

# **Familial breast cancer**

## **The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care**

**Update**

**July 2006**

**National Collaborating Centre for Primary  
Care**

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## 1. Introduction

The Familial Breast Cancer Guideline (NICE) was published in 2004. The recommendation made on the use of MRI in diagnosing breast cancer was as follows:

***On the basis of current evidence, MRI and ultrasound should not be used in routine surveillance practice but may have a role in problem-solving mammographically detected abnormalities.***

***(Note: several MRI studies have already been presented at major cancer meetings and will report in the next 2 years. This recommendation should be reviewed when they become available.)***

These studies have now been published and this review updates the evidence.

Guidance on other issues was not considered by this review and remains current.

Recent evidence has suggested that MRI screening increases the sensitivity of breast cancer screening at the expense of specificity.[Leach et al., 2005] This additional sensitivity has the potential to identify cases sooner which ought to lead to more promising prognoses. Furthermore, a hastening of a correct identification can prevent disutility associated with false negatives prior to their eventual diagnosis. Similarly, evidence has suggested that the sensitivity of the mammography options is partially compromised in younger groups, due to breast tissue density issues.[Kerlikowske et al., 1996] The benefit of MRI screening has to be contrasted between different groups of women, and then compared with the cost implications that MRI screening has, both in the screening programme (such as the cost of those incorrectly brought back for further investigation) and in the wider National Health Service.

The primary question that this investigation is looking to answer is whether MRI screening can be recommended on clinical and cost-effectiveness grounds in particular populations of women.

## 2. Recommendations

**These recommendations should be read in conjunction with the existing NICE guidance (National Institute for Clinical Excellence, 2004), in particular, the recommendations on mammographic surveillance.**

**These recommendations indicate when Magnetic Resonance Imaging (MRI) is to be used. This is in addition to, or as an alternative to, mammography as per the recommendations in the original guideline.**

- 1 At entry to an MRI surveillance programme, and at each subsequent change in the programme, women should be provided with a documented plan which includes:
  - a clear description of the method(s) and intervals, including the risks and benefits
  - the reasons for any changes to the surveillance plan
  - sources of support and further information.
- 2 MRI of both breasts should be performed to high quality standards ensuring both high temporal and spatial resolution. Dynamic sequences are recommended post contrast. They should be double-read where possible.
- 3 When mammography is recommended in women under 50, digital mammography should be used in preference to conventional mammography at centres where this is available to NHS Breast Screening Programme standards.
- 4 Women who are known to have a genetic mutation should be offered annual MRI surveillance if they are:
  - *BRCA1* and *BRCA2* mutation carriers aged 30–49 years

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- *TP53* mutation carriers aged 20 years or older

Women who have been referred to a clinical genetics centre who are not known to have a genetic mutation should be offered an assessment of their 10-year breast cancer risk using a validated risk assessment tool (for example Tyrer-Cuzick or BOADICEA; Antoniou, 2004, Amir, 2003) to assess whether they are or will be eligible for MRI.

5 MRI surveillance should be offered annually when indicated:

### **From 30–39 years:**

- to women at a 10-year risk of greater than 8%

### **From 40–49 years:**

- to women at a 10-year risk of greater than 20%, or
- to women at a 10-year risk of greater than 12% where mammography has shown a dense breast pattern<sup>3</sup>.

## **Guidance Notes**

1. For the purposes these calculations, a woman's age should be assumed to be 30 years of age for a woman in her thirties and 40 years of age for a woman in her forties. A 10-year risk should then be calculated for the age range 30–39 and 40–49, respectively.

2. A 10-year risk of 8% aged 30–39 and a 10-year risk of 12% risk aged 40–49 years would be fulfilled by women with the following family histories:

- 2 close relatives diagnosed with average age under 30 years\*
- 3 close relatives diagnosed with average age under 40 years\*
- 4 close relatives diagnosed with average age under 50 years\*

\*All relatives must be on the same side of the family and one must be a mother or sister of the woman

3. As defined by the 3-point mammographic classification used by UK breast radiologists (Breast Group of the Royal College of Radiologists 1989]

- 6 Women who have not been tested but have a high chance of carrying a *BRCA1* or *TP53* genetic mutation should be offered annual MRI surveillance from 30–49 years if they are at:
  - a 50% risk of carrying one of these mutations in a tested family, or
  - a 50% risk of carrying a *BRCA1* or *TP53* mutation in an untested or inconclusively tested family with at least a 60% chance of carrying a *BRCA1* or *TP53* mutation (that is, a 30% risk of carrying one of these mutations themselves).
- 7 MRI and any accompanying mammography data should be collected for audit purposes to support a national database.

### 3. Evidence statements

- 1 MRI in combination with mammography has increased sensitivity relative to mammography alone in surveillance for breast cancer in women at high risk of familial breast cancer and particularly *BRCA1* & *BRCA2* carriers. (Ib)
- 2 Four out of five studies showed that mammography had a greater specificity than MRI in the high risk group. (Ib)
- 3 Mammography has been shown to be a useful adjunct to MRI in the high risk group, particularly for *BRCA2* carriers because of their high incidence of ductal carcinoma insitu (DCIS). There is also some evidence that within the *BRCA2* population mammography has a higher sensitivity than MRI in detecting DCIS.(Ib).
- 4 In two studies there was a greater differential in sensitivity in favour of MRI over mammography in *BRCA1* carriers. (Ib)
- 5 No studies were found comparing the diagnostic sensitivity of digital mammography versus MRI in women at high risk of FBC

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- 6 Digital mammography has increased sensitivity over film-screen mammography in the surveillance of women from the general population under 50 years of age, pre-menopausal & peri-menopausal and those with dense breast tissue. (Ib)
- 7 No economic evaluations were identified that dealt with the cost-effectiveness of surveillance tools in those at a familial risk of breast cancer.
- 8 A cost utility model developed for this work showed that a combined approach of annual mammography and Magnetic Resonance Imaging (MRI) is a cost-effective intervention in all women with a *BRCA1* mutation aged 30–49 (Ib)
- 9 A cost utility model developed for this work showed that the use of a combined approach of annual Magnetic Resonance Imaging and mammography is a cost-effective intervention in non-*BRCA1* women aged 30-39 with an 8% or greater 10-year risk (Ib)
- 10 A cost utility model developed for this work showed that the use of a combined approach of annual Magnetic Resonance Imaging and mammography is a cost-effective intervention in non-*BRCA1* women aged 40-49 with a 20% or greater 10-year risk (Ib)

### **3.1. *Responsibility and support for guideline development***

#### **3.1.1. The National Collaborating Centre for Primary Care (NCC-PC)**

The NCC-PC is a partnership of primary care professional associations and academic units, formed as collaborating centre to develop guidelines under contract to the National Institute for Health and Clinical Excellence (NICE).

#### **3.1.2. The Technical Team**

The Technical Team had the responsibility for this guideline throughout its development. It is responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The Technical team working on this guideline consisted of the:

- Information Scientist, who searched the bibliographic databases for evidence to answer the questions posed by the Guideline Development Group (GDG)
- Reviewer, with a knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG.
- Health Economist who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness
- Project Manager, who was responsible for organising and planning the development, for meetings and minutes and for liaising the Institute and external bodies.

#### **3.1.3. The Guideline Development Group (GDG)**

Guideline Development Groups are not committees but working groups.. The aim is to get the range of experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations who were sent the draft scope of the guideline and some guidance on the expertise needed. From the nominations, three consumer representatives and the following healthcare professionals joined the GDG.

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The GDG members of the original guideline were re-convened under the same chairmanship. Because of the topic to new members were invited to join

The GDG Members are listed below:

From Previous GDG

### **Professor Gareth Evans (Chair)**

Consultant Clinical Geneticist, St Mary's Hospital, Manchester

### **Nasim Bahar**

Patient Representative

### **Professor Doug Easton**

Principle Research Fellow, Cancer Research UK

### **Dr Jane Halpin**

Public Health, Watford & Three Rivers PCT, St. Albans

### **Dr Penny Hopwood**

Consultant Psychiatrist and Psycho-Oncologist, Christie Hospital NHS Trust, Manchester

### **Aileen McIntosh**

Deputy Director, Sheffield Evidence Based Guidelines Programme, Public Health, SCHARR, University of Sheffield

### **Carmel Sheppard**

Consultant Nurse Breast Care, Portsmouth Hospitals NHS Trust/University of Southampton

### **Mr Mark Sibbering**

Consultant Breast Surgeon, Derby City General Hospital, Derby

### **Wendy Watson**

Patient representative,

### **Dr Sue Barter**

Radiologist, Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge

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*New Members*

**Dr Cristina Parsons Perez**

Senior Genetics, Policy and Information Officer, Breakthrough Breast Cancer

**Dr Ken Young**

Consultant Physicist , National Co-ordination Centre for the Physics of Mammography, Royal Surrey County Hospital NHS Trust, Guildford,

**Prof Fiona Gilbert**

Radiologist, Foresterhill Aberdeen

*Technical Team*

**Richard Norman**, Health Economist

**Gill Ritchie**, Systematic Reviewer

**Yolanda Jozeph**s, Project Manager

**Nancy Turnbull**, Chief Executive

## **4. Clinical Effectiveness of MRI**

### **4.1. Methods**

The question being addressed - is as follows:

**“What is the effectiveness and cost effectiveness of MRI versus mammography versus MRI and mammography in surveillance for breast cancer in women at increased risk compared to the general population?”**

Population: Asymptomatic women at an increased risk of breast cancer

Intervention: MRI or MRI & mammography (digital or film)

Comparator: Mammography (digital or film)

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Outcomes: sensitivity, specificity, cases identified, positive predictive values, negative predictive values, mortality, cost effectiveness

**Inclusion criteria:** RCT's, cohort or case-control studies evaluating MRI Vs mammography (X-ray mammography is the gold standard) or MRI and mammography Vs mammography in the detection of breast cancer in asymptomatic women with an increased risk of breast cancer.

**Exclusion criteria:** Insufficient information to allow construction of 2x2 table,. women without an increased risk of breast cancer (unless reported by sub group), computed radiography.

It was not within our remit to consider quality of life issues surrounding the use of MRI. However, this may be a question to be addressed when the full guideline is updated.

The search strategy used in the original guideline was repeated and updated from December 2002 when the last searches were conducted. Foreign language papers were excluded.

The Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), CENTRAL, Medline, Embase, Cinahl, & PsycInfo databases were searched from 2003 until 30th November 2005. The abstracts were read and 17 papers obtained. 12 papers were rejected because they were not relevant or did not meet the inclusion criteria. 5 papers were included for review that assessed the diagnostic accuracy of MRI vs mammography in women at increased risk of developing breast cancer.

### **Areas without evidence:**

It was anticipated that we would not find studies on the accuracy of digital imaging in an increased risk population group. Therefore we included any studies conducted in a normal population where subgroup analysis had been undertaken in the under 50 age group

An additional search was carried out for diagnostic studies of digital mammography in an average risk breast cancer population . The databases above were searched between 2003 and 22<sup>nd</sup> December 2005. Foreign language studies were excluded.

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Seven studies were obtained. Five studies were excluded because they were not relevant or did not meet the inclusion criteria. Two papers were included for review because they had carried out subgroup analysis in the population of interest to this guideline.

Where possible the data from each of the included studies have been reproduced in a 2x2 table to give figures of the true positive, false positive, false negative and true negative results of the diagnostic tests undertaken.

### 4.2. MRI Evidence

MARIBS study (Leach et al 2005)

**Table 1 Sensitivity and Specificity Table adapted from MARIBS study [Leach et al., 2005]**

	Mammography			MRI			MRI & mammography		
	All women	<i>BRCA1</i>	<i>BRCA2</i>	All women	<i>BRCA1</i>	<i>BRCA2</i>	All women	<i>BRCA1</i>	<i>BRCA2</i>
No. women	649	139	86	649	139	86	649	139	86
No positive screens									
True positive	14	3	6	27	12	7	33	12	11
False positive	121	30	13	344	76	41	428	95	51
No negative screens									
True negative	1725	335	219	1502	289	191	1418	270	181
False negative	21	10	6	8	1	5	2	1	1
Sensitivity %	40%	23%	50%	77%	92%	58%	94%	92%	92%
Specificity %	93%	92%	94%	81%	79%	82%	77%	74%	78%
predictive value % positive	10%	9%	32%	7%	14%	15%	7%	11%	18%
negative	99%	97%	97%	99%	100%	97%	100%	100%	99%

The MARIBS study was a multicentre prospective cohort study of 649 women aged 35-49 years with a *BRCA1*, *BRCA2*, *TP53* mutation or strong family history of breast cancer. Annual screening of MRI and mammography was carried out for 2-7 years (1881 screens). A total of 35 cancers were diagnosed. 19 by MRI only, six by

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mammography only and eight by both, with two interval cases. 11 invasive cancers were less than 10 mm in greatest dimension. Of these, six were detected by MRI, three by mammography, one by both modalities, and one interval case. Four invasive cancers were between 10-14 mm. Three were detected by MRI and one by both modalities. Five invasive cancers were between 15-19 mm. Four were detected by MRI and one by both modalities. Nine cancers were 20 mm or larger in dimension, six were detected by MRI and three by both modalities. There were six cases of ductal carcinomas in situ (DCIS), of which four were less than 10 mm in diameter. Three were detected by mammography, two were detected by both modalities and one was an interval cancer. Of the 29 invasive cancers, three were grade 1, seven were grade 2, 19 were grade 3. Of cancers detected by screening or in a screening interval, 21 of 26 were node negative.

Sensitivity was significantly higher for MRI than for mammography and was particularly pronounced in *BRCA1* carriers (13 cancers). The authors note that MRI is able to detect tumours earlier in their development compared with mammography, although mammography is relatively good at detecting DCIS compared with MRI. In spite of annual screening with two modalities, some large, node positive tumours were identified. This reflects the rapid growth characteristics of cancers in women with germline mutations.

Overall the study shows that the combination of MRI with mammography is the most effective screening examination for *BRCA1* and *BRCA2* carriers and the full high-risk cohort studied here. The authors also conclude that their results suggest that MRI screening would be of most benefit to *BRCA1* carriers.

MRISC study (Kriege et al 2004)

**Table 2 Sensitivity and Specificity Table adapted from [Kriege et al., 2004]**

	Mammography	MRI
Total screens	4169	4169
No positive screens		
True positive	18	32
False positive	207	420
No negative screens		
True negative	3917	3704
False negative	27	13
Sensitivity %	40	71
Specificity%	95	90
predictive value %		

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True	8	7
Negative	99	100

Women who had a cumulative lifetime risk of breast cancer of 15 percent or more were included in this cohort study [Kriege et al., 2004]. 1909 asymptomatic women including: 358 carriers of germline mutations, 1052 high risk (30-50% cumulative lifetime risk), 499 moderate risk (15-30% cumulative lifetime risk) were screened, with a mean follow-up of 2.9 years. Among the women examined by both methods at the same screening visit, 45 tumours were detected including 6 ductal carcinomas in situ (DCIS). Five patients were excluded from analysis.

Of the invasive cancers 19 were 1cm or less in diameter, 14 were between 1-2 cm, 11 were more than 2 cm in diameter. Six of the 42 invasive tumours with known axillary status were node positive.

11 grade 1 cancers were found in women at high risk (68.8%), 6 in moderate risk women (75.0%), 2 in mutation carriers (10.5%).

One Grade 2 cancer was found in women at high risk (6.2%), 2 in moderate risk (25.0%), 5 in mutation carriers (26.3%).

Four Grade 3 tumours were found in women at high risk (25.0%), 1 in moderate risk (12.5%), 12 in mutation carriers (63.2%).

The authors comment that larger tumours were found in women with *BRCA1*, *BRCA2* and *TP53* mutations than the other two risk groups in the study, suggesting that more frequent screening is necessary for this group of women.

The study found that the sensitivity of MRI was higher than mammography, but that the specificity and positive predictive value were lower. MRI detected 20 cancers (including 1 DCIS) that were not found by mammography, and the stage of these cancers was favourable, 11 of the 19 invasive tumours being less than 10 mm.

The study also showed that mammography had a higher sensitivity than MRI for detecting ductal carcinoma in situ (DCIS) 83% (five out of six cancers detected), compared with 17% (one out of six) for MRI. In this study, screening with MRI led to twice as many unneeded additional examinations compared with mammography

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(420 versus 207) and three times as many unneeded biopsies (24 versus 7). The authors conclude that the MRI can detect breast cancer at an earlier stage in women at risk for breast cancer.

Warner et al study 2004

**Table 3 Sensitivity and Specificity Table adapted from [Warner et al., 2004].**

	Mammography				MRI			
	Year 1	Year 2	Year 3	Total	Year 1	Year 2	Year 3	Total
Total screens	236	136	85	457	236	136	85	457
No positive screens								
True Positive	5	3	0	8	11	5	1	17
False positive	1	0	0	1	15	4	1	20
No negative screens								
True negative	222	129	83	434	208	125	82	415
False negative	8	4	2	14	2	2	1	5
Sensitivity %	38	43	0	36	85	71	50	77
Specificity %*	99.6	100	100	99	93	97	99	95.4
Predictive value %								
True	83	100	N/A	88	42	56	50	46
Negative	97	97	98	97	99	98	99	99

Abbreviations: MRI magnetic resonance imaging; N/A not applicable  
\*Definition of specificity is based on biopsy rates

A cohort study of 236 asymptomatic women with *BRCA1* or *BRCA2* mutations underwent 1-3 annual screenings [Warner et al., 2001]. The study found that MRI was more sensitive for detecting breast cancer than mammography or CBE alone. 22 cancers were detected in total; 16 invasive, 6 ductal carcinoma in situ (DCIS). There was one interval cancer.

All six of the DCIS cancers were found in the *BRCA2* group. Four in year 1, (two detected by MRI, tumour size between 3.0-4.0 cm, one detected by mammography, tumour size not given because specimen consisted of few small scattered foci, one detected by both modalities, tumour size 1.5 cm). One in year 2, (detected by mammography, no remaining cancer was observed at time of excisional biopsy). One in year 3, (detected by MRI, tumour size 6.0 cm).

Nine invasive cancers in year 1 were detected. Six had tumour sizes between 0.5-1.0 cm (3 detected by MRI, 1 detected by mammography, 2 detected by both modalities), three had tumour sizes of 1.5-2.0 cm (2 detected by MRI, 1 by neither (ultrasound.)) Six invasive cancers were detected in year two. Three had tumour sizes of 0.6-1.0 cm (3 detected by MRI), three had tumour sizes of 1.5-2 cm (2

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detected by both modalities, 1 by neither (ultrasound). One cancer was node positive.

The study shows that the addition of annual MRI to mammography improves the sensitivity of surveillance for detecting early breast cancers. The authors suggest that mammography appears to be a useful adjunct to MRI for *BRCA2* carriers because of the high incidence of ductal carcinoma insitu (DCIS) in this group.

The authors note that MRI recall rates decreased from 26% on the first round of screening to 13% on the second round and 10% on the third. The authors conclude that the study supports the position that MRI-based screening should be used for breast cancer surveillance for *BRCA1* and *BRCA2* mutation carriers. Further research is required to demonstrate whether this modality lowers breast cancer mortality before it can be recommended for general use.

Kuhl et al study 2005

**Table 4 Sensitivity and Specificity Table adapted from [Kuhl et al., 2005].**

	Mammography				MRI				MRI & Mammography			
	All	Risk 20%	Risk 20-40%	Mutation Carriers	All	Risk 20%	Risk 20-40%	Mutation carrier	All	Risk 20%	Risk 20-40%	Mutation carrier
Total screens	1701	352	751	167	1701	352	751	167	1701	352	751	167
No positive screens												
True positive	14	3	5	2	39	6	20	8	40	6	20	8
False positive	45	11	18	5	39	10	16	4	55	14	14	9
No negative screens												
True negative	1364	302	676	154	1370	254	678	155	1354	299	673	150
False negative	29	3	15	6	4	0	0	0	3	0	0	0
Sensitivity %	32.6	50	25	25	90.7	100.0	100.0	100.0	93.0	100.0	100.0	100.0
Specificity %	96.8	96.5	97.4	96.9	97.2	97.4	97.7	97.5	96.1	95.5	97.0	94.4
Predictive rates %												
Positive PV	23.7	21.4	21.7	28.6	50.0	42.9	55.6	66.7	42.1	30.0	51.2	47.1
Negative PV	97.91	99.0	97.4	96.8	99.7	100	100	100	99.7	100	100	100

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This cohort study comprised of 529 asymptomatic women who were suspected or proven to carry a breast cancer susceptibility gene [Kuhl et al., 2005]. A total of 1542 surveillance rounds were completed with a mean follow-up of 5.3 years. This study found that in patients at high familial risk for breast cancer MRI had the highest sensitivity, specificity and positive predictive rates for the detection of cancer. Forty three cancers were identified in the total cohort (34 invasive, 9 ductal carcinoma in situ (DCIS)). Forty of the forty three were diagnosed by imaging studies. Two cancers were palpable at the time of diagnosis (one at the regular screening interval, one was an interval cancer diagnosed in between screening rounds). These two clinically palpable cancers were also visualised by MRI but not mammography.

Nineteen cancers were diagnosed by means of MRI only. These included five intraductal (all high grade) and 14 invasive cancers with a median size of 7.5 mm. All fourteen invasive cancers were staged pT1 and all had negative axillary lymph nodes.

14 cancers diagnosed by mammography. These included three intraductal and ten invasive cancers with a median size of 12.0 mm, four were node positive.

39 cancers were detected by MRI. These included eight intraductal and 31 invasive cancers with a median size of 11.0 mm, five were node positive.

This study found that MRI had the highest sensitivity, specificity and positive predictive value for the detection of invasive as well as intraductal cancer. The addition of mammography to MRI did not improve sensitivity to a statistically significant degree. The authors conclude that compared with mammography, surveillance with MRI allows an earlier diagnosis of familial breast cancer and at an earlier stage. The specificity of MRI was equivalent to that achieved with mammography, which the authors suggest is due to the highly experienced readers used in the study. The number of cancers in the subgroup at moderate risk was too low to make valid recommendations regarding which surveillance modalities to recommend. The findings of this study lead the authors to recommend that MRI should be an integral part of surveillance for women at high familial risk, particularly in documented mutation carriers, but also for women without documented mutation. The authors also note that further work is required to assess the risk/benefit ratio of

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mammography and MRI in young *BRCA1* mutation carriers who may exhibit an increased radiosensitivity.

International Breast MRI Consortium Working Group study (Lehman et al 2005)

**Table 5 Sensitivity and Specificity Table adapted from [Lehman et al., 2005]**

	Mammography	MRI
Total screens	367	367
No of positive screens		
True Positive	1	4
False positive	3	20
No of negative screens		
True negative	360	343
False negative	3	0
Sensitivity %	25.0	100.0
Specificity %	99.0	95.0
Predictive rates %		
Positive Predictive value	25.0	17.0
Negative predictive value	99.0	100.0

This prospective study compared the performance of screening mammography with MRI on 367 asymptomatic high risk women age 25 or above [Lehman et al., 2005]. The objective of this study was also to ascertain if imaging and biopsy procedures are reliable and do not result in excessive false positive examinations. Imaging results recommended 38 biopsies of which 27 were performed. 4 cancers were detected overall, all were detected by MRI, and mammography detected 1 of these. The biopsy recommendation rates for MRI and mammography were 8.5% (95% CI 5.8-11.8) and 2.2% (95% CI 0.1-4.4), respectively. Twenty four women underwent biopsy based on a positive MRI and four based on a positive mammogram. Of the lesions that were identified as malignant, two were identified in women with scattered fibroglandular density, and two were identified in women with heterogeneously dense breast tissue. Three of the four lesions were identified as infiltrating ductal carcinomas ranging in size from 5 mm to 13 mm, and one lesion was DCIS. All were lymph node negative.

The limitations of this study are that only one screening round was undertaken and no follow-up was carried out to identify potential false negative MRI results or delayed diagnoses of those who declined biopsies. The authors conclude that although the specificity of MRI has been challenged they found only 5% of women

underwent benign biopsy and the PPV of biopsies performed was 17%. They recommend that MRI should be considered as a complement to mammography.

### **4.3. Digital mammography Vs film mammography Evidence**

DMIST study (Pisano et al 2005)

There was insufficient data provided to construct a 2 x 2 table.

This prospective study was conducted to assess whether the use of digital mammography had a higher sensitivity than film mammography [Pisano et al., 2005].

The results from 42,760 asymptomatic women entered into the trial were reported. Sub group analysis was undertaken in the following: under 50 age group, pre-menopausal and peri-menopausal n=15803, and those with heterogeneously or extremely dense breasts n=19897. In the entire population the diagnostic accuracy of digital and film mammography was similar. The accuracy was significantly higher for digital mammography in the under 50 age group, women with dense breasts and pre-menopausal & peri-menopausal women.

A total of 335 cancers were diagnosed. Of these 254 (75.8%) were diagnosed within 365 days after study mammography and 81 (24.2%) were diagnosed between 366-455 days after study mammography.

In the pre-menopausal & peri-menopausal subgroup film mammography identified seven (2.1%) invasive cancers, four (1.2%) ductal carcinoma in situ (DCIS), three were node positive. Digital mammography identified 19 (5.7) invasive cancers, 14 (4.2%) DCIS, five were node positive.

In the heterogeneously dense or extremely dense breast subgroup, film mammography identified 12 (3.6%) invasive cancers, seven (2.1%) DCIS, five were node positive. Digital mammography identified 26 (7.8%) invasive cancers, 14 (4.2%) DCIS, five were node positive.

The authors conclude that digital mammography was significantly better than conventional film mammography at detecting breast cancer in these groups. The cancers detected by digital mammography and missed by conventional mammography included many invasive and high-grade in situ cases. The authors conclude that this justifies the use of digital mammography in these groups.

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### Oslo II study (Skaane et al 2004)

This randomised controlled trial [Skaane and Skjennald, 2004] was conducted to compare cancer detection rates, recall rates and positive predictive value of film mammography (FM) with digital mammography (DM). 25,263 women aged 45-69 years were randomised to either film or digital mammography. Sub group analysis was carried out on the 45-49 age group (n=7607). 17 cancers were detected with FM (10 invasive cancers, seven DCIS). The median size of invasive cancers detected by FM was 11mm. 8 cancers were detected with DM (six invasive cancers, two DCIS). The median size of invasive cancers detected by DM was 10 mm.

Recall rates in both groups were significantly higher with DM than FM ( $P < 0.05$ ), but positive predictive value was not significantly different. In the 45-49 age group the cancer detection rate was nearly equal for the two modalities ( $P = 0.686$ .) The authors state that a limitation of the study was that comparisons between FM and DM were available only during review of positive mammograms. Low recall rates and no follow-up for probably benign lesions might have caused cancers represented by a positive score on images in either modality to be dismissed at consensus meetings, where decisions about which women should continue in the screening programme and which be recalled for diagnostic workup were taken. Follow-up for two years would be necessary to detect incorrectly dismissed cancers and to evaluate interval cancers in a subsequent screening round.

The number of breast cancers in the group was small and the authors state that the results do not permit any final conclusions regarding the comparison of FM and DM in women younger than 50 years.

## **5. Cost-Utility Analysis**

### **5.1. Executive Summary**

#### **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***

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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 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 to be 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***

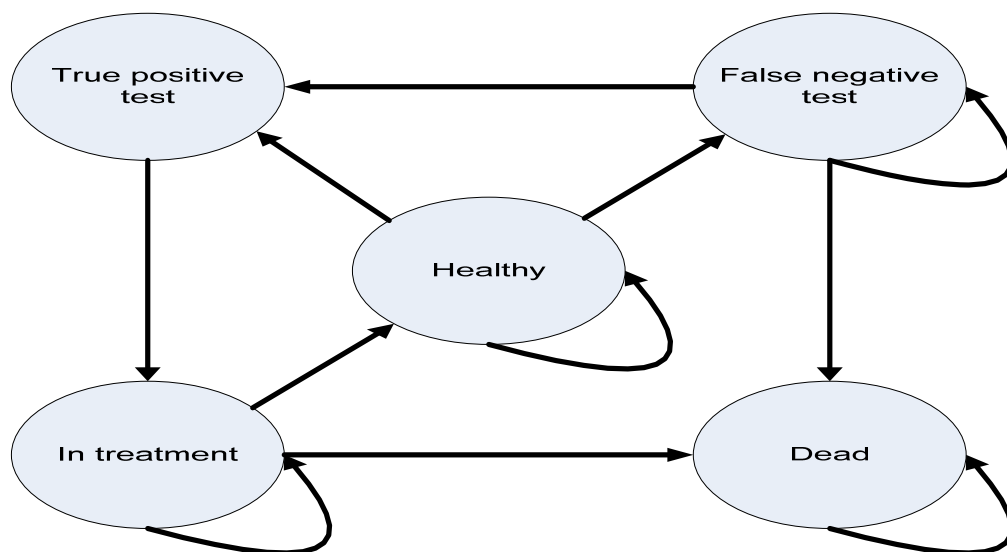
This analysis suggests that MRI screening has a role in play in routine surveillance of women at a high risk of breast cancer between 30 and 49. Despite the relatively small size of the population in question, there is an issue with regards to the provision of these services.

## 5.2. 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 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.

### 5.2.1. 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.

### 5.2.2. 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 6 The Sensitivity and Specificity of Screening Techniques**

	No screening	Annual Mammography	Annual MRI scans	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

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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.

### 5.2.3. 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

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*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 7 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.

#### **5.2.4. 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](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.

#### **5.2.5. 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

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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.

### 5.2.6. 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 8 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 9 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.

### 5.2.7. 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 1 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 1) in proportion to the expected increase in the breast cancer risk level for each sub-group considered.

**Table 10 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 <b>mGy</b>
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.

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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]

### **5.2.8. 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.

### **5.2.9. 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].

### **5.2.10. Discounting**

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

### **5.2.11. 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.

### **5.2.12. 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) =  $(\text{Cost (A)} - \text{Cost (B)}) / (\text{Q (A)} - \text{Q (B)})$

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.

### 5.3. Results

#### 5.3.1. 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 11 BRCA1 population (31% 10-year risk for a 40-year old)**

Screening method	Total cost (£ million)	Cost relative to no screening (£M)	Total QALY's	QALY's relative to no screening
No screening	4.915	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 12 High risk (12% 10-year risk for a 40-year old)**

Screening method	Total cost (£ million)	Cost relative to no screening (£M)	Total QALY's	QALY's relative to no screening
No screening	1.679	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 13 Raised risk (6% 10-year risk for a 40-year old)**

Screening method	Total cost (£ million)	Cost relative to no screening (£M)	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 14 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	1.675	575	2 913
Combined	Mammography	2.250	289	7 781

**Table 15 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	1.576	141	11 226
Combined	Mammography	2.192	74	29 622

**Table 16 Incremental Analysis in the Raised Risk Group**

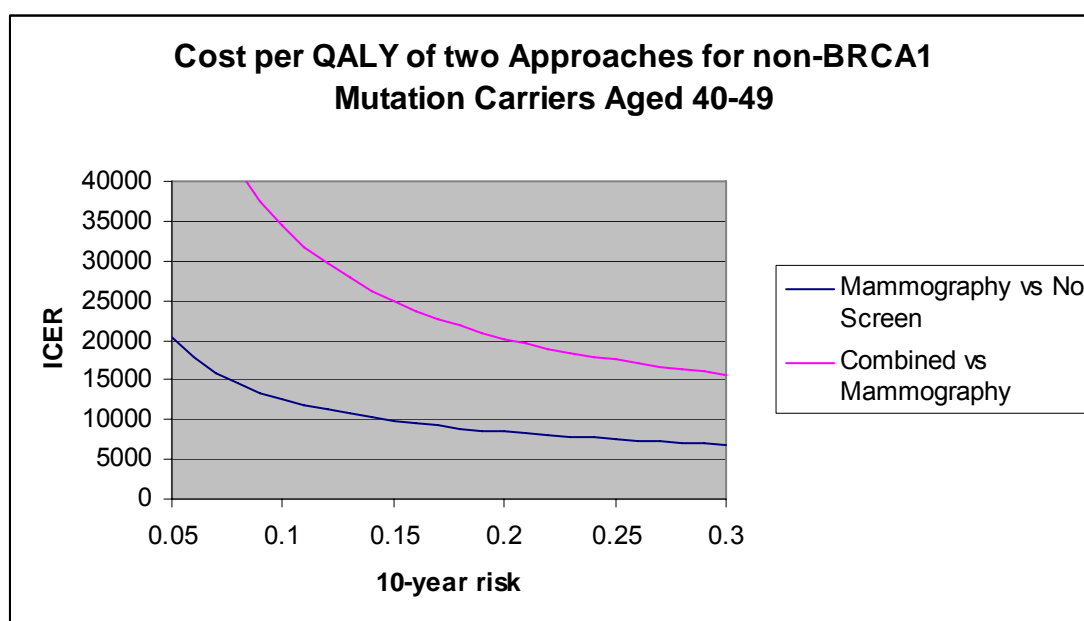
Option A	Option B	Incremental cost (A vs. B) (£M)	Incremental QALY's (A vs. B)	ICER
Mammography	No screening	1.224	70	17 427
Combined	Mammography	2.185	41	53 544

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-

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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.

### 5.3.2. 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

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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 17 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 18 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 19 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,

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alongside the comparison of MRI alone relative to no screening (for the reasons outlined previously).

**Table 20 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 21 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

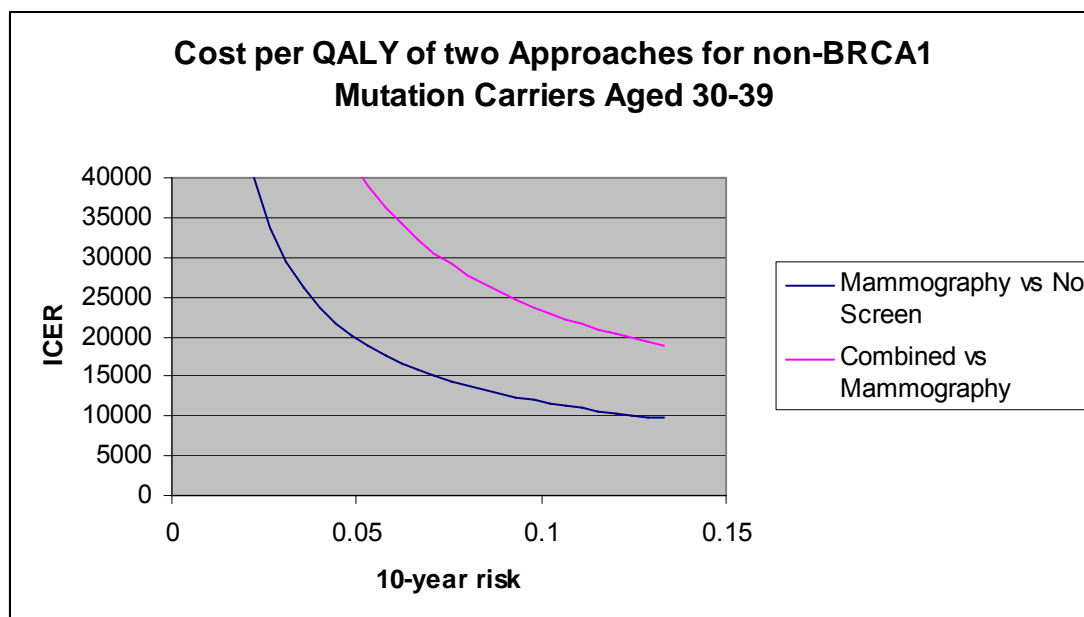
**Table 22 Incremental Analysis in the Raised Risk Group**

Option A	Option B	Incremental cost (A vs. B) (£M)	Incremental QALY's (A vs. B)	ICER
MRI	No screening	3.189	60	53 111

### 1.1.1.1 *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.



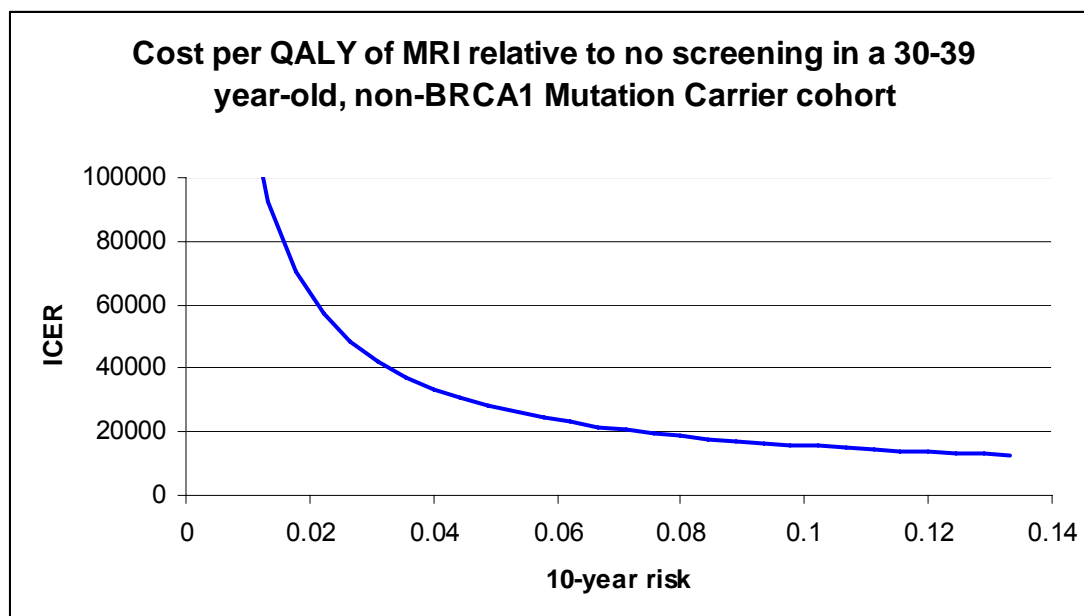
The annual mammography crosses the £20 000 value at a 10-year risk below 5%. The combined approach becomes cost-effective when 10-year risk at 30 rises to 12.3%. The figure is lower than that for the older age group since successfully identified and treated individuals have a greater lifespan. However,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

#### 1.1.1.2 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.

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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.



### 5.3.3. 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

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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).

## **5.4. 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).

### **5.4.1. 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

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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.

### 5.5. References

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## 5.6. Appendices

### 5.6.1. Appendix 1: Assumed distributions and parameters used in 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 1 <sup>st</sup> possible opportunity	0.85 (non- <i>BRCA1</i> ) 0.8 ( <i>BRCA1</i> )	Beta	0.085	14.15	2.497059
	Prognosis in those identified at the 2 <sup>nd</sup> possible opportunity	0.75 (non- <i>BRCA1</i> ) 0.65 ( <i>BRCA1</i> )	Beta	0.075	24.25	8.083333
	Prognosis in those identified at the 3 <sup>rd</sup> possible opportunity	0.65 (non- <i>BRCA1</i> ) 0.5 ( <i>BRCA1</i> )	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	984	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

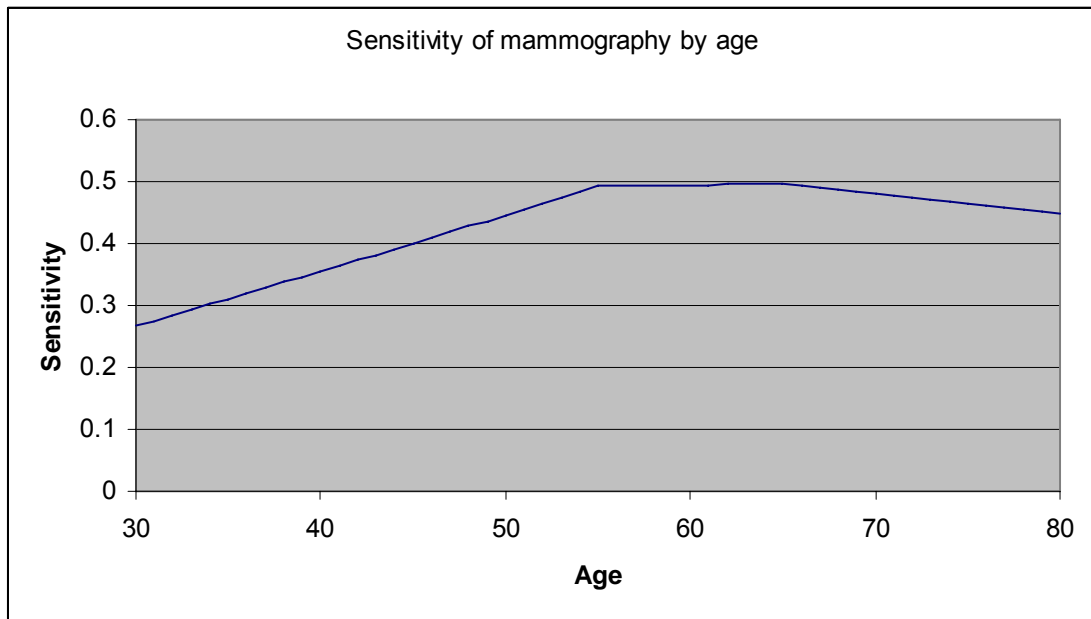
### 5.6.2. Appendix 2: Sensitivity of Mammography by Age

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
60-69	0.932
70+	0.87

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.

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### 5.6.3. Appendix 3: Unit costs

**Table 23 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 evaluation
Ultrasound scan	Unit	48.8	MARIBS economic evaluation
Biopsy	Unit	176	MARIBS economic evaluation
MR-guided biopsy	Unit	955	MARIBS economic evaluation
Chemotherapy	Unit	922	NHS Reference Costs 2004
Wide local excision	Unit	984	NHS Reference Costs 2004*
Mastectomy	Unit	2 058	MARIBS economic evaluation
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.**

**5.6.4. Appendix 4: Utility Multipliers Used in the Model A**

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

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

Figure 2 : Costs and Outcomes (*BRCA1*, aged 40-49)

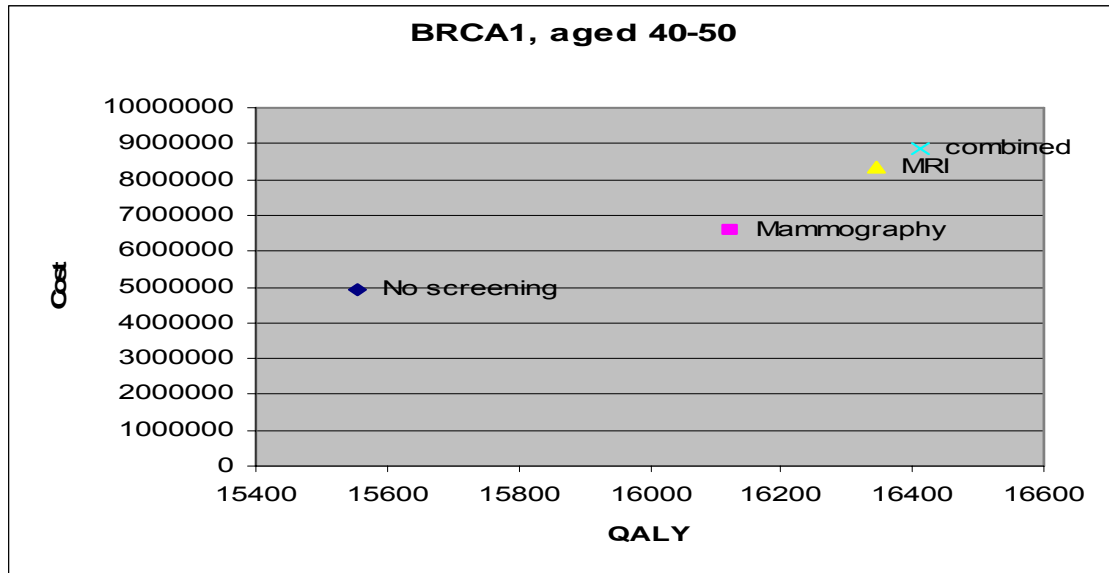


Figure 3 : Costs and Outcomes (high risk, aged 40-49)

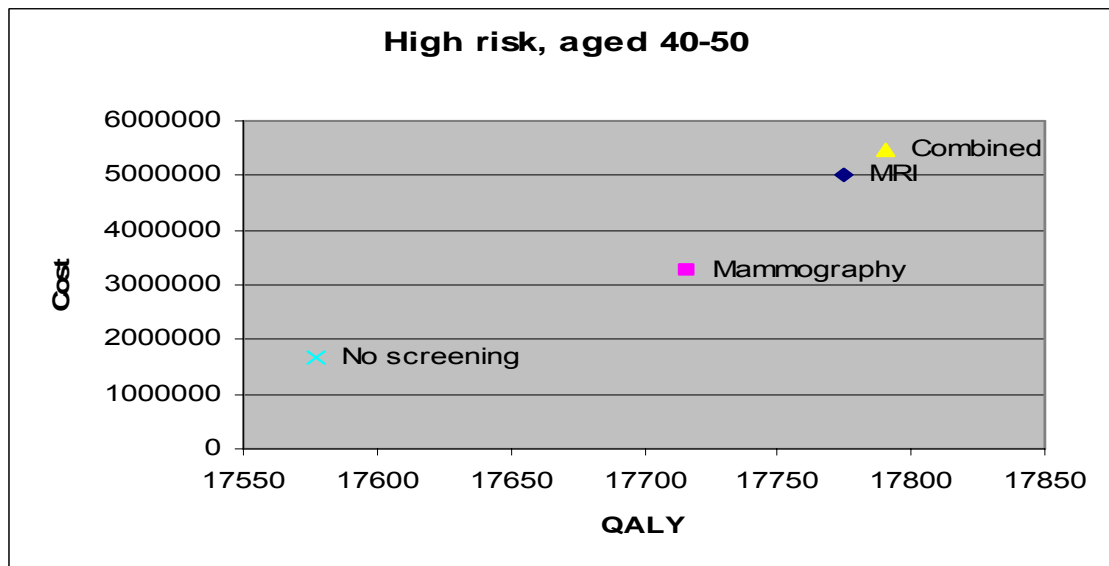


Figure 4 Costs and Outcomes (raised risk, aged 40-49)

# Familial Breast Cancer

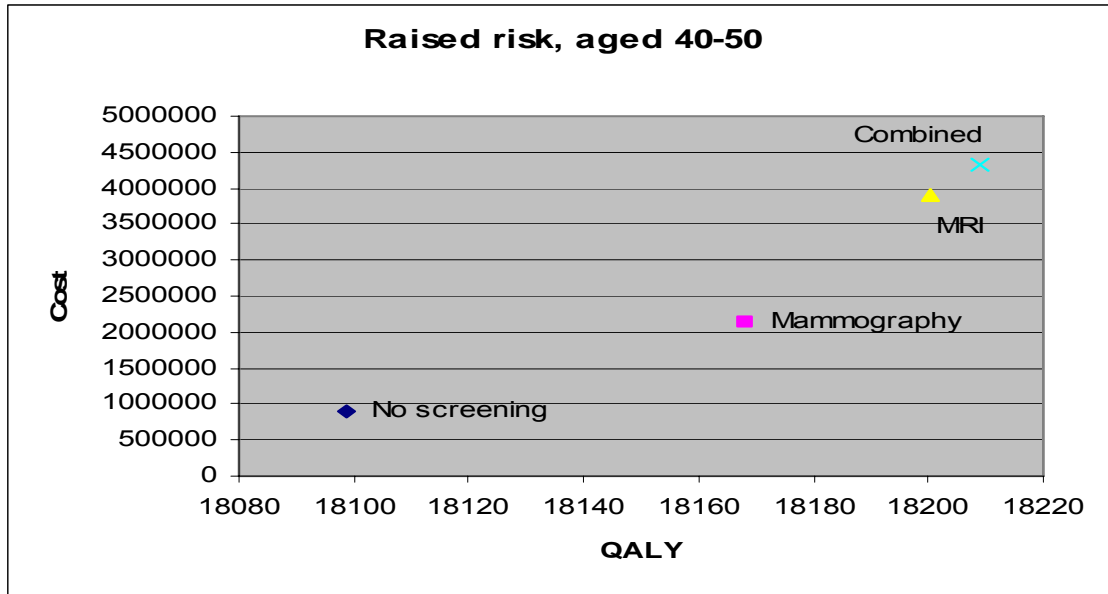
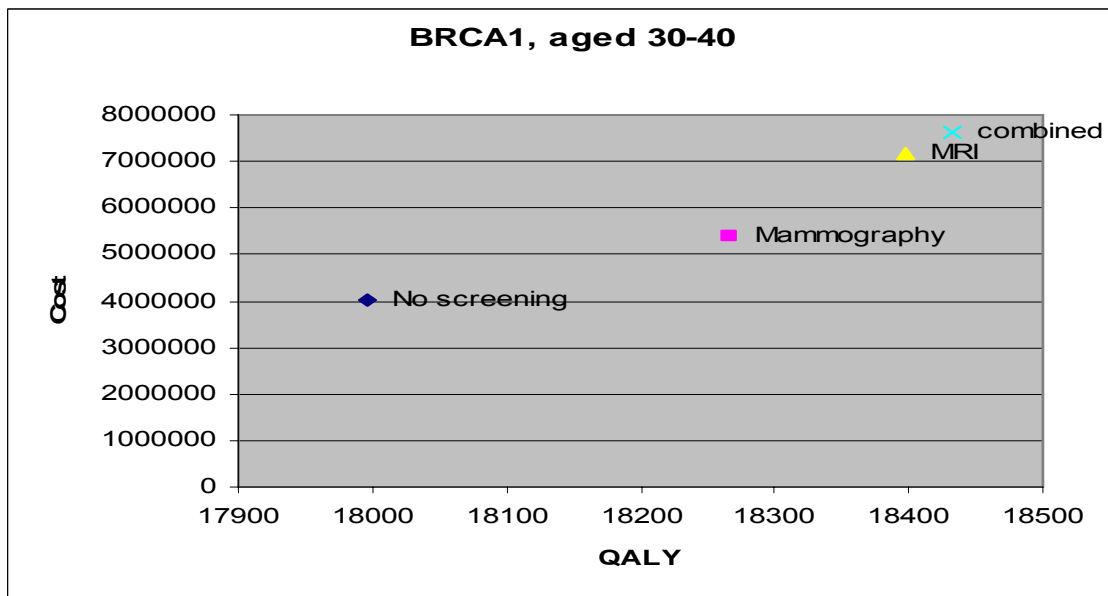


Figure 5 Costs and Outcomes (BRCA1, aged 30-39)



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Figure 6: Costs and Outcomes (high risk, aged 30-39)

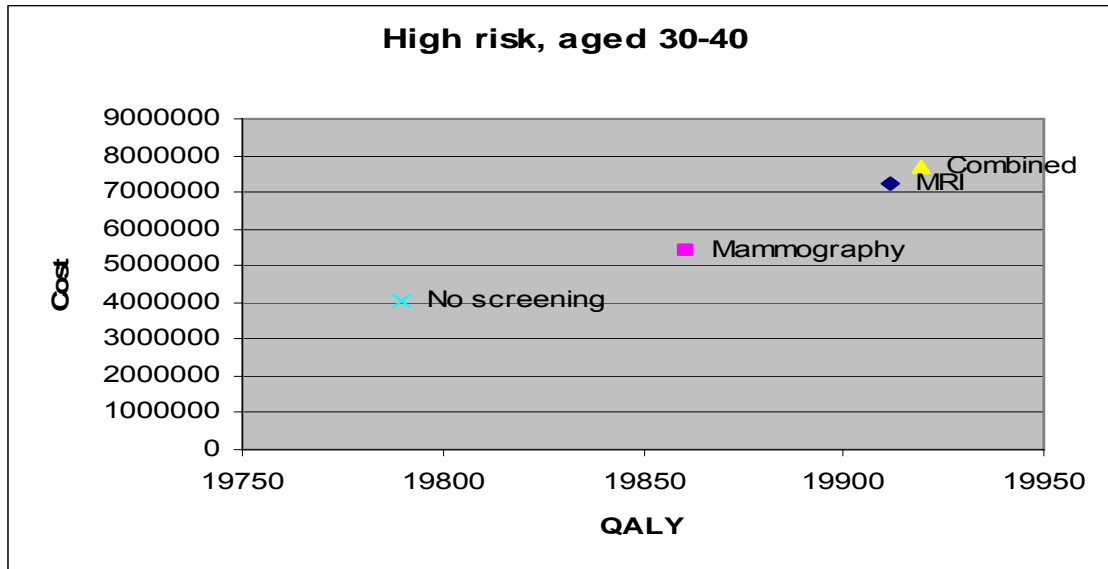
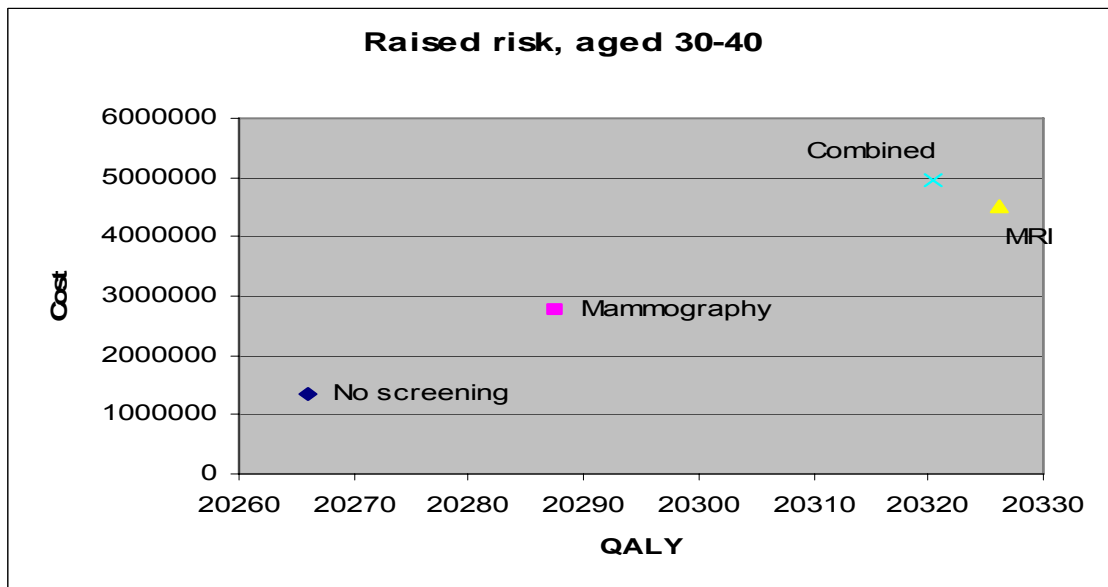


Figure 7 : Costs and Outcomes (Raised risk, aged 30-39)



**5.6.6. 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 negatives	0.005	0.008	0
	Prognosis (1) <i>BRCA1</i>	0.8	0.9	0.7
	Prognosis (2) <i>BRCA1</i>	0.65	0.75	0.55
	Prognosis (3) <i>BRCA1</i>	0.5	0.6	0.4
	Prognosis (1) non- <i>BRCA1</i>	0.85	0.95	0.75
	Prognosis (2) non- <i>BRCA1</i>	0.75	0.85	0.65
	Prognosis (3) non- <i>BRCA1</i>	0.65	0.75	0.55
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

**5.6.7. 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	<i>BRCA1</i> range	High risk range	Raised risk range
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## Familial Breast Cancer

Probabilities	Mortality of false negatives	5 145 - 5 413	17 926 – 20 331	39 093 - 45 444
	Prognosis (1) <i>BRCA1</i>	4 342 - 6 629	N/A	N/A
	Prognosis (2) <i>BRCA1</i>	4 735 - 5 872	N/A	N/A
	Prognosis (3) <i>BRCA1</i>	4 015 - 7 843	N/A	N/A
	Prognosis (1) non- <i>BRCA1</i>	N/A	13 530 - 30 766	28 510 - 74 551
	Prognosis (2) non- <i>BRCA1</i>	N/A	15 535 - 23 677	33 325 - 54 123
	Prognosis (3) non- <i>BRCA1</i>	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 - 5 269	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	<i>BRCA1</i> 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) <i>BRCA1</i>	2 301 – 4 019	N/A	N/A
	Prognosis (2) <i>BRCA1</i>	2 566 – 3 379	N/A	N/A
	Prognosis (3) <i>BRCA1</i>	2 147 – 4 799	N/A	N/A
	Prognosis (1) non- <i>BRCA1</i>	N/A	7 651 – 21 159	11 570 - 35 221
	Prognosis (2) non- <i>BRCA1</i>	N/A	9 184 – 14 451	14 057 - 22 926
	Prognosis (3) non- <i>BRCA1</i>	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 - 17 769

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### 5.6.8. Appendix 6c Results for Univariate Sensitivity Analysis (Combined approach relative to mammography)

#### 6c(i) 30-39 year olds

Type of parameter	Parameter	<i>BRCA1</i> 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) <i>BRCA1</i>	8 651 - 31 016	N/A	N/A
	Prognosis (2) <i>BRCA1</i>	11 918 - 15 543	N/A	N/A
	Prognosis (3) <i>BRCA1</i>	10 294 - 20 226	N/A	N/A
	Prognosis (1) non- <i>BRCA1</i>	N/A	21 151 - 260 940	38 819 - 421 436
	Prognosis (2) non- <i>BRCA1</i>	N/A	32 449 - 48 670	59 395 - 88 517
	Prognosis (3) non- <i>BRCA1</i>	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

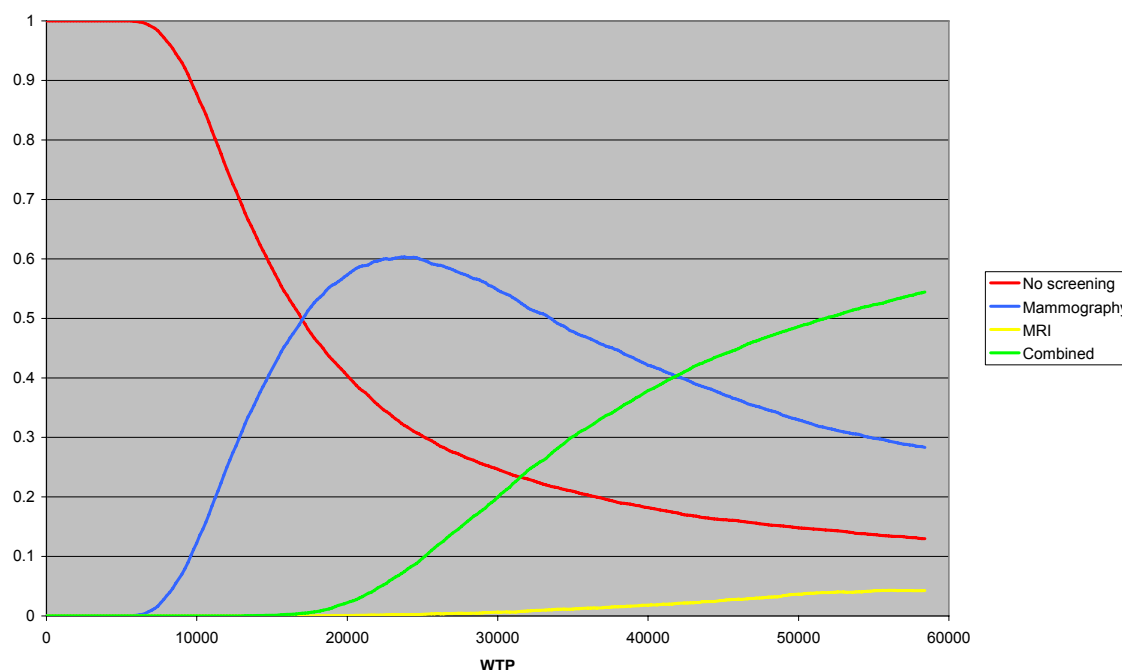
Type of parameter	Parameter	<i>BRCA1</i> range	High risk range	Raised risk range
Probabilities	Mortality of false negatives	7 525 – 8 262	27 605 - 33 819	49 911 - 61 060
	Prognosis (1) <i>BRCA1</i>	4 744 – 22 634	N/A	N/A
	Prognosis (2) <i>BRCA1</i>	6 389 – 9 990	N/A	N/A
	Prognosis (3) <i>BRCA1</i>	5 972 – 11 479	N/A	N/A
	Prognosis (1) non- <i>BRCA1</i>	N/A	Dominated - 14 804	27 168 - 1.644M
	Prognosis (2) non- <i>BRCA1</i>	N/A	22 289 - 44 242	40 551 - 78 855
	Prognosis (3) non- <i>BRCA1</i>	N/A	19 382 - 65 114	35020 - 115 648

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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 incidence	Increase in annual incidence due to mammography	7 771 – 7 790	29 612 - 29 632	53 535 - 53 553

### 5.6.9. Appendix 7: Probabilistic Sensitivity Analysis

Figure 8: Cost-Effectiveness Acceptability Curves for Raised Risk Individuals Aged 40



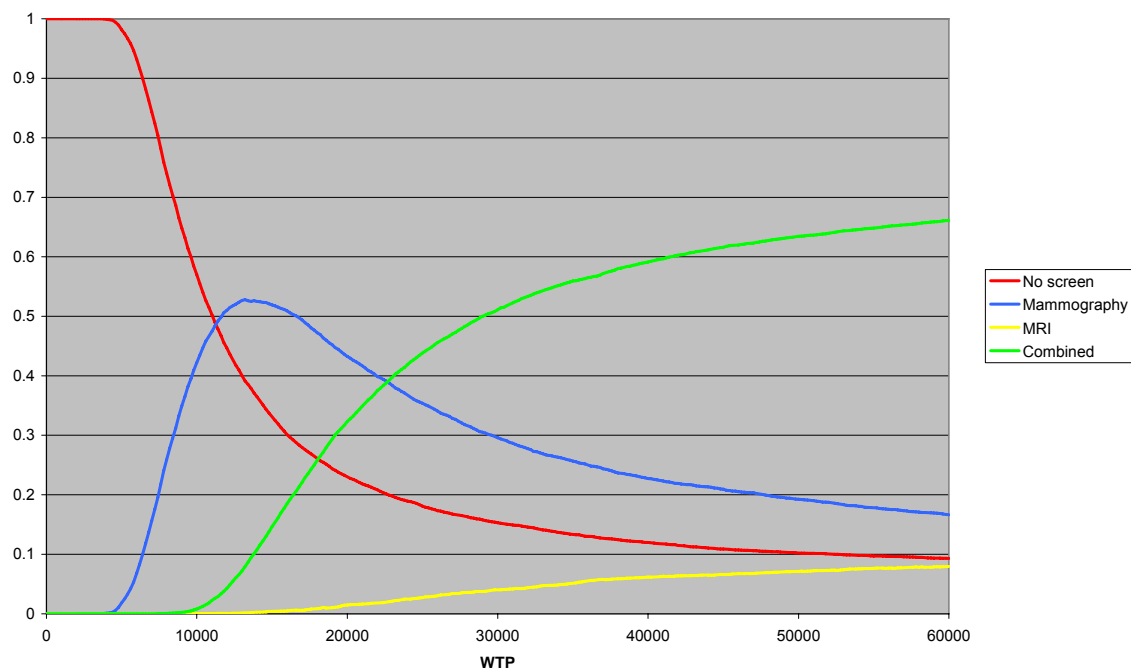
This contrasts the societal willingness to pay for a QALY with the probability of each intervention being cost-effective relative to the other three (thus, at any point, the probabilities sum to 1). Firstly, it should be noted that, as expected, the more expensive and more sensitive interventions are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

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**Figure 9 : Cost-Effectiveness Acceptability Curves for High Risk, non-*BRCA1* Individuals Aged 40**



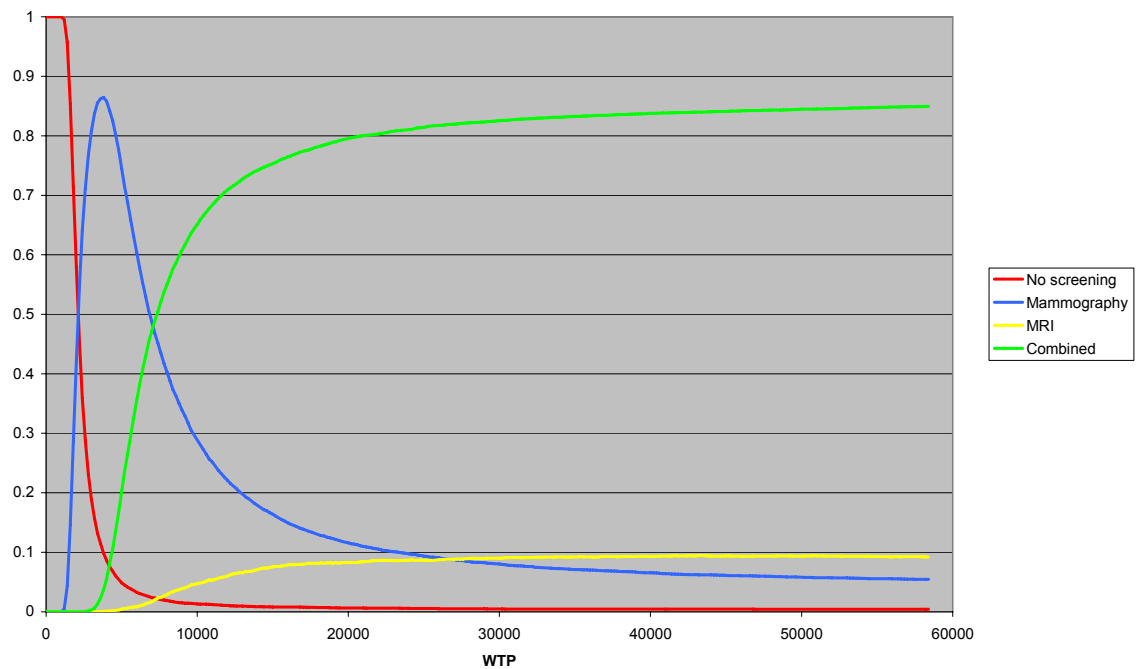
As the diagram suggests, more expensive interventions are relatively more likely to be cost-effective in this higher risk group. This is reasonable as the screening method would identify more tumours since there is likely to be a higher incidence in the period prior to screening. At a societal valuation 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.<sup>1</sup>

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<sup>1</sup> 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.

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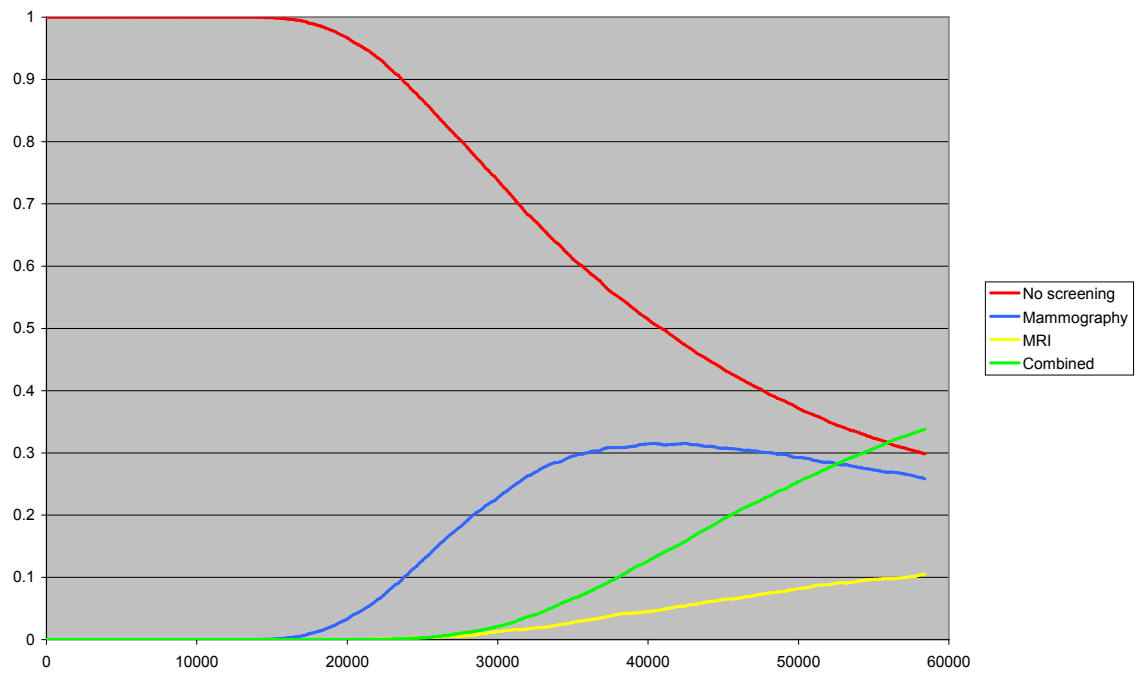
**Figure 10: Cost-Effectiveness Acceptability Curves for *BRCA1* Mutation Individuals Aged 40**



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%.

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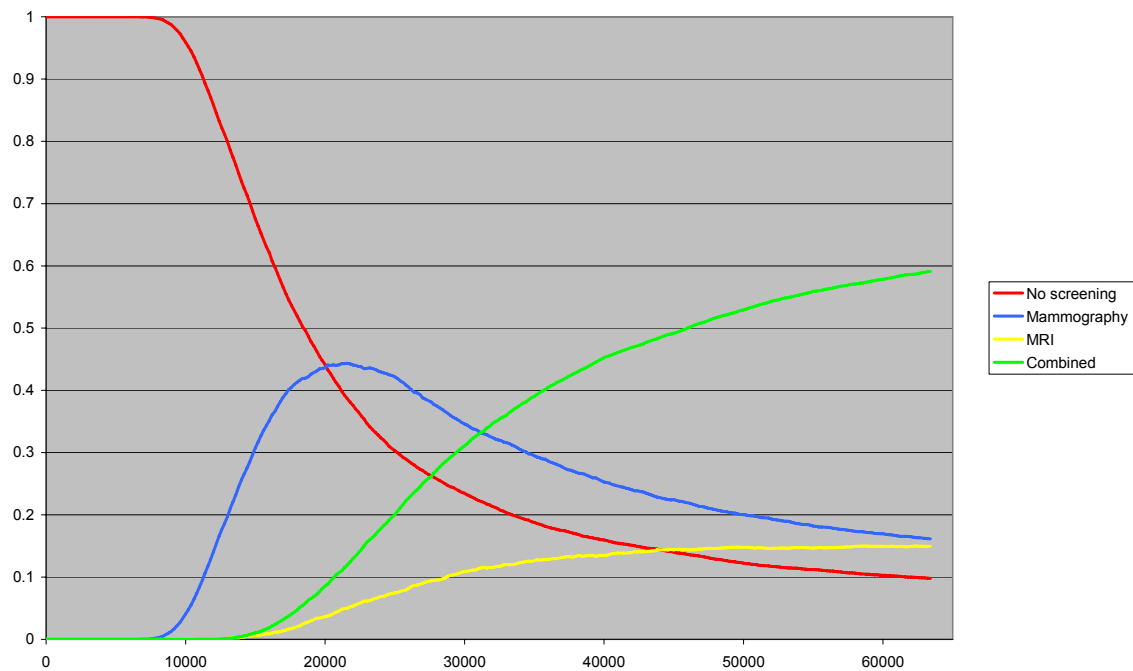
Figure 11: Cost-Effectiveness Acceptability Curves for Raised Risk Individuals Aged 30



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.

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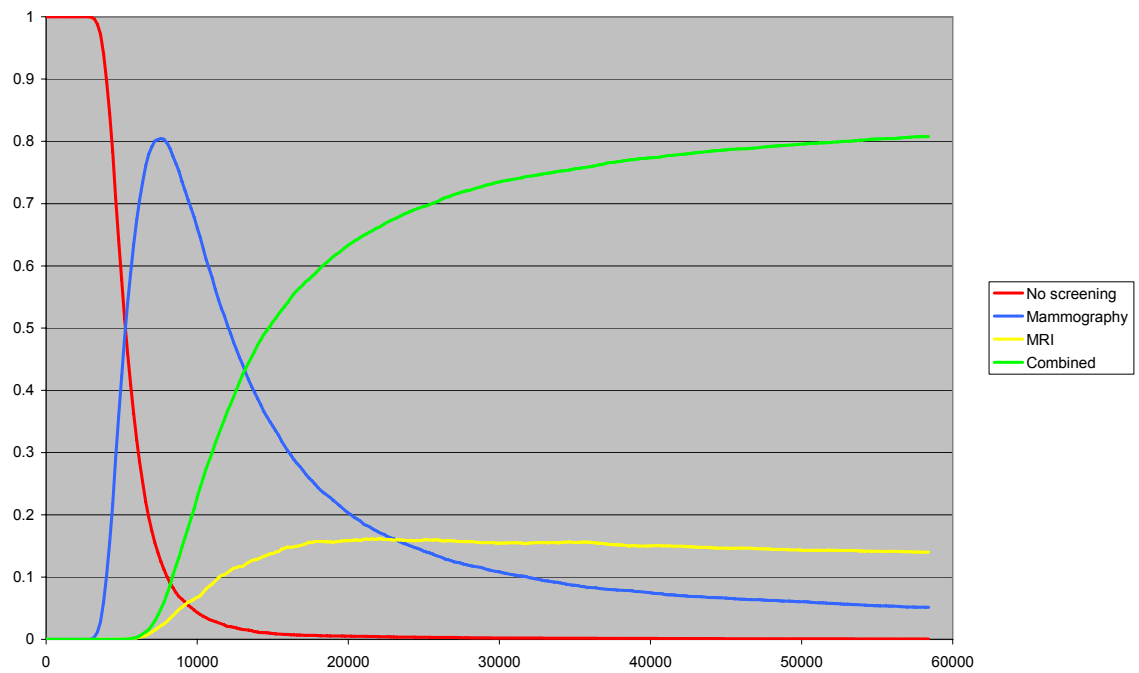
**Figure 12: Cost-Effectiveness Acceptability Curves for High Risk, non-*BRCA1* Individuals Aged 30**



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.

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**Figure 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 likelihoods at these two values are 0.633 and 0.735).

5.6.10. Appendix 8 Clinical effectiveness evidence tables

Evidence Table: MRI surveillance

Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
<p>Leach, M. O., Boggis, C. R., Dixon, A. K., et al 2005, "Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS)", Lancet, vol. 365, no. 9473, pp. 1769-1778.</p> <p>UK Multi-centre study carried out between Aug 1997 and May 2004</p>	Prospective cohort	++	A Comparison of contrast enhanced magnetic resonance imaging (CE MRI) with mammography for screening in women at high familial risk of breast cancer.	<p>Total n=649</p> <p>n = strong family history of breast cancer or high probability of <i>BRCA1</i>, <i>BRCA2</i> or <i>TP53</i></p> <p>n=139 <i>BRCA1</i> mutation or first degree relative with mutation (known <i>BRCA1</i> n=82)</p> <p>n=86 <i>BRCA2</i> mutation or first degree relative with mutation</p>	<p>All women: 2% <i>BRCA1</i> 3% of increased risk <i>BRCA2</i> 5% of increased risk</p>	<p>Inclusion criteria: Known carriers of <i>BRCA1</i>, <i>BRCA2</i> <i>TP53</i> mutation; first degree relative of someone with <i>BRCA1</i>, <i>BRCA2</i> or <i>TP53</i> (the latter screened from age 25); strong family history of breast or ovarian cancer (annual risk of breast cancer of at least 0.9%); or family history consistent with classic Li-fraumeni syndrome</p> <p>Aged between 31-55 (mean age 40)</p> <p>No previous breast cancer or with any other cancer if their expected prognosis was &lt;5 years.</p>	<p>Women had the opportunity to have at least two annual scans.</p> <p>76% (1437 of 1881) of mammography and MRI examinations were performed on the same day. 4% (71 of 1881) were performed more than one month apart.</p> <p>Both MRI and mammography screenings were double reported and the results were blinded.</p> <p>BIRADS category 3 (indeterminate, probably benign) or above used as definition of a</p>	mammography	<p>Sensitivity: 95% CI All women: MRI 77% (60-90) mammography 40% (24-58) p=0.01 (MRI versus mammography) combined 94% (81-99)</p> <p>Women with <i>BRCA1</i> or first degree relative with <i>BRCA1</i> n=139 MRI 92% (64-100), mammography 23% (5-54) p=0.004 (MRI versus mammography) Combined 92% (64-100)</p> <p>Women with <i>BRCA2</i> or first degree relative with <i>BRCA2</i> n=86 MRI 58% (28-84)</p>	<p>PPV: 95% CI MRI 7.3% (4.9-10), mammography 10% (5.8-17) Combined 7% (6-8) NPV: MRI 99% (99-100) mammography 99% Combined 100%</p> <p><i>BRCA1</i> group: PPV MRI 14% (7.2-23), mammography 9.1% (1.9-23) Combined 11% (8-14) NPV MRI 100%, mammography 97% (95-99) Combined 100%</p> <p><i>BRCA2</i> PPV MRI 15% (10-19), mammography 32% (26-37), combined 18%</p>	Medical Research Council, National Health Service	<p>1881 screening tests performed</p> <p>35 cancers detected, 19 by MRI, 6 by mammography, 8 by both MRI and mammography, with two interval cases.</p> <p><i>BRCA1</i> or first degree relative with <i>BRCA1</i> 13 cancers detected. 9 by MRI, 0 by mammography, 3 by both, 1</p>

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
				(Known <i>BRCA2</i> n=38)		Exclusion criteria: women who underwent predictive genetic testing and had a negative result or those who developed cancer during the study.	positive test.  The MRI score and the Mammography score were compared every year with the woman's true cancer status as ascertained by pathology or by the absence or presence of an interval cancer in the year after examination		mammography 50% (21-79) p=1.0 (MRI versus mammography) Combined 92% (62-100)  Specificity: 95% CI All women: MRI 81%(80-83), mammography 93% (92-95) p<0.0001(MRI versus mammography) Combined 77% (75-79)  Women with <i>BRCA1</i> or first degree relative with <i>BRCA1</i> n=139 MRI 79% (75-83), mammography 92% (88-94) p<0.0001 (MRI versus mammography) Combined 74% (69-78)  Women with <i>BRCA2</i> or first degree relative with <i>BRCA2</i>	(13-23)  NPV MRI 97% (95-99), mammography 97% (95-99) Combined 99% (99-100)		interval case  <i>BRCA2</i> or first degree relative with <i>BRCA2</i> 12 cancers detected 5 by MRI, 4 by mammography, 2 by both, 1 interval cancer

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
									n=86 MRI 82% (77-87) mammography 94% (91-97), p=0.0001 (MRI versus mammography) Combined 78% (72-83)			
<p>Kriege, M., Brekelmans, C. T., Boetes, et al. 2004, "Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition", New England Journal of Medicine, vol. 351, no. 5, pp. 427-437.</p> <p>Multi-centre study carried out in the Netherlands between Nov 1999 and Oct 2003</p>	Prospective cohort study	++	The value of regular surveillance in women at high risk, efficacy of MRI compared to mammography, quality of life effects during screening, cost-effectiveness of regular screening	<p>Total n= 1909</p> <p>n=358 mutation carriers (<i>BRCA1</i>, <i>BRCA2</i>, <i>PTEN</i>, <i>TP53</i>)</p> <p>n=1052 high risk group (30-49 % cumulative lifetime risk)</p> <p>n=499 moderate risk (15-29% cumulative lifetime risk)</p>	1%	<p>Inclusion criteria: Life time risk for breast cancer of 15% or more,</p> <p>Aged 25-70 (mean 40), or younger than 25 from families with very young age onset (&lt;30 years),</p> <p>Exclusion criteria: Previous breast cancer or a personal history of breast cancer</p>	Women screened every 6 months with clinical breast examination, and once a year with mammography and MRI independently. Both tests were carried out on the same day, or in the same time period, between day 5 and 15 of the menstrual cycle. BIRADS category 3 (probably benign) or above used as definition of a positive test. The results were blinded	mammography	<p>Sensitivity for all cancers: mammography 40%, MRI 71.1%</p> <p>For invasive breast cancer: Sensitivity: mammography 33.3%, MRI 79.5 %</p> <p>Specificity: mammography 95.0%, MRI 89.8 %</p>	<p>PPV: mammography 8%, MRI 7.1%</p> <p>NPV: 100%</p>	Dutch Health insurance Council	<p>Median Follow-up 2.9 years (mean 2.7, range, 0.1 to 3.9 years) 50 cancers detected in total ( 5 excluded from analysis).</p> <p>Cancers detected: In total. 32 by MRI, 22 by MRI only. 18 by mammography, 8 mammography only, 10 by both</p>

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
							so the two examinations were not linked.  Characteristics of cancers detected were compared with the characteristics of those in two different age-matched control groups					mammography and MRI
Warner, E., Plewes, D. B., Hill, K. et al. 2004, "Surveillance of <i>BRCA1</i> and <i>BRCA2</i> mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination", JAMA, vol. 292, no. 11, pp. 1317-1325  Single centre study carried out in Canada between Nov	Prospective cohort study	++	Compare the sensitivity and specificity of four methods of breast cancer surveillance (mammography, MRI, ultrasound (not extracted) & clinical breast examination (CBE) (not extracted)	Total n=236 With <i>BRCA1</i> or <i>BRCA2</i> mutations	5%	Inclusion criteria: <i>BRCA1</i> or <i>BRCA2</i> , between ages 25-65, (mean 46.6 years)  Exclusion criteria: history of bilateral breast cancer, undergoing chemotherapy, known to have metastatic disease, women who weighed more than 91 kg	Between 1-3 annual screening examinations using 4 screening modalities (CBE, mammography, ultrasound and MRI performed on the same day. Each imaging read and scored independently by different radiologist. Radiologists were blinded to results of CBE. BIRADS category 4 (suspicious	Mammography	Sensitivity: 95% CI MRI 77% (73-81), Mammography 36% (32-41),  Specificity: 95% CI MRI 95.4% (93-97), mammography 99.8% (99-100)	PPV: 95% CI MRI 46% (41-51) Mammography 89% (86-92)  NPV: 95% CI MRI 99% (98-100) Mammography 97% (95-98)	Canadian Breast Cancer Research Alliance, The Terry Fox Foundation, International Breast MRI Consortium, Canadian national Breast Cancer Fund, Papoff Family	(Results broken down by year. Total for all years not given in original table, this has been calculated )  Participants were followed up for 1 year from the date of last screening  22 cancers

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
1997 and March 2003.							<p>abnormality, biopsy should be considered) or above used as definition of a positive test.</p> <p>All lesions with a score of 4 or 5 were biopsied</p>					<p>detected (16 invasive, 6 ductal carcinoma in situ). 17 by MRI alone, 8 by mammography 2 by mammography alone.</p> <p>MRI detected 9 (75%) of 12 cancers missed by conventional surveillance (mammography &amp; CBE)</p> <p>All 22 patients who had a cancer detected are currently alive and disease free</p>

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
<p>Kuhl, C. K., Schrading, S., Leutner, C. C., Morakkabati-Spitz, N., Wardelmann, E., Fimmers, R., Kuhn, W., &amp; Schild, H. H. 2005, "Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer", <i>Journal of Clinical Oncology</i>, vol. 23, no. 33, pp. 8469-8476. Ref ID: 224</p> <p>single study centre study carried out at the University of Bonn Medical School, Germany between</p>	Prospective cohort	++	Comparison of sensitivity & specificity of mammography, breast ultrasound (not reported) and MRI imaging.	Total n= 529, previous history of breast cancer n=139, no previous history of breast cancer n=390 lifetime risk of 20% n=110, lifetime risk of 21-40% n= 241, mutation carriers n=43	All women: 3% Lifetime risk of 20%: 2%  Lifetime risk of 21-40%: 3%  Mutation carriers: 5%	<p>Inclusion criteria: asymptomatic, meet criteria for high familial risk defined by consortium on Familial Breast and Ovarian Cancer of the German Cancer Aid, corresponding to life time risk of breast cancer of at least 20%</p> <p>Exclusion criteria: current signs or symptoms of breast cancer, or had undergone bilateral mastectomy, or diagnosed with metastatic disease</p>	<p>Annual surveillance consisting of clinical breast examination (CBE), ultrasound, mammography and MRI performed within a time frame of 8 weeks.</p> <p>Each imaging study was read and scored by a different radiologist. Readers were informed of clinical findings of CBE and risk status of patient, but blinded to results of imaging modalities. Diagnosis was coded using BI-RADS categories on a five point</p>	Mammography	<p>Sensitivity: All women: mammography 32.6% (30-35), MRI 90.7% (89-92), mammography + MRI 93.0% (92-94)</p> <p>Risk 20%: mammography 50.0% (45-55), MRI 100.0% (100), mammography + MRI 100.0% (100)</p> <p>Risk 21-40% mammography 25.0% (22-28) MRI 100.0% (100), mammography + MRI 100.0% (100)</p> <p>Mutation carriers: mammography 25.0% (18-32). MRI 100% (100), mammography + MRI 100%</p>	<p>PPV All women: mammography 23.7% (22-26), MRI 50.0% (47-53), mammography + MRI 42.1% (40-45)</p> <p>Risk 20%: mammography 21.4% (17-26), MRI 42.9% (32-43), mammography + MRI 30.0% (25-35)</p> <p>Risk 21-40% mammography 21.7% (19-25) MRI 55.6% (52-59), mammography + MRI 51.2% (55-62)</p> <p>Mutation carriers: mammography 28.6% (22-35). MRI 66.7% (60-74), mammography + MRI 47.1%</p>	Förderverein für Radiologie an der Universität Bonn, German Cancer Aid	<p>a total of 1452 annual surveillance rounds with a mean followup of 5.3 years (range, 2-7 years)</p> <p>Total of 43 cancers identified in 41 patients (34 invasive, 9 DCIS).</p> <p>40 diagnosed by imaging.</p> <p>14 by mammography, 39 by MRI, 40 by MRI &amp; mammography</p>

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
February 1996 and February 2002							scale. 4 or above was treated as a positive result and biopsied.		<p>(100)</p> <p>Specificity: All women: mammography 96.8% (96-98), MRI 97.2% (96-98), mammography + MRI 96.1% (95-97)</p> <p>Risk 20%: mammography 96.5% (94-99), MRI 97.4% (94-98), mammography + MRI 95.5% (93-98)</p> <p>Risk 21-40% mammography 97.4% (96-99) MRI 97.7% (97-99), mammography + MRI 97.0% (97-99)</p> <p>Mutation carriers: mammography 96.9% (94-100). MRI 97.5% (95-100), mammography + MRI 94.4% (91-98)</p>	(39-55)  NPV not reported		

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
<p>Lehman, C. D., Blume, J. D., Weatherall, P., et al. 2005, "Screening women at high risk for breast cancer with mammography and magnetic resonance imaging", <i>Cancer.</i>, vol. 103, no. 9, pp. 1898-1905.</p> <p>Multicentre study carried out by the International Breast MRI Consortium in the USA and Canada between July 1999 and Jan 2002</p>	Prospective study	+	Comparison of sensitivity, specificity, PPV and diagnostic yield of MRI and mammography	Total n=367	1%	<p>Inclusion criteria: Asymptomatic high risk women age <math>\geq</math> 25 years (mean 45) and lifetime risk of breast cancer &gt; 25% based on family history or genetic testing. Women who had prior history of breast cancer within 5 years of entry date were eligible by having contralateral breast screened. Women who had breast cancer diagnosed &gt; 5 years prior to study entry were eligible for bilateral screening provided they had a probability &gt; 50% for breast cancer or were <i>BRCA1</i> or <i>BRCA2</i></p> <p>Exclusion</p>	<p>Clinical breast examination (CBE), mammogram, MRI. CBE and mammogram performed within 90 days of MRI examination.</p> <p>MRI and mammography were interpreted without knowledge of the results of the other test. Separate MRI and mammogram readers were assigned for each institution</p> <p>Diagnosis was coded using the BI-ADS scoring system. All lesions given a score of 4 or 5 (positive for disease) were recommended for biopsy</p>	mammography	<p>Sensitivity 95% CI MRI 100% (100)</p> <p>Mammography 25% (21-29)</p> <p>Specificity 95% CI; MRI 95% (92-97)</p> <p>Mammography 99% (98-100)</p>	<p>PPV MRI 17.0% (CI 95% 14-21)</p> <p>mammography 25% (CI 95% 21-29)</p> <p>NPV MRI 100% (CI 95% 100)</p> <p>Mammography % (CI 95% 98-100)</p>	National Cancer Institute, Office of National women's Health	<p>One screening round performed</p> <p>No follow-up carried out.</p> <p>27 biopsies performed of 38 that were recommended</p> <p>4 cancers detected in total. 4 by MRI, 1 by mammography.</p>

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
						criteria: pregnancy, pacemaker, magnetic aneurysm clip or other implanted magnetic device, severe claustrophobia, palpable lesions or mammographic abnormalities prior to assessment						
Pisano, E. D., Gatsonis, C., Hendrick, E., Yaffe, M., Baum, J. K., Acharyya, S., Conant, E. F., Fajardo, L. L., Bassett, L., D'Orsi, C., Jong, R., & Rebner, M. 2005, "Diagnostic performance of digital versus film mammography for breast-cancer screening", <i>New England Journal of Medicine</i> , vol.	Prospective study	++	To assess the diagnostic accuracy between digital and film mammography	Total n=42,760  premenopausal and perimenopausal n=15803  heterogeneously or extremely dense breasts n=19897		Inclusion criteria: Asymptomatic  Exclusion criteria: reported symptoms, pregnancy, breast implants, had undergone mammography within the preceding 11 months, had a history of breast cancer treated with lumpectomy and radiation	A digital and film mammogram taken in random order. Digital and film examinations were independently interpreted by two radiologists.  Readers rated mammograms using a seven-point malignancy scale suitable for ROC analysis and the BIRADS classification scale. Readers	Film mammogram	Sensitivity Means  Digital mammography (DM)  All women 0.70±0.03;  <50 years 0.78±0.05  Premenopausal/perimenopausal 0.72± 0.05  Heterogeneously dense or extremely dense breasts 0.70±0.04  Film	PPV Digital mammography  All women 0.05±0.004  <50 years 0.03±0.005  Premenopausal/perimenopausal 0.04±0.005  Heterogeneously dense or extremely dense breasts 0.04±0.005  Film	National Cancer Institute	Follow-up carried out at one year  Participants were classified as positive for cancer if pathologically verified within 455 after initial screening and negative if their study records showed

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics [6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
353, no. 17, pp. 1773-1783.  Multicentre study carried out by the American college of Radiology Imaging Network during a two year period in the USA and Canada							also rated breast density according to the BIRADS scale scores of 0, 4 or 5 were recorded as positive		mammography  All women ; 0.66±0.03  <50 years 0.51±0.07  Premenopausal /perimenopausal 0.51±0.06  Heterogeneously dense or extremely dense breasts 0.55±0.04   Specificity Digital mammography  All women 0.92±0.001  <50 years 0.90±0.003  Premenopausal /perimenopausal 0.90±0.002  Heterogeneously dense or extremely dense breasts 0.91±0.002	mammography  All women 0.05±0.003  <50 years 0.02±0.004  Premenopausal/perimenopausal 0.03±0.004  Heterogeneously dense or extremely dense breasts  0.03±0.004  NPV not reported		negative findings after biopsy, if the followup mammogram at 1 year was normal.

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
									Film mammography  All women 0.92±0.001  <50 years 0.90±0.003  Premenopausal /perimenopausal 0.90±0.002  Heterogeneously dense or extremely dense breasts  0.90±0.002			
Skaane, P. & Skjennald, A. 2004, "Screen-film mammography versus full-field digital mammography with soft-copy reading: randomized trial in a population-based screening program--the Oslo II Study", <i>Radiology</i> , vol. 232, no. 1, pp. 197-204.	RCT	+	Comparison of cancer detection rates, recall rates and PPV of screen-film mammography (SFM) with full-field digital mammography (FFDM) carried out between Nov 2000 and Dec 2001 by the Breast Cancer Screening Programme in Oslo.	Total n=25,263 aged 45-69  Total 45-49 age group n=10,619 (mean 47.4)	Not reported	Women aged 50-69 were part of the Norwegian Breast Cancer Screening Program. Women aged 45-49 were offered screening mammography only in Oslo county. All women were invited by letter to attend screening. Randomisation to either SFM or	Digital mammography  SFM and FFDM images were interpreted independently by two of a team of eight radiologists. A five-point rating scale for probability of cancer was used for interpretation of both SFM and FFDM. A	Film mammography	N= 7,607 (71%) SFM Cancer detection rate 0.22%  N=3,012 (29%) FFDM cancer detection rate 0.27% P=.686  Recall rate for SFM n=231 (3.0%) of 7,607  Recall rate for FFDM n=112 (3.7%) of 3,012	PPV SFM 7.4%  FFDM 7.1%  NPV not reported	Norwegian Breast Cancer Screening Programme	No followup undertaken.  SFM total of 17 cancers detected. 7 (41%) ductal carcinoma in situ, 10 (59%) invasive breast cancer.  FFDM total of 8

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Bibliographic reference [1]	Study type [2]	Evidence level [3]	Aim of study	Number of patients [4]	Prevalence [5]	Patient characteristics[6]	Type of test* [7]	Reference standard [8]	Sensitivity and specificity [9]	Positive and negative predictive value [10]	Source of funding [11]	Additional comments [12]
Ref ID: 231 Norway						<p>FFDM was based on the last digit of the invitation number, with adjustments for age and area of residence</p> <p>From the 45-49 year age group 7,607 (71%) women allocated to SFM 3,164 (29%) allocated to FFDM</p>	<p>score of 2 or higher (probably benign) was automatically selected for a consensus meeting. The consensus meeting would decide which women should continue in the screening programme and which be recalled for diagnostic workup. A score of 4 (probable malignancy) or higher resulted in biopsy being undertaken</p> <p>Recall rate was defined as the percentage of patients requiring further imaging workup</p>					<p>cancers detected. 2 (25%) ductal carcinom as in situ, 6 (75%) invasive breast cancers</p> <p>Comparisons between SFM and FFDM were available only during review of positive mammograms.</p>

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- [1] *Bibliographic reference*: author, title, journal, volume, year, pages.
- [2] *Study type*: observational, cohort, case studies, etc.
- [3] *Evidence level*: classified using levels of evidence for studies of diagnostic test accuracy.
- [4] *Number of patients*: total number of patients included in the study, with inclusion/exclusion criteria.
- [5] *Prevalence*: proportion of people with the disease in the population at risk.
- [6] *Patient characteristics*: relevant characteristics to the area of interest: age, sex, ethnic origin, comorbidity, disease status, community/hospital based.
- [7] *Type of test*: description of the test used in the study. \*Specify the test threshold where applicable.
- [8] *Reference standard*: reference standard used as measure of outcome. Specify if it is a 'gold' standard or 'current best practice'.
- [9] *Sensitivity*: proportion of individuals classified as *positive* by the gold (or reference) standard, who are correctly identified by the study test. *Specificity*: proportion of individuals classified as *negative* by the gold (or reference) standard, who are correctly identified by the study test.
- [10] *Positive predictive value*: proportion of individuals with a positive test result who actually have the disease. *Negative predictive value*: proportion of individuals with a negative test result who do NOT have the disease.
- [11] *Source of funding*: government funding (for example, NHS), voluntary/charity (for example, Wellcome Trust), pharmaceutical company.
- [12] *Additional comments*: additional characteristics/interpretations of the studies. Important flaws in the study not identifiable from other data in the table. A range of additional questions or issues that will need to be considered, but do not figure in the results table – for example, if a test is one of a sequence of tests, if its utility was determined.

J Evidence table for studies of diagnostic test accuracy © National Institute for Clinical Excellence February 2004 (updated March 2005)