoma	0.803 (0.490 to 1.277)
CTC Sensitivity to LR adenoma	0.627 (0.381 to 1.018)
CTC Specificity	0.881 (0.873 to 0.889)

Endoscopy Complications

The model includes a small risk of complications associated with colonoscopy, FS and CTC; including perforation, major bleed and death. Given the very small numbers involved, a single estimate for the probability of each harm was applied to all individuals in the model. Incidence of hospitalisation for bleeding and perforation following FS with or without polypectomy were taken from the UKFSST [42]. In total, 12 patients suffered a major bleed out of the 40,621 who underwent FS. No individuals undergoing FS without polypectomy suffered perforation whereas only one individual out of 9,494 patients undergoing polypectomy suffered perforation.

The rate of perforation for colonoscopy was taken from a more recent study of 130,831 patients undergoing colonoscopy in the BCSP [49]. This reported a colonoscopy perforation rate of 0.031% without polypectomy, and 0.091% with polypectomy, with an average of 2.3 polypectomies per patient. The rate of bleeding requiring transfusion (represented in the model as hospitalisation) was 0.04%. Gatto et al (2003) [50] 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 English screening population; however, no alternative source was identified.

Risk of perforation following CTC is even lower than for colonoscopy. A rate of 0.02% was assumed, in line with results from a systematic review and meta-analysis of the data [51]. No individuals died following perforation in any of the included studies, so mortality rate following CTC was assumed to be 0%. Endoscopy complications are summarised in Table 26.

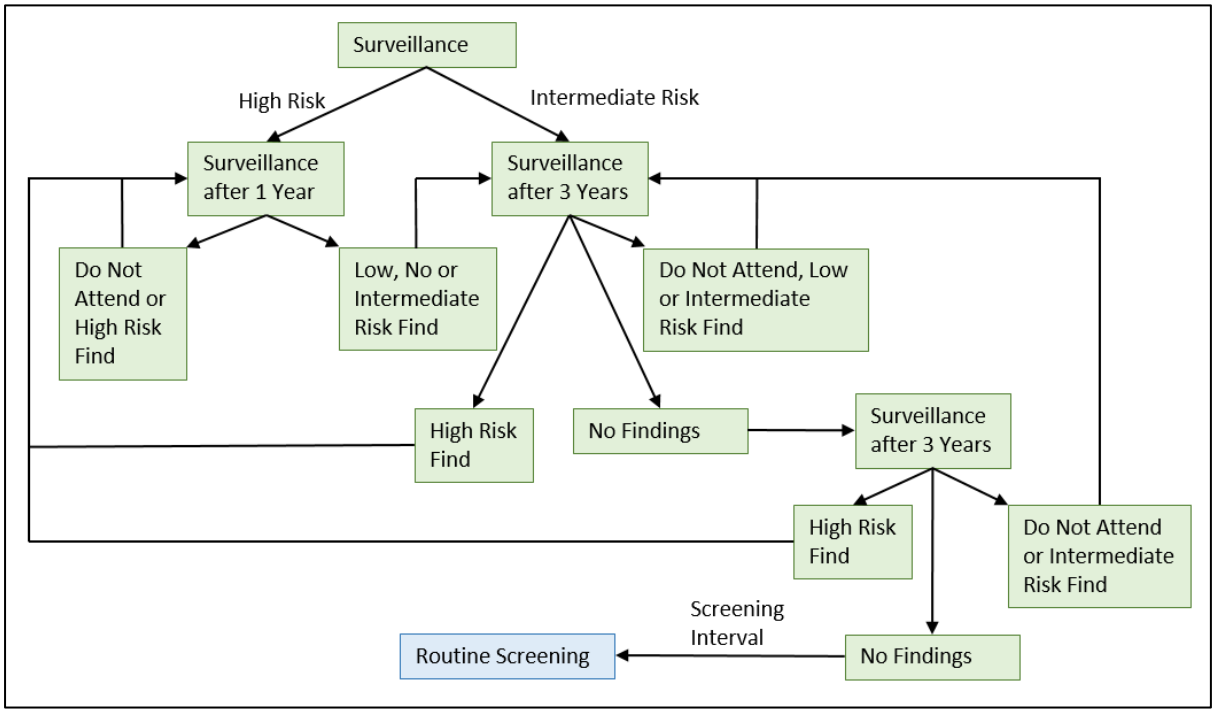
Table 26: Probability of endoscopy harms

Parameter	**Value (95% CI)**
FS with polypectomy probability of perforation	0.000105 (0.000003 to 0.00039)
FS without polypectomy probability of perforation	0
FS probability of hospitalisation for bleeding	0.000295 (0.00015 to 0.00048)
FS probability of death following perforation	0.0645 (0.0818 to 0.1722)
Colonoscopy with polypectomy probability of perforation	0.00091 (0.00061 to 0.00128)
Colonoscopy without polypectomy probability of perforation	0.00031 (0.00014 to 0.00054)
Colonoscopy probability of hospitalisation for bleeding	0.0004 (0.0003 to 0.00052)
Colonoscopy probability of death following perforation	0.0519 (0.0145 to 0.1111)
CTC probability of perforation	0.0002 (0.00007 to 0.00039)
CTC probability of death following perforation	0

Surveillance

The default surveillance pathway in the model follows current NHS BCSP guidelines (Figure 24) [1]. The model natural history includes only two adenoma health states; low risk and high risk. All individuals detected with high risk adenomas are eligible for surveillance; however, these high risk individuals are first divided further into intermediate risk and high risk categories. Intermediate risk is defined as 3-4 small adenomas or one adenoma of at least 1cm in diameter, whereas high risk is defined as either five or more small adenomas, or three or more adenomas of which one is at least 1cm in diameter. Those at high risk are eligible for surveillance after one year, whilst those at intermediate risk are eligible for surveillance after three years. As the model natural history does not explicitly model these as two separate health states, a different method was required to determine which individuals would be assigned to high risk and which to intermediate risk adenoma categories.

Figure 24: Surveillance pathway recommended by NHS BCSP guidelines and replicated in the model



No data was available to inform the proportions of high risk versus intermediate risk detected after FIT screening; however, the NHS BCSP records this by age and sex after gFOBT screening [40]. The proportion of high risk adenomas found (compared with all high and intermediate risk adenomas) was plotted by age for males and females separately using data from 44,000 individuals screened between 2011 and 2015 (Figure 25). This indicated that male sex and age are both predictors for high-risk adenomas. Screening round did not appear to be a predictor for the proportion high risk (not shown). The age trend appeared to be reasonably linear, enabling estimation of regression coefficients for calculating individualised probabilities of having a high risk adenoma (Table 27).

Figure 25: Plot showing the proportion of individuals with high risk (rather than intermediate risk) adenomas by age and sex, following gFOBT screening in the BCSP, 2001 to 2015 [40]

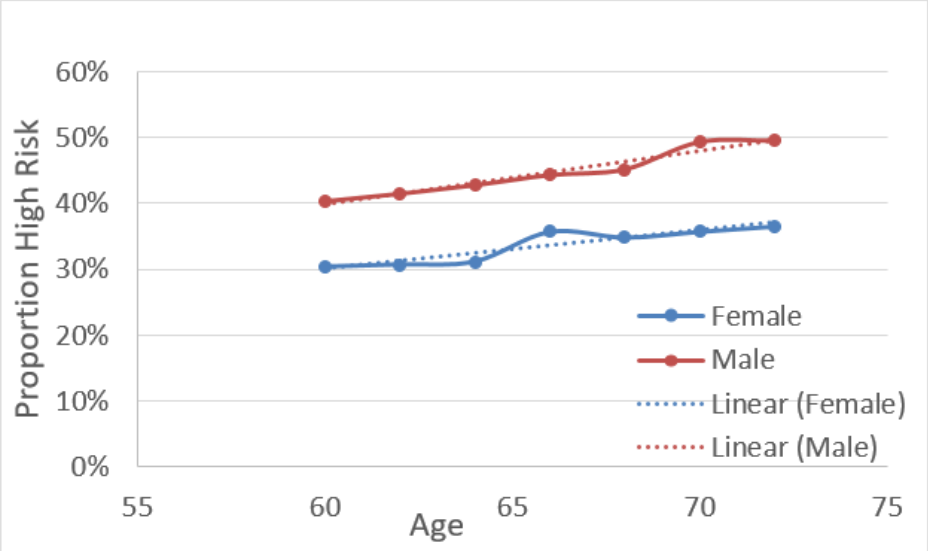


Table 27: Regression coefficients used in the model to predict the probability that an individual has a high risk adenoma rather than an intermediate risk adenoma following detection through screening.

Variable	**Mean**	**Lower 95% CI**	**Upper 95% CI**
Intercept	-0.0458	-0.0588	-0.0328
Male Sex	-0.0463	-0.055	-0.0376
Age	0.0058	0.0057	0.0059
Age*Male Sex	0.0024	0.0023	0.0024

Individuals who are invited to surveillance colonoscopy may or may not attend. Uptake of surveillance colonoscopy was assumed to be 82.5% in line with data from the BCSP [40]. In line with the BCSP guidelines, individuals in the model who do not attend are invited back for another surveillance colonoscopy after the interval relevant to their risk status has passed (i.e. after a further three years if they were previously classified as intermediate risk). Individuals found to have high risk adenomas at surveillance will undergo polypectomy and then be reinvited after one year. Individuals found to have low or intermediate risk findings will undergo polypectomy and then be reinvited after three years. Individuals who do not have any adenomas upon surveillance will be reinvited after three years; however, if they were originally high risk and then have three consecutive clear colonoscopies, or were originally medium risk and then have two consecutive clear colonoscopies they are assumed to be very low risk and return to routine screening. Any modelled individual who is diagnosed with cancer during surveillance is removed from the screening and surveillance pathway

and instead follows a disease pathway which includes treatment costs, utility reductions and reduced survival compared to the general population.

Whilst it is known from a study by Bressler et al (2007) that not all adenomas are cleared from the bowel upon polypectomy (particularly low risk adenomas) [46], the current model structure incorporating only a limited number of health states, rather than individual adenomas, does not enable this to be represented. Instead, the Bressler data is used to inform colonoscopy sensitivity (i.e. whether or not adenomas are detected), and then it is assumed that polypectomy that takes place during screening and surveillance returns all detected individuals back to the normal epithelium health state. This is likely to mean that the people undergoing surveillance in the model are healthier than in practice, whilst more unhealthy people are returned to the screening pool, although it is unclear what impact this would have on model comparisons of different screening strategies. Future versions of the model will simulate individual adenomas, enabling colonoscopy sensitivity estimates to be applied to each individual adenoma and allowing incomplete adenoma clearance upon polypectomy to be simulated. This will be essential for accurate comparison of different surveillance strategies.

Surveillance data from the BCSP indicates that individuals who are undergoing surveillance have a much higher risk of developing CRC and adenomas than individuals in the general population (personal communication from Stuart Bonnington). It is thought that this is partly due to incomplete clearance of adenomas from the bowel during polypectomy (as discussed above), and partly due to surveilled individuals being at higher risk of adenoma and CRC development than individuals in the general population. However, it was decided that this data should not be used to adjust the natural history transition probabilities in people undergoing surveillance, as this could result in surveillance inadvertently increasing cancer risk in the model, whereas in reality surveillance should reduce risk. This was particularly important given that one of the objectives of MiMiC-Bowel was to enable evaluation of different surveillance strategies. If natural variation in cancer risk is accurately represented in the model, then individuals who are at high risk due to environmental and genetic factors will be those most likely to be picked up with adenomas during screening and therefore to undergo surveillance. This should mean that those undergoing surveillance will naturally transition faster to adenomas and cancers than individuals in the general screening population.

Utilities

Utility decrements due to age were calculated as described in the Modelling Changes in Phenotypic Characteristics by Age section, and are shown in Table 28.

A recent review and meta-analysis of CRC utilities by Djalalov et al (2014) was used to estimate utility multipliers for CRC [52]. The meta-analysis included a linear mixed-effects model for utilities that took into account differences in utility measurements by cancer site, stage, time since surgery, measurement instrument and method of administration. The reference case was chosen for cancer site (colorectal cancer) and method of administration (interviewer), whilst EQ-5D was chosen as the measurement instrument. The model indicated that individuals with stage D cancer would have a 0.19 lower utility than individuals with stage A-C cancer. The model also indicated that utility increased after surgery, with values given for before surgery, three months after surgery, one year after surgery and more than one year after surgery. This meant that it was possible to estimate utilities in the first year after diagnosis (which would likely include treatment with surgery), and for subsequent years. The three months after surgery values were chosen to represent the first year after surgery, and the more than one year after surgery values were chosen to represent subsequent years.

The values described above are absolute utilities rather than multipliers or decrements. However, no average age is given against which to compare values from the general population. An analysis from Ara & Brazier (2011) indicates that the average utility of people with a history of cancer is 14% lower than that for the general population or for people without a cancer history, and that this doesn't change significantly with age [5]. Given that the utility value estimated in the Djalalov model for mixed stages, more than one year after surgery is 0.86 [52], this implies that it would be reasonable to use the Djalalov values as utility multipliers rather than as absolute utilities (which would overestimate health related quality of life in cancer). The utility multipliers used in the model by stage and year since diagnosis are presented in Table 28.

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.

Screening harms are associated with transient reductions in utility. It was not possible to find utility decrements relating specifically to screening adverse events. As an alternative, utility decrements for bleeding were estimated by assuming they would be similar to a major gastrointestinal bleed and

used the value from Dorian et al. (2014) of 0.1511 for two weeks, i.e. a total QALY loss of 0.00581 in the year of occurrence [53]. Values for perforation were assumed to be the same as for stomach ulcer/abdominal hernia/rupture taken from Ara and Brazier (2011) [5]. The disutility value was 0.118 for one month, i.e. total QALY loss of 0.00983 over a year.

Individual utility values were modelled annually by first applying the total age decrement calculated using the baseline age and EQ-5D for each individual, then applying multipliers due to CRC, then applying any transient screening harm decrements. Any individual with utility values greater than 1 had utility adjusted to 1, whilst any individual with utility values lower than -0.594 had utility adjusted to -0.594, reflecting the upper and lower bounds of the EQ-5D score.

Table 28: A summary of utility decrements and multipliers used in the model

	Utility Change (95% CI)	Multiplier or Decrement
Age	-0.00432 (-0.00460; -0.00404)	Decrement
CRC Stage A-C Year 1	0.87 (0.67; 1.07)	Multiplier
CRC Stage A-C Subsequent Years	0.92 (0.76; 1.08)	Multiplier
CRC Stage D Year 1	0.68 (0.42; 0.93)	Multiplier
CRC Stage D Subsequent Years	0.73 (0.51; 0.94)	Multiplier
Bowel Perforation	-0.00983 (-0.01058; -0.00917)	Decrement
Intestinal Bleed	-0.00581 (-0.00883; -0.00279)	Decrement

Costs

Screening and Further Investigation Costs

FIT screening programme costs were taken from the ScHARR bowel cancer screening cohort model, which used costings from the Southern screening hub [37]. Previously, costs of individual components were combined to give for example separate costs for FIT non-compliers, FIT compliers with normal results and FIT compliers with positive results. Costs were structured in a slightly different way for MiMiC-Bowel to enable each individual to accumulate costs as they travelled along the screening pathway, gathering one cost for being invited, and then separately gathering the additional costs of complying (e.g. the cost of processing the test kit) and then getting a positive test (e.g. the cost of an appointment with a specialised screening practitioner to discuss further investigation) (Table 29).
For FS screening, costs from the Southern screening hub were used to estimate all screening costs in a similar way to that described for FIT screening, apart from the cost of the FS exam itself, which was costed using NHS Reference Costs 2017/18 [54]. Southern Hub screening costs were inflated from 2008/09 values to 2013/14 values using the Hospital and Community Health Services (HCHS) pay and prices index, and then to 2017/18 values using the new Health Services Index [55].

Table 29: Screening costs taken from Southern Hub Costings [37], inflated to 2017/18 values

Screening Procedure	**Components Included in Costing**	**Cost (95% CI)**
FIT Invite	FIT kit, invitation letter, reminder letters in non-responders, helpline costs, postage, packaging, staff costs and overheads.	£7.45 (£6.71; £8.20)
Additional Costs of FIT Normal Result	FIT processing, retests (required in 3% of people), normal result letter to patient & GP	£1.09 (£0.98; £1.19)
Additional Costs of FIT Positive Result	Additional costs of positive result letter to patient & GP. Specialised screening practitioner appointment.	£10.23 (£9.21; £11.25)
FS Invite	Invitation letter, bowel preparation kit, reminder letters in non-responders, helpline costs, postage, packaging, staff costs and overheads.	£5.82 (£5.24; £6.40)
Additional Costs of FS Normal Result	Normal result letter to patient & GP with postage. FS procedure NOT included.	£1.14 (£1.03; £1.26)
Additional Costs of FS Positive Result	Positive result letter to patient & GP with postage. Specialised screening practitioner appointment. FS procedure NOT included.	£11.37 (£10.24; £12.51)

Individuals undergoing further investigations (CTC or colonoscopy) or surveillance colonoscopy incur further costs relating to these procedures and the harms arising from these procedures. All further investigations and screening harms were costed using NHS Reference costs 2017/18 [54]. Previous versions of NHS Reference costs have provided interquartile ranges, allowing calculation of a standard error if it is assumed that the interquartile range is distributed symmetrically around the mean. However, the 2017/18 version does not include this. Interquartile ranges from NHS Reference costs 2016/17 were therefore combined with the mean from NHS Reference costs 2017/18 to provide an estimate of interquartile ranges around the new mean that were proportional to the 2016/17 values.

No cost was assigned to invitation to further investigations or surveillance. For CTC, all costs were assumed to be incurred upon attending CTC and no additional costs were given for a positive result. The cost for CTC was estimated from diagnostic imaging CTC costs relating to CTC for more than three areas (Table 30). Different costs were incurred for FS and colonoscopy with and without polypectomy. Individuals who did not have any adenomas or cancer detected were assumed to have a diagnostic FS or colonoscopy (without polypectomy) whereas those diagnosed with adenomas were assumed to have therapeutic FS or colonoscopy (with polypectomy). All of these were costed as day case procedures. People diagnosed with cancer were also costed as though they had therapeutic FS/colonoscopy – whilst these individuals will not have a polyp removed, they will likely have some tissue removed for biopsy instead. Cost of biopsy (costed as histopathology and histology within direct access pathology services) was assumed to be incurred by all individuals diagnosed with cancer and those with adenomas removed. In individuals with cancer, a single biopsy was costed, whilst in those with adenomas removed, the cost of biopsy was multiplied by an estimate of the average number of adenomas removed during screening, given as 2.3 in a study of the NHS BCSP [49]. Note that this estimate comes from gFOBT screening rather than FIT or FS screening; however, no other data informing this could be found.

Individuals who suffer screening harms are also expected to incur costs of these harms. Perforation from CTC, FS or colonoscopy was calculated as a weighted average of the cost of major large intestine procedures with CC score of 0 to 3+, 19 years and over. Bleed from FS or colonoscopy was calculated as a weighted average of the cost of gastrointestinal bleed without interventions, with single intervention and with multiple interventions. All harms were costed as non-elective short-stay procedures.

Table 30: Costs of screening, further investigation and harm taken from NHS Reference Costs 2017/18 [54]

Procedure	Description	Cost (Interquartile Range)
Diagnostic FS	FS without polypectomy, Day case	£402 (£316; £472)
Therapeutic FS	FS with polypectomy, Day case	£512 (£420; £595)
Diagnostic Colonoscopy	Colonoscopy without polypectomy, Day case	£525 (£406; £601)
Therapeutic Colonoscopy	Colonoscopy with polypectomy, Day case	£641 (£508; £735)
Biopsy	Histopathology and histology	£33 (£12; £38)
CTC Scan	CT scan of more than three areas	£139 (£69; £191)
Bowel Perforation	Weighted average of major large intestine procedures with CC score 0-3+	£1,554 (£472; £2,295)
Intestinal Bleed	Weighted average of gastrointestinal bleed without intervention or with single or multiple intervention	£474 (£391; £532)

CRC Treatment Costs

Cancer treatment costs were taken from a 2016 costing study by Laudicella et al (2016) that used population based, patient level data to estimate the costs of treating four different types of cancer, including colorectal cancer, in each year following diagnosis in England [56]. The study is limited in that it groups early stage (Dukes A & B) and later stage (Dukes C & D), and groups individuals aged 18-64 or 65+, rather than providing data on a wider range of ages. However, it has two advantages. Firstly, it reports costs for up to nine years following diagnosis, which enables treatment costs to be allocated to the year they are incurred (rather than assuming they are all incurred in the first year after diagnosis), and should mean that most costs of relapse are incorporated. Secondly, costs include all healthcare costs incurred by individuals and not those specifically incurred through colorectal cancer treatment. This has the advantage that healthcare costs indirectly attributed to cancer are included (for example extra care required to treat unrelated conditions in individuals with cancer), but the disadvantage that completely unrelated healthcare costs that would also be incurred in individuals without cancer are also included. The study does not estimate healthcare costs in individuals without cancer as comparison, but does estimate healthcare costs for the three years prior to cancer diagnosis. This means that cancer-related healthcare costs over the nine years following diagnosis could be estimated by subtracting the three-years pre- diagnosis costs from the

costs for each year post-diagnosis. Costs in the year immediately prior to diagnosis were significantly higher than costs two or three years prior to diagnosis suggesting that these might represent the costs of diagnosis. These costs were not included in the model to avoid double counting the costs of diagnosis through screening and surveillance. The costing study was carried out in 2010, so costs were inflated to 2013/14 values using the Hospital and Community Health Services (HCHS) pay and prices index, and then to 2017/18 values using the new Health Services Index [55].

Table 31: CRC–related healthcare costs from Laudicella et al 2016 [56], inflated to 2017/18 values.

	Age 18-64		Age 65+	
	Stage A-B	Stage C-D	Stage A-B	Stage C-D
Year One	£16,302	£21,051	£15,233	£16,625
Year Two	£3,826	£6,895	£3,508	£5,242
Year Three	£3,175	£4,713	£2,860	£4,047
Year Four	£2,452	£3,850	£2,379	£3,169
Year Five	£2,206	£2,748	£2,414	£2,965
Year Six	£1,509	£2,300	£2,440	£2,816
Year Seven	£1,569	£2,680	£2,217	£1,800
Year Eight	£1,438	£2,055	£2,458	£2,338
Year Nine	£1,239	£1,413	£2,052	£1,818

Appendix A: Parameter Table

No	Parameter Name	Mean	95% CI		Distribution	Source
1	CRC Relative Risk Current Smoker	1.38	1.12	1.72	Lognormal	Calibrated based on Brown et al. 2018 [17]
2	CRC Relative Risk Former Smoker	1.19	1.06	1.35	Lognormal	
3	CRC Relative Risk Overweight Males (BMI 25-29.99)	1.29	1.20	1.38	Lognormal	
4	CRC Relative Risk Overweight Females (BMI 25-29.99)	1.11	1.02	1.23	Lognormal	
5	CRC Relative Risk Obese Males (BMI >=30)	1.74	1.62	1.88	Lognormal	
6	CRC Relative Risk Obese Females (BMI >=30)	1.33	1.11	1.61	Lognormal	
7	CRC Relative Risk Light Alcohol Drinker (<12.5g per day)	0.85	0.79	0.90	Lognormal	
8	CRC Relative Risk Moderate Alcohol Drinker (12.5-50g per day)	1.03	1.02	1.05	Lognormal	
9	CRC Relative Risk Heavy Alcohol Drinker (>50g per day)	1.16	1.07	1.26	Lognormal	
10	CRC Relative Risk High Physical Activity (150+ mins per week)	0.84	0.75	0.92	Lognormal	
11	CRC Relative Risk Black Ethnicity Males	0.57	0.34	0.95	Lognormal	Calibrated based on Hippisley-Cox et al. 2015[19]
12	CRC Relative Risk Black Ethnicity Females	0.65	0.45	0.95	Lognormal	
13	CRC Relative Risk Asian Ethnicity Males	0.41	0.26	0.67	Lognormal	
14	CRC Relative Risk Asian Ethnicity Females	0.42	0.25	0.72	Lognormal	
15	CRC Relative Risk Other Ethnicity Males	0.43	0.23	0.80	Lognormal	
16	CRC Relative Risk Other Ethnicity Females	0.70	0.47	1.04	Lognormal	
17	CRC Relative Risk Family History (genetic risk subtracted)	3.05	1.86	4.31	Lognormal	Calibrated based on Lowery et al. 2016 [18]
18	Multiplier used for genetic risk	1.73	NA	NA	Constant	Model calibration
19	Coefficients for proportion with family history: Intercept	-0.073	-0.08	-0.06	Normal	Calculated from UK Biobank data [7]
20	Coefficients for proportion with family history: Age	0.003	0.0032	0.0035	Normal	
21	Transition probability: Norm to LR Adenoma Age 35 Male	2.01E-03	NA	NA	Correlated set	Model calibration
22	Transition probability: Norm to LR Adenoma Age 45 Male	2.68E-02	NA	NA	Correlated set	Model calibration
23	Transition probability: Norm to LR Adenoma Age 55 Male	1.49E-02	NA	NA	Correlated set	Model calibration
24	Transition probability: Norm to LR Adenoma Age 65 Male	8.17E-03	NA	NA	Correlated set	Model calibration
25	Transition probability: Norm to LR Adenoma Age 75 Male	4.36E-03	NA	NA	Correlated set	Model calibration

26	Transition probability: Norm to LR Adenoma Age 85 Male	3.15E-03	NA	NA	Correlated set	Model calibration
27	Transition probability: Norm to LR Adenoma Age 35 Female	1.15E-03	NA	NA	Correlated set	Model calibration
28	Transition probability: Norm to LR Adenoma Age 45 Female	1.62E-02	NA	NA	Correlated set	Model calibration
29	Transition probability: Norm to LR Adenoma Age 55 Female	1.15E-02	NA	NA	Correlated set	Model calibration
30	Transition probability: Norm to LR Adenoma Age 65 Female	8.28E-03	NA	NA	Correlated set	Model calibration
31	Transition probability: Norm to LR Adenoma Age 75 Female	4.01E-03	NA	NA	Correlated set	Model calibration
32	Transition probability: Norm to LR Adenoma Age 85 Female	3.05E-03	NA	NA	Correlated set	Model calibration
33	Transition probability: LR to HR Adenoma Age 35 Male	2.82E-02	NA	NA	Correlated set	Model calibration
34	Transition probability: LR to HR Adenoma Age 45 Male	3.13E-02	NA	NA	Correlated set	Model calibration
35	Transition probability: LR to HR Adenoma Age 55 Male	2.06E-02	NA	NA	Correlated set	Model calibration
36	Transition probability: LR to HR Adenoma Age 65 Male	1.21E-02	NA	NA	Correlated set	Model calibration
37	Transition probability: LR to HR Adenoma Age 75 Male	1.55E-02	NA	NA	Correlated set	Model calibration
38	Transition probability: LR to HR Adenoma Age 85 Male	9.27E-03	NA	NA	Correlated set	Model calibration
39	Transition probability: LR to HR Adenoma Age 35 Female	1.75E-02	NA	NA	Correlated set	Model calibration
40	Transition probability: LR to HR Adenoma Age 45 Female	2.85E-02	NA	NA	Correlated set	Model calibration
41	Transition probability: LR to HR Adenoma Age 55 Female	1.45E-02	NA	NA	Correlated set	Model calibration
42	Transition probability: LR to HR Adenoma Age 65 Female	1.44E-02	NA	NA	Correlated set	Model calibration
43	Transition probability: LR to HR Adenoma Age 75 Female	1.99E-02	NA	NA	Correlated set	Model calibration
44	Transition probability: LR to HR Adenoma Age 85 Female	1.14E-02	NA	NA	Correlated set	Model calibration
45	Transition probability: HR to Cancer Age 35 Male	9.24E-03	NA	NA	Correlated set	Model calibration
46	Transition probability: HR to Cancer Age 45 Male	1.63E-02	NA	NA	Correlated set	Model calibration
47	Transition probability: HR to Cancer Age 55 Male	1.81E-02	NA	NA	Correlated set	Model calibration
48	Transition probability: HR to Cancer Age 65 Male	2.84E-02	NA	NA	Correlated set	Model calibration
49	Transition probability: HR to Cancer Age 75 Male	5.02E-02	NA	NA	Correlated set	Model calibration
50	Transition probability: HR to Cancer Age 85 Male	3.52E-02	NA	NA	Correlated set	Model calibration
51	Transition probability: HR to Cancer Age 35 Female	4.69E-03	NA	NA	Correlated set	Model calibration
52	Transition probability: HR to Cancer Age 45 Female	2.08E-02	NA	NA	Correlated set	Model calibration
53	Transition probability: HR to Cancer Age 55 Female	2.72E-02	NA	NA	Correlated set	Model calibration
54	Transition probability: HR to Cancer Age 65 Female	3.59E-02	NA	NA	Correlated set	Model calibration

55	Transition probability: HR to Cancer Age 75 Female	6.50E-02	NA	NA	Correlated set	Model calibration
56	Transition probability: HR to Cancer Age 85 Female	5.31E-02	NA	NA	Correlated set	Model calibration
57	Transition probability: Norm to CRC Dukes A Age 15 Male	0	NA	NA	Correlated set	Model calibration
58	Transition probability: Norm to CRC Dukes A Age 101 Male	5.77E-04	NA	NA	Correlated set	Model calibration
59	Transition probability: Norm to CRC Dukes A Age 15 Female	0	NA	NA	Correlated set	Model calibration
60	Transition probability: Norm to CRC Dukes A Age 101 Female	5.74E-04	NA	NA	Correlated set	Model calibration
61	Transition probability: Dukes Stage A to B undiagnosed	2.93E-01	NA	NA	Correlated set	Model calibration
62	Transition probability: Dukes Stage B to C undiagnosed	5.54E-01	NA	NA	Correlated set	Model calibration
63	Transition probability: Dukes Stage C to D undiagnosed	3.50E-01	NA	NA	Correlated set	Model calibration
64	Proportion CRC_D deaths undiagnosed as a function of age > 75	0.04	NA	NA	Correlated set	Model calibration
65	Symptomatic presentation with CRC Dukes A	2.03E-02	NA	NA	Correlated set	Model calibration
66	Symptomatic presentation with CRC Dukes B	1.43E-01	NA	NA	Correlated set	Model calibration
67	Symptomatic presentation with CRC Dukes C	2.74E-01	NA	NA	Correlated set	Model calibration
68	Symptomatic presentation with CRC Dukes D	2.50E-01	NA	NA	Correlated set	Model calibration
69	Symptomatic presentation annual decrement in those aged > 75	3.61E-02	NA	NA	Correlated set	Model calibration
70	Average number of adenomas present in patient with at least one adenoma	2.3	2.3	2.3	Lognormal	Rutter et al 2014 (note based on gFOBT screening) [49]
71	Proportion of advanced adenoma classified as high risk coefficients: Intercept	-0.0458	-0.0583	-0.0323	Normal	NHS BCSP data 2014/15 (note based on gFOBT screening) [40]
72	Proportion of advanced adenoma classified as high risk coefficients: Male	-0.0463	-0.0553	-0.0379	Normal	
73	Proportion of advanced adenoma classified as high risk coefficients: Age	0.0058	0.0057	0.0059	Normal	
74	Proportion of advanced adenoma classified as high risk coefficients: Male * Age	0.0024	0.0023	0.0024	Normal	
75	FIT Uptake Regression Coefficients: Intercept	0.7096	0.6269	0.8023	Normal	UK FIT Pilot (Moss et al 2016) [33]
76	FIT Uptake Regression Coefficients: Age 65+	-0.1165	-0.1278	-0.1054	Normal	
77	FIT Uptake Regression Coefficients: Age 70+	-0.1192	-0.1206	-0.1178	Normal	
78	FIT Uptake Regression Coefficients: Sex Female	0.1398	0.1310	0.1484	Normal	
79	FIT Uptake Regression Coefficients: Previous non responder	-1.8326	-1.8579	-1.8264	Normal	
80	FIT Uptake Regression Coefficients: Incident	1.8795	1.8640	1.8779	Normal	

81	FIT Uptake Regression Coefficients: IMD2	-0.0726	-0.0943	-0.0619	Normal	
82	FIT Uptake Regression Coefficients: IMD3	-0.1508	-0.1625	-0.1278	Normal	
83	FIT Uptake Regression Coefficients: IMD4	-0.2877	-0.3147	-0.2744	Normal	
84	FIT Uptake Regression Coefficients: IMD5 most deprived	-0.5978	-0.6162	-0.5978	Normal	
85	FIT Uptake Regression Coefficients: Age 50-54	-0.3647	-0.3659	-0.3635	Normal	Scottish FIT Data 2017-18[34]
86	FIT Uptake Regression Coefficients: Age 55-59	-0.2516	-0.2519	-0.2512	Normal	
87	FIT Uptake Regression Coefficients: Asian	-0.9406	-1.0405	-0.8345	Normal	Szczepura et al 2008 [35] (note based on gFOBT screening England)
88	FS Uptake Regression Coefficients: Intercept	-0.7780	-0.8701	-0.6889	Normal	McGregor et al 2016 [41]
89	FS Uptake Regression Coefficients: Males	0.1389	0.0834	0.1939	Normal	
90	FS Uptake Regression Coefficients: IMD1 least deprived	0.7158	0.6141	0.8180	Normal	
91	FS Uptake Regression Coefficients: IMD2	0.5687	0.4713	0.6663	Normal	
92	FS Uptake Regression Coefficients: IMD3	0.3667	0.2738	0.4600	Normal	
93	FS Uptake Regression Coefficients: IMD4	0.1807	0.0899	0.2716	Normal	
94	FS Uptake: Per Year of Age above 55	-0.00163	-0.00223	-0.00108	Normal	UKFSST [42], normalised to BCSP mean uptake
95	FS Uptake: Asian	-0.384	-0.673	-0.132	Normal	Robb et al 2008 [43] (note based on gFOBT screening)
96	Colonoscopy uptake after FIT coefficients: Intercept	1.1691	1.1666	1.1715	Normal	NHS BCSP data 2014/15 (note based on gFOBT screening) [40]
97	Colonoscopy uptake after FIT coefficients: Prevalent screen	0.0993	0.062799	0.1372	Normal	
98	Colonoscopy uptake after FIT coefficients: Female * Prevalent	0.0555	0.0473	0.0638	Normal	
99	Colonoscopy uptake after FIT coefficients: Age	-0.00453	-0.00473	-0.00457	Normal	
100	Colonoscopy uptake after FIT coefficients: Age * Prevalent	-0.00227	-0.00287	-0.00153	Normal	
101	Colonoscopy uptake after FIT coefficients: Age * Female * Prevalent	-0.0012	-0.0014	-0.001	Normal	
102	Colonoscopy uptake after FS	0.9625	0.950	0.974	Beta	UKFSST [42]
103	CTC uptake after FIT	0.9920	0.988	0.995	Beta	Plumb et al 2013 [45]
104	Surveillance colonoscopy uptake	0.825	NA	NA	Constant	
105	Proportion CTC of all referrals Age 60-61	0.0315	0.028	0.035	Beta	NHS BCSP data 2014/15 [40]
106	Proportion CTC of all referrals Age 62-63	0.03697	0.033	0.041	Beta	
107	Proportion CTC of all referrals Age 64-65	0.04495	0.041	0.049	Beta	

108	Proportion CTC of all referrals Age 66-67	0.04424	0.040	0.048	Beta	
109	Proportion CTC of all referrals Age 68-69	0.04700	0.043	0.052	Beta	
110	Proportion CTC of all referrals Age 70-71	0.05309	0.048	0.059	Beta	
111	Proportion CTC of all referrals Age 72-74	0.06071	0.055	0.067	Beta	
112	FIT probability second kit sent	0.02	0.018	0.022	Beta	Murphy and Gray 2015 [57]
113	FS repeat test rate	0.02065	0.019	0.022	Beta	UKFSST [42]
114	Colonoscopy repeat test rate	0.06963	0.068	0.071	Beta	NHS BCSP data 2014/15 [40]
115	CTC additional investigation rate	0.35445	0.337	0.372	Beta	Plumb et al 2013 [45]
116	Colonoscopy (with polypectomy) perforation rate	0.00091	0.001	0.001	Beta	Rutter et al 2014 [49]
117	Colonoscopy (without polypectomy) perforation rate	0.00031	0.000	0.001	Beta	Rutter et al 2014 [49]
118	FS (with polypectomy) perforation rate	0.000105	0.000	0.000	Beta	UKFSST [42]
119	FS (without polypectomy) perforation rate	0	NA	NA	Constant	
120	CTC perforation rate	0.0002	0.00007	0.00039	Beta	Bellini et al 2014 [51]
121	Colonoscopy probability of hospitalisation for bleeding	0.0004	0.000	0.001	Beta	Rutter et al 2014 [49]
122	FS probability of hospitalisation for bleeding	0.000295	0.000	0.000	Beta	UKFSST [42]
123	Colonoscopy probability of death following perforation	0.05195	0.015	0.111	Beta	Gatto et al 2003
124	FS probability of death following perforation	0.06452	0.008	0.172	Beta	
125	CTC probability of death following perforation	0	NA	NA	Constant	Bellini et al 2014 [51]
126	Colonoscopy Sensitivity for LR adenomas	0.7651	0.733	0.796	Beta	Van Rijn et al 2006 [13]
127	Colonoscopy Sensitivity for HR adenomas	0.9791	0.943	0.997	Beta	
128	Colonoscopy Sensitivity for CRC	0.9656	0.962	0.969	Beta	Bressler et al 2007 [46]
129	Colonoscopy Specificity	1	NA	NA	Constant	Assumption due to nature of the test
130	CTC Sensitivity for LR adenomas	0.6274	0.381	1.018	Beta	Assumption based on detection rates relative to colonoscopy in Atkin et al. 2013 [47]
131	CTC Sensitivity for HR adenomas	0.8029	0.490	1.277	Beta	
132	CTC Sensitivity for CRC	0.9463	0.606	1.472	Beta	
133	CTC Specificity	0.8812	0.8729	0.8893	Beta	Lin et al 2015 [48]
134	FS Sensitivity for LR adenomas Male Intercept	0.394	0.369	0.418	Beta	Calculated from UKFSST detection rates and modelled prevalence [42]
135	FS Sensitivity for LR adenomas Male Age Param	0.999	0.988	1.011	Normal	

136	FS Sensitivity for HR adenomas Male Intercept	0.486	0.447	0.526	Beta	Calculated from NHS BCSP 2014/15 detection rates and modelled prevalence [40]
137	FS Sensitivity for HR adenomas Male Age Param	0.988	0.972	1.005	Normal	Calculated from UKFSST detection rates and modelled prevalence [42]
138	FS Sensitivity for CRC Male Intercept	0.438	0.295	0.581	Beta	Calculated from NHS BCSP 2014/15 detection rates and modelled prevalence [40]
139	FS Sensitivity for CRC Male Age Param	1.034	0.969	1.140	Normal	Calculated from UKFSST detection rates and modelled prevalence [42]
140	FS Sensitivity for LR adenomas Female Intercept	0.321	0.294	0.348	Beta	
141	FS Sensitivity for LR adenomas Female Age Param	0.978	0.964	0.994	Normal	
142	FS Sensitivity for HR adenomas Female Intercept	0.380	0.329	0.431	Beta	Calculated from NHS BCSP 2014/15 detection rates and modelled prevalence [40]
143	FS Sensitivity for HR adenomas Female Age Param	0.947	0.927	0.969	Normal	Calculated from UKFSST detection rates and modelled prevalence [42]
144	FS Sensitivity for CRC Female Intercept	0.366	0.213	0.519	Beta	Calculated from NHS BCSP 2014/15 detection rates and modelled prevalence [40]
145	FS Sensitivity for CRC Female Age Param	0.916	0.910	1.106	Normal	Calculated from UKFSST detection rates and modelled prevalence [42]
146	FS Specificity	1	NA	NA	Constant	Assumption due to nature of the test
147	FIT Sensitivity LR adenomas Males: Power Curve Intercept	0.841	0.7057	1.2074	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
148	FIT Sensitivity LR adenomas Males: Power Curve FIT_Param	-0.784	-0.9810	-0.6540	Normal	
149	FIT Sensitivity LR adenomas Males: Age effect > 60	1.034	1.0259	1.0428	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
150	FIT Sensitivity LR adenomas Males: Round 2 effect	0.823	0.7362	0.9094	Normal	
151	FIT Sensitivity LR adenomas Females: Power Curve Intercept	0.630	0.5288	0.9050	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
152	FIT Sensitivity LR adenomas Females: Power Curve FIT_Param	-0.852	-1.0500	-0.7230	Normal	
153	FIT Sensitivity LR adenomas Females: Age effect > 60	1.026	1.0179	1.0347	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
154	FIT Sensitivity LR adenomas Females: Round 2 effect	0.801	0.7166	0.8852	Normal	
155	FIT Sensitivity HR adenomas Males: Power Curve Intercept	1.071	1.0818	1.1313	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
156	FIT Sensitivity HR adenomas Males: Power Curve FIT_Param	-0.487	-0.5910	-0.4130	Normal	
157	FIT Sensitivity HR adenomas Males: Age effect > 60	1.027	1.0207	1.0336	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
158	FIT Sensitivity HR adenomas Males: Round 2 effect	0.827	0.7626	0.9086	Normal	
159	FIT Sensitivity HR adenomas Females: Power Curve Intercept	1.205	1.2165	1.2731	Beta	

160	FIT Sensitivity HR adenomas Females: Power Curve FIT_Param	-0.555	-0.6590	-0.4810	Normal	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
161	FIT Sensitivity HR adenomas Females: Age effect > 60	1.014	1.0072	1.0200	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
162	FIT Sensitivity HR adenomas Females: Round 2 effect	0.829	0.7638	0.9100	Normal	
163	FIT Sensitivity CRC Males: Power Curve Intercept	0.526	0.2702	0.8675	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
164	FIT Sensitivity CRC Males: Power Curve FIT_Param	-0.083	-0.1450	-0.0540	Normal	
165	FIT Sensitivity CRC Males: Age effect > 60	0.999	0.9852	1.0141	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
166	FIT Sensitivity CRC Males: Round 2 effect	0.991	0.8259	1.1768	Normal	
167	FIT Sensitivity CRC Males: Round 3 effect	0.845	0.6758	1.0813	Normal	
168	FIT Sensitivity CRC Females: Power Curve Intercept	0.353	0.1764	0.5820	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
169	FIT Sensitivity CRC Females: Power Curve FIT_Param	-0.171	-0.2320	-0.1420	Normal	
170	FIT Sensitivity CRC Females: Age effect > 60	1.008	0.9935	1.0226	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
171	FIT Sensitivity CRC Females: Round 2 effect	1.016	0.8467	1.2065	Normal	
172	FIT Sensitivity CRC Females: Round 3 effect	0.863	0.6900	1.1040	Normal	
173	FIT False Positives Males: Power Curve Intercept	0.510	0.3616	0.9747	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
174	FIT False Positives Males: Power Curve FIT_Param	-1.020	-1.2930	-0.8470	Normal	
175	FIT False Positives Males: Age effect > 60	1.056	1.0401	1.0714	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
176	FIT False Positives Males: Round 2 effect	0.604	0.5952	0.6135	Normal	
177	FIT False Positives Males: Round 3 effect	0.517	0.4994	0.5261	Normal	
178	FIT False Positives Females: Power Curve Intercept	0.538	0.3816	1.0287	Beta	Calculated from Moss et al. 2016 detection rates and modelled prevalence [33]
179	FIT False Positives Females: Power Curve FIT_Param	-1.082	-1.3550	-0.9090	Normal	
180	FIT False Positives Females: Age effect > 60	1.056	1.0404	1.0717	Normal	Calculated from Zorzi et al. 2018 estimates of age effects on detection rates [38]
181	FIT False Positives Females: Round 2 effect	0.634	0.6244	0.6436	Normal	
182	FIT False Positives Females: Round 3 effect	0.550	0.5311	0.5596	Normal	
183	Utility decrement age	0.00432	0.00404	0.0046	Normal	Ara & Brazier 2010 [5]
184	Utility multiplier CRC Yr1 Stage A-C	0.87	0.67	1.07	Normal	Djalalov et al 2014 [52]
185	Utility multiplier CRC Yr1 Stage D	0.68	0.42	0.93	Normal	
186	Utility multiplier CRC Yr2+ Stage A-C	0.92	0.76	1.08	Normal	
187	Utility multiplier CRC Yr2+ Stage D	0.73	0.51	0.94	Normal	

188	Annual utility decrement perforation (based on 1 month data)	-0.0098	-0.0106	-0.0092	Normal	Ara & Brazier 2010 [5]
189	Annual utility decrement bleeding (based on 2 week data)	-0.0058	-0.0088	-0.0028	Normal	Dorian et al. 2014 [53]
190	CRC Treatment Costs: Dukes' A & B, Age <64, Year 1	£16,302	£13,264	£19,649	Gamma	Laudicella et al. 2016 [56], Excess costs compared with pre cancer, inflated to 2017/18
191	CRC Treatment Costs: Dukes' A & B, Age <64, Year 2	£3,826	£3,113	£4,611	Gamma	
192	CRC Treatment Costs: Dukes' A & B, Age <64, Year 3	£3,175	£2,583	£3,827	Gamma	
193	CRC Treatment Costs: Dukes' A & B, Age <64, Year 4	£2,452	£1,995	£2,955	Gamma	
194	CRC Treatment Costs: Dukes' A & B, Age <64, Year 5	£2,206	£1,795	£2,659	Gamma	
195	CRC Treatment Costs: Dukes' A & B, Age <64, Year 6	£1,509	£1,228	£1,818	Gamma	
196	CRC Treatment Costs: Dukes' A & B, Age <64, Year 7	£1,569	£1,276	£1,891	Gamma	
197	CRC Treatment Costs: Dukes' A & B, Age <64, Year 8	£1,438	£1,170	£1,733	Gamma	
198	CRC Treatment Costs: Dukes' A & B, Age <64, Year 9	£1,239	£1,008	£1,494	Gamma	
199	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 1	£15,233	£12,395	£18,361	Gamma	
200	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 2	£3,508	£2,855	£4,229	Gamma	
201	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 3	£2,860	£2,327	£3,447	Gamma	
202	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 4	£2,379	£1,936	£2,867	Gamma	
203	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 5	£2,414	£1,964	£2,910	Gamma	
204	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 6	£2,440	£1,985	£2,941	Gamma	
205	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 7	£2,217	£1,804	£2,672	Gamma	
206	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 8	£2,458	£2,000	£2,962	Gamma	
207	CRC Treatment Costs: Dukes' A & B, Age 65+, Year 9	£2,052	£1,669	£2,473	Gamma	
208	CRC Treatment Costs: Dukes' C & D, Age <64, Year 1	£21,051	£17,128	£25,373	Gamma	
209	CRC Treatment Costs: Dukes' C & D, Age <64, Year 2	£6,895	£5,610	£8,311	Gamma	
210	CRC Treatment Costs: Dukes' C & D, Age <64, Year 3	£4,713	£3,835	£5,681	Gamma	
211	CRC Treatment Costs: Dukes' C & D, Age <64, Year 4	£3,850	£3,132	£4,640	Gamma	
212	CRC Treatment Costs: Dukes' C & D, Age <64, Year 5	£2,748	£2,236	£3,312	Gamma	
213	CRC Treatment Costs: Dukes' C & D, Age <64, Year 6	£2,300	£1,872	£2,772	Gamma	
214	CRC Treatment Costs: Dukes' C & D, Age <64, Year 7	£2,680	£2,181	£3,231	Gamma	
215	CRC Treatment Costs: Dukes' C & D, Age <64, Year 8	£2,055	£1,672	£2,477	Gamma	
216	CRC Treatment Costs: Dukes' C & D, Age <64, Year 9	£1,413	£1,150	£1,704	Gamma	

217	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 1	£16,625	£13,526	£20,037	Gamma	
218	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 2	£5,242	£4,265	£6,318	Gamma	
219	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 3	£4,047	£3,293	£4,878	Gamma	
220	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 4	£3,169	£2,579	£3,820	Gamma	
221	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 5	£2,965	£2,413	£3,574	Gamma	
222	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 6	£2,816	£2,291	£3,394	Gamma	
223	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 7	£1,800	£1,465	£2,170	Gamma	
224	CRC Treatment Costs: Dukes' C & D, Age 65+, Year 8	£2,338	£1,902	£2,818	Gamma	
225	CRC cTreatment Costs: Dukes' C & D, Age 65+, Year 9	£1,818	£1,479	£2,191	Gamma	
226	Cost of FIT invite	£7.45	£6.74	£8.16	Uniform	Southern Hub screening costings model inflated to 2017/18 [37]
227	Additional cost of FIT performed	£1.09	£0.98	£1.19	Uniform	
228	Additional cost of FIT positive result	£10.23	£9.26	£11.20	Uniform	
229	Cost of FS invite	£5.82	£5.27	£6.37	Uniform	
230	Cost of FS attend diagnostic (not including FS exam)	£1.14	£1.04	£1.25	Uniform	
231	Cost of FS attend therapeutic (not including FS exam)	£11.37	£10.29	£12.45	Uniform	
232	Cost of FS (without polypectomy)	£402	£320	£469	Uniform	NHS reference costs 17/18 (IQR estimated from 16/17) [54]
233	Cost of FS (with polypectomy)	£512	£425	£591	Uniform	
234	Cost of COL (without polypectomy)	£525	£412	£597	Uniform	
235	Cost of COL (with polypectomy)	£641	£515	£730	Uniform	
236	Cost of CTC	£121	£97	£141	Uniform	
237	Cost of treating bowel perforation (major surgery)	£1,554	£526	£2,258	Uniform	
238	Cost of admittance for bleeding (overnight stay on medical ward)	£474	£395	£529	Uniform	
239	Pathology cost	£32.75	£13.11	£37.31	Uniform	

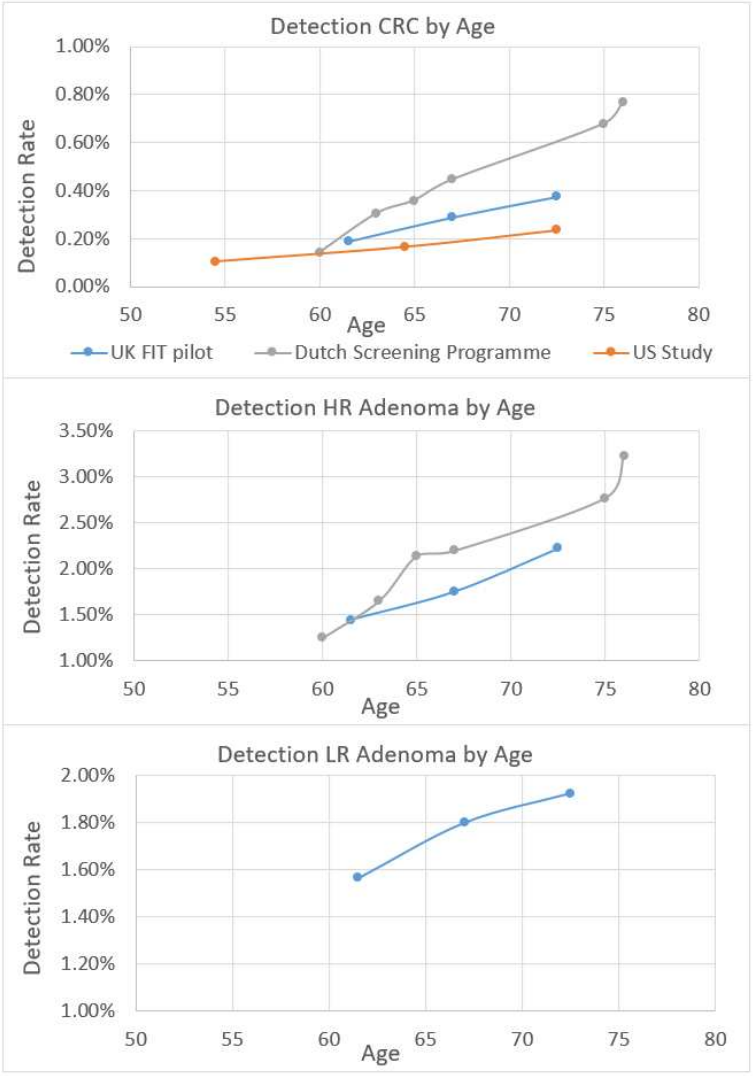
Appendix B: Comparison of FIT Detection Rates across Studies

To investigate the accuracy of the FIT sensitivity estimates based on the UK FIT pilot and to investigate trends by age, sex, screening round and FIT threshold, a comparison of UK FIT pilot detection with data from other countries was carried out. This included data from the Italian screening programme (and from Veneto specifically), the Dutch screening programme, the Swedish FIT pilot and a US large scale study [33 38 39 58-61].

Detection by age

Only two studies reported detection rates of CRC by age, and one reported detection rates of HR adenomas by age. However, we were also able to obtain unpublished information about detection rates for all three disease types from the UK FIT pilot through an ODR request. The slope of increase appears to be reasonably linear but varies depending between screening studies so for CRC may be as small as 0.007% (US data) [60] or as large as 0.039% (Dutch data) [39] per year of age (Figure 26).

Figure 26: Trends in detection rates following FIT screening by age



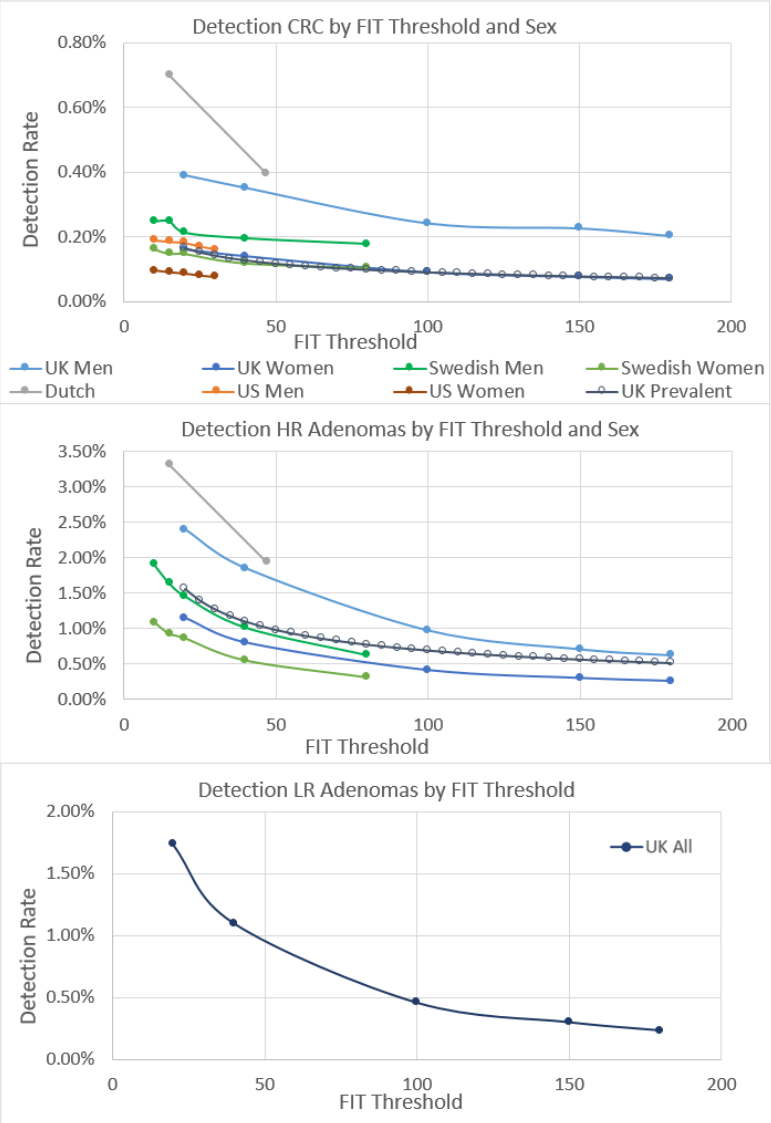
The Dutch data was from the first round of a new screening programme, so represented a previously unscreened population [39]; whilst the US and UK data was from mixed screening populations, including individuals who had previously been screened [33 60]. Given that lower detection rates are observed in subsequent screening rounds, it is likely that the slope represented by the Dutch data is the most accurate representation of the age effect, independent from other effects.

It is important to note that whilst detection rate does appear to increase with age, prevalence also increases with age, therefore the sensitivity may not change with age.

Detection by sex and FIT threshold

In all screening studies where male and female data is gathered separately, detection rate is higher in males than females (Figure 27). As with age, it is unclear how much of this difference is related to the difference in underlying prevalence between men and women.

Figure 27: Trends in detection rates by FIT threshold and sex



The absolute values are very different between studies, which is likely to be due to the different average ages represented in each study and the differing mixture of first time screening and subsequent screening, in addition to country-specific differences in prevalence and FIT test kit.

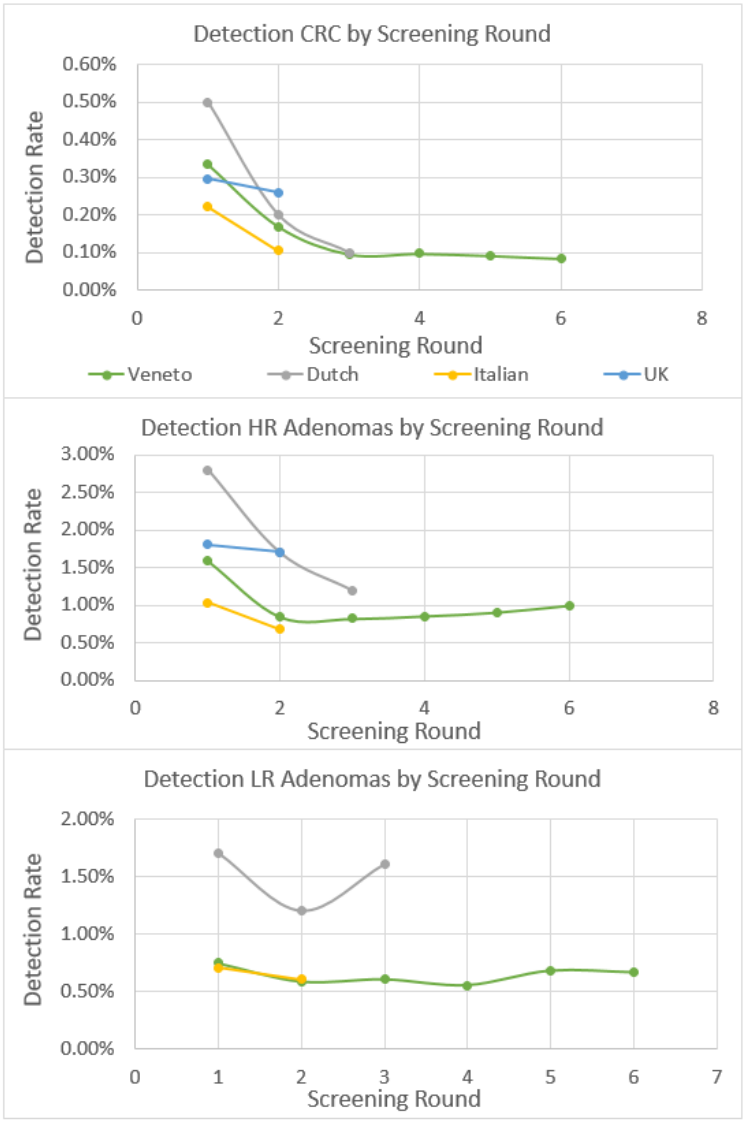
Detection rate decreases as FIT threshold rises, in a non-linear way. The curve appears to be steeper for LR adenomas than HR adenomas, and for HR adenomas than CRC. Our previous model used data from the prevalent round of the UK FIT pilot only (shown as UK prevalent on the graphs) [33]. There is extremely high uncertainty around the estimates of CRC detection due to the small numbers involved in the pilot. The plots indicate that whilst HR adenoma detection rates for the UK FIT pilot prevalent round fall roughly between the separate male and female detection rates for all screening rounds in the UK FIT pilot, and close to the male detection rates for Sweden [59], CRC detection rates are much lower, indicating that the prevalent round data could be underestimating CRC detection.

Detection by screening round

There is large variation between studies in differences by screening round (Figure 28). For the UK and Italian studies data is not provided by actual screening round and instead is reported as either prevalent (first screen) or incident (subsequent screen) round [33 61]; the incident screen has been represented on the graph as screen two, but in fact will contain individuals who have been screened two or more times.

The general trend is for detection rates to be reduced in subsequent screening rounds; however, the data from the Veneto screening programme [38], which is most comprehensive in terms of providing information about a large number of screening rounds, shows the detection rate for CRC flat-lining after the third screen, and actually increasing for HR and LR adenoma. This is likely due to confounding with age. Indeed, the authors have performed multivariate analysis adjusting for age which indicates that CRC detection rates are likely to keep reducing until screening round three, whilst HR and LR adenoma detection rates are likely to flat-line after the second screen rather than increase.

Figure 28: Trends in detection rates following FIT screening by screening round



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