Cost-effectiveness evidence review

Familial breast cancer:

Classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.

Update of clinical guideline 14 and 41

Health economics evidence reviews & full reports 2004, 2006 & 2013

Health economics plan, 2013

Developed for NICE by the National Collaborating Centre for Cancer

Contents

1 Genetic Testing

1.1 Genetic testing for people with a family history but no personal history of breast cancer (2004) (Chapter 6.2)

1.1.1 Cost-effectiveness of genetic testing studies (2004)

Grann et al. (1999)

This is a US study that models the cost-effectiveness in terms of additional costs per life year saved of genetic testing of Ashkenazi Jewish women for BRCA1/2 gene mutations. A Markov model was constructed and analysed using Monte Carlo simulation. Costs were reported in 1995 US dollars and discounted at 3% per annum. Four prophylactic strategies were available for women testing positive: mastectomy and/or oophorectomy, or surveillance and cost-effectiveness results presented separately depending on the treatment strategy adopted.

Parameter values were taken from existing literature. No account was taken of costs associated with lost productivity.

Results with 95% confidence intervals derived from Monte Carlo simulation were as follows:

	Cost per life year gained (95% CI)
• Combined surgery	$20,717 (9507 – 46998)
• Mastectomy	$29,970 (15333 – 65281)
• oophorectomy	$72,780 (23014 – 240275)
• Surveillance	$134,273 (82838 – 267605)

These base case figures were based on a cost of $450 but a sensitivity analysis used a figure of $2,400. This increases the cost per life year gained in excess of $65,000 for each treatment strategy. Furthermore, it must be recognised that no quality adjustment of health gains was made.

Tengs et al. (1998) & Tengs and Berry (2000)

The first of these papers is a decision analysis that calculates the health implications of genetic testing in terms of additional life expectancy and QALYs. It is an outcomes study only, not an economic analysis, but is presented here since the second, cost-effectiveness analyses builds on it. The study attempts to synthesise evidence relating to likelihood of developing cancer with/without BRCA1/2 gene, error rate in genetic test, likelihood of prophylactic surgery, quality of life and length of life.

The alternative prophylactic strategies considered are mastectomy, mastectomy and oophorectomy, oophorectomy and no prophylactic measure.

There was a large range of data sources used which cannot be evaluated without reference to the original studies. Some estimates were made by a panel of cancer experts. Quality of life estimates associated with different states were also assumed.

Results show that, taking quality of life into account, a 30 year old (with the preferences described in the base case) would benefit from allowing a test to inform her decision. This is dependent on the pretest probability of carrying BRCA1/2. For example, at 0.5 the test is useful in helping women decide between oophorectomy vs. mastectomy and oophorectomy and generates an expected QALY gain of 0.45.

A range of sensitivities were explored. The general conclusion from these analyses is that women of "average" risk would not benefit substantially from testing but that women of "moderate to high" risk with no more than moderate concern about the quality of life implications of prophylactic surgery could benefit substantially from testing.

The second paper is a US cost-utility analysis based on a Markov decision model which compares testing vs. no testing. It builds upon the decision analysis presented in Tengs et al (1998) but updates several of the values. Principally, estimates are drawn from existing literature. A societal perspective is taken and sources used are a range of recently published evidence, government databases, company websites and a survey of breast cancer experts. Results are reported in 1998 US $'s and a discount rate of 3% applied to both costs and benefits.

Results are presented for different pre-test risks of BRCA1 and BRCA2 mutations. In the base case analysis, testing women with average population risk does not appear cost-effective ($1.6m per QALY). However, the ICER falls rapidly as the risk level rises and is well within conventionally accepted boundaries even for women of only a slightly elevated risk (p= 0.05 BRCA1, 0.05 BRCA2).

Base case results for low risk women $1,600,000 per QALY

Slightly higher risk	$34,000
Moderate risk	$15,000
High risk	$3500 to $4900

The sensitivity analysis revealed that this is sensitive to the penetrance of breast and ovarian cancers (lifetime probability of BRCA1 carriers developing cancer) although in "high risk" women (p=0.5 BRCA1) this does not take results above conventional cost-effectiveness thresholds. Altering the quality of life impact of mastectomy and oophorectomy could change the optimal strategy following a positive test but did not substantially alter the ICERs relating to testing.

Increasing the cost of the test from $2580 to $5000 takes the ICER beyond $50,000 for women at slightly increased risk.

Sevilla et al. (2002)

This study examines the cost-effectiveness of numerous alternative genetic testing techniques. These techniques were direct DNA sequencing (DS), denaturing high performance liquid chromatography (DHPLC), single-strand conformation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), heteroduplex analysis (HA), fluorescent assisted mismatch analysis (FAMA) and the protein truncation test (PTT). A total of twenty strategies were assessed. The motivation for the analysis is that the gene patent owner (Myriad genetics) may wish to restrict testing to the DS method only.
Comparisons are made in terms of cost per mutations diagnosed in a hypothetical population of 10,000 individuals with a 15% chance of harbouring the mutation. This was altered in sensitivity analyses.

Costs are presented in 2002 Euros. Direct costs were based on studies in three French laboratories.

Results indicate that, 15 of the 20 strategies can be eliminated on the basis of dominance, including DS. FAMA → DSF and FAMA → DS21 detect as many mutations as the DS method and are less costly. Of the approaches which are not dominated, ICERS are as follows;

PTT11+HA21→ DSF	971 euros
PTT11+ DHPLC21 → DSF	1873 euros
DHPLC→ DSF	9669 euros
FAMA11+DHPLC21 → DSF	18140 euros
FAMA → DSF	163173 euros

1.2 Estimating the Cost Effectiveness of Genetic Testing for BRCA1/BRCA2 (2004) (Chapter 6.2)

1.2.1 Background

The following model was built to provide an insight into the cost-effectiveness of genetic testing for BRCA1/2 breast/ovarian cancer mutations in a UK setting. The model was made available to the GDG but was not discussed by the group or used to determine guideline recommendations. It must be stressed that the modelling presented here is a preliminary piece of work which is intended to highlight the important uncertainties that exist in this area but is not sufficiently well developed to be used for decision making.

1.2.2 Overview of model

The analysis compares a full gene genetic test to no testing for women at high risk of developing breast cancer due to familial history using a Markov decision tree model developed in DATA Professional1. An overview of the model structure is shown in figure 1.1.

If genetic screening is available then only a proportion of women eligible for the program will be carriers of the BRCA1/2 genetic mutation. For women that enter the program and undergo testing, the test provides either a positive or negative result. The model also allows for the possibility that women enter the program but decide not to undergo testing. Following testing a woman may decide to undergo prophylactic surgery (either mastectomy and/or oophorectomy) in order to reduce her risk of breast and ovarian cancer. Four Markov states are included in the model; no cancer, breast cancer, ovarian cancer and death. The model runs annually for a maximum of fifty cycles.

The analysis is undertaken from a health service perspective for women aged 25, 35, 45, and 65 years of age. Health benefits are expressed in terms of Quality Adjusted Life Years (QALYS). Costs are discounted at 6% per annum and benefits are discounted at 1.5% per annum. Costs are expressed in 2002 UK sterling.

Assumptions of the model:

- Breast cancer and ovarian cancer cannot be experienced simultaneously
- Prophylactic surgery, if undertaken, is immediate
- Prophylactic oophorectomy is only undertaken in conjunction with prophylactic mastectomy
- Women in a cancer state experience a constant decrement in Quality of life whilst in that state. There is distinction made between different stages of disease
- Women that undergo prophylactic surgery experience a constant decrement in quality of life.
- Reductions in quality of life from prophylactic surgery and cancer states are multiplicative
- Cancer states may be experienced for a maximum of 5 years. Women that have not progressed to death after 5 years return to the normal health state
- Progression from the normal health state to cancer states is not dependent on previous health states i.e. the model has no memory

[1] 1998-2003 Treeage Software Inc.

- No account is taken of the possible gains that might accrue from individuals choosing not to undergo surgery given the information from a negative test who would have undergone surgery if no test were available
- No genetic testing takes place without counselling

Values used in the analysis

A table of base case values and sources is provided in Table A.

If genetic testing is available then women will be eligible for the program dependent on their level of risk. Clearly, the effectiveness and cost-effectiveness will differ according to the threshold at which this risk level is set. This threshold determines the probability that a woman is BRCA1/2 positive. The base case model uses a value of 0.15, which corresponds to the level of risk associated with women whose family history corresponds to the "high" risk definition used in the guideline, Sevilla et al. (2002).

For each woman entering the program, it is assumed that a preliminary counselling session is required. The cost of this session (£49.84) has been taken from Cohen et al. (in submission) In order to test for BRCA mutations an affected family member is tested to see if a family mutation can be found. In the base case analysis it is assumed that 100% of individuals entering the program have a living affected relative that is willing to be tested. This will depend on the criteria adopted for entry to the program. In the TRACE trial, for example, only 36 out of 48 women had such a relative (75%) and this value is used in the sensitivity analysis. It is recognised that the TRACE trial was not a trial of full gene testing. However, some of the cost elements are common to alternative testing programs.

The cost of this test is that for full sequencing in Manchester (Evans personal communication). Where a family mutation is detected in the affected woman then family members can be tested. Therefore, the cost per woman will depend both on the cost of the subsequent testing and the number of relatives that undergo testing per affected relative. We assume that a mean of two relatives will be tested per affected woman found positive. The unit cost for testing unaffected women is £28.84 for single batch cascade testing from the TRACE trial. Additionally, a positive test in the affected relative requires appropriate counselling to be provided both to that relative and to the unaffected relatives. This cost was estimated at £115.78 (Cohen et al. in submission - table 5 excluding patient travel costs) for affected women, plus £148.21 for pre and post test counselling in the unaffected relative.

The sensitivity and specificity of full gene sequencing is taken from myriad genetics (quoted in Tengs and Berry 2000). Women that receive a positive test result are more likely to undergo risk reducing surgery (either mastectomy, or mastectomy and oophorectomy) with these probabilities taken from Evans (personal communication). Expected health outcomes are therefore dependent on age dependent cancer risks and other cause mortality (ONS, Stratton et al 1998, Grann et al 2002), adjusted according to true BRCA1/2 status and whether risk reducing surgery has been taken. Quality of life values for all cancer and risk reducing surgery states are taken from Grann et al. (2002) and Tengs et al (1998).

Costs for cancer states and prophylactic surgery are taken from NHS reference costs (2002). Cancer costs accrue are assumed to accrue for each year that a person remains in a cancer state.

1.2.3 Results

Base case results, shown in Table A, show that genetic testing women at a very young age is dominated compared to a no testing alternative. The reason for this is that the model

assumes that those women that undertake risk reducing surgery do so immediately. At a young age the risk of breast or ovarian cancer is relatively low compared to the reduction in quality of life suffered from risk reducing surgery. The benefits of risk reducing surgery are experienced to a greater extent in later years and are consequently not valued particularly highly due to discounting.

The base case results for testing at all other ages (except 65 years and over) indicate that health benefits are generated at a relatively low additional cost. The cost per QALY is relatively high (£55k) for women aged 65 years. The reason for this is that whilst the costs of providing testing and surgery are immediate (financial and quality of life reduction for women), the benefits occur in later years (reduced incidence of disease). However, all cause mortality in older women is obviously higher and therefore the benefits accrued in future years are limited.

Sensitivity analyses

Only simple, one-way sensitivity analyses have been performed with the aim of showing those key estimates that have substantial impact on the model. Results are shown in Table B.

Firstly, it can be seen that the results are relatively insensitive to the probability that a woman entering the scheme has an affected relative and therefore receives the test.

The prior probability of women entering the program having genetic mutations has a substantial impact. If the true proportion is 20% instead of 15% then, except in women aged 25 and below, then testing becomes a relatively cost effective option and in some case (women aged 45 and 55 years) dominates the no test option. Table B also shows that the results are sensitive to the QALY values used for the relevant health states, to the proportion of women that undertake risk reducing surgery that would not have done so in the absence of genetic testing and to the cost of the test. For the latter value, the Myriad quoted cost was used although the result here may not be a completely accurate reflection of such testing arrangements since the myriad system would not require the involvement of affected relatives.

1.2.4 Discussion and Limitations

There is no combined ovarian and breast cancer health state in the model.
It is assumed that no women undergo risk reducing oophorectomy without mastectomy.
There is little evidence that genetic testing alters the likelihood that women undergo risk reducing surgery (or any other type of risk reducing behaviour that is not accounted for in the model). These estimates are therefore extremely uncertain.

No comparison of different genetic testing programs has been undertaken. Sevilla et al (2002) suggest that the incremental cost effectiveness of some full gene testing programs is extremely high compared to less sensitive/specific alternatives. Such an analysis should be undertaken from an NHS perspective.

Only health benefits are included in the model. There may be an inherent value of information and there is also likely to be utility in waiting less time for results. If this wider perspective were adopted then it would be important to compare different types of genetic testing, including the private provision of testing by Myriad genetics (for example, comprehensive BRCA testing results can be received in 10 days for a unit cost of $4,140).

The costs and benefits associated with breast and ovarian cancers are relatively crude.

The results for women aged 25 years should not be interpreted as an indication that genetic testing is not cost-effective at this age but that surgery undertaken in the light of additional information may be best delayed (as many women choose currently).

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Parameter	Value		Source
Probability that woman entering the program is BRCA1/2+ve		0.15	Sevilla et al.
Sensitivity of test		0.98	Myriad genetics
Specificity of test		0.99	Myriad genetics
Mortality Rates (per 1000 population per year) for women by age			ONS
	35-44	1.51	
	45-54	3.93	
	55-64	10.9	
	65-74	31.6	
	75-84	80.1	
	85 and over	187.9	
Rates of breast cancer by age			ONS
	25	6.67E-05	
	26-30	0.000526	
	31-40	0.005	
	41-50	0.02	
	51-60	0.043478	
	61-70	0.066667	
	71-80	0.090909	
	81-85	0.1	
Rates of ovarian cancer by age			ONS
	25	0.00002	
	26-30	0.00004	
	31-40	0.00007	
	41-50	0.0002	
	51-60	0.00046	
	61-70	0.00075	
	71-80	0.00076	
	81-85	0.00061	
5 year survival breast cancer			ONS
	less than 40	0.7	
	40-49	0.78	
	50-59	0.8	
	60-69	0.78	
	70-79	0.68	
	80-99	0.48	

Parameter	Value		Source
5 year survival ovarian cancer	less than 40	0.69	ONS
	40-49	0.43	
	50-59	0.34	
	60-69	0.25	
	70-79	0.17	
	80-99	0.12	
Lifetime risk breast cancer BRCA carrier		0.84	Guideline Easton et al. quoted in Grann et al (2000)
Relative risk ovarian cancer BRCA carrier		27.05	
Relative risk breast cancer after prophylactic mastectomy		0.1	Guideline evidence statement
Relative risk breast cancer after prophylactic oophorectomy		0.37	Guideline evidence statement
Relative risk ovarian cancer after prophylactic oophorectomy		0.04	Grann et al. (2002)
Probability of mastectomy and oophorectomy following positive test result		0.25	Evans (personal communication
Probability of mastectomy after positive test result		0.5	Evans (personal communication)
QALYs			
Mastectomy		0.76	Grann et al (2002)
oophorectomy (before 50 with hormone replacement)		0.82	Grann et al (2002)
oophorectomy (before 50 without hormone replacement)		0.8	Grann et al (2002)
Mast and ooph		0.73	Grann et al (2002)
Breast cancer		0.77	Grann et al (2002)
Ovarian cancer		0.65	Grann et al (2002)
Costs			
Genetic testing cost in affected woman - Whole Gene NHS		891.17	Evans personal communication
Genetic testing in affected woman - Myriad		1569.6	Myriad genetics personal communication (adjusted to UK sterling using OECD PPP)
Mastectomy		1989	NHS reference costs J02
Breast cancer treatment each year		2387	NHS reference costs J09
oophorectomy		2144	NHS reference costs M07
Ovarian cancer treatment cost each year		588	NHS reference costs M98
Number of women in family tested per affected relative		2	Assumption
Cost of counselling		49.84	Cohen et al. (2003)

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Table A: Base case results for Genetic Testing Model (£'s per QALY)					
Age in Years					
	25	35	45	55	65
	Dominated	14478	3075	4137	54563

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Table B: Sensitivity Analyses for genetic Testing Model (£'s per QALY)					
Age in Years					
Parameter value in sensitivity analysis (base case)	25	35	45	55	65
75% (100%) have affected relative	Dominated	15013	3326	4642	58298
Prob BRCA 0.2 (0.15)	Dominated	7351	Dominates	Dominates	5851
Prob mastectomy 0.25 (0.5) and prob mast and ooph 0.1 (0.25) after a positive test	Dominated	55983	21204	43733	958256
Cost of gene test £1569 per person (£891per affected relative)	Dominated	36459	13306	24783	207080
QALY mastectomy 0.6 (0.76)	Dominated	Dominated	Dominated	Dominated	Dominated
QALY mastectomy and oophorectomy 0.5 (0.73)	Dominated	Dominated	Dominated	Dominated	Dominated
QALY breast cancer 0.6 (0.77)	Dominated	2597	942	772	1954

Note: An option is said to dominate an alternative if it is both less costly and more effective. "Dominated" indicates scenarios where genetic testing is more costly and less effective than no testing. "Dominates" indicates scenarios where genetic testing is less costly and more effective then no testing.

2

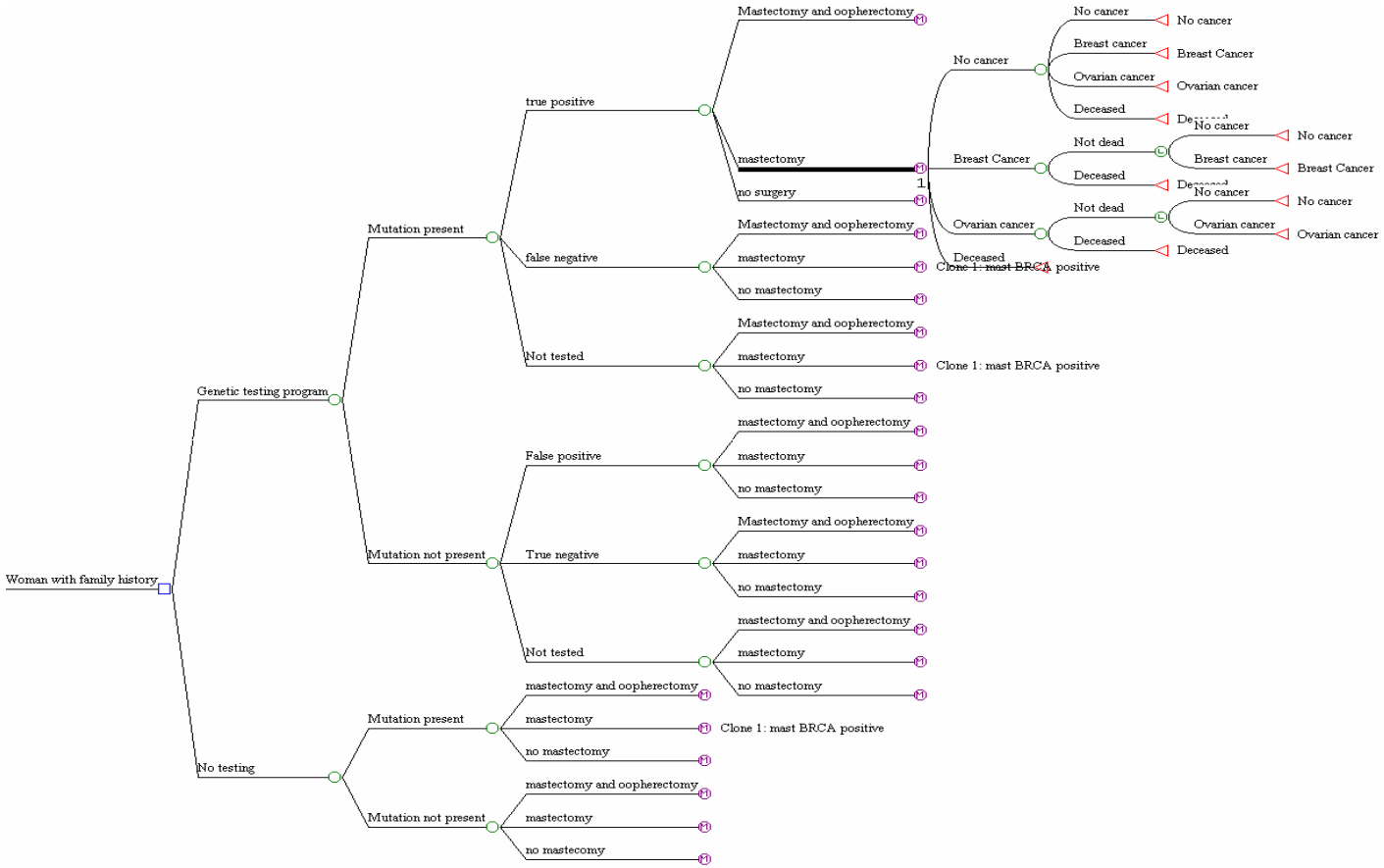

Figure 1.1: Genetic Testing Decision Model

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1.3 The carrier probability at which genetic testing should be offered to people (2013) (Chapter 6.3)

1.3.1 Review question

The risk threshold at which genetic testing should be offered to people (women and men)?

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Women and men Unaffected (without cancer) with a living relative with a family history Unaffected (without cancer) without a living relative with a family history Affected patients (breast/ovarian/prostate)	Genetic Testing at different carrier probability thresholds 5% 10% 15% 20% 30% 40%	Genetic testing No Genetic Testing	Cost Effectiveness Cost Effectiveness Incremental cost effectiveness ratio (ICER) Results of sensitivity analysis Results of supplementary analysis

1.3.2 Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED). Focus was put on studies/reviews reporting HE evidence for topic A including systematic reviews of economic evidence (or systematic reviews which contain economic evaluations), published economic evaluations (including conference proceedings), economic evaluations as part of randomized controlled trials, economic evaluations as part of observational studies and economic modelling studies (all types). Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Selection criteria for included evidence:

Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included.

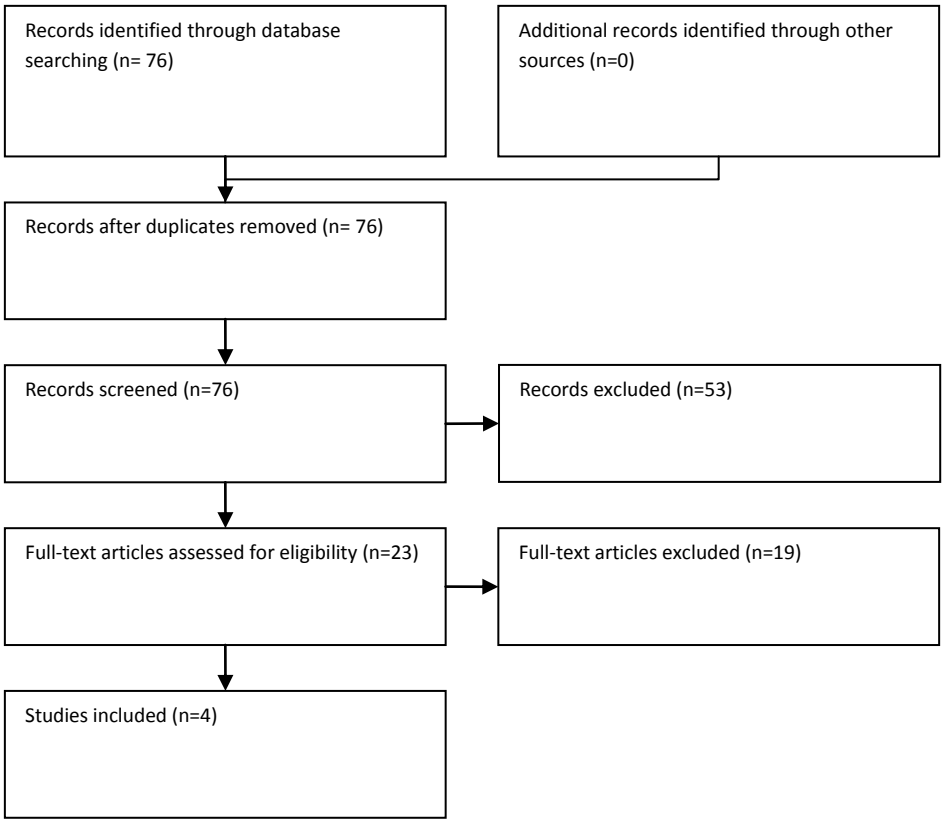
Studies that were conducted in OECD countries (other than the UK) were included

Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economists screened the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. Full articles were obtained for 23 studies and checked against the inclusion criteria.

1.3.3 Results



Quality and applicability of the included studies

All four studies were deemed partially applicable to the guideline. The reasons for partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. All papers were deemed to have very serious limitations because they did not meet one or more aspects of the NICE reference case. In particular, data was extracted from literature but no systematic literature review was reported (all papers), time horizon (Kwon et al 2010a; Kwon et al. 2010 b), cost year (Balmana et al. 2004) and probabilistic sensitivity analysis (Balmana et al. 2004) were not reported and discounting structure did not conform with the NICE reference case (all papers).

		Applicability	
		Directly applicable	Partially applicable
Methodological quality	Minor limitations		
	Potentially serious limitations		
	Very serious limitations		Balmana et al., 2004, Holland et al., 2009, Kwon et al., 2010a, Kwon et al., 2010b

1.3.4 Evidence statements

Balmana et al 2004 showed that the cost-effectiveness ratio of their genetic counselling and screening program was €4,294 per life-year gained. The model was sensitive to the prevalence of mutation carriers, the lifetime risk of breast cancer and the effectiveness of the screening, suggesting that testing for breast cancer in a high risk population may be cost-effective. Holland et al 2009 suggested that at a 10% probability of mutation (the current US guideline), the test strategy generated 22.9 QALYs over a lifetime and cost $118,000, while the no-test strategy generated 22.7 QALYs and cost $117,000. The incremental cost-effectiveness ratio of the test strategy was $9,000 and the differences between costs and effects were not substantial. The test strategy remained cost-effective to a probability of mutation of 0% as long as utility gained from a negative test result was 0.006 or greater. These results were sensitive to the frequency of inconclusive test results and utility gains from a negative test result. In a cohort of women with a personal history of ovarian cancer, Kwon et al 2010a showed that BRCA testing based on personal/family history and ancestry could prevent future cases in first degree relatives with an ICER of $32,018 per year of life (LY) gained compared with the reference strategy. In a cohort of women with a personal history of breast cancer, Kwon et al 2010b showed that whilst BRCA mutation testing for all women with breast cancer who were younger than 50 years could prevent the highest number of breast and ovarian cancer cases, this was not cost-effective. Testing women with triple negative breast cancers who were younger than 50 years was cost-effective with an ICER of $8,027 per year of life gained ($9,084 per quality-adjusted life-year), and could reduce subsequent breast and ovarian cancer risks. (see table 1.1 & 1.2)

Population

Balmana et al did not provide explicit population criteria, stating only those with a family history and breast cancer risk assessed by the Claus Model were included. Only an average age of 47 years was reported. Holland et al 2009 examined a 35 year old woman who had an associated family risk of breast and/or ovarian cancer. Kwon et al 2010a included women with ovarian cancer with a population including those with a family history of breast and/or ovarian cancer. Kwon et al 2010b included women in the general population with a previous history of breast cancer aged 50 years and younger.

Intervention & Comparator

Balmana et al looked at genetic testing with/without annual mammography compared to no screening. Holland et al compared genetic testing followed by preventative surgery if applicable compared to no testing but on-going surveillance. Kwon et al 2010 a and b compared genetic testing to no testing. In all studies, the interventions and comparator were only briefly described.

Outcome

Health effects were quantified in terms of QALYs in Holland et al 2009, Kwon et al 2010 a and b. Balmana et al, Kwon et al 2010 a and b examined incremental cost per life year gained.

Source of effectiveness data

Balmana et al derived effectiveness data from local registry data and literature and used local cost data. Holland et al, Kwon et al 2010 a and b derived effectiveness and costs from published literature.

Table 1.1 Economic evidence profile:Table of included studies

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
Balmana, 2004	Very serious limitations 1	Partially applicable 2	Families [...] having several relatives affected by breast cancer, frequently of an early onset, and might be associated with the presence of ovarian and male breast cancer. Age unknown	Genetic counselling (GC), genetic study of the index case (GSIC), clinical breast examination (CBE) and annual mammography (Mx) from 30 to 80 years or until breast cancer diagnosis	Determination of genetic status (GC and GSIC), no screening	£1010 3 for scrrening compared to no screening	Life expectancy: 0.19 years gained with screening compared to no screening	Cost/LYG: £5267.174	One-way sensitivity analysis showed that results were sensitive to the estimated probability of being a mutation carrier and thus detection rate of BRCA mutations, number of BCs without lymph node involvement as well as changes in life-time risk of BC in mutation carriers. No PSA reported.
Holland 2009	Very serious limitations 5	Partially applicable 6	35-year-old women with an associated	Genetic testing for BRCA	No genetic testing or prophylactic	£742.16 7	Utility scores: Screening (cumulative):	£6679.48/QALY8	One-way sensitivity analysis and

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
			family risk of breast and/or ovarian cancer 35-year-old women who were concerned about having a mutation	mutation at age 35 followed by the possibility of preventative surgery if mutation was found	surgery but ongoing surveillance according to recommendations		22.9 QALYs No screening (cumulative): 22.7 QALYs Incremental QALYs of screening: 0.2		probabilistic sensitivity analysis performed and reported. Costs and effects of both strategies were found to be similar and not sensitive to parameter estimates. Probability of test-strategy cost-effective at 73 % when a QALY was valued at $100,000 and 70 % at $50,000.
Kwon 2010a	Very serious limitations 9	Partially applicable 10	Theoretical cohort of women in the general population with ovarian cancer	BRCA testing only if Ashkenazi Jewish, personal or family history of BC and/or	No BRCA mutation testing	Incremental cost compared to no testing11: SGO criteria: £735.87 Test serous:	Life expectancy (years): Compared to no testing SGO criteria: 0.0326 Test serous:	Compared to no testing12 SGO criteria: £23,049.58/ QALY	Results were found stable over a wide range of plausible parameter estimates

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
				OC (SGO criteria); BRCA testing only if invasive serous cancer; BRCA testing if any ovarian cancer		£1644.58 Test all: £2431.95	0.0426 Test all: 0.0502 Utility score (QALYs): Compared to no testing SGO criteria: 0.0319 Test serous: 0.0415 Test all: 0.0491	Test serous: £92,503.83/QALY Test all: £106,837.32/QALY	(including proportion of first-degree relatives undergoing testing and prophylactic surgery).
Kwon 2010b	Very serious limitations 13	Partially applicable 14	Theoretical cohort of women in the general population with breast cancer diagnosed at 50 or younger	Testing of women with medullary breast cancer younger than 50; Testing of women with any breast cancer younger than 40; Testing of women with triple-negative BC younger	No testing	Compared to no testing Medullary breast cancer: £57.33 Triple-negative BC <40: £199.25 Any BC <40: £634.80 Triple-negative BC <50: £649.48 Any BC <50: £3018.79	Life expectancy (years): Compared to no testing Medullary breast cancer: 0.011 Triple-negative BC <40: 0.040 Any BC <40: 0.103 Triple-negative BC <50: 0.121 Any BC <50: 0.178 Utility score	Compared to no testing Medullary breast cancer: £6075.33/QALY Triple-negative BC <40: £5495.06/QALY Any BC <40: £7688.89/Q	Results were found stable over a wide range of plausible parameter estimates.

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
				than 40; Testing of women with triple-negative BC younger than 50			(QALYs): Compared to no testing Medullary breast cancer: 0.008 Triple-negative BC <40: 0.032 Any BC <40: 0.086 Triple-negative BC <50: 0.098 Any BC <50: 0.127	ALY Triple-negative BC <50: £195.75/QALY Any BC <50: £78,935.88/QALY	

[1] Effectiveness data is based on one single hospital register; no cost year or discounting rates reported, exclusion and inclusion criteria unclear. Therefore the relevance of these results for informing the current guideline is limited.
[2] The analysis does not meet one or more aspects of the NICE reference case.
[3,4] Converted from 2000 Euros using a PPP exchange rate of 0.88 then uprated by inflation factor of 139% (http://eppi.ioe.ac.uk/costconversion/default.aspx). Cost year of 2000 assumed as not stated in publication.
[5] Effectiveness, cost and utility data is based on literature review (no methodology reported), exclusion and inclusion criteria unclear. Therefore the relevance of these results for informing the current guideline is limited.
[6] The analysis does not meet one or more aspects of the NICE reference case.
[7,8] Converted from 2006 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[9] Effectiveness, cost and utility data is based on literature review (no methodology reported), exclusion criteria and time horizon unclear. General population used for analysis, no separate analysis of family history, no risk groups reported. Therefore the relevance of these results for informing the current guideline is limited.
[10] The analysis does not meet one or more aspects of the NICE reference case.
[11,12] Converted from 2008 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 103% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[13] Effectiveness, cost and utility data is based on literature review (no methodology reported), exclusion criteria and time horizon unclear. Only ovarian cancer patients included in analysis. Therefore the relevance of these results for informing the current guideline is limited.
[14] The analysis does not meet one or more aspects of the NICE reference case.
[15,16] Converted from 2009 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 102% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Table 1.2: Evidence table of included economic studies

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author: Balmana J. Year: 2004 Country: Spain Setting: Primary prophylaxis (screening)	Type of analysis: Cost-effectiveness analysis Model structure: Decision tree Time horizon: Observational data collection: 1995 to 2001 Model: 50 years (30 to 80 years of age) Perspective: Not explicitly stated. Only healthcare resources	Inclusion criteria: Not explicitly reported. "Families [...] having several relatives affected by breast cancer, frequently of an early onset, and might be associated with the presence of ovarian and male breast cancer." Breast cancer risk was assessed by the Claus model which is not described. Exclusions criteria: Not explicitly reported. ""Those families not meeting the criteria for the genetic analysis are excluded". Criteria not described.	Genetic testing: Group 1 and 2: genetic counselling (GC), genetic study of the index case (GSIC), clinical breast examination (CBE) and annual mammography (Mx) from 30 to 80 years or until breast cancer diagnosis Group 3: determination of genetic status (GC and GSIC), no screening	Clinical data: Risk classification (of family): High risk Moderate risk Number of mutations identified: Breast cancer: Diagnosed Diagnosed through screening protocol Node-negative diagnosed by screening protocol Node-negative diagnosed	73 % 27 % 29 probands (20 %) 70 21/70 (30 %) 71 % (95%CI=50-86) 49 % (95%CI=35-63)	Conflict of interest: None disclosed. Sponsored by the Health Technology Assessment Agency of the Instituto de Salud Carlos III Applicability: Partially applicable Limitations: Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	included. Source of baseline data: Literature review Methodology not reported. Source of effectiveness data: Familial breast cancer registry, Hospital de la Santa Creu i Sant Pau Source of utility data: No QALYs measured.	Sample size: 143 probands/family; 858 family members (estimated) Age: Not explicitly reported. Average age at diagnosis of BC was 47 years. Gender: Not explicitly reported. 100 % women 0 % men		outside screening protocol Prophylactic mastectomies Life expectancy (years): Screening strategy No screening strategy Utility score: None reported Cost: Total Screening strategy No screening strategy Breakdown Genetic counselling (GC +	13 52.69 52.50 € 1157.80 € 334.40	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of cost data: Management Control Department, Hospital de la Santa Creu i Sant Pau Currency unit: EUR Cost year: Not reported Discounting: Cost: 5 % Health effect: not reported	Subgroup analysis: Reported in table III. Participants divided in 3 groups: Group 1: females from high-risk families without an identified mutation (n=684) Group 2: BRCA1 or BRCA2 female mutation carriers (n=87) Group 3: female nonmutation carriers from families with a pathological BRCA1 or BRCA2 gene mutation		GSIC) Per family Per woman First CBE Following CBE Mammography Breast biopsy Determination of genetic status ICER: Cost/LYG Uncertainty: One-way sensitivity analysis showed that results were sensitive to the estimated probability of being a mutation carrier	€ 2328.9 € 388.15 € 48.08 €27.05 €27.05 €48.08 €120.20 € 4294.00	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				and thus detection rate of BRCA mutations, number of BCs without lymph node involvement as well as changes in life-time risk of BC in mutation carriers. No PSA reported.		
Author: Holland M.L. Year: 2009 Country: USA	Type of analysis: Cost-utility analysis Model structure: Semi-Markov model Time horizon: 70 years (starting at 35 years of	Inclusion criteria: 35-year-old women with an associated family risk of breast and/or ovarian cancer 35-year-old women who were concerned about having a mutation Exclusions criteria: Not explicitly reported	Genetic testing: Group 1("test strategy"): Genetic testing for BRCA mutation at age 35 followed by the possibility of preventative surgery if mutation was found Group 2 ("no-test strategy"): no genetic testing or prophylactic surgery but ongoing surveillance according	Utility score: Cumulative Test strategy Mutation positive Mutation negative No-test strategy Cost: Cumulative	22.9 QALYs 20.5 QALYs 23.1 QALYs 22.7 QALYs	Conflict of interest: Project partially funded by the Agency for Healthcare Research and Quality NRSA Institutional Research Training Grant Applicability: Partially

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Setting: Primary prevention	age) Perspective: Societal perspective Only patient-specific costs and benefits included Effects of patient's genetic status on family members not included Productivity losses not considered Source of baseline data: Literature review (no methodology reported)	Sample size: Not stated Age: 35 years Gender: 100 % women 0 % men Subgroup analysis: None	to recommendations	Test strategy No-test strategy ICER: Uncertainty: One-way sensitivity analysis and probabilistic sensitivity analysis (using Monte Carlo simulation) performed and reported. All ranges used for SA reported in Table 4 (page 211). Costs and effects of both strategies were found to be similar and not sensitive to parameter estimates. PSA showed that test-strategy dominates for 11	$ 118,000 $ 117,000 $ 9000/QALY	applicable Limitations: Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of effectiveness data: Literature review (no methodology reported) Source of utility data: Literature review (no methodology reported) Authors' assumptions Source of cost data: Literature review (no methodology reported)			% of results and was dominated by no-test strategy for 24 %. Probability of test-strategy to be cost-effective was 73 % when a QALY was valued at $100,000 and 70 % at $50,000.		

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Currency unit: US $ Cost year: 2006 Discounting: QALYs: 3 % Costs: 3 %					
Author: Kwon J. Year: 2010a Country:	Type of analysis: Cost-effectiveness and cost-utility analyses Model structure: Markov Monte Carlo simulation	Inclusion criteria: Theoretical cohort of women in the general population with ovarian cancer Exclusions criteria: Not stated	Genetic testing: No BRCA mutation testing BRCA testing only if Ashkenazi Jewish ancestry, a personal or family history of BC and/or OC (SGO criteria) BRCA testing only if	Clinical data: Life expectancy (years): No testing SGO criteria Test serous Test all	 19.0140 19.0466 19.0566 19.0642	Comment: Most cost-effective strategy is testing women with triple-negative BC younger than 50 years. Conflict of

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
USA Setting: Primary prevention	model Time horizon: Not reported Perspective: Societal Source of baseline data: Literature review (methods not described) Source of effectiveness data: Literature review (methods not described)	Sample size: 45,000 (simulated) Age: 50 Gender: 100 % women 0 % men Subgroup analysis: None	invasive serous cancer BRCA testing if any invasive, nonmuinous epithelial ovarian cancer	Utility score (QALYs): No testing SGO criteria Test serous Test all Cost (US$): No testing SGO criteria Test serous Test all ICER: Cost per life year gained No testing SGO criteria	 16.6171 16.6490 16.6589 16.6662 2637 3680 4968 6084 - 32,018	interest: None reported Applicability: Partially applicable Limitations: Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of utility data: Literature review (methods not described) Source of cost data: Literature review (methods not described) Currency unit: US$ Cost year: 2008 Discounting:			Test serous Test all Cost per QALY No testing SGO criteria Test serous Test all Uncertainty: Results were found stable over a wide range of plausible parameter estimates (including proportion of first-degree relatives undergoing testing and prophylactic surgery).	128,465 148,363 - 32,670 131,113 151,429	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Costs: 3 % Health benefits; 3 %					
Author: Kwon J. Year: 2010b Country: USA Setting: Primary prevention	Type of analysis: Cost-effectiveness and cost-utility analyses Model structure: Markov Monte Carlo simulation model Time horizon: Not reported Perspective: Societal	Inclusion criteria: Theoretical cohort of women in the general population with breast cancer diagnosed at 50 or younger Exclusions criteria: Not stated Sample size: 45,000 (simulated) Age: 50	Genetic testing: No testing Testing of women with medullary breast cancer younger than 50 Testing of women with any breast cancer younger than 40 Testing of women with triple-negative BC younger than 40 Testing of women with triple-negative BC younger than 50	Clinical data: Number of mutations identified: No testing Medullary breast cancer Triple-negative BC <40 Any BC <40 Triple-negative BC <50 Any BC <50 Number of new breast cancer cases: No testing Medullary breast cancer	0 168 651 1254 1724 3681 3611 3455	Comment: Most cost-effective strategy is testing women with triple-negative BC younger than 50 years. Conflict of interest: None reported Applicability: Partially applicable

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of baseline data: Literature review (methods not described) Source of effectiveness data: Literature review (methods not described) Source of utility data: Literature review (methods not described) Source of cost data:	Gender: 100 % women 0 % men Subgroup analysis: None		Triple-negative BC <40 Any BC <40 Triple-negative BC <50 Any BC <50 Life expectancy (years): No testing Medullary breast cancer Triple-negative BC <40 Any BC <40 Triple-negative BC <50 Any BC <50 Utility score (QALYs): No testing Medullary breast cancer Triple-negative BC <40	3234 2763 2643 2131 19.762 19.773 19.802 19.865 19.883 19.940 16.433 16.441 16.465	Limitations: Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Literature review (methods not described) Currency unit: US$ Cost year: 2009 Discounting: Costs: 3 % Health benefits; 3 %			Any BC <40 Triple-negative BC <50 Any BC <50 Cost (US$): No testing Medullary breast cancer Triple-negative BC <40 Any BC <40 Triple-negative BC <50 Any BC <50 ICER: Cost per life year gained No testing Medullary breast cancer Triple-negative BC <40	16.519 16.531 16.560 2424 2506 2709 3332 3353 6742 - 7642 6861	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
				Any BC <40 Triple-negative BC <50 Any BC <50 Cost per QALY No testing Medullary breast cancer Triple-negative BC <40 Any BC <40 Triple-negative BC <50 Any BC <50 Uncertainty: Results were found stable over a wide range of plausible parameter estimates.	10022 1160 59503 - 8690 7860 10998 280 112908	

1.3.5 References

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Holland ML, Huston A & Noyes K (2009) Cost-effectiveness of testing for breast cancer susceptibility genes. Value in Health, 12: 207-216.

Kwon JS, Daniels MS, Sun CC & Lu KH (2010a) Preventing future cancers by testing women with ovarian cancer for BRCA mutations. Journal of Clinical Oncology, 28: 675-682.

Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH & Arun B (2010b) Expanding the criteria for BRCA mutation testing in breast cancer survivors. Journal of Clinical Oncology, 28: 4214-4220.

1.4 A cost-utility analysis of genetic testing for individuals with a family history of breast cancer (2013) (Chapter 6.3)

1.4.1 Introduction

The existing NICE Guideline (CG14) recommends that the carrier probability threshold at which genetic testing for mutations in BRCA1 and BRCA2 (or TP53) is offered to individuals affected by breast or ovarian cancer is set at 20%. The patient's mutation probability is estimated by assessment of the family history. Genetic testing is offered in Tertiary Care if an affected individual's mutation risk exceeds the established threshold. Related to this is the recommendation that unaffected family members should be managed in Tertiary Care if their risk assessment gives a lifetime breast cancer risk equal or greater than 30%, or the 10 year risk from 40 to 50 years is more than 8%. High-risk unaffected family members may harbour a substantial mutation carrier probability, depending on context. Currently there is no recommendation for offering tests to unaffected patients with a strong family history.

Since publication of CG14 in 2004, the threshold for testing has fallen, albeit inconsistently across all Tertiary Care Centres, with some adopting a 10% mutation probability for affected cases. Moreover, some centres now offer genetic testing to unaffected patients with a substantial risk of being mutation carriers, mostly in circumstances where no living affected family member is available to offer a direct diagnostic test. Changes in practice are related to declining costs of genetic testing and the increasing rapidity with which results can be achieved.

In view of these variations in practice this topic is intended to assess the scope for changing the current probability threshold at which testing is offered to affected patients (male or female), that is with a current or previous diagnosis of breast or ovarian cancer. Furthermore, the economic evaluation will determine whether a probability threshold should be established for offering 'indirect' genetic testing to unaffected patients (no personal history of cancer) with a family history suggestive of a strong dominant genetic susceptibility to cancer, where there is no living affected relative available to test. Also, the cost-effectiveness of testing unaffected relatives of affected individuals will be assessed.

BRCA mutation testing

Mutations in several genes are known to be associated with an inherited risk of breast cancer, ranging from moderate to highly increased lifetime risks compared to the general population. Of the known genes, inherited mutations BRCA1 and BRCA2 are the most common cause of a high lifetime risk of breast cancer of between 40% and 85% depending on gene and context. Female mutation carriers also have a high risk of ovarian cancer (10 to 50% depending on the gene involved), whereas male carriers of BRCA2 mutations have an increased risk of prostate cancer (an estimated 25% risk in BRCA2 carriers) and breast cancer (7% for BRCA2). A large proportion of very high-risk families with a strong history of breast cancer (classically defined as four or more invasive breast cancers in close relatives) are attributed to mutations in either BRCA1 or BRCA2, more so if there is also a history of epithelial ovarian cancer or male breast cancer. Mutations in BRCA1/BRCA2 are very rare in the population as a whole. Overall they account for up to 5% of all breast cancers.

In current practice, the great majority of clinical diagnostic genetic tests for familial breast cancer target the identification of mutations in BRCA1 or BRCA2 as is indicated by the extent of the family history of cancer (principally breast and ovarian cancer). Since mutations in BRCA1 and BRCA2 are rare in the population as a whole, genetic testing is mostly

targeted at 'high-risk families' where there is a strong family history of breast/ovarian cancer. For genetic testing to be maximally informative, testing is usually carried out first on an individual affected with breast or ovarian cancer, who is likely to carry a mutation if one is present in the family. If a mutation is identified, other individuals in the family may be offered a 'predictive' genetic test to determine whether they carry the mutation. Since this test is based on a single mutation, it is more straightforward than the initial genomic mutation screen, but there are substantial clinical implications for risk management following a positive test result.

Consequences of genetic testing

The benefits and risks of diagnostic genetic testing for familial breast cancer (essentially for BRCA1 and BRCA2) are manifold. Identifying a strong hereditary factor as the overwhelming contribution to the patient's cancer diagnosis has significant clinical implications in terms of their overall treatment and future cancer risk management. With the likely availability of genetically-targeted chemotherapies, mutation detection is increasingly likely to inform cancer treatment depending on the time course and timing of genetic testing in relation to other treatments given. Furthermore, decisions around risk-reducing surgery (mastectomy versus lumpectomy, contra lateral/bilateral mastectomy, and salpingo-oophorectomy for ovarian cancer risk management) may depend on the result.

The potential exists for substantial psychosocial and emotional benefits and harms as a consequence of giving information concerning the risk of cancer in the family and how the risk is managed in mutation carriers/potential carriers. Identifying a causal gene mutation provides information about the future risk of cancer (contralateral breast cancer and ovarian cancer) for the affected patient. Secondary predictive testing has substantial implications for at-risk relatives and for offspring of carriers (male and female) who also may not have completed their families.

Health economic priority

Because decisions about who is eligible for genetic testing will significantly impact upon NHS resources and patient benefits, this topic was identified as a high economic priority by the GDG.

1.4.2 De novo economic model (overview)

Aim

The aim of the economic evaluation was to assess at which carrier probability probability and at which age genetic testing should be offered to people with a family history of breast/ovarian cancer.

The following strategies were considered:

- Genetic testing
- No genetic testing (comparator)

Subgroup analyses were conducted for the following subgroups:

- People affected by breast/ovarian cancer (population 1)
- People unaffected by cancer with an affected relative available to test (population 2)
- People unaffected by cancer without an affected relative available to test (population 3)
- Subgroup analyses were undertaken for the following age groups:
- 20-29 years

- 30-39 years
- 40-49 years
- 50-59 years
- 60-69 years
- >70 years

Subgroup analyses were conducted for the following carrier probabilities:

- 5% carrier probability
- 10% carrier probability
- 15% carrier probability
- 20% carrier probability
- 30% carrier probability
- 40% carrier probability

An illustration of all subgroups for analysis can be found in Table 1.3.

Table 1.3: Summary of all subgroups analysed for topic A

Population	Age	Carrier probability					
1 -Women affected by cancer	20-29	5%	10%	15%	20%	30%	40%
	30-39	5%	10%	15%	20%	30%	40%
	40-49	5%	10%	15%	20%	30%	40%
	50-59	5%	10%	15%	20%	30%	40%
	60-69	5%	10%	15%	20%	30%	40%
	>70	5%	10%	15%	20%	30%	40%
2 -Women unaffected by cancer, with an affected relative available to test	20-29	5%	10%	15%	20%	30%	40%
	30-39	5%	10%	15%	20%	30%	40%
	40-49	5%	10%	15%	20%	30%	40%
	50-59	5%	10%	15%	20%	30%	40%
	60-69	5%	10%	15%	20%	30%	40%
	>70	5%	10%	15%	20%	30%	40%
3 -Women unaffected by cancer – with no affected relative available to test	20-29	5%	10%	15%	20%	30%	40%
	30-39	5%	10%	15%	20%	30%	40%
	40-49	5%	10%	15%	20%	30%	40%
	50-59	5%	10%	15%	20%	30%	40%
	60-69	5%	10%	15%	20%	30%	40%
	>70	5%	10%	15%	20%	30%	40%

The economic model does not cover:

- Indirect effects of genetic testing on the relatives of the individual modelled as part of the populations described above
- Incidence of both breast and ovarian cancer within one year. This occurs in a very small proportion of patients.
-

Supplementary analysis

An important cost-effectiveness question raised by the GDG was the effect on family member(s) if an individual was tested and found to be a BRCA 1 or BRCA 2 gene carrier. As outlined in the background to this topic (chapter 6), an economic appraisal of the potential benefits and risks in terms of the number of genetically at-risk relatives identified as a result of indirect testing would be helpful. Due to the complexity of modelling only the direct impact

of genetic testing on the individual, defined by populations above, were considered in the base case analysis. It was agreed to consider this within a supplementary analysis to provide an indication of the potential impact for family members.

Inclusion of women and men

This topic was to be up-dated to include men, as this population had not been considered in CG14. However, the paucity of evidence on men was considered a potential challenge in developing the model. It was agreed by the GDG that men would be considered within the same population as women. A separate model for men would be built to allow specific analysis of men, if and when appropriate data became available.

1.4.3 Model structure

The model for topic A was constructed in two stages:

Stage 1: A decision tree was used to reflect key events in the clinical pathway from diagnostic genetic testing through to risk reducing surgery and disease progression (stage 2) There are two arms in each tree: no genetic testing is offered (a) and genetic testing is offered (b). In populations 1 (Figure 1.1) and 3 (Figure 1.3), genetic testing is offered directly to the population member. The decision tree for population 2 (Figure 1.2) includes an additional step in arm b, in which genetic testing is offered to the population member (unaffected individual) only if a positive result is obtained as a result of genetic testing in their relative, who is affected by cancer.

Figure 1.1: Stage 1 decision tree schematic – Population 1

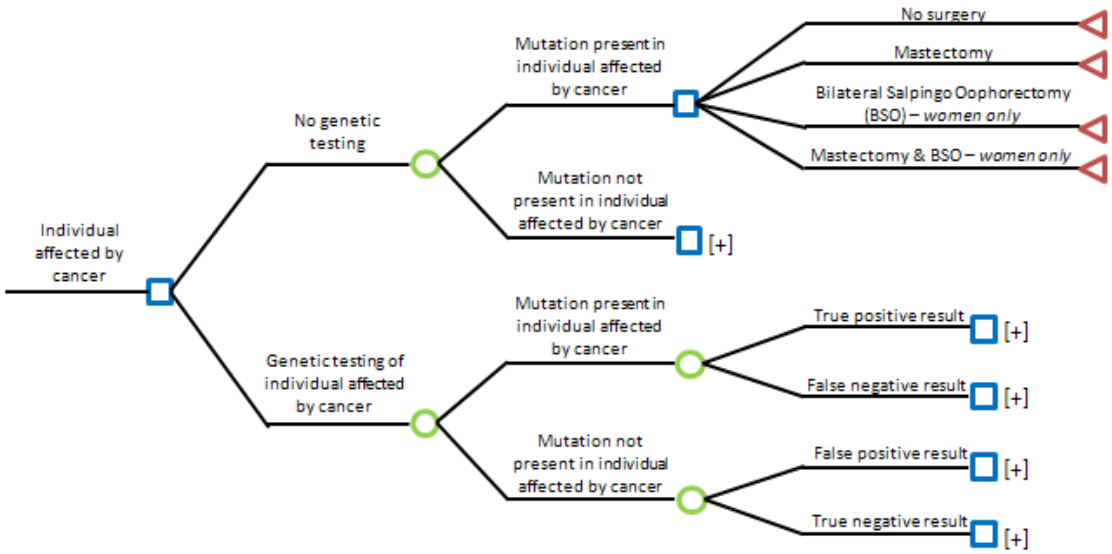


Figure 1.2: Stage 1 decision tree schematic – Population 2

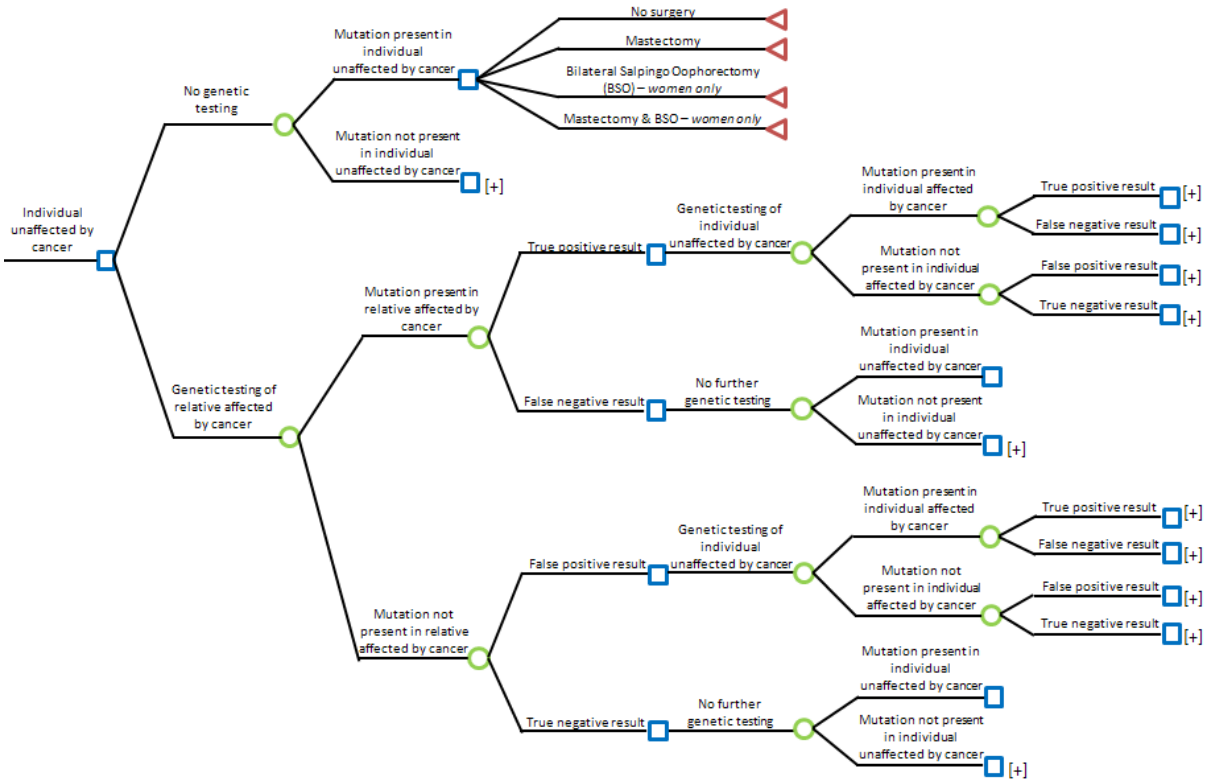
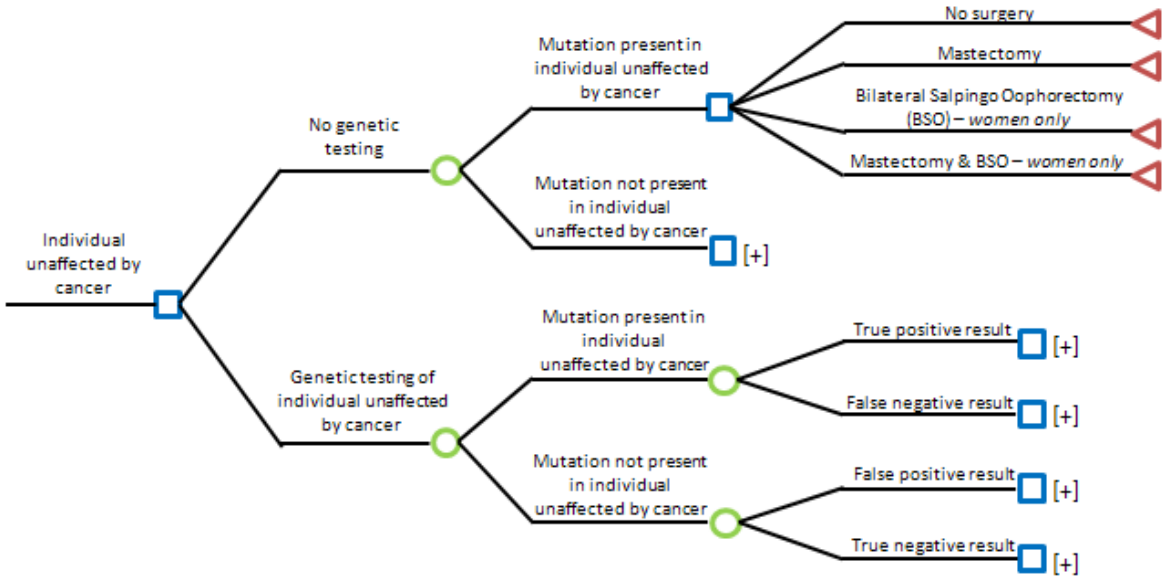


Figure 1.3: Stage 1 decision tree schematic – Population 3



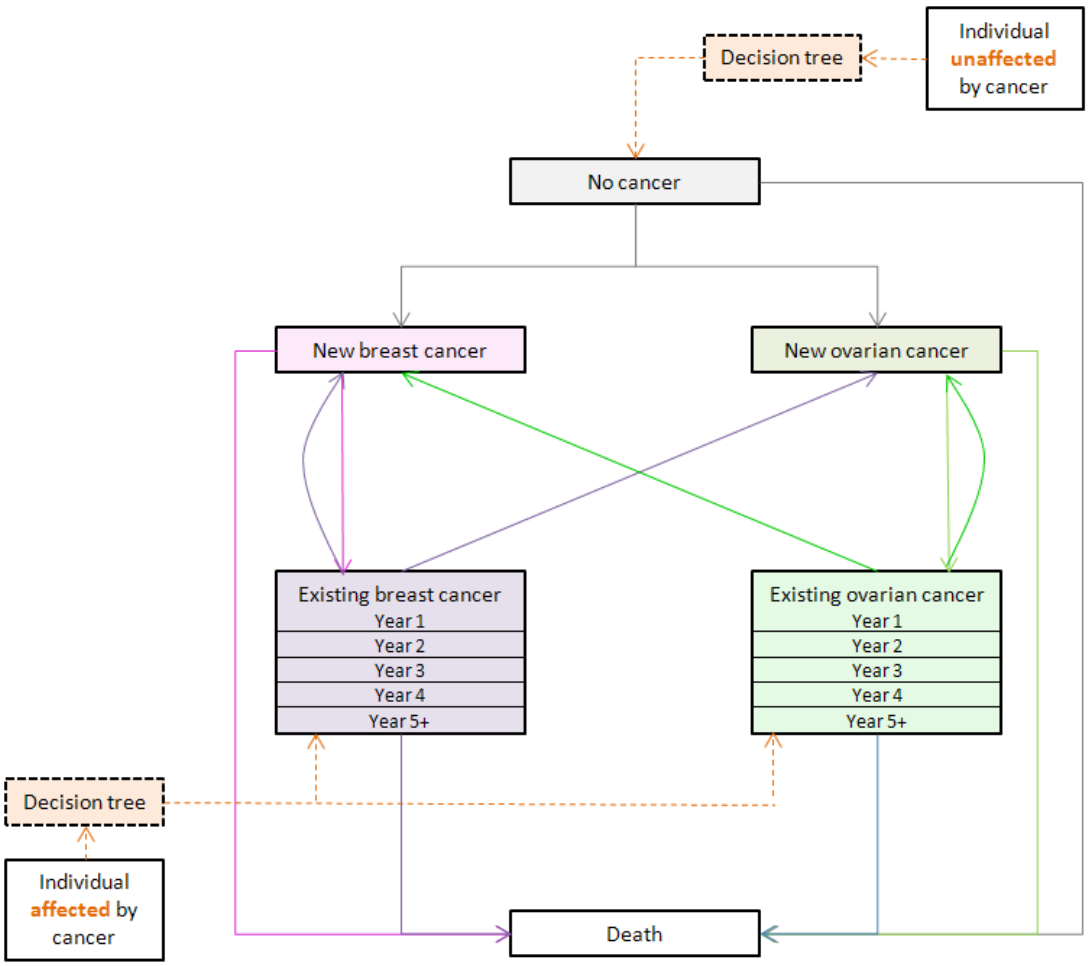
Decision node Chance node Terminal node [+] Branches as for the node above

It was assumed that the only risk reducing surgery option available to men is mastectomy. Whilst rare, the GDG felt it should be reflected in the model.

Stage 2: A semi-Markov model was constructed to replicate the natural progression of disease following risk reducing surgery decisions, made as a result of genetic testing or in its absence. A number of health states were included to model the incidence of new cancers, survival and death. Both cancer-related deaths and all-cause mortality were included. Transitions between health states were evaluated over annual cycles, over a modelled horizon of up to 50 years.

Separate models were developed for women and men (Figures 1.4 and 1.5).

Figure 1.4: Model schematic of disease progression in women

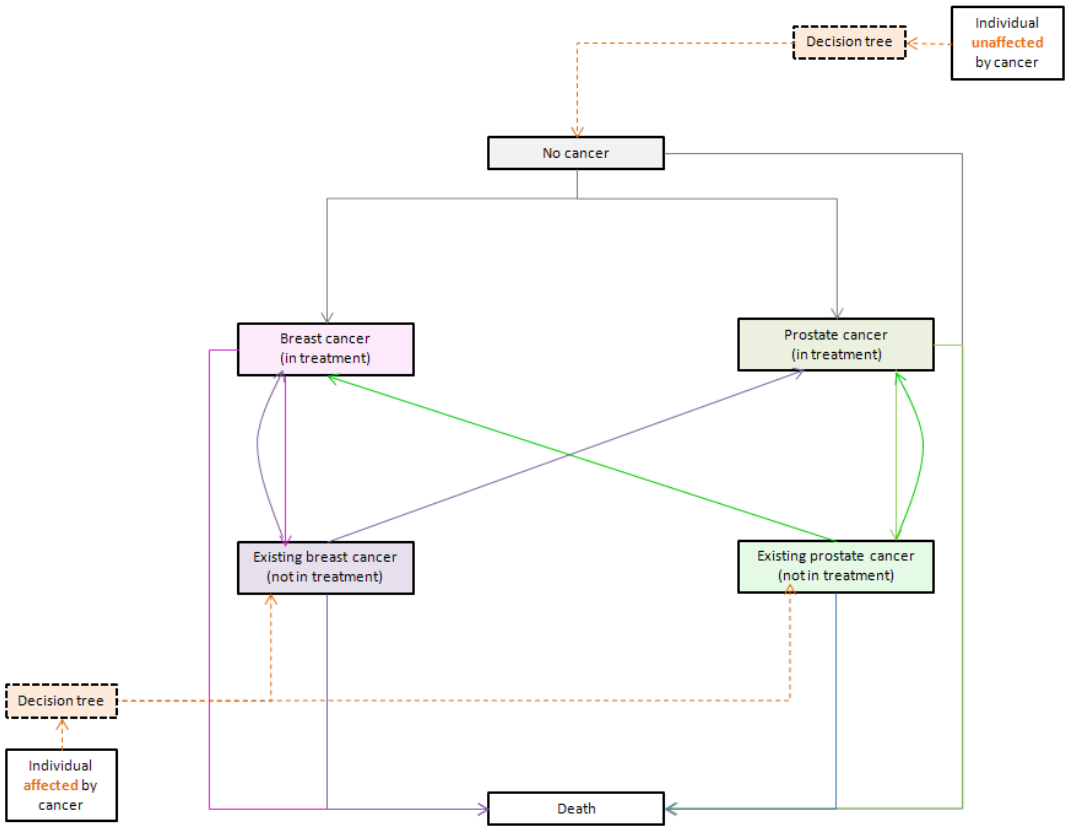


Women

The model assumes that women unaffected by cancer would start in a state of no cancer from which they could enter a state of new breast cancer or new ovarian cancer. It was agreed by the GDG that whilst the detection of breast and ovarian cancers may occur simultaneously/within a short time period, this was uncommon. It was agreed that the number of patients in whom both cancers were detected within one year was small enough not to be considered in the model. While primary peritoneal cancer should be considered, it was agreed that this diagnosis should be incorporated in the ovarian cancer state, as the literature often considers primary peritoneal together with ovarian cancer.

Surviving patients enter a state of existing cancer and remain in this state until the development of a new cancer or death. The existing cancer states are divided into 5 sub-states, defined by time since incidence of the most recently developed cancer. This allows the application of costs, quality of life and survival rates specific to time since diagnosis. Women affected by cancer (population 1) enter the model in the first sub-state of one of the two existing cancer states (Figure 1.4).

Figure 1.5: Model schematic of disease progression in men



Men

As in the model for women, men unaffected by cancer start in a state of no cancer from which they could enter a state of breast cancer (in treatment), or prostate cancer (in treatment). It was agreed by the GDG that a simultaneous detection of breast and prostate cancer would be rare and should not be included in the model. Surviving patients enter a state of existing cancer and remain in this state until the development of a new cancer or death. Men affected by cancer (population 1) enter the model in one of the two existing cancer states (Figure 1.5).

A UK NHS perspective has been adopted in the analysis, in line with NICE methodological recommendations. Health outcomes have been expressed in terms of quality-adjusted life years (QALYs). The analysis undertaken was a cost-utility analysis producing cost/QALY results expressed as incremental cost effectiveness ratios (ICERs).

Key model assumptions

- The base case analysis follows current standard practice and incorporates current recommendations for surveillance and treatment.
- A proportion of individuals may refuse diagnostic genetic testing if offered; these individuals follow the same pathway as those in the no testing arm.
- In individuals unaffected by cancer and with a living relative affected by cancer (Population 2), the assumption made is that the relative is willing to undergo diagnostic genetic testing. Any individual unaffected by cancer, with a living relative affected by cancer but whose relative was unwilling or unable to undergo genetic testing would fall into population 3.
- Regardless of whether a mutation is identified or not, a proportion of individuals may refuse or delay the uptake of risk-reducing surgery. The model simulates individuals delaying surgery by up to 5 years after genetic testing, if no new cancers have developed in that time.
- Affected individuals enter the model in an existing cancer health state.
- Unaffected individuals who are subsequently diagnosed and treated for cancer progress to an existing cancer health state on survival i.e. they become an affected individual.
- All individuals in an existing cancer health state are at increased risk of developing a new cancer
- Individuals with disease progression fully complete the treatment pathway, as per current standard practice, identified by the GDG.
- Menopausal status has consequences for the typical treatments given for breast cancer. As the mean age of menopause is approximately 51 years (Mishra and Kuh, 2012), it is assumed that all patients treated for breast cancer in age groups <50 years receive treatment typical of a premenopausal patient, while patients >50 years receive treatment typical of a postmenopausal patient.
- The surveillance of individuals with unknown BRCA status is assumed to consist of annual mammography for individuals with carrier probability up to 30% and annual MRI for individuals with carrier probability exceeding 30%.
- It is assumed that nobody has had risk-reducing surgery before genetic testing, or that the first uptake rate (year 1) of risk-reducing surgery includes those who have it before genetic testing.

Time horizon

A 50 year horizon was chosen for this model as the GDG were interested in the long-term benefits of diagnostic genetic testing. Since genetic testing has implications for survival a lifetime horizon is necessary to fully evaluate the differences between strategies, in terms of their likely impact on health-related utility and healthcare costs.

Software

The cost-effectiveness model was developed in Microsoft Excel 2007, with coding written in Visual Basic for Applications (VBA).

Cost effectiveness model: Inputs

The cost-effectiveness analysis required relevant clinical evidence, health-related preferences (utilities), healthcare resource use and costs. A considerable challenge was presented when no relevant clinical evidence was identified under the PICO for this topic. Therefore, structured searches had to be undertaken for all relevant parameters and, where

published evidence was limited, the expert opinion of the GDG was used to estimate relevant parameters.

Men were not considered separately as a population due to lack of data.

1.4.4 Clinical data

Uptake of genetic testing

Not every individual who is eligible for genetic testing and is therefore offered a test will choose to undergo genetic testing. The proportion of eligible and invited unaffected and affected individuals who choose not to take up genetic testing has been retrieved from published literature (Schwartz et al., 2004, Evans et al., 2009) (table 1.4). Individuals who choose not to undergo testing follow the same pathway as the "no testing" branch of the decision tree in the model.

Table 1.4: Percentage of eligible individuals who choose not to undergo genetic testing

Parameter	Value (%)	Source
Affected individual	14.00	Schwartz et al. 2004
Unaffected individual	51.80	Evans et al. 2009

Accuracy of genetic testing

Like any diagnostic test, genetic testing is not 100% accurate and can produce false positive and false negative results. The model accounts for this by applying sensitivity (Smith et al., 2012) and specificity values to the process of genetic testing (table 1.5).

Table 1.5: Diagnostic accuracy of genetic testing

Parameter	Value (%)	Source
Sensitivity	90.00	Smith et al. 2012
Specificity	99.00	Assumption based on GDG opinion

Uptake of risk-reducing surgery (RRS)

The model assumes that regardless of the outcome of testing, or whether testing is undertaken at all, some people will choose to undergo risk-reducing surgery i.e. mastectomy, bilateral salpingo-oophorectomy (BSO), or both (Table 1.6). Risk-reducing surgery has been shown to significantly decrease breast and ovarian cancer incidence as well as improve cancer-specific survival in people with a family history of breast and ovarian cancer (Rebbeck et al., 2004, Domchek et al., 2006, Boughey et al., 2010, Domchek et al., 2010, Mavaddat et al., 2012). The model therefore applies cancer incidence and survival rates specific to the risk-reducing surgery undertaken, if any.

The model assumes that people who undergo risk-reducing surgery will do so within the first 5 years of modelling, with the majority taking up RRS within the first 2 years. Individuals below the age of 35 who have not completed family planning are assumed to postpone BSO for 5 years. Table 1.6 summarises the data used in the model over the entire 5-year uptake period. In the model, this was applied as annual uptake with approximately 50% of people who decide to undergo RRS having surgery in year 1, 15% in year 2, 13% in year 3, 12% in year 4 and 10% in year 5 (these yearly proportions varied slightly based on the available data). The "no surgery" option for each year was calculated by adding all uptake values for all surgery options for each year and subtracting it from 100%.

Table 1.6: Uptake of risk-reducing surgery

Population subgroup	Surgery type	P Surgery uptake (over 5 years)	Source
BRCA+ unaffected woman	Mastectomy	0.417	Based on Evans et al. 2009
	BSO	0.542	Based on Sidon et al. 2012
	Both	0.145	Based on Uyei et al. 2006
BRCA- unaffected woman	Mastectomy	0.064	Based on Evans et al. 2009
	BSO	0.041	Based on Uyei et al. 2006
	Both	0.010	Based on Uyei et al. 2006
BRCA unknown unaffected woman	Mastectomy	0.033	Based on Evans et al. 2009
	BSO	0.185	Manchanda et al. 2012
	Both	0.014	Assumption
BRCA+ affected woman	Mastectomy	0.079	Based on Uyei et al. 2006
	BSO	0.432	Based on Sidon et al. 2012
	Both	0.410	Based on Uyei et al. 2006
BRCA- affected woman	Mastectomy	0.225	Based on Uyei et al. 2006
	BSO	0.031	Based on Uyei et al. 2006
	Both	0.072	Based on Uyei et al. 2006
BRCA unknown affected woman	Mastectomy	0.066	Assumption
	BSO	0.360	Manchanda et al. 2012
	Both	0.028	Assumption

Cancer type

Current literature suggest that 84% of people affected by cancer (population 1) will suffer from breast cancer whereas 11% will develop ovarian cancer based on current literature (Antoniou et al., 2008). The remaining 5% suffer from more than one cancer type and were excluded from the analysis according to GDG advice. The model assumes that people affected by cancer (population 1) had either breast or ovarian cancer and the proportions stated above were inflated to reflect this; i.e. 88.40% affected by breast cancer and 11.60% affected by ovarian cancer. Due to the uncertainty that might arise from this slight discrepancy these input parameters were included in the sensitivity analysis.

Breast cancer was assumed to be node-positive in BRCA2 carriers and triple-negative in BRCA1 carriers. Ovarian cancer includes fallopian and peritoneal cancer.

Cancer incidence

Cancer incidence data for people with a family history of breast cancer is relatively sparse and the available data is often based on small patient numbers (especially for BRCA1 and BRCA2 mutation carriers). Furthermore, studies of different designs have been conducted in different countries and sometimes do not distinguish between affected and unaffected individuals or concentrate on a single subpopulation (e.g. BRCA positives or BRCA negatives). This makes incidence data inconsistent between the subpopulations which caused concern. It was therefore decided to use incidence data produced by BOADICEA, based on a 45-year old affected index individual (for the affected subpopulation) and her 20

year old unaffected daughter (for the unaffected subpopulation) from example families with a carrier probability of 5%, 10%, 15%, 20%, 30% and 40%, respectively.

No new cancer incidence data was available for affected individuals aged 20 to 39 years as the calculations were based on a 45 year old affected woman.

Table 1.7 summarises the values for breast and ovarian cancer incidence per age group for individuals who have not undergone risk-reducing surgery as calculated by BOADICEA.

Table 1.7: Annual incidence of new breast and ovarian cancer for different subpopulations and age groups

Population subgroup	New cancer	Age group	Annual cancer incidence based on carrier probability					
			5%	10%	15%	20%	30%	40%
BRCA+ women unaffected by cancer	Breast	20-29	0.02778	0.02840	0.02799	0.02665	0.02737	0.02778
		30-39	0.09772	0.09927	0.09827	0.09497	0.09673	0.09794
		40-49	0.13034	0.13136	0.13068	0.12863	0.12977	0.13056
		50-59	0.08741	0.08741	0.08730	0.08741	0.08741	0.08741
		60-69	0.04343	0.04312	0.04343	0.04395	0.04364	0.04343
		>70	0.02645	0.02614	0.02634	0.02706	0.02665	0.02634
	Ovarian	20-29	0.00010	0.00010	0.00010	0.00010	0.00010	0.00010
		30-39	0.01694	0.01694	0.01694	0.01694	0.01694	0.01694
		40-49	0.04972	0.04972	0.04972	0.04972	0.04972	0.04972
		50-59	0.06156	0.06156	0.06156	0.06156	0.06156	0.06156
		60-69	0.06060	0.06060	0.06060	0.06060	0.06060	0.06060
		>70	0.04636	0.04636	0.04636	0.04636	0.04636	0.04636
BRCA- women unaffected by cancer	Breast	20-29	0.00060	0.00060	0.00060	0.00060	0.00060	0.00060
		30-39	0.00431	0.00451	0.00441	0.00431	0.00431	0.00431
		40-49	0.01228	0.01248	0.01238	0.01187	0.01207	0.01228
		50-59	0.01664	0.01674	0.01664	0.01613	0.01643	0.01654
		60-69	0.01522	0.01532	0.01522	0.01491	0.01511	0.01532
		>70	0.01542	0.01552	0.01542	0.01532	0.01532	0.01542
	Ovarian	20-29	0.00010	0.00010	0.00010	0.00010	0.00010	0.00010
		30-39	0.00030	0.00030	0.00030	0.00030	0.00030	0.00030
		40-49	0.00100	0.00100	0.00100	0.00100	0.00100	0.00100
		50-59	0.00190	0.00190	0.00190	0.00190	0.00190	0.00190
		60-69	0.00270	0.00270	0.00270	0.00270	0.00270	0.00270
		>70	0.00290	0.00290	0.00290	0.00290	0.00290	0.00290
BRCA+ women existing cancer	Breast	20-29	n/a	n/a	n/a	n/a	n/a	n/a
		30-39	n/a	n/a	n/a	n/a	n/a	n/a
		40-49	0.02634	0.02696	0.02655	0.02511	0.02583	0.02634
		50-59	0.09387	0.09398	0.09431	0.09420	0.09453	0.09464

Population	New cancer	Age group	Annual cancer incidence based on carrier probability					
		60-69	0.04103	0.04041	0.04103	0.04239	0.04166	0.04124
		>70	0.01959	0.01908	0.01939	0.02061	0.02000	0.01959
	Ovarian	20-29	n/a	n/a	n/a	n/a	n/a	n/a
		30-39	n/a	n/a	n/a	n/a	n/a	n/a
		40-49	0.00944	0.00944	0.00944	0.00944	0.00944	0.00944
		50-59	0.06166	0.06166	0.06166	0.06166	0.06166	0.06166
		60-69	0.06049	0.06049	0.06049	0.06049	0.06049	0.06049
		>70	0.04646	0.04646	0.04646	0.04646	0.04646	0.04646
BRCA- women existing cancer	Breast	20-29	n/a	n/a	n/a	n/a	n/a	n/a
		30-39	n/a	n/a	n/a	n/a	n/a	n/a
		40-49	0.00501	0.00592	0.00642	0.00642	0.00702	0.00844
		50-59	0.03087	0.03563	0.03698	0.03687	0.03791	0.04364
		60-69	0.02122	0.02378	0.02409	0.02419	0.02440	0.02737
		>70	0.01319	0.01410	0.01410	0.01430	0.01450	0.01552
	Ovarian	20-29	n/a	n/a	n/a	n/a	n/a	n/a
		30-39	n/a	n/a	n/a	n/a	n/a	n/a
		40-49	0.00020	0.00030	0.00050	0.00060	0.00090	0.00110
		50-59	0.00260	0.00331	0.00451	0.00552	0.00793	0.00995
		60-69	0.00310	0.00341	0.00481	0.00531	0.00743	0.00854
		>70	0.00331	0.00331	0.00441	0.00491	0.00642	0.00723

The baseline annual incidences (no RRS) as shown in Table 1.8 for each subpopulation and age group were then adjusted using risk reduction rates as published in the literature to account for the effects of the different risk-reducing surgery options on new cancer incidence. Risk reduction rates and multipliers applied to baseline values in the model are shown in Table 1.8.

Table 1.8: Risk reduction rates and multipliers applied to baseline incidences

Subpopulation/cancer	Surgery type	Risk reduction (%)	Source	Multiplier
Affected/breast	Mastectomy	95.00	Boughey et al. 2010	0.05
	BSO	41.00	Mavaddat et al. (submitted)	0.59
	both	97.00	Assumption	0.03
Affected/ovarian	Mastectomy	0.00	Assumption	1.00
	BSO	86.00	Domchek et al. 2010	0.14
	both	89.00	Assumption	0.14
Unaffected/ovarian	Mastectomy	91.00	Rebbeck et al. 2004	0.09
	BSO	38.00	Mavaddat et al. (submitted)	0.62
	both	95.00	Rebbeck et al. 2004	0.05
Unaffected/ovarian	Mastectomy	0.00	Assumption	1.00
	BSO	72.00	Domchek et al. 2010	0.28
	both	72.00	Assumption	0.28

Cancer-related mortality

Data on cancer-specific mortality have been taken from published literature and validated by the GDG.

Published data was only available for individual age groups. However, an increase of mortality by 1% per additional life year based on a cohort of 637 breast cancer patients with a family history of breast/ovarian cancer was reported (Brekelmans et al., 2007). This was used to estimate mortality for other age groups. Furthermore, the reported 3 and 5-year survival rates were converted into annual probability of death (Table 1.9).

Table 1.9: Annual probability of death from cancer (no risk-reducing surgery)

Subpopulation	Age group	P(death)	Source
BRCA+ women with breast cancer	20-29	0.03985	Brekelmans et al. 2007
BRCA+ women with breast cancer	30-39	0.04533	Brekelmans et al. 2007
BRCA+ women with breast cancer	40-49	0.05093	Brekelmans et al. 2007
BRCA+ women with breast cancer	50-59	0.05667	Brekelmans et al. 2007
BRCA+ women with breast cancer	60-69	0.06255	Brekelmans et al. 2007
BRCA+ women with breast cancer	>70	0.06858	Brekelmans et al. 2007
BRCA- women with breast	20-29	0.02172	Brekelmans et al. 2007

Subpopulation	Age group	P(death)	Source
cancer			
BRCA- women with breast cancer	30-39	0.02458	Brekelmans et al. 2007
BRCA- women with breast cancer	40-49	0.02747	Brekelmans et al. 2007
BRCA- women with breast cancer	50-59	0.03039	Brekelmans et al. 2007
BRCA- women with breast cancer	60-69	0.03335	Brekelmans et al. 2007
BRCA- women with breast cancer	>70	0.03635	Brekelmans et al. 2007
BRCA+ women with ovarian cancer	20-29	0.08718	Assumption (-1% per life year)
BRCA+ women with ovarian cancer	30-39	0.10107	Assumption (-1% per life year)
BRCA+ women with ovarian cancer	40-49	0.11541	Assumption (-1% per life year)
BRCA+ women with ovarian cancer	50-59	0.13022	Ben David et al. 2002
BRCA+ women with ovarian cancer	60-69	0.14556	Assumption (+1% per life year)
BRCA+ women with ovarian cancer	>70	0.16147	Assumption (+1% per life year)
BRCA- women with ovarian cancer	20-29	0.12789	Assumption (-1% per life year)
BRCA- women with ovarian cancer	30-39	0.14950	Assumption (-1% per life year)
BRCA- women with ovarian cancer	40-49	0.17227	Assumption (-1% per life year)
BRCA- women with ovarian cancer	50-59	0.19637	Ben David et al. 2002
BRCA- women with ovarian cancer	60-69	0.22201	Assumption (+1% per life year)
BRCA- women with ovarian cancer	>70	0.24945	Assumption (+1% per life year)

The baseline annual incidences (no RRS) as shown in Table 1.9 for each subpopulation and age group were then adjusted using risk reduction rates as published in the literature to account for the effects of the different risk-reducing surgery options on cancer mortality. Risk reduction rates and multipliers applied to baseline values in the model are shown in Table 1.10.

Table 1.10: Mortality reduction rates and multipliers applied to baseline mortality

Subpopulation/cancer	Surgery type	Risk reduction (%)	Source	Multiplier
Breast cancer	Mastectomy	74.00	van Sprundel et al. 2005	0.26
	BSO	85.00	Domchek et al. 2006	0.15
	both	88.00	Assumption	0.12
Ovarian cancer	Mastectomy	0.00	Assumption	1.00
	BSO	77.00	Domchek et al. 2006	0.23
	both	77.00	Assumption	0.23

Mortality (non-disease specific)

In order to estimate the quantitative benefit of genetic testing and its potential consequences (risk-reducing surgery, lower incidence, better survival), it was necessary to calculate how many additional life years the individual and cohort will accumulate due to decreased mortality associated with genetic testing. For this reason, interim life tables (2008-2010) were obtained from the Office for National Statistics2. All cause mortality events were estimated using gender specific life tables for the United Kingdom. These life tables define the annual probability of death in female subjects at each age. By applying this non-disease specific life expectancy to each individual the effects of genetic testing on quantity of life could be estimated.

1.4.5 Utility data

The model calculates the cost of genetic testing per quality adjusted life year (QALY) gained. This means that the analysis considers a change in quality of life as well as any additional life years which result from genetic testing. It was therefore necessary to estimate QALYs associated with various health states and events, such as cancer treatment and risk-reducing surgery. However, during the systematic review it became clear that there is a distinct lack of QALY data based on EQ-5D measures in the published literature which made it necessary for the GDG to make assumptions for some parameters based on their clinical expertise and experience.

All utilities were discounted by 3.50%.

Baseline utility and effect of genetic testing

Baseline utilities were taken from literature and were based on UK data and EQ-5D wherever possible. The baseline utility of an individual affected by breast cancer was determined to be 0.68 (Peasgood et al., 2010). The baseline utility of an individual who is not suffering from breast cancer is assumed to be the same as the average person in the general population.

Based on previous findings (Grann et al., 2011), genetic testing and especially a positive result can lead to anxiety in affected individuals. Comparing an average quality of life score of 0.90 for a person not suffering from breast cancer (Younis et al., 2011) and the value for a person who is well but with a positive BRCA testing result of 0.895 reported by Grann et al. (2011), the utility decrement of genetic testing was set to 0.005. This decrement was only applied once at the time of testing.

[2] Office for National Statistics (http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables).

Utility decrement associated with risk-reducing surgery

Previously, it has been suggested that risk-reducing surgery causes a person's utility score to drop temporarily due the effect of surgery on quality of life (Griffith et al., 2004, Peasgood et al., 2010). The model therefore assumes a utility decrement of 0.03 for mastectomy (Peasgood et al., 2010) and 0.08 for oophorectomy (Griffith et al., 2004) in the year surgery is performed. The GDG advised that it would be very rare for both surgeries to be done at the same time, so an additive utility decrement of 0.11 was used for people who undergo both surgeries. No utility decrement is applied in subsequent years on GDG advice.

Utility during cancer treatment

Utility values for patients undergoing treatment for breast and ovarian cancer in year 1 were taken from literature (Havrilesky et al., 2009, Peasgood et al., 2010). Following GDG advice, a steady improvement in quality of life was then assumed to occur over the following 5 years. However, utility of these affected individuals was assumed to never return to the baseline value of the general population (Table 1.11).

Table 1.11: Utility during and following cancer treatment

Time from diagnosis	Utility		Source
	Breast cancer	Ovarian cancer	
Year 1	0.71	0.50	Peasgood et al. (2010); Havrilesky et al. 2009
Year 2	0.72	0.65	Assumption
Year 3	0.73	0.67	Assumption
Year 4	0.74	0.69	Assumption
Year 5	0.76	0.70	Assumption
Year 5+	0.77	0.72	Assumption

1.4.6 Resource use and cost data

The costs considered in this analysis were those relevant to the UK NHS setting and included the cost of diagnostic genetic testing, treatment (including expected in-patient and out-patient costs) and surveillance. Unit costs were based on the BNF, NHS Reference Costs (2011) and Unit Costs of Health and Social Care (Curtis 2011).

All costs were discounted by 3.50%.

Costs of diagnostic genetic testing

The cost of genetic testing for an index individual and an unaffected relative (cascade testing) was deducted from GDG advice and micro-costing reported in literature (Griffith et al., 2005). Cost of genetic testing was made up of counselling (including administration costs) and the cost of genetic testing (laboratory cost). For the index individual, the cost of counselling (two sessions) was calculated as £798.20 by converting the cost published by Griffith et al. (2005) to 2011 prices. According to GDG recommendation a testing cost of £700.00 was added, giving a total cost of genetic testing for an index individual of £1498.20. For family members of the index individual, a counselling cost £894.40 (three sessions) and a lower testing cost of £240.00 (GDG recommendation) were applied, due to the fact that the type of mutation will already be known. Testing an affected family member therefore costs £1134.40.

Costs of risk-reducing surgery

Cost of risk-reducing surgery was taken from NHS reference costs 2011. Cost of mastectomy was weighted according to complications and co-morbidities and uptake of unilateral versus bilateral surgery with or without reconstruction based on figures for the general population. Cost of bilateral salpingo-oophorectomy (BSO) was weighted for complications and co-morbidities. The cost of both surgeries was calculated additively as the GDG agreed that it would be extremely rare for both surgeries to be done at once. Table 1.12 summarises the cost of risk-reducing surgery as used in the model.

Table 1.12: Cost of different risk-reducing surgery options

Surgery type	Cost (£)	Source
Mastectomy	2811.59	NHS reference costs 2011
BSO	3355.43	NHS reference costs 2011
Both	6167.02	NHS reference costs 2011

Costs of surveillance

People who choose not to undergo risk-reducing surgery will be offered annual surveillance screening for breast cancer. Costs of different screening strategies are applied dependant on BRCA status and personal history of breast cancer. According to GDG guidance it was assumed that unaffected individuals known to be BRCA-positive and those with unknown mutation status but whose family carrier probability is at least 30% would receive annual MRI scans costing £216.00 per year (NHS, 2011). Unaffected individuals with unknown mutation status with a risk below 30% are offered annual mammography costing £93.00 per year (Tosteson et al., 2008). Unaffected individuals known to be BRCA negative are offered no surveillance. Affected individuals known to be BRCA positive are offered annual MRI, while all other affected individuals are offered mammography.

Cost of cancer treatment

Cost of cancer treatment was micro-costed based on GDG expertise and under the assumption that all BRCA2 breast cancers would be node-positive, while all BRCA1 breast cancers would be triple-negative. Micro-costing was performed for node-positive and triple-negative breast cancer for pre- and post-menopausal women and for ovarian cancer. Table 1.13 presents the costs included in the cancer treatment micro-costing exercise.

Table 1.13: Costs included in cancer treatment micro-costing

Cancer type/patient	Resource	Dose	Cost, whole course (£)	Proportion	Source
Breast cancer, node-positive pre-menopausal	FEC	6 cycles	714.00	0.34	BNF 63
	FECT	6 cycles	3565.50	0.08	BNF 63
	Epi-CMF	8 cycles	576.80	0.16	BNF 63
	Other (treated as FEC)	6 cycles	714.00	0.42	BNF 63
	Neutropenic sepsis	n/a	5373.00	0.15	NHS reference costs 2011
	Outpatient appointments	1/cycle	147.00/cycle	1.00	PSSRU 2011
	Dexamethasone	16mg for 2 days	13.00	1.00	BNF 63
	Ondansetron	16mg for 2 days	100.90	1.00	BNF 63
	Maxolan	40mg for 5 days	7.50	1.00	BNF 63
	Neulasta	6 mg after each dose	4118.20	0.50	BNF 63
	Tamoxifen	20mg daily for 5 years	35.40/year	1.00	BNF 63
	Lumpectomy	n/a	1447.83	1.00	NHS reference costs 2011
	Mastectomy	n/a	2811.59	0.40	NHS reference costs 2011
	Adjuvant radiotherapy	15 fractions	1807.80	0.40	NHS reference costs 2011
	Herceptin	8 mg/kg loading dose, then 6 mg/kg, 3 weekly over 18 weeks	7210.98	0.125	BNF 63
	Total cost per patient		**9326.02**		
Breast cancer, node-positive post-menopausal	FEC	6 cycles	714.00	0.34	BNF 63
	FECT	6 cycles	3565.50	0.08	BNF 63
	Epi-CMF	8 cycles	576.80	0.16	BNF 63
	Other (treated as FEC)	6 cycles	714.00	0.42	BNF 63
	Neutropenic sepsis	n/a	5373.00	0.15	NHS reference costs 2011
	Outpatient appointments	1/cycle	147.00/cycle	1.00	PSSRU 2011
	Dexamethasone	16mg for 2 days	13.00	1.00	BNF 63
	Ondansetron	16mg for 2 days	100.90	1.00	BNF 63
	Maxolan	40mg for 5 days	7.50	1.00	BNF 63
	Neulasta	6 mg after each dose	4118.20	0.50	BNF 63
	Tamoxifen	20mg daily for 5 years	35.40 per year	1.00	BNF 63
	Lumpectomy	n/a	1447.83	1.00	NHS reference costs 2011
	Mastectomy	n/a	2811.59	0.20	NHS reference costs 2011

Cancer type/patient	Resource	Dose	Cost, whole course (£)	Proportion	Source
	Adjuvant radiotherapy	15 fractions	1807.80	0.40	NHS reference costs 2011
	Herceptin	8 mg/kg loading dose, then6 mg/kg, 3 weekly over 18 weeks	7210.98	0.125	BNF 63
	Total cost per patient		**8763.70**		
Breast cancer, triple-negative pre-menopausal	FEC	6 cycles	714.00	0.33	BNF 63
	FECT	6 cycles	3565.50	0.12	BNF 63
	Epi-CMF	8 cycles	576.80	0.21	BNF 63
	Other (treated as FEC)	6 cycles	714.00	0.34	BNF 63
	Neutropenic sepsis	n/a	5373.00	0.15	NHS reference costs 2011
	Outpatient appointments	1/cycle	147.00/cycle	1.00	PSSRU 2011
	Dexamethasone	16mg for 2 days	13.00	1.00	BNF 63
	Ondansetron	16mg for 2 days	100.90	1.00	BNF 63
	Maxolan	40mg for 5 days	7.50	1.00	BNF 63
	Neulasta	6 mg after each dose	4118.20	0.50	BNF 63
	Lumpectomy	n/a	1447.83	1.00	NHS reference costs 2011
	Mastectomy	n/a	2811.59	0.40	NHS reference costs 2011
	Adjuvant radiotherapy	15 fractions	1807.80	0.40	NHS reference costs 2011
	Total cost per patient		**8372.61**		
Breast cancer, triple-negative post-menopausal	FEC	6 cycles	714.00	0.33	BNF 63
	FECT	6 cycles	3565.50	0.12	BNF 63
	Epi-CMF	8 cycles	576.80	0.21	BNF 63
	Other (treated as FEC)	6 cycles	714.00	0.34	BNF 63
	Neutropenic sepsis	n/a	5373.00	0.15	NHS reference costs 2011
	Outpatient appointments	1/cycle	147.00/cycle	1.00	PSSRU 2011
	Dexamethasone	16mg for 2 days	13.00	1.00	BNF 63
	Ondansetron	16mg for 2 days	100.90	1.00	BNF 63
	Maxolan	40mg for 5 days	7.50	1.00	BNF 63
	Neulasta	6 mg after each dose	4118.20	0.50	BNF 63
	Lumpectomy	n/a	1447.83	1.00	NHS reference costs 2011
	Mastectomy	n/a	2811.59	0.20	NHS reference costs 2011

Cancer type/patient	Resource	Dose	Cost, whole course (£)	Proportion	Source
	Adjuvant radiotherapy	15 fractions	1807.80	0.40	NHS reference costs 2011
	Total cost per patient		**7810.29**		
Metastatic breast cancer	**Total cost per patient**		**20860.65**	**0.05**	**NICE 2009**
Breast cancer treatment year 2-5	Tamoxifen	20mg/day	35.40	0.42	BNF 63
	Anastrozole	1mg/day	71.88	0.31	BNF 63
	Exemestane	25mg/day	1018.32	0.10	BNF 63
	Total cost per patient	**Per year**	**143.89**		
Ovarian cancer	Carboplatin	6 cycles	1897.74	0.33	BNF 63
	Docetaxol/paclitaxel + carboplatin	6 cycles	5905.02	0.67	BNF 63
	Neutropenic sepsis	n/a	5373.00	0.15	NHS reference costs 2011
	Dexamethasone	16mg for 2 days	13.00	1.00	BNF 63
	Ondansetron	16mg for 2 days	100.90	1.00	BNF 63
	Maxolan	40mg for 5 days	7.50	1.00	BNF 63
	Neulasta	6 mg after each dose	4118.20	0.50	BNF 63
	Surgery (major debulking)	n/a	3482.73	1.00	NHS reference costs 2011
	Total cost per patient		**9454.35**		

Proportion = proportion of patients receiving treatment

Following micro-costing of each treatment, costs were weighted according to percentage of BRCA1 and BRCA2 carriers, probability of early breast cancer versus advanced breast cancer and pre-menopausal versus post-menopausal to obtain an overall estimate of costs of breast and ovarian cancer (Table 1.14). Breast cancers experienced by BRCA-negative patients were assumed to be node-positive

Table 1.14: Costs of cancer treatment used in model

Cancer type	Cost (£)	Source
Cost of breast cancer treatment for BRCA+ patient - premenopausal	£9,486	Micro-costing/weighted
Cost of breast cancer treatment for BRCA- patient - premenopausal	£9,903	Micro-costing/weighted
Cost of breast cancer treatment for BRCA+ patient - postmenopausal	£8,960	Micro-costing/weighted
Cost of breast cancer treatment for BRCA- patient - postmenopausal	£9,369	Micro-costing/weighted
Cost of ovarian cancer treatment for BRCA+ patient	£9,454	Micro-costing
Cost of ovarian cancer treatment for BRCA- patient	£9,454	Micro-costing

Cost of death

Cost of palliative care was taken from literature (Guest et al., 2006) and NHS reference costs (2011). Cost of cancer-related death was inflated to 2011 costs, weighted for breast and ovarian cancer and was estimated to be £ 4134.00. Cost of non-cancer specific death was obtained from NHS reference cost (2011) for Hospital Specialist Palliative Care Support (19 years and over) and was determined to be £ 110.00.

1.4.7 Sensitivity analysis

Three different sensitivity analyses were conducted to test the robustness of the results of each economic model.

One-way sensitivity analysis

Table 1.15 presents the range of parameter estimates applied to the comparison of genetic testing versus no genetic testing during one-way sensitivity analysis.

Table 1.15: Parameter variation during one-way sensitivity analysis

Parameter varied	Low	High	Justification/source
Costs			
Genetic testing (index)	1099.10	1773.80	Varied number of counselling sessions
Genetic testing (relative)	687.20	1536.10	Varied number of counselling sessions
Cost of palliative care	3598.60	6943.50	All breast cancer vs. all ovarian cancer (Guest et al., 2006)
Utilities			
Utility associated with breast cancer in treatment	0.475	0.774	Cancer progression vs. response to treatment (Peasgood et al., 2010)
Utility associated with ovarian cancer in treatment	0.400	0.620	Advanced vs. early ovarian cancer (Havrilesky et al., 2009)
Decrement associated with genetic testing	0.00	0.01	Assumption
Rates			
% eligible individuals affected by cancer who choose not to undergo genetic testing	11.10	16.70	+/- 20 % of base case value (Schwartz et al., 2004)
% eligible individuals unaffected by cancer who choose not to undergo genetic testing	41.40	62.10	+/- 20 % of base case value (Evans et al., 2009)
Probability that an affected family member of unaffected individual is BRCA+	0.05	0.50	Low/high carrier probabilities
Probability of affected person suffering from breast cancer	0.756	0.924	+/- 10 % of base case value (Antoniou et al., 2008)

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed to test the robustness of the modelling conclusions in the face of uncertainty surrounding the choice of modelling inputs. Parameter values were varied within a reasonable range in each of 1,000 runs and the results averaged across runs. While more stable estimates may have been obtained over a greater number of runs, a pragmatic approach was taken due to the vast number of subgroups included in the analysis.

Costs were sampled from gamma distributions, utilities from beta distributions and probabilities from normal distributions. Due to the number of parameters included in the model it is not practical to present the individual values of all parameters for each sampled variable; however they may be easily summarised. The mean was taken as described in previous sections. Due to the limitations of available data and the vast number of parameters, the standard error of the mean was assumed to be 10% of the mean for all parameters. For gamma and beta distributions, the alpha and beta parameters required for sampling were derived from the mean and standard error.

1.4.8 Supplementary analysis

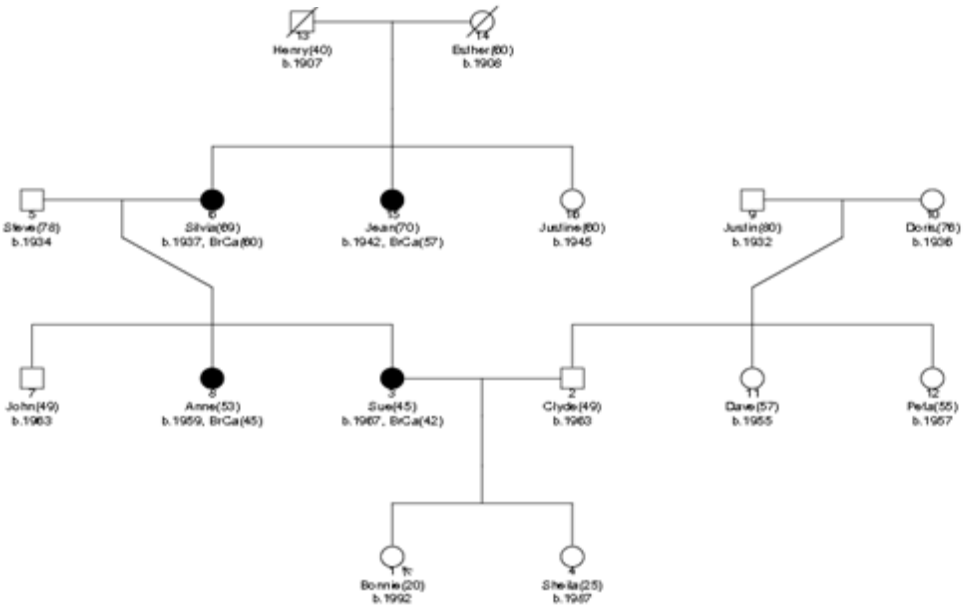
Base case analyses consider the impact of genetic testing for the individual described by the PICO population only. However, genetic testing is likely to have further impact on family members of this modelled individual. For this reason, supplementary analyses were

conducted to give an indication of the potential costs and benefits for family members of individuals identified as BRCA-positive.

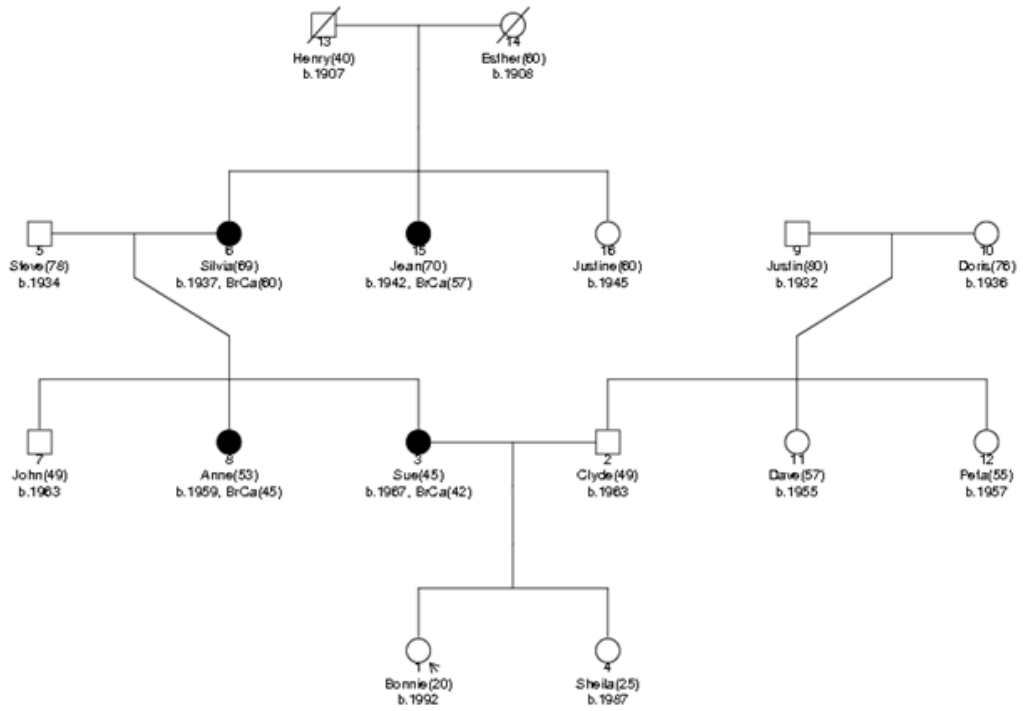
In order to conduct analysis of the cost-effectiveness of genetic testing for a family at a certain carrier probability, hypothetical families were drawn up from BOADICEA for each carrier probability threshold of interest (see Figure 1.6, a-f).

Figure 1.6: Example families of different carrier probability

a) 5% carrier risk



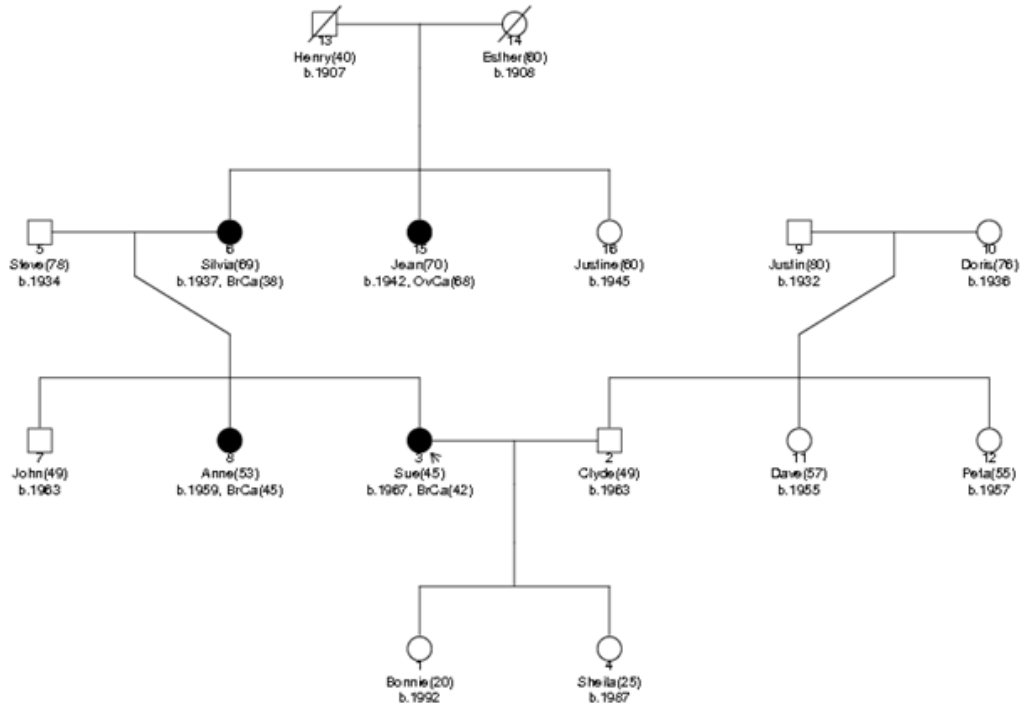
b) 10% carrier risk



1

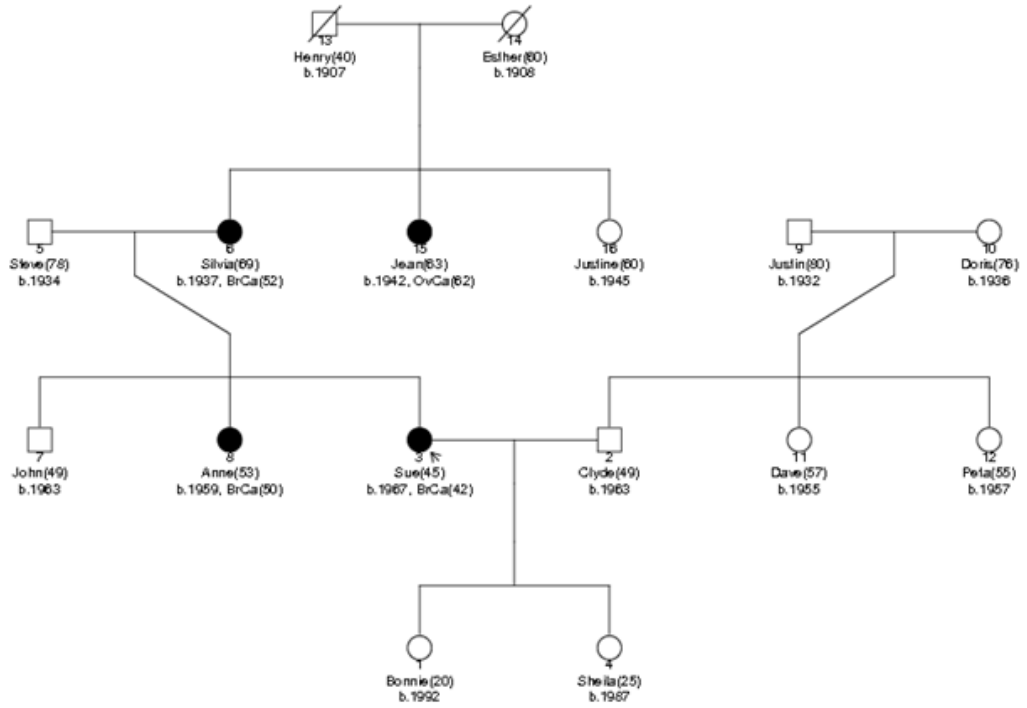
2

c) 15% carrier risk

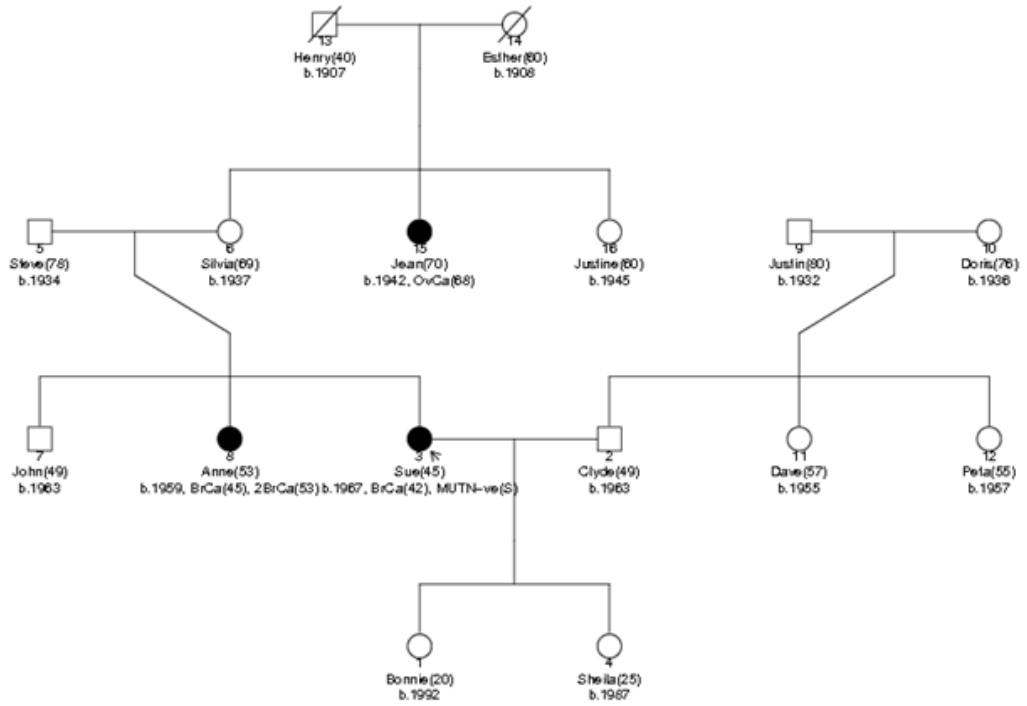


3

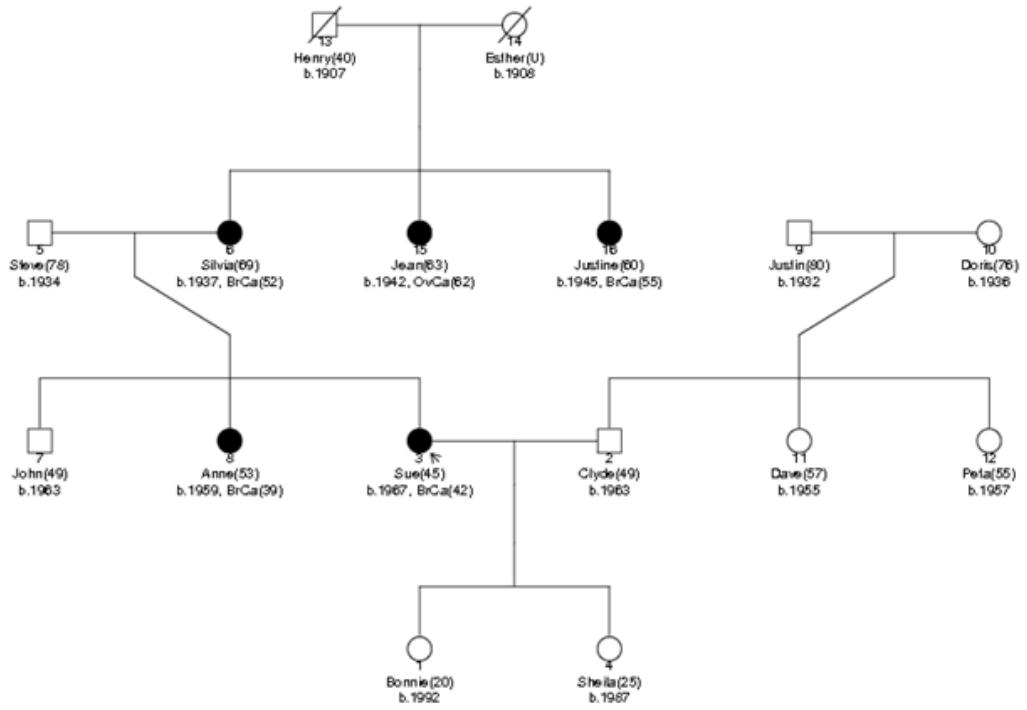
d) 20% carrier risk



e) 30% carrier risk



f) 40% carrier risk



1

The model was set up according to the characteristics of each family member (carrier probability of the family, individual age and affected/unaffected by cancer), run and the results recorded for each individual. The total costs and QALYs accumulated by each individual with and without genetic testing were combined to give total costs and benefits experienced by each hypothetical family of an BRCA positive index individual as shown in Table 1.16.

Table 1.16: Schematic table for calculations of cost-effectiveness of genetic testing on a family level

(Please note that these are examples for illustration only)		**Without Testing**		**With testing at 30% carrier probability**	
	Characteristics	**Lifetime Costs**	**Lifetime QALY**	**Lifetime Costs**	**Lifetime QALY**
Relative 1	Woman, age 20, no history of cancer	Cost(NT,1)	QALY(NT,1)	Cost(T,1)	QALY(T,1)
Relative 2	Woman, age 53, history of breast cancer	Cost(NT,2)	QALY(NT,2)	Cost(T,2)	QALY(T,2)
Relative 3	Woman, age 60, history of breast cancer	Cost(NT,3)	QALY(NT,3)	Cost(T,3)	QALY(T,3)
Relative 4	Woman, age 25, no history of cancer	Cost(NT,4)	QALY(NT,4)	Cost(T,4)	QALY(T,4)
Relative 5	Man, age 50, no history of cancer	Cost(NT,5)	QALY(NT,5)	Cost(T,5)	QALY(T,5)
Family of index individual with positive mutation		Total Cost(NT)	Total QALY(NT)	Total Cost(T)	Total QALY(T)
Family of index individual with positive mutation		Incremental costs (Δ Cost):		Total Cost(T) - Total Cost(NT)	
		Incremental QALYs (Δ QALY):		Total QALY(T) - Total QALY(NT)	

This analysis provides an estimate of the potential incremental costs and benefits (Δ Cost and Δ QALY above) associated with the knock on effect of genetic testing of relatives of every index individual in whom a positive BRCA mutation is identified. The incremental costs and QALYs from the family analysis were then multiplied by the probability of a positive mutation in the index individual and added to the base case results per index individual to produce an adjusted ICER, including these potential further benefits to family members.

Interpreting results

The results of cost-effectiveness analyses are expressed as incremental cost-effectiveness ratios (ICERs) which are calculated by dividing the cost difference between the two alternatives being compared by the difference in the effect/benefit.

In cost-utility analysis, the effect is expressed in quality-adjusted life years (QALYs) which incorporate quantity of life (additional life years) and quality of life in one measure. Thus, by dividing the difference in costs by the difference in QALYs, cost per QALY can be calculated for each comparison.

Generally, NICE considers an intervention cost-effective if one of the following applies.

The intervention is less costly and more clinically effective compared with all other relevant alternatives. In this case, no ICER is calculated as the strategy in question dominates the alternatives.

The intervention has an ICER of less than £ 20,000 per QALY compared to the next best alternative. This means that an investment of up to £ 20,000 in order to achieve an additional QALY is considered cost-effective.

During one-way or univariate sensitivity analysis all ICERs are recalculated after changing the value of a single parameter within a reasonable range. This is done for many parameters independently and provides an estimate of the robustness of the ICER to changes in specific parameters. In this way, sensitivity analysis accounts for uncertainty as it will become evident whether changes in parameters will affect the cost-effectiveness of an intervention.

Probabilistic sensitivity analysis changes the values of all chosen parameters at once (usually within the 95% confidence interval or one standard error) and calculates how probable it is that the intervention is cost-effective if all uncertainty associated with the individual parameter inputs is considered.

1.4.9 Results

Women affected by breast cancer (population 1)

Age groups: 20-29 years and 30-39 years

The incidence of new breast cancer data generated by BOADICEA was based on an affected woman of age 45 years. For this reason, no incidence data was available for affected individuals below the age of 40 years.

Age group: 40-49 years

Table 1.17 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.17: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 40 to 49 years under each screening strategy (population 1)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£21,818	£22,815	£997
	QALY	13.40	13.45	0.0519
	Life years	17.72	17.80	0.0748
10%	Cost	£23,313	£24,349	£1,037
	QALY	13.24	13.29	0.0572
	Life years	17.53	17.61	0.0812
15%	Cost	£24,755	£25,841	£1,086
	QALY	13.06	13.12	0.0616
	Life years	17.32	17.41	0.0866
20%	Cost	£25,786	£26,931	£1,145
	QALY	12.93	12.99	0.0647
	Life years	17.17	17.26	0.0905
30%	Cost	£28,024	£29,284	£1,260
	QALY	12.65	12.72	0.0714
	Life years	16.84	16.94	0.0988
40%	Cost	£30,085	£31,458	£1,373
	QALY	12.40	12.48	0.0780
	Life years	16.56	16.66	0.1070

Table 1.18 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 1.18: Incremental cost effectiveness ratios of genetic testing for individuals aged 40 to 49 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£19,218	Genetic testing cost-effective at £20,000 CE threshold
10%	£18,114	Genetic testing cost-effective at £20,000 CE threshold
15%	£17,627	Genetic testing cost-effective at £20,000 CE threshold
20%	£17,697	Genetic testing cost-effective at £20,000 CE threshold
30%	£17,650	Genetic testing cost-effective at £20,000 CE threshold
40%	£17,591	Genetic testing cost-effective at £20,000 CE threshold

Age group: 50-59 years

The Table 1.19 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.19: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 50 to 59 years under each screening strategy (population 1)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£22,920	£23,966	£1,046
	QALY	11.39	11.43	0.0400
	Life years	15.08	15.14	0.0597
10%	Cost	£24,261	£25,361	£1,100
	QALY	11.26	11.30	0.0427
	Life years	14.94	15.00	0.0629
15%	Cost	£25,772	£26,926	£1,155
	QALY	11.10	11.15	0.0454
	Life years	14.75	14.82	0.0661
20%	Cost	£26,838	£28,054	£1,217
	QALY	10.99	11.03	0.0472
	Life years	14.62	14.69	0.0683
30%	Cost	£29,133	£30,474	£1,341
	QALY	10.74	10.79	0.0511
	Life years	14.34	14.41	0.0730
40%	Cost	£31,108	£32,577	£1,469
	QALY	10.54	10.59	0.0546
	Life years	14.11	14.18	0.0771

Table 1.20 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 1.20: Incremental cost effectiveness ratios of genetic testing for individuals aged 50 to 59 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£26,127	Genetic testing cost-effective at £30,000 CE threshold
10%	£25,729	Genetic testing cost-effective at £30,000 CE threshold
15%	£25,419	Genetic testing cost-effective at £30,000 CE threshold
20%	£25,760	Genetic testing cost-effective at £30,000 CE threshold
30%	£26,237	Genetic testing cost-effective at £30,000 CE threshold
40%	£26,915	Genetic testing cost-effective at £30,000 CE threshold

Age group: 60-69 years

Table 1.21 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.21: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 60 to 69 years under each screening strategy (population 1)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£22,160	£23,265	£1,105
	QALY	9.04	9.07	0.0262
	Life years	12.00	12.04	0.0424
10%	Cost	£22,954	£24,121	£1,167
	QALY	8.98	9.01	0.0274
	Life years	11.93	11.97	0.0438
15%	Cost	£24,100	£25,325	£1,225
	QALY	8.88	8.91	0.0290
	Life years	11.82	11.87	0.0457
20%	Cost	£24,897	£26,184	£1,288
	QALY	8.82	8.85	0.0302
	Life years	11.75	11.79	0.0471
30%	Cost	£26,587	£28,002	£1,414
	QALY	8.68	8.71	0.0326
	Life years	11.59	11.64	0.0498
40%	Cost	£27,926	£29,473	£1,547
	QALY	8.57	8.60	0.0346
	Life years	11.47	11.52	0.0521

Table 1.22 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 1.22: Incremental cost effectiveness ratios of genetic testing for individuals aged 60 to 69 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£42,178	Genetic testing not cost-effective
10%	£42,534	Genetic testing not cost-effective
15%	£42,207	Genetic testing not cost-effective
20%	£42,622	Genetic testing not cost-effective
30%	£43,410	Genetic testing not cost-effective
40%	£44,744	Genetic testing not cost-effective

Age group: 70+ years

Table 1.23 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.23: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 70+ years under each screening strategy (population 1)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£21,337	£22,489	£1,152
	QALY	6.32	6.33	0.0138
	Life years	8.41	8.44	0.0267
10%	Cost	£21,799	£23,011	£1,212
	QALY	6.29	6.30	0.0144
	Life years	8.39	8.42	0.0273
15%	Cost	£22,553	£23,822	£1,268
	QALY	6.24	6.26	0.0151
	Life years	8.34	8.37	0.0282
20%	Cost	£23,103	£24,430	£1,327
	QALY	6.21	6.23	0.0158
	Life years	8.31	8.34	0.0289
30%	Cost	£24,217	£25,664	£1,446
	QALY	6.15	6.16	0.0170
	Life years	8.24	8.27	0.0302
40%	Cost	£25,086	£26,655	£1,569
	QALY	6.09	6.11	0.0180
	Life years	8.19	8.22	0.0312

Table 1.24 presents the full range of ICERs calculated for various screening strategies in individuals aged >70 years.

Table 1.24: Incremental cost effectiveness ratios of genetic testing for individuals aged 70+ years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£83,698	Genetic testing not cost-effective
10%	£84,410	Genetic testing not cost-effective
15%	£83,789	Genetic testing not cost-effective
20%	£84,206	Genetic testing not cost-effective
30%	£85,215	Genetic testing not cost-effective
40%	£87,153	Genetic testing not cost-effective

Women unaffected by cancer (with no personal history) – with an affected relative available to test (population 2)

Age group: 20-29 years

Table 1.25 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.25: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 20 to 29 years under each screening strategy (population 2)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£7,805	£9,081	£1,275
	QALY	20.32	20.39	0.0627
	Life years	23.04	23.09	0.0471
10%	Cost	£9,142	£10,386	£1,244
	QALY	20.08	20.15	0.0743
	Life years	22.85	22.91	0.0587
15%	Cost	£10,385	£11,602	£1,218
	QALY	19.84	19.93	0.0845
	Life years	22.66	22.73	0.0694
20%	Cost	£11,518	£12,719	£1,200
	QALY	19.63	19.72	0.0932
	Life years	22.48	22.56	0.0789
30%	Cost	£16,075	£16,783	£707
	QALY	19.15	19.26	0.1147
	Life years	22.10	22.20	0.1006
40%	Cost	£18,447	£19,137	£690
	QALY	18.67	18.81	0.1357
	Life years	21.72	21.84	0.1220

Table 1.26 presents the full range of ICERs calculated for various screening strategies in individuals aged 20-29 years.

Table 1.26: Incremental cost effectiveness ratios of genetic testing for individuals aged 20 to 29 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£20,348	Genetic testing cost-effective at £30,000 CE threshold
10%	£16,741	Genetic testing cost-effective at £20,000 CE threshold
15%	£14,406	Genetic testing cost-effective at £20,000 CE threshold
20%	£12,870	Genetic testing cost-effective at £20,000 CE threshold
30%	£6,168	Genetic testing cost-effective at £20,000 CE threshold
40%	£5,083	Genetic testing cost-effective at £20,000 CE threshold

Age group: 30-39 years

Table 1.27 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.27: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 30 to 39 years under each screening strategy (population 2)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£10,279	£11,458	£1,179
	QALY	19.11	19.20	0.0880
	Life years	21.85	21.92	0.0670
10%	Cost	£12,086	£13,227	£1,140
	QALY	18.80	18.89	0.0986
	Life years	21.58	21.66	0.0788
15%	Cost	£13,799	£14,904	£1,105
	QALY	18.49	18.60	0.1082
	Life years	21.31	21.40	0.0902
20%	Cost	£15,357	£16,437	£1,080
	QALY	18.22	18.33	0.1158
	Life years	21.07	21.17	0.0999
30%	Cost	£20,566	£21,199	£633
	QALY	17.60	17.74	0.1357
	Life years	20.53	20.65	0.1223
40%	Cost	£23,827	£24,432	£605
	QALY	16.99	17.15	0.1546
	Life years	20.01	20.15	0.1438

Table 1.28 presents the full range of ICERs calculated for various screening strategies in individuals aged 30-39 years.

Table 1.28: Incremental cost effectiveness ratios of genetic testing for individuals aged 30 to 39 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£13,402	Genetic testing cost-effective at £20,000 CE threshold
10%	£11,571	Genetic testing cost-effective at £20,000 CE threshold
15%	£10,208	Genetic testing cost-effective at £20,000 CE threshold
20%	£9,327	Genetic testing cost-effective at £20,000 CE threshold
30%	£4,665	Genetic testing cost-effective at £20,000 CE threshold
40%	£3,911	Genetic testing cost-effective at £20,000 CE threshold

Age group: 40-49 years

Table 1.29 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.29: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 40 to 49 years under each screening strategy (population 2)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£11,886	£13,062	£1,176
	QALY	17.31	17.39	0.0863
	Life years	19.87	19.93	0.0666
10%	Cost	£13,906	£15,048	£1,143
	QALY	16.99	17.09	0.0944
	Life years	19.58	19.66	0.0760
15%	Cost	£15,880	£16,988	£1,108
	QALY	16.68	16.78	0.1022
	Life years	19.29	19.38	0.0856
20%	Cost	£17,698	£18,781	£1,083
	QALY	16.40	16.50	0.1084
	Life years	19.03	19.12	0.0936
30%	Cost	£23,199	£23,881	£682
	QALY	15.77	15.89	0.1242
	Life years	18.46	18.57	0.1121
40%	Cost	£26,930	£27,587	£657
	QALY	15.16	15.29	0.1389
	Life years	17.90	18.03	0.1293

Table 1.30 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 1.30: Incremental cost effectiveness ratios of genetic testing for individuals aged 40 to 49 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£13,625	Genetic testing cost-effective at £20,000 CE threshold
10%	£12,108	Genetic testing cost-effective at £20,000 CE threshold
15%	£10,838	Genetic testing cost-effective at £20,000 CE threshold
20%	£9,996	Genetic testing cost-effective at £20,000 CE threshold
30%	£5,493	Genetic testing cost-effective at £20,000 CE threshold
40%	£4,730	Genetic testing cost-effective at £20,000 CE threshold

Age group: 50-59 years

Table 1.31 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.31: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 50 to 59 years under each screening strategy (population 2)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£11,500	£12,773	£1,273
	QALY	14.97	15.03	0.0611
	Life years	17.14	17.19	0.0476
10%	Cost	£13,147	£14,403	£1,257
	QALY	14.74	14.81	0.0663
	Life years	16.94	16.99	0.0534
15%	Cost	£14,805	£16,042	£1,237
	QALY	14.52	14.59	0.0715
	Life years	16.73	16.79	0.0595
20%	Cost	£16,376	£17,599	£1,222
	QALY	14.31	14.38	0.0759
	Life years	16.54	16.60	0.0649
30%	Cost	£21,096	£21,975	£879
	QALY	13.85	13.94	0.0864
	Life years	16.13	16.21	0.0767
40%	Cost	£24,209	£25,082	£873
	QALY	13.41	13.51	0.0963
	Life years	15.73	15.82	0.0879

Table 1.32 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 1.32: Incremental cost effectiveness ratios of genetic testing for individuals aged 50 to 59 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£20,821	Genetic testing cost-effective at £30,000 CE threshold
10%	£18,954	Genetic testing cost-effective at £20,000 CE threshold
15%	£17,295	Genetic testing cost-effective at £20,000 CE threshold
20%	£16,097	Genetic testing cost-effective at £20,000 CE threshold
30%	£10,176	Genetic testing cost-effective at £20,000 CE threshold
40%	£9,070	Genetic testing cost-effective at £20,000 CE threshold

Age group: 60-69 years

Table 1.33 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.33: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 60 to 69 years under each screening strategy (population 2)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£10,138	£11,541	£1,403
	QALY	12.05	12.09	0.0352
	Life years	13.73	13.76	0.0280
10%	Cost	£11,350	£12,747	£1,397
	QALY	11.93	11.96	0.0381
	Life years	13.62	13.65	0.0311
15%	Cost	£12,576	£13,965	£1,389
	QALY	11.80	11.84	0.0410
	Life years	13.51	13.54	0.0343
20%	Cost	£13,777	£15,159	£1,382
	QALY	11.67	11.71	0.0437
	Life years	13.39	13.43	0.0374
30%	Cost	£17,457	£18,557	£1,100
	QALY	11.41	11.46	0.0495
	Life years	13.17	13.21	0.0436
40%	Cost	£19,785	£20,889	£1,104
	QALY	11.15	11.21	0.0550
	Life years	12.94	12.99	0.0496

Table 1.34 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 1.34: Incremental cost effectiveness ratios of genetic testing for individuals aged 60 to 69 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£39,823	Genetic testing not cost-effective
10%	£36,647	Genetic testing not cost-effective
15%	£33,882	Genetic testing not cost-effective
20%	£31,590	Genetic testing not cost-effective
30%	£22,231	Genetic testing cost-effective at £30,000 CE threshold
40%	£20,056	Genetic testing cost-effective at £30,000 CE threshold

Age group: 70+ years

Table 1.35 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.35: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 70+ years under each screening strategy (population 2)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£8,187	£9,762	£1,575
	QALY	8.56	8.57	0.0139
	Life years	9.71	9.72	0.0121
10%	Cost	£9,002	£10,577	£1,575
	QALY	8.50	8.51	0.0153
	Life years	9.66	9.67	0.0135
15%	Cost	£9,819	£11,393	£1,574
	QALY	8.44	8.45	0.0167
	Life years	9.61	9.62	0.0149
20%	Cost	£10,638	£12,211	£1,573
	QALY	8.38	8.39	0.0181
	Life years	9.56	9.57	0.0163
30%	Cost	£13,210	£14,580	£1,369
	QALY	8.26	8.28	0.0208
	Life years	9.46	9.48	0.0190
40%	Cost	£14,783	£16,161	£1,378
	QALY	8.14	8.16	0.0236
	Life years	9.36	9.38	0.0217

Table 1.36 presents the full range of ICERs calculated for various screening strategies in individuals aged >70 years.

Table 1.36: Incremental cost effectiveness ratios of genetic testing for individuals aged 70+ years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£113,629	Genetic testing not cost-effective
10%	£102,968	Genetic testing not cost-effective
15%	£94,395	Genetic testing not cost-effective
20%	£87,029	Genetic testing not cost-effective
30%	£65,682	Genetic testing not cost-effective
40%	£58,390	Genetic testing not cost-effective

Women unaffected by cancer (with no personal history) – without an affected relative available to test (population 3)

Age group: 20-29 years

Table 1.37 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.37: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 20 to 29 years under each screening strategy (population 3)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£7,727	£7,515	-£212
	QALY	20.34	20.40	0.0601
	Life years	23.06	23.10	0.0459
10%	Cost	£8,925	£8,775	-£150
	QALY	20.11	20.18	0.0694
	Life years	22.88	22.94	0.0553
15%	Cost	£10,030	£9,946	-£84
	QALY	19.90	19.98	0.0774
	Life years	22.71	22.78	0.0639
20%	Cost	£11,029	£11,018	-£11
	QALY	19.71	19.79	0.0838
	Life years	22.56	22.63	0.0711
30%	Cost	£15,283	£14,365	-£918
	QALY	19.27	19.37	0.1006
	Life years	22.22	22.31	0.0885
40%	Cost	£17,370	£16,667	-£703
	QALY	18.84	18.96	0.1170
	Life years	21.88	21.99	0.1055

Table 1.38 presents the full range of ICERs calculated for various screening strategies in individuals aged 20-29 years.

Table 1.38: Incremental cost effectiveness ratios of genetic testing for individuals aged 20 to 29 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
10%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
15%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
20%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
30%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
40%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold

Age group: 30-39 years

Table 1.39 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.39: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 30 to 39 years under each screening strategy (population 3)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£10,192	£9,930	-£262
	QALY	19.13	19.21	0.0860
	Life years	21.87	21.93	0.0661
10%	Cost	£11,817	£11,604	-£213
	QALY	18.84	18.93	0.0943
	Life years	21.63	21.70	0.0756
15%	Cost	£13,348	£13,186	-£162
	QALY	18.56	18.67	0.1016
	Life years	21.39	21.47	0.0847
20%	Cost	£14,724	£14,623	-£101
	QALY	18.31	18.42	0.1068
	Life years	21.17	21.26	0.0919
30%	Cost	£19,550	£18,653	-£897
	QALY	17.76	17.88	0.1220
	Life years	20.69	20.80	0.1096
40%	Cost	£22,441	£21,739	-£702
	QALY	17.21	17.34	0.1362
	Life years	20.23	20.36	0.1264

Table 1.40 presents the full range of ICERs calculated for various screening strategies in individuals aged 30-39 years.

Table 1.40: Incremental cost effectiveness ratios of genetic testing for individuals aged 30 to 39 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
10%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
15%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
20%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
30%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
40%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold

Age group: 40-49 years

Table 1.41 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.41: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 40 to 49 years under each screening strategy (population 3)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£11,796	£11,579	-£217
	QALY	17.32	17.41	0.0847
	Life years	19.88	19.95	0.0661
10%	Cost	£13,602	£13,433	-£169
	QALY	17.03	17.13	0.0908
	Life years	19.63	19.70	0.0735
15%	Cost	£15,363	£15,240	-£123
	QALY	16.75	16.85	0.0966
	Life years	19.37	19.45	0.0810
20%	Cost	£16,965	£16,897	-£68
	QALY	16.50	16.60	0.1007
	Life years	19.14	19.22	0.0869
30%	Cost	£22,026	£21,253	-£773
	QALY	15.93	16.04	0.1125
	Life years	18.63	18.73	0.1014
40%	Cost	£25,325	£24,731	-£595
	QALY	15.38	15.50	0.1232
	Life years	18.14	18.25	0.1146

Table 1.42 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 1.42: Incremental cost effectiveness ratios of genetic testing for individuals aged 40 to 49 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
10%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
15%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
20%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
30%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
40%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold

Age group: 50-59 years

Table 1.43 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.43: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 50 to 59 years under each screening strategy (population 3)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£11,444	£11,373	-£72
	QALY	14.98	15.04	0.0596
	Life years	17.15	17.19	0.0473
10%	Cost	£12,909	£12,896	-£12
	QALY	14.77	14.84	0.0633
	Life years	16.97	17.02	0.0518
15%	Cost	£14,385	£14,427	£43
	QALY	14.57	14.64	0.0671
	Life years	16.79	16.84	0.0565
20%	Cost	£15,769	£15,872	£103
	QALY	14.38	14.45	0.0701
	Life years	16.61	16.67	0.0605
30%	Cost	£20,110	£19,594	-£516
	QALY	13.97	14.05	0.0778
	Life years	16.25	16.32	0.0696
40%	Cost	£22,855	£22,514	-£341
	QALY	13.57	13.66	0.0849
	Life years	15.90	15.98	0.0780

Table 1.44 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 1.44: Incremental cost effectiveness ratios of genetic testing for individuals aged 50 to 59 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
10%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
15%	£636	Genetic testing cost-effective at £20,000 CE threshold
20%	£1,467	Genetic testing cost-effective at £20,000 CE threshold
30%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
40%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold

Age group: 60-69 years

Table 1.45 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.45: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 60 to 69 years under each screening strategy (population 3)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£10,110	£10,227	£117
	QALY	12.06	12.09	0.0336
	Life years	13.74	13.77	0.0279
10%	Cost	£11,181	£11,360	£180
	QALY	11.94	11.98	0.0357
	Life years	13.64	13.67	0.0302
15%	Cost	£12,265	£12,505	£239
	QALY	11.83	11.86	0.0378
	Life years	13.54	13.57	0.0326
20%	Cost	£13,322	£13,622	£300
	QALY	11.71	11.75	0.0397
	Life years	13.44	13.47	0.0349
30%	Cost	£16,704	£16,486	-£218
	QALY	11.48	11.52	0.0438
	Life years	13.24	13.27	0.0396
40%	Cost	£18,747	£18,688	-£58
	QALY	11.25	11.30	0.0477
	Life years	13.04	13.08	0.0441

The Table 1.46 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 1.46: Incremental cost effectiveness ratios of genetic testing for individuals aged 60 to 69 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£3,491	Genetic testing cost-effective at £20,000 CE threshold
10%	£5,030	Genetic testing cost-effective at £20,000 CE threshold
15%	£6,329	Genetic testing cost-effective at £20,000 CE threshold
20%	£7,555	Genetic testing cost-effective at £20,000 CE threshold
30%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold
40%	Testing dominates	Genetic testing cost-effective at £20,000 CE threshold

Age group: 70+ years

Table 1.47 presents the total and incremental costs, QALYs and life years estimated over a lifetime for an individual under each screening strategy.

Table 1.47: Summary of costs, QALYs and life years estimated over a lifetime for an individual aged 70+ years under each screening strategy (population 3)

Percentage carrier probability	Outcome/patient	No Testing	Genetic testing at threshold	Difference
5%	Cost	£8,171	£8,538	£366
	QALY	8.56	8.57	0.0122
	Life years	9.71	9.72	0.0120
10%	Cost	£8,888	£9,312	£423
	QALY	8.51	8.52	0.0133
	Life years	9.67	9.68	0.0130
15%	Cost	£9,606	£10,085	£479
	QALY	8.45	8.47	0.0143
	Life years	9.62	9.64	0.0141
20%	Cost	£10,322	£10,858	£536
	QALY	8.40	8.41	0.0153
	Life years	9.58	9.59	0.0151
30%	Cost	£12,680	£12,846	£166
	QALY	8.29	8.31	0.0173
	Life years	9.49	9.51	0.0172
40%	Cost	£14,052	£14,352	£300
	QALY	8.18	8.20	0.0193
	Life years	9.40	9.42	0.0192

Table 1.48 presents the full range of ICERs calculated for various screening strategies in individual aged >70 years.

Table 1.48: Incremental cost effectiveness ratios of genetic testing for individuals aged 70+ years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£30,015	Genetic testing not cost-effective
10%	£31,913	Genetic testing not cost-effective
15%	£33,600	Genetic testing not cost-effective
20%	£35,057	Genetic testing not cost-effective
30%	£9,616	Genetic testing cost-effective at £20,000 CE threshold
40%	£15,534	Genetic testing cost-effective at £20,000 CE threshold

One-way sensitivity analysis

Due to the very high number of subgroups that were analysed for this topic, one-way sensitivity analysis was conducted in spot checks for several age groups and carrier probabilitys rather than as a complete analysis for all subgroups. All spot checks demonstrated that the results of the analyses are reasonably robust to changes of single parameter values.

Probabilistic sensitivity analysis

Women affected by cancer (population 1)

Age group: 40-49 years

Table 1.49 presents the mean incremental costs and QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.49: Summary of mean incremental costs and QALYs of genetic testing in the age group 40 to 49 years (population 1)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,003	CI: (£201, £1798)
	Incremental QALY	0.051	CI: (0.0194, 0.0873)
10%	Incremental cost	£1,043	CI: (£225, £1833)
	Incremental QALY	0.056	CI: (0.0219, 0.0954)
15%	Incremental cost	£1,091	CI: (£290, £1852)
	Incremental QALY	0.061	CI: (0.0238, 0.1026)
20%	Incremental cost	£1,150	CI: (£378, £1880)
	Incremental QALY	0.064	CI: (0.0255, 0.1072)
30%	Incremental cost	£1,263	CI: (£549, £1971)
	Incremental QALY	0.071	CI: (0.0281, 0.1183)
40%	Incremental cost	£1,375	CI: (£671, £2077)
	Incremental QALY	0.077	CI: (0.0308, 0.1286)

Table 1.50 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 40-49 years.

Table 1.50: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 40 to 49 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	£19,624	Genetic testing	0.501
10%	£18,487	Genetic testing	0.543
15%	£17,953	Genetic testing	0.573
20%	£18,003	Genetic testing	0.573
30%	£17,915	Genetic testing	0.580
40%	£17,808	Genetic testing	0.594

Age group: 50-59 years

The Table 1.51 presents the mean incremental costs and QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.51: Summary of mean incremental costs and QALYs of genetic testing in the age group 50 to 59 years (population 1)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,051	CI: (£295, £1799)
	Incremental QALY	0.039	CI: (0.0125, 0.0692)
10%	Incremental cost	£1,107	CI: (£341, £1868)
	Incremental QALY	0.042	CI: (0.013, 0.0741)
15%	Incremental cost	£1,160	CI: (£411, £1890)
	Incremental QALY	0.045	CI: (0.0139, 0.0784)
20%	Incremental cost	£1,221	CI: (£495, £1933)
	Incremental QALY	0.047	CI: (0.0145, 0.0815)
30%	Incremental cost	£1,343	CI: (£661, £2029)
	Incremental QALY	0.051	CI: (0.015, 0.0889)
40%	Incremental cost	£1,470	CI: (£797, £2132)
	Incremental QALY	0.054	CI: (0.0161, 0.0944)

Table 1.52 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 50-59 years.

Table 1.52: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 50 to 59 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	£26,695	No genetic testing	0.311
10%	£26,282	No genetic testing	0.317
15%	£25,888	No genetic testing	0.326
20%	£26,219	No genetic testing	0.306
30%	£26,583	No genetic testing	0.284
40%	£27,234	No genetic testing	0.262

Age group: 60-69 years

Table 1.53 presents the mean incremental costs and QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.53: Summary of mean incremental costs and QALYs of genetic testing in the age group 60 to 69 years (population 1)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,108	CI: (£507, £1748)
	Incremental QALY	0.026	CI: (0.0057, 0.0475)
10%	Incremental cost	£1,170	CI: (£578, £1791)
	Incremental QALY	0.027	CI: (0.0065, 0.0496)
15%	Incremental cost	£1,228	CI: (£640, £1832)
	Incremental QALY	0.029	CI: (0.0069, 0.0521)
20%	Incremental cost	£1,289	CI: (£720, £1891)
	Incremental QALY	0.030	CI: (0.0073, 0.0537)
30%	Incremental cost	£1,415	CI: (£865, £1989)
	Incremental QALY	0.032	CI: (0.0076, 0.0578)
40%	Incremental cost	£1,547	CI: (£1002, £2098)
	Incremental QALY	0.034	CI: (0.008, 0.0611)

Table 1.54 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 60-69 years.

Table 1.54: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 60 to 69 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	£42,880	No genetic testing	0.076
10%	£43,253	No genetic testing	0.074
15%	£42,849	No genetic testing	0.070
20%	£43,224	No genetic testing	0.059
30%	£43,931	No genetic testing	0.051
40%	£45,228	No genetic testing	0.043

Age group: >70 years

Table 1.55 presents the mean incremental costs and QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.55: Summary of mean incremental costs and QALYs of genetic testing in the age group 70+ years (population 1)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£775	CI: (£1588, £1191)
	Incremental QALY	0.013	CI: (0.0091, 0.0073)
10%	Incremental cost	£1,215	CI: (£717, £1742)
	Incremental QALY	0.014	CI: (0.0016, 0.0277)
15%	Incremental cost	£1,271	CI: (£764, £1783)
	Incremental QALY	0.015	CI: (0.0018, 0.0288)
20%	Incremental cost	£1,329	CI: (£852, £1829)
	Incremental QALY	0.015	CI: (0.002, 0.0298)
30%	Incremental cost	£1,447	CI: (£967, £1923)
	Incremental QALY	0.017	CI: (0.0023, 0.0317)
40%	Incremental cost	£1,569	CI: (£1110, £2037)
	Incremental QALY	0.018	CI: (0.0026, 0.0331)

Table 1.56 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged at least 70 years.

Table 1.56: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 70+ years (population 1)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	£86,025	No genetic testing	0.006
10%	£86,631	No genetic testing	0.003
15%	£85,784	No genetic testing	0.003
20%	£86,068	No genetic testing	0.002
30%	£86,821	No genetic testing	0.001
40%	£88,603	No genetic testing	0.000

Women unaffected by cancer – with a living affected relative to test (population 2)

Age group: 20-29 years

Table 1.57 presents the mean incremental costs and QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.57: Summary of mean incremental costs and QALYs of genetic testing in the age group 20 to 29 years (population 2)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,295	CI: (£829, £1775)
	Incremental QALY	0.063	CI: (0.0106, 0.1004)
10%	Incremental cost	£1,262	CI: (£798, £1743)
	Incremental QALY	0.075	CI: (0.0179, 0.1154)
15%	Incremental cost	£1,235	CI: (£790, £1718)
	Incremental QALY	0.085	CI: (0.024, 0.1282)
20%	Incremental cost	£1,216	CI: (£785, £1705)
	Incremental QALY	0.094	CI: (0.0301, 0.1395)
30%	Incremental cost	£723	CI: (£286, £1166)
	Incremental QALY	0.115	CI: (0.0439, 0.167)
40%	Incremental cost	£703	CI: (£293, £1144)
	Incremental QALY	0.136	CI: (0.0568, 0.1947)

Table 1.58 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 20-29 years.

Table 1.58: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 20 to 29 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	£20,591	No genetic testing	0.510
10%	£16,939	Genetic testing	0.692
15%	£14,570	Genetic testing	0.796
20%	£13,005	Genetic testing	0.857
30%	£6,293	Genetic testing	0.977
40%	£5,170	Genetic testing	0.987

Age group: 30-39 years

Table 1.59 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.59: Summary of mean incremental costs and QALYs of genetic testing in the age group 30 to 39 years (population 2)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,200	CI: (£631, £1766)
	Incremental QALY	0.088	CI: (0.019, 0.1373)
10%	Incremental cost	£1,160	CI: (£589, £1726)
	Incremental QALY	0.099	CI: (0.0262, 0.1492)
15%	Incremental cost	£1,123	CI: (£572, £1684)
	Incremental QALY	0.108	CI: (0.0343, 0.1604)
20%	Incremental cost	£1,098	CI: (£573, £1637)
	Incremental QALY	0.116	CI: (0.0409, 0.1674)
30%	Incremental cost	£650	CI: (£165, £1159)
	Incremental QALY	0.136	CI: (0.0569, 0.1897)
40%	Incremental cost	£619	CI: (£139, £1127)
	Incremental QALY	0.154	CI: (0.0707, 0.2118)

Table 1.60 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 30-39 years.

Table 1.60: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 30 to 39 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	13621.34	Genetic testing	0.813
10%	11765.32	Genetic testing	0.873
15%	10379.81	Genetic testing	0.918
20%	9478.33	Genetic testing	0.939
30%	4795.77	Genetic testing	0.991
40%	4011.86	Genetic testing	0.996

Age group: 40-49 years

Table 1.61 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.61: Summary of mean incremental costs and QALYs of genetic testing in the age group 40 to 49 years (population 2)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,196.46	CI: (£560, £1851)
	Incremental QALY	£0.09	CI: (0.021, 0.1349)
10%	Incremental cost	£1,162.10	CI: (£535, £1828)
	Incremental QALY	£0.09	CI: (0.0275, 0.1431)
15%	Incremental cost	£1,126.14	CI: (£517, £1762)
	Incremental QALY	£0.10	CI: (0.0351, 0.15)
20%	Incremental cost	£1,099.91	CI: (£519, £1723)
	Incremental QALY	£0.11	CI: (0.0403, 0.1562)
30%	Incremental cost	£698.95	CI: (£140, £1273)
	Incremental QALY	£0.12	CI: (0.054, 0.1743)
40%	Incremental cost	£671.00	CI: (£132, £1234)
	Incremental QALY	£0.14	CI: (0.0669, 0.1914)

Table 1.62 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 40-49 years.

Table 1.62: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 40 to 49 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	13852.10	Genetic testing	0.80
10%	12311.08	Genetic testing	0.86
15%	11016.10	Genetic testing	0.90
20%	10152.79	Genetic testing	0.92
30%	5630.15	Genetic testing	0.99
40%	4834.23	Genetic testing	0.99

Age group: 50-59 years

Table 1.63 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.63: Summary of mean incremental costs and QALYs of genetic testing in the age group 50 to 59 years (population 2)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,288.96	CI: (£645, £1958)
	Incremental QALY	£0.06	CI: (0.0131, 0.098)
10%	Incremental cost	£1,271.74	CI: (£643, £1926)
	Incremental QALY	£0.07	CI: (0.0165, 0.1033)
15%	Incremental cost	£1,250.76	CI: (£637, £1883)
	Incremental QALY	£0.07	CI: (0.0212, 0.1085)
20%	Incremental cost	£1,235.22	CI: (£632, £1844)
	Incremental QALY	£0.08	CI: (0.0251, 0.113)
30%	Incremental cost	£892.03	CI: (£361, £1456)
	Incremental QALY	£0.09	CI: (0.0335, 0.1246)
40%	Incremental cost	£883.73	CI: (£348, £1422)
	Incremental QALY	£0.10	CI: (0.0409, 0.1372)

Table 1.64 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 50-59 years.

Table 1.64: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 50 to 59 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	20998.35	No genetic testing	0.48
10%	19113.58	Genetic testing	0.58
15%	17436.94	Genetic testing	0.67
20%	16225.32	Genetic testing	0.72
30%	10301.64	Genetic testing	0.91
40%	9163.54	Genetic testing	0.95

Age group: 60-69 years

Table 1.65 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.65: Summary of mean incremental costs and QALYs of genetic testing in the age group 60 to 69 years (population 2)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,415.00	CI: (£857, £1978)
	Incremental QALY	£0.04	CI: (0.0056, 0.0597)
10%	Incremental cost	£1,409.00	CI: (£863, £1962)
	Incremental QALY	£0.04	CI: (0.0081, 0.0633)
15%	Incremental cost	£1,400.00	CI: (£862, £1943)
	Incremental QALY	£0.04	CI: (0.0105, 0.0662)
20%	Incremental cost	£1,392.00	CI: (£862, £1921)
	Incremental QALY	£0.04	CI: (0.012, 0.0687)
30%	Incremental cost	£1,110.00	CI: (£615, £1603)
	Incremental QALY	£0.05	CI: (0.0164, 0.0766)
40%	Incremental cost	£1,112.00	CI: (£631, £1597)
	Incremental QALY	£0.06	CI: (0.0202, 0.0838)

Table 1.66 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 60-69 years.

Table 1.66: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 60 to 69 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	40004.00	No genetic testing	0.03
10%	36801.00	No genetic testing	0.04
15%	34010.00	No genetic testing	0.06
20%	31694.00	No genetic testing	0.09
30%	22350.00	No genetic testing	0.41
40%	20133.00	No genetic testing	0.50

Age group: >70 years

Table 1.67 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.67: Summary of mean incremental costs and QALYs of genetic testing in the age group 70+ years (population 2)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£1,584	CI: (£1125, £2059)
	Incremental QALY	0.014	CI: (-0.0009, 0.0262)
10%	Incremental cost	£1,583	CI: (£1127, £2045)
	Incremental QALY	0.015	CI: (0.0002, 0.0279)
15%	Incremental cost	£1,581	CI: (£1129, £2035)
	Incremental QALY	0.017	CI: (0.0014, 0.0292)
20%	Incremental cost	£1,579	CI: (£1135, £2035)
	Incremental QALY	0.018	CI: (0.0026, 0.0309)
30%	Incremental cost	£1,376	CI: (£949, £1796)
	Incremental QALY	0.021	CI: (0.0043, 0.035)
40%	Incremental cost	£1,383	CI: (£957, £1821)
	Incremental QALY	0.024	CI: (0.0057, 0.0391)

Table 1.68 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged >70 years.

Table 1.68: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 70+ years (population 2)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	113857.98	No genetic testing	0.000
10%	103138.19	No genetic testing	0.000
15%	94513.36	No genetic testing	0.000
20%	87106.80	No genetic testing	0.000
30%	65780.75	No genetic testing	0.000
40%	58465.59	No genetic testing	0.001

Women unaffected by cancer – without a living affected relative to test (population 3)

Age group: 20-29 years

Table 1.69 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.69: Summary of mean incremental costs and QALYs of genetic testing in the age group 20 to 29 years (population 3)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	-£206	CI: (£-891, £485)
	Incremental QALY	0.060	CI: (0.0078, 0.0986)
10%	Incremental cost	-£144	CI: (£-787, £521)
	Incremental QALY	0.070	CI: (0.0144, 0.1103)
15%	Incremental cost	-£79	CI: (£-697, £562)
	Incremental QALY	0.078	CI: (0.0195, 0.1197)
20%	Incremental cost	-£6	CI: (£-592, £624)
	Incremental QALY	0.084	CI: (0.0247, 0.1273)
30%	Incremental cost	-£910	CI: (£-1554, £-289)
	Incremental QALY	£0	CI: (0.0357, 0.1485)
40%	Incremental cost	-£697	CI: (£-1275, £-118)
	Incremental QALY	0.117	CI: (0.0463, 0.1697)

Table 1.70 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 20-29 years.

Table 1.70: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 20 to 29 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	-3402.00	Genetic testing	0.982
10%	-2068.00	Genetic testing	0.984
15%	-1016.00	Genetic testing	0.985
20%	-73.00	Genetic testing	0.987
30%	-9025.00	Genetic testing	1.000
40%	-5945.00	Genetic testing	0.999

Age group: 30-39 years

Table 1.71 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.71: Summary of mean incremental costs and QALYs of genetic testing in the age group 30 to 39 years (population 3)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	-£254	CI: (£-990, £441)
	Incremental QALY	0.086	CI: (0.0172, 0.1355)
10%	Incremental cost	-£205	CI: (£-922, £483)
	Incremental QALY	0.095	CI: (0.0228, 0.1442)
15%	Incremental cost	-£154	CI: (£-823, £509)
	Incremental QALY	0.102	CI: (0.0292, 0.1526)
20%	Incremental cost	-£94	CI: (£-732, £546)
	Incremental QALY	0.107	CI: (0.0356, 0.1578)
30%	Incremental cost	-£888	CI: (£-1549, £-272)
	Incremental QALY	0.122	CI: (0.0483, 0.1754)
40%	Incremental cost	-£694	CI: (£-1287, £-118)
	Incremental QALY	0.136	CI: (0.0592, 0.1917)

Table 1.72 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 30-39 years.

Table 1.72: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 30 to 39 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	-2941.25	Genetic testing	0.989
10%	-2167.28	Genetic testing	0.992
15%	-1516.32	Genetic testing	0.996
20%	-877.15	Genetic testing	0.997
30%	-7277.21	Genetic testing	1.000
40%	-5102.02	Genetic testing	1.000

Age group: 40-49 years

Table 1.73 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.73: Summary of mean incremental costs and QALYs of genetic testing in the age group 40 to 49 years (population 3)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	-£208	CI: (£-989, £557)
	Incremental QALY	0.0849	CI: (0.0183, 0.1343)
10%	Incremental cost	-£161	CI: (£-907, £588)
	Incremental QALY	0.0910	CI: (0.0237, 0.1407)
15%	Incremental cost	-£115	CI: (£-818, £603)
	Incremental QALY	0.0968	CI: (0.03, 0.1452)
20%	Incremental cost	-£61	CI: (£-726, £619)
	Incremental QALY	0.1008	CI: (0.034, 0.1494)
30%	Incremental cost	-£765	CI: (£-1415, £-127)
	Incremental QALY	0.1126	CI: (0.044, 0.1635)
40%	Incremental cost	-£587	CI: (£-1194, £23)
	Incremental QALY	0.1232	CI: (0.0574, 0.175)

Table 1.74 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 40-49 years.

Table 1.74: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 40 to 49 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	-£2,454	Genetic testing	0.988
10%	-£1,765	Genetic testing	0.991
15%	-£1,190	Genetic testing	0.995
20%	-£605	Genetic testing	0.997
30%	-£6,790	Genetic testing	1.000
40%	-£4,763	Genetic testing	1.000

Age group: 50-59 years

Table 1.75 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.75: Summary of mean incremental costs and QALYs of genetic testing in the age group 50 to 59 years (population 3)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	-£66	CI: (£-797, £689)
	Incremental QALY	0.0599	CI: (0.0111, 0.097)
10%	Incremental cost	-£7	CI: (£-711, £716)
	Incremental QALY	0.0637	CI: (0.0136, 0.1006)
15%	Incremental cost	£48	CI: (£-622, £747)
	Incremental QALY	0.0675	CI: (0.0174, 0.1039)
20%	Incremental cost	£107	CI: (£-525, £775)
	Incremental QALY	0.0704	CI: (0.0206, 0.106)
30%	Incremental cost	-£510	CI: (£-1129, £128)
	Incremental QALY	0.0781	CI: (0.0275, 0.1142)
40%	Incremental cost	-£335	CI: (£-912, £257)
	Incremental QALY	0.0851	CI: (0.0343, 0.1224)

The Table 1.76 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 50-59 years.

Table 1.76: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 50 to 59 years (population 3)

Percentage carrier probability	**ICER (£/QALY)**	**Strategy with highest NMB at £20,000?**	**Probability that genetic testing is cost-effective at £20,000**
5%	-£1,102	Genetic testing	0.973
10%	-£107	Genetic testing	0.974
15%	£709	Genetic testing	0.978
20%	£1,526	Genetic testing	0.982
30%	-£6,532	Genetic testing	1.000
40%	-£3,941	Genetic testing	1.000

Age group: 60-69 years

Table 1.77 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.77: Summary of mean incremental costs and QALYs of genetic testing in the age group 60 to 69 years (population 3)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£122	CI: (£-484, £762)
	Incremental QALY	0.0339	CI: (0.0038, 0.0583)
10%	Incremental cost	£184	CI: (£-408, £799)
	Incremental QALY	0.0360	CI: (0.0055, 0.0608)
15%	Incremental cost	£243	CI: (£-321, £844)
	Incremental QALY	0.0380	CI: (0.0081, 0.0629)
20%	Incremental cost	£303	CI: (£-233, £874)
	Incremental QALY	0.0399	CI: (0.0093, 0.0648)
30%	Incremental cost	-£213	CI: (£-728, £321)
	Incremental QALY	0.0440	CI: (0.0127, 0.0693)
40%	Incremental cost	-£54	CI: (£-537, £446)
	Incremental QALY	0.0480	CI: (0.0155, 0.0747)

Table 1.78 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 60-69 years.

Table 1.78: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 60 to 69 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	£3,594	Genetic testing	0.892
10%	£5,110	Genetic testing	0.887
15%	£6,386	Genetic testing	0.880
20%	£7,594	Genetic testing	0.866
30%	-£4,834	Genetic testing	0.993
40%	-£1,134	Genetic testing	0.990

Age group: >70 years

Table 1.79 presents the mean incremental costs, QALYs together with the 95% confidence intervals estimated over a lifetime per person for genetic testing at each carrier probability threshold versus no testing.

Table 1.79: Summary of mean incremental costs and QALYs of genetic testing in the age group 70+ years (population 3)

Percentage carrier probability	Outcome / patient	Mean	95% Confidence Interval
5%	Incremental cost	£369	CI: (£-112, £884)
	Incremental QALY	0.012	CI: (-0.0028, 0.0246)
10%	Incremental cost	£426	CI: (£-44, £928)
	Incremental QALY	0.013	CI: (-0.0019, 0.0258)
15%	Incremental cost	£482	CI: (£30, £961)
	Incremental QALY	0.014	CI: (-0.0008, 0.027)
20%	Incremental cost	£538	CI: (£95, £1001)
	Incremental QALY	0.015	CI: (0, 0.028)
30%	Incremental cost	£170	CI: (£-251, £611)
	Incremental QALY	0.017	CI: (0.0018, 0.0305)
40%	Incremental cost	£303	CI: (£-91, £728)
	Incremental QALY	0.019	CI: (0.0035, 0.0338)

Table 1.80 presents the mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged >70 years.

Table 1.80: Mean ICERs calculated over a PSA of 1,000 runs for various screening strategies in individuals aged 70+ years (population 3)

Percentage carrier probability	ICER (£/QALY)	Strategy with highest NMB at £20,000?	Probability that genetic testing is cost-effective at £20,000
5%	30037.59	No genetic testing	0.349
10%	31902.13	No genetic testing	0.305
15%	33558.01	No genetic testing	0.254
20%	34991.59	No genetic testing	0.213
30%	9740.56	Genetic testing	0.736
40%	15592.08	Genetic testing	0.619

Supplementary analysis

Two sets of analyses were conducted in order to investigate the potential cost-effectiveness of family testing. There were difficulties estimating the potential impact of genetic testing for male relatives of a BRCA positive index individual, since a lack of data had proved the population of a male specific model to be impossible at this time. As such, the analyses were conducted in which A. male relatives were excluded and B. male relatives were run through the model built for women. The consequent range of results gives an indication of the potential impact on a hypothetical family.

Table 1.81 summarises the total incremental costs and benefits (QALYs) associated with the relatives of a BRCA-positive index individual at different family carrier probability levels. Genetic testing for the family members of an index individual found to be BRCA-positive was estimated to be cost-effective for all scenarios tested. (This excludes the costs and benefits associated with the index individual themselves.)

Cost-effectiveness results are better in lower carrier probability families due to the higher proportion of unaffected relatives in the hypothetical families tested.

Table 1.81: Incremental cost and QALYs generated by genetic testing of family members

Percentage Carrier probability	A: Men excluded from analysis			B: Men included in analysis		
	Incremental Cost	Incremental Benefit	ICER	Incremental Cost	Incremental Benefit	ICER
5%	£691	0.237	£2,912	£622	0.321	£1,938
10%	£1,837	0.260	£7,063	£1,875	0.350	£5,358
15%	£2,109	0.288	£7,321	£2,250	0.384	£5,861
20%	£2,524	0.306	£8,251	£2,776	0.406	£6,833
30%*	-£884	0.355	Dominates	-£1,619	0.468	Dominates
40%	£3,083	0.373	£8,277	£2,648	0.496	£5,339

*note the particular family profile tested for 30% risk included fewer relatives affected by cancer (however one relative with history of multiple cancers)

When combined with the base case results, results remain cost-effective for all scenarios that were estimated to be cost-effective in the base case and are improved for some patient subgroups (tables 1.82-1.87).

Table 1.82: Improved cost-effectiveness (shaded) for base case individuals aged 20-29 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (20-29 years)		
	Population 1	Population 2	Population 3
5%	N/A	Cost-effective	Cost-effective
10%	N/A	Cost-effective	Cost-effective
15%	N/A	Cost-effective	Cost-effective
20%	N/A	Cost-effective	Cost-effective
30%	N/A	Cost-effective	Cost-effective
40%	N/A	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 1.83: Improved cost-effectiveness (shaded for base case individuals aged 30-39 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (30-39 years)		
	Population 1	Population 2	Population 3
5%	N/A	Cost-effective	Cost-effective
10%	N/A	Cost-effective	Cost-effective
15%	N/A	Cost-effective	Cost-effective
20%	N/A	Cost-effective	Cost-effective
30%	N/A	Cost-effective	Cost-effective
40%	N/A	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 1.84: Improved cost-effectiveness (shaded) for base case individuals aged 40-49 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (40-49 years)		
	Population 1	Population 2	Population 3
5%	Cost-effective	Cost-effective	Cost-effective
10%	Cost-effective	Cost-effective	Cost-effective
15%	Cost-effective	Cost-effective	Cost-effective
20%	Cost-effective	Cost-effective	Cost-effective
30%	Cost-effective	Cost-effective	Cost-effective
40%	Cost-effective	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 1.85: Improved cost-effectiveness (shaded) for base case individuals aged 50-59 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (50-59 years)		
	Population 1	Population 2	Population 3
5%	(£19,204 - £20,822)	Cost-effective	Cost-effective
10%	Cost-effective	Cost-effective	Cost-effective
15%	Cost-effective	Cost-effective	Cost-effective
20%	Cost-effective	Cost-effective	Cost-effective
30%	Cost-effective	Cost-effective	Cost-effective
40%	Cost-effective	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 1.86: Improved cost-effectiveness (shaded) for base case individuals aged 60-69 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (60-69 years)		
	Population 1	Population 2	Population 3
5%	Not cost-effective	Not cost-effective	Cost-effective
10%	Not cost-effective	Not cost-effective	Cost-effective
15%	(£18,043 - £21,341)	(£17,513 - £20,252)	Cost-effective
20%	Cost-effective	Cost-effective	Cost-effective
30%	Cost-effective	Cost-effective	Cost-effective
40%	Cost-effective	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 1.87: Improved cost-effectiveness (shaded) for base case individuals aged >70 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (>70 years)		
	Population 1	Population 2	Population 3
5%	Not cost-effective	Not cost-effective	Cost-effective
10%	Not cost-effective	Not cost-effective	Cost-effective
15%	Not cost-effective	Not cost-effective	Cost-effective
20%	(£19,400 - £23,808)	Not cost-effective	Cost-effective
30%	Cost-effective	Cost-effective	Cost-effective
40%	Cost-effective	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

1.4.10 Discussion

Summary of results

The aim of this economic analysis was to assess the cost-effectiveness of genetic testing compared to no genetic testing in different patient populations, age groups and carrier probability groups and to estimate the effect of relative cascade testing on cost-effectiveness of genetic testing.

Affected individuals (population 1)

- Genetic testing is expected to be cost-effective for all carrier probability groups between the age of 40 and 49 years if only the impact on the index individual is considered in the analysis
- Incidence of new breast cancer was based on an affected individual aged 45 years. For this reason no analyses were conducted for affected individuals below the age of 40. However, since incidence of new breast cancer increases as the age of diagnosis of primary cancer decreases (Malone et al., 2010), it is expected that genetic testing will be cost-effective for all risk groups between the ages 20 to 39 years.
- Genetic testing of the affected index individual only is not expected to be cost-effective for individuals aged 50 years and over.

Affected individuals (population 1) have a higher incidence of developing new breast and ovarian cancer compared to unaffected individuals. All individuals in this population will receive cancer treatment at least once during their lifetime. Risk-reducing surgery and genetic testing uptake are also higher in affected individuals. Furthermore, mortality is higher in the affected population and they are more likely to die from cancer than from other causes when compared to the unaffected population. Thus, the overall costs of the affected population are considerably higher and their quality of life is lower than the unaffected populations. Consequently, genetic testing provides fewer cost savings and quality of life benefits later in life for the affected population and is not particularly cost-effective if only the cost and benefits of the affected index individual are included in the analysis.

Unaffected individuals with an affected relative available to be tested (population 2)

- Genetic testing is expected to be cost-effective for 20-29 year old unaffected individuals whose affected relative has been tested first from 10% carrier probability upwards.

- Genetic testing is expected to be cost-effective for all carrier probability thresholds tested for unaffected individuals between the ages of 30 and 49 years.
- Genetic testing is expected to be cost-effective for 50-59 year old unaffected individuals whose affected relative has been tested first from 10% carrier probability upwards.
- Genetic testing for this population is not expected to be cost-effective at a £ 20,000/QALY threshold for any carrier probability from 60 years onwards.
-

Analyses suggest that genetic testing will be cost-effective for most age and carrier probability groups when the focus of analysis is the impact of testing on an unaffected individual, who undergoes genetic testing based on the prior result of testing in an affected relative. These results suggest that in many scenarios the cost of testing an affected index individual is sufficiently offset by the costs and benefits of one unaffected relative (population 2 member) to be considered cost-effective.

An unaffected individual is expected to receive the optimum benefits of genetic testing such as reduced incidence of primary breast and ovarian cancers and subsequent morbidity and mortality in individuals found to be BRCA positive and who choose to undergo risk reducing surgery as a result, or the reduction of unnecessary risk-reducing surgery in individuals found to be BRCA negative. Furthermore, cost savings may be achieved as a result of genetic testing for the same reasons, and also as a result of reduced surveillance in those individuals found to be BRCA negative.

Unaffected individuals without an affected relative available to be tested (population 3)

- Genetic testing is expected to dominate for all carrier probabilities for age groups 20 to 49 years. That is, it is more effective and less expensive than no testing.
- Genetic testing is expected to be highly cost-effective for all carrier probabilities for age groups 50 to 69 years.
- Genetic testing is expected to be cost-effective for unaffected individuals over 70 years with at least a 30% carrier probability.

The results of population 3 (unaffected individuals who have no affected relative available to test) are highly cost-effective if only the costs and benefits of this single individual are considered. Unaffected individuals in population 3 accumulate all benefits and cost savings described for population 2 however the total cost of testing is lower in this scenario. With no unaffected relative available to test the unaffected individual is the index individual and only one test is conducted to determine whether this individual carries a mutation, while in population 2 one index test was conducted and a possible further test of the unaffected individual. Furthermore, all unaffected individuals in this scenario are offered testing leading to higher potential cost savings in surveillance for those identified as BRCA negative.

Supplementary analysis

- Cost-effectiveness is expected to be significantly improved if cascade testing of relatives is taken into account in addition to testing the single individuals of populations 1 to 3.
- Analysis of hypothetical family profiles suggests that at 10% carrier probability genetic testing will be cost-effective in all individuals aged 20-59 years and in unaffected individuals with no affected relative to test aged at least 60 years.
- The family profiles tested did not show significantly improved cost-effectiveness of genetic testing in several family members with increasing carrier probability. This may be due to the following reasons:

1. Lower risk families have a greater proportion of family members with no personal history of cancer, for whom genetic testing is expected to be more cost-effective than affected individuals.
2. Genetic testing in low risk families identifies a higher proportion of BRCA-negative individuals, for whom greater cost savings may be generated while they remain in the “no cancer” state due to reduced screening.

Potential limitations of the model

- The model did not include the possibility of developing new breast and ovarian cancers within the same annual cycle. While this does occur in reality, it happens rarely affecting a very small proportion of individuals. The further assumptions and additional model complexity required to replicate this situation far outweigh the additional information it could potentially provide. Modelling conclusions are not expected to be affected by the exclusion of this very small minority of patients.
- All women affected by breast cancer (population 1) were assumed to enter the model in the first year of the existing cancer state. However, it is unclear what proportion of affected individuals will take up genetic testing immediately and how many decide to postpone testing.
- The uptake of risk reducing surgery is only modelled during the first five years following genetic testing. Some women may choose to undergo risk reducing surgery at a later date. However, the majority of women that have not chosen to undergo such procedures within five years post-testing will not do so. The exception to the situation modelled may be for very young women who delay risk reducing surgery for many years, in order to start a family. Consequently, it is possible that the estimation of benefits in the youngest age group may be conservative.
- The availability of relevant quality of life data was limited. While utility decrements associated with mastectomy and BSO were identified, no equivalent was found describing the loss of quality of life associated with both procedures. The decrements associated with mastectomy and BSO were treated additively to produce an estimation of the decrement associated with mastectomy and BSO, due to the unlikelihood that both procedures would be conducted simultaneously and hence incur a decrement less than the sum of the two independent procedures. While utilities associated with breast cancer treatment and ovarian cancer treatment were identified in the literature, no published utilities were identified describing the quality of life experienced by individuals after the initial treatment of their cancers. In the absence of such data estimation of the pattern of improvement in quality of life for individuals in the “existing cancer” states were derived through discussions amongst the GDG, including patient representatives.
- Quality of life is known to alter over time as people age. While this could be reflected in the baseline utility of a member of the general population, limited data availability prohibited the inclusion of varied quality of life estimates for individuals with a familial risk of breast cancer and developing breast or ovarian cancer according to age. As such age specific quality of life estimates were not included in the model.
- At this point in time, data on men with a family history of breast cancer was very rare and men could therefore not be modelled separately.
- The modelling horizon was limited to 50 years. This is a sufficient horizon to be considered a lifetime for most population subgroups, however for the youngest group considered (20-29 years) individuals are followed up only until their 70s. As the life expectancy of a female of this age is almost 83 years, the full lifetime costs and benefits may be underestimated in this analysis. The effects of discounting both costs and effects mean this underestimation is expected to be only slight.

- As no incidence data was available for affected index individuals (population 1) under 40 years no analyses could be run for affected individuals in the two lowest age groups.

Comparison with other published studies

A total of 4 studies were identified in the systematic review of economic evidence for this topic (see full evidence review). All four papers reported modelling results of different populations and were only partially applicable to the PICO. Serious limitations were identified in all four studies. None of these studies considered all of the populations (including age groups), risk thresholds, and inclusion of men that the GDG considered relevant for the topic. One of the significant limitations of all these papers is that the intervention and comparator were only briefly described.

Overall, the 4 studies showed that in general genetic testing is cost-effective, except when only ovarian cancer patients are considered. One study which considered those affected by breast cancer with a BRCA mutation (Kwon et al 2010b), genetic testing was not cost-effective for any breast cancer in women aged <50 years. Our analysis demonstrated that overall genetic testing is expected to be cost-effective except in testing affected individuals (population 1)aged 50 years and over, in unaffected individuals with an affected individual (population 2) for all carrier probabilities aged 60 years and over; and in unaffected individuals with an affected relative (population 3) aged over 70 years. However, direct comparisons are very difficult to make from the results of our analysis to these studies.

Implications for future research

Further research that could improve this model would include the following data/information:
Specific data on health outcomes of men with a familial risk of breast cancer

Further consideration of the impact of disease stage

Prospective information on age-specific HRQOL/utilities of people with a familial risk of breast cancer in both affected and unaffected populations.

Further evidence on the impact of genetic testing on relatives

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1.5 Genetic testing for BRCA1, BRCA2 and TP53 within 4 weeks of diagnosis of breast. (2013) (Chapter 6.5)

1.5.1 Review question

Genetic testing for BRCA1 BRCA2 and TP53 within 4 weeks of diagnosis of breast cancer to inform treatment and future surveillance: Is delayed genetic testing cost-effective?

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients recently diagnosed with first breast cancer	Treatment with knowledge of patient mutation status	Treatment without knowledge of patient mutation status	Incremental cost-effectiveness analysis (ICER) Sensitivity analysis

1.5.2 Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED).

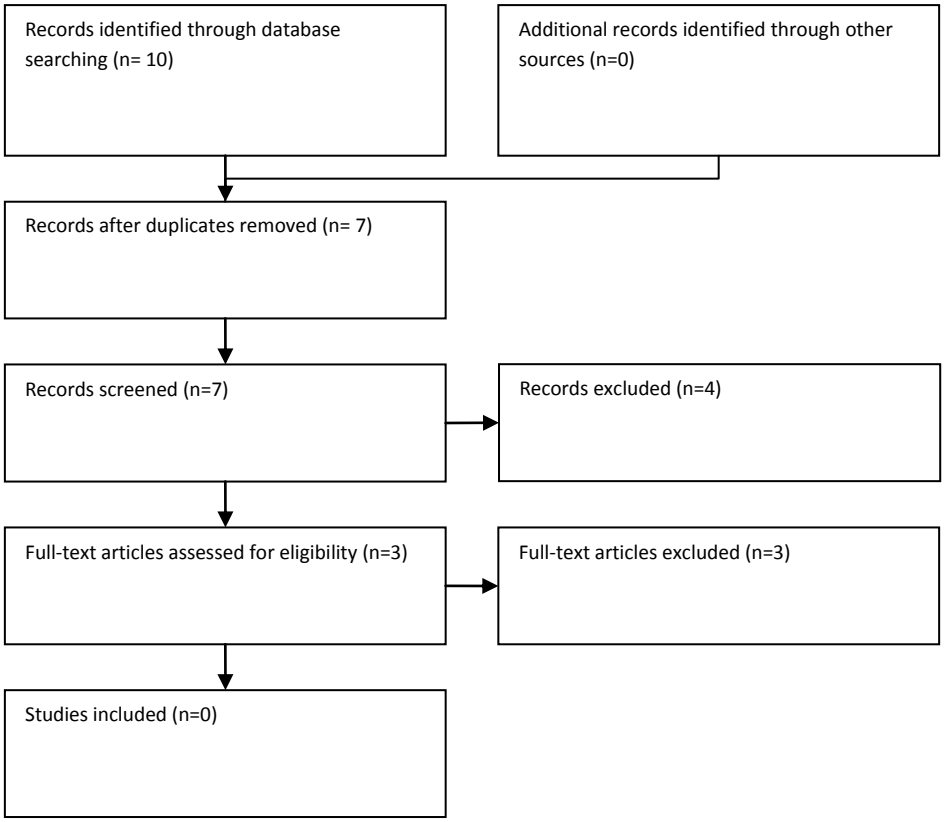
Selection criteria for included evidence:

- Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included
- Studies that were conducted in OECD countries (other than the UK) were included
- Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economists (BD and DF) did the screen of the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for and checked against the inclusion criteria.

1.5.3 Results



Volume of evidence

Three potentially relevant papers were reviewed. All papers were considered not relevant for this topic. All papers were deemed to have a population not sufficiently specific to the PICO for this topic. Serious methodological limitations were identified in all papers.

Excluded studies

Bahaman J, Saenz J, Bonillo X et al. Genetic counselling program in familial breast cancer: Analysis of its effectiveness, cost and cost-effectiveness ratio. Int J Cancer 2004;112: 647-652.

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2 Surveillance and strategies for early detection of breast cancer

2.1 Surveillance for women with no personal history of breast cancer (chapter 7.2)

2.1.1 Review question

What is the cost-effectiveness of mammography, MRI and combined screening in people with a family history who have no personal history of breast cancer?

Question in PICO Format

Patients/population	Intervention	Comparison	Outcomes
Women with no personal history of breast cancer aged: 18-29 30-39 40-49 50-70 70+	Mammography MRI Ultrasound Clinical Breast Examination Any combination of tests at different timings and/or frequencies No Screening	Each Other	Cost-effectiveness Incremental cost effectiveness ratio (ICER) Results of sensitivity analysis

Economic Priority

This was considered by the GDG to be in literature- a formal cost-effectiveness analysis was conducted in CG41.

2.1.2 Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED). Focus was put on studies/reviews reporting HE evidence for topic A including systematic reviews of economic evidence (or systematic reviews which contain economic evaluations), published economic evaluations (including conference proceedings), economic evaluations as part of randomized controlled trials, economic evaluations as part of observational studies and economic modelling studies (all types). Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Selection criteria for included evidence:

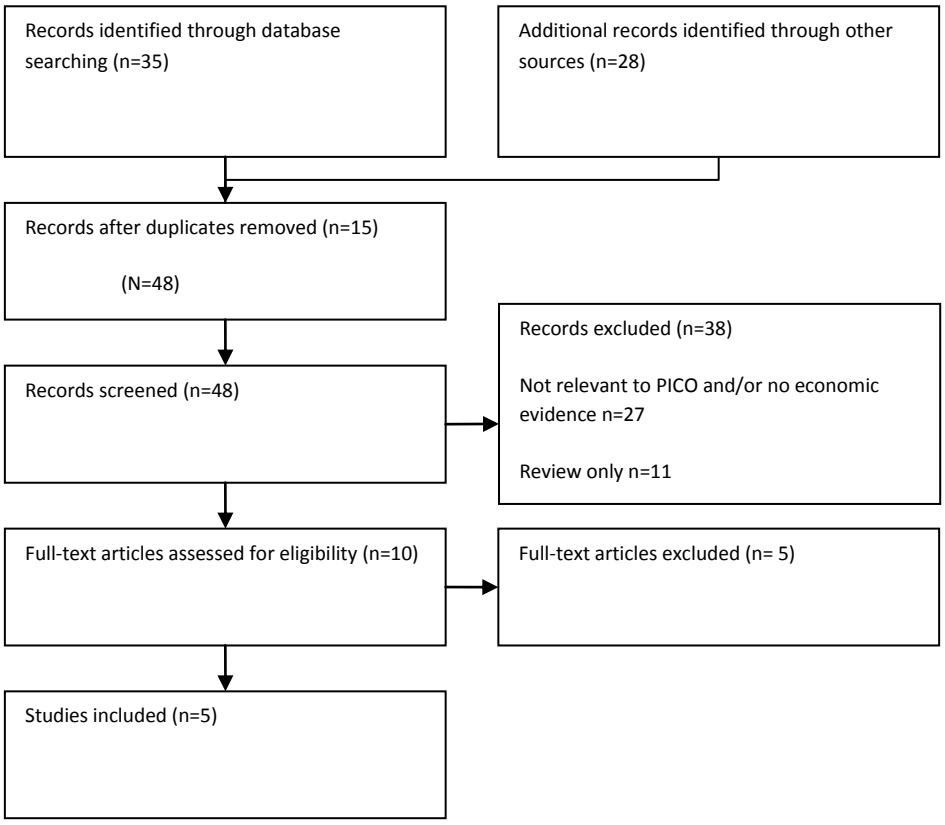
- Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included
- Studies that were conducted in OECD countries (other than the UK) were included
- Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS
-

Selection of studies

The health economists screened the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. Full articles were obtained for ten studies and checked against the inclusion criteria.

2.1.3 Results

The literature searches identified 10 relevant economic papers for topic D. All studies exhibited limitations in the quality of the sources of data.



Quality and applicability of the included studies

The included studies were deemed partially applicable to the guideline. The reasons for partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. The papers were deemed to have very serious limitations because they did not meet one or more aspects of the NICE reference case. In particular, data sources (all papers), time horizons (Griebsch et al. 2006; Plevritis et al 2006), perspective (Moore et al. 2009) and discounting structure (Moore et al. 2009) were unclear or did not conform to the NICE reference case (Lee et al. 2010; Plevritis et al. 2006; Taneja et al. 2009) and no QALYs (Griebsch et al. 2006; Taneja et al. 2009), ICERs (Taneja et al. 2009) or probabilistic sensitivity analysis (Taneja et al. 2009; Lee et al. 2010) were reported.

		Applicability	
		Directly applicable	Partially applicable
Methodological quality	Minor limitations		
	Potentially serious limitations		
	Very serious limitations		Griebsch et al., 2006, Plevritis et al., 2006, Moore et al., 2009, Taneja et al., 2009, Lee et al., 2010

2.1.4 Evidence statements

The evidence review for topic D included five papers which reported the cost-effectiveness of different screening strategies compared to no screening or each other. Four studies were conducted in the USA (Plevritis et al., 2006, Moore et al., 2009, Taneja et al., 2009, Lee et al., 2010) and one was based in a UK healthcare setting (Griebsch et al., 2006). The papers report varying degrees of cost-effectiveness and inconsistent results of cost-effectiveness of the different screening strategies. (see table 2.1 & 2.2)

Population

Griebsch et al. (2006) reported results of a population of women aged 35-49 years at high genetic risk of breast cancer (>0.9%per annum) who were tested carriers of BRCA 1, 2 or TP53 mutations, a first degree relative of someone with a mutation or could demonstrate a strong family history of breast or ovarian cancer. Lee et al. (2010) modelled cost-effectiveness of screening for initially 25-year old BRCA1 carriers whereas Plevritis et al. (2006) included 25-year old BRCA1 and BRCA2 carriers in their model. Moore et al (2009) looked at a hypothetical cohort of women with a strong family history of breast cancer and Taneja et al. (2009) investigated cost-effectiveness of screening in a simulated cohort of 40-year old women with BRCA1/2 mutation or a strong family history.

Intervention & Comparator

Griebsch et al. (2006) compared annual screening with a combined approach of MRI and mammography to mammography recall alone while Moore et al. (2009) compared annual mammography with MRI only and Plevritis et al. (2006) investigated the cost-effectiveness of MRI and the combined approach against no screening. Lee at al. (2010) looked at annual film-screen mammography, annual MRI and annual combined approach in comparison to clinical examination. Taneja et al. (2009) estimated the cost-effectiveness of a single event of MRI and the combined approach when compared to mammography.

Outcome

Griebsch et al. (2006) did not report cost/QALY results but calculated that the combined approach cost £34,951.33 per additional cancer detected (converted to 2011 GPB). They concluded that assuming a maximum acceptable ICER of £20,000 MRI+XRM only had 0.07 probability of being cost-effective and 0.67 cost effective when the threshold was raised to £30,000.

Lee et al. (2010) found that compared to clinical surveillance mammography had an ICER of £12,076.57, MRI of £148,791.75 and the combined approach cost £49,835.40/QALY (converted to 2011 GPB). Moore et al. (2009) concluded that MRI was not cost-effective when compared to mammography in people with a strong family history while Plevritis found that mammography is cost-effective for BRCA1/2 carriers up to 69 years and MRI is cost-

effective for BRCA1 carriers up to 49 years of age. In contrast, Taneja et al. (2009) suggested that MRI and the combined approach were cost-effective compared to mammography.

Source of effectiveness data

Effectiveness data used in Griebsch et al. (2006) was derived from a single multi-centre prospective study, whereas Lee et al, Moore et al and Taneja et al. used data from published literature and Plevritis et al used SEER data.

Table 2.1:Table of included economic studies

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
Griebsch, 2006	Very serious limitations 1	Partially applicable 2	Women aged 35-49 years at high genetic risk of breast cancer who were: Tested carriers of BRCA 1, 2 or TP53 mutation; first degree relative of someone with above mutation or strong family history of breast or ovarian cancer.	Annual screening with CE MRI and both CE MRI and XRM	Recall by XRM alone	Compared to mammography alone:3 MRI: £324.13 MRI+XRM: £371.58	Number of cancers detected per screen compared to mammography: MRI: 0.00744 MRI+XRM: 0.01063	MRI+XRM £34,951.33 per additional cancer detected 4	Assuming a maximum acceptable ICER of £20,000 MRI+XRM 0.07 probability of being cost-effective. When raised to £30,000 cost effective was 0.67.
Lee 2010	Very serious limitations 5	Partially applicable 6	25 year old BRCA1 mutation carriers	Annual screening strategies of Screen film mammography MRI Mammography and MRI	Clinical surveillance	Compared to strategy mentioned before:7 Clinical surveillance: - Mammography: £3095.74 MRI: £5987.46 Combination:	Incremental QALYs Compared to strategy mentioned before: Clinical surveillance: - Mammography 0.25 MRI 0.04 Combined 0.12	Mammo-graphy £12,076.57 MRI eliminated - £148,791.75 Combined £49,835.408	Univariate analysis included mutation penetrence, diagnostic test, costs of screening, discount and quality of life weights, sensitivity/sp

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
						£1681.25			ecificity value of screening and effect of risk reducing BSO
Moore 2009	Very serious limitations 9	Partially applicable 10	Hypothetical cohort of women with >-15% cumulative risk based on Claus criteria (strong family history)	Annual breast screening XRM MRI	Each other	Of MRI compared to mammography: £9950.2011	Incremental QALYs of MRI compared to mammography: 0.1	MRI: £133,292.0212	PSA: MRI superior in 0% <$50,000 per QALY, 22% >$50,000 per QALY; MRI not cost-effective
Plevritis 2006	Very serious limitations 13	Partially applicable 14	Simulated cohort of female 25 year old BRCA1/2 mutation carriers with no prior history and no prior prophylactic mastectomy or chemoprevention	Mammography + MRI; Mammography alone	No screening	Compared to no screening:15 BRCA1 Mammography (25-69 years): £2420.86 MRI (40-49 years): £4841.72 MRI (25-69 years): £4708.37	Incremental QALYs compared to no screening: BRCA1 Mammography (25-69 years): 0.167 MRI (40-49 years): 0.145 MRI (25-69 years): 0.013 BRCA2 Mammography (25-69 years): 0.113 MRI (40-49 years):	Compared to no screening:16 BRCA1 Mammography (25-69 years): £14,523.62/QALY MRI (40-49 years): £33,323.39/QALY MRI (25-	MRI becomes more cost effective as risk increases and less cost-effective as risk decreases.. For women aged 50 years and younger with extremely dense breast

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
						BRCA2 Mammography (25-69 years): £2460.71 MRI (40-49 years): £5224.12 MRI (25-69 years): 4680.02	0.061 MRI (25-69 years): 0.008	69 years): £364,724.25/QALY BRCA2 Mammography (25-69 years): £21,780/QALY MRI (40-49 years): £85,523.2/QALY MRI (25-69 years): £560,616.06/QALY	adds $41,183 per QALY for BRCA1 and $98,454 per QALY for BRCA2. It is sensitive to cost of MRI – sensitive to discounting.
Taneja 2009	Very serious limitations 17	Partially applicable 18	Hypothetical cohort of women aged 40 years at high risk of undetected cancer, invasive or DCIS - BRCA 1 or 2 mutation carriers or strong family	Single episode within established screening programme MRI XRM + MRI	XRM	Not stated	Not stated	Compared with mammography:19 MRI: £19418.98/QALY MRI+XRM: £19370.70/QALY	Sensitivity to prevalence. BRCA1/2- $65,094 if prevalence 2% (Base case was 4%), $12,007 if 6%. BRCA 1 or 2 cost-effective for

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
			history with >20% life-time risk.						MRI alone or in combination compared with XRM alone.

[1] Effectiveness data is based on one single prospective study; no cost-utility analysis undertaken, no quality of life data considered. Therefore the relevance of these results for informing the current guideline is limited.
[2] The analysis does not meet one or more aspects of the NICE reference case.
[3,4] Converted from 2003 GPB using a PPP exchange rate of 1.00 then uprated by inflation factor of 124% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[5] Data is based on published literature; only BRCA1 carriers considered, no cost inputs reported. Therefore the relevance of these results for informing the current guideline is limited.
[6] The analysis does not meet one or more aspects of the NICE reference case.
[7,8] Converted from 2007 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 105% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[9] Data is based on published literature; no distinguishing in different risk groups, costs not discounted but outcomes discounted at 5%. Therefore the relevance of these results for informing the current guideline is limited.
[10] The analysis does not meet one or more aspects of the NICE reference case.
[11,12] Converted from 2006 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[13] Cost and utility data is based on published literature; only BRCA1 and BRCA2 carriers considered, no PSA reported. Therefore the relevance of these results for informing the current guideline is limited.
[14] The analysis does not meet one or more aspects of the NICE reference case.
[15,16] Converted from 2005 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 112% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[17] Data sources not reported, no PSA reported, only single screening event considered. Therefore the relevance of these results for informing the current guideline is limited.
[18] The analysis does not meet one or more aspects of the NICE reference case.
[19] Converted from 2005 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 112% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Table 2.2: Summary of economic evidence

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author Griebsch et al Year 2006 Country UK Setting Secondary care	Analysis Cost effectiveness analysis Model Not applicable Time horizon Not clear Perspective UK NHS Sources of clinical/epidemiological data Single prospective study (Leach et al 2005) Cost NHS reference costs Utility Not applicable Discount 3.5%	Women aged 35-49 years at high genetic risk of breast cancer (>0.9%per annum) recruited between 1997-2004 in 22 centres who were: Tested carriers of BRCA 1, 2 or TP53 mutation; first degree relative of someone with above mutation or strong family history of breast or ovarian cancer. Sample size not reported	Annual screening with both CE MRI and XRM Versus recall by XRM alone	Costs (price year 2003) Screening Further investigations (recorded within MARIBIS study) Cost effectiveness Cost per cancer detected ICERs Uncertainty Probabilistic sensitivity analysis reported	ICER CE MRI was dominated MRI+XRM £28,284 per additional cancer detected BRCA 1 only combined did not result in any additional cancers detected. CE MRI resulted in £11,731 per additional cancer detected BRCA 2 only CE MRI was dominated. MRI +XRM £15,302 per additional cancer detected. Assuming a maximum acceptable ICER of £20,000 MRI+XRM 0.07 probability of being cost-effective. When raised to £30,000 cost effective was 0.67. When restricted to BRCA1 (2) probability of XRM +MRI was cost effective was 0.57 (0.82) on	Conflict of Interest No statement Funding No statement Applicability Partially applicable Limitations Very serious limitations This study did not incorporate a cost utility analysis but is deemed useful for GDG decision making.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
					£20,000 and 0.71 (0.96) of £30,000	
Author Lee et al Year 2010 Country USA Setting Secondary care	Analysis Cost-utility analysis Model Monte Carlo simulation- model has been previous published (Lee et al 2008, Radiology:246:763-771 Time horizon Life time Perspective Societal Sources of literature Clinical/Epidemiological Critical review of the literature and public databases Costs Medicare reimbursement and medical literature HRQOL	Inclusion criteria 25 year old BRCA1 mutation carriers	Annual screening strategies of Screen film mammography MRI Mammography and MRI V clinical surveillance	Costs (price year 2007) Not specified in this paper but previous paper refers to resources related to screening and treatment Cost- Utility Cost per QALYS ICERS presented Sensitivity analysis Univariate analysis performed to identify parameters that could cause the ICER for annual combined screening either to decrease below $50,000 per QALY or increase to above $100,00 per QALY Included mutation penetrance, diagnostic test, costs of screening, discount and quality of life weights, sensitivity/specificity value of screening and effect of risk reducing BSO As transient QOL effects have been shown to affect CE of breast cancer	Costs Clinical surveillance $96,042 Mammography $100,336 MRI $108,641 Combined $110,973 Incremental cost Mammography $4294 MRI $8305 Combined $2,332 QALYs Clinical surveillance 44.21 Mammography 44.46 MRI 44.50 Combined 44.624 Incremental QALYs Mammography 0.25 MRI 0.04 Combined 0,12 ICERs Mammography $16,751 MRI eliminated- $206,384 Combined $69,125 Sensitivity analysis indicated that when MRI cost is increased to $960 (base case 4577) or risk by aged 70 years decreased to below 58% (65% in BCA) or sensitivity	Conflict of interest None reported Funding National Cancer Institute grant and breast cancer surveillance consortium grant Applicability Partial applicability Limitations Very serious limitations

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Medical literature (QOL weights applied for 5 years at which time QOL reverted to that of a healthy cancer-free woman of same age. Discount 3% per annum			screening and QOL for biopsy have been identified, these short term effects were included in the sensitivity analysis. Probability sensitivity analysis not referred to.	decreased below 76% (BCA94%) cost of adding MRI to mammography exceeded $100,000 per QALY.	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author Moore et al. Year 2009 Country USA Setting Secondary care	Analysis Cost-utility analysis Model Markov Time horizon Life time Perspective Not reported Sources of clinical/epidemiological data Literature Costs Medicare/Medicaid reimbursement data Utilities Published data Discount No discounts on costs- outcomes 5%	Inclusion criteria Hypothetical cohort of women with >-15% cumulative risk based on claus criteria (strong family history))	Annual breast screening XRM MRI	Costs (price year 2006) Costs for physician, hospital and laboratory services using centres for medicare and Medicaid service reimbursement. Medication costs obtained from Federal supply scale Cost –utility analysis Cost per QALY Uncertainty Univariate analysis Cost of MRI, probability of living with node negative cancer, false positive mammography or MRI reading Probability sensitivity analysis Maximum acceptable ICER at $50,000 threshold.	Costs MRI $18,167 XRM $4,760 QALYs MRI 14.1 XRM 14.0 ICER MRI $179,599 Undiscounted MRI $30,380 XRM $7,765 QALYs MRI 23.6 XRM 23.4 ICER MRI	Conflict of interest None declared Funding PhRMA health outcomes award, Georgia cancer coalition, American Society of haematology and Robert wood Johnson Foundation Applicability Partial applicability Limitations Very serious limitations

					$124,291 PSA MRI superior in 0% <$50,000 per QALY, 22% >$50,000 per QALY MRI not cost-effective	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author Plevritis Year 2006 Country USA Setting Secondary care	Analysis Cost-utility analysis Model Continuous-time monte carlo simulation model Time horizon Not clear Perspective Societal Clinical epidemiological SEER data Costs Literature Medicare reimbursement Utilities Published adjustments for QOL associated with ageing and breast/ovarian cancer with	Inclusion criteria A simulated cohort of female 25 year old BRCA1/2 mutation carriers born in 1980 and followed up starting in 2005. No prior history and not undergone prophylactic mastectomy or chemoprevention. Sample size Not stated Uncertainty	Mammography and MRI Mammography alone No screening	Costs (2005 Prices) Resource utilisation prompted by screening MRI: Follow up MRI Biopsy Follow up DXM Other imaging Ultrasound Biopsy Costs due to screening, diagnosis and treatment Mammography Biopsy MRI guided biopsy Mastectomy with reconstruction (uni/bilateral) Adjuvant treatment for node negative/positive cancers Metastatic breast cancer treatment Annual surveillance costs after treatment Cost utility analysis ICERS Cost per QALY 1 way and multi-way	ICER BRCA 1 Mammography $18,952 MRI 40-49 $43,834 35-49 $71,401 35-54 $89,661 35-59 $111,387 30-59 $124,820 30-64 $154,654 30-69 $164,762 25-69 $475,932 BRCA2 DXM $28,421 MRI 40-49 $111,600 40-54 $154,876 35-54 $158,839 35-59 $165,702 35-64 $198,429 35-69 $209,585 30-69 $266,334 25-69 $731,553 MRI becomes more cost	Conflict of interest None reported Funding NIH grant and California Breast Cancer Research Programme Fellowship Applicability Partial applicability Limitations Very serious limitations

	BRCA1/2 or general population Discount 3%			sensitivity analysis	effective as risk increases and less cost-effective as risk decrease. When relative to mammography to performance of mammography. For women aged 50 years younger with extremely dense breast adds $41,183 per QALY for BRCA1 and $98,454 per QALY for BRCA2. It is sensitive to cost of MRI – sensitive to discounting.	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author Taneja et al. Year 2009 Country USA Setting Secondary care	Analysis Cost-utility analysis Model Decision analysis Time horizon Life-time Perspective Healthcare system Sources of clinical/epidemiological data Literature Cost Unclear Utility Unclear Discount 3% per annum	Inclusion criteria A hypothetical cohort of women aged 40 years at high risk for undetected cancer, invasive or DCIS-BRCA 1 or 2 mutation carriers or strong family history with >20% life-time risk. Sample size 10,000	Single episode within established screening programme MRI XRM XRM + MRI	Costs (price year2005)) Current screening Follow-up diagnostic evaluation Treatment of local or regional disease Cost of diagnosis Treatment Cost-utility Cost per QALYs ICERs Not reported Uncertainty Series of one-way sensitivity analysis Probabilistic sensitivity analysis not reported	Cost per QALYs MRI + XRM for BRCA ½ $25,277 MRI v XRM $25,340 0.5% risk MRI +XRM v XRM $310,616 3.0% risk MRI +XRM v XRM $45,566 Sensitivity analysis showed sensitivity to prevalence BRCA ½- -$65,094 if prevalence 2% (Base case was 4%) $12,007 if 6% BRCA 1 or 2 CE for MRI alone or in combination compared with XRM alone. Other at risk -CE depends	Conflict of Interest No statement Funding No statement Applicability Partially applicable Limitations Very serious limitations

					on prevalence	

2.1.5 References

Griebsch I, Brown J, Boggis C, Dixon A, Dixon M, Easton DF, Eeles R, Evans DG, Gilbert FJ, Hawnaur J, Kessar P, Lakhani SR, Moss SM, Nerurkar A, Padhani AR, Pointon LJ, Potterton J, Thompson D, Turnbull LW, Walker LG, Warren R & Leach MO (2006) Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high risk of breast cancer. British Journal of Cancer, 95: 801-810.

Lee JM, McMahon PM, Kong CY, Kopans DB, Ryan PD, Ozanne EM, Halpern EF & Gazelle GS (2010) Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. Radiology, 254: 793-800.

Moore SG, Shenoy PJ, Fanucchi L, Tumeh JW & Flowers CR (2009) Cost-effectiveness of MRI compared to mammography for breast cancer screening in a high risk population. BMC Health Services Research, 9: 9-17.

Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE & Garber AM (2006) Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. Journal of the American Medical Association, 295: 2374-2384.

Taneja C, Edelsberg J, Weycker D, Guo A, Oster G & Weinreb J (2009) Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. Journal of the American College of Radiology, 6: 171-179.

1

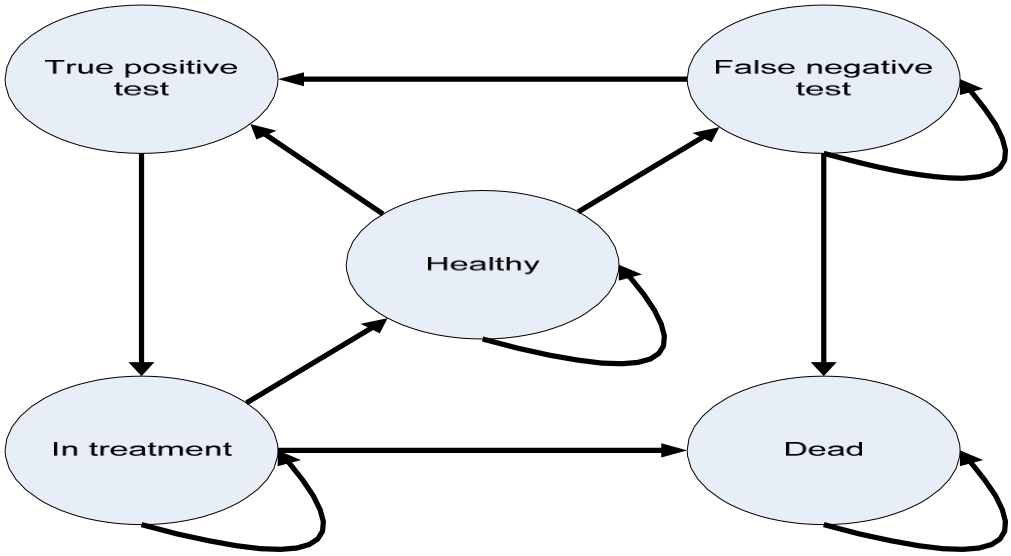
2.2 Cost Utility Analysis of annual mammography, annual MRI and annual combined screening (2006). (Chapter 7.2)

2.2.1 Methodology

A Markov model was constructed for each of four scenarios, specifically no screening, annual mammography, annual MRI scans and both annual mammography and MRI scans in parallel. These scenarios were selected as they best matched the options investigated in the MARIBs study. [Leach et al., 2005] The decision rule for assigning positive or negative results to these approaches are taken from a large clinical trial. [Leach et al., 2005] It should be noted that an assumption was made that the mammography was film-screen. The implication of using digital mammography is investigated in the discussion.

Markov models follow a cohort through a disease transition over time. This means that a hypothetical cohort of 1 000 individuals of a particular age and risk profile are introduced into model and given a 10-year regime of one of the four screening options. Their transition between the states outlined below is followed, assigning appropriate system costs and benefits until death.

Figure 2.1: The Model Structure



It should be noted that the models assumes false positives are assessed and identified immediately and return to the healthy population for the subsequent cycle.

The Model

The clinical benefit of more sensitive approaches lies in three major areas,

- The reduced quality of life of an individual between a false negative and eventual detection.
- The raised mortality of an individual between a false negative and eventual detection.
- The differential prognosis of an individual post-diagnosis dependent on the number of false negative experienced.

This benefit must in turn be balanced against a likely reduction in specificity. Thus, the approaches using MRI screening are likely to lead to a greater number of false positives. There is likely to be a disutility associated with being a false positive (through anxiety for instance). However, the model does not include this due to a lack of evidence amenable to a cost-effectiveness analysis. This greater number of false positives will lead to a resource

implication for the system since further investigative work will be undertaken before the incorrect diagnosis is detected. This component has been estimated in the model.

The structure of the model is provided above. There are a number of key parameters in the analysis of cost-effectiveness, each of which needs discussion.

Sensitivity and Specificity

In the construction of the model, the major difference between treatment in the wings were the relative sensitivity and specificity of the approaches. These figures are derived from a recent trial. [Leach et al., 2005]

Table 2.2: Sensitivity and Specificity of Screening Techniques

	No screening	Annual	Annual MRI	Combined screening
Sensitivity	0	0.4	0.77	0.94
Specificity	1	0.93	0.81	0.77

The first clarification on these figures concerns the sensitivity of mammography. There is evidence to suggest that younger women have a lower sensitivity value under mammography due to thicker breast tissue impedes successful identification. Therefore, relative sensitivity figures were drawn from the literature [Kerlikowske et al., 1996] and applied to the MARIBS sensitivities and specificities given above to give sensitivity by age. Details of this procedure are given in Appendix 2.

The second clarification refers to the types of tumours identified. It has been suggested that mammography is relatively more likely to identify DCI (ductal carcinoma in situ). Thus, it could be argued that the types of tumours identified in MRI screening are more important identifications. Thus, it could further be claimed that the outcomes from MRI screening and the combined approach are underestimated in the analysis. There is evidence on the sensitivity and specificity of the screening tools to different types of tumours. [Leach et al., 2005] However, this was based on some small population groups and hence sensitive to random variation in the trial population.

The model assumes that, following two cycles of false negatives, the case will be identified in Primary Care. This was a necessary assumption to reflect that tumours will eventually present independent of screening. The choice of two years is an assumption suggested within the Guideline Development Group.

Risk

The risk of developing a tumour depends on the age and family history of the individual. The previous guidance suggested two categories of risk and defined them as follows,

Risk - High Risk

Risk is estimated based on family history. High risk of developing breast cancer is defined as an estimated risk of

- greater than 8% between age 40 and 50 years
- or a lifetime risk of 30% or greater

High risk also includes a 20% or greater chance of a faulty BRCA1, BRCA2 or TP53 gene in the family. (If, however, a person has a genetic test and is found not to be carrying the identified faulty gene, their risk is then, in most cases, average.)

Less than 1% of women will have are at high risk of developing breast cancer.

Risk - Moderate risk

When the frequency of breast cancer within a family suggests that there may be a faulty gene or combinations of genes that are passed down through generations and may contribute to the development of breast cancer. Moderate family history is more common than strong family history and accounts for an estimated 20% of all breast cancers. However, relatively little is currently understood about this form of familial breast cancer and it cannot currently be identified through genetic testing.

Moderate risk of developing breast cancer is defined as a risk of

- 3–8% between age 40 and 50 years
- or a lifetime risk of 17% or greater but less than 30%.

Note that in this guidance, it was felt that the term 'moderate risk' has been replaced with the term 'raised risk'. The definition however remains the same. In the base case modelling, a figure for risk in both groups was assumed. These figures were 6% risk between 40 and 49 in the raised risk group and 12% risk in the high risk group.

It was felt that individuals with an identified BRCA1 mutation should be considered separately from the high risk group, due to increased risk and increased aggression of tumours. Therefore, this sub-population was addressed as a further group. Information on this group was taken from a case series analysis and is presented below. [Antoniou et al., 2003]

Table 2.3: The Annual Incidence of Cancer in Women with a BRCA1 Mutation

Age	Annual incidence for carriers of mutations in BRCA1 (%)
30-34	0.74
35-39	1.59
40-44	2.92
45-49	4.28

The increased aggression of tumours in this population is addressed later.

The model includes the BRCA2 individuals in the high risk group (thus assigning them a 12% 10-year risk at 40). However, evidence suggests that, while this assumption is reasonable for the entire BRCA2 population (approximately 14% risk), it may not be appropriate for women with maternal mortality at 50. [Antoniou et al., 2003] Indeed, if the mother has died at 50, and two sisters of 45 and 50 have developed tumours, the 10-year risk rises to approximately 29%.

Clearly, there are a large number of possible subgroups of the BRCA2 population. Therefore, it is not appropriate to produce sub-group analysis for each of these. The solution to these multiple levels of risk is to investigate what level of risk is required to justify each approach. This is known as threshold analysis and will be investigated in the results.

The relative risk by age was taken from a study identified in the previous guidance [Claus et al., 1994]. Using these two sources, risk at any age can be identified by age and risk classification.

Life Expectancy (non-disease specific)

In measuring the outcome of a successful identification and treatment of a breast cancer patient, it is of importance how much the individual will benefit as a result of being saved. Thus, life expectancy for each age group between 30 and 90 was identified from

government figures and applied to each individual remaining at the end of a 10-year screening programme (http://www.gad.gov.uk/Life_Tables/docs/wltewf0204.xls). While non-cancer specific mortality would occur within the 10-year period, it was felt that this would balance across cohorts so not affect the conclusion.

Typical Treatment

Since the correctly diagnosed individuals go on to receive treatment, it is important to consider that there is both resource use and benefit in this area. It should be noted that, since the majority of individuals in the twelve cohorts (BRCA1 / high risk / raised risk and four screening options) eventually enter treatment, the cost of treatment will largely cancel out between groups. The assumed typical treatment path is as follows.

Following a positive test, all individuals receive a further MRI scan and an ultrasound. Those who were false positives are identified and returned to the negative population. Those who are positive undergo a biopsy (of which 1 in 15 are MR guided). Of these, one third are benign and are returned to the population. Of the remainder, 80% receive standard chemotherapy and taxol, 50% undergo a wide local excision, 50% have a mastectomy and 20% receive tamoxifen. It is expected that the typical patient remains in the treatment group for two years before returning to the population. Inevitably, clinical practice will show a wide variation around this figure. This variation, while important in practice, will not affect the results generated by the model.

Life expectancy (disease specific)

The most relevant area of mortality in the model occurs in the treatment phase. Since the 5-year survival rate is approximately 77% following diagnosis (Coleman MP et al. Cancer Survival Trends in England and Wales 1971-1995, deprivation and NHS Region OUP (1999)). However, it is very difficult to estimate the differential prognosis for individuals identified after particular numbers of false negatives since even re-appraising false negatives may not reveal a tumour. Therefore, the model makes the following assumption for the all non-BRCA1 populations.

Table 2.4: Assumed 5-year survival rates for all non-BRCA1 mutation populations

Identified at which stage?	5-year survival rates
First possible opportunity	85%
Second possible opportunity	75%
Third possible opportunity	65%

For the BRCA1 population, it was suggested that the gradient of the 5-year survival rate curve based on time before diagnosis will be steeper. This is because they represent a group in which the tumour is likely to be more aggressive. Thus, the assumed figures for this group are as follows

Table 2.5: Assumed 5-year survival rates for a BRCA1 population

Identified at which stage?	5-year survival rates
First possible opportunity	80%
Second possible opportunity	65%
Third possible opportunity	50%

Also, to reflect a slightly increased mortality in the false negative group, the model assumes a 0.5% increased mortality risk across risk groups during the cycle following the false result.

Radiation Risk

There is a significant literature estimating the risk associated with medical radiation exposures. For breast screening this risk is based on the estimation of the number of induced cancers expected following repeated attendance for regular mammograms. [Law, 1995] [Preston et al., 2002] [Law and Faulkner, 2002] [Berrington de Gonzalez and Reeves, 2005] [European Commission, 1996] [Young et al., 2003] [Law and Faulkner, 2001] The effect of this is cumulative: Thus, it is likely to be of particular importance in questions surrounding screening techniques in younger age groups. Figures on risk used here for women with an average incidence of breast cancer were taken from a major paper on this issue [European Commission, 1996] and are shown in the table 2.6 and are similar to those used previously by the NHS Breast Screening programme. [Young et al., 2003] It is thought that women with a higher incidence of breast cancer may be more susceptible to radiation induced cancers. To take account of this possibility the modelling assumes an increase in the radiation risk (shown in Table 2.6) in proportion to the expected increase in the breast cancer risk level for each sub-group considered.

Table 2.6: Lifetime risk of radiation-induced breast cancer by age at exposure for the general population of women.

Age	Increase in lifetime risk of breast cancer per million women per mGy
30-34	18
35-39	17
40-44	16
45-49	15
50-54	14

The model assumes that each woman receives a mean glandular radiation dose of 4.5 mGy for each two-view mammography screening. This is the typical of the radiation dose reported for two view mammography within the NHS Breast Screening Programme [Law, 1995]. A study has reported that the doses for women attending for screening at younger ages are not significantly different from those reported for older women. [Law and Faulkner, 2001] It is assumed that the increase in lifetime risk due to radiation induction occurs at a uniform rate after a 10 year latent period following exposure.

The factors used for the induction of breast cancer are subject to considerable uncertainty and may be a factor of two higher or lower in the underlying rate, with further uncertainties in the estimation of risks to specific age ranges and sub-groups of the population. [Law, 1995]

Utilities

The quality of life of individuals was also considered in the model. This is important as the model ought to acknowledge the disutility associated with treatment and being undiagnosed, and the quality of extra life years gained through the successful treatment of breast cancer. The assumptions are given in Appendix 4.

Costs

The costs were split into the following areas: the cost of screening (be it mammography, MRI or both); the cost of false positives and the cost of typical treatment. The unit costs of each of the components of these three areas are given in the Appendix. Much of this data comes from an unpublished economic analysis run parallel to the MARIBS trial [Griebsch, 2006].

Discounting

As per guidance from the Institute, both costs and benefits were discounted at 3.5% per annum.

Perspective

Only costs to the NHS and Personal Social Services were considered. Thus, issues such as the effect of the condition on productivity were not addressed.

The Measurement of Cost-Effectiveness

The tool for analysing one intervention relative to another is the incremental cost-effectiveness ratio (ICER) This is defined as

Incremental cost per QALY (of intervention A relative to B) = (Cost (A) – Cost (B)) / (Q (A) – Q (B))

Where:

Q (A) = Estimated quality-adjusted life years from intervention A
Q (B) = Estimated quality-adjusted life years from intervention B

Defining an 'acceptable' cost for a QALY has not yet been adequately formalised in the economic evaluation of healthcare. A value of between £20 000 and £30 000 is most commonly used in NICE guidance.

2.2.2 Results

Women Aged Between 40 and 49

The total costs and outcomes were discounted and summed until all individuals reached life expectancy. The base case results depend on the risk profile and initial age of the cohort. The results from the three risk groups are presented below for a 40-year old cohort.

Table 2.7: BRCA1 population (31% 10-year risk for a 40-year old)

Screening method	Total cost (£ million)	Cost relative to no screening	Total QALY's	QALY's relative to no screening
No screening	4.915	0	15 554	0
Mammography	6.590	1.675	16 129	575
MRI	8.364	3.449	16 346	792
Combined	8.840	3.925	16 418	864

Table 2.8: High risk (12% 10-year risk for a 40-year old)

Screening method	Total cost (£ million)	Cost relative to no screening	Total QALY's	QALY's relative to no screening
No screening	1.679	0	17 577	0
Mammography	3.255	1.576	17 718	141
MRI	5.022	3.343	17 775	198
Combined	5.447	3.768	17 792	215

Table 2.9: Raised risk (6% 10-year risk for a 40-year old)

Screening method	Total cost (£ million)	Cost relative to no screening	Total QALY's	QALY's relative to no screening
No screening	0.907	0	18 099	0
Mammography	2.131	1.224	18 169	70
MRI	3.897	2.990	18 200	101
Combined	4.316	3.409	18 210	111

This figures, and those for the 30-39 age group are presented diagrammatically in Appendix 5.

In all groups, the MRI option is extendedly dominated by mammography and dual approach. Under standard economic approaches, this means that it should be excluded from any incremental analysis (but not from probabilistic sensitivity analysis). This can be explained as, if MRI is cost-effective relative to mammography, the dual approach is necessarily cost-effective relative to it. Therefore, incremental analysis was performed on the base case for the remaining three screening options (no screening, mammography and combined).

Table 2.10: Incremental Analysis in the BRCA1 Group

Option A	Option B	Incremental cost	Incremental	ICER
Mammography	No screening	1.675	575	2 913
Combined	Mammography	2.250	289	7 781

Table 2.11: Incremental Analysis in the High Risk Group

Option A	Option B	Incremental cost	Incremental	ICER
Mammography	No screening	1.576	141	11 226
Combined	Mammography	2.192	74	29 622

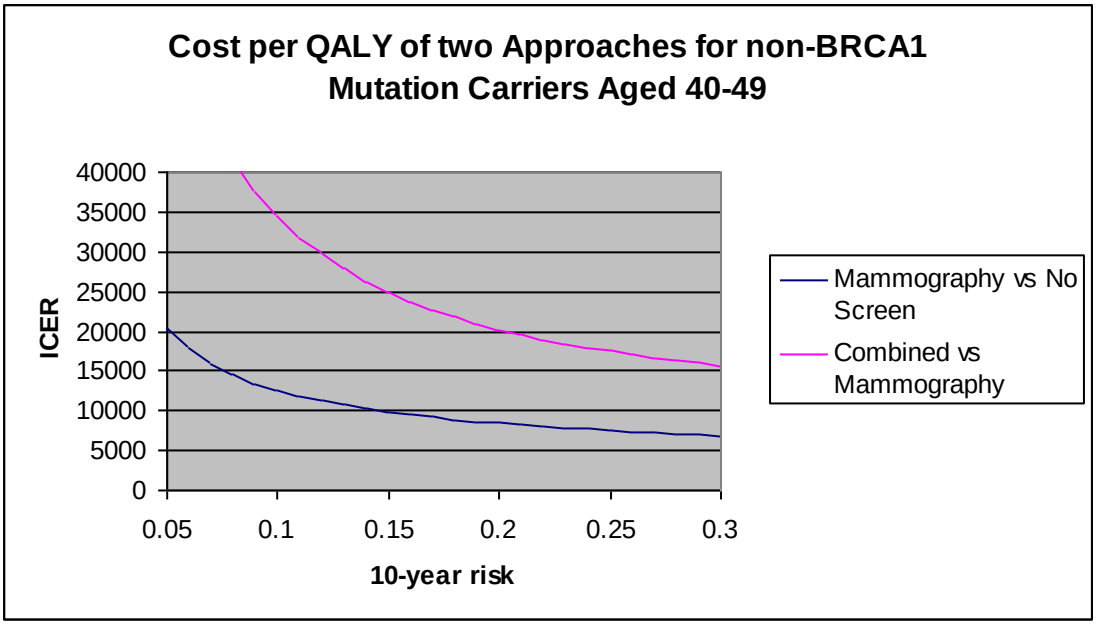
Table 2.12: Incremental Analysis in the Raised Risk Group

Option A	Option B	Incremental cost	Incremental	ICER
Mammography	No screening	1.224	70	17 427
Combined	Mammography	2.185	41	53 544

Thus, in the 40-49 year age group, the point estimates suggest that individuals with BRCA1 mutations should receive both annual mammography and MRI scans (since both estimated ICERs lies below the lower £20 000 per QALY limit). Other high risk individuals should certainly receive mammography but the cost-effectiveness of extending screening to either MRI screening or a combined approach is uncertain (since the ICER lies between £20 000 and £30 000). Raised risk individuals should receive annual mammography but it does not seem that further investigation is cost-effective. The robustness of each of these conclusions is addressed in the section on sensitivity analysis.

As discussed in the Methods section, the selection of these levels of risk is arbitrary. A more interesting investigation is to consider at what level of 10-year risk each screening modality become cost-effective. This requires a figure for the value of each QALY. NICE methodology does not set a particular level for this parameter.

The modelling will assume a figure of £20 000.



The combined screening approach crosses the £20 000 figure at 20.3% (it crosses the £30 000 value at 11.8%). Thus, a 10-year risk at 40 of 20.3% is suggestive of cost-effectiveness of using MRI alongside mammography relative to mammography alone. This analysis confirms that MRI screening is cost-effective in BRCA1 mutation carriers aged 40-49 since their risk is greater than this level, and any cancer is likely to be more aggressive.

Women Aged Between 30 and 39

In the younger age group, the cost-effectiveness of screening techniques will differ from the older age group. This is for three major reasons. Firstly, the sensitivity of mammography is reduced due to interaction between it and breast tissue density. Secondly, the incidence rate in this age group across risk groups is consistently lower, thus increasing the number needed to screen to identify a case. Finally, the life expectancy of women in the younger group is higher, meaning they have a greater capacity to benefit.

Results comparable to those presented in the previous section are provided below. One caveat to be noted is that it was felt that the uncertainty surrounding the effect of radiation, given its cumulative effect, the group were unwilling to recommend routine annual mammography in this age group. Thus, while the results of the model are given here including the options which contain mammography, these were not considered in the recommendation phase.

Table 2.13: BRCA1 population (11% 10-year risk for a 30-year old)

Screening method	Total cost (£ million)	Cost relative to no screening (£M)	Total QALY's	QALY's relative to no screening
No screening	4.004	0	17 995	0
Mammography	5.392	1.388	18 260	265
MRI	7.184	3.180	18 397	402
Combined	7.638	3.634	18 427	432

Table 2.14: High risk (5% 10-year risk for a 30-year old)

Screening method	Total cost (£ million)	Cost relative to no screening (£M)	Total QALY's	QALY's relative to no screening
No screening	4.023	0	19 789	0
Mammography	5.398	1.375	19 863	74
MRI	7.215	3.192	19 911	122
Combined	7.656	3.633	19 921	132

Table 2.15: Raised risk (3% 10-year risk for a 30-year old)

Screening method	Total cost (£ million)	Cost relative to no screening (£M)	Total QALY's	QALY's relative to no screening
No screening	1.340	0	20 266	0
Mammography	2.742	1.402	20 300	34
MRI	4.529	3.189	20 326	60
Combined	4.950	3.610	20 331	65

In the BRCA1 and other high risk groups, the MRI alone approach is extendedly dominated. In the raised risk group, the effect of radiation risk is sufficient to exclude the combined approach as it is dominated, and the mammography alone modality since it is extendedly dominated. The appropriate comparisons are presented here, alongside the comparison of MRI alone relative to no screening (for the reasons outlined previously).

Table 2.16: Incremental Analysis in the BRCA1 Group

Option A	Option B	Incremental cost (A vs. B) (£M)	Incremental QALY's (A vs. B)	ICER
Mammography	No screening	1.388	265	5 240
Combined	Mammography	2.246	167	13 486
MRI	No screening	3.180	402	7 918

Table 2.17: Incremental Analysis in the High Risk Group

Option A	Option B	Incremental cost (A vs. B) (£M)	Incremental QALY's (A vs. B)	ICER
Mammography	No screening	1.375	74	18 746
Combined	Mammography	2.258	58	38 919
MRI	No screening	3.192	122	26 170

Table 2.18: Incremental Analysis in the Raised Risk Group

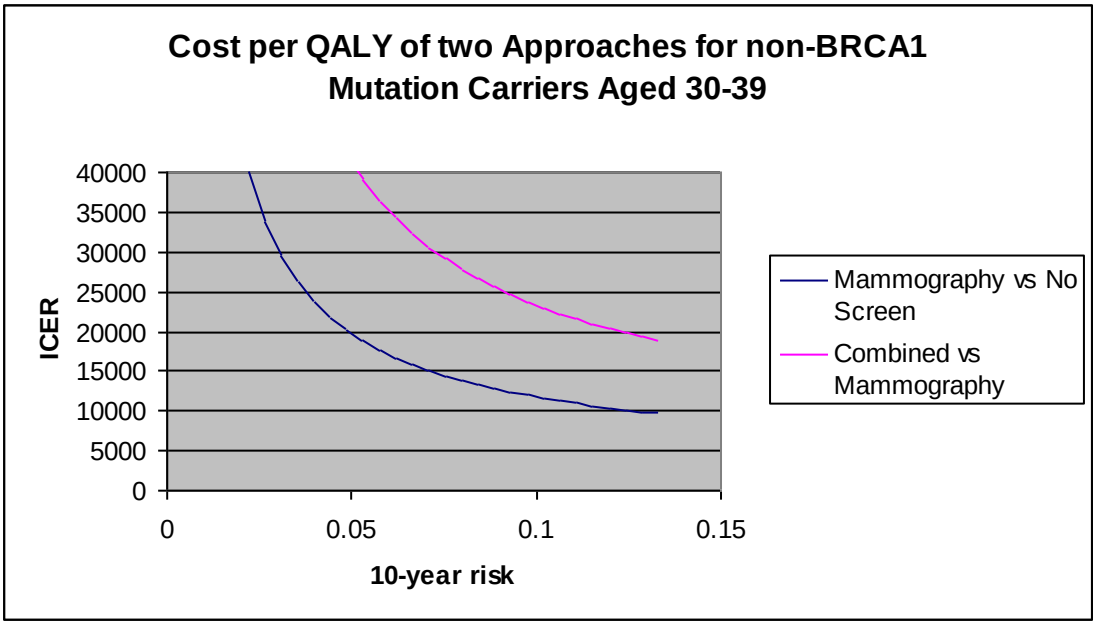
Option A	Option B	Incremental cost	Incremental	ICER
MRI	No screening	3.189	60	53 111

Base case results (mammography not excluded)

In the younger age-group, the use of the combined screening approach seems to be recommended on the basis of cost-effectiveness in those with a BRCA1 mutation (since the ICER is below £20 000). In the high risk group, there is supportive evidence for the use of annual mammography, with evidence against the use of more expensive screening tool as an adjunct. However, if MRI screening is to be employed, it should be as an alternative to mammography, rather than as an adjunct. In the raised risk group, there is no evidence

supporting cost-effectiveness of annual screening. As with the results for the older age group, these conclusions will be addressed in the section on sensitivity analysis.

As with the 40-49 age group, it is worthwhile to consider what level of risk for the non-BRCA2 individuals is required to generate an ICER of £20 000. The results are displayed diagrammatically.

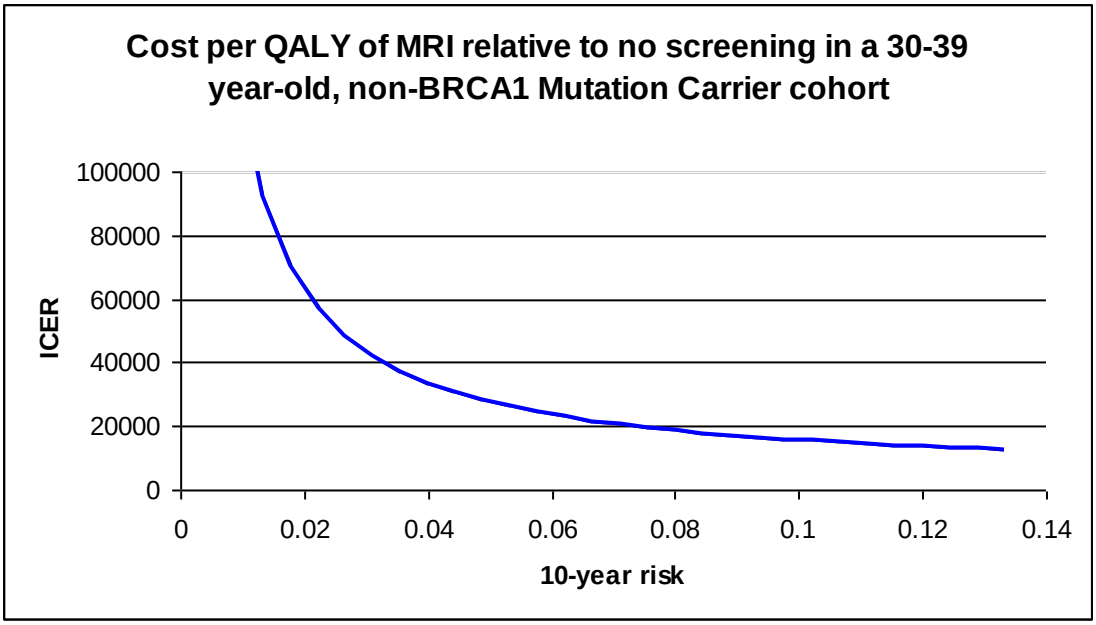


The annual mammography crosses the £20 000 value at a 10-year risk below 5%. The combined approach becomes cost-effective when 10-year risk at 30 rises to 12.3%. The figure is lower than that for the older age group since successfully identified and treated individuals have a greater lifespan. However, the proportion of individuals for whom the combined approach is cost-effective is lower in the younger population since the risk in this age group is lower.

Base case results (mammography excluded)

If the sole options are annual MRI or no screening, the incremental analysis suggests the MRI approach is cost-effective in BRCA1 mutation carrier population. In the high risk group, the cost per QALY suggests that the cost-effectiveness of the MRI screening is uncertain (since the ICER falls between £20 000 and £30 000). For raised risk individuals, estimates of the model suggest that MRI screening is not cost-effective relative to no screening.

Repeating the analysis on the required risk to generate a cost per QALY of £20 000 for non-BRCA1 mutation carriers, the model predicts that a 7.36% 10-year risk is required to produce an ICER of £20 000.



Sensitivity Analysis

In this investigation, two major approaches were taken to sensitivity analysis. Firstly, a simple univariate sensitivity analysis was undertaken. Thus, model parameters were adjusted within reasonable upper and lower boundaries. This is intended to show the key drivers of the cost-effectiveness results.

The parameters selected were varied within ranges considered reasonable. Costs were generally increased or decreased by 20%. One exception was the costing of MRI scans and mammography. In the base case result, the cost of MRI scans was taken from NHS Reference Costs. (Department of Health Reference Costs Non- maternity ultrasound and MRI). However, the economic evaluation undertaken alongside the MARIBS research suggests different cost levels. These costs are set as the upper boundary of the range to investigate the effect of using these figures.

Utility multipliers were increased or decreased by 0.1. The increased incidence of cancer as a result of mammography is doubled or removed to represent the greater uncertainty surrounding this parameter. Results of this analysis are given in Appendix 6.

The results of this univariate sensitivity analysis suggest that mammography remains cost-effective relative to no screening under the changes given in the sensitivity analysis approach table. Therefore, the conclusion that mammography is cost- effective in all BRCA1 and high risk populations is robust. Regarding the cost- effectiveness of a combined MRI / mammography approach relative to mammography alone, the analysis suggests that the result is most sensitive to the differential 5-year survival rates and to the cost of MRI screening.

The second component of the sensitivity analysis, designed to reflect the uncertainty surrounding multiple variables, was probabilistic sensitivity analysis (PSA). This was used to show the likelihood of different screening methods being cost-effective at different societal thresholds of willingness to pay for a QALY . The varied parameters, with their assumed standard errors and distributions are given in Appendix 1. The cost-effectiveness

acceptability curves for all options in the two populations are given in Appendix 5 (note that each diagram takes 10 000 iterations).

2.2.3 Discussion

Under the base case assumptions, the use of mammography on both raised and high risk populations (age 40-49) can be recommended on cost-effectiveness grounds. However, the use of more expensive techniques, specifically magnetic resonance imaging (MRI) is supported in only high-risk groups. This evidence is strengthened in a BRCA1 group since the evidence suggested (albeit in a small sample) that the difference in sensitivity between mammography and a combined approach is greatest in this population group. [Leach et al., 2005]

It should be noted that this conclusion is driven largely by the cost of MRI screening. This is important as there were two sources of cost data for the scan. The NHS Reference Cost figure is used in the base case analysis. The effect of using the alternative figure, taken from the unpublished economic evaluation run parallel to MARIBS is presented in the univariate sensitivity analysis (as the upper boundary of £405.10 is that suggested in this document).

Limitations of the model

The classification of what constitutes high risk and raised risk are largely arbitrary figures. In the initial guidance from the Institute (NICE), a range of risk was specified as representing these two groups. For the purposes of economic modelling, it was felt to be necessary that a point estimate of risk was identified.

Due to the lack of patient level data, probabilistic sensitivity analysis was undertaken rather than a non-parametric approach, such as bootstrapping. Thus, possible correlation between model parameters is ignored.

A key limitation of the model is that the mammography is limited to film-screen mammography. This decision was made since the recommendation of digital mammography is unrealistic given the current prevalence of the two options for this technique. Evidence has suggested that the key benefit of digital mammography is that they increase the sensitivity in younger women. As previously stated, the nature the breast tissue of younger women reduces the sensitivity of film-screen mammography. The effect of investigating digital mammography is potentially large. Evidence suggests that the sensitivity of this approach can exceed that of film- screen mammography by 27% (78% vs. 51%). [Pisano et al., 2005] This figure compares with the annual MRI approach in terms of sensitivity and exceeds it in terms of specificity (90%). The effect on cost is undetermined as yet.

Little published evidence on utility weights or costs was identified. Therefore, the work relies on one unpublished economic appraisal conducted alongside a major clinical trial and on assumptions. However, the sensitivity analysis suggests the result to be relatively robust to uncertainty in these areas.

2.3 Appendices for cost utility analysis of annual mammography,annual MRI and annual combined screening (2006).(Chapter 7.2)

2.3.1 Appendix 1: Probabilistic Sensitivity Analysis

The sources of the deterministic values are given previously. The source of assumptions surrounding the standard error of the means are all assumptions.

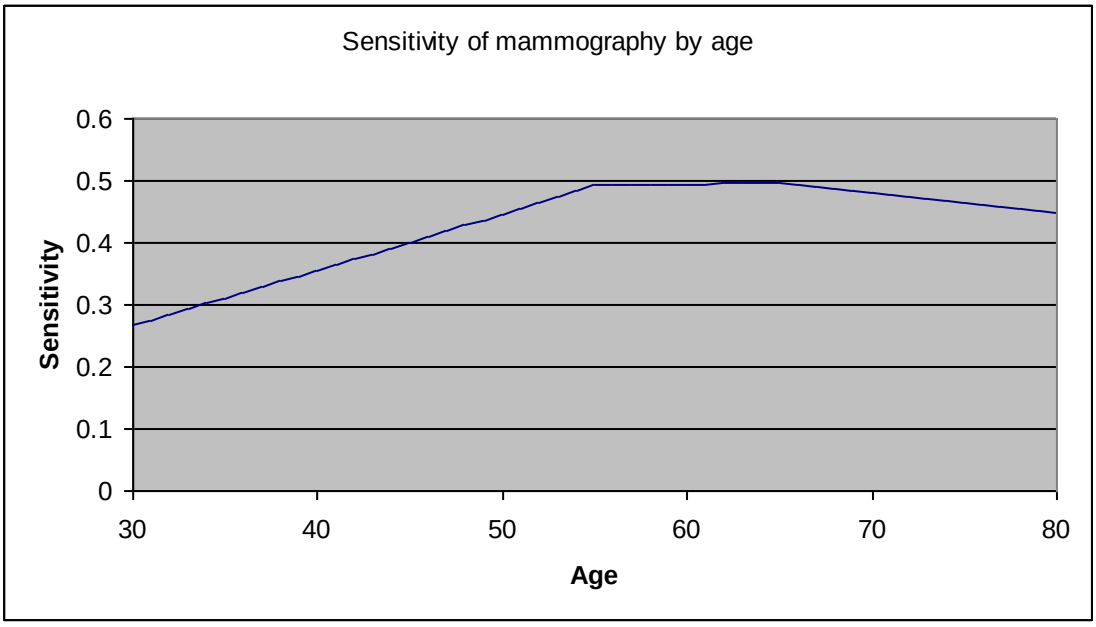
		Deterministic value	Assumed distribution	Standard Error	Alpha	Beta
Probabilities	6-month mortality of false negatives	0.005	Beta	0.005	99.495	19799.51
	Prognosis in those identified at the 1st possible opportunity	0.85 (non-BRCA1) 0.8 (BRCA1)	Beta	0.085	14.15	2.497059
	Prognosis in those identified at the 2nd possible opportunity	0.75 (non-BRCA1) 0.65 (BRCA1)	Beta	0.075	24.25	8.083333
	Prognosis in those identified at the 3rd possible opportunity	0.65 (non-BRCA1) 0.5 (BRCA1)	Beta	0.065	34.35	18.49615
Costs	Biopsy	176	Gamma	17.6	100	1.76
	MR guided biopsy	955	Gamma	95.5	100	9.55
	Wide local excision	84	Gamma	50	100	9.842875
	Mastectomy	2058	Gamma	205.8	100	20.58
	Chemotherapy	922	Gamma	200	100	20
	Taxol	80	Fixed			
	Tamoxifen	27.25	Fixed			
	MRI scan	224	Gamma	22.4	100	4.051
	USS	48.8	Gamma	4.88	100	0.488
	Mammography	33.5	Gamma	3.35	100	0.335
Utility multipliers	In treatment	0.7	Beta	0.07	29.3	12.55714
	False negative	0.9	Beta	0.09	19.2	4.8
Screening effect on incidence	Increase in annual incidence due to mammography	Age-dependent	Uniform	N/A	0	Deterministic value multiplied by 2

2.3.2 Appendix 2: Sensitivity of Mammography by Age

The MARIBs trial gives sensitivity for mammography of 0.4. A trial gives sensitivity by age, as given below. [Kerlikowske et al., 1996]

Age	Sensitivity
30-39	0.583
40-49	0.75
50-59	0.923

This does not intersect with the MARIBs result. It was assumed that this was because the trials had chosen alternative points on the Receiver Operating Characteristic (ROC) curve (thus one was relatively more conservative in assigning a positive result). The average age of participants in the MARIBs trial fell in the 40-49 range. Therefore, all of the sensitivities by age described above were multiplied by 0.4 / 0.75 to generate the sensitivities displayed below. Since the age bands are wide, the line was smoothed to give a more accurate increase in sensitivity as age increases.



2.3.3 Appendix 3: Unit costs

Table 2.19. Major Costs in the Model

Intervention	Type of cost	Cost (£)	Source
MRI scan	Unit	224	NHS Reference Costs 2004
Mammography	Unit	33.5	MARIBS economic
Ultrasound scan	Unit	48.8	MARIBS economic
Biopsy	Unit	176	MARIBS economic evaluation
MR-guided biopsy	Unit	955	MARIBS economic
Chemotherapy	Unit	922	NHS Reference Costs 2004
Wide local excision	Unit	984	NHS Reference Costs 2004*
Mastectomy	Unit	2 058	MARIBS economic
Tamoxifen	1 year (20mg daily)	29.08	British National Formulary cost

* It should be noted that no identified source of information on the cost of wide local excision was identified. Therefore, it was assumed that it entailed a comparable resource use to a surgical biopsy. It should be noted that the importance of this assumption is highly limited (as shown in the univariate sensitivity analysis) since the treatment costs approximately balance between the cohorts in different screening programmes.

2.3.4 Appendix 4: Utility Multipliers Used in the Model A

State	Utility multiplier	Source
Undiagnosed breast	0.9	Assumption
In treatment	0.7	Assumption
Baseline utility by age		Health Survey for

2.3.5 Appendix 5: ICER's on the cost-effectiveness plane for the six population groups

Figure 2.2 : Costs and Outcomes (BRCA1, aged 40-49)

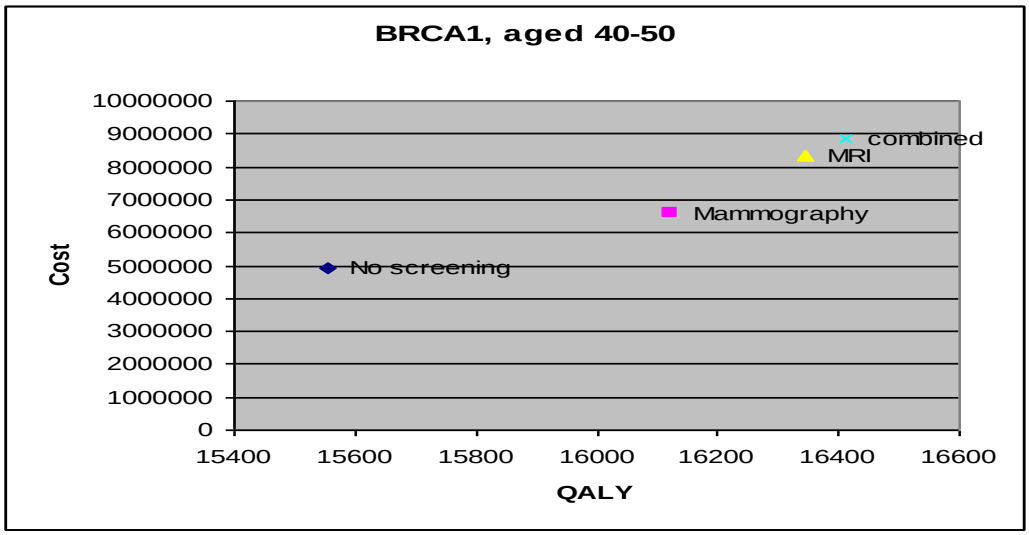


Figure 2.3 : Costs and Outcomes (high risk, aged 40-49)

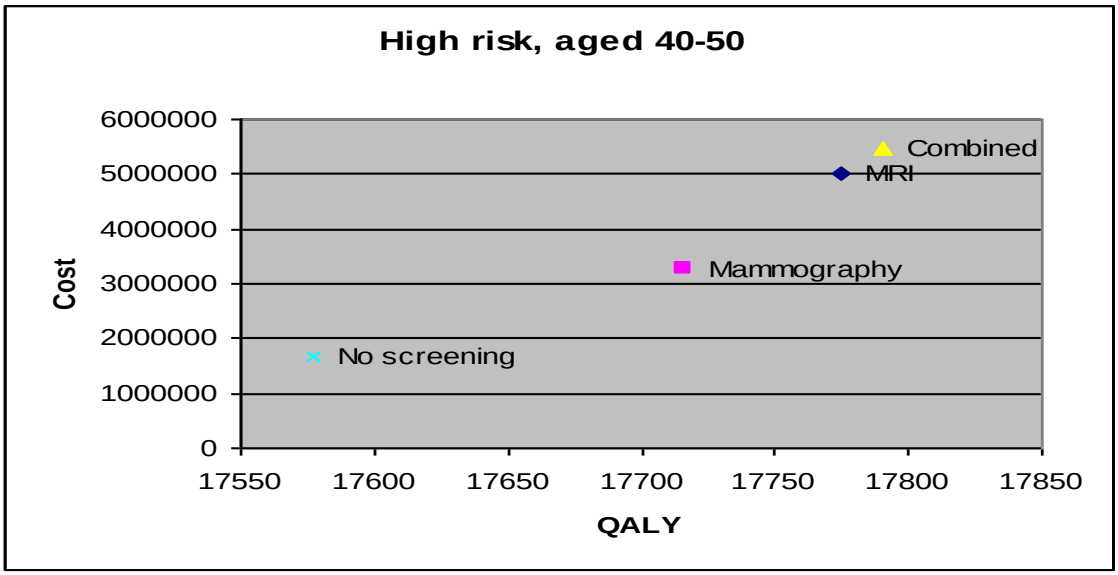


Figure 2.4 Costs and Outcomes (raised risk, aged 40-49)

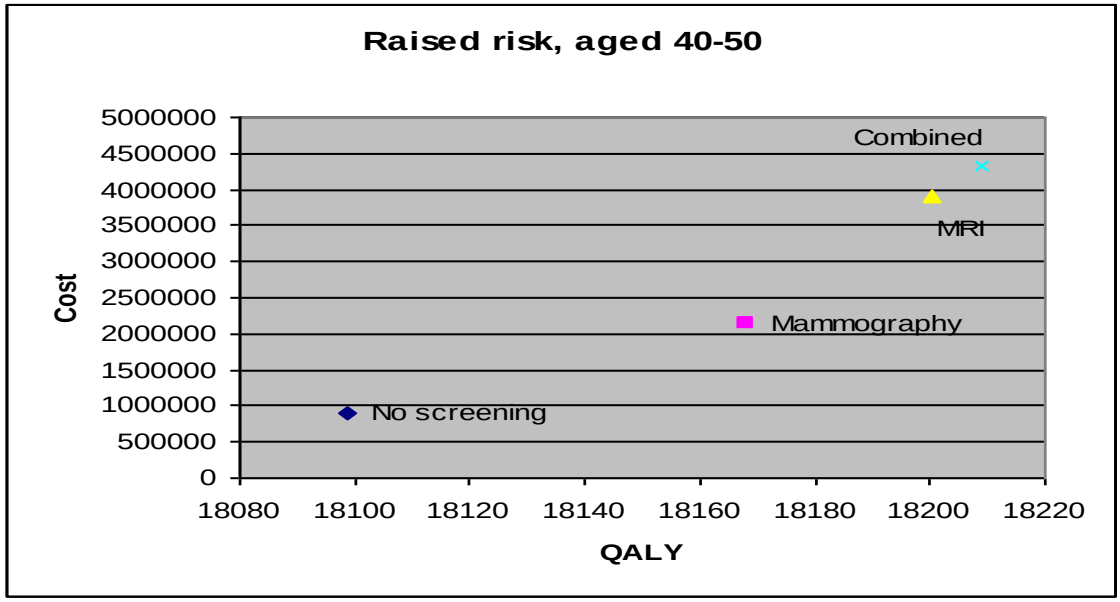


Figure 2.5 Costs and Outcomes (BRCA1, aged 30-39)

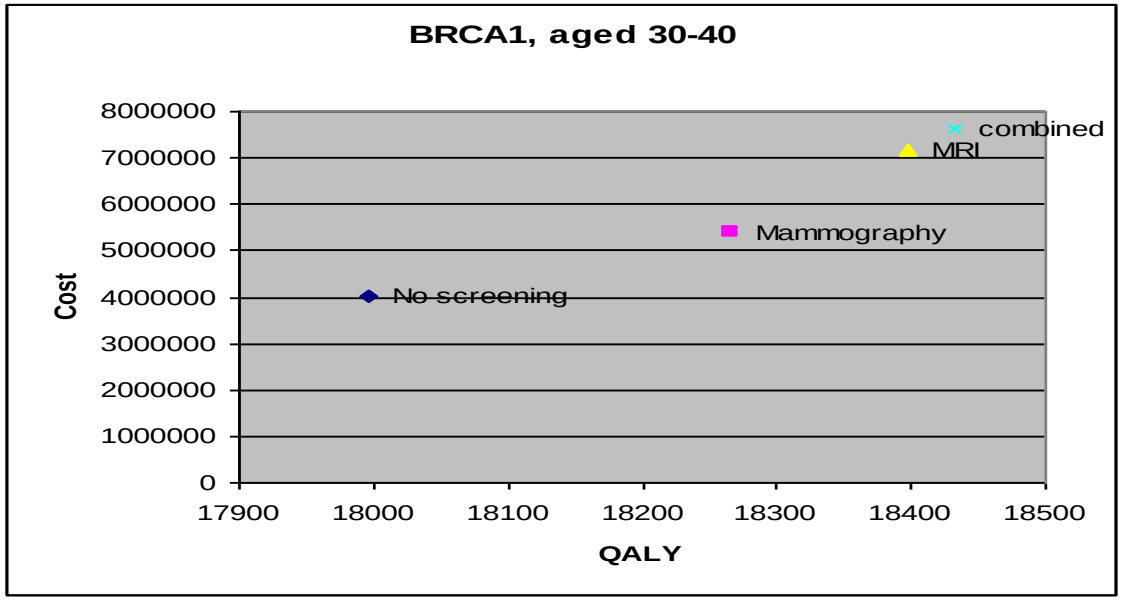


Figure 2.6: Costs and Outcomes (high risk, aged 30-39)

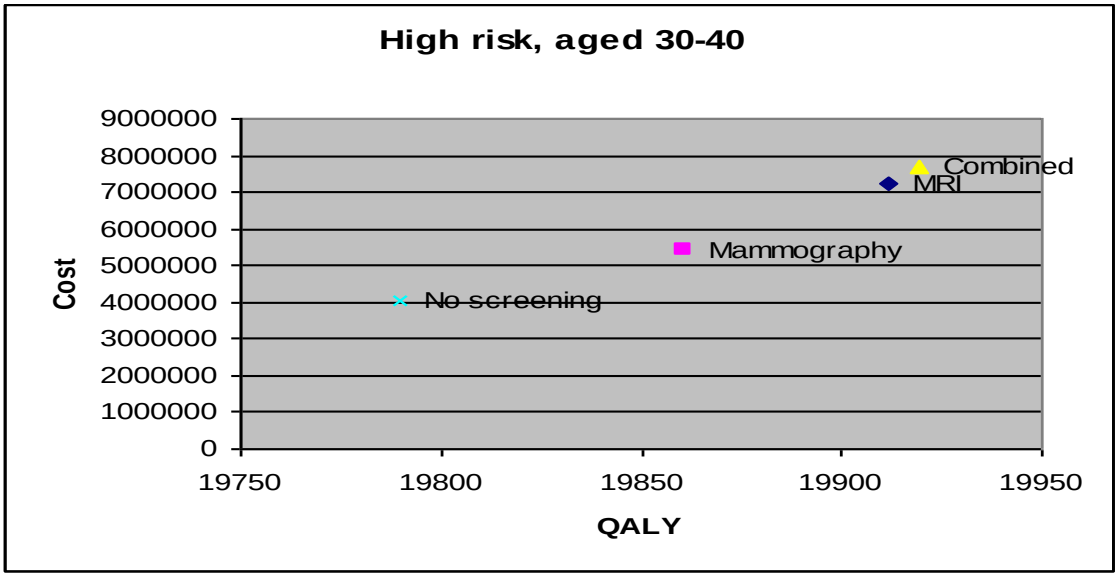
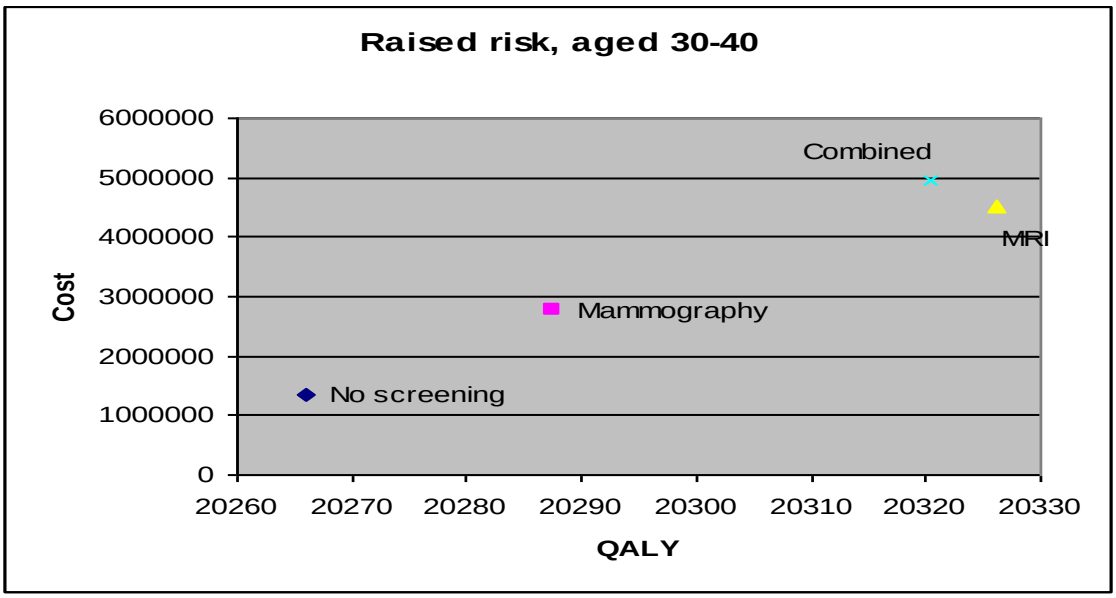


Figure 2.7 : Costs and Outcomes (Raised risk, aged 30-39)



2.3.6 Appendix 6: Univariate Sensitivity Analysis Strategy and Detailed Results

(Note that any pairwise comparison involving MRI-alone was excluded since this option was extendedly dominated)

Appendix 6a: Strategy for Univariate Sensitivity Analysis

Type of parameter	Parameter	Base case value	High value	Low value
Probabilities	Mortality of false			
	Prognosis (1) non-			
	Prognosis (2) non-			
	Prognosis (3) non-			
Costs	Biopsy	176	211	141
	MR guided biopsy	955	1 146	764
	Wide local excision	984	1 181	787
	Mastectomy	2058	2 469	1 647
	Chemotherapy	922	1106	738
	MRI scan	224	405.1	112
	USS	48.8	58.56	39.04
	Mammography	33.5	40	32
Utilities	In treatment	0.7	0.8	0.6
	False negatives	0.9	1	0.8
Screening effect on incidence	Increase in annual incidence due to mammography		+100%	No effect

Appendix 6b Results for Univariate Sensitivity Analysis

(Mammography relative to no screening)

6b(i) 30-39 year olds*(Note that the change in ICERs in the areas not given are minimal)*

Type of parameter	Parameter	BRCA1 range	High risk range	Raised risk range
Probabilities	Mortality of false	5 145 - 5 413	17 926 – 20 331	39 093 - 45 444
	Prognosis (1)	4 342 - 6 629	N/A	N/A
	Prognosis (2)	4 735 - 5 872	N/A	N/A
	Prognosis (3)	4 015 - 7 843	N/A	N/A
	Prognosis (1) non-	N/A	13 530 - 30 766	28 510 - 74 551
	Prognosis (2) non-	N/A	15 535 - 23 677	33 325 - 54 123
	Prognosis (3) non-	N/A	11 940 - 46 404	25 050 - 118 222
Costs	MRI scan	4 413 -6 578	15 757 - 23 578	34 804 - 51 657
	USS	5 168 - 5 312	18 485 - 19 006	40 683 - 41 805
	Mammography	5 189 - 5 464	18 557 - 19 563	40 835 - 43 016
Utilities	In treatment	5 212 - 5	18 661 - 18 832	41 205 - 41 283
	False negatives	4 973 - 5 538	17 270 - 20 497	37 918 - 45 210
Screening effect on incidence	Increase in annual incidence due to mammography	5 010 - 5 482	17 932 - 19 622	39 379 - 43 284

6b(ii) 40-49 year olds

Type of parameter	Parameter	BRCA1 range	High risk range	Raised risk range
Probabilities	Mortality of false negatives	2 859 – 3 012	10 634 – 12 392	16 464 - 19 336
	Prognosis (1)	2 301 – 4 019	N/A	N/A
	Prognosis (2)	2 566 – 3 379	N/A	N/A
	Prognosis (3)	2 147 – 4 799	N/A	N/A
	Prognosis (1) non-	N/A	7 651 – 21 159	11 570 - 35 221
	Prognosis (2) non-	N/A	9 184 – 14 451	14 057 - 22 926
	Prognosis (3) non-	N/A	6 858 – 32 477	10 389 - 55 507
Costs	MRI scan	2 522 – 3 545	9 647 – 13 780	14 419 - 22 291
	USS	2 879 – 2 947	11 089 – 11 364	17 165 - 17 689
	Mammography	2 891 – 3 011	11 129 – 11 648	17 230 - 18 279
Utilities	In treatment	2 901 – 2 926	11 193 – 11 260	17 331 - 17 524
	False negatives	2 736 – 3 115	10 192 – 12 494	15 797 - 19 432
Screening effect on incidence	Increase in annual incidence due to mammography	2 839 – 2 989	11 018 – 11 441	17 096 - 17769

Appendix 6c Results for Univariate Sensitivity Analysis

(Combined approach relative to mammography)

6c(i) 30-39 year olds

Type of	Parameter	BRCA1 range	High risk range	Raised risk range
Probabilities	Mortality of false negatives	13 069 - 14 264	36 613 - 43 598	66 771 - 79 790
	Prognosis (1)	8 651 - 31 016	N/A	N/A
	Prognosis (2)	11 918 - 15 543	N/A	N/A
	Prognosis (3)	10 294 - 20 226	N/A	N/A
	Prognosis (1) non-	N/A	21 151 - 260 940	38 819 - 421 436
	Prognosis (2) non-	N/A	32 449 - 48 670	59 395 - 88 517
	Prognosis (3) non-	N/A	25 519 - 85 647	46 344 - 155 596
Costs	MRI scan	7 101 – 23 812	20 375 - 68 903	36 290 - 127 327
	USS	13463 - 13510	38 853 - 38 985	70 957 - 71 197
	Mammography	13 486 – 13 487	38 918 - 38 919	No change
Utilities	In treatment	13 252 – 13 729	38 353 - 39 501	70 284 - 71 888
	False negatives	12 486 – 14 660	34 814 - 44 120	63 743 - 80 318
Screening effect on incidence	Increase in annual incidence due to mammography	13 471 – 13 502	38 904 - 38 933	71 064 - 71 090

6c(ii) 40-49 year olds

Type of parameter	Parameter	BRCA1 range	High risk range	Raised risk range
Probabilities	Mortality of false negatives	7 525 – 8 262	27 605 - 33 819	49 911 - 61 060
	Prognosis (1)	4 744 – 22 634	N/A	N/A
	Prognosis (2)	6 389 – 9 990	N/A	N/A
	Prognosis (3)	5 972 – 11 479	N/A	N/A
	Prognosis (1) non-	N/A	Dominated -	27 168 - 1.644M
	Prognosis (2) non-	N/A	22 289 - 44 242	40 551 - 78 855
	Prognosis (3) non-	N/A	19 382 - 65 114	35020 - 115 648

Costs	MRI scan	4 272 – 13 454	15 271 - 52 827	27 243 - 96 072
	USS	7 767 – 7 795	29 571 - 29 673	53 454 - 53 634
	Mammography	7780 – 7781	29 621 - 29 622	No change
Utilities	In treatment	7 622 – 7 946	29 066 - 30 199	52 798 - 54 312
	False negatives	7 096 – 8 612	25 818 - 34 740	46 871 - 62 433
Screening effect on	Increase in annual incidence due to	7 771 – 7 790	29 612 - 29 632	53 535 - 53 553

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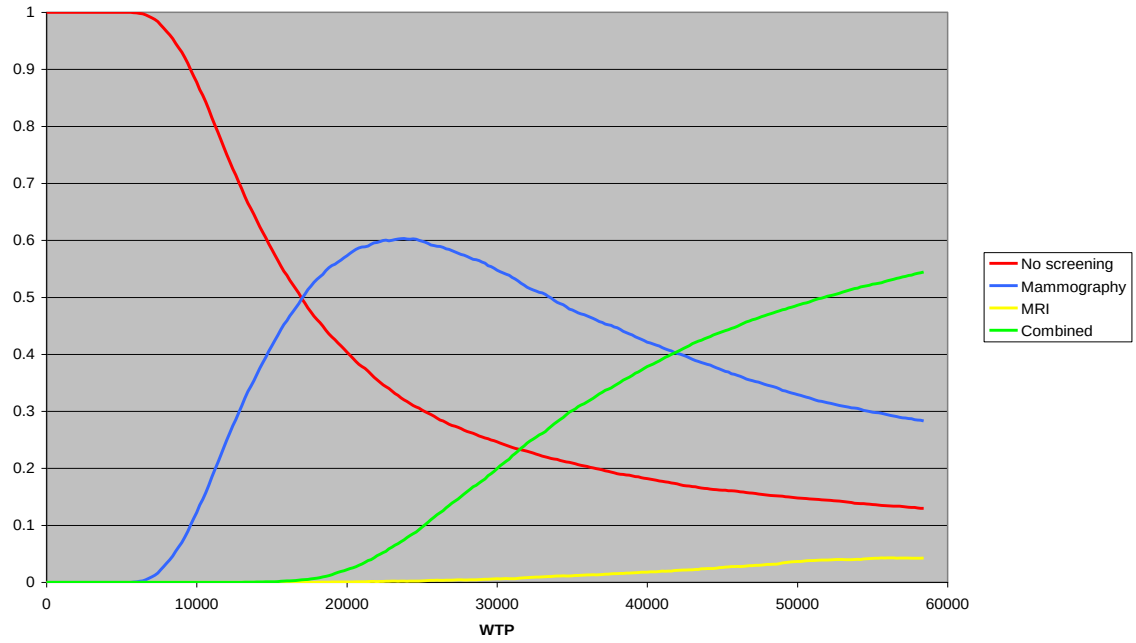
2.3.7 Appendix 7: Probabilistic Sensitivity Analysis

Figure 2.8: Cost-Effectiveness Acceptability Curves for Raised Risk Individuals Aged 40

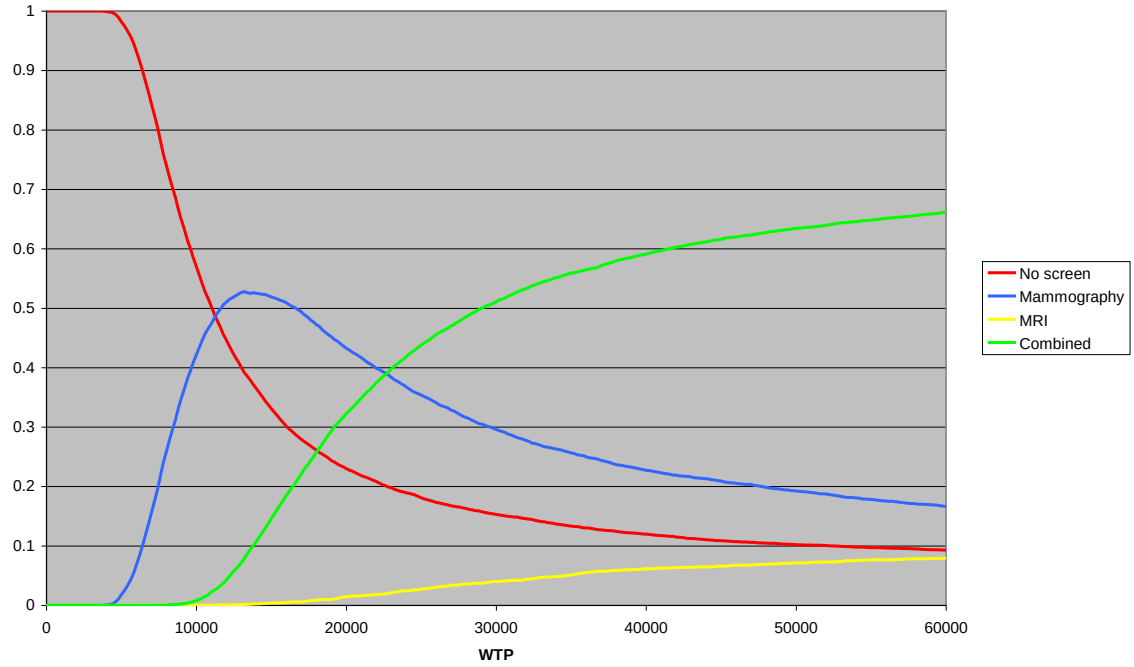


This contrasts the societal willingness to pay for a QALY with the probability of each intervention being cost-effective relative to the other three (thus, at any point, the probabilities sum to 1). Firstly, it should be noted that, as expected, the more expensive and more sensitive interventions are increasingly likely to be cost-effective as the societal valuation of a QALY increases.

It is apparent that this evidence suggests that the recommendation of MRI in this population group is not supported. As the mammography becomes likely to be the cost-effective option at a QALY value of approximately £20 000, the evidence on using annual mammography is equivocal.

The comparable figure for the high risk, non-BRCA1 population at 40 is presented below.

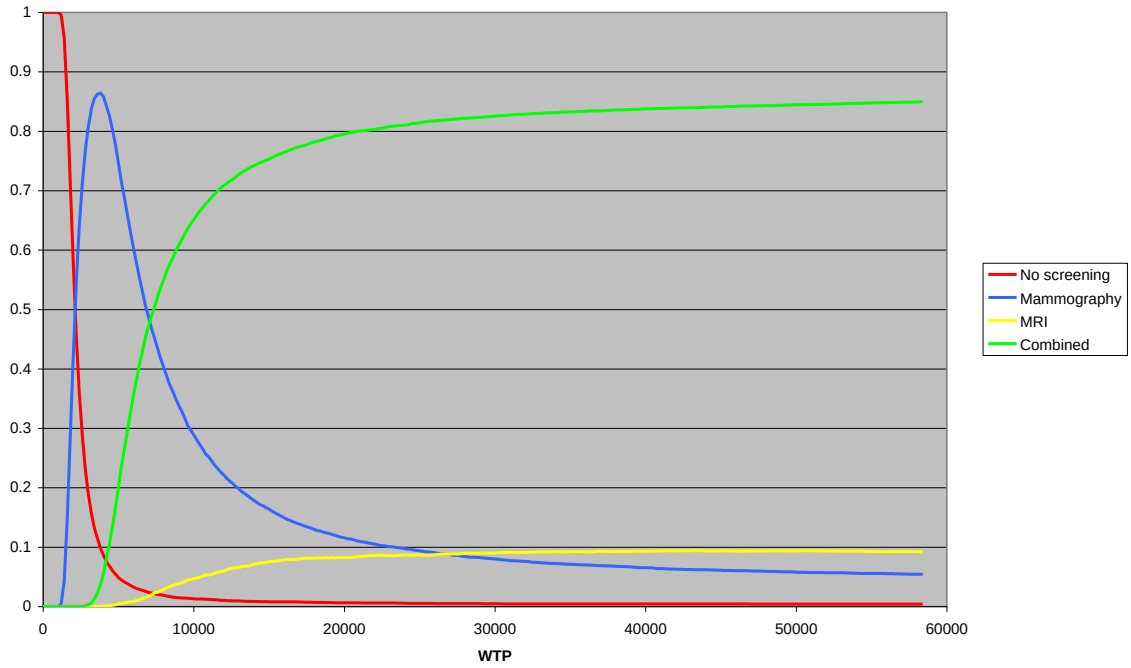
Figure 2.9: Cost-Effectiveness Acceptability Curves for High Risk, non-BRCA1 Individuals Aged 40



As the diagram suggests, more expensive interventions are relatively more likely to be cost-effective in this higher risk group. This is reasonable as the screening method would identify more tumours since there is likely to be a higher incidence in the period prior to screening. At a societal valuation of a QALY above £11 300, a screening method per se is the most cost-effective. From £11 300 to £22 700, the mammography is the intervention most likely to be cost-effective. Beyond £22 700, combined screening is most likely to be cost-effective.[3]

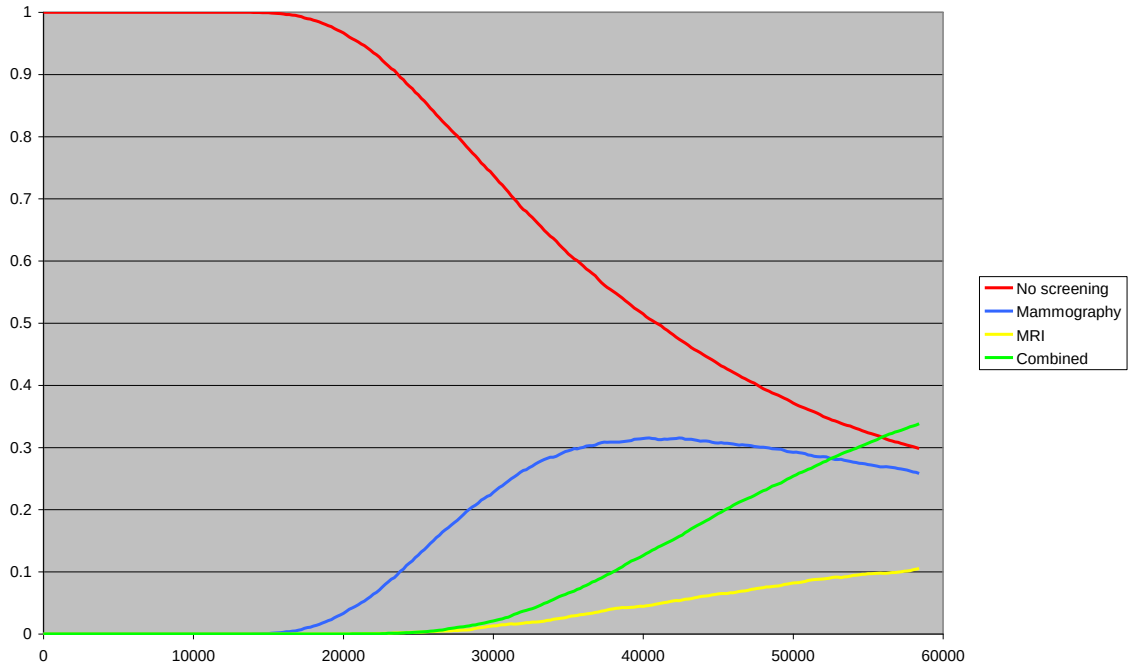
[3] It should be noted that the values at which interventions switch from being cost-effective to not being so do not fall at exactly the same points as the lines intersect. This is because the switching value is based on the expected net benefit, thus accounting for skewness. For further details, see Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ. 2004 May;13(5):405-15.

Figure 2.10: Cost-Effectiveness Acceptability Curves for BRCA1 Mutation Individuals Aged 40



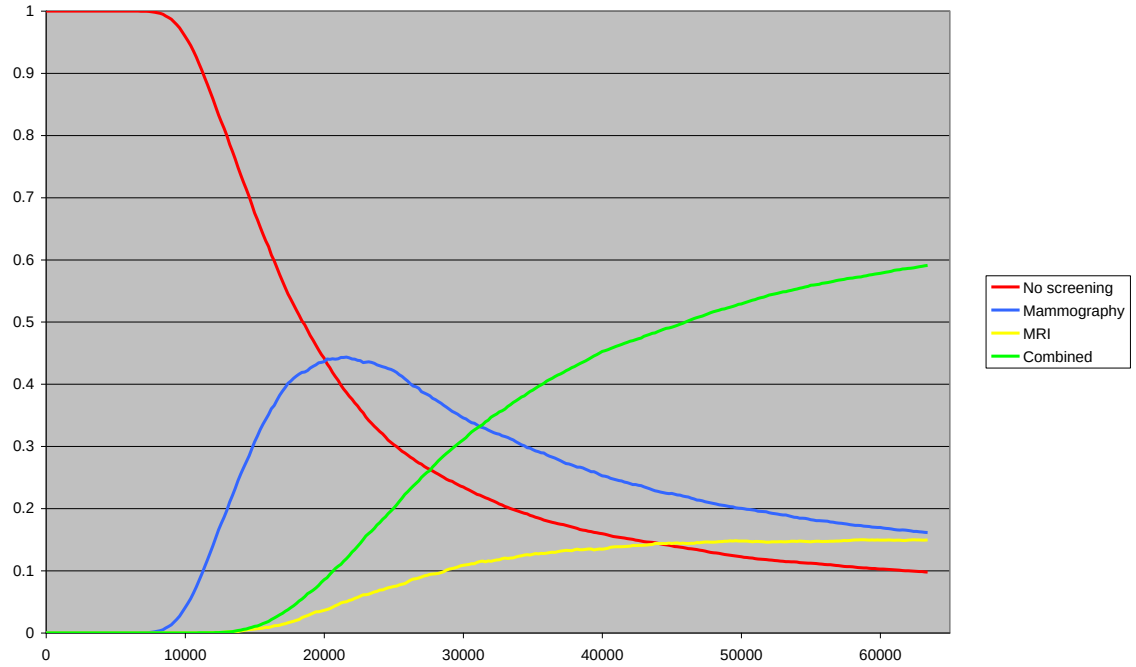
As with the high risk, non-BRCA1 group in relation to the raised risk group, the BRCA1 group have screening interventions recommended at a considerably lower societal willingness to pay. Thus, at a threshold of £20 000 per QALY, the model suggests that the likelihood of the combined approach being the most cost-effective is 79.6%.

Figure 2.11: Cost-Effectiveness Acceptability Curves for Raised Risk Individuals Aged 30



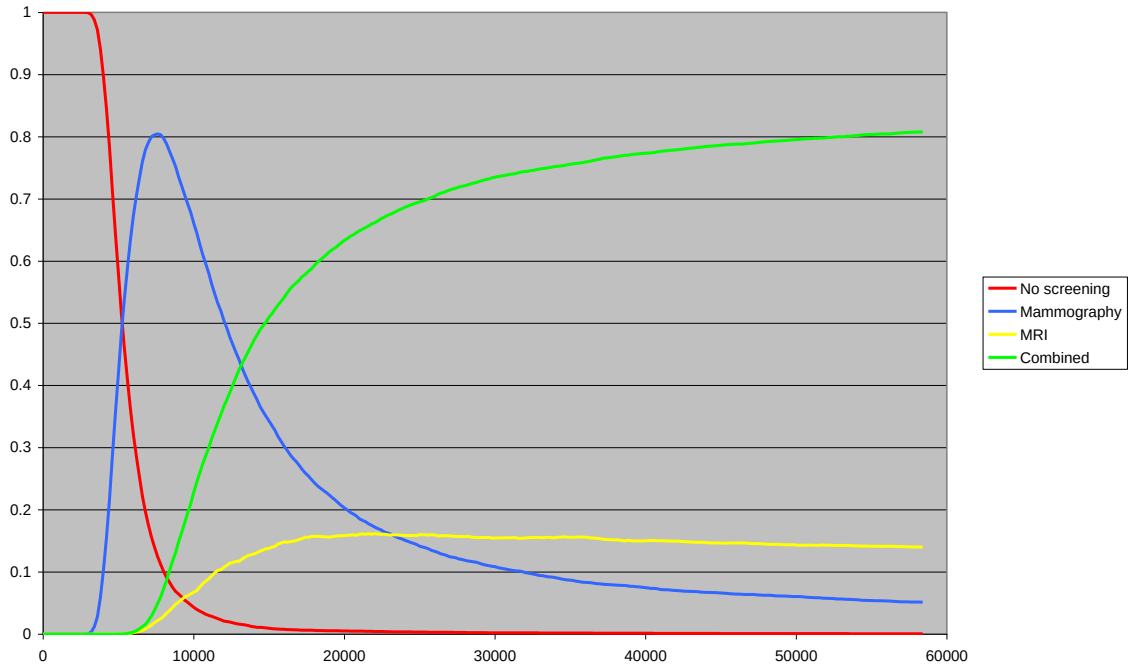
In the younger population, the probabilistic sensitivity analysis agrees with the base case results given previously. At most recognised thresholds, the evidence for annual mammography is weak. This is due to a relatively low risk of tumours, a reduced sensitivity of mammography, and the potential harm of radiation from such a programme.

Figure 2.12: Cost-Effectiveness Acceptability Curves for High Risk, non-BRCA1 Individuals Aged 30



In the higher risk (but not BRCA1) group, three approaches have a likelihood of being cost-effective of greater than 0.3 if we assume various thresholds for the value of a QALY between £20 000 and £30 000. Thus, the probabilistic sensitivity analysis cannot provide strong evidence in support of any of not screening, using mammography alone, and using both approaches.

Figure 2.13: Cost-Effectiveness Acceptability Curves for BRCA1 Mutation Individuals Aged 30



In the BRCA1 group, the combined approach is most likely to be cost-effective at a QALY threshold between £20 000 and £30 000 (the likelihood's at these two values are 0.633 and 0.735).

2.4 Health economic summary of annual mammography, annual MRI and annual combined screening (2006) (Chapter 7.2)

Aims of the review

To assess the relative cost-effectiveness of annual mammography, annual MRI screening and annual combined screening in women aged 30-49 at a familial risk of breast cancer.

Methods

Search strategy

A systematic search of the Social Science Citation Index (SSCI), Embase, Medline and NHSEED was undertaken looking for cost-effectiveness papers in this area. A similar clinical search was undertaken, with any data amenable to Health Economics identified.

Inclusion and exclusion criteria

Since the likelihood of finding significant numbers of cost-effectiveness studies was small, no major study design was designated a priori. However, any included analysis had to be a cost-effectiveness or cost-utility paper, written in English, and looking at the economics of screening methods for individuals at a familial raised risk of breast cancer.

Results

Results of search strategy

No published economic evaluations were identified in the search. Two economic evaluations looked at the cost-effectiveness of mammography in population-level risk women. [Kerlikowske et al., 1999] [Salzmann et al., 1997] These were not considered since the intervention they investigate is not the primary tool under investigation in this work. An unpublished economic evaluation of a clinical trial covering a raised risk population group was included for costing data.

Results for cost-effectiveness

A model was constructed looking at the costs and outcomes of no screening, annual mammography, annual MRI or a combined annual approach of both mammography and MRI. Using 10-year risk values for 40 year olds of 6%, 12% and 31% for raised risk, high risk and *BRCA1* subpopulation groups respectively, the incremental cost-effectiveness ratio (ICER) of annual mammography relative to no screening was £17 209, £11 090 and £2 865 per QALY gained respectively. The ICER of MRI screening or a combined approach of both MRI and mammography differed across risk groups and are fully outlined in the results section.

Focusing first on the 40-49 age group, the results suggest that annual mammography can be recommended in all population groups considered. The combined (or dual) approach, using both MRI screening and mammography has good evidence supporting its use in the *BRCA1* mutation population. In the high risk population group, there is some support for the cost-effectiveness of the approach.

The results for 30-39 year olds suggest that, as before, annual mammography can be recommended as a cost-effective intervention in high-risk populations (including a *BRCA1* subgroup). However, unlike the older age cohort, this result is not transferable to the raised risk group. Beyond mammography, providing parallel MRI screening is cost-effective in the *BRCA1* population. In the high risk group, the evidence suggests that the use of MRI screening as an adjunct to mammography in this younger age group is not cost-effective.

If mammography is excluded from the analysis a priori as a result of concern regarding radiation risk in this younger cohort, the evidence suggests that annual MRI screening is cost-effective relative to no screening if the 10-year risk is at least 7.4%.

Sensitivity analysis suggested that these result is dependent on two major areas. Firstly, cases identified at an earlier stage are likely to have a better 5-year survival rate. The degree of improvement as cases are identified earlier has significant implications for the conclusion. The second area is the cost of MRI screening. The model selects one of the two identified costs for MRI scans. Sensitivity analysis investigates the effect of this selection and, as outlined later, the choice affects certain conclusions in particular sub-populations.

Conclusions

Implications for future research

The issue of whether to extend screening to include routine MRI scans is sensitive to the cost of these scans, and to the effect on prognosis of being identified at an earlier stage. It is likely that further investigation in these areas represents the best extension of this work.

Implications for clinical practice

This analysis suggests that MRI screening has a role in play in routine surveillance of women at a high risk of breast cancer between 30 and 49. Despite the relatively small size of the population in question, there is an issue with regards to the provision of these services.

2.5 Surveillance for people with a personal history of breast cancer (chapter 7.3)

Review question

What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk-reducing mastectomy?

Question in PICO format

Patients/population	Intervention	Comparison	Outcomes
Patients with a personal history of breast cancer and a familial risk aged: 18-29 30-39 40-49 50-70 70 +	Mammography MRI Ultrasound Clinical Breast Exam Any combinations of tests at different frequencies/timings No screening	Each Other	Cost-effectiveness Incremental cost effectiveness ratio (ICER) Results of sensitivity analysis

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED). Focus was put on studies/reviews reporting HE evidence for topic A including systematic reviews of economic evidence (or systematic reviews which contain economic evaluations), published economic evaluations (including conference proceedings), economic evaluations as part of randomized controlled trials, economic evaluations as part of observational studies and economic modelling studies (all types). Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

Selection criteria for included evidence:

Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included

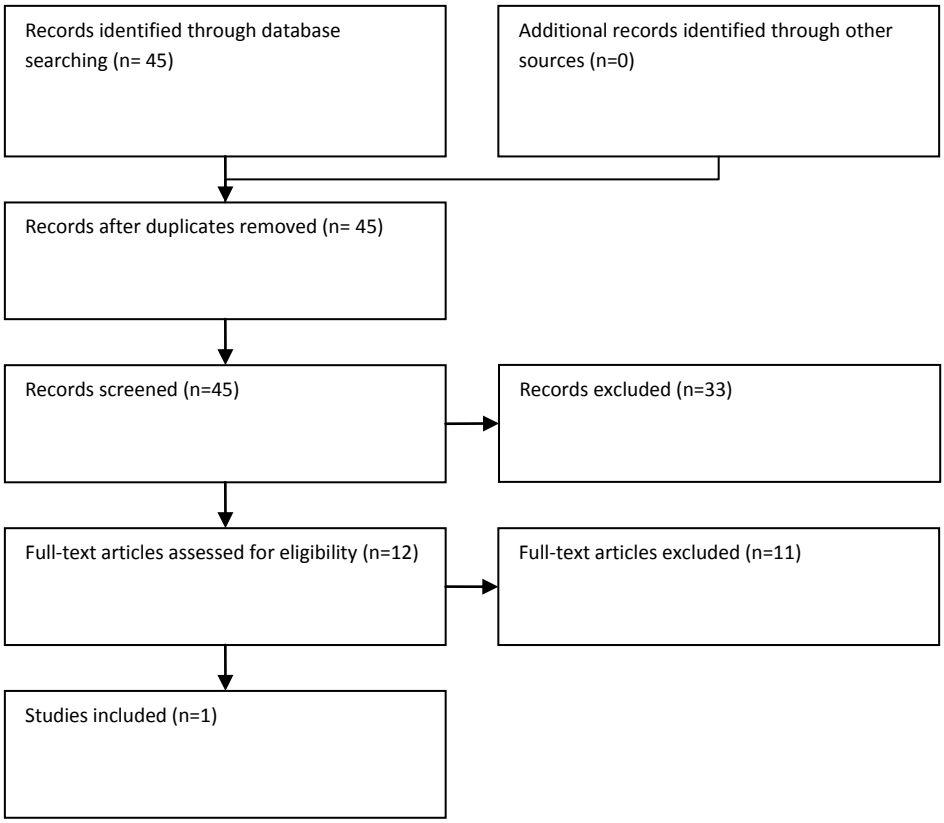
Studies that were conducted in OECD countries (other than the UK) were included

Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economists screened the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. Full articles were obtained for twelve studies and checked against the inclusion criteria.

Results



Quality and applicability of the included studies

The included study (Schousboe et al., 2011) was deemed partially applicable to the guideline. The reasons for partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. The paper was deemed to have very serious limitations because they did not meet one or more aspects of the NICE reference case. In particular, justification of the use of QALY data from a Swedish cohort was unclear (no systematic literature review reported) and the discount structure used did not conform to the NICE reference case.

		Applicability	
		Directly applicable	Partially applicable
Methodological quality	Minor limitations		
	Potentially serious limitations		
	Very serious limitations		Schousboe et al., 2011

2.5.1Evidence statements

One study was included for this topic. The study (Schousboe et al., 2011) was conducted in the USA and showed that biennial mammography cost less than $100,000 per QALY gained

for women aged 40 to 79 years with both a family history of breast cancer and a previous breast biopsy, regardless of breast density. Annual mammography was not cost-effective for any group, regardless of age or breast density. (see table 2.20 & 2.21)

Population

The population included US women with a familial risk and previous breast biopsy of different age groups. The base case assumes no family history or personal history but secondary analysis included family and personal history of breast cancer. It is not specifically stated whether the population included BRCA1/2 carriers.

Intervention & Comparator

This paper compared annual mammography, biannual mammography, mammography every 3-4 years compared with no mammography/screening.

Outcome

Health effects were quantified in terms of QALYs and number of women screened over 10 years to prevent 1 death from breast cancer.

Source of effectiveness data

Clinical and epidemiological data were derived from the Surveillance, Epidemiology and End Results (SEER) database, Breast Cancer Surveillance Consortium (BCSC), literature and assumptions. Utility data was derived from the literature. Cost data was derived from national health care reimbursement data and literature.

Table 2.20: Modified GRADE table of included economic studies

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
Schousboe, 2011	Very serious limitations 1	Partially applicable 2	Cohort of US women aged over 40 with a family and personal history of breast cancer (secondary analysis)	Annual mammography, biannual mammography and mammography every 3 to 4 years	No mammography	Not specifically reported	Number of women screened over 10 years to prevent 1 death from breast cancer: Screening strategy: Mammography every 3 to 4 years (age 70-79, BI-RADS 4) — 337 Mammography every 3 to 4 years (age 40-49, BI-RADS 2) — 4870 Biannual mammography (age 60-69, BI-RADS 4) — 2041 Biannual mammography (age 40-49, BI-RADS 2) — 12195	Mammography every 3 to 4 years (age 50-59, BI-RADS 1 and personal as well as family history of BC): £17,680.523	Univariate sensitivity analysis and probabilistic sensitivity analysis reported. Results (ICERs) are sensitive to detection rate of false-positives, magnitude of excess DCIS detection, shift from advanced to local disease, breast cancer incidence.

1 Quality of life data is based on one single publication of a Swedish research group; model is based on US population data and makes several assumptions due to lack of published data. Family and personal history are only considered in the secondary analysis and results are not applicable to BRCA1/2 mutation carriers. Therefore the relevance of these results for informing the current guideline is limited.

2 The analysis does not meet one or more aspects of the NICE reference case.

3 Converted from 2008 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 103% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Table 2.21: Evidence table of included economic studies

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Schousboe Year: 2011 Country: USA Setting: Primary prophylaxis	Type of analysis: Cost-utility Model structure: Markov model (Monte Carlo simulations) Time horizon: Lifetime Perspective: National Health payer Source of baseline data: Surveillance, Epidemiology and End Results (SEER) database, Breast Cancer Surveillance Consortium (BCSC), literature and assumptions Source of effectiveness data: SEER, BCSC Source of utility data: Literature (Sweden)	Inclusion criteria: Not explicitly reported "women in the United States" Exclusions criteria: Not explicitly reported Sample size: 1,000,000 Age: Initial mammography at 40 years Gender: Female: 100% Subgroup analysis: By age: 40 to 49 years 50 to 59 years 60 to 69 years 70 to 79 years By risk: Family history of BC Previous breast biopsy By breast density	Group 1: Annual mammography Group 2: Biannual mammography Group 3: Mammography every 3 to 4 years Group 4: No mammography	Clinical data: Number of women screened over 10 years to prevent 1 death from breast cancer Mammography every 3 to 4 years (age 70-79, BI-RADS 4) Mammography every 3 to 4 years (age 40-49, BI-RADS 2) Biannual mammography (age 60-69, BI-RADS 4) Biannual mammography (age 40-49, BI-RADS 2) Utility score: None reported Cost: None reported ICER: Cost-effective ($100,000/QALY): Biannual mammography (age 40-49, BI-RADS 3-4)	337 4870 2041 12,195 Cost (US$)/QALY 74,482-87,769	Notes: The base case assumes no family history or personal history but secondary analysis included family and personal history of BC Results not applicable to BRCA1/2 carriers Conflict of interest: Research was funded by Eli Lilly, Da Costa Family Foundation for Research in Breast Cnacer Prevention of the Californian Pacific Medical Center and Breast Cancer Surveillance Consortium

	Source of cost data: Medicare reimbursement data, literature Others: Currency unit: US $ Cost year: 2008 Discounting: Costs: 3% Health benefits: 3%	Breast Imaging Reporting and Data System (BI-RADS) categories 1 to 4		Biannual mammography (age 40-49, personal and family history of BC) Biannual mammography (age 50-59, BI-RADS 2,3 or 4) Biannual mammography (age 50-59, BI-RADS 1 and personal and family history of BC) Mammography every 3-4 years (age 50-59, BI-RADS 1) Biannual mammography (age 70-79, BI-RADS 3 and 4) Biannual mammography (age 70-79, personal history) Biannual mammography (age 70-79, family history) Cost-effective ($ 50,000): Biannual mammography (age 40-49, BI-RADS 3 and 4 and either personal or family history of BC) Biannual mammography (age 50-79, BI-RADS 3 and 4) Biannual mammography (age 50-79, BI-RADS 2 and either personal	9.114-79,793 23,962-89,189 57,956 72,184 40,540-50,982 40,630-78,684 47,508-84,079 23,779-38,946 21,425-50,982 28,903-47,508	Applicability: Partially applicable Limitations: Very serious limitations

				or family history of BC) Mammography every 3 to 4 years (age 50-59, BI-RADS 1 and personal as well as family history of BC) Mammography every 3 to 4 years (age 70-79, BI-RADS 1 or 2) Uncertainty: Univariate sensitivity analysis and probabilistic sensitivity analysis reported. Results (ICERs) are sensitive to detection rate of false-positives, magnitude of excess DCIS detection, shift from advanced to local disease, breast cancer incidence. Probability of mammography every 3 to 4 years being cost-effective for 40 to 49 years with no additional risk Probability of mammography every 3 to 4 years being cost-effective for 40 to 49 years with no additional risk was and BI-RADS 1 or 2	 25,060 13,574-18,223 <1 % 5.4 %	

2.5.2 References

Schousboe JT, Kerlikowske K, Loh A & Cummings SR (2011) Personalizing mammography by breast cancer density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Annals of Internal Medicine, 155: 10-20.

2.6 A cost utility analysis of the specific surveillance needs for people with a personal history and family history of breast cancer (2013). (Chapter 7.3)

2.6.1 Introduction

Women who are affected by primary breast cancer are at an increased risk of developing second breast cancers in the remaining breast tissue with those women with a familial history at an even higher risk. Risk-reducing mastectomy has been shown to significantly decrease the risk of contralateral breast cancer in women with a family history of breast cancer when compared to women who underwent therapeutic mastectomy of the affected breast only (Boughey et al., 2010). However, not all women who are offered risk-reducing mastectomy choose to have this done. For those women who have breast tissue remaining it is important to offer regular surveillance screening as early detection confers a survival advantage (Houssami et al., 2011, Robertson et al., 2011). However, it is unknown whether this is also the same for women at familial risk. Little evidence is available on surveillance in women with a personal history as well as a family history of breast cancer and it is therefore not clear which surveillance method should be offered to which risk group at which age.

2.6.2 Screening methods

Different surveillance methods and strategies are available to screen women with a personal history of breast cancer for contralateral and ipsilateral recurrences. These include mammography (digital and film-screen), MRI, clinical examination, ultrasound and combinations of the aforementioned tests (Robertson et al., 2011). At present all women are offered mammography annually or biennially for between 3-5 years and some for longer than this. Even though digital mammography is known to be slightly more sensitive than film-screen mammography, especially for the detection of breast cancer in premenopausal women and in those women with dense breasts (Kerlikowske et al., 2011), it has been shown that overall mammography performance is lower for women with a personal history of breast cancer than for unaffected women. This is thought to be due to lower detection of invasive cancers (Houssami et al., 2011). Furthermore, MRI generally has been shown to be more sensitive than mammography, especially in high-risk populations such as BRCA1/2 carriers (FH01, 2010). For these reasons, it has been suggested that MRI may be the more appropriate surveillance method when compared to mammography in women who have previously been treated for primary breast cancer (Robertson et al., 2011).

Health economic priority

The decision to offer certain types/frequencies of surveillance will impact on NHS resources and patient benefits. This cannot be answered by qualitative methods as one surveillance strategy may be more expensive but may be more effective. The GDG identified this topic as a high economic priority.

Economic model (overview)

Update of CG41

CG41 assessed the relative cost-effectiveness of annual film-screen mammography, annual MRI screening and annual combined screening in women aged 30-49 years at a familial risk of breast cancer. It was agreed by the GDG that this evaluation would be based on adapting and updating the economic model in CG41. The adaptation would include people with a personal history of breast cancer and consider the surveillance needs for different sub-groups.

The topic would also be adapted and up-dated to include men if feasible, as this population had not been considered in CG41. However, the paucity of evidence on men was considered a potential challenge in developing the model. It was therefore agreed by the GDG that men would be considered within the same population as women.

Aim

The aim of this economic analysis was to compare the cost-effectiveness of different surveillance methods for women and men with a family history and a personal history of breast cancer who have not undergone risk-reducing mastectomy. The following screening methods were included in the analysis:

- No screening (comparator)
- Annual mammography (digital)
- Annual MRI
- Annual combined approach (mammography plus MRI)

Subgroup analyses were conducted on the following patient groups:

- High risk patients (age 30-39 years)
- High risk patients (age 40-49 years)
- High risk patients (age 50-59 years)
- High risk patients (age 60-69 years)
- BRCA2-positive patients (age 30-39 years)
- BRCA2-positive patients (age 40-49 years)
- BRCA2-positive patients (age 50-59 years)
- BRCA2-positive patients (age 60-69 years)
- BRCA1-positive patients (age 30-39 years)
- BRCA1-positive patients (age 40-49 years)
- BRCA1-positive patients (age 50-59 years)
- BRCA1-positive patients (age 60-69 years)

The economic analysis does not cover:

Surveillance needs of annual mammography, annual MRI and annual combined screening in women or men at a familial risk of breast cancer but without a personal history. This was considered in CG41 and the GDG decided that this topic was considered a low priority for economic modelling in this update.

2.6.3 Model Structure

CG41 was considered an appropriate model structure for adaptation with no major structural changes required.

An outline of the model structure is presented in Figure 2.14. In brief, the CG41 model comprised a deterministic decision tree and Markov model, which aimed to model the surveillance needs of individuals with a family history but no personal history of breast cancer. The decision tree modelled the probability of an individual developing breast cancer and the conditional probability of its subsequent diagnosis, dependent on the screening strategy in use. The Markov model then followed patients over time, modelling disease progression amongst the cohort. Appropriate costs and benefits were then accumulated according to the progression of each individual until death.

The following adaptations were made:

- Change of patient population to men and women with a family history and a personal history of breast cancer
- Digital mammography was considered instead of film-screen mammography
- Age groups were extended from 30-49 to 30-69 years; modelled over 4 age groups: 30-39, 40-49, 50-59, 60-69 years
- BRCA2-positives (previously included as part of the high risk group for CG41) were considered as a separate patient group, in addition to BRCA1-postives and high risk individuals
- The moderate risk group (included in CG41) was not again considered due to lack of cost-effectiveness in previous analyses, and in favour of the specification of the three patient groups defined above
- Additional capability to apply distinct breast cancer survival rates for each of the patient groups
- Additional capability to run automated probabilistic sensitivity analysis (PSA)

The model evaluates the screening of a cohort of patients and the subsequent diagnoses of disease over annual cycles. All individuals enter the Markov model (Figure 2.15) in the "healthy" state. Whereas the true condition of each individual's health in this state will vary, in simplified terms, these individuals do not have a newly developed breast cancer that could be potentially identified through screening and are not in treatment for breast cancer. Individuals in the "healthy" state are subject to one of the four screening strategies under consideration) for the first ten years of the model.

Screening can result in either a true positive, true negative, false positive or a false negative result, as derived in the decision tree model. Individuals diagnosed with breast cancer (true positives) receive treatment in the year of diagnosis and for two further years, after which time they return to the "healthy" population. It is assumed that false positives are assessed, immediately identified as false positives and return to the healthy population for the subsequent cycle. Within the ten year screening stage, false negatives will be subject to screening in the following cycle, in which they may be identified as a true positive. As detailed in the list of modelling assumptions, should a cancer go undiagnosed for two consecutive annual cycles, they will be diagnosed in the third year, reflecting the assumption that all breast cancers will present eventually in the absence of screening.

Cancer-related death is modelled for individuals who have been diagnosed with cancer and are in treatment. Survival is modelled dependent on the patient group (high risk, BRCA 1, BRCA 2) and the time at which the cancer was detected (first, second or third annual opportunity in which the cancer may have been detected by screening). As detailed in the list of modelling assumptions, in the base case, an increased rate of mortality for individuals with undiagnosed cancer is not applied during the time between the development of cancer and its identification (up to two years). However, this delay in diagnosis does have a negative impact on survival once the cancer is detected.

Figure 2.14: Model schematic of decision tree and Markov process for CG41 model, adapted for specific surveillance needs of people with a personal history and family history of breast cancer.

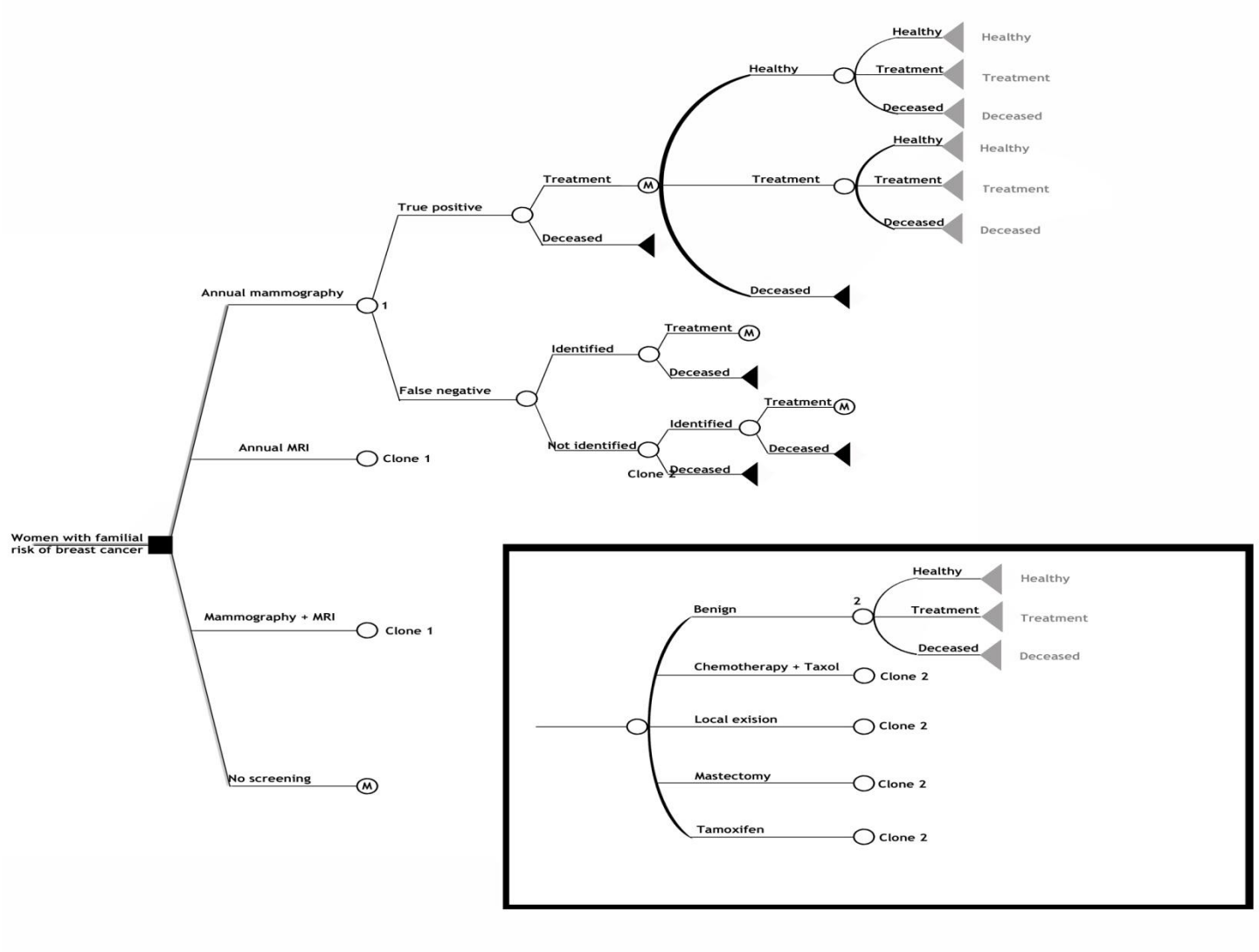
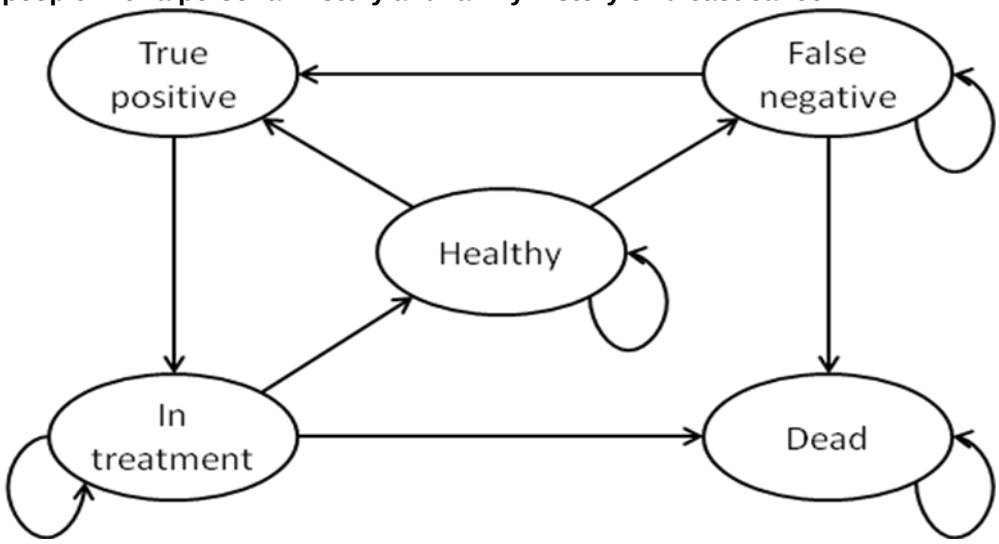


Figure 2.15: Markov chain modelling disease progression for specific surveillance needs of people with a personal history and family history of breast cancer.



A UK NHS perspective has been adopted in the analysis, in line with NICE methodological recommendations. Health outcomes have been expressed in terms of quality-adjusted life years (QALYs). The analysis undertaken was a cost-utility analysis producing cost/QALY results expressed as incremental cost effectiveness ratios (ICERs).

Key model assumptions

- The model assumes false positives are assessed and identified immediately and returned to the healthy population for the subsequent annual cycle.
- False negatives will be identified in primary care after 2 annual cycles.
- Mortality of false negatives within the following cycle is not increased (this differs from the model in CG41, which was decided by the GDG on 05/07/2012).
- High risk patients have a 5-year risk of recurrent breast cancer of 3.4% for a 30 year old (according to Malone et al. 2010).
- BRCA2-positive patients have a 5-year risk of recurrent breast cancer of 15.5% for a 30 year old (according to Malone et al. 2010).
- BRCA1-positive patients have a 5-year risk of recurrent breast cancer of 17.0% for a 30 year old (according to Malone et al. 2010).
- Typical treatment consists of a further MRI and ultrasound following a positive screening result during which false positives would be identified and returned to the negative population. Positives undergo biopsy (of which one in 15 is assumed to be MRI guided). One third of biopsies is assumed to be benign and is returned to the population. Eighty percent of remaining patients receive standard chemotherapy and taxol, whereas 20% receive tamoxifen. Fifty percent of patients undergo wide local excision and the other 50 % undergo mastectomy (weighted for unilateral, bilateral and with/without reconstruction according to NHS reference costs 2011). Patients remain in the treatment group for 1 year before they return to the population.
- An increase of lifetime risk of breast cancer due to radiation during screening occurs at a uniform rate after a latent period of 10 years.
- The model gives no consideration to different cancer types.
- Undiagnosed breast cancer does not decrease utility within the cycle.

Time horizon

A life time horizon was modelled to capture the long term consequences of annual screening for people with a personal history of breast cancer. Since the chosen screening strategy has implications for survival a lifetime horizon is necessary to fully evaluate the differences between strategies, in terms of their likely impact on health-related utility and healthcare costs.

Software

The cost-effectiveness analysis was conducted using a model developed in Microsoft Excel 2007, with coding written in Visual Basic for Applications (VBA).

Cost-effectiveness model: Inputs

The cost-effectiveness model required population with clinical evidence, health related preferences (utilities) and resource use/cost data. High quality evidence was needed for all parameters. Where this was not available, consideration was given to the clinical evidence used in CG41 and the expert opinion of the GDG was used to estimate relevant parameters. All data inputs were verified and validated by the GDG before analysis was undertaken.

Men were not considered separately as a population due to lack of data.

2.6.4 Clinical data

Risk of recurrent breast cancer

The baseline values for risk of developing an episode of recurrent breast cancer in patients with a family and personal history of breast cancer were taken from literature recommended by the GDG (Schaapveld et al., 2008, Malone et al., 2010) and converted from 5-year risk to annual probabilities. The data used in the model is presented in Table 2.22. A range of different risks based on the 95% confidence interval (CI) reported by Malone et al. 2010 were used for the one-way sensitivity analysis.

Table 2.22: Baseline 5-year risk and annual probability of recurrent breast cancer

q	Age group	5-year risk (in %)	Annual probability	Probability distribution	95 % CI of 5-year risk	Source
High risk	30-39	n/a*	0.01600	Log normal	n/a	Schaapveld et al. 2008
	40-49	n/a*	0.01350	Log normal	n/a	Schaapveld et al. 2008
	50-59	n/a*	0.01290	Log normal	n/a	Schaapveld et al. 2008
	60-69	n/a*	0.01200	Log normal	n/a	Schaapveld et al. 2008
BRCA2	30-34	15.5	0.03312	Log normal	7.1 to 33.7	Malone et al. 2010
	35-39	12.0	0.02524	Log normal	5.6 to 26.0	Malone et al. 2010
	40-44	8.9	0.01847	Log normal	4.1 to 19.3	Malone et al. 2010
	45-49	6.5	0.01335	Log normal	2.9 to 14.4	Malone et al. 2010
	50-54	5.3	0.01083	Log normal	2.4 to 11.9	Malone et al. 2010
	55-59	4.5	0.00917	Log normal	n/a	Assumption
	60-69	3.8	0.00772	Log normal	n/a	Assumption
BRCA1	30-34	17.0	0.03658	Log normal	9.5 to 30.5	Malone et al. 2010
	35-39	13.2	0.02792	Log normal	7.4 to 23.5	Malone et al. 2010
	40-44	9.8	0.02042	Log normal	5.5 to 17.4	Malone et al. 2010
	45-49	7.3	0.01505	Log normal	2.7 to 19.7	Malone et al. 2010
	50-54	6.0	0.01230	Log normal	2.2 to 16.3	Malone et al. 2010
	55-59	5.0	0.01021	Log normal	n/a	Assumption
	60-69	4.0	0.00813	Log normal	n/a	Assumption

*Annual probability data extrapolated by GDG based on 5-year risk reported.

Breast cancer risk has been found to be significantly higher in women with a personal history of breast cancer when compared to unaffected women (Houssami et al., 2011, Sardanelli et

al., 2011). Furthermore, BRCA1 and BRCA2 patients are 4.5 and 3.4 times more likely to present with contralateral breast cancer than BRCA-negative high-risk patients and risk increases with decreasing age at first diagnosis (Malone et al., 2010).

Mortality (non-disease specific)

In order to estimate the quantitative benefit of early cancer detection (and thus increased chance of survival), it was necessary to calculate how many additional life years the individual and cohort will accumulate due to decreased mortality associated with screening. For this reason, interim life tables (2008-2010) were obtained from the Office for National Statistics[4]. These allowed the identification of the life expectancy for each age group based on the general population. By applying this non-disease specific life expectancy to each individual remaining at the end of the 10-year screening programme, the effects of the screening methods on quantity of life could be estimated. While non-cancer specific mortality would still occur within the 10 year screening period, it was assumed that this would be near equal in all subgroups and would thus not affect the conclusions.

Mortality (disease specific)

No high-quality published data could be found on the differential prognosis for individuals whose cancer is identified after a certain number of false negative results during screening. It was therefore necessary to adapt the assumptions made during CG41 for these parameters according to the current GDG's expertise and opinion (Table 2.23).

Table 2.23: Assumed 5-year mortality and survival for all mutation subgroups

	5-year mortality (%)			5-year survival (%)		
Identified at which stage?	**High-risk**	**BRCA2**	**BRCA1**	**High-risk**	**BRCA2**	**BRCA1**
First possible opportunity	15	15	20	85	85	80
Second possible opportunity	25	25	30	75	75	70
Third possible opportunity	35	35	40	65	65	60

Tumours of BRCA1-positive patients are often more aggressive than in the other mutation subgroups (high proportion of triple negative breast cancers). For this reason, mortality for this subgroup was assumed to be higher.

Following GDG consensus, no increase of mortality was applied in the false negative state during the cycle following the false result.

[4] Office for National Statistics- http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables)

Radiation risk

CG41 found significant evidence that medical radiation exposure can increase the risk of cancer and it is now commonly accepted that this risk exists. During every mammography, a patient is exposed to a mean of 3.6 mGy (milli-Gray) for each two-view mammography screening (FH01, 2010). The risk of radiation-induced cancer following repeated attendance of regular mammographies is cumulative and may be higher for women with a higher incidence of breast cancer. It is therefore particularly important for younger age groups especially as their breast cancer risk is highest if they have a personal history of breast cancer. The values for the increase in lifetime risk of breast cancer per mGy of radiation have been adopted from CG41 and account for the increased risk for younger women.

Sensitivity/specificity of surveillance methods

The major difference between CG41 and the current model is that digital mammography has since started to replace film-screen mammography in practice and was therefore used for the model population, thus requiring appropriate sensitivity/ specificity values for this technique. Sensitivity and specificity data of all other techniques were updated according to recent literature.

The sensitivity/specificity values are presented in Table 2.24. The evidence suggests a slightly higher sensitivity and similar specificity for digital mammography compared to film-screen mammography (Kerlikowske et al., 2011). However, MRI performance has also improved in recent years and is still higher than mammography (Robertson et al., 2011, Sardanelli et al., 2011). Furthermore, the sensitivity of mammography is lower for people with a history of breast cancer than for people without a personal history (Houssami et al., 2011). All values were checked with the GDG who validated the inputs and agreed that the more recent data should be incorporated into the model as these studies were more relevant to the population (i.e. considered people with a personal history of breast cancer) and values applied to the detection of ipsilateral or contralateral recurrence of breast cancer.

Table 2.24: Sensitivity and specificity of the different annual screening techniques

	No screening	Mammography (digital)	MRI	Combined screening
Sensitivity	0	0.654 (all ages)	0.910	0.932
Specificity	1	0.904	0.915	0.963

It is known that sensitivity (and to a certain but much smaller degree specificity) of mammography depends on the breast density as dense tissue impedes successful identification. Sensitivity therefore increases with age. The model accounts for this by applying different mammography sensitivity values to women of different age groups according to data published by Houssami et al. 2011 (Table 2.25)

Table 2.25: Sensitivity of mammography for different age groups

Age	Sensitivity	Source
30-39	0.51	Assumption
40-49	0.51	Houssami et al. 2011
50-59	0.64	Houssami et al. 2011
60-69	0.72	Houssami et al. 2011

The model assumes that, following two cycles of false negatives, a cancer would be identified in Primary Care, as per CG41 which made the necessary assumption that a cancer would eventually present independent of screening.

2.6.5 Utility data

The model calculates the cost of different screening regimes per quality adjusted life year (QALY) gained. This means that the analysis considers a change in quality of life as well as any additional life years which result from regular surveillance. It was therefore necessary to estimate QALYs of the different methods. However, during the systematic review it became clear that there is a distinct lack of QALY data based on EQ-5D measures in the published literature which made it necessary to adapt the assumptions made for CG41 according to the GDG's expertise.

The baseline utility which describes the quality of life of an individual who is not suffering from breast cancer is assumed to be the same as the average person in the general population. Quality of life is highly variable according to age and as such, an age dependant baseline utility from the Health Survey for England is applied as in CG41. An individual who is diagnosed and treated for breast cancer is expected to experience a lower quality of life. This utility was taken from recent literature (Peasgood et al., 2010). In CG41, the assumption was made that individuals who had undiagnosed breast cancer (false negatives) also experienced quality of life lower than baseline, applying a utility multiplier of 0.9 to the baseline utility in the annual cycle following every false negative. However, the GDG concurred that a person with undiagnosed breast cancer was unlikely to experience any decrement in their quality of life. Consequently, this model applies a utility multiplier of 1 (no change) in the annual cycle following a false negative result. Table 2.26 summarises the utility scores used in the model.

Table: 2.26: Utility values used in the model

	Value	SE	Distribution	Source
Baseline	Per age	n/a	n/a	Health Survey for England
BC in treatment	0.71	0.071	Beta	Peasgood et al. (2010) SE assumed to be 10% of mean
Multiplier applied to false negative	1.00	n/a	n/a	Assumption

All utilities were discounted at a rate of 3.5%.

Resource use and cost data

The analysis was undertaken from an NHS perspective and the costs considered included cost of the different surveillance methods, cost of staging as well as cost of breast cancer treatment and surgery. All unit costs, where available, were taken from the British National Formulary (BNF 63) for medications and drugs, NHS reference costs (2011) for treatments and published literature. Chemotherapy treatment was micro-costed according to GDG advice and expertise.

All costs are expressed in 2011/12 GBP (£) and were discounted at a rate of 3.5%.

Cost of surveillance

The costs of the different screening methods was taken from NHS reference costs (2011) and relevant literature (Tosteson et al., 2008) (Table 2.27).

Table 2.27: Cost of the different screening methods

	Value (£)	Range (£)	Distribution	Source
Mammography	92.96	74.4-111.6	Gamma	Tosteson et al. 2008 (converted to 2011 £)
MRI	216.00	162.0-303.0	Gamma	NHS reference costs 2011
MRI+mammography	308.96	247.2-370.8	Gamma	As above

Cost of staging

After a true or false positive result, all positive individuals receive a further MRI scan and an ultrasound to confirm the screening result. Any false positives are assumed to be identified at this stage and are returned to the healthy population.

True positives will then undergo a biopsy which is assumed to be MRI-guided in one of 15 procedures. One third of the true positives is assumed to be benign and is returned to the healthy population. All relevant costs of this confirmation and staging process are summarised in Table 2.28. Cost of confirmation and biopsy was taken from NHS reference costs 2011 and relevant literature (Griebsch et al., 2006).

Table 2.28: Cost of confirmation and staging

	Value (£)	Range (£)	Distribution	Source
Ultrasound	52.0	46.8-57.2	Gamma	NHS reference costs 2011
Biopsy	332.4	260.0-768.0	Gamma	NHS reference costs 2011
MRI-guided biopsy	1241.5	1117.4-1365.7	Gamma	Griebsch et al. 2006 (converted to 2011 £)

Biopsy costs were weighted according to unilateral/bilateral and level of complications in the general population.

Cost of cancer treatment

True positives with confirmed breast cancer will receive chemotherapy and taxol in the first year of treatment and will then receive tamoxifen for a further two years. Chemotherapy was micro-costed according to GDG advice and weighted for node-positive, triple negative and pre/postmenopausal.

Fifty percent of patients were assumed to undergo wide local excision, whereas the other 50% would have mastectomy. Cost of wide local excision and mastectomy was weighted for unilateral/bilateral and level of complications in the general population.

Table 2.29 summarises the costs of cancer treatment applied in the model.

Table 2.29: Cost of breast cancer treatment

	Value (£)	Range (£)	Distribution	Source
Chemotherapy	4924.0	4431.6-5416.4	Gamma	Micro-costed
Taxol (per year)	116.0	n/a	Gamma	BNF 63
Tamoxifen (per year)	35.4	n/a	Gamma	BNF 63
Wide local excision	1447.8	1237.0-1876.0	Gamma	NHS reference costs 2011
Mastectomy	2811.6	2297.0-3096.0	Gamma	NHS reference costs 2011

2.6.6 Sensitivity analysis

One-way sensitivity analysis

Table 2.30 presents the range of parameter estimates applied to the following comparisons during one-way sensitivity analysis:

- Mammography versus no screening
- MRI versus no screening
- MRI+mammography versus no screening
- MRI versus mammography
- MRI+ versus mammography
-

Table 2.30: Parameter variation during one-way sensitivity analysis

Parameter varied	Low	High	Justification/source
Costs			
MRI	£162	£303	Range of NHS reference costs
Mammography	-20%	+20%	Assumption
Biopsy, wide local excision & mastectomy	£260; £1,237; £2,297	£768; £1,876; £3,096	Unilateral versus bilateral
Utilities			
Baseline	-10%	+10%	Assumption
In treatment	-10%	+10%	Assumption
Undiagnosed breast cancer (multiplier)	0.95		Assumption. (No difference in base case)
Rates			
Mortality of individuals with undiagnosed cancer	0.5% per year		Assumption made in previous guidelines. (No increase in mortality in base case)
Survival of individual diagnosed at 1st opportunity	High risk: 0.75 BRCA 2: 0.75 BRCA 1: 0.70	High risk: 0.95 BRCA 2: 0.95 BRCA 1: 0.90	Assumption
Survival of individual diagnosed at 2nd opportunity	High risk: 0.65 BRCA 2: 0.65 BRCA 1: 0.60	High risk: 0.85 BRCA 2: 0.85 BRCA 1: 0.80	Assumption
Survival of individual diagnosed at 3rd opportunity	High risk: 0.55 BRCA 2: 0.55 BRCA 1: 0.50	High risk: 0.75 BRCA 2: 0.75 BRCA 1: 0.70	Assumption

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted in which parameter values were varied in each of 1000 runs and the results averaged across runs.

Parameters were varied according to the criteria set out in Table 2.31. To summarise, costs were sampled from gamma distributions, utilities from beta distributions and rates and probabilities from log normal or beta distributions. Standard errors of the means were estimated from confidence intervals reported by the source publication. Where no information was reported or the deterministic value was based on an assumption, the standard error of the mean was assumed to be a proportion of the mean e.g. 10 %. In the case of breast cancer incidences, where published values were available for some age groups but not for others, the missing standard errors were assumed to be a similar proportion of the mean to those that could be estimated.

Table 2.31: Variation of parameters during probabilistic sensitivity analysis

Parameter varied	Mean	SE	Assumed distribution	Alpha	Beta	Source of parameters
Costs						
Normal biopsy	332.39	33.24	Gamma	100	3.3239	Assumed 10% of mean
MR guided biopsy	1241.50	124.15	Gamma	100	12.4150	
Wide local excision	1447.83	144.78	Gamma	100	14.4783	
Mastectomy	2811.59	281.16	Gamma	100	28.1159	
First year treatment*	4924.00	492.40	Gamma	100	49.2400	
Taxol ×	116.00	11.60	Gamma	100	1.1600	
Tamoxifen ×	35.40	3.54	Gamma	100	0.3540	
MRI scan	216.00	21.60	Gamma	100	2.1600	
Ultrasound scan	52.00	5.20	Gamma	100	0.5200	
Mammography	92.96	9.30	Gamma	100	0.9296	
* (excludes mastectomy & tamoxifen) × (annual cost)						
Utilities						
In treatment	0.71	0.071	Beta	28.29	11.5551	Assumed 10% of mean
Rates and probabilities						
5-year cumulative incidence of breast cancer						
High risk, age 25-29 years	0.032	-	Log Normal	-3.4420	0.1655	Estimated from 95% CIs reported by Malone et al
High risk, age 30-34 years	0.034	-	Log Normal	-3.3814	0.1579	
High risk, age 35-39 years	0.026	-	Log Normal	-3.6497	0.0875	
High risk, age 40-44 years	0.019	-	Log Normal	-3.9633	0.0926	
High risk, age 45-49 years	0.028	-	Log Normal	-3.5756	0.0449	
High risk, age 50-54 years	0.023	-	Log Normal	-3.7723	0.0545	
High risk, age 55-59 years	0.02	-	Log Normal	-3.9120	0.1174	Assumed to be approximate proportion of mean as those reported
High risk, age 60-69 years	0.015	-	Log Normal	-4.1997	0.1260	
High risk, age >70 years	0.01	-	Log Normal	-4.6052	0.1382	
BRCA 2, age 25-29 years	0.146	-	Log Normal	-1.9241	0.4137	Estimated from 95% CIs

BRCA 2, age 30-34 years	0.155	-	Log Normal	-1.8643	0.3973	reported by Malone et al
BRCA 2, age 35-39 years	0.12	-	Log Normal	-2.1203	0.3917	
BRCA 2, age 40-44 years	0.089	-	Log Normal	-2.4191	0.3952	
BRCA 2, age 45-49 years	0.065	-	Log Normal	-2.7334	0.4088	
BRCA 2, age 50-54 years	0.053	-	Log Normal	-2.9375	0.4084	
BRCA 2, age 55-59 years	0.045	-	Log Normal	-3.1011	0.5582	Assumed to be approximate proportion of mean as those reported
BRCA 2, age 60-69 years	0.038	-	Log Normal	-3.2702	0.5886	
BRCA 2, age >70 years	0.03	-	Log Normal	-3.5066	0.6312	
BRCA 1, age 25-29 years	0.16	-	Log Normal	-1.8326	0.3226	Estimated from 95% CIs reported by Malone et al
BRCA 1, age 30-34 years	0.17	-	Log Normal	-1.7720	0.2976	
BRCA 1, age 35-39 years	0.132	-	Log Normal	-2.0250	0.2948	
BRCA 1, age 40-44 years	0.098	-	Log Normal	-2.3228	0.2938	
BRCA 1, age 45-49 years	0.073	-	Log Normal	-2.6173	0.5070	
BRCA 1, age 50-54 years	0.06	-	Log Normal	-2.8134	0.5109	
BRCA 1, age 55-59 years	0.05	-	Log Normal	-2.9957	0.5093	Assumed to be approximate proportion of mean as those reported
BRCA 1, age 60-69 years	0.04	-	Log Normal	-3.2189	0.5472	
BRCA 1, age >70 years	0.035	-	Log Normal	-3.3524	0.5699	
5-year survival						
High risk, identified at 1st opportunity	0.85	0.085	Beta	14.1500	2.4971	Assumed 10% of mean
High risk, identified at 2nd opportunity	0.75	0.075	Beta	24.2500	8.0833	
High risk, identified at 3rd opportunity	0.65	0.065	Beta	34.3500	18.4962	
BRCA 2, identified at 1st opportunity	0.85	0.085	Beta	14.1500	2.4971	
BRCA 2, identified at 2nd opportunity	0.75	0.075	Beta	24.2500	8.0833	

BRCA 2, identified at 3rd opportunity	0.65	0.065	Beta	34.3500	18.4962	
BRCA 1, identified at 1st opportunity	0.8	0.08	Beta	19.2000	4.8000	
BRCA 1, identified at 2nd opportunity	0.7	0.07	Beta	29.3000	12.5571	
BRCA 1, identified at 3rd opportunity	0.6	0.06	Beta	39.4000	26.2667	
Sensitivity and specificity						
Sensitivity mammography (age 30-39)	0.51	0.0485	Beta	53.7402	51.6327	Estimated from 95% CIs reported by Houssami et al
Sensitivity mammography (age 40-49)	0.51	0.0485	Beta	53.7402	51.6327	
Sensitivity mammography (age 50-59)	0.64	0.0390	Beta	96.1547	54.0870	
Sensitivity mammography (age 60-69)	0.72	0.0398	Beta	90.9328	35.3628	
Specificity mammography	0.904	0.0398	Beta	48.6332	5.1646	
Sensitivity MRI	0.91	0.0469	Beta	32.9169	3.2555	Estimated from 95% CIs reported by Sardanelli et al
Specificity MRI	0.915	0.0222	Beta	143.5607	13.3362	Estimated from range reported by Sardanelli et al
Sensitivity combined approach	0.932	0.0441	Beta	29.3944	2.1447	Estimated from 95% CIs reported by Sardanelli et al
Specificity combined approach	0.963	0.0061	Beta	914.4223	35.1336	

Interpreting results

The results of cost-effectiveness analyses are expressed as incremental cost-effectiveness ratios (ICERs) which are calculated by dividing the cost difference between the two alternatives being compared by the difference in the effect/benefit.

In cost-utility analysis, the effect is expressed in quality-adjusted life years (QALYs) which incorporate quantity of life (additional life years) and quality of life in one measure.

Thus, by dividing the difference in costs by the difference in QALYs, cost per QALY can be calculated for each comparison.

Generally, NICE considers an intervention cost-effective if one of the following applies.

The intervention is less costly and more clinically effective compared with all other relevant alternatives. In this case, no ICER is calculated as the strategy in question dominates the alternatives.

The intervention has an ICER of less than £ 20,000 per QALY compared to the next best alternative. This means that an investment of up to £ 20,000 in order to achieve an additional QALY is considered cost-effective.

During one-way or univariate sensitivity analysis all ICERs are recalculated after changing the value of a single parameter within a reasonable range. This is done for a range of parameters and provides an estimate of the robustness of the ICER to changes in specific parameters. In this way, sensitivity analysis accounts for uncertainty as it will become evident whether changes in parameters will affect the cost-effectiveness of an intervention.
Probabilistic sensitivity analysis changes the values of all chosen parameters at once (usually within the 95% confidence interval or one standard error) and calculates how probable it is that the intervention is cost-effective if all uncertainty associated with the individual parameters is considered.

2.6.7 Results:

Age group 30 to 39 years

Base case analysis

Table 2.32 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 2.32: Base case results for the age group 30 to 39 years

	High risk		BRCA 2		BRCA 1	
	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	Total costs
No screening	19766.35	£2,050,154	19363.11	£2,536,313	19009.83	£2,758,506
Mammography	19916.30	£3,111,010	19625.31	£3,627,730	19290.18	£3,871,473
MRI	19998.21	£4,146,673	19767.93	£4,664,445	19442.86	£4,927,887
MRI+	20000.00	£4,823,684	19772.27	£5,342,108	19447.45	£5,570,690

Table 2.33 presents the full range of ICERs calculated for various screening strategies in individuals aged 30-39 years.

Table 2.33: ICERs for comparison of different screening strategies (30-39 years)

High risk	vs. No screening		ICER
Mammography	£7,075	vs. Mammography	
MRI	£9,042	£12,643	vs. MRI
MRI+	£11,871	£20,461	£379,167
BRCA 2	vs. No screening		
Mammography	£4,162	vs. Mammography	
MRI	£5,257	£7,269	vs. MRI
MRI+	£6,857	£11,666	£156,014
BRCA 1	vs. No screening		
Mammography	£3,970	vs. Mammography	
MRI	£5,010	£6,919	vs. MRI
MRI+	£6,426	£10,804	£140,171

The results suggest that all screening strategies are expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. Furthermore MRI is expected to be cost effective compared to mammography at this threshold, providing the highest net monetary benefit (NMB*) at £20,000. Combination MRI plus mammography is not expected to be cost effective compared to MRI or mammography alone at the £20,000 threshold (Figure F3). There is little difference in the total QALYs associated with combination MRI+mammography compared to MRI alone and with a slightly negative difference in QALYs, MRI+mammography is not expected to be cost-effective compared to MRI in any population.

Screening strategies have a much higher potential impact on quality of life for BRCA 1 and BRCA 2 carriers (Figure F4). For BRCA 1 and BRCA 2 carriers, all screening strategies are expected to be cost-effective compared to no screening at a £20,000/QALY threshold. Furthermore, MRI and combination MRI+mammography are expected to be cost-effective compared to mammography at £20,000/QALY.

Tables 2.34 and 2.35 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 2.34: Incremental cost for all comparisons (30-39 years)

High risk	vs. No screening		Δ Cost
Mammography	£1,061	vs. Mammography	
MRI	£2,097	£1,036	vs. MRI
MRI+	£2,774	£1,713	£677
BRCA 2	vs. No screening		
Mammography	£1,091	vs. Mammography	
MRI	£2,128	£1,037	vs. MRI
MRI+	£2,806	£1,714	£678
BRCA 1	vs. No screening		
Mammography	£1,113	vs. Mammography	
MRI	£2,169	£1,056	vs. MRI
MRI+	£2,812	£1,699	£643

Table 2.35: Incremental QALYs for all comparisons (30-39 years)

High risk	vs. No screening		Δ QALY
Mammography	0.150	vs. Mammography	
MRI	0.232	0.082	vs. MRI
MRI+	0.234	0.084	0.002
BRCA 2	vs. No screening		
Mammography	0.262	vs. Mammography	
MRI	0.405	0.143	vs. MRI
MRI+	0.409	0.147	0.004
BRCA 1	vs. No screening		
Mammography	0.280	vs. Mammography	
MRI	0.433	0.153	vs. MRI
MRI+	0.438	0.157	0.005

One-way sensitivity analysis

Tables 2.36 to 2.37 present the results of the one-way sensitivity analyses for all 3 risk groups for individuals aged 30 t0 39 years.

Table2.36: Results of the one-way sensitivity analysis for the high-risk group (30-39 years)

HIGH RISK Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£6789 - 7535	£6830 - 12445	£9866 - 15101	£7187 - 21432	£15376 - 28653
Mammography	£6037 - 8113	£9042 - 9042	£11206 - 12535	£14543 - 10743	£20465 - 20457
Biopsy, wide local excision & mastectomy	£7046 - 7127	£9015 - 9090	£11842 - 11921	£12619 - 12684	£20434 - 20510
Utilities					
Baseline	£7704 - 6541	£9857 - 8352	£12931 - 10971	£13809 - 11658	£22305 - 18899
In breast cancer treatment	£6948 - 7704	£8888 - 9857	£11661 - 12931	£12449 - 13809	£20113 - 22305
Undiagnosed breast cancer (multiplier)	£6768	£8651	£11356	£12097	£19574
Rates					
Mortality of individuals with undiagnosed cancer	£6641	£8473	£11109	£11823	£19096
Survival of individual diagnosed at 1st opportunity	£14374 - 4791	£22124 - 5811	£29811 - 7573	£49463 - 7432	£88738 - 11839
Survival of individual diagnosed at 2nd opportunity	£9194 - 5815	£9510 - 8641	£12338 - 11460	£9854 – 17306	£15629 - 28975
Survival of individual diagnosed at 3rd opportunity	£4145 - 22989	£5597 - 22548	£7351 - 29391	£8758 - 22115	£14213 - 35463
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Table 2.37: Results of the one-way sensitivity analysis for the BRCA2 group (30-39 years)

BRCA 2 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£4005 - 4417	£4087 - 7142	£5741 - 8657	£4239 - 12152	£8838 - 16221
Mammography	£3588 - 4737	£5257 - 5257	£6488 - 7227	£8326 - 6213	£11661 - 11670
Biopsy, wide local excision & mastectomy	£4131 - 4219	£5226 - 5311	£6826 - 6913	£7241 - 7320	£11635 - 11720
Utilities					
Baseline	£4527 - 3853	£5720 - 4863	£7459 - 6346	£7919 - 6748	£12693 - 10792
In breast cancer treatment	£4247 - 4082	£5359 - 5159	£6993 - 6727	£7402 - 7141	£11892 - 11448
Undiagnosed breast cancer (multiplier)	£3979	£5025	£6555	£6949	£11150
Rates					
Mortality of individuals with undiagnosed cancer	£3918	£4936	£6427	£6804	£10891
Survival of individual diagnosed at 1st opportunity	£8599 - 2815	£13338 - 3364	£17838 - 4353	£31893 - 4321	£56118 - 6685
Survival of individual diagnosed at 2nd opportunity	£5466 - 3414	£5562 - 5038	£7137 - 6613	£5666 - 10145	£8846 - 16701
Survival of individual diagnosed at 3rd opportunity	£2437 - 14047	£3247 - 13433	£4237 - 17359	£5023 - 12847	£8084 - 20383
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Table 2.38: Results of the one-way sensitivity analysis for the BRCA1 group (30-39 years)

BRCA 1 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£3824 - 4207	£3908 - 6785	£5391 - 8095	£4063 - 11521	£8183 - 15027
Mammography	£3428 - 4512	£5010 - 5010	£6083 - 6769	£7913 - 5926	£10816 - 10796
Biopsy, wide local excision & mastectomy	£3936 - 4030	£4977 - 5068	£6393 - 6485	£6888 - 6973	£10772 - 10863
Utilities					
Baseline	£4312 - 3678	£5445 - 4639	£6982 - 5953	£7528- 6401	£11742 - 10005
In breast cancer treatment	£4054 - 3890	£5113 - 4911	£6560 - 6297	£7054 - 6789	£11026 - 10591
Undiagnosed breast cancer (multiplier)	£3792	£4785	£6137	£6609	£10318
Rates					
Mortality of individuals with undiagnosed cancer	£3748	£4717	£6039	£6493	£10111
Survival of individual diagnosed at 1st opportunity	£8547 - 2658	£13526 - 3168	£17823 - 4033	£35125 - 3968	£61308 - 6106
Survival of individual diagnosed at 2nd opportunity	£3161 - 3225	£3263 - 4771	£4137 - 6189	£3376 - 9741	£5169 - 15760
Survival of individual diagnosed at 3rd opportunity	£2290 - 14871	£3050 - 13669	£3912 - 17363	£4723 - 12607	£7393 - 19469
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Probabilistic sensitivity analysis

Table 2.39 to 2.41 present the mean incremental costs, QALYs and cost-effectiveness ratio (ICER) estimated over a lifetime per person under each screening strategy, calculated over 1,000 PSA runs. The 95% confidence intervals for incremental costs and QALYs are also presented. High risk group values for incremental cost and QALYs are presented for the entire cohort whereas BRCA1 and BRCA2 results apply to every single individual in the model.

Table 2.39: Results of the probabilistic sensitivity analysis for the high-risk group (30-39 years)

ICER	vs. No screening		High risk
Mammography	£7,122	vs. Mammography	
MRI	£9,084	£12,684	vs. MRI
MRI+	£11,931	£20,566	£388,302
Δ Cost	vs. No screening		
	£1,063,169		
Mammography	(£1051777, £1074562)	vs Mammography	
	£2,095,317	£1,032,147	
MRI	(£2081467, £2109166)	(£1016746, £1047549)	vs MRI
	£2,772,645	£1,709,475	£677,328
MRI+	(£2758411, £2786879)	(£1693727, £1725224)	(£659720, £694936)
Δ QALY	vs. No screening		
	149.28		
Mammography	(137, 162)	vs Mammography	
	230.65	81.38	
MRI	(217, 244)	(70, 93)	vs MRI
	232.40	83.12	1.74
MRI+	(219, 246)	(72, 95)	(-10, 14)

Table 2.40: Results of the probabilistic sensitivity analysis for the BRCA2 group (30-39 years)

ICER	vs. No screening		BRCA2
Mammography	£3,938	vs. Mammography	
MRI	£4,969	£6,889	vs. MRI
MRI+	£6,443	£10,975	£144,203
Δ Cost	vs. No screening		
	£1,112		
Mammography	(£1070, £1154)	vs. Mammography	
	£2,156	£1,044	
MRI	(£2112, £2200)	(£998, £1090)	vs. MRI
	£2,826	£1,714	£670
MRI+	(£2783, £2869)	(£1669, £1759)	(£623, £717)
Δ QALY	vs. No screening		
	0.282		
Mammography	(0.254, 0.311)	vs. Mammography	
	0.434	0.152	
MRI	(0.405, 0.463)	(0.127, 0.176)	vs. MRI
	0.439	0.156	0.005
MRI+	(0.409, 0.468)	(0.131, 0.181)	(-0.021, 0.030)

Table 2.41: Results of the probabilistic sensitivity analysis for the BRCA1 group (30-39 years)

ICER	vs. No screening		BRCA1
Mammography	£3,812	vs. Mammography	
MRI	£4,783	£6,561	vs. MRI
MRI+	£6,135	£10,265	£130,630
Δ Cost	vs. No screening		
Mammography	£1,124 (£1090, £1158)	vs. Mammography	
MRI	£2,179 (£2143, £2215)	£1,055 (£1017, £1093)	vs. MRI
MRI+	£2,826 (£2790, £2861)	£1,702 (£1665, £1739)	£646 (£608, £685)
Δ QALY	vs. No screening		
Mammography	0.295 (0.266, 0.323)	vs. Mammography	
MRI	0.456 (0.427, 0.485)	0.161 (0.135, 0.187)	vs. MRI
MRI+	0.461 (0.431, 0.490)	0.166 (0.140, 0.192)	0.005 (-0.021, 0.031)

Table 2.42 presents the screening strategy that is the most cost-effective (highest net monetary benefit (NMB) and the probability of each strategy being cost-effective at thresholds of £20,000 and £30,000. At a cost-effectiveness threshold of £20,000, MRI is expected to be the most-cost effective screening strategy in all risk groups considered within the analysis, with a high probability of cost-effectiveness (High risk: 0.711, BRCA2: 0.798, BRCA1: 0.829).

Table 2.42: Results of the probabilistic sensitivity analysis (age 30-39 years)

High risk	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.148	0.118
Mammography	0.141	0.094
MRI	0.711	0.788
MRI+	0	0
Highest NMB:	MRI	MRI
BRCA 2	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.094	0.083
Mammography	0.106	0.085
MRI	0.798	0.818
MRI+	0.002	0.014
Highest NMB:	MRI	MRI
BRCA 1	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.084	0.071
Mammography	0.086	0.076
MRI	0.829	0.838
MRI+	0.001	0.015
Highest NMB:	MRI	MRI

Age group 40 to 49 years

Base case analysis

Table 2.43 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 2.43: Base case results for the age group 40 to 49 years

	High risk		BRCA 2		BRCA 1	
	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	Total costs
No screening	17958.23	£1,771,033	17975.12	£1,560,443	17787.72	£1,716,315
Mammography	18070.10	£2,823,582	18110.24	£2,609,404	17935.24	£2,776,125
MRI	18131.14	£3,856,560	18183.37	£3,634,600	18015.18	£3,811,963
MRI+	18132.45	£4,536,122	18185.13	£4,319,839	18017.06	£4,476,184

Table 2.44 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 2.44: ICERs for comparison of different screening strategies (40-49 years)

High risk	vs. No screening		ICER
Mammography	£9,409	vs. Mammography	
MRI	£12,062	£16,925	vs. MRI
MRI+	£15,871	£27,468	£516,670
BRCA 2	vs. No screening		
Mammography	£7,763	vs. Mammography	
MRI	£9,960	£14,020	vs. MRI
MRI+	£13,140	£22,841	£389,187
BRCA 1	vs. No screening		
Mammography	£7,184	vs. Mammography	
MRI	£9,213	£12,959	vs. MRI
MRI+	£12,034	£20,780	£353,033

The results suggest that all screening strategies are expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. Furthermore MRI is expected to be cost effective compared to mammography at this threshold, providing the highest net monetary benefit (NMB) at £20,000. Combination MRI plus mammography is not expected to be cost effective compared to either MRI or mammography alone at £20,000 per QALY gained. There is some uncertainty around this conclusion due to possible variance in the parameter values chosen, however MRI was found to provide the highest NMB over 60% of 1,000 runs.

Tables 2.45 and 2.46 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 2.45: Incremental cost for all comparisons (40-49 years)

High risk	vs. No screening		Δ Cost
Mammography	£1,053	vs. Mammography	
MRI	£2,086	£1,033	vs. MRI
MRI+	£2,765	£1,713	£680
BRCA 2	vs. No screening		
Mammography	£1,049	vs. Mammography	
MRI	£2,074	£1,025	vs. MRI
MRI+	£2,759	£1,710	£685
BRCA 1	vs. No screening		
Mammography	£1,060	vs. Mammography	
MRI	£2,096	£1,036	vs. MRI
MRI+	£2,760	£1,700	£664

Table 2.46: Incremental QALYs for all comparisons (40-49 years)

High risk	vs. No screening		Δ QALY
Mammography	0.112	vs. Mammography	
MRI	0.173	0.061	vs. MRI
MRI+	0.174	0.062	0.001
BRCA 2	vs. No screening		
Mammography	0.135	vs. Mammography	
MRI	0.208	0.073	vs. MRI
MRI+	0.210	0.075	0.002
BRCA 1	vs. No screening		
Mammography	0.148	vs. Mammography	
MRI	0.227	0.080	vs. MRI
MRI+	0.229	0.082	0.002

One-way sensitivity analysis

Tables 2.47to 2.49 present the results of the one-way sensitivity analyses for all 3 risk groups for individuals aged 40 t0 49 years.

1 **Table 2.47: Results of the one-way sensitivity analysis for the high-risk group (40-49 years)**

HIGH RISK Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£9023 - 10029	£9217 - 16646	£13171 - 20222	£9571 - 28773	£20613 - 38513
Mammography	£8011 - 10806	£12062 - 12062	£14976 - 16767	£19487 - 14364	£27472 - 27464
Biopsy, wide local excision & mastectomy	£9376 - 9465	£12033 - 12114	£15840 - 15927	£16901 - 16968	£27439 - 27520
Utilities					
Baseline	£10224 - 8714	£13126 - 11158	£17226 - 14693	£18466 - 15622	£29891 - 25408
In breast cancer treatment	£9222 - 10224	£11837 - 13126	£15564 - 17256	£16649 - 18466	£26958 - 29891
Undiagnosed breast cancer (multiplier)	£8961	£11489	£15116	£16122	£26162
Rates					
Mortality of individuals with undiagnosed cancer	£8811	£11279	£14825	£15798	£25592
Survival of individual diagnosed at 1st opportunity	£19325 - 6342	£29915 - 7718	£40410 - 10083	£67804 - 9906	£122387 - 15830
Survival of individual diagnosed at 2nd opportunity	£12259 - 7719	£12691 - 11522	£16501 - 15319	£13161 - 23245	£20934 - 39034
Survival of individual diagnosed at 3rd opportunity	£5479 - 30866	£7430 - 30270	£9785 - 39527	£11657 - 29689	£19029 - 47710
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

2

1 **Table 2.48: Results of the one-way sensitivity analysis for the BRCA2 group (40-49 years)**

BRCA 2 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£7447 - 8272	£7623 - 13726	£10913 - 16728	£7948 - 23803	£17165 - 31986
Mammography	£6618 - 8908	£9960 - 9960	£12401 - 13879	£16135 - 11905	£22835 - 22847
Biopsy, wide local excision & mastectomy	£7734 - 7816	£9933 - 10009	£13111 - 13191	£13997 - 14061	£22814 - 22890
Utilities					
Baseline	£8447 - 7182	£10850 - 9205	£14303 - 12152	£15307 - 12933	£24882 - 21110
In breast cancer treatment	£7914 - 7618	£10143 - 9784	£13390 - 12899	£14247 - 13800	£23259 - 22438
Undiagnosed breast cancer (multiplier)	£7395	£9489	£12517	£13357	£21759
Rates					
Mortality of individuals with undiagnosed cancer	£7274	£9317	£12276	£13087	£21280
Survival of individual diagnosed at 1st opportunity	£15879 - 5239	£24685 - 6375	£33395 - 8352	£57199 - 8188	£103092 - 13143
Survival of individual diagnosed at 2nd opportunity	£10163 - 6363	£10515 - 9532	£13669 - 12676	£10897 - 19471	£17326 - 32667
Survival of individual diagnosed at 3rd opportunity	£4502 - 25682	£6113 - 25137	£8076 - 32870	£9664 - 24604	£15806 - 39463
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

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Table 2.49: Results of the one-way sensitivity analysis for the BRCA1 group (40-49 years)

BRCA 1 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£6896 - 7348	£7064 - 12676	£10004 - 15301	£7375 - 21956	£15609 - 29110
Mammography	£6131 - 8237	£9213 - 9213	£11361 - 12707	£14903 - 11015	£20792 - 2093767
Biopsy, wide local excision & mastectomy	£7153 - 7238	£9184 - 9264	£12004 - 12087	£12934 - 13003	£20751 - 20831
Utilities					
Baseline	£7811 - 6650	£10030 - 8521	£13089 - 11137	£14133 - 11965	£22616 - 19219
In breast cancer treatment	£7329 - 7045	£9390 - 9044	£12272 - 11805	£13182 - 12743	£21177 - 20396
Undiagnosed breast cancer (multiplier)	£6840	£8773	£11458	£12341	£19784
Rates					
Mortality of individuals with undiagnosed cancer	£6751	£8643	£11273	£12129	£19409
Survival of individual diagnosed at 1st opportunity	£15233 - 4803	£24057 - 5833	£32291 - 7568	£59178 - 7471	£106868 - 11806
Survival of individual diagnosed at 2nd opportunity	£5720 - 5843	£6017 - 8780	£7762 - 11596	£6353 - 18158	£9967 - 30184
Survival of individual diagnosed at 3rd opportunity	£4102 - 26007	£5573 - 24628	£7286 - 31887	£8828 - 23366	£14201 - 37084
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Probabilistic sensitivity analysis

Tables 2.50 to 2.52 present the mean incremental costs, QALYs and cost-effectiveness ratio (ICER) estimated over a lifetime per person under each screening strategy, calculated over 1,000 PSA runs. The 95% confidence intervals for incremental costs and QALYs are also presented. High risk group values for incremental cost and QALYs are presented for the entire cohort whereas BRCA1 and BRCA2 results apply to every single individual in the model.

Table 2.50: Results of the probabilistic sensitivity analysis for high-risk group (40-49 years)

ICER	vs. No screening		High risk
Mammography	£9,467	vs Mammography	
MRI	£12,114	£16,979	vs MRI
MRI+	£15,946	£27,609	£530,510
Δ Cost	vs. No screening		
Mammography	£1,054,910 (£1044540, £1065279)	vs Mammography	
MRI	£2,084,378 (£2071365, £2097391)	£1,029,468 (£1014831, £1044105)	vs MRI
MRI+	£2,764,268 (£2750843, £2777692)	£1,709,358 (£1694354, £1724363)	£679,890 (£662951, £696829)
Δ QALY	vs. No screening		
Mammography	111.44 (102, 121)	vs Mammography	
MRI	172.07 (162, 182)	60.63 (52, 69)	vs MRI
MRI+	173.35 (164, 183)	61.91 (53, 70)	1.28 (-8, 10)

Table 2.51: Results of the probabilistic sensitivity analysis for BRCA2 group (40-49 years)

ICER	vs. No screening		BRCA 2
Mammography	£7,339	vs. Mammography	
MRI	£9,411	£13,283	vs. MRI
MRI+	£12,401	£21,628	£358,019
Δ Cost	vs. No screening		
Mammography	£1,056 (£1029, £1084)	vs. Mammography	
MRI	£2,080 (£2050, £2110)	£1,024 (£993, £1055)	vs. MRI
MRI+	£2,765 (£2735, £2794)	£1,708 (£1678, £1739)	£685 (£652, £717)
Δ QALY	vs. No screening		
Mammography	0.144 (0.129, 0.159)	vs. Mammography	
MRI	0.221 (0.206, 0.236)	0.077 (0.064, 0.090)	vs. MRI
MRI+	0.223 (0.208, 0.238)	0.079 (0.066, 0.092)	0.002 (-0.012, 0.016)

Table 2.52: Results of the probabilistic sensitivity analysis for BRCA1 group (40-49 years)

ICER	vs. No screening		BRCA1
Mammography	£6,583	vs. Mammography	
MRI	£8,401	£11,753	vs. MRI
MRI+	£10,948	£18,797	£296,344
Δ Cost	vs. No screening		
Mammography	£1,070 (£1042, £1098)	vs. Mammography	
MRI	£2,106 (£2076, £2135)	£1,036 (£1005, £1067)	vs. MRI
MRI+	£2,768 (£2739, £2798)	£1,698 (£1668, £1729)	£663 (£631, £695)
Δ QALY	vs. No screening		
Mammography	0.163 (0.145, 0.180)	vs. Mammography	
MRI	0.251 (0.233, 0.268)	0.088 (0.073, 0.103)	vs. MRI
MRI+	0.253 (0.235, 0.270)	0.090 (0.075, 0.106)	0.002 (-0.013, 0.018)

Table 2.53 presents the screening strategy that is the most cost-effective (highest net monetary benefit (NMB) and the probability of each strategy being cost-effective at thresholds of £20,000 and £30,000. At a cost-effectiveness threshold of £20,000, MRI is expected to be the most-cost effective screening strategy in all risk groups considered within the analysis, with a high probability of cost-effectiveness (High risk: 0.599, BRCA2: 0.656, BRCA1: 0.713).

Table 2.54: Results of the probabilistic sensitivity analysis (age 40-49 years)

High risk	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.185	0.138
Mammography	0.216	0.127
MRI	0.599	0.735
MRI+	0	0
Highest NMB:	MRI	MRI
BRCA 2	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.148	0.107
Mammography	0.196	0.124
MRI	0.656	0.768
MRI+	0	0.001
Highest NMB:	MRI	MRI
BRCA 1	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.128	0.093
Mammography	0.159	0.104
MRI	0.713	0.803
MRI+	0	0
Highest NMB:	MRI	MRI

Age group 50 to 59 years

Base case analysis

Table 2.55 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 2.55: Base case results for the age group 50 to 59 years

	High risk		BRCA 2		BRCA 1	
	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	Total costs
No screening	15671.62	£1,547,168	15815.56	£1,038,364	15719.15	£1,147,246
Mammography	15775.89	£2,606,070	15899.33	£2,081,643	15812.24	£2,198,142
MRI	15805.87	£3,627,845	15923.51	£3,099,128	15839.10	£3,221,268
MRI+	15807.05	£4,307,940	15924.25	£3,788,335	15839.90	£3,895,894

Table 2.56 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 2.56: ICERs for comparison of different screening strategies (50-59 years)

High risk	vs. No screening		ICER
Mammography	£10,155	vs. Mammography	
MRI	£15,498	£34,082	vs. MRI
MRI+	£20,384	£54,612	£574,640
BRCA 2	vs. No screening		
Mammography	£12,453	vs. Mammography	
MRI	£19,090	£42,090	vs. MRI
MRI+	£25,300	£68,489	£925,448
BRCA 1	vs. No screening		
Mammography	£11,290	vs. Mammography	
MRI	£17,292	£38,089	vs. MRI
MRI+	£22,763	£61,363	£836,821

The results suggest that mammography and MRI are expected to be cost-effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. However, MRI is not expected to be cost-effective compared to mammography. Combination MRI plus mammography is not expected to be cost-effective compared to any other screening strategy at a threshold of £20,000 per QALY gained. While the PSA results suggest that uncertainty surrounding the parameter values chosen could affect the conclusion regarding the most cost-effective strategy, mammography provided the highest NMB in almost 60% of 1,000 PSA runs, with a further 20% provided by MRI.

Tables 2.57 and 2.58 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 2.57: Incremental cost for all comparisons (50-59 years)

High risk	vs. No screening		Δ Cost
Mammography	£1,059	vs. Mammography	
MRI	£2,081	£1,022	vs. MRI
MRI+	£2,761	£1,702	£680
BRCA 2	vs. No screening		
Mammography	£1,049	vs. Mammography	
MRI	£2,074	£1,025	vs. MRI
MRI+	£2,759	£1,710	£685
BRCA 1	vs. No screening		
Mammography	£1,051	vs. Mammography	
MRI	£2,074	£1,023	vs. MRI
MRI+	£2,749	£1,698	£675

Table 2.58: Incremental QALYs for all comparisons (50-59 years)

High risk	vs. No screening		Δ QALY
Mammography	0.104	vs. Mammography	
MRI	0.134	0.030	vs. MRI
MRI+	0.135	0.031	0.001
BRCA 2	vs. No screening		
Mammography	0.084	vs. Mammography	
MRI	0.108	0.024	vs. MRI
MRI+	0.109	0.025	0.001
BRCA 1	vs. No screening		
Mammography	0.093	vs. Mammography	
MRI	0.120	0.027	vs. MRI
MRI+	0.121	0.028	0.001

One-way sensitivity analysis

Tables 2.59 to 2.61 present the results of the one-way sensitivity analyses for all 3 risk groups for individuals aged 50 to 59 years.

1 **Table 2.59: Results of the one-way sensitivity analysis for the high-risk group (50-59 years)**

HIGH RISK Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£9740 - 10824	£11830 - 21408	£16907 - 25987	£19101 - 58218	£40888 - 76722
Mammography	£8655 - 11655	£15498 - 15498	£19231 - 21538	£39299 - 28866	£54617 - 54607
Biopsy, wide local excision & mastectomy	£10118 - 10221	£15464 - 15559	£20348 - 20449	£34058 - 34126	£54577 - 54673
Utilities					
Baseline	£10991 - 16798	£16798 - 14385	£22070 - 18938	£37125 - 31501	£59198 - 50685
In breast cancer treatment	£9918 - 10991	£15155 - 16798	£19914 - 22070	£33478 - 37125	£53408 - 59198
Undiagnosed breast cancer (multiplier)	£9594	£14641	£19258	£32193	£51596
Rates					
Mortality of individuals with undiagnosed cancer	£9478	£14436	£18967	£31652	£50638
Survival of individual diagnosed at 1st opportunity	£22950 - 6659	£40670 - 9780	£54924 - 12780	£201927 - 19055	£404,617 – 29,967
Survival of individual diagnosed at 2nd opportunity	£12457 - 8639	£16336 - 14782	£21220 - 19652	£24077 - 56284	£37645 - 95375
Survival of individual diagnosed at 3rd opportunity	£5932 - 32318	£9421 - 40553	£12410 - 52831	£24343 - 55000	£39236 - 86978
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

2

1 **Table 2.60: Results of the one-way sensitivity analysis for the BRCA2 group (50-59 years)**

BRCA 2 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£11934 - 13290	£14521 - 26450	£20947 - 323121	£23489 - 72058	£51250 - 96264
Mammography	£10584 - 14322	£19090 - 19090	£23855 - 26744	£48567 - 35612	£68473 - 68506
Biopsy, wide local excision & mastectomy	£12420 - 12512	£19060 - 19142	£25267 - 25357	£42073 - 42118	£68460 - 68542
Utilities					
Baseline	£13508 - 11551	£20745 - 17679	£27454 - 23459	£46033 - 38768	£74433 - 63425
In breast cancer treatment	£12732 - 12186	£19484 - 18711	£25856 - 24767	£42702 - 42495	£69898 - 67137
Undiagnosed breast cancer (multiplier)	£11770	£18041	£23911	£39767	£64731
Rates					
Mortality of individuals with undiagnosed cancer	£11610	£17768	£23528	£39088	£63498
Survival of individual diagnosed at 1st opportunity	£27886 - 8172	£49308 - 12076	£67240 - 15893	£231849 - 23679	£485312 - 37684
Survival of individual diagnosed at 2nd opportunity	£15297 - 10611	£20152 - 18237	£26338 - 24391	£29829 - 69445	£47125 - 119816
Survival of individual diagnosed at 3rd opportunity	£7240 - 39572	£11571 - 49796	£15361 - 65441	£30063 – 67678	£49196 - 108790
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

2

Table 2.61: Results of the one-way sensitivity analysis for the BRCA1 group (50-59 years)

BRCA 1 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£10824 - 12040	£13168 - 23935	£18858 - 29055	£21289 - 65156	£45887 - 86297
Mammography	£9602 - 12978	£17292 - 17292	£21467 - 24059	£43938 - 32241	£61386 - 61340
Biopsy, wide local excision & mastectomy	£11256 - 11350	£17261 - 17346	£22730 - 22822	£38071 - 38123	£61332 - 61417
Utilities					
Baseline	£12239 - 10477	£18776 - 16024	£24687 - 21118	£41598 - 35126	£666637 - 56863
In breast cancer treatment	£11549 - 11042	£17661 - 16937	£23277 - 22271	£38695 - 37502	£62670 - 60109
Undiagnosed breast cancer (multiplier)	£10665	£16334	£21503	£35980	£57966
Rates					
Mortality of individuals with undiagnosed cancer	£10556	£16139	£21224	£35466	£57027
Survival of individual diagnosed at 1st opportunity	£26394 - 7334	£47244 - 10815	£64163 - 14140	£249339 - 21127	£555910 - 33285
Survival of individual diagnosed at 2nd opportunity	£8366 - 9558	£11171 - 16464	£14507 - 21917	£17035 - 64178	£26543 - 110440
Survival of individual diagnosed at 3rd opportunity	£6452 - 39158	£10313 - 48033	£13595 - 62712	£26908 - 62543	£43554 - 99695
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Probabilistic sensitivity analysis

Tables 2.62 to 2.64 present the mean incremental costs, QALYs and cost-effectiveness ratio (ICER) estimated over a lifetime per person under each screening strategy, calculated over 1,000 PSA runs. The 95% confidence intervals for incremental costs and QALYs are also presented. High risk group values for incremental cost and QALYs are presented for the entire cohort whereas BRCA1 and BRCA2 results apply to every single individual in the model.

Table 2.62: Results of the probabilistic sensitivity analysis for high-risk group (50-59 years)

ICER	vs. No screening		High risk
Mammography	£10,216	vs Mammography	
MRI	£15,561	£34,213	vs MRI
MRI+	£20,475	£54,940	£588,654
Δ Cost	vs. No screening		
Mammography	1061273.93 (£1051661, £1070887)	vs Mammography	
MRI	2079553.14 (£2067161, £2091946)	1018279.22 (£1004194, £1032364)	vs MRI
MRI+	2759979.69 (£2747154, £2772806)	1698705.76 (£1684238, £1713173)	680426.55 (£663981, £696873)
Δ QALY	vs. No screening		
Mammography	103.88 (97, 111)	vs Mammography	
MRI	133.64 (126, 141)	29.76 (23, 36)	vs MRI
MRI+	134.80 (128, 142)	30.92 (24, 37)	1.16 (-6, 8)

Table 2.63: Results of the probabilistic sensitivity analysis for BRCA2 group (50-59 years)

ICER	vs. No screening		BRCA 2
Mammography	£11,591	vs. Mammography	
MRI	£17,771	£39,702	vs. MRI
MRI+	£23,571	£64,752	£842,193
Δ Cost	vs. No screening		
Mammography	£1,049 (£1023, £1075)	vs. Mammography	
MRI	£2,061 (£2033, £2089)	£1,012 (£984, £1041)	vs. MRI
MRI+	£2,753 (£2726, £2780)	£1,704 (£1676, £1733)	£692 (£662, £722)
Δ QALY	vs. No screening		
Mammography	0.090 (0.080, 0.101)	vs. Mammography	
MRI	0.116 (0.106, 0.126)	0.026 (0.016, 0.035)	vs. MRI
MRI+	0.117 (0.107, 0.127)	0.026 (0.017, 0.035)	0.001 (-0.008, 0.010)

Table 2.64: Results of the probabilistic sensitivity analysis for BRCA1 group (50-59 years)

ICER	vs. No screening		BRCA1
Mammography	£9,639	vs. Mammography	
MRI	£14,681	£32,171	vs. MRI
MRI+	£19,246	£51,416	£588,318
Δ Cost	vs. No screening		
	£1,062		
Mammography	(£1033, £1090)	vs. Mammography	
	£2,083	£1,021	
MRI	(£2054, £2112)	(£991, £1052)	vs. MRI
	£2,753	£1,691	£670
MRI+	(£2724, £2781)	(£1661, £172)	(£638, £701)
Δ QALY	vs. No screening		
	0.110		
Mammography	(0.098, 0.122)	vs. Mammography	
	0.142	0.032	
MRI	(0.130, 0.154)	(0.021, 0.042)	vs. MRI
	0.143	0.033	0.001
MRI+	(0.131, 0.155)	(0.022, 0.043)	(-0.009, 0.012)

Table 2.65 presents the screening strategy that is the most cost-effective (highest net monetary benefit (NMB) and the probability of each strategy being cost-effective at thresholds of £20,000 and £30,000. At a cost-effectiveness threshold of £20,000, mammography is expected to be the most-cost effective screening strategy in all risk groups considered within the analysis, with a high probability of cost-effectiveness (High risk: 0.577, BRCA2: 0.584, BRCA1: 0.536).

Table 2.65: Results of the probabilistic sensitivity analysis (age 50-59 years)

High risk	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.217	0.154
Mammography	0.577	0.382
MRI	0.206	0.464
MRI+	0	0
Highest NMB:	Mammography	MRI
BRCA 2	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.283	0.181
Mammography	0.584	0.49
MRI	0.133	0.329
MRI+	0	0
Highest NMB:	Mammography	Mammography
BRCA 1	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.245	0.15
Mammography	0.536	0.411
MRI	0.219	0.439
MRI+	0	0
Highest NMB:	Mammography	Mammography

Age group 60 to 69 years

Base case analysis

Table 2.66 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 2.66: Base case results for the age group 60 to 69 years

	High risk		BRCA 2		BRCA 1	
	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	Total costs
No screening	12927.34	£1,274,262	13053.01	£726,734	13011.02	£796,532
Mammography	13012.78	£2,330,289	13105.78	£1,762,911	13065.59	£1,835,740
MRI	13027.43	£3,350,394	13114.78	£2,785,982	13074.89	£2,860,793
MRI+	13028.91	£4,025,952	13115.69	£3,469,556	13075.82	£3,538,269

Table 2.67 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 2.67: ICERs for comparison of different screening strategies (60-69 years)

High risk	vs. No screening		ICER
Mammography	£12,359	vs. Mammography	
MRI	£20,742	£69,641	vs. MRI
MRI+	£27,092	£105,150	£457,079
BRCA 2	vs. No screening		
Mammography	£19,637	vs. Mammography	
MRI	£33,340	£113,698	vs. MRI
MRI+	£43,765	£172,297	£753,553
BRCA 1	vs. No screening		
Mammography	£19,044	vs. Mammography	
MRI	£32,322	£110,274	vs. MRI
MRI+	£42,309	£166,390	£723,293

The results suggest that mammography is expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. MRI and combination MRI plus mammography is expected to be cost effective compared to no screening at a threshold of £30,000 per QALY gained for the high risk group. Neither MRI alone nor combination MRI plus mammography are expected to be cost effective compared to mammography alone.

The PSA results suggest we can be fairly confident of this conclusion when accounting for possible variance in the parameter values chosen since mammography is found to provide the highest NMB over 72% of 1,000 runs.

Tables 2.68 and 2.69 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 2.68: Incremental cost for all comparisons (60-69 years)

High risk	vs. No screening		Δ Cost
Mammography	£1,056	vs. Mammography	
MRI	£2,076	£1,020	vs. MRI
MRI+	£2,752	£1,696	£676
BRCA 2	vs. No screening		
Mammography	£1,036	vs. Mammography	
MRI	£2,059	£1,023	vs. MRI
MRI+	£2,743	£1,707	£684
BRCA 1	vs. No screening		
Mammography	£1,039	vs. Mammography	
MRI	£2,064	£1,025	vs. MRI
MRI+	£2,742	£1,703	£677

Table 2.69: Incremental QALYs for all comparisons (60-69 years)

High risk	vs. No screening		Δ QALY
Mammography	0.085	vs. Mammography	
MRI	0.100	0.015	vs. MRI
MRI+	0.102	0.016	0.001
BRCA 2	vs. No screening		
Mammography	0.053	vs. Mammography	
MRI	0.062	0.009	vs. MRI
MRI+	0.063	0.010	0.001
BRCA 1	vs. No screening		
Mammography	0.055	vs. Mammography	
MRI	0.064	0.009	vs. MRI
MRI+	0.065	0.010	0.001

One-way sensitivity analysis

Tables 2.70 to 2.72 present the results of the one-way sensitivity analyses for all 3 risk groups for individuals aged 60 to 69 years.

Table 2.70: Results of the one-way sensitivity analysis for the high-risk group (60-69 years)

HIGH RISK Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£11852 - 13176	£15823 - 28668	£22455 - 34561	£38984 - 119033	£78636 - 147868
Mammography	£10530 - 14189	£20742 - 20742	£25553 - 28630	£80314 - 58968	£105157 - 105144
Biopsy, wide local excision & mastectomy	£12316 - 12436	£20699 - 20819	£27048 - 26169	£69598 - 69718	£105107 - 105227
Utilities					
Baseline	-	-	-	-	-
In breast cancer treatment	-	-	-	-	-
Undiagnosed breast cancer (multiplier)	£11494	£19291	£25196	£64788	£51596
Rates					
Mortality of individuals with undiagnosed cancer	£11489	£19232	£25098	£64283	£97018
Survival of individual diagnosed at 1st opportunity	£30483 - 7920	£58234 - 12892	£77447 - 16767	£970216 - 36994	£1780482 - 55471
Survival of individual diagnosed at 2nd opportunity	£14578 - 10808	£21903 - 19753	£28,234 - 26094	£45529 - 139777	£67570 - 222153
Survival of individual diagnosed at 3rd opportunity	£7247 - 37813	£12510 - 55293	£16392 - 71095	£51169 - 105586	£78020 - 156422
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Table 2.71: Results of the one-way sensitivity analysis for the BRCA2 group (60-69 years)

BRCA 2 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£18807 - 20974	£25303 - 46289	£36182 - 55982	£63396 - 194740	£128739 - 242474
Mammography	£16651 - 22624	£33340 - 33340	£41248 - 46282	£131212 - 96185	£172282 - 172313
Biopsy, wide local excision & mastectomy	£19601 - 19702	£33304 - 33405	£43728 - 43830	£113662 - 113763	£172261 - 172361
Utilities					
Baseline	-	-	-	-	-
In breast cancer treatment	-	-	-	-	-
Undiagnosed breast cancer (multiplier)	£18269	£31019	£40718	£105818	£160357
Rates					
Mortality of individuals with undiagnosed cancer	£18221	£30882	£40518	£104954	£158998
Survival of individual diagnosed at 1st opportunity	£47558 - 12614	£91364 - 20799	£121989 - 27197	£1348413 - 60757	£2401047 - 91455
Survival of individual diagnosed at 2nd opportunity	£23134 - 17205	£35220 - 31803	£45586 - 42173	£74658 - 226310	£111031 - 359850
Survival of individual diagnosed at 3rd opportunity	£11497 - 59270	£20101 - 87933	£26482 - 113635	£83543 - 172074	£127850 - 255891
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Table 2.72: Results of the one-way sensitivity analysis for the BRCA1 group (60-69 years)

BRCA 1 Parameter varied	Mamm vs. NS	MRI vs. NS	MRI+ vs. NS	MRI vs. mamm	MRI+ vs. mamm
Costs					
MRI	£18242 - 20335	£24540 - 44860	£34986 - 54109	£61510 - 188838	£124282 - 234231
Mammography	£16152 - 21935	£32322 - 32322	£39879 - 44740	£127250 - 93298	£166418 - 166362
Biopsy, wide local excision & mastectomy	£19006 - 19111	£32284 - 32389	£42271 - 42376	£110236 - 110341	£166352 - 166457
Utilities					
Baseline	-	-	-	-	-
In breast cancer treatment	-	-	-	-	-
Undiagnosed breast cancer (multiplier)	£17698	£30039	£39321	£102513	£154682
Rates					
Mortality of individuals with undiagnosed cancer	£17706	£29997	£39244	£101965	£153804
Survival of individual diagnosed at 1st opportunity	£49112 - 12064	£95760 - 19867	£127764 - 25906	£2514562 - 57817	£5416521 - 86663
Survival of individual diagnosed at 2nd opportunity	£13387 - 16582	£20538 - 30733	£26585 - 40706	£44821 - 229208	£66655 - 365349
Survival of individual diagnosed at 3rd opportunity	£10917 - 63497	£19095 - 92370	£25087 - 118790	£79908 - 171070	£121807 - 252957
NS: no screening, Mamm: Mammography, MRI+: combination MRI+mammography					

Probabilistic sensitivity analysis

Tables 2.73 to 2.75 present the mean incremental costs, QALYs and cost-effectiveness ratio (ICER) estimated over a lifetime per person under each screening strategy, calculated over 1,000 PSA runs. The 95% confidence intervals for incremental costs and QALYs are also presented. High risk group values for incremental cost and QALYs are presented for the entire cohort whereas BRCA1 and BRCA2 results apply to every single individual in the model.

Table 2.73: Results of the probabilistic sensitivity analysis for high-risk group (60-69 years)

ICER	vs. No screening		High risk
Mammography	£12,433	vs Mammography	
MRI	£20,823	£70,006	vs MRI
MRI+	£27,206	£105,887	£462,258
Δ Cost	vs. No screening		
Mammography	1058406.36 (£1049671, £1067142)	vs Mammography	
MRI	2075027.58 (£2063317, £2086738)	1016621.22 (£1003159, £1030084)	vs MRI
MRI+	2750917.42 (£2738754, £2763081)	1692511.06 (£1678653, £1706370)	675889.84 (£659988, £691792)
Δ QALY	vs. No screening		
Mammography	85.13 (80, 90)	vs Mammography	
MRI	99.65 (95, 105)	14.52 (10, 19)	vs MRI
MRI+	101.11 (96, 106)	15.98 (11, 21)	1.46 (-4, 7)

Table 2.74: Results of the probabilistic sensitivity analysis for BRCA2 group (60-69 years)

ICER	vs. No screening		BRCA 2
Mammography	£16,339	vs. Mammography	
MRI	£27,636	£95,383	vs. MRI
MRI+	£36,216	£144,611	£638,613
Δ Cost	vs. No screening		
Mammography	£1,047 (£1015, £1079)	vs. Mammography	
MRI	£2,067 (£2033, £2100)	£1,019 (£985, £1054)	vs. MRI
MRI+	£2,747 (£2714, £2780)	£1,700 (£1665, £1734)	£680 (£645, £716)
Δ QALY	vs. No screening		
Mammography	0.064 (0.056, 0.073)	vs. Mammography	
MRI	0.075 (0.066, 0.083)	0.011 (0.004, 0.0017)	vs. MRI
MRI+	0.076 (0.067, 0.084)	0.012 (0.005, 0.018)	0.001 (-0.005, 0.007)

Table 2.75: Results of the probabilistic sensitivity analysis for BRCA1 group (60-69 years)

ICER	vs. No screening		BRCA1
Mammography	£16,800	vs. Mammography	
MRI	£28,299	£94,981	vs. MRI
MRI+	£37,047	£143,668	£624,839
Δ Cost	vs. No screening		
Mammography	£1,046 (£1018, £1074)	vs. Mammography	
MRI	£2,065 (£2036, £2095)	£1,020 (£989, £1050)	vs. MRI
MRI+	£2,744 (£2715, £2773)	£1,698 (£1668, £1729)	£679 (£647, £710)
Δ QALY	vs. No screening		
Mammography	0.062 (0.054, 0.070)	vs. Mammography	
MRI	0.073 (0.065, 0.081)	0.011 (0.004, 0.0018)	vs. MRI
MRI+	0.074 (0.066, 0.082)	0.012 (0.005, 0.019)	0.001 (-0.006, 0.008)

At a threshold of £20,000, mammography is expected to be the most-cost effective screening strategy in the high risk group and in BRCA 1 and BRCA 2 carriers with a probability of it being cost-effective of 0.716, 0.584 and 0.536 respectively (Table 2.76).

Table 2.76: Results of the probabilistic sensitivity analysis (age 60-69 years)

High risk	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.270	0.182
Mammography	0.716	0.737
MRI	0.014	0.081
MRI+	0	0
Highest NMB:	Mammography	Mammography
BRCA 2	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.515	0.359
Mammography	0.461	0.586
MRI	0.023	0.054
MRI+	0.001	0.001
Highest NMB:	Mammography	Mammography
BRCA 1	CE threshold = £20,000	CE threshold = £30,000
Probability cost-effective:		
No Screening	0.507	0.347
Mammography	0.476	0.610
MRI	0.017	0.043
MRI+	0	0
Highest NMB:	Mammography	Mammography

2.6.8 Discussion

Summary of results

The aim of this economic evaluation was to assess the cost-effectiveness of different screening strategies for breast cancer in patients with a previous history of breast cancer.

All results appear to be reasonably robust to changes in the key parameters in both one-way and probabilistic sensitivity analyses. Results will be summarised for the three subgroups below for a NICE WTP threshold of £20,000.

High-risk group (non-carrier)

For high-risk patients with a primary breast cancer between the ages of 30 and 49, MRI is the most cost-effective screening strategy

For high-risk patients with a primary breast cancer between the ages of 50 and 69, mammography is the most cost-effective screening strategy

BRCA2 group

For BRCA2-positive patients with a primary breast cancer between the ages of 30 and 49, MRI is the most cost-effective screening strategy

For BRCA2-positive patients with a primary breast cancer between the ages of 50 and 69, mammography is the most cost-effective screening strategy

BRCA1 group

For BRCA1-positive patients with a primary breast cancer between the ages of 30 and 49, MRI is the most cost-effective screening strategy

For BRCA1-positive patients with a primary breast cancer between the ages of 50 and 69, mammography is the most cost-effective screening strategy

Potential limitations of the model

Mortality and survival

The model is likely to underestimate the full extent to which breast cancer patients are at risk of cancer-related mortality, due to the limited number of annual cycles over which patients are modelled as being “true positives” or “in treatment”. Patients return to the “healthy” state after three years, in which they are no longer at risk of cancer related mortality. While this is sufficient to evaluate the differences between screening strategies and their impact on improved survival, due to earlier detection and treatment of breast cancer, it is a significant simplification of reality.

The absence of all cause mortality from the Markov chain is a further simplification of reality. While death from cancer is directly modelled, death from other causes is not. However, the exact model horizon (lifetime) is defined by the life expectancy of the cohort following ten years of screening. The assumption was made in CG41 that the absence of non-cancer specific mortality within the initial 10-year period would balance across cohorts and would

not affect the conclusions of modelling. This may be a more significant issue amongst the eldest cohort here modelled of 60-69 years.

Cancer treatment

The treatment of breast cancer is modelled over three years only. The use of tamoxifen and aromatase inhibitors commonly spans five years. Hence the estimated cost of treatment included in the model may be viewed as conservative.

Differentiation of cancer type

The model does not differentiate between different cancer types. There is now evidence that mammography has a significantly higher sensitivity to ductal carcinoma in situ (DCI) when compared to invasive cancer (Houssami et al., 2011). This could result in the underestimation of the outcomes of MRI and combined screening. However, since MRI and the combined approach are cost-effective against mammography in many age groups and especially for BRCA1 and BRCA2-positive patients, this underestimation will not significantly alter the outcomes of the model.

Furthermore, sensitivity of mammography is slightly higher for the detection of ipsilateral breast cancer than for contralateral breast cancer (Houssami et al., 2011). However, this difference is very small und non-significant and is not expected to impact on the model outcomes.

Data limitations

Quality of life

The paucity of published quality of life data necessitates a high level of dependence on expert opinion. Health related utility associated with breast cancer in treatment has been sourced from the literature. However:- it is not age specific as we have a utility during breast cancer treatment rather than a utility multiplier or a decrement. - it is not BRCA status or breast cancer type specific- it is modelled as constant over three years, while quality of life may be expected to be lower during the first year of more intensive treatment

Breast cancer survival according to timing of diagnosis is based on GDG estimations only.

Sensitivity of combined approach is not age specific, even though mammography is known to be more sensitive in older patients.

The modelled sensitivities of MRI and mammography are not specific to the patient group.

Breast cancer incidence data

Due to a lack of satisfactory data regarding breast cancer incidence in the different risk groups, the GDG decided to use a mixed data approach with BRCA1/2 incidence data derived from Malone et al. (2010) and high risk incidence data derived from Schaapveld et al. (2008). Even though this approach produced satisfactory results, the mixing of different data sets from different countries does cause slight inconsistencies especially in the older age groups.

Comparison with published literature

Only one study was identified in the systematic review for this topic (see full evidence review). This study was considered partially applicable and had very serious limitations.

This study assumed no family history or personal history but secondary analysis included family and personal history of breast cancer. It is not specifically stated whether the population included BRCA1/2 carriers and the interventions only included mammography; thus making the results difficult to compare to our analysis. However, this analysis did include different timings of surveillance, whereas our analysis only looks at annual surveillance. This study showed that biannual mammography was cost-effective for women aged 40 to 79 years with both a family history of breast cancer and a previous breast biopsy, regardless of breast density. Annual mammography was not cost-effective for any group, regardless of age or breast density. This is in contrast to our analysis which identified that mammography was cost-effective across all populations and ages examined when compared to no screening. However, when compared with annual MRI, MRI was a more cost-effective method of surveillance for those aged <50 years.

Implications for future research

Further research that could improve the model for this topic would include collecting the data/information and further analysis:

Considering the impact of different timings/ frequency of surveillance at 2 and 3 years

Specific data on health outcomes of men with a familial history and personal history of breast cancer

Prospective information on age-specific HRQOL/utilities of people with a familial risk of breast cancer in both affected and unaffected populations.

Specific data on sensitivity/specificity of MRI and mammography in this patient group

Consistent published cancer incidence data for different risk and age groups

2.6.9 References (2013)

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3 Risk reduction and treatment strategies

3.1 Chemoprevention for women with no personal history of breast cancer (chapter 8.2)

3.1.1 Review question

What is the cost- effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Patients/population	Intervention	Comparison	Outcomes
Women with a family history of breast, ovarian or related (prostate/pancreatic) cancer And/or Women at risk of breast cancer based on the results of genetic testing (i.e. positive for BRCA1, BRCA2 and/or TP53)	Chemoprevention Tamoxifen Raloxifene Aromatase Inhibitors	Each Other No chemoprevention	Incremental cost-effectiveness analysis (ICER) Sensitivity analysis

3.1.2 Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED).

Selection criteria for included evidence:

Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included

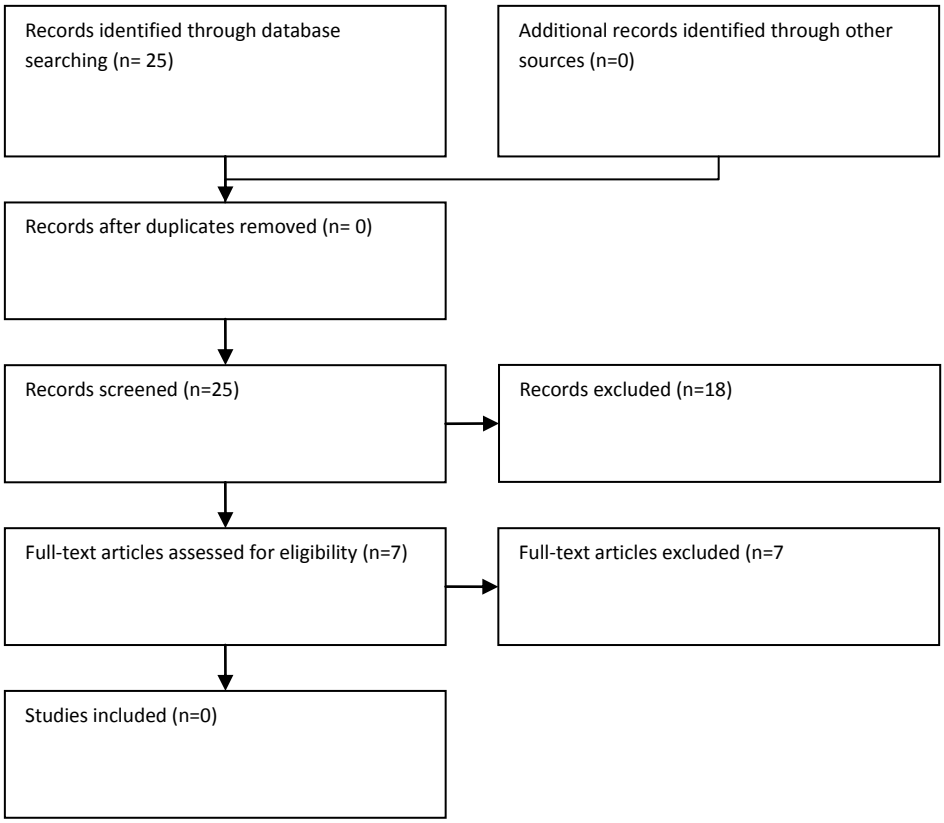
Studies that were conducted in OECD countries (other than the UK) were included

Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economist (BD) did the screen of the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for and checked against the inclusion criteria.

3.1.3 Results



Volume of evidence

Seven potentially relevant papers were reviewed. All papers were considered not relevant for this topic. Two studies (Anderson et al., 2006, Grann et al., 2011) were considered not relevant as the papers did not consider the same comparator as specified in the PICO for this topic. Dinh et al., 2010 and Palli et al., 2010 were excluded as they did not contain sufficient information on the population. Grann et al., 2000, Ozanne and Esserman, 2004 and Kondo et al., 2009 were excluded as the population was not specific to the topic (family history or known BRCA1 or 2 mutation).

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3.2 A cost consequence analysis for chemoprevention for women with no personal history of breast cancer

3.2.1 Introduction

Background

Since the previous guidance on Familial Breast Cancer (NICE 2006) was developed, two trials have been published on chemoprevention. These have provided high quality evidence that shows tamoxifen is effective in reducing breast cancer incidence when used for chemoprevention in pre and post menopausal women who do not have a diagnosis of breast cancer (Fisher et al., 2005 and Cuzick et al., 2007). There was also high quality evidence which suggests raloxifene has similar effectiveness to tamoxifen when used for chemoprevention in post menopausal women who do not have a diagnosis of breast cancer (Vogel et al., 2006).

3.2.2 Modelling methods

Type of economic evaluation

Though a full cost-utility analysis would be recommended for this topic, other topics were identified by the GDG as higher priorities for health economic modelling and therefore no modelling on chemoprevention was conducted as part of the guideline development process. Time restraints limit the scope of the current analysis presented. A simplified cost-consequence analysis has been conducted to provide estimates of the incremental costs and outcomes associated with offering chemoprevention in line with the new guideline recommendations compared to current practice. The analysis is based primarily on the accompanying NICE costing report.

Target population

The target population is high risk women with no personal history of breast cancer, who have no history or increased risk of thromboembolic disease or endometrial cancer and who are eligible for the offer of chemoprevention as described by the new guidelines.

Comparators

The comparator is the current standard of care in the NHS, assumed to be no chemoprevention.

Time horizon

Since chemoprevention has the potential to reduce the long-term incidence of cancer, and hence mortality, a long-term horizon of 50 years has been used in this analysis.

Health outcomes

The primary measurement of benefit in the analysis is cases of breast cancer avoided as a result of chemoprevention.

Healthcare resources and costs

The perspective of the NHS and personal and social services (PSS) has been taken for all costing purposes. A discount rate of 3.5% was applied to all costs incurred after the first year.

Health-related quality of life

Estimates of health-related quality of life were beyond the scope of this analysis.

Model structure and main limitations

Chemoprevention costs are estimated over a 5-year period, dependent on rates of treatment uptake and continuation after 1 year. Associated adverse event rates and costs of treatment are also estimated over this period.

The incidence of breast cancer under current standard of care is projected over 50 years according to age group.

The relative risk reductions of breast cancer in the chemoprevention trials are applied to estimate comparative incidence rates (this does not include cases of oestrogen negative breast cancers which can occur in women having chemoprevention).

Half cycle corrections are applied to incidence of future breast cancer cases.

All patients below the age of 50 are assumed to be pre-menopausal and all those aged at least 50 post-menopausal

Treatment that reduces the incidence of cancer has the potential to prevent future mortality. However, only the first instance of breast cancer is considered, with no evaluation of consequent morbidity and mortality.

Possible differences in the occurrence of fractures, as a result of chemoprevention, have not been accounted for. Since some evidence suggests that fractures are less frequent with tamoxifen compared to placebo, any potential bias introduced by this limitation will be in favour of the current standard of care.

The availability of chemoprevention may reduce the number of risk reducing surgeries carried out. However, it is not considered within this analysis. Many factors influence the choice of preventive action, including age, level of cancer risk, the strength of the benefits and significance of the possible harms, and any contraindications to treatment, making it difficult to include here.

3.2.3 Data inputs and key assumptions

Chemoprevention eligibility, uptake and continuance

Not all women who are eligible for and are offered the option of chemoprevention will choose to undergo such treatment. It was assumed that 25% of the target population (eligible women) will choose to take up chemoprevention.

The treatment regimen offered is dependent on menopausal status therefore the population distribution of age amongst eligible women is required. These data were derived from 2010 primary care data for England. (See table 3.1]

Table 3.1: Age distribution among women aged at least 20 in England

Age (years)	20-29	30-39	40-49	50-59	60-69	70+
Proportion of women	17.0%	17.0%	19.1%	15.6%	13.9%	17.4%

All pre menopausal women who chose to undergo chemoprevention will be treated with tamoxifen. Due to its absence in current clinical practice, the expected uptake of tamoxifen versus raloxifene in post menopausal women is unknown. For this analysis an equal split of tamoxifen versus raloxifene uptake was therefore assumed in post menopausal women.

In certain cases, chemoprevention may not be tolerable to the woman and as a result be discontinued after one year. Expert opinion suggests that 50% of women may end treatment after one year therefore this has been used in the base-case analysis.

Adverse events

Endometrial cancer

A systematic review identified high quality evidence (Nelson, et al., 2009) that the incidence of endometrial cancer is higher in patients treated with prophylactic tamoxifen than in those given placebo RR 2.13;(95% CI, 1.36-3.32).

There was moderate quality evidence (Nelson, et al., 2009) of uncertainty about the relative incidence of endometrial cancer in those given prophylactic raloxifene compared to those given placebo RR 1.14; (95% CI, 0.65-1.98). Further moderate quality evidence from one randomised trial (Vogel, et al., 2006) showed uncertainty about the relative incidence of endometrial cancer in patients who received tamoxifen compared to those given raloxifene RR 0.62; (95% CI, 0.35-1.08). Uncertainty in both trials was due to the low number of incident cases of endometrial cancer.

Base case model inputs were based on results presented by Nelson et al., (2009). The baseline risk of endometrial cancer with no chemoprevention was assumed to be the placebo result (0.4% over median 4 years), and relative risks for tamoxifen and raloxifene applied.

Thromboembolic events

The systematic review also identified high quality evidence (Nelson, et al., 2009) that thromboembolic events are more common in patients treated with tamoxifen or raloxifene compared with placebo. For tamoxifen versus placebo RR = 1.93 (95% CI, 1.41-2.64) and for raloxifene versus placebo RR = 1.60 (95% CI, 1.15-2.23). Further high quality evidence (Vogel. et al., 2006) suggests that thromboembolic events are more common in patients treated with tamoxifen than in those given raloxifene RR 0.70; (95% CI, 0.54-0.91).

Base case model inputs were based on results presented by Nelson et al., (2009). The baseline risk with no chemoprevention was assumed to be the placebo result seen in the tamoxifen trials (0.4% over median 4 years), and relative risks for tamoxifen and raloxifene applied to this rate.

Other events

Though the tamoxifen and raloxifene trials reported other less serious side effects such as increased frequency of hot flushes (with both drugs) and vaginal discharge (especially with

tamoxifen), these were assumed to have no significant cost impact and as such were not included in the analysis.

Though there is some evidence showing that tamoxifen may reduce the incidence of fractures compared to placebo, this has not been included in the analysis.

Incidence of breast cancer and effect of chemoprevention

The incidence of breast cancer in high risk women in the absence of chemoprevention was taken from an unpublished UK clinical trial (Evans (personal communication), 2013). The estimated annual probabilities of breast cancer applied are shown in Table 3.2.

Table 3.2: Breast cancer incidence in women eligible for chemoprevention

Age (years)	20-29	30-39	40-49	50-59	60-69	70+
Annual probability of breast cancer	0.27%	0.47%	0.65%	0.91%	1.06%	1.75%

Two trials comparing tamoxifen with placebo, reported breast cancer incidence and the rate was lower in the tamoxifen arm of both trials (Cuzick et al., (2007) and Fisher et al., (2005)). Pooled analysis of the data from both trials resulted in a statistically significantly lower rate of breast cancer (invasive and non-invasive) in the Tamoxifen group versus the placebo group: Pooled RR 0.65, (95% CI, 0.56-0.74).

From one high quality randomised trial comparing Tamoxifen and Raloxifene (Vogel et al., 2006), there was no significant difference in the incidence of either invasive or non-invasive breast cancer between women receiving Tamoxifen or Raloxifene: Invasive breast cancer RR=1.02, (95% CI, 0.82-1.28), Non-invasive breast cancer RR=1.40, (95% CI, 0.98-2.00).

The base case analysis assumes that tamoxifen and raloxifene are equally effective and reduce the risk of breast cancer by 35%, based on this evidence.

Cost of chemoprevention and associated adverse events.

The annual costs of tamoxifen and raloxifene are £36 and £222 respectively (electronic drugs tariff 2012/13) [accessed 13.02.2013].

Additional six monthly visits to a GP / clinic are needed to monitor women and give them a repeat prescription. The cost of a GP visit is estimated to be £40 per 11.7 minute consultation (Curtis L 2012).

The cost of endometrial cancer (£4,375.90) was taken from Hind et al., 2007 and inflated to 2011/12 costs using the Hospital & Community Health Services (HCHS) index (Curtis L 2012).

The cost of thromboembolic events (£821) was assumed to be that of deep vein thrombosis, taken from the total HRG cost in the 2011/12 NHS reference costs.

Cost of breast cancer

The cost of breast cancer was estimated as £14,511 per case according to the details in the table 3.3. These data were derived from the NICE costing report, which was based on the micro costing exercise carried out for the economic model on surveillance published in the full guideline (see full health economic evidence review). The cost of endocrine therapy

(including aromatase inhibitors) and the use of neulasta as an integral part of breast cancer treatment are also included.

Table 3.3: Example of potential costs of breast cancer treatment

Description	Unit cost £	Units	Total £
Breast surgery (weighted average cost)[1]	2783	1	2,783
Adjuvant radiotherapy (fractions)[2]	123	15	1,845
Chemotherapy delivery – first attendance[3]	482	1	482
Chemotherapy delivery – subsequent cycles[4]	321	5	1,605
Chemotherapy – drug costs[5]	289	6	1,736
Other drug costs			
Neulasta[6]	686	6	4,118
Dexamethasone[7]			13
Ondansetron[7]			101
Maxolan[7]			8
Endocrine Therapy[8]			1,820
Total			14,511

[1]. This is a weighted average using HES activity data for breast surgery 2011/12 and national tariff 2013/14 for codes JA06Z, JA09D and JA16Z
[2]. Tariff 2013/14 code SC23Z Adjuvant radiotherapy – 15 fractions
[3]. Tariff 2013/14 code SB14Z Deliver complex chemotherapy, including prolonged infusional treatment at first attendance
[4]. Tariff 2013/14 Deliver subsequent elements of a chemotherapy cycle
[5]. Drug costs for Epirubicin, cyclphosphamide and fluourouracil (assumption this is the standard regimen based on TA109 Breast cancer (early) - docetaxel)
[6]. Standard treatment to reduce infection risk due to chemotherapy induced neutropenia price taken from electronic drug tariff 2013
[7]. Full cost-effectiveness evidence review and reports – familial breast cancer (table 1.13 costs included in cancer treatment micro-costing)
[8]. Weighted average of 5 endocrine therapies.

3.2.4 Results

Base case

The results based on a cohort of 1,000 eligible women are presented in Table 3.4. Of 1,000 women eligible for treatment, 250 women would be expected to choose to undergo chemoprevention at a cost of £79,088 (discounted drug cost only). The total cost of chemoprevention with associated GP visits and adverse events is estimated as £138,564 higher than the current standard of care.

Over 50 years, it is estimated that 11 cases of breast cancer could be avoided per 1,000 women offered chemoprevention. At a cost of £14,511 per breast cancer case, this equates to a saving approaching £160,000.

Offsetting the cost of chemoprevention by the potential savings of breast cancers avoided, the cost of chemoprevention is estimated as £34,264 per 1,000 eligible women, or £34 per woman eligible for chemoprevention.

Table 3.4: Results of base case analysis for 1,000 eligible women

	Current standard of care	Chemoprevention offered	Difference
Discounted costs			
Chemoprevention drugs	£0	£79,088	£79,088
Chemoprevention monitoring	£0	£56,731	£56,731
Endometrial cancer & thromboembolic events	£24,322	£27,068	£2,746
Breast cancer	£2,649,226	£2,544,925	-£104,301
Total costs	£2,673,548	£2,707,812	£34,264
Outcomes			
Breast cancer cases	300	289	11
Endometrial cancer cases	5.00	5.60	0.60
Thromboembolic events	5.00	5.60	0.60

Results suggest that chemoprevention would cost £3,010 per breast cancer case prevented. Based on this analysis, if the offer of chemoprevention in accordance with the recommendations were to be cost-effective at a threshold of £20,000 per QALY, a gain of at least 1.71 QALYs would be required per 1,000 eligible women.

3.2.5 Sensitivity Analyses

The results show that the analysis is sensitive to various input parameters within the model. In particular, a reduction or increase in the total cost of breast cancer and the effectiveness of chemoprevention were found to be the most influential. By altering the total cost of breast cancer to £19,300 a cost saving result of -£0.92 per breast cancer case prevented is achieved.

Table 3.5: Results of the Sensitivity Analysis

Input Parameter	Input for sensitivity analysis	Cost per Breast Cancer case prevented	Percentage change from Base-case
Uptake of Chemoprevention			
Base-case	25%		
	50%	£3,010.50	0%
	75%	£3,010.50	0%
Discontinuation of Chemoprevention after 1 Year			
Base-case	50%		
	20%	£1,400.96	-53%
	40%	£2,295.15	-24%
	60%	£4,083.53	36%
	70%	£5,871.91	95%
Relative Risk Reduction of Chemoprevention			
Base-case	35%		
	25%	£8,194.70	172%
	30%	£5,165.86	72%
	40%	£1,401.08	-53%
	45%	£155.63	-95%
Total Cost of Breast Cancer			
Base-case	£14,511.45		
	£4,200.00	£9,522.37	216%
	£12,700.00	£4,154.47	38%
	£15,800.00	£2,196.76	-27%
	£20,000.00	- £455.61	-115%

3.2.6 Conclusion

The results of this cost-consequence analysis show, that a cohort of 1,000 women with a high risk of breast cancer given a 5 year course of chemoprevention with Tamoxifen or Raloxifene, 11 possible cases of breast cancer are averted. The total cost savings associated with this reduction in breast cancer were estimated to be £160,000. Overall, when considering the total difference in costs associated with chemoprevention vs no chemoprevention and the number of breast cancer cases avoided, the total cost per breast cancer case prevented was found to be £3,010.

The overall cost-effectiveness of chemoprevention cannot be determined from this analysis alone as there is no willingness to pay threshold against which it can be compared. Further analysis showed that if a cost-utility analysis was undertaken, assuming a willingness to pay threshold of £20,000 per QALY, the chemoprevention strategy would need to provide a gain of 1.71 QALYs per 1,000 women to be cost-effective.

In conclusion although the analysis is limited to modelling only those women with a first incidence of breast cancer and does not specify type including node positive or negative, the costs of preventing a case of breast cancer are likely to be considered acceptable from an NHS perspective.

3.2.7 References

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3.3 Contra-indications to risk reducing surgery for people with a personal history of breast cancer (chapter 8.3.5)

3.3.1 Review question

What are the factors that indicate that offering risk reducing surgery is not cost-effective?

Question in PICO format

Patients/population	Intervention	Factors	Outcomes
Women who have had a diagnosis of breast cancer and who are at risk of future primary breast cancer due to an inherited risk of breast/ovarian cancer	Risk reducing breast or ovarian surgery Mastectomy Oophorectomy Hysterectomy	Risk Group/Threshold Parity Age Menopausal Status Co morbidities Patient Choice Life Expectancy Metastatic Disease	Incremental cost-effectiveness ratio (ICER) Results of sensitivity analysis

3.3.2 Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED), HTA (Health Technology Assessment) and the Health Economic Evaluations Database (HEED).

Selection criteria for included evidence:

Studies that compare both costs and health consequences (in terms of ICER) of different strategies were included (from 2000 to current)

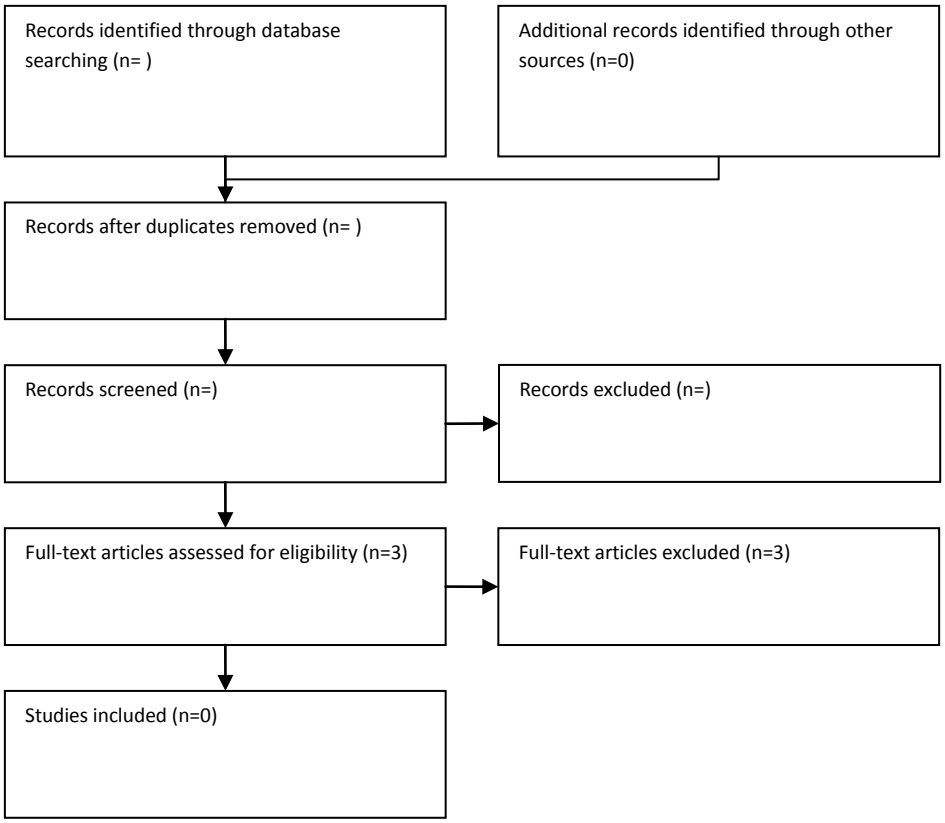
Studies that were conducted in OECD countries (other than the UK) were included

Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS

Selection of studies

The health economist (BD) did the screen of the literature search results, by comparing their title and abstract to the inclusion criteria in the PICO question. The full articles were then obtained for and checked against the inclusion criteria.

3.3.3 Results



Volume of evidence

Three potentially relevant papers were identified. All Papers were deemed not relevant as the population focused on women without breast cancer at baseline (Grann et al 2011, Anderson et al 2006, Norum et al 2008). No direct evidence was found to inform this topic.

3.3.4 References

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4 Health economic plan (2013)

Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 7.1.3 of the Guidelines Manual (2009).

Guideline

Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (update), including the management of women and men diagnosed with breast cancer who also have a history of familial breast cancer. Short title: Familial breast cancer (update)

Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on 29th September 2011 by the following people 5:

For the NCC and GDG:

NCC economist:	Ceri Phillips, Deb Fitzsimmons, Bernadette Diethart, Hayley Bennett (Swansea Centre for Health Economics, College of Human and Health Sciences, Swansea University)
NCC representative(s) 6:	John Graham, Lianne Gwillim, Susan O'Connell
GDG representative(s) 7:	Maggie Alexander, Gareth Evans

For NICE (completed by NICE):

CCP lead:	Fergus Macbeth
Commissioning manager:	Claire Turner
Economic lead:	Prashanth Kandaswamy
Costing lead:	

Proposals for any changes to the agreed priorities will be circulated by email to this group. If substansive revisions are agreed, they will require to be recorded as addenda to this document (section 7) or as an updated version of the document.

[5] This may be done by face-to-face meeting, teleconference, or email as convenient.
[6] May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.
[7] May be GDG chair, clinical lead and/or other members as appropriate.
[d] In case clinical questions are changed, for example, section 4 requires updating as well as other sections if modelling priorities are affected.

Topic priorities identified in the Scope

This section contains all topics covered by the scope. These topics usually reflect selected clinical issues. Please indicate if an area is relevant for economic consideration and if modelling is deemed appropriate to address it.

Area[h]	Relevant?[i]	Appropriate for modelling?[j]	Existing economic evaluations
Topic A The risk threshold at which genetic testing should be offered to people (for the update this part of the topic will be extended to include the threshold for offering testing to men as well as women).	High It is possible to compare different groups (with different risk thresholds and ages), providing the data exists, in order to calculate the relative costs and benefits of the alternatives.	This topic is appropriate for modelling. Decisions about who is eligible for genetic testing will significantly impact NHS resources and patient benefits. No good quality economic evidence has been found to address the updated topic.	A preliminary search of the literature has suggested 13 papers published that would be relevant for A with potential feasibility to use this evidence to adapt the existing economic model CG14. Summary of approach: Adaptation and updating of the CG14 economic model. The suggested adaptation would be to run model for populations with different risk thresholds (e.g. 5, 10, 15, 20%) and age groups to ascertain relative cost effectiveness and gauge which threshold would be the most efficient. The GDG will be asked to consider timing (e.g. delay versus rapid testing) and surgical options may also need to

h This corresponds to the "Key clinical issues that will be covered " section in the scope

[i] Please state if this area is deemed relevant for considering opportunity costs and likely disinvestments. Areas might pose a decision problem directly or implicitly infomr the choice between options. Categories should include information on relevance and if of high or low priority for health economic work (see below).

[j] Health economic work comprises literature reviews, qualitative consideration of expected costs and effects and/or formal decision modelling. Decision modelling is particularly useful where it can reduce uncertainty over cost effectiveness and/or where a recommendation is likely to result in considerable changes in health and/or costs. For further details please see section 7.1 of the Guidelines Manual (2009). It may not be feasible or efficient to address every relevant decision problem by de novo work. There rationale for choosing areas for cost effectiveness modelling should be discussed in detail in Section 5.

			be concidered (although GDG deemed this a low priority). Although not specified in the research questions chemotherapy and other treatments may need to be considered in the adapted model. Published economic evaluations have been identifed. However the applicability of this evidence (e.g. relevance to the UK healthcare setting) would need to be confirmed with the GDG and views obtained so as to validate the model from a clinical perspective.
Topic B Methods of assessing the risk threshold for genetic testing (for the update this part of the topic will be extended to include the threshold for testing for men as well as women).	Not applicable There are few methodological papers in existence with no easy identification of consequences to patients	Unlikely to yield significant health benefits according to choice of method.	
Topic C Chemoprevention to reduce the incidence of breast cancer in women.	Medium It is relevant to compare giving chemoprevention, to not giving chemoprevention and to calculate the costs and benefits of each alternative.	This topic is appropriate for modelling. The decision to give or not give chemoprevention will impact signficantly on NHS resources and patient benefits.	A preliminary literature search identified 7 economic evaluations addressing the cost effectiveness of chemoprevention (mostly concentrating on tamoxifen). The suitability of these papers in the UK healthcare context and the amount and quality of data that can be extracted will have to be assessed in order to decide which model design is feasible and how

			much data is available for model population.
Topic D Specific surveillance needs of women with no personal history of breast cancer.	Priority classed as “In literature” It is relevant to compare different methods and frequencies of surveillance and to calculate the costs and benefits of each alternative.	Appropriate for modelling. The decision to give certain types/frequencies of surveillance will impact NHS sources and patient benefits. No good quality economic evidence has been found in our preliminary searches to update this topic.	Recent economic evaluations of screening methods (MRI, mammography, ultrasound) as well as clinical and self examination have been found in the preliminary literature search. The quality of the data presented in these publications as well as the suitability for the UK healthcare setting will have to be assessed.
Topic E HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause.	Low While it may be possible to model giving HRT versus not giving it, this decision is governed by safety issues which are well documented in the literature. Cost-effectiveness evidence is unlikely to add any additional relevant information to this topic.	The value of modelling for this topic is considered limited. This refers to a small sub-set of people, for whom the clinical literature should serve as a good guide regarding whether or not to take HRT.	
Topic F The risk thresholds at which genetic testing should be offered to an affected person to: Inform future care Initiate genetic tests for their relatives.	Low There are few methodological papers in existence with no easy identification of consequences to patients	Unlikely to yield significant health benefits according to choice of method.	

Topic G1 Genetic testing for BRCA1 BRCA2 and TP53 within 4 weeks of diagnosis of breast cancer to inform treatment and future surveillance: Does a delay in genetic testing at diagnosis affect outcome?	Medium G1) Potentially relevant for modelling if the data exist. It may be possible to compare the costs/benefits of testing at diagnosis versus delayed testing.	G1) Potentially appropriate for modelling if the data exist. Testing at diagnosis may have a significant economic impact and resource impact versus a delayed approach. The quality of economic evidence avaliable is variable.	A preliminary search of the literature has suggested some papers published for G1 but evidence is limited as most papers and models available concentrate on testing or no testing (sometimes with distinguishing age groups) and do not incorporate a time frame for testing (i.e. within or after 4 weeks of diagnosis of breast cancer.
Topic G2 Genetic testing for BRCA1 BRCA2 and TP53 within 4 weeks of diagnosis of breast cancer to inform treatment and future surveillance: Who should discuss the outcomes of genetic testing with the patient and when?	Not applicable G2) This is a clinical judgement question with no appropriate comparison of costs and benefits adn is therfore not suitable for economic evaluation.	N/A	
Topic H1 Risk-reducing breast or ovarian surgery: At what level of risk of future primary breast cancer, and in what circumstances, should the option of risk-reducing surgery be discussed?	Low H1) Risk threshold for “discussions” is not relevant for modelling as there will not be quantifiable comparable costs and benefits. Risk threshold for giving surgery might have	N/A	

	been relevant but has not been specified here.		
Topic H2 Risk-reducing breast or ovarian surgery: In what circumstances is offering risk-reducing surgery not appropriate?	Low H2) Relevant for modelling. The decision to give or not give surgey will result in comparable costs and benefits.	Appropriate for modelling. While this was deemed low priority, a screening model (as proposed for Topic A) will, as a by-product, assess treatment/consequences including surgery.	Some economic evaluations on the cost-effectiveness of prophylactic mastectomy and oophorectomy have been identified in an initial literature search. The data extracted from these publications (according to quality and availability) will be used to inform the genetic testing model as prophylactic surgery is a possible consequence of a positive genetic result and its costs and outcomes/consequences will therefore need to be incorporated in the model analysis.
Topic I The specific surveillance needs of people with a personal history of breast cancer	High It is relevant to compare different methods and frequencies of surveillance and to calculate the costs and benefits of each alternative.	The decision to give certain types/frequencies of surveillance will impact on NHS resources and patient benefits. This cannot be answered by qualitative methods as one survelillance strategy may be more expensive but may be more effective.	A preliminary search of the literature has suggested papers published that would be relevant for I, with potential feasibility to use this evidence to adapt the existing economic model CG41. Summary of approach:Adaptation and updating of the CG41 economic model . According to the scope, the suggested adaptation would be to include men without breast cancer and women and men with breast cancer to establish the specific surveillance needs for different sub-groups. It will be necessary to include and update all the various

			surveillance options/consequences and various treatment options/outcomes to ascertain relative cost effectiveness and gauge which surveliance approach would be the most efficient. Published economic evaluations have been identifed. However the applicability of this evidence (e.g. relevance to the UK healthcare setting) would need to be confirmed with the GDG and views obtained so as to validate the model from a clinical perspective.
Topic J The effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ with a TP53 mutation or at high risk of TP53 mutation.	Low While there are two comparisons, the patient group is so small and condition so rare that there are unlikely to be large impacts on NHS budgets.	Limited applicability for modeling. There are unlikely to be large impacts on NHS budgets.	

1

1 **List of clinical questions**

2 Insert a list of all clinical questions in a 'PICO' format that are covered by the guideline.k

#	Clinical questions by scope area
	Area 1 - The risk threshold at which genetic testing should be offered to people (for the update this part of the topic will be extended to include the threshold for offering testing to men as well as women.
1	Question A What is the carrier probability at which genetic testing should be offered to people who are (a) unaffected with a family history of breast/ovarian/related cancer (b)unaffected with a family history and no living relative and (c) affected patients?
	Area 2 - Assessing the risk threshold for genetic testing (for the update this part of the topic will be extended to include the threshold for testing for men as well as women.
2	Question B What are the optimal models for assessing the carrier probability at different thresholds for genetic testing in women and men at risk of familial breast cancer?
	Area 3 (Chemoprevention to reduce the incidence of breast cancer in women).
3	Question C What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related cancer?
	Area 4 - Specific surveillance needs of women with no personal history of breast cancer.
4	Question D What are the specific surveillance needs of women with a family history who have no personal history of breast cancer?
	Area 5 - HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause.
5	Question E What are the risks and benefits of HRT for women under the age of 50, with a BRCA1 or BRCA2 mutation who have undergone a bilateral salpingo

[k]This is the list of clinical questions to be covered by the guideline.

oophorectomy?

Area 6 - The risk thresholds at which genetic testing should be offered to an affected person to:

Inform future care

Initiate genetic tests for their relatives

6 Question F

What are the familial risk thresholds at which genetic testing should be offered to an affected person with a family history of breast cancer to:

Inform future care

inform predictive genetic testing for relatives

Area 7 - Genetic testing for BRCA1/ BRCA2 and TP53 within 4 weeks of diagnosis of breast cancer to inform treatment and future surveillance:

Does a delay in genetic testing at diagnosis affect outcome

Who should discuss the outcomes of genetic testing with the patient and when?

7 Question G1

Does the mutation status of patient affect the rate of uptake of different treatment option and outcome of the different treatment options?

8 Question G2

Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur?

Area 8 - Risk-reducing breast or ovarian surgery:

At what level of risk of future primary breast cancer, and in what circumstances, should the option of risk-reducing surgery be discussed?

In what circumstances is offering risk-reducing surgery not appropriate?

9 Question H1

What level of risk indicates that risk reducing surgery is a viable option?

10 Question H2

What are the factors that indicate that offering risk reducing surgery is not appropriate?

Area 11 - The specific surveillance needs of people with a personal history of breast cancer

11 Question I

What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk reducing mastectomy?

Area 12 - The effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ with a TP53 mutation or at high risk of TP53 mutation.

12 Question J

What is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high-grade ductal carcinoma in situ (DCIS) with a BRCA1, BRCA2 or TP53 mutation or at high risk of BRCA1, BRCA2 or TP53 mutation?

1

Planned de novo modelling

This section will specify modelling work prioritised by the GDG. It will provide details on how cost effectiveness will be considered for relevant, prioritised clinical areas/decision problems. Proposed modelling work should be listed in chronological order. For each decision model, please state the proposed analytical methods, relevant references and any comments on, for example, possible diversions from the reference case.

Scope areal (clinical question(s) m)	Outline proposed analysis
a) The risk threshold at which genetic testing should be offered to people (for the update this part of the topic will be extended to include the threshold for offering testing to men as well as women).	A new model will be developedfrom the outline model schematicfor CG14 (appendix 1).. We would run the model with different subgroups of varying risks to help establish the most efficient risk threshold and inform at which threshold genetic testing should be offered. It will be neccesary to include all the various treatment options/consequences (including risk reducing treatments)). Patient population The model will include men and women, those at risk with breast cancer and those without. Intervention Genetic testing at different risk thresholds Comparision No testing Outcomes Diagnosis Treatment Mortality Prognosis and survival Health related quality of life Time horizon We will follow through to life expectancy with 1, 5, 10 and expected life-time horizons. Proposed Model

[l] This should be the key areas relevant for considering opportunity costs and high priority for de novo modelling, as identified in section 3.

[m] Two or more questions may be addressed by a single analysis if appropriate.

	A model using a decision tree and semi markov structure will be developed based on an adaptation of the model used for CG14, to reflect the clinical pathway and a cost-utility analysis will be peformed using QALYs a the measure of health outcomes. Clinical/economic evidence The data used to populate the model will be mainly derived from the systematic reviews conducted to identify clinical and cost-effectiveness evidence for the topic. Interviews with the clinical members of the GDG will be used to validate the model and assumptions. To populate the model, the following data will be needed The risk estimates for each sub-group of people. The previous model looked at testing versus not testing. We would put different subgroups of varying risks through the model to help establish the risk threshold at which genetic testing should be offered. Proportion of patients who receive treatment strategies (including preventative) Probability of death for patients with cancer Probability of death for patients from other causes Estimates of QALY gain including; Estimates of QALY gain for people who are diagnosed with breast cancer compared to those who are not E stimates of QALY for patients during standard treatments Estimates of QALY gain for people at different time horizons Costs To populate the model the following data will be required Costs associated with genetic testing Costs associated with survelliance Costs associated with typical treatment e.g. chemoprevention, surgery, chemotherapy Costs and benefits will be discounted at 3.5% per year. A UK NHS and personal social services perspective will be taken. NB- It will be neccesary to consider resource implications of those with a living relative versus those

	without. We will also consider different types of genetic testing (e.g. sanger sequencing versus next generation), lab capacity and NHS infrastructure issues in delivering genetic testing services and consider the impact of false positives. National published unit costs (PSSRU) and NHS reference costs will be used. Analysis A cost-utility analysis will be performed and ICERs presented. Univariate sensitivity analysis will be to examine the sensitivity of the results to a range of assumptions and changes in parameter estimates , while a probabilistic sensitivity analysis will assess the likelihood that the intervention can be regarded as representing value for money as measured by society's willingness to pay. Feasibility issues A cursory search of the literature has identified 13 economic studies on this topic. Three models were identified using a Markov model but these models were outside the UK. The model for CG14 simulated clinical outcomes and mortality in a cohort of women without breast cancer but with a family history of breast cancer and follows them up until all individuals reached life expectancy . This model didn't doesn't consider men or those with BC, doesn't have chemoprevention treatment options, doesn't include risk threshold identification, and doesn't include impact of delay vs. rapid testing. We suggest that these should be included in our updated model. These will need to be considered by the GDG
I) The specific surveillance needs of people with a personal history of breast cancer	A model will adapted from the original model for CG41 (appendix 2) This model looked at surveillance needs for at risk women without breast cancer. In this update, we would run the model to women and men with breast cancer to establish the specific survellience needs for different sub-groups. It will be necessary to include and update all the various survelliance options/consequences and various treatment options/outcomes. Patient population The model will include men and women who have a personal history of breast cancer.

	Intervention Surveillance Comparision No surveillance Outcomes Diagnosis Treatment Mortality Prognosis and survival Health related Quality of life Time horizon We will follow through to life expectancy with 1, 5, 10 and expected life-time horizons. Proposed model A Markov model will be developed based on an adaptation of the model used for CG41, to reflect the clinical pathway and a cost-utility analysis will be peformed using QALYs a the measure of health outcomes. Clinical/economic evidence The data used to populate the model will be mainly derived from the systematic reviews conducted to identify clinical and cost-effectiveness evidence for the topic. Interviews with the clinical members of the GDG will be used to validate our model and assumptions. To populate the model, the following data will be needed: The proportion of patients who receive different survelliance methods. Proportion of patients who receive treatment strategies (including preventative) Probability of death for patients with cancer Probability of death for patients from other causes Estimates of QALY gain including; Estimates of QALY gain for people who are diagnosed with breast cancer compared to those who are

	not E stimates of QALY gain for patients during standard treatments Estimates of QALY gain for people at different time horizons Costs To populate the model the following data will be required Costs associated with survelliance Costs associated with typical treatment e.g. surgery, chemotherapy Costs and benefits will be discounted at 3.5% per year. A UK NHS and personal social services perspective will be taken. National published unit costs (PSSRU) and NHS reference costs will be used. NB- We will also consider different types of survelliance and NHS infrastructure issues in delivering survelliances services and consider the impact of false positives/ negatives. Analysis A cost-utility analysis will be performed and ICERs presented. Univariate sensitivity analysis will be to examine the sensitivity of the results to a range of assumptions and changes in parameter estimates , while a probabilistic sensitivity analysis will assess the likelihood that the intervention can be regarded as representing value for money as measured by society's willingness to pay. Feasibility issues A cursory search of the literature has identified 19 economic studies on this topic including from the UK. The model for CG41 simulated clinical outcomes and mortality in a cohort of women without breast cancer but with a family history of breast cancer and follows them up until all individuals reached life expectancy . This model didn't doesn't consider men or those with Breast Cancer and does not consider other surveillance methods (e.g. ultrasound). We suggest that these should be included in our updated model. These will need to be considered by the GDG.

It is not the intention of the economic model(s) to answer the below questions. However, as a default of assessing the cost effectiveness of screening, it is neccesary to include the treatments/consequences. The models will therefore provide some evidence to contribute to the below topics even though they were deemed low-moderate priority by GDG.	
C) Chemoprevention to reduce the incidence of breast cancer in women.	This may be a default of the modelling done for topics A, if the GDG decide to include chemoprevention in the model.
H2) Risk-reducing breast or ovarian surgery: In what circumstances is offering risk-reducing surgery not appropriate?	This will be a default of the modelling done for topic A

1

Clinical Guidelines technical support unit14

Please indicate if any of the analyses or areas suggested in section 3 require or would benefit from the Clinical Guidelines Technical Support Unit support or validation.

References

McIntosh A, Shaw C, Evans G, Turnbull N, Bahar N, Barclay M, Easton D, Emery J, Gray J, Halpin J, Hopwood P, McCay J, Sheppard C, Sibbering M, Watson M, Wailoo A, Hutchinson A (2004). Clinical Guidelines and Evidence Review for the Classification and Care of Women at Risk of Familial Breast Cancer, London: National Collaborating Centre for Primary Care/University of Sheffield.

Evans G, Bahar N, Easton D, Halpin, J, Hopwood P, McInstosh A, Sheppard C, Sibbering M, Watson W, Barter S, Parsons Perez C, Young K, Gilbert F, Norman R, Ritchie G, Jozephs Y, Turnbill N (2006).Familial Breast Cancer. The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. Update. London: National Collaborating Centre for Primary Care

Addenda to economic plan

Please state any changes that have been made to the above agreed plan, together with date. If clinical questions have changed since the economic plan was signed off, include a new list with all clinical questions as part of the addenda, together with a comment where questions were inserted, deleted or altered and an explanation.

Scope area15 (clinical question(s) 16)	Proposed changes	Date agreed

[14] The Clinical guidelines technical support unit provides academic support to guidelive developers at any point in guideline development: Conduct, or support the NCC/SCG team in the development of, advanced evidence synthesis, Support complex economic analyses, conduct validation of or amendments to, existing evidence syntheses used in guideline models and address concerns from stakeholder (via consultation). Please contact the Senior technical adviser for further details

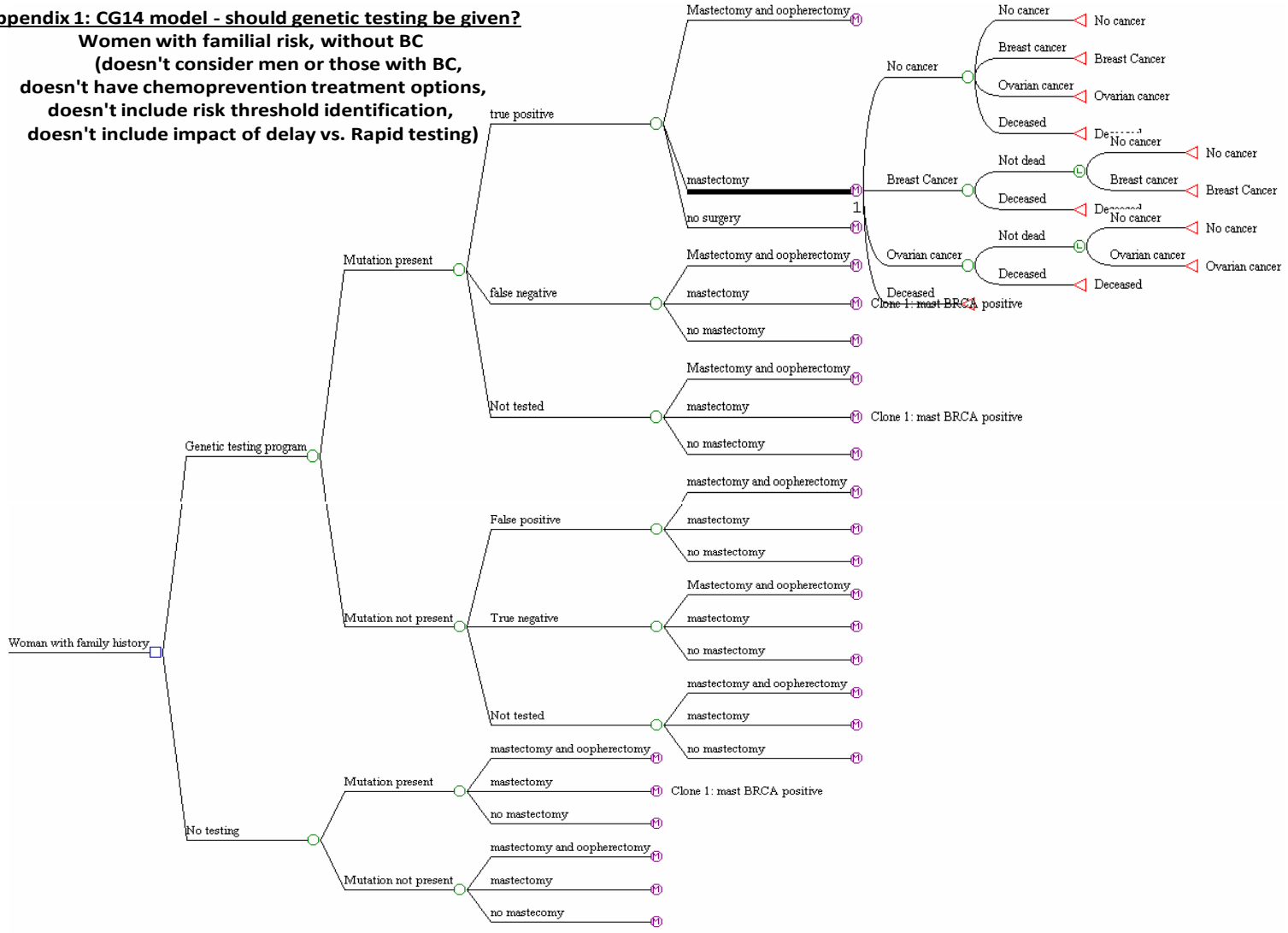
[15] This should be the key areas relevant for considering opportunity costs and high priority for de novo modelling, as identified in section 3.

[16] Two or more questions may be addressed by a single analysis if appropriate.

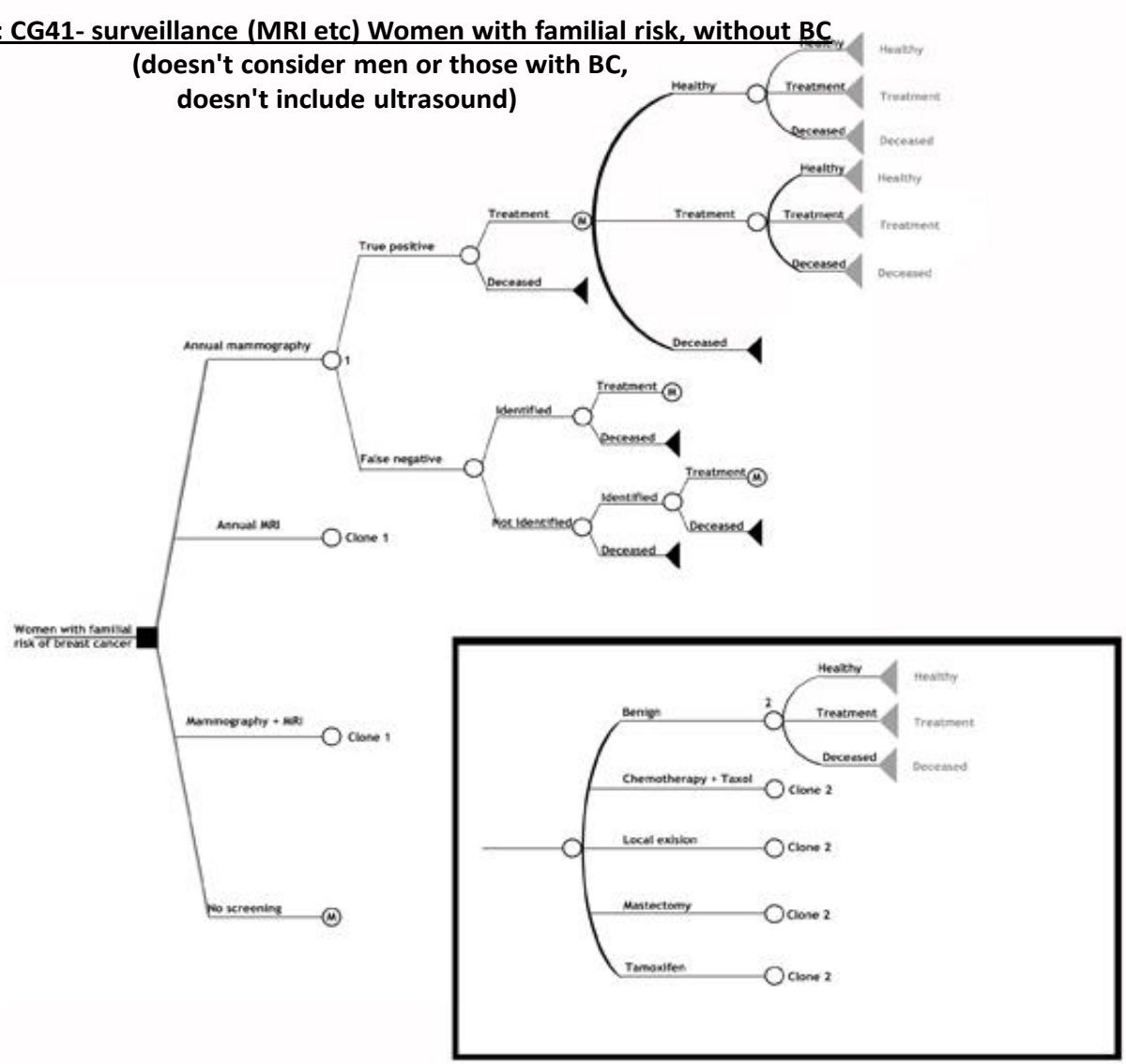
1

Appendix 1: CG14 model - should genetic testing be given?

Women with familial risk, without BC
(doesn't consider men or those with BC,
doesn't have chemoprevention treatment options,
doesn't include risk threshold identification,
doesn't include impact of delay vs. Rapid testing)



Appendix 2: CG41- surveillance (MRI etc) Women with familial risk, without BC (doesn't consider men or those with BC, doesn't include ultrasound)



5 Health Economics Search Strategies

Topic A and F: What is the carrier probability at which genetic testing should be offered to people who are (a) unaffected but with a family history of breast/ovarian/related cancer and an affected relative willing to have a test; (b) unaffected with a family history and no living relative and (c) affected people?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. 1 or 2 or 3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetic Predisposition to Disease/
12. (BRCA1 or BRCA2 or TP53).tw.
13. ((high adj risk) or (increas$ adj risk)).tw.
14. (mutation adj1 risk*).tw.
15. lifetime breast cancer risk*.tw.
16. (mutation adj carrier*).tw.
17. (genetic adj susceptib*).tw.
18. (inherited adj mutation*).tw.
19. or/9-18
20. 8 and 19
21. diagnostic genetic test*.tw.
22. predictive genetic test*.tw.
23. (Sanger adj sequenc*).tw.
24. MLPA*.tw.
25. Multiplex Ligation-dependent Probe Amplification*.tw.
26. Genetic Screening/
27. (probability adj1 threshold*).tw.
28. exp Genetic Testing/
29. exp Risk Assessment/
30. or/21-29
31. 20 and 30

SIGN Health Economics filter was added to search.
(Other database searches were performed by the Swansea University Health Economics team)

Database name	No of references found	Finish date of search
Medline	58	21/11/2011
Update search	3	04/07/2012
Embase	61	21/11/2011
Update search	4	04/07/2012

Total References retrieved (after de-duplication): 96
Total References retrieved for Update Search (after de-duplication): 6

Topic B: What are the optimal methods for assessing the carrier probability of people (whether or not they have a personal history of breast cancer) at different thresholds for genetic testing in women and men at risk of familial breast cancer?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. 1 or 2 or 3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetic Predisposition to Disease/
12. (mutation adj1 risk*).tw.
13. lifetime breast cancer risk*.tw.
14. (mutation adj carrier*).tw.
15. (inherited adj mutation*).tw.
16. predictive genetic test*.tw.
17. (probability adj1 threshold*).tw.
18. lifetime risk*.tw.
19. interval risk*.tw.
20. assessment tool*.tw.
21. mutation probability*.tw.
22. cancer risk assessment*.tw.
23. risk estimation tool*.tw.
24. mutation frequenc*.tw.
25. BRCAPRO*.tw.
26. BOADICEA*.tw.
27. Tyrer-Cuzick*.tw.
28. exp Risk Assessment/mt [Methods]
29. exp Genetic Testing/mt [Methods]
30. exp "Predictive Value of Tests"/
31. exp Models, Statistical/
32. 9 or 10 or 11

33. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

34. 8 and 32

35. 33 and 34

SIGN Health Economics filter was added to search.
(Other database searches were performed by the Swansea University Health Economics team)

Database name	**No of references found**	**Finish date of search**
Medline	63	26/03/2012
Update Search	1	04/07/2012
Embase	66	26/03/2012
Update Search	4	04/07/2012

Total References retrieved (after de-duplication): 121
Total References retrieved for Update Search (after de-duplication): 5

Topic C: What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Medline search strategy for Part One *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp ovarian neoplasms/
6. (ovar$ adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
7. 5 or 6
8. exp Prostatic Neoplasms/
9. (prostat$ adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
10. 8 or 9
11. exp Pancreatic Neoplasms/
12. (pancrea$ adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.
13. 11 or 12
14. 4 or 7 or 10 or 13
15. (familial or family histor$).tw.
16. (heredit$ or inherit$ or predispos$).tw.
17. exp Genetics/
18. genetic$.tw.
19. (gene or genes or mutation$).tw.
20. Genetic Screening/
21. exp Genetic Predisposition to Disease/
22. exp Neoplastic Syndromes, Hereditary/
23. Genetic Counseling/
24. exp Genetic Techniques/
25. (BRCA1 or BRCA2 or TP53).tw.
26. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
27. ((high adj risk) or (increas$ adj risk)).tw.
28. or/15-27
29. 14 and 28
30. 4 and 29
31. exp Chemoprevention/
32. (chemoprevent$ or chemoprophyla$).tw.
33. exp Tamoxifen/
34. exp Raloxifene/
35. exp Aromatase Inhibitors/
36. aromatase inhibitor$.tw.
37. (reduction adj3 (cancer$ or tumo?r$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$)).tw.

38. (exemestane$ or aromasin$).tw.
39. anastr?zol$.tw.
40. letrozol$.tw.
41. or/31-40
42. 30 and 41
43. limit 42 to yr="2003 -Current"

(Other searches were performed by the Swansea University Health Economics team)

Part One – Chemoprevention of familial breast cancer

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2003-current	24	8	31/10/2011
Embase	2003-current	251	13	31/10/2011

Total references retrieved after duplicates removed: 14

Part Two – Chemoprevention of breast cancer with adverse effects filter

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2003-current	75	39	01/11/2011
Embase	2003-current	667	87	01/11/2011

Total references retrieved after duplicates removed: 87

Update Searches*:*

Part One:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	/09/2011-09/07/2012	5	3	09/07/2012
Embase	/09/2011-09/07/2012	3	0	09/07/2012

Total references retrieved after duplicates removed: 4

Part Two:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	/09/2011-09/07/2012	6	3	09/07/2012
Embase	/09/2011-09/07/2012	23	3	09/07/2012

Total references retrieved after duplicates removed: 4

Topic D: What are the specific surveillance needs of women with a family history who have no personal history of breast cancer?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. exp Mammography/
25. (breast$ and screen$).ti.
26. (mammogra$ or echomammogra$).tw.
27. Ultrasonography, Mammary/
28. (ultraso$ or sonogra$ or echosonogra$).tw.
29. Magnetic Resonance Imaging/
30. "magnetic resonance imag$".tw.
31. MRI.tw.
32. ((non-invasive$ or noninvasive$) and (imag$ or diagnos$)).tw.
33. Mass Screening/
34. surveillance.tw.
35. Physical Examination/
36. Breast self-examination/
37. ("physical exam$" or "self exam$" or "self-exam$" or "clinical exam$" or "breast exam$").tw.
38. or/24-37
39. 23 and 38
40. limit 39 to yr="2003 -Current"

Database name	No of references found	No of references retrieved	Finish date of search
Medline	8	3	17/07/2012
Embase	9	1	17/07/2012

Total references retrieved after duplicates removed: 4

Topic E: What are the risks and benefits of HRT for women under the age of 50, with a *BRCA1* or *BRCA2* mutation who have undergone a bilateral salpingo-oophorectomy?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplas$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. Ovariectomy/
25. (ovariectom$ or oophorectom$).tw.
26. (ovar$ removal or ovar$ surger$ or ovar$ ablat$).tw.
27. (prophylactic adj surger$).tw.
28. or/24-27
29. 23 and 28
30. exp Hormone Replacement Therapy/
31. ((hormon$ or oestrogen$ or estrogen$ or oestradiol or estradiol or progesterone$ or progestin) and replacement).tw.
32. hormone substitution.tw.
33. hrt.tw.
34. ((hormon$ or oestrogen$ or estrogen$ or oestradiol or estradiol or progesterone$ or progestin) adj2 (therap$ or treatment$)).tw.
35. or/30-34
36. 29 and 35
37. limit 36 to yr="1995 -Current"

(Other database searches were performed by the Swansea University Health Economics team)

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1995-current	7	0	07/09/2011
Embase	1995-current	16	0	07/09//2011

Total references retrieved after duplicates removed: 0

Topic F: Does knowing the mutation status of a patient at or soon after cancer diagnosis affect the different cancer treatment options and/or does it usefully inform immediate decisions about risk reducing options?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. exp Mastectomy/
25. mastectom$.tw.
26. mammaplast$.tw.
27. mammoplast$.tw.
28. mammectom$.tw.
29. or/24-28
30. *Ovariectomy/
31. (oophorectom$ or salpingooophorectom$).tw.
32. 30 or 31
33. Surgery/
34. (risk reduc$ adj surger$).tw.
35. (breast conserv$ adj surger$).tw.
36. or/33-35
37. Antineoplastic Combined Chemotherapy Protocols/
38. chemotherap$.tw.
39. exp Antineoplastic Agents/
40. or/37-39
41. exp Radiotherapy/

42. radiotherap$.tw.
43. (radiation adj (therap$ or treatment$)).tw.
44. or/41-43
45. ((therap$ or treatment$) adj adjuvant).tw.
46. Combined Modality Therapy/
47. 45 or 46
48. 29 or 32 or 36 or 40 or 44 or 47
49. 23 and 48
50. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
51. (primary or first or new or prior).tw.
52. 50 and 51
53. 49 and 52
54. (mutation$ or BRCA1 or BRCA2 or TP53).tw.
55. (gene$ adj status).tw.
56. exp Mutation/
57. genes, brca1/ or genes, brca2/
58. brca1 protein/ or brca2 protein/
59. Tumor Suppressor Protein p53/tu [Therapeutic Use]
60. Genes, p53/
61. or/54-60
62. 53 and 61

(Other searches were performed by the Swansea University Health Economics team)

Database name	**Dates Covered**	**No of references found**	**No of references retrieved**	**Finish date of search**
Medline	1998-current	3	1	22/02/2012
Embase	1998-current	31	1	05/03/2012

Total references retrieved (after duplicates removed): 2

Topic G2: Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur?

Medline search strategy for Part One *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or family histor$).tw.
10. (heredit$ or inherit$ or predispos$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes or mutation$).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. exp Neoplastic Syndromes, Hereditary/
17. Genetic Counseling/
18. exp Genetic Techniques/
19. (BRCA1 or BRCA2 or TP53).tw.
20. Genes, BRCA1/ or Genes, BRCA2/ or Genes, p53/
21. ((high adj risk) or (increas$ adj risk)).tw.
22. or/9-21
23. 8 and 22
24. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
25. (primary or first or new).tw.
26. 24 and 25
27. 23 and 26
28. (mutation$ or BRCA1 or BRCA2 or TP53).tw.
29. (gene$ adj status).tw.
30. genes, brca1/ or genes, brca2/
31. brca1 protein/ or brca2 protein/
32. Tumor Suppressor Protein p53/
33. Genes, p53/
34. exp Mutation/
35. or/28-34
36. 27 and 35
37. exp Medical Staff/
38. exp Nurses/
39. exp Physicians/
40. exp Family/
41. Patient Care Team/

42. 37 or 38 or 39 or 40 or 41
43. (surgeon$ or specialist$ or doctor$ or physician$ or clinician$ or oncologist$ or MDT$ or nurse$ or health$ worker$ or health$ professional$ or general practioner$ or gp).tw.
44. (geneticist$ or counsel?or$).tw.
45. (famil$ or relati$).tw.
46. 43 or 44 or 45
47. 42 or 46
48. 36 and 47
49. Patient Education as Topic/
50. Attitude of Health Personnel/
51. Physician-Patient Relations/
52. Nurse-Patient Relations/
53. Patient Participation/
54. exp Patient Satisfaction/
55. Professional-Family Relations/
56. exp Decision Making/
57. exp Ethics, Medical/
58. (discuss$ or disseminat$ or inform$ or communicat$ or interview$ or counsel$ or talk$ or tell$ or decid$ or decision$ or written or document$).tw.
59. or/49-58
60. 48 and 59

(Other searches were performed by the Swansea University Health Economics team)

Database name	**Dates Covered**	**No of references found**	**No of references retrieved**	**Finish date of search**
Medline	1996-current	19	4	23/04/2012
Embase	1996-current	33	4	23/04/2012

Total references retrieved (after duplicates removed): 7

Topic H1: What level of risk indicates that risk reducing surgery is a viable option?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. Genetic Counseling/
17. exp Genetic Techniques/
18. (BRCA1 or BRCA2 or TP53).tw.
19. ((high adj risk) or (increas$ adj risk)).tw.
20. or/9-19
21. 8 and 20
22. exp Mastectomy/
23. mastectom$.tw.
24. mammaplast$.tw.
25. mammoplast$.tw.
26. mammectom$.tw.
27. or/22-26
28. *Ovariectomy/
29. (oophorectom$ or ovariectom$ or salpingooophorectom$).tw.
30. 28 or 29
31. ((risk reduc$ or preventive or prophylactic) adj surg$).tw.
32. 27 or 30 or 31
33. 21 and 32
34. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis) adj3 (diagnos$ or confirm$ or past or histor$ or affect$)).tw.
35. 33 and 34
36. risk$.tw.
37. 35 and 36

(Other database searches were performed by the Swansea University Health Economics team)

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All dates	11	3	06/02/2012
Embase	All dates	26	2	08/02/2012

Total references retrieved after duplicates removed: 4

Topic H2: What are the factors that indicate that offering risk reducing surgery is not appropriate?

Medline search strategy *(This search strategy is adapted to each database.)*
1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. Genetic Counseling/
17. exp Genetic Techniques/
18. (BRCA1 or BRCA2 or TP53).tw.
19. ((high adj risk) or (increas$ adj risk)).tw.
20. or/9-19
21. 8 and 20
22. exp Mastectomy/
23. mastectom$.tw.
24. mammaplast$.tw.
25. mammoplast$.tw.
26. mammectom$.tw.
27. or/22-26
28. *Ovariectomy/
29. (oophorectom$ or ovariectom$ or salpingooophorectom$).tw.
30. 28 or 29
31. ((risk reduc$ or preventive or prophylactic) adj surg$).tw.
32. 27 or 30 or 31
33. 21 and 32
34. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis) adj3 (diagnos$ or confirm$ or past or histor$ or affect$)).tw.
35. 33 and 34

(Other database searches were performed by the Swansea University Health Economics team)

Database name	Dates	No of	No of	Finish date

	Covered	references found	references retrieved	of search
Medline	All dates	12	4	30/01/2012
Embase	All dates	32	4	30/01/2012

Total references retrieved after duplicates removed: 7

Topic I: What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk reducing bi-lateral mastectomy?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. (familial or (family adj histor$)).tw.
10. (hereditary or inherit$).tw.
11. exp Genetics/
12. genetic$.tw.
13. (gene or genes).tw.
14. Genetic Screening/
15. exp Genetic Predisposition to Disease/
16. Genetic Counseling/
17. exp Genetic Techniques/
18. (BRCA1 or BRCA2 or TP53).tw.
19. or/9-18
20. 8 and 19
21. Neoplasms, Second Primary/
22. Neoplasm Recurrence, Local/
23. 21 or 22
24. exp Breast Neoplasms/
25. exp "Neoplasms, Ductal, Lobular, and Medullary"/
26. 24 or 25
27. 23 and 26
28. (breast$ adj3 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
29. (mammar$ adj3 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
30. 28 or 29
31. ("second primar$" or secondary or recurren$ or metachronous or ipsilateral or history).tw.
32. 30 and 31
33. 27 or 32
34. 20 and 33
35. exp Mammography/
36. (breast$ and screen$).ti.
37. mammogra$.tw.
38. Ultrasonography, Mammary/

39. (ultraso$ or sonogra$ or echosonogra$).tw.
40. Magnetic Resonance Imaging/
41. "magnetic resonance imag$".tw.
42. MRI.tw.
43. ((non-invasive$ or noninvasive$) and (imag$ or diagnos$)).tw.
44. Mass Screening/
45. surveillance.tw.
46. Physical Examination/
47. Breast self-examination/
48. ("physical exam$" or "self exam$" or "self-exam$" or "clinical exam$" or "breast exam$").tw.
49. or/35-48
50. 34 and 49

(Other database searches were performed by the Swansea University Health Economics team)

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1970-current	63	8	21/11/2011
Embase	1970-current	209	8	21/11/2011

Total references retrieved after duplicates removed: 12

Topic J: What is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer including high-grade ductal carcinoma in situ (DCIS) with a *TP53* mutation or at high risk of *TP53* mutation?

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp breast neoplasms/
2. exp "Neoplasms, Ductal, Lobular, and Medullary"/
3. ((breast or mammary) adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or metasta$ or dcis)).tw.
4. or/1-3
5. exp Ovarian Neoplasms/
6. (ovar$ adj3 (cancer$ or tumour$ or tumor$ or neoplasm$ or carcinoma$ or metasta$)).tw.
7. 5 or 6
8. 4 or 7
9. Tumor Suppressor Protein p53/
10. Genes, p53/
11. (TP53 or P53 gene).tw.
12. Li-Fraumeni Syndrome/
13. or/9-12
14. 8 and 13
15. exp Mastectomy/
16. (mastectomy$ or mammaplast$ or mammoplast$ or mammectom$).tw.
17. 15 or 16
18. (risk reduc$ adj surg$).tw.
19. (breast conserv$ adj surg$).tw.
20. (breast sparing adj surg$).tw.
21. ((local excision or segmental or partial or limited) adj2 (surg$ or resection$ or mastectom$)).tw.
22. lumpectom$.tw.
23. segmentectom$.tw.
24. or/18-23
25. exp radiotherapy/
26. radiotherap$.tw.
27. (radiation adj (therap$ or treatment$)).tw.
28. irradiati$.tw.
29. 25 or 26 or 27 or 28
30. 24 and 29
31. 17 or 30
32. 14 and 31

(Other database searches were performed by the Swansea University Health Economics team)

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1970-current	0	0	09/01/12
Embase	1970-current	2	0	09/01/12

Total references retrieved after duplicates removed: