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Generic Cancer Screen - Economic modelling report

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Early Cancer Detection Consortium

Generic Cancer Screen - Economic modelling report

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1 Executive Summary

Introduction

Screening for multiple cancer types in a single test has the potential to offer both cost savings and health gains in comparison to offering several separate type-specific programmes. There are a large number of blood based biomarkers which are common to multiple cancer types. If used individually, these biomarkers are generally not sufficiently sensitive or specific to be used for early detection of cancer, nor is their yield of cancers detected per cohort of patients screened sufficiently high to make them economically efficient. It is possible that by combining several different biomarkers a blood based cancer screening test with sufficiently high sensitivity, specificity, and efficiency could be developed. The UK Early Cancer Detection Consortium (ECDC) was formed in 2012 to develop a multi-marker, multi-cancer, blood based generic screening test to be used in national screening programmes. The intention of the ECDC is to develop a test will both indicate the possibility of cancer, and provide guidance on which type of cancer is suspected.

The objectives of this study are to develop an early economic model to evaluate an early generic cancer screening programme and to identify what evidence needs to be generated to allow for robust economic evaluation in the future.

Methods

A conceptual model was developed to assess the potential cost and health impacts of a new generic cancer screening programme which included impacts such as changes in treatment costs and improvements in overall survival due to earlier diagnosis. The conceptual model highlighted the data required to populate an economic model.

Literature searches and expert elicitation were undertaken to obtain data on: proposed screening pathways; costs (cost of treatment by stage of disease, cost of a screening test and cost of follow-up); screening characteristics (uptake, test characteristics, completion rates, harms, positivity rate, and stage shift); health related quality of life (for cancer patients, decrement associated with false positives); cancer incidence; and survival. For reasons of feasibility the scope of literature searches and the economic modelling was restricted to five cancer types (bladder; breast; colorectal; lung; and ovarian). The available data for each of these areas were summarised and critiqued.

An economic model was developed using available data. A simple structure was employed where the health gains from screening were based solely on stage shift (moving diagnoses from late stage disease to early stage). The model was used to predict cost outcomes and resource use for one round of the screening programme. The new programme was modelled as an addition rather than a replacement to standard care (type specific programmes for breast and colorectal cancer). The model was used to conduct scenario analyses to explore the impact of model parameters on cost-effectiveness.

Results

For several parameters obtained from the literature reviews available, potentially biased or of poor quality. Due to the early stage of the evaluation some data were not available such as: the test sensitivity and specificity; the proposed generic cancer screening pathways; and the unclear rate of

the test. The data available on the lifetime costs of treatment of cancer by stage at diagnosis was unsatisfactory for modelling; where lifetime costs were available, they were often based on old data or on treatment pathways which did not reflect heterogeneity in patient care. Data on disease natural history were not available for all cancer types. These data limitations meant that populating some model structures (such as modelling of precancerous conditions) was not possible. Due to these data limitations, accurate estimation of the cost-effectiveness of such a screening programme was not possible.

The study highlighted the extent to which certain model parameters vary by cancer type and the importance of this in relation to economic modelling. Data analysis undertaken as part of this study illustrated that the QALY gains from earlier diagnosis (for diagnosis in stages I/II instead of III/IV) of cancer varied widely by cancer type ranging from 6.1 discounted QALYs (13.7 life years) for ovarian cancer to 1.1 discounted QALYs (2.3 life years) for small cell lung cancer.

ICER values were generated using the early economic model, however these values should be interpreted with caution, as the model structure was associated with structural limitations. The ICER values from this early economic model ranged from £12,277 to £185,911 per QALY gained demonstrating a high degree of uncertainty. However, it is important to note that when data and structural issues are addressed, the ICER could well be lower than this range. Indeed, the health economic reappraisal of the NHS bowel cancer screening programme found that bowel cancer screening dominated no screening (i.e. cost savings and QALY gains). The wide range of ICER values and the structural limitations highlight the need to improve the evidence base to support economic evaluations of generic cancer screening programmes.

The study allowed the identification of key future research priorities. The literature searches undertaken established areas where data was associated with significant uncertainty. The expert elicitation component of this study illustrated that identifying pathways for people with a positive test result in a generic cancer screening programme is much more difficult than for a type specific programme. The exploratory modelling undertaken showed that the important drivers of cost-effectiveness were the same as would be expected for a type specific cancer screening programme, i.e.: the stage shift associated with screening (which would depend on test sensitivity and specificity and the natural history of each cancer), the cost of the screening test, the positivity rate of the programme (which would depend on the sensitivity, the specificity and the prevalence) and the cost of follow up for false positives. It is expected that further data to inform the majority of these parameters will be generated during development of a new test.

Discussion

The study found that there was a substantial degree of uncertainty in the health economic effects of a generic cancer screening programme, which was largely due to several data issues. To address this limitation, future research is needed into: the lifetime treatment costs for each cancer type by stage at diagnosis; the natural history of multiple cancer types; the follow up pathways for false positive screens; and the QALY gains from earlier detection of cancer.

The lifetime cancer treatment costs were found to be poorly understood. A recent research study attempted to address this gap, however 1) costing was restricted to four cancer types, 2) the pathways were based on national guidelines and expert opinion so may not reflect actual use and 3)

some parts of the pathway were implausible to ECDC experts. Research should be conducted to establish the lifetime treatment costs by stage at diagnosis and cancer type. Two study designs are possible to calculate the lifetime cost: 1) using observational data on the actual pathways which patients follow or 2) using recommended pathways from NICE guidelines and expert opinion. There may be value in comparing costing obtained using both methods. As treatment pathways for cancer will continue to change, regular updating of the costs (e.g. every five years) is suggested

The natural history of each cancer type detected by a generic screening programme needs to be understood in order to adequately represent the benefits of screening within a model. Natural history parameters include: the rate at which precancerous conditions develop; the rate of progression between the different precancerous; and cancerous stages of the disease and an understanding of symptomatic presentation rates. An understanding of the natural history of the disease is also one of the criteria that the National Screening Committee uses to approve or reject new screening programmes. Further research by experts in the field of cancer into the natural history of cancer types which would not have previously been considered for detection in a cancer screening programme is recommended.

QALY gains associated with earlier detection were calculated in this study using published incidence and survival data. The available data was adequate however it is essential that up to date incidence and survival data for all cancer types is regularly published. This will enable accurate estimation of QALY gains in health economic modelling which incorporate improvements in survival over time due to the introduction of new treatments and technologies.

Further research should be conducted into the follow up pathways for positive results from a generic cancer screening test prior to a trial of the test. In contrast to, a type specific cancer screening programme it is not obvious which follow up procedure(s) a person with a positive test result should receive. It is recommended that further research in this area be undertaken by experts in the field prior to the trial of the test. Furthermore the model results were sensitive to the cost of diagnosing false positives, indicating that controlling these costs may be a key driver of the overall cost-effectiveness of a generic cancer screening programme.

Conclusions

A generic cancer screening programme could potentially offer benefits over type specific programmes. This study highlights future research required to test this hypothesis. Further clinical research needs to be conducted before it will be possible to determine if a blood based approach would be a cost-effective method for screening for multiple cancer types.

In order to allow a future economic evaluation of a generic cancer screening programme research funding in the following areas should be prioritised: lifetime cancer treatment costs by stage at diagnosis, the natural history of different cancer types and the QALY gains associated with earlier detection of cancer. If these limitations in the evidence base are not addressed, then accurate assessment of the cost-effectiveness of early detection strategies for multiple cancer types will not be possible.

Researchers developing tests suitable for a generic cancer screening programme should carefully consider the follow up pathways for people with positive results in order to efficiently determine if

the result is a false positive. Currently for many cancers there is insufficient understanding of the biological and/or radiological characteristics of false positives. This is evidenced by high false positive rates even within established single-tumour screening programmes. In addition, it is essential to understand whether the screening test will detect precancerous conditions (and for which cancer types). If the test does detect pre-cancerous conditions, then using the test in a screening programme for the general population may alter the observed incidence of cancerous conditions, as early treatment may prevent cancerous tumours from developing.

In conclusion, it is not yet possible to robustly assess the cost-effectiveness of a new generic cancer screening programme using only currently available evidence.

2 Introduction

2.1 Background

There are a large number of blood based biomarkers which are common to many cancer types. If used individually these biomarkers are not sufficiently sensitive or specific to be used for the earlier detection of cancer. One prominent example of this is circulating cell free DNA, which is present in higher concentrations in a cancer patient's blood (1). However cell free DNA alone is not a viable biomarker alone, as it is not sufficiently specific. Elevated levels of cell free DNA have been observed in patients with a variety of noncancerous conditions including sepsis, inflammatory conditions, myocardial infarction, obstructive sleep apnoea and after exercise (1)(2).

The UK Early Cancer Detection Consortium (ECDC) was formed to develop a blood based generic cancer screening test which combines multiple biomarkers(3). It is proposed that by combining several different biomarkers a blood based generic cancer screening test with sufficiently high sensitivity and specificity can be developed. The test will consist of two components: the initial test which will be a high sensitivity test to detect all patients with cancer and a reflex test which will be a high specificity test for those patients identified by the initial test. It is intended that this screening test will be used as part of a generic cancer screening programme. The aim of the generic cancer screening test is earlier diagnosis of cancer, which can lead to earlier treatment and better survival.

The proposed generic cancer screening programme requires that a blood sample is taken, the samples are sent to an external laboratory for testing and the results are sent to the person in the screening programme and their GP. This offers the potential to conduct the generic cancer screening programme at the same time as any other regular health interventions that take a blood sample, for example the NHS health checks. Currently there are three cancer type specific screening programmes in the UK for colorectal (in the NHS bowel screening programme), breast and cervical cancers. The generic cancer screening programme is currently not intended to replace these screening programmes, but to operate alongside them.

The ECDC has undertaken systematic reviews to identify potentially useful biomarkers and the acceptability to patients of a blood based cancer screening programme.(4;5) A Delphi exercise has also been undertaken to establish what information decision makers in the NHS may need at the local and national level prior to the introduction of a new blood based generic cancer screening programme. The Delphi exercise was undertaken between August and November 2014, 27 persons who were involved in research or treatment of cancer were surveyed by the ECDC (6). They found that at least 75% of those responding considered affordability, cost utility and implications of false positives/negatives to be of high or very high importance in designing a generic cancer screening programme.(6)

2.2 Aims

The aims of this project are to:

- Develop a conceptual model to assess the potential cost and health impacts of a new cancer screening programme and identify data required to populate an economic model.
- Obtain data to populate an economic model through literature searching and clinical input.

- Describe available data and establish any key data gaps.
- Construct a draft economic model using available data and produce outputs to inform the development of the generic cancer screen.

Section 2 describes the conceptual model and data requirements. Section 3 describes the data including how it was identified and data quality. Sections 4 and 5 describe the draft economic model and results. Conclusions are provided in section 6.

3 Economic model

3.1 Conceptual Model

A conceptual model of the health and cost impacts of a generic cancer screening programme was developed. The conceptual model was presented to the ECDC at a meeting in March 2014 to ensure that all important impacts were included. The conceptual model is shown in Figure 3.1.

The main potential benefits of a generic cancer screening programme were lower treatment costs and improved survival due to earlier diagnosis of cancer. It is also possible that the screening programme will result in the diagnosis and treatment of non-cancer conditions which are detected incidentally.

There are several potential harms and costs of the screening programme. The definitions of these harms are given in Table 3.1. Follow up of false positive results will incur a cost to the NHS and may be associated with adverse psychological impact that may impact on HRQoL. It is also possible that the generic cancer screening programme will lead to the treatment of false positives. Treatment of false positives is unnecessary but may occur if a 100% specific diagnostic test for the cancer type is not available (e.g. for ovarian cancer). False reassurance may occur for persons with false negative results who may then be less willing to present if they have symptoms. There may be increases in overdiagnosis which is the diagnosis of a cancer that would not have led to symptoms or mortality during the remaining lifetime of the patient.(7) Overdiagnosis will lead to overtreatment and hence people will receive unnecessary treatment.

Figure 3.1: A conceptual model of the health and cost impact of generic cancer screening programme

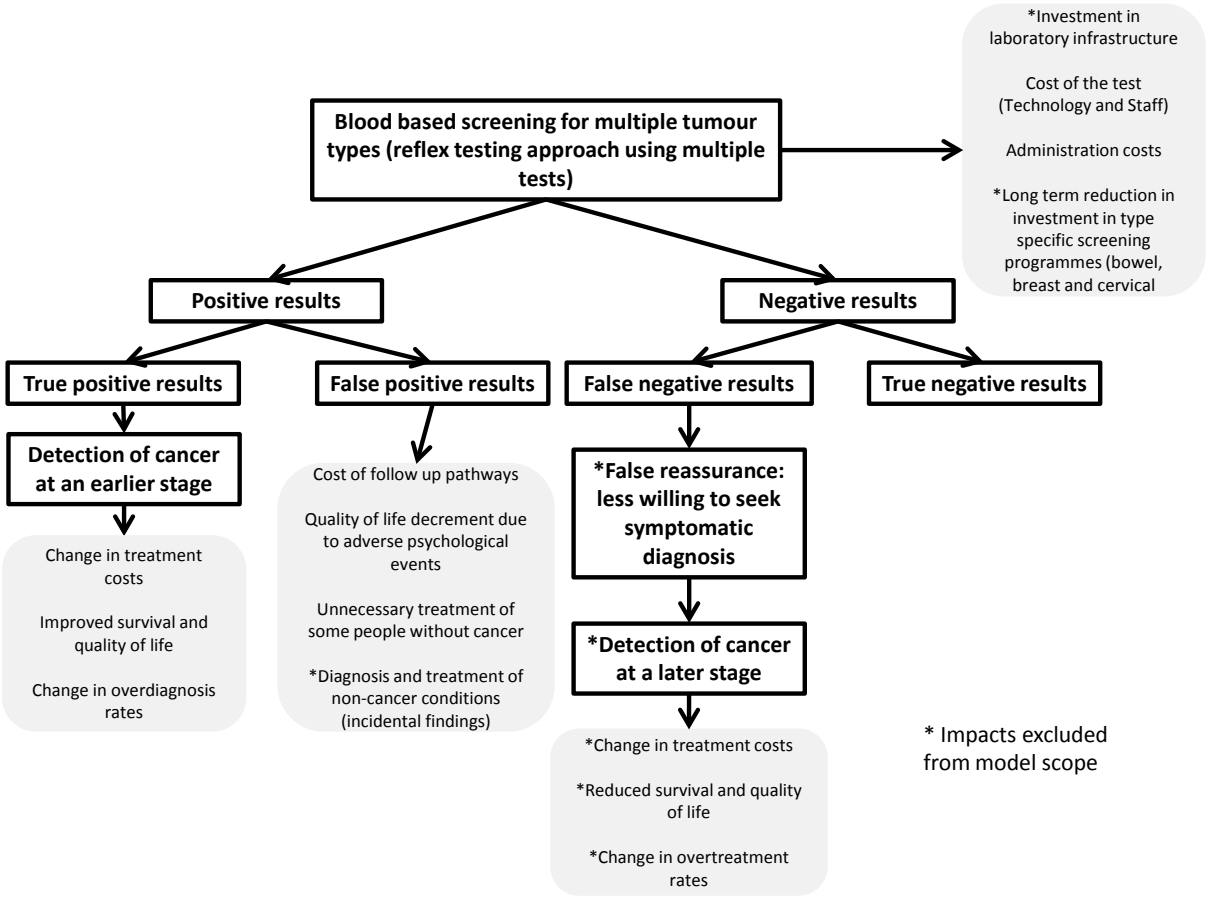


Table 3.1: Definitions used in this report

Name	Definition
Generic cancer screening test	The test which will be used in the proposed screening programme
Stage at diagnosis	The stage of cancer at the time the patient is diagnosed
Overdiagnosis	The diagnosis of a disease in an individual through a screening programme, which otherwise would not have caused symptoms or death (7)
Overtreatment	The treatment of those patients who have been over diagnosed
Treatment of false positives	The treatment of those patients who have had a positive cancer screening test, but who do not have cancer
HRQoL	Health related quality of life

3.2 Model Scope

The conceptual model was simplified to form a model structure which could be used for the economic evaluation. Several potential impacts of the generic cancer screening programme on the NHS were not included in the model. The effect of false reassurance (less willing to seek symptomatic diagnosis following false negative result) was excluded from the modelling due to insufficient data on the mechanisms of this effect in cancer screening programmes. (8)

The cost-effectiveness analysis follows methods guidance from the National Institute for Health and Care Excellence (NICE) and take an NHS and personal social services perspective (9). The initial investment in laboratory infrastructure was excluded as one off costs are not usually included within a cost-effectiveness analysis. The model compares the introduction of a generic cancer screening programme to current practice which includes three site specific screening programmes (bowel, breast and cervix).

The generic cancer screening test is intended to detect multiple cancer types. The model scope was restricted to five cancer types (bladder, breast, colorectal, lung and ovarian) as it would be unfeasible to model all types of cancer. These five cancer types were selected by the ECDC based on prevalence and potential for the generic cancer screen to be beneficial and together they account for 45.1% of cancer incidence. It should be noted that, type specific screening programmes exist for breast and colorectal cancer therefore the benefits of screening for these cancer types will be lower than if no type specific screening programme existed for these cancer types.

4 Data to inform an economic model of the generic cancer screen

4.1 Data requirements

The conceptual model illustrates the data required to estimate the cost-effectiveness of a generic cancer screening test. As the aim of the generic cancer screening test is to alter the distribution of stage at diagnosis. Data on survival and treatment costs by stage at diagnosis was required. Information on the proposed screening and follow-up pathways for the generic cancer screen are required.

To summarise the following data are required:

- Proposed screening pathways
- Cost data: Cost of treating cancer by stage, Cost of generic cancer screening test and follow-up
- Screening data: uptake, test characteristics, completion rates, harms, over diagnosis, positivity rate, and stage shift due to screening
- HRQoL: for cancer patients, decrement associated with false positive result
- Cancer incidence and survival data

Data was obtained via: discussion with the ECDC; elicitation from experts; and literature searches and is described in Sections 4.2 to 4.8

4.2 Proposed Screening Pathways

To allow the costs and health impacts of the generic cancer screen to be modelled the patient pathways associated with the proposed screening programme were determined. The pathways were established via numerous discussions with the ECDC in 2014. These pathways are described within this Section and are summarised in Figure 4.2.

Persons are invited to complete a screen via an invitation letter. This is the same as the mode of invitation used by the existing breast, bowel and cervical screening programmes. If no response is received a second invitation letter will be sent. It is also possible to opt out of the screening programme at the invitation stage. An option to complete consent paperwork online will be available. Persons declining or failing to make an appointment will be re-invited at the subsequent screening round.

The options for screening age range and screening intervals to consider were obtained via ECDC opinion (Ian Cree and Sian Taylor-Phillips). In the base case an age range of 40-72 years was considered with 4 yearly screening intervals.

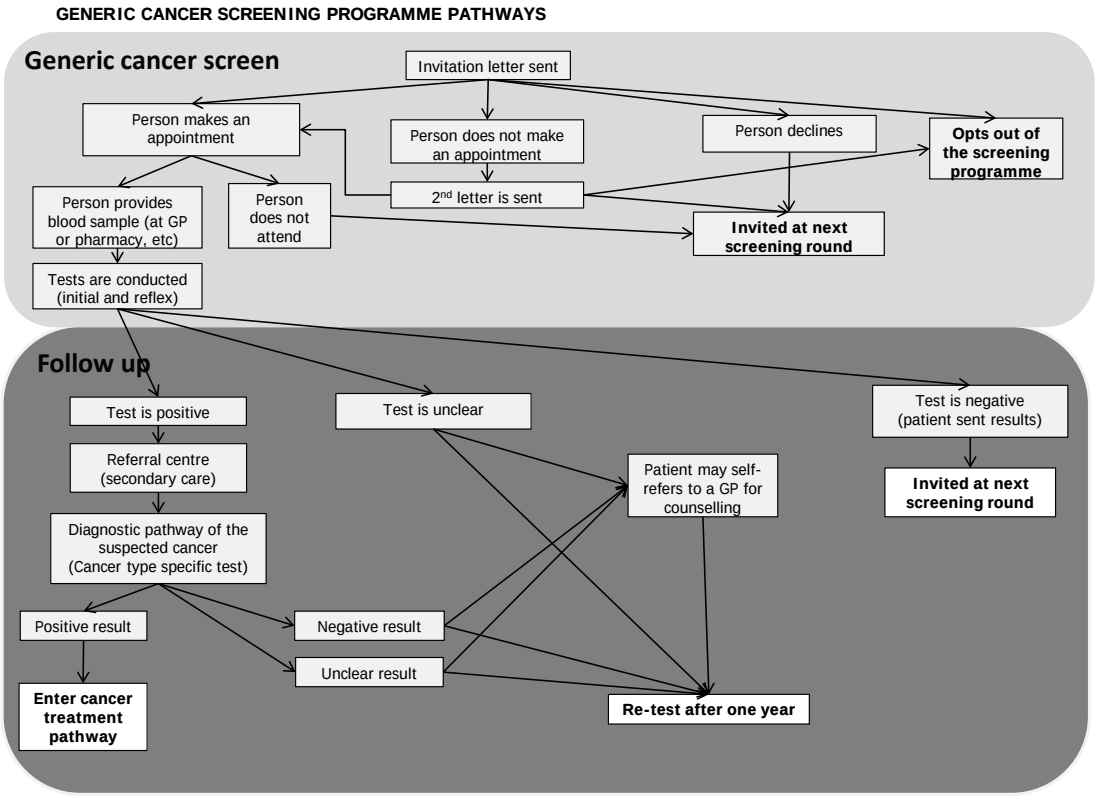
It was assumed that the blood sample would be taken at a GP surgery. Four options were considered for the mode of taking the blood sample: (1) the sample may be taken by either a practice nurse or a

phlebotomist; (2) the sample may be taken as part of the NHS health checks or separate to the health checks.

The proposed follow-up pathways were discussed by the ECDC at a (meeting in October 2014, ECDC input summarised in Appendix 1) and are presented in the Figure below. A summary of the input given regarding the pathways are given in Appendix 1. Positive test results will receive a letter inviting them to attend a referral centre (secondary care) which will be followed by a cancer type specific diagnostic test. In addition it was assumed that all persons with a positive result would see a cancer nurse specialist to reduce their anxiety in the recall period. The staffing requirements to provide this cancer nurse specialist support were based on data from the NHS breast cancer screening programme.

Persons with an unclear result following diagnosis investigations may be retested after a year. Persons with a negative or unclear result following diagnostic investigations may self-refer themselves to a GP to discuss their outcomes. Due to an absence of data on the proportion of the number of patients who self-refer is 40%. This number was tested in scenario analyses. They will be offered a repeat test after just one year. Those with negative results will receive a letter confirming this and will be re-invited at the subsequent screening round. Due to the lack of evidence, it was assumed that40% of patients with false positive results self-refer to a GP to discuss their results in the base case.

Figure 4.2: Proposed pathways for the generic cancer screening test



4.3 Cost of generic cancer screening test and follow-up

The cost of the generic cancer screen can be split into the following four components:

1. Cost of inviting patients to attend and communicating the results
2. Cost of taking the blood sample (including test consumables, and transportation of sample to laboratory)
3. Cost of the biomarker tests on blood sample
4. The cost of cancer nurse specialist support
5. Cost of follow-up pathways

The data used to inform these costs is described here and is summarised in Tables 4.3 a, b and c.

Cost of inviting patients to attend and communicating the results

The cost of inviting people to the screening programme, the cost of running a helpline for the screening programme and the cost of communicating the results to patients and their GP were based on costs estimated by the Southern Hub for the Bowel cancer screening programme (10). The total cost of this was £2.09 per screening invitee.

Cost of taking the blood sample

It was assumed that the blood sample would be taken at a GP surgery. Two options were considered for the mode of taking the blood sample: 1) the sample may be taken by either a practice nurse or a phlebotomist; 2) the sample may be taken as part of the NHS health checks or separate to the health checks. It has been assumed that in the NHS health checks the blood samples will be sent to the laboratories at no additional cost as they will already be sent there as part of standard practice. The staff costs were taken from Curtis 2013 and the staff time was obtained by expert clinical opinion (11). The cost of taking a blood sample is given in Table 4.3a for the costs used in the model and for the breakdown of this cost, see Table 4.3b. As the staff time is relatively uncertain a scenario analysis was conducted where the staff time for nurse outside the NHS health was halved to 5 minutes. A scenario analysis was also conducted were the blood tests were conducted within the health checks. In this scenario, the staff time involved was 5 minutes to ensure that the staff had time to ensure that the patient had consented to the generic cancer screening test. The cost in the base case is therefore £6.17 per sample, assuming a phlebotomist does this as part of a health check.

Cost of the biomarker tests on blood sample

It is envisaged that the generic cancer screen will use tests for several different biomarkers. Blood-based biomarkers that can be used for early identification of cancer in the general population will be used possibly including some of the following types of tests: adhesion and matrix proteins, auto-antibodies and immunological markers, classical tumour markers, coagulation and angiogenic proteins, cytokines, chemokines and insulin-like growth factors, circulating-free DNA, hormones, metabolomics, micro RNA and other RNAs, novel proteins, nuclear proteins, viral proteins, volatile organic compounds. The test will consist of two components: the initial test which will be a high

sensitivity test to detect all patients with cancer and a reflex test which will be a high specificity test for those patients identified by the initial test. The cost of the biomarker tests will be:

Cost of biomarkers in initial test + (proportion of samples requiring reflex test cost of biomarkers in reflex test)*

As not all samples will require reflex testing the average number of biomarker tests performed (including initial and reflex) will not be an integer. For example, if 75% of samples receive 1 test and the remaining 25% receive 3 tests then the average number of tests is 1.5. The average number of biomarker tests performed per sample was assumed to range from 1.5 to 3 with 2 being assumed in the base case. The costs of testing for 8 biomarkers were provided by Ian Cree (ECDC) (12). These biomarkers will not necessarily be included in the generic cancer screening test, but were instead used to inform the potential cost of biomarkers in the generic cancer screening test. Some of the values were estimates and some values were obtained from a large district general hospital (2011/12 financial year). The cost of all reported biomarkers is given in Table 4.3c. The average cost of the CA, prostate specific antigen (PSA) and Carcinoembryonic antigen (CEA) biomarkers is £33. It may be possible to test for all biomarkers of a certain type for a fixed cost. The cost of testing for multiple volatile organic compounds (VOCs) was taken to be £10 (13). This cost estimate does not include any consumables related to VOCs (gas, vials, pre-concentrator or nurse time). Given the estimate of the cost of biomarkers and the assumption on the number of biomarkers in the generic cancer screening test, it was assumed that the base case cost of the biomarkers in the generic cancer screening test was £66.

The cost of cancer nurse specialist support

It was assumed that ongoing support would be given to people identified as having cancer by cancer nurse specialists, as in The NHS breast screening programme. The minimum staffing level is 0.1 whole time equivalent cancer specialist nurses per 10,000 patients screened (4% positivity rate so 400 positives) (14).It was assumed that this staffing level was related to the positivity of the NHS breast screening programme hence a minimum staffing level of 0.1 whole time equivalent cancer specialist nurses per 400 positive people was assumed. A cancer specialist nurse is equivalent to a nurse advanced in the unit costs of health and social care. The yearly cost (including salary, salary on costs and overheads but excluding qualifications) of an average nurse advanced was £81,705 per year. Whether or not this service would be provided alongside a new screening programme is uncertain, therefore a scenario analyses excluding these costs was undertaken.

Cost of follow-up pathways

It is expected that the generic cancer screening test results will indicate the type of cancer present. It has been assumed that patients who have a positive generic cancer screening test result will be referred to an appropriate secondary care clinician. For example, a person suspected of having bladder cancer will be referred to an urologist or oncologist. Therefore the costs of follow up were assumed to be the costs of procedures used to diagnose patients in secondary care, see Section 4 of Table 4.3a. For people without cancer (false positives) it has been assumed that they will receive the

most expensive diagnostic pathway. It was assumed that people with unclear screening test results did not receive further follow up but were invited to receive another screening test in one year.

Summary

Table 4.3a: Summary of generic cancer screening test and follow-up costs

1. Cost of inviting patients to attend and communicating the results	
Sending invitations and reminders, processing opt-outs, sending results letters, follow-up invitations	£1.51
Helpline costs per screening invitee	£0.58
Total cost	£2.09
2. Cost of taking the blood sample (including test consumables, and transportation of sample to laboratory)	
Assumes 10 minutes required to take sample	
Nurse takes blood sample at a GP surgery (within the health checks)	£9.33
Nurse takes blood sample at a GP surgery	£32.33
Phlebotomist takes blood sample at a GP surgery (within the health checks)	£6.17
Phlebotomist takes blood sample at a GP surgery	£29.17
3. Cost of the biomarker tests on blood sample	
Cost of tumour marker tests (each, average cost)	£33
Average number of tumour marker tests per person screened	2
Cost of tumour marker tests	£66
4. Cost of follow-up pathways	
Cost of follow-up for true positive screens (assumed to be the cost of diagnosing cancer)	See treatment costs Table
Cost of follow-up for false positive screens (assumed to be the maximum cost of diagnosing cancer)	See treatment costs Table

Table 4.3b: Component costs of taking blood sample for generic cancer screen

	Cost	Source
Practice nurse cost per hour	£44	Unit costs of health and social care 2013
Phlenotomist cost per hour	£25	Unit costs of health and social care 2013
Time taken for nurse/phlebotomist to take blood sample (minutes)	10	ECDC opinion (IC)
Time taken for nurse/phlebotomist to take blood sample (minutes)	5	ECDC opinion (IC)
Within health checks: Test consumables (needles, vials, etc.)	£2	ECDC opinion (IC)
Outside health checks: Cost of consumables and transporting the blood samples to the laboratory	£25	ECDC opinion (IC), from Sputnik trial

Table 4.3c: Costs of tumour markers

Tumour marker	Costs of tumour markers		Source
	2011/12	*2012/13 (Inflated using HCHS)*	
CA 125	£23	£24	NICE ovarian cancer guidelines
CA 125	£34	£35	
CA19.9	£35	£35	IC personal communication. Costs were obtained from a large district hospital in the 2011/12 financial year
CA15.3	£36	£36	
PSA	£34	£35	
CEA	£31	£31	
	2015		
FAIMS	£20		Expert opinion IC
cfDNA	£50		Expert opinion IC
Mutation analysis cfDNA	£200		Expert opinion IC

4.4 Cost of Cancer Diagnosis and Treatment

4.4.1 Literature searches

A series of literature searches were conducted to obtain cost-effectiveness and costing studies which might contain data on the cost of treating each of the five cancer types within the model scope. The searches were conducted in MEDLINE and MEDLINE in PROCESS in October 2014. In addition, the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) journal was searched for publications on the treatment of each of the five cancer types. The search terms relating to each disease were obtained and adapted where necessary from single technology appraisal submissions to the National Institute for Health and Care Excellence. The Scottish Intercollegiate Guidelines Network (SIGN) economic search filters (15) were used and search terms were added to remove any potentially irrelevant materials from the searches. The search strategies are presented in the Appendix.

The following exclusion criteria were applied to all search results:

1. It did not only include patients with the cancer type under consideration
2. The studies only contained qualitative data
3. Only costs to the NHS were included
4. It was not an original study; in this case the original study referenced was included in its place
5. It did not consider UK patients
6. It did not present treatment costs specific to cancer stage
7. It did not present a cost for all patients with the cancer type

These exclusion criteria were identified so that: the study results were relevant to the UK population and studies which reported consistent methodologies for calculating the cost of cancer across the different cancer stages were identified.

In addition to the published literature a report by Incisive Health for Cancer Research UK was identified in the grey literature (dated September 2014). This reports the financial implications of earlier diagnosis of ovarian, lung, colon and rectal cancer. (16) The Incisive Health report uses national pathways and British sources for unit costs to create a cost of treating a patient by stage at diagnosis. The national pathways were simplified and amended according to clinical input to better reflect the cost of treating cancer patients in the UK.

A group of clinical experts were contacted to ensure that key studies had not been missed. Details of the experts contacted are provided in the Appendix. No additional studies were identified via the experts.

The studies identified for each of the five cancer types are presented in Table 4.4a. Where appropriate prices were inflated to 2012/13 using the hospital & community health services (HCHS) pay and prices index(11;17).

Table 4.4a: Results of literature search for cancer treatment costs

Cancer Type	Studies found in literature search	Included studies	Included studies references	Other studies identified
Bladder	3	1	(18)	
Breast*	108	7	(19-26)	
Colorectal	106	1	(27)	(10;16)
Lung	58	1	(28)	(16)
Ovarian	6	0		(16)

*, A modified set of exclusion criteria was applied

4.4.2 Studies of cancer diagnosis and treatment

Bladder cancer

The search identified three potentially useful studies of which two studies were excluded: one was an opinion piece and one considered patients with haematuria. (29) (30) Mowatt et al. was published in 2010, the study assessed the clinical benefit and cost-effectiveness of different strategies for the detection and diagnosis of bladder cancer in the UK. (18) Unit costs of procedures used in treating bladder cancer were reported, however the lifetime cost of treating non muscle invasive bladder cancer, muscle invasive bladder cancer and metastatic bladder cancer was not presented.

As no existing studies providing data on bladder cancer treatment costs in the UK were identified by the search, a de novo bladder cancer costing study was undertaken as part of this project. This study is presented in a separate Appendix. National Collaborating Centre for Cancer (NCC-C) draft clinical guidelines (31), expert opinion, NHS reference costs (32) and the unit costs of health and social care (11) were used in the bladder cancer costing study. However, due to insufficient clinical input the proportion of patients who followed each part of the bladder cancer treatment and diagnosis pathways could not be determined hence the costing study remains incomplete.

In the absence of an estimate from the de novo costing study, it was assumed that stage specific costs of diagnosing and treating bladder cancer are the same as the costs of diagnosing and treating colorectal cancer. This assumption was made for three reasons. Firstly, both types of cancer can be treated during the diagnostic procedure in the very earliest stages. Secondly, both cancer types use surgery to treat more advanced tumours. Finally, both cancers are in similar areas of the body therefore the costs of surgery in these two cancers may be similar.

Breast cancer

The search identified 108 articles potentially relevant to the cost of treating breast cancer. When all criteria were applied only one study on the cost of treating breast cancer remained (19). There were concerns about the applicability of this study for the cost of treating breast cancer in the UK. Therefore, criteria 6 and 7 were removed from the exclusion criteria to obtain studies which

reported the average cost of treating breast cancer. 7 articles were included using the modified exclusion criteria. Of these 7 articles, two articles contained lifetime treatment costs by stage for all breast cancer patients (19;20) and five (21-26) articles had information on the lifetime treatment costs for either late or early stage breast cancer patients.

The study by Madan *et al.* (20) used the costs from Johnston (33) which report the cost of treating breast cancer by a patient's Nottingham prognostic index (NPI). As NPI cannot be matched to stage at diagnosis groups, these costs were excluded.

Table 4.4b: Breast cancer lifetime treatment costs identified by the literature review

Study	**Cost reported in the study**	**Original price year**	**Inflated cost (2012/13)**	**Study Details**
Late Stage				
Remak and Brazil (22)	£12,502	2000/1	£18,394	The population is women presenting with stage IV breast cancer. Less than 40% of patients who present with late stage breast cancer have a stage IV cancer.
Cameron *et al.* (23)	£11,424	2005/6	£13,710	The population is post-menopausal women with ER+ advanced breast cancer. About 80% of breast tumours are ER positive in post-menopausal women (34).
Reis *et al*. (19)	£45,328	2009/10	£48,542	The population is those patients at an increased familial risk of breast cancer. Most patients in the UK are not at an increased risk of breast cancer (35). The palliative care costs were at least five times higher than other studies on late stage breast cancer.
Fleeman *et al*. (26)	£15,661	2008/9	£16,957	The population is those women who receive anastrozole as a first line treatment for metastatic breast cancer. This population represents less than 10% of patients with metastatic breast cancer.
Fleeman *et al*. (26)	£13,992	2008/9	£15,150	The population is those women who receive laptinib as a first line treatment for metastatic breast cancer only. This population represents less than 10% of patients with metastatic breast cancer.
Early stage				
Ward *et al.* (24)	£23,690	2005/6	£28,430	The population is those women eligible to receive anthracycline based chemotherapy. Currently the only recommended adjuvant chemotherapy option by NICE includes an anthrcycline

				(doxorubicin). This chemotherapy option is only recommended for patients who are node positive (30% of breast cancers).
Wolowacz *et al.* (25)	£15,587	2005/6	£18,706	The population is those women with node positive early breast cancer. Out of all breast cancers, approximately 30% are node positive.
Reis *et al*. (19)	£17,456	2009/10	£18,694	The population is those women at an increased familial risk of breast cancer. Most patients in the UK are not at an increased risk of breast cancer (35)..

The costs from Cameron *et al*. (23) will be used for the lifetime treatment costs of late stage breast cancer as the study included around 80% of the late stage breast cancer population. The costs from Ward *et al*. (24) will be used for the lifetime treatment costs of early stage breast cancer. This study was selected as it generally uses more recent sources for the cost inputs in the model than Wolowcaz et *al*. (25), it incorporates a cost of death in the model, clearly takes into account the cost of recurrence and covers a similar proportion of the population with breast cancer. Reis *et al*. (19) was not considered as relevant to the cost of treating early stage breast cancer, as it appeared to cover a smaller proportion of the UK population with breast cancer.

No information was available on the cost of diagnosing breast cancer, as all studies looked at treatments for patients after they had been diagnosed. Therefore it was assumed that the stage specific cost of diagnosing breast cancer was the average of the stage specific costs of treating colorectal, NSCLC, SCLC and ovarian cancer.

Colorectal cancer

The search identified 106 articles potentially relevant to the cost of treating colorectal cancer. Only one of these articles, by Sweet *et al*. (27) was deemed relevant. Further to the articles discovered in the search two reports were identified from grey literature: one by Incisive Health (16) and one by Whyte *et al.*(a) (36).

Sweet *et al.* defined treatment costs as any costs that occurred after diagnosis. (27) They calculated the long term treatment costs by dividing the average lifetime treatment costs by the average life expectancy of patients diagnosed with CRC. It is unclear how they calculate the initial cost, or the length of time that the initial cost covers. The costs are calculated from data collected by the department of health in the payments by results scheme. The prices are not discounted; however it would be possible to use the model to calculate the lifetime treatment costs of colorectal cancer patients. The costs are reported in 2007 prices, Table 4.4c reports the inflated values that would be used in the economic model.

Table 4.4c: The cost of treating and follow up of colorectal cancer in England in 2012 prices

Dukes' stage	**Initial cost**	**Yearly follow up cost**
Stage A – Screen detected	£5,928	£175
Stage A – not screen detected	£4,564	£175
Stage B	£11,319	£175
Stage C	£19,959	£175
Stage D	£13,680	£414

Source; Sweet *et al*.(27)

Whyte et al.(a) (36) report the lifetime cost of diagnosing, treating, follow up and recurrence of colorectal cancer by stage and age diagnosis. The costs were obtained from a whole disease model of colorectal cancer by Tappenden (37).

Table 4.4d: The lifetime treatment cost of colorectal cancer in the UK

	Dukes' stage at diagnosis			
Age at diagnosis	**A**	**B**	**C**	**D**
40-49	£8,375	£8,362	£13,862	£11,198
50-59	£5,465	£6,712	£9,272	£8,078
60-69	£4,423	£5,120	£6,945	£6,227
70-79	£3,040	£3,305	£4,291	£4,176
80-100	£1,320	£1,479	£1,493	£772
Incidence weighted average	£3,651	£3,918	£5,318	£4,574

Source; Whyte *et al.*(a)(36)

In the Incisive Health report, the costs for colon and rectal cancer were calculated independently (16). To allow for recurrence it has been assumed that all of patients with stage I, II or III cancer shown not to survive to 5 years after being diagnosed suffer a recurrence of their disease. Further to this, the incisive health report assumed that the cost of treating a recurrence of the disease was the same as treating a patient with stage IV cancer. The weighted average cost of diagnosing and cost of treatment, follow up and recurrence of colon and rectal cancer were calculated using the number of patients with colon and rectal cancer from a study by Maringe *et al*.(38) .

Table 4.4e: The costs of diagnosing, treating, follow up and recurrence of colorectal cancer

	Colorectal cancer		
TNM stage	**Cost of diagnosis**	**Cost of treatment, follow up and recurrences**	**Total cost**
Stage I	£561	£3,526	£4,088
Stage II	£561	£10,296	£10,857
Stage III	£498	£16,327	£16,825
Stage IV	£463	£11,829	£12,293

Source; Incisive Health (16)

Data from the ICBP indicates that the mean age at which patients present with colon cancer is 72 and with rectal cancer is 70 (38). The lifetime treatment costs are generally lower in the 70-79 age group in Whyte *et al.*(a).(36) than the Incisive Health report (16). This is likely due to the assumption made in the Incisive Health report that only patients with stage I-III colorectal cancer at initial diagnosis could suffer from a recurrence and at recurrence all cancers were stage IV colorectal cancer. Not all recurrences of colorectal cancer will be stage IV at recurrence, indeed ,(one clinical opinion suggests that stage III would be the most common stage of recurrent cancers, hence this assumption will likely lead to an overstatement of the cost of treating colorectal cancer in the UK population. The lifetime treatment costs of stage IV colorectal cancer in the incisive health report are generally much higher than the costs of treating stage D colorectal cancer in Whyte *et al.*(a)(36).

As the costs are significantly different and it is unclear why they are so different, the costs from Whyte et al.(a) (36)will be used in the base case and the values from the Incisive health report will be included as a scenario analysis. The costs reported by Sweet et al. (27) will not be used in scenario analyses as it is unclear how long the initial costs should apply for. Diagnosis costs will be estimated from the Incisive Health report, assuming that stage I, II, III and IV colorectal cancer correspond to Duke's stage A, B, C and D respectively.

Lung cancer

The search identified 58 articles potentially relevant to the cost of treating lung cancer. Only one of studies from the search by Fleming et al. was deemed to be relevant (28). Fleming *et al*. conducted a costing study using patient charts and prices obtained from a survey of Northern Irish hospitals. All patients registered with the Northern Ireland Cancer Registry in 2001 were included in the study. The resource use for each patient was established using hospital notes for each patient in the 12 months after they presented with lung cancer. Unit costs were obtained from the British National Formulary and a survey of local service providers. The cost of diagnosis, surgery, chemotherapy, radiotherapy, inpatient care and total costs were calculated and expressed in 2004 prices.

Table 4.4f: The diagnosis and treatment costs 12 months after presentation of small cell and non-small cell lung cancer in Northern Ireland.

Stage	Diagnosis costs	Treatment and follow up costs
Small cell lung cancer		
Limited (stage I and II)	£1,174	£9,389
Extensive (stage III and IV)	£935	£5,578
Un-staged	£1,052	£6,225
Overall	£1,005	£6,311
Non-small cell lung cancer		
Limited (stage I and II)	£1,003	£7,646
Advanced (stage III)	£1,014	£7,131
Extensive (stage IV)	£884	£4,802
Un-staged	£936	£6,423
Overall	£957	£6,458

Source; Fleming *et al*(28)

Data from 2004 inflated to 2012/13 prices

In the Incisive health report, to allow for recurrence it has been assumed that all patients with stage I,II or III small cell lung cancer shown not to survive to 5 years after being diagnosed suffer a recurrence of their disease (16). Further to this, it has been assumed that the cost of treating a recurrence of the disease was the same as treating a patient with stage IV Lung cancer.

The clinical experts had concerns that the proportion of patients receiving CT scans, spirometry and chemotherapy were too low in patients with stage 1-3 lung cancer. This could lead to an understatement of the cost of treating lung cancer in the early stages of the disease. The clinical experts also had concerns that too many patients with stage 3 lung cancers were receiving surgery. This could lead to an overstatement of the cost of treating lung cancer in the early stages of the disease. However it could also reflect local variations in the treatment of patients with lung cancer. The cost in the Incisive Health report for each stage of non-small cell lung cancer is given in Table 4.4g

Table 4.4g: The cost of diagnosing, treating, follow up and recurrence of non-small cell lung cancer in English patients in 2012/13

TNM stage	Cost of diagnosis	Cost of treatment, follow up and recurrences
Stage I	£2,939	£6,517
Stage II	£2,939	£14,033
Stage III	£3,124	£17,885
Stage IV	£2,906	£10,172

Incisive Health report (16)

The cost of treating non-small cell lung cancer used in the model will be taken from the Incisive Health report, as this data estimates the lifetime treatment cost of small cell lung cancer rather than the treatment costs which occur within a year of diagnosis. In Fleming et al. (4), limited stage disease

refers to stage I and II tumours, advanced stage disease refers to stage III tumours and extensive disease refers to stage IV tumours. The cost of treating non-small cell lung cancer is generally higher in the Incisive Health report than Fleming et al. (4). There are two reasons why this is likely to be the case. Firstly, Fleming et al. (4) only follow up patients with non-small cell lung cancer for one year. As such, the cost of treating some recurrences will have been missed from this data set. Secondly, the Incisive Health report assumes that all patients who do not survive up until the fifth year suffer from a stage IV recurrence of their lung cancer. This likely overstates the lifetime treatment cost of non-small cell lung cancer, as this assumption ignores the fact that a small number of lung cancer recurrences may be non-metastatic. As the costs in the Incisive Health report are more recent, it is likely that they are a better reflection of the cost of treating non-small cell lung cancer in the UK. Due to the potential limitations that using the Incisive health report pose, a scenario analysis will be conducted where the cost of treating patients with stage 1, 2 or 3 lung cancer is increased by 10%.

As the one year net survival of small cell lung cancer patients is less than 25%, the cost of treating and follow up for a small cell lung cancer patient is likely to be appropriately captured within the first year. For small cell lung cancer patients, the data from Fleming et al. (4) inflated to 2012/13 prices, will be used in the economic model. However, it should be noted that the information presented in Fleming et al.(28) is now likely to be out of date.

Ovarian cancer

The search identified 6 articles potentially relevant to the cost of treating ovarian cancer. None of these articles were deemed to be relevant, however one article which was not published in a peer reviewed journal was known. The Incisive Health report (16) uses national pathways and British sources for unit costs to estimate the cost of treating a patient by stage at diagnosis. The national pathways were simplified and amended according to clinical input to better reflect the lifetime cost of treating ovarian cancer patients in the UK. In calculating the lifetime cost of treatment, the cost of diagnosing, treating and following up ovarian cancer was considered. To allow for recurrence it was assumed that all of patients with stage I, II or III ovarian cancer shown not to survive to 5 years after being diagnosed suffer a recurrence of their disease. Further to this, the incisive health report assumed that the cost of treating a recurrence of the disease was the same as treating a patient with stage IV ovarian cancer. The cost reported for each stage of ovarian cancer is given in Table 4.4h.

Table 4.4h: The cost of treating ovarian cancer in English cancer patients in 2012/13

FIGO Stage	Cost of diagnosing ovarian cancer	Cost of treatment, follow up and recurrences of ovarian cancer
Stage I	£462	£6,370
Stage II	£505	£18,335
Stage III	£548	£22,935
Stage IV	£361	£14,720

Source, Incisive Health report (16)

Summary

A summary of the diagnosis and treatment costs used in the economic model for each of the five cancer types by stage at diagnosis is presented in Table 4.4i.

Table 4.4i: Summary of diagnosis and treatment costs

Cancer type and Stage	Diagnosis costs	Lifetime treatment costs (excludes diagnosis cost)	Source
Bladder cancer stage I	£561	£3,533	Assumed to be the same as colorectal cancer costs
Bladder cancer stage II	£561	£3,989	
Bladder cancer stage III	£498	£5,338	
Bladder cancer stage IV	£463	£4,671	
Breast cancer stage 1	£1,284	£23,690	Diagnosis costs: assumption based on other cancer types. Treatment costs: stage 1&2 Ward *et al.* (24), stage 3&4 Cameron *et al*.(23)
Breast cancer stage 2	£1,295	£23,690	
Breast cancer stage 3	£1,276	£11,725	
Breast cancer stage 4	£1,166	£11,725	
Colorectal Cancer Dukes' Stage A	£561	£3,533	Diagnosis costs: Incisive Health (16), Treatment costs: Whyte *et al.*(36)
Colorectal Cancer Dukes' Stage B	£561	£3,989	
Colorectal Cancer Dukes' Stage C	£498	£5,338	
Colorectal Cancer Dukes' Stage D	£463	£4,671	
NSC Lung cancer Stage 1	£2,939	£6,517	Incisive Health (16)
NSC Lung cancer Stage 2	£2,939	£14,033	
NSC Lung cancer Stage 3	£3,124	£17,885	
NSC Lung cancer Stage 4	£2,906	£10,172	
SC Lung cancer Stage 1	£1,174	£9,389	Fleming *et al.*(28)
SC Lung cancer Stage 2	£1,174	£9,389	
SC Lung cancer Stage 3	£935	£5,578	
SC Lung cancer Stage 4	£935	£5,578	
Ovarian cancer stage 1	£462	£6,370	Incisive Health (16)
Ovarian cancer stage 2	£505	£18,335	
Ovarian cancer stage 3	£548	£22,935	
Ovarian cancer stage 4	£361	£14,720	

NSC; non-small cell, SC; small cell

4.5 Screening Data

4.5.1 Uptake

The uptake of the generic cancer screening test is unknown hence values from other screening programmes may be informative. The uptake in the existing NHS screening programmes is: NHS breast screening 74%, NHS Cervical screening 74%, NHS bowel cancer screening 55% and the uptake in the NHS health checks is 48.8%.(10;39-41) Based on this data a range of values between 55% and 74% will be considered in the economic model, with 55% been used as the base case.

4.5.2 Generic screening test characteristics

Sensitivity and specificity

The generic cancer screening test will utilise a combination of biomarkers to ensure that high sensitivity and specificity are obtained. At the time of the project the test characteristics were not known; however they will be estimated via a study as part of a subsequent ECDC work package. To a certain extent it is envisaged that it will be possible to design the generic cancer test to have the optimal trade-off between sensitivity and specificity. The sensitivity of the test is likely to vary by cancer type and cancer stage but as no data on this is available a constant sensitivity will be assumed for the purposes of this project. Sensitivity and specificity were not used in the economic model, as there was no natural history model. Consequently there was no way of estimating the prevalence of asymptomatic cancer in the current model structure. Without the prevalence of asymptomatic cancer it was not possible to apply the sensitivity and specificity in the model.

Unclear result rate

The proportion of samples which will result in an 'unclear' result is unknown. An unclear rate of 0.096 was observed for the cervical screening programme in 2000-01 and this was used in the base case.(41) A range for the unclear rate of 0.05-0.2 was considered in the scenario analyses.

Positivity rate

Positivity is the percentage of the population who received a positive result from a screening programme including patients with both true positive and false positive results. The positivity associated with the generic cancer screening test will be dependent on the test characteristics of the generic cancer screening test and the prevalence of disease in the population. It is anticipated that positivity rates for the generic screening test will be available following ECDC work package 3. Positivity data was obtained for the NHS bowel, breast and cervical screening programmes; see

Table 4.5a. Based on the data available from other screening programmes a rate of 2% will be considered in the base case with a range of 1%-4% in scenario analyses.

Table 4.5a: The positivity rates of the current NHS screening programmes

Type of screening	**Positivity rate**	**Screening programme**	**Source**
Bowel	2.1%	NHS bowel cancer screening programme.	Logan et al. (42)
Breast	4%	NHS breast cancer screening programme.	NHS breast cancer screening programme annual review 2012. (39)
Cervical	4.2%	NHS cervical cancer screening programme.	Number of people screened: NHS cervical screening programme annual review 2012. (41) Number of people receiving follow up: NHS Cervical Screening Programme Statistical Bulletin 2012-13.(43)

False positivity rate

The false positive rate is the proportion of patients out of the whole population who receive false positive results. This can be obtained by multiplying the positivity rate by the complement of the positive predictive value (note positive predictive value (PPV) =true positives/positives).

To inform the false positive rate data from existing UK screening programmes was considered. Data available from the NHS cervical cancer screening programme did not allow calculation of a false positive rate. (43) In the evaluation of the first million cases in the NHS bowel screening programme, the positivity was 2.0% and the PPV ranged from 10.1% to 58.8% depending on whether low to high risk cases were counted as cancers. This gives a range of false positive rate to be 0.8% to 1.8%. From the NHS breast cancer screening annual review, the PPV was 19.6% in women aged 50-70 in 2010/11(39). In the model base case the positivity is 2% using this data and the data from the NHS breast screening programme the base case false positive rate is 1.6%. As this value is likely to be sensitive to the screening test used, the false positivity rate was varied between 0.8% and 1.8% whilst the positivity rate was 2% in the scenario analyses.

4.5.3 Overdiagnosis

Overdiagnosis is the diagnosis of a cancer that otherwise would not have caused symptoms or death within a patient's remaining lifetime (7). Overdiagnosis can occur either as a result of a screening programme or as an incidental finding. Treatment of precancerous conditions can prevent cases of cancer and thus result in QALY gains. However, overdiagnosis usually incurs costs and will harm a patient's HRQoL thus reducing QALYs.

It would be useful to understand: 1) what the current rates of overdiagnosis are for the cancer types in the scope, and 2) how overdiagnosis rates will change as a result of the generic cancer screening programme. However, there is little data available to answer these questions. It is unknown if the generic cancer screen will result in the detection of a significant number of precancerous conditions.

In the NHS breast screening programme there are an estimated 2.3 cases of overtreatment per 1000 people screened (44). The overtreatment rate within the NHS bowel cancer screening programme is not known. Overdiagnosis was excluded from the economic model for two reasons. Firstly, the economic model does not include a natural history component to estimate the prevalence of asymptomatic cancer. Therefore the rates of overdiagnosis cannot be directly estimated in the model results. Secondly, there was no information on a plausible range of overdiagnosed cases in a blood based screening programme. It is envisaged that more information on this will become available in future ECDC work packages. The exclusion of overdiagnosis will mean that the ICERs are lower bounds, as total costs will be lower bounds and total QALYs will be upper bounds. See Section 7.5 for more details.

4.5.4 Treatment of people who receive a false positive

In screening, false positives may receive cancer treatment unnecessarily if there is no 100% specific diagnostic test available. For example, in the UKCTOCs trial first screening round a false positive treatment rate of 0.01-1.70% was observed (depending on screening arm and tumour definition used). So, 0.01-1.70% of persons screened received treatment for ovarian cancer (assumed to be an oophorectomy) but did not have ovarian cancer (45) (46;47). In the base case, 0.87% of female attendees received an unnecessary operation for ovarian cancer. As the generic cancer screen will have a different false positive rate to the UKCTOCs trial a scenario analysis in which no patient receives false positive treatment will also be considered.

For colorectal cancer colonoscopy is assumed to be 100% specific so no treatment of false positives will occur. For lung cancer diagnosis, a CT scan is assumed to be 100% specific so i.e. no treatment of false positives could occur. Clinical advice on whether treatment of false positives may be possible for bladder or breast cancer was not available so an assumption that no unnecessary treatment would occur was made. In conclusion, it was assumed that treatment of persons who receive a false positive result in the generic cancer screening programme is possible for ovarian cancer only.

4.5.5 Stage shift due to screening

Stage shift was defined as the percentage of patients who in the presence of screening do not present with an early stage cancer (stage I or II) but would have been detected with a late stage (stage III or IV) cancer without screening.

The formulae for stage shift, S, was:

$S = 1 - (\frac{P_{screening}}{P_{no\ screening}})$, where P = the proportion of cancers that were detected at stage III or IV.

Stage shift due to the generic cancer screen was not available, so data on stage shift from other UK screening programmes was considered. The stage shift for the NHS breast cancer screening programme was obtained from a cost-effectiveness study on the extending the age range of women eligible to routinely participate in the NHS breast screening programme (20;48). The stage shift observed in the trial data underlying the cost-effectiveness study was between prognostic groups and not stage at diagnosis groups, this is a limitation of using this data for a stage shift in the economic model. The observed stage shift was that 21% of patients who would have been diagnosed with late stage cancer in the absence of screening were diagnosed with early stage cancer in the presence of screening. After adjusting for the uptake of the screening programme, the observed stage shift was 31% in those patients who attended the screening programme.

Data was obtained on the stage distribution of cancers observed in the NHS bowel screening programme from the evaluation of the screening pilot (49). Data on the stage distribution prior to the UK bowel screening programme was obtained from the incidence data available from Oxford, Northern and Yorkshire and Eastern regions in 2004-6 used by Whyte et al (50).The calculated stage shift from this data was 57%. This may be an overestimate of the stage shift as the screening pilot only includes those cancers at screening and not interval cancers.

The base case stage shift used in the economic modelling was assumed to be 31% in the base case. This value was the stage shift observed for breast cancer, adjusted for the stage shift in the NHS breast cancer screening programme. A range of other values were considered in scenario analyses.

Table 4.5b: The stage shift associated with UK cancer screening

	Screened population		Unscreened population	
Stage	Number	Percentage	Number	Percentage
Bowel cancer				
Stage A/B	345	72.3%	11991	35.8%
Stage C/D	132	27.7%	21519	64.2%
Stage Shift		56.9%		
Breast cancer				
DCIS/Excellent/Good	184	39.2%	183	23.5%
Poor/Moderate	285	60.8%	595	76.5%
Stage Shift		21%		

Sources; Evaluation of the UK Colorectal Cancer Screening Pilot Final Report (49),Whyte *et al*. (50) and Madan *et al*.(51)

4.6 Cancer incidence and survival data

The main benefit of the proposed generic screening programme is improved survival and increased QALYs as a result of earlier diagnosis. Hence data on cancer incidence and survival by stage at diagnosis for each of the five cancer types included in the model scope was required.

The international cancer benchmarking partnership (ICBP) has published a series of papers comparing international differences in survival between countries in breast, colorectal, lung and ovarian cancers. The UK is one of the countries included in these comparisons.

In addition to the ICBP data the following sources were searched for data on cancer incidence and survival by age and stage: National Lung Cancer Audit, the lead Knowledge and Intelligence Team for each cancer, ICBP, Cancer Research UK, references mentioned in the NICE bladder cancer draft guidelines (52). A summary of incidence and survival information is presented in Tables 4.6a and b respectively.

Table 4.6a: Summary of cancer incidence data available

Cancer Type	**Incidence data available**	**Sources and references**
Bladder	by stage at diagnosis: in England in 2012	National Collaborating Centre for Cancer (NCC-C) draft clinical guidelines (31)
	by age at diagnosis: in England in 2012	National Collaborating Centre for Cancer (NCC-C) draft clinical guidelines (31)
	no data by age and stage obtained	
Breast	by stage at diagnosis : in England, Wales and Northern Ireland in 2000-7 In the West Midlands 1980-2002	Walters *et al.* (53) Woods *et al*. (54)
	by age at diagnosis: in UK in 2009-11 In the West Midlands 1980-2002	Cancer Research UK Woods *et al.* (54)
	no data by age and stage obtained	
Colorectal	by age at diagnosis: in England and Northern Ireland in 2000-7	Maringe *et al*. (38)
	by stage at diagnosis: in England and Wales in 2012	Cancer Research UK
	by age and stage at diagnosis: in England	Whyte *et al*. (10)
Lung	by stage at diagnosis: in England and Northern Ireland in 2004-7	Walters *et al. (55)*
	by age at diagnosis: in UK in 2013	National Lung Cancer Audit (LUCADA) (56)
	no data by age and stage obtained	
Ovarian	by stage at diagnosis in England and Northern Ireland in 2004-7	Maringe *et al*. (57)
	by age at diagnosis: in England in 2009 in UK in 2009-11	Trent Cancer registry (58) Cancer Research UK
	no data by age and stage obtained	

Table 4.6b: Summary of cancer survival data available

Cancer Type	Survival data available	Sources and references
Bladder	by stage at diagnosis: in England in 2012	National Collaborating Centre for Cancer (NCC-C) draft clinical guidelines (31)
	by age at diagnosis: in England in 2012	National Collaborating Centre for Cancer (NCC-C) draft clinical guidelines (31)
	No data was obtained by age and stage at diagnosis	
Breast	By stage and age at diagnosis: in England, Wales and Northern Ireland in 2000-7	Walters *et al.* (53)
	By stage at diagnosis in Former Anglia Cancer Network in 2006-10	Cancer Research UK (52)
Colorectal	By stage and age at diagnosis: in England and Northern Ireland in 2000-7	Maringe *et al*. (38)
Lung	By stage and age at diagnosis: in England and Northern Ireland in 2004-7	Walters *et al. (55)*
Ovarian	By stage and age at diagnosis: in England and Northern Ireland in 2004-7	Maringe *et al*. (57)
	By stage at diagnosis in Former Anglia Cancer Network in 2006-10	Cancer Research UK (52)

4.7 Health related quality of life data

4.7.1 Cancer HRQoL data

A literature search was conducted (in November 2014) using the ScHARR health utilities database for each of the five cancer types within the scope. These searches identified 28 studies. Studies were excluded if 1) there were no British patients, 2) it did not consider all patients with a stage at diagnosis, 3) the treatments under consideration were not available in the UK, 4) it was not specific to a cancer type or 5) the HRQoL was higher than the utility used for people without cancer. Full details are provided in the Appendix. After exclusions there was one relevant study which was on the utility of advanced lung cancer patients. (59)

Chouaid *et al*. (59) consider the utility of patients with advanced non-small cell lung cancer (Stage IIIb or Stage IV). The study was a cross sectional study of the utility of adult patients with advanced non-small cell lung cancer across nine countries, one of which is the UK. One of the ways in which utility was estimated was using the EQ-5D-3L questionnaire and EQ-5D preference weights on the

preferences of the UK population for different EQ-5D health states (60). A utility value of 0.66 (95% CI 0.62-0.69) was reported.

In addition to cancer specific studies, generic HRQoL values for patients with and without cancer are available from a study by Ara and Brazier (61). Ara and Brazier pool the data from four consecutive health surveys for England. These surveys contain information on whether an individual has one of several health conditions, including cancer, and their HRQoL measured using the EQ-5D questionnaire. When completing an EQ-5D questionnaire patients assign themselves to one health state. These health states are valued using a study on the preferences of the UK population for different EQ-5D health states (60). A HRQoL of 0.697 (95% CI 0.657-0.736) for persons with cancer and 0.798 (95% CI 0.755-0.839) for persons without cancer was reported.

A brief search for systematic reviews of HRQoL data also found one additional study, a meta-analysis for lung cancer patients HRQoL. (62) The systematic review included any article which: had a previously unpublished HRQoL for lung cancer, reported the elicitation technique and noted who had provided the HRQoL value. A hierarchal linear model was used to estimate the HRQOL for patients with different types of lung cancer. Using the results of the hierarchal linear model, the HRQoL for lung cancer patients with the patient as a respondent, an EQ-5D valuation of health states, and death to perfect health as bounds to the scale was calculated. The HRQoLs obtained from Sturza (62) are given in Table 4.7. No country specific criteria were applied to the study by Sturza (62).

Table 4.7: The health state utility values of lung cancer patients

Stage	Small cell lung cancer	Non-small cell lung cancer
Non metastatic	0.494	0.716
Mixed/not specified	0.443	0.665
Metastatic	0.244	0.466

Source; Sturza (62)

The HRQoLs from Sturza (62) will be used for patients with lung cancer and the values from Ara and Brazier will be used for all other cancers. The values from Chouaid *et al*. (59) will not be used, as they would not be consistent with the utility values used for other patients with lung cancer.

4.7.2 Psychological impact of false positive screening test results

It is hypothesised that a false positive screening test result may cause harm to an individual's HRQoL through increased anxiety. A brief search was conducted using Google scholar to obtain the psychological and clinical literature on the impact of a false positive screening test result. Several economic models of screening were assessed to determine what approach, if any, had been taken to address the psychological impact of a false positive screening test result.

These searches identified very little literature supporting an impact of false positives on QALYs. In one potentially relevant study by Collins et al. (63) conducted a meta-analysis of 12 randomized controlled trials of screening interventions, 6 of trials included in the meta-analysis were trials of cancer screening programmes. The results of this study suggest that there is no detectable impact of

false positive screening test results on a patient's anxiety, depression and mental quality of life after 4 weeks. Therefore, it was assumed that any impact of false positive screening test results on HRQOL values lasted for less than four weeks.

Madan et al. (20) explore the effect of the psychological impact of a false positive screening test result on the cost-effectiveness of an extension of the NHS breast screening programme. QALY decrements of 0, 0.01, 0.02, 0.03 and 0.04 (0, 3.5, 7, 10.5 and 14 days in a year spent in a health state equivalent to death) per false positive were applied.

Based on the Madan et al study a range of 0-0.04 will be considered in the model to reflect 'no QALY decrement due to false positive' and 'the maximum plausible QALY decrement (0.04 = HRQOL of 0.5 for 4 weeks)'. In the base case no utility decrement was assumed.

4.8 Summary of data availability and quality

Proposed screening pathways
The proposed screening pathways were elicited from the ECDC. There was uncertainty in several areas of the pathways. For example, who would take the blood sample and whether or not it would be taken as part of the health checks. In addition there was uncertainty and discussion around the follow-up pathways for unclear results. Establishing these is important as they are likely to be a key determinant of costs.

Cost of treating cancer by stage
An extensive literature search was undertaken to obtain treatment and diagnosis costs for the five cancers in the scope by stage at diagnosis. Published literature in this area is very limited indeed. One unpublished study by Incisive health contained useful estimates but the study may not be of high quality. Clinical opinion suggested that some of the assumptions and values used in the Incisive study may not be reliable. No data was available for bladder cancer treatment. Therefore, it was assumed that the cost of treating and diagnosing bladder cancer was the same as the cost of treating and diagnosing colorectal cancer.

Cost of generic cancer screening test and follow-up
As the generic cancer screening test is still in development, costs were not available. Costs for several aspects of the screening test were taken from other NHS screening programs. Costs of follow up were estimated using NHS reference costs for procedures and consultations. There was considerable uncertainty surrounding the costs of the biomarkers tested for as part of the screen.

Screening data
Data on uptake rates, completions rates, and rates of over diagnosis were estimated based on other NHS screening programmes. There was no data available on the test characteristics of the proposed generic cancer screen as it is still in development. A range of acceptable values for sensitivity and specificity was available from the Delphi exercise so this could be used to inform scenario analyses. It is anticipated that further data will be available to inform the full model in later work packages.

HRQoL

Literature searches were undertaken for HRQoL values relating to the five cancer types within the model scope. Limited cancer type specific values were identified. However, general cancer utility values were available which were suitable for use in the economic model. One study which provided a HRQoL decrement value for a false positive screening test result was identified.

Cancer incidence and survival data

Data on cancer incidence and survival by stage at diagnosis was available for each of the five cancer types. Incidence data by age and stage was available for colorectal cancer only. Incidence data by age and incidence data by stage was available separately for each of the other four cancer types. The proportion of cancer cases which were unstaged in the data sets available ranged from 25.3% (breast cancer to 65% (bladder cancer). Survival data was available by stage at 1 year for all 5 cancer types, at 3 years for breast and colorectal cancer and at 5 years for bladder cancer. Generally the cancer incidence and survival data was satisfactory for the economic modelling.

5 Draft economic model: methods

5.1 Modelling assumptions

Cohort modelled

The cohort modelled was the 2015 population of England and Wales who would be eligible for screening in a generic cancer screening programme. The two comparisons of interest are:

- Generic cancer screening programme **in addition to** the type specific cancer screening programmes (breast, bowel and cervical).
- Generic cancer screening programme **as a replacement to** the type specific cancer screening programmes (breast, bowel and cervical).

This analysis considers the first comparison in which the new generic cancer screening programme is additional.

The model represents the lifetime impact of one cohort being screened once. However, a screening programme may reduce the incidence of cancer in later screening rounds, as some of the cancers have been detected earlier. Also, any interaction between the generic cancer screening programme and the type specific screening programmes in terms of reducing future incidence of cancer is not included in the model. As there is no current example of two concurrent screening programmes, estimating these effects would be exceptionally difficult. The approach taken of excluding these effects and using incidence and survival data from after the introduction of the NHS breast and bowel cancer screening programmes provides the best available estimate of the benefits of a new screening programme without clinical data.

Cancer types

The modelling is restricted to five cancer types for reasons of feasibility. The included types consist of 45.1% of the incidence of all cancers in the UK.(64) This means that the benefits of screening on QALYs (due to earlier detection) will be underestimated; hence the incremental cost-effectiveness ratio (ICER) evaluated here provides an upper bound on the ICER for all cancer types.

Precancerous conditions

The intention is that the generic cancer screening test is designed to detect cancer and not precancerous conditions. Hence the economic modelling excludes precancerous conditions. If following development of the generic cancer screening test it is found that precancerous conditions are detected then this will have significant impacts on the health economics and a more complex model will be required to capture these effects.

Treating precancerous conditions may result in a QALY gain where cases of cancer are prevented. Treating precancerous conditions can also cause a QALY decrement where cancer would never have presented symptomatically within a person's lifetime as unnecessary treatment can be harmful to HRQoL. These two effects will influence the ICER in different ways; if treating precancerous conditions prevents cases of cancer then the ICER will be an upper bound. If treating precancerous

conditions harms patients, then the ICER will be a lower bound. Hence the impact may well vary between cancer types and is difficult to predict.

5.2 Predicted outcomes of screening

A common approach to screening modelling is to develop a disease natural history model which estimates the number of persons with precancerous disease and cancer at any given time point. This can then be used in combination with data on the sensitivity and specificity of a cancer screening test to generate predicted screening outcomes. Screening outcomes, such as incidence by stage, can be used to determine predicted outcomes in terms of life years gained and QALYs.

As the draft economic model is being constructed ahead of any estimates of screening test sensitivity and specificity being available a different approach to modelling predicted screening outcomes was taken. A parameter, the stage shift of cancer incidence, was used to describe the impact of the cancer screen on the stage distribution of cancer incidence. In addition to this parameters for positivity rates and false positivity were included.

The definition of early stage is not always precisely known and varies by cancer type. References were identified which suggest that for ovarian cancer stages 1 and 2 are early (45) and for SCLC early is TNM stages I and II (55). Definitions for colon and bladder cancer classify into early/intermediate/late with stage 1 being early. (38) (31) No information was found for NSCLC, rectal or breast cancer.

For this analysis it was assumed that cancer diagnosed in stage 3 or 4 were late stage and those diagnosed in stage 1 or 2 are referred to as early stage.(45;47) For persons attending screening the stage shift is defined to be the proportion of late stage incidence which is picked up at an early stage as a result of the screen.

5.3 Estimating the incidence of cancer

The future incidence of each cancer type by age was estimated using ONS population projections and the age specific incidence rates for each cancer type (65). Details on the sources for the age specific incidence rates are given in the Appendix. Data on the total incidence of cancer in 2012 was taken from the ONS and the Welsh cancer intelligence and surveillance unit (66;67). This data was compared to the modelled incidence in a 2012 cohort.

To test the modelling approach the model predicted incidence and observed incidence was compared for the incidence of cancer in the 2012 population in England and Wales, see Table 5.3. The age-specific incidence data used varies in the countries and years included as shown in the Appendix. These differences are expected to be responsible for the differences in observed and modelled incidence seen.

Table 5.3: Comparison of modelled and observed incidence

	Cancer type				
	Bladder	Breast	Colorectal	Lung	Ovarian
Observed incidence in England and Wales in 2012	9,660	44,718	36,497	38,240	6,225
Model predicted incidence in England and Wales for 2012 population	8,990	43,628	38,026	36,087	6,088
Percentage difference	-6.9%	-2.4%	4.2%	-5.6%	-2.2%
Model predicted incidence in England and Wales for 2015 population	9,458	45,047	39,968	38,137	6,315

5.4 Estimating life expectancy and mortality with cancer

For the economic model to represent the benefits of a stage shift the life expectancy for cancer patients by stage is required. The life expectancy of cancer patients was estimated by calculating their probability of death in each year since diagnosis, calculating the cumulative survival of patients (applying a half-cycle correction) and adding the average life years gained. To calculate a patient's probability of death, two pieces of information were required in each year after a patient was diagnosed: 1) Cancer survival and 2) Other cause survival. All cause survival was calculated by multiplying the other cause survival with the fitted cancer survival models.

1) Cancer survival

A fractional survival model assumes that the population is split into two fractions: those who will die from their cancer (which we will refer to as terminal cancer patients) and those who will not (which we will refer to as non-terminal cancer patients). Fractional survival models were used to model stage specific cancer survival as this fits with the observation that some patients (particularly those diagnoses at an early stage) may have non-terminal cancer. The first model parameter is the proportion of patients with non-terminal cancer, which we will refer to as γ. For the proportion of patients with terminal cancer, (1- γ), an exponential model was fitted (as there were insufficient data points to allow statistical testing of other curve types) parameterised by λ, the constant risk of death. The formula for the survival model used is:

$$S(t) = \gamma + [1 - \gamma] * exp(- \lambda * t)$$

Firstly we estimated the proportion of patients who have non-terminal cancer for each stage, γ. Long term survival information was not available by stage at diagnosis; therefore γ could not be obtained from observed data. An estimate for γ was calculated using long term all stage survival data which was available for up to 10 or 20 years.(52) The parameter γ was estimated as follows: if the most recent stage specific survival data was from year T, then for stage A γ =(T year stage A specific survival)*(10/20 year all stage survival/T year all stage survival). For example, for breast cancer stage 1: γ = (5 year stage 1 survival)*(20 year all stage survival/5 year all stage survival) = 74.4%. The precise value for γ was then calibrated (using the Microsoft Excel® solver add-in) so that the predicted and observed mortality matched. When comparing predicted to observed mortality, the observed mortality was adjusted for the modelled incidence rates. All calibrations were conducted

for the year 2012 which had the most recent observed incidence data for England and Wales available.

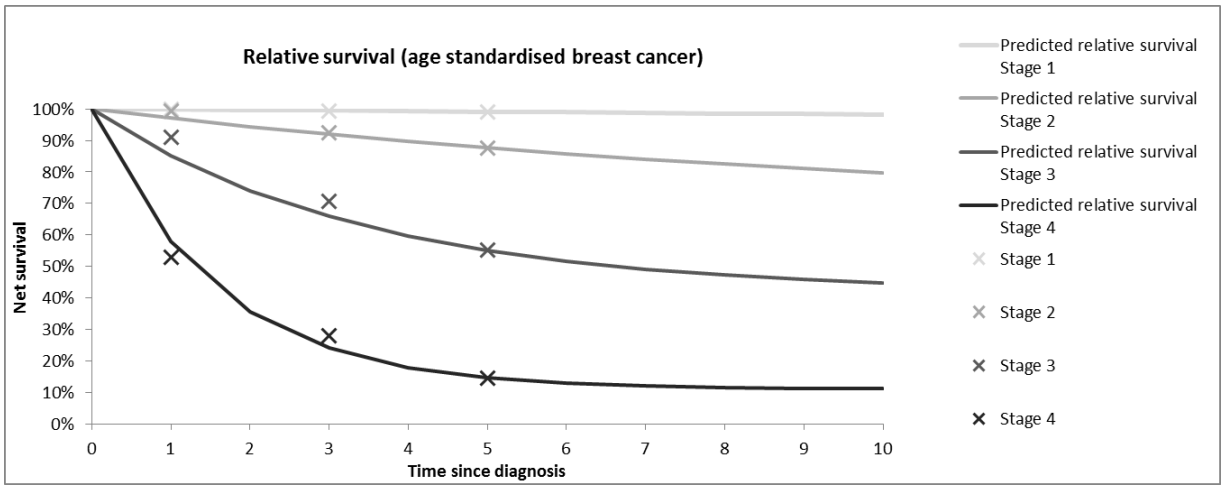
The calibration used the assumption that the ratio (long term survival: short term survival) was the same for all stages of cancer, but could vary between cancer types. Scenario analyses were undertaken to test the impact of this assumption. The rationale behind these analyses was the belief that patients with an earlier stage of cancer were more likely to have non-terminal cancer than patients with a later stage of cancer. In the first scenario analysis, γ was increased by 10% for stage 1 patients and decreased by 10% for stage 4 patients. In the second scenario analysis γ was: increased by 10% for stage 1 patients, increased by 5% for stage 2 patients, decreased by 5% for stage 3 patients and decreased by 10% for stage 4 patients. The relative survival of Stage 2 patients is generally lower than Stage 1 patients and the relative survival of Stage 3 patients generally higher than Stage 4 patients. Therefore it was expected that the impact on γ would be smaller in Stage 2 and 3 patients than Stage 1 and 4 patients respectively. As can be seen in the formula below, by changing γ the constant risk of death changes as a different proportion of patients have a terminal cancer.

For the fraction with terminal cancer, (1 - γ), the formula for the constant risk of death, λ, for the exponential distribution is as follows:

$\lambda = \left(-\frac{1}{T}\right) * \ln\left(\frac{S(T)-\gamma}{(1-\gamma)}\right)$, where T = time at which the last stage specific survival data is available.

The fitted survival curve for breast cancer is shown in Figure 5.4. The modelled survival curves for the other cancer types are provided in the Appendix. A good fit was observed for all cancer types except bladder cancer. For bladder cancer modelled survival was better than observed survival but it is suspected that this is because survival may have improved between the date of the survival data (2006-2010) and the date of the mortality data. The method used ensures a perfect fit to the most recent mortality data (2012) for all cancer types.

Figure 5.4: The fitted survival curve for breast cancer by stage at diagnosis



2) Other cause survival

The probability that a patient would die from any cause other than their cancer was calculated by taking the office for national statistics (ONS) life tables and subtracting the average proportion of mortality associated with each cancer type from the ONS mortality statistics in 2011- 2013 (to match the all cause death data used) (68-70). The probability that a patient would die from any cause other than their cancer varies by age, so the life expectancy of cancer patients was calculated for patients with different ages at diagnosis.

To obtain the mortality for each type of cancer, it was necessary to use the ICD-10 code associated with each cancer type: (Bladder C67, Breast C50, Colon C18, Rectal C19-C20& C21.8, Lung C34, and Ovarian C56-57). There were no separate ICD – 10 codes for small cell and non-small cell lung cancer. Therefore all lung cancer deaths were removed from the all cause death in the ONS life tables for both types of lung cancer. This approach of removing all lung cancer related deaths, was previously used in a cost-effectiveness study on the early detection of non-small cell lung cancer(71).

5.4.1 Predictions of cancer life expectancy and mortality

The incidence and survival models were used to estimate the life expectancy and number of deaths of patients with cancer by age and stage at diagnosis for each cancer type.

From the survival data, life years gained were calculated assuming that the patients who died in any given year died at 6 months (half-cycle correction). The life years gained were summed across all years after the patient was diagnosed with cancer. An incidence weighted average over age was taken to calculate the life expectancy of patients with cancer by stage, see Tables 5.4a and 5.4b.

Table 5.4a: Model-predicted life expectancy by cancer type (2015)

Life expectancy (years)						
	Bladder	Breast	Colorectal	NSCLC	SCLC	Ovarian
Stage 1/Duke's stage A	10.3	23.8	14.4	5.2	4.2	18.7
Stage 2/Duke's stage B	7.0	19.2	12.8	4.1	4.2	9.5
Stage 3/ Duke's stage C	6.3	12.3	9.6	2.5	2.9	4.8
Stage 4/stage D	4.3	4.6	3.0	1.4	1.4	1.6
Early stage	8.8	21.3	13.2	4.8	4.2	17.3
Late stage	4.6	9.5	7.4	1.8	1.9	3.6
Difference between early and late stage	4.2	11.9	5.8	3.0	2.3	13.7

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

Table 5.4b: Model-predicted life expectancy by cancer type (2015, discounted)

Discounted life expectancy (years)						
	Bladder	Breast	Colorectal	NSCLC	SCLC	Ovarian
Stage 1/Duke's stage A	7.8	14.2	10.0	4.1	3.3	12.3
Stage 2/Duke's stage B	5.3	11.6	8.9	3.2	3.2	6.5
Stage 3/ Duke's stage C	4.8	7.2	6.7	2.0	2.3	3.4
Stage 4/stage D	3.2	2.1	2.0	1.0	1.2	1.4
Early stage	6.6	12.9	9.2	3.8	3.3	11.4
Late stage	3.5	5.3	5.1	1.5	1.5	2.7
Difference between early and late stage	3.1	7.5	4.1	2.3	1.7	8.7

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

Table 5.4c: Model-predicted life expectancy by cancer type: scenario analyses testing alternate modelling assumptions (2015)

		Base Case	Scenario 1: γ increased by 10% for stage 1 patients and decreased by 10% for stage 4 patients	Scenario 2: γ +10% for stage 1 patients, +5% for stage 2 patients, -5% for stage 3 patients and -10% for stage 4 patients
Cancer type	Cancer Stage	Undiscounted Life Expectancy (years)		
Bladder	Early	8.8	9.0	9.1
	Late	4.6	4.3	4.3
	Difference	4.2	4.7	4.8
Breast	Early	21.4	21.4	21.5
	Late	9.4	9.4	9.2
	Difference	11.9	11.9	12.3
Colorectal	Early	13.2	13.2	13.6
	Late	7.4	7.4	7.2
	Difference	5.8	5.8	6.4
NSCLC	Early	4.8	5.0	5.0
	Late	1.8	1.7	1.7
	Difference	3.0	3.2	3.3
SCLC	Early	4.2	4.4	4.4
	Late	1.8	1.8	1.8
	Difference	2.3	2.5	2.6
Ovarian	Early	17.3	18.1	18.1
	Late	3.6	3.6	3.6
	Difference	13.7	14.5	14.5

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; γ, proportion of patients who have non-terminal cancer for each stage

The scenario analyses testing different survival modelling assumptions resulted in a slightly greater difference between life expectancy for early and late stage cancers than in the base case. The effect

of these scenarios on the cost-effectiveness of the generic cancer screening programme will be shown in the results.

The number of deaths due to cancer was calculated as follows. The proportion of deaths attributable to other causes was calculated for each year after the patient was diagnosed with cancer. All deaths that were not attributable to other causes were attributable to cancer. The number of deaths is not calculated as simply the difference between the relative survival and cumulative other cause survival curves. Taking this approach would wrongly count most of those patients whose cause of death was due to cancer as having died from other causes.

Table 5.4d: Model-predicted number of deaths attributable to each cancer type

	Bladder	Breast	Colorectal	Lung	Ovarian
Observed mortality in England and Wales in 2012	4646	10311	14191	30257	3769
Expected mortality (The observed mortality in England and Wales in 2012 adjusted for the modelled incidence rates)	4324	10060	14786	30175	3686
Model predictions of deaths in 2015	4548	10371	15536	32520	3824

Source, Office for National Statistics (69)

Table 5.4d shows that the model predicts a higher number of cancer deaths in 2015 than 2012. It is expected these differences are due to differences in population size and population age distributions (2012 (56.6 million) and 2015 (58.1 million)). The model predictions in the 2012 English and Welsh exactly match the expected mortality in 2012.

5.5 Model structure

As no data on the test characteristics of the generic cancer screen was available a simple approach to modelling was taken. It was assumed that the screening intervention would result in a proportion of individuals who presented with a late stage cancer (stage III or IV) at a given age being stage shifted to having an early stage cancer (stage I or II). This approach only enabled the evaluation of impacts (costs and QALYs) for one screening round. This approach was appropriate given data available however it was associated with the following limitations:

- The model scope only includes five cancer types, rather than all cancer types
- Any effects of overdiagnosis are excluded from the economic model
- Any survival improvements within stages, due to an individual's cancer been detected in the screening programme is not included
- Precancerous conditions are excluded from the model
- Multiple screening rounds cannot be included in the current model structure

- Scenarios around the use of the new screening programme as a replacement to rather than an addition to current screening programmes cannot be conducted
- The individual's disease history remains unknown. Therefore the health benefits of repeat screening for individuals with an unclear result cannot be included in the model.
- Much of the data for the generic cancer screening programme comes from the existing type specific screening programmes.

Due to the limitations and exclusions discussed ICER values presented are not considered robust or reliable. However the analyses do identify key parameters which are likely to influential on the cost-effectiveness of a new generic cancer screening programme

5.6 Analyses undertaken

The model was run for the population of England and Wales in 2015 undertaking one round of screening as an addition to the type specific screening programmes. The total costs associated with the screening programme were estimated including: cost of generic cancer screen; cost of follow-up; and cancer treatment costs. The totals QALYs gained were estimated which incorporated: QALY gains due to earlier diagnosis (as a result of better survival) and QALY decrements due to false positives. The following model outputs were produced: cancer deaths prevented, life years saved, QALY gain, change in cancer treatment costs, cost of screening and follow up, total costs and ICER. The first base case analysis was conducted where parameters mostly took average from the existing screening programmes (details in Table 5.6a). A second base case analysis (base case 2) was conducted where parameters took favourable values from the existing screening programme data (details in Table 5.6a). The parameters used in all model runs are detailed in Table 5.6a. If there is no parameter value in the base case 2 column, then it took the same value in both base case 1 and base case 2. In addition to the base case deterministic analysis several scenario analyses were run to explore the impact of key modelling assumptions. These analyses are detailed below.

Table 5.6a: The model parameters used in in the base cases and all scenario analyses

Screening Parameters				
	Base case 1	***Base case 2***	***Scenario analysis values***	**Source**
Screening starting age	40	*	45, 50	ECDC opinion
Screening finishing age	75	*	70, 80	ECDC opinion
Screening interval	4 years	*	1 year, 3 years, 5 years, 10 years	ECDC opinion
Uptake	55%	73.4%	45%, 73.4%	NHS bowel screening programme, Other NHS screening programmes and ECDC opinion
Positivity rate	2%	*	1%, 4%	NHS bowel screening programme, exploratory value, Other NHS screening programmes
False positive rate	1.6%	1.5%	1.5%, 1.8%, 0%	NHS breast cancer screening programme, exploratory value, NHS bowel screening programme.
Unclear rate	9.7%	*	5%, 20%	NHS cervical screening programme & exploratory values
Screening costs parameters and pathway assumptions				
Stage shift due to screening	31%	56.9%	90%	NHS Breast cancer screening programme, NHS bowel cancer screening programme, exploratory value
Percentage of patients with unclear or false positive results who visit their GP	40%	*	0%	
Cost of a GP appointment	£37			Curtis *et al*.(11)
Cost of invitations per invitee	£2.09	*	*	Whyte *et al*.(10)
Cost of taking the blood sample (including staff time)	£6.17	£4.08	£9.33, £4.08	ECDC opinion & exploratory values
Cost of the biomarkers	£66	£10	£10, £49, £99	ECDC opinion & the cost of individual biomarkers at a large district hospital
Cost of follow up for false positive patients	£3,124	£361	£361	The cost of the most expensive and the cheapest follow up pathway
Cost of cancer nurse specialist support per positive patient	£20	*	£0	NHS breast cancer screening programme
Health state utility values				
HRQoL for non-lung	0.697	*	None	Ara and Brazier(61)

cancer patients				
HRQoL for non-metastatic NSCLC	0.718	*	*	Sturza(62)
HRQoL for metastatic NSCLC	0.466	*	*	
HRQoL for non-metastatic SCLC	0.496	*	*	
HRQoL for metastatic SCLC	0.244	*	*	
HRQoL decrement due to false positives	0	*	-0.02, -0.04	Madan *et al(20)*
Cancer treatment & diagnosis costs				
Stage 1 Bladder cancer	£4,094	*	(+25%, -25%)	Assumed to be equal to colorectal cancer
Stage 2 Bladder cancer	£4,551	*	(+25%, -25%)	
Stage 3 Bladder cancer	£5,836	*	(-25%, +25%)	
Stage 4 Bladder cancer	£5,134	*	(-25%, +25%)	
Stage 1 Breast cancer	£24,974	*	(+25%, -25%)	Assumption, Ward *et al.(24),* Cameron *et al*. (23)
Stage 2 Breast cancer	£24,985	*	(+25%, -25%)	
Stage 3 Breast cancer	£13,001	*	(-25%, +25%)	
Stage 4 Breast cancer	£12,891	*	(-25%, +25%)	
Stage 1 CRC	£4,094	*	(+25%, -25%)	Incisive Health (16), Whyte *et al*.(36)
Stage 2 CRC	£4,551	*	(+25%, -25%)	
Stage 3 CRC	£5,836	*	(-25%, +25%)	
Stage 4 CRC	£5,134	*	(-25%, +25%)	
Stage 1 NSCLC	£9,456	*	(+25%, -25%)	Fleming *et al*.(28)
Stage 2 NSCLC	£16,972	*	(+25%, -25%)	
Stage 3 NSCLC	£21,009	*	(-25%, +25%)	
Stage 4 NSCLC	£13,078	*	(-25%, +25%)	
Stage 1 SCLC	£10,563	*	(+25%, -25%)	Incisive Health(16)
Stage 2 SCLC	£10,563	*	(+25%, -25%)	
Stage 3 SCLC	£6,513	*	(-25%, +25%)	
Stage 4 SCLC	£6,513	*	(-25%, +25%)	
Stage 1 Ovarian cancer	£6,832	*	(+25%, -25%)	Incisive Health (16)
Stage 2 Ovarian cancer	£18,840	*	(+25%, -25%)	
Stage 3 Ovarian cancer	£23,483	*	(-25%, +25%)	
Stage 4 Ovarian cancer	£15,081	*	(-25%, +25%)	
Predicted life years gained (undiscounted)				
Stage 1 bladder cancer	10.3	*	10.8, 10.7	ONS(68-70;72), National Collaborating Centre for Cancer(31), calculation
Stage 2 bladder cancer	7.0	*	7.0, 7.2	
Stage 3 bladder cancer	6.3	*	6.3, 6.1	
Stage 4 bladder cancer	4.3	*	3.9, 4.0	
Stage 1 breast cancer	23.8	*	23.8, 23.8	ONS(68-70;72), Cancer Research UK, calculation
Stage 2 breast cancer	19.2	*	19.2, 19.5	
Stage 3 breast cancer	12.3	*	12.3, 12.0	
Stage 4 breast cancer	4.6	*	4.5, 4.5	
Stage 1 CRC	14.4	*	14.9, 14.9	ONS (68-70;72), Maringe *et al*.(38), calculation
Stage 2 CRC	12.8	*	12.8, 13.1	

Stage 3 CRC	9.6	*	9.6, 9.3	
Stage 4 CRC	3.0	*	2.9, 2.9	
Stage 1 NSCLC	5.2	*	5.4, 5.4	
Stage 2 NSCLC	4.1	*	4.1, 4.2	ONS (68-70;72), Walters *et al*.(55), calculation
Stage 3 NSCLC	2.5	*	2.5, 2.4	
Stage 4 NSCLC	1.4	*	1.3, 1.3	
Stage 1 SCLC	4.2	*	4.5, 4.5	
Stage 2 SCLC	4.2	*	4.2, 4.3	ONS (68-70;72), Walters *et al*.(55), calculation
Stage 3 SCLC	2.9	*	2.9, 2.8	
Stage 4 SCLC	1.4	*	1.3, 1.3	
Stage 1 Ovarian cancer	18.7	*	19.6, 19.6	ONS (68-70;72), Cancer Research UK, calculation
Stage 2 Ovarian cancer	9.5	*	9.5, 9.7	
Stage 3 Ovarian cancer	4.8	*	4.8, 4.7	
Stage 4 Ovarian cancer	1.6	*	1.6, 1.6	

*, Base case 2 uses the same parameter values as base case 1 for these parameters
HRQoL, health related quality of life; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

5.6.1 Scenario analysis: Impact of generic cancer screen on stage distribution

As stated in Section 5.2, stage shift was defined in the model as the proportion of patients who would have been detected as a stage 3 or 4 cancer in the absence of screening but in the presence of screening were detected as having a stage 1 or 2 cancer. In the base case 1, the stage shift associated with breast screening was used (51). As data was also available on the stage shift associated with colorectal cancer screening in the UK, this was used as a scenario analysis(49;50). As the new screening programme may have a different effectiveness than breast or bowel screening in the UK, a scenario analysis was conducted where the stage shift was assumed to be 90%.

5.6.2 Scenario analysis: Modelling life expectancy gains associated with stage shift

Predicted life expectancy gains are dependent on the stage distribution of long term survivors. Two different scenarios were considered and full details are in Section 5.4. In summary, the proportion of long term survivors with stage 1 cancer will increase by 10% from the base case and the proportion of long term survivors with stage 4 cancer will decrease by 10% from the base case in the scenario 1. In scenario 2, the proportion of long term survivors with stage 1 and 4 cancer will be the same as the scenario 1 and the proportion of long term survivors with stage 2 cancer will increase by 5% from the base case and the proportion of long term survivors with stage 3 cancer will decrease by 5% from the base case

5.6.3 Scenario analysis: Screening costs

Three components of the cost of the screening programme were varied in the scenario analyses: the cost of the biomarkers used in the generic cancer screening test, the cost of conducting the generic cancer screening test and the cost of follow up for people with a positive screening test result.

Cost of biomarkers

As stated in Section 4.3, it was assumed that the cost of a single biomarker was £33 and the number of biomarkers in the generic cancer screening programme would be between 1.5 and 3 biomarkers per test. In base case 1, it was assumed that the average cost of the biomarkers was £66 (on average 2 biomarkers per test). Scenario analyses were conducted in which the cost of biomarkers in the generic cancer screening programme were assumed to be £99 and £49 (on average 3 and 1.5 biomarkers per test respectively). Currently the cancer biomarkers reported in Section 4.3 are not used in the UK for a cancer screening programme. Therefore, there is the potential for economies of scale if these biomarkers were to be used in a cancer screening programme. With this in mind a further scenario analysis was conducted where the cost of the biomarkers used in the generic cancer screening programme was assumed to be £10.

Cost of delivering generic cancer screening test

The impact of lowering the cost of the generic cancer screening programme on the ICER was assessed. One way in which this may be possible would be to deliver the generic cancer screening as

part of the NHS health checks. In base case 1 the cost of taking the blood sample for the generic cancer screening programme includes: delivering the sample to laboratory, consumables which will be used when the sample is taken, additional staff time and the cost of vials, needles and labels for the blood sample. In the scenario analyses, only the cost of staff time and the cost of vials, needles and labels for the blood sample will be included in the cost of taking the blood sample. The cost of conducting the generic cancer screening test is £27 per attendee in base case 1, and this will be changed to £4 and £9 per attendee in the scenario analyses.

Cost of screening follow up

The cost of follow up given to a patient with a false positive result was varied from £3,124 in the base case 1 (the most expensive diagnostic pathway) to £361 (the least expensive diagnostic pathway) in the scenario analyses.

A scenario analysis was also conducted where the cost of the biomarkers, the cost of delivering the generic cancer screening programme and the cost of follow up for people with false positive screening results were set to their minimum values (£10, £4 and £361 respectively).

Scenario analyses excluding the cost of additional cancer nurse specialists to support people through the diagnosis pathways, and excluding the cost of self-referrals of false positive results to GPs were also undertaken.

5.6.4 Scenario analysis: HRQoL decrement for false positives

As stated in Section 5.5, scenario analyses were conducted on the QALY decrement due to a person receiving a false positive result. In base case 1 a QALY decrement of -0.02 per false positive was applied; this was varied to 0 and -0.04 in the scenario analyses.

5.6.5 Scenario analysis: Screening age ranges and interval

As the generic cancer screening test is yet to be developed, the ages at which people will be screened and the screening interval are highly uncertain. The age at which the screening programme starts was varied from 40 in base case 1 to 45 and 50 in the scenario analyses. Further scenario analyses were conducted on the age at which screening was stopped was varied from 75 in base case 1 to 70 in the scenario analyses. Finally the interval between screening rounds was varied from every 4 years in base case 1 to every year, every 3 years, every 5 years and every 10 years in the scenario analyses.

5.6.6 Scenario analysis: Unclear results, positivity rate, false positivity rate and uptake

As the generic cancer screening test is yet to be developed, the uptake, unclear, and positivity rates of the programme are uncertain. The unclear results rate was varied from 9.7% in base case 1 to 5% and 20% in the scenario analyses. The positivity rate was varied in a separate analysis from 2% in

base case 1 to 1% and 4% in the scenario analyses. The false positivity will adjust to be just over 80% of the positivity rate based on the NHS breast screening programme (39) Given the positivity rate of 2% in base case 1, the false positive rate was varied from 1.6% in the base case to 0.8% and 1.8% in the scenario analyses. This analysis was conducted by varying the proportion of patients with positive results who were assumed to be truly false positives. The uptake of the generic cancer screening programme was varied from 55% in base case 1 to 45% and 74% in the scenario analyses.

5.6.7 Scenario analysis: The cost of cancer treatment

The cost of treating each cancer stage is highly uncertain. In the future, treating each cancer stage may become more expensive as new cancer drugs become available. However, treating each cancer stage may become cheaper as existing drugs come off patent. The important consideration for cost-effectiveness will be how the cost of treating early stage and late stage cancer changes over time. Therefore two scenario analyses were conducted. In the first scenario analysis, the cost of treating early stage cancer was increased by 25% whilst the cost of treating late stage cancer was reduced by 25%. In the second scenario analysis, early stage cancer been 25% cheaper to treat and late stage cancer been 25% more expensive to treat.

5.6.8 Two-way sensitivity analyses

To understand how the ICER may change when the cost of the biomarkers and the effectiveness of screening were varied, a two way sensitivity analysis was conducted were both of these parameters were varied at the same time.

5.6.9 Validation exercise

Comparison of QALY gains

As a way of validating the model predictions of QALY gains, the ECDC economic model was compared to the ScHARR Bowel cancer screening model (BCSP model). The BCSP model represents up to 8 screening rounds (biennial from 60-74) so it was run for a single screening round (single screen at age 64 for a cohort of size 100,000) to allow comparison with base case 2 from the ECDC economic model. In both models discounting was applied from age 65 at 3.5%.

The BSCP model includes QALY gains as a result of 1) earlier diagnosis of cancer (leading to better survival) and 2) reduced cancer incidence (due to removal of precancerous conditions). The ECDC economic model does not include the impacts on cancer incidence of treatment of precancerous conditions because 1) the generics screening test is not designed to detect pre-cancerous conditions and 2) the simple model structure used does not include a natural history component to allow such impacts to be modelled.

6 Draft economic model: Results

6.1 Model Results (base-case)

The model outputs were intended to be used to inform the development of the generic cancer screening test. Several outcomes are presented which include: cancer deaths prevented, life years saved, QALY gain, change in cancer treatment costs, cost of screening and follow up, total costs and ICER. Model predictions were generated relating to one year of screening although the lifetime benefits associated with earlier stage of diagnosis are included.

Table 6.1a shows that in base case 1; 24.5 million people were predicted to be eligible for screening in 2015. The model predicts that 3.5 million people attend the screening programme resulting in 1,341 cancers being detected at an earlier stage and the prevention of 403 cancer deaths. The model also predicts that 337,490 people required repeat tests due to an unclear test result. The results show that screening leads to more life years accrued by people and the number of cancer cases diagnosed in an early stage increases.

The cost of the screening programme includes the cost of inviting people to be screened and the cost of conducting the screening test. This cost is more than double the follow up costs for those patients who have been screened. The follow up costs include all diagnosis costs, cost of GP appointments for some patients who received a false positive screening test result, the cost of cancer nurse specialists, the cost of unnecessarily treating people with false positive screening test results and the cost of re-inviting and re-screening people with unclear test results. The cost savings from treating cancer patients earlier are much smaller than the cost increases associated with the screening programme. The model predicts a cost saving from earlier treatment of £0.5 million and a cost increase from introducing screening of £447.5 million in 2012/13 prices. The incremental cost-effectiveness ratio (ICER) of this screening programme is around £98,000 per QALY gained.

Table 6.1b shows that in base case 2, 24.5 million people were predicted to be eligible for screening in 2015 and 3.5 million people attended the screening programme. 10,447 cancers were detected by the screening programme with 3,294 of these cancers been detected at an earlier stage preventing 991 cancer deaths. The model predicts that the same number of people require repeat tests in both base case 2 and base case 1. This is as; both base cases use the same parameter value for the unclear rate which determines the number of people who were invited for a repeat screening test.

The cost of conducting screening in base case 2 is approximately double the cost of follow up. However both the cost of conducting screening in base case 2 is less than 1/3 of the cost of conducting screening in base case 1. A similar reduction in the cost of follow up was observed between base case 1 and 2. The cost savings associated with earlier diagnosis are higher than in base case 1, but are still much smaller than the cost increases caused by introducing the generic cancer screening programme. The model predicts a cost saving from earlier treatment of £1.3 million and a cost from introducing screening of £138.5m in 2012/13 prices. The ICER of this screening programme is around £12,000 per QALY gained.

Table 6.1a: The descriptive statistics and cost-effectiveness results for the generic cancer screening programme in base case 1 (Population: England and Wales 2015)

Population			
Population in screening age range	-	24,455,078	
Persons invited to attend screening	-	6,325,952	
Persons completing screening	-	3,479,274	
Unclear results	-	337,490	
Positive results	-	69,585	
False positive results	-	55,933	
True positive results (screen detected cancer cases)	-	13,653	
True positive results (screen detected cancer cases) of 5 included cancer types	-	6,144	
Cancer cases presenting symptomatically of the 5 included cancer types (in screening years)	21,875	15,731	-6,144
Cost of conducting screening			
The cost of inviting people to screening	£0.0m	£13.9m	
The cost of conducting the screening test (excluding biomarker costs)	£0.0m	£23.7m	
The cost of the biomarkers in the screening test	£0.0m	£240.7m	
Cost of screening follow up			
Cost of follow up for true positives	included in diagnositc costs below		
Cost of diagnositic follow up for false postives	£0.0m	£145.0m	
Cost of unnescessary treatment (false positives)	£0.0m	£21.8m	
GP self referals	£0.0m	£0.8m	
Cost of cancer nurse specalist support to the screening programme	£0.0m	£1.4m	
Cancer diagnosis and treatment costs			
Cost of diagnosing cancer (in screening years)	£30.1m	£30.1m	£0.0m
Cancer treatment costs (in screening years)	£296.5m	£295.9m	-£0.5m
Clinical benefits			
Cancer deaths (in screening years)	10,493	10,090	-403
Cancer cases diagnosed in an early stage (in screening years)	74,552	75,893	1,341
Life years gained (in screening years)	303,371	312,804	9,433
Quality adjusted life years (QALYs)			
QALY decrement due to false positives	0	0	0
QALYs accured by persons diagnosed with one of the 5 included cancer types (in screening years)	132,894	137,444	4,550
Summary			
Total cost of conducting screening	£0.0m	£278.4m	£278.4m
Total cost of follow up	£0.0m	£169.1m	£169.1m
Cancer diagnosis and treatment costs	£326.6m	£326.0m	-£0.5m
TOTAL COST	£326.6m	£773.5m	£447.0m
TOTAL QALYs	132,894	137,444	4,550
Incremental cost-effectiveness ratio (ICER) (£/QALY)			£98,246

Table 6.1b: The descriptive statistics and cost-effectiveness results for the generic cancer screening programme in base case 2 (Population: England and Wales 2015)

	No Screening	Screening	Incremental
Population			
Population in screening age range	-	24,455,078	
Persons invited to attend screening	-	6,325,952	
Persons completing screening	-	4,643,249	
Unclear results	-	450,395	
Positive results	-	92,865	
False positive results	-	69,649	
True positive results (screen detected cancer cases)	-	23,216	
True positive results (screen detected cancer cases) of 5 included cancer types	-	10,447	
Cancer cases presenting symptomatically of the 5 included cancer types (in screening years)	21,875	11,428	-10,447
Cost of conducting screening			
The cost of inviting people to screening	£0.0m	£14.2m	
The cost of conducting the screening test (excluding biomarker costs)	£0.0m	£21.7m	
The cost of the biomarkers in the screening test	£0.0m	£49.7m	
Cost of screening follow up			
Cost of follow up for true positives	included in diagnositc costs below		
Cost of diagnositic follow up for false postives	£0.0m	£20.9m	
Cost of unnescessary treatment (false positives)	£0.0m	£29.1m	
GP self referals	£0.0m	£1.0m	
Cost of cancer nurse specalist support to the screening programme	£0.0m	£1.9m	
Cancer diagnosis and treatment costs			
Cost of diagnosing cancer (in screening years)	£30.1m	£30.2m	£0.1m
Cancer treatment costs (in screening years)	£296.5m	£295.1m	-£1.3m
Clinical benefits			
Cancer deaths (in screening years)	10,493	9,502	-991
Cancer cases diagnosed in an early stage (in screening years)	74,552	77,846	3,294
Life years gained (in screening years)	303,371	326,551	23,181
Quality adjusted life years (QALYs)			
QALY decrement due to false positives	0	0	0
QALYs accured by persons diagnosed with one of the 5 included cancer types (in screening years)	132,894	144,074	11,180
Summary			
Total cost of conducting screening	£0.0m	£85.6m	£85.6m
Total cost of follow up	£0.0m	£52.9m	£52.9m
Cancer diagnosis and treatment costs	£326.6m	£325.3m	-£1.3m
TOTAL COST	£326.6m	£463.8m	£137.3m
TOTAL QALYs	132,894	144,074	11,180
Incremental cost-effectiveness ratio (ICER) (£/QALY)			£12,277

6.2 Scenario analyses

A series of scenario analyses are presented to demonstrate the impact of model parameters on the cost-effectiveness of the screening programme, see Tables 6.2a and 6.2b. Several outcomes are presented which include: cancer deaths prevented, life years saved, QALY gain, change in cancer treatment costs, cost of screening and follow up, total costs and ICER.

Table 6.2a: Scenario analysis results

	Cost of screening and follow up	Cancer treatment costs	Total costs	Total QALYs gained	ICER (£/QALY)
Scenario analyses					
Base Case 1	£447.5m	-£0.5m	£447.0m	4,550	£98,246
Scenario analyses: The stage shift associated with screening					
Base case 1: the stage shift associated with screening = 31%	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The stage shift associated with screening = 57%	£447.5m	-£0.9m	£446.6m	8,377	£53,304
The stage shift associated with screening = 90%	£447.5m	-£1.5m	£446.0m	13,259	£33,638
Scenario analyses: Survival modelling					
Base case 1: The base case survival models are used	£447.5m	-£0.5m	£447.0m	4,550	£98,246
Survival model scenario 1	£447.5m	-£0.5m	£447.0m	4,716	£94,782
Survival model scenario 2	£447.5m	-£0.5m	£447.0m	4,864	£91,888
Scenario analyses: The cost of generic cancer screening test					
Base case 1: cost = £66	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The cost of the biomarkers in the generic cancer screening test = £10	£243.4m	-£0.5m	£242.9m	4,550	£53,394
The cost of the biomarkers in the generic cancer screening test = £49	£387.3m	-£0.5m	£386.8m	4,550	£85,019
The cost of the biomarkers in the generic cancer screening test = £99	£567.8m	-£0.5m	£567.3m	4,550	£124,699
Scenario analyses: The cost of delivering the generic cancer screening					
Base case 1: cost = £6	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The cost of delivering the generic cancer screening programme = £4	£439.5m	-£0.5m	£439.0m	4,550	£96,482
The cost of delivering the generic cancer screening programme = £9	£459.7m	-£0.5m	£459.2m	4,550	£100,926
Scenario analyses: The cost of following up false positives					
Base case 1: cost = £3,124	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The cost of follow up for false positives is £361	£319.2m	-£0.5m	£318.7m	4,550	£70,056
Scenario analysis: No cancer nurse specalist support					
Base case 1: cost of support = £1.4m	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The cost of cancer nurse specalists and GPs are £0	£445.2m	-£0.5m	£444.7m	4,550	£97,751
Scenario analysis: Multiple costs are changed					
Base case 1	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The cost of follow up for patients with false positive test results = £361, the cost of delivering the generic cancer screening programme = £4 the cost of the biomarkers = £10 no cancer nurse specalist support or GP self-referals	£104.9m	-£0.5m	£104.4m	4,550	£22,946
Scenario analyses: HRQoL decrement due to false positive screening results					
Base case 1: HRQoL decrement = 0	£447.5m	-£0.5m	£447.0m	4,550	£98,246
HRQoL decrement due to false positive results is -0.02	£447.5m	-£0.5m	£447.0m	3,431	£130,278
The HRQoL decrement due to patients receiving false positive results = -0.04	£447.5m	-£0.5m	£447.0m	2,404	£185,911
Scenario analyses: Screening age range and interval					
Base case 1: age 40-75, interval = 4 years	£447.5m	-£0.5m	£447.0m	4,550	£98,246
Age range is 45-75 and interval = 4years	£378.8m	-£0.6m	£378.3m	4,376	£86,433
Age range is 50-75 and interval = 4 years	£315.2m	-£0.9m	£314.3m	4,254	£73,891
Age range is 40-70 and interval = 4 years	£412.2m	-£0.1m	£412.1m	3,823	£107,810
Age range is 40 - 75 and interval = 1 year	£1,730.1m	-£2.7m	£1,727.4m	18,678	£92,487
Age range is 40 - 75 and interval = 3 years	£582.7m	-£0.8m	£581.9m	6,019	£96,681
Age range is 40 - 75 and interval = 5 years	£372.4m	-£0.9m	£371.5m	4,523	£82,138
Age range is 40 - 75 and interval = 10 years	£191.6m	-£0.4m	£191.3m	2,163	£88,443
Age range is 50 - 70 and interval = 4 years	£287.0m	-£0.6m	£286.5m	3,715	£77,114
Age range is 50-75 and interval = 1 year	£1,173.0m	-£3.6m	£1,169.4m	16,425	£71,193
Scenario analyses: The unclear and positivity rates associated with screening					
Base case 1: unclear rate 9.7%, positivity rate 2%	£447.5m	-£0.5m	£447.0m	4,550	£98,246
unclear rate 5%	£440.1m	-£0.5m	£439.6m	4,550	£96,628
unclear rate 20%	£463.6m	-£0.5m	£463.1m	4,550	£101,790
The positivity rate = 1%, false positivity rate = 0.8%	£369.0m	-£0.5m	£368.5m	4,550	£80,989
The positivity rate = 4%, false positivity rate = 3.2%	£608.9m	-£0.5m	£608.4m	4,550	£133,726
Scenario analyses: The uptake of the generic cancer screening					
Base case 1: uptake rate 55%	£447.5m	-£0.5m	£447.0m	4,550	£98,246
Uptake rate = 45%	£366.4m	-£0.4m	£366.0m	3,722	£98,313
Uptake rate = 73%	£599.2m	-£0.7m	£598.6m	6,072	£98,581
Scenario analyses: The false positive rate of the generic cancer screening programme					
Base case 1: false positive rate = 1.6%	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The false positive rate = 1.5%, positivity rate = 2%	£437.7m	-£0.5m	£437.2m	4,550	£96,100
The false positive rate = 1.8%, positivity rate = 2%	£465.0m	-£0.5m	£464.4m	4,550	£102,082
Scenario analyses: The cost of cancer treatment					
Base case 1	£447.5m	-£0.5m	£447.0m	4,550	£98,246
The cost of treating early stage cancer is 25% higher and the cost of treating late stage cancer is 25% lower than the base case	£447.5m	£6.2m	£453.7m	4,550	£99,722
The cost of treating early stage cancer is 25% lower and the cost of treating late stage cancer is 25% higher than the base case	£447.5m	-£7.2m	£440.3m	4,550	£96,770

6.2.1 Scenario analysis: Impact of generic cancer screen on stage distribution

The scenario analysis results demonstrate that when the stage shift associated with screening is increased, the screening programme is more effective thus the ICER is lower. In base case 1, the stage shift is 31% and the ICER is £98,000per QALY gained. When the stage shift is 90%, the ICER falls to £37,000per QALY gained.

6.2.2 Scenario analysis: Modelling life expectancy gains associated with stage shift

The scenario analyses testing different survival modelling assumptions resulted in a slightly greater difference between life expectancy for early and late stage cancers than in base case 1. It is expected that when the survival models used in Scenario 1 and Scenario 2 are used, that the QALYs associated with early detection will increase. This is as those patients who are detected with an early stage cancer are expected to live longer than in base case 1. Conversely, those patients who are detected with a late stage cancer are expected to have a shorter life expectancy than in base case 1. Therefore, it is expected that the incremental gains in life expectancy due to the introduction of a new screening programme will be greater in these scenarios. This expectation was matched by an increase in the total QALYs and a fall in the ICER, as costs remained constant. The overall impact on the ICER is smaller than some of the other scenarios, in scenario 1 the ICER is £94,000per QALY gained and in scenario 2 the ICER is £91,000 per QALY gained. The ICER has fallen by £4,000per QALY gained from base case 1 in scenario 1 and £7,000per QALY gained from base case 1 in scenario 2.

6.2.3 Scenario analysis: Screening costs

The scenario analyses on the costs of screening demonstrate that as the costs increase, the total cost of the generic cancer screening programme also increases but the effectiveness is constant which results in a significant increase in ICER values. The ICER varies from £53, 000per QALY gained when the cost of the biomarkers are £10 to £125,000 per QALY gained when the cost of the biomarkers are £99. This suggests that the cost of the biomarkers will have a substantial impact upon the ICER. The ICER varies from £96,000per QALY gained when the cost of conducting the screening test is £4 to £101,000per QALY gained when the cost of conducting the screening test is £9. This suggests that controlling the cost of conducting the test is important in controlling the cost of a new screening programme when the cost of following up of false positives falls from £3,124 to £361 the ICER falls to £70,000per QALY gained. Finally, when the cost of cancer nurse specialists and GPs are removed from the costs of screening the ICER falls by around £500 per QALY gained compared to base case 1. This is as the overall cost of the providing these services is £2.2m and this is very small compared to the overall screening costs of £447.0m This would suggest that thought needs to be given as to how people with positive results will be followed up in a generic cancer screening programme, as the overall cost of follow up will have a significant impact on the cost-effectiveness of the new screening programme.

When the cost of follow up for false positives, the cost of delivering the screening programme and the cost of the biomarkers are set to their lowest parameter values and the cancer nurse specialists and GPs are removed from the screening programme costs, the total cost of the screening programme is £350m lower than base case 1. Again there is no change in the effectiveness of the screening programme. The ICER in this scenario is £23,000per QALY gained, which is lower than when only one aspect of the screening programme costs is varied. This demonstrates that the cost of all aspects of the screening, not just the cost of the biomarkers in the generic cancer test, need to be minimised to increase the chance that the programme will be considered cost-effective.

6.2.4 Scenario analysis: HRQoL decrement for false positives

These scenario analyses show that for higher HRQoL decrements for false positives the QALY gain associated with screening is lower and hence the ICER increases. The ICER ranges from £186,000per QALY gained when the HRQoL decrement for false positives is -0.04 to £98,000 per QALY gained when there is no HRQoL decrement for false positives (base case 1).

6.2.5 Scenario analysis: Screening age ranges and screening interval

In this analysis the age ranges in which people are eligible for screening and the screening intervals have been varied. As the model used here does not represent the natural history of cancer disease the cumulative effect of several screening rounds cannot be estimated. Hence the optimal screening age range and interval cannot be established.

However, these analyses provide useful information on the first year costs associated with running a screening programme in different age ranges and screening intervals. It can be seen that as the interval is decreased and as the age range of people who are screened is widened, the cost of running the screening programme increases. This expected as increasing the screening interval and widening the age range of the population been screened increases the number of people been screened every year. In these analyses the cost of the generic cancer screening programme ranges from £191.3m to £1,727.4m.

6.2.6 Scenario analysis: Unclear rate, positivity rate and uptake

For higher unclear rates, the cost of screening is higher but there is no effect on QALYs gained hence the screening programme is less cost-effective. This is likely due to the limitations with the model structure, as without a more complicated model it is unknown how many individuals with an unclear result will have a cancer one year later. As the positivity rate is increased, the costs of screening increase and the QALYs gained decrease. It is expected that the total QALYs will decrease as the false positivity rate in the model is increases with the positivity rate. Therefore, when the number of people who receive positive results increase, the number of people who receive false positives also increases. This increase in people who receive false positives drives the fall in QALYs due to the QALY decrement experienced by people who receive false positive results. Overall, as the positivity of the

screening programme increases, the programme is less likely to be cost-effective. When the positivity of the generic cancer screening programme is 1%, the ICER is £80,000per QALY gained and when the positivity of the generic cancer screening programme is 4%, the ICER is £133,000 per QALY gained.

The false positive rate was also changed independently from the positivity rate. When the positivity was 2% and the false positive rate was 0.8%, the ICER was £96,000 per QALY gained. When the positivity was 2% and the false positive rate was 1.8%, the ICER was £102,000 per QALY gained. This would indicate that controlling the number of people who receive false positive screening test results will be an important determinant of the cost-effectiveness of the generic cancer screening programme.

6.2.7 Scenario analysis: The cost of cancer treatment

Changing the cost of cancer treatment overall had very little impact on the ICER. In the first scenario the cost of treating early stage cancer was 25% higher and the cost of treating late stage cancer was 25% lower than base case 1. In the first scenario lead the total costs were £453.7m and the ICER was £100,000per QALY gained. In the second scenario the cost of treating early stage cancer was 25% lower and the cost of treating late stage cancer was 25% higher than base case 1. In this scenario, the total costs were £440.3m and the ICER was £97,000per QALY gained. The reason for the relatively small changes in the ICER is due to the relatively small changes in total cost. The total cost changed from base case 1 by +£6.7m in the first scenario and -£6.7m in the second scenario. These changes in total cost are just over 1% of base case 1 total cost, hence the relatively small differences in the ICERs.

6.2.8 Scenario analysis: Summary of the one way scenario analyses

In conclusion, the one way scenario analyses which reflect the costs of the screening programme (cost of the test, cost of conducting the test and the cost of follow up) and the clinical characteristics of the test (stage shift associated with screening, positivity and false positivity) have the largest impact on the ICER. Therefore the cost of the generic cancer screening programme should be considered whilst the generic cancer screening test is being developed as well as the clinical effectiveness of the test. Another parameter which has relatively large impacts on the ICER is the HRQoL decrement due to false positives.

6.2.9 Two-way sensitivity analyses

The two way sensitivity analyses show that when the impact of generic cancer screen on stage distribution is 90% and the cost of the biomarkers is £10, then the ICER is £18,248. Two other ICERs in the Two way sensitivity analyses are within the £20,000 to £30,000 per QALY gained threshold used by NICE when considering whether a technology is a cost-effective use of NHS resources(9). This confirms that the combined cost and effectiveness of the generic cancer screening test will be one of the key drivers of the cost-effectiveness of any generic cancer screening programme.

Therefore both of these factors should be considered when the generic cancer screening test is being developed.

Table 6.2b: Two way scenario analysis on cost of screening test and impact of screening test of stage distribution

		Impact of generic cancer screen on stage distribution: reduction in late stage incidence for those complying with screening			
		25%	31%	57%	90%
Cost of the biomarkers in the generic cancer screening test	£10	Incr. Costs= £243.0m Inc. QALYs= 3,683 ICER= £65,984	Incr. Costs= £242.9m Inc. QALYs= 4,550 ICER= £53,394	Incr. Costs= £242.5m Inc. QALYs= 8,377 ICER= £28,946	Incr. Costs= £241.9m Inc. QALYs= 13,259 ICER= £18,248
	£49	Incr. Costs= £386.9m Inc. QALYs= 3,683 ICER= £105,050	Incr. Costs= £386.8m Inc. QALYs= 4,550 ICER= £85,019	Incr. Costs= £386.4m Inc. QALYs= 8,377 ICER= £46,121	Incr. Costs= £385.8m Inc. QALYs= 13,259 ICER= £29,099
	£66	Incr. Costs= £446.0m Inc. QALYs= 13,259 ICER= £33,638	Incr. Costs= £447.0m Inc. QALYs= 4,550 ICER= £98,246	Incr. Costs= £446.6m Inc. QALYs= 8,377 ICER= £53,304	Incr. Costs= £446.0m Inc. QALYs= 13,259 ICER= £33,638
	£99	Incr. Costs= £567.4m Inc. QALYs= 3,683 ICER= £154,066	Incr. Costs= £567.3m Inc. QALYs= 4,550 ICER= £124,699	Incr. Costs= £566.9m Inc. QALYs= 8,377 ICER= £67,671	Incr. Costs= £566.4m Inc. QALYs= 13,259 ICER= £42,715

6.2.10 Validation exercise

The results of the validation exercise illustrate that the total QALYs associated with the ECDC are less than with the BCSP model because the treatment of precancerous conditions does not occur with the generic cancer screen. In the BCSP model 66% of QALYs gained are predicted to be associated with the treatment of precancerous conditions rather than earlier diagnosis. Hence the diagnosis of precancerous conditions is important for colorectal cancer. However, the same may not be the case for other cancer types and each cancer type will need to be considered individually. The results of the validation exercise are in Table 6.2c.

Table 6.2c: Comparison of ECDC economic model and ScHARR Bowel cancer screening model predictions for a cohort of 100,000 64 year old being offered one screen

	ECDC economic model (five modelled cancers)	ECDC economic model (restricted to colorectal cancer)	ScHARR Bowel cancer screening model	ScHARR Bowel cancer screening model (excluding detection of precancerous conditions)
Reduction in symptomatically presenting cancers	165	45	191	191
Persons with a screen detected cancer	165	45	67	67
Persons with precancerous conditions detected	0	0	356	0
Total QALYs gained	974	95	511	176

Therefore there are three reasons why the QALYs gained due to the earlier detection of colorectal cancer are lower in the ECDC economic model and BCSP model: 1) differences in the survival models, 2) differences in the stage distribution of colorectal cancer incidence in the UK before and after the NHS bowel cancer screening programme and 3) differences in the model structures.

The survival models used in the ECDC and BCSP models to predict the life expectancy of colorectal cancer patients used the same technique. The models use the same data source, however in the ECDC economic model bowel and colon cancers are treated separately as the combined information is not in the public domain. Any difference between expected colorectal cancer survival used in the two models is likely to be small.

Table 6.2c shows the difference in stage distribution in the absence of the bowel cancer screening programme and in 2012 when the bowel cancer programme was running (but not fully rolled out up to age 74). This has important implications when modelling the ECDC proposed screening programme. The potential for shifting diagnoses to earlier stages is obviously greater in the absence of the Bowel cancer screening programme. This partly explains why a smaller QALY gain is seen for the ECDC compared with the BCSP.

Table 3: The Stage distribution of colorectal cancer before and after the introduction of the NHS bowel cancer screening programme.

	Dukes A	Dukes B	Dukes C	Dukes D	Dukes A and B	Dukes C and D
Stage distribution of bowel cancer based on 2004-6 incidence rates (pre NHS bowel screening)	11%	25%	35%	29%	36%	64%
Stage distribution of bowel cancer based on 2012 incidence rates (post NHS bowel screening)	13%	35%	35%	17%	48%	52%

It should be noted that these results also support the hypothesis that a simple model structure is not accurately capturing the full benefits of a new screening programme, as a simple cannot include any benefits due to the early treatment of precancerous conditions.

6.2.11 Extrapolation of the model results to all cancer types

The base cases and scenario analyses undertaken just incorporate QALY gains and treatment cost differences due to earlier diagnosis of the five included cancer types. The five included cancer types account for 45.1% of the incidence of all cancer types in the UK in 2011. Intuitively, it would be expected that if all cancer types could be detected by this test then the QALY gains by cancer type would increase. The cost of treating early stage cancer was lower than treating late stage cancer for most, but not all of the cancers included in the model. The direction of effect due to including more cancer types in the model is unknown, as the treatment cost differences between late and early stage cancer may not be similar to the cancers currently included in the model.

As life expectancy gain due to earlier diagnosis varies significantly by cancer type (ranging from 1.7 years for non-small cell lung cancer and 8.7 years for ovarian cancer) the average QALY gain for the five modelled cancer types may differ significantly from the average QALY gain for all cancer types. Therefore the same fall in the ICER may not be achieved when all cancer types are accurately included in the economic model. Although this analysis is merely exploratory it does indicate that

the potential for the generic cancer screening programme ICER to be significantly lower if the benefits of early diagnosis of all cancer types are included.

7 Conclusions

7.1 Key considerations for the cost-effectiveness of screening programme

An economic model was developed to assess the economic headroom of introducing a new generic cancer screening programme which would detect multiple cancer types. The scope of the economic model was restricted to include five cancer types (bladder, breast, colorectal, lung and ovarian) for feasibility reasons. The effect of a stage shift due to a single round of generic cancer screening on the stage distribution of cancer incidence for the English and Welsh population in 2015 is modelled. The lifetime effect of earlier cancer detection on the stage distribution, life expectancy of cancer patients, total QALYs gained, cost of conducting the generic cancer screening programme, cost of diagnosing each cancer type and the cost of treating each cancer were calculated. All analyses took an NHS and personal social services perspective.

In the base case analysis: one screening round was modelled, the screening effectiveness data was based on the stage shift from the breast cancer screening programme, and people aged 40 to 72 were invited to be screened at four yearly intervals. Full details on all the parameters and assumptions used in the base case are given in Section 4. In base case 1, the ICER of a new generic cancer screening programme in addition to the existing UK type specific screening programmes compared to no generic cancer screening programme was around £96,770 per QALY gained. In base case 2, the ICER of a new generic cancer screening programme in addition to the existing UK type specific screening programmes compared to no generic cancer screening programme was around £12,000 per QALY gained. In base case 1, the model parameters were the average values in a range and in base case 2 the model parameters were generally the most favourable values from the parameter range. Several scenario analyses were undertaken on base case 1 which resulted in ICERs ranging from £18,248 per QALY gained to £185,911 per QALY gained. The parameters with the biggest impact on the ICER are total cost of screening (includes: biomarker costs, the costs of delivering screening and the cost of following up false positives), the stage shift associated with screening, the positivity and false positivity of the screening programme and the HRQoL decrement due to false positive results. All of these factors should be considered when designing screening programme. The ICER values estimated here only incorporate the benefits of earlier diagnosis for 5 cancer types (45.1% of incidence) and an exploratory analysis indicates that the ICER could be significantly lower if the impact on all cancer types is included.

Considering the normal NICE cost-effectiveness threshold (£20,000 to £30,000 per QALY gained) the screening programme may be cost-effective (9). As the generic cancer screening programme is predicted to result in a QALY gain, controlling the cost of all aspects of the screening programme, not just the cost of the generic cancer screening test, will be a key determinant of the cost-effectiveness of the screening programme.

It is intended that the generic cancer screening programme will detect most cancer types, however not all cancer types are included in the economic model. Hence the results presented here provide a lower bound for the likely QALY gain. Whether the estimates of total costs are an upper or lower

bound will depend on whether the cost of diagnosing and treating the other cancer types is cheaper in the earlier or later stages of the disease. If the cost of diagnosing and treating other cancer types is cheaper in the earlier stage of the disease, then total costs will be upper bounds. Conversely if the cost of diagnosing and treating other cancer types is more expensive in the earlier stages of the disease, then total costs will be lower bounds.

7.2 Cost of cancer screening programmes

The estimated annual cost of the generic cancer screening programme ranges between £104.4m and £1,727.4m. This is associated with considerable uncertainty as the cost of the biomarkers, the cost of follow up and the screening intervals have not yet been established.

For comparative purposes the annual cost of the current NHS screening programmes is given in Table 7.2. The estimated annual cost of the type specific screening programmes in England is £348.3 m. In the long term the need for the cervical cancer screening programme will decrease as younger cohorts receive vaccination. If a successful generic cancer screening programme can be developed then disinvestment in type specific cancer screening programmes may be considered.

The cost of the current NHS screening programmes is given in Table 7.2 and they vary from £77.3m to £175m per year. The cost of the generic cancer screening programme varies from £104.4m to £1,727.4m. Whilst the range of costs for the generic cancer screening programme are higher than the cost of the current cancer type specific screening programmes, it should be kept in mind that the generic cancer screening programme is intended to be able to detect multiple cancer types. If the existing type specific programmes were to be replaced with the generic cancer screening programme, this would result in substantially lower incremental total costs than are presented in this report as £348.3 million could be saved. The current model cannot assess the health consequences of removing the existing screening programme, as it does not contain the prevalence of a symptomatic cancer (in the absence of all screening) therefore the impact on the ICER cannot be quantified.

Table 7.2: Comparison of costs from the generic cancer screen, type specific cancer screening programmes and the NHS health check

Programme	Total cost of programme	Source	Annual number of people invited	Source	Annual number of people screened	Source	Cost per invitee	Cost per person screened	Cost per test	Cost of followup
NHS breast cancer screening	£96.0m	NHS breast cancer screening programme website*	2,862,370	NHS breast cancer screening programme annual review 2012	2,100,799	NHS breast cancer screening programme annual review 2012	£33.54	£45.70	Mammography: £47.92 (NHS reference costs 2005/6 inflated to 2012/13 prices)	Biopsy : £304 NHS reference costs 2005/6 inflated to 2012/13 prices
NHS bowel cancer screening	£77.3m	NHS bowel cancer screening programme website*	4,641,593	Calculated from the ECDC economic model	2,552,876	Calculated from the ECDC economic model	£16.65	£30.28	gFOBT test: £2.13 Whyte et al 2011 inflated to 2012/13 prices	Colonoscopy: £222 to £596 Whyte et al. 2011 inflated to 2012/13 prices
NHS cervical cancer screening	£175.0m	NHS cervical cancer screening programme website*	4,240,000	Health & Social Care Information Centre 2013	3,320,000	NHS cervical cancer screening programme annual review 2012	£41.27	£52.71	LBC: £29.32 Karnon et al 2004 inflated to 2012/13 prices	Coloposcopy and conisation: £238 (range £174 to £302) Karnon et al 2004 inflated to 2012/13 prices
Total cost of 3 cancer screening programmes	*£348.3m*	*total of above*								
NHS Health checks	£373.5m	Department of Health 2008	3,045,628	Department of Health,NHS health check - data for England from July 2015	1,352,020	Department of Health,NHS health check - data for England from July 2015	£123	£276	Test costs range from £0.79 to £13.84 per test used. Department of Health 2008 inflated to 2012/13 prices	Unclear
Generic cancer screening programme- base case 1	£447.0m	ECDC economic model	6,325,952		3,479,274		£70.66	£128	£73.94	£3,124
Generic cancer screening programme- base case 2	£137.3m	ECDC economic model	6,325,952		4,643,249		£21.70	£29.56	£16.18	£361

* date not provided and it is unclear if the costs include follow up costs

7.3 The cost-effectiveness of other cancer screening programmes

Incremental cost-effectiveness ratios (ICERs) are used by NICE to determine whether new technologies should be funded on the NHS. Generally technologies are considered if the ICER is less than £20,000-£30,000 per QALY gained (9). A recent study suggests that the threshold should in fact be £13,000 per QALY gained.(73). The ICERs associated with screening programmes are often considerably below this threshold, see Table 7.3.

Table 7.3: A summary of estimated cost-effectiveness of screening programmes

Screening Programme	**Setting**	**Year**	**Methods**	**Results**	**Source**
Breast screening programme	UK NHS	1986	Cost-effectiveness analysis	£3,309 per QALY gained	Forrest report (74)
Breast Screening programme	UK NHS	1993	Cost-effectiveness analysis	£1,800 per life year gained	Van Ineveld *et al*. (75)
Breast screening programme	UK NHS	2013	Cost-effectiveness analysis	£20,800 per QALY gained	Pharoah *et al.* (76)
Bowel screening programme	UK NHS	2012	Cost-effectiveness analysis	Screening dominates no screening	Whyte *et al.*(10)
Bowel screening programme	US third party payer	2002	Systematic review of cost-effectiveness analyses	$10,000 to $25,000 per life year gained	Pignone *et al.* (77)
Cervical screening programme	UK NHS	2004	Cost-effectiveness analysis	New method dominated the old method	Karnon *et al*. (78)
Cervical screening programme	UK NHS	2004	Cost-effectiveness analysis	£4588 per life year gained	Sherlaw-Johnson *et al*. (79)

The highest ICER associated with an existing screening programme is £20,800 per QALY gained, see Table 7.3. The lowest ICER of the generic cancer screening programme is about £12,000per QALY gained. This would suggest that it is plausible that the generic cancer screening programme may be considered cost-effective by UK decision makers. Whether or not the generic cancer screening test is considered to be cost-effective will depend on many variables which are outlined in Section 6.2.

7.4 The criteria for the implementation of a new screening programme

The National Screening Committee has a list of criteria which must be satisfied by a potential new screening programme. The full list of criteria is included in the Appendix. (80) One of the criteria is the opportunity cost of a new screening programme, which can be assessed using a cost-effectiveness analysis. However, the natural history of the disease must be adequately understood for a new screening programme to be approved. At this stage, it is unclear whether or not all

included cancers would meet these criteria. It is also worth noting that evidence from a high quality randomised controlled trial on the impact of the new screening programme mortality or morbidity must also be available. Therefore a full randomised controlled trial would be necessary after work package three if a generic cancer screening test is to be implemented as part of a screening programme in the UK.

7.5 Limitations: Areas where further data is required

This study has identified several areas where additional data is required for the economic model. These areas are the cost of diagnosing, treating and following up cancer; the clinical characteristics of the generic cancer screening test; and the screening pathways. As was discussed in detail in Section4, these parameters were a significant limitation for the economic modelling. It was not feasible to develop a natural history model for each included cancer type in the economic modelling in the time frames of this project. However the data discovered in this project suggests that developing these models also be subject to data limitations. It is expected that more information on the clinical characteristics of the generic cancer screening test and the screening pathways will be generated by future ECDC work packages. It should also be noted that more recent cancer incidence and survival data may be available at a later date, where available this data will be included in the economic model. This research has highlighted both the areas where data is most sparse/uncertain and the model parameters which are most important in reducing uncertainty in cost-effectiveness estimates.

7.6 Limitations: modelling approach

7.6.1 The model scope

The economic modelling is restricted to five cancer types however it is the intention that the generic cancer screening test will cover numerous cancer types. Therefore the benefits (QALY gains) of detecting other cancer types (outside the five modelled) are not accounted for. Similarly the cost differences associated with diagnosing other cancer types are not included.

If the missing cancers were to be included it would be expected that the screening programme would yield more benefits, as more cases of cancer would be detected in an earlier stage. This would result in patients with cancer living longer, increasing the QALY gains from introducing the generic cancer screening programme.

The net effect of the inclusion of other cancer types is likely to be a decrease in total costs, as this is observed on average for the five currently included cancer types. However for breast and small cell lung cancer the cost of diagnosing and treating patients in a later stage is less than the cost of treating and diagnosing patients in an earlier stage. If the cost of diagnosis and treatment for the other cancer types are similar to breast and small cell lung cancer (i.e. more expensive in earlier stages) then the total costs may increase. This would lead to the current estimates of ICER being a lower bound. Conversely, if the cost of diagnosis and treatment is lower in earlier stages than the later stages for other cancer types then the incremental total costs will decrease. This will lead to the ICER's presented in the results being upper bounds. On average for the five included cancer types, the costs are lower in the earlier disease stages than the later disease stages. This would indicate that this is likely to be the case for other cancer types, hence the ICERs are likely to be upper bounds.

Inclusion of other cancer types in the model could also result in higher costs of follow up for false positives (due to potentially more complicated follow up pathways) than have been included in this model so this should also be considered.

Future research will expand this analysis to include more cancer types to obtain a more accurate estimate of the ICER. The five cancers included in this analysis comprise 45.1% of all cancer incidence. Expanding the analysis to the 11 most common cancers could cover 75% of cancer incidence.

7.6.2 Overdiagnosis

The economic model does not include overdiagnosis. Therefore the estimates of total cost were lower bounds, as the cost of treating overdiagnosed cases has not been included. The QALYs are upper bounds, as any HRQoL decrements for someone getting cancer who would not have presented symptomatically within their remaining lifetime is also not included. As total costs are likely to be higher when overdiagnosis is included and the total QALYs are likely to be lower, the ICERs are likely to be higher than those found here when overdiagnosis is included.

7.6.3 Survival improvements due to screening

Basing the improvements in survival between the screening and non-screening model arms on shifts in the stage distribution will not include any survival differences that may occur between screen detected cancers and a non-screen detected cancers with the same stage at diagnosis. Evidence for this effect exists in one trial of ovarian cancer screening in which there were statistically significant survival differences in the trial arms, but there was no statistically significant difference in the stage distributions.(81)

7.6.4 Model structure

Due to an absence of data on the test characteristics of the generic cancer screen a simple approach to modelling was taken here (without cancer natural history models). This approach was appropriate given the level of data available however it is associated with limitations which we describe here:

<u>Pre-cancerous conditions</u>

It is unknown if the generic cancer screen will result in the detection of a significant number of precancerous conditions. Treatment of precancerous conditions can prevent cases of cancer and thus result in QALY gains. Without a natural history model it is not possible to estimate the number of pre-cancerous conditions in a population or the number detected by a screening test. If detected, pre-cancerous conditions can be treated, although the benefits/disbenefits associated with treating some precancerous conditions (e.g. ductal carcinoma in situ for breast cancer) are unclear. Hence the possible benefits/disbenefits associated with treating precancerous conditions are not included within the economic model results.

<u>Screen detection of undiagnosed (primarily asymptomatic) cancers</u>

The economic model is restricted to five cancer types (for reasons of feasibility) which account for 45% of cancer incidence. Hence the model predictions do not describe the likely cost-effectiveness in relation to all cancer types. In addition the model is assumed to result in a stage shift in current cancer incidence but may also result in the diagnosis of cases of cancer which would not present symptomatically (likely asymptomatic cancer cases). This would only be possible for cases of cancer which remain undiagnosed for over 1 year hence this limitation is not expected to have a significant impact on model results.

7.6.5 Stage shift

The stage shift was calculated using a definition of Stage I and II cancers as early stage cancers and Stage III and IV cancers as late stage cancers for all included cancer types. However, after a new generic cancer screening test could stage shift all individuals to Stage I from Stages II to IV. The exact mechanism of a stage shift due to a new test would have to be determined based upon the clinical evidence developed during the creation of such a test. However, the net effect of using this definition of the stage shift distribution remains unknown. This is because, more QALYs would be achieved by detecting people at Stage I rather than Stage II. However the number of people who would experience a Stage shift remains unknown. If sufficiently less people are detected at an early stage using this definition, then the overall QALY gains could be smaller than a test that shifts people with Stage III or IV cancer to Stage I or II.

7.6.6 Reassurance from a negative generic cancer screening test result

It was believed by some members of the ECDC that it was possible that a screening programme would reassure people that they did not have cancer leading to 1) fewer people without cancer seeking symptomatic diagnosis and 2) people with false positive results potentially been diagnosed at a later stage than in the absence of screening. These effects were not included in the model as: 1) there was limited evidence for these effects in the existing type specific programmes and 2) these effects had not been considered in cost-effectiveness model to reappraise the NHS bowel screening programme for the national screening committee.(10)

Figure 7.6a: Cancer types and incidence included within the economic modelling

Cancer Type			Prevalence			
			Incidence			*
Included in the economic model (45.1% of incidence)	{	Bladder	Symptomatic presentation			Undiagnosed
		Breast	Symptomatic presentation	&	Screen detected	Undiagnosed
		Colorectal	Symptomatic presentation	&	Screen detected	Undiagnosed
		Lung	Symptomatic presentation			Undiagnosed
		Ovarian	Symptomatic presentation			Undiagnosed
Excluded from the economic model (54.9% of incidence)	{	Cervical	Symptomatic presentation	&	Screen detected	Undiagnosed
		Prostate	Symptomatic presentation			Undiagnosed
		Malignant Melanom	Symptomatic presentation			Undiagnosed
		etc.	Symptomatic presentation			Undiagnosed

* Cancer type specific natural history models are require to predict the prevalence of undiagnosed cancer. Hence detection of undiagnosed cancer by the generic screening test is not included within economic model.

Reduced cancer prevalence at subsequent screening rounds

Screening may result in the detection of cancers that would have presented symptomatically in years after the screening round has taken place i.e. a screening round will impact on the future incidence and prevalence of cancer. Without a natural history model this future change in cancer incidence/prevalence cannot be predicted hence the economic model cannot predict the cost-effectiveness of more than one screening round. Hence the optimal screening interval and age ranges cannot be determined by the model developed here.

7.7 Recommendations for future research

The study has highlighted that further research is required to generate data to enable a robust economic analysis of a generic cancer screening programme. The three key areas for further research are: the lifetime cost of treating cancer by stage at diagnosis, the natural history of each cancer type and the QALY gains associated with earlier cancer detection. These research areas should be prioritised, as this information is necessary for a robust economic assessment of any early cancer detection strategy, not just the ECDC workpackages.

The lifetime cancer treatment costs were found to be poorly understood. A recent research study attempted to address this gap.(16) The study is useful, however it had some limitations 1) costing was restricted to four cancer types, 2) the pathways were based on national guidelines and expert opinion so may not reflect actual use and 3) some parts of the pathway were implausible to ECDC experts. Research should be conducted to establish the lifetime treatment costs by stage at diagnosis and cancer type. Two study designs are possible to calculate the lifetime cost: 1) using observational data on the actual pathways which patients follow or 2) using recommended

pathways from NICE guidelines and expert opinion. There may be value in comparing costing obtained using both methods. As treatment pathways for cancer will continue to change, a research programme involving regular updating of the costs (e.g. every five years) is suggested

The natural history of each cancer type detected by a generic screening programme needs to be understood in order to adequately represent the benefits of screening within a model. Natural history parameters include: the rate at which precancerous conditions develop; the rate of progression between the different precancerous and cancerous stages of the disease, and an understanding of symptomatic presentation rates. An understanding of the natural history of the disease is also one of the criteria that the National Screening Committee uses to approve or reject new screening programmes. Further research by experts in the field of cancer into the natural history of cancer types which would not have previously been considered for detection in a cancer screening programme is recommended.

QALY gains associated with earlier detection were calculated in this study using published incidence and survival data. The available data was adequate however; it is essential that up to date incidence and survival data for all cancer types is regularly published. This will enable accurate estimation of QALY gains in health economic modelling which incorporate improvements in survival over time due to the introduction of new treatments and technologies.

7.8 The ECDC planned research programme

The report details a draft economic model which was constructed as part of the ECDC WP2. A case control study which will result in a combination of biomarkers being identified for the screening test (WP3) and a screening trial (WP4) are planned.

<u>WP3</u>
The existing draft model will be refined further. The economic modelling will inform decisions regarding the screening programme to be trialled in WP4. This will include: The screening age range and interval; the range of acceptable costs for the screening test; the importance of parameters such as false positive rate, the unclear rate, the cost of following up false positives etc. on the cost-effectiveness of the programme.

Alongside case control study:

- Seek more robust data on treatment costs by stage: Data obtained in WP2 however data quality is poor. In WP3 we will look into obtaining better data e.g. from NHS Leeds (Michael Messenger).
- the follow up pathways costings will be finalised
- Cancer incidence and survival data used in the model will be updated with newer data when available.

Following results of case control study:

- The biomarkers to be included will be identified and the cost estimates can be refined further.
- Estimates of test characteristics from the case control study will be incorporated into the economic model.

- Detection of pre-cancerous conditions. WP2 assumed that the test would be designed so that pre-cancerous conditions are not detected. If the test developed in the case control study identifies pre-cancerous conditions then their prevalence and cost and benefits of treating them will be incorporated into the modelling.
- Mode of delivering test will be finalised: 1) sample taken by nurse or phlebotomist and 2) within or outside health checks.

WP4

The results of the trial can be used to update the economic model. In particular the trial will provide data on the following:

- Screening uptake
- Stage shift due to screening
- Positivity rate in the general population
- Cost of running the screening programme
- Will capture any false reassurance effects (later diagnosis) in the results

The following data could be collected in WP4 and would inform the health economics:

- HRQoL decrement associated with false positive result
- HRQoL of patients with different cancers by stage at diagnosis
- Data on the treatment of false positives
- The treatment costs of cancer types by stage at diagnosis in the last screening round

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University of Sheffield

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School of Health and Related Research

Early Cancer Detection Consortium

Generic Cancer Screen - Economic modelling report

APPENDICES

May 2016

Sophie Whyte, Daniel Pollard, Ian Cree on behalf of the Early Cancer Detection Consortium

Contents

1 Appendix: Expert Input

This appendix addresses the expert input into the economic model.

1.1 Expert input received from members of the Early Cancer Detection Consortium

Robert Dann (Strategic Marketing Leader, GE Healthcare) suggested that instead of having a CT scan, people with a positive generic cancer screening test would be referred to the suspected cancer site. This approach was adopted in the model. Robert Dann also suggested that people with multiple suspected cancer sites would be treated as having an unclear test result. As the model did not have a complex natural history component, this advice was not incorporated into the analyses but will be considered in future work.

Professor Frank Sullivan (Professor, Department of Family & Community Medicine, University of Toronto; Honorary Professor, Population health sciences, University of Dundee and academic general practioner) advised that patients in a new screening programme would consult with their GP. As such, additional training should be provided to GPs.

Sian Taylor Phillips (NIHR postdoctoral Research Fellow, University of Warwick) advised that:

- using the NHS health checks as the basis of a new cancer screening programme could be problematic.
- screening older people could increase the harms from over treatment
- All results which we don't know are clinically meaningful (unclears) should be suppressed as far as possible
- The new test may detect pre-cancerous conditions which we don't know exist yet.
- GPs should be avoided in the screening pathways as far as possible, as this may lead to increases in off-protocol referrals and they are relatively expensive.
- Counselling on negative results would be provided by a cancer care nurse. This care should be modelled on data from the NHS breast cancer screening programme.

This advice informed the age ranges for the new screening programme, the screening interval, the method of test delivery and how unclear results were treated in the screening pathways

Professor Ian Cree (Yvonne Carter Professor of Pathology, Warwick Medical School. Hon. Consultant Pathologist, University Hospitals Coventry and Warwickshire NHS Trust. Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, EME programme) advised that:

- That the screening interval of the new screening programme would be somewhere between 1 and 5 years
- That unclear test results would be followed up with a further blood test within a year.
- Screening test cost may be £10 per case.
- The cost of several tumour markers
- The NHS health checks will likely take a large enough blood sample to be used in the generic cancer screening programme

- Screening would not be delivered by GPs. Screening would be delivered by nurses or phlebotomists
- Screening would take no more than five minutes
- Cost of taking the blood sample would be £25 outside of the NHS health checks and £2 inside the NHS health checks. This advice was based upon the SPUTNIK trial.
- The lifetime cost of late stage breast cancer should be in the region of £23,500.

Ian Cree also provided the current cost of several known biomarkers.

James Covington provided information on the cost of testing volatile organic compounds.

1.2 Lung cancer expert advice

Lesley Bishop (Consultant Respiratory Physician, Portsmouth NHS) and Emma Helm (Consultant radiologist, University Hospitals Coventry and Warwickshire) provided clinical input to the cost, health related quality of life, incidence and survival of lung cancer patients. There were clinical concerns about the appropriateness of the operations used in the Incisive Health report (1). The clinical belief was that more patients would receive CT scans, spirometry and chemotherapy than was the case in the Incisive Health report. Another concern with the Incisive Health report was that the surgery figures for people with stage 3 lung cancer were too low.

There were concerns that the one year net survival statistics were too low, another source on the survival of lung cancer patients was found (2). This source presented the survival of patients in 20 countries. It was not clear if the UK was included in this data set. As such, these survival statistics were not used in the model

It was also established that there was not a 100% specific test for the diagnosis of lung cancer. However, a CT scan would be close to achieving 100% specificity.

Judith Drought (University Hospitals of Coventry and Warwickshire), Jo Hamiliton (University Hospitals of Coventry and Warwickshire), Anoop Chauhan (Portsmouth Hospitals Trust) and Mya Gui (Portsmouth Hospitals Trust) were approached but did not respond.

1.3 Colorectal cancer expert advice

Ramesh P Arasaradnam (Honorary Associate Professor of Medicine and Consultant Gastroenterologist, University of Warwick and University Hospitals Coventry and Warwickshire) and Steve Smith (Director Midlands & NW bowel cancer screening hub) provided clinical input to the cost, health related quality of life, incidence and survival of colorectal cancer patients. No issues were raised with the data obtained.

Peter Correa (University Hospitals of Coventry and Warwickshire), Chris Harmston (University Hospitals of Coventry and Warwickshire),were also approached but did not respond.

1.4 Breast cancer expert advice

Dr Tim Gulliford (Consultant, Oncologist, Spire Portsmouth Hospital) responded, but did not feel qualified to answer the questions.

Constantinos Yiangou (Portsmouth Hospitals Trust), Martin Wise (Portsmouth Hospitals Trust), *Ramsey* Cutress (Associate professor in Breast Surgery, University of Southampton) were also approached.

1.5 Ovarian cancer expert advice

Francis Gardener (Portsmouth Hospitals Trust), Christopher Poole (Professor of Oncology, Warwick University), Dirk Brinkman (Portsmouth Hospitals Trust), Alison Franks (University Hospitals of Coventry and Warwickshire) were approached for clinical input on ovarian cancer, but did not respond.

1.6 Bladder Cancer expert advice

Dr Siriram Rajapolan (University Hospitals of Coventry and Warwickshire), Mr Donald Macdonald (University Hospitals of Coventry and Warwickshire) and Mr Kieran Jefferson (University Hospitals of Coventry and Warwickshire) provided input into the costs of treating people with bladder cancer. However, even with their substantial input it was not possible to develop a robust model to estimate the cost of treating bladder cancer by stage at diagnosis.

2 Appendix: HRQoL literature searches and results

All searches were conducted using the ScHARR health utilities database. This database is an online resource that contains bibliographic details on studies reporting health state utility values.(3) The search terms used only included the name of the cancer. For example the search for bladder cancer used the search terms bladder and cancer. No restrictions were placed on the instrument used to obtain the HSUV, the country of origin or the treatments used.

Studies were deemed to be potentially relevant if they included UK patients, had an appropriate number of patients to draw inferences and if they considered all patients with a stage of disease (e.g. metastatic cancer). The searches were conducted in November 2014. 28 studies were found (this figure includes duplicates in the searches conducted for the different cancer types. One study was included after the exclusion criteria were applied. The results of the searches and the reason why the studies were or were not included are given in Tables 2.1 – 2.4 below. The results for bladder cancer are not presented, as these searches returned no results.

Table 2.1: The results of the health state utility value search for breast cancer

Author	**Title**	**Journal**	**Year**	**Accept / reject**	**Why?**
Bastani,P., Kiadaliri,A.A.	Cost-utility analysis of adjuvant therapies for breast cancer in Iran	International Journal of Technology Assessment In Health Care	2012	Reject	No British patients
Lee,C.F., Ng,R., Luo,N., Wong,N.S., Yap,Y.S., Lo,S.K., Chia,W.K., Yee,A., Krishna,L., Wong,C., Goh,C., Cheung,Y.B.	The English and Chinese versions of the five-level EuroQoL Group's five-dimension questionnaire (EQ-5D) were valid and reliable and provided comparable scores in Asian breast cancer patients	Supportive Care In Cancer	2013	Reject	No British patients
Moro-Valdezate,D., Peiro,S., Buch-Villa,E., Caballero-Garate,A., Morales-Monsalve,M.D., Martinez-Agullo,A., Checa-Ayet,F., Ortega-Serrano,J.	Evolution of Health-Related Quality of Life in Breast Cancer Patients during the First Year of Follow-Up	Journal of Breast Cancer	2013	Reject	No British patients
Moro-Valdezate,D.,	Factors associated with health-related quality of	Breast Cancer	2012	Reject	No British patients

Buch-Villa,E., Peiro,S., Morales-Monsalve,M.D., Caballero-Garate,A., Martinez-Agullo,A., Checa-Ayet,F., Ortega-Serrano,J.	life in a cohort of Spanish breast cancer patients				
Postma,E.L., Koffijberg,H., Verkooijen,H.M., Witkamp,A.J., van den Bosch,M.A., van,Hillegersberg R.	Cost-Effectiveness of Radioguided Occult Lesion Localization (ROLL) Versus Wire-Guided Localization (WGL) in Breast Conserving Surgery for Nonpalpable Breast Cancer: Results from a Randomized Controlled Multicenter Trial	Annals of Surgical Oncology	2013	Reject	No British patients
Teckle,P., Peacock,S., McTaggart-Cowan,H., van der Hoek,K., Chia,S., Melosky,B., Gelmon,K.	The ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities	Health and Quality of Life Outcomes	2011	Reject	No British patients

Table 2.2: The results of the health state utility value search for colorectal cancer

Author	Title	Journal	Year	Accept / reject	Why?
Farkkila,N., Sintonen,H., Saarto,T., Jarvinen,H., Hanninen,J., Taari,K., Roine,R.P.	Health-related quality of life in colorectal cancer	Colorectal Disease	2013	No	No British patients.
Kim,S.H., Hwang,J.S., Kim,T.W., Hong,Y.S., Jo,M.W.	Validity and reliability of the EQ-5D for cancer patients in Korea	Supportive Care In Cancer	2012	No	No British patients
Schwandner,O.	Sacral neuromodulation for fecal incontinence and "low anterior resection syndrome" following neoadjuvant therapy for rectal cancer	International Journal of Colorectal Disease	2013	No	Only offered to a small subgroup of UK patients
Teckle,P., Peacock,S., McTaggart-Cowan,H., van der Hoek,K., Chia,S., Melosky,B., Gelmon,K.	The ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities	Health and Quality of Life Outcomes	2011	No	No British patients
Bennett,L., Zhao,Z., Barber,B., Zhou,X., Peeters,M., Zhang,J., Xu,F., Wiezorek,J., Douillard,J.Y.	Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment	British Journal of Cancer	2011	No	Treatment is not recommended in the UK

Table 2.3: The results of the health state utility value search for lung cancer

Author	Title	Source	Year	Reject/ Accept	Reason
Chouaid,C., Agulnik,J., Goker,E., Herder,G.J., Lester,J.F., Vansteenkiste,J., Finnern,H.W., Lungershausen,J., Eriksson,J., Kim,K., Mitchell,P.L.	Health-Related Quality of Life and Utility in Patients with Advanced Non-Small-Cell Lung Cancer: A Prospective Cross-Sectional Patient Survey in a Real-World Setting	Journal of Thoracic oncology	2013	Accept	
Iyer,S., Taylor-Stokes,G., Roughley,A.	Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany	Lung Cancer	2013	Reject	No British patients
Pickard,A.S., Ray,S., Ganguli,A., Cella,D.	Comparison of FACT- and EQ-5D-based utility scores in cancer	Value in Health	2012	Reject	No British patients
Roulston,A., Bickerstaff,D., Haynes,T., Rutherford,L., Jones,L.	A pilot study to evaluate an outpatient service for people with advanced lung cancer	International Journal of Palliative Nursing	2012	Reject	Based on six patients
Schuette,W., Tesch,H., Buttner,H., Krause,T., Soldatenkova,V., Stoffregen,C.	Second-line treatment of stage III/IV non-small-cell lung cancer (NSCLC) with pemetrexed in routine clinical practice: evaluation of performance status and health-related quality of life	BMC Cancer	2012	Reject	Not recommended for these patients in the UK
Sharples,L.D., Jackson,C., Wheaton,E., Griffith,G., Annema,J.T., Dooms,C., Tournoy,K.G., Deschepper,E., Hughes,V., Magee,L., Buxton,M., Rintoul,R.C.	Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised	Health Technology Assessment	2012	Reject	HSUV are higher than the HSUV used for patient's without cancer

	controlled trial				
Teckle,P., Peacock,S., McTaggart-Cowan,H., van der Hoek,K., Chia,S., Melosky,B., Gelmon,K.	The ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities	Health and Quality of Life Outcomes	2011	Reject	No British patients
Vogl,M., Wenig,C.M., Leidl,R., Pokhrel,S.	Smoking and health-related quality of life in English general population: implications for economic evaluations	BMC Public Health	2012	Reject	HSUVs for smokers not lung cancer patients
Barton,R., English,A., Nabb,S., Rigby,A.S., Johnson,M.J.	A randomised trial of high vs low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study	Lung Cancer	2010	Reject	Based on eleven patients in each arm
Basch,E., Jia,X., Heller,G., Barz,A., Sit,L., Fruscione,M., Appawu,M., Iasonos,A., Atkinson,T., Goldfarb,S., Culkin,A., Kris,M.G., Schrag,D.	Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes	Journal of the National Cancer Institute	2009	Reject	No British patients
Grutters,J.P., Joore,M.A., Wiegman,E.M., Langendijk,J.A., de,Ruysscher D., Hochstenbag,M., Botterweck,A., Lambin,P., Pijls-Johannesma,M.	Health-related quality of life in patients surviving non-small cell lung cancer	Thorax	2010	Reject	No UK patients

Table 2.4: The results of the health state utility value search for ovarian cancer

Author	Title	Journal	Year	Accept/ reject	Why?
Fisher, M., Gore,M.	Cost-effectiveness of trabectedin plus pegylated liposomal doxorubicin for the treatment of women with relapsed platinum-sensitive ovarian cancer in the UK: analysis based on the final survival data of the OVA-301 trial	Value in health	2013	Reject	Only considered patients with relapsed platinum sensitive ovarian cancer
Duffy, S.W., Mackay, J., Thomas, S., Anderson, E., Chen, T.H., Ellis, I., Evans, G., Fielder, H., Fox, R., Gui, G., Macmillan, D., Moss, S., Rogers, C., Sibbering, M., Wallis, M., Warren, R., Watson, E., Whynes, D., Allgood, P., Caunt, J.	Evaluation of mammographic surveillance services in women aged 40-49 years with a moderate family history of breast cancer: a single-arm cohort study	Health Technology Assessment	2013	Reject	Considers the screening of breast cancer.
Harding, V., Fenu, E., Medani, H ., Shaboodien, R., Ngan, S., Li, H.K., Burt, R., Diamantis, N., Tuthill,M., Blagden,S., Gabra,H., Urch,C.E., Moser,S., Agarwal,R.	Safety, cost-effectiveness and feasibility of daycase paracentesis in the management of malignant ascites with a focus on ovarian cancer	British Journal of Cancer	2012	Reject	Does not report HSUV or QALY values
Haldar, K., Giaougiannis,P., Wilson,C., Crawford,R.	Laparoscopic salpingo-oophorectomy for ovarian ablation in women with hormone-sensitive breast cancer	International Journal of Gynaecology & Obstetrics	2011	Reject	Considers breast cancer patients
Guest, J.F., Ruiz,F.J., Greener, M.J., Trotman,I.F.	Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK	European Journal of Cancer Care	2006	Reject	Costing study
Snowsill, T., Huxley, N., Hoyle, M., Jones-Hughes, T., Coelho, H., Cooper, C., Frayling, I., Hyde, C.	A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome	Health Technology Assessment	2014	Reject	Does not consider ovarian cancer

3 Appendix: Cost data literature searches

A search was conducted to obtain cost-effectiveness and costing studies which reported the cost of treating the different cancer types. The searches were conducted in MEDLINE and MEDLINE in PROCESS in October 2014. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) journal was searched for publications on the treatment of all five cancer typescancer. The search terms relating to each disease were obtained and adpated were necessary from single technology appriasla submissions to the National Institute for Health and Care Excellence. The SIGN economic filters (4) were used and search terms were added to remove any potentially irrelevant materials from the searches. Additional terms were added to limit the search to UK studies, studies in English and studies published in 2006 or later. The search strategies are presented in Tables 3.1 – 3.6.

Articles were considered to be potentially relevant if they were published after December 2005. Cost data prior to this date was not included in the search, as it was deemed that data prior to this date may not reflect current practice in the UK for the treatment of breast cancer. Studies were limited to UK studies as the cost of treating cancer in other countries was deemed to be irrelevant.

Table 3.1: The adapted SIGN filter for economic studies

1	Economics/
2	"costs and cost analysis"/
3	Cost-benefit analysis/
4	Cost control/
5	Cost savings/
6	Cost of illness/
7	Cost sharing/
8	"deductibles and coinsurance"/
9	Medical savings accounts/
10	Health care costs/
11	Direct service costs/
12	Drug costs/
13	Employer health costs/
14	Hospital costs/
15	Health expenditures/
16	Capital expenditures/
17	Value of life/
18	exp economics, hospital/
19	exp economics, medical/
20	Economics, nursing/
21	Economics, pharmaceutical/
22	exp "fees and charges"/
23	exp budgets/
24	(low adj cost).mp.
25	(high adj cost).mp.
26	(health?care adj cost$).mp.

27	(fiscal or funding or financial or finance).tw.
28	(cost adj estimate$).mp.
29	(cost adj variable).mp.
30	(unit adj cost$).mp.
31	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
32	or/1-31
33	Cancer specific filter and 32
34	limit 33 to yr="2006 -Current"
35	(Britain or British or United Kingdom or UK or GB or Wales or Welsh or Scottish or Scots or Scotland or England or Northern Ireland).tw.
36	great britain/ or england/ or scotland/ or wales/ or northern ireland/
37	35 or 37
38	34 and 37
39	limit 38 to English
40	(cost or costs or cost-effectiveness or cost-effectiveness analysis or cost effectiveness or cost effectiveness or CEA or cost benefit or cost benefit analysis or cost-benefit or cost-benefit analysis or CBA).tw.
41	39 and 40

The cancer type specific search terms which were added to the search terms given in Table 3.1 are detailed in Table 3.2.

Table 3.2: The search strategy used to identify economic and cost studies for patients with bladder cancer in the UK.

Bladder Cancer	**?**
Search Term	Terms Searched
1.	Urinary Bladder Neoplasms/
2.	(bladder adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcinoma$ or adenoma$ or adenocarcinoma$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3.	1 or 2
Breast Cancer	**Adapted from Eisai ltd. (5)**
Search Term	Terms Searched
1	breast cancer.mp. or exp Breast Neoplasms/
2	(cancer or tumor* or tumour* or carcinoma* or sarcoma* or neoplasm* or adenocarcinoma* or polyp*).mp.
3	(breast* or mamma*).mp.
4	2 and 3
5	1 or 4
Colorectal Cancer	**Adapted from; Merck Serono Ltd., (6)**
Search Term	Terms Searched
1	(((Colorect* or Colon* or Rect* or Duoden* or Ile* or Jejun* or Stomach* or gastri* or gastro* or GI) adj3 (cancer* or tumor* or tumour* or neoplasm* or malignan* or carcinom*)) or CRC).mp. or exp Colorectal Neoplasms/
Lung Cancer	**Adapted from; Hinde *et al*. (7)**
Search Term	Terms searched
1	exp Lung Neoplasms/
2	exp Carcinoma, Non-Small-Cell Lung/
3	exp Carcinoma, Small-Cell Lung/
4	(lung$ adj3 (canc$ or carcinoma$ or tumo?r$ or neoplasm$)).ti,ab.
5	1 or 2 or 3 or 4
Ovarian Cancer	**Source: National Institute for Health and Care Excellence (8)**
Search Terms	Terms Searched
1	(ovar* adj4 (cancer* or tumo*r* or malignan* or oncolog* or carcinoma* or neoplas* or mass* or growth* or cyst*)).ti,ab.
2	(adenexa* adj4 mass*).ti,ab.
3	exp OVARY CANCER/
4	exp OVARIAN NEOPLASMS/
5	1 or 2 or 3 or 4

The search for bladder cancer costing studies identified 3 articles.

The search for breast cancer costing studies identified 108 articles.

The search for colorectal cancer costing studies returned 106 articles.

The search for lung cancer costing studies returned 58 studies.

The search for ovarian cancer studies returned six articles.

Studies were not considered relevant if they did not consider the cost of treating cancer after diagnosis

4 Appendix: Cancer Incidence Data summary

4.1 Bladder cancer

The National Collaborating Centre for Cancer (NCC-C) draft clinical guidelines for the treatment and diagnosis of bladder cancer contain information on the incidence of bladder cancer by stage at diagnosis in England and Wales in 2012 (9). There was no information presented on the incidence of bladder cancer by stage and age in England or Wales. As the English data is based upon a larger sample size, this data will be used in the model. The NCC-C draft clinical guidelines present the incidence of bladder cancer by age and the incidence of bladder cancer by stage separately. The incidence of bladder cancer by stage in England in 2012 is presented in Table 4.1a. The incidence of bladder cancer by age in England is presented in Table 4.1b.

Table 4.1a: The stage specific incidence of bladder cancer in England in 2012

Stage	**Percentage of cancers in England**
Unknown	65.0%
Stage I	11.9%
Stage II	10.2%
Stage III	2.1%
Stage IV	10.5%

Source; National Collaborating Centre for Cancer (9)

Table 4.1b: The age standardized incidence rate of bladder cancer in the UK

Age group	**Age standardised rate per 100,000 population in England in 2012**		
	Men	*Women*	*Both*
under 40	0.2	0.1	0.1
40-49	3.2	1.5	2.4
50-59	13.6	5.5	9.5
60-69	48.1	14.4	31.3
70-79	127.5	34.7	81.1
80+	236.6	66.7	151.6

Source; National Collaborating Centre for Cancer (9)

To use both data sources in the model it will be necessary to assume that age and stage specific incidence rates are independent. This means that the stage distribution of cancers will not change with patient's age.

4.2 Breast cancer

The data on breast cancer incidence was obtained from multiple sources, as no source had the incidence by stage at diagnosis for different age groups. The stage distribution of breast cancer was obtained from Walters et al. (10) and the age distribution of breast cancer was obtained from Cancer

Research UK (11). A study by Woods *et al*. (12) reported the age and stage distributions of breast cancer incidence in the UK separately.

4.2.1 Stage distribution

Walters *et al*. (10) report the stage distribution but not the age distribution of breast cancer incidence in the UK for breast cancers diagnosed between 2000-07. It should be noted that cancer sites with a missing stage will be underreported in Table 4.2a, as all cancer registries in the UK with over 50% missing stage information (three English regional registries) were excluded from the analyses.

Table 4.2a: The incidence of breast cancer by stage at diagnosis in the UK from 2000-7

TNM Stage	Number	Mean Age	Percentage
All patients	140,568	63	
Missing Stage	35,517	67.7	
Stage 1	44,135	60.6	42.0%
Stage 2	47,738	61.2	45.4%
Stage 3	8,663	63.3	8.2%
Stage 4	4,515	67.6	4.3%

Source; Walters *et al*. (10)

A study by Woods et al. (12) compared the incidence by age and stage of breast cancer incidence over time from 1980 -2002. Data was collected over this time period from the West Midlands cancer registry and in the period of 1990-94 for the whole of the UK. The age specific incidence rates by stage at diagnosis are presented in Figure 2 of the paper.

4.2.2 Age distribution

Cancer research UK present data on the age specific incidence rates breast cancer in females in the UK from 2009-11 (11). Table 4.2b shows a clear pattern in that incidence is increasing with age until age 70 to 74, were there is a decrease in the incidence rate. This is unsurprising as the age extension of breast cancer screening did not start until 2011. Screening stopped for the women in this cohort at age 70.

Table 4.2b: The incidence of breast cancer by age in the UK from 2009-11

Age Range	Female Cases	Rate per 100,000 female population
0 to 04	0	0
05 to 09	0	0
10 to 14	1	0
15 to 19	4	0.2
20 to 24	34	1.6
25 to 29	180	8.4
30 to 34	537	26.5
35 to 39	1331	61.9
40 to 44	2899	123.3
45 to 49	4844	209.2
50 to 54	5608	277.3
55 to 59	4982	272.8
60 to 64	6805	354.9
65 to 69	6089	399.7
70 to 74	4188	323.2
75 to 79	4228	382.7
80 to 84	3639	414.5
85+	4187	447.4
All Ages	49557	155.2

Source; Cancer Research UK (11)

Woods *et al*. (12) present data on the three-year rolling average incidence rate for a primary invasive breast cancer in the West Midlands from 1980-2002. This data is presented in Figure 3 of Woods *et al.*(12).

4.3 Colorectal cancer

There were multiple sources on the incidence of colorectal cancer across different age groups and stage at diagnosis groups. The stage distribution of colorectal cancer was obtained from Maringe *et al.*(13) and the age distribution of colorectal cancer was obtained from Cancer Research UK(11). Both of these data sources include data collected after the NHS bowel screening programme was introduced in England in 2006. Data on CRC cancer incidence prior to 2006 was obtained from Whyte *et al.*(b) (14).

4.3.1 Stage distribution of colorectal cancer incidence

Maringe *et al*. (13) report the stage distribution but not the age distribution of colorectal cancer incidence in the UK for colorectal cancers diagnosed from 2000-07. This data was used for the stage distribution of colorectal cancer as it based upon the same dataset that was used to estimate the one year net survival. It should be noted that cancer sites with a missing stage will be underreported in Table 4.3a, as all cancer registries in the UK with over 50% missing stage information (Wales and one English regional registry) were excluded from the analyses. This data only includes two out of seven years in which the NHS bowel screening programme was active. This is the most recent data known on the stage distribution of the incidence of colorectal cancer.

Table 4.3a: The stage distribution of colorectal cancer incidence in the UK from 2000-07.

Dukes' stage	**Rectal**			**Colon**			**Colorectal**		
	Observed	Mean age	%	Observed	Mean age	%	Observed	Mean age	%
All patients	67,399	70.4	0%	142,410	72.3	0.0%	209,809	71.7	0%
Missing Stage	20,630	73.3	30.6%	39,585	74.8	27.8%	60,215	74.3	28.7%
Stage A	9,693	69.5	14.4%	9,644	71.2	6.8%	19,337	70.3	12.9%
Stage B	13,355	70.1	19.8%	39,588	72.4	27.8%	52,943	71.8	35.4%
Stage C	15,802	68.2	23.4%	36,037	70.7	25.3%	51,839	69.9	34.7%
Stage D	7,919	68.9	11.7%	17,286	70.6	12.1%	25,205	70.1	16.8%

Source; Maringe *et al*. (13)

4.3.2 Age distribution of colorectal cancer incidence

Data on the age profile of colorectal cancer incidence was obtained from Cancer Research UK statistics on the incidence of bowel cancer across age groups. This data was only available from 2009-11, so it reflects the age distribution of colorectal cancer when all patients have been screened for colorectal cancer. This data is presented in Table 4.3b.

Table 4.3b: The age distribution of colorectal cancer in the UK 2009-11

Age Range	Cases		Rate per 100,000 population	
	Male	Female	Male	Female
0 to 04	0	0	0.00	0.00
05 to 09	0	1	0.00	0.10
10 to 14	6	6	0.30	0.30
15 to 19	11	14	0.50	0.70
20 to 24	22	28	1.00	1.30
25 to 29	53	55	2.50	2.60
30 to 34	96	79	4.70	3.90
35 to 39	119	109	5.60	5.10
40 to 44	257	263	11.20	11.20
45 to 49	518	462	22.90	20.00
50 to 54	923	730	46.50	36.10
55 to 59	1,510	1052	84.80	57.60
60 to 64	3,066	1895	166.00	98.80
65 to 69	3,605	2245	252.20	147.40
70 to 74	3,789	2505	327.70	193.30
75 to 79	3,719	2842	415.70	257.20
80 to 84	2,960	2760	490.50	314.40
85+	2,280	3119	518.10	333.30
All Ages	22,934	18166	74.50	56.90

Source; Cancer Research UK (15)

To use the stage profile of colorectal cancer incidence and the age profile of colorectal cancer incidence in the model, it will be necessary to assume that age and stage specific incidence rates are independent. This means that the stage distribution of cancers will not change with patient's age.

4.3.3 Stage and age distribution of colorectal cancer incidence

Whyte *et al.*(b) (14) obtained the data on CRC cancer incidence from English cancer registry data for Oxford, Northern and Yorkshire and Eastern regions from 2004-06. This data shows the incidence of colorectal cancer across age groups prior to the implementation of the NHS bowel screening programme. Table 4.3c shows that the rate of colorectal cancer incidence is generally increasing in age and that the most common stage that people will present is Dukes stage C.

Table 4.3c: The incidence of colorectal cancer from 2004 - 06.

	Incidence rates per 100,000 population				
Age Range	**Dukes stage A**	**Dukes stage B**	**Dukes stage C**	**Stage D**	**CRC (all stages)**
0-29	0.03	0.10	0.17	0.19	0.48
30-34	0.20	0.50	1.02	0.77	2.48
35-39	0.67	0.90	2.04	1.51	5.11
40-44	0.87	1.45	3.25	3.11	8.68
45-49	2.04	5.54	7.87	6.56	22.02
50-54	4.11	8.51	14.92	12.60	40.15
55-59	7.69	15.77	25.49	19.76	68.70
60-64	13.32	26.35	39.78	31.19	110.65
65-69	20.78	44.20	60.87	46.90	172.74
70-74	29.73	67.14	84.04	63.47	244.38
75-79	35.38	89.36	109.04	86.18	319.95
80-84	33.30	96.01	129.00	106.64	364.96
85+	22.69	76.42	135.90	129.00	364.02

Source; Whyte *et al*.(b) (14)

In the model the data from Cancer Research UK and Maringe *et al*. will be used to model the incidence of colorectal cancer. This the data in both sources covers the period in which the NHS bowel screening programme was operating (2006 onwards).

4.4 Lung cancer

The data on Lung cancer incidence was obtained from multiple sources, as no source had the incidence by stage at diagnosis for different age groups. The stage distribution of Lung cancer was obtained from Walters *et al.*(16),the proportion of Lung cancers which were NSCLC or SCLC was obtained from a the national lung cancer audit (17) and the age profile of lung cancer incidence was obtained from cancer research UK(18).

4.4.1 Stage distribution

Walters *et al*. (16) report the stage distribution but not the age distribution of Lung cancer incidence in the UK for Lung cancers diagnosed from 2000-07. This data was used for the stage distribution of Lung cancer as it based upon the same dataset that was used to estimate the one year net survival. It should be noted that cancer sites with a missing stage will be underreported in Table 4.4a, as all cancer registries in the UK with over 50% missing stage information (Wales and six English regional registries) were excluded from the analyses.

Table 4.4a: The stage distribution of Lung cancer incidence in the UK from 2004-07(16).

	Small cell lung cancer		Non-small cell lung cancer	
TNM Stage	**Number**	**Percentage**	**Number**	**Percentage**
All patients	3,250		22,993	
Stage I	96	2.95%	2,376	10.3%
Stage II	67	2.06%	1,165	5.1%
Stage III	529	16.28%	4,718	20.5%
Stage IV	1,309	40.28%	7,759	33.7%
Missing Stage	1,249	38.43%	6,975	30.3%

Source, Walters *et al*. (16)

4.4.2 The age profile of non small cell and small cell lung cancer

Data on the age profile of non small cell and small cell lung cancer incidence was obtained from lung cancer cases that first presented in 2013 (19). When calculating these rates it was assumed that carcinoid lung cancers were counted as lung cancers, despite these cancers not been included in the economic model.Therefore the percentage of NSCLC and SCLC cases do not add to 100%.

Table 4.4b: The percentage of lung cancers which are non small cell or small cell lung cancer from a subsection of cases in England, Scotland and Wales in 2013

	Proportion of male cases NSCLC	Proportion of female cases NSCLC	Proportion of male cases SCLC	Proportion of female cases of SCLC
0-54	87.3%	81.6%	12.3%	17.5%
55-59	84.7%	83.6%	15.2%	16.3%
60-64	84.9%	83.2%	14.9%	16.6%
65-69	87.6%	84.7%	12.3%	15.1%
70-74	88.3%	86.6%	11.7%	13.2%
75-79	90.1%	89.1%	9.9%	10.8%
80-84	92.0%	91.7%	7.9%	8.2%
85+	95.5%	96.7%	4.5%	3.3%
Total	89.2%	87.7%	10.8%	12.1%

Source, National lung cancer audit(17); NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

4.4.3 The age profile of lung cancer

The age profile of lung cancer was obtained from cancer research UK(20). This information was presented seperately for males and females.

Table 4.4c: The age distribution of lung cancer in the UK 2009-11

Age Range	Male Cases	Female Cases	Male Rates	Female Rates
0 to 04	1	1	0	0.1
05 to 09	0	0	0	0
10 to 14	0	1	0	0
15 to 19	4	5	0.2	0.3
20 to 24	6	7	0.3	0.3
25 to 29	13	11	0.6	0.5
30 to 34	23	20	1.1	1
35 to 39	58	48	2.7	2.2
40 to 44	157	140	6.8	6
45 to 49	353	368	15.6	15.9
50 to 54	751	722	37.8	35.7
55 to 59	1,553	1,294	87.3	70.8
60 to 64	2,737	2,253	148.2	117.5
65 to 69	3,596	2,774	251.5	182.1
70 to 74	4,271	3,100	369.4	239.3
75 to 79	4,146	3,118	463.5	282.2
80 to 84	3,411	2,838	565.2	323.3
85+	2,563	2,570	582.3	274.6
All Ages	23,642	19,271	76.8	60.3

Source, Cancer Research UK (20)

To use the stage profile of Lung cancer incidence, the age profile of non small cell lung cancer incidence in the model amd the age profile of lung cancer incidence it was necessary to assume that these rates are independent. This means that the stage distribution of cancers will not change with patient's age, however the proportion of lung cancer cases that are non small cell lung cancer will change with a patient's age.

4.5 Ovarian cancer

The data on ovarian cancer incidence was obtained from multiple sources, as no source had the incidence by stage at diagnosis for different age groups. The stage distribution of ovarian cancer was obtained from Maringe *et al.*(21) and the age distribution of ovarian cancer was obtained from a report by the Trent cancer registry (22).

4.5.1 Stage distribution

Maringe *et al*. (21) present the stage distribution of ovarian cancer incidence in the UK for cancers diagnosed from 2004-07. This data is calculated from the same dataset that was used to estimate the one year net survival. It should be noted that cancer sites with a missing stage are underreported in Table 4.5a, as all cancer registries in the UK with over 50% missing stage information (Wales and four English regional registries) were excluded from the analyses.

Table 4.5a: The stage distribution of ovarian cancer incidence in the UK from 2004-07.

FIGO Stage	Number	Percentage of cases
All patients	11909	
Stage I	2681	22.5%
Stage II	478	4.0%
Stage III	3127	26.3%
Stage IV	1842	15.5%
Missing stage	3781	31.7%

Source, Maringe *et al*.(21)

4.5.2 Age distribution

Data on the age profile of ovarian cancer incidence was obtained from a 2012 Trent cancer registry report on the incidence, survival and mortality from ovarian cancer in England (22). Table 4.5b shows that the age specific incidence rate is increasing in age for women, the incidence rate after age 75 is broadly similar for all age groups.

Table 4.5b: The age distribution of ovarian cancer in England in 2009.

Age Band	Total Cases	Rate *
15-19	26	1.6
20-24	64	3.7
25-29	89	5.2
30-34	95	5.9
35-39	161	8.8
40-44	255	12.9
45-49	332	17.6
50-54	441	27.1
55-59	560	36.9
60-64	767	48.3
65-69	709	58.2
70-74	732	68.2
75-79	609	66.2
80-84	462	63.1
85+	547	69.5

Source, Trent cancer registry (22);

* Rate is the age specific incidence rate per 100,000 female population

To use the stage profile of ovarian cancer incidence and the age profile of ovarian cancer incidence in the model it was necessary to assume that age and stage specific incidence rates are independent. This means that the stage distribution of cancers does not change with patient's age.

5 Appendix: Cancer Survival Data summary

5.1 Bladder cancer

The NCC-C draft clinical guidelines were used as the source of survival data in the model (9). The NCC-C draft clinical guidelines for the diagnosis and management of bladder cancer use relative survival statistics to show the effect of stage of diagnosis on the probability that a patient will be alive after one or five years. The NCC-C draft clinical guidelines for the treatment and diagnosis of bladder cancer (9) present the one and five year relative survival of bladder cancer patients in England and Wales separately. To estimate these survival figures, data was collected from the National Cancer Registration Service (NCRS) in England and the Welsh Cancer Intelligence and Surveillance Unit (WCISU). Data from Wales is not presented, as it will not be used in the model due to the lower sample size of the Welsh population. The one year and five year relative survival of all bladder cancer patients in England is shown Table 5.1.

Table 5.1: The one year and five year relative survival of bladder cancer patients in England

TNM Stage	**One year relative survival, (95% confidence interval)**		**Five year relative survival, (95% confidence interval)**	
	Men	*Women*	*Men*	*Women*
Stage I	95.3%, (93.8%, 96.4%)	90.9%, (87.5%, 93.5%)	78.5%, (72.7%, 83.3%)	76.2%, (65.1%, 84.2%)
Stage II	72.6%, (70.0%, 74.9%)	58.3%, (53.8%, 62.5%)	39.6%, (34.4%, 44.7%)	36.8%, (30.9%, 42.8%)
Stage III	63.8%, (57.8%, 69.2%)	55.5%, (47.0%, 63.3%)	29.4%, (19.9%, 39.5%)	33.8%, (22.6%, 45.3%)
Stage IV	42.2%, (39.6%, 44.8%)	34.4%, (30.6%, 38.3%)	11.4%, (7.5%, 16.2%)	12.4%, (8.9%, 16.6%)
Unknown	78.8% (78.1%, 79.4%)	65.2%, (64.1%, 66.3%)	61.1%, (59.7%, 62.5%)	48.1%, (45.9%, 50.3%)

Source; National Collaborating Centre for Cancer (9)

The NCC-C draft clinical guidelines present the relative survival of bladder cancer by age and the relative survival of bladder cancer by stage separately. This data does not include a breakdown of the relative survival of patients across age groups and stage at diagnosis groups. This data will not be used in the model, as it would be necessary to make the following assumptions:

1. Which age group was the baseline for shifting the stage distribution.

2. Independence of stage and age effects.

Also the results of combining the stage and age data would have to be consistent with the information presented in Table X.

5.2 Breast cancer

As part of the ICBP, Walters *et al*. (10) published estimates of the one and three year net-survival of breast cancer patients in the UK from 2000-07. Data for the UK covered England, Wales and Northern Ireland, but not Scotland (10). In the study all cancer registries with less than 50% of patients with a valid stage were excluded from the analyses. This lead to the exclusion of three out of the eight English cancer registries for the TNM stage analysis. Walters *et al.* (10) also present the survival of breast cancer by SEER summary stage. The SEER summary stage could only be calculated if there are records for each patient's T, N and M separate from the overall stage. The English cancer registries did not collect this data. Therefore, the net survival estimates using the SEER summary stages are based upon Northern Irish and Welsh data only. Table 5.2a shows that patients who are diagnosed at an earlier stage have higher survival. For patients who are diagnosed at Stage I or II, age appears to have little impact on net survival. However for Stages III and IV, patients who are diagnosed at a younger age have higher survival.

Table 5.2a: Survival of breast cancer patients in the UK from 2000-07

TNM Stage	One year net survival, (95% confidence interval)			
	Age Standardised	15-49	50-69	70-99
All patients	94.3%, (94.2%, 94.4%)	98%, (97.8%, 96.1%)	96.9%, (96.8%, 97%)	87.9%, (87.6%, 88.2%)
Stage I	100%, (100%, 100%)	100%, (99.9%, 100%)	100%, (100%, 100%)	100%, (100%, 100%)
Stage II	99.2%, (99.2%, 99.3%)	99.2%, (99.1%, 99.3%)	99.3%, (99.2%, 99.4%)	99.1%, (99.0%, 99.3%)
Stage III	90.9%, (90.5%, 91.4%)	95.5%, (94.8%, 96.2%)	93.9%, (93.3%, 94.5%)	84.2%, (82.9%, 85.4%)
Stage IV	53%, (52%, 54%)	68.3%, (65.5%, 71.1%)	60%, (58.2%, 61.9%)	42.2%, (40.3%, 44.1%)
Missing Stage	87.3%, (87.1%, 87.6%)	96.4%, (96%, 96.7%)	93.2%, (92.9%, 93.6%)	79.9%, (79.2%, 80.5%)
	Three year net survival, (95% confidence interval)			
All patients	87.4%, (87.3%, 87.6%)	91.1%, (90.8%, 91.4%)	91.6%, (91.4%, 91.8%)	78.6%, (78.1%, 79.1%)
Stage I	99.3%, (99.2%, 99.4%)	98.5%, (98.2%, 98.8%)	99.4%, (99.2%, 99.5%)	99.7%, (99.6%, 99.9%)
Stage II	92.4%, (92.2%, 92.7%)	92.4%, (92%, 92.9%)	93.1%, (92.8%, 93.5%)	91.2%, (90.4%, 92.1%)
Stage III	70.7%, (69.9%, 71.5%)	76.5%, (74.8%, 78.1%)	74.6%, (73.3%, 76%)	61.9%, (59.9%, 63.9%)
Stage IV	27.9%, (26.9%, 28.9%)	36.2%, (33.1%, 39.4%)	33.1%, (31.2%, 35%)	20.8%, (19.0%, 22.6%)
Missing Stage	77.1%, (76.7%, 77.5%)	88%, (87.2%, 88.7%)	85.7%, (85.2%, 86.3%)	66.9%, (66.0%, 67.9%)

Source; Walters et al.(10)

Five year relative survival information was obtained from the Cancer Research UK website, this information is presented in Table X below. This information includes all women diagnosed with breast cancer in 2002-06 in the Former Anglia cancer network.

Table 5.2b: The five year relative survival of female breast cancer patients in the former Anglia cancer network in 2002-06

Stage	Relative survival
Stage I	99.1%
Stage II	87.6%
Stage III	55.1%
Stage IV	14.7%
All Stages	85.8%
Stage Not Known	63.7%

Source, Cancer Research UK (20)

5.3 Colorectal cancer

The one year and three-year net-survival of colorectal cancer patients in the UK from 2000-07 was reported in Maringe *et al.*(13). In the study all cancer registries with less than 50% of patients with a valid stage were excluded from the analyses. In the colon cancer analysis the Welsh registry was excluded and in the rectal cancer analysis one English registry and the Welsh registry were excluded. Tables 5.3a and 5.3b show that patients who are diagnosed at an earlier stage or a younger age, have higher survival. Tables 5.3a and 5.3b also show that patients diagnosed with colon cancer tend to have a worse prognosis than a patient diagnosed with rectal cancer.

Table 5.3a: The one year net survival of colorectal cancer patients in the UK from 2000-07 in different stage at diagnosis and age groups

Duke's stage	**One year net survival, (95% Confidence Interval)**			
	Age standardised	15-49	50-69	70-99
	Colon cancer			
All patients	67.4%, (67.2%, 67.6%)	80.6%, (79.9%, 81.4%)	76.5%, (76.1%, 76.8%)	61.6% (61.3%, 61.9%)
Stage A	95.7%, (95.3%, 96.2%)	98.8%, (98%, 99.6%)	97.8%, (97.3%, 98.3%)	94.4% (93.5%, 95.2%)
Stage B	90.1%, (89.8%, 90.4%)	96.8%, (96.2%, 97.4%)	94.4%, (94%, 94.7%)	87.6% (87.1%, 88%)
Stage C	76.8%, (76.4%, 77.1%)	87.2%, (86%, 88.3%)	83.6%, (83.1%, 84.1%)	71.4% (70.8%, 72%)
Stage D	34.2%, (33.7%, 34.7%)	50.8%, (48.4%, 53.2%)	43.6%, (42.6%, 44.7%)	26% (25.2%, 26.8%)
Missing Stage	42.9%, (42.6%, 43.3%)	72.4%, (70.6%, 74.1%)	58.9%, (58.1%, 59.7%)	35.3% (34.7%, 35.8%)
Rectal Cancer				
All patients	75.2%, (75%, 75.5%)	86%, (85.2%, 86.9%)	83.2%, (82.8%, 83.6%)	67.7%, (67.2%, 68.2%)
Stage A	95.7%, (95.4%, 96%)	99.2%, (98.9%, 99.4%)	97.5%, (97.1%, 97.9%)	93.8%, (93%, 94.6%)
Stage B	91.5%, (91.1%, 91.8%)	98.1%, (97.8%, 98.5%)	95%, (94.5%, 95.4%)	88.2%, (87.4%, 89%)
Stage C	87.4%, (87%, 87.8%)	94.5%, (93.4%, 95.5%)	92.1%, (91.6%, 92.6%)	81.7%, (80.8%, 82.6%)
Stage D	43.2%, (42.5%, 43.8%)	57.9%, (55.2%, 60.7%)	52.5%, (51.2%, 53.8%)	31.7%, (30.4%, 32.9%)
Missing Stage	59.4%, (58.9%, 59.9%)	79.4%, (77.3%, 81.4%)	70.1%, (69.2%, 71.1%)	49%, (48.1%, 49.8%)

Source; Maringe *et al. (13)*

Table 5.3b: The three year net survival of colorectal cancer patients in the UK from 2000-07 in different stage at diagnosis and age groups

Dukes' stage	**Three year net survival, (95% Confidence Interval)**			
	Age standardised	15-49	50-69	70-99
Colon cancer				
All patients	54.9%, (54.7%, 55.1%)	65.1%, (64.1%, 66.1%)	62%, (61.6%, 62.5%)	50.4%, (50.0%, 50.7%)
Stage A	94.9%, (94.2%, 95.5%)	96.7%, (95.1%, 98.3%)	95.9%, (95.1%, 96.7%)	94.2%, (92.9%, 95.4%)
Stage B	84.8%, (84.4%, 85.2%)	90.1%, (88.9%, 91.4%)	88.1%, (87.5%, 88.6%)	82.8%, (82.1%, 83.5%)
Stage C	58.1%, (57.7%, 58.6%)	65.8%, (63.9%, 67.7%)	64.4%, (63.6%, 65.2%)	53.4%, (52.6%, 54.2%)
Stage D	11.6%, (11.3%, 12%)	18.3%, (16.3%, 20.3%)	16.0%, (15.1%, 16.8%)	8.0%, (7.4%, 8.5%)
Missing Stage	31.2%, (30.8%, 31.6%)	58.2%, (56.2%, 60.2%)	44.8%, (43.9%, 45.7%)	24.6% (24.0%, 25.1%)
Rectal Cancer				
All patients	59.9%, (59.5%, 60.2%)	69.7%, (68.3%, 71%)	67.8%, (67.2%, 68.3%)	52.5%, (51.9%, 53.1%)
Stage A	94%, (93.5%, 94.5%)	97.7%, (97%, 98.3%)	95.6%, (95%, 96.2%)	92.3%, (91.1%, 93.5%)
Stage B	84.1%, (83.6%, 84.6%)	91.9%, (90.9%, 93%)	87.2%, (86.4%, 88%)	81%, (79.8%, 82.2%)
Stage C	67.5%, (66.8%, 68.2%)	75.8%, (73.4%, 78.2%)	72.7%, (71.6%, 73.7%)	61.1%, (59.8%, 62.5%)
Stage D	14.4%, (13.9%, 15%)	20.3%, (17.9%, 22.7%)	18.9%, (17.8%, 20.1%)	9.1%, (8.3%, 10.0%)
Missing Stage	40.7%, (40.1%, 41.2%)	63.2%, (60.6%, 65.8%)	52.4%, (51.3%, 53.6%)	29.1%, (28.2%, 30.0%)

Source; Maringe *et al*.(13) In tables III and IV of the supplementary material

5.4 Lung cancer

The one year net-survival of lung cancer patients in the UK from 2004-07 was reported in Walters *et al*.(16). In the study all cancer registries with less than 50% of patients with a valid stage were excluded from the analyses, this lead to the exclusion six English cancer registries and the Welsh cancer registry. Table 5.4a shows that patients who are diagnosed at an earlier stage have a better chance of survival than someone who is diagnosed at a later stage and that a patient who is diagnosed at a younger age have a better chance of survival than someone who is diagnosed at an older age.

Table 5.4a: The one year net survival of lung cancer patients in the UK from 2004-07 in different stage at diagnosis and age groups.

TNM Stage	One year net survival, (95% confidence interval)			
	Age standardised	*15-54*	*55-74*	*75-99*
Non small cell lung cancer				
All patients	29.6% (29.1%,30%)	41.5% (39.6%,43.5%)	32.5% (31.7%,33.2%)	22.6% (21.8%,23.3%)
Stage I	72.5% (71.4%,73.6%)	90.0% (88%,92%)	77.5% (75.6%,79.3%)	60.9% (58.2%,63.6%)
Stage II	59.8% (57.9%,61.7%)	79.9% (74.5%,85.2%)	65.3% (62.1%,68.5%)	45.5% (41.6%,49.4%)
Stage III	35.3% (34.3%,36.3%)	44.4% (40.2%,48.6%)	39.6% (37.9%,41.4%)	26.3% (24.6%,28.1%)
Stage IV	15.9% (15.3%,16.4%)	24.5% (22%,27.1%)	17.1% (16.1%,18%)	10.9% (9.9%,11.8%)
Missing Stage	20.6% (19.9%,21.2%)	42.1% (38%,46.1%)	23.7% (22.4%,25%)	16.0% (14.9%,17%)
Small cell lung cancer				
All patients	24.9%, (23.7%,26.1%)	33.2%, (33.9%,40.7%)	27.9%, (26.2%,29.6%)	14.4%, (12.5%,16.2%)
Stage I and II*	55.9%*, (49.6%,62.2%)	82.2%*, (70.5%,93.8%)	57.3%*, (48.7%,65.9%)	44.9%*, (32.4%,57.5%)
Stage III	37.3%, (33.9%,40.7%)	50.8%, (40.5%,61%)	42.2%, (37.3%,47.1%)	18.8%, (13.1%,24.5%)
Stage IV	14.4%, (13.1%,15.8%)	19.9%, (15.8%,24%)	14.7%, (12.9%,16.5%)	11.1%, (8.7%,13.6%)
Missing Stage	24.2%, (22.4%,26.1%)	38.2%, (30.8%,45.6%)	28.0%, (25.3%,30.8%)	13.7%, (11%,16.4%)

Source, Walters *et al.* (16);

* due to small patient numbers stage I and II small cell lung cancer were grouped in the survival analyses

The clinical advisors believed that the survival figures present in Walters *et al.* (16) were likely to be lower than current survival of lung cancer patients in the UK. These figures will be used in the model as they are likely to be unfavorable to an early cancer detection strategy.

5.5 Ovarian cancer

The one year net-survival of ovarian cancer patients in the UK from 2004-07 was reported in Maringe *et al*. (21). In the study all cancer registries with less than 50% of patients with a valid stage were excluded from the analyses, this lead to the exclusion four English cancer registries and the Welsh cancer registry. Table 5.5a shows that patients who are diagnosed at an earlier stage has a

better chance of survival than someone who is diagnosed at a later stage and that a patient who is diagnosed at a younger age has a better chance of survival than someone who is diagnosed at an older age.

Table 5.5a: The one year net survival of ovarian cancer patients in the UK from 2004-07 in different stage at diagnosis and age groups.

FIGO Stage	**One year net survival, (95% Confidence Interval)**			
	Age standardised	*15-49 year olds*	*50-69 year olds*	*70-99 year olds*
All patients	68.7%, (68.3%, 69.1%)	92.8%, (92.3%, 93.2%)	78.0%, (77.3%, 78.7%)	48.3%, (47.1%, 49.5%)
Stage I	97.2%, (96.9%, 97.6%)	98.9%, (98.4%, 99.3%)	97.4%, (96.8%, 98%)	94.6%, (92.9%, 96.4%)
Stage II	89.9%, (88.5%, 91.3%)	95.9%, (94%, 97.8%)	91.5%, (89.1%, 93.9%)	83.7%, (78.8%, 88.6%)
Stage III	70.3%, (69.2%, 71.4%)	84.1%, (81.1%, 87.0%)	76.4%, (74.6%, 78.2%)	57.1%, (54.5%, 59.6%)
Stage IV	52.6%, (51.1%, 54.1%)	71.5%, (65.9%, 77.1%)	66.3%, (63.6%, 69.1%)	35.7%, (32.8%, 69.1%)
Missing stage	51.0%, (50.0%, 52.0%)	88.2%, (86.0%, 90.4%)	67.9%, (65.9%, 70%)	31.2%, (29.3%, 33.1%)

Source, Maringe *et al*. (21)

Five year relative survival information was obtained from the Cancer Research UK website, this information is presented in Table 5.5b below. This information includes all women diagnosed with breast cancer in 2002-06 in the Former Anglia cancer network.

Table 5.5b: The five year relative survival of ovarian cancer patients in the former Anglia cancer network in 2002-06

Stage	Relative survival
Stage I	90%
Stage II	42.8%
Stage III	18.6%
Stage IV	3.5%
All Stages	39.3%
Stage Not Known	12.5%

Source, Cancer Research UK (20)

6 Appendix: Fitted survival curves

Cancer Research UK and Brenner et al. were searched for information on wether the fraction of cancer survivors (in the last year in which there was survival information) who had non-terminal cancer would vary by stage for each cancer type(20;23). There was no information to indicate that the fraction of cancer survivors who had non-terminal cancer patients varied by stage for any of the cancer types. Therefore in each cancer type, the fraction of cancer survivors who had non-terminal cancer was assumed to be constant. The solver function in Microsfot Excel® was used to calculate the fraction of patients who have non-terminal cancer by matching the modelled mortality (in a 2012 population) to the observed mortality in 2012 (adjusted for the modelled incidence rates). Exponential curves were fitted to the proportion of patients who were assumed to have a terminal cancer using the last in which there was stage specific survival.

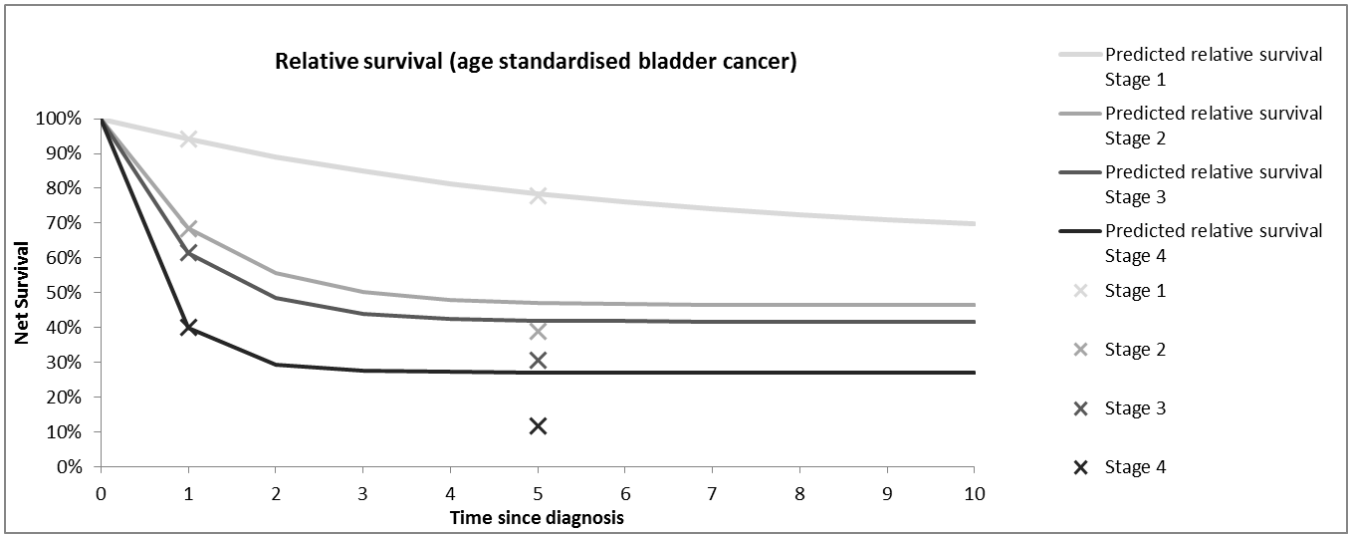
6.1 Bladder cancer

For bladder cancer one year and five year relative survival information was available by stage at diagnosis. When the curves were fitted to the five year survival data, the modelled moratlity was higher than the observed mortality even when 100% of patients who survived until five years were assumed to have non-terminal cancer. This is likely due to the fact that the survival data was based on a 2006-10 cohort of English patients. The difference between modelled and expected mortality could be due to improvements in the survival of bladder cancer patients between 2006 and 2012. Therefore, a fractional survival model was fitted using the one year survival information. The parameters used in the survival model are given in Table 6.1a and the fitted survival curves are shown in Figure 6.1a.

Table 6.1a: The parameters used in the fractional survival model for bladder cancer

Stage	1 year survival	Fraction of 1 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage 1	94.0%	69.9%	63.9%	0.18
Stage 2	68.5%	69.9%	46.5%	0.89
Stage 3	61.5%	69.9%	41.7%	1.08
Stage 4	40.0%	69.9%	27.1%	1.74

Figure 6.1a: The fitted survival curve for bladder cancer by stage at diagnosis



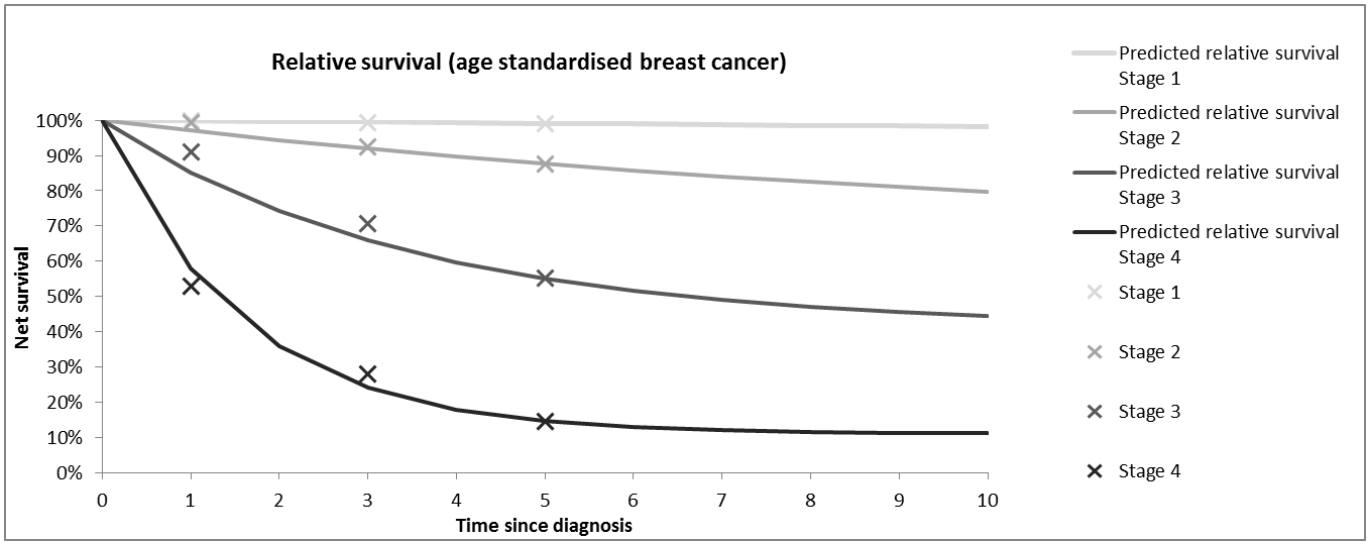
6.2 Breast cancer

Five year stage specific relative survival information was available for breast cancer so the fractional survival model was fitted using this data. The parameters used in the survival model are given in Table 6.2a and the fitted survival curves are shown in Figure 6.2a.

Table 6.2a: The parameters used in the fractional survival model for breast cancer

Stage	5 year survival	Fraction of 5 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage 1	99.1%	75.1%	74.41%	0.01
Stage 2	87.6%	75.1%	65.8%	0.09
Stage 3	55.1%	75.1%	41.4%	0.29
Stage 4	14.7%	75.1%	11.0%	0.64

Figure 6.2a: The fitted survival curve for breast cancer by stage at diagnosis



6.3 Colorectal cancer

Short term survival was presented separately for colon and rectal cancer. As there were differences in the relative survival of patients with colon and rectal cancer up until year three, survival curves were fitted to each cancer type. To enable the use of the curves in the model, an incidence weighted average of colon and rectal cancer was applied to combine the survival curves in the model. No data was available on the stage specific survival of colon or rectal cancer patients after three years. The fractional survival model was fitted to the three year relative survival information for clon and rectal cancer separately.The parameters used in the survival model are given in Tables 6.3a and 6.3b and the fitted survival curves are shown in Figures 6.3a and 6.3b.

Table 6.3a The parameters used in the fractional survival model for colon cancer

Stage	3 year survival	Fraction of 3 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage A	94.9%	87.1%	82.7%	0.12
Stage B	84.8%	87.1%	73.9%	0.29
Stage C	58.1%	87.1%	50.6%	0.63
Stage D	11.6%	87.1%	10.1%	1.37

Table 6.3b: The parameters used in the fractional survival model for rectal cancer

Stage	3 year survival	Fraction of 3 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage A	94.0%	87.1%	81.9%	0.13
Stage B	84.1%	87.1%	73.3%	0.30
Stage C	67.5%	87.1%	58.8%	0.52
Stage D	14.4%	87.1%	12.5%	1.29

Figure 6.3a: The fitted survival curve for colon cancer by stage at diagnosis

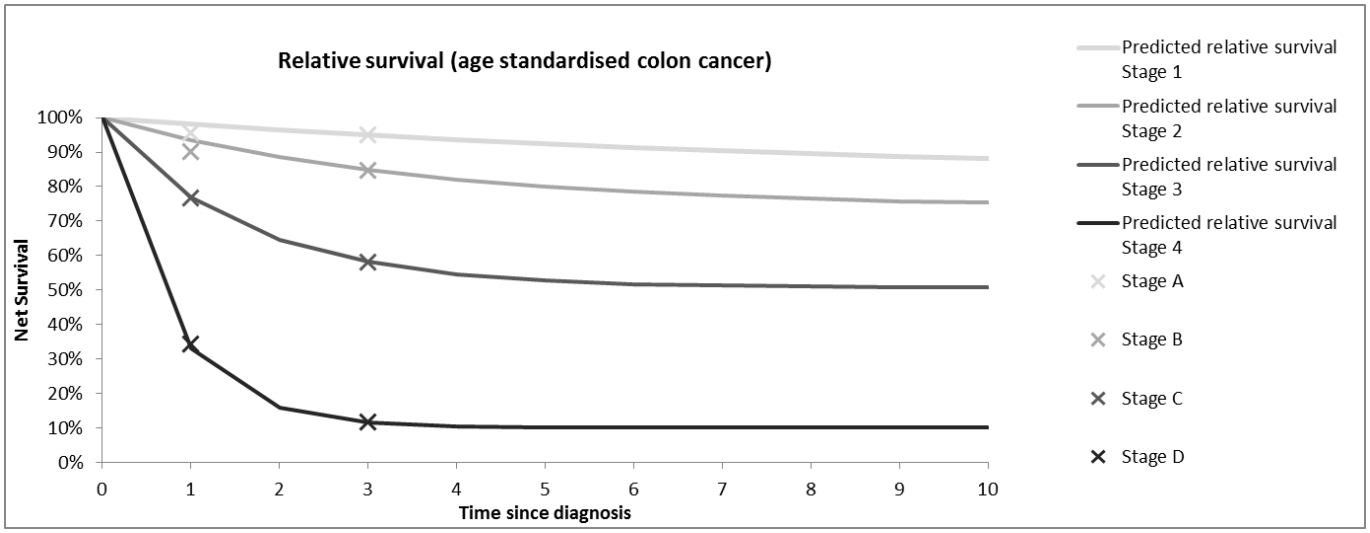
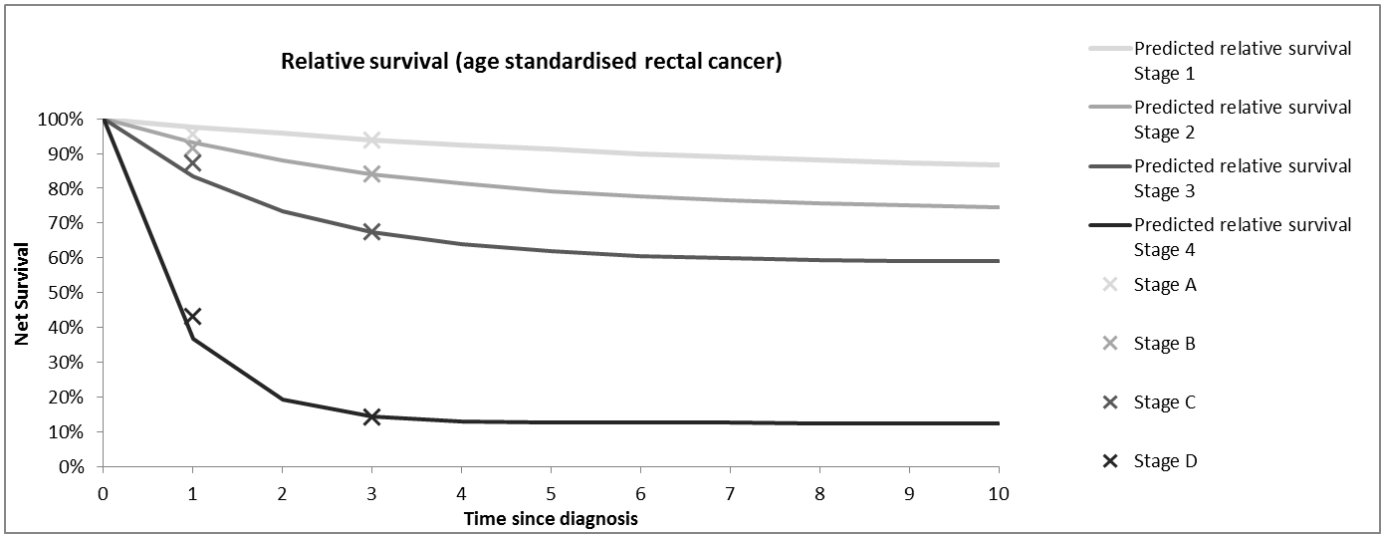


Figure 6.3b: The fitted survival curve for rectal cancer by stage at diagnosis



6.4 Lung cancer

Short term survival was presented separately for non-small cell and small cell lung cancer. As there were differences in the one year relative survival of patients with non-small cell and small cell lung, survival curves were fitted to each cancer type. The incidence of non-small cell and small cell lung cancer was modelled separately, so there was no need to combine the survival curves. No data was available on the stage specific survival of non small cell lung cancer or small cell lung cancer patients after one year years. The fractional survival model was fitted to the one year relative survival information for non-small cell and small cell lung cancer separately.The parameters used in the survival model are given in Tables 6.4a and 6.4b and the fitted survival curves are shown in Figures 6.4a and 6.4b.

Table 6.4a: The parameters used in the fractional survival model for for non small cell lung cancer

Stage	1 year survival	Fraction of 1 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage 1	72.5%	32%	23%	0.44
Stage 2	59.8%	32%	19%	0.69
Stage 3	35.3%	32%	11%	1.31
Stage 4	15.9%	32%	5%	2.17

Table 6.4b: The parameters used in the fractional survival model for small cell lung cancer

Stage	1 year survival	Fraction of 1 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage 1 and 2	56%	32%	18%	0.77
Stage 3	37%	32%	12%	1.24
Stage 4	14%	32%	5%	2.27

Figure 6.4a: The fitted survival curve for non-small cell lung cancer

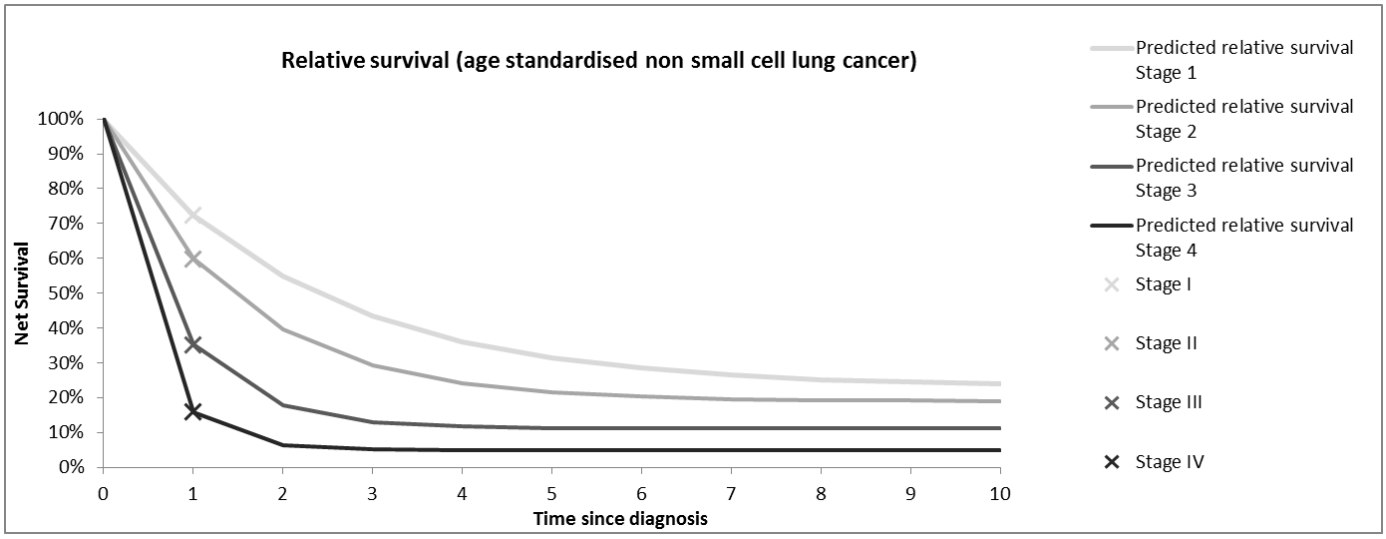
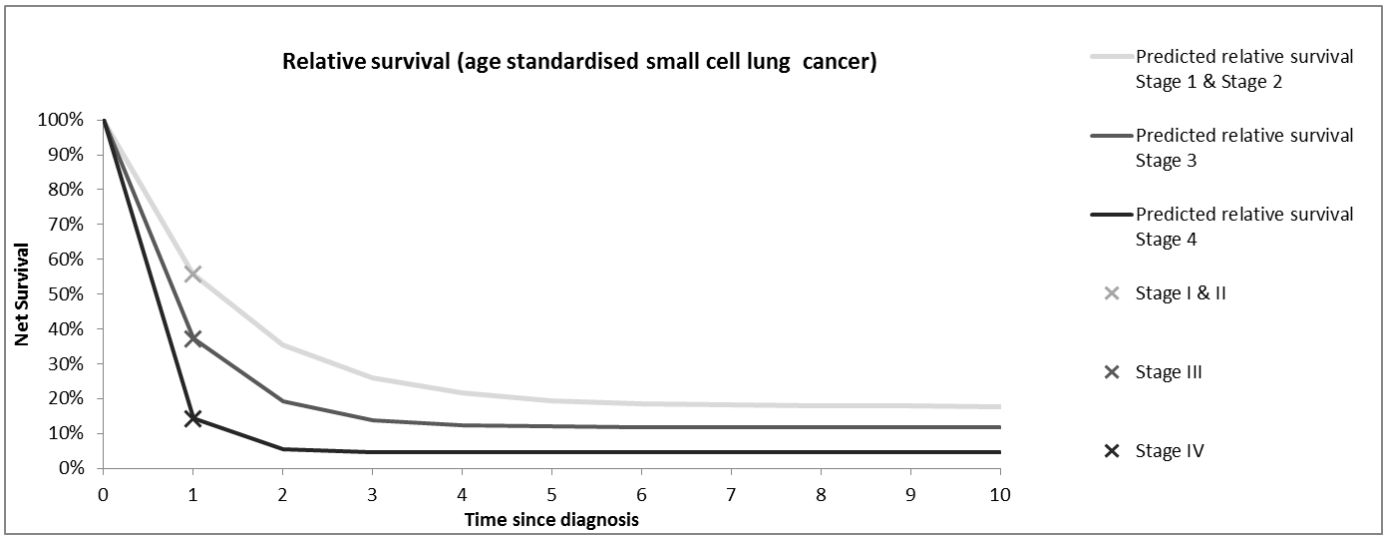


Figure 6.4b: The fitted survival curve for small cell lung cancer



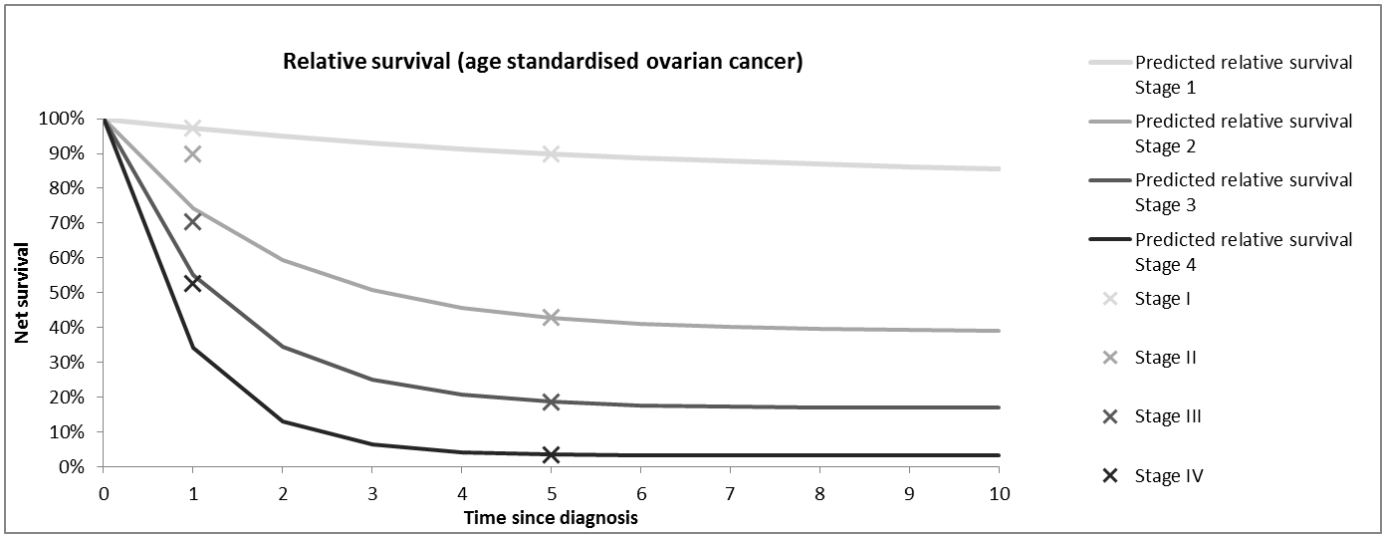
6.5 Ovarian cancer

Five year stage specific relative survival information was available for ovarian cancer so the fractional survival model was fitted using this data. The parameters used in the survival model are given in Table 6.5a and the fitted survival curves are shown in Figure 6.5a.

Table 6.5a: The parameters used in the fractional survival model for ovarian cancer

Stage	5 year survival	Fraction of 5 year survivors, who have a non-terminal cancer	Total proportion of patients who have a non-terminal cancer (γ)	Lambda (λ)
Stage 1	90%	91%	82%	0.16
Stage 2	43%	91%	39%	0.55
Stage 3	19%	91%	17%	0.78
Stage 4	4%	91%	3%	1.14

Figure 6.5a: The fitted survival curve for ovarian cancer



7 The National Screening Committee's criteria for a new screening programme in the UK

All 21 criteria used by the national screening committee when considering whetheror not to implement a new screening programme are listed below (23):

1. The condition should be an important health problem

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

5. There should be a simple, safe, precise and validated screening test.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

7. The test should be acceptable to the population.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

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