WASHINGTON STATE HEALTH CARE AUTHORITY

# HTA Report: Breast MRI

## In Diagnosis and Treatment of Cancer in Women at High Risk

## Health Technology Assessment

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# Breast MRI in Diagnosis and Treatment of Cancer in Women at High Risk

## Provided by:

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*This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.*

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## ABBREVIATIONS USED IN THIS REPORT

Other abbreviations, with their explanations, are found, at times in individual critical appraisals and study reviews.

| Abbreviation | Definition |
|---|---|
| ACR | American College of Radiology |
| ACS | American Cancer Society |
| BCS | Breast conserving surgery |
| CBE | Clinical breast exam |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CLTR | Cumulative lifetime risk |
| DCIS | Ductal carcinoma in situ |
| DM | Digital mammography |
| ESRD | End stage renal disease |
| FH | Family history |
| FN | False negative |
| FNA | Fine needle aspiration |
| FP | False positive |
| FSM | Film screen mammogram |
| HTA | Health Technology Assessment |
| HTAP | Health Care Authority's Health Technology Assessment Program |
| ICDR | Incremental cancer detection rate |
| IDC | Infiltrating or invasive ductal carcinoma |
| ILC | Invasive lobular carcinoma |
| LCIS | Lobular carcinoma in situ |
| LOE | Level of evidence |
| MCC | Multicentric cancer |
| MFC | Multifocal cancer |
| MRI | Magnetic resonance imaging |
| MX | Mammography |
| NA or N/A | Not applicable |
| NPV | Negative predictive value |
| NR | Not reported |
| NS | Not significant |
| OHSU | Oregon Health Services University |
| PPV | Positive predictive value |
| QALY | Quality adjusted life years |
| RCT | Randomized controlled trial |
| RD | Absolute risk difference |
| ROC | Receiver operating curve |
| RR | Relative risk |
| SN | Sensitivity |
| SP | Specificity |
| SR | Systematic review |
| TN | True negative |
| TP | True positive |
| TP:FP Ratio | True positive to false positive ratio |

| Abbreviation | Definition |
|---|---|
| USPSTF | United States Preventive Services Task Force |
| WBUS | Whole breast ultrasound |
| WLE | Wide local excision |

## CONTENTS

## EXECUTIVE SUMMARY

## 1. BACKGROUND

In 2009, an estimated 192,370 cases and 40,170 deaths occurred in women with breast cancer (National Cancer Institute 2010). In 2002, the United States Preventive Services Task Force found adequate evidence of film mammography's sensitivity and specificity and evidence of mammography's effectiveness in decreasing breast cancer mortality in women at average risk based on randomized controlled trials (RCTs) and concluded that film mammography was the standard for detecting breast cancer in women at average risk of developing breast cancer (USPSTF 2002). In 2007, the American Cancer Society (ACS) issued guidelines recommending that women at high risk of developing breast cancer be screened with MRI (Saslow 07). The ACS recommends annual mammography and MRI screening for women starting at age 30 if their lifetime risk is approximately 20% to 25%. (For various models available to calculate breast cancer risk for women with various risk factors see III. BREAST CANCER RISK ASSESSMENT). Women with *BRCA1* mutations are estimated to have a 65% risk by age 70 years for developing breast cancer, 95% confidence interval [CI],( 44% to 78%); the corresponding risk for for *BRCA2* mutations is 45% , 95% CI, (31% to56%) (Anoniou 03). Because of recent clinical guideline recommendations and the perceived greater accuracy of detecting breast cancer using MRI in high risk women, there is a need to review the evidence of benefits and magnitude of harms by adding MRI to screening programs for women at increased risk of developing breast cancer.

This evidence review summarizes the evidence on the accuracy and efficacy of MRI compared with conventional techniques (always mammography, sometimes with ultrasound and sometimes with clinical breast exam) for detecting breast cancer and its role in reducing breast cancer mortality and other meaningful health outcomes in women at increased risk for breast cancer and those with recently diagnosed breast cancer undergoing preoperative surgical staging and planning. Evidence included in this review was obtained through systematic searches of the medical literature for relevant systematic reviews including meta-analyses, other diagnostic studies, randomized controlled trials and economic studies. Selected national guidelines and previous technology assessments are also summarized in this review.

## 2. AIM

The primary aim of this assessment was to systematically review, critically appraise and analyze research evidence regarding the accuracy, efficacy, effectiveness and safety of MRI in the detection of breast cancer in women with a recent diagnosis of breast cancer and those at high for breast cancer because of other risk factors such as a positive family history, known genetic mutations and high lifetime risk of developing breast cancer. Available information on the economic impact of MRI and from current clinical guidelines is also summarized.

## 3. CONCLUSIONS

### Diagnostic Accuracy

Adding yearly screening with MRI to mammographic (+/- US+/- clinical breast exam) screening in women at high risk of breast cancer (family history of breast cancer, ≥ approximately 20% lifetime risk of breast cancer, known BRCA1/2 carriers and/or previous history of breast cancer) will increase detection of breast cancer. Increased breast cancer detection will also occur in women with increased breast density or fibroglandular breast tissue. The increase in cancer detection of approximately 2 to 5 breast cancers per 100 screenings is offset by a higher rate of false positive tests (lower specificity).

### Changes in Treatment

Changes in care, such as recall of patients, subsequent benign breast biopsies and possibly unnecessarily more extensive breast tissue resections and unnecessary mastectomies will occur in some women who

undergo MRI testing. Approximately 11 additional benign biopsies will occur per 100 screenings, and many women will undergo more extensive breast resection surgery (up to 44% change in treatment plans). The evidence regarding the effect of adding MRI to mammographic screening on incomplete cancer excision rates or breast cancer recurrence rates is inconclusive. No RCTs have assessed the effect of adding MRI to conventional breast cancer screening on mortality rates.

**Safety**

Gadolinium-based MRI contrast agents appear to be safe. We found no evidence of adverse events associated with MRI radiation exposure. We found no evidence that breast implants increase the risk of developing breast cancer. The evidence is insufficient to conclude that false-positive breast cancer screening or testing results lead to clinically meaningful negative psychological outcomes.

**Technical and Provider Issues in MRI Testing**

The evidence is insufficient to establish technical MRI specifications or provider qualifications.

**Cost and Cost-effectiveness**

The evidence suggests that adding MRI to mammographic breast cancer screening in women at high risk of developing breast cancer will increase the detection of breast cancers, lead to false positive tests with increased diagnostic and therapeutic interventions and costs and may increase the number of women who undergo unnecessary mastectomies. However, accurately estimating cost-effectiveness may not be possible because RCTs evaluating the mortality reduction with screening or testing women at high-risk for breast cancer have not been conducted. QALYs gained by adding MRI to mammographic breast cancer screening vary greatly depending upon assumptions about sensitivity of MRI, yearly cancer risk, the number and frequency of diagnostic tests, the type and costs of therapeutic interventions, risk of recurrence, development of cancer in the contralateral breast and mortality assumptions. Examples of QALY estimates can be seen below (Taneja 09) and details from cost-effectiveness studies can be found under FINDINGS KEY QUESTION 5).

| Population At High Risk For Breast Cancer | Breast Cancer Prevalence Rate* | Cost Per QALYs Gained With Addition of Annual MRI Screening to MX Screening |
|---|---|---|
| Women With BRCA 1/2 | 4% | $25,277 |
| High Risk Without BRCA 1/2: Seconario 1 | 3% | $45,000 |
| High Risk Without BRCA 1/2: Seconario 2 | 2% | $72,360 |
| High Risk Without BRCA 1/2: Seconario 3 | 1% | $151,642 |
| High Risk Without BRCA 1/2: Seconario 4 | O.5% | $310,616 |

***5 Year Risk of Developing Breast Cancer Based on Results From NCI Breast Cancer Assessment Tool (available at http://www.cancer.gov/bcrisktool/Default.aspx)**

A 35 year old African American woman without BRCA1/2, but with a strong FH of breast cancer, no children, no previous breast biopsies: 0.8%

A 35 year old white woman without BRCA1/2, but with a strong FH of breast cancer, no children, no previous breast biopsies: 1%

A 35 year old white woman without BRCA1/2, but with a strong FH of breast cancer, one child born when the mother was between ages 20 to 24, no previous breast biopsies: 1.2%

A 40 year old African American woman without BRCA1/2, but with a strong FH of breast cancer, two children born when the mother was between ages 20 to 24, 1 normal previous breast biopsy: 1.6%

A 40 year old white woman without BRCA1/2, but with a strong FH of breast cancer, no children, no previous breast biopsies: 1.9%

A 45 year old white woman without BRCA1/2, but with a strong FH of breast cancer, no children, no previous breast biopsies: 2.9%

A 40 year old white woman without BRCA1/2, but with a strong FH of breast cancer, two children born when the mother was between ages 20 to 24, 1 normal previous breast biopsy: 3.6%

## 4. KEY QUESTION FINDINGS

This review is specific to women at risk of breast cancer based on presentation with an abnormal mammogram, palpable breast abnormality or relevant demographic and clinical risk factors.

**FINDINGS KEY QUESTION 1: DIAGNOSTIC ACCURACY**

What is the evidence that breast MRI has the ability to diagnose or exclude breast cancer compared to current tests including mammography?

a. Describe sensitivity, specificity and other key test characteristics

**The evidence is sufficient to conclude that adding yearly screening with MRI to mammographic screening will increase detection of breast cancer. The increase in cancer detection is offset by a higher rate of false positive tests, benign breast biopsies, more extensive surgeries including an increase in more unnecessary mastectomies (LOE: Borderline).**

**Sensitivity of MRI: LOE Borderline**

**The addition of MRI to annual breast cancer screening with mammography will detect an estimated additional 2 to 5 breast cancers per 100 screenings. Accurate estimates of increased case-finding are not possible because of different study populations and study methods in the studies.**

Screening women at high risk for breast cancer (family history of breast cancer, ≥ approximately 20% lifetime risk of breast cancer, known BRCA1/2 carriers and/or previous history of breast cancer) with the addition of MRI to mammography, ultrasound and clinical breast exam (CBE) provides increased sensitivity.

**Ranges for Sensitivity and Specificity***

| Screening Modalities | Ranges for Sensitivity | Ranges for Specificity |
|---|---|---|
| CBE | 9% to 50% | NR |
| MX | 25% to 59% | 93% to 100% |
| MRI | 64% to 100% | 75% to 100% |
| MX+MRI | 80% to 100% | 73% to 97% |
| US | 33% to 65% | NR |
| MX+US | 49% | 93% |
| CBE+MX+US+MRI | 95% | NR |

| | | |
|---|---|---|
| CBE+MX | 45% | NR |
| CBE+MX+US | 64% | NR |
| CBE+MX+MRI | 86% | NR |

***** Data from Lord 07 and Warner 08 meta-analyses and the individual studies included in the meta-analysis. See sections below for more detail.

**Specificity of MRI: LOE Inconclusive**
**Risk of experiencing a benign biopsy: Up to an estimated 11 additional benign biopsies per 100 screening rounds will occur by adding MRI to annual mammographic screening in women at high risk for breast cancer. Accurate estimates of false positive tests are not possible because of different study populations and study methods in the studies.**

Specificity of MRI plus conventional testing (mammography+/-ultrasound +/- clinical breast exam) varied across studies—range 77–96%

- Relative risk of recall for further investigation of false positives is 3.4 to 4.9

**Contralateral Breast Cancer: LOE Borderline**
**MRI detects contralateral breast lesions in a substantial proportion of women with breast cancer, but does not reliably distinguish benign from malignant findings.**

- **The evidence is sufficient to conclude that MRI increases the detection of contralateral breast cancer and false positives in women recently diagnosed as having invasive breast cancer. MRI compared to conventional (mammography+/-ultrasound +/- clinical breast exam) testing increases the detection rate.**
    - Detection of suspicious findings (true positives plus false positives): 9.3% (95% CI, 5.8% to 14.7%)
    - Incremental cancer detection rate (ICDR): 4.1% (95% CI, 2.7% to 6.0%)
    - PPV, 47.9% (95% CI, 31.8% to 64.6%)
    - True positive: false positive ratio, 0.92 (95% CI, 0.47 to 1.82).

**FINDINGS KEY QUESTION 2: IMPROVED OUTCOMES**
What is the evidence that breast MRI improves health outcomes for patients with suspected or diagnosed breast cancer? Including consideration of—

a. reduced need for other tests
b. more accurate diagnosis
c. change in treatment plan
d. reduced mortality and morbidity

**The evidence is insufficient to conclude that, in high risk women, the addition of MRI to mammographic screening reduces the need for mammography or ultrasound. (LOE: Inconclusive). Adding MRI will change treatment plans and result in more extensive surgery for some women (LOE: Borderline), but may not change incomplete excision rates or breast cancer recurrence rates (LOE: Inconclusive). We found no evidence that adding MRI to conventional screening in women at high risk of breast cancer will reduce mortality rates (LOE: Inconclusive).**

**Reduced need for other tests: LOE Inconclusive**
**The evidence regarding the reduced need for mammography and ultrasound screening if MRI screening is utilized to screen women at high risk of breast cancer is inconclusive. Several other considerations are important in deciding whether or not to forgo mammography or ultrasound testing in women at high risk.**

- The increased likelihood of missing breast cancers in high-risk women and those with increased breast density;
- Contraindications to MRI contrast, or inability to undergo MRI testing for other reasons;
- Patient preference; and,
- Economic considerations.

**Change in treatment plans: LOE Borderline**
**The evidence is sufficient to conclude that adding MRI screening in high risk women and preoperative MRI testing in women with recently diagnosed breast cancer will change treatment plans for some women.**

- 15.7% of women with recently diagnosed breast cancer will have changes in treatment plans following MRI.
- Conversion of wide local excision to more extensive surgery will occur in up to 11.3% of women.
- Conversion from wide excision to mastectomy will occur in up to 8.1% of women.
- In women with breast cancer with dense breast tissue, microcalcifications suspicious for carcinoma in situ or discordance between mammography and ultrasound, MRI may add clinical information which may alter treatment plans (44.3% of the time in one retrospective observational study).
- Some women will undergo treatment changes based on false positive tests.
    - One study reported that 6.9% of women with changes in treatment based on MRI were found to have benign lesions.

**Incomplete cancer excision: LOE Inconclusive**
**The evidence is insufficient to determine whether MRI affects the rate of incomplete cancer excision.**

- The evidence regarding incomplete excision rates is conflicting ranging from no difference between groups to 18% decrease in re-excision rates in women who underwent MRI preoperatively. The study reporting of no difference between groups may have been underpowered to find a difference if one existed.

**Potential benefits of changes in treatment plans: LOE Inconclusive**
**The evidence is insufficient to determine whether changes in treatment plans based on the results of preoperative MRI testing are beneficial.**

**Breast cancer recurrence rates: LOE Inconclusive**
**The evidence regarding the effect of preoperative MRI testing in women with early invasive breast cancer on recurrence rates is inconclusive.**

- One retrospective observational study reported a 5.6% reduction in recurrence rates in patients receiving preoperative MRI before breast conservation surgery. Another larger observational study found that MRI was not associated with a lower recurrence rate or 8-year rate of local failure.

**Breast cancer mortality: LOE Inconclusive**
**We found no RCTs which assessed the effect of adding MRI to conventional breast cancer screening on mortality rates.**

**FINDINGS KEY QUESTION 3: SAFETY**
What is the evidence of the safety of breast MRI?

**We found no evidence to suggest that MRI radiation exposure results in adverse outcomes for women at high risk of breast cancer being screened with MRI. There is little evidence that false-**

**positive test results lead to meaningful adverse psychological outcomes (LOE: Borderline to Inconclusive).**

**Safety of gadolinium-based contrast agents in MRI testing: LOE Inconclusive**
**The evidence from observational studies suggests that gadolinium-based agents (with the possible exception of gadodiamide) may be safely used as MRI contrast agents in non-pregnant adults without chronic kidney disease (CKD).**

- Gadolinium crosses the placenta and is classified as a category C drug* by the U.S. Food and Drug Administration and can be used "if the potential benefit justifies the potential risk to the fetus." No adverse effects of MRI on fetus, infants or children, including a theoretical concern of acoustic nerve injury, have been demonstrated.
- There is low quality evidence with conflicting safety results reported for gadolinium-based agents in CKD. One review concluded that renal and extra-renal toxicity may occur in patient with advanced renal disease (GFR <20 ml/minute) and those with end-stage renal disease (ESRD) on dialysis even though no cause and effect relationship has been established.

* Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available.

**Radiation risk of MRI testing in women at high for breast cancer: LOE Inconclusive**
**The evidence is insufficient to conclude that MRI radiation exposure results in adverse events for women at high risk of breast cancer or women recently diagnosed with breast cancer undergoing staging procedures or preoperative surgical planning.**

- MRI uses non-ionizing radiation and short-term and long-term adverse effects of MRI in screening or testing for breast cancer have not been established. We found no evidence to suggest a cause and effect relationship between MRI radiation exposure and adverse events for women being tested with MRI.

**Psychological Issues: LOE Borderline to Inconclusive**
**There is insufficient evidence to conclude that false-positive breast cancer screening tests or recalling patients for false positive tests leads to clinically meaningful negative psychological outcomes.**

- One narrative review of 313,967 women at average risk for breast cancer reported no long-term symptoms of depression in women with false positive mammograms (Brewer 07).
- A cross-sectional survey of 479 women without a history of breast cancer, who were randomly selected from telephone listings, reported that women were highly tolerant of false positive mammograms. When asked how many false positives would be acceptable for each life saved, women showed a high tolerance: 63% would tolerate 500 or more false positives and 37% would tolerate 10,000 or more (Schwartz 00).

**FINDINGS KEY QUESTION 4: SUBPOPULATIONS**

What is the evidence that breast MRI has differential efficacy or safety issues in subpopulations? Including consideration of—

a. Age, breast tissue characteristics; breast implants
b. Other patient characteristics or evidence of appropriate patient selection criteria
c. Type of scanning machine and software, reader training, and other operational factors
d. Provider type, setting or other provider characteristics
e. Health care system type, including worker's compensation, Medicaid, state employees

**There is insufficient evidence to conclude that breast implants increase the risk of developing breast cancer. Adding MRI to mammography appears to increase the detection rate for breast cancer in women with increased breast density. The evidence is insufficient for establishing technical MRI specifications or establishing provider qualifications (LOE: Inconclusive).**

**Breast Implants: LOE Inconclusive**
**There is insufficient evidence to conclude that breast implants increase the risk of developing breast cancer or that benefit is derived from MRI screening in women, who have had breast implants, and who are not otherwise at high risk.**

- A meta-analysis of 10 cohort and case-control studies totaling more than 152,000 women with implants followed from 10 to 20 years found no increased risk in breast cancer in women with implants.

**Increased breast density: LOE Inconclusive**
**The evidence is suggestive that adding MRI to mammography is more sensitive for detecting breast cancer in women with increased breast density or fibroglandular breast tissue.**

- Observational studies have reported increased cancer detection rates in this setting.

**Technical specifications and provider issues in MRI testing: LOE Inconclusive**
**The evidence is insufficient to establish technical MRI specifications or provider qualifications.**

- In one assessment of technical specifications based on a meta-analysis of observational studies, none of the following parameters were associated with the TP:FP ratio: year of study, slice thickness and repetitions after contrast-medium injection. Details of imaging techniques were frequently lacking (Warren 09). Experts (e.g., EUSOMA group – see Guidelines) have recommended technical specifications and provider qualifications.

**FINDINGS KEY QUESTION 5: COST IMPLICATIONS**
What is the evidence about the cost implications and cost effectiveness of breast MRI?

**Adding MRI to mammographic breast cancer screening in high-risk women will increase diagnostic and therapeutic costs. Estimating cost-effectiveness is problematic because mortality reduction with the addition of MRI screening in this population has not been addressed in RCTs (LOE: Mixed)**

**Costs and Cost-effectiveness: LOE Mixed (see below)**
**The evidence is suggestive that adding MRI to mammographic breast cancer screening in women at high risk of breast cancer will increase diagnostic and therapeutic costs** (**LOE for cost outcomes: Moderate**).

**Accurately estimating cost-effectiveness may not be possible because RCTs evaluating the mortality reduction with screening or testing women at high-risk for breast cancer have not been conducted (LOE for cost-effectiveness of adding of MRI to breast cancer testing in women at high risk of breast cancer or those with recently diagnosed breast cancer undergoing preoperative staging: Inconclusive**).

Estimates of cost-effectiveness of adding yearly MRI screening to mammographic screening in women at increased risk of breast cancer from 3 economic analyses are reported below:

1. The cost per QALY gained by adding MRI from ages 35 to 54 years was reported to be $55,420 for BRCA1 mutation carriers, $130,695 for BRCA2 mutation carriers, and $98,454 for BRCA2 mutation carriers who have mammographically dense breasts. Screening strategies that incorporate annual MRI as well as annual mammography have a cost per quality-

adjusted life-year (QALY) gained ranging from approximately $25,000 to more than $300,000, depending on the ages selected for MRI screening and the specific *BRCA* mutation. The study assumed a cumulative breast cancer incidence by age 70 of 65% for women with BRCA 1 mutations and 45% for women with BRCA 2 mutations. The risks of a second breast cancer within 10 years were assumed to be 43.4% and 34.6% respectively. The study assumed a 14% breast cancer mortality reduction for yearly mammography alone from age 25 to 69 years in women with BRCA 1 mutations and a 38% mortality reduction for mammography plus MRI. For BRCA 2 the respective mortality reduction assumptions were 16% and 38%. (Plevritis 06).

2. The cost per QALY gained with MRI and mammography compared with mammography alone for women with BRCA1/2 mutations was reported to be $25,277. The investigators based survival on a mathemathical model that uses observational data including stage of disease at diagnosis and observed survival. They based QALYs gained with the addition of MRI on prevalence rates (investigators used a 4% prevalence rates for BRCA 1/2 and a range down to 0.5% for strong FH without BRCA 1/2 women based on selected observational studies). Among other high-risk women without BRCA mutations, cost per QALY gained with MRI and mammography compared with mammography alone varied depending on the prevalence of breast cancer, ranging from $45,566 (prevalence rate of 3%) to $72,360 (prevalence rate of 2%) to $151,642 (prevalence rate of 1%) to $310,616 (prevalence rate of 0.5%). The cost effectiveness of MRI alone compared with mammography alone was similar (Tanjea 09).
3. The cost of adding annual MR imaging to annual mammographic screening in high-risk women was reported to be $69,125 for each additional QALY gained. Sensitivity analysis indicated that, when the screening MR imaging cost increased to $960 (base case, $577), or the sensitivity of combined screening decreased below 76% (base case, 94%), the cost of adding MR imaging to mammography exceeded $100,000 per QALY (Lee 10).

## Washington State Agency Data

The following data is provided by the Washington State agencies on their utilization and cost information.

Figure 1. Washington State Agency Annual Reimbursement Costs for Breast MRI, 2005-2009

| Year/Agency | 2005 | 2006 | 2007 | 2008 | 2009 | 5 Year Total |
|---|---|---|---|---|---|---|
| **UMP/PEP** | | | | | | |
| Annual Total Cost | $388,836 | $434,526 | $707,429 | $787,489 | $793,663 | $3,111,943 |
| BMRI Count[1] | 352 | 391 | 676 | 761 | 756 | 2936 |
| Average cost[1] | $1,105 | $1,111 | $1,046 | $1,035 | $1,050 | $1,060 |
| **DSHS** | | | | | | |
| Annual Total Cost | $95,210 | $112,996 | $46,520 | $93,869 | $117,854 | $466,449 |
| BMRI Count[2] | 160 | 180 | 90 | 156 | 248 | 834 |
| Average cost[2] | $595 | $628 | $517 | $602 | $475 | $559 |
| **Totals** | | | | | | |
| Annual Total Cost | $484,046 | $547,522 | $753,949 | $881,358 | $911,517 | $3,578,392 |
| BMRI Count | 512 | 571 | 766 | 917 | 1004 | 3770 |
| Average cost | $945 | $959 | $984 | $961 | $908 | $949 |

[1] Average payments and counts include zero $ reimbursement claims (5-6% of claims overall).

[2] Average reimbursements and patient counts do not include zero $ reimbursement claims where DSHS is a secondary payer. Secondary payer BMRI counts are highly variable by year, so BMRI counts of patients in this table reflect claims reimbursed, and not necessarily usage trends. Zero payment claim counts were 34/194 (.18) in 2005, 25/205 (.12) in 2006, 157/247 (.61) in 2007, 136/292 (.47) in 2008, 5/252 (.02) in 2009.

Figure 2. Washington State Agency Breast MRI Patients with and without prior Mammogram, 2005-2009

Combined UMP/PEP (2005-2009) and DSHS (2005-2008) data

| Count of BMRI Patients | 2005 | 2006 | 2007 | 2008 | 2009* | Grand Total |
|---|---|---|---|---|---|---|
| **With a prior Mammogram** | **122** | **215** | **725** | **912** | **714** | **2688** |
| **Without a prior Mammogram** | **424** | **381** | **198** | **141** | **42** | **1186** |
| **Total** | **546** | **596** | **923** | **1053** | **756** | **3874** |
| **Percent of BMRI Patients** | | | | | | |
| **With a prior Mammogram** | 22% | 36% | 79% | 87% | 94% | 69% |
| **Without a prior Mammogram** | 78% | 64% | 21% | 13% | 6% | 31% |

*2009 BMRI data for DSHS excluded due to loss of link with prior year member identification.
Note that 2005 and 2006 results are skewed by insufficient timeframe in the data to capture prior mammograms.

Figure 3. UMP/PEP BMRI Diagnosis Classification, 2005-2009

| Diagnosis Code Classification | 2005 | 2006 | 2007 | 2008 | 2009 | Grand Total |
|---|---|---|---|---|---|---|
| Diagnosis | $118,257 | $118,942 | $216,980 | $288,686 | $275,490 | $1,018,355 |
| Follow-up | $9,105 | $3,181 | $15,090 | $17,845 | $20,813 | $66,034 |
| Other | $4,150 | $4,655 | $13,715 | $14,625 | $11,378 | $48,523 |
| Prevention | $0 | $100 | $0 | $0 | $0 | $100 |
| Screening | $29,445 | $31,173 | $67,426 | $67,686 | $113,388 | $309,118 |
| Staging | $199,780 | $232,001 | $293,363 | $281,643 | $263,671 | $1,270,458 |
| Surveillance | $28,099 | $44,474 | $100,855 | $117,004 | $108,923 | $399,355 |
| **Grand Total** | **$388,836** | **$434,526** | **$707,429** | **$787,489** | **$793,663** | **$3,111,943** |

Figure 4. UMP/PEP BMRI Counts by Diagnosis Classification, 2005-2009

| Diagnosis Code Classification | 2005 | 2006 | 2007 | 2008 | 2009 | Grand Total |
|---|---|---|---|---|---|---|
| Diagnosis | 126 | 114 | 237 | 290 | 276 | 1043 |
| Follow-up | 3 | 5 | 9 | 11 | 13 | 41 |
| Other | 3 | 4 | 11 | 7 | 5 | 30 |
| Prevention | 0 | 1 | 0 | 0 | 0 | 1 |
| Screening | 21 | 22 | 58 | 60 | 97 | 258 |
| Staging | 168 | 196 | 264 | 272 | 243 | 1143 |
| Surveillance | 31 | 49 | 97 | 120 | 122 | 419 |
| **Grand Total** | **352** | **390** | **676** | **760** | **756** | **2935** |

Figure 5. UMP/PEP BMRI Patient Counts by Diagnosis Classification

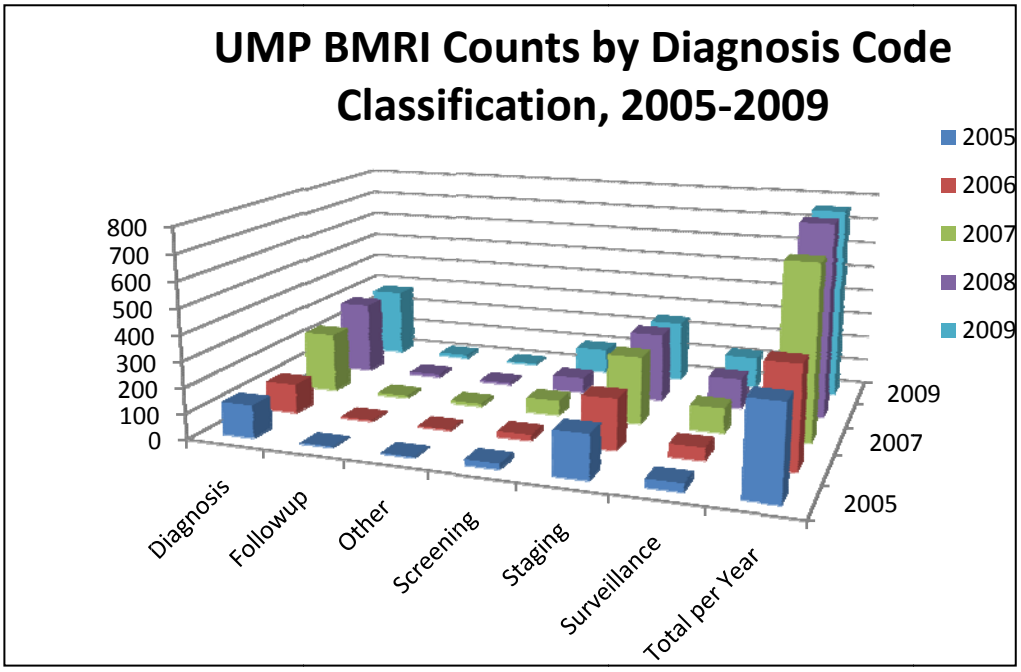


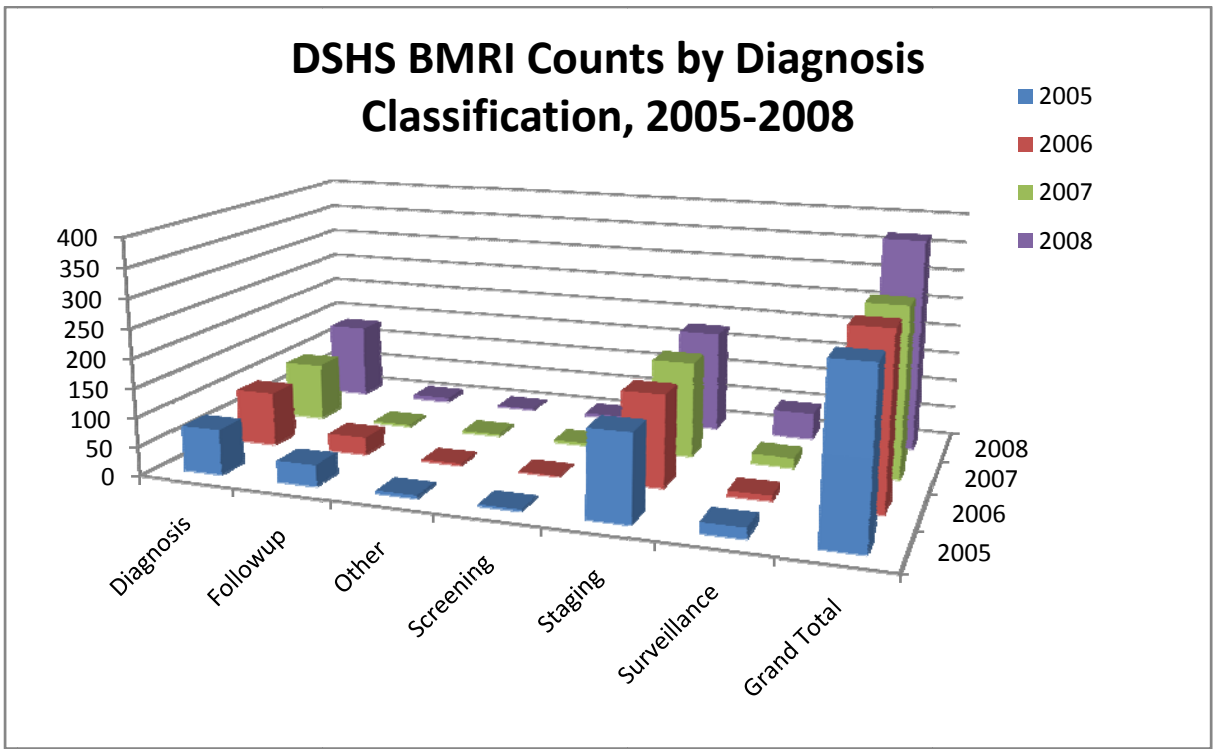

Figure 6. DSHS BMRI Costs by Diagnosis Classification, 2005-2009

| Diagnosis Code Classification | 2005 | 2006 | 2007 | 2008 | 2009 | Grand Total |
|---|---|---|---|---|---|---|
| Diagnosis | $25,836 | $38,125 | $14,111 | $34,752 | $39,824 | $152,648 |
| Follow-up | $17,942 | $15,882 | $1,499 | $578 | $629 | $36,530 |
| Other | $1,536 | $1,289 | $823 | $590 | $3,220 | $7,456 |
| Screening | $1,821 | $626 | $1,058 | $1,051 | $0 | $4,555 |
| Staging | $42,252 | $53,319 | $27,973 | $43,985 | $64,367 | $231,896 |
| Surveillance | $5,822 | $3,755 | $1,058 | $12,914 | $9,815 | $33,364 |
| **Grand Total** | **$95,210** | **$112,996** | **$46,520** | **$93,869** | **$117,854** | **$466,449** |

Figure 7. DSHS BMRI Counts by Diagnosis Classification, 2005-2009

| Diagnosis Code Classification | 2005 | 2006 | 2007 | 2008 | 2009 | Grand Total |
|---|---|---|---|---|---|---|
| Diagnosis | 68 | 85 | 104 | 79 | 397 | 397 |
| Follow-up | 3 | 3 | 3 | 6 | 2 | 17 |
| Other | 3 | 2 | 3 | 2 | 8 | 18 |
| Screening | 2 | 1 | 2 | 5 | 0 | 10 |
| Staging | 113 | 123 | 139 | 141 | 148 | 664 |
| Surveillance | 12 | 7 | 15 | 34 | 25 | 93 |
| **Grand Total** | **194** | **205** | **247** | **292** | **262** | **1200** |

Figure 8. DSHS BMRI Patient Counts by Diagnosis




| Related Medical Codes | | |
|---|---|---|
| **Code Type** | **Code** | **Description** |
| **CPT - MRI** | 77058 | MRI, single breast (since 2006) |
| | 77059 | MRI, both breasts (since 2006) |
| | 0159T | MRI add-on (since 2006) (use as part of cost, not a separate procedure) |
| | 76093-4 | DEL-MRI Breast w/wo contrast, uni/bi (until 2005-6) |
| **HCPCS- MRI** | C8903-8 | MRI of the Breast (still in use) |
| **Breast Surgery** | 19301-7 | Breast surgery – mastectomy partial-radical |
| **Diagnosis codes** | 174.* | Primary malignant breast cancer, female |
| | 233.0,233.3 239.3 | Neoplasm, cancer in situ, breast |
| **Other diagnostic procedures for breast cancer** | | |
| Mammogram | 77051-77057 | Mammogram, diagnostic or screening, interpretation and guidance |
| | G0202-7 | Screening mammogram, digital, bilateral |

**:: END OF EXECUTIVE SUMMARY ::**

## 5. RATING OF INDIVIDUAL STUDIES AND THE OVERALL QUALITY OF THE EVIDENCE

**Delfini Validity & Usability Grading Scale for Summarizing the Evidence for Interventions**

| Grade of Usability | Strength of Evidence Advice<br>Grades can be applied to individual studies, to conclusions within studies, a body of evidence or to secondary sources such as guidelines or clinical recommendations. General advice is provided below. |
|---|---|
| **Grade A: Useful** | The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.)<br><br>Advice: Studies achieving this grade should be outstanding in design, execution and reporting with useful information to aid clinical decision-making, enabling reasonable certitude in drawing conclusions.<br><br>For a body of evidence:<br>Several well-designed and conducted studies that consistently show similar results<br>• For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient; however, without confirmation from other studies results could be due to chance, undetected significant biases, fraud, etc. In such instance the study might receive a Grade A, but the Strength of the Evidence should include a cautionary note.<br>• For natural history and prognosis: Cohort studies |
| **Grade B: Possibly Useful** | The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified<br><br>Advice: Studies achieving this grade should be of high quality in design, execution and reporting with non-lethal threats to validity and with sufficiently useful information to aid clinical decision-making, enabling reasonable certitude in drawing conclusions.<br><br>For a body of evidence:<br>The evidence is strong enough to conclude that the results are probably valid and useful (see above); however, study results from multiple studies are inconsistent or the studies may have some (but not lethal) threats to validity.<br>• For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient; however, without confirmation from other studies results could be due to chance, undetected significant biases, fraud, etc. In such instance the study might receive a Grade A, but the Strength of the Evidence should include a cautionary note.<br>• Also for diagnosis, valid studies assessing test accuracy for detecting a condition when there is evidence of effectiveness from valid, applicable RCTs.<br>▪ For natural history and prognosis: Cohort studies |
| **Grade B-U: Possible to uncertain usefulness** | The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U.<br>Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality. |

| | |
|---|---|
| **Grade U: Uncertain Validity and/or Usefulness** | There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.<br>• Uncertain Validity: This may be due to uncertain validity due to methodology (enough threats to validity to raise concern – our suggestion would be to **not** use such a study in most circumstances) or may be due to conflicting results.<br>• Uncertain Usefulness: Or this may be due to uncertain applicability due to results (good methodology, but questions due to effect size, applicability of results when relating to biologic markers, or other issues). These latter studies may be useful and should be viewed in the context of the weight of the evidence.<br>• Uncertain Validity and Usefulness: This is a combination of the above.<br>• Uncertainty of Author: If the author has reached a conclusion that the findings are uncertain, doing a critical appraisal is unlikely to result in a different conclusion. The evidence leaves us uncertain regardless of whether the study is valid or not. Critical appraisal is at the discretion of the reviewer. |

**AHRQ Risk of Bias Ratings**

Overall quality of the evidence was rated by applying the domains recently selected by the Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program (EHCP) group (Owens 09). These domains were selected by AHRQ EHCP after reviewing choices made by the U.S. Preventive Services Task Force (USPSF) (Sawaya 07), the GRADE working group (Guyatt 08) and other evidence-based practice centers (West 02, Treadwell 06). Briefly, The AHRQ EHCP approach assesses the risk of bias, consistency, directness and precision for each outcome or comparison of interest (in some instances, paraphrased below):

**AHRQ Overall Risk of Bias Domains**

- **Bias** is scored as low, medium, or high risk of bias.
- **Consistency** is the degree of similarity of effect sizes of included studies and is scored as consistent, inconsistent, or unknown/not applicable.
- **Directness** is the linkage between the intervention and health outcomes scored as direct or indirect (meaning intermediate or surrogate outcome measures).
- **Precision** concerns the ability to draw a clinically useful conclusion from the confidence intervals. An imprecise estimate, for example, is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., favoring both the interventions being compared).

**The overall level of evidence (LOE)** for each outcome of interest utilized by the AHRQ and EHCP group includes three grades—high, moderate and inconclusive. For example, if the LOE is high, further research is unlikely to change confidence in the estimate of effect. If evidence is unavailable or does not permit a conclusion, the outcome in the AHRQ EHCP system is graded as inconclusive. For this review, we modified this grading system for overall LOE by adding a fourth category—"borderline" to increase clarity as we believe "moderate" is not precise enough to address evidence of borderline usefulness. We grade the overall LOE as "high" if we find more than one grade B (valid and possibly useful) study reporting consistent results, "moderate" if we find at least one grade B study, "borderline" if we find at least two grade B-U (possible to uncertain validity and usefulness) studies with consistent findings and "inconclusive" if we find single grade B-U studies or grade B-U studies with conflicting results or only grade U studies (uncertain usefulness or validity).

- Critical appraisals of individual studies and search documentation are produced in two separate documents titled—
  - **Breast MRI in Diagnosis and Treatment of Cancer in Women at High Risk: Search Documentation**
  - **Breast MRI in Diagnosis and Treatment of Cancer in Women at High Risk: Critical Appraisal Documentation**.
- Peer reviewer comments are included in the appendices.
- Comments from members of the public, agency medical directors and other interested parties will be addressed and incorporated as appropriate in the final report.

## 6. DETAILS OF EVIDENCE FINDINGS

This review is specific to women at risk of breast cancer based on presentation of with an abnormal mammogram, palpable breast abnormality or relevant demographic and clinical risk factors.

### DETAILS QUESTION 1: DIAGNOSTIC ACCURACY

**What is the evidence that breast MRI has the ability to diagnose or exclude breast cancer compared to current tests including mammography?**

**a. Describe sensitivity, specificity and other key test characteristics**

**Test Accuracy in Women at High Risk For Breast Cancer (Tables 1 & 3): LOE Borderline to Inconclusive**

The evidence is sufficient to conclude that 2 to 5 additional cancers will be detected for every 100 high risk women receiving MRI screening in addition to yearly mammography breast cancer screening (LOE for sensitivity: Borderline). The increase in sensitivity and additional cases of breast cancer detected are offset by a higher biopsy rate and up to an 11% recall rate for false positive tests (LOE for specificity: Inconclusive).

We found two recent large systematic reviews of acceptable quality (medium risk of bias by AHRQ rating system) that assessed the accuracy of magnetic resonance imaging (MRI) when added to conventional (mammography+/-ultrasound +/- clinical breast exam) screening in women at high risk of breast cancer.

**Study and Details**

**Lord 07 Systematic Review**

This meta-analysis was rated as medium risk of bias. The authors provide evidence regarding the sensitivity and specificity of screening high risk women with and without the addition of MRI to mammography, ultrasound and clinical breast exam (CBE) in women at high risk for breast cancer because of genetic mutations, family history or history of previous breast cancer (≥ approximately 20% lifetime risk of breast cancer or known BRCA1/2 carriers).

Two of the authors independently assessed the quality of included studies. The authors classified studies as high quality if they were conducted prospectively using well-defined selection criteria and recruited consecutive eligible subjects; reported on the execution of study tests and test threshold for a positive test in sufficient detail to allow test replication; applied the same reference standard to validate the results of study tests; interpreted test results without the knowledge of the reference standard or comparator tests; conducted study tests within two weeks; reported indeterminate test results; and explained study withdrawals. Studies not conducted prospectively or not meeting the criteria for an adequate reference standard or test interval were classified as low quality and other studies were classified as fair quality. The meta-analysis also examined and updated four previous systematic reviews.

The investigators constructed two by two tables and per-patient sensitivity and specificity, and the associated 95% confidence intervals (CI) for test strategies with and without MRI were calculated and the differences between strategies were reported.

3,309 studies were screened for retrieval. 91 relevant studies were retrieved for further evaluation after excluding ineligible studies because of design and methodological problems. The investigators found no RCTs of MRI in breast screening of high risk women. Five adequate quality diagnostic studies were included in the review and used to estimate the sensitivity and specificity of MRI as an additional test to the combination of mammography, ultrasound and/or mammography alone. The review did not identify any studies that compared mortality as an outcome or interval cancer rates in high risk women screened with and without MRI.

The study found consistent evidence based on the 5 included studies that adding MRI to conventional screening (mammography+/-ultrasound +/- clinical breast exam) in high-risk women provides a highly sensitive screening strategy (sensitivity range: 93-100%) compared to mammography alone (sensitivity range: 25-59%) or mammography plus ultrasound +/- clinical breast exam (CBE) (sensitivity range: 49-67%). Meta-analysis of the three studies that compared MRI plus mammography versus mammography alone found the sensitivity of MRI plus mammography to be 94% (95% CI, 86 to 98%) and the incremental sensitivity of MRI to be 58% (95% CI, 47 to 70%). Incremental sensitivity of MRI when added to mammography plus ultrasound 44% (95% CI, 27 to 61%) was lower as was the incremental sensitivity of MRI when added to the combination of mammography, ultrasound plus clinical breast exam (95% CI, 31 to 33%).

Estimates of screening specificity with MRI were not consistent in the studies but suggested a 3-5-fold higher risk of patient recall for investigation of false positive results with the addition of MRI to screening. Based on 2 of the included studies, the risk for undergoing a percutaneous biopsy without finding cancer was approximately 3-fold higher. One study suggested that the risk of undergoing a surgical biopsy with benign findings was approximately doubled. False positive recall rates ranged from 6 to 106 per 1000 MRI exams in the two studies reporting recall rates. No studies assessed whether adding MRI reduces patient mortality, recurrence rates or earlier stage disease. This meta-analysis was rated as being at medium risk of bias. Details are summarized in Table 1 and 2 below.

**Warner 08 Meta-analysis**

This more recent meta-analysis included some additional studies and compared the diagnostic accuracy of mammography and MRI alone and in combination in women at high risk of breast cancer (known BRCA1/2 mutations, untested first-degree relative of a person with such a gene mutation, having a family history consistent with a hereditary breast cancer syndrome, atypical or lobular carcinoma in situ on previous biopsy or radiation therapy to chest before age 30 years and at least 8 years previously). This meta-analysis was rated as at medium risk of bias.

The investigators reported measures of test function by American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) scores using only BI-RADS scores of 4 or 5 as positive. (BI-RADS details are provided in the appendices.) The authors reported sensitivity, specificity, likelihood ratios, and posttest probability associated with adding MRI to annual mammography screening in women at high risk for breast cancer. Threats to validity include heterogeneity of population, potentially distorting statistical adjustments, lack of blinding in 2 studies and lack of information about missing values.

Reported sensitivity of the combination of MRI and mammography ranged from 80% to 100%, compared with 25% to 59% for mammography alone. In every study except one, the specificity of MRI was lower than that of mammography; the specificity of the MRI combined with mammography ranged from 73% to 93%. The combination of MRI and mammography with a BI-RADS score of 4 or higher as the definition of a positive test provided the best balance of performance in terms of all measures investigated (sensitivity, specificity, diagnostic odds ratios, likelihood ratios and posttest probabilities). The summary negative likelihood ratio and probability of a BI-RADS–suspicious lesion (given negative test findings and assuming a 2% pretest probability of disease) for the combination of MRI plus mammography were 0.14 and 0.3%, respectively, compared with 0.70 and 1.4% for mammography alone. None of the included studies assessed recurrence rates or mortality. Details are summarized in Tables 3 and 4 below.

Test Accuracy of MRI in Detecting Breast Cancer in the Contralateral Breast in Women At High Risk For Breast Cancer: LOE Borderline

The evidence is sufficient to determine that MRI increases the detection of contralateral breast cancer in women recently diagnosed as having invasive breast cancer.

| Study and Details |
| --- |
| **Brennan 09**<br>A recent meta-analysis of 22 studies evaluating MRI detection in the contralateral breast compared to conventional (mammography+/-ultrasound +/- clinical breast exam) imaging reported that MRI detected 131 malignancies in 3,253 women with breast cancer. Sensitivity and specificity were not reported because cancer outcomes were not ascertained in subjects with negative MRIs. MRI-detected suspicious findings (true positives plus false positives) was 9.3% (95% CI, 5.8% to 14.7%); incremental cancer detection rate (ICDR) was 4.1% (95% CI, 2.7% to 6.0%), PPV, 47.9% (95% CI, 31.8% to 64.6%); true positive: false positive ratio, 0.92 (95% CI, 0.47 to 1.82). The authors concluded that MRI detects contralateral lesions in a substantial proportion of women, but does not reliably distinguish benign from malignant findings. Where reported, 35.1% of MRI-detected cancers were ductal carcinoma in situ, 64.9% were invasive cancers and the majority were node negative. Changes in treatment plans were inconsistently reported, but many women underwent contralateral mastectomy. |
| **Lehman 07**<br>In an observational diagnostic study of 969 women with a recent diagnosis of unilateral breast cancer and no abnormalities on mammographic and clinical examination of the contralateral breast, MRI detected clinically and mammographically occult breast cancer in the contralateral breast in 30 of 969 women (3.1%).<br><br>The sensitivity of MRI in the contralateral breast was 91%, and the specificity was 88%. The negative predictive value of MRI was 99%. A biopsy was performed on the basis of a positive MRI finding in 121 of the 969 women (12.5%), 30 of whom had specimens that were positive for cancer (24.8%). |

**Table 1: Sensitivity / Specificity Breast Cancer Detection in High Risk Women (Lord 07 Meta-analysis)**

| Diagnostic Test | Sensitivity | Specificity | |
|---|---|---|---|
| Mammography Alone | 25% to 59% | NR | |
| Mammography + US | 49% to 67% | NR | |
| Mammography + MRI versus Mammography Alone | 94% (95% CI, 86 to 98); incremental sensitivity of MRI 58% (95% CI, 47 to 70%) | Specificity of MRI plus conventional testing varied across studies (range 77 to 96%) and precluded meta-analysis to estimate the "true" relative specificity of screening strategies versus without MRI. | |
| MRI + Mammography + US | 86% to 100%; incremental sensitivity of MRI 44%, (95% CI, 27 to 61%) | | |
| MRI + Mammography + CBE | Incremental sensitivity of MRI 31%to 33% | | |
| Relative Risk of Recall Rates: Further Investigation of False Positives And / Or Benign Percutaneous Biopsy (Core or Fine Needle) When MRI was added to mammography versus mammography alone | | | 3.43 to 4.86 |
| Estimated Additional False Positive Recalls Per 1000 Screening Rounds | | | 71 to 74 |
| Relative Risk of Undergoing Benign Percutaneous Biopsy Due to Addition of MRI to Mammography + US | | | 1.22 to 9.50 |
| Additional Benign Biopsies per 1000 Screening Rounds | | | 7 to 46 |

**Table 2: Results From 5 Included Studies (Lord 07)**
**NR = Not reported**

**Notes**

- Number: Alphabetically arranged; reference number applies to the order in this table only (i.e., is not tied to **References**)

| # | Author, Year, Population, Screening Strategy for Studies Included in Lord 07 | Sensitivity (SN) and Specificity (SP) Conventional Screening Without MRI | Sensitivity (SN) and Specificity (SP) of MRI and Combined With MRI | Incremental Cancer Yield and Test Sensitivity Using MRI | Relative Risk and Absolute Risk Difference (95% CI) of False Positive Patient Recall and Benign biopsies With and Without MRI |
|---|---|---|---|---|---|
| 1. | Kuhl 2005<br>N=529<br>Mean observation period 5.3 years<br>Median age 40 years; range 27 to 59 years)<br>At least 20% lifetime risk<br>Strong FH ca of breast or ovary<br>Mutation carriers: 8.1%<br>Prior history of breast cancer: 26%<br><br>Conventional testing = mammography + ultrasound | MX + US<br>SN 49% (33 to 65%)<br>SP 89% (87 to 91%) | MX + MRI<br>SN 93% (81 to 99%)<br>SP NR | Incremental yield 19/1452;<br>13.1 additional cancers with MRI per 1000 screening rounds;<br>Incremental SN 44% (27 to 61%) | False positive patient recall rate and benign biopsy rate NR |
| 2. | Leach 2005 (magnetic resonance imaging breast screening (MARIBS)) United Kingdom<br>22 sites 1997–2004<br>N=649<br>Screening intervals of 6–54 months in length (median 12 months)<br>Median age 40 years (range 31 to 55 years)<br>*BRCA1* mutation:13%<br>*BRCA2* mutation:6%<br>65% strong FH ca breast or ovary:65%<br>Prior history of breast cancer: 0%<br>Conventional testing = mammography | MX<br>SN 40% (24 to 58%)<br>SP 93% (92 to 95%) | MX + MRI<br>SN 94% (81 to 99%)<br>SP 77% (75 to 79%) | Incremental yield 19/1881;<br>10.1 additional cancers with MRI per 1000 screening rounds;<br>Incremental SN 54% (36 to 72%) | False positive patient recall<br>rate NR;<br>Benign percutaneous biopsy rate:<br>RR: 1.22 (0.83 to 1.80);<br>RD: 7 (6 to 20) additional benign percutaneous biopsies per<br>1000 screening rounds |
| 3. | Lehman 2005<br>(International Breast MRI Consortium Working Group (IBMC)) USA, Canada<br>13 sites<br>1999–2002<br>N=367<br>Single screening (MRI done within 90 days of MX)<br>Mean age 45 years, standard deviation 9.7 years (range NR)<br>Lifetime risk >25%<br>Prior history of breast cancer: 10%<br>Conventional testing = CBE + mammography | MX<br>SN 25% (0.6 to 81%)<br>SP 98% (96 to 99%) | MRI<br>SN 100%<br>SP NR | 8.2 additional cancers with MRI per 1000 screening rounds;<br>Incremental SN 75% | False positive patient recall:<br>RR: 4.86 (2.18 to 10.82);<br>RD: 74 (41 to 106) additional recalls per 1000 screening rounds;<br>RR: 9.50 (2.23 to 40.49)<br>RD: 46 (22 to 70) additional<br>biopsies per 1000 screening<br>rounds |

| | | | | | |
|---|---|---|---|---|---|
| 4. | Sardanelli 2007<br>N=278<br>2 annual screenings<br>Mean age 46 years (range 25 to 79 years)<br>BRCA1 mutations:35%<br>BRCA2 mutations:24.5%<br>strong FH ca breast or ovary:37%<br>Prior history of breast cancer: 44%<br>Conventional testing = mammography + ultrasound + CBE | CBE<br>SN 50% (29% to 71%)<br>MS<br>SN 59% (36% to 78%)<br>US<br>SN 65% (41% to 83%) | MRI<br>SN 94% (82% to 99%)<br>SP MRI 96% (94 to 98%) | 15.9 additional cancers with MRI per 1000 screening rounds;<br>Incremental SN 33% (11 to 55%) | False positive patient recall rate and benign biopsy rate NR |
| 5. | Warner 2004<br>N=236<br>1 to three annual screenings<br>Median age: 47 years (range 25 to 65 years)<br>BRCA1: 58%<br>BRCA2: 42%<br>Prior history of breast cancer: 30%<br>Prior history of ovarian cancer:9%<br><br>Risk classification<br>BRCA1/2 mutation carriers 100%<br>Conventional testing = mammography + ultrasound + CBE | CBE<br>SN 9.1%<br>US<br>SN 33%<br>MX<br>SN 36% (17–59%)<br>SP 99.8% (99–100%)<br>CBE+MX<br>SN 45% (24 to 68%)<br>CBE+US+MX<br>SN 64% (41 to 83%) | MRI<br>SN 77%<br>CBE+MX+MRI<br>SN 86% (65–97%)<br>CBE+US+MX+MRI<br>SN 95% (77 to 100%) | MX+MRI<br>24.1 additional cancers per 1000 screening rounds; incremental SN with MRI 50% (25 to 75%)<br><br>CBE+MX+MRI 19.7 additional cancers per 1000 screening; incremental SN with MRI 41% (16–66%)<br><br>CBE+US+MX+MRI 15.3 additional cancers per 1000 screening rounds; incremental SN with MRI 31% (10 to 54%) | False positive patient recall rate and benign biopsy rate NR |

**Table 3: Sensitivity / Specificity Breast Cancer Detection in High Risk Women (Warner 08 Meta-analysis)**

| Screening Strategy, BI-RADS* Cutoff Value | Diagnostic Odds Ratio (95% CI) | Sensitivity (95% CI), % | Specificity (95% CI), % | Positive Likelihood Ratio (95% CI) | Negative Likelihood Ratio (95% CI) |
|---|---|---|---|---|---|
| **Mammography**<br>≥3<br>≥4 | 14.7 (6.1 to 35.6)<br>38.5 (15.9 to 93.3) | 39 (37 to 41)<br>32 (23 to 41) | 94.7 (93.0 to 96.5)<br>98.5 (97.8 to 99.2) | 8.7 (4.4 to 17.5)<br>24.8 (11.6 to 53.0) | 0.64 (0.55 to 0.75)<br>0.70 (0.59 to 0.82) |
| **MRI**<br>≥3<br>≥4 | 18.3 (11.7 to 28.7)<br>88.7 (34.6 to 227.5) | 77 (70 to 84)<br>75 (62 to 88) | 86.3 (80.9 to 91.7)<br>96.1 (94.8 to 97.4) | 4.2 (3.0 to 5.9)<br>16.6 (11.1 to 25.0) | 0.29 (0.21 to 0.41)<br>0.22 (0.12 to 0.43) |
| **Mammography and MRI**<br>≥3<br>≥4 | 45.9 (17.5 to 120.9)<br>124.8 (36.4 to 427.4) | 94 (90 to 97)<br>84 (70 to 97) | 77.2 (74.7 to 79.7)<br>95.2 (93.7 to 96.6) | 4.1 (3.6 to 4.7)<br>16.4 (11.1 to 24.1) | 0.09 (0.04 to 0.23)<br>0.14 (0.05 to 0.42) |

*BI-RADS _ Breast Imaging Reporting and Data System

**Table 4: Results from 11 Individual Studies Reported in Warner 08**

**Notes**

- Number: Alphabetically arranged; reference number applies to the order in this table only (i.e., is not tied to **References**)

| # | Author, Year, Population, Screening Strategy for Studies Included in Warner 08 | Sensitivity<br>Specificity<br>PPV<br>Mammography | Sensitivity<br>Specificity<br>PPV<br>MRI | Sensitivity<br>Specificity<br>PPV<br>MRI + Mammography | Cases Breast Ca / Total Examinations (Some cases may have been detected by US) |
|---|---|---|---|---|---|
| 1. | Hagen 07<br>N=491<br>Mean age 41<br>No risk criteria<br>BI-RADS 3-5 | Sensitivity 32%<br>Specificity NR<br>PPV NR | Sensitivity 68%<br>Specificity NR<br>PPV NR | Sensitivity 80%<br>Specificity NR<br>PPV NR | 25/867=2.9% |
| 2. | Hartman 04*<br>N=41<br>High Family Risk (>1%/yr)<br>Median age 42.5<br>BI-RADS 4 or 5<br>Blinding not reported | Sensitivity 0%<br>Specificity NR<br>PPV NR | Sensitivity 100%<br>Specificity 75%<br>PPV 9% | Sensitivity 100%<br>Specificity NR<br>PPV NR | 1/41=2.4% |
| 3. | Kriege et al.,2004<br>N=1909<br>Mean age 40 years<br>High familial risk (≥20% lifetime)<br>BI-RADS score 4 or 5 | Sensitivity 33%<br>Specificity 99%<br>PPV 27% | Sensitivity 64%<br>Specificity 96%<br>PPV 16% | Sensitivity NR<br>Specificity NR<br>PPV NR | 45/4169=1.1% |
| 4. | Kuhl 2005<br>N=529<br>Median age 40 years (range 27 to 59 years)<br>Prior history of breast cancer: 26%<br>High familial risk (≥15% lifetime)<br>Conventional testing = mammography + ultrasound<br>BI-RADS score 4 or 5 | Sensitivity 32%<br>Specificity 97%<br>PPV 24% | Sensitivity 91%<br>Specificity 97%<br>PPV 50% | Sensitivity 93%<br>Specificity 96%<br>PPV 42% | 43/1452=3% |
| 5. | Leach 2005 (magnetic resonance imaging breast screening (MARIBS)) United Kingdom 22 sites 1997 to 2004<br>N=649<br>Median age 40 years (range 31 to 55 years)<br>High familial risk (≥0.9% per year)<br>Prior history of breast cancer: 0%<br>BI-RADS score 4 or 5 | Sensitivity 40%<br>Specificity 93%<br>PPV 15% | Sensitivity 77%<br>Specificity 81%<br>PPV 21% | Sensitivity 94%<br>Specificity 77%<br>PPV 20% | 35/1881=1.9% |
| 6. | Lehman 07<br>N=171<br>Mean age 45<br>High Risk (>25% lifetime risk) | Sensitivity 33%<br>Specificity 91%<br>PPV 12% | Sensitivity 100%<br>Specificity 79%<br>PPV 15% | Sensitivity 100%<br>Specificity 73%<br>PPV 12% | 6/171=3.5% |

| # | Author, Year, Population, Screening Strategy for Studies Included in Warner 08 | Sensitivity<br>Specificity<br>PPV<br>Mammography | Sensitivity<br>Specificity<br>PPV<br>MRI | Sensitivity<br>Specificity<br>PPV<br>MRI + Mammography | Cases Breast Ca / Total Examinations (Some cases may have been detected by US) |
|---|---|---|---|---|---|
| 7. | Lehman 2005<br>(International Breast MRI Consortium Working Group (IBMC))<br>USA, Canada 13 sites 1999 to 2002<br>N=367<br>Mean age 45 years<br>High familial risk (≥25% lifetime)<br>Prior history of breast cancer: 10%<br>Conventional testing = mammography<br>BI-RADS score 4 or 5 | Sensitivity 25%<br>Specificity NR<br>PPV 25% | Sensitivity 100%<br>Specificity NR<br>PPV 17% | NR | 3/367 additional cases=0.8% |
| 8. | Sardanelli 2007<br>N=278<br>Mean age 46 years (range 25 to 79 years)<br>High familial risk<br>Prior history of breast cancer: 39%<br>Conventional testing = mammography + ultrasound + CBE | Sensitivity 59%<br>Specificity 99%<br>PPV 77% | Sensitivity 94%<br>Specificity 98%<br>PPV 63% | Sensitivity 100%<br>Specificity NR<br>PPV NR | 18/377=4.7% |
| 9. | Trecate 2006<br>N=116<br>High Familial Risk<br>Ages 23-81<br>BI-RADS 4 or 5<br>Blinding not reported | Sensitivity 33%<br>Specificity 100%<br>PPV 100% | Sensitivity 100%<br>Specificity 97%<br>PPV 79% | Sensitivity 100%<br>Specificity 97%<br>PPV 79% | 12/116=10.3% |
| 10. | Warner 2001<br>N=196<br>Mean age 43<br>High familial risk (≥25% lifetime)<br>BI-RADS score 4 or 5 | Sensitivity 43%<br>Specificity 99%<br>PPV 55% | Sensitivity 86%<br>Specificity 91%<br>PPV 26% | Sensitivity 100%<br>Specificity NR<br>PPV NR | 7/196=3.6% |
| 11. | Warner 2004<br>N=236<br>Median age: 47 years<br>Prior history of breast cancer: 30%<br>Risk classification<br>BRCA1/2 mutation carriers 100%<br>No family history criteria<br>Conventional testing = mammography + ultrasound + CBE | Sensitivity 36%<br>Specificity 100%<br>PPV 88% | Sensitivity 77%<br>Specificity 95%<br>PPV 46% | Sensitivity 86%<br>Specificity 95%<br>PPV 48% | 22/457=4.8% |

* Small study with atypical SN for MX; Data not included in estimates of SN ranges

**DETAILS QUESTION 2: IMPROVED OUTCOMES**

**What is the evidence that breast MRI improves health outcomes for patients with suspected or diagnosed breast cancer? Including consideration of—**

a. **reduced need for other tests**
b. **more accurate diagnosis**
c. **change in treatment plan**
d. **reduced mortality and morbidity**

**Reducing Need for Other Tests: LOE Inconclusive**

Breast cancers may be missed if MRI, mammography or ultrasound are omitted from screening high risk women, and reducing need for other tests becomes a judgment call based on evidence and other factors such as patient preference, breast density, contraindications to MRI contrast and cost.

| Study and Details |
|---|
| **Berg 08**<br>In a prospective cohort study, forty participants at elevated risk as determined by study personnel and who had heterogeneously dense or extremely dense parenchyma in at least 1 quadrant by prior mammography, 41 breasts were diagnosed with cancer: 8 suspicious on both ultrasound and mammography, 12 on ultrasound alone, 12 on mammography alone and 8 participants (9 breasts) on neither. The diagnostic yield for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 women screened (95% CI, 1.1 to 7.2 per 1000; P = .003 that supplemental yield is 0). The diagnostic accuracy for mammography was 0.78 (95% CI, 0.67 to 0.87) and increased to 0.91 (95% CI, 0.84 to 0.96) for mammography plus ultrasound (P = .003). |
| **Kuhl 10**<br>In a more recent study conducted in four German centers, investigators reported cancer yield for CBE, mammography, ultrasound and breast MRI used alone and in different combinations in screening women at elevated risk for breast cancer. Calculated cancer yield achieved by MRI alone was found to be 14.9 of 1,000 and was not significantly improved by adding mammography (MRI plus mammography: 16.0 of 1,000). The cancer detection rate was not improved by adding ultrasound to MRI (14.9 of 1,000). PPV was 36% for ultrasound, 39% for mammography and 48% for MRI. Thirty of 687 women (4.4%) underwent biopsy for false positive diagnosis. All women were diagnosed with the combination of MRI and mammography, but 2 of 27 cancers were missed by MRI when mammography was omitted. |
| **Lord 07, Warner 08**<br>As demonstrated in the two meta-analyses above, sensitivity was increased when MRI and US were added to mammography screening in women at high risk of breast cancer. In the Lord 07 meta-analysis, the sensitivity of MRI plus mammography was 94% (95% CI, 86 to 98%) with the incremental sensitivity of MRI of 58% (95% CI, 47 to 70%) when added to mammography. When ultrasound was added to mammography sensitivity ranged from 49% to 67%. Incremental sensitivity of adding MRI to mammography plus ultrasound was 44% (95% CI, 27 to 61%). Specificity and PPV of MRI plus mammography were lower than with mammography alone in the Warner 08 meta-analysis. |
| **Weinstein 09**<br>A prospective screening 2 year cohort study of 609 asymptomatic high risk women (positive test for a mutation in *BRCA1* or *BRCA2*, ≥25% lifetime risk based on the Claus or Gail models, previous diagnosis of lobular carcinoma in situ or atypical hyperplasia (atypical ductal hyperplasia or atypical lobular hyperplasia), history of chest wall radiation before puberty and a recent diagnosis of breast cancer in the contralateral breast) with nonactionable mammograms (not suspicious for cancer) were screened with digital mammography (DM), whole breast ultrasound (WBUS) and MRI and yielded 20 breast cancers. Nine ductal carcinomas in situ and 11 invasive breast cancers were detected. The overall cancer yield on a |

per-patient basis was 3.0% (18 of 609 patients). The cancer yield by modality was 1.0% for FSM (6 of 597 women), 1.2% for DM (7 of 569 women), 0.53% for WBUS (3 of 567 women) and 2.1% for MRI (12 of 571 women). Of the 20 cancers detected, some were only detected by one imaging modality (FSM, n= 1; DM, n = 3; WBUS, n = 1; and MRI, n = 8).

**Ultrasound: LOE Inconclusive**

Performing supplemental screening with ultrasound in women at high risk for breast cancer was judged by the authors to add no additional benefit over screening with mammography and MRI in most instances. However, as stated in the American College of Radiology (ACR) 2010 guidelines (see CLINICAL GUIDELINES below), breast ultrasound may have a role as a supplemental screening tool for some high-risk women such as those with dense breast tissue, those who have contraindications to MRI or in those whose levels of risk do not reach the level recommended for breast MRI screening by the American Cancer Society (ACS).

**Change in Treatment Plans: LOE Inconclusive**

Based on one meta-analysis and two observational studies, there is sufficient evidence to conclude that adding MRI screening in high risk women and in the preoperative setting will change treatment plans for some women, and some women will undergo treatment changes based on false positive tests (LOE for change in treatment plans: Borderline). Widening of surgical margins during local excisions and increased rates of mastectomy are likely to occur. There is insufficient evidence to determine if these changes in treatment based on MRI are beneficial.

| **Study and Details** |
|---|
| **Houssami 08**<br>A meta-analysis of 19 diagnostic studies of 2610 women with established index breast cancer, rated as at moderate risk of bias, reported that MRI detected additional disease in both breasts (16% increase) and the rate of conversion from wide local excision (WLE) to mastectomy was 8.1% (95% CI, 5.9 to 11.3). The conversion rate from WLE to more extensive surgery was 11.3%. However, pathologic examination did not identify additional disease in 13.6% (1.1% divided by 8.1%) of the former group and in 52.2% (5.9% divided by 11.3%) of the latter group. Thus, an additional 1.1% of women underwent an unnecessary mastectomy, and 5.5% undergoing more extensive local excision were found by histopathology to have no additional malignancy to what was found without MRI testing, i.e., underwent an unnecessary wider local excision. |
| **Lim 10**<br>In a recent observational study of 535 newly diagnosed breast cancer patients who planned to undergo breast conserving surgery, ninety-eight (18.3%) patients had additional lesions, shown as suspicious lesions on breast MRI, but not detected with conventional (mammography + ultrasound + clinical breast exam) methods. Eighty-four (15.7%) of these patients had a change in surgical treatment plans based on the MRI results. Forty-seven (8.8%) of the 84 patients had additional malignancies; the other 37 patients (6.9%) had benign lesions. However, during the period of study, the mastectomy rate did not change significantly (OR 0.98; 95% CI, 0.95 to 1.00; P = 0.059). |
| **Pengel 09**<br>A cohort study of 349 women with invasive breast carcinoma reported that, in the entire cohort, there was no significant difference in incomplete excision rates between the MRI and the non-MRI group (P = 0.17). However, MRI led to treatment changes: mastectomy (8.7%) or wider excision (2.3%). |
| **Scomersi 10**<br>In a retrospective record review of the therapeutic impact MRI in 493 breast cancer patients who could not be imaged adequately with mammography or ultrasound (dense breasts, microcalcifications suspicious for carcinoma in situ or discordance between mammography and ultrasound), MRI added |

clinical information in 52.9% of patients and resulted in 44.3% of management changes.

**Turnbull 10**

The first randomized controlled trial (RCT) to assess whether preoperative breast MRI in early-stage breast cancer can decrease reoperation rates for incompletely excised breast cancer included 1623 women with early breast cancer and reported that further wide local excision rates were not statistically different whether breast MRI was used (10.4%) or not (11.2%), and total reoperation rates were the same (19%) with or without breast MRI. However, the results of this RCT are inconclusive because 15 (26%) of the 58 women undergoing mastectomy did not have preoperative verification of breast cancer, and this may have diminished the reported effect of preoperative MRI on reoperation rates. Plus, authors' claims of no difference for repeat operation, mastectomy at further operation within 6 months of randomization or a pathologically avoidable mastectomy at initial surgery appear to be unfounded as the results were not statistically significant, and a review of the confidence intervals reveals that roughly 4 to 5 patients—a clinically significant number—within a 5 percent play of chance, could face a repeat operation or mastectomy at further operation within 6 months of randomization or a pathologically avoidable mastectomy either way. Thus, these results are inconclusive.

Further, because some benign lesions are indistinguishable from suspicious or malignant lesions prior to surgery, excessive surgical procedures are likely to be unnecessarily performed in a significant portion of patients undergoing preoperative MRI. Data are suggestive that Triple Assessment (mammography, ultrasound, CBE) Plus MRI may increase the number of mastectomies performed as compared to Triple Assessment No MRI. Reviewers computed confidence intervals for patients undergoing a clinically recommended mastectomy. Data suggest that MRI, compared to no MRI, may result in 4 to 8 more mastectomies, utilizing a triple assessment approach, outside a 5 percent play of chance. Some uncertainty is due to not knowing if there was an imbalance in lack or loss of histological data between the groups.

Also data are suggestive that Triple Assessment Plus MRI may increase the number of pathologically avoidable mastectomies performed as compared to Triple Assessment No MRI. Reviewers computed confidence intervals for patients undergoing a clinically recommended mastectomy. Data suggest that MRI compared to no MRI may result in 1 to 3 more pathologically avoidable mastectomies per 100 testings, when utilizing a triple assessment approach, outside a 5 percent play of chance. Some uncertainty is due to not knowing if there was an imbalance in lack or loss of histological data between the groups.

**Re-excision Rates: LOE Inconclusive**

The evidence regarding the effect of preoperative MRI testing on re-excision rates following surgical treatment is inconclusive. Studies report conflicting results which may be due to insufficient numbers of subjects to show a difference if there is one (power issues).

**Study and Details**

**Pengel 09**

Authors reported no significant difference in incomplete excision rates between the MRI and the non-MRI groups (P = 0.17). The authors reported a sub-group analysis showing that incompletely excised infiltrating ductal carcinoma (IDC) was significantly associated with not receiving MRI: 11/136 (8.1%) versus 2/126 in the MRI group (1.6%), P = 0.02.

**Mann 10**

In a retrospective cohort study of patients with invasive lobular carcinoma, the reported a re-excision rate was 27% in patients not receiving preoperative MRI compared to 9% in the MRI group, OR 3.64 (95% CI, 1.30 to 10.20, P = 0.010). The mastectomy rate in the MRI group compared to the no-MRI group was 48%

versus 59%, P = 0.098.

**Recurrence Rates: LOE Inconclusive**

There is insufficient evidence to determine if preoperative MRI testing in women with early invasive breast cancer reduces recurrence rates or mortality rates. Adequately powered prospective trials are lacking.

| Study and Details |
|---|
| **Fischer 04**<br>A retrospective study of 346 patients reported a local recurrence rate after breast conservation treatment of 6.8% (9/133) in patients without a breast MRI and 1.2% (1/86) in patients with a breast MRI (P < .001). |
| **Solin 08**<br>In a retrospective cohort study of 756 women with early stage invasive breast carcinoma or ductal carcinoma in situ who underwent breast conserving surgery (BCS) including definitive breast irradiation, it was reported that MRI was not associated with a lower recurrence rate. The 8-year rate of any local failure was similar in both groups: 3% for the patients receiving breast MRI study and 4% for patients not receiving a breast MRI study. The local-only first failure rates (3% *v* 4%, respectively; *P* =.32) were not statistically different. There were also no differences between the two groups for the 8-year rates of overall survival (86% *v* 87%, respectively; *P*=.51), cause-specific survival (94% *v* 95%, respectively; *P* =.63), freedom from distant metastases (89% *v* 92%, respectively; *P*=.16), or contralateral breast cancer (6% *v* 6%, respectively; *P*=.39). |

**Patient Acceptance of MRI Testing: LOE Borderline**

The evidence suggests that the MRI testing in women at high risk for breast cancer is acceptable.

| Study and Details |
|---|
| **Essink-Bot 06**<br>One study addressed women's acceptance of MRI in breast cancer surveillance in patients with familial or genetic predisposition. Discomfort and preferences were evaluated. The authors concluded that MRI is accepted by this population of women and was preferred over mammography. However, this study was conducted in the Netherlands and may not be generalizable to the US population as "discomfort" and "acceptance" may be cultural. However, this study suggests acceptability of MRI. |

**DETAILS QUESTION 3: SAFETY**
**What is the evidence of the safety of breast MRI?**

It is useful to consider potential harms of MRI testing in women at high risk for breast cancer and women undergoing staging and surgical planning for recently diagnosed breast cancer by considering the evidence in three areas: 1) safety of gadolinium-based contrast agents used in MRI testing; 2) evidence about MRI safety; and, 3) the potential harms of false positive tests which could result in an increased number of unnecessary procedures, decreased quality of life or functioning and psychological distress.

**Safety of Gadolinium-based MRI Contrast Agents: LOE Borderline**
We found no evidence to conclude that gadolinium-based agents (with the possible exception of gadodiamide) present safety issues in non-pregnant adults without CKD. Numerous gadolinium-based MRI contrast agents have been approved for clinical use in the United States.

| Study and Details |
|---|
| **Chen 08**<br>Intravenous gadolinium in high doses is teratogenic in animal studies, albeit at high and repeated doses. Gadolinium crosses the placenta, where it is presumably excreted by the fetal kidneys into the amniotic fluid. Gadolinium-induced nephrogenic systemic fibrosis has been reported, but valid evidence regarding a cause and effect relationship is lacking. The 2007 American College of Radiology guidance document for safe MRI practices recommended that intravenous gadolinium be avoided during pregnancy and used only if absolutely essential and that the risks and benefits of gadolinium use be discussed with the pregnant patient and referring clinicians. Gadolinium is classified as a category C drug* by the U.S. Food and Drug Administration and can be used if considered critical (only to be administered "if the potential benefit justifies the potential risk to the fetus").<br>* Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. |
| **Perazella 07**<br>One review of safety studies conducted in patients with CKD found low quality evidence with conflicting safety results but concluded that renal and extra-renal toxicity may occur even though no cause and effect relationship has been established. Based on expert opinion the authors recommend avoidance of gadolinium agents in patients with advanced kidney disease (GFR <20 ml/minute) and those with ESRD on dialysis. |
| **Shellock 06**<br>The most recent review of gadolinium-based agents included 79 observational studies (some patients with hepatic or renal impairment or coronary artery disease) who received various preparations of gadolinium chelates in conjunction with MRI imaging. Most gadolinium-based agents are similar with regard to their physical properties, mode of action and general safety profiles. The review compared adverse events reported in patients receiving contrast agents to placebo and included postmarketing safety surveillance data and totaled more than 1.5 million applications of gadolinium agents. The reported adverse event rates were similar in the contrast agent group (13%) and placebo group (17%), but this could represent a power issue. Serious adverse events were rarely reported and included dyspnea, nausea, urticaria, hypotension, and anaphylactoid reactions. The authors also reviewed previous studies and reported that none showed a discernible difference between the various gadolinium-based MRI contrast agents in terms of the incidence or type of adverse event reported. The authors found one report of "spurious hypocalcemia" with an observed decrease from normal serum calcium levels in as many as 16% of patients given preparations of the agent gadodiamide. |

**Safety of MRI—Radiation Exposure: LOE Inconclusive**

MRI uses non-ionizing radiation, and short-term and long-term adverse effects have not been established. We found no studies addressing the effects of MRI radiation exposure on adverse events in women at high risk of breast cancer screened or tested with MRI or women recently diagnosed with breast cancer undergoing staging procedures or preoperative surgical planning.

**Safety of MRI—The Fetus, Infants and Children: LOE Inconclusive**

There is insufficient evidence to determine the effect of breast cancer screening or testing with MRI on the fetus, infants and children.

| Study and Details |
| --- |
| **Chen 08** |
| A recent review found no evidence that MRI is associated with adverse outcomes in the fetus, infants or children including a theoretical concern of acoustic injury. |

**Safety of MRI—MRI Testings in Women with Breast Implants: LOE Borderline**

There is insufficient evidence to conclude that breast implants increase the risk of breast cancer or that benefit is derived from MRI screening women with breast implants.

| Study and Details |
| --- |
| **Hoshaw 01** |
| In a meta-analysis of observational studies assessing the association of breast implants and breast cancer and qualitative review of risk for other cancers, no persuasive evidence of a causal association between breast implants and any type of cancer was found. The meta-analysis supports the overall conclusion that breast implants do not pose any additional risk for breast cancer (relative risk, 0.72; 95% CI, 0.61 to 0.85) or for other cancers (relative risk, 1.03; 95% CI, 0.87 to 1.24). The authors conclude that there is no evidence that women with implants are diagnosed with later-stage breast malignancies, that they are at increased risk for breast cancer recurrence or that if they develop breast cancer they have a decreased length of survival. |

**MRI and Psychological Issues: LOE Borderline to Inconclusive**

The evidence is insufficient to conclude that false-positive breast cancer screening test results or recalling patients because of false positive tests is associated with clinically meaningful negative psychological outcomes. The evidence is suggestive that many women might suffer no clinically meaningful negative psychological outcomes. However, the evidence is of medium to potentially high risk of bias, is highly limited due to many factors, and non-significant findings raise the possibility of insufficient population numbers to show a difference between groups if one exists (power issues).

| Study and Details |
| --- |
| **Brewer 07 Systematic Review** |
| One systematic review of abnormal screening mammograms of women 40 years of age and older undergoing routine screening concluded that *some* women with false-positive results on mammography may have differences in whether they return for mammography, occurrence of breast self-examinations and levels of anxiety compared with women with normal results. While this is entirely reasonable to conclude that this is the case for "some women," this systematic review did not identify any generalizable clinically meaningful findings. Reported results may not be useful for the US population as these outcomes may be culturally based and study findings suggest some cultural differences (US, Canadian and European). There is no indication that studies were critically appraised; for each outcome of interest, the included studies were characterized as finding statistically significant findings of greater symptoms of |

| |
|---|
| distress, higher levels of anxiety, or—conversely—lower levels of depression, no effects (which could be attributable to power issues wherein any non-significant findings raise the possibility of insufficient population numbers to show a difference if one exists) or mixed results. Authors also cited limitations of included studies: correlational study designs, a small number of studies, a lack of clinical validation for many measures and possible heterogeneity. |
| **Feig 04**<br>This narrative review reported on 24 studies addressing psychological effects of screening and found some evidence of anxiety prior to testing but no evidence of clinically meaningful depression or psychological distress from false positives or recall for further evaluation. |
| **O'Neill 09**<br>This observational study reported a small increase in psychological disturbance in high-risk women whose MRI results prompted recall. However, study was small and included mostly Caucasian women in Chicago who were highly motivated and willing to try a new modality. |
| **Schwartz 00**<br>This cross-sectional survey of 479 women without a history of breast cancer randomly selected from telephone books, reported that the subjects were highly tolerant of false positive mammograms. When asked how many false positives would be acceptable for each life saved 63% of the subjects answered that they would tolerate 500 or more false positives and 37% would tolerate 10,000 or more. |

**DETAILS QUESTION 4: SUBPOPULATIONS**

**What is the evidence that breast MRI has differential efficacy or safety issues in subpopulations? Including consideration of—**

a. **Age, breast tissue characteristics; breast implants**
b. **Other patient characteristics or evidence of appropriate patient selection criteria**
c. **Type of scanning machine and software, reader training, and other operational factors**
d. **Provider type, setting or other provider characteristics**
e. **Health care system type, including worker's compensation, Medicaid, state employees**

**MRI and Ultrasound Testing in Women at High Risk of Breast Cancer With Dense Breast Tissue: LOE Borderline**

Mammography has been compared to MRI in detecting breast cancer in the setting of increased breast density pattern by mammography. The evidence is sufficient to conclude that some additional cases of breast cancer will be detected with the addition of MRI and ultrasound to mammography testing.

| Study and Details |
|---|
| **Sardanelli 04**<br>In a study of ninety patients with planned mastectomies, patients underwent mammography and dynamic gadolinium-enhanced MRI. The gold standard was pathologic examination of the whole excised breast (slice thickness, 5 mm). The overall positive predictive value (PPV) was 76% (124/164) for mammography and 68% (152/222) for MRI (difference NS). In breasts with an almost entirely fatty pattern, sensitivity was 75% for mammography and 80% for MRI (NS) and the PPV was 73% and 65% (NS) respectively. In breasts with fibroglandular or dense pattern, the sensitivity was 60% for mammography and 81% for MRI ($P < 0.001$), and the PPV was 78% and 71% (NS), respectively. The authors concluded that MRI was more sensitive than mammography for the detection of multiple malignant foci in fibroglandular or dense breasts. |
| **Berg 08**<br>In a prospective cohort study of forty participants at elevated risk for breast cancer and who had heterogeneously dense or extremely dense parenchyma in at least 1 quadrant by prior mammography, diagnostic yield for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 women screened (95% CI, 1.1 to 7.2) per 1000. The diagnostic accuracy for mammography was 0.78 (95% CI, 0.67 to 0.87) and increased to 0.91 (95% CI, 0.84 to 0.96) for mammography plus ultrasound ($P = .003$). |

**Technical and Provider Issues: LOE Inconclusive**

The evidence is insufficient for establishing optimal technical specifications for MRI testing.

| **Study and Details** |
|---|
| **Warren 09**<br>This was a post-hoc assessment of the effect of technical aspects of MRI on diagnostic performance based on the Houssami meta-analysis summarized above (Houssami 08). Where technical parameters were complete, authors examined their effect on summary ROC models and the TP:FP ratio and PPV, using random-effects logistic regression analysis. None of the technical parameters (year of study, slice thickness or repetitions after contrast-medium injection) were associated with TP:FP ratio or significant performance differences. Tesla strength was reported in 2,801 cases. Other key information was omitted including whether both breasts were examined for 1683 (60%), position of the patient in 1,375 (49%), and imaging planes used in 688 (25%). Contrast agent and dose were reported for 2,646 (95%) breasts. Reporting technique was inconsistently reported. Single radiology reports were found in 1,637 (58%) cases, double in 347 (12.4%). In 960 (34%) knowledge of mammography or ultrasound findings was not stated. Although evidence is lacking technical and provider issues have been addressed in clinical guidelines (See CLINICAL GUIDELINES below: Magnetic resonance imaging of the breast: technical recommendations from the European Society of Breast Cancer Specialists (EUSOMA) working group) |

**DETAILS QUESTION 5: COST IMPLICATIONS**
**What is the evidence about the cost implications and cost effectiveness of breast MRI?**

- The evidence is suggestive that adding MRI to mammographic breast cancer screening in women at high risk of breast cancer will increase diagnostic and therapeutic costs (LOE for cost outcomes: Moderate).
- The evidence is insufficient for reliably estimating cost-effectiveness (LOE: Inconclusive).

Accurately estimating cost-effectiveness may not be possible because RCTs evaluating the mortality reduction with screening or testing women at high-risk for breast cancer have not been conducted and mortality estimates are based on mathematical modeling using data from studies of tumor size and nodal metastases and their association with observed mortality outcomes (LOE for cost-effectiveness of adding of MRI to breast cancer testing in women at high risk of breast cancer or those with recently diagnosed breast cancer undergoing preoperative staging: Inconclusive).

- Estimates of cost-effectiveness of adding yearly MRI screening to mammographic screening in women at increased risk of breast cancer from 3 economic analyses are reported below:The cost per QALY gained by adding MRI from ages 35 to 54 years was reported to be $55,420 for BRCA1 mutation carriers, $130,695 for BRCA2 mutation carriers, and $98,454 for BRCA2 mutation carriers who have mammographically dense breasts. Screening strategies that incorporate annual MRI as well as annual mammography have a cost per quality-adjusted life-year (QALY) gained ranging from approximately $25,000 to more than $300,000, depending on the ages selected for MRI screening and the specific *BRCA* mutation. The study assumed a cumulative breast cancer incidence by age 70 of 65% for women with BRCA 1 mutations and 45% for women with BRCA 2 mutations. The risks of a second breast cancer within 10 years were assumed to be 43.4% and 34.6% respectively. The study assumed a 14% breast cancer mortality reduction for yearly mammography alone from age 25 to 69 years in women with BRCA 1 mutations and a 38% mortality reduction for mammography plus MRI. For BRCA 2 the respective mortality reduction assumptions were 16% and 38%. (Plevritis 06).
- The cost per QALY gained with MRI and mammography compared with mammography alone for women with BRCA1/2 mutations was reported to be $25,277. The investigators based survival on a mathemathical model that uses observational data including stage of disease at diagnosis and observed survival. They based QALYs gained with the addition of MRI on prevalence rates (investigators used a 4% prevalence rates for BRCA 1/2 and a

range down to 0.5% for strong FH without BRCA 1/2 women based on selected observational studies). Among other high-risk women without BRCA mutations, cost per QALY gained with MRI and mammography compared with mammography alone varied depending on the prevalence of breast cancer, ranging from $45,566 (prevalence rate of 3%) to $72,360 (prevalence rate of 2%) to $151,642 (prevalence rate of 1%) to $310,616 (prevalence rate of 0.5%). The cost effectiveness of MRI alone compared with mammography alone was similar (Tanjea 09).

- The cost of adding annual MR imaging to annual mammographic screening in high-risk women was reported to be $69,125 for each additional QALY gained. Sensitivity analysis indicated that, when the screening MR imaging cost increased to $960 (base case, $577), or the sensitivity of combined screening decreased below 76% (base case, 94%), the cost of adding MR imaging to mammography exceeded $100,000 per QALY (Lee 10).

## APPENDICES TABLE OF CONTENTS

## I. EVIDENCE GRADES (DELFINI) AND RISK OF BIAS ASSESSMENTS (AHRQ) FOR CRITICALLY APPRAISED STUDIES

**Notes**

- Number: Alphabetically arranged; reference number applies to the order in this table only (i.e., is not tied to **References**)

| # | Study | Grades: Delfini AHRQ | Study Type | High Risk Women? | Outcome | Other/Comments |
|---|---|---|---|---|---|---|
| 1. | Berg 08 | BU Medium | Prospective Cohort | Yes | Ultrasound for detection of cancer in dense breast tissue | Diagnostic yield for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 women screened (95% CI, 1.1 to 7.2) per 1000. The diagnostic accuracy for mammography was 0.78 (95% CI, 0.67 to 0.87) and increased to 0.91 (95% CI, 0.84 to 0.96) for mammography plus ultrasound (P = .003). |
| 2. | Brennan 09 | BU Medium | Meta-analysis | Yes | Detection cancer contralateral breast | MRI-detected suspicious findings (true positives plus false positives) was 9.3% (95% CI, 5.8% to 14.7%); incremental cancer detection rate (ICDR) was 4.1% (95% CI, 2.7% to 6.0%), PPV, 47.9% (95% CI, 31.8% to 64.6%); true positive: false positive ratio, 0.92 (95% CI, 0.47 to 1.82). MRI does not reliably distinguish benign from malignant findings. |
| 3. | Brewer 07 | BU Medium | Systematic Review of Observational Studies | No | Psychological well-being | 23 studies of 313,967 women with false-positive mammograms. Narrative review. Authors conclude that results suggest no long-term symptoms of depression in women who receive false-positive mammograms. |
| 4. | Chen 08 | U High | Guidelines Use of MRI In Pregnancy | No | Safety: Adverse Events Fetus and Children | The 2007 American College of Radiology guidance document for safe MRI practices recommended that intravenous gadolinium should be avoided during pregnancy and should be used only if absolutely essential and that the risks and benefits of gadolinium use be discussed with the pregnant patient and referring clinicians. Gadolinium is classified as a category C drug by the U.S. Food and Drug Administration and can be used if considered critical (only to be administered "if the potential benefit justifies the potential risk to the fetus). |

| # | Study | Grades: Delfini AHRQ | Study Type | High Risk Women? | Outcome | Other/Comments |
|---|---|---|---|---|---|---|
| 5. | Essink-Bot 06 | BU Medium | Observational | Yes | Acceptance of MRI | Single site observational study in Holland reporting that 44.4% (75/169) women expressed a preference for MRI as a screening test, 41.4% (70/169) for CBE and 14.2% (24/169) for mammography. Further, 64.4% (114/177) reported that they would feel completely reassured by a favorable MRI result, whereas this was 40.1% (71/177) for mammography and 27.8% (49/177) for CBE, respectively. |
| 6. | Feig 04 | U High | Narrative Review | No | Psychological Impacts | Narrative review of 24 studies reporting on psychological impacts: some anxiety prior to mammography but no significant psychological impact. |
| 7. | Fischer 04 | U High | Retrospective Cohort | Yes | Recurrence Rate Breast Cancer | 6.8% (9/133) in patients without a breast MRI and 1.2% (1/86) in patients with a breast MRI (P< .001). |
| 8. | Houssami 08 | BU Medium | Meta-analysis | Yes | Change in treatment plans | Increased rates of case finding, false positives, wide excision and mastectomy. |
| 9. | Hoshaw 01 | U High | Observational Studies | No | Safety: Breast Implants | No reliable evidence of a causal association between breast implants and any type of cancer was found. A metaanalysis of implants and breast cancer concludes that breast implants do not pose any additional risk for breast cancer (relative risk, 0.72; 95% confidence interval, 0.61 to 0.85) or for other cancers (relative risk, 1.03; 95% confidence interval, 0.87 to 1.24). |
| 10. | Kuhl 10 | BU Medium | Cohort | Yes | Diagnostic Accuracy | Positive predictive value was 39% for mammography, 36% for ultrasound and 48% for MRI. All women were diagnosed with the combination of MRI and mammography. Missed 2/27 cancers diagnosed by mammography + MRI. The high diagnostic accuracy of MRI as shown by receiver operating characteristic (ROC) analysis was not significantly improved by the addition of one or any combination of the other screening modalities. |

| # | Study | Grades: Delfini AHRQ | Study Type | High Risk Women? | Outcome | Other/Comments |
|---|---|---|---|---|---|---|
| 11. | Lee 10 | U<br>High | Model | Yes | Cost Effectiveness MRI in women with BRCA 1 Mutations | The cost of adding annual MR imaging to annual mammographic screening was reported to be $69,125 for each additional QALY gained. Sensitivity analysis indicated that, when the screening MR imaging cost increased to $960 (base case, $577), or the sensitivity of combined screening decreased below 76% (base case, 94%), the cost of adding MR imaging to mammography exceeded $100,000 per QALY. |
| 12. | Lehman 07 | BU<br>Medium | Observational | Yes | Detection cancer in contralateral breast | Detection rate 3.1%; biopsy rate: 12.5%; positive for cancer: 24.8%. |
| 13. | Lim 10 | BU<br>Medium | Observational | Yes | Change in treatment plans | Ninety-eight (18.3%) newly diagnosed breast cancer patients had additional lesions, shown as suspicious lesions on breast MRI, but not detected with conventional methods. Eighty-four (15.7%) of these patients had a change in surgical treatment plans based on the MRI results. |
| 14. | Lord 07 | BU<br>Medium | Meta-analysis of observational diagnostic studies | Yes | Diagnostic Accuracy | Useful sensitivity, specificity information. |
| 15. | Mann 10 | BU<br>Medium | Retrospective Cohort | Yes | Re-excision rates in invasive lobular carcinoma (ILC) | In the group not receiving MRI, 27% of the patients underwent a re-excision after initial BCS. In the group receiving MR, this rate was significantly lower at 9%. The odds ratio was 3.64 (95% CI, 1.30 to 10.20, P = 0.010). The mastectomy rate in the MR+ group compared to the MR- group was (48% vs. 59%, P = 0.098). |
| 16. | O'Neil 09 | BU<br>Medium | Observational Study | Yes | Psychological Impacts from false positive test | Impact of Event Scale (IES) questionnaire used to assess psychological impact of false positives (15 items with 75 points, higher score indicating greater breast cancer-specific distress). Difficult to interpret "avoidance" in results. Authors conclude "little increase in psychological disturbance" based on mean avoidance score changes from 7.5 to 9.9. |

| # | Study | Grades: Delfini AHRQ | Study Type | High Risk Women? | Outcome | Other/Comments |
|---|---|---|---|---|---|---|
| 17. | Pengel 09 | BU Medium | Observational Study | Yes | Change in treatment plans + Incomplete excision rates | The larger extent of breast cancer detected by MRI led to treatment changes: mastectomy (8.7%) or wider excision (2.3%). |
| 18. | Perazella 07 | U High | Narrative Review | No | Safety of gadolinium MRI contrast agents | Experts recommend avoidance of gadolinium agents in patients with advanced kidney disease (GFR <20 ml/ minute) and those with ESRD on dialysis |
| 20. | Plevritis 06 | U High | Model | Yes | Cost Effectiveness MRI in women with BRCA 1/2 Mutations | The cost per QALY for adding MRI to mammography from ages 35 to 54 years reported to be $55,420 for BRCA1 mutation carriers and $130,695 for BRCA2 mutation carriers. Cost per QALY for BRCA2 mutation carriers who have mammographically dense breasts was reported to be $98,454. |
| 21. | Saranelli 04 | BU Medium | Observational | Yes | MRI detection of cancer in dense breasts | In breasts with fibroglandular or dense pattern, the sensitivity was 60% for mammography and 81% for MRI (P< 0.001), and the PPV was 78% and 71% (NS), respectively. |
| 22. | Schwartz 00 | BU Medium | Cross-sectional survey | No | Tolerance of false positive mammograms | 63% of the subjects would tolerate 500 or more false positives and 37% would tolerate 10,000 or more for one life saved. |
| 23. | Scomersi 10 | U Medium | Chart Review | Yes | Change in treatment plans | 493 breast cancer patients who could not be imaged adequately with traditional radiology (dense breasts, microcalcifications suspicious for carcinoma in situ or discordance between mammography and ultrasound), MRI added clinical information in 52.9% of patients that resulted in 44.3% of management changes. |
| 24. | Shellock 06 | U High | Review | No | Safety: Gadolinium | Adverse events similar in gadolinium and placebo groups. |
| 25. | Solin 08 | U High | Retrospective Cohort | Yes | Recurrence Rate Breast Cancer 8 years | MRI was not associated with a lower recurrence rate at 8 years. |

| # | Study | Grades: Delfini AHRQ | Study Type | High Risk Women? | Outcome | Other/Comments |
|---|---|---|---|---|---|---|
| 26. | Taneja 09 | U<br>High | Model | Yes | Cost Effectiveness MRI in women with BRCA 1/2 Mutations | The cost per QALY gained with MRI and mammography compared with mammography alone for women with BRCA1/2 mutations was reported to be $25,277. Among other high-risk women, cost per QALY gained with MRI and mammography compared with mammography alone varied depending on the prevalence of breast cancer, ranging from $45,566 to $310,616. The cost effectiveness of MRI alone compared with mammography alone was similar. |
| 27. | Turnbull 10 | Change mastect-omy rate: BU/Medium<br><br>Repeat opera-tion: U/High Avoid-able mastec-tomy: U/High<br><br>Cost effective ness: U/High | RCT | Yes | Change in management plans | Preoperative staging early breast cancer. 26% of women undergoing mastectomy did not have preoperative verification of breast cancer. |
| 28. | Warner 08 | BU<br>Medium | Meta-analysis | Yes | Diagnostic Accuracy | Useful sensitivity/specificity information. |
| 29. | Warren 09 | U<br>High | Review from meta-analysis | Yes | Technical Parameters of MRI | Technical parameters examined for effect on summary ROC models, and the TP:FP ratio and PPV, using random-effects logistic regression analysis. Analyzed technical parameters: year of study, slice thickness and repetitions after contrast-medium injection. None of the technical parameters were associated with TP:FP ratio. |

| # | Study | Grades: Delfini AHRQ | Study Type | High Risk Women? | Outcome | Other/Comments |
|---|---|---|---|---|---|---|
| 30. | Weinstein 09 | BU Medium | Observational Study | Yes | Diagnostic Accuracy | The cancer yield by modality was 1.0% for mammography (six of 597 women), 1.2% for digital mammography (seven of 569 women), 0.53% for whole breast US (three of 567 women) and 2.1% for MRI (12 of 571 women). Of the 20 cancers detected, some were only detected by one imaging modality (FSM, n= 1; DM, n = 3; WBUS, n = 1; and MRI, n = 8). |

## II. OVERALL GRADE FOR LEVEL OF EVIDENCE (LOE) FOR OUTCOMES

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| **Sensitivity** | Lord 07<br>Warner 08 | Consistent | Indirect | Imprecise | Borderline | Meta-analysis: Evidence is sufficient for drawing conclusions about the sensitivity of MRI |
| **Specificity** | Lord 07<br>Warner 08 | Inconsistent | Indirect | Imprecise | Inconclusive | Meta-analysis: Evidence is sufficient for drawing conclusions about specificity of MRI |
| **Detection in Dense Breast Tissue** | ↓ | N/A | N/A | N/A | N/A | Some additional cases of breast cancer will be detected with the addition of MRI and ultrasound to mammography testing in women with increased breast tissue density. |
| | Sardanelli 04 | N/A | N/A | N/A | N/A | In breasts with fibroglandular or dense pattern, the sensitivity was 60% for mammography and 81% for MRI. |
| | Berg 08 | N/A | N/A | N/A | N/A | Diagnostic yield |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 women screened (95% CI, 1.1 to 7.2) per 1000. |
| **Detection in Contralateral Breast** | ↓ | Consistent | Direct | Imprecise | Borderline | Meta-analysis and observational studies |
| | Lehman 07 | N/A | N/A | N/A | N/A | Observational diagnostic study: cancer detected in 30 of 969 women (3.1%). The sensitivity of MRI in the contralateral breast was 91%, and the specificity was 88%. The negative predictive value of MRI was 99%. Biopsy rate: 12.5%, positive for cancer |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | 24.8%. |
| | Brennan 09 | N/A | N/A | N/A | N/A | Meta-analysis: MRI-detected suspicious findings (true positives plus false positives) was 9.3% (95% CI, 5.8% to 14.7%); incremental cancer detection rate (ICDR) was 4.1% (95% CI, 2.7% to 6.0%), PPV, 47.9% (95% CI, 31.8% to 64.6%); true positive: false positive ratio, 0.92 (95% CI, 0.47 to 1.82). MRI does not reliably distinguish benign from malignant findings. |
| **Reducing Need for Other Tests** | ↓ | Inconsistent | Indirect | Imprecise | Inconclusive | Risk of bias is high because reducing need for tests requires judgment and will vary with decision-makers—if conventional testing is decreased breast cancers are likely to be missed. |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | Lord 07<br>Warner 08 | N/A | N/A | N/A | N/A | See above |
| | Kuhl 10 | N/A | N/A | N/A | N/A | Cohort Study: The high diagnostic accuracy of MRI by receiver operating (ROC) analysis was not significantly improved by the addition of one or any combination of the other screening modalities. All tumors were detected with MRI + mammography. However, MRI missed 2/27 tumors. |
| | Weinstein 09 | N/A | N/A | N/A | N/A | Meta-analysis: Some cancers were detected by only one imaging modality |
| | Kuhl 10 | N/A | N/A | N/A | N/A | Cohort Study: Calculated cancer yield achieved by MRI alone was not significantly improved by adding mammography. However, all |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | women were diagnosed with the combination of MRI and mammography, but 2 of 27 cancers were missed by MRI alone. The cancer detection rate was not improved by adding ultrasound to MRI. |
| **Change in Treatment Plans** | ↓ | Inconsistent | Direct | Imprecise | Borderline | MRI detected additional abnormalities in both breasts (16%) with 8.1% converting to mastectomy and 11.3% to more extensive resection. |
| | Houssami 08 | N/A | N/A | N/A | N/A | Meta-analysis: Increased rates of case finding, false positives, wide excision and mastectomy. |
| | Turnbull 10 | N/A | N/A | N/A | N/A | RCT: 50/1623 women experienced changes in treatment plans. |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | Lim 10 | N/A | N/A | N/A | N/A | Cohort Study: 15.7% of patients with recently diagnosed breast cancer had a change in surgical treatment plans based on the preop MRI results. Mastectomy rates did not change |
| | Brennan 09 | N/A | N/A | N/A | N/A | Meta-analysis: incremental cancer detection rate (ICDR) in contralateral breast was 4.1% (95% CI, 2.7% to 6.0%). MRI detects contralateral breast lesions in a substantial proportion of women, but does not reliably distinguish benign from malignant findings. Effect on treatment was inconsistently reported, but many women underwent contralateral |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | mastectomy based on MRI. |
| | Scomersi 10 | N/A | N/A | N/A | N/A | In 493 breast cancer patients who could not be imaged adequately with traditional radiology (dense breasts, microcalcifications suspicious for carcinoma in situ or discordance between mammography and ultrasound), MRI added clinical information in 52.9% of patients that resulted in management changes in 44.3% of women. |
| **Re-excision Rates** | ↓ | Inconsistent | Direct | Imprecise | Inconclusive | Conflicting results reported |
| | Pengel 09 | N/A | N/A | N/A | N/A | Cohort study of invasive breast cancer reported no significant difference in incomplete excision rates between the MRI |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | and the non-MRI groups (P = 0.17). |
| | Mann 10 | N/A | N/A | N/A | N/A | Retrospective cohort study of patients with invasive lobular carcinoma reported a re-excision rate of 27% in patients not receiving preoperative MRI compared to 9% in the MRI group, OR 3.64 (95% CI, 1.30 to 10.20, P = 0.010). The mastectomy rate in the MRI group compared to the no-MRI group was (48% vs.59%,P = 0.098). |
| **Recurrence Breast Cancer** | ↓ | Inconsistent | Imprecise | Direct | Inconclusive | Conflicting Evidence |
| | Fischer 04 | N/A | N/A | N/A | N/A | Retrospective cohort study which found MRI was associated with lower recurrence rate in women |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | undergoing BCS. 6.8% (9/133) in patients without a breast MRI and 1.2% (1/86) in patients with a breast MRI (p< .001). |
| | Solin 08 | N/A | N/A | N/A | N/A | Retrospective cohort study which found that MRI was not associated with a lower recurrence rate in women with breast conservation surgery with radiation. The 8-year rate of any local failure was 3% for the patients with a breast MRI study and 4% for the patients without a breast MRI study. |
| **Psychological Impact** | ↓ N/A | Inconsistent | Indirect | Imprecise | Borderline to Inconclusive | Insufficient evidence to conclude MRI results in clinically meaningful psychological distress; there |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | appears to be high tolerance for false positives. |
| | Brewer 07 | N/A | N/A | N/A | N/A | No long term symptoms of depression in women with false positive mammograms. |
| | Feig 04 | N/A | N/A | N/A | N/A | Narrative review of 24 studies addressing psychological effects of screening and found some evidence of anxiety prior to mammography, but no evidence of clinically meaningful psychological distress. |
| | O'Neil 09 | N/A | N/A | N/A | N/A | Mean avoidance scores changed from 7.5 to 9.9 (Impact of Event Scale) which authors interpret as "little increase" in psychological disturbance. |
| | Schwartz | N/A | N/A | N/A | N/A | Mammography |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | study: Women not at high risk would tolerate 500 or more false positives for one life saved. |
| **Technical and Provider Issues** | ↓ | Inconsistent | Indirect | Imprecise | Inconclusive | Insufficient evidence to establish optimal technical specifications or provider qualifications. |
| | Warren 09<br>↓ | N/A | N/A | N/A | N/A | Post-hoc analysis of meta-analysis of diagnostic studies. None of the technical parameters evaluated by the authors were associated with TP:FP ratio. |
| **Cost-Effectiveness** | ↓ | Consistent | Indirect | Imprecise | Inconclusive | Insufficient evidence for accurately estimating cost-effectiveness. |
| | Lee 10 | N/A | N/A | N/A | N/A | The cost of adding annual MR imaging to annual mammographic screening was reported to be |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | $69,125 for each additional QALY gained. Sensitivity analysis indicated that, when the screening MR imaging cost increased to $960 (base case, $577) or when the sensitivity of combined screening decreased below 76% (base case, 94%), the cost of adding MR imaging to mammography exceeded $100,000 per QALY. |
| | Plevritis 06 | N/A | N/A | N/A | N/A | The cost per QALY for adding MRI to mammography from ages 35 to 54 years reported to be $55,420 for BRCA1 mutation carriers and $130,695 for BRCA2 mutation carriers. Cost per QALY for BRCA2 |

| Outcome | Reference | Overall Consistency (consistent, inconsistent, N/A) | Directness (direct, indirect = proxy marker) | Precision (precise, imprecise; precise allows conclusion re: superiority, equiv, or inferiority) | Overall Level of Evidence (high=confidence that the evidence represents the true effect, moderate, borderline, inconclusive evidence) | Comments<br>• Moderate LOE requires grade B for clinical outcomes, but BU evidence for test accuracy<br>• Borderline: more than 1 BU for clinical outcomes; for safety grade U may be sufficient<br>• Insufficient: conflicting grade BU or grade U. |
|---|---|---|---|---|---|---|
| | | | | | | mutation carriers with mammographically dense breasts was reported to be $98,454. |
| | Taneja 09 | N/A | N/A | N/A | N/A | The cost per QALY gained with adding MRI to mammography for women with BRCA1/2 mutations was reported to be $25,277. Among other high-risk women, cost per QALY varied depending on the prevalence of breast cancer, ranging from $45,566 to $310,616. |

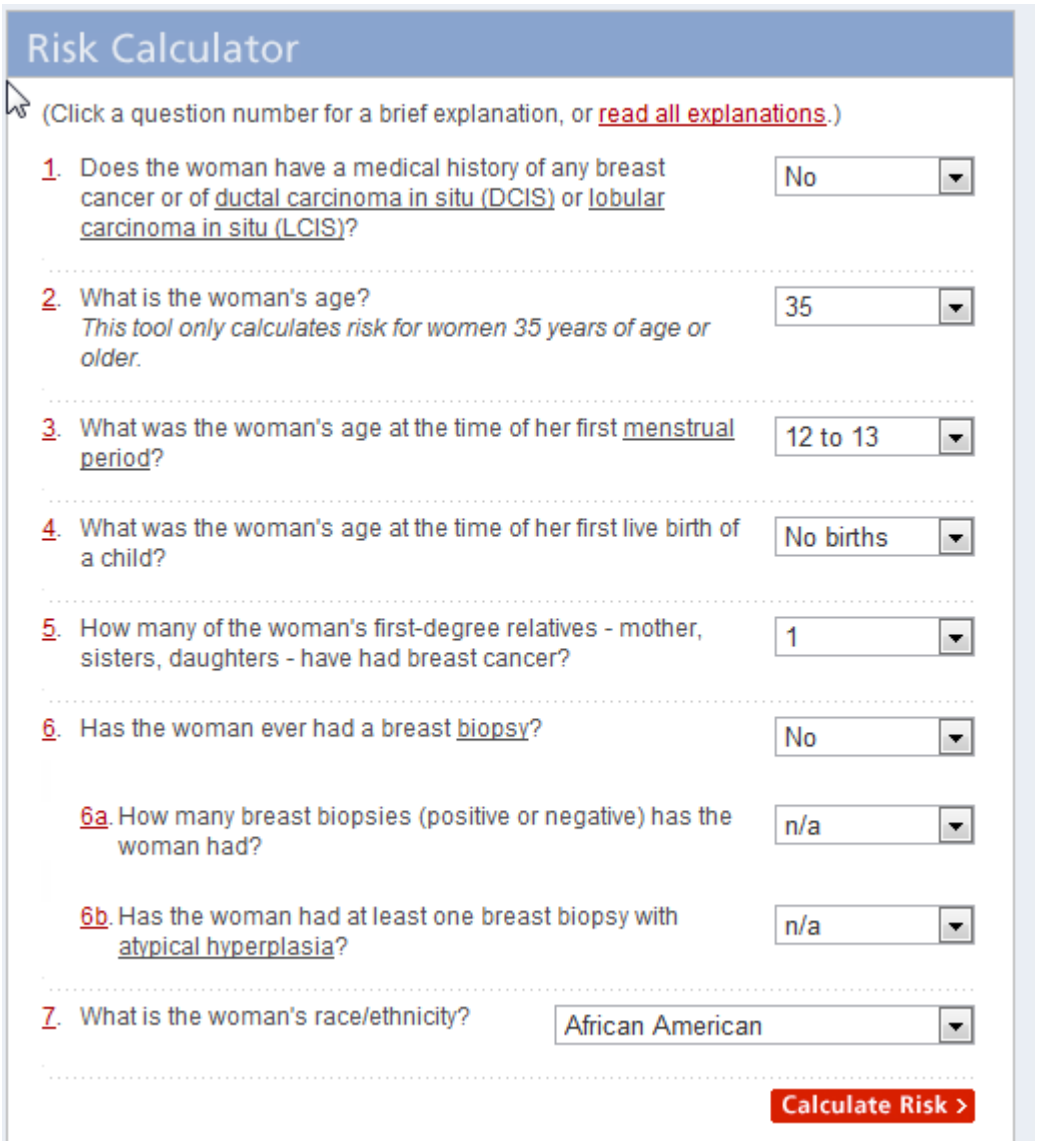
## III. BREAST CANCER RISK ASSESSMENT

### Risk Assessment Models

The American Cancer Society and other guidelines groups base recommendations for screening, at least in part, on lifetime risk of breast cancer. The ACS recommends annual mammography and MRI screening for women starting at age 30 if their lifetime risk is approximately 20% to 25%. There are several models available to calculate cancer risk. Some models use pedigree analysis of first- and second-degree relatives on both the maternal and paternal sides. Several models can estimate risk based on complex family histories and assist in both estimating breast cancer risk and the likelihood that a *BRCA* mutation is present, including the Claus, Tirer-Cusick, BRCAPRO, and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm models. Some of the models include complex family histories as well as conventional risk factors, such as reproductive history or a history of prior breast biopsy. The Breast Cancer Risk Assessment Tool (Gail model) provides a good generalized measure of short and long-term risk based on a woman's age, ethnicity, history of breast biopsy and breast cancer, age at menarche, parity, and age at first live birth (see below), but it does not have the capacity to analyze detailed family histories, including first- and second-degree relatives on both the maternal and paternal sides. To estimate risk of breast cancer in women with a significant family history who have not undergone genetic testing and do not have an affected relative who has tested positive, health professionals may wish to obtain specialized software that can address family history in first- and second-degree relatives on both the maternal and paternal sides. See below for details.

**National Cancer Institute (NCI) Breast Cancer Assessment Tool**

- Last modified: 4/28/08
- URL: http://www.cancer.gov/bcrisktool/
- The Breast Cancer Risk Assessment Tool is based on a statistical model known as the "Gail model," which uses a woman's personal medical history (number of previous breast biopsies and the presence of atypical hyperplasia in any previous breast biopsy specimen), her reproductive history (age at the start of menstruation and age at the first live birth of a child), and the history of breast cancer among her first-degree relatives (mother, sisters, daughters) to estimate her risk of developing invasive breast cancer over specific periods of time. An example is provided below:



Risk Calculator

(Click a question number for a brief explanation, or read all explanations.)

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)? — No

2. What is the woman's age?
*This tool only calculates risk for women 35 years of age or older.* — 35

3. What was the woman's age at the time of her first menstrual period? — 12 to 13

4. What was the woman's age at the time of her first live birth of a child? — No births

5. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer? — 1

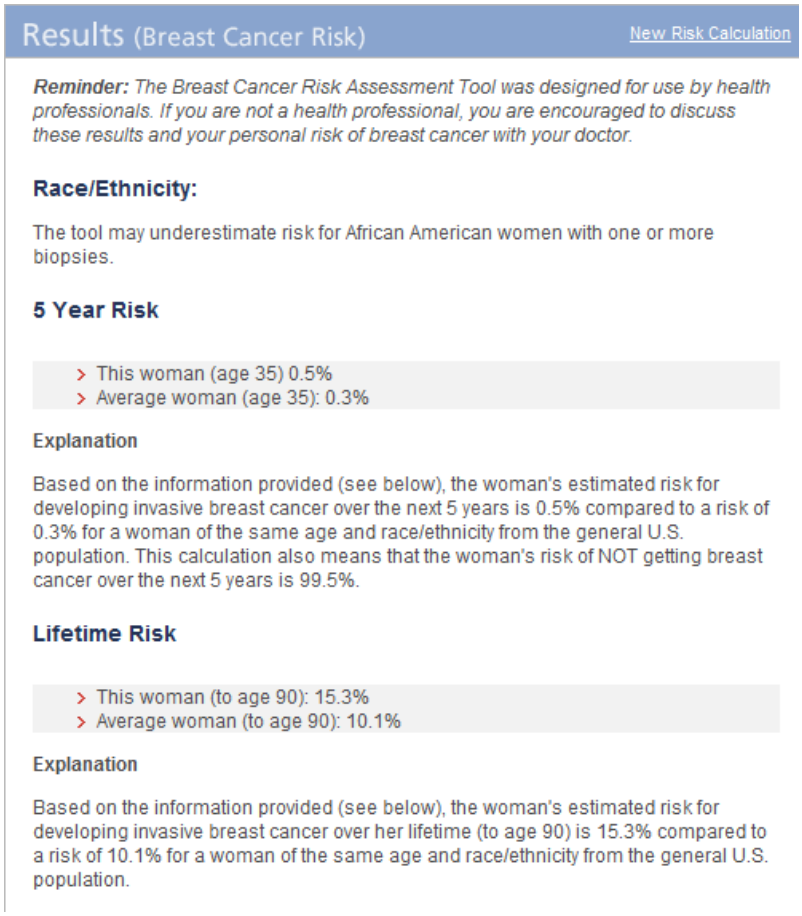
6. Has the woman ever had a breast biopsy? — No

6a. How many breast biopsies (positive or negative) has the woman had? — n/a

6b. Has the woman had at least one breast biopsy with atypical hyperplasia? — n/a

7. What is the woman's race/ethnicity? — African American

Calculate Risk >



Results (Breast Cancer Risk) New Risk Calculation

***Reminder:*** *The Breast Cancer Risk Assessment Tool was designed for use by health professionals. If you are not a health professional, you are encouraged to discuss these results and your personal risk of breast cancer with your doctor.*

**Race/Ethnicity:**

The tool may underestimate risk for African American women with one or more biopsies.

**5 Year Risk**

- This woman (age 35) 0.5%
- Average woman (age 35): 0.3%

**Explanation**

Based on the information provided (see below), the woman's estimated risk for developing invasive breast cancer over the next 5 years is 0.5% compared to a risk of 0.3% for a woman of the same age and race/ethnicity from the general U.S. population. This calculation also means that the woman's risk of NOT getting breast cancer over the next 5 years is 99.5%.

**Lifetime Risk**

- This woman (to age 90): 15.3%
- Average woman (to age 90): 10.1%

**Explanation**

Based on the information provided (see below), the woman's estimated risk for developing invasive breast cancer over her lifetime (to age 90) is 15.3% compared to a risk of 10.1% for a woman of the same age and race/ethnicity from the general U.S. population.

- BRCAPRO Version 4.3, http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp
- BOADICEA Versions, http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_home.html
- Claus model (BreastCa for Palm, version 1.0, copyright 2001) http://www.palmgear.com/index.cfm?fuseaction=software.showsoftware&prodID=29820
- Tyrer-Cuzick (IBIS Breast Cancer Risk Evaluation Tool, RiskFileCalc version 1.0, copyright 2004) Available by email request from IBIS: ibis@cancer.org.uk

## IV. BI-RADS (THE BREAST IMAGING REPORTING AND DATA SYSTEM)

BI-RADS was developed in 1993 by the American College of Radiology (ACR) to standardize mammographic reporting, improve communication, reduce confusion regarding mammographic findings, aid research and facilitate outcomes monitoring. The classification system is summarized below. Details are available at—
http://www.acr.org/SecondaryMainMenuCategories/quality_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext.aspx

**Clinical Management Recommendations for Mammograms by Breast Imaging Reporting and Data System (BI-RADS) Category**

| BI-RADS Category | Assessment | Clinical Management Recommendation |
|---|---|---|
| 0 | Incomplete Assessment | Need to review prior studies and/or complete additional imaging |
| 1 | Negative | Continue routine screening |
| 2 | Benign Finding | Continue routine screening |
| 3 | Probably Benign Finding | Short-term follow-up mammogram at 6 months, then every 6 to 12 months for 1 to 2 years |
| 4 | Suspicious Abnormality | Perform biopsy, preferably needle biopsy |
| 5 | Highly suspicious of malignancy; appropriate action should be taken | Biopsy and treatment, as necessary |
| 6 | Known biopsy-proven malignancy, treatment Pending | Assure that treatment is completed |

## V. CLINICAL GUIDELINES

**National Guideline Clearinghouse (NGC)**
We found 7 recent MRI guidelines providing specific recommendations for women at increased risk of breast cancer. We also found recommendations for this population in the National Institute for Health and Clinical Excellence (NICE) database.

**a. American College of Radiologists (ACR)**
Lee CH, Dershaw DD, Kopans D, Evans P, Monsees B, Monticciolo D, Brenner RJ, Bassett L, Berg W, Feig S, Hendrick E, Mendelson E, D'Orsi C, Sickles E, Burhenne LW. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol. 2010 Jan;7(1):18-27. PubMed PMID: 20129267.

In 2010 The Society of Breast Imaging (SBI) and the American College of Radiologists (ACR) issued guidelines for breast cancer screening in high risk (Lee 2010). The recommendations are based on a combination of evidence and consensus. Therefore risk of bias is at least medium.

Recommendations:

- BRCA1 or BRCA2 mutation carriers, untested first degree relatives of BRCA mutation carrier
    - Recommendation: Annual mammogram and annual MRI starting by age 30, but not before age 25
- Women with ≥20% lifetime risk for breast cancer on the basis of family history
    - Recommendation: Annual mammography and annual MRI starting by age 30, but not before age 25, or 10 years before the age of the youngest affected relative, whichever is later. Performing supplemental screening with ultrasound in these women adds no additional benefit over screening with mammography and MRI. However, screening breast ultrasound may have a role as a supplemental screening tool for high-risk women who have contraindications to MRI or in those whose levels of risk do not reach the level recommended for breast MRI screening by the ACS.
- History of chest irradiation received between the ages of 10 and 30
    - Recommendation: Annual mammogram and annual MRI starting 8 years after treatment; mammography is not recommended before age 25
- Personal history of breast cancer (invasive carcinoma or DCIS), ovarian cancer, or biopsy diagnosis of lobular neoplasia or ADH
    - Recommendation: Annual mammography from time of diagnosis; either annual MRI or ultrasound can also be considered; if screening MRI is performed in addition to mammography, also performing screening ultrasound is not necessary
- Women with dense breasts as the only risk factor
    - The addition of ultrasound to screening mammography may be useful for incremental cancer detection

**b. Magnetic resonance imaging of the breast: technical recommendations from the European Society of Breast Cancer Specialists (EUSOMA) working group**
Sardanelli F, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, Helbich T, Heywang-Köbrunner SH, Kaiser WA, Kerin MJ, Mansel RE, Marotti L, Martincich L, Mauriac L, Meijers-Heijboer H, Orecchia R, Panizza P, Ponti A, Purushotham AD, Regitnig P, Del Turco MR, Thibault F, Wilson R. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer. 2010 May;46(8):1296-316. Epub 2010 Mar 19. PubMed PMID: 2030462.

Expert opinion: The consensus group recommends—

- Use of MR units with magnets with intensity field P1.0 T and gradients P20 mT/m, equipped with bilateral dedicated coils, preferably multichannel
- Regular checks using standardized quality control of MR units, including magnetic field homogeneity, breast coil performance, etc., according to national regulations
- In order to reduce the risk of false positives, premenopausal women undergo the examination ideally on day 6–13 of the menstrual cycle, even when oral contraception is used
- In case of hormone replacement therapy, MRI be performed at least 4 weeks after discontinuation of treatment

These schedule protocols can be waived in urgent cases. The minimal MRI protocol for breast cancer detection can be defined as follows: bilateral (with the exception of prior mastectomy) morphological study using at least one unenhanced high-contrast sequence such as T2-weighted fast/turbo spin-echo with or without fat saturation, short tau inversion recovery (STIR), or spectral presaturation with inversion recovery (SPIR) sequences, with scan plane chosen by the radiologist; bilateral (with the exception of prior mastectomy) 2D or 3D gradient-echo T1-weighted dynamic sequence, with or without fat saturation, thickness 63 mm, spatial in-plane resolution 61.5 mm2 (preferably 61 mm2), temporal resolution 6120 s), scan plane chosen by the radiologist. They recommend the use of two-compartment (vascular/ interstitial) gadolinium-chelates at the standard dose of 0.1 mmol/kg with an injection rate of 2–3 ml/s, followed by saline flushing (20–30 ml at 2 ml/s), preferably using an automatic injector. Additional techniques, i.e. MR approaches not yet validated on a large scale (such as proton spectroscopy, diffusion-weighted and perfusion imaging), must be considered as additional and not a replacement for the above recommended imaging protocols.

The image postprocessing should include temporal subtraction (contrast-enhanced minus unenhanced images) for dynamic studies without fat saturation. Dynamic analysis with generation of percent enhancement versus time curves should be performed through positioning of region of interests at least for all identified enhancing lesions with a diameter P5mm and mass-like morphology according to the MR imaging Breast Imaging Reporting and Data System (BI-RADS) classification, documenting a representative curve for the most suspicious enhancement dynamics.

Subtraction technique and dynamic measurements may not be useful or needed if partial volume effect or patient motion exists. If such artefacts are suspected, unsubtracted images should be visually evaluated and this technical limitation needs to be included in the report. They recommend the use of standardized interpretation systems such as the BI-RADS lexicon or equivalent.

There is some evidence that software for breast MR computer-aided diagnosis (CAD) may be of benefit, but it is insufficient to recommend the routine use of such systems. A comprehensive diagnostic statement should be included at the end of the report, including the evaluation of the previous conventional (mammography+/-ultrasound +/- clinical breast exam) breast imaging modalities when they are available. A final practical recommendation should be suggested at the end of the report.

They suggest also attaching to the report itself a selection of paper- or film-printed images that show the relevant findings as described in the report, even though all the images are supplied through the picture archiving and communication system (inpatients) or a DICOM compatible compact disc (outpatients).

They highlight the need of MR-guided procedures (needle biopsy, presurgical localization) for findings visible only at MRI judged to be suspicious with potential influence on therapeutic decision, as mentioned above. For these procedures, they recommend the use of dedicated coils and devices, officially approved

for the procedure. Tissue sampling for histopathology using core biopsy or preferably vacuum-assisted biopsy is required when MR-guidance is used.

**c. USPSTF: Breast Cancer Screening, 2009**

Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L; U.S. Preventive Services Task Force. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151:727-37, W237-42.

The focus of the guideline is on women at average risk of breast cancer. Relevant evidence mentioned by the USPSTF is retrospective observational data and from expert opinion and is rated as at medium risk or high risk of bias.

- Contrast-enhanced magnetic resonance imaging (MRI) has traditionally been used to evaluate women who have already received a diagnosis of breast cancer. Recommendations for its use in screening pertain to certain high-risk groups only. If a woman has an abnormal mammographic finding on screening or a concerning finding on physical examination, additional imaging and biopsy may be recommended. Additional imaging may consist of diagnostic mammography or mammography done with additional or special views, targeted breast ultrasonography or breast MRI. Additional imaging may help classify the lesion as a benign or suspicious finding to determine the need for biopsy. Biopsy techniques vary in the level of invasiveness and amount of tissue acquired, which affects yield and patient experience. One retrospective study cited in the guideline, reported the following: planned surgical management was altered in 69 of 267 patients (26%) and, in 49 of those patients (71%), there was pathologic verification of malignancy in the surgical specimen that confirmed the need for wider or separate excision or mastectomy. Forty-four of 267 patients (16.5%) had conversion of planned breast conservation to mastectomy. In a univariate analysis, change in management was associated significantly with histology; management was altered in 11 of 24 lobular tumors (46%) compared with 58 of 243 ductal tumors (24%; P = 0.02). The authors concluded that breast MRI improved local staging in almost 20% of patients and that preoperative breast MRI studies may be particularly useful in surgical planning for, and management of, patients with lobular carcinoma.

**d. National Comprehensive Cancer Network (NCCN), 2009**

Bevers TB, Anderson BO, Bonaccio E, Buys S, Daly MB, Dempsey PJ, Farrar WB, Fleming I, Garber JE, Harris RE, Heerdt AS, Helvie M, Huff JG, Khakpour N, Khan SA, Krontiras H, Lyman G, Rafferty E, Shaw S, Smith ML, Tsangaris TN, Williams C, Yankeelov T; National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. J Natl Compr Canc Netw. 2009 Nov;7(10):1060-96. Review. Erratum in: J Natl Compr Canc Netw. 2010 Feb;8(2):xxxvii. Buys, Sandra [corrected to Buys, Saundra]; Yaneeklov, Thomas [corrected to Yankeelov, Thomas]. PubMed PMID: 1993097

The recommendations are based on a combination of "lower quality" evidence and consensus. Therefore, risk of bias is at least medium.

- Women with a strong family history of breast cancer, genetic predisposition or hereditary ovarian cancer should undergo mammography, MRI and clinical breast exam starting at age 25 every 6-12 months or annually.
- Consider MRI as an adjunct to mammography and clinical breast exam every 6 to 12 months if a woman has a lobular carcinoma in situ (LCIS) or atypical hyperplasia.

**e. Institute for Clinical Systems Improvement (ICSI), 2010**

URL :http://www.icsi.org/guidelines_and_more/guidelines__order_sets__protocols/womens_health/breast_disease_diagnosis/breast_disease__diagnosis_of__guideline_.html

Recommendations were adopted from the American Cancer Society (see below).

**f. American Cancer Society Guideline for breast screening with MRI as an adjunct to mammography (2007)**

Saslow, D., Boetes, C., Burke, W., Harms, S., Leach, M., et al. (2007). American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography. *CA Cancer Journal for Clinicians,* 57, 75-89. The recommendations are based on a combination of evidence and consensus. Therefore risk of bias is at least medium.

- Screening MRI is recommended for women with—
    - Approximately 20-25% or greater lifetime risk of breast cancer, including women with—
        - A strong family history of breast or ovarian cancer.
        - Women who were treated for Hodgkin disease.

**g. National Institute for Health and Clinical Excellence: The Familial Breast Cancer Guideline (NICE), 2006**

URL: http://www.nice.org.uk/CG41

Accuracy estimates were based on two studies at medium risk of bias:

- Adding MRI added to mammography increases sensitivity over mammography alone in screening for breast cancer in women at high risk.
- Four out of five studies reported greater specificity with mammography than MRI in high risk women.
- Mammography may be a useful adjunct to MRI in the high risk group, particularly for BRCA2 carriers because of their high incidence of ductal carcinoma insitu (DCIS) and, in women with BRCA2 mutations, mammography has a higher sensitivity than MRI in detecting DCIS.
- MRI is more sensitive than mammography in BRCA1 carriers.
- MRI combined with mammography is a cost-effective intervention in women with a BRCA1 mutation aged 30–49.
- Annual MRI combined with mammography is a cost-effective intervention in non-BRCA1 women aged 30-39 with an 8% or greater 10-year risk.
- MRI combined with mammography is a cost-effective intervention in non-BRCA1 women aged 40-49 with a 20% or greater 10-year risk.

## VI. PREVIOUS TECHNOLOGY ASSESSMENTS

### Table 5. Overview of Relevant Recent Systematic Reviews and Technology Assessments of Breast Cancer Screening and MRI Screening in Women at High Risk of Breast Cancer

**Notes**

- Number: Alphabetically arranged; reference number applies to the order in this table only (i.e., is not tied to **References**)

| # | Reference | Quality Assessment of Studies | Findings |
|---|---|---|---|
| 1. | AHRQ:<br>Bruening W, Launders J, Pinkney N, Kostinsky H, Schoelles K, Turkelson C. Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities. Comparative Effectiveness Review No. 2. (Prepared by ECRI Evidence-based Practice Center under Contract No. 290-02-0019.) Rockville, MD: Agency for Healthcare Research and Quality. February 2006. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. | Yes | This review did not formally address women at high risk for breast cancer.<br><br>For suspicious lesions in general, at a fixed 95% sensitivity, the specificity of MRI was 62.8%. At the mean threshold of the studies, the sensitivity was 92.5%, the specificity was 72.4% and the negative predictive value was 90.5% (for a population with a prevalence of disease of 50.3%). For lesions with microcalcifications, the analysis found that the sensitivity of MRI was 85.9%, the specificity was 75.5% and the negative predictive value was 84.7% (for a population with a prevalence of disease of 50.3%). If a woman with a suspicious lesion tests negative for breast cancer by MRI, her chance of actually having breast cancer drops from 20% to 3.8%. For every 1,000 women who had a negative MRI, about 962 women would have avoided an unnecessary biopsy, but 38 women would have missed cancers. Of interest, this review cites the Ontario Ministry of Health which has suggested that a 98% negative predictive value threshold would be societally acceptable to reliably preclude breast biopsy. Evidence suggests that for women at average risk of breast cancer receiving a biopsy in the US, all four of the diagnostic tests evaluated in this report fall short of this 98% threshold. While MRI was more sensitive than the other technologies in typical usage, MRI would result in a 96% negative predictive value for a woman at average risk; women at higher risk would have an even lower negative predictive value. |
| 2. | Dunfield L, Severn M. *Effectiveness of magnetic resonance imaging (MRI) screening for women at high risk of breast cancer* [Technology report number 93]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007. | Yes | Found sensitivity range from 96% to 100% for MRI and 33% to 44% for mammography. The specificity was reported to be 91% to 95% for MRI and 92% to 99.5% for mammography. The results indicate that some breast cancers would have been missed with mammography screening alone, and the addition of MRI resulted in more cancers being detected. High-risk women, such as those with BRCA1/2 mutations, those having a first-degree relative with a mutation or those with a strong family history of breast cancer, seem to benefit most from the addition of MRI to the |

| # | Reference | Quality Assessment of Studies | Findings |
|---|---|---|---|
| | | | screening modality. The American Cancer Society's guidelines were evaluated, and authors report that the rigor of development was low because the inclusion and exclusion criteria, the external review process and the process for updating the guidelines were not reported. The editorial independence from the funding body and the conflicts of interest were not reported, making the editorial independence score zero. The cost-effectiveness studies suggest that MRI for breast cancer screening could be cost effective, depending on the willingness to pay and the value attributed to one QALY. |
| 3. | ECRI Evidence Report:<br>Screening women at high risk of breast cancer by MRI, July 2007 | Yes | Initial evaluation of breast symptoms should be accomplished with MRI and ultrasound.<br>MRI is more accurate than mammography in detecting breast cancers in high risk women. MRI added to mammography is more accurate than mammography in detecting breast cancer in high risk women. The addition of MRI to mammography increases the rate of false-positives. An estimated 16 additional false positives will occur for every 1 additional cancer identified. Screening of women at high risk of breast cancer with MRI only reduces X-ray exposure and reduces false positives (3 fewer false positives for every 10 additional cancers). |
| 4. | Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database of Systematic Reviews 2009,Issue 4. Art. No.: CD001877. DOI:10.1002/14651858.CD001877.pub3. | Yes | Not a review of MR screening in high risk women, but relevant when attempting to project mortality and morbidity benefits from interventions if screening tests are positive. Objective was to assess the effect of screening for breast cancer with mammography on mortality and morbidity. Screening is likely to reduce breast cancer mortality. As the effect was lowest in the adequately randomized trials, a reasonable estimate is a 15% reduction corresponding to an absolute risk reduction of 0.05%. Screening led to 30% overdiagnosis and overtreatment or an absolute risk increase of 0.5%. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged, and 10 healthy women, who would not have been diagnosed if there had not been screening, will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress for many months because of false positive findings. [Note: audit of Cochrane references by reviewers suggests the evidence may not support the conclusion "will experience important psychological distress" because of the low quality of evidence.] It is thus not clear whether screening does more good than harm. To help ensure that the women are fully informed of both benefits and harms before they decide whether or not to attend screening, the authors summarized the |

| # | Reference | Quality Assessment of Studies | Findings |
|---|---|---|---|
| | | | above information in a leaflet for lay people that is available in several languages on www.cochrane.dk. |
| 5. | Medical Services Advisory Committee (MSAC), 2007: Breast magnetic resonance imaging | Yes | Accuracy studies have provided strong evidence that MRI is a more sensitive and less specific test than mammography for detecting breast cancer. There was consistent evidence that adding MRI to mammography provides a 2.6-fold increase in test sensitivity (MRI+mammography sensitivity 94% [95% CI, 86 to 98%]; mammography sensitivity 36% [95% CI, 25 to 48%; incremental sensitivity of MRI 58% [95% CI, 46 to 70%]). Estimates of test specificity using MRI varied, but one study showed a 3-fold increase in the rate of investigations for false positive findings. Existing evidence that mammography has a higher sensitivity in older women suggests the incremental accuracy of MRI is likely to be lower in this age group. There was a lack of clinical evidence to determine the health benefits gained by earlier detection of breast cancer in women at high risk.<br><br>Cost-effectiveness: Based on modeled estimates of the effects of early detection, MRI may potentially be cost-effective for screening very high-risk women such as BRCA1 mutation carriers aged 35-54 years, but is unlikely to be cost-effective for screening BRCA2 carriers or women with a wider risk or age distribution. The total additional cost of implementing MRI for breast cancer screening will depend on the cost and uptake of the procedure, the sensitivity of standard mammography screening protocols that include the option of performing a screening ultrasound and patient baseline risk. |
| 6. | Oregon Health and Sciences University MEDICAID EVIDENCE-BASED DECISIONS PROJECT (MED) RAPID APPRAISAL<br>Magnetic Resonance Imaging (MRI) in Breast Cancer January 15, 2008 | Yes | Evidence of moderate strength showed that both MRI and alone and MRI plus x-ray mammography detect greater numbers of cancers than x-ray mammography and that there is an increase in false positive findings in women screened with MRI. There is no evidence that breast MRI improves life expectancy, survival or quality of life in any patient population. Improved diagnostic efficacy may or may not lead to improved clinical outcomes. Safety, effects on processes of care and economic impacts were not considered. |

## VII. METHODS

### Scope of Work Statement (SOW)

Patients identified as being at high risk for breast cancer from family history, personal history, genetic testing or possible abnormalities on screening mammography or physical examination may undergo additional tests. An ideal diagnostic test to evaluate risk of breast abnormalities would provide accurate information appropriate to guide patient-management decisions. Such testing would accurately distinguish patients who require biopsy from those who can safely avoid biopsy as well as accurately identify the extent or location of malignancy (e.g. detection of contra lateral disease) for optimizing treatment if breast cancer has been diagnosed.

In order to appropriately guide decisions, a person who has a positive diagnostic or screening test should be reasonably confident that the positive result is correct. Likewise a person who has a negative test result should be reasonably confident that the result is correct.

Finally, there should be reasonable confidence that any test results are likely to result in improved clinical outcomes and that the benefits outweigh harms for the person who has undergone diagnostic testing or screening.

### Key Questions

For women at risk of breast cancer based on presentation of with an abnormal mammogram; palpable breast abnormality; or relevant demographic and clinical risk factors:

1. What is the evidence that breast MRI has the ability to diagnose or exclude breast cancer compared to current tests including mammography?
    a. Describe sensitivity, specificity, and other key test characteristics
2. What is the evidence that breast MRI improves health outcomes for patients with suspected or diagnosed breast cancer? Including consideration of:
    a. reduced need for other tests
    b. more accurate diagnosis
    c. change in treatment plan
    d. reduced mortality and morbidity
3. What is the evidence of the safety of breast MRI?
4. What is the evidence that breast MRI has differential efficacy or safety issues in subpopulations? Including consideration of:
    a. Age, breast tissue characteristics; breast implants
    b. Other patient characteristics or evidence of appropriate patient selection criteria
    c. Type of scanning machine and software, reader training, and other operational factors
    d. Provider type, setting or other provider characteristics
    e. Health care system type, including worker's compensation, Medicaid, state employees
5. What is the evidence about the cost implications and cost effectiveness of breast MRI?

### Assumptions Regarding Project Scope

Specific exclusions to scope —

- This HTA will not include formal decision analyses or performance of detailed, primary economic analyses (e.g. cost-utility or cost-effectiveness analyses).
- Detailed analysis of data on costs, etc. is not currently part of this work plan.

**Work Approach and Sequence**

- We received approval for our work plan after discussing our report objectives, key questions and analytic framework with HCA/Agency and OHSU
- We conducted a systematic literature search to identify relevant studies published in peer-reviewed publications, critically appraised, documented and synthesized the evidence from the obtained literature.
- Deliverables include a final report and one-time formal presentation of the report.

**Searching and Filtering**

- Multiple searches were performed applying various search terms and limits to maximize potentially relevant studies.
- A systematic search of the specified databases was conducted using standard, accepted methods for systematic reviews.
- Search terms for the PubMed searches dealing with test accuracy included the following terms: "breast cancer" and "MRI" and "high risk" and "screening" or "diagnosis."
- Search dates for individual studies were based on search dates of systematic reviews or meta-analyses obtained from our initial searches. Details of the search include search date, search terms, limits (e.g., randomized controlled trial (RCT) or systematic review (SR)) and were documented, as were the number of hits and whether or not each reference was relevant.
- Titles and abstracts were evaluated to determine relevancy. Studies found to have fatal flaws identifiable within the title or abstract are excluded at this stage and the reason for exclusion was documented.

**Exclusions**

We excluded studies not published in the English language, studies not relevant to the question, animal studies, editorials, opinion pieces, abstracts without full documentation of research, narrative reviews, observational studies for determining efficacy of interventions, studies deemed to be fatally flawed from bias due to study design or methodology and studies not useful for answering key clinical questions:

- Clinically useful studies were defined as those with clinically meaningful size of benefits in prespecified outcomes of importance to patients (defined as "mortality, morbidity, symptom relief, emotional and physical functioning and health-related quality-of-life").
- Studies of therapeutic interventions reporting pre-specified intermediate outcomes were included if potentially relevant.
- Diagnostic studies were excluded if the test of interest was not compared to a reasonable comparator. We looked carefully at the possibility that new tests detected abnormalities that are meaningfully different from those detected by the reference test and prioritized studies where assessors of the new test were blinded to results of reference tests and vice-versa.
- We sought screening studies attempting to determine if earlier diagnosis and subsequent treatments in women at high risk for breast cancer improved outcomes more than later diagnosis and treatment and where reported beneficial outcomes would not be due to bias (e.g., lead time, length, overdiagnosis or volunteer bias).

**Table 6: Inclusion & Exclusion Criteria of Studies Included in the Review**

| Study Component | Inclusion | Exclusion |
|---|---|---|
| **Participants** | ◆ Adult females with various risk factors for breast cancer placing them at increased risk for breast cancer | ◆ Children<br>◆ Men |
| **Intervention** | ◆ Contrast-enhanced MRI | |
| **Comparators** | ◆ Mammography<br>◆ Ultrasound<br>◆ No screening or diagnostic intervention | Non-standard technologies |
| **Outcomes** | ◆ Diagnostic Accuracy<br>◆ Mortality and various morbidities<br>◆ Other benefits<br>◆ Changes in treatment plans<br>◆ Adverse Events<br>◆ Cost | |
| **Study Design** | ◆ For efficacy outcomes: valid, RCTs<br>◆ For diagnostic studies: New test requires better outcomes or value than existing tests for the population of interest. The new test should be compared to gold standard or reasonable comparator and should find the same abnormality as found by the gold standard. Assessors of new test are blinded to results of reference test and vice-versa. There is minimal bias from indeterminate results. Measures of test function are useful clinically.<br>◆ For screening studies: as above for diagnostic tests with additional evidence that earlier diagnosis and subsequent treatments improved outcomes more than later diagnosis and treatment and where reported beneficial outcomes were not be due to bias (e.g., lead time, length, overdiagnosis or volunteer bias). | ◆ Case reports<br>◆ Case series other than for context<br>◆ Non-clinical studies |
| **Publication** | ◆ Studies published in English in peer reviewed journals, published health technology assessments (HTAs) or publicly available FDA reports<br>◆ Valid economic analyses (e.g. cost-utility studies) published in English in an HTA, or in a peer-reviewed journal published after those represented in previous HTAs. | ◆ Abstracts, editorials, letters, opinion pieces<br>◆ Duplicate publications of the same study which do not report on different outcomes<br>◆ Single reports from multicenter trials<br>◆ Older studies by same authors including some of the same subjects as a newer study<br>◆ White papers<br>◆ Narrative reviews<br>◆ Articles identified as preliminary reports when results are published in later versions<br>◆ Incomplete economic evaluations or economic evaluations based on flawed efficacy data<br>◆ Studies deemed to be at high risk of bias |

**Study Selection, Quality Assessment and Rating of the Body of Evidence**

One or two Delfini reviewers assessed the methodological quality of studies selected for critical appraisal after examining titles and abstracts for relevance, design and methodological issues. For primary and secondary studies of diagnosis and therapy we used checklists developed by Delfini. Relevant, reliable research published following the date of the secondary studies' search dates was obtained and evaluated. Studies selected for further review were evaluated for selection, performance, attrition and assessment bias along with other threats to validity. Individual studies were assessed for bias and usefulness using the Delfini Evidence Grading Scale. Studies (see below) with Delfini evidence grades of B-U or higher were assigned a risk of bias score using the Agency for Healthcare Research and Quality (AHRQ) and the

Effective Health Care Program (EHCP) group ratings of low, medium or high risk of bias. In most instances, we excluded studies graded U because of the high risk of bias. Exceptions were made if there was a conclusion that was deemed to be reasonably reliable, an important safety issue or information that was considered important enough that readers should be alerted. Details of searches are provided in a separate document titled, **Breast MRI in Diagnosis and Treatment of Cancer in Women at High Risk: Search and Critical Appraisal Documentation**.

**Project Team**

This HTA project was managed and completed by the Delfini Group, LLC. The Delfini Group is composed of Michael Stuart MD and Sheri Ann Strite, herein after referred to as "Delfini" or "We" meaning, "We, the Project Team."

**Conflict of Interest**

No team member working on this project has any conflict of interest.

**Searches and Data Sources**

The following electronic databases were searched to identify relevant peer-reviewed studies:

- PubMed (includes MEDLINE, OLDMEDLINE, HealthStar)
- Cochrane Databases (including Systematic Reviews, Registry of Clinical Trials, Review Methodology Database, Database of Reviews of Effectiveness)
- USPSTF
- HSTAT
- AHRQ
- Relevant FDA documentation or reports
- National Guideline Clearinghouse
- Professional organization publications and guidelines not indexed with the National Library of Medicine, AHRQ or similar sources
- Selected studies from bibliographies of retrieved studies

We attempted to obtain relevant, comparative studies. We sought systematic reviews, including meta-analyses, of high quality, RCTS for efficacy and safety and well-done observational studies for diagnostic accuracy and safety. Searches were conducted using standard MeSH terms (controlled vocabulary) as well as specific free-text terms and combinations of terms related to the key questions. The search terms and limits are listed below. Details of multiple searches performed starting on 4/23/10 and ending on 5/30/10 are provided in a separate document titled, **Breast MRI in Diagnosis and Treatment of Cancer in Women at High Risk: Search and Critical Appraisal Documentation**.

**Flowchart Summarizing Search and Application of Relevance and Inclusion Criteria**

We screened 879 potentially relevant publications from our 20 database and hand searches. We retrieved 97 studies for further abstract and/or full text evaluation after excluding ineligible studies because of problems with topic, population, intervention, comparison, outcome, design or methodology. We included 36 publications in our systematic review.

Potentially relevant publications screened for retrieval (n = 879)

Retrieved (n=97) publications for abstract or full-text evaluation after excluding ineligible studies because of problems with topic, population, intervention, comparison, outcome, design or methodology

Publications included in systematic review (n=36)

**Search Sources, Terms and Limits**

**Search 1**

| | |
|---|---|
| Source | PubMed |
| Terms | Breast cancer (screening OR diagnosis) MRI |
| Limits | Meta-analysis |

**Search 2**

| | |
|---|---|
| Source | PubMed |
| Terms | Breast cancer (screening OR diagnosis) MRI |
| Limits | Systematic review |

**Search 3**

| | |
|---|---|
| Source | Cochrane Library: Other Reviews |
| Terms | MRI Breast Cancer |
| Limits | None |

**Search 4**

| | |
|---|---|
| Source | Cochrane Library: Clinical Trials |
| Terms | MRI Breast Cancer |
| Limits | None |

**Search 5**

| | |
|---|---|
| Source | Cochrane Library: Technology Assessments |
| Terms | MRI Breast Cancer |
| Limits | None |

**Search 6**

| | |
|---|---|
| Source | PubMed |

| | |
|---|---|
| Terms | Breast cancer (screening OR diagnosis) MRI |
| Limits | Clinical trial |
| Date limits | 2008/12/01 to 2010/04/24 |

**Search 7**

| | |
|---|---|
| Source | PubMed |
| Terms | MRI Breast Cancer cost-effectiveness |
| Limits | None |

**Search 8**

| | |
|---|---|
| Source | PubMed |
| Terms | MRI Breast Cancer cost-effectiveness |
| Limits | High Sensitivity |

**Search 9**

| | |
|---|---|
| Source | PubMed |
| Terms | (mri) AND (high risk breast cancer (screening OR diagnosis)) AND (Diagnosis/Broad[filter]) |
| Limits | Dates only |
| Date limits | March 1, 2007 to May 9, 2010 |

**Search 10**

| | |
|---|---|
| Source | PubMed |
| Terms | breast cancer mri contralateral |
| Limits | None |

**Search 11**

| | |
|---|---|
| Source | PubMed |
| Terms | (risk OR adverse) AND (breast implants or breast augmentation) AND english [lang] |
| Limits | Meta-Analysis |
| Date limits | None |

**Search 12**

| | |
|---|---|
| Source | PubMed |
| Terms | MRI AND (breast implants or breast augmentation) AND english [lang] |
| Limits | Meta-Analysis |

**Search 13**

| | |
|---|---|
| Source | PubMed |
| Terms | MRI AND (breast implants or breast augmentation) AND english [lang] |
| Limits | None |

**Search 14**

| | |
|---|---|
| Source | PubMed |
| Terms | breast cancer management (elevated OR high) familial risk NOT treatment |
| Limits | Dates |
| Date limits | 2008 to May 16, 2010 |

**Search 15a**

| | |
|---|---|
| Source | PubMed (displayed as abstracts) |
| Terms | [change surgical management MRI breast] OR [assessment preoperative MRI breast] |
| Limits | None |

**Search 15b**

| | |
|---|---|
| Source | PubMed (displayed as citations) |
| Terms | [change surgical management MRI breast] OR [assessment preoperative MRI breast] |
| Limits | None |

**Search 16**

| | |
|---|---|
| Source | PubMed |
| Terms | MRI technical aspects breast |
| Limits | None |

**Search 17**

| | |
|---|---|
| Source | COCHRANE LIBRARY: Cost Effectiveness |
| Terms | MRI Breast Cancer |
| Limits | None |

**Search 18**

| | |
|---|---|
| Source | Search of References (Safety) |

## VIII. PEER REVIEW COMMENTS

| | |
|---|---|
| Name | Harry A. Taylor, MD, MPH |
| Affiliations, Academic | Assistant Professor, Department of Family Medicine, Oregon Health Sciences University |
| Affiliations, Professional | Medical Director, Oregon Health Information Technology Extension Center |
| Affiliations, Manufacturer | None |
| Email Address | taylorc@ochin.org or taylorha@ohsu.edu |
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| Telephone | 503-943-2500 |
| Conflicts of Interest* | None |

*Please disclose any potential intellectual or financial conflicts of interest such as research in progress, consulting arrangements or other financial involvements with companies related to the technologies evaluated in this draft.

**Date of Review:** June 18, 2010

| | |
|---|---|
| Clarity of purpose | Very good to excellent |
| Clarity of scope | Very good to excellent |
| Currency of information | Very good to excellent |
| Adequacy of search and filtering | Search – Very good to excellent<br>Filtering – Very good |
| Supportable analyses | Very good to excellent |
| Clarity of conclusions | Very good to excellent – clear and concise |
| Supportability of conclusions | Very good to excellent |
| Sufficient transparency and documentation | Very good to excellent |
| Significant report limitations | Very good to excellent |
| Other | |

## IX. COMMENTS FROM MEMBERS OF THE PUBLIC AND OTHER INTERESTED PARTIES WITH RESPONSES

Delfini Responses To Public Comment

*GE Healthcare comment that additional cancers are detected in all cases with the addition of MRI to mammography*
The increase in sensitivity and detectionof breast cancer with the addition of MRI to mammography is documented in the diagnostic accuracy section of the review and in the section, FINDINGS KEY QUESTION 1: DIAGNOSTIC ACCURACY.

*GE Healthcare comment about uncertainty that the additional cancer yield is "offset by a higher rate of false positives…".*
The evidence for a higher rate of false positives is found in Section 6, DETAILS QUESTION 1: DIAGNOSTIC ACCURACY.

*GE Healthcare comment that since the goal of screening is not to miss anyone, the sensitivity of the test should be weighted more heavily in this evaluation than the specificity.*

The evidence review presents a summary of the best evidence by answering specific key questions posed by the Washington State Health Technology program. For this review, measures of test function (e.g., sensitivity and specificity) were included. Weighting of the evidence findings in making screening decisions or recommendations is outside the scope of the review.

*GE Healthcare comment about lack of clarity regarding reasons for assigning a level of evidence (LOE) of borderline to sensitivity of MRI when added to mammography in detecting breast cancer in women at high risk for breast cancer.*

The LOE reflects the degree of confidence that the evidence reflects the true effect of the diagnostic or therapeutic intervention. A borderline LOE rating was assigned to the sensitivity of adding MRI to mammography for detecting breast cancer in women at high risk for breast cancer because the best diagnostic studies were at medium risk of bias (e.g., there were no RCTs, all studies had methodological flaws) and the reported sensitivity of adding MRI ranged widely in studies. The evidence can be found in section 6, DETAILS OF EVIDENCE FINDINGS.

*GE Healthcare comment about lack of clarity regarding reasons for assigning a level of evidence (LOE) of borderline to "change in treatment plans" in women with recently diagnosed breast cancer when MRI is added to mammography.*

A borderline LOE rating was assigned to "change in treatment plans" because of conflicting results and risk of bias due to employing observational study designs. All studies were observational except the most recent randomized, controlled trial (Turnbull 10). In the Turnbull study (first RCT to report change in treatment plans) the study results were inconclusive because of threats to validity (e.g., 26% of the women undergoing mastectomy did not have preoperative verification of breast cancer, the study was underpowered for detecting a clinically meaningful difference between groups). The evidence can be found in section 6, DETAILS OF EVIDENCE FINDINGS.

## X. REFERENCES

**Notes**

- References are alphabetically arranged; reference number applies to the order in this table only.


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