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Title: Development of the Microsimulation Model in Cancers of Bladder and Kidney (MiMiC-BlaKy)

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Development of the Microsimulation Model in Cancers of Bladder and Kidney (MiMiC-BlaKy)

Technical Document

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Abbreviations

BC	Bladder Cancer
CT	Computerised Tomography Scan
CRUK	Cancer Research UK
EQ-5D	EuroQol - 5 Dimensions
FIT	Faecal Immunochemical Test
GOF	Goodness of Fit
HSE	Health Survey for England
IMD	Indices of Multiple Deprivation
KC	Kidney Cancer
LYS	Life Years Saved
MRI	Magnetic Resonance Imaging
NHD	Natural History Disease
ONS	Office for National Statistics
RR	Relative Risk
QALYs	Quality-Adjusted Life Years

Background

The Microsimulation Model in Bladder [BC] and Kidney [KC] cancers has been developed as part of the YORKSURe trial, a feasibility assessment for implementing a targeted study in populations with a high risk of disease-specific mortality in Yorkshire. YORKSURe is a feasibility trial aimed at the early diagnosis of BC through the detection of haematuria in asymptomatic individuals at high risk of mortality from BC[1]. Following results of the feasibility trial, the aim is to then conduct a large-scale trial, with sufficient power to test any differences in survival. The feasibility trial aims to understand if the proposed approach is robust, appropriate, necessary, and acceptable to participants.

The trial investigates the efficacy of urine dipstick testing for BC detection. A urine dipstick test is a simple diagnostic tool used to screen for abnormalities in the urine. It involves a specially treated strip that is dipped into a urine sample. The strip has reagent pads that change colour upon exposure to various substances such as glucose, protein, blood, and leukocytes, among others. The colour changes on the dipstick are compared to a chart that provides an indication of the presence and approximate concentration of different substances, which can help in the diagnosis of conditions like urinary tract infections, as well as bladder and (much less accurately) kidney cancers. This quick and non-invasive test is routinely used in clinical settings for its speed and convenience in providing immediate results.

To inform the trial design, the mathematical disease model was created with the objective to assess the long-term impact and cost-effectiveness of home dipstick test screening in a population cohort similar to one of the cohorts enrolled in the YORKSURe trial—current and former smokers. The original model focused solely on simulating the natural history of BC. The initial calibration of the BC model revealed that haematuria screening is not cost-effective. However, drawing such a conclusion was deemed premature without factoring in the potential additional benefits of screening, such as the detection of KC. As a result, a combined Bladder and Kidney cancers model, referred to as MiMiC-BlaKy, was subsequently developed.

MiMiC-BlaKy is an individual patient simulation model constructed using the R programming language. Its primary purpose is to facilitate comparisons of the effectiveness, cost-effectiveness, and resource utilisation associated with screening strategies for urological cancers, specifically BC and KC, across diverse population groups. The model simulates the life trajectories of patients and can be tailored to represent various populations, chosen based on predefined criteria.

Each individual within the model possesses a unique set of characteristics that govern their susceptibility to cancer and how they respond to screening and surveillance protocols. Notably, the

model spans a lifetime horizon and adopts the perspective of the NHS (National Health Service). In its simulations, MiMiC-BlaKy treats both BC and KC as mutually exclusive events. This means that if an individual develops either BC or KC, they will not experience a primary case of the second disease during their lifetime. This approach is argued by the rarity of such concurrent primary cases and the assumption that patients with history of urological cancers could be followed up for all urological conditions.

Model Structure

At the core of the model lie natural history disease (NHD) modules for both diseases. The model posits that only cancer onset, and not the progression of the disease, is influenced by risk factors. Within the model, the probability of transitioning to each progressive disease state is time-dependent, contingent on the time elapsed since disease onset. Simultaneously, the probability of receiving a diagnosis is not directly time dependent as it is determined by the model state in which the individual is situated.

For BC, each patient may develop either low-risk or high-risk BC with the Stages 1 to 4 aligning with the criteria utilised by the Office for National Statistics in the UK and Cancer Research UK (CRUK) (Figure 1). For KC, following the onset of cancer, each patient is assigned one of four undiagnosed stages (1 to 4), as depicted in Figure 2. These stages feature varying probabilities of being diagnosed and, when diagnosed, differing risks of cancer-related mortality.

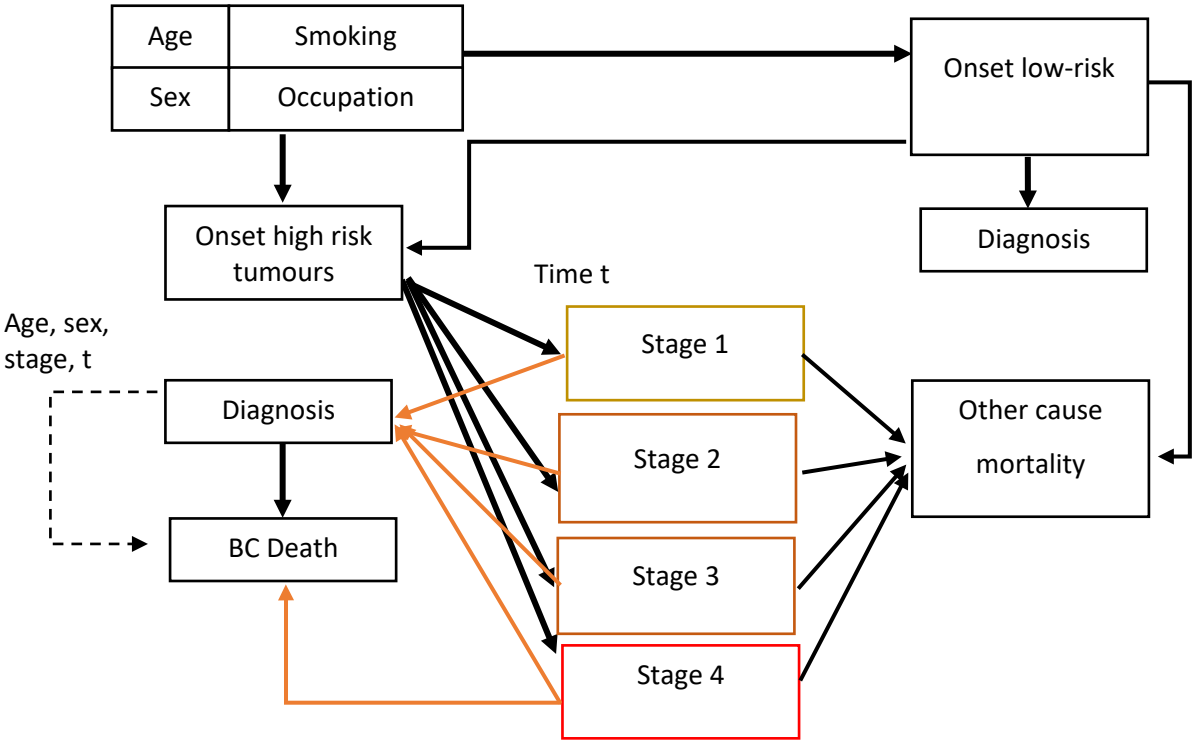


Figure 1: Structure of the natural history disease in the bladder cancer model

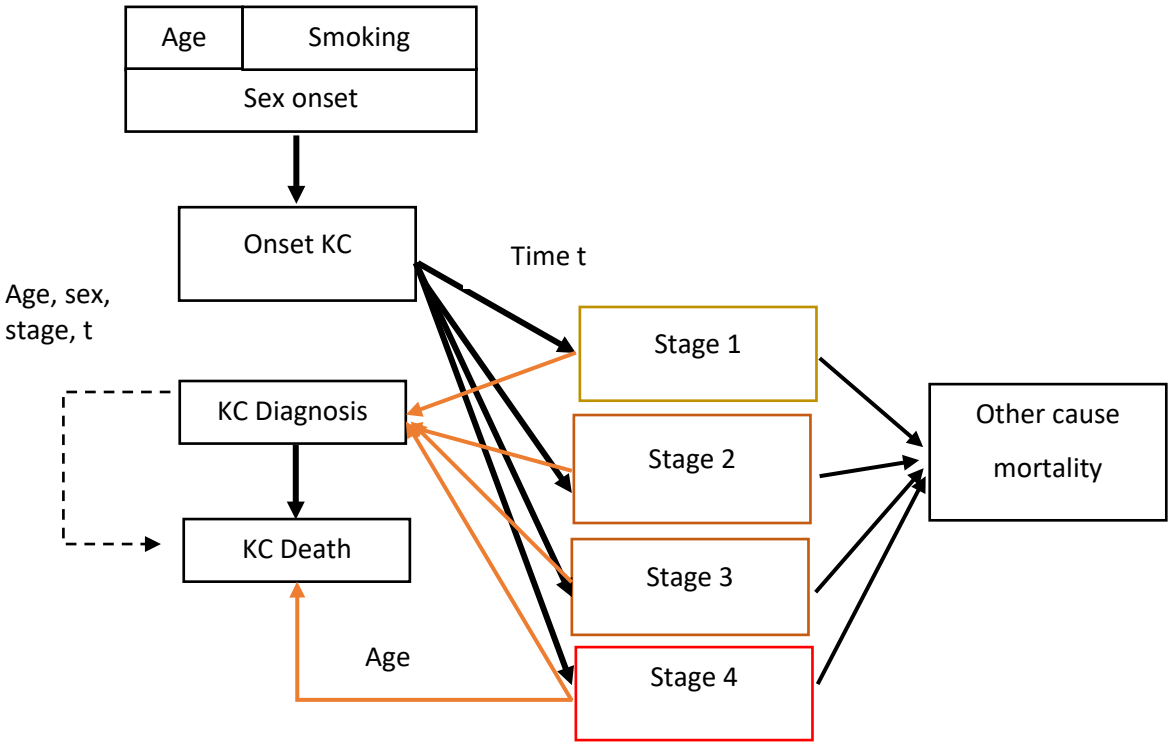


Figure 2: Structure of the natural history disease in the kidney cancer model

For people who have an onset of high-risk BC or KC, from stage 1 to stage 4, a disease progression event was assigned as a function of the time since cancer onset. It is assumed that patients who become symptomatically diagnosed will follow the treatment pathway, which includes treatment costs, utility reductions, and reduced survival compared to the general population. This means that each diagnosed stages have different quality of life and costs associated with it.

The model has two absorbing states. Whilst all individuals have a probability of dying from other causes, only those high-risk cancers who have Stage 1-4 BC can die from BC. For KC, the cancer deaths may happen at Stages 1-4. It is not possible that individuals can die from undiagnosed cancer, assuming that all cancers are diagnosed before death or post-mortem (reflecting the national incidence and mortality data) unless a person with cancer reaches the age of 70 years when symptomatic presentation rate lowers, and they have a stage 4 cancer. This was added to the model to reflect the observed lower symptomatic presentation rate among elderly individuals potentially associated with higher rates of comorbidities.

The screening module is integrated atop the natural history models, providing a critical input. This module extends an invitation for screening to each individual meeting the eligibility criteria, which are determined by age, smoking status, and the absence of symptomatic cancer. Upon diagnosis via

the screening process, individuals are guided through a diagnostic pathway. Should they continue to test positive at the conclusion of this pathway—owing to an actual cancer diagnosis or a false-positive result—these individuals are then ascribed annual treatment expenses and associated disutilities.

Following model setup, the model simulation progresses by first evaluating whether the person has a tumour at time t. The next step is to decide the stage of the disease and who is diagnosed with cancer symptomatically, and if diagnosed, who dies from cancer; then if screening is selected, the screening and surveillance modules of the model are run. Finally, model outcomes are gathered. Costs, quality-adjusted life years (QALYs) and other outcomes such as resource use and cancer cases are aggregated; half cycle correction and discounting are applied to costs, QALYs and life years saved (LYS), and incremental results are estimated.

The calibrated model can be run in two modes: probabilistic and deterministic. Both modes can be run with different populations varied by their demographic characteristics (age, sex, smoking status) to analyse the impact of implementation of the home dipstick test.

Model Population

Baseline Phenotypic Characteristics

The model baseline population is composed of individuals from the Health Survey for England (HSE) 2018[2], an annual survey which is designed to provide a snapshot of the nation's health. The year 2018 was selected as the most recent dataset that included population baseline quality of life values. Individuals aged under 30 years were excluded from the model as it was assumed that the number of BC cases in this group are very small. This resulted in a sample of 6,928 individuals. The individual phenotypic attributes extracted from HSE 2018 for use in the model included age, sex, ethnicity, EuroQol - 5 Dimensions (EQ-5D), indices of multiple deprivation (IMD) quintile (a measurement of socioeconomic deprivation), smoking status, occupation (in particular whether a person is a manufacturing worker [as it is specified in HSE] or not), and region (whether the respondent is from Yorkshire and the Humber region or not). 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. Table 1 summarises the individual characteristics extracted from HSE 2018.

Table 1: Summary of individual characteristics extracted from HSE 2018, their coding in the model and the numbers with missing data.

Characteristic (Unit)	**HSE 2019/2014 Survey Code**	**How Coded in the Model**	**Number with Missing Data**
Age (Years)	Age16g5	Continuous variable	0 (0%)
Sex	Sex	Binary; 1 = Male, 0 = Female.	0 (0%)
Ethnicity	origin2	Numeric; 1 = White; 2 = Black; 3 = Asian; 4 = Mixed; 5 = other	23 (0.34%)
IMD Quintile	qimd	Numeric: 1 = least deprived; 5 = most deprived.	0 (0%)
Smoking Status	cigsta3	Split into two binary variables: Current Smoker (1 = yes; 0 = no); Former Smoker (1 = yes; 0 = no).	20 (0.30%)
Occupation	HRPSIC7B3	Binary; 1 – manufacturing worker, 0 – other occupation	150 (2.24%)
Region	GOR1	Binary; 1 - Yorkshire and the Humber, 2 – other region	0 (0%)
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].	683 (10.19%) 681 (10.16%) 674 (10.06%) 691 (10.31%) 695 (10.37%)
weighting	wt_int	Continuous variable.	0 (0%)

HSE = Health Survey for England; IMD = Indices of Multiple Deprivation; 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, those missing smoking data were never regular smokers, and those who had missing occupation were not manufacturing workers.

HSE 2018 did not report the age as a continuous variable but as a categorical one within 5-year categories. To assign a continuous value, we randomly sampled assuming a uniform distribution in each age category the age within the 5-year category for each individual.

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 0.32 indicating that 32% 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	1.1042713	0.0255135
Age	-0.0046997	0.0003289
Sex	0.0316358	0.0120132
IMD Quintile	-0.0352753	0.0042573

Risk factors included in the model

The relative risk (RR) for current and former smokers was calculated using the outcomes of a systematic review and meta-analysis conducted by Cumberbatch et al (2016). The review reported a pooled RR of BC incidence of 3.47 (3.07–3.91) for current smokers and 2.04 (1.85–2.25) for former smokers compared to never smokers and the RR of KC incidence for renal cell cancer of 1.36 (1.19–1.56) for current smokers and 1.16 (1.08–1.25) for former smokers.[4]

The RR for manufacture workers was incorporated into the model by conducting a random effect meta-analysis using the data from the systematic review on the occupational BC within the UK.[5] From the systematic review of Cumberbatch et al (2016), the studies reporting cases, controls, and the total population size for any manufacture workers were included. This resulted in three studies included into the synthesis. The test for heterogeneity results: I2 = 0%; Q(df = 2) = 0.3868, p-val = 0.8242. Using a random effect model the pooled RR for manufacture workers compared to everyone else was 1.99, 95%CI (1.22; 3.26). The log of the RR is reported on the plot (Figure 3). There is no consistency in the literature regarding the impact of occupation on KC incidence; thus, the distribution of risk of KC by occupation was not included into the model [6].

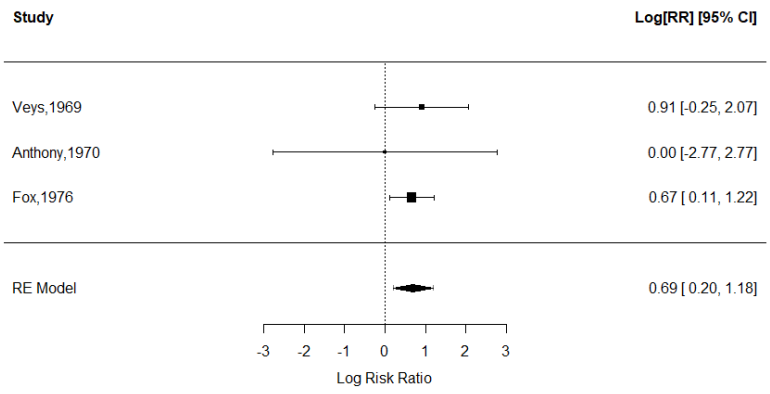


Figure 3: Random effect meta-analysis of RR of BC for manufacture workers compared to non-manufacture workers

The risk of BC and KC onset by age and sex was informed through the calibration and is reported in the relevant section below. Because the individual risks were informed through different sources which did not consider correlations between the relevant risk factors, re-calibration of the individual RR was necessary (see the calibration section).

Other risk factors not included in the model

HSE 2018 does not contain any information about environmental carcinogens. A review on epidemiology of BC identifies exposure to arsenic in drinking water as a cause of BC[7]. There is no data suggesting that English regions differ by their arsenic exposure in drinking water, although one source reported that arsenic concentrations >10 μg L−1 were previously measured in 5% of private water supplies. According to Public Health England report from 2019, there is no risk of high content of arsenic in drinking water in England and so this risk factor was currently not included into the model[8].

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 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. While occupational exposure is also likely to change and risks may be cumulative over time, it was considered to be a binary risk factor in the model because of lack of evidence on the dynamics of occupational exposure among the population in England and RR of occupational exposure after retirement age.

Smoking

Data from HSE 2018 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. This is supported by ONS data demonstrating that the proportion of current smokers in England has fallen significantly, and that those aged 25 to 34 years had the highest proportion of current smokers in the UK (19.0%). It is therefore assumed that no individuals who were surveyed as non-smokers in HSE 2018 would start smoking after the age of 30. The probability to remain a smoker after one year was based on the estimated number of quitters (self-reported) per 100,000 smokers (from April 2020 to March 2021) according to NHS digital data: 0.0167 was the estimated probability to quit smoking after one year and 0.9833 was the estimated probability to remain a smoker.[9] While smoking cessation is much more complex and dynamic than modelled here, we used this simplified approach for project feasibility.

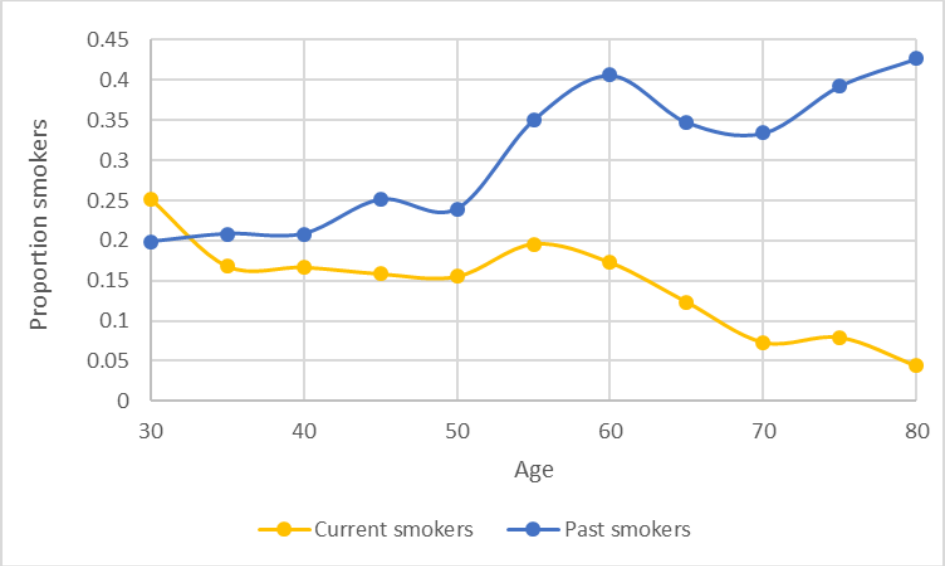


Figure 4: The proportion of current and former smokers by age in the HSE 2018 population [10]

EQ-5D

EQ-5D decreases with age, therefore annual 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. [11] 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 the population ages 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.

Reconstructing the population of England for model calibration and analysis

The model was set up to enable a single-aged cohort to be modelled, in order to answer cost-effectiveness questions.

Single-age cohort

A starting age of 30 was chosen, as incidence of BC and KC among those younger than 30 years is close to negligible [12]. The cohort was created by artificially setting the ages of all individuals from HSE 2018 to 30. At the same time, adjustments were made to individual EQ-5D to reflect the change in age, based on the methods described above. Summary statistics for this population are shown in Table 3. The cohort was modelled over their lifetime to provide estimates of the parameters in the calibration (see the section on the model calibration).

Multi-age population

For representing the trial population or for resource use inquiries, it is of utmost importance that the baseline population accurately mirrors the target population (i.e. the trial population or the present demographic composition of England), encompassing a multi-aged cohort. Currently, this functionality has not been integrated into the model but is planned for incorporation in future model iterations. The process of re-creating the multi-age cohort (that is going to be used in the future) is described below.

As the baseline individuals within the model initiate their journey at various ages, it is necessary to simulate an initial health state for each individual rather than assuming that no individuals have cancer at the model start. In essence, the approximation of multi-cohort modelling can be achieved by utilising the HSE 2018 population data in conjunction with survey weights (as illustrated in Table 3). To do this, a population of 3.35 million individuals will be simulated, starting at the age of 30 at baseline using the cohort model. For this simulated population, individual probabilities of occupying one of health states in BC (normal epithelium, low-risk BC, or one of the high-risk BC stages) and in KC (normal epithelium or one of the KC stages) at their actual (HSE) age was calculated.

Subsequently, a health state is randomly allocated to each person based on the defined probabilities. Likewise, the probability of diagnosis for each individual within the HSE population assessed. Given that this population would not participate in the BC screening programme, they were excluded from the simulation population by assigning a weight of zero in the sampling function.

YORKSURe Trial Screening Population

The all-England population will likely differ from the population in Yorkshire by their phenotypic characteristics, including smoking prevalence, age, and occupational exposure (Table 3), though the difference between the HSE population from all-England and Yorkshire is small.

Table 3: Summary statistics for the model population at baseline, for multi-aged and single-aged cohorts from HSE 2018

Characteristic	**Mean (HSE 2018)**	**Standard Deviation**	**Weighted Mean at Multi-Aged Cohort Model Start, England**	**Weighted Mean at Single-Aged Cohort Model Start (Age 30), England**	**Weighted Mean for Yorkshire population (Age 30)**
Age (years)	55.99	15.78	54.84	30	
	Number in HSE 2018	**Percentage in HSE 2018**	**Weighted Percentage (Multi-Aged Cohort)**	**Weighted Percentage Single-Aged Cohort)**	**Weighted Percentage for Yorkshire population**
Male	3110	44.9%	44.9%	44.9%	47.2%
Ethnicity: White	6078	87.7%	87.7%	87.7%	86.3%
Ethnicity: Asian	478	6.9%	9.0%	9.0%	8.2%
Ethnicity: Black	201	2.9%	2.9%	2.9%	2.7%
IMD1	1366	19.7%	19.7%	19.7%	10.9%
IMD2	1493	21.6%	21.6%	21.6%	22.0%
IMD3	1466	21.2%	21.2%	21.2%	17.2%
IMD4	1398	20.2%	20.2%	20.2%	20.7%
IMD5	1205	17.4%	17.4%	17.4%	29.2%
Current Smoker	1034	14.9%	14.9%	14.9%	15.9%
Former Smoker	2126	30.7%	30.7%	30.7%	29.0%
Manufacture workers	998	14.4%	13.1%	13.1%	16.5%

Yorksure trial includes three different population cohorts with health economic modelling aiming to predict the outcomes for two asymptomatic cohorts (cohort 1 and cohort 2). Cohort 1 & 2 were invited to take part in a 'Bladder Health Check' through the mailout of a urine self-testing kit. Urine test strips suitable for self-testing will test for glucose, leukocytes, nitrite, protein, and erythrocytes (blood) in the urine (haematuria). Participants with a positive test result for haematuria (Cohort 1 & 2) or glycosuria (Cohort 2 only as per randomisation) will be invited to attend an Early Detection Clinic for further investigations (urinary tract USS and urine cytology for haematuria or a HbA1c

blood test for glycosuria). Those with abnormalities found at the Early Detection Clinic will be referred to their local urology centre as per 2WW criteria.

The description of the two cohorts is the following[1]:

Cohort 1: Men and women aged 55-80 years within those already participating in the Yorkshire Lung Screening Trial. The test to be used is The Roche Combur 5 HC test. Those verbally consenting will be asked to home self-test their urine up to 6 times over consecutive days for haematuria. The protocol plan assumes to invite 2,000 persons leading to the detection of 1-7 cancers and so will not be able to inform clinical outcomes.

Cohort 2: Men aged 65-79 years registered with a selected GP in a region with a high BC mortality risk. Participants and GPs will receive only the haematuria result or the glycosuria result (as per randomisation).

Simulation of the trial population in the model required reconstructing the multi-age population as it described above, and then reassigning the weights for each person in HSE based on the trial selection criteria. For the cohort 1, the sampling eligibility for the HSE population included age 55-80 years and being either current or former smoker. For the cohort 2, the new weights to the HSE population were allocated based on sex, age, smoking status, and factory work characteristics.

Model population size

The size of population to model was defined by the standard error around the predicted mortality by age and sex (not to exceed 5% for each 5-year age group). The calculated minimum model population size is 1.3 mln. people (if the general population is simulated).

Natural History of Bladder and Kidney Cancers

The natural history module of the model (Figure 1 and Figure 2) relies upon: (a) cancer onset, (b) cancer growth, and (c) the probability distributions for being in each health state based on tumour size.

Probability of cancer onset

Cancer onset is dependent on age, sex, occupation, and smoking status. For binary characteristics (current smokers, former smokers, and manufacture workers), the individual value was considered to be 1 for an individual possessing those characteristics, and 0 for an individual not possessing the characteristics, with the population mean value representing the proportion of people with the characteristic in the population.

Considering the non-linear relationship between age and the diagnosed incidence of cancers (Figure 5a and 5b), the relationship between the age, sex, smoking status, and manufacturing work status and the risk of cancer onset was modelled using multiplications of the RR (where smoking and manufacturing workers [for BC] statuses are based on published data while risks for age and sex parameters are calibrated). The risk by age is accessed as:

$$risk\ at\ age\ x = age\_30y(^{Age\ x - Age\ 30})$$

where age_30y – risk of BC onset for 30 years old.

The RR impacting disease onset by demographic factors was multiplied by the probability of cancer onset for a 30-year-old non-smoking non-manufacture worker female.

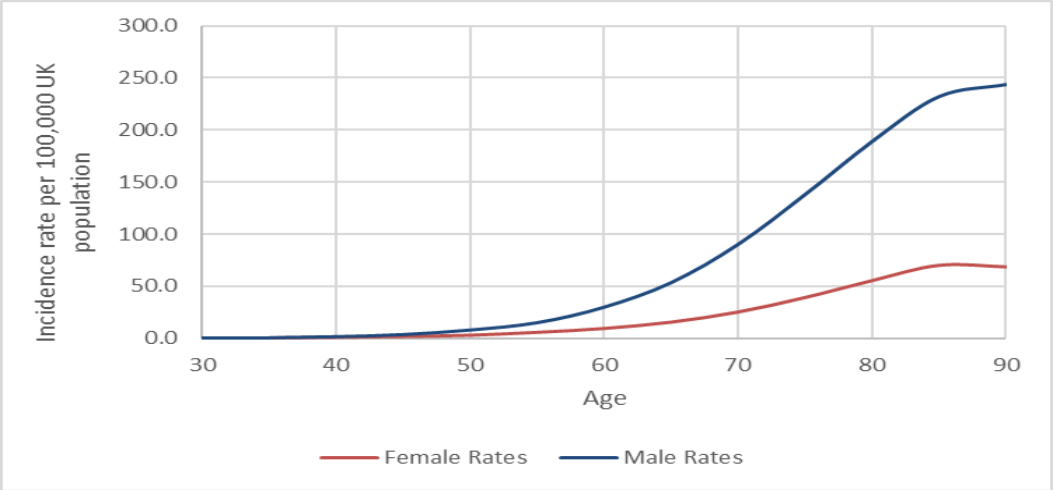


Figure 5a: CRUK data on incidence of BC by age per 100,000 population for males and females (2016-2018)[12]

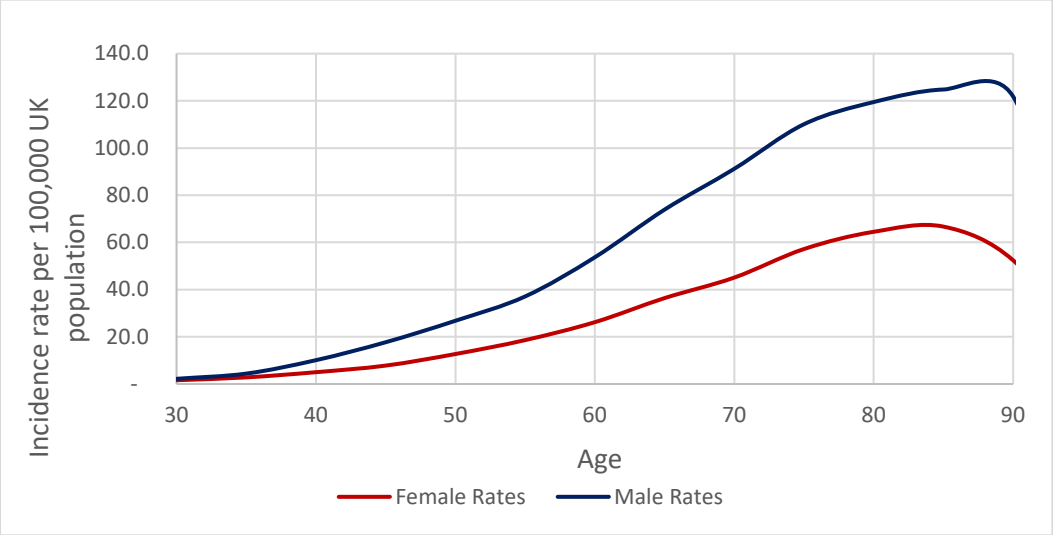


Figure 5b: CRUK data on incidence of KC by age per 100,000 population for males and females (2016-2018)[13]

Probability of disease progression

For any patients who experience an onset of cancer, a specific disease pathway is sampled. In BC cases where individuals follow a low-risk pathway, the model calibrates the probability of transitioning to the high-risk pathway. The prior for this parameter was informed by expert input and published sources, as direct evidence to inform this probability was lacking. Linton et al. (2013)[14], in their study of low-risk patients with a median follow-up of 61 months (interquartile range 24–105), documented progression and subsequent mortality in 2.4% of patients. Assuming a uniform distribution for the progression rate over five years, this implies that at least 2.4% of patients experience progression over that period, or 0.48% annually. Given the associated uncertainty, this value was employed as a starting parameter in model calibration and was not directly used in the model. It was assumed that patients diagnosed with low-risk BC do not experience progression during surveillance within the first year following diagnosis. Their likelihood of progressing after the surveillance period is contingent upon the combined probabilities of cancer recurrence and transitioning from low-risk to high-risk BC.

Regarding the pathway for high-risk BC and KC, the allocation of stages was executed probabilistically by sampling the time required to reach each stage from a distribution with a calibrated mean. This time was stochastically drawn from a Weibull distribution, with considerations for the calibrated mean (μ), calibrated shape (k), and computed scale (lambda).

$$Lambda = \frac{\mu}{Gamma(1 + \frac{1}{k})}$$

The mean time from cancer onset to the disease state was calibrated with the calibration priors based on the reported range of the time to progression of undiagnosed cancer retrieved from the literature based on the clinical experts' elicitation (used as a strong prior defined as having more than 10% of value in the initial likelihood)[15 16] and the reported median value of the time to progression used as a starting parameter value, Table 5. The reported time of progression from the start of one stage to the start of the next stage across different cancers based on consensus methodology (RAND/UCLA modified Delphi panel method) was the only source found to inform the progression of undiagnosed BC and KC.

Table 4: Median time of BC progression reported by Schwartzberg et al (2022)[16]

Median time of cancer progression:	Median and range in years, BC	Median and range in years, KC
Stage I to Stage II	3 (2-5)	5 (<1–7)
Stage II to Stage III	2 (1-5)	3 (<1–5)
Stage III to Stage IV	<1(<1-2)	2 (<1–2)

Recurrence

According to the same study and the clinical experts, low risk BC has a high recurrence rate. Linton et al (2013) informed that during 13.5 months of the follow up 28.5%, 95% CI(25.3–31.9) patients had a recurrence of low risk cancer[14]. In the BOXIT trial[17] the recurrence rate of NMIBC was > 8 times more common than was progression to MIBC. Linton et al (2013)[14] also report that the probability of developing recurrence with low-risk BC was 0.285 with 13 months of the follow up. While recurrence was not explicitly modelled, the annual probability of recurrence was used as a direct parameter in the model (0.285 (0.253-0.319))[14] to estimate the proportion of the patients who progress from low-risk to high-risk cancers after the low-risk cancer diagnosis (i.e. the probability to progress to high-risk cancers is equal to probability to have a recurrence after the surveillance ends, multiplied by the probability to progress from low-risk to high-risk cancer).

Calibration

Calibration is necessary to inform the unobserved parameters or transitions. In this model calibration was applied for some of the RRs and for the natural history disease parameters. The RR of cancer for manufacture workers resulted in a similar prediction of BC risk in the population over their lifetime (the mean predicted risk was 1.96 vs 1.99 in the published sources). However, for the smoking status, the variable parameter in the model simulation, the implemented RR (see the section “Risk factors included in the model”) resulted in different lifetime risk prediction for both BC and KC. This means that an application of the RR at the level of the transitions from no cancer-to-cancer onset did not translate into equivalent relative risk of BC or KC because of correlation between risk factors in the modelled population, because smoking is a variable factor in the model, and because the studies used report the RR of cancer incidence (and not cancer onset as it is in the model). Thus, the risk of smoking in the model was calibrated to predict the lifetime risk reported in the studies.

Relative risk calibration

A simple iterative process to calibrate the RR for current and former smokers was chosen which incorporated the following steps:

1. The model was run for 200 sets of individuals in HSE 2018 population using a starting set of the RRs used from the published sources (see the section “Risk factors included in the model”).

2. Following model running, the weighted incidence of BC in individuals with and without each characteristic was calculated and a modelled relative risk of BC calculated.

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.

In the model for BC, the calibrated relative risk (RR) was 1.9 for past smokers and 6.40 for current smokers, to predict the risk published in the lifetime literature of 2.04 and 3.47, respectively. For KC, the input RRs were 1.011 for past smokers and 1.98 for current smokers, to predict the lifetime risk of 1.16 and 1.31 reported in the literature. It is important to note that these figures represent the RRs used as parameters to initiate cancer in the model. However, the model's output for the RR of diagnosed cancer aligns with the RRs reported in published sources, indicating no difference in risk estimates post-modelling.

Natural History of cancer calibration

Calibration parameters

The following parameters related to the NHD were calibrated:

1. The annual probability of cancer onset for 30-year-old non-smoking females who are not employed in manufacturing.
2. For BC specifically: the probability of presenting with a low-risk tumour at onset, applied as a singular probability at the moment of onset.
3. The RR of cancer onset by age and gender, specifically comparing male to female and an incremental year of age beyond 30, are denoted as RR_age and RR_sex in the equation that determines the individual’s probability of BC onset.
4. Annual probabilities diagnosis, i.e. transition to a symptomatic state for each stage of undiagnosed cancer, with four distinct probabilities for KC and five for BC.
5. A yearly reduction in the probability of symptomatic diagnosis for individuals over the age of 75 years.
6. Parameters dictating tumour progression through stages, as defined by two out of three Weibull parameters (the mean and shape of the time to progression).

7. Exclusively for BC: the annual probability of moving from a low-risk to a high-risk progression pathway.

Calibration targets

Considering that there is currently no BC screening in England, the model was calibrated to the current epidemiological data:

- Incidence of BC and KC in England by age and sex in 2016-2018 (Figure 5).
- Incidence of BC and KC by stages 1 to 4.
- Incidence of low-risk BC.

The model was validated to BC and KC mortality by age and sex using this validation target in an iterative way: the fit mortality was not included in the GOF calculation but the visual fit to mortality by age and sex was assessed after each calibration attempt and after the warm-up period in the final calibration runs.

Incidence of high-risk BC and KC: total and by stage

Age-specific incidence rates for high-risk BC and KC among males and females registered between 2016 and 2018 have been sourced from Cancer Research UK [12 13].

When it comes to incidence rates by cancer stage two primary challenges were encountered. Firstly, no available data pertaining to the distribution of BC and KC stages at diagnosis, stratified by age and gender, could be identified. The stage at diagnosis was initially sources from the NHS reports (Table 6). Considering no data to inform otherwise, constant stage distribution by age and sex for classified stages 1 to 4 were assumed.

Table 5: Distribution for stage at diagnosis for bladder and kidney cancers

Stage at diagnosis	**Bladder cancer**	**Kidney cancer**
Stage 1	32.5%	34.13%
Stage 2	19.4%	5.14%
Stage 3	9.5%	14.3%
Stage 4	7.3%	15.8%
Missing stage at diagnosis	31.3%	30.62%

While we encountered a lack of available data regarding how the missing cases of BC and KC should be allocated among the defined stages 1 to 4, Girolamo et al (2018)[18], conducted a study that linked the National Cancer Registration dataset with the Routes to Diagnosis and Hospital Episode Statistics

datasets in the UK. Their study aimed to explore the characteristics of patients with missing stage information, focusing on colon, lung, and breast cancer cases. For colon cancer, they reported the odds ratio (OR) for experiencing missing stage information based on age, with an OR of 0.78 for individuals aged 65-74 years, 1.61 for those aged 75-84 years, and 2.8 for those aged 85 years and above, in comparison to individuals aged 15-64 years. Additionally, they provided the stage distribution for patients with missing stage information following imputations, which included Stage 1 - 0.093, Stage 2 - 0.218, Stage 3 - 0.184, and Stage 4 - 0.505. These findings pertaining to colon cancer were utilised to compute the distribution of BC incidence by age and stage, as detailed in Table 6.

Table 6: Incidence of high-risk bladder cancer by stages, used as a calibration target, average number of new cases in the UK per year

Age, lower bond, years	**Incidence in females**	**Incidence in males**	**Females**				**Males**			
			Stage 1	Stage 2	Stage 3	Stage 4	Stage 1	Stage 2	Stage 3	Stage 4
30	5	6	2	1	1	1	2	2	1	1
35	8	14	3	2	1	2	6	4	2	3
40	21	35	8	6	3	4	14	9	5	7
45	41	83	16	11	6	8	33	22	12	16
50	72	186	28	19	11	14	73	50	27	35
55	124	310	49	33	18	23	122	83	46	59
60	174	529	69	47	26	33	209	142	78	100
65	281	907	116	76	41	48	373	247	132	155
70	406	1,324	167	110	59	69	545	360	193	226
75	463	1,389	160	121	71	111	481	362	213	332
80	514	1,343	178	134	79	123	465	350	206	321
85	434	908	110	106	72	147	229	222	150	307
90	275	433	69	67	45	93	109	106	71	146

For KC, when the same approach was used to allocate the missing stage at diagnosis to one of the four stages, the calibration demonstrated implausibility of this assumption on missing data allocation, as the model was overpredicting mortality, when it fit the incidence and incidence by stages. The emergency presentation rate among KC with missed stage at diagnosis was similar to combined Stage 1-2 KC [https://www.cancerdata.nhs.uk/]. This demonstrated that the missing cancer cases likely belong to earlier cancer stage and were allocated equally among Stage 1 and Stage 2 KC, supported by the feedback from the clinical experts. The KC incidence and incidence by stage are reported in Table 7.

Table 7: Incidence of kidney cancer by stages, used as a calibration target, average number of new cases in the UK per year

Age, lower bond, years	Incidence in females	Incidence in males	Females				Males			
			Stage 1	Stage 2	Stage 3	Stage 4	Stage 1	Stage 2	Stage 3	Stage 4
30	36	49	18	6	6	7	24	8	8	9
35	61	94	30	9	10	11	46	15	16	17
40	102	205	50	16	17	19	101	32	34	38
45	181	399	89	28	30	33	197	62	67	73
50	301	614	149	47	50	55	303	96	102	113
55	395	765	195	61	66	73	378	119	128	141
60	481	948	237	75	80	89	468	147	158	175
65	656	1,255	324	90	115	127	619	173	220	243
70	724	1,339	357	100	127	140	660	184	235	259
75	676	1,109	334	139	96	107	548	228	158	175
80	598	851	296	123	85	94	421	175	121	134
85	413	489	205	125	40	44	243	148	47	52
90	210	217	104	63	20	22	108	66	21	23

Incidence of low-risk bladder cancer

Incidence and incidence by stage reported by the Office for National statistics and Cancer Research UK reports the number of BC cases being significantly lower than the National Cancer Registration and Analysis Service (NCRAS) Data Repository, NHS Digital. This is because, according to the clinical experts, the national statistical data includes only high-risk BC. To estimate the incidence of low-risk BC, we used the NCRAS Data Repository that reports the total number of BC cases registered in 2019 (18,595 cases) and subtracted from it the number of low-risk cancers reported by the CRUK, 2019 (8,951 cases). The ratio of low-to high-risk BC was used to calculate the estimated incidence of low-risk cancers by age and sex (assuming the same age- and sex- trend as for high-risk BC considering the lack of data to inform otherwise) (Table 8).

Table 8: Incidence of low-risk bladder cancers by sex, average number of new cases per year in the UK

Age, lower bond, years	Low-risk cancers, females	Low-risk cancers, males
30	5	6
35	9	15
40	23	38
45	44	90
50	78	200
55	134	334
60	187	570
65	303	977
70	437	1,427
75	499	1,497
80	554	1,447
85	468	978
90	296	467

Mortality from bladder and kidney cancer

Mortality data for BC and KC in the UK based on Cancer Research UK reports, stratified by age and sex for the years 2016 to 2018 (Figure 6a and Figure 6b), were initially employed for the purpose of validating the calibrated model, and then used as a calibration target in the last version of the calibration[19].

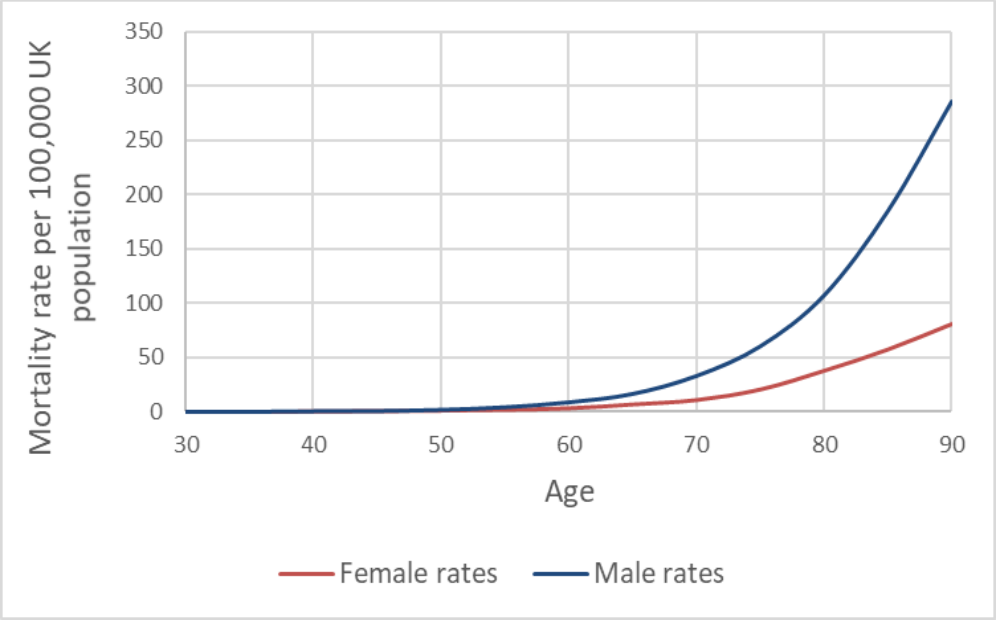


Figure 6a: Mortality of BC per 100,000 population for males and females in the UK (2016-2018)

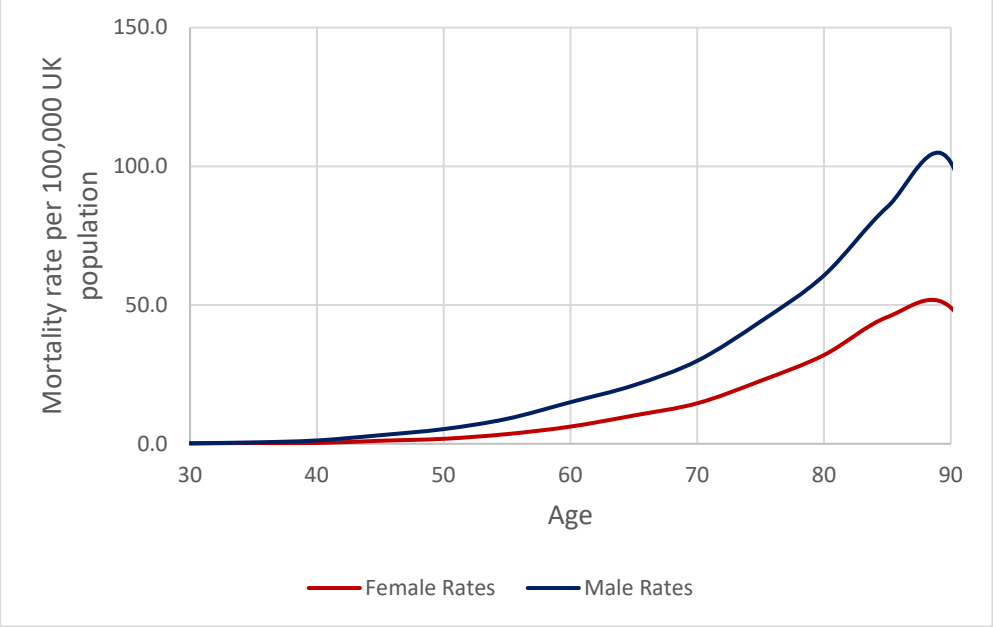


Figure 6b: Mortality of KC per 100,000 population for males and females in the UK (2016-2018)

Calibration approach

The approach to generating parameters in model calibration can be Bayesian or non-Bayesian. Non-Bayesian methods aim to improve the model's predictive power by identifying the optimal set of calibration parameters for which the model reproduces the calibration target[20]. In contrast, a Bayesian calibration seeks to generate a posterior distribution of calibration parameters and model outputs, conditional on the calibration target[20 21]. The benefit of Bayesian calibration over the

optimisation approach is that uncertainty around the NHD parameters is fully explored and integrated into the probabilistic sensitivity analysis, thereby reducing bias in the modelling outputs. Thus, one of the most common Bayesian approaches in calibration of the NHD models, the Metropolis-Hasting algorithm (MHA) was used.

MHA has some limitations. The calibration theory says that if the MHA is run for sufficient iterations it will fully explore the parameter space. This approach though is computationally expensive since simulation of the population with rare events (such as cancer) requires a substantial running time. With limited processing time, there is a risk that the parameter space is not adequately explored. That is to say that one cannot be sure that if convergence is achieved, there are no other alternative acceptable parameter regions. To minimize the risk, the calibration was run with five chains (five parallel processes) using as the starting parameter set the sets from the previous calibration attempts. The parameter space for the first calibration runs was defined by running a random calibration with the Latin Hypercube Sample which generates a near-random sample of parameter values from a multidimensional distribution. The parameters that had the starting value informed by the literature, were not varied in the random calibration.

Population size: The model was run with the population size of around 700,000 (100 HSE populations) during the warmup period and then 1.4m (200 HSE) during the parameter spacewalk.

Goodness of fit (GOF): likelihood. Since the model is run with a population who are all of the same age, the number of events at each age are dependent and represent events in time. Thus, likelihood was calculated as lifetime incidence (e.g. Likelihood of BC incidence for females). Higher weights (using 20 as a multiplier to the individual GOF) were used for total incidence and mortality, as the only data based on the national statistics by age and sex.

Priors and parameters sampling: The transition probabilities were restricted to be sampled in the range of zero to one. In addition, strong priors (defined as taking 20% or more from the initial likelihood value) were set up for:

- A symptomatic presentation rate for each more advanced stage is not lower than for the previous one.
- Probability of symptomatic diagnosis at Stage 1 is less than 0.2, Stage 2 – 0.05-0.4, Stage 3 – 0.1-0.7, Stage 4 – 0.2 – 0.9.
- The mean parameters defining the stage allocation in the Weibull distribution is within the reported ranges for each cancer.

- The relative risk for males does not exceed 10 and the relative risk for each year of age does not exceed 2.

There is an increased hazard for the shape parameter in Weibull distribution describing the progression between stages. The hazard increases with more advanced stages (progression to stage 2, stage 3, and stage 4) and the shape parameters takes a minimum value of 3 which was estimated based on the visual plot evaluation for the individual values of time to progression with the identified Weibull distribution parameters.

Maximum step size (epsilon): 20% of each parameter value at the first iteration. As the algorithm converges the maximum step size was reduced from the original value based on the acceptance rate (each 100 cycles it was reduced 10% if the acceptance rate was less than 10%). The warmup period was defined by reaching the positive likelihood (i.e. the parameters included in the outcomes were those with the positive likelihood).

The proposal parameter set in calibration was always accepted if the proposal parameter set had higher likelihood than the current parameter set; in addition, 0.5% of calibration runs with lower likelihoods (if the difference in likelihoods was not exceeding 50%) after the warmup period were accepted. The five chains of the MHA were run for each cancer. Because of the wide distributions for parameters, the parameters for PSA were sampled with replacement from retrieved calibrated correlated parameter sets.

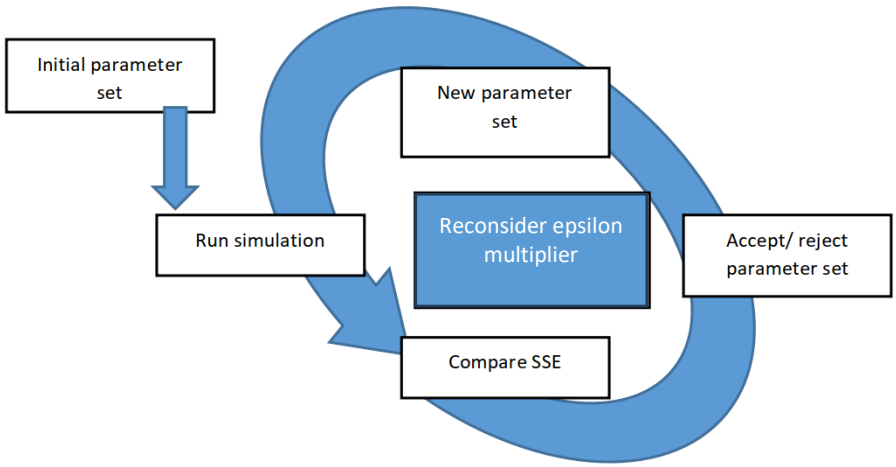


Figure 7: Metropolis-Hastings algorithm used to calibrate model parameters

Calibration outcomes, fit and validation

To perform probabilistic sensitivity analysis, the first 1,000 runs during warm-up period were excluded, and then correlated parameter sets were obtained by combining positively likelihood

parameters from different chains. These parameters were then sampled with replacement. The best-fit parameters are reported in the Table 9 and the characteristics of the distribution for parameters are reported in the Appendix A.

Table 9: Best-fit calibrated parameters: bladder and kidney cancer

Parameter	Best fit BC parameters	Best fit KC parameters
Annual probability of cancer onset for age 30 female, non-smoker, and not manufacturing worker	9.11E-06	4.44E-05
Probability of having low-risk BC at onset	0.69	
RR for increase in cancer onset with each year of age	1.11	1.07
RR of increase of cancer risk with male sex	3.65	2.08
Probability of being diagnosed (annually):		
Low-risk BC	0.08	NA
Stage 1	0.10	0.10
Stage 2	0.22	0.15
Stage 3	0.41	0.56
Stage 4	0.79	0.60
A multiplier to reflect a decrease in symptomatic presentation rate for cancer (after age 75 years)	0.96	0.92
Shape in the Weibull distribution for progression to stage 2	5.25	3.92
Shape in the Weibull distribution for progression to stage 3	6.42	5.54
Shape in the Weibull distribution for progression to stage 4	7.19	6.12
Probability of progressing from low-risk to high-risk BC (annual)	1.6E-03	NA
Probability of dying undiagnosed (after age 75 years)	0.05	0.20
Mean in the Weibull distribution for progression to stage 2	4.21	5.89
Mean in the Weibull distribution for progression to stage 3	2.36	2.14
Mean in the Weibull distribution for progression to stage 4	1.39	1.02

In the model, cancer progresses more quickly with subsequent stages (Tables 10). Most of the patients with BC progressed to stage 2 within 3-5 years (Table 10a) while more than 98% of patients progressed from Stage 3 to Stage 4 in less than 2 years.

Table 10a: Proportion of population with BC progressed between the stages

Time limit	**Stage 1 to Stage 2**	**Stage 2 to Stage 3**	**Stage 3 to Stage 4**
Less than 1 year	0.04%	0.40%	4.8%
Less than 2 years	1.34%	24.4%	98.3%
Less than 3 years	9.40%	95.61%	100.0%
More than 5 years	24.21%	0%	0%

For KC, there was a wider spread on the progression time from Stage 1 to Stage 2 KC (Table 10b) while progression to later stages was quicker and with lower variability with all patients progressing from Stage 3 to Stage 4 in less than 2 years.

Table 10b: Proportion of population with KC progressed between the stages

Time limit	Stage 1 to Stage 2	Stage 2 to Stage 3	Stage 3 to Stage 4
Less than 1 year	0.06%	1.41%	46.7%
Less than 2 years	1.00%	47.31%	100%
Less than 3 years	4.50%	99.73%	100%
Within 5 -7 years	43.30%	0%	0%
More than 7 years	27.14%	0%	0%

In the data used to calibrate the model[15], the range from BC onset to progression to Stage 2 was reported as 0-5 years. In the model, 76% of patients progressed to stage 2 within this time (Table 11a).

Table 11a: Percentage of population progressed from onset time (stage 1) to other stages: bladder cancer

Progression from onset to stage	The range of the time to stage reported in the qualitative study of Broder et al (2021)[15]	The model predictions of the proportion of patients who progress within this indicated range
to Stage 2	0-5 years	76%
to Stage 3	0-10 years	99%
to Stage 4	0-12 years	99%

In the data used to calibrate the model[15], the range from KC onset to progression to Stage 2 was reported as 0-7 years. In the model, 73% of patients progressed to stage 2 within this time (Table 11b).

Table 11b: Percentage of population progressed from onset time (stage 1) to other stages: kidney cancer

Progression from onset to stage	The range of the time to stage reported in the qualitative study of Broder et al (2021)[15]	The model predictions of the proportion of patients who progress within this indicated range
to Stage 2	0-7 years	73%
to Stage 3	0-12 years	99%
to Stage 4	0-14 years	99%

Calibration resulted in a good fit for the main calibration targets. Sex-specific mortality was also effectively predicted (Figure 8a- 8d).

Figure 8. Comparison of the model predictions to bladder cancer calibration and validation targets: red - the predictions with calibrated parameter sets, black - the targets with confidence interval

Figure 8a: Distribution of incidence by age and sex (random 200 calibrated parameter sets): number of cases per year. The top plots – high-risk BC incidence, the bottom plots –bladder cancer mortality. The left side – males, the right side -females

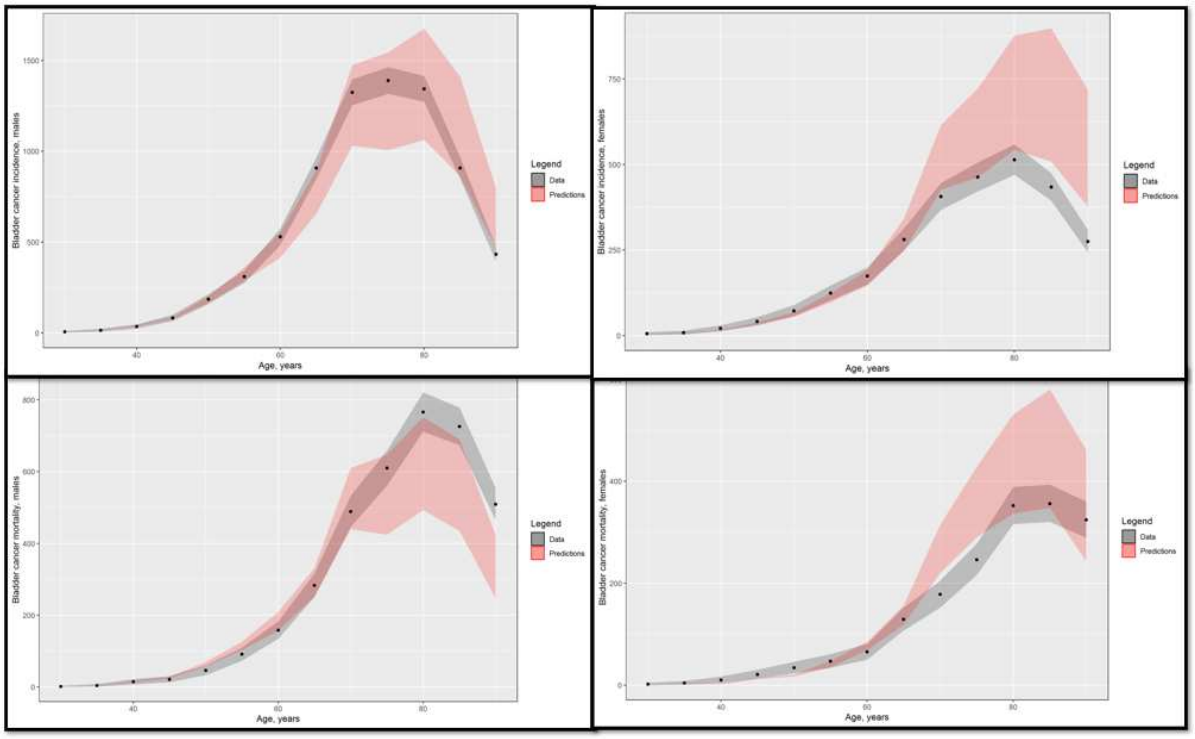


Figure 8b: Incidence by age and sex (best fit sets): number of cases per year. The top plots – high-risk BC incidence, the bottom plots –bladder cancer mortality. The left side – males, the right side -females

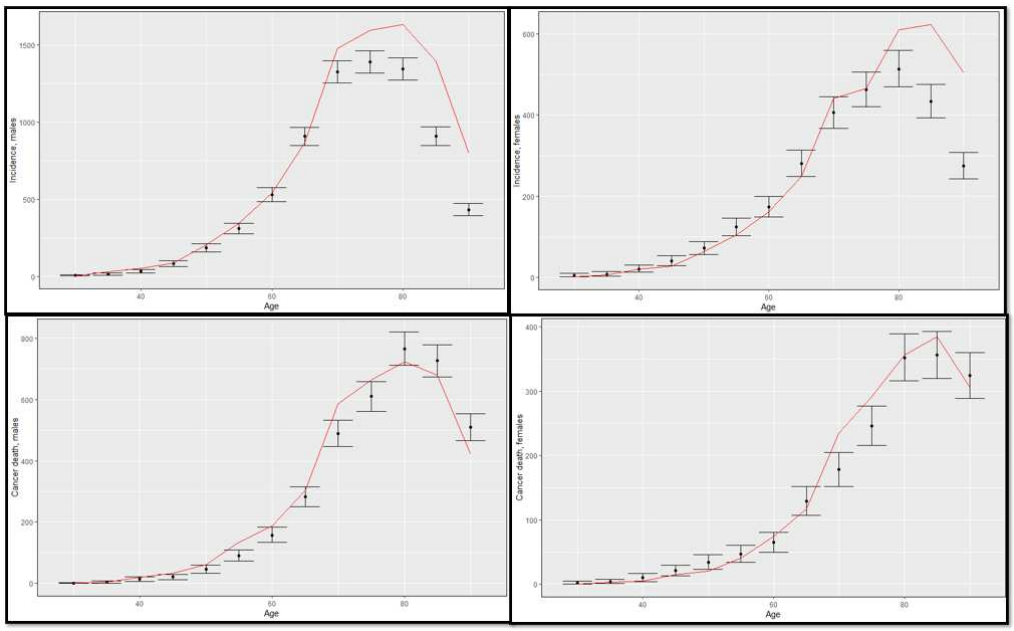


Figure 8c: Best fit to incidence by age and Stages 1 to 4 (from top left to the bottom left) for males: number of cases per year

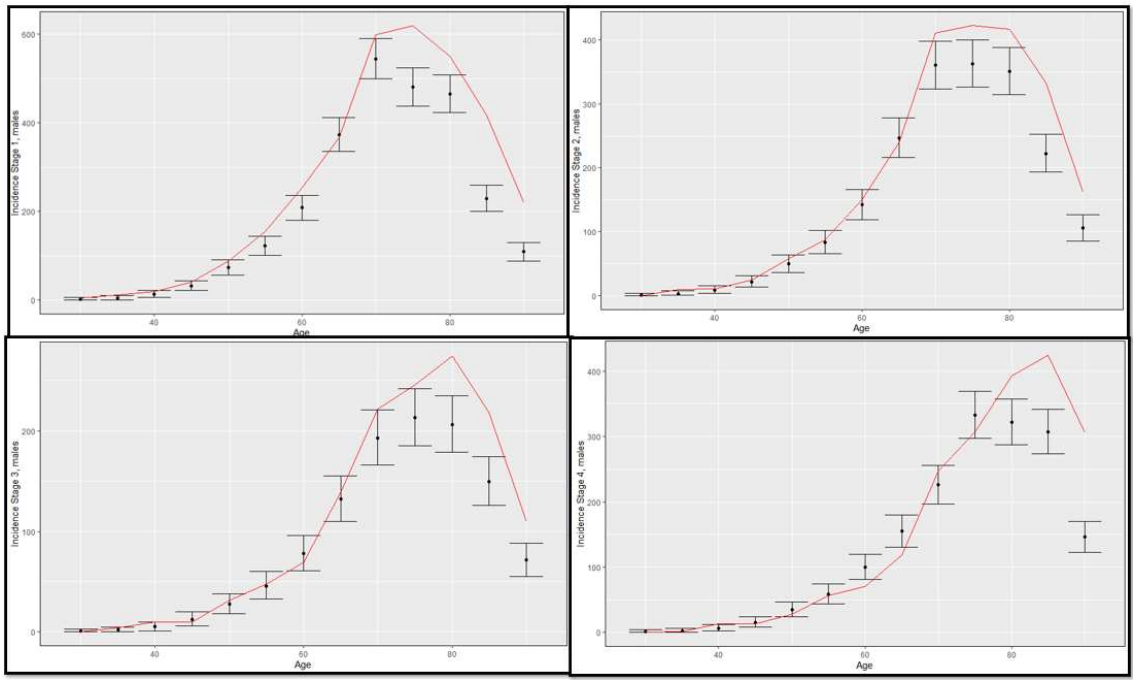


Figure 8d: Best fit to incidence by age and Stages 1 to 4 4 (from top left to the bottom left) for females: number of cases per year

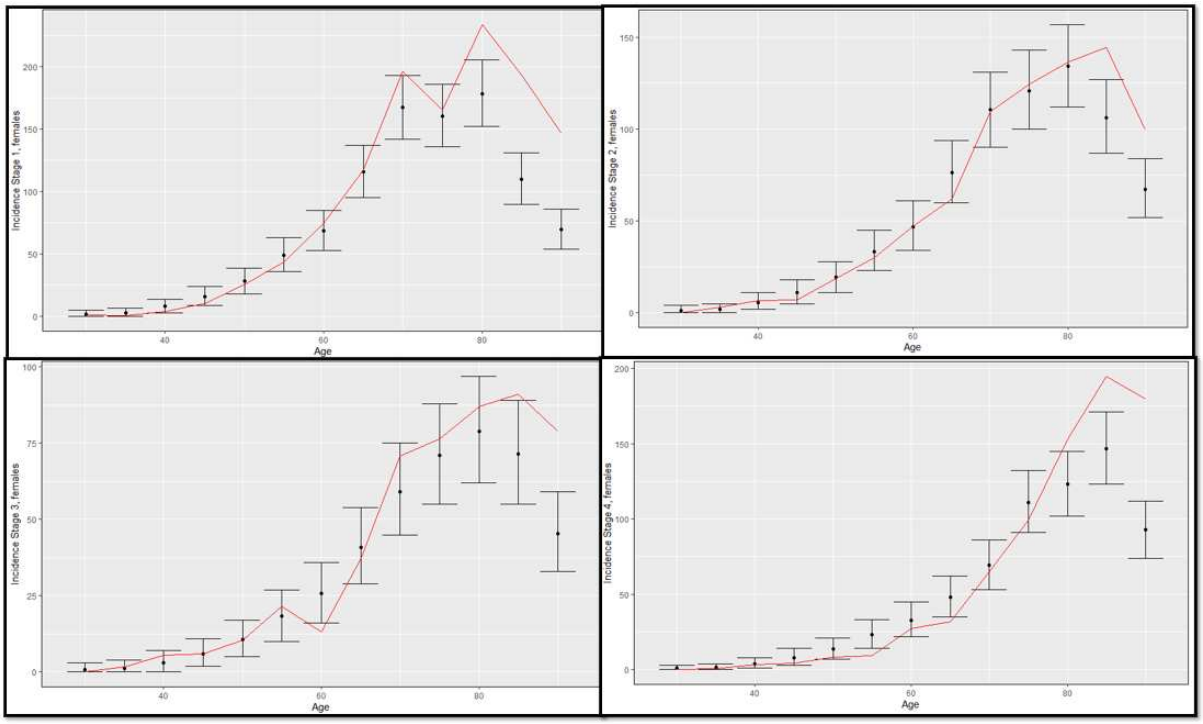


Figure 9. Comparison of the model predictions to kidney cancer calibration and validation targets: red - the predictions with calibrated parameter sets, black - the targets with confidence interval

Figure 9a: Distribution of incidence by age and sex (random 200 calibrated parameter sets): number of cases per year. The top plots – kidney cancer incidence, the bottom plots – kidney cancer mortality. The left side – males, the right side -females

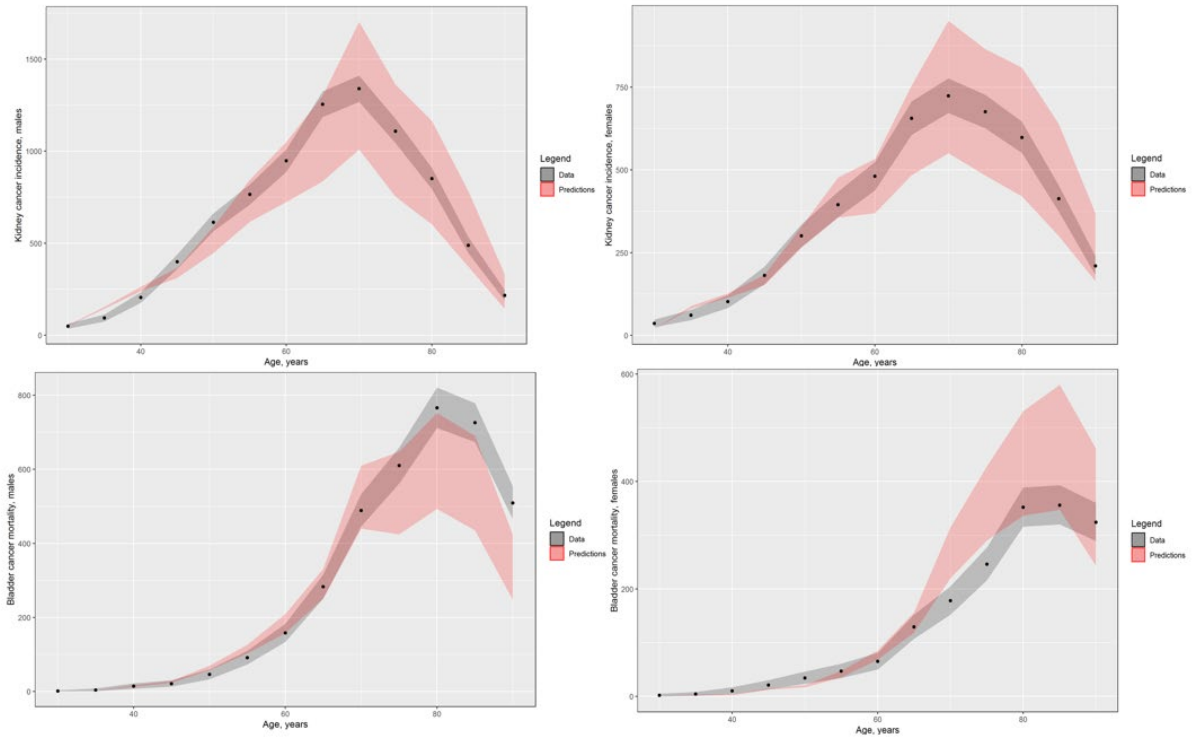


Figure 9b: Incidence by age and sex (best fit sets): number of cases per year. The top plots – kidney cancer incidence, the bottom plots – kidney cancer mortality. The left side – males, the right side - females

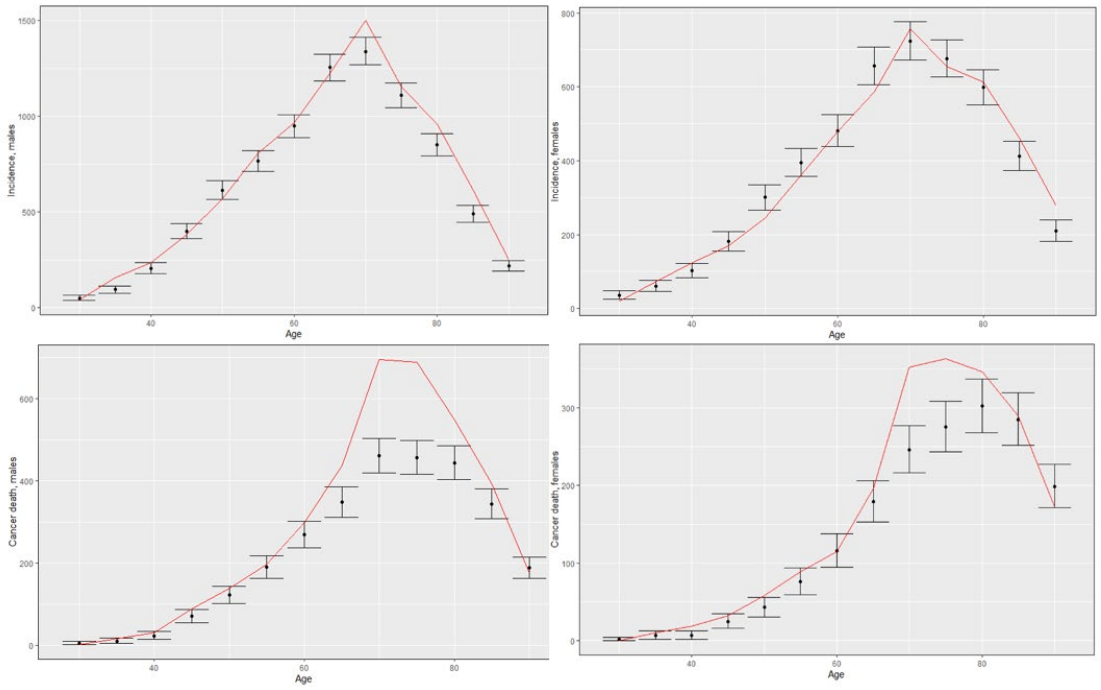


Figure 9c: Best fit to incidence by age and Stages 1 to 4 (from top left to the bottom left) for males: number of cases per year

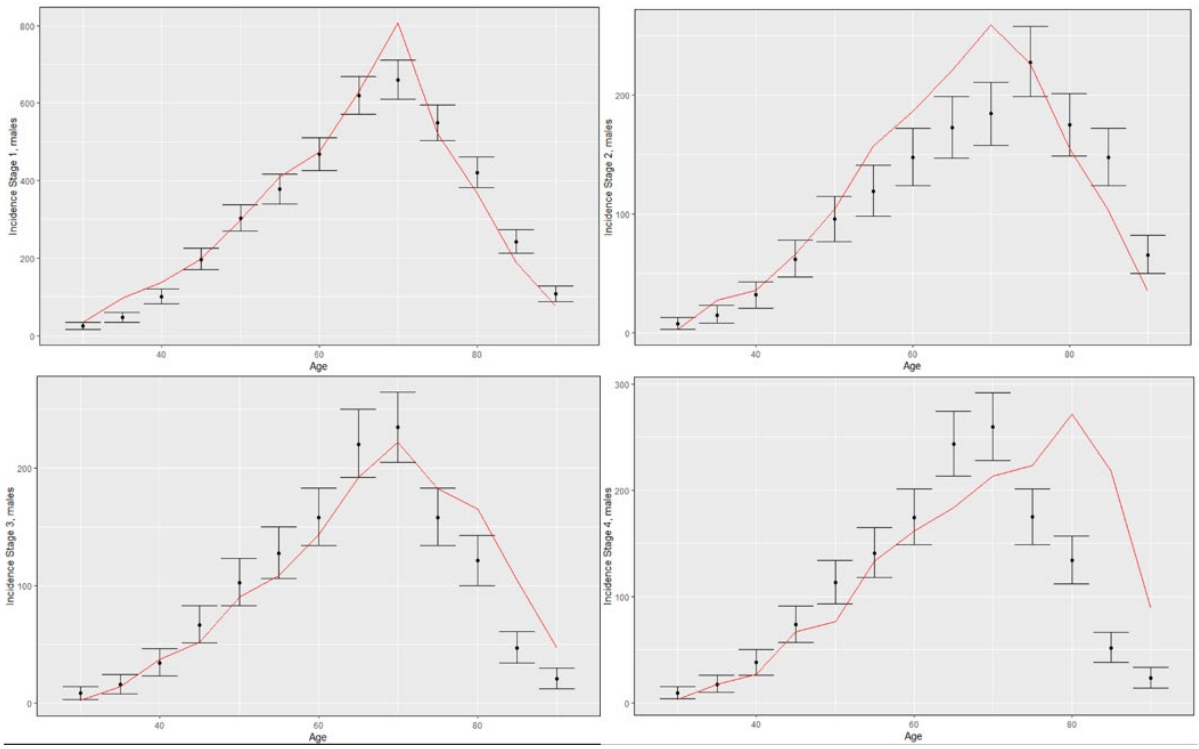
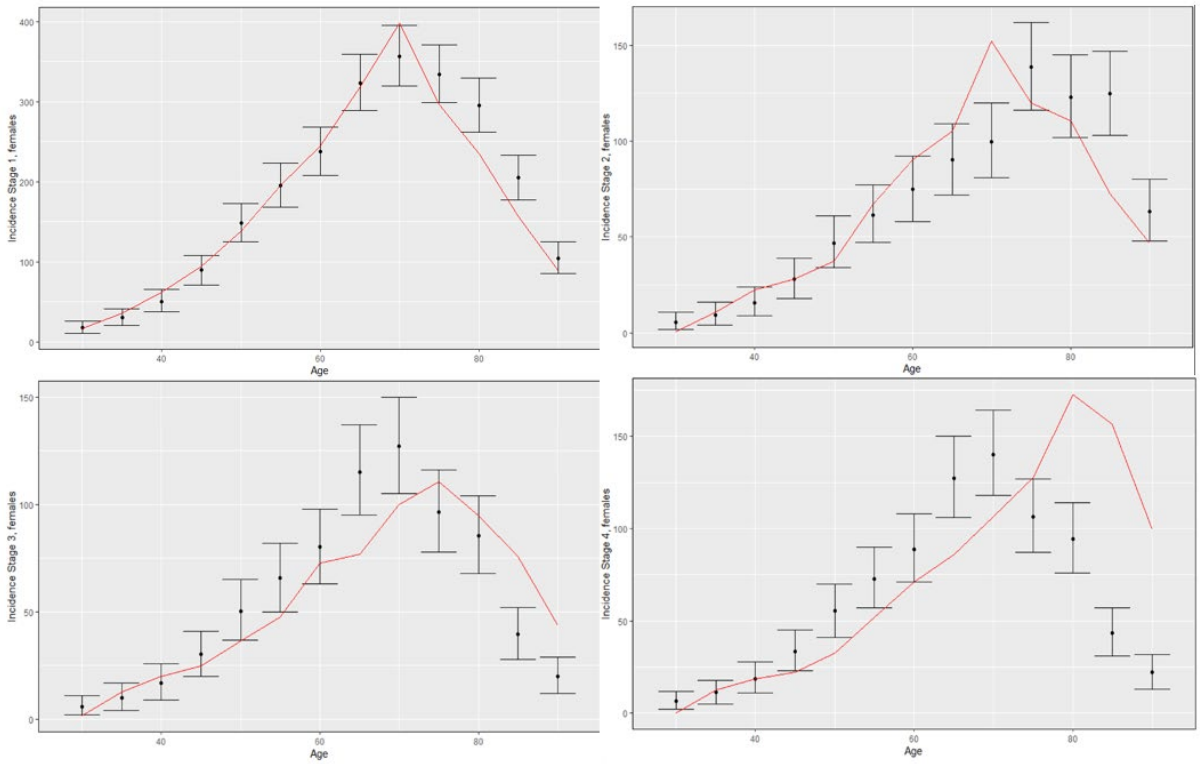


Figure 9d: Best fit to incidence by age and Stages 1 to 4 4 (from top left to the bottom left) for females: number of cases per year



Survival

Individuals can either die from BC (if they have BC), KC (if they have KC), or from other causes. Survival following cancer diagnosis is known to vary by age, sex, cancer stage, and time since diagnosis[22]. While there are number of sources reporting 1-, 5- and 10-year survival from BC and KC, these data are incomplete, and so a combination of sources was necessary to assess the cancer survival including different factors. It was assumed that anyone surviving for ten years post-diagnosis was cured and would have no further risk of death from cancer.

One and five year net BC 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 [22] (Table 12). However, the data for some subgroups, in particular 5-year survival by age among women diagnosed at stage 4 was missing. ONS data do not report 10-year survival. To assess 10-year survival, the ratio between 5- and 10-year survival among males and females was calculated from CRUK data in 2013-2017[23]. 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. The calculated ratio was applied to 5-year survival by age to assess 10-year survival by age (Table 12). For the subgroups of the population with missing 5-year data, the survival was assumed to be similar to the next available age-group. For kidney cancer, when survival in more advanced stage was higher than in less advanced stage in a specific age group, weighted average was applied for both stages (though acknowledging that stage classification system is not linear and it may be plausible that less advanced stages may have higher mortality than more advanced stages for some patients).

Table 12: Net one and five year survival by age group, sex and stage for 2013-2017 from ONS [22] and 10-year survival from CRUK[23] [24]

Sex	Age group	Bladder cancer			Kidney caner		
		1-year survival	5-year survival	10-year survival	1-year survival	5-year survival	10-year survival
Stage 1							
Men	15-44	97.2	84.7	72.9	99.4	97.2	78.9
	45-54	97.9	84.7	74.2	98.9	95.8	77.8
	55-64	98.0	87.6	75.4	98.3	91.8	74.5
	65-74	96.5	81.2	69.9	97.6	89.1	72.3
	75-99	92.7	69.7	60.0	89.9	72.5	58.9
Women	15-44	92.3	81.6	76.3	99.8	98.3	79.8
	45-54	97.6	86.3	80.7	99.8	98.3	79.8
	55-64	97.8	86.5	80.8	99.1	94.5	76.7
	65-74	94.7	81.0	75.7	97.2	90.4	73.4

	75-99	86.5	67.6	63.2	90.6	76.0	61.7
Stage 2							
Men	15-44	80.1	57.9	49.8	98.2	84.4	68.5
	45-54	85.0	54.7	47.1	98.3	87.5	71.0
	55-64	85.6	54.0	46.5	97.8	92.4	75.0
	65-74	80.6	34.0	29.3	93.0	81.5	66.2
	75-99	64.3	53.9	29.7	83.6	56.2	45.6
Women	15-44	61.6	57.9	48.9	98.1	91.8	74.5
	45-54	78.4	54.7	48.9	99.0	91.8	74.5
	55-64	78.2	48.3	45.1	97.1	87.8	71.3
	65-74	72.6	44.8	41.9	93.9	81.3	66.0
	75-99	55.5	27.3	25.5	85.0	58.5	47.5
Stage 3							
Men	15-44	81.1	50.1	43.1	94.8	81.1	65.8
	45-54	83.4	51.5	44.3	96.4	81.1	65.8
	55-64	78.2	51.5	44.3	94.5	79.7	64.7
	65-74	75.5	51.5	27.4	95.2	77.4	62.8
	75-99	59.8	48.0	27.4	87.2	66.6	54.1
Women	15-44	75.1	43.0	40.2	96.6	77.1	62.6
	45-54	72.4	43.0	40.2	92.0	77.1	62.6
	55-64	76.0	43.0	40.2	93.0	76.9	62.4
	65-74	65.8	18.1	16.9	93.1	77.6	63.0
	75-99	42.9	11.8	11.0	83.6	61.4	49.9
Stage 4							
Men	15-44	47.9	16.1	13.8	52.1	19.6	15.9
	45-54	44.9	14.0	12.0	50.1	17.4	14.1
	55-64	42.3	14.2	12.2	46.5	16.7	13.6
	65-74	43.0	15.4	13.3	41.5	13.5	11.0
	75-99	28.3	15.4	13.3	29.3	6.1	5.0
Women	15-44	36.0	11.22	7.8	43.1	18.5	15.0
	45-54	37.3	8.3	7.8	45.5	18.5	15.0
	55-64	38.7	8.3	7.8	45.8	16.9	13.7
	65-74	34.8	8.3	7.8	40.3	13.7	11.1
	75-99	19.9	8.3	7.8	24.2	8.3	6.7

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

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

It was assumed that the probability of dying from cancer beyond ten years post diagnosis was 0.

Mortality from other causes

Individuals defined as a target screened population, such as smokers, are likely to be at a higher risk of mortality from other causes as well (e.g. cardio-vascular diseases, lung and other cancers). Thus, it

is important for other cause mortality to be correctly reflected in the model. To accurately reflect the mortality from other causes, the RR for non-cancer mortality among smokers, former smokers, and never smokers were applied using the all-cause mortality data by age and sex and the data on relative risk of smoking status on all-cause mortality reported by the prospective study in the UK which recruited 1,3 million UK women in 1996–2001[25]. The study reports that among ex-smokers who had stopped smoking permanently at ages 35–44 years, the relative risk was 1.20 (1.14–1.26) for all-cause mortality. For 12-year mortality, those smoking at baseline had a mortality rate ratio of 2.76 (95% CI 2.71–2.81) compared with never-smokers. We assumed a constant rate for the RR of all-cause mortality among smokers and past smokers compared to non -smokers considering a lack of quantitative data to inform the time trend based on smoking duration or smoking cessation. Whilst mortality was age and sex specific, the model assumes that smoking status affects other cause mortality in a similar way as it does for all-cause mortality.

The other cause mortality was calculated separately for the model to be run in the modes BC, KC, and BC with KC combined. Cancer mortality was subtracted from all-cause mortality to retrieve other-cause mortality.

(1) The RR(no smoke/all pop) is = Rd.nsm / Rd. all-pop

(2) Rd. all-pop = N Death all pop / Size all pop= (Nd.sm + Nd.past.sm + Nd.no.sm)/ Size all pop = (Rd.sm*Nsm + Rd.psm*Npsm + Rd.nsm*Nno.sm) / Size all pop

Where Rd.sm, Rd.psm, and Rd.nsm, Rc. all-pop – rate of death in current, past, no smoker, and all populations. Nsm, Npsm, Nno.sm – number of current, past, and no smokers.

From (1) and (2) and dividing both the nominator and denominator to Rd.nsm:

(3) The RR(no smoke/all pop) is = Rd. all-pop/(RRsm/no.sm *Nsm + RRpsm/ no.sm *Npsm + Nnsm)

The calculated RR (OC death for no smoke/all pop) is 0.7547219.

Screening

The model can simulate a single, one-off screening intervention (home urine dipstick test) or repetitive screening: annual or biennial. Considering the lack of data on the efficacy of repetitive screening, the model assumes that screening accuracy does not change with subsequent screens, but the amount of disease found during each screening episode may change, being dependent on the underlying model health states (i.e. the prevalence and stage of undiagnosed cancer). As with the symptomatic population (and as it is in the YORKSURe trial), the population with a positive screening test will get a cytology test plus ultrasound (US), and, if positive, cystoscopy, and then white-light-guided TURBT. The symptomatic pathway, however, was not explicitly modelled for

cancers diagnosed symptomatically; instead, the diagnostic costs were attributed to all patients diagnosed with symptoms, in addition to the treatment costs.

Model scenarios

We simulated the cohorts to mirror the demographics of the lung cancer screening population, encompassing both males and females, including both current and former smokers. The one-time intervention occurred at different screening ages (55 to 70 years). We also modelled the population cohort 1 and cohort 2 similar to the Yorksure trial (see the section "Yorksure trial population").

Modelling screening impact

The following comparative outcomes of different screening scenarios (vs no screening) are reported:

- Screening costs, additional diagnostic costs and total costs.
- Screening-diagnosed and all cancers (total and by stage) and cancer deaths.
- Life-years saved and quality adjusted life years.
- Incremental cost-effectiveness ratio.

For the most cost-effective scenario we report resources required for screening: number of dipstick tests, supplementary diagnostic procedures and surgeries, and overdiagnosis.

Screening Uptake

In the base case (pre-trial) modelling 100% uptake with the screening test was considered to assess the cost-effectiveness of the intervention under complete population compliance. Differential uptake (the uptake observed in the feasibility study and in the FIT screening population) was considered in the scenario analyses.

Similar to other cancer screening programmes, the uptake is likely to differ by age and sex, as well as deprivation, and ethnicity. Considering the lack of data around screening uptake for home-based haematuria testing, the impact of age, sex, and IMD was considered to be identical to the home faecal immunochemical test (FIT) used in colorectal cancer screening (MiMiC-Bowel model). The trial data onuptake by age, IMD, and ethnicity will be incorporated upon trial completion.

In the MiMiC-Bowel model an impact of different characteristics on screening uptake was informed through the FIT pilot. The English FIT pilot results included a multivariate analysis of adequate uptake which provided odds ratios for uptake by age group, sex, and deprivation (IMD quintiles) [26]. This indicates that uptake is lower in males, older age groups, and more highly socioeconomically deprived groups. Model coefficients were calculated by taking the log of each odds ratio. Uptake in the reference group (male, age 59-64, IMD1 [least deprived], first screening round) was 53.6%. This

information was used to calculate an intercept for the model using the formula: intercept = -LN((1/x)-1) where x = baseline uptake. The intercept was then adjusted to represent country-wide FIT screening. Odds ratios and model coefficients are shown in Table 12.

Table 133: Odds Ratios from Moss et al (2017) [26] and calculated model coefficients used to predict screening 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)

Sensitivity and specificity of screening and diagnostic tests

Sensitivity of the home urine dipstick test is likely to depend upon a range of factors including sex, and age. There is no data though on how sensitivity of the dipstick test varies by age and sex and so in the base-case modelling the sensitivity of the test was assumed to be independent of the demographic parameters.

Accuracy of the dipstick for bladder cancer

Accuracy of screening tests was assessed on symptomatic patients only.

Lotan et al (2003) conducted a hierarchical Bayesian meta-analysis on sensitivity and specificity of different diagnostic tests, including the dipstick; they report sensitivity of 0.52 (0.27–0.76) and specificity of 0.82 (0.62–0.93) based on pulled data from 3 studies with 196 and 322 patients respectively. Because they don't report the sensitivity values by BC state, only the test specificity was informed by this study.[27]

Saad et al (2002) report the sensitivity by stage and specificity for the dipstick test for tumours by Grade and T category, with the patients assessed with the different tests before the surgery to evaluate sensitivity and specificity assessed on patients free of bladder carcinoma. The overall sensitivity is comparable to the values reported in the meta-analysis of Lotan et al (2003): 0.55 vs

0.52[28]. We used the sensitivity by stage reported by Saad et al the following way: the dipstick sensitivity to low-risk BC was assumed to be similar to grade 1 tumours (0.23), the dipstick sensitivity to Stage 1 BC was assumed to be similar to pT1 tumours as they are referred in the publication of Saad et al (2002) (0.5), the dipstick sensitivity to Stage 2-4 BC was assumed to be similar to pT2 tumours (0.88).

Accuracy of the follow up tests for bladder cancer

According to the diagnostic pathway described in the YORKSURe trial protocol, the screen-positive cases detected with the dipstick, will be invited to attend an Early Detection Clinic run in a nearby GP surgery, where they get personal data collected, and will undergo a urinary tract ultrasonography (US), and urine sample collection for cytology, for the investigation of haematuria. To estimate the joint sensitivity of the tests, the results of two meta-analyses on accuracy of the urine cytology test and US were used[29 30]. It was assumed that if any test is positive, a patient is redirected to further investigation. Thus, the joint sensitivity of both tests was calculated using the formula:

$$Sensitivity_{2_{tests}} = 1 - \left(1 - Sensitivity_{cytology}\right) * \left(1 - Sensitivity_{US}\right)$$

The joint specificity of the tests was calculated using the formula:

$$Specificity_{2_{tests}} = Specificity_{cytology} * Specificity_{US}$$

The calculated joint sensitivity of the tests was 0.90 95%CI (0.878; 0.923) and specificity 0.87 95%CI (0.8450.89). We assumed that this sensitivity was only related to all high-risk BC, since the sensitivity to low-risk cancers was significantly lower when stage was considered[31]. The sensitivity of the test to low-risk BC was assumed to be similar to one reported by Yafi et al (2015) for cytology test (0.16)[31].

Those with abnormal results will be redirected to their local urology haematuria service which includes flexible cystoscopy and additional assessments. Diagnostic flexible cystoscopy and clinical oncology services are assigned only to those patients who tested positive with the previous diagnostic tools. For the accuracy of cystoscopy, we used the outcomes of the study by Blick et al (2012) [32], who used urine samples from 109 diagnosed patients to explore the accuracy of biomarkers compared to the cystoscopy test and report the accuracy for low-risk and high-risk cancers separately (Table 14).

In the base-case analysis, both sensitivity and specificity of TURBT were assumed to be 1.

Accuracy of the dipstick and follow up tests for kidney cancer

There is no reliable data regarding the accuracy of urine dipsticks for detecting KC, although it is widely acknowledged that their sensitivity is relatively low, particularly when compared to their

sensitivity for detecting BC, while their specificity remains high, typically ranging from 97% to 100%[33-35].

Bezinque et al. (2017)[36] reported that only 21.7% (n=221 out of 1016) of KC patients had evidence of proteinuria detected in their urine dipstick tests. Additionally, they noted that 57.4% of patients with KC had negative dipstick results, indicating the absence of positive findings for blood, leukocyte esterase, nitrite, glucose, ketones, urobilinogen, and bilirubin. As a result, we assumed that even in case of negative proteinuria people with undiagnosed KC may be redirected to further diagnostic because of other abnormalities in their dipstick test, assuming the sensitivity of the test for Stage 2-4 KC was similar to the proportion of patients redirected to further investigation because of the positive dipstick test with suspected KC, as reported by Bezinque et al. (2017)[36] - 42.6%. To estimate sensitivity for Stage 1 KC, we calculated it proportionally from the sensitivity of the dipstick for BC: (0.50/0.88)0.426= 0.242. We also assumed a specificity of 0.98, aligning with the commonly expected ranges reported in the literature.

In accordance with the NHS England guidelines for symptomatic patients[37], the diagnostic pathway considers individuals with suspected KC (i.e., those who tested positive and have kidney cancer, as well as those who tested positive for KC but do not have the condition). These individuals are referred for a Computerised Tomography Scan (CT) scan and then surgery if positive. Notably, the NICE Guidelines for the Management of Renal Cancer indicate that biopsy is rarely employed; therefore, it has been included in the diagnostic pathway only as an accompanying part to the surgery. The scenario analysis includes a follow up for CT positive cases by a Magnetic Resonance Imaging (MRI). The sensitivities and specificities of CT and MRI for KC were retrieved from a systematic review of Vogel et al (2018)[38]. For CT, median sensitivity and specificity were 88% (interquartile range [IQR] 81%-94%) and 75% (IQR 51%-90%), and for MRI they were 87.5% (IQR 75.25%-100%) and 89% (IQR 75%-96%). This reported accuracy of the test was similar to the accuracy reported in another review by Furrer et al (2020), which suggested slightly higher accuracy rate if benign cancers are considered.[39]

We assumed the mortality rate during the surgery for screen-detected KC was similar to that for BC (Table 14).

Scenarios:

(a) Scenario A. A more recent review and meta-analysis reported much lower sensitivity values for urine cytology and much higher specificity values. Several of the included retrospective studies had small sample sizes with no true or false-positive patients detected (which could

explain the wide confidence interval and the difference in means: sensitivity in seven studies was 20% (95% CI 2.5–72%) and specificity in seven studies was 99.8% (95% CI 94–100%)). Meanwhile the data from this meta-analysis were used in the scenario analysis with sensitivity by stage being readjusted to fit the total sensitivity values[33].

(b) Scenario B. YORKSURe trial assumes not one dipstick test, but 6 consecutive tests in the screened population. From preliminary data, those who chose to participate in screening, completed on average 4.7 tests. This scenario considers higher sensitivity value of the dipstick test (arbitrary values of 1.2 and 1.5 times difference) and the average costs of 4.7 screening tests instead of one test only.

(c) CT positive cases with suspected kidney cancer are followed by an MRI test.

Table 14: Accuracy of the screening and diagnostic tests for screen-detected cases and screening-related harms

	Bladder cancer		**Kidney Cancer**	
Parameter	Value	Source	Value	Source
Sensitivity of home dipstick for LG cancers	0.23	Saad (2002)[28]	NA	NA
Sensitivity of home dipstick for HG Stage 1	0.50	Saad (2002)[28]	0.242	Bezinque et al. (2017)[36]
Sensitivity of home dipstick for HG Stage 2-4	0.88	Saad (2002)[28]	0.426	Bezinque et al. (2017)[36]
Specificity haematuria dipstick (home)	0.82 (0.62–0.93)	hierarchical Bayesian meta-analysis, Lotan (2003)[27]	0.98	Assumption
Sensitivity of US / cytology for high-risk cancer	0.90 (0.87-0.93)	Meta-analyses of RCTs Qu (2011) & He(2016)[29 30]		
Sensitivity of US / cytology for low-risk cancer	0.16	Yafi et al (2015)[31]		
Specificity of US / cytology	0.87(0.85-0.89)	Meta-analyses of RCTs Qu (2011) & He(2016)[29 30]		
Sensitivity of flexible cystoscopy (all stages)	0.98 (95% CI 0.94–0.99)	Blick (2012)[32]; scenario: Meta-analysis Zheng (2012): 0.943 (95% CI 0.914−0.964)[40]		
Specificity of flexible cystoscopy	0.94 (95% CI 0.92–0.96)	Blick (2012)[32]; scenario: Meta-analysis Zheng (2012): 0.847 (95% CI 0.812−0.878)[40]		
Sensitivity of biopsy during TURBT / kidney surgery	1	Assumption	0.991	Marconi (2016)[41]
Specificity of biopsy during TURBT / kidney surgery	1	Assumption	0.997	Marconi (2016)[41]

Sensitivity of CT		88% (IQR 81%-94%)	Vogel et al (2019)[38 39]
Specificity of CT		75% (IQR 51%-90%)	Vogel et al (2019) [38 39]
Sensitivity of MRI (Scenario analysis)		87.5% (IQR 75.25%-100%)	Vogel et al (2019) [38]
Specificity of MRI (Scenario analysis)		89% (IQR 75%-96%).	Vogel et al (2019) [38]
Mortality rate during surgery	0.008 (0.003-0.013)[42 43]	0.008 (0.003-0.013)	Assumption

Surveillance

The surveillance programme refers to the follow up of people with BC and KC after the treatment received. The NICE guidelines suggest offering the following surveillance interventions:

- Low-risk NMIBC: cystoscopic follow up 3 months and 12 months after diagnosis.
- Intermediate-risk NMIBC: cystoscopic follow up at 3, 9 and 18 months, and once a year thereafter.
- High risk NMIBC: cystoscopic follow up every 3 months for the first 2 years then every 6 months for the next 2 years then once a year thereafter[44].

Surveillance is not explicitly modelled since treatment costs already include the costs of surveillance.

Modelling diagnostic pathway

The diagnostic pathway for both symptomatically and screening-diagnosed BC (Figure 9a) assumes the following:

1) Since neither dipstick nor cystoscopy have 100% specificity, there is a small proportion of patients who will have no cancer and will receive surgery for both BC (TURBT) and KC. These patients also have a small probability of diagnostic-related harms (death during the surgery).
2) The costs of the surgery are already included in the 1-year costs of treatment and so are not costed separately. For false-positive cases, the costs of surgery are added separately.
3) Since the duration of the surveillance (2 years since diagnosis for LRBC and 5 years for HRBC and KC) is less than the treatment cost period, no additional surveillance costs are assigned. Since the patients are following the survival pathway, the probability of relapse in HRBC is not included in the model as it is already reflected in the survival function. Patients in LRBC do not progress to HRBC if they are diagnosed and are in the surveillance period (2 years). They can progress to HRBC if they are undiagnosed (see the calibration section) or if they are

diagnosed and leave the surveillance programme (i.e. diagnosed for more than 2 years); in the latter case their probability to progress is calculated as a joint probability of relapse in LRBC and progression to HRBC.

4) In the model, the probability to become false-positive for either BC or KC is sampled independently for both diseases. Considering that the specificity of the dipstick is much higher for KC than for BC, if a person is tested false-positive for both BC and KC, they follow the BC diagnostic pathway.

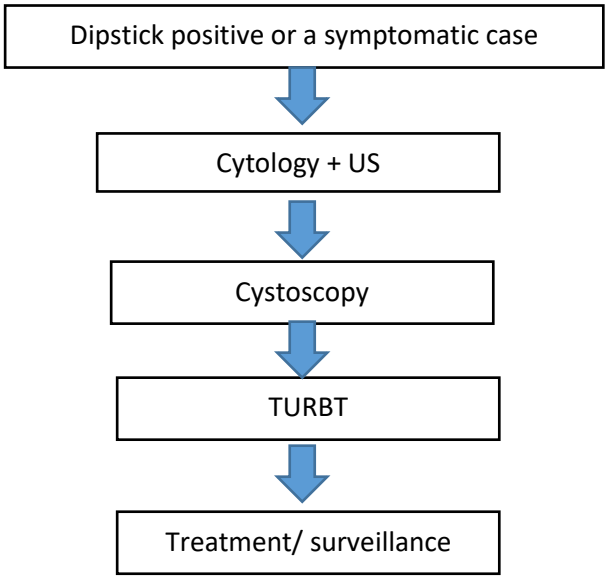


Figure 10a: Diagnostic pathway for BC

For KC, the diagnostic pathway assumed the following steps (10b) [37]:

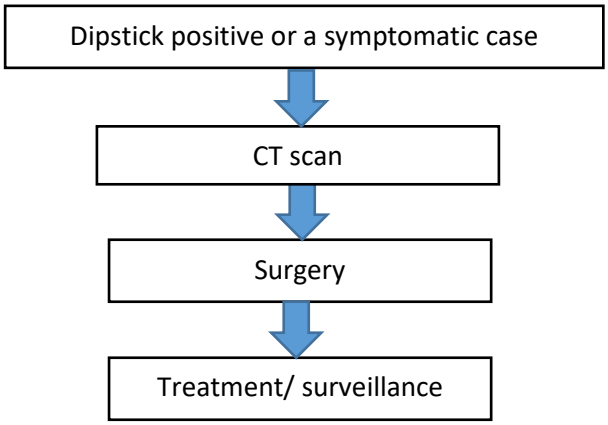


Figure 10b: Diagnostic pathway for KC

Utilities

The methodology for calculating individual utility values and the decrement in utility due to age was detailed in the "Modelling Changes in Phenotypic Characteristics by Age" section. In determining the utility multipliers associated with BC and KC diagnoses, we referred to the 2023 NHS Cancer Quality of Life Survey[45]. This entailed examining EQ-5D scores across stages 1-4 for BC (2,847 patients), KC (3,404 patients), and a collective group of all cancers (146,193 patients). The weighted average utilities were computed as follows: 73.44 with a 95% confidence interval (CI) of 71.72 to 75.17 for BC; 71.47 with a 95% CI of 69.63 to 73.30 for KC; and 73.91 with a 95% CI of 73.64 to 74.19 for all cancers. Utilities for BC and KC at each stage were assessed in proportion to those in all cancers at corresponding stages. The utility multipliers were then calculated by comparing these stage-specific utilities with the average utility values in the general population, taking into account the mean age at cancer diagnosis (73 years for bladder cancer and 67 years for kidney cancers)[11]. The derived utility values are presented in Table 15.

Table 15: Utility multipliers in bladder and kidney cancer states

Stages				**Calculated multipliers**	
	Utilities				
	All cancers	Bladder	Kidney	Bladder	Kidney
1	76.2 (76.0;76.4)	75.72	73.68	0.97(0.96;0.98)	0.92(0.91;0.93)
2	73.86 (73.6;74.11)	73.39	71.42	0.94(0.93,0.95)	0.89(0.88;0.90)
3	73.83 (73.56;74.10)	73.36	71.39	0.94(0.93;0.95)	0.89(0.88;0.90)
4	68.98 (68.57;69.39)	68.54	66.70	0.88 (0.87;0.89)	0.83 (0.82; 0.84)

The impact of the disease on utilities is assumed to last for 10 years, while the patient receives the treatment and cancer impacts the survival. The scenario analysis will be conducted with utility multipliers used over the patients' lifetime rather than the 10-year time frame.

Resource use and costs

Diagnostic costs for symptomatic and screen-detected patients

The cost of primary care diagnosis for symptomatic patients was based on the mean weighted costs among males and females using data on resource use reported by Lyratzopoulos (2013) for number of GP consultations, a haematuria test, US scan, or blood (cytology) test (Table 16)[46], plus the cystoscopy and clinical oncology service costs.

Table 16: Data on resource use reported by Lyratzopoulos (2013)[46]

		Men	Women	Men	Women
Sample size		538	202	73%	27%
Consultations					
	1	320	102	59%	50%
	2	158	46	29%	23%
	3	40	23	7%	11%
	4	8	11	1%	5%
	5	12	20	2%	10%
Dipstick					
Yes		394	143	73%	71%
No		144	59	27%	29%
US					
Yes		39	36	7%	18%
No		499	166	93%	82%
Blood test					
Yes		207	47	38%	23%
No		331	155	62%	77%

The unit costs were retrieved from the National tariffs / NHS reference costs (2022/23). The costs of the dipstick test were not available in the NHS reference costs and was assessed from the costs for pre-operative tests from the National clinical guideline centre (2015). Costs of the dipstick test were inflated from the published values using the consumer price inflation rate for health to inflate to the 2022 values. For screen-positive cases detected with the dipstick, the model accounts for the test accuracy and costs according to the YORKSURe trial protocol[1].

Participants with a positive screening result will be invited to attend an Early Detection Clinic run in a nearby GP surgery, where they get personal data collected, and will undergo a urinary tract ultrasound scan and urine sample collection for cytology. For the US scan, the weighted unit costs (£49.10) were calculated considering the frequency of the procedure duration of less than 20 and more than 20 minutes. Those with abnormal results with assumed suspected BC will be redirected to their local urology haematuria service which includes flexible cystoscopy and additional assessments. It will be considered that screen-diagnosed patients require only one GP consultation but also get one US scan each. Diagnostic flexible cystoscopy and clinical oncology services are assigned only to those patients who are tested positive with the previous diagnostic tools. The costs of white-light-guided TURBT and the costs of surgery for KC patients were not included in diagnostic costs since they are assumed to be already reflected in the Year 1 treatment costs, except for false-positive cases.

Participants with a suspected KC after the positive dipstick test (those with no KC but who get a positive test and those with KC tested as positive), will get CT scan. Those with positive CT scan in

the base case will receive a surgery and biopsy and in a scenario analysis will also get Magnetic Resonance Imaging Scan (MRI). For both CT and MRI scans the costs of scan of one area and with post-contrast (as the more expensive one) were included. The unit costs and the mean calculated diagnostic costs are reported in the Table 17.

Table 17: Unit costs for bladder and kidney cancer diagnostic in symptomatic patients (inflated to 2022 when necessary)

Item	**Unit costs (uninflated)**	**Year**	**Inflated costs**
GP consultation costs	£33.00	2020	£36.92
Blood test	£3.42	2022	£3.42
Cytology (haematuria)	£6.00	2020	£6.01
Dipstick (screening)	£3.85	2015	£3.86
US	£79.58	2020	£89.04
Diagnostic Flexible Cystoscopy, 19 years and over	£358.00	2020	£401.00
Clinical oncology service	£134.00	2022	£134.00
Magnetic Resonance Imaging	£169.00	2022/2023	£169.00
Computerised Tomography Scan of One Area	£86.00	2022/2023	£86.00
Average diagnostic costs for symptomatic BC patients			£612.14
Average diagnostic costs for symptomatic KC patients			£466.18
Average costs for diagnostic procedures if dipstick screening resulted in a suspected BC (GP consultation, blood test, cytology and US)			£135.39
Average costs for diagnostic procedures if dipstick screening resulted in a suspected KC (GP consultation, blood test, Urology service and CT scan)			£132.35
Average costs for diagnostic procedures if the US + cytology resulted in a suspected BC (Urology service + flexible cystoscopy)			£534.96
Average costs for diagnostic procedures if the CT scan resulted in a suspected KC: MRI in Scenario analysis			£303.00
Costs of surgery/ biopsy for false-positive cases that lead to biopsy but not the surgery			£646.00

Treatment and surveillance costs

Cox et al (2020)[17] reported annual costs for NMBC during the first three years after diagnosis. The costs were weighted to the number of patients in recurrent and not recurrent state for each stage. The assumptions on how the costs by stage were retrieved from the costs by grade and the costs summary are reported in the Table 18. For patients diagnosed with LRBC, a unique consideration was necessary. LRBC does not have a direct transition to mortality. Therefore, we included costs for up to 12 months post-diagnosis to account for this specific scenario. Additionally, taking into account

the existing surveillance practices for LRBC, the second-year post-diagnosis also incorporates surveillance costs, amounting to £401.00 annually, based on National Tariffs/NHS Reference Costs for the year 2022/23. Thus, the costs in year 1 were calculated as costs in Grade 1 for patients with intermediate risk (no costs for low-risk patients was reported) and no recurrence; costs in year 2: costs of recurrence for Grade 1 cancers multiplied to a probability of recurrence (see Parameters Sheet) and surveillance costs; Costs in years 3-10: costs of recurrence for Grade 1 cancers multiplied to probability of recurrence.

For the KC analysis, Rossi et al. (2021)[47] conducted a comprehensive assessment of the costs associated with KC across various health states. Due to disparities in model structures, direct incorporation of these costs into our model was not feasible. Instead, we utilised the costs associated with each stage for newly diagnosed KC cases, specifically those occurring in Year 1, inflating them from 2020 to 2022. For the Stage 4 costs, we included both the costs of the newly diagnosed patients in Stage 4, and the costs of systemic therapy, multiplying the annual therapy costs to the proportion of patients receiving the therapy. Subsequently, we applied the proportional difference in costs in Year 2 and Year 3 from Cox et al (2020) to adjust the in the later years. The outcomes of this cost estimation process are detailed in Table 19.

Table 18: Costs of bladder cancer reported by Cox et al (2020)[17]

Stage in the model	Costs of state in Cox et al (2020)	Not inflated costs, £			Inflated costs, £		
		Y1	Y2	Y3-10	Y1	Y2	Y3-10
LR	Y1: Costs in Grade 1 for patients with intermediate risk and no recurrence; Y2: costs of recurrence for Grade 1 cancers multiplied to a probability of recurrence (see Parameters Sheet) and surveillance costs; Y3: costs of recurrence for Grade 1 cancers multiplied to a probability of recurrence.	£ 2,828	£ 1,554	£ 1,153	£ 3,191	£1,754	£ 1,301
Stage 1 HR	Costs for Grade 1 High risk patients weighted by number of patients in no recurrence and recurrence states.	£ 5,114	£ 2,681	£ 1,705	£ 5,770	£ 3,025	1,924
Stage 2	Costs for Grade 2 High risk patients weighted by number of patients in no recurrence and recurrence states.	£ 6,472	£ 4,039	£ 3,063	£ 7,303	£ 4,558	£ 3,456
Stage 3	Costs for Grade 3 High risk patients weighted by number of patients in no recurrence and recurrence states.	£ 8,753	£ 6,320	£ 5,344	£ 9,877	£ 7,132	£ 6,030
Stage 4	MIBC Progression costs	£ 10,374	£ 7,940	£ 6,964	£ 11,706	£ 8,960	£ 7,858

Table 19: Costs of kidney cancer in the model[47]

Stage in the model	Not inflated costs, £			Inflated costs, £		
	Y1	Y2	Y3-10	Y1	Y2	Y3-10
Stage 1	£ 7,165.5	£ 3,756	£ 2,389	£ 8,086	£ 4,239	£ 2,696
Stage 2	£ 8,110.0	£ 5,061	£ 3,838	£ 9,151	£ 5,711	£ 4,331
Stage 3	£ 8,595.0	£ 6,206	£ 5,248	£ 9,700	£ 7,003	£ 5,921
Stage 4	£ 39,982.4	£ 30,602	£ 26,840	£ 45,117	£ 34,531	£ 30,286

In our study, we extended the cost analysis beyond the initial three years by assuming the costs in years 4 to 10 similar to the year 3. This choice was made to address a possibility of cancer relapse in the later years and align with the 10-year survival data utilised within our model. Beyond this 10-year horizon, we assumed that patients do not experience cancer relapse, resulting in no further cancer-related mortalities or associated costs and utility decrements.

BC screening Costs

The screening costs included the costs of the test (assumed to be identical to the unit costs of the diagnostic dipstick test), and the additional costs such as the costs of invites and postage, assumed to be similar to the FIT screening costs in colorectal cancer. Al costs were inflated to 2022 values (Table 20).

Table 20: Costs of screening, inflated to 2022

Screening Procedure	Components Included in Costing	Cost (95% CI)
Invite	invitation letter, reminder letters in non-responders, helpline costs, postage, packaging, staff costs and overheads.	£8.57 (7.1 -10.3)
Additional Costs of Normal Result	processing, retests (required in x% of people), normal result letter to patient & GP	£1.3 (1.1-1.6)
Additional Costs of Positive Result	Additional costs of positive result letter to patient & GP. Specialised screening practitioner appointment.	£11.8 (9.6-14.2)
Dipstick test		£3.86 (3.1-4.7)

Appendix A: Parameter tables

General parameters

Parameter Description	Parameter Name	Mean		95% CI	
RR of other-cause mortality for former smokers vs never smokers	RR.All.Death.past_smoke	1.2	lognormal	1.14	1.26
RR of other-cause mortality for current smokers vs never smokers	RR.All.Death.current_smoke	2.76	lognormal	2.71	2.81
RR of other-cause mortality for non-smokers compared to the whole population	RR.All.Death.no_smoke	0.754722	normal	0.7520552	0.7573886
Probability of quitting smoking per year	P.quit.smoke	0.0167	trunc.norm	0.0159057	0.0174943
Distick Uptake Regression Coefs: Intercept	DT.UPTK.CONS	0.709576	normal	0.6268837	0.8023417
Distick Uptake Regression Coefs: Age 50-54	DT.UPTK.50	-0.36469	normal	-0.3658866	-0.3634971
Distick Uptake Regression Coefs: Age 55-59	DT.UPTK.55	-0.25156	normal	-0.2519249	-0.2512075
Distick Uptake Regression Coefs: Age 65-69	DT.UPTK.65	-0.11653	normal	-0.1278334	-0.1053605
Distick Uptake Regression Coefs: Age 70+	DT.UPTK.70	-0.23572	normal	-0.2484614	-0.2231436
Distick Uptake Regression Coefs: Sex Female	DT.UPTK.F	0.139762	normal	0.1310283	0.14842
Distick Uptake Regression Coefs: Previous non responder	DT.UPTK.NRESP	-1.83258	normal	-1.8578993	-1.8263509
Distick Uptake Regression Coefs: Incident	DT.UPTK.INC	1.879465	Normal	1.8640801	1.8779372
Distick Uptake Regression Coefs: IMD2	DT.UPTK.IMD2	-0.07257	normal	-0.0943107	-0.0618754
Distick Uptake Regression Coefs: IMD3	DT.UPTK.IMD3	-0.15082	normal	-0.1625189	-0.1278334
Distick Uptake Regression Coefs: IMD4	DT.UPTK.IMD4	-0.28768	normal	-0.3147107	-0.2744368
Distick Uptake Regression Coefs: IMD5 most deprived	DT.UPTK.IMD5	-0.59784	normal	-0.6161861	-0.597837
Distick Uptake Regression Coefs: Asian	DT.UPTK.ASIAN	-0.94057	normal	-1.040504	-0.8344767
Uptake with all the diagnostic to follow up screen positive result	Diag.UPTK	1	Constant		
Utility decrement age	Utility.age	0.00432	normal	0.00404	0.0046
Cost of dipstick invite	Cost.dipstick.invite	8.57	Gamma	6.973	10.329

Additional cost of dipstick performed	Cost.ad.dipstick	1.3	Gamma	1.058	1.567
Additional cost of dipstick positive result	Cost.dipstick.positive	11.8	Gamma	9.601	14.222
Cost of dipstick test	Cost.dipstick	3.86	Gamma	3.141	4.652

Bladder cancer parameters

Parameter Description	Parameter Name	Best-fit	Mean	Distribution and parameters	
Probability of cancer onset (females, age 30, non smokers, not manufacture workers)	P.onset	9.11E-06	9.75E-06	Beta	Alpha: 18.20; Beta: 1866800.38
Probability that at a time of onset (t0) the tumour is a low-risk BC	P.onset_low.risk	0.643	0.687	Beta	Alpha: 6.416; Beta: 3.559
RR of cancer onset by age (compared to age 30)	RR.onset_age	1.111	1.130	Norm	Mean: 1.130; sd: 0.019
RR of cancer onset for male sex compared to the female sex	RR.onset_sex	3.650	3.226	Norm	Mean: 3.226; sd: 0.352
Annual probability to become a symptomatic patient for LRBC	P.sympt.diag_LRBC	0.079	0.056	Beta	Alpha: 24.27; Beta: 406.20
Annual probability to become a symptomatic at HRBC stage 1	P.sympt.diag_St1	0.101	0.085	Beta	Alpha: 14.08; Beta: 151.21
Annual probability to become a symptomatic at HRBC stage 2	P.sympt.diag_St2	0.219	0.200	Beta	Alpha: 31.91; Beta: 127.38
Annual probability to become a symptomatic at HRBC stage 3	P.sympt.diag_St3	0.411	0.391	Beta	Alpha: 13.52; Beta: 21.05
Annual probability to become a symptomatic at HRBC stage 4	P.sympt.diag_St4	0.786	0.616	Beta	Alpha: 5.41; Beta: 3.37
Age (for those who are older than 75 yo) coefficient affecting a possibility of different symptomatic presentation rate among older people	P.sympt.diag_Age	0.959	0.933	Beta	Alpha: 43.73; Beta: 3.13
Shape of the Weibull distribution for time of BC progression from Stage I to Stage II	shape.t.StI.StII	5.25	4.98	Norm	Mean: 4.98; sd:0.50
Shape of the Weibull distribution for time of BC progression from Stage II to Stage III	shape.t.StII.StIII	5.25	5.89	Norm	Mean: 5.89; sd: 0.65

Shape of the Weibull distribution for time of BC progression from Stage III to Stage IV	shape.t.StIII.StIV	7.19	6.92	Norm	Mean: 6.92; s.d.: 0.78.
Probability of patients progressing from low-risk BC to high-risk BC	P.LRtoHRBC	0.00161	0.00156	Beta	Alpha: 32.88; Beta: 21059.23
Probability to die at stage 4 undiagnosed	P.ungiag.dead	0.0495	0.0051	Beta	Alpha: 16.48; Beta: 306.75
Mean of the Weibull distribution for time of BC progression from Stage I to Stage II	Mean.t.StI.StII	4.21	4.28	Norm	Mean: 4.28; sd: 0.56
Mean of the Weibull distribution for time of BC progression from Stage II to Stage III	Mean.t.StII.StIII	2.36	2.35	Norm	Mean: 2.35; sd: 0.28
Mean of the Weibull distribution for time of BC progression from Stage III to Stage IV	Mean.t.StIII.StIV	1.38	1.51	Norm	Mean: 1.51; sd: 0.29

Parameter Description	**Parameter Name**	**Mean**	**Distribution**	**95% CI**	
RR of cancer onset for manufacturing workers vs no manufacturing workers	RR.manufacture	1.99	lognormal	1.22	3.26
RR of cancer onset for former smokers vs never smokers	RR.past_smoke	2.174497	lognormal	0.790348	3.558646
RR of cancer onset for current smokers vs never smokers	RR.current_smoke	5.997746	lognormal	4.613597	7.381895
Recurrence for LR non-MIBC during one year	P.Recurrence.LR	0.285	normal	0.253	0.319
Sensitivity haematuria dipstick (home) for low-risk cancers	Sens.dipstick.LR	0.23	Beta	0.1309696	0.3471015
Sensitivity haematuria dipstick (home) to high-risk Stage 1 BC	Sens.dipstick.St1	0.5	Beta	0.3546468	0.6453532
Sensitivity haematuria dipstick (home) to high-risk Stage 2-4 BC	Sens.dipstick.St2.4	0.88	Beta	0.6174801	0.9955459
Specificity haematuria dipstick (home)	Spec.dipstick	0.82	Beta	0.62	0.93
Sensitivity of flexible cystoscopy (all stages high-risk BC)	Sens.diag2	0.98	Beta	0.9699535	0.9891559
Specificity of flexible cystoscopy	Spec.diag2	0.94	Beta	0.9258939	0.9586881
Sensitivity of flexible cystoscopy (low-risk BC)	Sens.diag2.LR	0.98	Beta	0.9699535	0.9891559
Joined sensitivity of US+cytology (high-risk BC)	Sens.diag1	0.904086	normal	0.877376	0.926868

Joined sensitivity of US+cytology (low-risk BC)	Sens.diag1.LR	0.16	normal	0.1286406	0.1913594
Joined specificity of US+cytology	Spec.diag1	0.996428	normal	0.994689	0.997613
Sensitivity of biopsy	Sens.biopsy	1	constant	1	1
Specificity of biopsy	Spec.biopsy	1	constant	1	1
Mortality rate of TURBT	Mort.surg	0.000463	normal	0.000373	0.000554
Utility multiplier for HG stages 1-3, compared to LG BC or no cancer	Disutility.St1.3	0.901827	normal	0.8545599	0.9476379
Utility multiplier HG stage 4, compared to no cancer	Disutility.St4	0.882892	normal	0.8081088	0.9476379
Utility multiplier for LG BC	Disutility.LG	1	Constant	1	1
Costs for treatment and surveillance: intercept (Regression)	Cost.treat.intercept	£2,349	Gamma	£1,911	£2,831
Costs for treatment and surveillance: previous smoke (Regression)	Cost.treat.past.smoke	-£57	normal	-£68	-£46
Costs for treatment and surveillance: current smoke (Regression)	Cost.treat.current.smoke	-£242	normal	-£289	-£195
Costs for treatment and surveillance: Y2 (Regression)	Cost.treat.Y2	-£921	normal	-£1,102	-£741
Costs for treatment and surveillance: Y3 (Regression)	Cost.treat.Y3	-£1,514	normal	-£1,811	-£1,217
Costs for treatment and surveillance: stage 1 (Regression)	Cost.treat.St1	£1,447	normal	£1,163	£1,730
Costs for treatment and surveillance: stage 2 (Regression)	Cost.treat.St2	£1,676	normal	£1,348	£2,005
Costs for treatment and surveillance: stage 3 (Regression)	Cost.treat.St3	£3,957	normal	£3,181	£4,732
Costs for treatment and surveillance: stage 4 (Regression)	Cost.treat.St4	£5,407	normal	£4,347	£6,467
Costs for treatment and surveillance: low-risk BC (Regression)	Cost.treat.LR	£1,217	normal	£979	£1,456
Costs for surveillance (absolute for high-risk BC only in Y4 and Y5)	Cost.surv	£401	Gamma	£326	£483
Average diagnostic costs for symptomatic patients	Cost.diag.sympt	£612	Gamma	£498	£738
Average diagnostic costs for screen-detected cases, 2st stage in urology center	Cost.diag.screen2	£535	Gamma	£435	£645
Average diagnostic costs for screen-detected cases, tests + CT scan	Cost.diag.screen1	£135	Gamma	£110	£163
Costs of biopsy for FP cases	Cost.biopsy	£646	Gamma	£526	£779

Kidney cancer parameters

Parameter Description	Parameter Name	Best-fit	Mean		Distribution and parameters
Probability of cancer onset (females, age 30, non smokers, not manufacture workers)	P.onset	4.43E-05	3.97E-05	Beta	Alpha: 17.78; Beta: 447412.78
RR of cancer onset by age (compared to age 30)	P.onset_age	1.073	1.070	Norm	Mean: 1.079; s.d.: 1.015
RR of cancer onset for male sex compared to the female sex	RR.onset_sex	2.076	1.790	Norm	Mean: 1.79; s.d.: 0.26.
Annual probability to become a symptomatic at HRBC stage 1	P.sympt.diag_St1	0.100	0.140	Beta	Alpha: 20.85; Beta: 162.64
Annual probability to become a symptomatic at HRBC stage 2	P.sympt.diag_St2	0.151	0.210	Beta	Alpha:24.14 ; Beta: 91.04
Annual probability to become a symptomatic at HRBC stage 3	P.sympt.diag_St3	0.565	0.511	Beta	Alpha: 16.04 ; Beta: 15.39
Annual probability to become a symptomatic at HRBC stage 4	P.sympt.diag_St4	0.610	0.652	Beta	Alpha: 11.23; Beta: 5.99
Age (for those who are older than 75 yo) coefficient affecting a possibility of different symptomatic presentation rate among older people	P.sympt.diag_Age	0.916	0.920	Beta	Alpha: 162.89; Beta:14.09
Shape of the Weibull distribution for time of BC progression from Stage I to Stage II	shape.t.StI.StII	3.927	4.070	Norm	Mean: 4.070; s.d.:0.46 .
Shape of the Weibull distribution for time of BC progression from Stage II to Stage III	shape.t.StII.StIII	5.535	5.280	Norm	Mean: 5.280; s.d.0.58.
Shape of the Weibull distribution for time of BC progression from Stage III to Stage IV	shape.t.StIII.StIV	6.106	6.22	Norm	Mean: 6.106; s.d. 0.79.
Probability to die at stage 4 undiagnosed	P.ungiag.dead	0.201	0.122	Beta	Alpha: 4.06; Beta 29.11:
Mean of the Weibull distribution for time of KC progression from Stage I to Stage II	Mean.t.StI.StII	5.88	5.63	Norm	Mean: .5.63; s.d.:0.46 .

Mean of the Weibull distribution for time of KC progression from Stage II to Stage III	Mean.t.StII.StIII	2.14	2.17	Norm	Mean: 2.17; s.d.: 0.27.
Mean of the Weibull distribution for time of KC progression from Stage III to Stage IV	Mean.t.StIII.StIV	1.02	1.01	Norm	Mean: 1.01; s.d: 0.28.
Parameter Description	**Parameter Name**	**Mean**	**Distribution**	**95% CI**	
RR of cancer onset for former smokers vs never smokers	RR.past_smoke	1.2	lognormal	1.14	1.27
RR of cancer onset for current smokers vs never smokers	RR.current_smoke	1.39	lognormal	1.28	1.51
Sensitivity haematuria dipstick (home) to high-risk Stage 1 KC	Sens.dipstick.St1	0.242	Beta	0.160	0.334
Sensitivity haematuria dipstick (home) to high-risk Stage 2-4 KC	Sens.dipstick.St2.4	0.426	Beta	0.218	0.648
Specificity haematuria dipstick (home)	Spec.dipstick	0.98	Beta	0.62	0.93
Sensitivity of CT scan diagnostic	Sens.diag1	0.88	Beta	0.81	0.94
Specificity of CT scan diagnostic	Spec.diag1	0.75	Beta	0.51	0.9
Sensitivity of MRI scan diagnostic	Sens.diag2	0.875	Beta	0.7525	1
Specificity of MRI scan diagnostic	Spec.diag2	0.89	Beta	0.75	0.96
Sensitivity of biopsy	Sens.biopsy	0.991	Beta	0.964	0.998
Specificity of biopsy	Spec.biopsy	0.996	Beta	0.937	1
Mortality rate of surgery	Mort.surg	0.000463	normal	0.00034	0.0005
Disutility for KC stages 1-3, compared to no cancer	Disutility.St1.3	0.91	normal	0.86	0.96
Disutility for KC stage 4, compared to no cancer	Disutility.St4	0.882892	normal	0.8081	0.9476
Costs for treatment and surveillance: intercept (Regression)	Cost.treat.intercept	£2,516	Gamma	£2,047	£3,032
Costs for treatment and surveillance: previous smoke (Regression)	Cost.treat.past.smoke	-£61	normal	-£265	£143
Costs for treatment and surveillance: current smoke (Regression)	Cost.treat.current.smoke	-£259	normal	-£516	-£2
Costs for treatment and surveillance: Y2 (Regression)	Cost.treat.Y2	-£987	normal	-£1,515	-£458
Costs for treatment and surveillance: Y3 (Regression)	Cost.treat.Y3	-£1,622	normal	-£2,113	-£1,131
Costs for treatment and surveillance: stage 1 (Regression)	Cost.treat.St1	£5,159	Gamma	£4,148	£6,170

Costs for treatment and surveillance: stage 2 (Regression)	Cost.treat.St2	£6,171	Gamma	£4,961	£7,380
Costs for treatment and surveillance: stage 3 (Regression)	Cost.treat.St3	£6,690	Gamma	£5,379	£8,001
Costs for treatment and surveillance: stage 4 (Regression)	Cost.treat.St4	£2,363	Gamma	£1,900	£2,826
Average diagnostic costs for symptomatic patients	Cost.diag.sympt	£297	Gamma	£242	£358
Average diagnostic costs for screen-detected cases, tests + CT scan	Cost.diag.screen1	£266	Gamma	£217	£321
Costs of biopsy for FP cases	Cost.biopsy	£646	Gamma	£526	£779

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