# *Breast magnetic resonance imaging (MRI) for screening of high-risk women*

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**Assessment report**

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This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of

evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

**MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

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# Abbreviations and acronyms

| | |
|---|---|
| ABS | Australian Bureau of Statistics |
| AIHW | Australian Institute of Health and Welfare |
| ANZCTR | Australian and New Zealand Clinical trials registry |
| AQoL | Assessment of Quality of Life |
| AUC | area under curve |
| BI-RADS | Breast Imaging Reporting and Data System (American College of Radiology) |
| *BRCA1* | breast cancer gene 1 |
| *BRCA2* | breast cancer gene 2 |
| CBE | clinical breast examination |
| CI | confidence interval |
| CUA | cost-utility analysis |
| DALY | disability-adjusted life year |
| DAP | Decision-Analytic Protocol |
| DCIS | ductal carcinoma in situ |
| FN | false-negative |
| FP | false-positive |
| FY | financial year |
| G-CSF | Granulocyte-colony Stimulating Factor |
| GP | general practitioner |
| HESP | Health Expert Standing Panel |
| HR | hazard ratio |
| HTA | health technology assessment |
| IBTR | ipsilateral breast tumour recurrence |
| ICER | incremental cost-effectiveness ratio |
| ICTRP | International Clinical Trials Registry Platform (WHO) |
| IV | intravenous |
| LCIS | lobular carcinoma in situ |
| LCL | lower control limit |
| MAM | mammography |
| MARIBS | magnetic resonance imaging breast screening |
| MBS | Medicare Benefits Schedule |
| MCBC | metachronous contralateral breast cancer |
| MRI | magnetic resonance imaging |
| MRISC | Magnetic Resonance Imaging Screening Study Group |
| MSAC | Medical Services Advisory Committee |
| NBCC | National Breast Cancer Centre |
| NBOCC | National Breast and Ovarian Cancer Centre |
| NHMRC | National Health and Medical Research Council |
| NHS | UK National Health Service |
| NICE | UK National Institute for Health and Clinical Excellence |
| NIH | US National Institutes of Health |
| NPV | negative predictive value |
| NR | not reported |
| OR | odds ratio |
| p53 | cellular tumour antigen p53 |
| PASC | Protocol Advisory Sub-committee |
| PBS | Pharmaceutical Benefits Scheme |

| | |
|---|---|
| PICO | population, intervention, comparator, outcome |
| PPV | positive predictive value |
| QALY | quality-adjusted life years |
| QUADAS | Quality Assessment of Diagnostic Accuracy Studies |
| RR | relative risk |
| RT | radiotherapy |
| SD | standard deviation |
| Sens | sensitivity |
| Spec | specificity |
| STAI | State-Trait Anxiety Inventory |
| TN | true-negative |
| TP | true-positive |
| *TP53* | tumour protein p53 gene |
| U/S | ultrasound |
| UCL | upper control limit |
| UK | United Kingdom |
| US | United States of America |
| WHO | World Health Organization |

# Executive summary

## Assessment of breast MRI for screening of high-risk women

### Purpose of the Application

In May 2011, the Department of Health and Ageing received an application ('the Application') from the Royal Australian and New Zealand College of Radiologists requesting the review of the Medicare Benefits Schedule (MBS) listing of breast magnetic resonance imaging (MRI) for screening of young women at high risk of breast cancer. The Application requested a review of:

- the use of breast MRI for the screening of high-risk women **in addition** to an organised screening program for women <50 years of age, as recommended by the Medical Services Advisory Committee in 2007 (MSAC, 2006); as such, no change is being proposed to the use of breast MRI in the clinical pathway from what was recommended in the 2006 review
- the inclusion of additional high-risk patient populations, namely women who are <50 years of age and have had either:
    a) a prior history of invasive breast cancer
    b) a prior history of treatment for lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS)
    c) a history of radiotherapy to the chest area between 10 and 35 years of age.

The change in the proposed patient population will see additional patients screened who would not previously have had access to MBS item 63464. In all populations, MRI is proposed as an additional test to standard imaging, which is mammography ± ultrasound.

### Proposal for public funding

The proposed MBS item descriptors as determined by the Protocol Advisory Sub-committee (PASC) are presented below, with proposed additions to the current wording shown in bold italic text.

**Proposed PASC-determined item descriptors.**

| Category 5—Diagnostic Imaging Services |
|---|
| MBS 63464<br>Magnetic resonance imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:<br>(a) a dedicated breast coil is used; and<br>(b) the request for scan identifies that the woman is asymptomatic and is <50 years of age; and<br>(c) the request for scan identifies either:<br>(i) that the patient is at high risk of developing breast cancer due to one of the following:<br>(A) 3 or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer<br>(B) 2 or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer, if any of the following applies to at least 1 of the relatives:<br>—has been diagnosed with bilateral breast cancer<br>—had onset of breast cancer before the age of 40 years<br>—had onset of ovarian cancer before the age of 50 years |

| Category 5—Diagnostic Imaging Services |
|---|
| —has been diagnosed with breast and ovarian cancer, at the same time or at different times<br>—has Ashkenazi Jewish ancestry<br>—is a male relative who has been diagnosed with breast cancer.<br>(C) 1 first- or second-degree relative diagnosed with breast cancer at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 years or younger; or (ii) that genetic testing has identified the presence of a high-risk breast cancer gene mutation<br>*(D) prior history of treatment for invasive breast cancer*<br>*(E) prior history of treatment for ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)*<br>*(F) with a history of therapeutic radiation treatment to the chest area between the ages of 10 and 35 years*<br>Scan of both breasts for:<br>—detection of cancer (R)<br>Note: Benefits are payable on one occasion only in any 12-month period.<br>Fee: $690.00 Benefit: 75% = $517.50, 85% = $613.80<br>Relevant explanatory note: Bulk bill incentive |
| MBS 63467<br>Magnetic resonance imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:<br>(a) a dedicated breast coil is used; and<br>(b) the woman has had an abnormality detected as a result of a service described in item 63464 performed in the previous 12 months<br>Scan of both breasts for:<br>—detection of cancer (R)<br>Note 1: Benefits are payable on one occasion only in any 12-month period.<br>Note 2: This item is intended for follow-up imaging of abnormalities diagnosed on a scan described by item 63464.<br>Bulk bill incentive<br>Fee: $690.00 Benefit: 75% = $517.50, 85% = $613.80 |

Source: Final Decision-Analytic Protocol, Table 2, p. 9. MBS = Medicare Benefits Schedule.

A team from the National Health and Medical Research Council (NHMRC)'s Clinical Trials Centre at the University of Sydney and THEMA Consulting was engaged to conduct a systematic review of the literature and an economic evaluation of breast MRI for surveillance in high-risk women.

## Current arrangements for public reimbursement

In 2007, MSAC recommended interim public funding for breast MRI in the surveillance of breast cancer in asymptomatic women with a high risk of developing breast cancer when used as part of an organised screening program. In February 2009, the government acted on MSAC's advice and listed breast MRI on the MBS as item numbers 63464 and 63467.

## Background

The NHMRC estimates that women at high risk of breast cancer due to genetic predisposition or family history account for <1% of the Australian female population, make up 5% to 10% of women

with breast cancers (NBOCC, 2009) and often develop breast cancer earlier in life. Risk reduction strategies for these women include:

- prophylactic surgical options (risk reduction for breast cancer of ~90%)
- chemoprevention (risk reduction for breast cancer of ~40%)
- intensified screening or surveillance.

This assessment includes women with a prior history of breast cancer (invasive, DCIS and LCIS) and women with a history of irradiation to the chest between 10 and 35 years of age, on the basis that they are at elevated risk of breast cancer.

In women with a history of breast cancer, the risk of a subsequent breast cancer (recurrence or second) is highly dependent on the prognostic factors associated with the tumour and on the treatment received (addition of radiotherapy and systemic therapies). Risk estimates therefore vary greatly in these groups (see sections A.1.2, page 2, and D.4.2, page 84, for detailed discussion), although rates appear to be declining with improved treatments.

In women treated with radiotherapy for mediastinal Hodgkin's lymphoma, breast cancer is the most common secondary malignancy. Factors which affect the risk of developing breast cancer are the patient's age at treatment, time since treatment, dose and field of radiotherapy, and whether alkylating chemotherapy has been received. Risk estimates are variable in these women.

## Prerequisites to implementation of any funding advice

MRI is currently available in public and private facilities in major centres in each state and territory; 337 units have been licensed throughout Australia to provide services eligible for funding under the MBS.

## Other relevant applications or reviews

**Other applications or reviews relevant to the current assessment.**

| No | Application title | Progress |
|---|---|---|
| 1333 | Breast magnetic resonance imaging (MRI) for staging in women with newly diagnosed breast cancer | Proposed DAP reviewed at PASC, 13 December 2013; awaiting release for public consultation |

DAP = Decision-Analytic Protocol; PASC = Protocol Advisory Sub-committee.
Source: MSAC website [accessed 8 January 2014].

## Clinical need

Breast MRI has been conditionally recommended for use as an **additional** test in the diagnosis of breast cancer in asymptomatic women <50 years of age with a high risk of developing breast cancer when used as part of organised screening, on the basis of the 2006 MSAC assessment. Under this scheme, women eligible for MRI in addition to organised screening programs include women with a genetic mutation (such as *BRCA1*, *BRCA2* or *TP53* defined by genetic testing) and familial history of breast or ovarian cancer or sarcoma (bone or soft tissue). Breast MRI occurs outside of the BreastScreen Australia program.

This assessment includes the proposal to include a new cohort of women at elevated risk of developing breast cancer; this would allow additional women to be screened with MRI who have not

previously had access to MBS item 63464. The new cohort includes women who have a previous history of invasive breast cancer, DCIS or LCIS, or chest irradiation from 10 to 35 years of age for Hodgkin's lymphoma.

### Comparator

Mammography is the most common form of breast imaging for asymptomatic and symptomatic women. BreastScreen Australia, the national population-based screening program, is targeted to asymptomatic women at average risk of breast cancer. It provides free screening mammograms at 2-yearly intervals for women aged 50 to 69 years, although women aged 40 to 49 and 70 years and older are also eligible. The MBS also provides a rebate for diagnostic mammography where there is a reason to suspect the presence of a malignancy, for example in women with breast symptoms and women with a personal or family history of breast cancer (MBS items 59300 and 59301). Breast ultrasound may be used to complement mammography (MBS items 55070, 55073 and 55076), with its use varying by centre. See Figure A.1 , page 16 for the clinical algorithm.

## Scientific basis of comparison

Evidence about the relative effectiveness of adding MRI to standard mammography is limited to studies reporting on test accuracy. These studies are designed to demonstrate differences in the performance of different screening strategies and do not provide evidence about the impact of these strategies on patient outcomes. Details of the included studies are provided in section B.3.2, Master list of studies. The included studies covered four areas:

- MBS interim-funded item (asymptomatic high-risk women)
    - 2 health technology assessment reports
    - 5 diagnostic accuracy studies
    - 1 patient outcomes study
- New additional high-risk group—women with a history of breast cancer
    - 2 health technology assessment reports
    - 2 diagnostic accuracy studies
- New additional high-risk group—women with a history of DCIS/LCIS
    - 1 diagnostic accuracy study
- New additional high-risk group—women with a history of chest irradiation
    - 3 diagnostic accuracy studies.

## Comparative safety

MSAC (2006) identified the following safety concerns in breast MRI screening for high-risk women:

- Adverse effects of false-positive findings (unnecessary investigation).
- Use in patients with contraindications to exposure to magnetic fields.
- Allergy to gadolinium contrast agent.
- Claustrophobia, which may preclude use in some patients.
- Patient discomfort due to the noise of the machine.
- Avoidance advised in pregnant women owing to limited evidence about the safety of MRI on the developing fetus.

The key safety issue with mammography is exposure to ionising radiation. Because there are documented harms from exposure to ionising radiation, relevant evidence is summarised in section B.10. However, given that mammography is proposed for both the intervention and the comparator, the harms associated with mammography would be expected to be the same regardless of the addition of MRI to the existing mammographic surveillance.

In conclusion, both breast MRI and mammography are considered to be safe procedures.

# Comparative effectiveness

## Asymptomatic, high-risk women: MBS interim-funded item

The conclusions largely mirror those of MSAC (2006, p. 71), as no new studies of diagnostic accuracy which provided evidence applicable to the proposed use of breast MRI in addition to mammography were included.

This review identified five level III-1/2 studies investigating the relative test accuracy of screening protocols with and without breast MRI in high-risk women. Four of these studies provided evidence applicable to the proposed use of breast MRI + mammography versus mammography. Risk classification varied across studies. Two studies included women who would be classified as at moderate rather than high risk (cumulative lifetime risk of >15% or 20%). All studies either had an average age of participants of <50 years or enabled the calculation of diagnostic accuracy for a subset of women who were <50 years or pre-menopausal (Table B.8, Table B.15 and Table B.16).

None of the studies were assessed as high quality; however, the consistency and precision of estimates of test sensitivity across these studies provide strong evidence that the combination of breast MRI and mammography is a highly sensitive test for the detection of breast cancer (range 0.85–0.94, HIQA [2013] meta-analysis 0.88 [0.78–0.93]) and offers approximately a 2.3 fold increase in the early detection of breast cancer over the use of mammography alone (range 0.36–0.40, HIQA [2013] meta-analysis 0.38 [0.26–0.51]) in the surveillance of high-risk women (Table B.25, Table B.26, Table B.27).

Less evidence was identified for an assessment of the relative accuracy of adding breast MRI to a mammography program that includes the use of ultrasound. Two studies reported an increased sensitivity of mammography combined with ultrasound (Kuhl et al, 2005; Warner et al, 2004) compared with mammography alone. They indicate that the incremental benefit of adding breast MRI to a screening program will be lower if standard imaging includes the routine or selected use of ultrasound than if it includes mammography alone.

Evidence about the specificity of screening protocols that include breast MRI was less consistent. This may be attributed, at least in part, to the different criteria used to define false-positives. The two studies which defined a false-positive as a test finding that initiated further testing to exclude malignancy provide the most relevant data and found specificities of 0.77 (0.75–0.79) (Leach, 2005) and 0.85 (0.84–0.86) (Kriege et al, 2006a), corresponding to false-positive rate of 23% and 15%, respectively, compared with rates for mammography alone of 7% and 5%, respectively. Leach (2005) reported that the biopsy rate for false-positive imaging was 5% for MRI + mammography, versus 1.5% for mammography alone.

### Women with a history of treatment for invasive breast cancer

This review identified two level III-2 studies of test accuracy investigating the relative accuracy of screening protocols with and without breast MRI in women with a history of treatment for invasive breast cancer. Both studies included women aged over 50 years (median of 57 and 55.7 years). Both studies had methodological flaws and were at high risk of bias across multiple domains (Table B.11, Table B.18, Table B.19).

The studies were consistent in showing that breast MRI combined with mammography is a highly sensitive test (no false-negatives identified) for the early detection of breast cancer in women with a previous history of invasive breast cancer. However, the small sample sizes reduced the precision of these estimates and the statistical power.

Evidence about specificity was inconsistent. Berg et al (2012) defined a false-positive as a test finding that initiated further testing to exclude malignancy and found a specificity of 0.79 (0.73–0.83) for breast MRI + mammography, corresponding to a false-positive rate of 21%, versus 5% for mammography alone. The false-positive biopsy rate in this study was 4.0% for breast MRI + mammography, versus 0.73% for mammography alone (Table B.31, Table B.32, Table B.33).

### Women with a history of treatment for DCIS or LCIS

This review did not identify any studies of test accuracy which compared screening protocols with and without breast MRI in women with a history of treatment for DCIS or LCIS. It did identify one level III-2 diagnostic accuracy study which compared breast MRI alone with mammography alone in women who had been treated for LCIS. The study was small and had a high risk of bias across multiple domains (Table B.12, Table B.20, Table B.21). It suggests that MRI may double the early detection of breast cancer in women with a history of LCIS (sensitivity: MRI 0.71 [0.42, 0.92], mammography 0.36 [0.13, 0.65]) (Sung et al, 2011b) (Table B.36, Table B.37), and found a 2.4-fold increase in the rate of biopsies for false-positive findings, but the body of evidence is too limited to allow any conclusions to be drawn.

### Women who have had chest irradiation between 10 and 35 years

This review identified one level III-1 test accuracy study investigating the relative accuracy of screening protocols with and without breast MRI for women who have had chest irradiation between the ages of 10 and 35 years (Ng et al, 2013). Two additional level III-2 test accuracy studies investigated the accuracy of breast MRI alone compared with mammography alone for women who have had chest irradiation between the ages of 10 and 35 years (Freitas et al, 2013; Sung et al, 2011a). All studies had a mean or median age of <50 years (Table B.13, Table B.22, Table B.23).

The Ng et al (2013) study is the most applicable and at a lower risk of bias than the other included studies. It provides weak evidence that the addition of breast MRI increases the early detection of breast cancer over mammography alone in women who have had chest irradiation (sensitivity: breast MRI + mammography 0.95 [0.74, 1.00], mammography alone 0.68 [0.43, 0.87]), an increase in the early detection of breast cancer of approximately 1.4-fold. The biopsy rate in this study was 18% (14.5%–22.6%) for the combined tests and 11% (8.0%–14.7%) for mammography alone, an increase in the rate of biopsy of 1.6 fold (Table B.38, Table B.39, Table B.40).

### Summary

Asymptomatic, high-risk women: MBS interim-funded item

- Breast MRI offers a 2.3 fold increase in the detection of breast cancer in younger high-risk women over mammography alone.
- Breast MRI increases by 3-fold the rate of investigations for false-positive findings.

Women with a history of treatment for invasive breast cancer

- Breast MRI may double the detection of breast cancer in women with a history of treatment for invasive breast cancer compared with mammography alone.
- Breast MRI may increase by 4-fold the rate of investigations for false-positive findings.

Women with a history of treatment for DCIS/LCIS

- Insufficient evidence to draw conclusions.

Women who have had chest irradiation between 10 and 35 years

- Breast MRI may offer an approximately 1.4-fold increase in the detection of breast cancer in women who have had chest irradiation between 10 and 35 years compared with mammography alone.
- Breast MRI may increase by approximately 1.6-foldthe rate of biopsy compared with mammography alone.

For all populations, any clinical benefits associated with earlier detection should be weighed against the potential distress and costs of additional investigations for false-positive MRI findings (see section B.6.3 Health outcomes, page 49, for a discussion of linked evidence regarding possible clinical benefits).

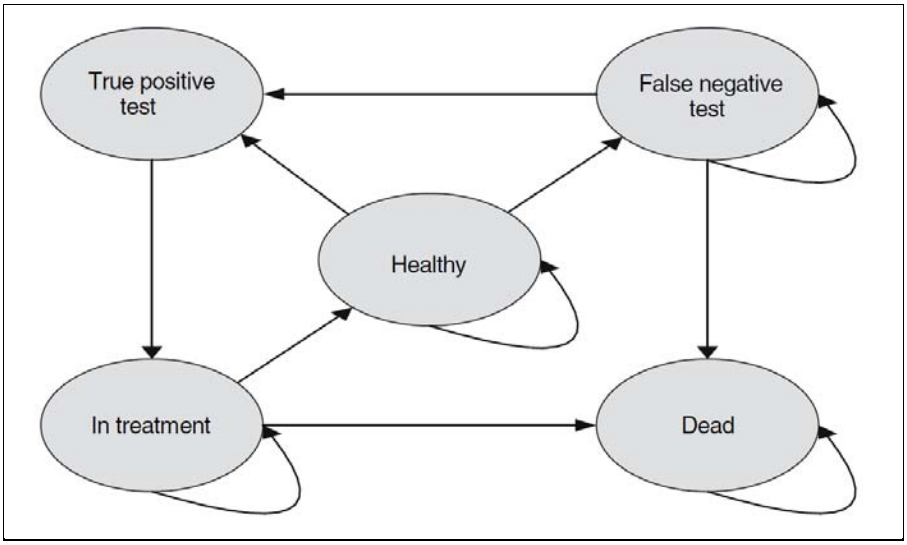
## Economic evaluation

### Method and approach

The economic evaluation presents a cost-utility analysis using an Australian adaptation of an economic model developed by the UK National Institute for Health and Clinical Excellence (NICE) to assess the cost-effectiveness of different surveillance strategies in women at high risk of breast cancer (NICE Clinical Guideline [CG] 41, 2006). A working version of the NICE (2006) model was provided to the assessment group with the permission of its developers, the National Collaborating Centre for Primary Care.

The structure of the economic model used in this assessment report is based on the Markov model structure used in the NICE (2006, 2013) clinical guidelines for familial breast cancer (CG41 and CG164). A diagram of the health states used in the model is shown in Figure 1. The model uses a 1-year cycle length and a lifetime time-horizon.

**Figure 1 Structure of economic model by NICE Clinical Guideline 41.**




Five key changes were made to the design of the model to adapt it to the Australian healthcare setting:

- Only two surveillance methodologies were compared in the current application: MRI + mammography and mammography alone.
- The revised model does not account for the risk of developing breast cancer as a result of radiation exposure through mammography, as the adapted model includes mammography in each arm and assumes that the risks would be approximately equal. This may be considered a conservative approach, as it underestimates the true risk of breast cancer and the full benefit of additional sensitivity.
- The revised model includes a background risk of death due to other causes on the basis of Australian life tables.
- The model allows patients to return to routine screening with mammography alone after the age of 50.
- A discount rate of 5% was applied to all costs and effects incurred after the first year of initial treatment.

The economic evaluation uses the same model structure to evaluate cost-effectiveness in five populations:

- High-risk based on confirmed breast cancer gene mutation (a sub-population of the current MBS-funded population).
- Familial high-risk (the current MBS-funded population).
- Prior history of invasive breast cancer.
- Prior history of treatment for DCIS or LCIS.
- Women with chest radiotherapy between 10 and 35 years of age.

For each population, updated clinical and cost data were incorporated into the model. See Table D.15 for a full list of all parameters used for each population. The key parameters were:

- the sensitivities and specificities of the different screening methods (Section D.4.3)

- the risk of developing breast cancer in women of different risk groups (including age; Section D.4.2)
- survival rate in women diagnosed with breast cancer (accounting for women with false diagnoses; Section D.4.2)
- utility values for women in different health states (Section D.4.5)
- costs (Section D.4.4).

## Results

The incremental cost per quality-adjusted life year (QALY) for the use of MRI + mammography compared with mammography alone is presented in the table below. The differences between the groups are driven largely by the baseline risk of breast cancer, the age at which each population begins screening and the population-specific diagnostic accuracy data for MRI + mammography compared with mammography alone (refer to Section D.4.3). In particular, the populations of women with prior breast cancer (DCIS, LCIS or invasive) begin screening at age 44, compared with age 30 in other populations, giving them a shorter period in which to accrue costs for MRI.

**Incremental cost per QALY (base-case population-specific data).**

| Population | Result | MRI + mammography | Mammography | Difference |
|---|---|---|---|---|
| *High-risk based on breast cancer gene mutation* | Total costs | $18,957 | $9,582 | $9,375 |
| | Total QALYs | 14.6762 | 14.4118 | 0.2644 |
| | ICER | | | $35,460 |
| *Familial high-risk* | Total costs | $16,022 | $6,696 | $9,326 |
| | Total QALYs | 15.3484 | 15.2465 | 0.1019 |
| | ICER | | | $91,488 |
| *Prior history of invasive breast cancer* | Total costs | $8,661 | $4,725 | $3,935 |
| | Total QALYs | 13.5186 | 13.4511 | 0.0676 |
| | ICER | | | $58,240 |
| *Prior history of treatment for DCIS or LCIS* | Total costs | $8,828 | $4,924 | $3,904 |
| | Total QALYs | 13.4765 | 13.4293 | 0.0471 |
| | ICER | | | $82,793 |
| *Chest radiotherapy between 10 and 35 years* | Total costs | $13,788 | $4,682 | $9,105 |
| | Total QALYs | 15.5053 | 15.4537 | 0.0516 |
| | ICER | | | $176,536 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

Variables tested in sensitivity analysis include diagnostic accuracy estimates, baseline risk of breast cancer, MRI screening age, clinical utility values, costs, time horizon and the discount rate. The model is extremely sensitive to the baseline risk of breast cancer and the estimated impact of delayed diagnosis on patient survival. The analyses for these two variables are shown in the table below. There was considerable variation in the incremental cost-effectiveness ratios (ICERs) for each

population when different age groups and different lengths of screening time were explored. Applying a decrement in health-related quality of life for 1 month in women with false-positive results substantially increases the ICER in populations where there is a low baseline risk of breast cancer, such as those with prior DCIS/LCIS or invasive breast cancer. For the results of all sensitivity analyses see Section D.4.2.

**Sensitivity analyses: risk of breast cancer and survival decrement due to delayed detection.**

| Variable tested | Value | Pop. 1 *BRCA1* | Pop. 2 Current MBS pop. | Pop. 3 Prior invasive breast cancer | Pop. 4 Prior DCIS/LCIS | Pop. 5 Prior chest irradiation |
|---|---|---|---|---|---|---|
| Baseline breast cancer risk (over 5 years from age 40) | 5% | $89,294 | $112,823 | $66,291 | $94,225 | $94,498 |
| | 10% | $46,958 | $57,774 | $33,489 | $47,646 | $47,599 |
| | 15% | $32,974 | $39,527 | $22,512 | $32,056 | $32,088 |
| | 20% | $26,066 | $30,464 | $16,980 | $24,201 | $24,415 |
| Decrement in 5-year overall survival due to delayed detection | 5% | $110,157 | $357,678 | $225,657 | $324,638 | $687,130 |
| | 10% | $53,658 | $174,247 | $110,894 | $158,210 | $337,273 |
| | 15% | $35,460 | $115,124 | $73,334 | $104,352 | $222,630 |
| | 20% | $26,414 | $85,911 | $54,672 | $77,704 | $165,637 |
| | 25% | $20,939 | $68,482 | $43,505 | $61,794 | $131,521 |
| | 30% | $17,185 | $56,895 | $36,067 | $51,213 | $108,789 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

## Key uncertainties in the economic evaluation

Five key uncertainties may affect the results of the economic model:

- The breast cancer risks used in the *BRCA1* and familial high-risk populations imply a lifetime risk of breast cancer at the upper end of (or slightly higher than) rates reported in the literature. This overestimate of breast cancer risk will overestimate the benefit of the additional sensitivity with MRI.
- The breast cancer risks used in the prior populations are based on a single study of women with prior DCIS. The risk of subsequent breast cancers (both recurrent and second) in women treated for both invasive and noninvasive breast cancer is variable across these populations and highly uncertain.
- The model assumes that early detection will improve 5-year overall survival by 18.8%. The assumptions and evidence required to link a change in diagnostic performance with improved survival are discussed in Section D.4.2. The benefits and harms of breast cancer screening in the general population are controversial, and an accurate estimate in these high-risk populations is not possible. However, it is clear that the cost-effectiveness of MRI relies heavily upon this assumption.

- The accuracy of mammography used in the model is based largely on evidence using film screen mammography, which may be inferior to the more commonly used digital mammography, thus overestimating the benefit of adding MRI to screening.
- The model does not incorporate the use of ultrasound, the inclusion of which is expected to reduce the incremental sensitivity of adding MRI to screening.

# Financial / budgetary impacts

## Method and approach

For the currently listed population, future use was estimated on the basis of projection (linear increase) of the actual use of MBS item 63464 since July 2009 (Table E.6, Figure E.1).

For the proposed new populations, future use was estimated using an epidemiological approach where possible, and assumptions where data were lacking (Section E.2.1).

The financial impact analyses focus on the additional cost of screening with MRI and the cost of the management of additional false-positive and true-positive findings from screening with MRI in addition to mammography.

## Key assumptions

The financial impact analyses use five key assumptions:

- Women who test negative with MRI receive no further follow-up.
- Women who test positive with MRI receive a follow-up biopsy.
- False-positives are detected at biopsy and are not treated.
- True-positives are confirmed at biopsy and receive treatment.
- Only additional true-positives and false-positives detected with MRI are included in the analysis of follow-up and treatment costs; management of all other women is not changed.

## Results

The total cost of the proposed listing for each of the populations is presented in the table below. The estimated total cost for all populations is $8.4 million in the first year of listing, and will increase to $20.3 million in year 5. Most this cost in each population comes from the cost of providing breast imaging with MRI (Sections E.2.2 and E.3.1). The contribution of follow-up and treatment costs is relatively minor (Sections E.4.1 and E.4.2).

**Total cost to the MBS of the requested listing.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,151,694 | $3,558,010 | $3,964,326 | $4,370,642 | $4,776,958 |
| Prior history of invasive breast cancer | $4,665,645 | $7,120,865 | $9,658,572 | $12,277,816 | $13,630,036 |
| Prior history of DCIS or LCIS | $551,969 | $842,029 | $1,141,791 | $1,451,502 | $1,611,986 |
| Prior history of therapeutic radiation to the chest | $52,469 | $106,721 | $162,802 | $220,759 | $255,783 |
| All populations | $8,421,778 | $11,627,624 | $14,927,491 | $18,320,718 | $20,274,762 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ.
Note: Rounding has been applied.

The total cost of the proposed listing to government health budgets, including the MBS, Pharmaceutical Benefits Scheme (PBS), and state and territory governments, is presented in the table below. The estimated total cost to government of the proposed listings is $9.7 million in 2015, rising to $23.3 million in 2019. See Sections E.5.1 and E.5.2 for details of the financial impact to the PBS and to the state and territory governments, respectively.

**Total cost to government health budgets.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,692,534 | $4,168,575 | $4,644,616 | $5,120,657 | $5,596,698 |
| Prior history of invasive breast cancer | $5,379,612 | $8,210,544 | $11,136,588 | $14,156,645 | $15,715,791 |
| Prior history of DCIS or LCIS | $611,543 | $932,909 | $1,265,024 | $1,608,162 | $1,785,967 |
| Prior history of therapeutic radiation to the chest | $52,500 | $106,751 | $162,832 | $220,789 | $255,813 |
| All populations | $9,736,188 | $13,418,779 | $17,209,060 | $21,106,253 | $23,354,268 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ.
Note: Rounding has been applied.

Sensitivity analyses were conducted to explore the effect of patient numbers, risk of breast cancer, estimates of diagnostic accuracy and MBS benefits for MRI (see Section E.6). The financial impact calculations for the proposed listing are most sensitive to changes in the numbers of women screened with breast MRI (see Section E.6.1). This is because the major contributor to the cost of the requested listing is the cost of performing the breast MRI service, including imaging and specialist attendance costs. Changes to variables that alter the number of women who receive biopsy and treatment have a low to moderate impact, as these costs account for a small proportion of the total cost of the proposed listing.

## Key uncertainties in the financial implications

Three key uncertainties may affect the results of the financial impact analysis:

- Patient numbers estimated for the new populations are uncertain, particularly the population of patients with a prior history of invasive breast cancer.
- The screening uptake rates used may be an underestimate, as high-risk patients may be more likely to comply with screening recommendations.
- The costs of treatment for women with prior breast cancer are uncertain as these patients may require a range of different treatment strategies, depending on their prior treatment history.

# Section A Details of the proposed medical service and its intended use

## A.1 Background

### A.1.1 Breast cancer in Australia

Breast cancer is a heterogeneous disease and can be divided into two main groups: *invasive* cancers, characterised by cancer cells that invade the breast stroma, and *noninvasive (in situ)* cancers, where cancer cells remain confined to the ducts or lobules. Generally, there are two types of noninvasive lesions: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), both of which differ in clinical features and morphology.

**(a) Overall incidence of breast cancer**

In Australia, data collection on the incidence of these different types of breast cancer is variable. Unlike the incidence of invasive breast cancer, collecting data on the incidence of DCIS and LCIS or recurrent secondary breast cancers is not the primary goal of data collection for cancer registries. Some data are derived by state and territory cancer registries in Australia (AIHW & NBOCC, 2010).

**(b) Invasive breast cancer**

In Australia, invasive breast cancer is the most frequently diagnosed cancer in women; 14,560 new cases were estimated in 2012 (based on 2000–2009 incidence data) (AIHW, 2012b). The age-standardised incidence rate in women was 114 per 100,000 in 2009, and the rates between 2010 and 2012 have been estimated to remain stable (AIHW, 2012b). Incidence varies by age: over half of invasive breast cancers diagnosed occur in women aged 50 to 69 years, and fewer than one in four (24%) in women who are <50 years of age (AIHW, 2012a).

**(c) DCIS and LCIS**

In 2005, there were 1,558 new DCIS cases reported in Australia. The lowest incidence rates occurred in women under 40 years of age (1.1 cases per 100,000 women) and 40 to 49 years of age (17.1 cases per 100,000 women), and the highest occurred in women 60 to 69 years of age (50.8 cases per 100,000 women; AIHW & NBOCC, 2010).

Data on the rates of LCIS are currently lacking in Australia. LCIS is rarely visible in mammography and is usually identified as an incidental finding at biopsy performed for other reasons (Sung et al, 2011b). In 1998 to 2001 in the United States, the rates of LCIS increased 2.5- to 3.8-fold in women aged <50 years (Li et al, 2005). These rates need to be considered with caution given the likelihood of differing interpretations of diagnostic criteria used by pathologists for LCIS in multiple institutions (Li et al, 2005).

**(d) Mortality**

In 2010, breast cancer was the second most common cause of cancer death in women (2,840 deaths per 100,000), following lung cancer (3,165 deaths per 100,000) in Australia (AIHW, 2012b). There has been a fall of 30% in the mortality rate of breast cancer in women over time, from 31 per 100,000 in

1994 to 22 per 100,000 in 2010 (AIHW, 2012b). Better survival has been attributed to improvements in treatment and, to some degree, screening programs (Jatoi & Miller, 2003; Burton et al, 2012).

**(e) Burden of disease**

Breast cancer is the leading cause of burden due to cancer in women, with the burden greatest in women 40 to 69 years of age (AIHW, 2012a, 2012b). The AIHW has estimated the burden of disease by using DALYs (disability-adjusted life years), where 'one DALY is one year of "healthy life" lost due to premature death, prolonged illness or disability' (AIHW, 2012b, p. 68). On the basis of 2012 estimates, breast cancer is expected to result in 61,300 DALYs. This represents more years of healthy life lost than are lost on account of disability, and is roughly equivalent to the burden of disease caused by stroke (AIHW, 2012b). From an international perspective, this places Australia and New Zealand (combined) as the third highest-ranked region for burden of disease from breast cancer, just after Northern Europe and Western Europe (Soerjomataram et al, 2012).

### A.1.2 Risk of breast cancer in high-risk groups

Sex and increasing age are the two main identifiable risk factors for breast cancer. However, additional factors are associated with an elevated risk of developing breast cancer.

The United Kingdom's NICE guidelines define three levels of risk classification for breast cancer (Table A.1): near population risk, moderate risk and high risk (NICE, 2013). The use of such categories may assist in determining the surveillance needs of specific women. The estimated risks of developing breast cancer for the populations under consideration in this assessment are discussed in the following sections.

**Table A.1 Summary of breast cancer risk categories used in UK guidelines (NICE, 2013).**

| Breast cancer risk category | Breast cancer risk between 40 and 50 years of age | Lifetime breast cancer risk from 20 years of age | Probability of a *BRCA1*, *BRCA2* or *TP53* mutation |
|---|---|---|---|
| Near population risk | <3% | <17% | Very low |
| Moderate risk | 3%–8% | 17%–30% | <10% |
| High risk | ≥8% | ≥30% | a ≥10% chance of a faulty *BRCA1*, *BRCA2* or *TP53* gene in the family |

Risk assessment models have been developed to help clinicians estimate the risk of breast cancer for individual patients. These models take into account known family history of breast cancer, yet each model estimates risk using different methods, populations and risk factors, and predicts different outcomes. The three main models are BRCAPRO, Claus and Tyrer–Cuzick.

Clinical guidelines suggest that women should receive personalised risk assessments and consider genetic testing if they have a strong family history of breast or ovarian cancer, or they have an *a priori* 10% to 20% probability of finding a mutation on the basis of risk assessment models such as BRCAPRO (NICE, 2013; USPSTF, 2005).

**(a) Gene mutations and family history**

Inherited breast cancer risk has been associated with mutations in some highly penetrant genes, including the breast cancer genes 1 (*BRCA1*) and 2 (*BRCA2*). In the Australian setting, the average cumulative risk of breast cancer for either *BRCA1* or *BRCA2* mutations was 27% (95% CI 16%–43%) to

50 years of age and 64% (95% CI 44%–83%) to 70 years (Scott et al, 2003). Inherited mutations of the tumour protein p53 gene (*TP53*) and *PTEN* genes have also been associated with a high risk of developing breast cancer, presenting as rare familial syndromes such as Li-Fraumeni and Cowden's, respectively (McPherson et al, 2000).

Generally, people with a first-degree relative affected by cancer are at a higher risk than the general population for cancer of the same site (Peto & Houlston, 2001; Turati et al, 2013). Compared with women who had no affected relatives, the risk ratio for breast cancer for women with one, two and three first-degree relatives increased from 1.80 (99% CI 1.69–1.01) to 2.93 (2.36–3.64) to 3.90 (2.03–7.49), respectively.

The probability of developing breast cancer in 10-year age bands by risk category is presented in Table A.2.

**Table A.2 Probability (%) of diagnosis with breast cancer within the next 10 years by familial risk category.**

| Age (years) | No affected relatives | One first-degree affected relative | Two first-degree affected relatives | *BRCA1* mutation | *BRCA2* mutation |
|---|---|---|---|---|---|
| 20 | 0.04 | 0.1 | 0.2 | 1.5 | 1.0 |
| 30 | 0.4 | 1.0 | 2.0 | 10 | 6.6 |
| 40 | 1.4 | 2.5 | 5.2 | 20 | 15 |
| 50 | 1.9 | 3.2 | 5.3 | 22 | 18 |
| 60 | 2.3 | 3.5 | 5.6 | 19 | 17 |

Source: Berg (2009).

The NHMRC estimates that women at high risk due to genetic predisposition or family history account for <1% of the Australian female population, although not all these women will go on to develop breast cancer (NBOCC, 2010). Women at high risk of breast cancer due to family history or genetic predisposition make up 5% to 10% of women with breast cancer (NBOCC, 2009). These women often develop breast cancer early in life and need more frequent screening and earlier start of screening than asymptomatic women at average risk of breast cancer.

In Australia, the current advice on the categorisation of breast cancer risk derives from the 2010 'guide for health professionals' from the NBOCC (2010). Risk for familial aspects of breast cancer is graded as:

1. at or slightly above average risk (>95% of the female population)
2. moderately increased risk (<4% of the female population)
3. potentially high risk (<1% of the female population).

The description of the potentially high-risk group coincides predominantly with the description outlined under the current MBS item 63464.

**(b) Prior history of invasive breast cancer**

Survival from breast cancer is increasing, with 5-year survival in Australia rising from 72% to 89% between 1982–87 and 2006–10. For those diagnosed between the ages of 40 and 49, 5-year relative

survival is >90%. Follow-up management of these women after treatment is therefore a significant question. Surveillance mammography is used to detect both ipsilateral breast tumour recurrence (IBTR) in the treated breast and new primary cancers in either the ipsilateral or contralateral breast.

Local recurrence tends to be a manifestation of aggressive disease, with risk varying by hormone receptor and *HER2* status. Rates of recurrence are also affected by systemic therapies, and as the effectiveness of these improve, as measured by rates of survival, the rates of IBTR also decrease (Houssami & Morrow, 2013). Therefore, rates of IBTR vary greatly depending on the tumour type and treatment regime. For example, rates of loco-regional recurrence over 10 years following breast conserving surgery are reduced from 25.1% without radiotherapy to 7.7% with radiotherapy (EBCTCG, 2005). A more recent study of women who underwent breast conserving surgery, most of whom also received adjuvant systemic therapy, found a 5-year cumulative incidence of local recurrence of 2.1%. This varied greatly by tumour type, from 0.8% for Luminal A to 10.8% for *HER2* (Arvold et al, 2011).

Like IBTR, rates of contralateral breast cancer are declining owing changes in treatment. It is estimated that rates in the United States have declined since 1985 at ~3% per year, predominantly in oestrogen receptor-positive women (Nichols et al, 2011). Using the Surveillance, Epidemiology, and End Results database (1973–1996), Gao et al (2003) found the risk of contralateral breast cancer to be 6.1% at 10 years and 12.0% at 20 years.

A more recent study based on US data estimated the risk of recurrent breast cancer to be 5.37 per 1000 woman-years and that of second primary breast cancers to be 5.88 per 1000 woman-years (Buist et al, 2010). The study included women with DCIS; rates of second primary cancers were 0.6%/year for invasive cancers and 0.8%/year for DCIS. Overall, the risks for both recurrence and new primary breast cancers are highly dependent on patients' prognostic factors; nevertheless, it appears likely that most patients would fall into the moderate- rather than high-risk category (Table A.1).

**(c) Prior history of DCIS or LCIS**

DCIS is considered to be a precursor to invasive breast cancer. A large systematic review notes that estimates of 5- or 10-year recurrence rates are remarkably unstable across studies, ranging from 2.4% to 15% for 5-year recurrence and from 10% to 24% for 10-year recurrence, and that the majority of important prognostic factors for DCIS outcomes are also prognostic factors for invasive breast cancer outcomes (Virnig et al, 2013). Australian data from 1995 to 2005 allowed an estimate that following a diagnosis of DCIS, the probability of being diagnosed with a subsequent invasive breast cancer is 5.3% within 5 years and 10.9% within 10 years (AIHW & NBOCC, 2010). Women who have the highest probability of invasive breast cancer are aged <40 years at the time of DCIS diagnosis: 8.4% within 5 years and 15.5% within 10 years (AIHW & NBOCC, 2010).

LCIS may be a precursor of invasive carcinoma and is associated with an increased risk of a subsequent breast cancer, with lifetime risk estimates of 10% to 20% (Arpino et al, 2005; Fisher et al, 1998). The average age of women diagnosed at biopsy with LCIS is 44 to 46 years (Page et al, 1991); however, these estimates are based on data derived from 1950 to 1968. Subsequent breast cancers that occur after LCIS may be ipsilateral or contralateral and are normally invasive lobular cancers, more than half being diagnosed >15 years after the index LCIS (Arpino et al, 2005; Page et al, 1991).

**(d) Previous history of irradiation to the chest from 10 to 35 years of age**

In women treated with radiotherapy for mediastinal Hodgkin's lymphoma, breast cancer is the most common secondary malignancy (Bhatia et al, 2003; Taylor et al, 2007). Several factors affect the risk of developing breast cancer: the patient's age at treatment, time since treatment, dose and field of radiotherapy, and whether alkylating chemotherapy has been received (Bhatia et al, 2003; De Bruin et al, 2009; Swerdlow et al, 2012; Travis et al, 2005). When diagnosed with breast cancer, women with prior Hodgkin's lymphoma are more likely to be younger than the average breast cancer patient, and to have bilateral disease and invasive ductal and lobular carcinoma (Cutuli et al, 2012).

A systematic review found that the cumulative incidence of breast cancer by age 40 to 45 years ranged from 13% to 20%, and by 25 to 30 years' follow-up ranged from 12% to 26%. This incidence is similar to that in women with a *BRCA* gene mutation, in whom the cumulative incidence by age 40 years ranges from 10% to 19% (Henderson et al, 2010).

### A.1.3 Risk reduction strategies for women at high risk

Risk reduction strategies for women at an increased risk of developing breast cancer include surgery, chemoprevention and screening tests. The information presented below provides a broad overview of the current state of knowledge.

**(a) Prophylactic surgical options**

The objective of surgical options is to reduce the risk of cancer and mortality. The surgical options are prophylactic bilateral mastectomy, prophylactic salipingo-oophorectomy (ie, the removal of the fallopian tubes and ovaries), and both mastectomy and salipingo-oophorectomy. Prophylactic bilateral mastectomy has been shown to reduce risk by at least 90% in mutation carriers, and salipingo-oophorectomy is likely to reduce the risk of ovarian cancer by 90% risk and of breast cancer by roughly 50% (Guillem et al, 2006).

**(b) Chemoprevention**

Selective oestrogen receptor modulators, such as tamoxifen, reduce breast cancer risk by ~40% (Cuzick et al, 2003, 2007; Fisher et al, 2005; Veronesi et al, 2007; Powles et al, 2007). Tamoxifen's preventive effect is sustained for 10 years (ie, 5 years of tamoxifen administration + 5 years after) (Cuzick et al, 2007). In a recent cohort study, tamoxifen was also found to reduce the risk of contralateral breast cancer in women who have a previous history of breast cancer and are *BRCA1*/*BRCA2* mutation carriers (Phillips et al, 2013).

**(c) Screening**

Intensified screening is advised for women at high risk of breast cancer who do not choose to undergo prophylactic mastectomy. The strategies are outlined below.

***Clinical breast examination***

Randomised controlled trials have shown that breast self-examination or clinical breast examination (CBE) by a trained health professional has a relatively low sensitivity both in population screening and in high-risk groups (Bobo et al, 2000; Kolb et al, 2002). In addition, no mortality benefit has been reported (Kösters & Gøtzsche, 2008).

***Mammography***

Participation in the population-based BreastScreen Australia mammography program is recommended for women aged 50 to 69 years, but women aged 40 years or above are also eligible (AIHW, 2012a). Screening mammography is less effective in women under 50 years, as it may lead to more investigations and missed breast cancers (false-negative results) owing to its lower sensitivity in this age group (Irwig et al, 1997).

Mammography is the only breast screening test to be evaluated by randomised controlled trials. Systematic reviews of these trials have reported that mammography reduces breast cancer mortality, but the extent of this effect remains controversial (Gøtzsche & Jorgensen, 2013). Patient, tumour and technical factors have been shown to influence its sensitivity. Technical factors, such as the quality of the mammogram film and reader interpretation, may also influence sensitivity.

***Ultrasound***

Breast ultrasound is commonly used to complement mammography, particularly in the investigation of breast symptoms in women younger than 35 years of age and in women who are pregnant or lactating (NBCC, 2002). Ultrasound is also used to evaluate palpable lesions not seen on mammography, to detect an associated underlying mass, to evaluate breast implants and to guide the biopsy or surgical excision of breast tumours (NBCC, 2002). A systematic review of the accuracy of screening tests for breast cancer identified evidence that ultrasound increases the sensitivity of mammography in detecting cancers in women with mammographically dense breasts and those assessed as at high risk of breast cancer, but also results in an increase in the rate of false-positive findings (Irwig et al, 2004).

### A.1.4 Items in the Decision-Analytic Protocol

The Final Decision-Analytic Protocol (DAP) for the current application, available on the MSAC website (www.msac.gov.au/internet/msac/publishing.nsf/Content/app1098.1-1), outlines the questions to be answered in this assessment report. Table A.3 summarizes how this assessment conforms to the Final DAP and any differences or changes that have occurred.

**Table A.3 Checklist against the Final Decision-Analytic Protocol (DAP) for Application 1098.1.**

| Items in the PASC-approved Decision-Analytic Protocol | Addressed in the assessment report | Reason or justification if not addressed |
|---|---|---|
| Details of the proposed intervention | Yes | N/A |
| Interim-funded MBS items and proposed MBS listing for new high-risk patient populations | Yes | N/A |
| Current place for proposed intervention and clinical algorithm with the proposed listing | Yes | N/A |
| Comparator | Yes | N/A |
| Comparative clinical effectiveness | Yes | N/A |
| Comparative safety | Yes | N/A |
| Comparative cost-effectiveness | Yes | The economic model does not incorporate the use of ultrasound, the inclusion of which is expected to reduce the incremental sensitivity of adding MRI to screening |

N/A = not applicable; PASC = Protocol Advisory Sub-committee; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging.

## A.2 Proposed medical service—MRI

### A.2.1 Proposed medical service and type

In May 2011, the Department of Health and Ageing received an application ('the Application') from the Royal Australian and New Zealand College of Radiologists requesting the review of the Medicare Benefits Schedule (MBS) listing of breast magnetic resonance imaging (MRI) for screening of young women at high risk of breast cancer. The Application requested a review of:

- the use of breast MRI for the screening of high-risk women **in addition** to an organised screening program for women <50 years of age, as recommended by the Medical Services Advisory Committee in 2007 (MSAC, 2006); as such, no change is being proposed to the use of breast MRI in the clinical pathway from what was recommended in the 2006 review
- the inclusion of additional high-risk patient populations, namely women who are <50 years of age and have had either:
    a) a prior history of invasive breast cancer
    b) a prior history of treatment for LCIS or DCIS
    c) a history of radiotherapy to the chest area between 10 and 35 years of age.

The change in the proposed patient population will see additional patients screened who would not previously have had access to MBS item 63464.

This inclusion of the additional high-risk patient populations is consistent with those risk factors that have been identified by NBOCC (2009, p. xi) as being associated with a strong, increased risk (relative risk > 4) of breast cancer.

### A.2.2 Health issue that this assessment addresses

This assessment is concerned with the screening of breast cancer in asymptomatic women at high risk of breast cancer. Women at high risk due to family history or genetic predisposition make up 5%–10% of women with breast cancer (NBOCC, 2009). These women often develop breast cancer early in life, and need more frequent screening and earlier start of screening than asymptomatic women at average risk of breast cancer. Breast MRI occurs outside of the BreastScreen Australia program and can include MRI or mammography, with or without the use of ultrasound. Currently women <50 years of age and assessed as being at high risk are offered annual screening, most starting no earlier than 25 years of age. However, this can depend on the age at onset of cancers in the family and the potential nature of the gene mutation.

### A.2.3 Mode of delivery and assessment

MRI can be used in both screening and diagnosis of breast cancer, including in women with a high risk due to family history or genetic predisposition. It is also used in preoperative staging, evaluating response to treatment, screening of women with breast augmentation or reconstruction, and identification of occult breast cancer in women with metastatic disease.

MRI uses a strong external magnetic field to produce images of biological tissues. This magnetic field stimulates hydrogen ions in body tissues to produce signals that vary according to the ions' chemical, structural and magnetic environment. MRI is particularly well suited to distinguishing between blood

vessels, other fluid-filled structures and surrounding soft tissues, and thus is especially useful in imaging the brain, muscles and heart, as well as in detecting abnormal tissues such as tumours.

In the breast, MRIs show parenchyma and fat, and abnormal tissue if present (Saslow et al, 2007). Breast MRI is performed in a dedicated MRI room using an MRI machine with a minimum magnet strength of 1.5 T. A dedicated breast coil, comprising seven or more channels, is also required, and an intravenous contrast agent is administered. As breast tissue generally has similar signal intensity to tumour tissue on routine MRI, the intravenous administration of a contrast agent containing gadolinium chelate is used to enhance breast lesions. Contrast-enhanced MRI provides detailed information about tumour morphology and vasculature, and can differentiate between benign and potentially malignant tumours (Bassett et al, 2008; Shah et al, 2005).

During the examination the patient lies prone on a scanning table inside a high-strength magnet, with the breast dependent in the dedicated breast coil (Rausch & Hendrick, 2006). A number of imaging sequences are obtained, before the administration of the contrast agent. Following contrast injection, further sequences are obtained, including evaluation of the uptake and washout of the contrast and any focal lesions, over several minutes (Saslow et al, 2007).

The MRI sequences are interpreted by a radiologist. Malignant lesions usually display an enhancement pattern (ie, a ≥70% increase in signal intensity) with rapid uptake and washout of contrast (Macura et al, 2006). They may also display rim-enhancement, which is related to a very high positive predictive value (PPV) for malignancy of 79% to 84% (Monticciolo, 2011; Nunes et al, 1997). In benign masses, such as fibroadenomas, the contrast uptake is usually slower and more prolonged, yet the signal can still be enhanced. Given the general differences in contrast uptake and washout in benign and malignant masses, it is important to examine images at early time-points (1–3 min) after contrast injection (Johnson, 2012; Saslow et al, 2007). Some lesions may have atypical or indeterminate findings.

Performing MRI requires appropriate techniques and equipment in addition to experienced staff. The supervising radiologist should have expertise in breast imaging and MRI interpretation. In addition, for an MRI scan to attract a Medicare rebate, the patient must be ≤50 years of age and fulfil the specified risk criteria (Table A.5). The scan must be requested by a specialist or consultant physician (not a GP) and be performed on a Medicare-eligible MRI unit by a Medicare-eligible provider, and be an MRI service listed in the MBS.

### A.2.4 Regulatory status

MRI is currently available in public and private facilities in major centres in each state and territory; 337 units have been licensed throughout Australia to provide services eligible for funding under the MBS.

Breast MRI requires both a breast coil and the use of a gadolinium-containing contrast agent. The Australian Register of Therapeutic Goods lists several coils and contrast agents that have been approved by the Therapeutic Goods Administration for use in diagnostic imaging procedures.

## A.3 Proposed MBS listing sought for breast MRI

### A.3.1 Proposed MBS listing

Breast MRI for screening of high-risk women is already listed on the MBS (items 63464 and 63467). As mentioned in section A.2, this assessment addresses:

- a review of interim-funded items 63464 and 63467—breast MRI for screening of high-risk, asymptomatic women (that is, women without breast changes) in terms of effectiveness and cost-effectiveness
- the inclusion of new high-risk patient populations in MBS item 63464, namely women with either:
  a) a prior history of invasive breast cancer
  b) a prior history of treatment for LCIS or DCIS
  c) a history of radiotherapy to the chest area between the ages of 10 and 35 years.

The proposed MBS item descriptor is presented in Table A.4, with proposed additions to the wording shown in bold italic text.

**Table A.4 Proposed MBS item descriptor for breast MRI.**

| Category 5—Diagnostic Imaging Services |
|---|
| MBS 63464 |
| Magnetic resonance imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where: |
| (a) a dedicated breast coil is used; and |
| (b) the request for scan identifies that the woman is asymptomatic and is <50 years of age; and |
| (c) the request for scan identifies either: |
| (i) that the patient is at high risk of developing breast cancer due to one of the following: |
| (A) 3 or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer; |
| (B) 2 or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer, if any of the following applies to at least 1 of the relatives: |
| —has been diagnosed with bilateral breast cancer |
| —had onset of breast cancer before the age of 40 years |
| —had onset of ovarian cancer before the age of 50 years |
| —has been diagnosed with breast and ovarian cancer, at the same time or at different times |
| —has Ashkenazi Jewish ancestry |
| —is a male relative who has been diagnosed with breast cancer. |
| (C) 1 first- or second-degree relative diagnosed with breast cancer at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 years or younger; or |
| (ii) that genetic testing has identified the presence of a high-risk breast cancer gene mutation |
| *(D) prior history of treatment for invasive breast cancer* |
| *(E) prior history of treatment for ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)* |
| *(F) with a history of therapeutic radiation treatment to the chest area between the ages of 10 and 35 years* |
| Scan of both breasts for: |

| Category 5—Diagnostic Imaging Services |
|---|
| —detection of cancer (R)<br>Note: Benefits are payable on one occasion only in any 12-month period.<br>Fee: $690.00 Benefit: 75% = $517.50, 85% = $613.80<br>Relevant explanatory note: Bulk bill incentive |
| MBS 63467<br>Magnetic resonance imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:<br>(a) a dedicated breast coil is used; and<br>(b) the woman has had an abnormality detected as a result of a service described in item 63464 performed in the previous 12 months<br>Scan of both breasts for:<br>—detection of cancer (R)<br>Note 1: Benefits are payable on one occasion only in any 12-month period.<br>Note 2: This item is intended for follow-up imaging of abnormalities diagnosed on a scan described by item 63464.<br>Bulk bill incentive<br>Fee: $690.00 Benefit: 75% = $517.50, 85% = $613.80 |

Source: Final Decision-Analytic Protocol, Table 2, p. 9; MBS = Medicare Benefits Schedule.

### A.3.2 Current arrangements for public reimbursement of breast MRI

In 2007, MSAC recommended **interim** public funding for breast MRI in the surveillance of breast cancer in asymptomatic women with a high risk of developing breast cancer when used as part of an organised screening program.

In February 2009, the government acted on MSAC advice and listed breast MRI on the MBS as item numbers 63464 and 63467 (Table A.5).

**Table A.5 Current MBS item descriptor for breast MRI.**

| Category 5—Diagnostic Imaging Services |
|---|
| MBS 63464<br>Magnetic resonance imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:<br>(a) a dedicated breast coil is used; and<br>(b) the request for scan identifies that the woman is asymptomatic and is <50 years of age; and<br>(c) the request for scan identifies either:<br>(i) that the patient is at high risk of developing breast cancer due to one of the following:<br>(A) 3 or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer;<br>(B) 2 or more first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer, if any of the following applies to at least 1 of the relatives:<br>—has been diagnosed with bilateral breast cancer<br>—had onset of breast cancer before the age of 40 years<br>—had onset of ovarian cancer before the age of 50 years |

| Category 5—Diagnostic Imaging Services |
|---|
| —has been diagnosed with breast and ovarian cancer, at the same time or at different times<br>—has Ashkenazi Jewish ancestry<br>—is a male relative who has been diagnosed with breast cancer.<br>(C) 1 first- or second-degree relative diagnosed with breast cancer at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 years or younger; or<br>(ii) that genetic testing has identified the presence of a high-risk breast cancer gene mutation<br>Scan of both breasts for:<br>—detection of cancer (R)<br>Note: Benefits are payable on one occasion only in any 12-month period.<br>(Anaes.) Fee: $690.00 Benefit: 75% = $517.50, 85% = $613.80<br>Relevant explanatory note: Bulk bill incentive |
| MBS 63467<br>Magnetic resonance imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:<br>(a) a dedicated breast coil is used; and<br>(b) the woman has had an abnormality detected as a result of a service described in item 63464 performed in the previous 12 months<br>Scan of both breasts for:<br>—detection of cancer (R)<br>Note 1: Benefits are payable on one occasion only in any 12-month period.<br>Note 2: This item is intended for follow-up imaging of abnormalities diagnosed on a scan described by item 63464.<br>Bulk bill incentive<br>(Anaes.)<br>Fee: $690.00 Benefit: 75% = $517.50, 85% = $613.80 |

Source: Final Decision-Analytic Protocol, Table 1, p. 7; MBS = Medicare Benefits Schedule.

To be eligible for the rebate, the patient must be a woman who is <50 years of age, with no current signs or symptoms of breast cancer, and who has been identified as at high risk of breast cancer as defined in the current MBS item descriptor (Table A.5).

In addition, for an MRI scan to attract a Medicare rebate, the scan must be requested by a specialist or consultant physician and be performed on a Medicare-eligible MRI unit by a Medicare-eligible provider, and be an MRI service listed in the MBS. Unlicensed sites that are ineligible for MBS funding may also provide breast MRI however the patient will need to pay for the scan themselves.

### A.3.3 Medical services likely to be co-administered with breast MRI

Women would first have a medical consultation including a clinical breast examination (CBE) (MBS items 3, 23, 36 and 44) and then be referred for a mammogram or a specialist appointment.

Breast MRI is currently used in addition to mammography with or without the use of ultrasound (MBS items 59300–59304, 593112–59317, 55070–55079), and as such, MRI and mammography may be given on the same day or within a week or so of one another. Factors such as menstrual cycles, availability of staff and equipment may have an impact on the length of time between tests but

should not result in only one test being given to eligible women as this may lead to women having a biopsy with less information than would have been supplied by having both tests.

To attract a rebate for a breast MRI, women will need to have a referral from a specialist medical practitioner or consultant physician (MBS items 104 and 110). Table A.6 outlines the MBS items associated with breast MRI. Table A.7 outlines the MBS items associated with breast ultrasound. Table A.8 outlines the consultation MBS items likely to be associated with breast MRI.

**Table A.6 Mammography MBS items associated with breast MRI.**

| Mammography | Category 5—Diagnostic Imaging Services |
|---|---|
| MBS 59300<br>Mammography of both breasts, if there is a reason to suspect the presence of malignancy because of:<br>(i) the past occurrence of breast malignancy in the patient or members of the patient's family; or<br>(ii) symptoms or indications of malignancy found on an examination of the patient by a medical practitioner.<br>Unless otherwise indicated, mammography includes both breasts (R).<br>Bulk bill incentive<br>Fee: $89.50 Benefit: 75% = $67.15, 85% = $76.10 | |
| MBS 59301*<br>Mammography of both breasts, if there is a reason to suspect the presence of malignancy because of:<br>(i) the past occurrence of breast malignancy in the patient or members of the patient's family; or<br>(ii) symptoms or indications of malignancy found on an examination of the patient by a medical practitioner.<br>Unless otherwise indicated, mammography includes both breasts (R) (NK)<br>Bulk bill incentive<br>Fee: $44.75 Benefit: 75% = $33.60, 85% = $38.05 | |
| MBS 59303<br>Mammography of one breast, if:<br>(a) the patient is referred with a specific request for a unilateral mammogram; and<br>(b) there is reason to suspect the presence of malignancy because of:<br>(i) the past occurrence of breast malignancy in the patient or members of the patient's family; or<br>(ii) symptoms or indications of malignancy found on an examination of the patient by a medical practitioner (R).<br>Bulk bill incentive<br>Fee: $53.95 Benefit: 75% = $40.50, 85% = $45.90 | |

| Mammography | Category 5—Diagnostic Imaging Services |
|---|---|
| MBS 59304*<br>Mammography of one breast, if:<br>(a) the patient is referred with a specific request for a unilateral mammogram; and<br>(b) there is reason to suspect the presence of malignancy because of:<br>(i) the past occurrence of breast malignancy in the patient or members of the patient's family; or<br>(ii) symptoms or indications of malignancy found on an examination of the patient by a medical practitioner (R) (NK).<br>Bulk bill incentive<br>Fee: $27.00 Benefit: 75% = $20.25, 85% = $22.95 | |

*From 1 July 2011 all services listed in the Diagnostic Imaging Services Table of the Medicare Benefits Schedule (MBS), excluding positron emission tomography services, preparation items 60918 and 60927 and MRI modifier items in subgroup 22 will have a mirror NK item (50% of the schedule fee) for diagnostic imaging services provided on aged equipment.

**Table A.7 Ultrasound MBS items associated with breast MRI.**

| Ultrasound | Category 5—Diagnostic Imaging Services |
|---|---|
| MBS 55070<br>Breast, one, ultrasound scan of, where:<br>(a) the patient is referred by a medical practitioner; and<br>(b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and<br>(c) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member (R).<br>Bulk bill incentive<br>Fee: $98.25 Benefit: 75% = $73.70, 85% = $83.55 | |
| MBS 55073<br>Breast, one, ultrasound scan of, where:<br>(a) the patient is not referred by a medical practitioner; and<br>(b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies (NR).<br>Bulk bill incentive<br>Fee: $34.05 Benefit: 75% = $25.55, 85% = $28.95 | |
| MBS 55076<br>Breasts, both, ultrasound scan of, where:<br>(a) the patient is referred by a medical practitioner; and<br>(b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and<br>(c) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member (R).<br>Bulk bill incentive<br>Fee: $109.10 Benefit: 75% = $81.85 85% = $92.75 | |

| Ultrasound | Category 5—Diagnostic Imaging Services |
|---|---|
| MBS 55079<br>Breasts, both, ultrasound scan of, where:<br>(a) the patient is not referred by a medical practitioner; and<br>(b) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies (NR).<br>Bulk bill incentive<br>Fee: $37.85 Benefit: 75% = $28.40 85% = $32.20 | |

MBS = Medicare Benefits Schedule

**Table A.8 Consultation MBS items associated with breast MRI.**

| Specialist consultation | Category 1—Professional Attendances |
|---|---|
| MBS 104<br>Specialist, referred consultation—surgery or hospital<br>(Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her speciality where the patient is referred to him or her)<br>—Initial attendance in a single course of treatment, not being a service to which ophthalmology items 106 or 109 or obstetric item 16401 apply.<br>Fee: $85.55 Benefit: 75% = $64.20, 85% = $72.75<br>Extended Medicare Safety Net Cap: $256.65 | |
| Consultant physician (other than in psychiatry), referred consultation—surgery or hospital<br>(Professional attendance at consulting rooms or hospital by a consultant physician in the practice of his or her specialty [other than in psychiatry] where the patient is referred to him or her by a medical practitioner)<br>—Initial attendance in a single course of treatment<br>Fee: $150.90 Benefit: 75% = $113.20, 85% = $128.30<br>Extended Medicare safety net cap: $452.70 | |

MBS = Medicare Benefits Schedule.

### A.3.4 Other relevant applications and reviews

Other applications and reviews relevant to the current assessment are summarised in Table A.9.

**Table A.9 Other applications and reviews relevant to the current assessment.**

| No | Application title | Progress |
|---|---|---|
| 1333 | Breast magnetic resonance imaging (MRI) for staging in women with newly diagnosed breast cancer | Proposed DAP reviewed at PASC 13 December 2013; awaiting release for public consultation |

DAP = Decision-Analytic Protocol; PASC = Protocol Advisory Sub-committee.

Source: MSAC website [accessed 8 January 2014].

## A.4 Comparator details

### A.4.1 Mammography through the BreastScreen Australia program

Mammography is the most common form of breast imaging for asymptomatic and symptomatic women and may be used for screening or diagnosis. BreastScreen Australia, the national population-based screening program, is targeted to asymptomatic women at average risk of breast cancer. It

provides free screening mammograms at 2-yearly intervals for women aged 50 to 69 years, although women aged 40 to 49 and 70 years and older are also eligible. A screening mammogram consists of two sets of low-dose x-rays to give views from the side (medio-lateral oblique) and top (cranio-caudal).

### A.4.2 Mammography outside the BreastScreen Australia program

Diagnostic mammography is recommended for women who have symptoms which may be due to breast cancer, who have a previous history of breast cancer or who are at familial risk of developing breast cancer. The MBS provides a rebate for diagnostic mammography where there is a reason to suspect the presence of a malignancy, for example in women with breast symptoms and women with a personal or family history of breast cancer (MBS items 59300 and 59301).

The MBS specifically excludes rebates for mammography for screening purposes except for personal or family history. However, it is apparent that some mammography services accessed through the MBS are non-diagnostic (IMS Health Pty Ltd for the Department of Health and Ageing, 2009).

### A.4.3 Ultrasound

Breast ultrasound may be used to complement mammography (MBS items 55070, 55073 and 55076). However, the role of breast ultrasound in screening young women at high risk of breast cancer has not been established (NBCC, 2002) and its use varies by centre in Australia. Some clinicians use ultrasound routinely to screen all young high-risk women; others use it selectively, for example in young women with increased mammographic density (Advisory Panel, March 2006).

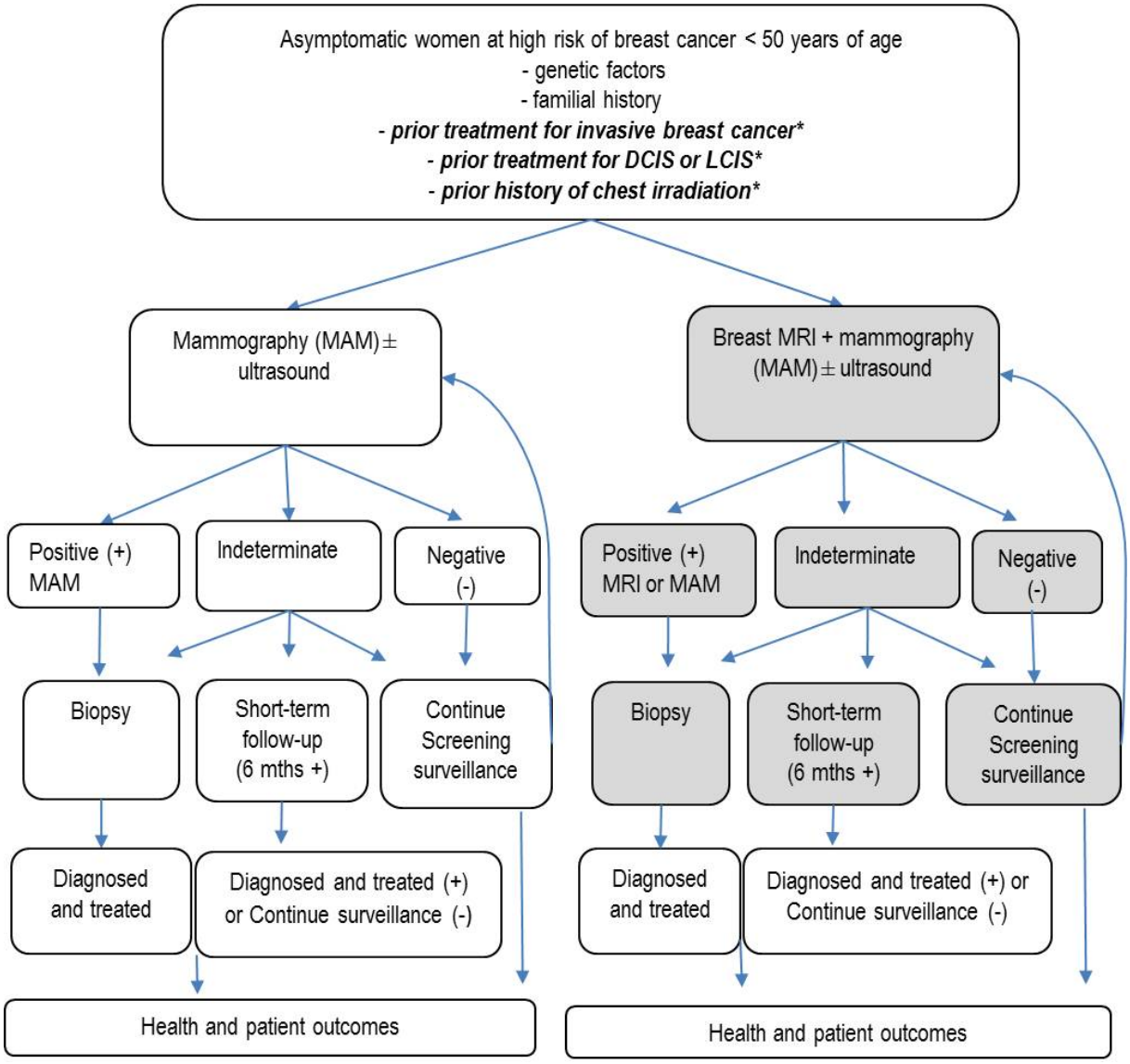
## A.5 Clinical management algorithm

Breast MRI has been conditionally recommended for use as an **additional** test in the diagnosis of breast cancer in asymptomatic women <50 years of age with a high risk of developing breast cancer when used as part of organised screening, on the basis of the 2006 MSAC assessment. Under this scheme, women eligible for MRI in addition to organised screening programs include women with a genetic mutation (such as *BRCA1*, *BRCA2* or *TP53* defined by genetic testing) and familial history of breast or ovarian cancer or sarcoma (bone or soft tissue). Breast MRI occurs outside of the BreastScreen Australia program.

In relation to the clinical algorithm, this assessment proposes no change in the use of breast MRI for the aforementioned cohort of high-risk women (ie, presence of genetic mutations or familial history); but includes a new cohort of women at high risk of developing breast cancer. This will see additional women screened with MRI who would not have previously had access to MBS item 63464. The new cohort includes women who have a previous history of invasive breast cancer, DCIS or LCIS, or chest irradiation from 10 to 35 years of age for Hodgkin's lymphoma.

Breast MRI will be considered in addition to mammography screening, with or without ultrasound. Figure A.1 includes the current and additional high-risk populations under consideration.

**Figure A.1 Clinical algorithm (clinical pathway) for screening asymptomatic high-risk women.**




*Proposed new cohort of women at high risk.

In clinical practice, the two tests may or may not be done simultaneously. While ultrasound is included in the above flow chart, it may not form part of routine screening in all centres.

## A.6 Differences between breast MRI and mammography

### A.6.1 Differences in the indication

There are three main differences in the indications between breast MRI and mammography:

- MRI is proposed as a more sensitive test than mammography for detecting early breast cancer. This means that breast MRI is capable of detecting a higher number of breast cancers that are not evidenced in mammography and clinical examinations.
- MRIs are not affected by increased radiological density. Mammography performs less well in young women, in particular in those with increased mammographic breast density.
- MRI is considered to be safer than mammography because it does not use ionising radiation.

The use of more than one imaging tool for breast cancer screening to increase the yield of cancer diagnosis in high-risk women has been reported in systematic reviews and primary studies (Lehman et al, 2005; Lord et al, 2007; Ojeda-Fournier & Comstock, 2009; Odle 2011).

### A.6.2 Differences in the contraindications

Contrast-enhanced breast MRI is unsuitable for various reasons:

- Potential reactions to gadolinium-based contrast agents, especially for patients with kidney disease (RANZCR, 2009).
- Women who weigh >136 kg or are unable to lie prone for an extended period.
- Women who are claustrophobic.
- Women who have cardiac pacemakers, aneurysm clips, insulin pumps or other surgically implanted metal objects (ACR, 2011).

### A.6.3 Differences in the likelihood and severity of adverse events

Breast MRI for screening has potential disadvantages:

- A possibly lower test specificity (ie, the ability to correctly exclude people without breast cancer) than mammography. This means that women receive a higher number of call-backs and biopsies to assess false-positive results than by mammography. This has been attributed to an overlap in enhancement features of benign and malignant breast lesions (Olsen et al, 2012; Saslow et al, 2007).
- Increased anxiety due to these false-positives.
- Psychological distress related to the MRI procedure itself (van Dooren et al, 2005).
- Lack of information about the effects of repeated imaging in high-risk groups.
- Failure to identify 5% to 12% of cancers (Friedrich, 1998; Schnall et al, 2006). In particular, MRI does not seem to detect all cases of DCIS or all small carcinomas (<3 mm).
- Variability in techniques and interpretation standards applied in institutions and criteria for excluding a diagnosis.
- The necessary exclusion of some groups of women from having MRI owing to contraindications such as cardiac pacemakers.

## A.7 Clinical claim

The clinical claims outlined in the DAP are related mainly to women at high risk due to genetic mutations or family history. This is because most of the research has focused on this high-risk group, not the proposed additional high-risk cohorts. The clinical claims to be addressed in the current assessment relate to the following potential benefits and harms.

Potential benefits:

- MRI in addition to mammography appears to increase the number of tumours detected.
- MRI in addition to mammography might reduce the incidence of advanced-stage breast cancer (Warner et al, 2011).
- Breast MRI is a safe procedure in patients without contraindications to exposure to magnetic fields.

Potential harms:

- MRI in addition to mammography leads to an increase in false-positive outcomes.

## A.8 Summary of the primary elements of the decision analysis

Table A.10 summarises the patient population, intervention, comparator and outcome (PICO) elements for this assessment report.

**Table A.10 Summary of the patient population, intervention, comparator and outcome (PICO) elements.**

| | |
|---|---|
| Population of interest | Asymptomatic women at high risk of breast cancer, <50 years of age with:<br>• genetic factors (such as *BRCA1*, *BRCA2* gene mutations)<br>• familial history of breast cancer, ovarian cancer or sarcoma (bone or soft tissue)<br>• prior treatment for invasive breast cancer<br>• prior treatment for DCIS or LCIS<br>• prior history of chest irradiation between the ages of 10 and 35 years |
| Intervention of interest | MRI in addition to mammography (with or without ultrasound)<br>If no studies exist with the combined intervention of MRI and mammography in the additional high-risk cohort, MRI vs mammography alone will be considered |
| Comparator | Mammography with or without ultrasound |
| Outcomes of interest | Report on at least one of the following:<br>• Health outcomes: overall survival, breast-cancer-specific mortality, breast cancer incidence or recurrence<br>• Diagnostic accuracy: sensitivity and specificity, positive and negative predictive value, true-positive to false-negative ratio, incremental rate of true-positive<br>• Change in management: definitive treatment instigated, biopsy rate, change of stage<br>• Patient-reported outcomes: quality of life, patient preference, satisfaction, anxiety, patient compliance, safety, adverse events |

*BRCA1/2* = breast cancer 1 or 2 gene; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging.

### Primary review question:

What are the safety, effectiveness and cost-effectiveness of breast MRI in addition to mammography with or without ultrasound for screening asymptomatic high-risk women less than 50 years of age?

# Section B Clinical evaluation for the indications

## B.1 Description of search strategies

The following exclusion criteria were applied to identify eligible studies for inclusion:

- Not an appropriate clinical study
    - Non-clinical studies are excluded.
    - Case series where the use or reporting of the reference standard is based on the breast MRI result (positive/negative) are excluded.
    - Case-control studies where patients were selected for inclusion in the study on the basis of their known disease status are excluded.
    - Systematic reviews which have been superseded are excluded.
    - Abstracts only are excluded.
- Wrong patient group
    - Studies must include the patients as described in the PICO table (Table A.10).
        - Age: studies including women >65 years old will be excluded (this criterion follows HIQA, 2013 and acknowledges the limited body of evidence for women aged <50 years). For indications in which no studies meet this criterion, the age range is extended.
    - Studies with <20 patients undergoing MRI are excluded.
- Wrong diagnostic tests
    - Studies must cover breast MRI and mammography.
    - Studies must report on MRI as an *additional* test to mammography. Where no studies report on MRI as an additional test, studies which compare MRI with mammography are included.
- Wrong reference standard or comparator
    - Reference standard: minimum of histology for positive tests and a consensus of all tests for negative tests.
    - Mammography with or without ultrasound as a comparator.
- Wrong outcomes
    - Studies must report on at least one of the outcomes described in the PICO table (Table A.10).
- Not in English

## B.2 Search strategies

Two search strategies were developed. (For full details, see Appendix 2.)

### B.2.1 Asymptomatic, high-risk women: MBS interim-funded item

The following electronic databases were searched:

- EMBASE.com (includes MEDLINE and EMBASE) and records retrieved 25 January 2013. Updated 6 November 2013.

- PreMEDLINE and records retrieved 25 January 2013. Updated 6 November 2013.
- The Cochrane Library (includes CDSR, DARE, CLEED, CLHTA and CLMCR). Records retrieved 9 December 2012.
- The World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), which include the US National Institutes of Health (NIH) and ANZCTR registries. Records retrieved 9 January 2013.

### B.2.2 Additional high-risk groups

The following electronic databases were searched:

- EMBASE.com (includes MEDLINE and EMBASE) and records retrieved 28 May 2013. PreMEDLINE and records retrieved 28 May 2013. Updated 6 November 2013.
- The Cochrane Library (includes CDSR, DARE, CLEED, CLHTA and CLMCR) and records retrieved 13 November 2012.
- The WHO's ICTRP, which includes the NIH and ANZCTR registries.

## B.3 All included studies

### B.3.1 Search results

The citations retrieved from the literature search were reviewed to assess their eligibility for inclusion in the assessment. At all stages in the review, studies were excluded if they did not meet the PICO criteria specified in Section A.8, if they were the wrong publication type (ie, editorial, non-systematic reviews, letters, articles before 2006), or if they were not published in English. Initially, the titles and abstracts of all citations were screened, and studies that did not meet the criteria were excluded. The full text of all remaining studies was retrieved and reviewed.

Studies reporting on a head-to-head comparison of breast MRI + mammography with mammography (with or without ultrasound) provide direct evidence about the relative effects of these tests to answer the clinical question. Studies comparing breast MRI with mammography were included only if no studies were identified which provided direct evidence. Information from studies that report data for only one of the tests of interest was not used, as indirect comparisons of results from different studies can introduce bias.

Studies investigating MRI in <20 patients were excluded because small studies are unlikely to achieve sufficient precision in their estimates of test outcomes for reliable interpretation. Large studies that identify few cancers would be unlikely to provide precise estimates of the sensitivity of a test but may still provide useful information about the relative specificity of tests, and were included in the review.

**(a) Asymptomatic, high-risk women: MBS interim-funded item**

Table B.1 presents a summary of the search results.

**Table B.1 Summary of identification of studies from the search of the published literature.**

| | EMBASE* | Pre-MEDLINE | Cochrane Library | WHO ICTRP | Total |
|---|---|---|---|---|---|
| Number of citations retrieved by search | 2382 | 222 | 174 | 120 | |
| Number of citations excluded after title/abstract review: | | | | | |
| • duplicates | 6 | 0 | 2 | | |
| • publication type (ie, editorial, non-systematic reviews, letters, articles before 2006) | 367 | 36 | 18 | | |
| • wrong participant group | 1360 | 126 | 71 | | |
| • wrong intervention | 301 | 26 | 29 | | |
| • wrong comparator | 205 | 9 | 14 | | |
| • did not report outcomes of interest | 10 | 0 | 2 | | |
| • non-English article | 1 | 0 | 2 | | |
| Total excluded | 2250 | 197 | 138 | 108 | |
| No. of citations potentially relevant | 132 | 25 | 36 | 12 | |
| Number of duplicates across EMBASE.com, PreMEDLINE and the Cochrane Library | | | | | 17 |
| No. of citations direct from 'additional high-risk group' searches | | | | | 24 |
| Total no. of citations potentially relevant | | | | | 212 |
| Number of citations excluded after full text review: | | | | | |
| • potentially relevant for 'additional high-risk' group | | | | | 26 |
| • publication type | | | | | 59 |
| • wrong participant group | | | | | 25 |
| • wrong intervention | | | | | 13 |
| • wrong comparator | | | | | 15 |
| • did not report outcomes of interest | | | | | 10 |
| • non-English article | | | | | 2 |
| • WHO ICTRP awaiting classification | | | | | 9 |
| Total excluded | | | | | 156 |
| No. of relevant citations | | | | | 53 |
| No. excluded with reasons | | | | | |
| Health technology assessments | | | | | 9 |
| Primary studies | | | | | 19 |
| Ongoing | | | | | 1 |
| No. included | | | | | |
| Health technology assessments & systematic reviews | | | | | 2 |
| Primary studies | | | | | 6 (22 pubs) |

*Includes EMBASE and MEDLINE. ICTRP = International Clinical Trials Registry Platform.

### (b) Additional high-risk groups

Table B.2 presents a summary of the search results.

**Table B.2 Summary of identification of studies from the search of the published literature.**

| | EMBASE* | Pre-MEDLINE | Cochrane Library | WHO ICTRP | Total |
|---|---|---|---|---|---|
| Number of citations retrieved by search | 614 | 48 | 110 | 120 | - |
| Combined EMBASE.com, PreMEDLINE and Cochrane Library | | | | | 772 |
| Number of citations excluded after title/abstract review: | | | | | |
| • duplicates | | | | | 33 |
| • publication type (ie, editorial, non-systematic reviews, letters, articles before 2006) | | | | | 187 |
| • wrong participant group | | | | | 136 |
| • wrong intervention | | | | | 129 |
| • wrong comparator | | | | | 59 |
| • did not report outcomes of interest | | | | | 12 |
| • non-English article | | | | | 4 |
| Total excluded | | | | 102 | 560 |
| Total remaining citations | | | | 12 | 212 |
| No. of relevant citations identified in MBS interim-funded search (Table B.1) | | | | 0 | 23 |
| Total no. of citations potentially relevant | | | | 12 | 235 |
| Number of citations excluded after full text review: | | | | | |
| • potentially relevant for interim-funded MBS item | | | | 9 | 24 |
| • publication type or study design | | | | | 61 |
| • wrong participant group | | | | | 50 |
| • wrong intervention | | | | | 36 |
| • wrong comparator | | | | | 0 |
| • did not report outcomes of interest | | | | | 2 |
| • non-English article | | | | | 1 |
| • duplicate | | | | | 40 |
| Total excluded | | | | | 214 |
| No. of relevant citations | | | | 3 | 21 |
| No. excluded with reasons | | | | | 3 HTAs & systematic reviews<br>13 primary studies |
| No. included | | | | | 2 HTAs & systematic reviews<br>5 primary studies |

*Includes EMBASE and MEDLINE. ICTRP = International Clinical Trials Registry Platform; MBS = Medicare Benefits Schedule. HTA = health technology assessment.

### B.3.2 Master list of studies

#### (a) Asymptomatic, high-risk women: MBS interim-funded item

A total of 53 relevant citations were identified for full-text review, after which two health technology assessment (HTA) reports and five primary studies were added. Master lists of the included studies are presented in Table B.3 (HTA reports) and Table B.4 (primary studies). The five primary diagnostic accuracy studies (Kriege et al, 2006a; Kuhl et al, 2005; Leach, 2005; Sardanelli et al, 2011; Warner et al, 2004; 22 publications, 2 of which were identified by hand searching) were all included in one or more of the included HTA reports (HIQA, 2013; NICE, 2013), and only the recent Sardanelli et al (2011) study was not included in the previous MSAC (2006) assessment. Two of the studies (Kriege et al, 2006a; Warner et al, 2004) have published updated results since the previous MSAC assessment (Passaperuma et al, 2012; Rijnsburger et al, 2010), although neither update included accuracy outcomes for MRI as an additional test. Sardanelli et al (2011) also did not include accuracy outcomes for MRI as an additional test in women <50 years of age, but it has been included as it had a high proportion of women with a history of breast cancer, as there were few studies of this patient population.

One primary patient outcomes study (two publications) was also included (Brédart et al, 2012a, b).

The EMBASE.com and PreMEDLINE search was updated in November 2013. No further studies were identified for inclusion.

**Table B.3 Master list of health technology assessments included for the assessment of asymptomatic, high-risk women.**

| Organisation | Reports |
|---|---|
| NICE, 2013 | National Institute of Clinical Excellence 2013, *Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.* CG164. London: NICE. |
| HIQA, 2013 | Health Information and Quality Authority 2013, *Health technology assessment (HTA) of surveillance of women aged less than 50 years at elevated risk of breast cancer: technical report.* Dublin: HIQA. |

**Table B.4 Master list of primary studies included for the assessment of asymptomatic, high-risk women.**

| Trial | Reports |
|---|---|
| | DIAGNOSTIC OUTCOMES |
| Leach, 2005<br>UK MARIBS study | Leach, MO 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*, 365 (9473), 1769–1778.<br>Gilbert, FJ, Warren, RML et al, 2009. Cancers in *BRCA1* and *BRCA2* carriers and in women at high risk for breast cancer: MR imaging and mammographic features, *Radiology*, 252 (2), 358–368.<br>Warren, RML, Pointon, L et al, 2002. What is the recall rate of breast MRI when used for screening asymptomatic women at high risk?, *Magnet Resonance Imag*, 20 (7), 557–565.<br>Hutton, J, Walker, LG et al, 2011. Psychological impact and acceptability of magnetic resonance imaging and x-ray mammography: The MARIBS Study, *B J Cancer*, 104 (4), 578–586. |

| Trial | Reports |
|---|---|
| Kuhl et al, 2005 | Kuhl, CK, Schrading, S et al, 2005. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer, *J Clin Oncol*, 23 (33), 8469–8476. |
| Kriege et al, 2006b<br>Dutch MRISC study | Kriege, M, Brekelmans, CTM et al, 2004. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition, *N Engl J Med*, 351 (5), 427–437+519.<br>Kriege, M, Brekelmans, CTM et al, 2006. Differences between first and subsequent rounds of the MRISC breast cancer screening program for women with a familial or genetic predisposition, *Cancer*, 106 (11), 2318–2326.<br>Kriege, M, Brekelmans, C et al, 2006. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer, *Breast Cancer Res Treat*, 100 (1), 109–119.<br>Kriege, M, Brekelmans, CTM et al, 2007. Tumor characteristics and detection method in the MRISC screening program for the early detection of hereditary breast cancer, *Breast Cancer Res Treat*, 102 (3), 357–363.<br>Obdeijn, IMA, Loo, CE et al, 2010. Assessment of false-negative cases of breast MR imaging in women with a familial or genetic predisposition, *Breast Cancer Res Treat*, 119 (2), 399–407.<br>Rijnsburger, AJ, Essink-Bot, ML et al, 2004. Impact of screening for breast cancer in high-risk women on health-related quality of life, *Br J Cancer*, 91 (1), 69–76.<br>Rijnsburger, AJ, Obdeijn, IM et al, 2010. *BRCA1*-associated breast cancers present differently from *BRCA2*-associated and familial cases: long-term follow-up of the Dutch MRISC screening study, *J Clin Oncol*, 28 (36), 5265–5273.<br>Essink-Bot, ML, Rijnsburger, AJ et al, 2006. Women's acceptance of MRI in breast cancer surveillance because of a familial or genetic predisposition, *Breast (Edinburgh, Scotland)*, 15 (5), 673–676.<br>van Dooren, S, Seynaeve, C et al, 2005. Exploring the course of psychological distress around two successive control visits in women at hereditary risk of breast cancer, *Eur J Cancer*, 41 (10), 1416–1425. |
| Warner et al, 2004<br>Canadian study | Warner, E, Plewes, DB et al, 2001. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer, *J Clin Oncol*, 19 (15), 3524–3531.<br>Warner, E, Plewes, DB et al, 2004. Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination, *JAMA*, 292 (11), 1317–1325.<br>Warner, E, Hill, K et al, 2011. Prospective study of breast cancer incidence in women with a *BRCA1* or *BRCA2* mutation under surveillance with and without magnetic resonance imaging, *J Clin Oncol*, 29 (13), 1664–1669.<br>Warner, E, Causer, PA et al, 2011. Improvement in DCIS detection rates by MRI over time in a high-risk breast screening study, *Breast J*, 17 (1), 9–17.<br>Passaperuma, K, Warner, E et al, 2012. Long-term results of screening with magnetic resonance imaging in women with *BRCA* mutations, *Br J Cancer*, 107 (1), 24–30.<br>Spiegel, TN, Esplen, MJ et al, 2011. Psychological impact of recall on women with *BRCA* mutations undergoing MRI surveillance, *Breast (Edinburgh, Scotland)*, 20 (5), 424–430. |

| Trial | Reports |
|---|---|
| Sardanelli et al, 2011<br>Italian / HIBCRIT study | Sardanelli, F, Podo, F et al, 2007. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT Study): Interim results, *Radiology*, 242 (3), 698–715.<br>Sardanelli, F, Podo, F et al, 2011. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): Final results, *Investig Radiol*, 46 (2), 94–105. |
| | PATIENT OUTCOMES |
| French study | Brédart, A, Kop, JL et al, 2012. Perception of care and experience of examination in women at risk of breast cancer undergoing intensive surveillance by standard imaging with or without MRI, *Patient Educ Counsel*, 86 (3), 405–413.<br>Brédart, A, Kop, JL et al, 2012. Anxiety and specific distress in women at intermediate and high risk of breast cancer before and after surveillance by magnetic resonance imaging and mammography versus standard mammography, *Psycho-Oncol*, 21 (11), 1185–1194. |

Bolded text highlights the report providing data on incremental accuracy used in this report.

Appendix 2 lists potentially eligible ongoing but excluded studies and reasons for their exclusion.

**(b) New, additional high-risk groups**

A total of 24 relevant citations were identified for full-text review, after which two HTA reports (NICE, 2013; Robertson et al, 2011b) and five primary studies (Berg et al, 2012; Freitas et al, 2013; Ng et al, 2013; Sung et al, 2011a, b) were included (Table B.5, Table B.6). One additional study (Viehweg et al, 2004) was identified for inclusion from an included HTA (Robertson et al, 2011a).

The search was updated in November 2013, and one further study was identified for inclusion (Ng et al, 2013), although this study had already been identified through hand searching.

**Table B.5 Systematic reviews and health technology assessments included for the assessment of additional high-risk groups.**

| Organisation | Reports |
|---|---|
| NICE, 2013 | National Institute of Clinical Excellence 2013, *Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.* CG164. London: NICE. |
| Robertson et al, 2011a | Robertson, C, Arcot Ragupathy, S et al, 2011. The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews, registry database analyses and economic evaluation, *Health Technol Assess*, 15 (34), 322. |

**Table B.6 Primary studies included for the assessment of additional high-risk groups.**

| Trial | Reports |
|---|---|
| | Women with a prior history of breast cancer |
| Berg et al, 2012 | Berg, WA, Zhang, Z et al, 2012. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk, *JAMA*, 307 (13), 1394–1404. |
| Viehweg et al, 2004 | Viehweg, P, Rotter, K et al, 2004. MR imaging of the contralateral breast in patients after breast-conserving therapy, *Eur Radiol*, 14 (3), 402–408. |

| Trial | Reports |
|---|---|
| | Women with a prior history of treatment for DCIS or LCIS |
| Sung et al, 2011b | Sung, JS, Malak, SF et al, 2011. Screening breast MR imaging in women with a history of lobular carcinoma in situ, *Radiology*, 261 (2), 414–420. |
| | Women with a history of chest irradiation between the ages of 10 and 35 years |
| Ng et al, 2013 | Ng, AK, Garber, JE et al, 2013. Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma, *J Clin Oncol*, 31 (18), 2282–2288. |
| Freitas et al, 2013 | Freitas, V, Scaranelo, A et al, 2013. Added cancer yield of breast magnetic resonance imaging screening in women with a prior history of chest radiation therapy, *Cancer*, 119 (3), 495–503. |
| Sung et al, 2011a | Sung, JS, Lee, CH et al, 2011. Screening breast MR imaging in women with a history of chest irradiation, *Radiology*, 259 (1), 65–71. |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Appendix 2 lists potentially eligible studies and the reasons for their exclusion.

# B.4 Assessment of included studies (quality appraisal)

## B.4.1 Asymptomatic, high-risk women: MBS interim-funded item

### HTAs and systematic reviews

Two systematic reviews evaluated the accuracy of breast MRI in addition to mammography as a surveillance test for high-risk populations (HIQA, 2013; NICE, 2013). The two systematic reviews met prespecified criteria for high-quality systematic reviews (Table B.7). The clinical questions and inclusion/exclusion criteria applied in the Irish review (HIQA, 2013) matched the current review. The current review therefore updates and broadens the scope of the Irish review. It also updates the MSAC (2006) review and takes into consideration the NICE (2013) review.

**Table B.7 Quality assessment of included systematic reviews.**

| Study | NICE, 2013 | HIQA, 2013 |
|---|---|---|
| Explicit review questions? | Yes | Yes |
| Explicit and appropriate eligibility criteria? | Yes | Yes |
| Explicit and comprehensive search strategy? | Yes | Yes |
| Quality of included studies appraised? | Yes | Yes |
| Methods of study appraisal reproducible? | Yes | Yes |
| Heterogeneity between studies assessed? | NA | No |
| Summary of main results clear and appropriate? | Yes | Yes |
| Applicability | High | High |

**Primary studies: diagnostic accuracy**

The five primary studies of diagnostic test accuracy (Warner et al, 2004; Kuhl et al, 2005; Leach, 2005; Kriege et al, 2006b; Sardanelli et al, 2011) all used a prospective design, but none reported that a consecutive sample of patients was tested. Studies presented results only for the subset of eligible patients who received both tests. The range of excluded patients was 9% to 21%; reasons for withdrawal included subsequent negative gene test, prophylactic mastectomy, development of breast cancer, loss to follow-up, claustrophobia or MRI refusal.

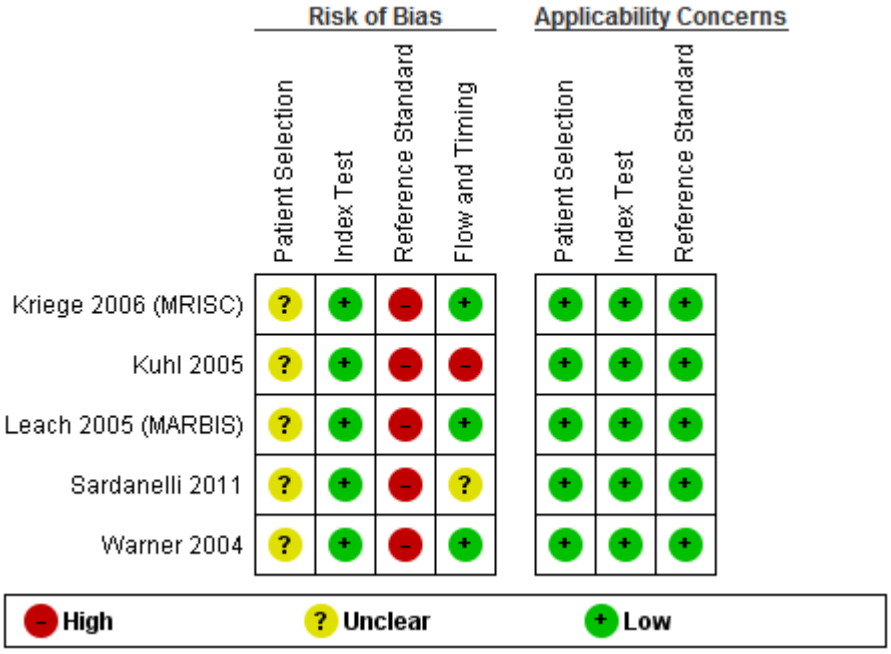
All studies had a high risk of bias associated with the reference standard, which was differentially applied on the basis of the test result (positive tests underwent histopathology and negative tests were followed up for interval cancers), leading to verification bias (see Table B.16). Furthermore, the biopsy was directed on the basis that the positive test result led to incorporation bias. Two of the studies used histopathology to verify only positive tests after review of all imaging tests (Leach, 2005; Warner et al, 2004). Three studies did not report whether interval cancers, which were identified as false-positives, were assessed on the basis of a review of films (Kriege et al, 2006b; Leach, 2005; Sardanelli et al, 2011).

Kuhl et al (2005) included results from tests performed >1 month apart in its assessment of test accuracy and therefore has a higher risk of bias in terms of flow and timing than the other studies, in which all tests were conducted within 2 weeks of each other and interpreted blind to the results of the reference standard and comparator test, using prespecified criteria. The timing of the index test was not reported in Sardanelli et al (2011).

Quality was assessed using the QUADAS-2 tool (Whiting et al, 2011) (Table B.8).

Applicability is discussed in greater detail in section B.5. In brief, all studies compared MRI + mammography with mammography alone and considered women at high risk of breast cancer aged <65 years, who generally represent the proposed population for breast MRI screening in Australia.

**Table B.8 Quality assessment of included primary diagnostic accuracy studies: asymptomatic, high-risk women.**



**Primary studies: patient outcomes**

Brédart et al (2012a, b) was a non-randomised, prospective, multicentre study. It used validated psychological scales to measure anxiety and distress in women undergoing MRI + mammography compared with mammography alone. Although it had explicit and appropriate inclusion and exclusion criteria, these differed between the group eligible for MRI and that eligible for mammography only, and therefore there are significant differences in the patient characteristics of the women who received the intervention compared with the comparator. This is the key risk of bias, and the study was otherwise considered high quality (Table B.9).

The patient population included women aged 20 to 70 and was therefore older than the population under review, limiting the applicability of the study, but the intervention and comparator were highly applicable.

**Table B.9 Quality assessment of included primary patient outcomes studies.**

| | Brédart et al 2012 |
|---|---|
| Was the study based on a representative sample selected from a relevant population? | Yes |
| Were the criteria for inclusion and exclusion explicit? | Yes |
| Were the data collection methods used adequately described? | Yes |
| Were outcomes assessed using valid and reliable instruments? | Yes |

### B.4.2 Additional high-risk groups

**Women with a history of treatment for invasive breast cancer**

Two HTAs evaluated the accuracy of breast MRI in comparison with mammography as a surveillance test for women with a history of treatment for invasive breast cancer (Table B.10). The NICE (2013) review met prespecified criteria for a high-quality systematic review, but its applicability is judged to be moderate, rather than high, because its population of women who have both a personal history of breast cancer and familial risk differs from the present review. The Robertson et al (2011a) review for the UK HTA Programme also met prespecified criteria for a high-quality review and was not judged to be superseded by the NICE (2013) review, as it had a higher level of applicability.

**Table B.10 Quality assessment of included systematic reviews.**

| Study | NICE, 2013 | Robertson et al, 2011a |
|---|---|---|
| Explicit review questions? | Yes | Yes |
| Explicit and appropriate eligibility criteria? | Yes | Yes |
| Explicit and comprehensive search strategy? | Yes | Yes |
| Quality of included studies appraised? | Yes | Yes |
| Methods of study appraisal reproducible? | Yes | Yes |
| Heterogeneity between studies assessed? | NA | NA |
| Summary of main results clear and appropriate? | Yes | Yes |

| Study | NICE, 2013 | Robertson et al, 2011a |
|---|---|---|
| Applicability | Moderate | High |

Of the two included primary studies (Berg et al, 2012; Viehweg et al, 2004), one used a prospective design (Berg et al, 2012), but it was unclear whether a consecutive sample of patients was tested. The other was a retrospective study, which therefore had a high risk of bias owing to patient selection (Viehweg et al, 2004).

Both studies had the same high risks of bias associated with the reference standard as described for the diagnostic accuracy studies assessed for the existing interim item. Neither study reported whether interval cancers, which were identified as false-positives, were assessed on the basis of a review of films.

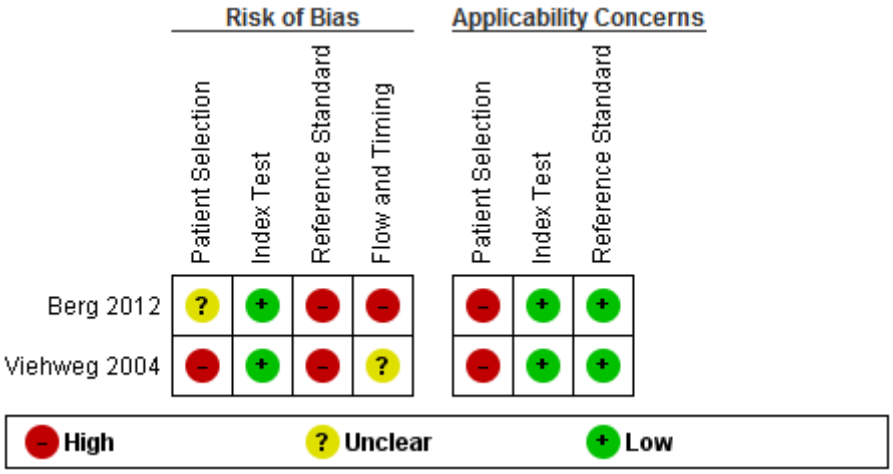
In the Berg et al (2012) study, patients underwent three rounds of mammogram and ultrasound screenings (12 months apart); only women who completed all three rounds of screening were eligible to undergo MRI screening. Only 58% of women eligible for MRI screening accepted it, and these women had a higher risk and were younger than those who declined; 612 (of 2,809 initially enrolled women) were included in the MRI analysis. In addition, 13% of patients registered for the were not included in the analysis. The reasons included withdrawal of consent, failure to undergo MRI and unreadable MRI.

Viehweg et al (2004) did not report the interval between index tests.

Applicability is discussed in greater detail in Section B.5. However, the applicability of Berg et al (2012) was limited because it was a mixed high-risk population which included patients with a personal history of cancer, as well as *BRCA1/2* mutations, a history of chest irradiation and those at familial risk. Of those in the MRI sub-study, 44.9% had a personal history of breast cancer, and diagnostic accuracy was presented separately for this subgroup. Both studies included women aged >50 years (and >65 years, which is the cut-off used for inclusion for the interim item indication), also limiting patient applicability. Twenty-four per cent of patients in Viehweg et al (2004) were referred for MRI on the basis of suspicion of disease.

Quality was assessed using the QUADAS-2 tool (Whiting et al, 2011) (Table B.11).

**Table B.11 Quality assessment of included primary accuracy studies: women with a history of treatment for invasive breast cancer.**

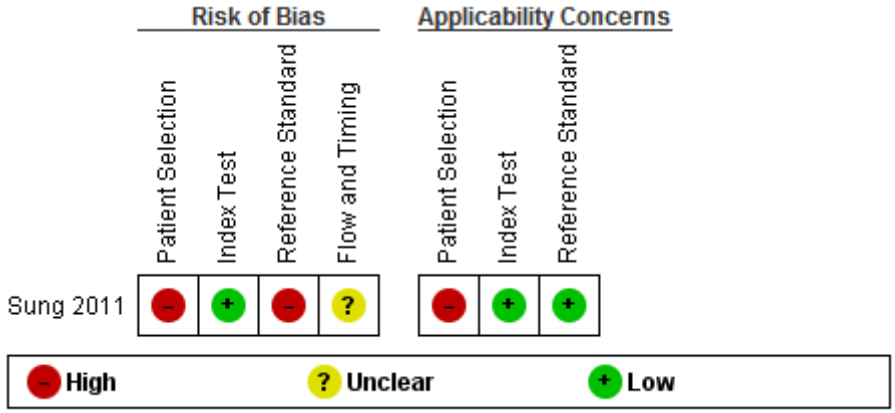



**Women with a history of treatment for DCIS or LCIS**

The one primary study of women with a history of treatment for DCIS or LCIS was a retrospective diagnostic accuracy study (Sung et al, 2011b). Owing to the design, the study had a high risk of bias in the selection of patients and an unclear risk of bias related to flow and timing. Similar to the other included diagnostic accuracy studies, there was also a high risk of bias in application of the reference standard.

The applicability of the patient population was problematic, as it included women aged 27 to 78 years, with a median age of 51 years (see Table B.20), which differs from the age of the population being considered in this assessment. A summary of the quality assessment using the QUADAS-2 tool (Whiting et al, 2011) is presented in Table B.12.

**Table B.12 Quality assessment of included primary diagnostic accuracy study: women with a history of treatment for DCIS or LCIS.**




DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

**Women who have had chest irradiation between the ages of 10 and 35 years**

One primary study of women who have had chest irradiation was prospective but did not report whether a consecutive sample of women was tested (Ng et al, 2013). The other two included studies were retrospective (Freitas et al, 2013; Sung et al, 2011a) and are therefore at high risk of bias regarding patient selection and flow and timing. In all studies, the reference standard had a high risk

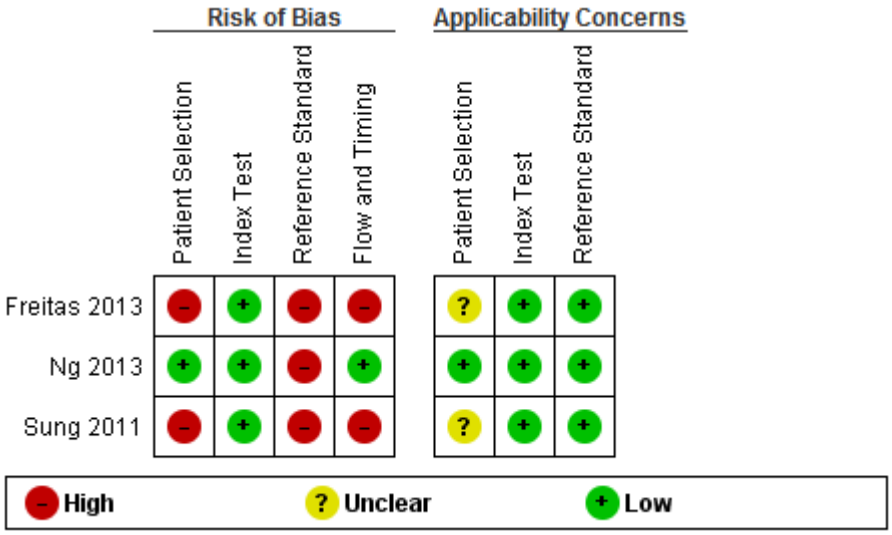
of bias as it was differentially applied on the basis of the index test, with positive tests leading to histopathology, indeterminate tests leading to short-term follow-up and negative tests leading to regular follow-up.

The study by Freitas et al (2013) excluded 22 women who had an interval of >4 months between MRI and mammography tests, but intervals up to 4 months could still introduce the risk of development of new disease between tests. The study by Sung et al (2011a) included 39 women who had an interval of between 7 and 12 months between MRI and mammography. In contrast, the two screening tests were conducted on the same day in Ng et al (2013).

All studies were considered broadly applicable, although Freitas et al (2013) did not report the age of patients at radiotherapy treatment, and the age range in Sung et al (2011a) was 5 to 54 years, which is broader than the population being assessed (women aged 10–35); however, the median in Sung et al (2011a) was 24.

The quality assessment using the QUADAS-2 tool (Whiting et al, 2011) is summarised in Table B.13.

**Table B.13 Quality assessment of included primary diagnostic accuracy study: women who have had chest irradiation between the ages of 10 and 35 years.**




# B.5 Characteristics of included studies

## B.5.1 Asymptomatic, high-risk women: MBS interim-funded item

### Systematic reviews and HTAs

The characteristics of the included systematic reviews (HIQA, 2013; NICE, 2013) plus the MSAC (2006) review are presented in Table B.14. The UK National Institute for Health and Clinical Excellence (NICE, 2013) evaluated breast MRI in the development of clinical guidelines for the classification and care of people at risk of familial breast cancer.

The studies included in the reviews varied owing to differences in inclusion criteria; in particular, the Irish HTA (HIQA, 2013) was limited to studies of women younger than 65 years. NICE (2013) updated an existing systematic review (Warner et al, 2008) and did not identify any further studies addressing the addition of MRI to mammography.

**Table B.14 Characteristics of included systematic reviews.**

| | Report objectives | Participants | Outcomes | Search date | Type of analysis, No. & date of included studies |
|---|---|---|---|---|---|
| MSAC, 2006 | What are the safety, effectiveness and cost-effectiveness of annual breast MRI in addition to annual mammography with or without breast ultrasound for screening asymptomatic high-risk women under the age of 50 years? | Population: asymptomatic women at high risk of breast cancer due to family history or genetic predisposition and no prior history of breast cancer, or women with an intact contralateral breast following mastectomy for a primary breast cancer<br>Intervention: MRI with or without mammography and breast ultrasound<br>Comparator: mammography | Test recall rate and/or biopsy rate among non-diseased<br>Diagnostic accuracy: Sens/Spec, PPV<br>stage, grade, size and/or nodal status of cancers detected<br>interval cancer rate<br>impact on clinical management<br>patient outcomes (morbidity, mortality, adverse events, quality of life) | To Mar 2006 | Narrative synthesis and meta-analysis<br>26 studies included (9 SR, 10 accuracy studies (15 articles), 2 others)<br>3 primary studies reporting on MRI + mammography<br>1. Kuhl et al, 2005<br>2. Leach, 2005<br>3. Warner et al, 2004 |
| NICE, 2013 | To update the previous NICE guidelines<br>What are the specific surveillance needs of women with a family history who have no personal history of breast cancer? | Population: women with no personal history of breast cancer aged 18–70+ (analysed by age)<br>Intervention: mammography, MRI, ultrasound, CBE, any combination of these<br>Comparator: each other | Part A: Sens/Spec, PPV/NPV in different age groups<br>Part B: stage at detection, disease-specific survival, incidence of breast cancer, incidence of radiation-induced cancer, health-related quality of life | From 2003 to 23 Nov 2011 with update search between 17 and 23 Jul 2012 | Narrative synthesis and meta-analysis (from Warner et al 2008)<br>Part A: 4 included studies (1 SR and 3 diagnostic accuracy)<br>7 primary studies reporting on MRI + mammography<br>1. Kuhl et al, 2005<br>2. Leach, 2005<br>3. Lehman et al, 2005<br>4. Lehman et al, 2007<br>5. Trecate et al, 2006<br>6. Warner et al, 2004<br>7. Warner 2001<br>Part B: 5 included studies (1 SR, 3 case series, 1 qualitative study) |
| HIQA, 2013 | To review evidence for the effectiveness and safety of | Population: women <65 years at an elevated risk of breast cancer through | Sens and Spec of each diagnostic test | To 7 Nov 2011 and updated | Narrative synthesis and meta-analysis |

| | Report objectives | Participants | Outcomes | Search date | Type of analysis, No. & date of included studies |
|---|---|---|---|---|---|
| | mammography, MRI surveillance or both in the specified populations, including different surveillance frequencies and age groups | either genetic factors or family history<br>Intervention: MRI, mammography or both<br>Comparator: MRI, mammography or both | | 18 Dec 2012 | 5 included studies, of which 3 report on MRI + mammography<br>1. Kriege et al, 2006<br>2. Kuhl et al, 2005<br>3. Leach, 2005 |

MRI = magnetic resonance imaging; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; SR = systematic review; CBE = clinical breast examination.

**Primary studies**

Five eligible studies of diagnostic test accuracy were identified (reported in 24 publications). Study size ranged from 496 to 1,909 women (reporting on a total of 10,941 MRI scans) (Table B.15). All of these studies included data from more than one screening round. All studies enrolled asymptomatic women with a known family history of or genetic predisposition to breast cancer. The risk criteria used to select patients differed between studies, as reflected in the number of women with known mutations, which ranged from 8% (Kuhl et al, 2005) to 100% (Warner et al, 2004). Three studies included women with both high familial risk and a personal history of breast cancer (Kuhl et al, 2005, 18%; Sardanelli et al, 2011, 26%; Warner et al, 2004, 44%).

No diagnostic accuracy study included only women aged ≤50 years, but the mean or median age was <50 years in all studies, or data were reported for this subgroup (Table B.15). The study by Kriege et al (2006b) included women aged up to 70 years but enabled calculation of sensitivity and specificity for a subset of pre-menopausal women; these data are used in this report. The study by Sardanelli et al (2011) included women aged up to 79 years but included diagnostic accuracy results for women aged <50 years; these data are used in this report, but data for this subgroup were not available for breast MRI + mammography.

The one patient outcomes study (Brédart et al, 2012a) included 1,561 women aged 20 to 70 years. It enrolled asymptomatic women with either a known genetic mutation or a high risk of having a genetic mutation for screening by MRI + mammography, whereas women who had a personal history of breast cancer or pathological breast lesion between the age of 40 and 50 years were enrolled for mammography only.

**Table B.15 Characteristics of included primary diagnostic accuracy studies—study setting and participants.**

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population —age range (years) | Popul.— pers. history of breast cancer (%) | Population —mutation carriers (%) |
|---|---|---|---|---|---|---|
| Leach, 2005 | UK | 649 (1,881) | Age 35–49<br>Asymptomatic women at high | 31–55 (median 40) | 0% | 18% |

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population —age range (years) | Popul.— pers. history of breast cancer (%) | Population —mutation carriers (%) |
|---|---|---|---|---|---|---|
| (MARIBS) | 22 sites<br>1997–2004 | | risk (known *BRCA1*/2 or *TP53* mutation; first-degree relative with known mutation; strong family history)<br>Excluded if had a prior history of breast cancer or tested negative to genetic test during study | 99% ≤50 | | |
| Kuhl et al, 2005 | Germany<br>Single centre<br>1996–2001 | 529 (1,452) | Asymptomatic, high risk (≥20% cumulative lifetime risk using Claus model)<br>Starting at age 30 or 5 years before youngest family member affected by breast cancer | 27–59 (median 40) | 26% | 8% |
| Warner et al, 2004 | Canada<br>Single centre<br>1997–2009 | 496 (1,847) | Asymptomatic (?), high risk (*BRCA1*/2 mutation carriers) or prior history of breast cancer (until 2004). Age 25–65 years<br>Excluded if history of bilateral breast cancer and undergoing chemotherapy, or had metastatic disease, or >91 kg | 25–66 (median 44) | 18%<br>(23% breast or ovarian) | 100% |
| Kriege et al, 2006b (MRISC) | Netherlands<br>Six sites<br>1999–2006 | 1,909 (4,169: 3,075 in pre-menopausal women) (2006 analysis)<br>2,275 (2010 analysis) | Asymptomatic, high risk (*BRCA1*/2 or other mutations, or cumulative lifetime risk ≥15%)<br>Age 25–70 years | 19–75 (mean 40.1)<br>NB: pre-menopausal women used for diagnostic accuracy | 0% | 19% (2006 analysis)<br>28% (2010 analysis) |
| Sardanelli et al, 2011 | Italy<br>18 centres (14 towns)<br>2000–2007 | 501 (1,592: 941 in women aged <50 years) | Inclusion: asymptomatic women, at high risk for breast cancer, ≥25; and either *BRCA1/2* or untested first-degree relatives of *BRCA1/2* mutation carriers' or strong family history of breast or ovarian cancer with ≥3 events in | Age 22–79 (mean 46)<br>NB: women aged <50 used for diagnostic accuracy | 44% | 63% |

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population —age range (years) | Popul.— pers. history of breast cancer (%) | Population —mutation carriers (%) |
|---|---|---|---|---|---|---|
| | | | first- or second-degree relatives<br>Exclusion: pregnancy, breast-feeding, current chemotherapy, terminal illness, contraindications to MRI or gadolinium-based contrast agent administration | | | |
| Brédart et al, 2012 | France<br>21 centres<br>2006–2008 | 1,561<br>900 in MRI group<br>661 in mammo-graphy group | Age 20–70 years<br>MRI eligible: asymptomatic, no ongoing treatment, no metastasis, no bilateral mastectomy. Women with a demonstrated mutation, untested women with a first-degree relative with a demonstrated mutation, women with a prob. of a mutation of at least 40% or women with a first-degree relative with a prob. of a mutation of at least 80%<br>Mammography eligible: personal history of breast cancer or pathological breast lesion between 40 and 50 years without family history or with only one first-degree relative, or women in whom MRI was contraindicated | MRI group: mean 47.7 (SD 10.3)<br>Mammo-graphy group: mean 53.2 (SD 6.7) | MRI: 51.6%<br>Mammo-graphy: 69.1% | MRI: 74.4% |

*n* = number; MRI = magnetic resonance imaging; *BRCA1/2* = breast cancer 1 or 2 gene; *TP53* = tumour protein p53 gene.

Most studies were performed using MRI machines with ≥1.5 T magnets (Table B.16). Two studies (Leach, 2005; Sardanelli et al, 2011) included tests performed on MRI machines with 1.0–1.5 T magnets, which may compromise test performance. Ultrasound was included routinely in the comparator tests in three studies (Kuhl et al, 2005; Sardanelli et al, 2011; Warner et al, 2004) and was used at the discretion of the clinical team in a fourth (Brédart et al, 2012a).

**Table B.16 Characteristics of included primary diagnostic accuracy studies—study design and outcomes.**

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Leach, 2005 (MARIBS) | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-2 | Annual MRI with contrast<br>1.0–1.5 T magnet | Annual film mammography (1 or 2 views) | Histopathology not performed for all test positives, on the basis of combination of all tests<br>No film review for interval cancers | Sens, Spec, AUC<br>Subgroup analysis: first vs subsequent screening rounds<br>Recall rate, biopsy rate<br>Cancer size, grade and lymph node status |
| Kuhl et al, 2005 | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-1 | Annual MRI with contrast<br>1.5 T magnet | Annual film mammography (2 views), biannual U/S | Histopathology for all test positives, 6-month follow-up for indeterminate findings<br>No film review for interval cancers | Sens, Spec<br>Cancer stage, size, lymph node status & grade in women with no prior history of breast cancer<br>Subgroup analysis by risk group, mutation status, prior history of breast cancer |
| Warner et al, 2004 | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-2 | Annual MRI with contrast<br>1.5 T magnet | Annual film mammography (4 views), annual U/S and biannual CBE | Histopathology not performed for all positive tests. If MRI finding positive and discordant with other tests, MRI repeated in 1 month<br>Film review for interval cancers | Sens, Spec<br>Subgroup analysis for first vs subsequent screening rounds<br>Cancer size & lymph node status |
| Kriege et al, 2006b (MRISC) | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-1 | Annual MRI with contrast<br>Magnet strength NR | Annual film mammography and biannual CBE | Histopathology for all test positives<br>Indeterminate finding for MRI or mammography verified by U/S ± biopsy or repeated test<br>Film review of interval cancers NR | Sens, Spec, AUC<br>Biopsy rate<br>Rate of cancer detection<br>Mortality<br>Subgroup analysis for 1 vs subsequent screening rounds |

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Sardanelli et al, 2011 | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-2 | Annual MRI with contrast<br>1.5 T magnet in 14 centres, 1.0 T in 4 centres | Annual clinical breast exam (CBE), mammography (film and digital) and U/S | Histopathology for all test positives, 6-month follow-up for indeterminate findings<br>Film review for interval cancers NR | Sens, Spec, PPV, NPV, LR+, LR–, ROC |
| Brédart et al, 2012a | Screening intervention<br>Prospective<br>Consecutive recruitment NR<br>Level III-2 | MRI with contrast<br>Magnet strength NR | Film/digital mammography ± U/S | NA | Psychological outcomes, perception of care and experience of examination |

NR = not reported; MRI = magnetic resonance imaging; U/S = ultrasound; CBE = clinical breast examination; Sens = sensitivity; Spec = specificity; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; ROC = receiver operating characteristic; AUC = area under curve; NPV = negative predictive value; PPV = positive predictive value.

### B.5.2 Additional high-risk groups

**Women with a history of treatment for invasive breast cancer**

The characteristics of the included systematic reviews (NICE, 2013; Robertson et al, 2011a) are presented in Table B.17. The NICE (2013) population included women with both a personal history and a family history of breast cancer, and is therefore a subset of that considered here. This population could also be considered applicable to the interim item indication.

NICE (2013) included four studies (Elmore & Margenthaler, 2010; Houssami et al, 2011; Robertson et al, 2011b; Sardanelli et al, 2011). Robertson et al (2011b) is a publication from the HTA included in this assessment (Robertson et al, 2011a). Houssami et al (2011) is a retrospective study comparing mammography results between women with and without a personal history of breast cancer; mammography results are not compared with MRI or any other screening modality and therefore the study is excluded. Elmore and Margenthaler (2010) is excluded as it does not assess diagnostic performance; it focuses on determining the factors predicting the use of breast MRI surveillance in women previously treated for breast cancer. Sardanelli et al (2011) met our inclusion criteria and was considered most applicable to the interim item indication; its characteristics are shown in Table B.15.

The Robertson et al (2011a) HTA included six studies with data on MRI surveillance. Three of these studies were excluded from this review as the population studied was women undergoing non-routine surveillance (ie, women with suspicion of recurrence) (Belli et al, 2002; Mumtaz et al, 1997; Rieber et al, 1997). Of the remaining three studies, one was excluded as it did not include any women younger than 50 years of age (Drew et al, 1998), and another because it included only women who had undergone mastectomy and received breast implants (Boné et al, 1995). The remaining study was included in the review (Viehweg et al, 2004).

**Table B.17 Characteristics of included systematic reviews.**

| | Report objectives | Participants | Outcomes | Search date | Type of analysis, No. & date of included studies |
|---|---|---|---|---|---|
| NICE, 2013 | To update the previous NICE guidelines.<br>What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk-reducing mastectomy? | Population: patients with a personal history of breast cancer and a familial risk, aged 18–70+ years<br>Intervention: mammography, MRI, ultrasound, CBE, any combination of these<br>Comparator: each other | Part A: Sens/Spec, PPV/NPV in different age groups<br>Part B: stage at detection, overall survival, incidence, radiation-induced cancer, interval cancers, health-related quality of life | 1970 – Nov 2011<br>Update search: Nov 2011 – Jul 2012 | Narrative synthesis<br>Included studies:<br>1. Robertson et al, 2011b<br>2. Elmore & Margenthaler, 2010<br>3. Houssami et al, 2011<br>4. Sardanelli et al, 2011 |
| Robertson et al, 2011a | To determine the performance of surveillance mammography, alone or in combination with other tests, in detecting IBTR and/or MCBC in women undergoing routine surveillance | Women previously treated for primary breast cancer without detectable metastatic disease at initial presentation | Test performance in diagnosing IBTR and MCBC in women undergoing routine and non-routine surveillance | 1990 to Mar 2009 | Narrative synthesis<br>Nine included studies, six with data on MRI:<br>1. Belli et al, 2002<br>2. Boné et al, 1995<br>3. Drew et al, 1998<br>4. Mumtaz et al, 1997<br>5. Rieber et al, 1997<br>6. Viehweg et al, 2004 |

MRI = magnetic resonance imaging; CBE = clinical breast examination; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; IBTR = ipsilateral breast tumour recurrence; MCBC = metachronous contralateral breast cancer.

Two eligible studies of diagnostic test accuracy were included (Berg et al, 2012; Viehweg et al, 2004), covering 395 women who underwent MRI and had a personal history of breast cancer (Table B.18). Berg et al (2012) was a surveillance study of women at high risk. It included women with a personal history of breast cancer, for whom diagnostic accuracy was reported, but details of their treatment for breast cancer and time since diagnosis were not provided, and the study did not differentiate between the detection of cancer in the contralateral breast or the detection or recurrence of cancer in the ipsilateral breast.

Both studies included women aged >50 years, limiting their applicability.

**Table B.18 Characteristics of included primary diagnostic accuracy studies—study setting and participants.**

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population—age range (years) | Had breast cancer treatment | Had radio-therapy |
|---|---|---|---|---|---|---|
| Berg et al, 2012 | UK, Argentina, Canada (Ontario)<br>21 sites<br>2004–2006 | Total: 2,662 (7,473)<br>MRI group: 612 (612)<br>MRI group with personal history: 275 (275) | Asymptomatic, heterogeneously dense or extremely dense breast tissue, and at least 1 other risk factor:<br>• *BRCA1/2* mutation<br>• history of prior chest, mediastinal or axillary irradiation<br>• pers. history of breast cancer<br>• lifetime risk Gail/Claus model ≥25%<br>• 5-year risk, Gail model ≥2.5%<br>• 5-year risk Gail model ≥1.7% and extremely dense breasts<br>• atypical ductal hyperplasia / atypical lobular hyperplasia / LCIS or atypical papilloma) | 25–91 (median 55)<br>MRI group: 27–87 (median 57) | NR | NR |
| Viehweg et al, 2004 | Germany<br>Single site<br>1994–2001 | 119 (145) | History of treated unilateral breast cancer | 25–78 (median 55.7) | 100% | 100% |

MRI = magnetic resonance imaging; NR = not reported; *BRCA1/2* = breast cancer gene 1/2; LCIS = lobular carcinoma in situ.

Viehweg et al (2004) used a 1.0 T machine, which may compromise MRI performance. Both studies compared the performance of MRI with mammography and ultrasound, but neither performed MRI over multiple screening rounds (Table B.19).

**Table B.19 Characteristics of included primary diagnostic accuracy studies—study design and outcomes.**

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Berg et al, 2012 | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-2 | Single MRI with contrast<br>1.5 T magnet | Annual film or digital mammography and ultrasound | Histopathology for test positives<br>12-month follow-up for test negatives | Sensitivity, specificity, PPV3 of biopsies performed, interval cancer rate |

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Viehweg et al, 2004 | Diagnostic accuracy<br>Retrospective<br>Level III-2 | Single MRI with contrast<br>1.0 T magnet | Annual film mammography, ultrasound on the basis of clinical decision | Histopathology for test positives<br>12-month follow-up for test negatives | |

NR = not reported; MRI = magnetic resonance imaging.

**Women with a history of treatment for DCIS or LCIS**

One diagnostic accuracy study was identified (Sung et al, 2011b). It included 220 women (840 MRI scans) who were retrospectively identified. Women with a personal history of breast cancer were excluded, and 29% of women had a family history of breast cancer defined as breast cancer in a first-degree relative (Table B.20).

**Table B.20 Characteristics of included primary diagnostic accuracy studies—study setting and participants.**

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population—age range (years) | LCIS (%) | Family history (%) |
|---|---|---|---|---|---|---|
| Sung et al, 2011 | US<br>Single centre<br>2003–2008 | 220 (840) | Women with a history of LCIS diagnosis before 2006 at percutaneous or surgical biopsy<br>Women with a personal history of breast cancer were excluded | 27–78 (median 51) | 100% | 29% |

LCIS = lobular carcinoma in situ.

The study was performed on MRI machines with either a 1.5 or 3.0 T magnet and used both film and digital mammography (Table B.21). There was no sub-group analysis according to magnet strength or type of mammography.

**Table B.21 Characteristics of included primary diagnostic accuracy studies for women—study design and outcomes.**

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Sung et al, 2011 | Diagnostic accuracy<br>Retrospective<br>Consecutive recruitment | MRI<br>1.5 or 3.0 T magnet | Film or digital mammography | Histopathology not performed for all positive tests. Indeterminate findings assigned to short interval follow-up<br>Film review of discordant results | Sens, Spec<br>Recall rate<br>Biopsy |

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| | NR<br>Level III-2 | | | | rate |

MRI = magnetic resonance imaging; NR = not reported; Sens = sensitivity; Spec = specificity.

**Women who have had chest irradiation between the ages of 10 and 35 years**

The characteristics of the three primary studies of women who had chest irradiation are presented in Table B.22 and Table B.23. All were single-centre studies conducted in North America and included women aged up to 65 years. The median latency from radiation therapy to surveillance was similar across the studies, but Ng et al (2013) excluded patients within 8 years of treatment, whereas the other two studies included women with recent treatment. The age at radiotherapy was not reported in Freitas et al (2013) and the radiation dose received was known for only 61% of patients.

**Table B.22 Characteristics of included primary diagnostic accuracy studies—study setting and participants.**

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population—age range (years) | Age at radio-therapy | Radiation dose (Gy) | Latency from radiation to surveillance (range) |
|---|---|---|---|---|---|---|---|
| Freitas et al, 2013 | Canada<br>Single centre<br>2004–2010 | 98 (262) | Asymptomatic women who received ≥15 Gy for paediatric or young adult cancer and were referred for screening mammography and MRI<br>Excluded patients with >4 months between MRI and mammography | 19–65 (mean 37) | NR | 15–35 (known for only 61% of patients) | 2–34 years (median 13 years) |
| Ng et al, 2013 | US<br>Single centre<br>2005–2010 | 148 (345) | Women previously treated with mantle irradiation for Hodgkin's lymphoma at age ≤35 years who were >8 years past treatment<br>Excluded women who were pregnant or lactating, had undergone bilateral mastectomy, were actively receiving breast cancer therapy, or with known contraindications for MRI | 22–65 (median 43) | 12–35 (median 23) | 19.6–58 (median 39.5) | Median 17.5 |
| Sung et | US | 91 (247) | Women with a history of | 18–62 | 5–54 | unkn. for | 3–43 |

| Study | Country<br>Setting<br>Recruitment period | *n* women (*n* tests) | Inclusion/exclusion criteria | Population—age range (years) | Age at radio-therapy | Radiation dose (Gy) | Latency from radiation to surveillance (range) |
|---|---|---|---|---|---|---|---|
| al, 2011 | Single centre<br>1999–2008 | | chest irradiation | (median 40) | (median 24) | 46%<br>35% >30<br>16% 20–29<br>2% 10–19 | (median 16) |

NR = not reported; MRI = magnetic resonance imaging.

All studies used at least 1.5 T magnets for MRI. Two exclusively used digital mammography.

**Table B.23 Characteristics of included primary diagnostic accuracy studies for women—study design and outcomes.**

| Study | Study design (prospective, consecutive) | Index test | Comparator tests | Reference standard | Outcomes |
|---|---|---|---|---|---|
| Freitas et al, 2013 | Diagnostic accuracy<br>Retrospective<br>Consecutive recruitment NR<br>Level III-2 | MRI<br>1.5 T magnet | Digital mammography | Histopathology for all positive tests. Indeterminate findings followed by short-term imaging follow-up<br>Film review of all cancers | Sens/Spec |
| Ng et al, 2013 | Diagnostic accuracy<br>Prospective<br>Consecutive recruitment NR<br>Level III-1 | Annual MRI<br>1.5 or 3.0 T magnet | Annual digital mammography | Histopathology for all positive tests. Indeterminate findings followed by short-term imaging follow-up<br>Film review of interval cancers NR | Sens/Spec |
| Sung et al, 2011 | Diagnostic accuracy<br>Retrospective<br>Consecutive recruitment NR<br>Level III-2 | MRI<br>1.5 or 3.0 T magnet | Mammography (Film or digital NR) | Histopathology for all positive tests. Indeterminate findings followed by short-term imaging follow-up<br>Film review of interval cancers NR | Sens/Spec |

NR = not reported; MRI = magnetic resonance imaging; Sens = sensitivity; Spec = specificity.

# B.6 Review of interim items

## B.6.1 Systematic review and HTA findings

The conclusions and recommendations from MSAC (2006), the two recent included HTAs, the NICE (2013) guidelines and the HIQA (2013) review are summarised in Table B.24. Although the MSAC

review was conducted in 2006, the overall body of evidence is largely unchanged, and the 2013 reviews considered the same key studies with some differences due to different inclusion criteria.

**Table B.24 Conclusions and recommendations for included systematic reviews.**

| Conclusions | Recommendations |
|---|---|
| MSAC, 2006 | |
| Overall, this review provides strong evidence that breast MRI is a safe test that offers a 160% increase in the detection of breast cancer in young high-risk women over mammography alone. It also produces a 200% increase in the rate of investigations for false-positive findings. However, owing to the lack of clinical evidence to determine the health benefits gained by earlier detection in this population and uncertainty about the applicability of estimates of cost-effectiveness derived from a US economic model, it does not provide adequate evidence to determine the potential effectiveness and cost-effectiveness of adopting breast MRI in Australia.<br>Other factors that may influence a decision to support funding for breast MRI for the surveillance of young high-risk women include judging the validity of linking evidence of mortality reduction from the early detection of breast cancer from screening trials in average-risk women >50 years to the early detection of breast cancer in younger high-risk women; the ethics and feasibility of conducting a trial to quantify these health benefits; the estimated total costs of introducing breast MRI; and the availability of facilities with appropriate expertise and equitable access to services. | Breast MRI, when combined with mammography, is safe and effective in the diagnosis of breast cancer in asymptomatic women at high risk, when used as part of an organised surveillance program.<br>Evidence suggests that breast MRI in combination with mammography may be cost-effective when compared with mammography alone in high-risk women aged <50 years.<br>MSAC recommends interim public funding for breast MRI in the diagnosis of breast cancer in asymptomatic women with a high risk of developing breast cancer when used as part of an organised surveillance program.<br>Evidence should be reviewed in not less than 3 years. |
| NICE, 2013 | |
| Part A:<br>Moderate-quality evidence suggests surveillance using MRI has better sensitivity for breast cancer than mammography, CBE or ultrasound. Surveillance with both MRI and mammography has better sensitivity than either test alone.<br>The Warner et al (2008) systematic review estimated breast cancer prevalence among high-risk women undergoing surveillance as ~2%. Using their pooled sensitivities and specificities, the results from 1000 combined MRI and mammography surveillance tests would include 17 true-positives, 49 false-positives, 931 true-negatives and 3 false-negatives.<br>Part B:<br>Stage at detection: Very low-quality evidence from two studies suggests that invasive breast cancers diagnosed in mammography-screened women aged ≤50 years with family history of breast cancer are significantly smaller than those | *Mammographic surveillance*<br>Offer annual mammographic surveillance to women:<br>– aged 40–49 years at moderate risk of breast cancer<br>– aged 40–59 years at high risk of breast cancer but with a ≤30% prob. of being a *BRCA* or *TP53* carrier<br>– aged 40–59 years who have not had genetic testing but have a >30% prob. of being a *BRCA* carrier<br>– aged 40–69 years with a known *BRCA1* or *BRCA2* mutation.<br>Offer mammographic surveillance as part of the population screening program to women:<br>– aged ≥50 years who have not had genetic |

| Conclusions | Recommendations |
|---|---|
| diagnosed in unscreened women of similar age (Maurice et al, 2006; Duffy et al, 2010). In these two studies, 28% to 30% of invasive tumours diagnosed during screening were >2 cm in diameter, compared with 45% to 61% of tumours diagnosed in the unscreened comparison groups. Very low-quality evidence from two studies suggests women aged ≤50 years with family history of breast cancer whose invasive breast cancer was diagnosed during screening were less likely to have positive nodes at diagnosis than unscreened women of similar age diagnosed with breast cancer (Maurice et al, 2006; Duffy et al, 2010). In these two studies, 32% to 34% women diagnosed with invasive breast cancer during screening had positive nodes, compared with 47% to 53% of those diagnosed in the unscreened comparison groups.<br><br>Disease-specific survival: Very low-quality evidence suggests a disease-specific survival benefit with mammographic surveillance in women aged <50 years with a family history of breast cancer. In Maurice et al (2006), death from breast cancer was less likely in women aged <50 with family history whose breast cancer was diagnosed during mammographic surveillance than in a control group of unscreened women of similar age who developed breast cancer (lead time adjusted HR 0.24 [95% CI 0.09–0.66]). Duffy et al (2010) modelled death from breast cancer in a mammographic surveillance study in women with familial history aged <50 years and a control group from another study, using prognostic features at diagnosis and underlying risk. Projected 10-year death from breast cancer was lower in the mammographic surveillance group than in the control group of unscreened women of similar age (RR 0.80 [95% CI 0.66–0.96]). In Maurice et al (2012), death from any cause was less likely in *BRCA1/2* carriers aged 28–77 years diagnosed with breast cancer during an intensive mammographic surveillance program than in those diagnosed outside this program (HR 0.44 [95% CI 0.25–0.77]). It was unclear, however, whether this estimate was adjusted for lead time bias.<br><br>Incidence of breast cancer, incidence of radiation-induced breast cancer: Low-quality evidence, from case-control studies (Jansen-van der Weide et al, 2010), suggests that exposure to low-dose radiation during screening mammography or chest x-ray is associated with an increased risk of breast cancer in women with a familial or genetic predisposition, OR 1.3 (95% CI 0.9–1.8). There was evidence of a dose–response relationship between low-dose radiation and breast cancer in this population: exposure to low-dose radiation before the age of 20 years (OR 2.0; 95% CI 1.3–3.1) and ≥5 exposures (OR 1.8; 95% CI 1.1–3.0). | testing but have a >30% prob. of being a *TP53* carrier<br>– aged ≥60 years at high risk of breast cancer but with a ≤30% prob. of being a *BRCA* or *TP53* carrier<br>– aged ≥60 at moderate risk of breast cancer<br>– aged ≥60 years who have not had genetic testing but have a >30% prob. of being a *BRCA* carrier<br>– aged ≥70 years with a known *BRCA1* or *BRCA2* mutation.<br><br>Consider annual mammographic surveillance for women:<br>– aged 30–39 years at high risk of breast cancer but with a ≤30% prob. of being a *BRCA* or *TP53* carrier<br>– aged 30–39 years who have not had genetic testing but have a >30% prob. of being a *BRCA* carrier<br>– aged 30–39 years with a known *BRCA1* or *BRCA2* mutation<br>– aged 50–59 years at moderate risk of breast cancer.<br><br>Do not offer mammographic surveillance to women:<br>– aged 29 years and under<br>– aged 30–39 years at moderate risk of breast cancer<br>– aged 30–49 years who have not had genetic testing but have a >30% prob. of being a *TP53* carrier<br>– of any age with a known *TP53* mutation.<br><br>*MRI surveillance*<br><br>Offer annual MRI surveillance to women:<br>– aged 30–49 years who have not had genetic testing but have a >30% prob. of being a *BRCA* carrier<br>– aged 30–49 years with a known *BRCA1* or *BRCA2* mutation<br>– aged 20–49 years who have not had genetic testing but have a >30% prob. of |

| Conclusions | Recommendations |
|---|---|
| Health-related quality of life: Low-quality evidence suggests that screening with biannual CBE, annual mammography, annual MRI, and recommendations for monthly breast self-examination has no unfavourable impact on generic short-term health-related quality of life (Rijnsburger et al, 2004). Rijnsburger et al (2004) recorded pain, discomfort and anxiety experienced by women at high risk of breast cancer during screening tests. The proportion of women who reported pain was 7% during CBE, 86% during mammography and 12% during MRI; 9% experienced discomfort during CBE, 69% during mammography and 45% during MRI; and 22% experienced anxiety during CBE, 28% during mammography and 37% during MRI. | being a *TP53* carrier<br>– aged 20–49 years with a known *TP53* mutation.<br>Consider annual MRI surveillance for women aged 50–69 years with a known *TP53* mutation.<br>Do not offer MRI to women:<br>– of any age at moderate risk of breast cancer<br>– of any age at high risk of breast cancer but with a ≤30% prob. of being a *BRCA* or *TP53* carrier<br>– aged 20–29 years who have not had genetic testing but have a >30% prob. of being a *BRCA* carrier<br>– aged 20–29 years with a known *BRCA1* or *BRCA2* mutation<br>– aged 50–69 years who have not had genetic testing but have a >30% prob. of being a *BRCA* or a *TP53* carrier, unless mammography has shown a dense breast pattern<br>– aged 50–69 years with a known *BRCA1* or *BRCA2* mutation, unless mammography has shown a dense breast pattern. |
| HIQA, 2013 | |
| There is limited evidence directly comparing surveillance MRI, film mammography and digital mammography in women <50 years at elevated risk of breast cancer.<br>The estimated sensitivity and specificity of MRI for the target population are 0.80 and 0.92, respectively. The estimated sensitivity and specificity of digital mammography for the target population are 0.38 and 0.97 respectively. These estimates are based mainly on film mammography owing to the lack of studies comparing digital mammography and MRI in women at elevated risk of breast cancer.<br>The estimated sensitivity and specificity of combined MRI and digital mammography for the target population are 0.88 and 0.88.<br>The overall effectiveness of a surveillance program for women at elevated risk of breast cancer depends on the combination of age range, imaging modality and surveillance interval used.<br>There is a lack of mortality data on surveillance in women under 50 years at elevated risk of breast cancer. However, there is | For women aged <50 years with identified high-penetrance genetic mutations other than *TP53*, annual MRI from age 30 to 49 years is recommended. The addition of annual digital mammography from age 40 to 49 years could be offered to maintain accordance with current international practice.<br>For the subgroup with a *TP53* mutation, annual MRI surveillance from age 20 to 49 years is recommended.<br>For women at high familial risk with no identified genetic mutations, annual digital mammography from age 40 to 49 years is preferable to existing ad hoc surveillance.<br>For women at moderate risk, annual digital mammography from age 40 to 49 years is preferable to existing ad hoc surveillance. |

| Conclusions | Recommendations |
|---|---|
| evidence of a mortality reduction in average-risk populations through earlier detection and treatment.<br>Surveillance has non-mortality effects that are both positive (eg, early detection leading to improved survival) and negative (eg, radiation-induced carcinoma, over-diagnosis and unnecessary biopsies). Ratio of benefits to harms depends on target population.<br>Frequent exposure to radiation through a mammography-based surveillance program from a young age may increase the risk of developing breast cancer. | An organised surveillance program will improve equity of access; it should have key performance indicators to measure performance against targets or expectations. |

MSAC = Medical Services Advisory Committee; MRI = magnetic resonance imaging; CBE = clinical breast examination; HR = hazard ratio; RR = risk ratio; OR = odds ratio; CI = confidence interval; *BRCA1/2* = breast cancer gene 1 or 2; *TP53* = tumour protein p53 gene.

## B.6.2 Diagnostic accuracy

**Sensitivity and specificity**

The results of all eligible primary studies that compare the sensitivity and specificity of MRI as an additional test to mammography for screening high-risk women (five studies) are summarised in Table B.25, Table B.26 and Table B.27. All studies reported diagnostic accuracy on a per test, rather than a per patient, basis.

Diagnostic accuracy was reported for two thresholds, either any lesions requiring follow-up as positive (BI-RADS [Breast Imaging Reporting and Data System] 0, 3, 4 or 5) or only suspicious lesions as positive (BI-RADS 4 and 5). In studies where results were reported for both thresholds, diagnostic accuracy followed the expected pattern of reduced sensitivity and increased specificity for the more stringent threshold. Similarly, where studies reported results for mammography alone and mammography combined with ultrasound and CBE, the diagnostic accuracy of the combined tests followed the expected pattern of increased sensitivity and decreased specificity.

Overall, the studies reported a sensitivity of mammography alone ranging from 0.14 to 0.49. The addition of MRI to mammography increased sensitivity, with a range of 0.85 to 0.94. The specificity of mammography alone ranged from 0.89 to 1.00. The addition of MRI to mammography was lower, with a range of 0.77 to 0.96.

**Table B.25 Diagnostic accuracy of breast MRI + mammography (± ultrasound).**

| Study | Tests | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Kriege et al, 2006b (MRISC)* | MRI+M+CBE | BI-RADS 0, 3, 4 & 5 | 28 | 456 | 5 | 2,619 | 0.85 [0.68, 0.95] | 0.85 [0.84, 0.86] |
| Kuhl et al, 2005 | MRI+M | BI-RADS 4 & 5 | 40 | 55 | 3 | 1,354 | 0.93 [0.81, 0.99] | 0.96 [0.95, 0.97] |
| Leach, 2005 (MARIBS) | MRI+M | BI-RADS 0, 3, 4 & 5 | 33 | 428 | 2 | 1,418 | 0.94 [0.81, 0.99] | 0.77 [0.75, 0.79] |
| Leach, 2005 | MRI+M | BI-RADS 4 & 5 | N | NR | NR | NR | 0.60† | 0.95† |

| Study | Tests | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| (MARIBS) | | | R | | | | | |
| Warner et al, 2004 | MRI+M+CBE | BI-RADS 0, 3, 4 & 5 | NR | NR | NR | NR | 0.90† | 0.80† |
| Warner et al, 2004 | MRI+M+CBE | BI-RADS 4 & 5 | 18 | NR | 3 | NR | 0.86 [0.64, 0.97] | 0.95† |
| Warner et al, 2004 | MRI+M+U/S+ CBE | BI-RADS 4 & 5 | 21 | NR | 1 | NR | 0.95 [0.77, 1.00] | NR |

* As reported in HIQA (2013) calculated from data in Table 1 of Kriege et al. (2006b).† Reported in Warner et al (2008). 95% CI not reported. M = mammography, MRI = magnetic resonance imaging, CBE = clinical breast examination, U/S = ultrasound; BI-RADS = American College of Radiology Breast Imaging Reporting and Data System; NR = not reported; CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Table B.26 Diagnostic accuracy of breast mammography (± ultrasound).**

| Study | Tests | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Kriege et al, 2006b (MRISC)* | M+CBE | BI-RADS 0, 3, 4 & 5 | 12 | 155 | 21 | 2,920 | 0.36 [0.20–0.55] | 0.95 [0.94–0.96] |
| Kuhl et al, 2005 | M | BI-RADS 4 & 5 | 14 | 45 | 29 | 1,364 | 0.33 [0.19–0.49] | 0.97 [0.96–0.98] |
| Kuhl et al, 2005 | M+U/S | BI-RADS 4 & 5 | 21 | 155 | 22 | 1,254 | 0.49 [0.33–0.65] | 0.89 [0.87–0.91] |
| Leach, 2005 (MARIBS) | M | BI-RADS 0, 3, 4 & 5 | 14 | 121 | 21 | 1,725 | 0.40 [0.24–0.58] | 0.93 [0.92–0.95] |
| Leach, 2005 (MARIBS) | M | BI-RADS 4 & 5 | NR | NR | NR | NR | 0.14† | 0.98† |
| Warner et al, 2004 | M | BI-RADS 0, 3, 4 & 5 | NR | NR | NR | NR | 0.36† | 0.99† |
| Warner et al, 2004 | M | BI-RADS 4 & 5 | 8 | 1 | 14 | 434 | 0.36 [0.17–0.59] | 1.00 [0.99–1.00] |
| Warner et al, 2004 | M+U/S+CBE | BI-RADS 4 & 5 | 14 | NR | 8 | NR | 0.64 [0.41–0.83] | NR |
| Sardanelli et al, 2011 | M | BI-RADS 4 & 5 | 10 | 8 | 12 | 628 | 0.45 [0.24–0.68] | 0.99 [0.98–0.99] |

* As reported in HIQA (2013) calculated from data in Table 1 of Kriege et al. (2006b). † Reported in Warner et al (2008). 95% CI not reported. M = mammography, CBE = clinical breast examination, U/S = ultrasound; BI-RADS = American college of Radiology Breast Imaging Reporting and Data System; NR = not reported; CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Table B.27 Diagnostic accuracy of breast MRI alone.**

| Study | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|
| Kriege et al, 2006b (MRISC)* | BI-RADS 0, 3, 4 & 5 | 23 | 328 | 10 | 2747 | 0.70 [0.51–0.84] | 0.89 [0.88–0.90] |
| Kuhl et al, 2005 | BI-RADS 4 & 5 | 39 | 39 | 4 | 1370 | 0.91 [0.78–0.97] | 0.97 [0.96–0.98] |
| Leach, 2005 (MARIBS) | BI-RADS 0, 3, 4 & 5 | 27 | 344 | 8 | 1502 | 0.77 [0.60–0.90] | 0.81 [0.80–0.83] |

| Study | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|
| Leach, 2005 (MARIBS) | BI-RADS 0, 3, 4 & 5 | NR | NR | NR | NR | 0.51† | 0.96† |
| Warner et al, 2004 | BI-RADS 0, 3, 4 & 5 | NR | NR | NR | NR | 0.82† | 0.81† |
| Warner et al, 2004 | BI-RADS 4 & 5 | 17 | 20 | 5 | 415 | 0.77 [0.55–0.92] | 0.95 [0.93–0.97] |
| Sardanelli et al, 2011 | BI-RADS 4 & 5 | 16 | 21 | 2 | 595 | 0.89 [0.65–0.99] | 0.97 [0.95–0.98] |

* As reported in HIQA (2013) calculated from data in Table 1 of Kriege et al. (2006b). † Reported in Warner et al (2008). 95% CI not reported. BI-RADS = American college of Radiology Breast Imaging Reporting and Data System; NR = not reported; CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

In a meta-analysis undertaken for the HIQA (2013) review, the combined sensitivity and specificity of breast MRI + mammography were 0.88 (0.78–0.93) and 0.88 (0.73–0.93) respectively. Those of mammography alone were 0.38 (0.26–0.51) and 0.92 (0.80–0.96) respectively.

**Additional cancer yield**

The additional cancer yield of MRI in women with negative findings on conventional testing ranged from 5.1 to 24.1 additional cancers per 1000 screening rounds (Table B.28). The incremental sensitivity was similar for studies at either end of this range (49%–50%), but the studies were conducted in populations with different risk levels, which are reflected in the different yields. The incremental yield and sensitivity were lower when MRI was added to mammography + ultrasound than in mammography alone.

**Table B.28 Incremental cancer yield of MRI over conventional testing.**

| Study | Conventional testing | Prevalence of breast cancer (1st screening round) | Total breast cancers detected | Incremental Cancer yield | Incremental yield per 1000 screening rounds | Incremental sensitivity (95% CI) using MRI |
|---|---|---|---|---|---|---|
| Kriege et al, 2006b (MRISC) | Mammography | 26/1723 (2%) | 33 | 16/3108 | 5.1 | 49% |
| Kuhl et al, 2005 | Mammography | 14/529 (3%) | 43 (41 patients) | 26/1452 | 17.9 | 60% (45–76) |
| Kuhl et al, 2005 | Mammography + ultrasound | 14/529 (3%) | 43 (41 patients) | 19/1452 | 13.1 | 44% (27–61) |
| Leach, 2005 (MARIBS) | Mammography | 20/649 (3%) | 35 | 19/1881 | 10.1 | 54% (36–72) |
| Warner et al, 2004 | Mammography | 13/236 (6%) | 22 (21 patients) | 11/457 | 24.1 | 50% (25–75) |
| Warner et al, 2004 | Mammography + ultrasound + CBE | 13/236 (6%) | 22 (21 patients) | 7/457 | 15.3 | 31% (10–54) |

MRI = magnetic resonance imaging; CBE = clinical breast examination; CI = confidence interval.

**Test recall rates**

One study reported patient recall rates following screening (Leach, 2005). The proportion of participants recalled for any further investigation was 15%, and that for fine-needle aspiration cytology or biopsy was 6%. That for MRI + mammography was higher than for mammography alone (12.7% vs 3.9% per woman year), as were false-positive biopsy rates (5% vs 1.5%).

### B.6.3 Health outcomes

**Overall survival**

Two included diagnostic accuracy studies and one excluded observational cohort study reported survival outcomes from women undergoing MRI surveillance. As there is no comparative group for these outcomes, they are not reported here. However, a brief description of their findings is presented in Appendix 3.

A prospective randomised controlled trial reporting on breast cancer mortality would provide the most valid assessment of the relative effectiveness of different screening programs for high-risk women. However, such a trial is not feasible owing to requirements for sample size and follow-up period, patient acceptability and the ethics of randomisation (see MSAC, 2006, p. 21, for further discussion).

Therefore, alternative methods for evaluating the impact of breast MRI screening are required, including large accuracy studies designed to test the hypothesis that the addition of breast MRI detects cases at an earlier stage or at a lower grade than cases mammography alone.

**Stage shift**

Four included primary studies reported on the size, lymph node status or grade of invasive cancers (Table B.29) by test type. The interpretation of these findings is limited by the small number of cases identified in each study (range 16–51).

Two studies reported on the characteristics of cancers detected by a combination of MRI and mammography versus mammography alone (Leach, 2005; Warner et al, 2008). Leach (2005) observed that the addition of breast MRI detected a similar proportion of invasive cancers <10 mm across as mammography (breast MRI 36% of cases detected, mammography 44%) but a higher proportion of node-negative invasive cancers (breast MRI 79%, mammography 67%). In contrast, Warner et al (2004) observed that breast MRI detected a higher proportion of cancers <10 mm across than mammography (breast MRI 38% of cases detected, mammography 20%) but a similar proportion of node-negative disease (breast MRI 92%, mammography 100%). None of these differences were statistically significant.

Kriege et al (2007) compared the characteristics of cancers detected by MRI only (20 cancers) with those of cancers detected by other screening (21 cancers). Tumour characteristics were not available for all evaluable cancers. Comparison of tumour size, lymph node status, histological differentiation grade, mitotic activity index, oestrogen receptor status and histology type by detection method showed that the extra cases detected by MRI alone were more often lymph node negative than the cases detected by other imaging or palpation (94% vs 59%, $P = 0.02$). MRI-only–detected cancers also appeared to be smaller than cancers detected by other methods, but this difference was not statistically significant (cancers <1 cm: MRI-only 58%, other methods 31%, $P = 0.11$).

These findings provide some evidence that including breast MRI in screening programs for high-risk women may lead to a favourable stage shift in the detection of breast cancer. However, the magnitude of the clinical benefit associated with the detection of earlier-stage disease has not been measured.

**Table B.29 Cancer stage, grade and nodal status for cases detected at screening of high-risk women.**

| Author | No. of invasive breast cancer cases (number of in-situ cancers) | | | Invasive cancer cases <10 mm (% of all invasive cancers detected by modality) | | | Negative lymph node/micrometastases (% of all invasive cancers detected by modality) | | | Histological grade | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MRI + M | M | MRI | MRI + M | M | MRI | MRI + M | M | MRI | MRI + M | M | MRI |
| Leach et al, 2005 | 28 | 9 | 19 | 11/29 (38%) | 4/9 (44%) *P* = 0.71[1] | 6/19 (32%) | 19/24 (79%) | 6/9 (67%) *P* = 0.65[1] | 13/15 (87%) | G1 3/28 (11%), G3 18/28 (64%) | G1 0/9 (0%), G3 7/9 (78%) | G1 3/25 (12%), G3 17/25 (68%) |
| Warner et al, 2004 | 13 | 5 | 13 | 5/13 (38%) | 1/5 (20%) *P* = 0.62[1] | 5/13 (38%) | 11/12 (92%) | 4/4 (100%) *P* = 1.00[1] | 11/12 (92%) | NR | NR | NR |
| Kriege et al, 2007[†] | 22 | 8 | 10 | | Other screen: 5/21 (31%) *P* = 0.11[3] | 11/20 (58%) | | Other screen: 9/21 (56%) *P* = 0.02[3] | 16/20 (94%) | | Other screen: G1 7/21 (44%), G3 5/21 (31%) | G1 11/20 (58%), G3 5/20 (26%) |
| Kuhl et al, 2005 | | 10 (4) | 31 (8) | | 5/14 (36%) *P* = 0.21[2] | 23/39 (59%) | | 6/10 (60%) *P* = 0.19[2] | 26/31 (84%) | NR | NR | NR |

[†] Study includes all women (Kriege et al, 2007), but sensitivity and specificity for this report include only pre-menopausal women (Kriege et al, 2006b). MRI = magnetic resonance imaging; G = histological grade of tumour; M = mammography; NR = not reported.

1. 2-sided Fisher's exact test MRI + mammography versus mammography.

2. 2-sided Fisher's exact test MRI versus mammography.

3. 2-sided Fisher's exact test MRI versus other screen detected.

### Treatment effect

If the addition of breast MRI is proposed to detect cases at an earlier stage or at a lower grade than mammography alone, treatment at this earlier stage or grade should reduce mortality. This review did not identify any studies comparing treatment outcomes for breast cancer cases detected by MRI and mammography in young high-risk women. Therefore, the relevant evidence comes from:

1. outcomes from mammogram screen-detected versus clinically detected cases in average-risk patients
2. outcomes for cases detected in high-risk women by stage and grade.

1. *Mammogram screen–detected versus clinically detected cases*

Meta-analyses of randomised controlled trials have established that early detection of breast cancer by mammography reduced breast cancer mortality in patients at average risk (Broeders et al, 2012; Gøtzsche & Jorgensen, 2013; Independent UK Panel on Breast Cancer Screening, 2012; US PSTF, 2009), but the magnitudes of the benefits and harms differ and the findings remain controversial. The benefits of mammographic screening may be more modest in women younger than 50 years. For women aged 39–49 years, US PSTF (2009) reported a relative risk for breast cancer death of 0.85 (95% CI 0.75–0.96; eight trials) and a number needed to invite for screening of 1904 (95% CI 929–6378) to prevent one breast cancer death.

The following factors were listed in the MSAC (2006) assessment as limiting the applicability of evidence from mammography screening trials:

- Breast cancers in women with a genetic predisposition show different characteristics, including a higher proportion of aggressive tumours, from sporadic breast cancers, and early detection may not bring the same survival benefits as for sporadic cancers.
- The extra cases of breast cancer detected by the addition of MRI may represent a different spectrum of disease from the extra cases detected by mammography versus clinical presentation. Differences in size, grade and stage of disease for MRI screen-detected versus mammogram screen-detected cases are not clearly defined (MSAC, 2006).

2. *High-risk women by tumour stage*

This review did not identify any studies comparing treatment outcomes for high-risk women by stage of disease at diagnosis. The MSAC (2006) review cited one large observational study which indicated that tumour size and nodal status are also important prognostic factors for *BRCA1*–associated breast cancers (Brekelmans & Seynaeve, 2006), which suggests that screening programs which detect a high proportion of early-stage disease will improve survival.

### B.6.4 Change in management

As all MRI-detected cancers are likely to be treated according to standard breast cancer treatment protocols, studies with the outcome of change in management are not required for the evaluation of the addition of breast MRI to mammography.

### B.6.5 Patient outcomes

Patient outcomes were included in two existing systematic reviews (MSAC, 2006; NICE, 2013), both of which relied extensively on one study (Rijnsburger et al, 2004), a survey of 288 women. In this study, 30% of women reported mammography as being 'quite' to 'very' painful, versus 1% who found breast MRI painful, but 5% reported anxiety about mammography, versus 10% about breast MRI. The study also found a small but significant reduction ($P \leq 0.01$) in self-rated health on a visual analogue score over time among women participating in an MRI breast cancer screening program, but no other generic quality of life score changed over time.

The primary study included in this review measured perception of breast cancer risk, the state anxiety component of the State-Trait Anxiety Inventory (STAI–state anxiety), and Impact of Events

Scale (IES) scores (Brédart et al, 2012a). The mean STAI–state anxiety score reflected low to moderate distress for both MRI + mammography and mammography alone. At baseline, MRI + mammography was associated with lower STAI–state anxiety ($P \leq 0.001$) and IES Avoidance scores ($P = 0.02$), but just after examination and 1 to 3 months later, no difference was found. These differences are likely to reflect the different patient characteristics between the two surveillance strategies. An abnormal surveillance result was associated with higher STAI–state anxiety ($P \leq 0.01$) and IES Intrusion ($P \leq 0.01$) scores, and a personal history of breast cancer and higher risk perception were associated with higher psychological distress following surveillance.

In a second publication of the same study (Brédart et al, 2012b), a relatively high percentage of women reported discomfort related to MRI associated with noise (65%), immobility (35%) and the duration of the examination (37%). Women younger than 50 years tended to have higher scores for quality of care for MRI than for mammography, and lower scores for psychological comfort for mammography than for MRI, showing that they had a more favourable perception and experience with MRI than women over 50, who reported more positive opinions for mammography.

# B.7 Women with a history of treatment for invasive breast cancer

## B.7.1 Systematic reviews and HTAs

The conclusions and recommendations from NICE (2013) and Robertson et al (2011a) are summarised in Table B.30. The NICE HTA was conducted as part of a guideline development process with the primary focus on familial breast cancer; therefore the population considered is narrower than is being considered in the current review.

**Table B.30 Conclusions and recommendations for included systematic reviews.**

| Conclusions | Recommendations |
|---|---|
| NICE, 2013 | |
| (Diagnostic outcomes) Moderate-quality evidence (Robertson et al, 2011b) suggests that MRI has the optimal combination of sensitivity and specificity for the detection of IBTR in patients undergoing routine and non-routine surveillance following breast conserving surgery. Moderate-quality evidence (Robertson et al, 2011b) suggests that MRI has higher sensitivity and specificity for the detection of IBTR in patients undergoing surveillance following breast conserving surgery. Surveillance mammography + CBE + ultrasound + MRI had the highest sensitivity (100%) for the detection of MCBC in surveillance following breast-conserving surgery (Robertson et al, 2011b). For patients undergoing routine surveillance following mastectomy, moderate-quality evidence (Roberston, et al, 2011b) suggests MRI has higher sensitivity than mammography or clinical examination for the detection of IBTR. In these patients surveillance mammography + | Ensure that all women with breast cancer are offered annual mammography for 5 years for follow-up imaging, in line with NICE CG80*. In conjunction, women who remain at high risk of breast cancer and have a family history should receive surveillance as outlined in this guideline.<br>Mammographic surveillance<br>Offer annual mammographic surveillance to all women aged 50–69 years with a personal history of breast cancer who:<br>—remain at high risk of breast cancer (including those who have a *BRCA1* or *BRCA2* mutation), and<br>—do not have a *TP53* mutation. [new 2013]<br>Offer mammography as part of the population screening program for all women aged ≥70 years with a personal history of breast cancer who: |

| Conclusions | Recommendations |
|---|---|
| ultrasound had the highest sensitivity (95%) and specificity (99%) for the detection of MCBC. Moderate-quality evidence from a surveillance study including women with and without a personal history of breast cancer (Sardanelli et al, 2011) suggests that MRI is more sensitive than mammography, ultrasonography, CBE or mammography + ultrasonography. Moderate-quality evidence from a surveillance study including women with and without a personal history of breast cancer (Sardanelli et al, 2011) suggests no significant difference in the sensitivity of MRI + mammography, MRI + ultrasonography, MRI + mammography + ultrasonography or MRI.<br><br>(Clinical outcomes) No evidence was found for the relative effect of surveillance MRI, mammography, ultrasound, CBE and no surveillance on stage at detection, overall survival, radiation-induced cancer or health-related quality of life.<br><br>Very low-quality evidence (Elmore & Margenthaler, 2010, Table 7.8) suggests a new breast cancer will be detected on ~1% of surveillance tests in women with a personal history of breast cancer and a familial risk. Low-quality evidence (Houssami, et al, 2011, Table 7.8) reported a cancer detection rate of 95.5/10,000 screens (95% CI 78.3–112.7) for screening with mammography. Although Sardanelli et al (2010) reported both clinical and diagnostic outcomes, the results for clinical outcomes are reported for all interventions combined and not for individual outcomes, and therefore there is a question mark over usefulness of the clinical data from this study in supporting the drafting of recommendations. | —remain at high risk of breast cancer (including those who have a *BRCA1* or *BRCA2* mutation, and<br><br>—do not have a *TP53* mutation. [new 2013]<br><br>MRI surveillance<br><br>Offer annual MRI surveillance to all women aged 30–49 years with a personal history of breast cancer who remain at high risk of breast cancer, including those who have a *BRCA1* or *BRCA2* mutation. [new 2013]<br><br>Do not offer MRI surveillance to any women aged ≥50 years without a *TP53* mutation unless mammography has shown a dense breast pattern. [new 2013]<br><br>Consider annual MRI surveillance for women aged 20–69 years with a known *TP53* mutation or who have not had a genetic test but have a >30% probability of being a *TP53* carrier. [new 2013]<br><br>Offer support (eg, risk counselling, psychological counselling, risk management advice) to women who have ongoing concerns but are not eligible for surveillance additional to that offered by the national breast screening programs. [2004, amended 2013]<br><br>Before deciding on surveillance, discuss and give written information on benefits and risks of surveillance, including:<br><br>—the possibility that mammography might miss a cancer in women with dense breasts and the increased likelihood of further investigations [new 2013]<br><br>—possible over-diagnosis<br><br>—risk associated with exposure to radiation<br><br>—possible psychological impact of a recall visit. [2004, amended 2013].<br><br>Review eligibility for surveillance if family history changes (eg, if another member of the family develops breast cancer or a mutation is identified). [new 2013]<br><br>At the start of a surveillance program and when there is a transition or change to the surveillance plan, give women:<br><br>—information about the surveillance program, including details of the tests, how often they will have them and the duration of the program<br><br>—information about the risks and benefits of surveillance—details of sources of support and further information. [2006, amended 2013] |

| Conclusions | Recommendations |
|---|---|
| | Ensure that women know and understand the reasons for any changes to the surveillance plan. [new 2013]<br><br>For women <50 years who are having mammography, use digital mammography at centres providing it to National Breast Screening Program standards. [new 2013]<br><br>Ensure that individual strategies are developed for all women having mammographic surveillance and that surveillance is:<br><br>—to national breast screening program standards<br><br>—audited<br><br>—undertaken only after written information is given about risks and benefits. [new 2013]<br><br>Ensure that MRI surveillance includes MRI of both breasts performed to National Breast Screening Program standards. [2006, amended 2013]<br><br>When women not known to have a genetic mutation are referred to a specialist genetic clinic, offer assessment of their carrier probability using a calculation method with acceptable performance (calibration and discrimination) to determine whether they meet or will meet the criteria for surveillance (eg, BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm). [new 2013]<br><br>Do not offer surveillance to women who have undergone a bilateral mastectomy. |
| Robertson et al, 2011a | |
| Nine studies, involving 3,775 women, were included in the systematic review of test performance. For the detection of IBTR in routine surveillance where there was no prior suspicion of recurrence, the highest sensitivity was shown for MRI and MRI + clinical examination at 100%, whereas the highest specificity was shown for surveillance mammography alone (97%), although this was obtained in a highly select population. Clinical examination alone had the lowest sensitivity (50%), and surveillance mammography + clinical examination had the lowest specificity (67%). In the detection of MCBC in routine surveillance, sensitivity ranged from 0% (clinical examination) to 100% for surveillance mammography + clinical examination + ultrasound + MRI. Specificity ranged from 50% for | • Surveillance, when combined with effective treatment of the cancers detected, is likely to improve survival.<br><br>• The evidence base on which to recommend any change in current practice is relatively weak.<br><br>• The current evidence base suggests that should the NHS choose to standardise surveillance for all women, then a regimen of mammography alone every 12–24 months appears to have the highest net benefits when society's willingness to pay for a QALY is £20,000 or £30,000.<br><br>• Rather than offering the same regimen to all patients, careful consideration should be given to stratification of patients to ensure maximum benefit to |

| Conclusions | Recommendations |
|---|---|
| surveillance mammography, MRI or clinical examination to 99% for surveillance mammography + ultrasound. The highly selected nature of the population should be borne in mind in the context of these results.<br><br>From the available data, MRI can be considered as a highly sensitive test for diagnosis of IBTR in both routine and non-routine surveillance patients. In both routine and non-routine surveillance aimed at detecting IBTR, MRI achieved higher reported specificities than surveillance mammography. For the purposes of detecting MCBC via routine surveillance, MRI had the highest reported sensitivity and specificity of any individual test. Combining tests increased both sensitivity and specificity for detecting MCBC. Surveillance mammography + clinical examination + ultrasound + MRI produced the highest reported sensitivity of 100%. It produced a lower reported specificity (89%) than surveillance mammography + ultrasound, which produced the highest reported specificity (99%) and the second highest reported sensitivity (95%). Of those test combinations reported here, surveillance mammography + ultrasound could be considered as the most accurate test combination for detecting MCBC via routine surveillance. | ensure optimal use of resources. How best to deliver a varying surveillance regimen would be challenging, and how such a service could be best organised needs consideration.<br><br>• The current evidence base suggests that should the NHS choose to tailor surveillance for those women with a greater likelihood of developing IBTR or MCBC, then more comprehensive (eg, mammography and clinical follow-up) and more frequent surveillance (every 12 months) would be associated with greatest net benefit.<br><br>• The current evidence base suggests that should the NHS choose to tailor surveillance for those women least likely to develop IBTR or MCBC, then only less frequent mammographic surveillance (eg, every 36 months) would be associated with the greatest net benefit.<br><br>• Variation in surveillance can be a source of anxiety to women. |

* NICE Guideline 80 (National Collaborating Centre for Cancer, 2009) makes the following recommendations on follow-up imaging:

Offer annual mammography to all patients with early breast cancer, including DCIS, until they enter the breast screening program. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.

On reaching screening age or after 5 years of annual mammography follow-up, stratify screening frequency in line with patient risk category.

Do not offer mammography of the ipsilateral soft tissues after mastectomy.

Do not offer ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.

MRI = magnetic resonance imaging; CBE = clinical breast examination; CI = confidence interval; *BRCA1/2* = breast cancer gene 1 or 2; *TP53* = tumour protein p53 gene; IBTR = ipsilateral breast tumour recurrence; MCBC = metachronous contralateral breast cancer; NHS = UK National Health Service; QALY = quality-adjusted life year.

## B.7.2 Diagnostic accuracy

### Sensitivity and specificity

The results of included studies that compare the sensitivity and specificity of MRI with mammography are summarised in Table B.31, Table B.32 and Table B.33. Viehweg et al (2004) reports results per test; in Berg et al (2012), the participant was the primary unit of analysis, although neither study was conducted over multiple rounds, so this doesn't affect the interpretation.

The sensitivity of breast MRI + mammography in patients who had a previous history of breast cancer was 1.00, and specificity was 0.79; this was a non-significant increase in sensitivity (0.50) and a significant decrease in specificity (0.95) compared with mammography alone (Berg et al, 2012). As only a subset of the study population underwent breast MRI and only a subset of these had a

previous history of breast cancer, interpretation of these results is limited by the small sample size (and therefore wide confidence intervals). Furthermore, the women included in this analysis may not be representative of the overall population and had already undergone three complete rounds of screening by mammography and ultrasound, so the prevalence of breast cancer is likely to be low, as only incident cancers will be detected. It was not reported whether the cancers detected were ipsilateral or contralateral.

Berg et al (2012) also reported on the addition of ultrasound to mammography, the primary objective of the study, over three rounds of screening in women with a history of breast cancer. Only a small subset of the study population had MRI but all had ultrasound. The sensitivity increased significantly (mammography alone, 0.56 [95% CI 0.42–0.69], mammography + ultrasound, 0.85 [95% CI 0.73–0.93]), while the specificity decreased significantly (mammography alone, 0.91 [95% CI 0.91–0.92], mammography + ultrasound, 0.83 [95% CI 0.82–0.84]). Diagnostic accuracy of mammography + ultrasound + MRI was not reported.

Viehweg et al (2004) reported only on the detection of contralateral breast cancers following breast-conserving surgery. The comparator to MRI was conventional imaging, which included ultrasound in 93 of 145 cases (64%). The addition of MRI to conventional imaging increased sensitivity (conventional imaging, 0.64, conventional imaging + MRI, 1.00) without a corresponding decrease in specificity (conventional imaging, 0.84, conventional imaging + MRI, 0.89); neither change was significant. This study had a high risk of bias; it was small and retrospective and did not use a standardised measure for positive tests, and therefore interpretation of these findings is limited.

Owing to the lack of evidence on the performance of breast MRI in women with a history of breast cancer, additional evidence from women who have been recently diagnosed with breast cancer is presented in Appendix 4.

**Table B.31 Diagnostic accuracy of breast MRI + mammography (± ultrasound).**

| Study | Test | Positive test | TP | FP | FN | TN | Sensitivity [95% CI] | Specificity [95% CI] |
|---|---|---|---|---|---|---|---|---|
| Berg et al, 2012** | MRI+M | BI-RADS 3, 4a, 4b, 4c, or 5 | 4 | 58 | 0 | 213 | 1.00 [0.40–1.00] | 0.79 [0.73–0.83] |
| Viehweg et al, 2004 | MRI+M+ U/S+CBE | Positive (Heywang-Köbrunner et al, 1997) | 11 | 15 | 0 | 119 | 1.00 [0.72, 1.00] | 0.89 [0.82, 0.94] |

**Previous history of breast cancer population & underwent MRI only (source: Berg et al, 2012 Supplementary Appendix). MRI = magnetic resonance imaging; M = mammography; U/S = ultrasound; CBE = clinical breast examination; BI-RADS = American College of Radiology Breast Imaging Reporting and Data System; CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Table B.32 Diagnostic accuracy of breast mammography (± ultrasound).**

| Study | Test | Positive test | TP | FP | FN | TN | Sensitivity [95% CI] | Specificity [95% CI] |
|---|---|---|---|---|---|---|---|---|
| Berg et al, 2012** | M | BI-RADS 3, 4a, 4b, 4c, or 5 | 2 | 13 | 2 | 258 | 0.50 [0.07–0.93] | 0.95 [0.92–0.97] |
| Viehweg et al, 2004 | M+U/S+ CBE | Positive (Heywang-Köbrunner et al, 1997) | 7 | 22 | 4 | 112 | 0.64 [0.31, 0.89] | 0.84 [0.76, 0.89] |

**Previous history of breast cancer population & underwent MRI only (source: Berg et al, 2012 Supplementary Appendix). M = mammography; U/S = ultrasound; CBE = clinical breast examination; BI-RADS = American College of Radiology Breast Imaging Reporting and Data System; CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Table B.33 Diagnostic accuracy of breast MRI alone.**

| Study | Test | Positive test | TP | FP | FN | TN | Sensitivity [95% CI] | Specificity [95% CI] |
|---|---|---|---|---|---|---|---|---|
| Berg et al, 2012** | MRI | BI-RADS 3, 4a, 4b, 4c, or 5 | 3 | 50 | 1 | 221 | 0.75 [0.19–0.99] | 0.82 [0.76–0.86] |
| Viehweg et al, 2004 | MRI | Positive (Heywang-Köbrunner et al, 1997) | 10 | 13 | 1 | 121 | 0.91 [0.59, 1.00] | 0.90 [0.84, 0.95] |

**Previous history of breast cancer population & underwent MRI only (source: Berg et al, 2012 Supplementary Appendix). MRI = magnetic resonance imaging; BI-RADS = American College of Radiology Breast Imaging Reporting and Data System; CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

### Additional cancer yield

The additional cancer yield of MRI (in women with negative findings on conventional testing) was 7.3 additional cancers per 1000 screening rounds in Berg et al (2012) and 2.8 additional cancers per 1000 screening rounds in Viehweg et al (2004) (Table B.34). The lower incremental yield in the latter may be partially explained by the inclusion of ultrasound in conventional testing.

**Table B.34 Incremental cancer yield of MRI over conventional testing.**

| Study | Conventional testing | Prevalence of breast cancer (1st screening round) | Total breast cancers detected | Incremental cancer yield | Incremental yield per 1000 screening rounds | Incremental sensitivity using MRI |
|---|---|---|---|---|---|---|
| Berg et al, 2012 | M | 36/2659 (1%) | 4 | 2/275 | 7.3 | 50% |
| Viehweg et al, 2004 | M+U/S+CBE | NR | 11 | 4/145 | 2.8 | 36% |

MRI = magnetic resonance imaging; M = mammography; U/S = ultrasound; CBE = clinical breast examination; NR = not reported.

### Test recall rates

Berg et al (2012) reported patient recall rates (Table B.35) for women with a personal history of breast cancer. The rates of recall for mammography alone were the lowest (5.5%); the rates of recall for MRI + mammography and MRI alone were comparable (22.5% vs 19.3% respectively). Similarly, the biopsy rates were lowest for mammography alone (1.6%), and comparable for MRI + mammography (5.5%) and MRI alone (4.0%). False-positive biopsy rates were lowest for mammography alone (0.7%) and highest for MRI + mammography (4.0%).

**Table B.35 Test recall and biopsy rates reported by Berg et al (2012).**

| Number of patients (number of screens) | Recall rate [95% CI] | Biopsy rate [95% CI] | False-positive biopsy rates |
|---|---|---|---|
| 275 (275) | M: 15/275 (5.5% [3.1–8.8])<br>MRI+M: 62/275 (22.5% [17.7–27.9])<br>MRI: 53/275 (19.3% [14.8–24.4]) | M: 4/275 (1.5% [0.4–3.7])<br>MRI+M: 15/275 (5.5% [3.1–8.8])<br>MRI: 11/275 (4.0% [2.0–7.0]) | M: 2/275 (0.73%)<br>MRI+M: 11/275 (4.0%)<br>MRI: 8/275 (2.9%) |

M = mammography; MRI = magnetic resonance imaging.

### B.7.3 Health outcomes

Neither study was large enough to report cancer size or stage as a proxy for health outcomes in women with a history of breast cancer.

### B.7.4 Patient outcomes

A study of the psychological outcomes associated with breast MRI and mammography screening (Brédart et al, 2012a) included a high number of women with a personal history of breast cancer; however, these women were eligible only for mammography. The findings from this study are discussed in Section B.6.5, Patient outcomes, on page 51.

## B.8 Women with a history of treatment for DCIS or LCIS

### B.8.1 Diagnostic accuracy

#### Sensitivity and specificity

One study with a high risk of bias reported on the sensitivity of breast MRI and mammography (but not breast MRI as an additional test to mammography) in women with a history of treatment for LCIS. This study reported sensitivity and specificity on a per patient basis and defined a positive test as one which required biopsy. This definition of a positive test is not independent of the reference standard and is a source of bias.

The sensitivity of breast MRI in this population was 0.71, compared with 0.36 for mammography. The difference was not significant, and the small number of patients limits the power of this study. The specificity of breast MRI was 0.76, significantly lower than mammography, with a specificity of 0.90 (Table B.36, Table B.37).

**Table B.36 Diagnostic accuracy of breast MRI.**

| Study | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|
| Sung et al, 2011 | Biopsy | 10 | 49 | 4 | 157 | 0.71 [0.42, 0.92] | 0.76 [0.70, 0.82] |

CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Table B.37 Diagnostic accuracy of mammography.**

| Study | Positive test | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|
| Sung et al, 2011 | Biopsy | 5 | 20 | 9 | 180 | 0.36 [0.13, 0.65] | 0.90 [0.85, 0.94] |

CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

# B.9 Women who have had chest irradiation between the ages of 10 and 35 years

## B.9.1 Diagnostic accuracy

**Sensitivity and specificity**

The results of the three eligible primary studies which compared the sensitivity and specificity of breast MRI and mammography in women who have had chest irradiation are presented in Table B.38, Table B.39 and Table B.40. All studies used a follow-up biopsy to define a positive test. This definition of a positive test is not independent of the reference standard and is a source of bias. Ng et al (2013) reported results on a per test basis, while Freitas et al (2013) and Sung et al (2011a) reported results on a per patient basis.

Only one study addressed the review question, which was the addition of breast MRI to mammography (Ng et al, 2013). This study was also of higher quality and more applicable than the other studies and was the largest study included. The addition of MRI to mammography increased sensitivity non-significantly from 0.68 to 0.95 with a corresponding non-significant reduction in specificity from 0.92 to 0.86.

The studies had comparable findings for sensitivity and specificity of the tests on their own, with the exception of the high sensitivity of breast MRI reported by Freitas et al (2013). The sensitivity of mammography in the three studies was higher than had been reported in other populations considered in this review, which would reduce the incremental benefit of adding breast MRI.

**Table B.38 Diagnostic accuracy of breast MRI and mammography.**

| Study | Positive test | TP | FP | FN | TN | Sensitivity [95% CI] | Specificity [95% CI] |
|---|---|---|---|---|---|---|---|
| Ng et al, 2013 | Biopsy | 18 | 45 | 1 | 274 | 0.95 [0.74, 1.00] | 0.86 [0.82, 0.90] |

CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Table B.39 Diagnostic accuracy of breast MRI.**

| Study | Positive test | TP | FP | FN | TN | Sensitivity [95% CI] | Specificity [95% CI] |
|---|---|---|---|---|---|---|---|
| Freitas et al, 2013 | Biopsy | 12 | 5 | 1 | 80 | 0.92 [0.64, 1.00] | 0.94 [0.87, 0.98] |
| Ng et al, 2013 | Biopsy | 12 | 30 | 7 | 289 | 0.63 [0.38, 0.84] | 0.91 [0.87, 0.94] |
| Sung et al, 2011 | Biopsy | 6 | 15 | 3 | 67 | 0.67 [0.30, 0.93] | 0.82 [0.72, 0.89] |

CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative

**Table B.40 Diagnostic accuracy of mammography.**

| Study | Positive test | TP | FP | FN | TN | Sensitivity [95% CI] | Specificity [95% CI] |
|---|---|---|---|---|---|---|---|
| Freitas et al, 2013 | Biopsy | 9 | 2 | 4 | 83 | 0.69 [0.39, 0.91] | 0.98 [0.92, 1.00] |
| Ng et al, 2013 | Biopsy | 13 | 25 | 6 | 294 | 0.68 [0.43, 0.87] | 0.92 [0.89, 0.95] |
| Sung et al, 2011 | Biopsy | 6 | 5 | 3 | 69 | 0.67 [0.30, 0.93] | 0.93 [0.85, 0.98] |

CI = confidence interval; TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative.

**Additional cancer yield**

The only study which compared MRI + mammography with mammography (Ng et al, 2013) reported an incremental yield of 14.8 cancers per 1000 screening rounds with the addition of MRI (Table B.41). This population had a high prevalence of disease and a lower incremental sensitivity than studies of women with high familial risk of breast cancer (see Table B.28, page 48). The prevalence of disease in this study may be affected by the very low number of women (4%) who had had prior breast MRI.

**Table B.41 Incremental cancer yield of MRI over conventional testing (Ng et al, 2013).**

| Conventional testing | Prevalence of breast cancer (1st screening round) | Total breast cancers detected | Incremental cancer yield | Incremental yield per 1000 screening rounds | Incremental sensitivity using MRI |
|---|---|---|---|---|---|
| Mammography | 7/134 (5%) | 18 | 5/338 | 14.8 | 27% |

MRI = magnetic resonance imaging; CI = confidence interval.

**Test recall rates**

The recall rate reported by Ng et al (2013) was 38% of screens (Table B.42). The biopsy rate of the combined tests (18%; 34% of patients) was higher than that of MRI (12%) or mammography (11%). The false-positive biopsy rate was 13% for the combined tests, 7% for mammography and 9% for MRI.

**Table B.42 Test recall and biopsy rates reported by Ng et al (2013).**

| No. of patients (No. of screens) | Recall rate | Biopsy rate | False-positive biopsy rates |
|---|---|---|---|
| 134 (345) | MRI+M: 132/345 (38%) | MRI+M: 63/345 (18%) (screens)<br>45/134 (34%) (patients)<br>M: 38/345 (11%)<br>MRI: 42/345 (12%) | 45 negative procedures in 29 patients (13%)<br>M: 25 negative in 16 patients (7%)<br>MRI: 30 negative in 23 patients (9%) |

MRI = magnetic resonance imaging; M = mammography.

## B.9.2 Health outcomes

### Stage shift

The small number of invasive screen-detected cancers detected in Ng et al (2013) limits the analysis, as seven of eight invasive cancers detected were both <10 mm across and node negative (Table B.43). This study identified a high number of DCIS cases (9 of 18 screen-detected cancers).

**Table B.43 Cancer stage, grade and nodal status for cases detected at screening of high-risk women (Ng et al, 2013).**

| Number of invasive breast cancer cases (number of in-situ cancers) | Invasive cancer cases <10 mm (% of all invasive cancers detected by modality) | Negative lymph node/micro-metastases (% of all invasive cancers detected by modality) | Histological grade |
|---|---|---|---|
| 8 (9)†<br>*MRI*: 7 (4) | 7/8 (88%) cases <10 mm<br>*MRI*: 6/7 | 7/8 (88%) cases node negative<br>*MRI:* 6/7 | *MRI + M:*<br>G1 1/8, G3 2/8 |

| Number of invasive breast cancer cases (number of in-situ cancers) | Invasive cancer cases <10 mm (% of all invasive cancers detected by modality) | Negative lymph node/micro-metastases (% of all invasive cancers detected by modality) | Histological grade |
|---|---|---|---|
| *M:* 7 (6) | *M*: 6/7 | *M:* 6/7 | |

† One phyllodes tumour was also diagnosed by MRI alone (not included). MRI = magnetic resonance imaging; M = mammography.

## B.10 Extended assessment of comparative harms

MSAC (2006) identified the following concerns in breast MRI screening for high-risk women:

- Adverse effects of false-positive findings (unnecessary investigation).
- Use in patients with contraindications to exposure to magnetic fields.
- Allergy to gadolinium contrast agent.
- Claustrophobia, which may preclude use in some patients.
- Patient discomfort due to the noise of the machine.
- Avoidance advised in pregnant women owing to limited evidence about the safety of MRI on the developing fetus.

The discussion of MRI contraindications in MSAC (2006) should be considered alongside this report.

The key safety issue with mammography is exposure to ionising radiation. Because there are documented harms from exposure to ionising radiation, relevant evidence is summarised below. However, given that mammography is proposed for both the intervention and the comparator, the harms associated with mammography would be expected to be the same regardless of the addition of MRI to the existing mammographic surveillance.

The NICE (2013) review included a 2010 meta-analysis (Jansen-van der Weide et al, 2010), which suggested, on the basis of low-quality evidence from case-control studies, that exposure to low-dose radiation during screening mammography or chest x-ray is associated with an increased risk of breast cancer in women with a familial or genetic predisposition (OR [odds ratio] 1.3, [95% CI 0.9–1.8]). There was evidence of a dose–response relationship between low-dose radiation and breast cancer in this population: exposure to low-dose radiation before the age of 20 years (OR 2.0, 95% CI 1.3–3.1) and five or more exposures (OR 1.8, 95% CI 1.1–3.0).

A review of the risk of exposure to low-dose radiation during screening was included as an appendix in a recent Canadian HTA (Medical Advisory Secretariat, 2010), which drew the following conclusions:

> *For women over 50 years of age, the benefits of mammography greatly outweigh the risk of radiation-induced breast cancer irrespective of the level of a woman's inherent breast cancer risk.*
>
> *Annual mammography for women aged 30–39 years who carry a breast cancer susceptibility gene or who have a strong family breast cancer history (defined as a first degree relative diagnosed in their thirties) has a favourable benefit:risk ratio. Mammography is estimated to detect 16 to 18 breast cancer cases for every one induced by radiation (Table 1). Initiation of screening at age 35 for this same group would increase the benefit:risk ratio to an even more favourable level of 34–50 cases detected for each one potentially induced.*
>
> *Mammography for women under 30 years of age has an unfavourable benefit:risk ratio due to the challenges of detecting cancer in younger breasts, the aggressiveness of cancers at this age, the potential for radiation susceptibility at younger ages and a greater cumulative radiation exposure.*

*Mammography when used in combination with MRI for women who carry a strong breast cancer susceptibility (eg, BRCA1/2 carriers), which if begun at age 35 and continued for 35 years, may confer greatly improved benefit:risk ratios which were estimated to be about 220 to one.*

*While there is considerable uncertainty in the risk of radiation-induced breast cancer, the risk expressed in published studies is almost certainly conservative as the radiation dose absorbed by women receiving mammography recently has been substantially reduced by newer technology.*

A large European study of *BRCA1/2* carriers published in 2012 was cited in the HIQA (2013) review. It found that exposure to any ionising radiation before the age of 30 years was associated with an increased risk of breast cancer (HR 1.90, 95% CI 1.20–3.00); this risk was dose related (Anouk et al, 2012). This increased risk was seen at doses substantially lower than those shown to be problematic in other cohorts exposed to ionising radiation, highlighting the potential increased radiosensitivity of *BRCA* mutation carriers.

## B.11 Interpretation of the clinical evidence

Evidence about the relative effectiveness of adding MRI to standard mammography is limited to studies reporting on test accuracy. These studies are designed to demonstrate differences in the performance of different screening strategies and do not provide evidence about the impact of these strategies on patient outcomes.

### B.11.1 Asymptomatic, high-risk women: MBS interim-funded item

The conclusions summarised in the following paragraphs largely mirror those of MSAC (2006, p. 71).

This review identified five level III-1/2 studies investigating the relative test accuracy of screening protocols with and without breast MRI in high-risk women. Four of these studies provided evidence applicable to the proposed use of breast MRI + mammography versus mammography. Risk classification varied across studies. Two studies included women who would be classified as at moderate rather than high risk (cumulative lifetime risk of >15% or 20%). Although only one study was designed to assess breast MRI in women under the age of 50 years (Leach, 2005), all studies either had an average age of participants of <50 years or enabled the calculation of diagnostic accuracy for a subset of women who were <50 years or pre-menopausal.

None of the studies were assessed as high quality; however, the consistency and precision of estimates of test sensitivity across these studies provide strong evidence that the combination of breast MRI and mammography is a highly sensitive test for the detection of breast cancer (range 0.85–0.94, HIQA [2013] meta-analysis 0.88 [0.78–0.93]) and offers approximately a 130% increase in the early detection of breast cancer over the use of mammography alone (range 0.36–0.40, HIQA [2013] meta-analysis 0.38 [0.26–0.51]) in the surveillance of high-risk women.

Less evidence was identified for an assessment of the relative accuracy of adding breast MRI to a mammography program that includes the use of ultrasound. Two studies reported an increased sensitivity of mammography combined with ultrasound (Kuhl et al, 2005; Warner et al, 2004) compared with mammography alone. They indicate that the incremental benefit of adding breast MRI to a screening program will be lower if standard imaging includes the routine or selected use of ultrasound than if it includes mammography alone.

Evidence about the specificity of screening protocols that include breast MRI was less consistent. This may be attributed, at least in part, to the different criteria used to define false-positives. The two studies which defined a false-positive as a test finding that initiated further testing to exclude malignancy provide the most relevant data and found specificities of 0.77 (0.75–0.79) (Leach, 2005) and 0.85 (0.84–0.86) (Kriege et al, 2006a), corresponding to a false-positive rate of 23% and 15%, respectively, compared with rates for mammography alone of 7% and 5%, respectively. Leach (2005) reported that the biopsy rate for false-positive imaging was 5% for MRI + mammography, versus 1.5% for mammography alone. Any clinical benefits associated with earlier detection should be weighed against the potential distress and costs of additional investigations for false-positive MRI findings.

**Overall conclusions: Asymptomatic, high-risk women: MBS interim-funded item**

- Breast MRI is a safe test.
- Breast MRI offers a 2.3 fold increase in the detection of breast cancer in younger high-risk women over mammography alone.
- Breast MRI increases by 3-fold the rate of investigations for false-positive findings.

### B.11.2 Women with a history of treatment for invasive breast cancer

This review identified two level III-2 studies of test accuracy investigating the relative accuracy of screening protocols with and without breast MRI in women with a history of treatment for invasive breast cancer. Both studies included women aged over 50 years (median of 57 and 55.7 years). Both studies had methodological flaws and were at high risk of bias across multiple domains.

The studies were consistent in showing that breast MRI combined with mammography is a highly sensitive test (no false-negatives identified) for the early detection of breast cancer in women with a previous history of invasive breast cancer. However, the small sample sizes reduced the precision of these estimates and the statistical power. The studies suggest that breast MRI may double the early detection of breast cancer compared with mammography alone.

Evidence about specificity was inconsistent. Viehweg et al (2004) did not use the standard BI-RADS nomenclature to define a positive/negative test, and the threshold used was unclear. Berg et al (2012) defined a false-positive as a test finding that initiated further testing to exclude malignancy and found a specificity of 0.79 (0.73–0.83) for breast MRI + mammography, corresponding to a false-positive rate of 21% compared with 5% for mammography alone. The false-positive biopsy rate in this study was 4.0% for breast MRI + mammography, versus 0.73% for mammography alone. Any clinical benefits associated with earlier detection should be weighed against the potential distress and costs of additional investigations for false-positive MRI findings.

**Overall conclusions: Women with a history of treatment for invasive breast cancer**

- Breast MRI is a safe test.
- Breast MRI may double the detection of breast cancer in women with a history of treatment for invasive breast cancer compared with mammography alone.
- Breast MRI may increase by 4-fold the rate of investigations for false-positive findings

### B.11.3 Women with a history of treatment for DCIS or LCIS

This review did not identify any studies of test accuracy which compared screening protocols with and without breast MRI in women with a history of treatment for DCIS or LCIS. It did identify one level III-2 diagnostic accuracy study which compared breast MRI alone with mammography alone in women who had been treated for LCIS. The study was small and had a high risk of bias across multiple domains. It suggests MRI may double the early detection of breast cancer in women with a history of LCIS (sensitivity: MRI 0.71 [0.42, 0.92], mammography 0.36 [0.13, 0.65]) (Sung et al, 2011b), and found a 140% increase in the rate of biopsies for false-positive findings, but the body of evidence if too limited to allow any conclusions to be drawn.

### B.11.4 Women who have had chest irradiation between 10 and 35 years

This review identified one level III-1 test accuracy study investigating the relative accuracy of screening protocols with and without breast MRI for women who have had chest irradiation between the ages of 10 and 35 years (Ng et al, 2013). Two additional level III-2 test accuracy studies investigated the accuracy of breast MRI alone compared with mammography alone (Freitas et al, 2013; Sung et al, 2011a). All studies had a mean or median age of <50 years.

The Ng et al (2013) study is the most applicable and at a lower risk of bias than the other included studies. It provides weak evidence that the addition of breast MRI increases the early detection of breast cancer over mammography alone in women who have had chest irradiation (sensitivity: breast MRI + mammography 0.95 [0.74, 1.00], mammography alone 0.68 [0.43, 0.87]), an increase in the early detection of breast cancer of approximately 1.4-fold. The biopsy rate in this study was 18% (14.5%–22.6%) for the combined tests and 11% (8.0%–14.7%) for mammography alone, an increase in the rate of biopsy of 1.6 fold.

Across all three studies, the sensitivity of mammography in this population was consistently higher than in other populations considered in this review (three studies: 0.67, 0.68 and 0.69), and while the sensitivity of breast MRI alone was less consistent (three studies: 0.63, 0.67 and 0.92), in two of the studies the sensitivity of MRI alone was not greater than that of mammography alone (Ng et al, 2013; Sung et al, 2011a). Despite their lack of precision, the consistency of these studies suggests that breast MRI alone is not more sensitive than mammography alone in women who have had chest irradiation, and likewise the techniques have similar specificity. The combination of the two tests is likely to increase the detection of early breast cancer compared with either test alone, although to a lesser degree than in other high-risk populations.

**Overall conclusions: Women who have had chest irradiation between 10 and 35 years**

- Breast MRI is a safe test.
- Breast MRI may offer an approximately 1.4-fold increase in the detection of breast cancer in women who have had chest irradiation between 10 and 35 years compared with mammography alone.
- Breast MRI may increase by approximately 1.6-fold the rate of biopsy compared with mammography alone.

# Section C Translating the clinical evaluation to economic evaluation

As shown in Section D, the results of the economic model presented in this assessment report are driven by several important differences between the surveillance using MRI + mammography and surveillance using mammography alone:

1. MRI + mammography has higher sensitivity than mammography alone, leading to earlier detection in a higher proportion of cancers.
2. Earlier detection of breast cancer leads to earlier treatment.
3. Earlier treatment of breast cancer leads to earlier accrual of treatment costs but improved prognosis.
4. The benefits of MRI + mammography are balanced against the incremental cost of MRI scans and reduced specificity, resulting in additional costs for the follow-up of false-positive diagnoses.

Five key translation issues were identified within this structure:

- Which accuracy data presented in Section B are most applicable to the populations being considered for MRI surveillance?
- What is the underlying risk of breast cancer in each of the proposed populations for screening; and, consequently, how many cancers would be detected earlier by MRI + mammography than by mammography alone?
- What is the prognosis for women with breast cancer, and how is prognosis affected by a delay in diagnosis?
- What are the resource use implications of the proposed screening program?
- What are the quality of life implications of the proposed screening program; that is, what utility values apply to patients with cancer and to those who are falsely identified as having cancer?

A review of economic evaluations, presented in Section D, found a number of economic models that address these key translation issues. Therefore, the approaches used to address these issues are explained within the description of the economic model itself in Section D.

# Section D Economic evaluation

## D.1 Overview of the economic evaluation

The model used in the MSAC (2006) application for breast MRI was adapted from a published evaluation of the cost-effectiveness of MRI for screening women at high risk of breast cancer in the United States (Plevritis et al, 2006). This evaluation applied evidence from diagnostic accuracy studies to a mathematical model of the natural history of breast cancer to estimate incremental effects, incremental cost and an incremental cost-effectiveness ratio (ICER) for MRI + mammography compared with mammography alone in different age groups and different risk groups in the United States. To translate this economic evaluation to an Australian setting and comply with MSAC decision-making processes, a secondary economic analysis was performed on the basis of the Plevritis model with the same assumptions about the diagnostic performance and effects of screening, but excluding indirect costs and applying Australian relative prices. This approach assumed that all parameters relating to the natural history and treatment of breast cancer in the United States would also apply in Australia, including prevalence, risk of breast cancer, treatments used, treatment efficacy and mortality. The overall economic conclusion of the MSAC (2006) report was that while

> *'breast MRI is potentially cost-effective for screening very high-risk women in the US such as BRCA1 mutation carriers between the ages of 35 and 54 years, it is unlikely to be cost-effective for screening BRCA2 carriers or a wider risk or age population such as that under consideration in Australia.*
>
> *'A secondary exploratory economic analysis for Australia, based on the Plevritis model with the same assumptions about diagnostic performance and the effects of screening, but excluding indirect costs and applying Australian relative prices, suggests the potential for breast MRI to be cost-effective in a select high-risk subgroup of the proposed screening population in Australia; for example, BRCA1 mutation carriers aged 35–54 years' (pages 77–78).*

Although interim funding was recommended for additional MRI screening, the MSAC concluded that there was considerable uncertainty surrounding the evaluation of cost-effectiveness and that the evidence presented in Assessment Report 1098 should be reviewed in not less than 3 years.

The economic evaluation presented in the current assessment report addresses some of the limitations of the previous assessment. The model presented here is an Australian adaptation of an economic model developed by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom to assess the cost-effectiveness of different surveillance strategies in women at high risk of breast cancer. The model was used to inform the development of NICE CG41 (2006) on the classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. The most recent iteration of the clinical guideline, an update of NICE CG41, was issued in June 2013 (NICE, 2013). A working version of the 2006 NICE model (Norman et al, 2007; National Collaborating Centre for Primary Care, 2006) was provided to the assessment group with the permission of its developers, the National Collaborating Centre for Primary Care.

In this assessment report, all relevant model parameters and assumptions from the NICE model were updated to reflect the proposed use of MRI in Australia as reflected in the Decision-Analytic Protocol (DAP) (see Section D.3.3 for a summary of how the model in this assessment report reflects the requirements of the DAP).

## D.2 Population and circumstances of use reflected in the economic evaluation

As discussed in Section A, this assessment report presents an economic evaluation of annual screening with MRI in addition to mammography in patients that are currently eligible for screening through interim funding, as well as a number of additional high-risk groups. The change in the proposed patient population will see additional patients screened who would not previously have had access using the existing (interim) MBS items (63464 and 63467).

On the basis of evidence presented in MSAC Application 1098, interim funding was made available to asymptomatic women, aged <50 years, at high risk of breast cancer due to familial risk factors. Alternatively, patients are eligible for screening if genetic testing has identified the presence of a high-risk breast cancer gene mutation (eg, *BRCA1*, *BRCA2* and *TP53*). Patients in either of these groups may access MRI screening using MBS items 63464 (screening) and 63467 (follow-up after the detection of an abnormality). The eligibility criteria for these items (Table A.5) were based on the evidence-based recommendations about categorising risk on the basis of family history, as outlined in NBCC (2000). Patients fitting this description are classified as 'high risk' and have an average lifetime risk of 25%–50% for developing breast cancer. The guidelines note that <1% of women will be categorised as at high risk by this definition. Although women with a confirmed gene mutation for breast cancer are listed in a separate category in the descriptor for MBS item 63464, the vast majority of these women would be identified only through genetic screening on the basis of a family history of breast cancer. The assessment report therefore presents a separate analysis of the cost-effectiveness of MRI screening in the subgroup of patients with a gene mutation for breast cancer, but notes that the analysis of the larger population of familial high-risk patients is most applicable to the population in which the MBS service is likely to be used.

In addition to the existing MBS population, the application requests the inclusion of additional high-risk patient populations, namely women who are <50 years of age and have had either:

- a prior history of invasive breast cancer
- a prior history of treatment for LCIS or DCIS
- radiotherapy to the chest area undertaken between 10 and 35 years of age.

In relation to patients with a prior history of breast cancer (DCIS, LCIS, invasive), those with a gene mutation that puts them at a high risk of breast cancer already have access to MRI screening under MBS items 63464 and 63467, since the item descriptors do not specifically exclude patients who have previously had breast cancer. Therefore, the population of primary concern in this application was considered to be patients with a prior history of breast cancer, *without* the presence of a high-risk gene mutation.

The five populations included in this economic evaluation are presented in Table D.1. The same model structure (based on the 2006 NICE economic model) is used to evaluate cost-effectiveness in

each population; however, the model parameters (eg, risk of breast cancer, breast cancer prognosis, diagnostic accuracy of screening and age at screening) differ to reflect the characteristics of each population group.

**Table D.1 Populations modelled in the economic evaluation.**

| Analysis | Population | Current funding |
|---|---|---|
| Analysis 1 | High-risk based on confirmed breast cancer gene mutation | Interim funding (MBS items 63464 and 63467) |
| Analysis 2 | Familial high-risk | Interim funding (MBS items 63464 and 63467) |
| Analysis 3 | Prior history of invasive breast cancer | Not reimbursed through Medicare |
| Analysis 4 | Prior history of treatment for DCIS or LCIS | Not reimbursed through Medicare |
| Analysis 5 | Women with chest radiotherapy between 10 and 35 years | Not reimbursed through Medicare |

# D.3 Structure and rationale of the economic evaluation

## D.3.1 Review of published economic evaluations

**Review of the primary economic literature 2006–2013**

The literature search, detailed in Appendix 2, identified 10 papers that included a formal economic evaluation relevant to this assessment report. An overview of the primary economic studies identified by the literature search is provided in Table D.2.

Substantial variation exists between the studies in terms of the populations analysed, the interventions and comparators, and the assumptions driving the economic models. Most studies were concerned with the screening of women with *BRCA1*/2 mutations; Griebsch et al (2006), Moore et al (2009), Taneja et al (2009) and Saadatmand et al (2013) included a broader population of women at high risk of breast cancer due to family history. None of the studies included all the populations of interest in this assessment report, and none provided results that would be directly applicable to the requested indications and the Australian healthcare setting. Nonetheless, the conclusions are relatively consistent, with mammography alone as the most cost-effective strategy after no screening, followed by MRI + mammography, and finally MRI alone.

Norman et al (2007) reports the economic evaluation associated with NICE CG41 on familial breast cancer (NICE, 2006). It reports the cost-effectiveness of MRI screening for breast cancer in *BRCA* mutation carriers aged 30 to 49 years, while the full clinical guidance by NICE presents a cost utility analysis (CUA) of various surveillance strategies in a range of high-risk populations. Therefore, while Norman et al (2007) is relevant to the economic evaluation presented in this application, the full report for NICE CG41 is the primary reference used here.

**Table D.2 Economic evaluations studies published since the MSAC (2006) report assessing MRI in combination with mammography.**

| Study | Location | Population | Intervention and comparator | Model approach, age of entry into model | Outcomes assessed | Costs included | Applicability | Incremental cost-effectiveness ratios |
|---|---|---|---|---|---|---|---|---|
| Cott Chubiz et al, 2013 | US | *BRCA1*/2 | Mammography vs<br>MRI (alone)<br>Mammography + MRI (alternating at 6-month intervals) | Markov model<br>Screening age: >25 years | QALYs | Screening, diagnostics and treatment and patient costs | Limited on the basis of intervention | *BRCA1*<br>Digital mammography and MRI alternating at 6-month intervals:<br>$74,200/QALY<br>*BRCA2*<br>$215,700/QALY |
| Grann et al, 2011 | US | *BRCA1*/2 | Mammography vs<br>Mammography + MRI<br>(other interventions associated with ovarian cancer also included) | Markov model<br>Screening age: 30–65 years | QALYs | Screening and cancer care costs | Limited owing to population (30–65 years) and no information on test performance to inform model | *BRCA1*<br>MRI+mammography: €123,900/QALY<br>*BRCA2*<br>MRI+mammography: €71,900/QALY |
| Griebsch et al, 2006 | UK | *BRCA1/2*, *TP53* carriers, their close relatives and others of high familial risk | Mammography vs<br>MRI (alone)<br>Mammography + MRI | Based on the results of MARIBS study<br>Screening age: 35–49 years | Cancers detected | Screening costs | Limited on the basis of source of data | MRI+mammography: £34,951.33 per additional cancer detected |

| Study | Location | Population | Intervention and comparator | Model approach, age of entry into model | Outcomes assessed | Costs included | Applicability | Incremental cost-effectiveness ratios |
|---|---|---|---|---|---|---|---|---|
| Lee et al, 2010 | US | *BRCA1* | Clinical surveillance vs<br>Mammography (alone)<br>MRI (alone)<br>Mammography + MRI | Probabilistic Markov model<br>Screening age: >25 years | QALYs | Screening costs, diagnostic evaluation, treatment and patient time | Limited on the basis of population and comparator; few details on cost | Mammography: £12,076.57/QALY<br>MRI alone: £148,791.75/QALY<br>Combined: £49,835.41/QALY |
| Moore et al, 2009 | US | ≥15% cumulative lifetime risk, based on family history | Mammography vs<br>MRI (alone) | Markov model<br>Screening age: >25 years | QALYs | Screening, diagnostics and treatment | Limited on the basis of comparator and location | Discounted:<br>$179,599/QALY<br>Undiscounted<br>$124,291/QALY |
| Norman et al, 2007 (also included in NICE 2006) | UK | *BRCA1* carriers 30–39 and 40–49 years | Clinical surveillance vs<br>Mammography (alone)<br>MRI (alone)<br>Mammography + MRI | Markov model<br>Screening age: 30–39; 40–49 years | QALYs | Screening, diagnostics and treatment | Limited on the basis of population (only *BRCA1*) | 40–49 years<br>Mammography: €5,600/QALY<br>MRI: dominated<br>MRI+mammography: €15,100/QALY<br>30–39 years<br>Mammography: €10,100/QALY<br>MRI: dominated<br>MRI+mammography: €26,200/QALY |

| Study | Location | Population | Intervention and comparator | Model approach, age of entry into model | Outcomes assessed | Costs included | Applicability | Incremental cost-effectiveness ratios |
|---|---|---|---|---|---|---|---|---|
| Pataky et al, 2013 | Canada | *BRCA1*/2 | Mammography vs<br>Mammography + MRI | Markov model<br>Screening age: ≥25 years | QALYs | Screening, diagnostics and treatment | Limited on the basis of population | $50,911/QALY |
| Plevritis et al, 2006 | US | *BRCA1*/2 | No screening vs mammography and<br>Mammography + MRI | Continuous-time Monte Carlo simulation<br>Model<br>Screening age: 25–69 years | QALYs | Screening, diagnostics and treatment | Limited on the basis of population | *BRCA1*<br>Mammography $18,952/QALY<br>MRI+mammography 35–49: $71,401/QALY<br>MRI+mammography 25–69: $475,932/QALY<br>*BRCA2*<br>Mammography $28421/QALY<br>MRI+mammography 35–54: $158,839/QALY<br>MRI+mammography 25–69: $731,553/QALY |

| Study | Location | Population | Intervention and comparator | Model approach, age of entry into model | Outcomes assessed | Costs included | Applicability | Incremental cost-effectiveness ratios |
|---|---|---|---|---|---|---|---|---|
| Saadatmand et al, 2013 | Netherlands | ≥15% cumulative lifetime risk, based on genetic or familial risk<br>Based on MRISC study | 1) Yearly mammography combined with clinical examination<br>2) Clinical examination every 6 months and yearly mammography + MRI (MRISC)<br>3) Yearly MRI, 6 months later mammography + clinical examination<br>4) Yearly clinical examination + alternating mammography or MRI | Microsimulation<br>Screening age: 35–50 and 35–60 years; plus biennial mammography to 75 years | Life years gained | Screening, diagnostics and treatment | Limited on the basis of population and intervention | Screening 33–50 years:<br>1) $54,665/LYG<br>2) $212,183/LYG<br>3) $338,743/LYG<br>4) Dominated<br>Screening 33–60 years:<br>1) $63,316/LYG<br>2) $268,399/LYG<br>3) $363,357/LYG<br>4) Dominated |
| Taneja et al, 2009 | US | *BRCA1/2* and ≥20% cumulative lifetime risk | Mammography vs<br>MRI (alone)<br>Mammography + MRI | Decision-analytic model<br>Screening age: 40 years (1 screening event only) | QALYs | Screening, diagnostic evaluation and treatment | Limited on the basis of population (age) | *BRCA1/2*<br>MRI: dominated<br>MRI+mammography: €33,200/QALY<br>≥20% risk<br>€59,900–€409,300/QALY |

*BRCA1*/2 = breast cancer gene 1/2; *TP53* = tumour protein p53 gene; LYG = life year gained; MRI = magnetic resonance imaging; QALY, quality adjusted life year.

### D.3.2 Review of HTAs 2006–2013

In addition to the primary economic studies identified above, the literature search identified five HTA reports including an economic evaluation of MRI in breast cancer screening. The key features and conclusions of these assessments are presented in Table D.3. The economic evaluations presented in both the Canadian and Spanish reports are relatively basic and of limited applicability to this assessment report. However, the models presented in the Irish and UK HTAs (HIQA, 2013; NICE, 2013; Robertson et al, 2011a) warrant further discussion.

**Table D.3 Health technology assessment reports including economic evaluations of surveillance using MRI in women at high risk of breast cancer.**

| Study | Locn | Population | Intervention and comparator | Model approach | Studies included | Outcomes assessed | Costs included | Economic conclusions |
|---|---|---|---|---|---|---|---|---|
| Robertson et al, 2011a | UK | Women treated for primary breast cancer | No surveillance mammography alone<br>Mammography + clinical examination<br>MRI + clinical exam | CUA | Viehweg et al, 2004<br>Rieber et al, 1997<br>Drew et al, 1998<br>Belli et al, 2002<br>*MRI studies only* | QALYs | Screening, diagnostic evaluation and treatment | In the base-case analysis the regimen with the highest net benefit and, therefore, most likely to be considered cost-effective was mammographic surveillance alone provided yearly |
| HIQA, 2013 | Ireland | Women aged <50 years at elevated risk of breast cancer | MRI<br>Mammography<br>MRI + mammography<br>No surveillance and 'no organised surveillance' | CUA | Kriege et al, 2006b<br>Kuhl et al, 2005<br>Leach, 2005<br>Warner et al, 2004 | QALYs<br>Breast cancer mortality at age 50 years also presented | Direct medical costs | Annual MRI from the ages of 30–49 years is the most cost-effective for women with *BRCA1* and BRCA2 mutations. The addition of mammography does not result in a substantial clinical benefit. Surveillance is not recommended for women with high familial risk before age 40 years. Mammography alone could be offered to women at high familial risk age 40–49 years |
| NICE, 2013 | UK | Women at risk of familial breast cancer and people with a family history of breast cancer | MRI<br>Digital mammography<br>MRI + mammography<br>No screening (comparator) | CUA/ Markov | MRI + mammography evidence (comparator not stated)<br>Lehman et al, 2007<br>Warner 2001<br>Warner et al, 2004<br>Kuhl et al, 2005<br>Leach, 2005 | QALYs | Screening, diagnostic evaluation and treatment | Offer annual MRI surveillance to women:<br>- aged 30–49 years who have not had genetic testing but have a >30% probability of being a *BRCA* carrier<br>- aged 30–49 years with a known *BRCA1* or *BRCA2* mutation<br>- aged 20–49 years who have not had genetic testing but have a >30% probability of being a *TP53* carrier<br>- aged 20–49 y with a known *TP53* mutation |

| Study | Locn | Population | Intervention and comparator | Model approach | Studies included | Outcomes assessed | Costs included | Economic conclusions |
|---|---|---|---|---|---|---|---|---|
| | | | | | Trecate et al, 2006 | | | - aged 30–49 years with a personal history of breast cancer who remain at high risk of breast cancer, including those who have a *BRCA1* or *BRCA2* mutation |
| Medical Advisory Secretariat, 2010 | Canada | Women at average and increased risk of breast cancer | MRI and digital mammography versus mammography | Basic decision analysis | Kriege et al, 2006b<br>Kuhl et al, 2005<br>Leach, 2005<br>Warner et al, 2004 | Costs to health system | Screening costs and cost of GPs to undertake MRI/mammography | Breast MRI + mammography is a cost-effective strategy for high-risk women and the budget impact is estimated at $7m–$27m annually |
| Cerezo Espinosa de los Monteros, 2008 | Spain | Women with a genetic predisposition to breast cancer<br>Women with suspected breast cancer | MRI<br>Mammography<br>MRI + mammography | Unclear | Unclear | Unclear | Unclear | MRI is effective as a screening method in women with a genetic predisposition to breast cancer. The studies retrieved do not form the basis for valid conclusions on whether MRI should be used in addition to mammography |

CUA = cost-utility analysis; MRI = magnetic resonance imaging; QALY = quality-adjusted life year; *BRCA1/2* = breast cancer 1/2 gene; *TP53* = tumour protein p53 gene.

**UK National Institute for Health Research HTA Programme (Robertson et al, 2011a)**

The economic model in the Robertson et al (2011a) report was a CUA designed to identify feasible management strategies for surveillance and follow-up of women after treatment for breast cancer in a UK setting, and to determine the cost-effectiveness of different regimens. The evaluation was concerned with the early detection of IBTR or ipsilateral secondary cancer in the treated breast and the detection of new primary cancers in the contralateral breast.

The model uses a Markov structure to represent the alternative surveillance regimens modelled at varying surveillance intervals. Patients can be in health states of no cancer, treated cancer (low, medium or high risk) and untreated cancer (low, medium or high risk). The absorbing state in the model is death. The cycle length for transitions between health states was 6 months. The primary intervention was routine surveillance mammography. The comparator consisted of any of:

- no surveillance mammography
- differences in frequency of surveillance mammography regimens
- alternative follow-up regimens; for example including, but not limited to, breast-care physician-led clinical examination.

Parameter estimates for the Markov model were determined from a survey of existing data sets, a series of systematic reviews, and focused searches for specific data. In addition, the evaluation included a review of individual patient data from two UK registries: the West Midlands Cancer Intelligence Unit breast cancer database and the Edinburgh breast cancer data set.

The results reported the cost-effectiveness of no surveillance, mammography alone, mammography + clinical examination and MRI + clinical examination. The interval between screenings could be 12, 18, 24 or 36 months. The starting age for screening in the base case was 57 years. A discount rate of 3.5% for costs and benefits was used following guidelines for NICE. In the base-case analysis the regimen with the highest net benefit and, therefore, most likely to be considered cost-effective was mammographic surveillance alone provided yearly. Sensitivity analyses showed that the results of the model were very sensitive to changes in the incidence of recurrent cancer.

**Health Information and Quality Authority (2013), Ireland**

The economic model in the HIQA (2013) report was a CUA that sought to assess the cost-effectiveness of digital mammography, MRI or both at different frequencies and starting ages for women younger than 50 years at an elevated risk of developing breast cancer. Elevated risk included moderate- and high-risk categories as defined by NICE (2013).

The comparators were no surveillance and the existing system of 'no organised surveillance'. The model made the following key assumptions:

- Women with *BRCA1*/2 or other identified mutations received MRI from age 30 years and digital mammography from 40 years.
- Women with *TP53* mutations received annual MRI from age 20 years and digital mammography from 30 to 35 years.
- Women with moderate or high familial risk underwent digital mammography with an annual surveillance rate of 70% and 85% respectively, and a biennial rate of 24% and 11%.

The model has a Markov structure and follows a hypothetical cohort of 1,000 women from age 20 years to life expectancy for women at age 50 years (assumed to be 83 years). Each individual was modelled from age 20 years using consecutive 6-month cycles. Ten states were included: healthy; undetected DCIS; undetected invasive cancer at 6, 12, 18 and 25 months; detected cancer; in treatment; terminal breast cancer; and deceased.

Strategies for surveillance were defined by the imaging method, starting age and frequency. Imaging methods were digital mammography, MRI and both. A discount rate of 4% was applied.

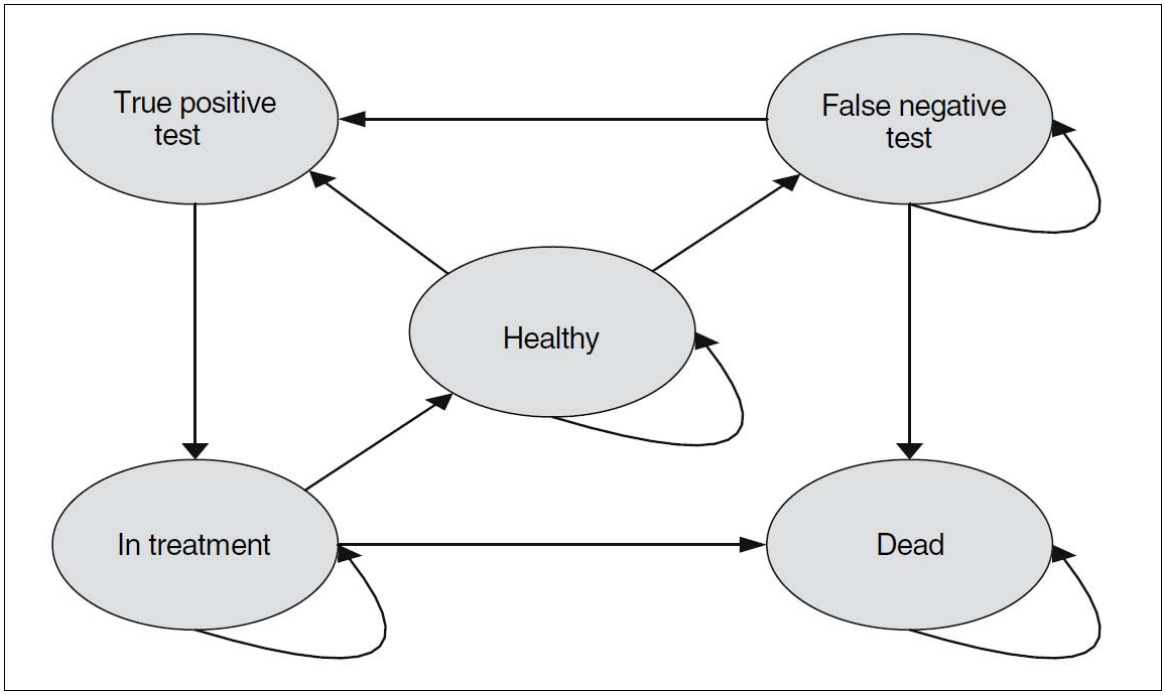
The economic model required a range of input parameters that describe the diagnostic test accuracy of the imaging modalities, the probability of developing breast cancer, the types of treatment given to identified cases of breast cancer, and the associated costs of surveillance, further testing and treatment. Overall, the economic evaluation concluded that annual MRI in women aged 30–49 years is the most cost-effective for women with *BRCA1* and *BRCA2* mutations. The addition of mammography did not result in a substantial clinical benefit. The report recommended that surveillance should not be used in women with high familial risk before age 40 years, and that mammography alone could be offered to women at high familial risk at age 40–49 years.

**National Institute of Clinical and Health Excellence (2013), United Kingdom**

The NICE (2013) guidance (CG164) on familial breast cancer presents a CUA of various surveillance strategies, including annual mammography, annual MRI and annual combined screening. The guideline, issued in June 2013, is an update of the NICE (2006) CG41 on the management of people at risk of familial breast cancer, developed by the National Collaborating Centre for Primary Care and published by Norman et al (2007).

In the original NICE (2006) model, 1000 hypothetical individuals (aged 30–39 or 40–49 years) were introduced into the model and received a screening option for 10 years. The model takes the perspective of the UK NHS and applies discounting at a rate of 3.5% per annum. The primary population of interest was women with a family history of breast cancer or a gene mutation for breast cancer. Four possible surveillance strategies were evaluated: no screening, annual mammography, annual MRI scans, and both annual mammography and MRI scans in parallel. The transition of patients between health states, presented in Figure D.1, was followed over consecutive 1-year cycles, assigning costs and benefits until death (ie, a lifetime time horizon). Death was assumed to occur when the woman reaches the life expectancy specific to her age when she exits the 10-year screening. The model assumed that false-positives are assessed and identified immediately through further MRI and ultrasound investigation, and the individuals are returned to the healthy population for the subsequent cycle. The model also assumes that individuals who have received two false-negative results will have their cancer diagnosed in primary care in the third screening cycle.

**Figure D.1 Structure of economic model by NICE Clinical Guideline 41.**




The model depends on three main assumptions. First, a false-negative result harms prognosis by giving these patients a poorer prognosis for each year that diagnosis is delayed. The model accounts for this by assigning different 5-year survival rates to individuals on the basis of whether their cancer is detected at the first, second or third possible opportunity.

Second, there is no way for patients to transition directly from 'true-positive' to 'dead', because people must pass through the 'in treatment' health state before they progress to death.

Third, the model does not incorporate a non-disease-specific death rate, as it assumes that the death rate would be low in the age groups considered.

The key parameters of the model were:

- the sensitivities and specificities of the different screening methods
- the risk of developing breast cancer in women of different risk groups (including age)
- survival rate in women diagnosed with breast cancer (accounting for women with false diagnoses)
- the risk of developing breast cancer as a result of radiation exposure through mammography
- utility values for women in different health states
- costs.

The 2013 update of NICE CG41 (CG164) is identical to the previous model (CG41; NICE, 2006) and does not include any new clinical data for the familial high-risk and *BRCA1* populations. It does, however, include an additional analysis of the cost-effectiveness of surveillance in people with a personal history of breast cancer and a familial risk. It includes new clinical parameters for the additional population, but also broadens the included age range to 30–69 years. Furthermore, it includes digital mammography instead of film-screen mammography (in the 2006 analysis).

For women with no previous history of breast cancer, the results reported in NICE CG41 suggested that individuals with *BRCA1* mutations should receive both annual mammography and MRI scans, since the ICER for combined testing was close to the £20,000 per QALY threshold used by NICE. Individuals at high risk for breast cancer on the basis of family history were recommended annual mammography, but the cost-effectiveness of MRI screening or a combined approach was uncertain, with ICERs between £20,000 and £30,000 per QALY. This evaluation was not updated in the NICE (2013) guideline on familial breast cancer.

For women with a previous history of breast cancer and a high familial risk, the results of the NICE (2013) CG164 indicate that in younger women (30–39 years), all screening strategies were cost-effective compared with no screening at a cost-effectiveness threshold of £20,000 per QALY gained. MRI alone was expected to be cost-effective compared with mammography, providing the highest net monetary benefit at a cost-effectiveness threshold of £20,000. MRI + mammography was not expected to be cost-effective compared with either test alone. The same conclusions were drawn for women aged 40–49 years with a high familial risk for breast cancer.

### D.3.3 Economic evaluation undertaken for this assessment

On the basis of the review of published economic evaluations above, the structure of the economic model used in this assessment report is based on the Markov model structure used in the NICE (2006, 2013) clinical guidelines for familial breast cancer (CG41 and CG164). A working version of the model used in the development of the NICE (2006) CG41 (National Collaborating Centre for Primary Care, 2006), also reported by Norman et al (2007), was provided to the assessment group with the permission of its developers, the National Collaborating Centre for Primary Care.

While the overall structure of the NICE model was considered suitable for adaptation, some modifications were required to ensure that the results were most applicable to the Australian healthcare setting. The following key changes were made to the design of the model:

- As per the final protocol for the assessment of breast MRI, only two surveillance methodologies were compared here: MRI + mammography and mammography alone.
- The revised model does not account for the risk of developing breast cancer as a result of radiation exposure through mammography, as the adapted model includes mammography in each arm and assumes that the risks would be approximately equal. This may be considered a conservative approach, as it underestimates the true risk of breast cancer and the full benefit of additional sensitivity.
- The revised model includes a background risk of death due to other causes on the basis of Australian life tables.
- The model allows patients to return to routine screening with mammography alone after the age of 50.

Apart from these minor structural changes, updated clinical and cost data were incorporated into the new model for each of the populations of interest. The Final DAP to guide the assessment of breast MRI for the screening of high-risk women outlined a number of parameters that should be considered when the cost-effectiveness of this intervention is evaluated in an Australian healthcare setting (Final DAP 2013; p. 22). Table D.4 outlines the approach used to address each issue in the current application.

**Table D.4 Issues raised in the Final Decision-Analytic Protocol.**

| Issue raised in Final Decision-Analytic Protocol (p. 22–23) | Approach used in economic model |
|---|---|
| Women considered at high risk of breast cancer begin screening at 25–30 years of age | The model assumes that women at high familial risk or with a gene mutation for breast cancer begin screening at the age of 30 years.<br>Populations with prior breast cancer (invasive or DCIS/LCIS) are assumed to commence screening at the age of 44 years to account for the time required to diagnose and treat their initial or primary cancer and the fact that a relatively small proportion of women are diagnosed with breast cancer before the age of 40 years.<br>Patients that have undergone radiotherapy to the chest area are likely to commence screening at 30 years as their increased risk for breast cancer is likely to have been identified at a relatively early age. |
| All women are compliant with screening | The model assumes full compliance in both screening arms. |
| Screening consists of mammography + MRI ± ultrasound | The proposed screening intervention includes MRI in addition to mammography; however, the diagnostic impact of ultrasound screening is not explicitly included as a clinical input. The cost of ultrasound is included in the model for those patients identified as being positive in surveillance screening. |
| Not all women will undergo ultrasound as part of screening | The model assumes zero use of ultrasound in routine screening. However, patients with a positive test undergo biopsy and ultrasound of one breast to confirm their diagnosis. |
| A proportion of women may get only one test ~10%–20%; ie, mammography or MRI | The use of MRI alone as a screening strategy was beyond the scope of the assessment. The inclusion of a proportion of patients receiving mammography alone in the screening arm with MRI + mammography was not considered necessary as this would essentially entail a comparison between mammography and itself. Therefore, the interventions compared were MRI + mammography and mammography alone. |
| Women with cancer who had positive findings on screening are designated true-positives and undergo further diagnostic evaluation (including ultrasound) followed by breast cancer treatment | Positive tests are directed to treatment according to Australian algorithms (Verry et al, 2012). Outcomes of treatment (ie, prognosis) are dependent on timing of detection, with a 1-year delay in cancer detection leading to a decrement in overall survival. |
| Those who do not have cancer and have negative examination results were classified as true-negatives and underwent no further diagnostic evaluation | True-negative patients do not receive additional tests, and are assumed to return for their next round of screening after 12 months. |

| Issue raised in Final Decision-Analytic Protocol (p. 22–23) | Approach used in economic model |
|---|---|
| Women who did not have cancer but had positive results (false-positive) underwent additional evaluation to rule out diagnosis | As per advice from the Health Expert Standing Panel, false-positives received an additional specialist consultation, ultrasound, and biopsy. |
| Women with false-negatives were diagnosed on average 10 months after initial screening and subsequently underwent breast cancer treatment | The model structure allows for only 12-month cycles and consequently assumes a delay in diagnosis of 1 year (in false-negative patients). |
| Women who have an indeterminate result will be divided between different pathways for short-term follow-up or further investigations (biopsy) dependent on the type of lesion | For simplification, indeterminate results are considered false-positives and are assigned the appropriate follow-up investigations.<br>Given the lower specificity of MRI this assumption may be biased against the proposed screening algorithm, leading to more costs than would be seen in practice. |
| Specifically when looking at breast MRI as an addition to an organised surveillance program:<br>• all women are screened with mammography<br>• discordant results are of interest | Discordant results are not specifically modelled. Rather, the model uses incremental analysis to isolate the effect of discordant results. That is to say, the impact of discordant results will be captured by the comparison between MRI in addition to mammography and mammography alone in terms of diagnostic accuracy. |
| Issues around the timing of the first scan for the proposed new populations (ie, diagnosis in comparison to after treatment) may also be need to be considered or addressed in the model, as the risk rates for the subsequent development of an invasive cancer relate to techniques used for the original diagnosis | The model assumes that women without prior breast cancer commence screening at the age of 30 years, while women with prior DCIS/LCIS or invasive breast cancer receive their first scan at the age of 44 years on the basis of AIHW data on the average age of diagnosis in patients diagnosed with cancer at <50 years of age. The model also incorporates age-specific cancer risks to ensure that the benefits of screening different age-groups are appropriately captured.<br>In the case of patients with prior history of cancer, the cancer recurrence risks are specific to the time since original diagnosis (AIHW data). |

AIHW = Australian Institute of Health and Welfare; DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging.

In conclusion, the Markov cost-utility model used in the economic evaluation for NICE CG41 (Norman et al, 2007) was adapted to suit the proposed MBS listings and the Australian healthcare setting. The key characteristics of the economic evaluation are summarised in Table D.5. A copy of the model built in Microsoft Excel is provided with this assessment report.

**Table D.5 Summary of the economic model.**

| Model feature | Description |
|---|---|
| Study question | What are the effectiveness and cost-effectiveness of the addition of MRI to an organised surveillance program of mammography in asymptomatic women <50 years of age with a high risk of developing breast cancer? |
| Type of economic evaluation | Cost utility analysis |
| Population | - Women in whom genetic testing has identified the presence of a high-risk breast cancer gene mutation (eg, *BRCA1*, *BRCA2* and *TP53*)<br>- Asymptomatic women, aged <50 years, at high risk of breast cancer due to familial risk factors<br>- Women with a prior history of treatment for invasive breast cancer<br>- Women with a prior history of treatment for DCIS or LCIS<br>- Women with a history of therapeutic radiation treatment to the chest area undertaken between the ages of 10 and 35 years |
| Intervention | Annual screening with combined MRI and mammography |
| Comparator | Annual screening with mammography alone |
| Outcomes and clinical parameters | - Diagnostic accuracy<br>- Breast cancer risk<br>- Health-related quality of life<br>- Survival |
| Time horizon | Lifetime (to capture the true extent of life years lost as a result of delayed breast cancer detection) |
| Discount rate | A discount rate of 5% was applied to all costs and effects incurred after the first year of initial treatment |
| Structure | A Markov model was developed, allowing patients transition through health states over the time horizon. Individual cycle lengths were 12 months, with a half-cycle correction to account for the continuous nature of transition probabilities. The model includes health states of true-positive test, false-negative test, healthy, in treatment and dead |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; *BRCA1/2* = breast cancer 1/2 gene; *TP53* = tumour protein p53 gene.

## D.4 Variables in the economic evaluation

The variables in the modelled economic evaluation can be broadly classified into:

- population variables and demographics
- natural history of breast cancer
- diagnostic accuracy
- cost variables
- utility values
- other model parameters
- Australian general population variables
- summary of model inputs and assumptions.

### D.4.1 Population variables and demographics

In Australia, the comparator for MRI screening in addition to mammography is surveillance with annual mammography alone. For each of the populations included in this assessment, it was necessary to estimate the average age at baseline; that is, the age at which screening would commence in each arm of the model. This parameter varies depending on whether patients are classified as at high risk on the basis of familial risk factors or because they have previously been treated for DCIS, LCIS or invasive breast cancer.

For patients with a known gene mutation or a family history that suggests a high predisposition to breast cancer, it is assumed that screening with either of the modelled surveillance strategies starts at the age of 30 years. This assumption is based on the fact that most diagnostic accuracy studies for MRI and mammography are in populations of at least this age. Furthermore, the benefits of any form of screening in very young women (ie, <30 years) are uncertain given these women's relatively low annual risk of breast cancer. Thus, NICE CG164 recommends no screening in women aged 20 to 29 years, with the exception of those with a high probability (>30%) of carrying a *TP53* mutation.

For women with prior DCIS, LCIS or invasive breast cancer, it is assumed that screening with either surveillance strategy would commence later, at the age of 44 years. This age was calculated using data on rates of breast cancer diagnosis in Australia for different age brackets (AIHW, 2012a). These data show that the average age of diagnosis for women under the age of 50 is 43 years, and it assumed that screening will commence 1 year after the primary diagnosis.

Women with a high risk of breast cancer due to prior chest radiotherapy have usually received the radiotherapy during treatment for paediatric or young adult cancer. Breast cancer risk is greatest among women treated with high-dose mantle irradiation for Hodgkin's lymphoma, but it is also elevated among women who received moderate-dose chest irradiation (for example, mediastinal or lung) for other paediatric and young adult cancers such as non-Hodgkin's lymphoma, Wilms' tumour, leukaemia, bone cancer, neuroblastoma and soft-tissue sarcoma. When diagnosed with breast cancer, women with prior Hodgkin's lymphoma are more likely to be younger than the average breast cancer patient (Cutuli et al, 2012). Therefore, it is also assumed that in this patient group, screening would begin also begin relatively early, at an average age of 30 years.

As specified in the Final DAP and MBS item 63464, it is assumed that at the age of 50 years, MRI surveillance would cease and women would thereafter be screened with annual mammography alone.

Sensitivity analysis considers different age ranges for the beginning and end of additional MRI screening in each of the populations being considered, as shown in Table D.6.

**Table D.6 Ages at which additional MRI screening begins and ends in the economic model.**

| Parameter | High-risk based on breast cancer gene mutation | Familial high-risk | Prior history of invasive breast cancer | Prior history of treatment for DCIS or LCIS | Women with chest radiotherapy between 10 and 35 years |
|---|---|---|---|---|---|
| Age at baseline (years) | 30 | 30 | 44 | 44 | 30 |
| Age at which MRI screening ends (years) | 50 | 50 | 50 | 50 | 50 |
| Duration of screening (years) | 20 | 20 | 6 | 6 | 20 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging.

### D.4.2 Natural history of breast cancer

The natural history of breast cancer is described in the economic model in terms of:

- the risk of disease over time
- prognosis following detection of the disease based on the stage at which it is detected.

**The annual risk of disease used in the economic model**

The breast cancer risks used in this economic model are based largely on the population-specific risks described in CG164 (NICE, 2013). In each population, the risk of cancer accounts for the woman's genetic background (ie, with or without a known gene mutation) and age at screening, both of which are known risk factors. Table D.7 presents the annual risks of breast cancer for each of the included populations at different ages. For women without prior breast cancer (ie, those with a confirmed gene mutation, a high familial risk or prior chest irradiation), the 5-year risks for an average 40-year-old woman are compared. For those with prior DCIS, LCIS or invasive breast cancer, the risks for a woman of average screening age (44 years) are compared. The age-specific cumulative incidence of breast cancer in each of the assessed populations is presented in Figure D.2. The figure provides an estimate of the lifetime risk of breast cancer in each population calculated from the annual risks used in the model. This analysis was performed to ensure that the estimated lifetime risks are broadly consistent with other estimates for lifetime risk reported in the literature.

**Table D.7 Annual risk of breast cancer by age.**

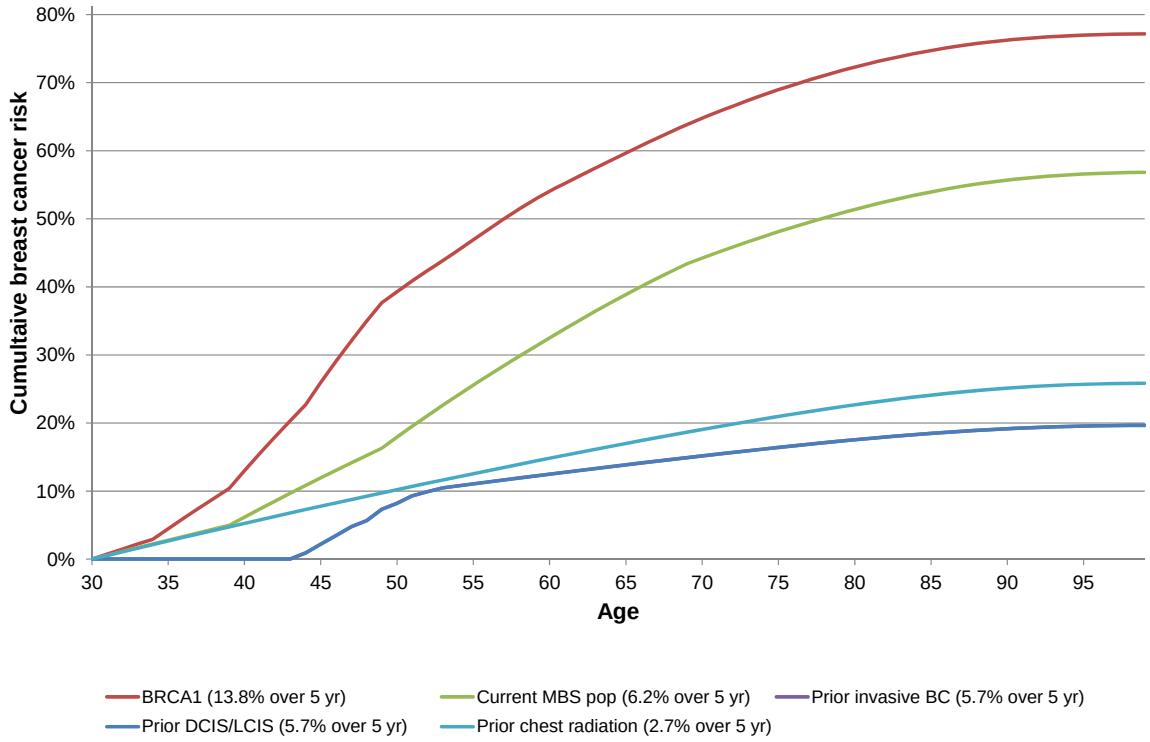
| Age (yrs) | High-risk based on breast cancer gene mutation (Antoniou et al, 2003) | Familial high-risk (Claus et al, 1994) | Prior history of invasive breast cancer (AIHW & NBOCC, 2010) | Prior history of treatment for DCIS or LCIS (AIHW & NBOCC, 2010) | Women with chest radiotherapy between 10 and 35 years (Henderson et al, 2010) |
|---|---|---|---|---|---|
| 30 | 0.74% | 0.56% | | | 0.54% |
| 35 | 1.59% | 0.56% | | | 0.54% |
| 40 | 2.92% | 1.27% | | | 0.54% |
| 45 | 4.28% | 1.27% | 1.31% | 1.31% | 0.54% |
| 50 | 2.65% | 1.98% | 0.97% | 0.97% | 0.54% |
| 55 | 3.01% | 1.98% | 0.33% | 0.33% | 0.54% |
| 60 | 2.70% | 2.08% | 0.33% | 0.33% | 0.54% |
| 65 | 2.96% | 2.08% | 0.33% | 0.33% | 0.54% |
| 70 | 2.96% | 1.65% | 0.33% | 0.33% | 0.54% |
| 75 | 2.96% | 1.65% | 0.33% | 0.33% | 0.54% |
| 80+ | 2.96% | 1.65% | 0.33% | 0.33% | 0.54% |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

***Women with a confirmed gene mutation***

Women with a confirmed gene mutation (eg, *BRCA1* or *BRCA2*) have the highest breast cancer incidence, followed by women with a high risk based on family history. As discussed previously, women at high risk for familial breast cancer include a relatively large proportion of women who carry gene mutations for breast cancer. Therefore, the elevated risk in the broader high-risk group is likely driven by the incidence of breast cancer in the subgroup of patients with a confirmed or unconfirmed gene mutation. Information on cancer risk in the mutation carrier population was taken from a case series analysis by Antoniou et al (2003) in women with *BRCA1* or *BRCA2* mutations; the study provides age-specific incidence rates for women aged 20 to 69 years with breast cancer.

**Figure D.2 Cumulative breast cancer incidence by age estimated in the economic model.**




Note: The cumulative incidence for prior invasive breast cancer and DCIS/LCIS are overlaid because these groups have identical risk.

The lifetime risk of breast cancer in women with a gene mutation calculated in the model was 77%. This compares well to estimates of cancer risk reported in the literature: Chen and Parmigiani (2007) suggested that 55% to 65% of women with a harmful BRCA1 mutation will develop breast cancer by the age of 70 years. Figure D.2 shows that the model is at the higher end of this range, with approximately 65% of the modelled population developing breast cancer by that age.

### *Women with a high risk of breast cancer based on family history*

For women with a high risk of breast cancer based on family history, the NICE (2013) model assumed that the 10-year risk of breast cancer for a 40-year-old was 12%. This corresponds to a 5-year risk of 6.2%. In the absence of other reliable data, this was the 5-year risk used in the economic model presented here. Within this group, age-specific rates of breast cancer were calculated using data from a study which compared the risk of breast cancer in a general population of women of various ages (Claus et al, 1994).

The annual risk of breast cancer by individual year of age used in the economic model was calculated relative to the 5-year risk of 6.2% in 40-year-olds. For example, 5-year risks of breast cancer reported by Claus et al (1994) were 1.2% for 30-year-olds and 2.7% for 40-year-olds. Thus, the 5-year risk for 30-year-olds in the economic model is estimated to be 2.8% ($2.8\% \approx 6.2\% \times 1.2/2.7$)[1]. This age adjustment is also the approach used in the original NICE (2013) model.

For women with a high familial risk for breast cancer, the calculated lifetime risk of 57% is slightly higher than lifetime risk according to the NBCC risk classification system (25%–50%). This

[1] The age adjustments made in the model convert the probabilities into hazards (odds), apply the age-specific odds ratio and convert back to probabilities. For illustration a relative risk approach is described above.

overestimation is likely to favour the MRI + mammography arm of the model because it overestimates the number of women likely to benefit from the improved sensitivity of MRI.

***Women with a prior history of DCIS, LCIS or invasive breast cancer***

Breast cancer incidence in this population includes new cancers in either breast or recurrent secondary breast cancers. There are relatively few published reports on the rates of breast cancer in women with prior breast cancer, as this information is not routinely collected by most registries. As discussed in Section A.1.2, published estimates vary widely depending on the population's disease characteristics, treatment, follow-up period and type of cancer being measured (eg, recurrent, ipsilateral or metastatic).

In the NICE (2013) model, the baseline values for the risks of developing breast cancer in women with prior breast cancer were determined by converting the 5-year risk reported by Malone et al (2010) to annual probabilities. This study consisted of women initially diagnosed with a primary invasive cancer, and risks were reported separately for *BRCA1* carriers, *BRCA2* carriers and non-carriers. This study reported the risk of only contralateral breast cancer. These data therefore underestimate the true risk of breast cancer in this group of women, which should include recurrent primary cancers and new breast cancers in both breasts. Thus, this assessment report takes a different approach from that used in the NICE (2013) model.

For women with a prior diagnosis of breast cancer, the model presented here relies primarily on data from an Australian Institute of Health and Welfare (AIHW) report on the risk of invasive breast cancer in women diagnosed with DCIS in Australia between 1995 and 2005 (AIHW & NBOCC, 2010). The report was considered highly applicable to this evaluation because the data are Australian, ipsilateral and contralateral breast cancers are included, and the risk of breast cancer is provided for different age groups by year from diagnosis. In the absence of similarly comprehensive data in women with prior invasive breast cancer, the model applies the same risks of cancer for women with prior DCIS or LCIS and prior invasive breast cancer based on the AIHW dataset. Sensitivity analysis examines different rates of breast cancer for patients with a prior diagnosis of breast cancer to reflect the fact that different cancers will have different treatments, which may affect the risk of future cancer.

The AIHW report estimates that in Australian women with a DCIS diagnosis made between 1995 and 2005, the probability of being diagnosed with a subsequent invasive breast cancer in all ages is 5.3% within 5 years and 10.9% within 10 years. Since the average age of screening in these women is 44 years, the age group of greatest relevance to this assessment report is women aged 40–49 years, in whom the risk of subsequent breast cancer is 5.7% within 5 years and 10.6% within 10 years (AIHW & NBOCC, 2010). For the base-case economic evaluation, the probability of breast cancer in the first 10 years of screening was based on the 5- and 10-year risks of breast cancer in that group. These risks were converted into annual probabilities. Beyond 10 years, women were given an ongoing low background risk for new breast cancer assumed to be half the annual risk observed in years 9 and 10 following original diagnosis. Women who have the highest probability of invasive breast cancer are aged <40 years at the time of DCIS diagnosis: 8.4% within 5 years and 15.5% within 10 years. The cost-effectiveness of commencing screening in the younger age group (patients originally diagnosed at <40 years) is included as a sensitivity analysis.

For populations with prior DCIS, LCIS or invasive breast cancer, several factors may contribute to uncertainty in the estimates of risk. Firstly, the same risks are used for women with prior invasive and

noninvasive breast cancers, as suitable data for the former population were not available. For both populations, information on the risk of breast cancer beyond 10 years was not available, and the overall lifetime risk was based on assumptions. In addition, as treatment for primary breast cancer improves over time, the probability of recurrence will decrease commensurately. Finally, there may be some overestimation of risk, because estimates of recurrence are based on a population that includes women with breast cancer mutations. Women at high risk for breast cancer due to family history or genetic predisposition are estimated to make up 5% to 10% of women with breast cancers, and this proportion is likely to be higher among younger cohorts (NBOCC, 2009). In this assessment report, the analysis of patients with prior breast cancer should theoretically exclude patients with a gene mutation, as these patients are already eligible for MRI screening under interim MBS item 63454. The lifetime risk of recurrent breast cancer in the model is approximately 20% in this population and is the lowest of all the populations examined here (Figure D.2).

***Women with prior chest radiotherapy***

Women that have had prior chest radiotherapy were not included in CG641 (NICE, 2013), and risk estimates for this population were therefore derived from a systematic review of surveillance in women treated with chest irradiation (Henderson et al, 2010). The review reported that the cumulative incidence of breast cancer by age 40 to 45 years ranged from 13% to 20% and by 25 to 30 years of follow-up ranged from 12% to 26%. However, in a number of the included studies, only some patients underwent chest radiotherapy. Including just those studies in which ≥95% of patients were exposed to chest irradiation, the pooled annual incidence of breast cancer is 0.54% (Hancock et al, 1993; Wolden et al, 1998; Alm El-Din et al, 2009; Ng et al, 2002). This is equivalent to a lifetime risk of 25.85%. Since the relationship between age and the incidence of breast cancer is unclear, the model assumes that the annual risk of breast cancer in this population remains constant over time.

**Breast cancer prognosis and survival**

The duration of survival after breast cancer is used to model how much clinical benefit a patient will gain as a result of being diagnosed and treated. Thus, life expectancy for patients diagnosed with breast cancer was sourced from AIHW (2012b), which reported that among women aged 40 to 49 years, 5-year relative survival from breast cancer is 91.9%. For patients that receive a false-negative diagnosis, it is assumed that the tumour will be identified at the following screening opportunity (ie, the next year). The delay in diagnosis is associated with a reduction in survival as a result of disease progression and tumour growth in the intervening period. Australian data (AIHW, 2012a) show that survival is considerably better for women diagnosed with smaller tumours (Table D.8).

**Table D.8 Relationship between tumour size at diagnosis and 5-year relative survival (AIHW, 2012a).**

| Size of cancer | 5-year relative survival | 95% CI |
|---|---|---|
| 1–10 mm | 98.2 | 96.9–99.4 |
| 11–15 mm | 94.7 | 93.2–96.1 |
| 16–19 mm | 93.0 | 90.6–95.1 |
| 20–29 mm | 87.9 | 86.0–89.6 |
| 30+ mm | 73.1 | 70.6–75.5 |
| Unknown | 49.1 | 45.7–52.5 |

In Australia, in the 40 to 49 year age group, the majority of tumours are between 0 and 30 mm at diagnosis (AIHW, 2012a). Similarly, in the MARIBS study of MRI in patients at high risk of breast cancer, of the 29 invasive tumours identified, eleven were <10 mm across in greatest dimension, four were 10–14 mm, five were 15–19 mm, and nine were >20 mm. The average invasive tumour size was 15 mm (Leach, 2005). In a study of breast cancer tumour growth estimated through mammography screening data, tumour growth varied considerably between patients, with 5% of tumours taking <1.2 months to grow from 10 mm to 20 mm, and another 5% taking >6.3 years (Weedon-Fekjær et al, 2008). The mean time a tumour needed to grow from 10 mm to 20 mm is estimated as 1.7 years, and the interval increases with age. For women aged 50 to 59 years, a 15-mm tumour in the 50th percentile (in relation to growth rate) was estimated to double in volume in 73 days. On the assumption that a tumour grows from 15 mm to >30 mm in the year after a false-negative test, the 5-year relative survival would decrease to 73.1%. On the basis of an age-specific 5-year relative survival estimate of 91.9% for women aged 40 to 49 years, there is likely to be an average 18.8% reduction in survival over 5 years in women who receive a false-negative diagnosis.

There is a considerable degree of uncertainty about the rates of growth of breast cancers and therefore the impact of delayed diagnosis on survival. To address this uncertainty, sensitivity analyses were performed in which the decrement in 5-year survival as a result of delayed detection was varied. These survival estimates were applied to all of the populations except patients with a confirmed gene mutation, who have faster-growing and more aggressive tumours. In the NICE model (and here), patients with a *BRCA1* mutation were assumed to have a survival rate of 80%, with a 15% decrement for each year following a false-negative result up to a maximum of two false-negative results (ie, a total decrement in overall survival of 30%). Given that the sensitivity of mammography is approximately 33%, two-thirds of the population with delayed detection will experience a decrement in survival of 30% and one-third a decrement of 15%. This corresponds to an average decrement in survival of approximately 25% (higher than the 18.8% used for the other populations). This assessment uses the same assumption for the population with a confirmed gene mutation for breast cancer (ie, a survival decrement of 15% over 2 years is applied to the baseline survival of 80%).

Recent improvements in breast cancer treatment have produced substantial improvements in survival, and this trend is likely to continue. As a result, the clinical consequences of delayed diagnosis are likely to become less serious. In addition, AIHW data suggest that among Australian women who had been diagnosed with invasive breast cancer, those women with a prior diagnosis of DCIS generally had smaller invasive tumours and the cancer was less likely to have spread to regional lymph nodes. Therefore, it is possible that women in the group with prior DCIS or LCIS have better 5-year survival rates than women with prior invasive breast cancer.

### D.4.3 Diagnostic accuracy

A detailed assessment of the quality of included diagnostic accuracy studies of MRI + mammography is presented in Section B.4. For each of the populations of interest, a number of studies were identified. The economic model uses data from those studies considered to be most applicable to the requested MBS indication (Table D.9).

For patients with a breast cancer gene mutation, evidence for diagnostic accuracy was sourced from a prospective, non-randomised, single-centre cohort study comparing the sensitivity and specificity of MRI, ultrasound, mammography and CBE in women aged between 26 and 65 years (median 44

years) with a confirmed *BRCA1* or *BRCA2* mutation (Warner et al, 2008). This was the only identified study in which all patients had a confirmed mutation for breast cancer. False-negatives were calculated through the monitoring of interval cancers over the 3-year follow-up period and through biopsy-confirmed cancers detected by other methods. Test results were scored using the BI-RADS classification, with a positive result being a BI-RADS score of 4 or 5.

For the broader population of women with a high risk for breast cancer based on family history, the model uses the results of a meta-analysis presented in the HTA by HIQA (2013). The comparison of mammography and MRI + mammography is based on three studies (Leach, 2005; Kuhl et al, 2005; Kriege et al, 2006a), all of which included a majority of patients with a high lifetime risk of breast cancer based on family history. A key limitation of this analysis is the lack of data on the sensitivity and specificity of digital mammography in younger women at elevated risk, since all studies meeting the inclusion criteria involved film mammography. It should also be noted that the studies used different definitions of a positive result, with some test results scored using a BI-RADS threshold of 0, 3, 4 or 5 (Kriege et al, 2006a; Leach, 2005) and others using a threshold of 4 or 5 (Kuhl et al, 2005). A sensitivity analysis presented in HIQA (2013) found only modest changes when the analysis was restricted to the two studies that used BI-RADS scores of 0, 3, 4 and 5 to define a positive test result.

For women with a prior history of invasive breast cancer, diagnostic accuracy data were drawn from a surveillance study of women at high risk, who included a subgroup of women with a personal history of breast cancer (Berg et al, 2012). Diagnostic accuracy was reported for the subgroup; however, details of their treatment for breast cancer and time since diagnosis were not provided. Because the analysis was based on a relatively small subgroup of the full study population, the confidence intervals around the estimates of sensitivity and specificity were relatively wide. The other potentially relevant study in this population (Viehweg et al, 2004) reported only on the detection of contralateral breast cancers following breast-conserving surgery, and the comparator with MRI was conventional imaging, which included ultrasound in 93 of 145 cases (64%).

One small diagnostic accuracy study was identified in patients with a history of treatment for DCIS or LCIS (Sung et al, 2011b). This retrospective analysis included 22 women (840 MRI scans) with a history of LCIS diagnosis. The study did not evaluate MRI + mammography; therefore, the results presented here pertain to a comparison between MRI alone and mammography alone. Overall, this was judged to be a poor-quality study with a high risk of bias.

Of the studies in women with a history of chest irradiation between the ages of 10 and 35 years, only one study addressed the review question, which was the addition of breast MRI to mammography (Ng et al, 2013). This study was of higher quality and more applicable than the other studies and was the largest study included. Across all populations, this was the only study that included digital mammography as opposed to film screen mammography.

**Table D.9 Diagnostic accuracy of mammography and MRI + mammography.**

| Population | Mammography | | Mammography + MRI | | Source |
|---|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity | |
| High-risk based on breast cancer gene mutation[a] | 0.36 (0.17–0.59) | 1.00 (0.99, 1.00) | 0.86 (0.64, 0.97) | 0.95 (0.94, 0.96)[b] | Warner 2008 |
| Familial high-risk | 0.38 (0.26, 0.51) | 0.97 (0.87, 0.98) | 0.88 (0.78, 0.93) | 0.88 (0.73, 0.93) | HIQA, 2013 |
| Prior history of invasive breast cancer | 0.50 (0.07, 0.93) | 0.95 (0.92, 0.97) | 1.00 (0.40, 1.00) | 0.79 (0.73, 0.83) | Berg et al, 2012 |
| Prior history of treatment for DCIS or LCIS | 0.36 (0.13, 0.65) | 0.9 (0.85, 0.94) | 0.71 (0.42, 0.92) | 0.76 (0.70, 0.82) | Sung et al, 2011 |
| Women with chest radiotherapy between 10 and 35 years | 0.68 (0.43, 0.87) | 0.92 (0.89, 0.95) | 0.95 (0.74, 1.00) | 0.86 (0.82, 0.90) | Ng et al, 2013 |

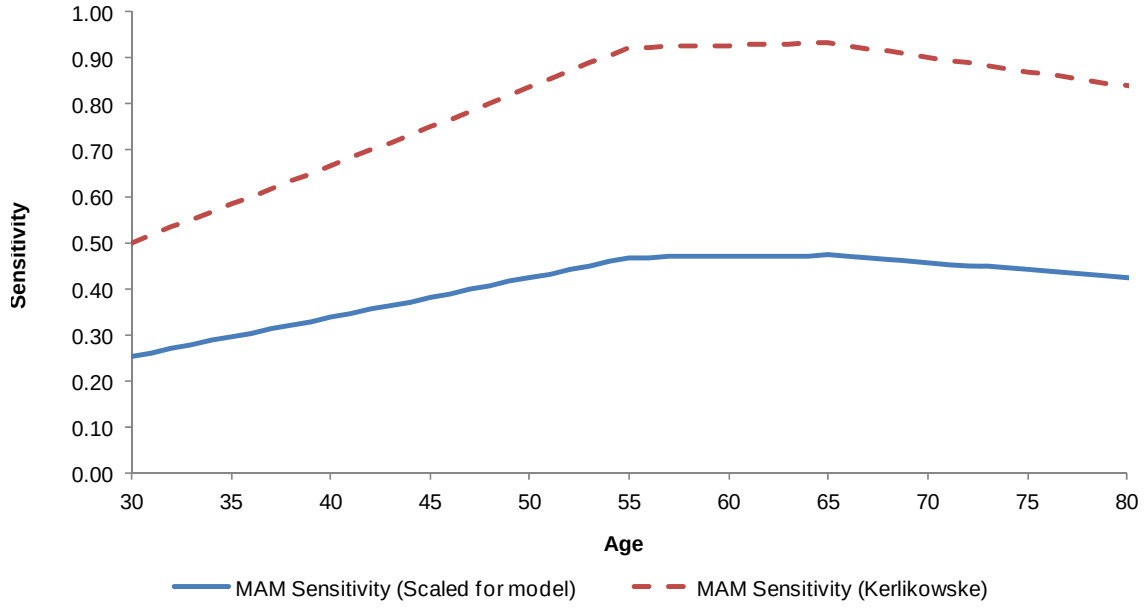
[a] *BRCA1*/*BRCA2* patients only BI-RADS 4 and 5.

[b] Confidence intervals were not reported; therefore, assume the same width (0.01 from the mean) as for mammography alone.

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging.

For mammography alone, age-specific sensitivity estimates were adjusted to account for the fact that mammography is associated with lower sensitivity in younger women owing to thicker breast tissue. This adjustment was done using the same approach as that described in the NICE (2013) economic evaluation, whereby relative sensitivity figures were drawn from the literature (Kerlikowske et al, 1996) and applied to the population-specific diagnostic accuracy data. As shown in Figure D.3, the age-adjusted sensitivity of mammography used in the model follows the same pattern as the sensitivity distribution reported by Kerlikowske et al (1996), albeit relative to the sensitivity data for women at high risk of breast cancer (presented in Section B).

**Figure D.3 Sensitivity of mammography by age.**




Note: The sensitivity data in this figure are for the familial high-risk population. The same age adjustment applies to the other populations, although the absolute sensitivity levels will differ.

### D.4.4 Cost variables

**Cost of screening**

The costs of screening consist of MRI + mammography for the intervention arm and mammography alone for the control arm. These costs were based on the current MBS item fees for MRI (item 63464) and mammography (item 59300), which are $690.00 and $89.50, respectively (Table D.10). True-negative individuals continue to accrue these costs annually.

**Table D.10 Cost of MRI and mammography.**

| Cost item | Reference | Unit cost |
|---|---|---|
| MRI scan | MBS item 63464 | $690.00 |
| Mammography | MBS item 59300 | $89.50 |
| Cost of MRI + mammography | MBS item 63464 and MBS item 59300 | $779.50 |

MRI = magnetic resonance imaging.

**Cost of a true-positive diagnosis**

In patients that receive a true-positive diagnosis of breast cancer, the cost of the first year of cancer treatment consists of a specialist consultation, biopsy, ultrasound, follow-up MRI, wide local excision or mastectomy (ARDRG J06A), chemotherapy and 1 year of tamoxifen therapy (Table D.11).

**Table D.11 Cost of the first year of cancer treatment in patients with a true-positive diagnosis.**

| Cost item | Unit cost | Reference | Units | Total cost |
|---|---|---|---|---|
| Specialist consultation—initial | $85.55 | MBS item 104 | 1 | $85.55 |
| MRI scan | $690.00 | MBS item 63467 | 1 | $690.00 |
| Biopsy | $137.90 | MBS item 31548 | 1 | $137.90 |
| Ultrasound | $98.25 | MBS item 55070 | 1 | $98.25 |
| Wide local excision or mastectomy | $7,295.00 | ARDRG v6 Public. J06A (MAJOR PR MALIG BREAST CONDTNS). http://www.health.gov.au/internet/main/publishing.nsf/Content/Round_14-cost-reports | 1 | $7,958.00 |
| Tamoxifen (1 year; 20 mg daily) | $42.40 (for 60 days) | PBS 2110C | 365 ÷ 60 = 6.08 | $257.93 |
| Adjuvant chemo (course) | $16,043.72 | Based on Verry et al (2012) | See Table D.12 | $16,043.72 |
| Total costs per first year of cancer | | | | $24,510.10 |

MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging; PBS = Pharmaceutical Benefits Scheme.

The cost of adjuvant chemotherapy was based on an Australian study (Verry et al, 2012). Patients are assumed to receive six intravenous administrations per treatment course (1 per cycle for 6 cycles) (Table D.12).

**Table D.12 Costs of adjuvant chemotherapy for first year of treatment (Verry et al, 2012).**

| Cost item | Unit cost | Reference | Units | Total cost |
|---|---|---|---|---|
| Initial consultation | $85.55 | MBS 104 | 1 | $85.55 |
| Follow-up consultation | $43.00 | MBS 105 | 1 | $43.00 |
| AC (doxorubicin [adriamycin]/ cyclophosphamide) chemo | $400.00 | Cancer Institute | 6 | $2,400.00 |
| Drug administration | $97.95 | MBS 13918 | 6 | $587.70 |
| G-CSF (IV, 6 mg) | $1971.52 | PBS 6363X | 5 (1 × 5) [a] | $9857.60 |
| G-CSF admin | $65.05 | MBS 13918 | 5 (1 × 5) | $325.25 |
| Metoclopramide (IV, 10 mg) | $1.31 | PBS 1206L | 6 (1 × 6) | $7.85 |
| Metoclopramide (PO, 10 mg) | $0.33 | PBS 1207M | 168 (28 × 6) | $55.78 |
| Dexamethasone (IV, 4 mg) | $3.26 | PBS 2509C | 6 (1 × 6) | $19.58 |
| Dexamethasone (PO, 0.5 mg) | $0.30 | PBS 1292B | 18 (3 × 6) | $5.36 |
| Ondansetron (IV, 4 mg) | $8.91 | PBS 1596B | 6 (1 × 6) | $53.46 |
| Ondansetron (PO, 4 mg) | $5.45 | PBS 1594X | 18 (3 × 6) | $98.08 |
| Aprepitant (PO, 125 mg) | $138.99 | PBS 8808N | 18 (3 × 6) | $2,501.82 |
| Total cost | | | | $16,043.72 |

[a]. G-CSF IV on day 2 after each cycle from cycle 2. G-CSF = Granulocyte-colony Stimulating Factor (Pegfilgrastim); IV = intravenous; PO = per oral; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.

Following the first year of treatment, it is assumed that in patients without disease recurrence, the annual costs of treatment (for a maximum of 5 years after diagnosis) are $175.50, consisting of 2 specialist consultations and one mammogram. After 5 years, these patients return to the model as 'true-negatives' with the same baseline risk of cancer as other patients in the model and the same annual surveillance routine.

A proportion of true-positive patients will not be successfully treated and will go on to receive treatment for distant metastases and other complications. Verry et al (2012) report an annual recurrence to distant metastases of 0.69% and an annual cost of distant metastases of $24,340.11. These costs are projected over a 5-year period to estimate an expected annual cost of cancer treatment after the first year of true-positive diagnosis of $341.45 ($341.45 ≈ $24,340.11 per year × 2.5 years of treatment on average over 5 years × 0.69% of patients per year; the exact calculations also allow for discounting and are provided in the Excel spreadsheet attachment).

**Cost of a false-negative diagnosis**

Patients with a false-negative diagnosis incur the same costs as patients who receive a true-negative diagnosis (ie, screening costs only). However, when the cancer is identified, these patients incur the same costs as for a true-positive diagnosis (Table D.11).

**Cost of a false-positive diagnosis**

Patients with a false-positive diagnosis are assumed to receive a follow-up biopsy (MBS item 31548), follow-up ultrasound (MBS item 55070) and specialist consultation (MBS item 104). The total cost of follow-up in these patients is therefore $321.70 (Table D.13). Note that the assumption that all false-

positives proceed to biopsy may lead to an overestimation of biopsy costs. Whereas true-positive patients receive a follow-up MRI as part of their first-year treatment costs, false-positive diagnoses are assumed to have no additional MRI screening owing to the lack of incremental clinical benefit associated with performing the same test twice.

**Table D.13 Cost of follow-up in false-positive patients.**

| Cost item | Unit cost | Reference |
|---|---|---|
| Biopsy | $137.90 | MBS item 31548 |
| Ultrasound | $98.25 | MBS item 55070 |
| Specialist consultation—initial | $85.55 | MBS item 104 |
| Total cost | $321.70 | MBS items 31548, 55070 and 104 |

### D.4.5 Utility values

Table D.14 presents the relative utility values applied to patients in different health states in the model. The utility values for patients undergoing treatment for breast cancer were derived from the same source as those used in the NICE economic model (Peasgood et al, 2010), and were applied for 1 year only. As in the NICE model, the base case here does not apply any utility decrement to patients who receive a false-positive diagnosis. While false-positives can lead to stress in the time between screening and follow-up biopsy, this time is likely to be short, as it is assumed that false-positives are identified during follow-up imaging and biopsy evaluations. It is important to note that including a disutility for any anxiety or inconvenience associated with a false-positive finding implicitly assumes that there is a finite (presumably high, but still finite) number of cancer deaths the community is willing to allow in order to avoid these inconveniences. For simplicity, the base-case model assumes that they cannot be measured against the overall objective of the screening program—to reduce cancer deaths—and are therefore ignored. The impact of including a 1-month disutility for women with a false-positive diagnosis is explored in sensitivity analyses (section D.6 Sensitivity analyses).

Unlike the NICE model, this model does not apply a utility decrement to women who received a false-negative diagnosis. These women do not know they have a false-negative diagnosis and are thus indistinguishable from the general population, and their utility value in the model reflects this until the tumour is detected (and the patient becomes a ‘true-positive’).

The relative utility values were applied to age-specific utility values representing Australian population norms, as reported by Hawthorne and Osborne (2005). These results were based on data from the 1998 South Australian Health Omnibus Survey, using the Assessment of Quality of Life instrument.

**Table D.14 Utility values for different health states in the model and Australian Assessment of Quality of Life population norms.**

| Health state | Relative utility value | Source |
|---|---|---|
| *Relative utilities* | | |
| In treatment (true-positive) | 0.68 | NICE model; Peasgood et al, 2010 |
| False-positives | 1.00 | Assumption |
| False-negatives | 1.00 | Assumption |
| *Australian AQoL population norms* | | |
| 30–39 years | 0.87 | Hawthorne and Osborne, 2005 |
| 40–49 years | 0.86 | Hawthorne and Osborne, 2005 |
| 50–59 years | 0.79 | Hawthorne and Osborne, 2005 |
| 60–69 years | 0.77 | Hawthorne and Osborne, 2005 |
| 70–79 years | 0.72 | Hawthorne and Osborne, 2005 |
| 80–89 years | 0.63 | Hawthorne and Osborne, 2005 |
| 90–99 years | 0.63 | Hawthorne and Osborne, 2005 |

AQoL = Assessment of Quality of Life.

### D.4.6 Other model parameters

The duration of the model is a lifetime horizon. Unlike the NICE model, which used a discount rate of 3.5%, this evaluation discounts costs and benefits at 5% per annum.

### D.4.7 Australian general population variables

As discussed above, the NICE economic model did not incorporate the probability of death in patients for reasons other than breast cancer, as it was thought that non-disease-specific mortality would be balanced across the cohorts. Since the model has a lifetime horizon and measures the possibility of distant cancer and death, it was considered appropriate to include a background rate of mortality for the purposes of the current assessment report.

Age-specific Australian mortality rates were derived from life tables produced by the Australian Bureau of Statistics (ABS, 2013). ABS data on causes of death (ABS, 2012) were used to determine the proportion of deaths that are attributable to breast cancer in each age group, so that these deaths could be removed from the estimates of non-disease-specific mortality to avoid double counting of breast cancer deaths within the model.

### D.4.8 Summary of model inputs and assumptions

Table D.15 summarises all parameters used in the model for the included populations.

**Table D.15 Summary of model inputs.**

| Category | Variable | High-risk based on breast cancer gene mutation | Familial high-risk | Prior history of invasive breast cancer | Prior history of treatment for DCIS or LCIS | Women with chest radiotherapy at 10–35 years | Reference |
|---|---|---|---|---|---|---|---|
| Population variables | Age at baseline (years) | 30 | 30 | 44 | 44 | 30 | Assumption |
| | Age at which MRI screening ends (years) | 50 | 50 | 50 | 50 | 50 | Assumption |
| | Duration of screening (years) | 20 | 20 | 6 | 6 | 20 | Assumption |
| Natural history of breast cancer | 5-year risk of breast cancer for 40-year-olds (44-year-olds for populations with prior breast cancer) | 13.77% | 6.20% | 5.70%[a] | 5.70%[a] | 2.67% | Antoniou et al, 2003; Claus et al, 1994; AIHW & NBOCC, 2010; Henderson et al, 2010 |
| | 5-year survival for breast cancer identified in Year 1 | 80.0% | 91.9% | 91.9% | 91.9% | 91.9% | NICE, 2013; AIHW, 2013 |
| | Decrement in 5-year survival due to delayed diagnosis | ~25% | 18.8% | 18.8% | 18.8% | 18.8% | Weedon-Fekjær et al, 2008 |
| Diagnostic accuracy | Sensitivity: mammography | 0.36 (0.17–0.59) | 0.38 (0.26, 0.51) | 0.50 (0.07, 0.93) | 0.36 (0.13, 0.65) | 0.68 (0.43, 0.87) | Warner 2008 |
| | Specificity: mammography | 1.00 (0.99, 1.00) | 0.97 (0.87, 0.98) | 0.95 (0.92, 0.97) | 0.90 (0.85, 0.94) | 0.92 (0.89, 0.95) | HIQA, 2013; Berg et al, 2012 |
| | Sensitivity: MRI + mammography | 0.86 (0.64, 0.97) | 0.88 (0.78, 0.93) | 1.00 (0.40, 1.00) | 0.71 (0.42, 0.92) | 0.95 (0.74, 1.00) | Sung et al, 2011; Ng et al, 2013 |
| | Specificity: MRI + mammography | 0.95 (0.94, 0.96)b | 0.88 (0.73, 0.93) | 0.79 (0.73, 0.83) | 0.76 (0.70, 0.82) | 0.86 (0.82, 0.90) | |
| Costs | MRI scan | $690.00 | $690.00 | $690.00 | $690.00 | $690.00 | MBS item 63464 |
| | Mammography | $89.50 | $89.50 | $89.50 | $89.50 | $89.50 | MBS item 59300 |

| Category | Variable | High-risk based on breast cancer gene mutation | Familial high-risk | Prior history of invasive breast cancer | Prior history of treatment for DCIS or LCIS | Women with chest radiotherapy at 10–35 years | Reference |
|---|---|---|---|---|---|---|---|
| | MRI + mammography | $779.50 | $779.50 | $779.50 | $779.50 | $779.50 | MBS items 63464 and 59300 |
| | Specialist consultation—Initial | $85.55 | $85.55 | $85.55 | $85.55 | $85.55 | MBS item 104 |
| | Biopsy | $137.90 | $137.90 | $137.90 | $137.90 | $137.90 | MBS item 31548 |
| | Ultrasound | $98.25 | $98.25 | $98.25 | $98.25 | $98.25 | MBS item 55070 |
| | Wide local excision / mastectomy | $7,958.00 | $7,958.00 | $7,958.00 | $7,958.00 | $7,958.00 | ARDRG v6 Public. J06A |
| | Tamoxifen (1 year; 20 mg daily) | $257.93 | $257.93 | $257.93 | $257.93 | $257.93 | PBS 2110C |
| | Adjuvant chemo (course) | $16,043.72 | $16,043.72 | $16,043.72 | $16,043.72 | $16,043.72 | Section D.4.4, Table D.12 |
| | Total costs per first year of cancer | $24,510.10 | $24,510.10 | $24,510.10 | $24,510.10 | $24,510.10 | Section D.4.4 |
| | Cost of follow-up in false-positive patients | $223.45 | $223.45 | $223.45 | $223.45 | $223.45 | MBS items 31548 and 104 |
| Utility values | Relative utility: in treatment | 0.68 | 0.68 | 0.68 | 0.68 | 0.68 | NICE model; Peasgood et al, 2010 |
| | Relative utility: false-positive | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | Assumption |
| | Relative utility: false-negative | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | Assumption |
| | Aust. population norms 30–39 | 0.87 | 0.87 | 0.87 | 0.87 | 0.87 | Hawthorne and Osborne, 2005 |
| | Aust. population norms 40–49 | 0.86 | 0.86 | 0.86 | 0.86 | 0.86 | Hawthorne and Osborne, 2005 |
| | Aust. population norms 50–59 | 0.79 | 0.79 | 0.79 | 0.79 | 0.79 | Hawthorne and Osborne, 2005 |

| Category | Variable | High-risk based on breast cancer gene mutation | Familial high-risk | Prior history of invasive breast cancer | Prior history of treatment for DCIS or LCIS | Women with chest radiotherapy at 10–35 years | Reference |
|---|---|---|---|---|---|---|---|
| | Aust. population norms 60–69 | 0.77 | 0.77 | 0.77 | 0.77 | 0.77 | Hawthorne and Osborne, 2005 |
| | Aust. population norms 70–79 | 0.72 | 0.72 | 0.72 | 0.72 | 0.72 | Hawthorne and Osborne, 2005 |
| | Aust. population norms 80–89 | 0.63 | 0.63 | 0.63 | 0.63 | 0.63 | Hawthorne and Osborne, 2005 |
| | Aust. population norms 90–99 | 0.63 | 0.63 | 0.63 | 0.63 | 0.63 | Hawthorne and Osborne, 2005 |
| Discount rate | Costs | 5% | 5% | 5% | 5% | 5% | Section D.4.6 |
| | Outcomes | 5% | 5% | 5% | 5% | 5% | Section D.4.6 |

[a] The 5-year risk of breast cancer in populations with prior invasive breast cancer or DCIS/LCIS is reported for women at the average age of screening, which is assumed to be 44 years.

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.

## D.5 Results of the economic evaluation

### D.5.1 Disaggregated costs

Disaggregated costs per patient are presented in Table D.16. In all populations, costs were higher for people in the MRI + mammography study arm than for those receiving mammography alone. This generally reflects the incremental cost of annual MRI surveillance. Costs were generally higher in populations that began screening earlier (those without prior breast cancer), owing to the longer period in which to accrue costs. Populations that started screening earlier also had a greater incremental difference between the two study arms because mammography is assumed to continue even when MRI screening stops. In addition, groups with a higher baseline risk of breast cancer had higher per-patient treatment costs.

The overall incremental cost per patient screened with MRI in addition to mammography in the currently reimbursed population was $9,326.

**Table D.16 Disaggregated costs.**

| Population | Result | MRI + mammography | Mammography | Difference |
|---|---|---|---|---|
| *High-risk based on breast cancer gene mutation* | Total screening costs | $9,898 | $1,486 | $8,412 |
| | Total false-positive costs | $192 | $0 | $192 |
| | Total treatment costs | $8,866 | $8,096 | $770 |
| | Total costs | $18,957 | $9,582 | $9,375 |
| *Familial high-risk* | Total screening costs | $10,343 | $1,619 | $8,724 |
| | Total false-positive costs | $536 | $173 | $364 |
| | Total treatment costs | $5,143 | $4,904 | $238 |
| | Total costs | $16,022 | $6,696 | $9,326 |
| *Prior history of invasive breast cancer* | Total screening costs | $5,117 | $1,533 | $3,584 |
| | Total false-positive costs | $539 | $274 | $265 |
| | Total treatment costs | $3,005 | $2,919 | $86 |
| | Total costs | $8,661 | $4,725 | $3,935 |
| *Prior history of treatment for DCIS or LCIS* | Total screening costs | $5,113 | $1,531 | $3,582 |
| | Total false-positive costs | $779 | $546 | $233 |
| | Total treatment costs | $2,936 | $2,848 | $89 |
| | Total costs | $8,828 | $4,924 | $3,904 |
| *Chest radiotherapy between 10 and 35 years* | Total screening costs | $10,469 | $1,676 | $8,794 |
| | Total false-positive costs | $725 | $479 | $246 |
| | Total treatment costs | $2,593 | $2,527 | $66 |
| | Total costs | $13,788 | $4,682 | $9,105 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging.

### D.5.2 Disaggregated outcomes

In Table D.17, life years (discounted and undiscounted) and QALYs (discounted and undiscounted) are presented for each of the study arms. In all of the included populations, the use of MRI screening in addition to mammography was associated with an increase in life years and QALYs as a result of improved overall survival. In the currently reimbursed population with high familial risk for breast cancer, MRI screening in addition to mammography was associated with greater life years (0.1313) and QALYs (0.1019) per patient. QALY gains were greatest in the population with the highest risk of breast cancer—that is, women with a confirmed breast cancer gene mutation.

There is a substantial difference between the discounted and undiscounted life years and QALYs. This reflects the fact that the clinical benefits (improved survival) of surveillance using MRI with or without mammography accrue over the long term, as the risk of breast cancer increases with age.

**Table D.17 Disaggregated outcomes.**

| Population | Result | MRI + mammography | Mammography | Difference |
|---|---|---|---|---|
| *High-risk based on breast cancer gene mutation* | Life years (undiscounted) | 48.4311 | 46.8635 | 1.5676 |
| | Life years (discounted) | 17.6901 | 17.3461 | 0.3441 |
| | QALYs (undiscounted) | 37.8137 | 36.6518 | 1.1619 |
| | QALYs (discounted) | 14.6762 | 14.4118 | 0.2644 |
| *Familial high-risk* | Life years (undiscounted) | 53.3475 | 52.7576 | 0.5898 |
| | Life years (discounted) | 18.5163 | 18.3849 | 0.1313 |
| | QALYs (undiscounted) | 41.4666 | 41.0275 | 0.4391 |
| | QALYs (discounted) | 15.3484 | 15.2465 | 0.1019 |
| *Prior history of invasive breast cancer* | Life years (undiscounted) | 41.0079 | 40.7469 | 0.2610 |
| | Life years (discounted) | 17.1947 | 17.1050 | 0.0897 |
| | QALYs (undiscounted) | 30.6773 | 30.4864 | 0.1909 |
| | QALYs (discounted) | 13.5186 | 13.4511 | 0.0676 |
| *Prior history of treatment for DCIS or LCIS* | Life years (undiscounted) | 40.8250 | 40.6418 | 0.1832 |
| | Life years (discounted) | 17.1380 | 17.0750 | 0.0630 |
| | QALYs (undiscounted) | 30.5458 | 30.4121 | 0.1338 |
| | QALYs (discounted) | 13.4765 | 13.4293 | 0.0471 |
| *Chest radiotherapy between 10 and 35 years* | Life years (undiscounted) | 54.5964 | 54.3285 | 0.2679 |
| | Life years (discounted) | 18.6936 | 18.6286 | 0.0650 |
| | QALYs (undiscounted) | 42.4651 | 42.2629 | 0.2022 |
| | QALYs (discounted) | 15.5053 | 15.4537 | 0.0516 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

Table D.18 presents the time (undiscounted years) that the average patient will spend in each health state for the lifetime of the model. In the model, patients that receive MRI in addition to

mammography spend fewer years in the dead health state, leading to the life year and QALY gains described above. Consistent with the QALY gains reported in Table D.17, the greatest reduction in time spent in the dead health state occurs in those women with the highest cumulative risk of breast cancer, that is, women with a confirmed gene mutation for breast cancer followed by those with a high familial risk. Figure D.4 presents the proportion of women alive at each age in the population with a high risk of breast cancer based on family history (ie, the currently reimbursed population).

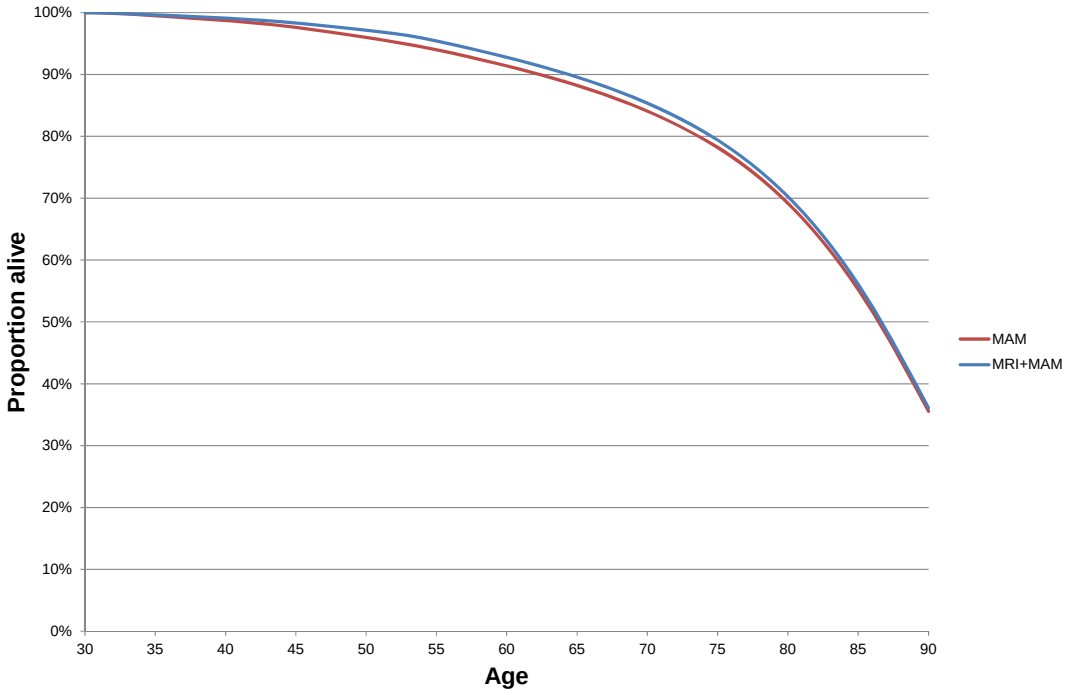
Owing to higher sensitivity, individuals undergoing surveillance using MRI in addition to mammography also spend more time in the healthy (true-negative) state and less time in the false-negative health state. Owing to poorer specificity, patients that receive MRI screening in addition to mammography also spend more time in the healthy (false-positive) health state.

**Table D.18 Time (undiscounted years) in each health state.**

| Population | Result | MRI + mammography | Mammography | Diff. |
|---|---|---|---|---|
| *High-risk based on breast cancer gene mutation* | Healthy (true-negative) | 42.4391 | 41.2491 | 1.19 |
| | Healthy (false-positive) | 0.0723 | 0 | 0.0723 |
| | False-negative | 0.7166 | 1.0635 | –0.3469 |
| | In treatment (true-positive) | 5.2031 | 4.5509 | 0.6522 |
| | Dead | 20.5689 | 22.1365 | –1.5676 |
| *Familial high-risk* | Healthy (true-negative) | 48.958 | 48.5964 | 0.3616 |
| | Healthy (false-positive) | 0.2619 | 0.1218 | 0.1401 |
| | False-negative | 0.5059 | 0.6641 | –0.1581 |
| | In treatment (true-positive) | 3.6217 | 3.3754 | 0.2463 |
| | Dead | 15.6525 | 16.2424 | –0.5898 |
| *Prior history of invasive breast cancer* | Healthy (true-negative) | 39.5742 | 39.4082 | 0.1660 |
| | Healthy (false-positive) | 0.2361 | 0.1649 | 0.0712 |
| | False-negative | 0.1053 | 0.1765 | –0.0712 |
| | In treatment (true-positive) | 1.0923 | 0.9973 | 0.0950 |
| | Dead | 13.9921 | 14.2531 | –0.2610 |
| *Prior history of treatment for DCIS or LCIS* | Healthy (true-negative) | 39.2552 | 39.1516 | 0.1037 |
| | Healthy (false-positive) | 0.3918 | 0.3290 | 0.0628 |
| | False-negative | 0.1739 | 0.2352 | –0.0614 |
| | In treatment (true-positive) | 1.0041 | 0.9260 | 0.0781 |
| | Dead | 14.1750 | 14.3582 | –0.1832 |
| *Chest radiotherapy between 10 and 35 years* | Healthy (true-negative) | 52.5059 | 52.357 | 0.1489 |
| | Healthy (false-positive) | 0.447 | 0.3514 | 0.0956 |
| | False-negative | 0.0498 | 0.106 | –0.0562 |
| | In treatment (true-positive) | 1.5936 | 1.5141 | 0.0795 |
| | Dead | 14.4036 | 14.6715 | –0.2679 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging.

**Figure D.4 Proportion of women alive with MRI + mammography or mammography alone (women with a high risk of breast cancer based on family history).**




## D.5.3 Incremental cost-effectiveness

The incremental cost per QALY for the use of MRI + mammography compared with mammography alone is presented in Table D.19. The ICER is lowest in women with a confirmed mutation for breast cancer ($35,460/QALY), followed by women with a prior history of invasive breast cancer ($58,240/QALY), and highest in women with a history of chest radiotherapy ($176,536/QALY).

The differences between these groups are driven largely by the baseline risk of breast cancer, the age at which each population begins screening and the population-specific diagnostic accuracy data for MRI + mammography compared with mammography alone (refer to Section D.4.3). That is to say, MRI + mammography is most cost-effective in populations where MRI has high sensitivity relative to mammography alone and the screened population has a high incidence of breast cancer. Since patients in the groups with prior breast cancer (DCIS, LCIS and invasive) have the same risk, the difference in the cost-effectiveness of these two populations is caused primarily by differences in the diagnostic accuracy data for these two populations. The accuracy data for the population with prior DCIS or LCIS were based on one poor-quality study that compared MRI alone with mammography (Sung et al, 2011b). For this population in particular, the analysis (Table D.20) using accuracy data from the HIQA (2013) meta-analysis might be more informative.

The high ICERs for women with a high familial risk for breast cancer or with prior chest radiotherapy are associated with the fact that the overall risk of breast cancer in these two populations does not appear high enough to justify the duration of screening (20 years), leading to high costs early in the model and insufficient QALY gains.

**Table D.19 Incremental cost per QALY (base-case population-specific data).**

| Population | Result | MRI + mammography | Mammography | Difference |
|---|---|---|---|---|
| *High-risk based on breast cancer gene mutation* | Total costs | $18,957 | $9,582 | $9,375 |
| | Total QALYs | 14.6762 | 14.4118 | 0.2644 |
| | ICER | | | $35,460 |
| *Familial high-risk* | Total costs | $16,022 | $6,696 | $9,326 |
| | Total QALYs | 15.3484 | 15.2465 | 0.1019 |
| | ICER | | | $91,488 |
| *Prior history of invasive breast cancer* | Total costs | $8,661 | $4,725 | $3,935 |
| | Total QALYs | 13.5186 | 13.4511 | 0.0676 |
| | ICER | | | $58,240 |
| *Prior history of treatment for DCIS or LCIS* | Total costs | $8,828 | $4,924 | $3,904 |
| | Total QALYs | 13.4765 | 13.4293 | 0.0471 |
| | ICER | | | $82,793 |
| *Chest radiotherapy between 10 and 35 years* | Total costs | $13,788 | $4,682 | $9,105 |
| | Total QALYs | 15.5053 | 15.4537 | 0.0516 |
| | ICER | | | $176,536 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

Table D.20 presents the same data but substitutes the estimates for diagnostic accuracy in each population with the single set of figures from the HIQA (2013) meta-analysis, previously used only for the group of women with a high familial risk for breast cancer. The HIQA (2013) diagnostic accuracy data have less variance than the population-specific results, as they are based on a large sample size. This is especially important for those populations supported by very poor-quality evidence, such as women with a prior history of treatment for DCIS or LCIS. However, using these data for all analyses assumes that the diagnostic accuracy of MRI + mammography compared with mammography alone does not vary for women of the same age in different populations (eg, the sensitivity of MRI in a 40-year-old woman with a *BRCA1* mutation would be the same as in a 40-year-old woman with prior invasive breast cancer).

Using the HIQA (2013) data, the ICER remains lowest in women with a confirmed mutation for breast cancer ($36,440/QALY), followed by women with prior invasive breast cancer and prior DCIS/LCIS (both $67,368/QALY). In the currently reimbursed population with a high familial risk for breast cancer, it remains unchanged, as the HIQA (2013) data were used in the base case ($91,488/QALY). In women with a prior history of invasive breast cancer, the ICER decreases to $125,687/QALY.

**Table D.20 Incremental cost per QALY (HIQA 2013 data).**

| Population | Result | MRI + mammography | Mammography | Difference |
|---|---|---|---|---|
| *High-risk based on breast cancer gene mutation* | Total costs | $19,314 | $9,797 | $9,517 |
| | Total QALYs | 14.6886 | 14.4275 | 0.2612 |
| | ICER | | | $36,440 |
| *Familial high-risk* | Total costs | $16,022 | $6,696 | $9,326 |
| | Total QALYs | 15.3484 | 15.2465 | 0.1019 |
| | ICER | | | $91,488 |
| *Prior history of invasive breast cancer* | Total costs | $8,416 | $4,600 | $3,816 |
| | Total QALYs | 13.5027 | 13.4460 | 0.0566 |
| | ICER | | | $67,368 |
| *Prior history of treatment for DCIS or LCIS* | Total costs | $8,416 | $4,600 | $3,816 |
| | Total QALYs | 13.5027 | 13.4460 | 0.0566 |
| | ICER | | | $67,368 |
| *Chest radiotherapy between 10 and 35 years* | Total costs | $13,550 | $4,252 | $9,297 |
| | Total QALYs | 15.4835 | 15.4095 | 0.0740 |
| | ICER | | | $125,687 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

# D.6 Sensitivity analyses

Categories of variables tested in sensitivity analysis include diagnostic accuracy data, patient characteristics, the natural history of breast cancer, clinical utility values and costs. As was the case for incremental costs per QALY, sensitivity analyses are presented using population-specific diagnostic accuracy data (Table D.21, p. 109) and the HIQA (2013) meta-analysis (Table D.22, p. 112).

## D.6.1 Diagnostic accuracy data

The upper and lower 95% CIs for each point estimate of diagnostic accuracy were used to establish the impact of sensitivity and specificity on ICERs for each population. As would be expected, increasing the sensitivity of MRI + mammography improved the ICERs for all populations. Since the point estimates for the sensitivity of screening were already very high, there was in effect a 'ceiling' on the extent to which sensitivity could be improved. By comparison, use of lower CIs significantly increased the ICERs, especially in populations where the diagnostic accuracy data came from small studies with high variance around the point estimates, such as in women with prior DCIS or LCIS.

Using data from the HIQA (2013) meta-analysis resulted in more stable results, owing to the narrower confidence intervals associated with these data (Table D.22). Note that using the HIQA (2013) data provides identical results for populations with prior invasive breast cancer and prior DCIS/LCIS in all sensitivity analyses. This reflects the fact that apart from the (population-specific) diagnostic accuracy data, these two populations have identical characteristics and parameters in the model.

### D.6.2 Patient characteristics

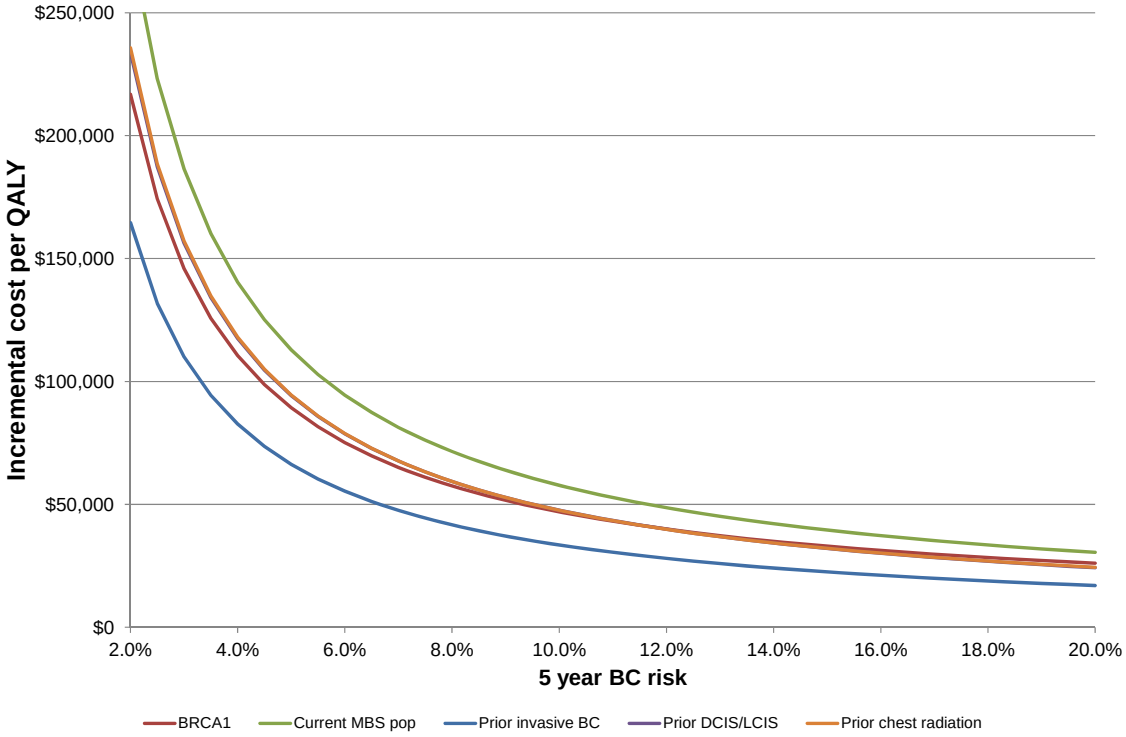
The model is extremely sensitive to the baseline risk of breast cancer in the screened population. The relationships between the incremental cost per QALY and 5-year breast cancer risk using the base-case population specific and HIQA (2013) data are presented in Figure D.5 and Figure D.6, respectively.

Note that for populations with prior breast cancer, the baseline population is women aged 44 years, whereas for populations without prior breast cancer, the 5-year risk presented is that for a 40-year-old. For all populations, changing the risk of breast cancer at one age results in an adjustment to the risk of breast cancer across all age groups.

Increasing the 5-year baseline risk of breast cancer at the beginning of screening to 10%, 15% or 20% produced substantial improvements to the ICERs in women with a high risk of familial breast cancer, those with a prior history of invasive or noninvasive breast cancer, and those with a history of chest radiotherapy. For those with a confirmed gene mutation for breast cancer, the effect of increasing the risk of breast cancer on the ICER was smaller, as these patients already have a very high 5-year risk for developing the disease (13.8% for a 40-year-old woman).

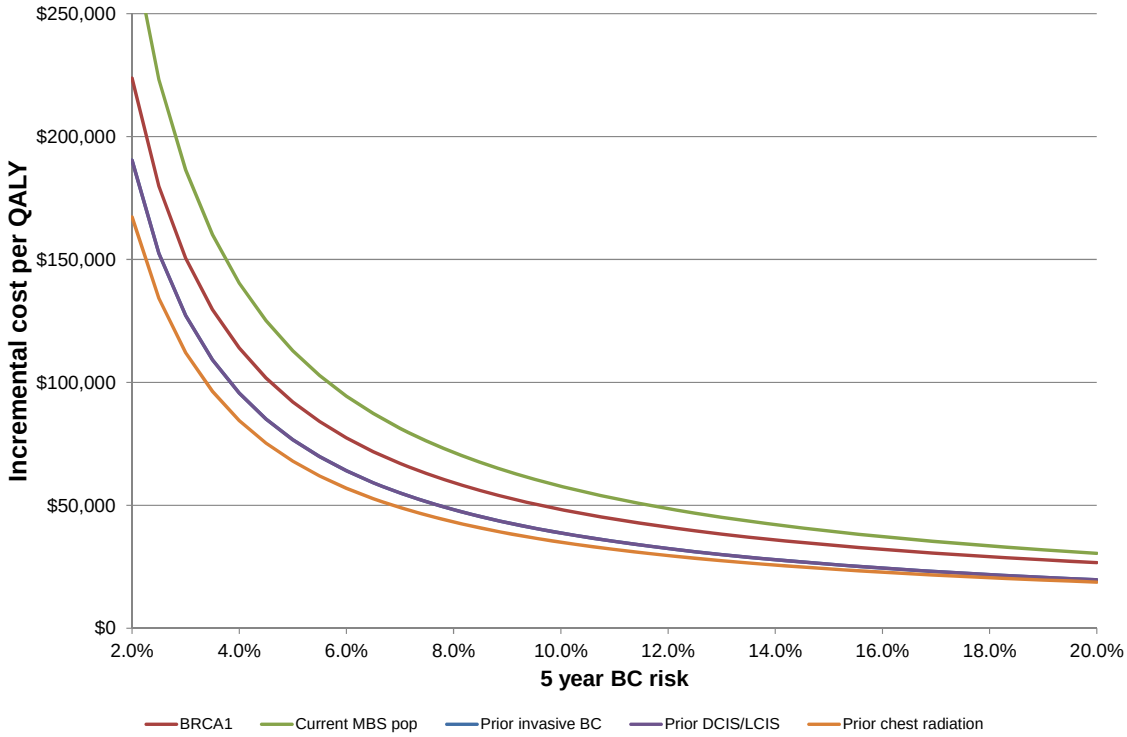
Women with prior breast cancer are generally more cost-effective at lower breast cancer risks because they accrue fewer costs over a shorter period of surveillance (6 years). By comparison, women in the population with a high familial risk of breast cancer require a higher 5-year breast cancer risk to achieve the same level of cost-effectiveness as other populations because of higher lifetime screening costs in this population.

**Figure D.5 Incremental cost/QALY by 5-year breast cancer risk (base-case population-specific data).**




Note: The curves for prior DCIS/LCIS and prior chest irradiation are overlaid by chance.

**Figure D.6 Incremental cost/QALY by 5-year breast cancer risk (HIQA, 2013 data).**




Note: The curves for prior invasive cancer and DCIS/LCIS are overlaid owing to identical breast cancer risk, survival and screening age.

Similarly, the model is sensitive to the estimated impact of delayed diagnosis on patient survival. It assumes that patients that receive a false-negative diagnosis in the first year but that are correctly identified as a true-positive in the following year have poorer clinical outcomes, because their tumour has grown in the intervening period. The base case assumes that there is an 18.8% reduction in survival as a result of delayed diagnosis in most of the assessed populations, and a 15% reduction over 2 years (30% overall) for patients with a confirmed breast cancer mutation. Patients with a confirmed breast cancer mutation also have a lower baseline probability of survival. This population is treated differently to account for the fact that tumours associated with a *BRCA1*, *BRCA2* or *TP53* mutation are often more aggressive and may produce a more significant decrement in survival if they are not detected early. The relationships between the incremental cost per QALY and the decrement in overall survival due to late detection using the base-case population-specific and HIQA (2013) data are presented in Figure D.7 and Figure D.8, respectively.

**Figure D.7 Incremental cost/QALY by decrement in overall survival due to late detection (base-case population-specific data).**

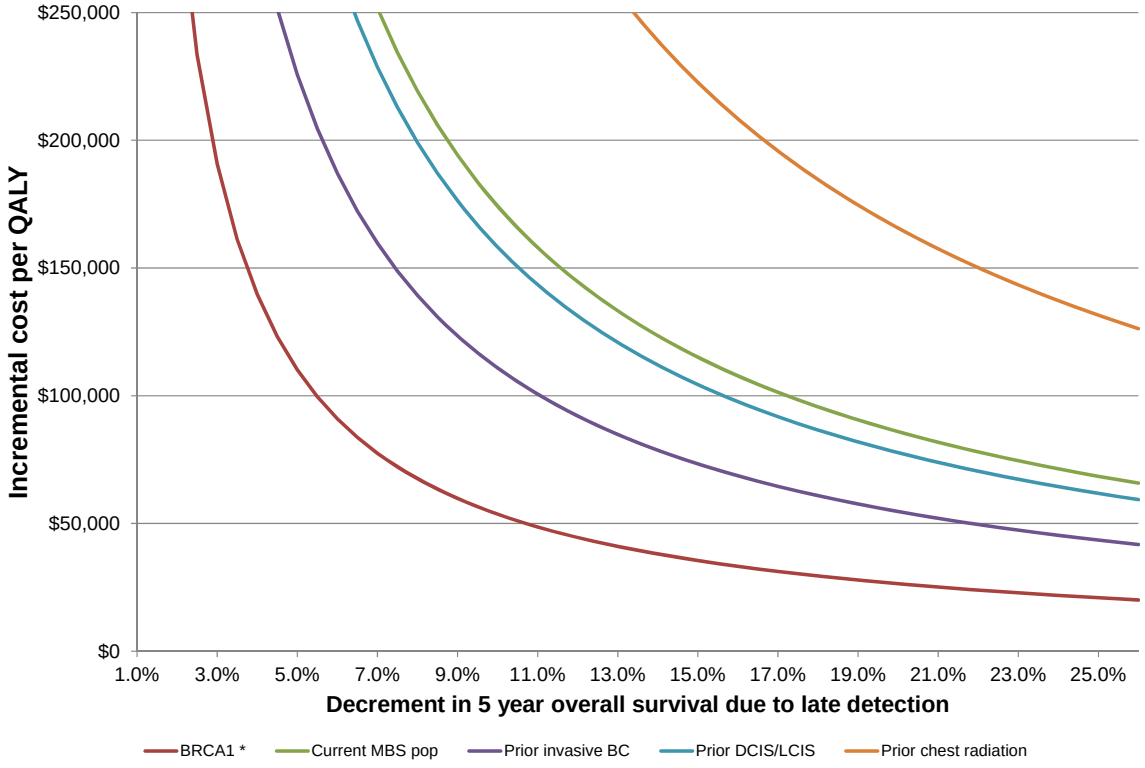
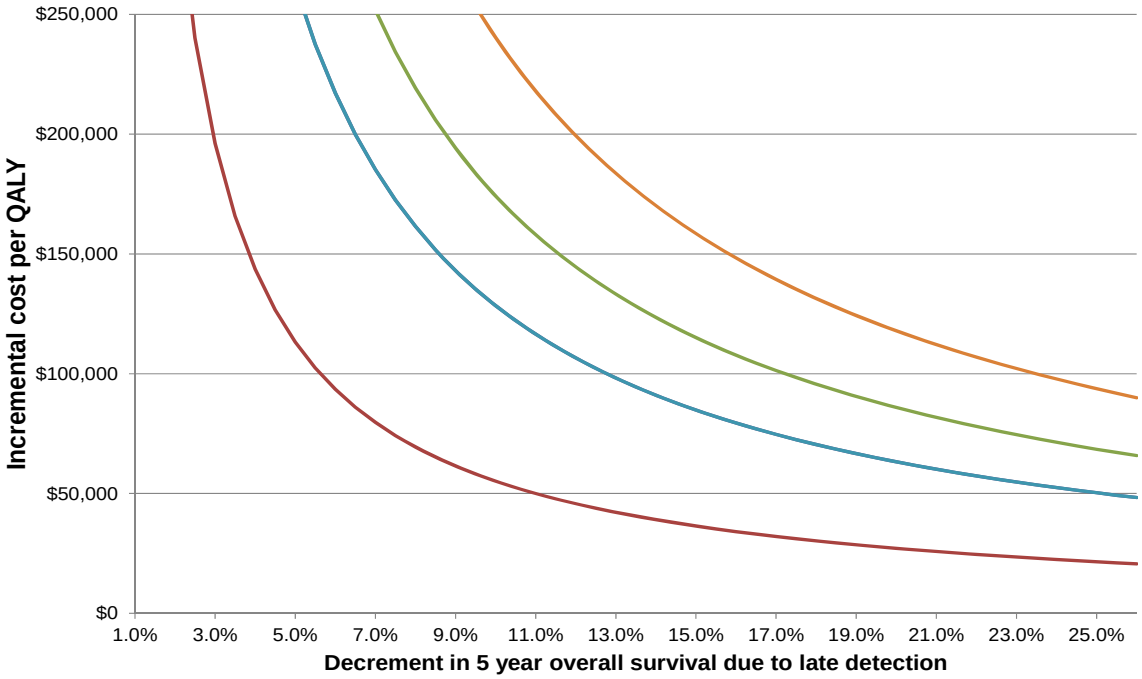


**Figure D.8 Incremental cost/QALY by decrement in overall survival due to late detection (HIQA, 2013).**




Note: The curves for prior invasive cancer and DCIS/LCIS are overlaid owing to identical breast cancer risk, survival and screening age.

For the currently reimbursed population with a high risk of familial breast cancer, decreasing the survival decrement to 5% or 10% increases the ICER substantially, while increasing it to >20% improves the result. For the subgroup with a confirmed breast cancer mutation, the ICER remains below $53,658 if the survival decrement is estimated to be >10%. Other populations included in the model maintain very high ICERs when the survival decrement is assumed to be <15%. In these groups, it is likely that the baseline risk of breast cancer remains the dominant factor influencing cost-effectiveness.

### D.6.3 MRI screening age

A sensitivity analysis was undertaken to assess the impact of limiting additional MRI screening to different age groups, for different lengths of time. Although the current MBS item for MRI surveillance specifies that it should be used in women below the age of 50 years, the sensitivity analysis shows that in the currently reimbursed population (with a high familial risk for breast cancer), the ICER decreases in older cohorts and is most cost-effective when women are screened between the ages of 40 and 60 years. This suggests that the impact of improving the sensitivity of screening with additional MRI is greater in populations with a higher baseline risk for breast cancer than it is in younger women, in whom mammography alone is said to be less effective. That is to say, despite the fact that the diagnostic accuracy of additional MRI screening is greater than mammography alone in younger cohorts, additional MRI in older cohorts will prevent more false-negative diagnoses.

In women with a history of prior breast cancer, the cost-effectiveness of screening at different ages is influenced by the fact that after 10 years of screening, the risk of recurrent breast cancer decreases substantially. Therefore, the most cost-effective strategies are those that limit screening to a 10-year

window (ie, 30–40 years or 40–50 years). In the small proportion of women with a primary cancer before the age of 40, the risk of recurrence is higher, resulting in greater QALY gains. However, since the average age of the population with prior breast cancer is 44, this result is not applicable to the overall population.

### D.6.4 Costs

Changing the cancer treatment costs has very little impact on the ICER in any of the populations. This reflects the fact that model assumes that screening does not prevent any cancers, so costs associated with treatment are delayed but not substantially reduced.

### D.6.5 Utility values

Increasing the utility values for women being treated in their first year of breast cancer slightly improves the ICER in all populations. This effect is largely related to the fact that the clinical outcomes for women with tumours that are identified earlier are not as affected by discounting.

Women with false-positive results may be subject to considerable stress and will undergo a follow-up biopsy to confirm the diagnosis. It may therefore be considered appropriate to apply a small disutility to these patients for a limited period. Applying a decrement in health-related quality of life for 1 month in women with false-positive results substantially increases the ICER in populations with a low baseline risk of breast cancer, such as those with prior DCIS, LCIS or invasive breast cancer.

The NICE economic model also applied a disutility to women that received a false-negative diagnosis after screening with either MRI or mammography. This improves the ICER in all screened populations owing to the greater sensitivity of MRI + mammography as a surveillance strategy. In the base case of the model presented here, a disutility was not considered appropriate, as it is assumed that women who have tumours that are detected in a subsequent round of screening would remain asymptomatic in the intervening period.

### D.6.6 Discount rate

Unlike the NICE model, which used a discount rate of 3.5%, costs and benefits in this evaluation are discounted at 5% per annum. The calculated ICERs are heavily dependent on the rate used to discount costs and outcomes, as, in general, costs accrue early in the model, whereas clinical benefits occur later. Reducing the discount rate therefore has a favourable impact on the ICERs in all of the assessed populations.

### D.6.7 Model duration

As noted above, the clinical benefits of MRI screening accrue over time. Therefore, decreasing the duration of the model reduces the cost-effectiveness of the intervention in all populations.

### D.6.8 Full results of the sensitivity analyses

**Table D.21 Univariate sensitivity analysis (base-case population-specific accuracy data).**

| Variable tested | Value(s) used | Pop. 1<br>*BRCA1* | Pop. 2<br>Current MBS pop. | Pop. 3<br>Prior invasive breast cancer | Pop. 4<br>Prior DCIS/LCIS | Pop. 5<br>Prior chest irradiation |
|---|---|---|---|---|---|---|
| Accuracy data | Base case | $35,460 | $91,488 | $58,240 | $82,793 | $176,536 |

| Variable tested | Value(s) used | Pop. 1<br>*BRCA1* | Pop. 2<br>Current MBS pop. | Pop. 3<br>Prior invasive breast cancer | Pop. 4<br>Prior DCIS/LCIS | Pop. 5<br>Prior chest irradiation |
|---|---|---|---|---|---|---|
| | MRI+MAM Sens—95% LCL | $53,070 | $111,466 | Dominated | $280,008 | $377,507 |
| | MRI+MAM Sens—95% UCL | $31,298 | $83,965 | $58,240 | $54,965 | $156,652 |
| | MRI+MAM Spec—95% LCL | $35,605 | $97,419 | $59,704 | $84,892 | $179,697 |
| | MRI+MAM Spec—95% UCL | $35,315 | $89,511 | $57,264 | $80,695 | $173,376 |
| | MRI+MAM Sens & Spec—95% LCL | $53,294 | $118,719 | Dominated | $287,224 | $384,292 |
| | MRI+MAM Sens & Spec—95% UCL | $31,171 | $82,153 | $57,264 | $53,582 | $153,849 |
| Baseline breast cancer risk (over 5 years from age 40) | 5% | $89,294 | $112,823 | $66,291 | $94,225 | $94,498 |
| | 10% | $46,958 | $57,774 | $33,489 | $47,646 | $47,599 |
| | 15% | $32,974 | $39,527 | $22,512 | $32,056 | $32,088 |
| | 20% | $26,066 | $30,464 | $16,980 | $24,201 | $24,415 |
| Decrement in 5-year overall survival due to delayed detection | 5% | $110,157 | $357,678 | $225,657 | $324,638 | $687,130 |
| | 10% | $53,658 | $174,247 | $110,894 | $158,210 | $337,273 |
| | 15% | $35,460 | $115,124 | $73,334 | $104,352 | $222,630 |
| | 20% | $26,414 | $85,911 | $54,672 | $77,704 | $165,637 |
| | 25% | $20,939 | $68,482 | $43,505 | $61,794 | $131,521 |
| | 30% | $17,185 | $56,895 | $36,067 | $51,213 | $108,789 |
| MRI age range | 30–40 | $48,122 | $106,522 | $48,639 | $68,593 | $143,131 |
| | 30–50 | $35,460 | $91,488 | $73,099 | $103,035 | $176,536 |
| | 30–60 | $36,111 | $85,768 | $87,557 | $123,395 | $204,367 |
| | 30–70 | $37,111 | $85,701 | $96,149 | $135,491 | $222,182 |
| | 40–50 | $21,264 | $63,039 | $61,408 | $87,133 | $242,901 |
| | 40–60 | $25,319 | $64,373 | $87,877 | $124,627 | $319,768 |
| | 40–70 | $27,674 | $67,234 | $102,822 | $145,784 | $367,345 |
| Cancer treatment costs Y1 | 0 | $32,855 | $89,511 | $57,306 | $81,314 | $175,548 |
| | 0.5 | $34,157 | $90,499 | $57,773 | $82,054 | $176,042 |
| | 1 | $35,460 | $91,488 | $58,240 | $82,793 | $176,536 |
| | 1.5 | $36,763 | $92,477 | $58,707 | $83,533 | $177,030 |

| Variable tested | Value(s) used | Pop. 1<br>*BRCA1* | Pop. 2<br>Current MBS pop. | Pop. 3<br>Prior invasive breast cancer | Pop. 4<br>Prior DCIS/LCIS | Pop. 5<br>Prior chest irradiation |
|---|---|---|---|---|---|---|
| | 2 | $38,065 | $93,465 | $59,174 | $84,273 | $177,524 |
| Cancer treatment costs subsequent years | 0 | $35,151 | $91,127 | $57,899 | $82,389 | $176,248 |
| | 0.5 | $35,305 | $91,308 | $58,070 | $82,591 | $176,392 |
| | 1 | $35,460 | $91,488 | $58,240 | $82,793 | $176,536 |
| | 1.5 | $35,615 | $91,669 | $58,410 | $82,996 | $176,680 |
| | 2 | $35,769 | $91,849 | $58,581 | $83,198 | $176,825 |
| False-positive costs | 0 | $34,734 | $87,920 | $54,317 | $77,860 | $171,768 |
| | 0.5 | $35,097 | $89,704 | $56,278 | $80,327 | $174,152 |
| | 1 | $35,460 | $91,488 | $58,240 | $82,793 | $176,536 |
| | 1.5 | $35,823 | $93,272 | $60,201 | $85,260 | $178,920 |
| | 2 | $36,186 | $95,057 | $62,163 | $87,727 | $181,304 |
| Utility in cancer treatment (Y1) | 0.5 | $36,039 | $92,630 | $58,631 | $83,661 | $177,638 |
| | 0.6 | $35,715 | $91,992 | $58,413 | $83,177 | $177,024 |
| | 0.7 | $35,397 | $91,363 | $58,197 | $82,698 | $176,415 |
| | 0.8 | $35,084 | $90,742 | $57,982 | $82,225 | $175,810 |
| | 0.9 | $34,777 | $90,130 | $57,769 | $81,758 | $175,209 |
| Utility: False-pos (1-month duration) | 0.8 | $36,604 | $108,111 | $69,159 | $103,300 | $222,196 |
| | 0.9 | $36,023 | $99,107 | $63,231 | $91,917 | $196,752 |
| Utility: False-neg (1-year duration) | 0.8 | $31,308 | $78,699 | $50,632 | $69,827 | $156,301 |
| | 0.9 | $33,255 | $84,613 | $54,170 | $75,759 | $165,804 |
| Discount rate (costs and outcomes) | 0 | $12,582 | $32,407 | $22,973 | $32,531 | $68,523 |
| | 0.035 | $26,783 | $69,592 | $45,489 | $64,572 | $138,586 |
| | 0.1 | $77,840 | $192,117 | $115,080 | $164,925 | $332,142 |
| Model follow-up/duration (to age …) | 60 | $52,827 | $134,844 | $117,487 | $168,109 | $243,081 |
| | 70 | $40,949 | $105,979 | $74,316 | $105,827 | $200,086 |
| | 80 | $36,965 | $95,602 | $62,477 | $88,854 | $183,328 |
| | 90 | $35,701 | $92,153 | $58,883 | $83,713 | $177,607 |
| | 99 | $35,460 | $91,488 | $58,240 | $82,793 | $176,536 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; MAM = mammography; Sens = sensitivity; Spec = specificity; LCL = lower control limit; UCL = upper control limit.

**Table D.22 Univariate sensitivity analysis (using HIQA, 2013 accuracy data in all populations).**

| Variable tested | Value(s) used | Pop. 1<br>*BRCA1* | Pop. 2<br>Current MBS pop. | Pop. 3<br>Prior invasive breast cancer | Pop. 4<br>Prior DCIS/LCIS | Pop. 5<br>Prior chest irradiation |
|---|---|---|---|---|---|---|
| Accuracy data | Base case | $36,440 | $91,488 | $67,368 | $67,368 | $125,687 |
| | MRI+MAM Sens—95% LCL | $42,289 | $111,466 | $84,494 | $84,494 | $152,397 |
| | MRI+MAM Sens—95% UCL | $34,298 | $83,965 | $61,164 | $61,164 | $115,548 |
| | MRI+MAM Spec—95% LCL | $38,646 | $97,419 | $71,735 | $71,735 | $133,949 |
| | MRI+MAM Spec—95% UCL | $35,704 | $89,511 | $65,912 | $65,912 | $122,933 |
| | MRI+MAM Sens & Spec—95% LCL | $44,879 | $118,719 | $89,990 | $89,990 | $162,434 |
| | MRI+MAM Sens & Spec—95% UCL | $33,610 | $82,153 | $59,845 | $59,845 | $113,018 |
| Baseline breast cancer risk (over 5 years form age 40) | 5% | $92,050 | $112,823 | $76,680 | $76,680 | $67,955 |
| | 10% | $48,321 | $57,774 | $38,740 | $38,740 | $34,996 |
| | 15% | $33,870 | $39,527 | $26,043 | $26,043 | $24,134 |
| | 20% | $26,726 | $30,464 | $19,646 | $19,646 | $18,786 |
| Decrement in 5-year overall survival due to delayed detection | 5% | $113,268 | $357,678 | $262,159 | $262,159 | $493,139 |
| | 10% | $55,159 | $174,247 | $128,454 | $128,454 | $240,431 |
| | 15% | $36,440 | $115,124 | $84,862 | $84,862 | $158,504 |
| | 20% | $27,136 | $85,911 | $63,234 | $63,234 | $117,938 |
| | 25% | $21,506 | $68,482 | $50,303 | $50,303 | $93,707 |
| | 30% | $17,648 | $56,895 | $41,694 | $41,694 | $77,585 |
| MRI age range | 30–40 | $49,230 | $106,522 | $55,190 | $55,190 | $109,392 |
| | 30–50 | $36,440 | $91,488 | $82,975 | $82,975 | $125,687 |
| | 30–60 | $37,200 | $85,768 | $99,445 | $99,445 | $137,298 |
| | 30–70 | $38,269 | $85,701 | $109,234 | $109,234 | $145,310 |
| | 40–50 | $21,883 | $63,039 | $70,679 | $70,679 | $143,125 |
| | 40–60 | $26,146 | $64,373 | $101,300 | $101,300 | $167,170 |
| | 40–70 | $28,617 | $67,234 | $118,615 | $118,615 | $182,618 |
| Cancer treatment costs Y1 | 0 | $33,852 | $89,511 | $66,246 | $66,246 | $124,185 |
| | 0.5 | $35,146 | $90,499 | $66,807 | $66,807 | $124,936 |

| Variable tested | Value(s) used | Pop. 1<br>*BRCA1* | Pop. 2<br>Current MBS pop. | Pop. 3<br>Prior invasive breast cancer | Pop. 4<br>Prior DCIS/LCIS | Pop. 5<br>Prior chest irradiation |
|---|---|---|---|---|---|---|
| | 1 | $36,440 | $91,488 | $67,368 | $67,368 | $125,687 |
| | 1.5 | $37,734 | $92,477 | $67,929 | $67,929 | $126,438 |
| | 2 | $39,027 | $93,465 | $68,490 | $68,490 | $127,189 |
| Cancer treatment costs subsequent years | 0 | $36,131 | $91,127 | $67,005 | $67,005 | $125,347 |
| | 0.5 | $36,285 | $91,308 | $67,186 | $67,186 | $125,517 |
| | 1 | $36,440 | $91,488 | $67,368 | $67,368 | $125,687 |
| | 1.5 | $36,594 | $91,669 | $67,549 | $67,549 | $125,857 |
| | 2 | $36,749 | $91,849 | $67,731 | $67,731 | $126,027 |
| False-positive costs | 0 | $35,107 | $87,920 | $64,737 | $64,737 | $120,720 |
| | 0.5 | $35,773 | $89,704 | $66,052 | $66,052 | $123,203 |
| | 1 | $36,440 | $91,488 | $67,368 | $67,368 | $125,687 |
| | 1.5 | $37,106 | $93,272 | $68,683 | $68,683 | $128,171 |
| | 2 | $37,773 | $95,057 | $69,999 | $69,999 | $130,655 |
| Utility in cancer treatment (Y1) | 0.5 | $37,031 | $92,630 | $67,908 | $67,908 | $126,890 |
| | 0.6 | $36,700 | $91,992 | $67,607 | $67,607 | $126,219 |
| | 0.7 | $36,375 | $91,363 | $67,308 | $67,308 | $125,555 |
| | 0.8 | $36,056 | $90,742 | $67,013 | $67,013 | $124,897 |
| | 0.9 | $35,743 | $90,130 | $66,720 | $66,720 | $124,247 |
| Utility: False-pos (1-month duration) | 0.8 | $38,656 | $108,111 | $75,346 | $75,346 | $159,932 |
| | 0.9 | $37,515 | $99,107 | $71,134 | $71,134 | $140,757 |
| Utility: False-neg (1-year duration) | 0.8 | $32,181 | $78,699 | $57,941 | $57,941 | $108,496 |
| | 0.9 | $34,178 | $84,613 | $62,300 | $62,300 | $116,460 |
| Discount rate (costs and outcomes) | 0 | $12,929 | $32,407 | $26,534 | $26,534 | $47,179 |
| | 0.035 | $27,528 | $69,592 | $52,594 | $52,594 | $97,577 |
| | 0.1 | $79,904 | $192,117 | $133,458 | $133,458 | $245,752 |
| Model follow-up/duration (to age …) | 60 | $54,271 | $134,844 | $136,186 | $136,186 | $176,946 |
| | 70 | $42,086 | $105,979 | $86,015 | $86,015 | $143,515 |
| | 80 | $37,990 | $95,602 | $72,280 | $72,280 | $130,787 |
| | 90 | $36,688 | $92,153 | $68,114 | $68,114 | $126,487 |
| | 99 | $36,440 | $91,488 | $67,368 | $67,368 | $125,687 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; MAM = mammography; Sens = sensitivity; Spec = specificity; LCL = lower control limit; UCL = upper control limit.

## D.7 Discussion of the results of the economic evaluation

The incremental costs per QALY of adding MRI to mammography in breast cancer screening estimated in the economic model were as follows:

- $35,460 in the *BRCA1* population (interim funded).
- $91,488 in the familial high-risk population (interim funded).
- $58,240 in the population with prior invasive breast cancer (not currently funded).
- $82,793 in the population with prior noninvasive breast cancer (not currently funded).
- $176,536 in the population with prior chest irradiation (not currently funded).

Importantly, these results were similar to corresponding results in the United Kingdom using the NICE model upon which this model is based. In the NICE (2013) assessment, the cost-effectiveness ratios for MRI in addition to mammography were £13,486 (A$24,949 at GB£1 = A$1.85) for the *BRCA1* population and £38,919 (A$72,000) for the high-familial-risk population (Tables 2.16 and 2.17 of NICE, 2013). The corresponding ICERs here were slightly higher for each population (A$35,460 and A$91,488). The increases can be explained by:

- a higher cost for MRI in Australia (A$690) than in the NICE model (£224 ≈ A$414)
- a higher discount rate in Australia, which puts more emphasis on the upfront costs of MRI and less emphasis on the downstream benefits relative to the NICE model, which uses a discount rate of 3.5%
- the costs of chemotherapy in this model, which are higher than the costs used in the NICE model, meaning there are more costs in the MRI arm of the model owing to the detection of more cancers.

Nevertheless, the cost-effectiveness results for MRI are similar to what has been predicted in this comparable, and important, jurisdiction.

The main drivers of the results of this model may be biased in favour of MRI. For example:

- The data for the accuracy of mammography used in the model are based largely on evidence using film screen mammography, which may be inferior to the more commonly used digital mammography, thus overestimating the benefit of adding MRI to screening.
- The model does not incorporate the use of ultrasound, the inclusion of which is expected to reduce the incremental sensitivity of adding MRI to screening.
- The breast cancer risks used in the *BRCA1* and high-familial-risk populations imply a lifetime risk of breast cancer at the upper end of (or slightly higher than) rates reported in the literature. This overestimate in breast cancer risk will overestimate the benefit of the additional sensitivity with MRI.
- The model is driven by an assumption that early detection will improve 5-year overall survival by 18.8%. The benefits and harms of breast cancer screening in the general population are controversial, and an accurate estimate in these high-risk populations is not possible; however, it is clear that the cost-effectiveness of MRI relies heavily upon accurate estimation of this assumption.

At $91,488 per QALY, the ICER for MRI screening is relatively high in the high-familial-risk population when considered against traditional thresholds of cost-effectiveness used in Australia. This suggests that alternative options to better stratify these women (eg, genetic testing for the *BRCA1* mutation) or a shorter duration of MRI screening in older women will help to improve the cost-effectiveness of MRI in this group. In sensitivity analyses where MRI screening is limited to a population aged 40 to 50 years, the ICER improves to $63,039. If MRI is used for only 5 years in women aged 40 to 45 years, the ICER improves again, to $53,915.

Despite having the lowest lifetime risk of breast cancer, the population with prior invasive cancer has a better ICER for MRI ($58,240) than all other populations except the *BRCA1* population. This appears to be because the duration of MRI screening is shorter (6 years) and is targeted to the period of time when the risk of disease recurrence is greatest (the period immediately following the original diagnosis and treatment).

In the population with prior chest irradiation, the model had to assume a constant risk of breast cancer over time owing to lack of data. This assumption means it is difficult for the model to appropriately target the use of MRI within this population, and the ICER for MRI in this population is consequently very high (close to $200,000 per QALY). Results from the other populations show that MRI use should be targeted to the period when the population is most at risk of breast cancer.

Overall, the results of the economic model suggest that (with the exception of the *BRCA1* population) MRI screening needs to be better targeted to shorter time periods when the risk of developing breast cancer is greatest, and not necessarily when mammography is least effective. The use of MRI in younger patients in whom the sensitivity of mammography is lower is not necessarily cost-effective, because the risk of breast cancer is lower and the lifetime costs of MRI will be greatest in these younger cohorts.

# Section E Estimated extent of use and financial implications

## E.1 Description of data sources used in the analysis

### E.1.1 Estimation of the size of the eligible populations

In Australia, data collection on the incidence and prevalence of different types of breast cancer is variable. Consequently, a range of sources have been used to support the estimation of the sizes of the following four eligible populations:

- Women with gene mutations and family history (population for the existing interim items).
- Women with a prior history of invasive breast cancer.
- Women with a prior history of DCIS or LCIS.
- Women with a prior history of irradiation to the chest from 10 to 35 years of age.

All four populations are restricted to women aged <50 years. The data sources used for each population are summarised below.

**Gene mutations or family history**

Estimation of the future use of the current interim items for breast MRI (MBS item numbers 63464 and 63467) is based on a projection of the actual use of the interim items since July 2009.

**Prior history of invasive breast cancer**

There is little data available on the prevalence of breast cancer in Australia. To estimate the number of women aged <50 years who have a prior history of invasive breast cancer, data on the prevalence of breast cancer and the type of breast cancer at diagnosis were taken from AIHW (2012b). The data used in the analyses are presented in Table E.1 and the calculations are explained in detail in Section E.2.1. Approximately 5% of breast cancer diagnoses are diagnosed in women with gene mutations or family history (NBOCC, 2009). These women are already eligible to receive breast MRI under the current interim items and were excluded from this population. The projected number of women in Australia was taken from ABS (2013).

**Table E.1 Data used to estimate the number of women aged <50 years with a prior history of invasive breast cancer.**

| Description | Source | Value |
|---|---|---|
| 27-year prevalence of breast cancer (number), 31 Dec 2008 | AIHW 2012b Table 5.1 p. 61 | 159325 |
| 27-year prevalence of breast cancer (rate per 10,000 females), 31 Dec 2008 | AIHW 2012b Table 5.1 p. 61 | 146.5 |
| 5-year prevalence of breast cancer (number), 31 Dec 2008 | AIHW 2012b Table 5.2 p. 62 | 57327 |
| 5-year prevalence of breast cancer at <50 years (number), 31 Dec 2008 | AIHW 2012b Table 5.2 p. 62 | 11376 |
| Proportion of 5-year prevalence of breast cancer at <50 years | Calculated | 19.8% |
| Proportion of diagnoses at <50 years that are invasive ductal or lobular cancer | AIHW 2012b Table 2.4 p. 15 | 90.6% |
| Proportion of diagnoses in women without gene mutations or family history | NBOCC 2009 p. 16 | 95.0% |

AIHW = Australian Institute of Health and Welfare.

**Prior history of DCIS or LCIS**

Women with a history of DCIS or LCIS are a much smaller group. A recent report (AIHW & NBOCC, 2010) found that 326 women <50 years of age were diagnosed with DCIS in 2005. No sources for the incidence of LCIS were identified, so it was assumed to be 50% of the DCIS incidence. These incidence data have been used to estimate the size of this population. Increases in the population over time were estimated using the ABS (2013) population projections.

**Prior history of irradiation to the chest from 10 to 35 years of age**

The Faculty of Radiation Oncology (2010) estimate that there may be, at most, 1000 additional women who would be considered as being at high risk as a result of receiving chest irradiation for Hodgkin's lymphoma and therefore potentially eligible for screening with MRI. This number has been used to estimate the size of this population. Increases in the population over time were estimated using the ABS (2013) population projections.

### E.1.2 Screening uptake rates for the new populations

The rate of uptake of breast MRI for women with a prior history of invasive breast cancer or of DCIS or LCIS was estimated from the participation rate of the BreastScreen Australia program. The most recent monitoring report for BreastScreen Australia (AIHW, 2013) indicated that in 2010–11, the age-standardised participation rate was 54.6%. For both populations it was assumed that this uptake rate will begin at 20% in Year 1 of listing, increasing to 54.6% in Year 5. The BreastScreen target participation rate of 70.0% was used in sensitivity analyses (see Section E.6.1 for details).

The rate of uptake for women with a prior history of chest irradiation was based on the published literature of breast cancer screening for survivors of Hodgkin's lymphoma. A number of studies have reported the participation rates for women with a history of Hodgkin's lymphoma who were invited to participate in a mammography screening program. The UK National Breast Cancer Screening Programme achieved a participation rate of 58.3% (Howell & Sebek, 2009). Three similar studies conducted in North America, which also invited participants, published participation rates of 75.0% (90/120) (Diller et al, 2002), 68.9% (115/167) (Kwong et al, 2008) and 31.9% (115/360) (Lee et al, 2008).

The base-case analysis used the participation rate from Lee et al (2008). This study reported the lowest participation rate, which was considered to be the best estimate of participation when women are not invited for screening. It was assumed that the uptake rate will begin at 7% in Year 1 of listing, increasing to 31.9% in Year 5. The participation rate from Howell and Sebek (2009) was used in sensitivity analyses (see Section E.6.1 for details).

The uptake rates for the first 5 years of listing for each population are shown in Table E.2.

**Table E.2 Uptake rates for breast MRI across 5 years.**

| Population | Data source | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|---|
| History of invasive breast cancer | AIHW 2013 Table 1.1 p. 11 | 20.0% | 30.0% | 40.0% | 50.0% | 54.6% |
| History of DCIS or LCIS | AIHW 2013 Table 1.1 p. 11 | 20.0% | 30.0% | 40.0% | 50.0% | 54.6% |
| History of chest irradiation | Lee 2008 p. 63 | 7.0% | 14.0% | 21.0% | 28.0% | 31.9% |

AIHW = Australian Institute of Health and Welfare; DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ.

### E.1.3 Follow-up MRI rates

The proportion of women in all populations who undergo follow-up MRI was estimated on the basis of the available data for the interim MBS items 63464 and 63467. Between July 2009 and June 2013 there were 9516 services for breast MRI (item 63464). During the same time, 708 follow-up MRI services (item 63467) were claimed, representing a follow-up imaging rate of 7.4%.

### E.1.4 Annual risk of breast cancer

The annual risk of breast cancer in each of the four populations in the base-case analysis was based on the 5-year risk calculated in the economic model. For women with gene mutations or family history and women with prior history of chest irradiation, the risk selected was that for a 40-year-old woman. For women with prior DCIS or LCIS, or a prior history of invasive breast cancer, the risk was that for a 44 year-old woman. For each population, the 5-year risk was divided by 5 to give an estimate of the annual risk of breast cancer.

**Table E.3 Annual risk of breast cancer in each of the included populations.**

| Population | Risk estimate |
|---|---|
| Women with gene mutations or family history | 1.2% |
| Women with history of invasive breast cancer | 1.1% |
| Women with previous DCIS or LCIS | 1.1% |
| Women with previous chest irradiation | 0.5% |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

### E.1.5 Diagnostic accuracy of mammography and MRI

The diagnostic accuracy of mammography and MRI in each of the four populations was based on the data presented in Section B (Table E.4). Where available, the data used for MRI were taken from studies where MRI was used in addition to mammography.

**Table E.4 Sensitivity and specificity of mammography and MRI in each population.**

| Population | Imaging modality | Sensitivity | Specificity | Source |
|---|---|---|---|---|
| Women with gene mutations or family history | MRI+MAM | 0.88 | 0.88 | HIQA, 2013 |
| | MAM | 0.38 | 0.92 | |
| Women with history of invasive breast cancer | MRI+MAM | 1.00 | 0.79 | Berg et al, 2012 |
| | MAM | 0.50 | 0.95 | |
| Women with previous DCIS or LCIS | MRI | 0.71 | 0.76 | Sung et al, 2011 |
| | MAM | 0.36 | 0.90 | |
| Women with previous chest irradiation | MRI+MAM | 0.95 | 0.86 | Ng et al, 2013 |
| | MAM | 0.68 | 0.92 | |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; MAM = mammography; MRI = magnetic resonance imaging.

### E.1.6 Assumptions used in the analysis of imaging follow-up and treatment

The key assumptions used to calculate the impact of MRI follow-up and breast cancer treatment costs are summarised in Table E.5. The financial impact analyses focus on the cost of screening with MRI and the cost of the additional false-positive and true-positive findings from MRI. It is assumed that only those additional findings with MRI result in changes in patient management. Management of all other women is not changed.

**Table E.5 Assumptions used in the follow-up and treatment cost analysis.**

| Details of assumption | Source |
|---|---|
| There is no change in the use of mammography with MRI. All women who would receive MRI currently receive mammography and this does not change with the addition of MRI | Assumption |
| MRI will replace ultrasound imaging in 25% of women. For the remaining 75% of women, use of ultrasound is not changed with the addition of MRI | HESP advice and assumption |
| Women who test negative with MRI receive no further follow-up | Assumption |
| Women who test positive with MRI receive a follow-up biopsy | Assumption |
| False-positives are detected at biopsy and not treated | Assumption |
| True-positives are confirmed with biopsy and receive treatment | Assumption |
| Only additional true-positives and false-positives detected with MRI are included in the analysis of follow-up and treatment costs; management of all other women is not changed | Assumption |

HESP = Health Expert Standing Panel; MRI = magnetic resonance imaging.

## E.2 Estimation of use and costs of the proposed medical service

### E.2.1 Estimation of the size of the eligible patient populations

#### Gene mutations or family history

The number of women with gene mutations or a family history of breast cancer that will receive MRI under the existing interim MBS items was estimated by extrapolation of the use data for MBS item 63464. The actual use data for MBS items 63464 and 63467 from July 2009 are shown in Table E.6.

**Table E.6 Use of MBS items 63464 and 63467, July 2009 – June 2013.**

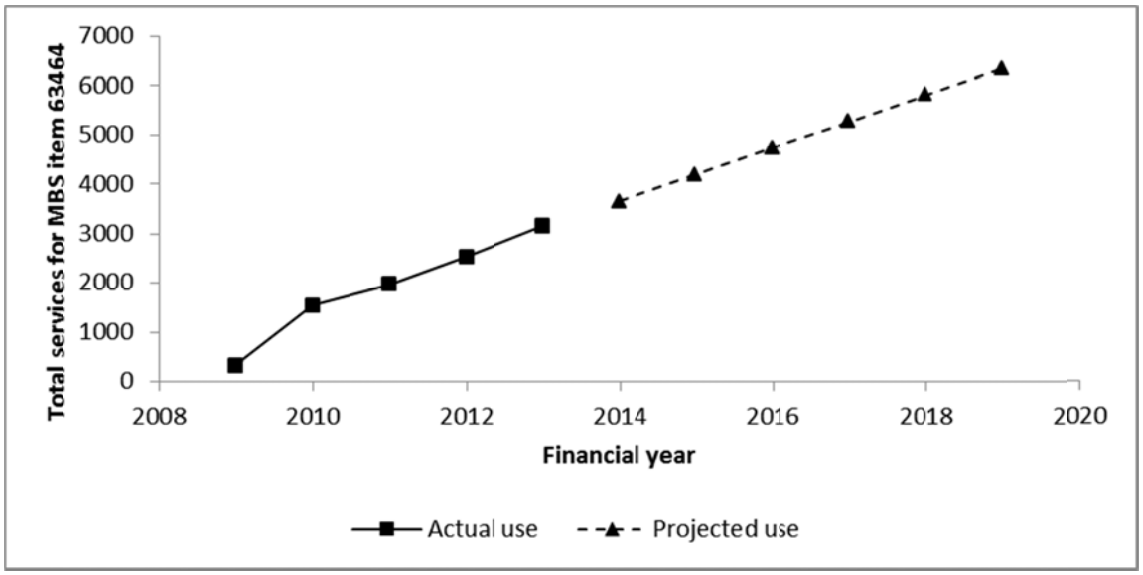
| Financial year | MBS 63464 Number of services | MBS 63467 Number of services |
|---|---|---|
| 2009 | 318 | 1 |
| 2010 | 1540 | 62 |
| 2011 | 1974 | 164 |
| 2012 | 2528 | 246 |
| 2013 | 3156 | 235 |
| Total | 9516 | 708 |

MBS = Medicare Benefits Schedule.

Source: Medicare Item reports accessed 27 November 2013.

The annual use of MBS item 63464 from July 2010 to June 2013 was extrapolated using linear regression, as shown in Figure E.1. The data for financial year 2009 were excluded, as this was the first year of listing and the item was available only from February 2009.

**Figure E.1 Projected use of MBS item 63464.**




MBS = Medicare Benefits Schedule.
Source: MBS item 63464 use July 2009 – June 2013; Medicare item reports accessed 27 November 2013.

The number of women who would receive MRI between financial years 2014 and 2019 is shown in Table E.7. It is estimated that 4,190 women will receive MRI in 2015, increasing to 6,351 in 2019. The proportion of women who carry a *BRCA* mutation has been estimated at 0.1% (NBOCC, 2009). Using the ABS populations projections, there will be approximately 7,934 women aged <50 years with a *BRCA* mutation in Australia in the 2015 financial year. As these women represent only a subgroup of the women eligible for MRI, the projected usage of MRI in Table E.7 is not excessive.

In each year the number of women who would have a follow-up MRI was calculated by applying the 7.4% follow-up MRI rate (see Section E.1.3). The number of ultrasounds replaced by MRI was calculated by applying the 25% ultrasound replacement rate (see Section E.1.6).

**Table E.7 Estimation of the number of women with gene mutations or family history who receive MRI.**

| Description | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women with gene mutations or family history who take up MRI screening | 4,190 | 4,730 | 5,271 | 5,811 | 6,351 |
| Number who have follow-up MRI | 312 | 352 | 392 | 432 | 473 |
| Number of ultrasounds replaced | 1,048 | 1,183 | 1,318 | 1,453 | 1,588 |

FY = financial year; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging. Note: Rounding has been applied.

**Prior history of invasive breast cancer**

The number of women with a prior history of invasive breast cancer who receive MRI was estimated using the following calculations:

1. The number of women in Australia with a prior history of breast cancer was calculated by applying the 27-year prevalence rate (146.5 per 10,000; AIHW, 2012b) to the ABS population projections.
2. The number of women aged <50 years with a prior history of breast cancer was calculated by applying the proportion of the 5-year prevalence of breast cancer among women aged <50 years (19.8%; AIHW, 2012b).
3. The number of women aged <50 years with a prior history of *invasive* breast cancer was calculated by applying the proportion of diagnoses in women aged <50 years for invasive ductal or lobular cancer (90.6%; AIHW, 2012b).
4. The number of women aged <50 years with a prior history of invasive breast cancer and who *do not* have gene mutations or family history was calculated by applying the proportion of breast cancer diagnoses among women without gene mutations or family history (95%; NBOOC, 2009).
5. The number of eligible women who take up MRI was calculated by applying the screening uptake rate.
6. The number of women who have follow-up MRI and the number of ultrasounds replaced were calculated by applying the 7.4% follow-up MRI rate and the 25% ultrasound replacement rate.

For a full explanation of the data and assumptions used in these calculations, see Section E.1. The results of the calculations are presented in Table E.8. Using this methodology, the estimated number of women aged <50 years with a prior history of breast cancer in the financial year 2015 is 34,953. This is approximately 10 times the incidence of breast cancer in the same age group in 2008, which was 3,208 (AIHW, 2012b). It is estimated that 6,017 women will receive MRI in 2015, increasing to 17,577 in 2019.

**Table E.8 Estimation of the number of women with prior history of invasive breast cancer who receive MRI.**

| Description | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of females in Australia | 12,022,954 | 12,233,224 | 12,444,642 | 12,655,537 | 12,865,712 |
| Number of women with a prior history of breast cancer | 176,136 | 179,217 | 182,314 | 185,404 | 188,483 |
| Number of women aged <50 years with a prior history of breast cancer | 34,953 | 35,564 | 36,178 | 36,792 | 37,403 |
| Number of women aged <50 years with a prior history of invasive breast cancer | 31,667 | 32,221 | 32,778 | 33,333 | 33,887 |
| Number of women aged <50 years with a prior history of invasive breast cancer with no gene mutations or family history | 30,084 | 30,610 | 31,139 | 31,667 | 32,192 |
| Number who take up MRI screening | 6,017 | 9,183 | 12,456 | 15,833 | 17,577 |
| Number who have follow-up MRI | 448 | 683 | 927 | 1,178 | 1,308 |
| Number of ultrasounds replaced | 1,504 | 2,296 | 3,114 | 3,958 | 4,394 |

FY = financial year; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging. Note: Rounding has been applied.

**Prior history of DCIS or LCIS**

The number of women with a prior history of DCIS or LCIS who would receive MRI was estimated using the following calculations:

1. The number of women in Australia in 2015 with a prior history of DCIS was estimated by multiplying the number of incident DCIS cases in women aged <50 years in 2005 (326: AIHW & NBOCC, 2010) by a factor of 6, selected because 44 was the screening start age used in the economic model, and a patient of this age would have 6 years of screening before becoming ineligible for MRI at age 50 years.
2. The number of women in Australia in 2016–2019 with a prior history of DCIS was estimated by applying the annual growth rate of the Australian population from the ABS population projections.
3. The number of women in Australia with a prior history of LCIS was estimated as 50% of the size of the DCIS population.
4. The total number of women who receive MRI was calculated by combining the numbers of women with a prior history of DCIS or LCIS.
5. The number of women who have follow-up MRI and the number of ultrasounds replaced were calculated by applying the 7.4% follow-up MRI rate and the 25% ultrasound replacement rate.

For a full explanation of the data and assumptions used in these calculations, see Section E.1. The results of the calculations are presented in Table E.9. It is estimated that 717 women will receive MRI in 2015, increasing to 2,095 in 2019.

**Table E.9 Estimation of the number of women with prior history of DCIS or LCIS who receive MRI.**

| Description | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women with a prior history of DCIS | 1,956 | 1,989 | 2,023 | 2,057 | 2,092 |
| Number of women with a prior history of LCIS | 1,630 | 1,658 | 1,686 | 1,715 | 1,744 |
| Number of women with a prior history of DCIS or LCIS | 3,586 | 3,647 | 3,709 | 3,772 | 3,836 |
| Number who take up MRI screening | 717 | 1,094 | 1,484 | 1,886 | 2,095 |
| Number who have follow-up MRI | 53 | 81 | 110 | 140 | 156 |
| Number of ultrasounds replaced | 179 | 274 | 371 | 472 | 524 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging. Note: Rounding has been applied.

**Prior history of irradiation to the chest from 10 to 35 years of age**

The number of women with a prior history of chest irradiation who would receive MRI was estimated on the basis of advice from the Faculty of Radiation Oncology (2010). The Faculty estimates that there may be, at most, 1000 women who would be considered as being at high risk as a result of receiving chest irradiation for Hodgkin's lymphoma. This number was used as the number of women eligible for MRI in 2015, and increases in the population over time were estimated using the ABS (2013) population projections. The number of women who have follow-up MRI and the number of

ultrasounds replaced were calculated by applying the 7.4% follow-up MRI rate and the 25% ultrasound replacement rate.

The results of the calculations are presented in Table E.10. It is estimated that 70 women will receive MRI in 2015, increasing to 341 in 2019.

**Table E.10 Estimation of the number of women with prior history of chest irradiation who receive MRI.**

| Description | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women with a history of chest irradiation | 1000 | 1017 | 1034 | 1052 | 1070 |
| Number who take up MRI screening | 70 | 142 | 217 | 295 | 341 |
| Number who have follow-up MRI | 5 | 11 | 16 | 22 | 25 |
| Number of ultrasounds replaced | 18 | 36 | 54 | 74 | 85 |

FY = financial year; MRI = magnetic resonance imaging. Note: Rounding has been applied.

### E.2.2 Estimated cost of breast MRI

Both the current and proposed listings for breast MRI are subject to the Bulk Billing Incentive. For items in Group I5—MRI, the Bulk Billing Incentive for out-of-hospital services is 100% of the Schedule Fee. As this affects the benefit paid for breast MRI, the average benefit per service for the interim items was calculated and used in the financial impact calculations. For each interim item, the total amount of benefits paid out between July 2009 and June 2013 was divided by the total number of services for the item over the same time period (Table E.11). The effect of using the average benefit per service for the financial year 2013 is explored in sensitivity analyses (see Section E.6.4).

**Table E.11 Average benefit per service for the breast MRI interim items (FY 2009–FY 2013).**

| Description | MBS item | Total services | Total benefits | Average benefit per service |
|---|---|---|---|---|
| Breast MRI, initial imaging | 63464 | 9516 | $6,227,309 | $654.40 |
| Breast MRI, follow-up imaging | 63467 | 708 | $466,207 | $658.48 |

FY = financial year; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging. Note: Rounding has been applied.

#### Initial breast MRI

The numbers of women in each of the populations who take up breast MRI screening each year in the first 5 years of listing are shown in Table E.12. Details of how patient numbers were estimated are explained in Section E.2.1.

**Table E.12 Numbers of women in the four populations who receive breast MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | 4,190 | 4,730 | 5,271 | 5,811 | 6,351 |
| Prior history of invasive breast cancer | 6,017 | 9,183 | 12,456 | 15,833 | 17,577 |
| Prior history of DCIS or LCIS | 717 | 1,094 | 1,484 | 1,886 | 2,095 |
| Prior history of therapeutic radiation to the chest | 70 | 142 | 217 | 295 | 341 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

The cost of initial breast MRI was calculated by multiplying the number of patients in each population who take up MRI screening by the average benefit per service for MBS item 63464 (breast MRI, initial imaging). The results of the calculations are shown in Table E.13. The total cost for all populations was estimated to be $7.2 million in 2015, rising to $17.3 million in 2019.

**Table E.13 Estimated cost of initial MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $2,742,084 | $3,095,593 | $3,449,102 | $3,802,611 | $4,156,120 |
| Prior history of invasive breast cancer | $3,937,377 | $6,009,356 | $8,150,949 | $10,361,350 | $11,502,500 |
| Prior history of DCIS or LCIS | $469,339 | $715,976 | $970,863 | $1,234,210 | $1,370,669 |
| Prior history of therapeutic radiation to the chest | $45,808 | $93,174 | $142,137 | $192,738 | $223,316 |
| All populations | $7,194,607 | $9,914,099 | $12,713,052 | $15,590,909 | $17,252,606 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Follow-up breast MRI**

The estimated number of women in each of the populations who have a follow-up breast MRI each year the first 5 years of listing is shown in Table E.14. Details of how patient numbers were estimated are explained in Section E.2.1.

**Table E.14 Number of women in the four populations who have a follow-up breast MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | 312 | 352 | 392 | 432 | 473 |
| Prior history of invasive breast cancer | 448 | 683 | 927 | 1,178 | 1,308 |
| Prior history of DCIS or LCIS | 53 | 81 | 110 | 140 | 156 |
| Prior history of therapeutic radiation to the chest | 5 | 11 | 16 | 22 | 25 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

The cost of follow-up breast MRI was calculated by multiplying the number of patients in each population who have follow-up MRI by the average benefit per service for MBS item 63467 (breast MRI, follow-up imaging). The results of the calculations are shown in Table E.15. The total cost for all populations was estimated to be $0.5 million in 2015, rising to $1.3 million in 2019.

**Table E.15 Estimated cost of follow-up MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $205,286 | $231,751 | $258,217 | $284,682 | $311,148 |
| Prior history of invasive breast cancer | $294,771 | $449,890 | $610,220 | $775,702 | $861,134 |
| Prior history of DCIS or LCIS | $35,137 | $53,601 | $72,684 | $92,399 | $102,615 |
| Prior history of therapeutic radiation to the chest | $3,429 | $6,975 | $10,641 | $14,429 | $16,719 |
| All populations | $538,624 | $742,218 | $951,762 | $1,167,212 | $1,291,615 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Total cost of initial and follow-up breast MRI**

The total cost of initial and follow-up breast MRI (MBS items 63464 and 63467) is shown in Table E.16. The total cost across all populations was estimated to be $7.7 million in 2015, rising to $18.6 million in 2019. The largest contributor to the total cost was the population of women with a prior history of invasive breast cancer. Given the moderately high level of bulk-billing for breast MRI, as reflected in the average benefit paid, the proposed listing could be expected to have a small to moderate impact on the Extended Medicare Safety Net.

**Table E.16 Total estimated cost of MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $2,947,370 | $3,327,344 | $3,707,319 | $4,087,293 | $4,467,268 |
| Prior history of invasive breast cancer | $4,232,148 | $6,459,246 | $8,761,169 | $11,137,052 | $12,363,634 |
| Prior history of DCIS or LCIS | $504,476 | $769,578 | $1,043,547 | $1,326,609 | $1,473,284 |
| Prior history of therapeutic radiation to the chest | $49,238 | $100,150 | $152,778 | $207,167 | $240,035 |
| All populations | $7,733,231 | $10,656,318 | $13,664,813 | $16,758,122 | $18,544,221 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

# E.3 Estimation of changes in use and cost of other medical services

## E.3.1 Cost of specialist attendance with breast MRI

It is assumed that for each episode of breast MRI, there will be an associated claim for specialist attendance. For initial breast MRI, the MBS item used to estimate cost was item 104, and for follow-up imaging it was item 105.

The cost of specialist attendance with initial breast MRI was calculated by multiplying the number of patients in each population who take up MRI screening by the 85% benefit for MBS item 104. The results of the analysis are shown in Table E.17. The total cost for specialist attendance with initial breast MRI was estimated to be $0.8 million in 2015, rising to $1.9 million in 2019.

**Table E.17 Cost of specialist attendance with initial MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $304,837 | $344,137 | $383,436 | $422,736 | $462,035 |
| Prior history of invasive breast cancer | $437,718 | $668,059 | $906,140 | $1,151,870 | $1,278,731 |
| Prior history of DCIS or LCIS | $52,176 | $79,595 | $107,931 | $137,207 | $152,377 |
| Prior history of therapeutic radiation to the chest | $5,093 | $10,358 | $15,801 | $21,427 | $24,826 |
| All populations | $799,823 | $1,102,149 | $1,413,308 | $1,733,239 | $1,917,970 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ.
Note: Rounding has been applied.

The cost of specialist attendance with follow-up breast MRI was calculated by multiplying the number of patients in each population who have follow-up MRI by the 85% benefit for MBS item

105. The results of the analysis are shown in Table E.18. The total cost for specialist attendance with follow-up breast MRI was estimated to be $29,897 in 2015, rising to $71,693 in 2019.

**Table E.18 Cost of specialist attendance with follow-up MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $11,395 | $12,864 | $14,333 | $15,802 | $17,271 |
| Prior history of invasive breast cancer | $16,362 | $24,972 | $33,871 | $43,056 | $47,798 |
| Prior history of DCIS or LCIS | $1,950 | $2,975 | $4,034 | $5,129 | $5,696 |
| Prior history of therapeutic radiation to the chest | $190 | $387 | $591 | $801 | $928 |
| All populations | $29,897 | $41,198 | $52,829 | $64,788 | $71,693 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

The total cost for consultations, both initial and follow-up, is shown in Table E.19. Across all populations, the total cost for specialist attendance was estimated to be $0.8 million in 2015, rising to $2.0 million in 2019.

**Table E.19 Total estimated cost of specialist attendance with MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $316,232 | $357,000 | $397,769 | $438,537 | $479,306 |
| Prior history of invasive breast cancer | $454,079 | $693,031 | $940,011 | $1,194,926 | $1,326,530 |
| Prior history of DCIS or LCIS | $54,127 | $82,570 | $111,965 | $142,336 | $158,073 |
| Prior history of therapeutic radiation to the chest | $5,283 | $10,745 | $16,392 | $22,228 | $25,754 |
| All populations | $829,720 | $1,143,347 | $1,466,137 | $1,798,027 | $1,989,662 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.3.2 Cost savings from replacement of ultrasound

The Health Expert Standing Panel advised that for a 25% of women, breast MRI would replace ultrasound. The estimated number of women in each population for whom breast MRI replaces ultrasound is shown in Table E.20. Details of how patient numbers were estimated are explained Section E.2.1.

**Table E.20 Number of women for who breast MRI replaces ultrasound.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | 1,048 | 1,183 | 1,318 | 1,453 | 1,588 |
| Prior history of invasive breast cancer | 1,504 | 2,296 | 3,114 | 3,958 | 4,394 |
| Prior history of DCIS or LCIS | 179 | 274 | 371 | 472 | 524 |
| Prior history of therapeutic radiation to the chest | 18 | 36 | 54 | 74 | 85 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

The MBS items included for women receiving ultrasound were specialist attendance (item 104) and ultrasound of both breasts (item 55076). The total MBS benefits paid per patient was $165.60 (85% benefit). The potential cost savings from the replacement of ultrasound with breast MRI are shown in

Table E.21. Across all populations, there was an estimated saving of $0.5 million in 2015, rising to $1.1 million in 2019.

**Table E.21 Total cost saving from replacement of ultrasound with MRI in the requested populations.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | –$173,370 | –$195,720 | –$218,071 | –$240,422 | –$262,773 |
| Prior history of invasive breast cancer | –$248,942 | –$379,944 | –$515,348 | –$655,101 | –$727,251 |
| Prior history of DCIS or LCIS | –$29,674 | –$45,268 | –$61,383 | –$78,034 | –$86,661 |
| Prior history of therapeutic radiation to the chest | –$2,896 | –$5,891 | –$8,987 | –$12,186 | –$14,119 |
| All populations | –$454,882 | –$626,824 | –$803,789 | –$985,742 | –$1,090,804 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

# E.4 Estimated financial implications for the MBS

## E.4.1 Cost of follow-up biopsy for additional positive findings with MRI

**Number of patients who receive a follow-up biopsy**

Patients who have a positive finding with mammography or MRI will undergo a biopsy to confirm the presence of a malignancy. The number of additional patients in each population who would receive a follow-up biopsy following a positive finding with MRI was estimated using the following calculations:

1. The numbers of true-positive and false-positive findings when MRI was and was not added to mammography were calculated using the sensitivity and specificity for each.
2. The number of additional positive findings with the addition of MRI was calculated by subtracting the number of positive findings with mammography from the number of positive findings with mammography + MRI.

Full details of these calculations are presented in Appendix 5. The results are shown in Table E.22. The population of women with a prior history of breast cancer had the highest number of women undergoing biopsy, increasing from 986 in 2015 to 2,880 in 2019. All of the remaining populations had <200 women receiving biopsy in the first year of listing.

**Table E.22 Number of additional positive findings with MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | 192 | 216 | 241 | 266 | 290 |
| Prior history of invasive breast cancer | 986 | 1,505 | 2,041 | 2,595 | 2,880 |
| Prior history of DCIS or LCIS | 102 | 156 | 211 | 269 | 298 |
| Prior history of therapeutic radiation to the chest | 4 | 9 | 13 | 18 | 20 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Costs included in the biopsy procedure**

The costs included for follow-up biopsies are shown in Table E.23. The total MBS cost per patient for a follow-up biopsy was $200.80.

**Table E.23 Breakdown of the included costs for biopsy procedure.**

| Description | MBS item | Benefit per service (85%) |
|---|---|---|
| Fine-needle aspiration biopsy or core-needle biopsy | 31533, 31548 | $117.25 |
| Ultrasound—one breast | 55070 | $83.55 |
| Total cost per patient | | $200.80 |

MBS = Medicare Benefits Schedule. Note: Rounding has been applied.

For the biopsy procedure, fine-needle aspiration biopsy (MBS item 31533) and core needle biopsy (item 31548) have been included. Both items have the same MBS schedule fee. Owing to very low use, stereotactic biopsy (items 31539 and 31545) and open biopsy (item 31506) have been excluded from the analyses. If the relative usage of these biopsy types should increase, it would be expected that the cost for follow-up would also increase, as these are higher-cost procedures. MRI-guided biopsy is not currently listed on the MBS. If MRI-guided biopsy gains a listing, this would also be expected to increase the costs of follow-up.

On advice from the Health Expert Standing Panel, the cost for imaging of a single breast with ultrasound (item 55070) has been included in the overall biopsy costs. Use of the corresponding 'NK' and non-referred items was very low, and these were excluded from the analysis.

**Total cost of additional follow-up biopsies with MRI**

The cost for additional biopsies with breast MRI was calculated by multiplying the number of additional patients who have a biopsy by the cost per patient. The results are shown in Table E.24. The estimated total cost for additional biopsies across all populations was $257,794 in 2015, increasing to $700,681 in 2019. The majority of this cost comes from the population of women with a prior history of invasive breast cancer, which reflects the higher patient numbers in this population.

**Table E.24 Total cost of additional biopsies with breast MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $38,455 | $43,413 | $48,370 | $53,328 | $58,285 |
| Prior history of invasive breast cancer | $197,989 | $302,177 | $409,865 | $521,014 | $578,396 |
| Prior history of DCIS or LCIS | $20,507 | $31,283 | $42,420 | $53,926 | $59,888 |
| Prior history of therapeutic radiation to the chest | $844 | $1,716 | $2,617 | $3,549 | $4,112 |
| All populations | $257,794 | $378,588 | $503,272 | $631,817 | $700,681 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.4.2 Cost of treatment for additional breast cancers identified by MRI

For the financial impact analyses it has been assumed that all patients who are true-positives have their diagnosis of breast cancer confirmed at biopsy and then proceed to treatment. The financial impact analyses of the additional true-positives identified with breast MRI have been included.

**Number of additional women who receive treatment for breast cancer**

The numbers of additional women in each of the populations who receive treatment for breast cancer each year in the first 5 years of listing is shown in Table E.25. Details of how patient numbers were estimated are explained in Section E.2.1. Overall, the numbers of additional women treated for

breast cancer are low. The population with the highest numbers is women with a prior history of invasive breast cancer. This population would have an additional 34 women undergo treatment in Year 1, rising to 100 women in Year 5. The population of women with a prior history of chest irradiation will not have any additional women treated, when the numbers are rounded to individual patients. This is due to the low numbers of women and the comparatively lower risk of breast cancer in this population.

**Table E.25 Number of additional women in the four populations who receive treatment for breast cancer.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | 26 | 29 | 33 | 36 | 39 |
| Prior history of invasive breast cancer | 34 | 52 | 71 | 90 | 100 |
| Prior history of DCIS or LCIS | 3 | 4 | 6 | 8 | 8 |
| Prior history of therapeutic radiation to the chest | 0 | 0 | 0 | 0 | 0 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**MBS costs for breast cancer treatment**

The MBS costs included in the analysis of breast cancer treatment costs are the same as those used in the economic model (Section D.4.4). The only exception is the cost for follow-up MRI, which has been incorporated earlier in the calculation of imaging costs (Section E.2.2). The MBS costs per patient are summarised in Table E.26.

**Table E.26 Breakdown of the included MBS costs for breast cancer treatment.**

| Description | MBS item | Benefit per service (85% ) | Number of services | Cost |
|---|---|---|---|---|
| Initial specialist attendance | 104 | $ 72.75 | 1 | $ 72.75 |
| Follow-up specialist attendance | 105 | $ 36.55 | 1 | $ 36.55 |
| Drug administration | 13918 | $ 83.30 | 6 | $ 499.80 |
| G-CSF administration (nurse cost) | 13915 | $ 55.30 | 5 | $ 276.50 |
| Total cost per patient | | | | $ 885.60 |

MBS = Medicare Benefits Schedule; G-CSF = Granulocyte-colony Stimulating Factor. Note: Rounding has been applied.

**Total cost to the MBS for treatment of additional breast cancers identified by MRI**

The cost to the MBS for the treatment of additional breast cancers identified with breast MRI was calculated by multiplying the number of additional patients who have a breast cancer treatment by the cost per patient. The results are shown in Table E.27. Overall, the cost is low. The cost across all populations is estimated to be $55,915 in 2015, increasing to $131,002 in 2019. The proposed listing may increase the costs of the Extended Medicare Safety Net for MBS items used in the treatment. However, as the number of additional patients undergoing treatment is low, the effects would be expected to be modest.

**Table E.27 Total cost to the MBS of treatment of additional breast cancers identified by MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $23,007 | $25,973 | $28,939 | $31,905 | $34,872 |
| Prior history of invasive breast cancer | $30,372 | $46,355 | $62,875 | $79,925 | $88,728 |
| Prior history of DCIS or LCIS | $2,534 | $3,866 | $5,242 | $6,664 | $7,401 |
| Prior history of therapeutic radiation to the chest | $1 | $1 | $1 | $1 | $1 |
| All populations | $55,915 | $76,195 | $97,058 | $118,496 | $131,002 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.4.3 Total cost to MBS associated with the requested listing

The total cost to the MBS for the requested listing includes the costs for breast MRI, specialist attendance for breast MRI, follow-up biopsy and breast cancer treatment. Cost savings to the MBS come from the replacement of ultrasound with breast MRI. The total cost of the proposed listing for each of the populations, incorporating cost savings, is presented in Table E.28. The estimated total cost for all populations is $8.4 million in the first year of listing, increasing to $20.3 million in Year 5. The majority of this cost in each population comes from the cost of providing breast imaging with MRI. The contribution of follow-up and treatment costs is relatively minor.

**Table E.28 Total cost to the MBS of the requested listing.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,151,694 | $3,558,010 | $3,964,326 | $4,370,642 | $4,776,958 |
| Prior history of invasive breast cancer | $4,665,645 | $7,120,865 | $9,658,572 | $12,277,816 | $13,630,036 |
| Prior history of DCIS or LCIS | $551,969 | $842,029 | $1,141,791 | $1,451,502 | $1,611,986 |
| Prior history of therapeutic radiation to the chest | $52,469 | $106,721 | $162,802 | $220,759 | $255,783 |
| All populations | $8,421,778 | $11,627,624 | $14,927,491 | $18,320,718 | $20,274,762 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

## E.5 Estimated financial implications for government health budgets

### E.5.1 Costs to the PBS associated with the requested listing

The requested listing for breast MRI will result in costs to the Pharmaceutical Benefits Scheme (PBS) for the treatment of additional patients diagnosed with breast cancer.

#### PBS costs for breast cancer treatment

The PBS costs included in the analysis of breast cancer treatment costs are the same as those used in the economic model (Section D.4.4). The PBS costs per patient are summarised in Table E.29.

**Table E.29 Breakdown of the included PBS costs for breast cancer treatment.**

| Description | PBS item | Unit cost | No. of units | Cost per patient |
|---|---|---|---|---|

| Description | PBS item | Unit cost | No. of units | Cost per patient |
|---|---|---|---|---|
| G-CSF | 6363X | $1,971.63 | 5 | $9,858.15 |
| Metoclopramide (IV) | 1206L | $1.32 | 6 | $7.92 |
| Metoclopramide (oral) | 1207M | $0.34 | 168 | $56.52 |
| Dexamethasone (IV) | 2509C | $3.00 | 6 | $18.00 |
| Dexamethasone (oral) | 1292B | $0.30 | 18 | $5.43 |
| Ondansetron (IV) | 1596B | $9.02 | 6 | $54.12 |
| Ondansetron (oral) | 1594X | $5.46 | 18 | $98.28 |
| Aprepitant (oral) | 8808N | $139.10 | 18 | $2,503.80 |
| Tamoxifen (1 year; 20 mg daily) | 2110C | $0.71 | 365 | $257.93 |
| Total cost per patient | | | | $12,860.15 |

G-CSF = Granulocyte-colony Stimulating Factor; IV = intravenous; mg = milligrams; PBS = Pharmaceutical Benefits Scheme. Note: Rounding has been applied.

**Total cost to the PBS for treatment of additional breast cancers identified by MRI**

The cost to the PBS for the treatment of additional breast cancers identified with breast MRI was calculated by multiplying the number of additional patients who have a breast cancer treatment (Table E.25) by the cost per patient. The results are shown in Table E.30. The total cost to the PBS for the treatment of additional breast cancers identified by MRI was $0.8 million in 2015, increasing to $1.9 million in 2019.

**Table E.30 Total cost to the PBS of treatment of additional breast cancers identified by MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $334,097 | $377,169 | $420,240 | $463,312 | $506,384 |
| Prior history of invasive breast cancer | $441,044 | $673,136 | $913,026 | $1,160,623 | $1,288,449 |
| Prior history of DCIS or LCIS | $36,801 | $56,140 | $76,126 | $96,775 | $107,475 |
| Prior history of therapeutic radiation to the chest | $19 | $19 | $19 | $19 | $19 |
| All populations | $811,960 | $1,106,463 | $1,409,411 | $1,720,729 | $1,902,326 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

## E.5.2 Costs to state and territory governments associated with the current listing

The costs to state and territory governments resulting from the requested listing are costs for the treatment of additional cases of breast cancer identified by MRI. The costs included in the analysis are the same as those used in the economic model (Section D.4.4) and are the costs of breast surgery following diagnosis. The cost per patient is $7,958 (AR-DRG code J06A). Patients who have previously had treatment for breast cancer may have a range of different treatment options for newly diagnosed cancer; this analysis may overestimate or underestimate the cost of surgery in this group.

The cost to state and territory governments for the treatment of additional breast cancers identified with breast MRI was calculated by multiplying the number of additional patients who have a breast

cancer treatment (Table E.25) by the cost per patient. The results are shown in Table E.31. Overall, the total cost of treating additional breast cancers was $0.5 million in 2015, increasing to $1.2 million in 2019.

**Table E.31 Total costs to state and territory governments for treatment of additional breast cancers identified by MRI.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $206,743 | $233,396 | $260,049 | $286,703 | $313,356 |
| Prior history of invasive breast cancer | $272,923 | $416,544 | $564,990 | $718,206 | $797,306 |
| Prior history of DCIS or LCIS | $22,773 | $34,740 | $47,107 | $59,885 | $66,506 |
| Prior history of therapeutic radiation to the chest | $12 | $12 | $12 | $12 | $12 |
| All populations | $502,450 | $684,691 | $872,159 | $1,064,806 | $1,177,180 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.5.3 Total cost to government health budgets

The total cost of the proposed listing to government health budgets is presented in Table E.32. This includes the estimated costs to the MBS, PBS, and state and territory governments. The estimated total cost to government of the proposed listings is $9.7 million in 2015, rising to $23.4 million in 2019. The majority of this cost comes from the cost of performing breast MRI, with treatment and follow-up costs making a minor contribution.

**Table E.32 Total costs to government health budgets.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,692,534 | $4,168,575 | $4,644,616 | $5,120,657 | $5,596,698 |
| Prior history of invasive breast cancer | $5,379,612 | $8,210,544 | $11,136,588 | $14,156,645 | $15,715,791 |
| Prior history of DCIS or LCIS | $611,543 | $932,909 | $1,265,024 | $1,608,162 | $1,785,967 |
| Prior history of therapeutic radiation to chest | $52,500 | $106,751 | $162,832 | $220,789 | $255,813 |
| All populations | $9,736,188 | $13,418,779 | $17,209,060 | $21,106,253 | $23,354,268 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

## E.6 Identification, estimation and reduction of uncertainty

### E.6.1 Higher patient numbers

The effect of higher patient numbers in all of the populations was explored. For women with gene mutation or family history of breast cancer (population for the current interim items), an alternative projection of screening uptake was based on monthly reports of services claimed for MBS items 63464 and 63467. On the basis of this projection, the number of women who have MRI will be 4,511 in 2015, increasing to 7,015 in 2019 (Table E.33).

**Table E.33 Estimation of the number of women with gene mutations or family history who receive MRI using monthly use data.**

| Description | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women with gene mutations or family history who take up MRI screening | 4,511 | 5,137 | 5,764 | 6,390 | 7,015 |

FY = financial year; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging. Note: Rounding has been applied.

For the three new populations, the effect of greater patient numbers was explored by increasing the screening uptake rates (Table E.34). For women with a prior history of DCIS, LCIS or invasive breast cancer, the uptake rate was set to 70% in Year 5 of listing, which is the target uptake rate for BreastScreen Australia. For those populations it was assumed that the uptake rate will begin at 30% in Year 1 of listing, increasing to 70% in Year 5. For women with a history of chest irradiation, the uptake rate at Year 5 of listing was set at 58.3%, which represents the high end of estimates available from the literature (Howell & Sebek, 2009; see also Section E.1.2). It was assumed that this uptake rate will begin at 20% in Year 1 of listing, increasing to 58.3% in Year 5.

**Table E.34 Alternative uptake rates for breast MRI across 5 years.**

| Population | Data source | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|---|
| History of invasive breast cancer | BreastScreen Australia target, AIHW 2013 p. 10 | 30.0% | 40.0% | 50.0% | 60.0% | 70.0% |
| History of DCIS or LCIS | BreastScreen Australia target, AIHW 2013 p. 10 | 30.0% | 40.0% | 50.0% | 60.0% | 70.0% |
| History of chest irradiation | Howell & Sebek, 2009 p. 101 | 20.0% | 30.0% | 40.0% | 50.0% | 58.3% |

AIHW = Australian Institute of Health and Welfare; DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ.

Using the higher uptake rates, the total costs of the proposed listing to the MBS and to government health budgets are shown in Table E.35 and Table E.36, respectively. The increase in screening uptake rates results in an increase in the number of women screened and treated, with a corresponding increase in costs. The total cost to government is estimated to be increased to $29.1 million in 2019, with the majority of the cost borne by the MBS. This represents an increase of $5.7 million from the base-case estimate.

**Table E.35 Total cost to the MBS of the requested listing using alternative uptake rates.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,393,189 | $3,864,168 | $4,335,577 | $4,806,126 | $5,276,675 |
| Prior history of invasive breast cancer | $6,998,468 | $9,494,486 | $12,073,215 | $14,733,379 | $17,474,405 |
| Prior history of DCIS or LCIS | $827,954 | $1,122,705 | $1,427,239 | $1,741,802 | $2,066,648 |
| Prior history of therapeutic radiation to the chest | $149,909 | $228,686 | $310,097 | $394,211 | $467,463 |
| All populations | $11,369,520 | $14,710,045 | $18,146,128 | $21,675,518 | $25,285,192 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Table E.36 Total cost to government health budgets using alternative uptake rates.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,975,470 | $4,527,270 | $5,079,574 | $5,630,871 | $6,182,168 |
| Prior history of invasive breast cancer | $8,069,418 | $10,947,393 | $13,920,736 | $16,987,974 | $20,148,450 |
| Prior history of DCIS or LCIS | $917,314 | $1,243,878 | $1,581,280 | $1,929,794 | $2,289,701 |
| Prior history of therapeutic radiation to the chest | $149,940 | $228,716 | $310,128 | $394,241 | $467,494 |
| All populations | $13,112,142 | $16,947,257 | $20,891,717 | $24,942,881 | $29,087,812 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.6.2 Higher risk of breast cancer

An increase in the risk of breast cancer would result in increases in the number of women who undergo biopsies and treatment for breast cancer. The effect of a higher risk of breast cancer was explored using the higher rates for each population shown in Table E.37.

**Table E.37 Higher estimates for the annual risk of breast cancer in each of the included populations.**

| Population | Risk estimate base case | Risk estimate sensitivity analysis | Source for sensitivity analysis |
|---|---|---|---|
| Women with gene mutations or family history | 1.2% | 2.0% | Assumption; based on 10-year risk estimates in Berg 2009 |
| Women with history of invasive breast cancer | 1.1% | 2.0% | ditto |
| Women with previous DCIS or LCIS | 1.1% | 2.0% | ditto |
| Women with previous chest irradiation | 0.5% | 1.2% | Assumption; same risk as women with gene mutation or family history (base-case risk) |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

The higher risk of breast cancer was incorporated into the cost calculations for each of the populations. The results of the analyses are shown in Table E.38 and Table E.39. Increasing the risk of breast cancer resulted in a modest increase in the overall cost of the requested listing. The total cost to government in 2019 was increased to $25.7 million, representing an increase of $2.3 million from the base-case estimate.

**Table E.38 Total cost to the MBS of the requested listing using higher breast cancer risk estimates.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,168,737 | $3,577,250 | $3,985,763 | $4,394,276 | $4,802,789 |
| Prior history of invasive breast cancer | $4,692,090 | $7,161,226 | $9,713,317 | $12,347,407 | $13,707,291 |
| Prior history of DCIS or LCIS | $554,141 | $845,342 | $1,146,284 | $1,457,213 | $1,618,328 |
| Prior history of therapeutic radiation to the chest | $52,471 | $106,723 | $162,804 | $220,761 | $255,784 |
| All populations | $8,467,439 | $11,690,540 | $15,008,168 | $18,419,657 | $20,384,193 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Table E.39 Total cost to government health budgets using higher breast cancer risk estimates.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $4,041,059 | $4,562,032 | $5,083,004 | $5,603,977 | $6,124,950 |
| Prior history of invasive breast cancer | $5,944,663 | $9,072,945 | $12,306,328 | $15,643,599 | $17,366,510 |
| Prior history of DCIS or LCIS | $658,656 | $1,004,780 | $1,362,482 | $1,732,055 | $1,923,558 |
| Prior history of therapeutic radiation to the chest | $52,539 | $106,790 | $162,871 | $220,828 | $255,852 |
| All populations | $10,696,917 | $14,746,547 | $18,914,685 | $23,200,459 | $25,670,870 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.6.3 Alternative accuracy estimates for MRI and mammography

The impact of varying the diagnostic accuracy of mammography and MRI in the new populations was explored. For each of the new populations, the sensitivity and specificity of mammography and MRI were set to the values from the meta-analysis in the HIQA (2013) report (Table E.4). The results of the analysis are shown in Table E.40 and Table E.41. The variation resulted in a very minor decrease in the overall cost of the proposed listing. The total cost to government in 2019 was $23.0 million, representing a decrease of $0.4 million from the base-case estimate.

**Table E.40 Total cost to the MBS of the requested listing using alternative diagnostic accuracy estimates.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,151,694 | $3,558,010 | $3,964,326 | $4,370,642 | $4,776,958 |
| Prior history of invasive breast cancer | $4,522,319 | $6,902,115 | $9,361,865 | $11,900,647 | $13,211,328 |
| Prior history of DCIS or LCIS | $539,064 | $822,342 | $1,115,096 | $1,417,566 | $1,574,298 |
| Prior history of therapeutic radiation to the chest | $52,189 | $106,150 | $161,931 | $219,577 | $254,413 |
| All populations | $8,265,267 | $11,388,618 | $14,603,219 | $17,908,433 | $19,816,997 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Table E.41 Total cost to government health budgets using alternative diagnostic accuracy estimates.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,692,534 | $4,168,575 | $4,644,616 | $5,120,657 | $5,596,698 |
| Prior history of invasive breast cancer | $5,236,285 | $7,991,795 | $10,839,881 | $13,779,476 | $15,297,082 |
| Prior history of DCIS or LCIS | $624,170 | $952,171 | $1,291,144 | $1,641,366 | $1,822,842 |
| Prior history of therapeutic radiation to chest | $52,246 | $106,207 | $161,987 | $219,633 | $254,470 |
| All populations | $9,605,235 | $13,218,747 | $16,937,628 | $20,761,133 | $22,971,092 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.6.4 Alternative average benefit for service for the breast MRI MBS items

The average benefit per service for the two interim MBS items for breast MRI has increased each year since 2009 owing to increasing use of bulk billing. The base-case financial impact analysis used the average benefit per service from 2009 to 2013. To explore the effect of varying this cost, a sensitivity analysis was performed using the average benefits per service from the financial year 2013. For MBS item 63464, the average benefit per service in 2013 was $669.18, and for MBS item 63467, it was $676.23. The results of the analysis are shown in Table E.42 and Table E.43. Using a higher cost for the breast MRI MBS items increased the total cost to the MBS and, consequently, to government. Overall, the increase in the cost to government was modest, being $0.4 million over the base-case estimates in 2019.

**Table E.42 Total cost to the MBS of the requested listing using alternative costs for breast MRI MBS items.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,219,140 | $3,634,152 | $4,049,163 | $4,464,174 | $4,879,185 |
| Prior history of invasive breast cancer | $4,762,492 | $7,268,675 | $9,859,059 | $12,532,671 | $13,912,960 |
| Prior history of DCIS or LCIS | $563,513 | $859,639 | $1,165,671 | $1,481,859 | $1,645,700 |
| Prior history of therapeutic radiation to chest | $53,596 | $109,013 | $166,298 | $225,499 | $261,275 |
| All populations | $8,598,741 | $11,871,478 | $15,240,190 | $18,704,204 | $20,699,120 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

**Table E.43 Total cost to government health budgets using alternative costs for breast MRI MBS items.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Gene mutation or family history | $3,759,980 | $4,244,716 | $4,729,452 | $5,214,188 | $5,698,925 |
| Prior history of invasive breast cancer | $5,476,459 | $8,358,355 | $11,337,075 | $14,411,501 | $15,998,715 |
| Prior history of DCIS or LCIS | $623,087 | $950,519 | $1,288,904 | $1,638,519 | $1,819,681 |
| Prior history of therapeutic radiation to chest | $53,626 | $109,043 | $166,328 | $225,530 | $261,306 |
| All populations | $9,913,152 | $13,662,633 | $17,521,760 | $21,489,738 | $23,778,625 |

DCIS = ductal carcinoma in situ; FY = financial year; LCIS = lobular carcinoma in situ. Note: Rounding has been applied.

### E.6.5 Summary

The financial impact calculations for the proposed listing are most sensitive to changes in the numbers of women screened with breast MRI. This is because the major contributor to the cost of the requested listing is the cost of performing the breast MRI service, including imaging and specialist attendance costs. Increases in the cost of the breast MRI MBS items due to greater use of bulk billing will increase the cost of the proposed listing to the MBS, although the extent of the increase would be modest. Changes to the diagnostic accuracy of mammography and MRI and changes to the risk of breast cancer result in only moderate changes to the financial impact. This is because changes to these variables alter the number of women who receive biopsy and treatment, which accounts for a small proportion of the total cost of the proposed listing.

# Appendix 1: Health Expert Standing Panel and Assessment Group

## Health Expert Standing Panel—Application Name No. 1098.1

| Member | Expertise or affiliation |
|---|---|
| A/Prof Jennifer Cawson | St. Vincent's Hospital Melbourne |
| Dr Gillian Mitchell | Peter MacCallum Cancer Centre |
| Mr Ian Morris | Princess Margaret Hospital for Children and King Edward Memorial Hospital for Women |
| Prof Christobel Saunders | Royal Perth Hospital |

## Evaluators

| Name | Organisation |
|---|---|
| Dr Briony Jack | NHMRC Clinical Trials Centre |
| Dr Samara Lewis | NHMRC Clinical Trials Centre |
| Dr Anna Stoklosa | NHMRC Clinical Trials Centre |
| Dr Melina Willson | NHMRC Clinical Trials Centre |
| Ms Sally Wortley | NHMRC Clinical Trials Centre |
| Ms Nimita Arora | THEMA Consulting |
| Mr Dan Jackson | THEMA Consulting |
| Mr Dominic Tilden | THEMA Consulting |

# Appendix 2: Search strategies

## Search strategies for asymptomatic high-risk women

**EMBASE.com search strategy.**

| Number | Search strategy |
|---|---|
| #1 | 'magnetic resonance imaging'/exp |
| #2 | 'mri'/mj |
| #3 | 'mri scan' |
| #4 | 'breast mri' |
| #5 | #1 OR #2 OR #3 OR #4 |
| #6 | 'breast cancer'/exp |
| #7 | 'breast tumour' |
| #8 | 'breast carcinoma'/mj |
| #9 | 'breast screening' |
| #10 | #6 OR #7 OR #8 OR #9 |
| #11 | #5 AND #10 |
| #12 | #11 AND [english]/lim AND [female]/lim |
| #13 | #12 AND [2006–2013]/py |

**PreMEDLINE search strategy.**

| Number | Search strategy |
|---|---|
| 1 | magnetic resonance imaging.mp. or exp Magnetic Resonance Imaging/ |
| 2 | MRI.ti,ab,kw. |
| 3 | MRI scan.ti,ab,kw. |
| 4 | breast MRI.ti,ab,kw. |
| 5 | 1 or 2 or 3 or 4 |
| 6 | breast cancer.mp. or exp Breast Neoplasms/ |
| 7 | breast tumour.ti,ab,kw. |
| 8 | breast carcinoma.ti,ab,kw. |
| 9 | breast screening.ti,ab,kw. |
| 10 | 6 or 7 or 8 or 9 |
| 11 | 5 and 10 |
| 12 | limit 11 to english language |

**Cochrane Library search strategy.**

| Number | Search strategy |
|---|---|
| 1 | MeSH descriptor: [Magnetic Resonance Imaging] explode all trees |
| 2 | "magnetic resonance imaging" (Word variations have been searched) |
| 3 | Magnetic resonance imag* (Word variations have been searched) |
| 4 | "MRI" (Word variations have been searched) |
| 5 | "MRI scan" (Word variations have been searched) |
| 6 | MR imag* (Word variations have been searched) |
| 7 | #1 or #2 or #3 or #4 or #5 or #6 |
| 8 | MeSH descriptor: [Breast Neoplasms] explode all trees |
| 9 | "breast cancer":ti,ab,kw (Word variations have been searched) |
| 10 | "breast carcinoma":ti,ab,kw (Word variations have been searched) |
| 11 | "breast tumour":ti,ab,kw (Word variations have been searched) |
| 12 | "breast tumours":ti,ab,kw (Word variations have been searched) |
| 13 | mammogram*:ti,ab,kw (Word variations have been searched) |
| 14 | breast screening:ti,ab,kw (Word variations have been searched) |
| 15 | #8 or #9 or #10 or #11 or #12 or #13 or #14 |
| 16 | #7 and #15 |

**WHO International Clinical Trials Registry Platform search strategy.**

| No. of search | Search terms |
|---|---|
| 1—Advanced search function | Condition = breast cancer<br>AND<br>Intervention = magnetic resonance imaging OR MRI<br>Recruitment status = ALL |
| 2—Advanced search function | Title = high risk<br>Condition = breast cancer<br>Intervention = MRI<br>Recruiting status = ALL |
| 3—Basic search function | Title = increased risk for breast cancer |

**Excluded health technology assessments and systematic reviews for the assessment of asymptomatic, high-risk women.**

| Citation | Reason for exclusion |
|---|---|
| Bermejo-Perez MJ, Marquez CS, Llanos MA (2008) Cancer surveillance based on imaging techniques in carriers of *BRCA1/2* gene mutations: a systematic review (Structured abstract). Br J Radiol 81:172–179. | Superseded |

| Citation | Reason for exclusion |
|---|---|
| Davidson E, Hancock S (2007) Surveillance of women at high risk of breast cancer: a tech brief (Structured abstract). No. 3, 309 New Zealand Health Technology Assessment (NZHTA). | Superseded |
| Dunfield L, Severn M (2007) Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer (Structured abstract). No. 3, 20. Canadian Agency for Drugs and Technologies in Health. | Superseded |
| Granader EJ, Dwamena B, Carlos RC (2008) MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach (Structured abstract). Acad Radiol 15:1590–1595. | Superseded |
| Health QO (2010) Cancer screening with digital mammography for women at average risk for breast cancer, magnetic resonance imaging (MRI) for women at high risk: an evidence-based analysis. pp 1–55. | Superseded |
| Lee JM, Halpern EF, Rafferty EA, Gazelle GS (2009) Evaluating the Correlation between Film Mammography and MRI for Screening Women with Increased Breast Cancer Risk. Acad Radiol 16:1323–1328. | Superseded |
| Lord SJ, Lei W, Craft P, Cawson JN, Morris I, Walleser S, Griffiths A, Parker S, Houssami N (2007) A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer (Structured abstract). Eur J Cancer 43:1905–1917. | Superseded |
| Morrow M, Waters J, Morris E (2011) MRI for breast cancer screening, diagnosis and treatment. Lancet 378(9805): 1804–11. | Superseded |
| Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D (2008) Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer (Structured abstract). Ann Intern Med 148:671–679. | Superseded |

**Excluded primary studies for the assessment of asymptomatic, high-risk women.**

| Trial ID | Citation | Reason for exclusion |
|---|---|---|
| Study type | | |
| Hoogerbrugge et al, 2008 | Hoogerbrugge N, Kamm YJL, Bult P, Landsbergen KM, Bongers EMHF, Brunner HG, Bonenkamp HJ, de Hullu JA, Ligtenberg MJL, Boetes C (2008) The impact of a false-positive MRI on the choice for mastectomy in *BRCA* mutation carriers is limited. Ann Oncol 19:655–659. | Non-comparative<br>Excluded from NICE, 2013 |
| Patrick-Miller et al, 2011 | Patrick-Miller LJ, Bradbury AR, Pius R, Wroblewski K, Verp MS, Jackson S, Gulden C, Newstead G, Abe H, Olopade OI (2011) Results from a longitudinal breast MRI surveillance study: Psychological impact for high-risk women. J Clin Oncol 29: (suppl; abstr 1563). | Abstract only |
| Shah et al, 2009 | Shah P, Rosen M, Stopfer J, Siegfried J, Kaltman R, Mason B, Armstrong K, Nathanson KL, Schnall M, Domchek SM (2009) Prospective study of breast MRI in *BRCA1* and *BRCA2* mutation carriers: Effect of mutation status on cancer incidence. Breast Cancer Res Treat 118:539–546. | Non-comparative<br>Excluded from NICE, 2013 |
| O'Neill et al, 2009 | O'Neill SM, Rubinstein WS, Sener SF, Weissman SM, Newlin AC, West DK, Ecanow DB, Rademaker AW, Edelman RR (2009) Psychological impact of recall in high-risk breast MRI screening. Breast Cancer Res Treat 115:365–371. | Non-comparative |
| Møller et al, 2013 | Møller P, Stormorken A, Jonsrud C, Holmen MM, Hagen AI, Clark N, Vabo A, Sun P, Narod SA, Maehle L (2013) Survival of patients with *BRCA1*- | Non-comparative |

| Trial ID | Citation | Reason for exclusion |
|---|---|---|
| | associated breast cancer diagnosed in an MRI-based surveillance program. Breast Cancer Res Treat 139:155–161. | |
| Patient characteristics | | |
| US study | Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, Pisano E, Schnitt SJ, Gatsonis C, Schnall M, DeAngelis GA, Stomper P, Rosen EL, O'Loughlin M, Harms S, Bluemke DA; International Breast MRI Consortium Working Group (2005) Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. Cancer May 1;103(9):1898–905. | Age: range NR (mean age 45 years, SD ± 9.7)<br>Included women ≥25 years |
| Zakaria et al, 2009 | Zakaria S, Brandt KR, Degnim AC, Thomsen KM. Patients' perceptions of breast MRI: A single-center study. Am J Roentgenol 2009; 192(4):1149–1154. | Includes women having MRI for staging |
| Berg et al, 2012 | Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. J Am Med Assoc 2012; 307(13):1394–1404. | Age: 21% of participants <50 years<br>NB: Excluded from HIQA, 2013 |
| Trecate et al, 2006 | Trecate G, Vergnaghi D, Manoukian S, Bergonzi S, Scaperrotta G, Marchesini M et al. MRI in the early detection of breast cancer in women with high genetic risk. Tumori 2006; 92(6):517–523.<br>Trecate G, Manoukian S, Suman L, Vergnaghi D, Marchesini M, Agresti R, Ferraris C, Peissel B, Scaramuzza D, Bergonzi S (2010) Is there a specific magnetic resonance phenotype characteristic of hereditary breast cancer? Tumori 96:363–384. | Age: range 23–81 years |
| Hagen et al, 2007 | Hagen AI, Kvistad KA, Maehle L, Holmen MM, Aase H, Styr B et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast 2007; 16(4):367–374. | Age: range 18–79 years |
| EVA trial<br>Kuhl et al, 2010 | Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, Konig R et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: The EVA trial. J Clin Oncol 2010; 28(9):1450–1457. | Age: range 25–71 years (mean 44.6) |
| Lehman et al, 2007 | Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT et al. Cancer yield of mammography, MR, and U/S in high-risk women: Prospective multi-institution breast cancer screening study. Radiology 2007; 244(2):381–388. | Age: range NR (mean 45.4 years). Included women age ≥25 years |
| Outcomes reported in the trial | | |
| Schrading et al, 2008 | Schrading S, Kuhl CK. Mammographic, U/S, and MR imaging phenotypes of familial breast cancer. Radiology 2008; 246(1):58–70. | No relevant outcomes reported |
| Peters et al, 2008 | Outcome data not presented | No specific data comparing mammography and MRI |
| Tilanus-Linthorst, 2000a, 2000b | Tilanus-Linthorst MMA, Bartels CCM, Obdeijn AIM, Oudkerk M. Earlier detection of breast cancer by surveillance of women at familial risk. Eur J Cancer 2000; 36(4):514–519.<br>Tilanus-Linthorst MMA, Obdeijn IMM, Bartels KCM, de Koning HJ, | Wrong outcomes |

| Trial ID | Citation | Reason for exclusion |
|---|---|---|
| | Oudkerk M. First experiences screening women at high risk for breast cancer with MR imaging. Breast Cancer Res Treat 2000; 63(1):53–60. | |
| Saunders et al, 2009 | Saunders CM, Peters G, Longman G, Thomson J, Taylor D, Hua J et al. A pilot study of trimodality breast imaging surveillance in young women at high risk of breast cancer in Western Australia. Med J Aust 2009; 191(6):330–333. | Insufficient data for accuracy outcomes |
| Popiela et al, 2013 | Popiela TJ, Kibil W, Herman-Sucharska I, Urbanik A. The use of magnetic resonance mammography in women at increased risk for developing breast cancer. Wideochir Inne Tech Małoinwazyjne 2013; 8(1):55–62. | Analysis limited to MRI detected lesions that were not visualised in U/S or mammography |
| Riedl et al, 2007 | Riedl CC, Ponhold L, Flory D, Weber M, Kroiss R, Wagner T et al. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. Clin Cancer Res 2007; 13(20):6144–6152. | Data not reported for MRI as an *additional* test to mammography |
| Trop et al, 2010 | Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D. Multimodality breast cancer screening in women with a familial or genetic predisposition. Curr Oncol 2010; 17(3):28–36. | Data not reported for MRI as an *additional* test to mammography |

NR = not reported.

**Identified ongoing studies.**

| Trial | Citation |
|---|---|
| FaMRIsc | Saadatmand S, Rutgers EJT, Tollenaar R, Zonderland HM, Ausems M, Keymeulen K, Schlooz-Vries MS, Koppert LB, Heijnsdijk EAM, Seynaeve C, Verhoef C, Oosterwijk JC, Obdeijn IM, de Koning HJ, Tilanus-Linthorst MMA (2012) Breast density as indicator for the use of mammography or MRI to screen women with familial risk for breast cancer (FaMRIsc): A multicentre randomized controlled trial. BMC Cancer 12. |

# Search strategies for additional high-risk groups

**EMBASE.com search strategy.**

| Number | Search strategy |
|---|---|
| #1 | 'magnetic resonance imaging'/exp OR 'magnetic resonance imaging' |
| #2 | 'mri'/exp OR 'mri' |
| #3 | 'mri scan' |
| #4 | 'breast mri' |
| #5 | #1 OR #2 OR #3 OR #4 |
| #6 | 'screening'/exp OR 'screening' |
| #7 | 'surveillance' |
| #8 | #6 OR #7 |
| #9 | 'breast cancer'/exp |
| #10 | 'breast tumour' |

| Number | Search strategy |
|---|---|
| #11 | 'breast carcinoma'/exp |
| #12 | 'invasive carcinoma'/exp |
| #13 | 'intraductal carcinoma'/exp |
| #14 | 'dcis'/exp |
| #15 | 'ductal carcinoma in situ'/exp |
| #16 | 'lobular carcinoma in situ' |
| #17 | 'lcis' |
| #18 | 'chest irradiation' |
| #19 | 'chest radiation' |
| #20 | 'hodgkins lymphoma' |
| #21 | #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 |
| #22 | #5 AND #8 AND #21 |
| #23 | #22 AND [female]/lim AND [humans]/lim AND [english]/lim |

**PreMEDLINE search strategy.**

| Number | Search strategy |
|---|---|
| 1 | magnetic resonance imaging.mp. or exp Magnetic Resonance Imaging/ |
| 2 | MRI.ti,ab,kw. |
| 3 | MRI scan.ti,ab,kw. |
| 4 | breast MRI.ti,ab,kw. |
| 5 | 1 or 2 or 3 or 4 |
| 6 | screening.ti,ab,kw. |
| 7 | surveillance.ti,ab,kw. |
| 8 | 6 or 7 |
| 9 | breast cancer.mp. or exp Breast Neoplasms/ |
| 10 | breast tumour.ti,ab,kw. |
| 11 | breast carcinoma.ti,ab,kw. |
| 13 | ductal carcinoma in situ.mp. or exp Carcinoma, Intraductal, Noninfiltrating/ |
| 14 | DCIS.ti,ab,kw. |
| 15 | lobular carcinoma in situ.ti,ab,kw. |
| 16 | LCIS.ti,ab,kw. |
| 17 | chest irradiation.ti,ab,kw. |
| 18 | chest radiation.ti,ab,kw. |

| Number | Search strategy |
|---|---|
| 19 | Hodgkin's lymphoma.mp. or exp Hodgkin Disease/ |
| 20 | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| 21 | 5 and 8 and 20 |

**Cochrane Library search strategy.**

| Number | Search strategy |
|---|---|
| #1 | MeSH descriptor: [Breast Neoplasms] explode all trees |
| #2 | "breast cancer":ti,ab,kw (Word variations have been searched) |
| #3 | "breast tumour":ti,ab,kw (Word variations have been searched) |
| #4 | "breast tumours":ti,ab,kw (Word variations have been searched) |
| #5 | "breast carcinoma":ti,ab,kw (Word variations have been searched) |
| #6 | "breast-cancer screening":ti,ab,kw (Word variations have been searched) |
| #7 | invasive carcinoma near/5 breast:ti,ab,kw (Word variations have been searched) |
| #8 | "ductal carcinoma in situ":ti,ab,kw (Word variations have been searched) |
| #9 | "DCIS":ti,ab,kw (Word variations have been searched) |
| #10 | "lobular carcinoma in situ":ti,ab,kw (Word variations have been searched) |
| #11 | "LCIS":ti,ab,kw (Word variations have been searched) |
| #12 | "lobular carcinoma":ti,ab,kw (Word variations have been searched) |
| #13 | "ductal carcinoma":ti,ab,kw (Word variations have been searched) |
| #14 | invasive breast carcinoma:ti,ab,kw (Word variations have been searched) |
| #15 | chest radiation:ti,ab,kw (Word variations have been searched) |
| #16 | chest irradiation:ti,ab,kw (Word variations have been searched) |
| #17 | "Hodgkin's lymphoma":ti,ab,kw (Word variations have been searched) |
| #18 | "Hodgkins lymphoma":ti,ab,kw (Word variations have been searched) |
| #19 | "Hodgkins lymphomas":ti,ab,kw (Word variations have been searched) |
| #20 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 |
| #21 | MeSH descriptor: [Magnetic Resonance Imaging] explode all trees |
| #22 | "magnetic resonance imaging":ti,ab,kw (Word variations have been searched) |
| #23 | magnetic resonance imag*:ti,ab,kw (Word variations have been searched) |
| #24 | "MRI":ti,ab,kw (Word variations have been searched) |
| #25 | "MRI scan":ti,ab,kw (Word variations have been searched) |
| #26 | MRI imag*:ti,ab,kw (Word variations have been searched) |
| #27 | #21 or #22 or #23 or #24 or #25 or #26 |

| Number | Search strategy |
|---|---|
| #28 | #20 and #27 |

**WHO International Clinical Trials Registry Platform.**

| No. of search | Search terms |
|---|---|
| 1—Advanced search function | Condition = breast cancer<br>AND<br>Intervention = magnetic resonance imaging OR MRI<br>Recruitment status = ALL |
| 2—Advanced search function | Title = high risk<br>Condition = breast cancer<br>Intervention = MRI<br>Recruiting status = ALL |
| 3—Basic search function | Title = increased risk for breast cancer |

**Excluded health technology assessments and systematic reviews for the assessment of additional high-risk groups.**

| Citation | Reason for exclusion |
|---|---|
| Women with a history of breast cancer | |
| Peters NH, Borel R, I, Zuithoff NP, Mali WP, Moons KG, Peeters PH (2008) Meta-analysis of MR imaging in the diagnosis of breast lesions (Structured abstract). Radiology 246:116–124. | Diagnostic population |
| Quinn EM, Coveney AP, Redmond HP (2012) Use of magnetic resonance imaging in detection of breast cancer recurrence: a systematic review. Ann Surg Oncol 19:3035–3041. | Wrong patient group |
| Women with a history of chest irradiation between the ages of 10 and 35 years | |
| Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, Diller LR, Constantine LS, Smith RA, Mahoney MC, Morris EA, Montgomery LL, Landier W, Smith SM, Robison LL, Oeffinger KC (2010) Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer (Structured abstract). Ann Intern Med 152:444–455. | Wrong research question |

**Excluded primary studies reviews for the assessment of additional high-risk groups.**

| Trial ID | Citation | Reason for exclusions |
|---|---|---|
| Women with a prior history of treatment for invasive breast cancer | | |
| Drew et al, 1998 | Drew, P. et al (1998). Routine screening for local recurrence following breast-conserving therapy for cancer with dynamic contrast-enhanced magnetic resonance imaging of the breast. Ann Surg Oncol, 5(3): 265–270. | Patient characteristics: age: does not include women <50 years |
| Schrading et al, 2008 | Schrading S, Kuhl CK (2008) Mammographic, U/S, and MR imaging phenotypes of familial breast cancer. Radiology 246:58–70. | No relevant outcomes |
| Brennan et al, 2010 | Brennan S, Liberman L, Dershaw DD, Morris E (2010) Breast MRI screening of women with a personal history of breast cancer. Am J Roentgenol 195:510–516. | Non-comparative (MRI only) |

| Trial ID | Citation | Reason for exclusions |
|---|---|---|
| Elmore & Margenthaler, 2010 | Elmore L, Margenthaler JA (2010) Breast MRI surveillance in women with prior curative-intent therapy for breast cancer. J Surg Res 163:58–62. | Non-comparative (MRI only) |
| Elmore & Margenthaler, 2010 | Elmore L, Margenthaler JA (2010) Use of breast MRI surveillance in women at high risk for breast cancer: A single-institutional experience. Ann Surg Oncol 17: S263–S267. | Non-comparative (MRI only) |
| Preda et al, 2006 | Preda L, Villa G, Rizzo S, Bazzi L, Origgi D, Cassano E, Bellomi M (2006) Magnetic resonance mammography in the evaluation of recurrence at the prior lumpectomy site after conservative surgery and radiotherapy. Breast Cancer Res 8. | Wrong comparator (MRI compared with histology) |
| Price et al, 2009 | Price J, Chen S (2009) Screening for breast cancer with MRI: Recent experience from the Australian Capital Territory. J Med Imaging Radiat Oncol 53:69–80. | Non-comparative (MRI only) |
| Sardanelli et al, 2011 | Sardanelli, F. et al (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the High Breast Cancer Risk Italian 1 Study). Investigative Radiol, vol. 46, no. 2, pp. 94–105.<br>Included in NICE, 2013: Familial breast cancer: classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (June 2013); update of clinical guideline 14 and 41. | Wrong patient group—all women also had high familial risk (included for interim item indication) |
| Women with a prior history of treatment for DCIS or LCIS | | |
| Port et al, 2007 | Port ER, Park A, Borgen PI, Morris E, Montgomery LL (2007) Results of MRI screening for breast cancer in high-risk patients with LCIS and atypical hyperplasia. Ann Surg Oncol 14:1051–1057 | Study type: non-comparative |
| Women with a history of chest irradiation between the ages of 10 and 35 years | | |
| Terenziani et al, 2013 | Terenziani M, Casalini P, Scaperrotta G, Gandola L, Trecate G, Catania S, Cefalo G, Conti A, Massimino M, Meazza C, Podda M, Spreafico F, Suman L, Gennaro M (2013) Occurrence of breast cancer after chest wall irradiation for pediatric cancer, as detected by a multimodal screening program. Int J Radiat Oncol Biol Phys 85:35–39. | Wrong intervention: MRI introduced late, and how many women had MRI was not reported |
| Lee et al, 2008 | Lee L, Pintilie M, Hodgson DC, Goss PE, Crump M (2008) Screening mammography for young women treated with supradiaphragmatic radiation for Hodgkin's lymphoma. Ann Oncol 19:62–67. | Wrong intervention: <20 women received MRI |
| Hudson et al, 2011 | Hudson MM, Metzger ML, Howard SC, Krasin M, Pai-Panandiker A, Li C, Srivastava DK, Robison L (2011) Mammography and magnetic resonance imaging for breast cancer surveillance in female survivors for pediatric Hodgkin lymphoma treated with chest radiation. Pediatr Blood Cancer 56:893. | Study type: abstract only |

# Appendix 3: Survival outcomes

Three studies reported survival outcomes for women at high familial risk of breast cancer diagnosed in a MRI surveillance program. Two of these are long-term follow-up studies of included diagnostic accuracy studies (Passaperuma et al, 2012; Rijnsburger et al, 2010). Passaperuma et al (2012) reported 28 invasive breast cancers in *BRCA1/2* carriers with no previous history of breast or ovarian cancer. At a median follow-up of 8.4 years, one woman had died of the disease, an overall distant recurrence rate of 3.6%. Rijnsburger et al (2010) reported that at a median follow-up of 5.0 years, 11 of 93 patients with breast cancer developed a recurrence (7 of 11 with a gene mutation), distant metastasis occurred in five patients (all with a gene mutation) and four patients died of the disease. The cumulative distant metastasis-free and overall survival at 6 years in the 42 *BRCA1/2* mutation carriers with invasive cancer was 83.9% (95% CI 64.1%–93.3%) and 92.7% (95% CI 79.0%–97.6%).

Rijnsburger et al (2010) also observed worse prognostic outcomes for *BRCA1* carriers than for *BRCA2* carriers and other women at high risk, with fewer tumours diagnosed at ≤1 cm diameter (21.4% *BRCA1* vs 61.5% *BRCA2, P* = 0.0045), a slightly lower proportion of DCIS (6.5% *BRCA1* vs 18.8% *BRCA2, P* = 0.32) and a higher interval cancer rate (32.3% *BRCA1* vs 6.3% *BRCA2, P* = 0.07).

The third study was an observational study of the Norwegian MRI surveillance program for women with *BRCA-1* mutations (Møller et al, 2013). Of 802 women, 68 were diagnosed with cancer (5 DCIS and 63 invasive cancers) and 10 died of the disease. The mean follow-up period was 4.2 years. The 5-year breast-cancer-specific survival for women with cancer was 75% (95% CI 56%–86%), and the 10-year survival was 69% (95% CI 48%–83%). The 10-year survival for women diagnosed from age 35 to 49 years was 62%, and that for women diagnosed at age ≥50 years was 81%. The 5-year survival for Stage 1 cancer was 82%, which was significantly lower ($P < 0.05$) than the population rate of 98% reported by the Norwegian Cancer Registry. The survival estimates from these included studies are of limited value owing to the small number of events and lack of an appropriate comparator.

# Appendix 4: Supplementary evidence on women with a history of breast cancer

The systematic review conducted to determine the clinical effectiveness of breast MRI in the surveillance of women with a previous history of DCIS, LCIS and invasive breast cancer identified very few studies, all of which had quality and applicability concerns. However, some literature reports on the use of breast MRI in the initial staging of breast cancer and the detection of contralateral cancer at diagnosis. Given the paucity of evidence identified in the systematic review, estimates of the accuracy and effectiveness of breast MRI at diagnosis may provide relevant data for consideration and inclusion in the economic model.

The following clinical uses for women recently diagnosed with breast cancer are addressed:

1. Breast MRI in the detection of multifocal and multicentric cancer.
2. Breast MRI in the detection of contralateral cancer.

For each of these clinical uses, the most recent, high-quality systematic reviews were sought. These were identified though the systematic review conducted in Section B and targeted literature searching. The identification of the studies did not follow standard systematic review methodology.

## Results

### Quality assessment

Two systematic reviews were identified through targeted searching; both met prespecified criteria for high-quality systematic reviews. However, both are considered to have limited applicability, as the included women are newly diagnosed with breast cancer and have not yet been treated. Furthermore, they included women of any age, and the median age is <50 years in two of 20 studies included in the Brennan et al (2009) review and in three of 16 studies in the Houssami et al (2008) review.

**Quality assessment of included systematic reviews.**

| Study | Brennan et al, 2009 | Houssami et al, 2008 |
|---|---|---|
| Explicit review questions? | Yes | Yes |
| Explicit and appropriate eligibility criteria? | Yes | Yes |
| Explicit and comprehensive search strategy? | Yes | Yes |
| Quality of included studies appraised? | Yes | Yes |
| Methods of study appraisal reproducible? | Yes | Yes |
| Heterogeneity between studies assessed? | Yes | Yes |
| Summary of main results clear and appropriate? | Yes | Yes |
| Applicability | Limited | Limited |

The following factors should be considered in assessing the translation of the findings from these studies to women who have been treated for breast cancer and are undergoing surveillance:

- Age: breast MRI is likely to be more effective than mammography in younger women with denser breasts.
- Effect of treatment:
  - Changes to breast tissue due to treatment, especially radiotherapy.
  - Reduction in risk of further cancers due to systemic treatments (see section A.1.2(b)).
- Effect of repeat imaging (ie, surveillance) rather than one-off imaging.

## Characteristics of studies

The characteristics of the two systematic reviews are presented in the table below. The Brennan et al (2009) review did not include estimates of sensitivity and specificity, as most studies did not verify the absence of disease in women with negative findings on MRI.

**Characteristics of included systematic reviews.**

| | Report objectives | Inclusion criteria | Outcomes | Search date | Type of analysis, No. incl. studies |
|---|---|---|---|---|---|
| Brennan et al, 2009 | To review the evidence for MRI screening of the contralateral breast in women with a new diagnosis of invasive breast cancer to determine its incremental yield and accuracy | (i) Studies of preoperative MRI in women with suspected or proven invasive breast cancer reporting contralateral findings relative to the index cancer which<br>(ii) provided data for both TP and FP detection in the contralateral breast as a minimum measure of accuracy<br>(iii) Studies not histologically verifying the majority of MRI detected abnorm-alities were excluded | Incremental yield, PPV, TP:FP ratio, change in management | April 2008 | Random effects logistic regression<br>22 studies included (3,253 women)<br>—Group 1: 18 for all invasive tumours<br>—Group 2: 4 for invasive lobular carcinoma only |
| Houssami et al, 2008 | To conduct a systematic review and meta-analysis of the incremental accuracy and impact of breast MRI in the context of local staging, with a focus on detection of multifocal and multicentric disease (detection of otherwise occult foci that are distinct from the index cancer) | MRI detection or accuracy in local staging (or in determining disease extent) in women with proven or suspected breast cancer; and provided a measure of MRI accuracy for the detection of additional tumour foci other than the index cancer | Incremental yield, PPV, TP:FP ratio, change in management | June 2007 | SROC curve, random effects logistic regression<br>19 studies included (2,610 women) |

MRI = magnetic resonance imaging; PPV = positive predictive value; TP = true-positive; FP = false-positive; SROC = summary receiver operating characteristics.

# Findings and conclusions

## Brennan et al (2009)

The pooled estimate for incremental cancer detection ratio in group 1 (all invasive cancers) was 4.1% (95% CI 2.7%–6.0%), and that for MRI positives (TP + FP) was 9.3% (95% CI 5.8%–14.7%). The summary estimate of PPV was 47.9% (95% CI 31.8%–64.6%) and the summary TP:FP ratio was 0.92 (95% CI 0.47–1.82). There was evidence that the PPV value decreased with increasing numbers of test positives (TP + FP) in a study ($P$ = 0.024). The PPV also varied according to conventional imaging: in five studies using mammography only, the estimated PPV was 31.0% (95% CI 16.0%–52.0%), and in eight studies using mammography with ultrasound, it was 57.0% (95% CI 39.0%–74.0%).

When reported, 35.1% of MRI detected cancers were DCIS (mean size 6.3 mm) and 64.9% were invasive cancers (mean size 9.3 mm). Clinical management was not reported for all cancers, but frequent use of mastectomy was indicated. There were 42 prophylactic mastectomies reported in women negative on MRI of which five were positive for malignancy (a false-negative rate of 11.9%).

The authors drew the following conclusion:

'*MRI detects contralateral lesions in a substantial proportion of women, but does not reliably distinguish benign from malignant findings. Relatively high incremental cancer detection ratio may be due to selection bias and/or over-detection. Women must be informed of the uncertain benefit and potential harm, including additional investigations and surgery.'*

## Houssami et al (2008)

The prevalence of detection of additional foci ranged from 6% to 34% across studies (median 16%). The incremental accuracy of MRI varied according to the quality of the reference standard: highest quality (two studies), AUC = 86%; intermediate quality (nine studies), AUC = 96%; lowest quality (eight studies), AUC = 99%. The overall summary estimate of PPV was 0.66 (95% CI 0.52–0.77), and the summary estimate of the TP:FP ratio was 1.91 (95% CI 1.09–3.34).

Thirteen studies provided data on change in surgical management; conversion from wide local excision to mastectomy in women with histologically proven additional foci was 8.1% (95% CI 5.9%–11.3%). The rate in women without histological verification (ie, FP detection) was 1.1% (95% CI 0.3%–3.6%).

The authors drew the following conclusion:

*'MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer, however there is a need to reduced FP MRI detection. Randomised trials are needed to determine the clinical value of detecting additional disease which changes surgical treatment in women with apparently localised breast cancer.'*

# Appendix 5: Patient number calculations for the financial impact analysis

The tables below show the results of each stage of the calculations to estimate the numbers of patients for the financial impact calculations.

**Women with gene mutations or family history.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women who receive MRI—extrapolated from claims for the interim MBS listings for breast MRI (see Breast MRI interim items worksheet) | 4,190 | 4,730 | 5,271 | 5,811 | 6,351 |
| Number who have follow-up MRI | 312 | 352 | 392 | 432 | 473 |
| Number of ultrasounds replaced | 1,048 | 1,183 | 1,318 | 1,453 | 1,588 |
| Number of screened women with breast cancer | 52 | 59 | 65 | 72 | 79 |
| Number of screened women without breast cancer | 4,138 | 4,672 | 5,205 | 5,739 | 6,272 |
| Number of true-positive findings with MRI | 46 | 52 | 58 | 63 | 69 |
| Number of true-positive findings with MAM | 20 | 22 | 25 | 27 | 30 |
| Number of additional true-positive findings with MRI | 26 | 29 | 33 | 36 | 39 |
| Number of false-positive findings with MRI | 497 | 561 | 625 | 689 | 753 |
| Number of false-positive findings with MAM | 331 | 374 | 416 | 459 | 502 |
| Number of additional false-positive findings with MRI | 166 | 187 | 208 | 230 | 251 |
| Number of additional positive findings with MRI | 192 | 216 | 241 | 266 | 290 |

FY = financial year; MAM = mammography; MRI = magnetic resonance imaging. Note: Rounding has been applied.

**Women with a prior history of invasive breast cancer.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of females in Australia | 12,022,954 | 12,233,224 | 12,444,642 | 12,655,537 | 12,865,712 |
| Number of women with a prior history of breast cancer | 176,136 | 179,217 | 182,314 | 185,404 | 188,483 |
| Number of women aged <50 years with a prior history of breast cancer | 34,953 | 35,564 | 36,178 | 36,792 | 37,403 |
| Number of women aged <50 years with a prior history of invasive breast cancer | 31,667 | 32,221 | 32,778 | 33,333 | 33,887 |
| Number of women aged <50 years with a prior history of invasive breast cancer who have no gene mutations or family history | 30,084 | 30,610 | 31,139 | 31,667 | 32,192 |
| Number who take up MRI screening | 6,017 | 9,183 | 12,456 | 15,833 | 17,577 |
| Number who have follow-up MRI | 448 | 683 | 927 | 1,178 | 1,308 |
| Number of ultrasounds replaced | 1,504 | 2,296 | 3,114 | 3,958 | 4,394 |

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of screened women with breast cancer | 69 | 105 | 142 | 180 | 200 |
| Number of screened women without breast cancer | 5,948 | 9,078 | 12,314 | 15,653 | 17,377 |
| Number of true-positive findings with MRI | 69 | 105 | 142 | 180 | 200 |
| Number of true-positive findings with MAM | 34 | 52 | 71 | 90 | 100 |
| Number of additional true-positive findings with MRI | 34 | 52 | 71 | 90 | 100 |
| Number of false-positive findings with MRI | 1,249 | 1,906 | 2,586 | 3,287 | 3,649 |
| Number of false-positive findings with MAM | 297 | 454 | 616 | 783 | 869 |
| Number of additional false-positive findings with MRI | 952 | 1,453 | 1,970 | 2,504 | 2,780 |
| Number of additional positive findings with MRI | 986 | 1,505 | 2,041 | 2,595 | 2,880 |

FY = financial year; MAM = mammography; MRI = magnetic resonance imaging. Note: Rounding has been applied.

**Women with a prior history of DCIS or LCIS.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women with a prior history of DCIS | 1,956 | 1,989 | 2,023 | 2,057 | 2,092 |
| Number of women with a prior history of LCIS | 1,630 | 1,658 | 1,686 | 1,715 | 1,744 |
| Number of women with a prior history of DCIS or LCIS | 3,586 | 3,647 | 3,709 | 3,772 | 3,836 |
| Number who take up MRI screening | 717 | 1,094 | 1,484 | 1,886 | 2,095 |
| Number who have follow-up MRI | 53 | 81 | 110 | 140 | 156 |
| Number of ultrasounds replaced | 179 | 274 | 371 | 472 | 524 |
| Number of screened women with breast cancer | 8 | 12 | 17 | 22 | 24 |
| Number of screened women without breast cancer | 709 | 1,082 | 1,467 | 1,865 | 2,071 |
| Number of true-positive findings with MRI | 6 | 9 | 12 | 15 | 17 |
| Number of true-positive findings with MAM | 3 | 4 | 6 | 8 | 9 |
| Number of additional true-positive findings with MRI | 3 | 4 | 6 | 8 | 8 |
| Number of false-positive findings with MRI | 170 | 260 | 352 | 447 | 497 |
| Number of false-positive findings with MAM | 71 | 108 | 147 | 186 | 207 |
| Number of additional false-positive findings with MRI | 99 | 151 | 205 | 261 | 290 |
| Number of additional positive findings with MRI | 102 | 156 | 211 | 269 | 298 |

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; FY = financial year; MAM = mammography; MRI = magnetic resonance imaging. Note: Rounding has been applied.

**Women with a prior history of chest irradiation.**

| Population | FY 2015 | FY 2016 | FY 2017 | FY 2018 | FY 2019 |
|---|---|---|---|---|---|
| Number of women with a history of chest irradiation | 1,000 | 1,017 | 1,034 | 1,052 | 1,070 |
| Number who take up MRI screening | 70 | 142 | 217 | 295 | 341 |
| Number who have follow-up MRI | 5 | 11 | 16 | 22 | 25 |
| Number of ultrasounds replaced | 18 | 36 | 54 | 74 | 85 |
| Number of screened women with breast cancer | 0 | 0 | 0 | 0 | 0 |
| Number of screened women without breast cancer | 70 | 142 | 217 | 295 | 341 |
| Number of true-positive findings with MRI | 0 | 0 | 0 | 0 | 0 |
| Number of true-positive findings with MAM | 0 | 0 | 0 | 0 | 0 |
| Number of additional true-positive findings with MRI | 0 | 0 | 0 | 0 | 0 |
| Number of false-positive findings with MRI | 10 | 20 | 30 | 41 | 48 |
| Number of false-positive findings with MAM | 6 | 11 | 17 | 24 | 27 |
| Number of additional false-positive findings with MRI | 4 | 9 | 13 | 18 | 20 |
| Number of additional positive findings with MRI | 4 | 9 | 13 | 18 | 20 |

FY = financial year; MAM = mammography; MRI = magnetic resonance imaging. Note: Rounding has been applied.

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