Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy #  00084  
Original Effective Date:  03/25/2002  
Current Effective Date:  06/01/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: All policy statements below refer to performing magnetic resonance imaging (MRI) of the breast with contrast and a breast coil. MRI of the breast without a breast coil, regardless of the clinical indication, is considered investigational. See additional comments in Policy Guidelines about the breast imaging team and the need for breast MRI centers to perform MRI-guided biopsy and localization.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

• Benefits are available in the member’s contract/certificate, and  
• Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of magnetic resonance imaging (MRI) of the breast with a breast coil and with contrast to be eligible for coverage for the following indications:

Screening Uses

• Annual MRI for screening of breast cancer in high risk patients. The following list includes individual risk factors known to indicate a high risk of breast cancer by themselves:
  o Lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH) or atypical ductal hyperplasia (ADH) on biopsy; or
  o A known BRCA1 or BRCA2 pathogenic or likely pathogenic variants in patient or first-degree relative of BRCA carrier if patient is untested; or
  o Another gene variant associated with high risk or increased risk of breast cancer, e.g. TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), CDH1, STK11, NF1, NBN, and PALB2 mutation; or
  o High risk (lifetime risk 20% or greater) of developing breast cancer as identified by models that are largely defined by family history, e.g. BRCA PRO, BOADICEA, Gail, Claus, Tyrer-Cuzick.; or
  o Received radiation therapy to the chest between 10 and 30 years of age

• Screening for breast cancer in any person previously diagnosed with breast cancer who has completed treatment, including a bilateral mastectomy, and was subsequently determined to be cancer free

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Detection Uses
- Detection of a suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma (ie, negative mammography and physical exam).
- A new diagnosis of breast cancer to evaluate the contralateral breast when clinical and mammographic findings are normal

Treatment-Related Uses
- Preoperative tumor mapping of the involved (ipsilateral) breast to evaluate the presence of multicentric disease in patients with clinically localized breast cancer who are candidates for breast-conservation therapy
- Pre-surgical planning in patients with locally advanced breast cancer before and after completion of neoadjuvant chemotherapy to permit tumor localization and characterization
- To determine the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumors
- To evaluate a documented abnormality of the breast before obtaining an MRI-guided biopsy when there is documentation that other methods, such as palpation or ultrasound, are not able to localize the lesion for biopsy

Other
Based on review of available data, the Company may consider the use of magnetic resonance imaging (MRI) of the breast to be eligible for coverage when used to assess breast implant rupture in symptomatic women who have undergone breast reconstruction for breast cancer, and the diagnosis of implant rupture cannot be confirmed by mammography or ultrasound.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers magnetic resonance imaging (MRI) of the breast without a breast coil for any clinical indication to be investigational

Based on review of available data, the Company considers all other uses of magnetic resonance imaging (MRI) of the breast to be investigational including but not limited to the following:

Screening Uses
- As a screening technique in average-risk patients
- As a screening technique for the detection of breast cancer when the sensitivity of mammography (ie, mammography using low-dose x-rays for imaging) is limited (ie, dense breasts, breast implants, scarring after treatment for breast cancer)

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Detection Uses
- For diagnosis of low-suspicion findings on conventional testing not indicated for immediate biopsy and referred for short-interval follow-up
- For diagnosis of a suspicious breast lesion in order to avoid biopsy

Treatment-Related Uses
- To determine response during neoadjuvant chemotherapy in patients with locally advanced breast cancer
- For evaluation of residual tumor in patients with positive margins after initial lumpectomy or breast conservation surgery.

When Services Are Not Covered
The use of magnetic resonance imaging (MRI) of the breast to assess breast implant rupture following cosmetic, non-covered breast surgery is not eligible for coverage.

Policy Guidelines
HIGH-RISK CONSIDERATIONS
There is no standardized method for determining a woman's risk of breast cancer that incorporates all possible risk factors. Clinical practice guidelines offer guidance on factors known to individually indicate a high risk of breast cancer.

A number of factors may increase the risk of breast cancer but do not by themselves indicate high risk. It is possible that combinations of factors may be indicative of high risk, but it is not possible to quantitate estimates of risk. As a result, it may be necessary to individualize the estimate of risk, whereby one would need to take into account the numerous risk factors. A number of risk factors, not individually indicating high risk, are included in the National Cancer Institute Breast Cancer Risk Assessment Tool (also called the Gail model). Risk factors in the model can be accessed online (http://www.cancer.gov/bcrisktool/Default.aspx).

CONSIDERATIONS FOR PERFORMING MRI
Breast MRI exams should be performed and interpreted by an expert breast imaging team working together with the multidisciplinary oncology treatment team.

As noted, breast MRI exams require a dedicated breast coil and the use of contrast by radiologists familiar with the optimal timing sequences and other technical aspects of image interpretation. The breast MRI center also should have the ability to perform MRI-guided biopsy and/or wire localization of findings detected by MRI.

CONSIDERATIONS FOR PREOPERATIVE MRI
Preoperative MRI in patients with localized disease results in higher rates of mastectomy and lower rates of breast-conserving therapy. There is uncertainty from the available evidence on whether outcomes are...
improved by changing to a more extensive operation. If biopsies are performed on all MRI-identified lesions, and if shared patient decision making is used for altering the surgical approach, then the probability of improved outcomes is increased.

**Background/Overview**

**MAGNETIC RESONANCE IMAGING**

MRI of the breast can be used to screen, detect, and/or diagnosis of breast cancer. MRI can be used as a replacement for mammography screening, or it can be used as an additional imaging test alone, or it can be used in combination with other imaging modalities. Each of these potential uses is described below.

**Screening Uses**

Screening uses include screening for breast cancer in patients who are at high genetic risk for breast cancer; screening also benefits patients who have breast characteristics that limit the sensitivity of a mammography.

MRI of the breast has been investigated as a screening tool in specific higher risk subgroups of patients. First, it has been studied in patients considered to be at high genetic risk of breast cancer, such as women with known *BRCA1* or *BRCA2* genetic variants or with a family history consistent with a hereditary pattern of breast cancer. Screening for breast cancer often begins at an earlier age in these patients, and mammography is considered less sensitive in younger patients due to the prevalence of dense breast tissue. In addition, screening MRI has been suggested for patients who may or may not be at increased risk but who have breast tissue characteristics that limit the sensitivity of a mammographic screening (these characteristics are dense breast tissue, breast implants, or scarring after breast-conserving therapy [BCT]). BCT consists of breast-conserving surgery followed by radiotherapy.

**Detection Uses**

The following are examples of how to detect suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma and negative mammography and clinical breast exam:

- Breast MRI has been advocated to help detect suspected occult primary breast cancer in patients with adenocarcinoma in the axillary lymph nodes after mammography and physical exam have failed to reveal a breast tumor. Localization of a breast primary might permit BCT instead of presumptive mastectomy.

The following are examples of how to detect breast cancer in the contralateral breast of patients with breast cancer:

- Patients with a diagnosed breast cancer are at higher risk for a synchronous or subsequent breast cancer in the contralateral breast, and breast MRI has been suggested as a more sensitive screening test compared with mammography.
- Diagnosis of low-suspicion findings on conventional testing not indicated for immediate biopsy but referred for short-interval follow-up
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The following are examples of how to detect breast cancer in the case of:

- Low-suspicion findings on conventional testing not indicated for immediate biopsy but referred for short-interval follow-up
- Further characterization of suspicious breast lesion to avoid biopsy

Treatment-Related Uses
The following are potential treatment-related uses of breast MRI:

- Preoperative tumor mapping (e.g., detection of multicentric disease [in a separate quadrant of the breast]) in patients with clinically localized breast cancer who are considered candidates for breast-conserving surgery followed by radiotherapy
- Preoperative tumor mapping in patients with locally advanced breast cancer before and after completion of neoadjuvant chemotherapy
- Evaluation of response during neoadjuvant chemotherapy in patients with locally advanced breast cancer
- Diagnosis of suspected chest wall involvement in posteriorly located tumors
- Evaluation of residual tumor after lumpectomy with positive surgical margins

Patients with abnormal findings on mammography are categorized according to the level of suspicion of the findings. Patients with low-suspicion findings are often recommended to undergo short-interval follow-up after 3 to 6 months (instead of immediate biopsy). This follow-up may continue for 2 years to demonstrate the stability of benign findings or to detect progression; progression would indicate the need for biopsy. MRI of the breast has been investigated as a technique to further characterize low-suspicion breast lesions, so that patients with MRI-negative lesions may be reassured and avoid the need for prolonged follow-up and those with MRI-positive lesions may be referred for early biopsy, possibly leading to earlier diagnosis and treatment.

Breast lesions detected by clinical exam or mammography that are considered suspicious frequently are referred for biopsy; however, only a minority of such biopsies reveal breast cancer due to the relatively low specificity of clinical and radiologic exams. MRI of the breast has been investigated as a technique to further characterize suspicious breast lesions so that patients with benign lesions may be spared a biopsy procedure. One infrequent situation (niche use) in which MRI of the breast may be helpful and improve health outcomes is in the management of patients who have a suspicious lesion that can only be seen on 1 mammographic view (i.e., the lesion cannot be seen in other views or on an ultrasound). Patients who fall under this category have a lesion that is not palpable, and therefore, percutaneous biopsy localization cannot be performed. Instead, MRI would be used to localize the suspicious lesion and permit biopsy (this technique would presumably lead to earlier diagnosis of breast cancer as opposed to waiting until the lesion was visible on 2 mammographic views or on ultrasound). The previously described scenario is an infrequent occurrence, so the evidence base addressing this use is mainly anecdotal, but the clinical rationale supporting this use is good.
Patients with localized breast cancer are considered candidates for breast-conserving surgery followed by radiotherapy. However, mastectomy may be considered in patients with multicentric disease. MRI has been investigated as a technique to assess the extent of the tumor in the breast, specifically to detect multicentric disease as an aid to surgical planning.

Patients with locally advanced breast cancer are usually offered neoadjuvant chemotherapy to reduce tumor size and permit BCT. Evaluation of tumor size and extent using conventional techniques (ie, mammography, clinical examination, ultrasonography) is suboptimal, and breast MRI has been proposed as a means to more accurately determine tumor size for surgical planning. MRI before chemotherapy is used to document tumor location, so that the tumor can be optimally evaluated after chemotherapy, especially if the size and degree of contrast enhancement are greatly reduced. Tumors that respond to chemotherapy get smaller and may even disappear; however, actual reduction in size is a delayed finding, and earlier changes in tumor vascularity have been observed in chemotherapy-responsive tumors. A decline in contrast enhancement on MRI has been noted in tumors relatively early in the course of chemotherapy. This MRI finding as an early predictor of tumor response has been explored as a means to optimize the choice of chemotherapeutic agent (eg, to alter chemotherapy regimen if the tumor appears unresponsive).

Tumors located near the chest wall may invade the pectoralis major muscle or extend deeper into chest wall tissues. Typically, modified radical mastectomy removes only the fascia of the pectoralis muscle; however, tumor involvement of the muscle would also necessitate removal of the muscle (or a portion of it). In smaller tumors, it is necessary to determine how closely the tumor abuts the pectoralis muscle and whether it invades the muscle to determine whether there is an adequate margin of normal breast tissue to permit BCT. Breast MRI has been suggested as a means of determining pectoralis muscle/chest wall involvement for surgical planning and to assist in the decision whether to use neoadjuvant chemotherapy.

BCT includes complete removal of the primary tumor along with a rim of normal surrounding tissue. Pathologic assessment of surgical margins is performed on excisional specimens to determine whether the tumor extends to the margins of resection. Surgical specimens are oriented and marked to direct re-excision if margins are shown to contain tumor; however, when the tumor is not grossly visible, the extent of residual tumor within the breast can only be determined through repeat excision and pathologic assessment. MRI has been proposed to evaluate the presence and extent of the residual tumor as a guide to re-excision when surgical margins are positive for tumor.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

MRI of the breast can be performed using commercially available magnetic resonance scanners and intravenous magnetic resonance contrast agents. Specialized breast coils such as the Access Breast Coil 4/SMS (Confirma, Kirkland, WA) and magnetic resonance–compatible equipment for performing biopsy have been developed and cleared for marketing by the U.S. FDA through the 510(k) process. The FDA determined that these devices are substantially equivalent to predicate devices for use “in conjunction with...”
a MRI to produce diagnostic and interventional images of the breast, chest wall and axillary tissues that can be interpreted by a trained physician.

**Rationale/Source**
Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve health outcomes). The following is a summary of the literature to date.

**SCREENING USES**
**Clinical Context and Test Purpose**
The question addressed in this portion of the evidence review is whether use of MRI as an adjunct to screen for breast cancer improves the net health outcome compared with standard mammographic techniques.

The question addressed in this evidence review is: Does the use of MRI improve the diagnostic accuracy compared with standard screening mammography methods, and is this degree of increased accuracy likely to improve health outcomes via earlier diagnosis and treatment?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is asymptomatic individuals being screened for breast cancer. Evaluation is stratified by those at high risk of breast cancer, those at average risk of breast cancer, and those with characteristics limiting the accuracy of the mammography (eg, dense breasts).

**Interventions**
The intervention of interest is MRI as an adjunct to screening with mammography.

**Comparators**
The comparator of interest is mammography alone.

**Outcomes**
The outcomes of interest for diagnostic accuracy include test accuracy and test validity (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility are overall mortality and breast cancer–specific mortality. Another outcome of interest for clinical utility is resource utilization (eg, need for additional testing or procedures).
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**Timing**
MRI would be performed as an adjunct to routine screening; timing can be guided by national guidelines on breast cancer screening.

**Setting**
The test would be performed in an outpatient imaging setting.

**Study Selection Criteria**
The evidence review focuses on systematic reviews when available. Additional comparative observational studies are included if the study captures longer periods of follow-up and/or larger populations and is published subsequent to the systematic reviews.

**Technical Reliability**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Screening Individuals at High Risk of Breast Cancer**

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Systematic Reviews**
The original evidence review was based on a 2003 TEC Assessment. This Assessment concluded that for high-risk women, the evidence appeared to show equivalent or better performance for MRI in terms of sensitivity in detecting breast cancer compared with mammography. In 2 published studies, however, there were only 15 cases of cancer. In both studies, MRI detected 100% of cancer cases; mammography detected 33%.

Three systematic reviews identified have included women at high risk of developing breast cancer. Warner et al (2008) review included 11 studies published through 2008. Two reviews by Phi et al (2015, 2017) reported 2 individual patient data meta-analyses from the same 6 studies published between 2010 and 2013. Phi et al (2015) included the women with BRCA1 or BRCA2 variants and Phi et al (2017) included the women with a strong family history of breast without a known variant. Characteristics of the systematic reviews are shown in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Studies</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Reference Standard</th>
</tr>
</thead>
</table>

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Table 2. Results of Systematic Reviews Assessing MRI Screening in High-Risk Women

<table>
<thead>
<tr>
<th>Study</th>
<th>MRI</th>
<th>Mammogram</th>
<th>MRI Plus Mammogram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
<td>Sensitivity, %</td>
</tr>
<tr>
<td>Phi et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>2226</td>
<td>2226</td>
<td>2226</td>
</tr>
<tr>
<td>PE (95% CI)</td>
<td>89 (76 to 96)</td>
<td>83 (77 to 88)</td>
<td>55 (41 to 69)</td>
</tr>
<tr>
<td>Phi et al (2015)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>1951</td>
<td>1951</td>
<td>1951</td>
</tr>
<tr>
<td>PE (95% CI)</td>
<td>85 (69 to 94)</td>
<td>85 (79 to 89)</td>
<td>40 (30 to 50)</td>
</tr>
<tr>
<td>Total N</td>
<td>15576</td>
<td>15576</td>
<td>15496</td>
</tr>
<tr>
<td>PE (95% CI)</td>
<td>77 (70 to 84)</td>
<td>86 (81 to 92)</td>
<td>39 (37 to 41)</td>
</tr>
</tbody>
</table>

CI: confidence interval; MRI: magnetic resonance imaging; PE: pooled estimate.
Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs assessing screening breast MRI in individuals at high risk of breast cancer were identified. It is unlikely that an RCT of screening breast MRI will be conducted given the support for the practice in clinical guidelines, which would likely preclude patients consenting to be assigned to a group without MRI screening.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical validity of MRI for screening in high-risk women has been demonstrated in good quality studies. MRI is more sensitive but less specific than mammography for detecting invasive cancers in high-risk women and the sensitivity of combined MRI and mammography is approximately 93% or higher. Given the high likelihood of malignancy among women at high risk for breast cancer, it is generally accepted that the benefits of detecting cancer earlier with adjunctive MRI outweigh the disadvantages of incurring more unnecessary workups and biopsies due to false-positive results.

Section Summary: Screening Individuals at High Risk of Breast Cancer
MRI is more sensitive than mammography in detecting malignancy during screening. Because of the high likelihood of malignancy among women at high risk for breast cancer, the benefits of detecting cancer earlier with adjunctive MRI outweigh the disadvantages of incurring more unnecessary workups and biopsies due to false-positive results.

Screening Individuals at Average Risk of Breast Cancer
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
In a systematic review of literature conducted by Nelson et al (2016) for the U.S. Preventive Services Task Force breast cancer screening recommendation update, no RCTs or nonrandomized observational studies identified evaluated adjunctive MRI for screening average-risk women for breast cancer. Because the
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prevalence of breast cancer is extremely low in average-risk young women, screening with a test such as MRI that has lower specificity would result in a lower positive predictive value (PPV) and many more false-positive results. Compared with mammography, there would be greater numbers of workups and biopsies with increased anxiety and morbidity with adjunctive MRI screening applied to young, average-risk women.

Health Quality Ontario (2016) published a systematic review of MRI as an adjunct to mammography for women not at high risk of breast cancer. Reviewers searched for studies evaluating screening breast MRI as an adjunct to mammography compared with mammography alone. Studies needed to use pathology results as a reference standard for positive tests and clinical follow-up as a reference standard for negative tests. In addition, studies needed to report one or more outcomes of interest, which included effectiveness outcomes (eg, mortality, health-related quality of life, screening-related harms) and diagnostic outcomes (eg, sensitivity, specificity), and biopsy and recall rates. Reviewers did not find any studies that met eligibility criteria. They concluded that there was a lack of evidence to inform the questions of the diagnostic accuracy of MRI plus mammography vs MRI alone and the impact of adjunct screening MRI on health outcomes in patients at less than high risk of breast cancer.

Observational Studies
One comparative observational study was published following the preceding systematic reviews. Kuhl et al (2017) reported results of a prospective study of supplemental MRI screening in addition to screening mammography with or without screening ultrasonography in women at average risk of breast cancer. Characteristics of the study are shown in Table 3.

Table 3. Characteristics of Clinical Validity Studies Assessing MRI Screening in Average-Risk Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Timing of Tests</th>
<th>Blinding of Assessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhl et al (2017)</td>
<td>Women 40-70 y without breast cancer– associated risk factors (lifetime risk &lt;15%) evaluated in Germany between 2005 and 2013</td>
<td>Prospective</td>
<td>Pathology for positive finding; 2-y FU for negative finding</td>
<td>Read by 9 breast radiologists with 5-18 y of experience; BIRADS category 4 or 5 referred for biopsy</td>
<td>Imaging completed within 4 wk of each other</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BIRADS: Breast Imaging Reporting and Data System; FU: follow-up; MRI: magnetic resonance imaging.

Results of the Kuhl (2017) clinical validity study of MRI screening in 2120 average-risk women are shown in Table 4. Forty-eight additional cancers were detected with MRI during the initial screening. MRI detected 13 of 13 incidence cancers during subsequent screening rounds; 12 of 13 incident cancers were found with MRI imaging alone. The specificity of MRI was 97%. The sensitivity of MRI was 100% compared with 8% for mammography and ultrasonography. Cancers diagnosed with MRI were small (median, 8 mm),
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predominantly node negative (93%), and dedifferentiated in 42% of cases at prevalence screening and in 46% of cases at incidence screening.

Table 4. Results of Clinical Validity Studies Assessing MRI Screening in Average-Risk Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Condition</th>
<th>Clinical Validity (95% Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Kuhl et al (2017)</td>
<td>2181</td>
<td>2120</td>
<td>Excluded if insufficient FU</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>100 (75 to 100)</td>
<td>97 (97 to 98)</td>
<td>36 (29 to 43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammography</td>
<td>8 (0.2 to 36)</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>8 (0.2 to 41)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

FU: follow-up; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

The purpose of the gaps tables (see Tables 5 and 6) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 5. Relevance Gaps of Clinical Validity Studies of MRI Screening in Average-Risk Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Duration of Follow-Upb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhl et al (2017)</td>
<td>1. Health outcomes not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

MRI: magnetic resonance imaging.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).
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Table 6. Study Design and Conduct Gaps of Clinical Validity Studies of MRI Screening in Average-Risk Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhl et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Only sensitivity comparisons provided</td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

MRI: magnetic resonance imaging.

- **Selection** key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
- **Blinding** key: 1. Not blinded to results of reference or other comparator tests.
- **Delivery of Test** key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
- **Selective Reporting** key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
- **Data Completeness** key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
- **Statistical** key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

The Kuhl (2017) study was a multicenter prospective study conducted in Germany that was well-reported with few concerns regarding risk of bias. While the comparison to mammography and ultrasonography for sensitivity was provided, other comparisons (specificity, PPV) were not provided.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing screening breast MRI in individuals at average risk of breast cancer were identified.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Given the limited published evidence on MRI screening of average-risk women, evaluations of clinical validity and clinical utility are not possible.
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Section Summary: Screening of Individuals at Average Risk of Breast Cancer
There is limited evidence on MRI screening for average-risk women; systematic reviews did not identify any RCTs or nonrandomized comparative studies. One study has been published since the systematic reviews. The PPV of screening tests would likely be lower in this lower prevalence population and there would be higher false-positive rates, morbidity, and anxiety.

Screening When Breast Characteristics Limit the Sensitivity of Mammography
The sensitivity of mammography is limited in patients after breast-conserving therapy (BCT) or in patients with dense or heterogeneously dense breasts; therefore, there is the potential for improved sensitivity with adjunctive MRI.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Evidence for individuals with a limited sensitivity of mammography was informed by a TEC Assessment (2004). No systematic reviews were identified.

Observational Studies: Dense Breasts
In the 2012 ACRIN (American College of Radiology Imaging Network) 6666 trial, mammography alone was compared with mammography plus ultrasound in women 25 years or older with at least heterogeneously dense breast tissue and at least one other breast cancer risk factor. Half (54%) of women had a personal history of breast cancer. In an MRI subanalysis, women who completed 3 rounds of screening and did not have contraindications or renal impairment were asked to undergo contrast-enhanced MRI within 8 weeks of the last screening mammography. Six hundred twenty-seven women consented and were eligible for this subanalysis, and 612 (98%) completed the needed tests; 16 cancers were detected in these women. Sensitivity increased from 44% (95% CI, 20% to 70%) for mammography plus ultrasound to 100% (95% CI, 79% to 100%; p=0.004) when MRI was added. Specificity declined from 84% (95% CI, 81% to 87%) for mammography plus ultrasound to 65% (95% CI, 61% to 69%; p<0.001) for all 3 tests. Over the 3-year study period, another 9 cancers were identified between screening tests, and 2 additional cancers were identified off-study.

Observational Studies: Following Breast-Conserving Therapy
Two prospective studies have reported on the performance of surveillance breast MRI following breast-conserving therapy (BCT). Study characteristics are shown in Table 7. Both studies were performed in Korea and it is unclear whether the populations overlapped.

Table 7. Characteristics of Clinical Validity Studies Assessing Surveillance Breast MRI After BCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Reference</th>
<th>Identification of</th>
<th>Timing of</th>
<th>Blinding of</th>
<th>Comment</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Images</th>
<th>Recurrence Rate, %</th>
<th>Clinical Validity (95% Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sens</td>
<td>Spec</td>
</tr>
<tr>
<td>Kim et al (2017)</td>
<td>421 women</td>
<td>414</td>
<td>Initial diagnosis of malignant phyllodes tumor, lobular carcinoma in situ (n=6), or developed supraclavicular lymph node metastasis within 12 mo (n=1)</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Cho et al (2017)</td>
<td>429 breast MRIs</td>
<td>422 breast MRIs</td>
<td>MRI within 4 wk of screening mammography and breast US</td>
<td>No (readers knew results of prior imaging studies)</td>
<td>Funded by Bayer Korea</td>
</tr>
</tbody>
</table>

BCT: breast-conserving therapy; BIRADS: Breast Imaging Reporting and Data System; mammography; MRI: magnetic resonance imaging; US: ultrasound.

Results of the clinical validity studies for surveillance of breast MRI following BCT are shown in Table 8. The sensitivity of MRI was higher than mammography and ultrasound with overlapping confidence intervals in both studies. Specificity of MRI was lower than mammography and ultrasound. The combination of mammography and MRI was 100% sensitive and 87% specific. The review by Cho et al (2017) reported that the recall rate was significantly higher for mammography plus MRI (13.8%; 95% CI, 12.0% to 15.5%) compared with mammography (4.4%; 95% CI, 3.3% to 5.5%), as was the biopsy rate (2.7% [95% CI, 2.0% to 3.4%] vs 0.5 [95% CI, 0.2% to 0.8%]). The yield per 1000 examinations was 8.2 (95% CI, 4.3 to 12.2) for mammography plus MRI vs 4.4 (95% CI, 1.5 to 7.2) for mammography.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>82</td>
<td>95</td>
<td>31</td>
<td>99</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Images</th>
<th>Recurrence Rate, % (95% Confidence Interval),%</th>
<th>Clinical Validity Rate, % (95% Confidence Interval),%</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>18</td>
<td>98</td>
<td></td>
<td>(2 to 52) (92 to 97) (15 to 51) (98 to 100)</td>
<td></td>
</tr>
<tr>
<td>Mammography</td>
<td>18</td>
<td>99</td>
<td></td>
<td>(2 to 52) (98 to 100) (5 to 85) (96 to 99)</td>
<td></td>
</tr>
<tr>
<td>Cho et al (2017)</td>
<td>801</td>
<td>754</td>
<td>Withdraw consent (n=39) or had systemic metastasis (n=7); unclear (n=1)</td>
<td>2.3 (92 to 97) (15 to 51) (98 to 100) (96 to 99)</td>
<td></td>
</tr>
</tbody>
</table>

MRI

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Images</th>
<th>Recurrence Rate, % (95% Confidence Interval),%</th>
<th>Clinical Validity Rate, % (95% Confidence Interval),%</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>65</td>
<td>90</td>
<td></td>
<td>(41 to 83) (89 to 92) (19 to 55) NR</td>
<td></td>
</tr>
<tr>
<td>Mammography</td>
<td>53</td>
<td>96</td>
<td></td>
<td>(31 to 74) (95 to 97) (43 to 90) NR</td>
<td></td>
</tr>
<tr>
<td>Mammography plus MRI</td>
<td>100</td>
<td>87</td>
<td></td>
<td>(82 to 100) (85 to 89) (18 to 42) NR</td>
<td></td>
</tr>
</tbody>
</table>

BCT: breast-conserving therapy; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; US: ultrasound.

Tables 9 and 10 display notable gaps identified in each study.

Table 9. Relevance Gaps of Clinical Validity Studies of Surveillance Breast MRI After BCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Duration of Follow-Upc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td>1. Health outcomes not reported</td>
<td></td>
</tr>
<tr>
<td>Cho et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td>1. Health outcomes not reported</td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

BCT: breast-conserving therapy; MRI: magnetic resonance imaging.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories

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not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 10. Study Design and Conduct Gaps of Clinical Validity Studies of Surveillance Breast MRI After BCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Selectiona</th>
<th>Blindingb</th>
<th>Delivery of Testc</th>
<th>Selective Reportingd</th>
<th>Data Completenesse</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al (2017)</td>
<td>1. Not blinded to results of mammography, US, or PET/CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. BCT: breast-conserving therapy; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound.

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing screening breast MRI in individuals with breast characteristics that limit the sensitivity of mammography were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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Section Summary: Screening When Breast Characteristics Limit the Sensitivity of Mammography
There are 2, possibly overlapping, prospective studies from Korea comparing the diagnostic accuracy of MRI with mammography in patients who have had BCT. One prospective study has reported on the performance of MRI plus mammography vs ultrasound in women with heterogeneously dense breast tissue and at least 1 other breast cancer risk factor. As in other indications, sensitivity increased when MRI was added and specificity decreased. For women who have breast characteristics that limit the sensitivity of mammography, the evidence on MRI screening is limited.

DETECTION USES
Clinical Context and Test Purpose
The question addressed in this portion of the evidence review is whether the use of MRI as an adjunct to detect breast cancer in the ipsilateral or contralateral breast improves the net health outcome compared with standard techniques.

The question addressed in this evidence review is: Does MRI improve the diagnostic accuracy beyond standard evaluation methods for detecting breast cancer and is this degree of increased accuracy likely to improve health outcomes via earlier diagnosis, better patient management decisions, and more appropriate treatment?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with suspicious lesions or with breast cancer in 1 breast.

Interventions
The intervention of interest is MRI examination as an adjunct to standard evaluation methods.

Comparators
The following tests and practices are currently being used to make decisions about managing breast cancer: mastectomy, mammography and clinical assessment, and biopsy.

Outcomes
The outcomes of interest for diagnostic accuracy include test accuracy and test validity (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility are the avoidance of invasive procedures (eg, biopsy, mastectomy), the ability to detect cancer that would require additional or earlier treatment, and overall mortality and breast cancer–specific mortality rates.
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**Timing**
MRI would be performed after a positive breast cancer screening or diagnostic examination.

**Setting**
Breast MRI is administered in an imaging setting.

**Study Selection Criteria**
The evidence review focuses on systematic reviews when available. Additional comparative observational studies are included if the study captures longer periods of follow-up and/or larger populations and was published subsequent to the systematic reviews.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Detecting Suspected Occult Breast Primary Tumor With Axillary Nodal Adenocarcinoma With a Negative Mammography and Physical Exam**

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

De Besser et al (2010) evaluated 8 retrospective studies in a systematic review of studies on the use of MRI in patients (total N=220 patients) with mammographically occult breast cancer and an axillary metastasis. In 7 studies, a potential primary lesion was detected in a mean of 72% of cases (range, 36%-86%). Pooling individual patient data yielded a sensitivity of 90% (range, 85%-100%) in detecting an actual malignant tumor. Specificity, however, was 31% (range, 22%-50%).

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.
Evidence on detection of suspected occult breast cancer is based on a TEC Assessment (2004) and a subsequent meta-analysis. The Assessment concluded that, in this small subgroup of patients, adjunctive use of breast MRI allowed a substantial portion of patients (25%-61%) to avoid the morbidity of mastectomy; risk of unnecessary biopsy was estimated to be 8%.

**Section Summary: Detecting Suspected Occult Breast Primary Tumor With Axillary Nodal Adenocarcinoma With a Negative Mammography and Physical Exam**

The use of MRI to guide breast-conserving surgery (BCS) rather than presumptive mastectomy appears to offer the substantial benefit of breast conservation for those patients in whom MRI detects the primary tumor.

**Detecting Contralateral Breast Cancer After Established Breast Cancer**

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Lehman et al (2007) reported on the results of the ACRIN-A6667 trial. They found that 30 (3%) of 969 women with a recent diagnosis of unilateral breast cancer had contralateral cancer at the time of initial diagnosis using MRI. Contralateral lesions were not detected by mammography or physical exam. Eighteen (60%) of the 30 cancers were invasive and 12 (40%) were ductal carcinoma in situ (DCIS). In this study, 121 (12.5%) patients had biopsies, with a positive biopsy rate of 24.8%. With 1-year follow-up, the sensitivity of MRI was 91% and specificity was 88%. Results of this trial in a diverse group of patients were similar to the findings of others.

Liberman et al (2003) reported on 212 women who had negative mammograms of the asymptomatic contralateral breast and found 12 cancers (prevalence, 5%) on MRI, including 6 DCIS and 6 infiltrating carcinomas. However, the PPV of these findings was only 20%, with a specificity of 76%. Lehman et al (2005) found 4 contralateral cancers in 103 patients; in this study, 10 biopsies were done.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.
No RCTs assessing diagnostic breast MRI in individuals with suspected contralateral breast cancer after established breast cancer were identified.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A trial with nearly 1000 women found that MRI had high sensitivity and reasonably high specificity for identifying contralateral lesions not detected by mammography or physical examination. Although long-term outcomes of contralateral breast cancers are not fully known, important management changes will occur based on such findings, and these management changes should lead to improved outcomes.

**Section Summary: Detecting Contralateral Breast Cancer After Established Breast Cancer**
The available evidence suggests that adjunctive MRI can identify contralateral breast cancers in women with negative mammograms. A trial with nearly 1000 women found that MRI had high sensitivity and reasonably high specificity for identifying contralateral lesions not detected by mammography or physical examination. Although long-term outcomes of contralateral breast cancers are not fully known, important changes in management will occur as a result of the findings, and these management changes should lead to improved outcomes. That is, in addition to the presumed benefits of early detection, simultaneous treatment of synchronous cancers can occur rather than multiple treatments on separate occasions.

**Detecting Breast Cancer in the Case of Low-Suspicion Findings on Conventional Mammography**

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the Clinically Useful section for discussion.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Evidence on low-suspicion findings is based on a TEC Assessment (2004). Available evidence has suggested that adjunctive MRI may be very sensitive and specific in patients with low-suspicion findings on
conventional testing and may provide a useful method to select patients for biopsy or to avoid prolonged short-interval follow-up. However, none of the available studies used prospective methods appropriate to patient populations to directly compare the sensitivity and specificity of short-interval mammographic follow-up with MRI and to determine the effects of adjunctive MRI on cancer detection rate and biopsy rate.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of adjunctive MRI has not been establishing, a chain of evidence supporting the clinical utility of this modality cannot be constructed.

Section Summary: Detecting Breast Cancer in the Case of Low-Suspicion Findings on Mammography
A TEC Assessment found insufficient evidence on the use of MRI to diagnose low-suspicion findings on conventional testing that are not indicated for an immediate biopsy. Well-designed prospective confirmatory studies would be necessary to permit conclusions on the effect this adjunctive use of breast MRI on health outcomes.

Detecting Breast Cancer by Further Characterizing Suspicious Breast Lesions

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Evidence on further characterization of suspicious breast lesions was summarized in 3 TEC Assessments (2000, 2001, 2004). Studies addressed a group of patients who have breast lesions of sufficient suspicion to warrant a recommendation to undergo biopsy for diagnosis. Therefore, MRI results were assumed to have an impact on the decision whether to undergo definitive biopsy, considered the criterion standard.

A systematic review published by Medeiros et al (2011) analyzed 69 studies including 9298 women. Pooled sensitivity was 90% (95% CI, 88% to 92%), and pooled specificity was 75% (95% CI, 70% to 79%). The pooled positive likelihood ratio of an abnormal MRI for malignancy was 3.6 (95% CI, 3.0 to 4.2) and the pooled negative likelihood ratio was 0.12 (95% CI, 0.09 to 0.15). For breast cancer or high risk lesions vs benign lesions, the area under the curve for MRI was 0.91.

Observational Studies
Two single-institution, prospective cohort studies examined the diagnostic accuracy of breast MRI for lesions identified by mammography or ultrasound. Strobel et al (2015) in Germany included lesions characterized as Breast Imaging Reporting and Data System (BIRADS) category 4 by conventional workup.
in 340 women. Most women were postmenopausal (61%), had no previous breast biopsy (64%), or family history of breast cancer (62%), and underwent initial evaluation for routine screening (88%). Of 353 lesions, 135 (38%) were biopsied; lesions down-graded to BIRADS categories 1, 2, or 3 on MRI were followed with imaging for 18 months, except for pure clustered microcalcifications (without accompanying mass), which were biopsied or followed with imaging for 24 months at patient discretion; none of the lesions monitored progressed during follow-up. Overall incidence of malignancy including DCIS was 20% (n=69). MRI down-graded 256 (28%) of 353 lesions, confirmed 37 (11%) lesions, and upgraded 50 (14%) lesions. The PPV of MRI was 73% compared with 19% for conventional imaging. The negative predictive value (NPV) of MRI was 99% (and could not be calculated for conventional imaging). For pure clustered microcalcifications, sensitivity was 89% (25/28 lesions) and the false-negative rate was 12% (3/28 lesions). False-positive MRI findings resulted in biopsy for 5 (1.5%) of 340 women.

In a similar study, Li et al (2014) in China included 84 women with BIRADS categories 3, 4, or 5 microcalcifications on mammography. Most patients were premenopausal (81%), had no family history of breast cancer (83%), and underwent initial evaluation for routine screening (56%). All lesions were biopsied surgically (n=91). The incidence of malignancy including DCIS was 46%. The PPV of MRI was 87% compared with 60% for mammography. The NPV of MRI was 91%.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing diagnostic breast MRI in individuals to further characterize suspicious breast lesions were identified.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Available evidence has not shown this use of breast MRI would improve health outcomes. Considering the relative ease of breast biopsy, the sensitivity of breast MRI would have to be virtually 100% to confidently avoid biopsy. Although MRI performs well, it is clear that the sensitivity is not 100%. False-negative results tend to occur, particularly in certain subcategories, such as DCIS, but invasive carcinomas may not be detected on MRI, also leading to false-negative results. The potential harm to health outcomes of failing to
diagnose breast cancer or at least of delaying the diagnosis of breast cancer is of significant concern. A TEC Assessment (2001) concluded that the potential benefits of sparing a fraction of patients from unnecessary biopsy did not outweigh potential harms considering the current level of diagnostic performance of breast MRI.

**Section Summary: Detecting Breast Cancer by Further Characterizing Suspicious Breast Lesions**

MRI for evaluation of suspicious breast lesions has a relatively high sensitivity and a moderately high specificity. However, it has not yet been established whether the NPV is sufficient to preclude the need for biopsy. Although 2 more recent studies have reported NPVs greater than 90% in certain types of breast lesions, these studies were conducted in single, non-U.S. institutions that require replication in larger, multicenter trials. Therefore, the use of MRI to further characterize suspicious lesions is currently unlikely to alter clinical management. In addition, the fairly high rate of false-positives will lead to substantial numbers of unnecessary biopsies.

**TREATMENT-RELATED USES**

For several indications (ie, preoperative mapping to identify multicentric disease with clinically localized breast cancer; guiding surgical decisions after neoadjuvant chemotherapy; evaluating suspected chest wall involvement; evaluating and localizing lesions prior to biopsy), the available RCT evidence is discussed; for the other indications, where RCT evidence is not available, direct and indirect evidence is discussed.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.
Clinical Context and Test Purpose
The question addressed in this portion of the evidence review is whether the use of MRI evaluation as an adjunct to guide treatment planning (e.g., surgical approach) for patients with known or suspected breast cancer improves the net health outcome compared with standard techniques.

The question addressed in this evidence review is: Does use of MRI as an adjunct to standard methods for pretreatment planning, posttreatment evaluation, or evaluation of response to treatment improve the diagnostic accuracy, and is this degree of increased accuracy likely to improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with suspicious lesions and individuals with breast cancer.

Interventions
The intervention of interest is MRI as an adjunct to standard evaluation methods.

Comparators
The following tests and practices are currently being used to make decisions about managing breast cancer: standard workup with MRI, mammography, clinical assessment, active surveillance, and/or pathologic inspection.

Outcomes
The relevant outcomes of interest for diagnostic accuracy include test accuracy and test validity (i.e., sensitivity, specificity). Primary outcomes of interest for clinical utility include avoidance of invasive procedures (e.g., biopsy, mastectomy), the ability to detect cancer requiring additional or earlier treatment, and overall mortality and breast cancer–specific mortality rates.

Timing
MRI would be performed after identification of suspicious breast lesions, or before or after treatment for breast cancer.

Setting
Breast MRI is administered in an outpatient imaging setting.

Study Selection Criteria
The evidence review focuses on systematic reviews and RCTs when available. Comparative observational studies are included if the study captures longer periods of follow-up and/or larger populations and is published subsequent to the systematic reviews.
Preoperative Mapping to Identify Multicentric Disease With Clinically Localized Breast Cancer Systematic Reviews

Evidence on preoperative mapping was based on a TEC Assessment (2004). The TEC Assessment concluded that ipsilateral MRI at the time of diagnosis did not meet TEC criteria because there was insufficient evidence to permit conclusions about the effect on health outcomes of adding MRI to the standard staging workup of early-stage invasive breast cancer. However, as noted in the Assessment, long-term recurrence rates after modified radical mastectomy compared with BCS plus whole-breast irradiation did differ, with lower long-term recurrence rates after mastectomy.

Subsequently, several meta-analyses have evaluated evidence on additional disease detected by MRI and changes in clinical management, most of which were by the same research group. The most recent and comprehensive meta-analysis was published by Houssami et al (2017). Studies included in the review were comparative (randomized or nonrandomized), evaluated preoperative MRI vs an alternative approach that did not include MRI, and reported quantitative data on surgical outcomes. The primary end point for the meta-analysis was whether patients underwent mastectomy as surgical treatment. Secondary end points were re-excision rates after BCS, positive margins after BCS, and receipt of contralateral prophylactic mastectomy.

Nineteen studies met the inclusion criteria—3 RCTs and 16 nonrandomized comparative studies. For the primary study end point, a pooled analysis of 15 studies (n=85,975 patients) found significantly greater odds of receiving a mastectomy after preoperative MRI than after no MRI (odds ratio [OR], 1.39; 95% CI, 1.23 to 1.57; p<0.001). Findings were the same in analyses stratified by publication dates, suggesting that the higher mastectomy rates were not limited to older studies conducted when the MRI-guided biopsy was less common. In an analysis limited to patients with invasive lobular cancer, there was no significant difference in the odds of mastectomy (6 studies: pooled OR=1.00; 95% CI, 0.75 to 1.33; p=0.988) or the odds of re-excision (5 studies: OR=0.65; 95% CI, 0.35 to 1.24; p=0.192).

Among the secondary outcomes, a pooled analysis of 3 studies found a significantly higher odds of contralateral prophylactic mastectomy after MRI (OR=1.91; 95% CI, 1.25 to 2.91). There were no significant differences between groups on other secondary outcomes (ie, re-excision rates, positive margins, reoperation rates).

One meta-analysis has addressed breast cancer recurrence rates. This meta-analysis, by Houssami et al (2014), analyzed individual patient data from 4 studies—1 RCTs and 3 nonrandomized comparative studies (total N=3180 patients). Most patients (62%-93%) had localized, invasive disease and received BCT and systemic chemotherapy. After a median follow-up of 2.9 years (interquartile range [IQR], 1.6-4.5 years), there was no difference in estimated 8-year ipsilateral local (adjusted hazard ratio [HR], 0.88; 95% CI, 0.52 to 1.51; p=0.65) or distant (adjusted HR=1.18; 95% CI, 0.76 to 2.27; p=0.48) recurrence-free survival overall or in patients who received BCT only.
Randomized Controlled Trials

A discussion of the 3 RCTs included in the Houssami meta-analysis (described above) is as follows.

The RCT by Gonzalez et al (2014) in Sweden assessed 440 women who underwent surgical treatment of invasive breast cancer with or without presurgical breast MRI. Breast MRI provided incremental information that altered treatment plan in 40 (18%) of 220 patients in the MRI group. Conversion from planned BCS to mastectomy occurred more often in the MRI group (20%) than in the control group (10%; p=0.024). However, more patients in the MRI group had planned BCS at baseline (70%) than in the control group (60%; p=0.036). The ipsilateral reoperation rate was 5% in the MRI group vs 15% in the control group (p<0.001). Reoperation rates among those initially planned for BCS were 5% and 22%, respectively (p<0.001).

A second RCT, the MONET trial, was reported by Peters et al (2011). It randomized 463 patients with suspicious, nonpalpable breast lesions identified by mammography or ultrasound to prebiopsy MRI or usual care. Of 207 evaluable patients in the MRI group, 11 additional suspicious lesions were identified on MRI and were occult on other imaging studies. All 11 additional lesions underwent biopsy, with 2 (18%) positive for malignancy. The incidence of mastectomy was similar between groups (32% vs 34%, p=0.776), as was the incidence of BCS (68% vs 66%). The incidence of re-excisions due to positive tumor margins was significantly greater in the MRI group (34%) than in the control group (12%; p=0.008).

A multicenter RCT from the U.K. (COMICE trial), reported by Turnbull et al (2010), examined the impact of presurgical MRI on the need for additional treatment within 6 months. This study was an open, parallel-group trial conducted at 45 centers in the U.K. and enrolled 1623 women with biopsy-proven breast cancer who were scheduled for wide local excision BCT. Of 816 patients in the MRI group, 58 (7%) underwent mastectomy as a result of MRI findings and/or patient choice, compared with 10 (1%) patients in the no-MRI group who underwent mastectomy by patient choice. There was no statistically significant reduction in reoperation rates in those who received MRI scans (19% in both groups; OR=0.96; 95% CI, 0.75 to 1.24; p=0.77). In the MRI group, 19 (2%) patients had a “pathologically avoidable” mastectomy, defined as a mastectomy based on MRI results showing more extensive disease, but histopathology showing only localized disease. Twelve months after surgery, there was no statistically significant difference in the quality of life between groups.

Since the publication of the Houssami meta-analysis, Bruck et al (2018) reported on the results of an RCT to evaluate the diagnostic value of preoperative MRI in 100 patients with newly diagnosed unifocal stage I invasive ductal carcinoma. Patients were randomized in a 1:1 ratio to preoperative breast MR or surgery without MRI. Breast MRI detected an additional finding in 14 patients (28%) and MRI detected lesions in 7 (14%) of patients undergoing MRI were confirmed to be malignant. Seven (14%) patients underwent breast reoperation in the MRI group compared with 12 (24%) patients in the control group (p=0.20). Definitive mastectomy was performed in 6 (12%) patients in the MRI group compared with 2 (4%) in the control group (p=0.14).
Observational Studies
In addition to the RCTs, Onega et al (2018) reported on the association between preoperative MRI and all-cause mortality in 5 registries (total N=4454 patients) of the National Cancer Institute-sponsored Breast Cancer Surveillance Consortium. Data from the Breast Cancer Surveillance Consortium registries were linked to Medicare claims data or electronic health records; women ages 66 and older with an initial nonmetastatic breast cancer (stage I–III) diagnosed from 2005 to 2010 were included with follow-up continuing through 2014. Nine hundred seventeen (21%) women underwent preoperative MRI. The unadjusted 5-year cumulative probability of death was 0.12 for women with MRI and 0.17 for those without (HR=0.67; 95% CI, 0.54 to 0.82). However, after adjustment for age, sociodemographic, and clinical factors, the association was attenuated (HR=0.90; 95% CI, 0.72 to 1.12).

Fortune-Greeley et al (2014) retrospectively examined case records of 20,332 women with invasive breast cancer in the Surveillance Epidemiology and End Results–Medicare-linked dataset. Twelve percent of patients had a preoperative MRI. Among patients with invasive lobular carcinoma, but not other histologic types, preoperative breast MRI was associated with lower odds of reoperation after initial partial mastectomy (adjusted OR=0.59; 95% CI, 0.40 to 0.86).

Section Summary: Preoperative Mapping to Identify Multicentric Disease With Clinically Localized Breast Cancer
Preoperative MRI as an adjunct to mammography and clinical assessment identifies additional foci of ipsilateral breast cancer and results in a higher rate of mastectomy. For example, a 2017 meta-analysis of 17 studies found significantly higher odds of receiving a mastectomy after preoperative MRI vs no MRI in women with breast cancer. Follow-up studies have reported mixed results, including no significant reduction in reoperations rates after MRI while other studies have reported lower odds of reoperation in patients with invasive lobular carcinoma. No significant differences in ipsilateral local or distant recurrence-free survival after MRI-guided treatment were found in meta-analyses. However, the meta-analysis might have been underpowered to detect differences in the overall population and further studies may help determine whether particular subgroups derive greater benefit.

Guiding Surgical Decisions After Neoadjuvant Chemotherapy
Systematic Reviews
Evidence on guiding surgical decisions is based on a TEC Assessment (2004) and more recent publications. Compared with conventional methods of evaluating tumor size and extent (ie, mammography, clinical exam, ultrasound), MRI of the breast provides an estimation of tumor size and extent that is at least as good as or better than that based on alternatives. Drew et al (2001) found MRI to be 100% sensitive and specific for defining residual tumor after chemotherapy. Conversely, mammography achieved 90% sensitivity and 57% specificity (mammography results considered equivocal), and clinical exam was only 50% sensitive and 86% specific. Similarly, Partridge et al (2002) reported on correlations of residual tumor size by histopathology of 0.89 with MRI and 0.60 with clinical exam. MRI results were well-correlated with...
results of histopathologic assessment (criterion standard) with correlation coefficients ranging from 0.72 to 0.98; however, MRI is not intended as a replacement for histopathologic assessment.

Several systematic reviews have been published since the 2004 TEC Assessment. Most recently, Marinovich et al (2015) published an individual patient data meta-analysis of agreement between MRI and pathologic tumor size and other evaluation methods after neoadjuvant chemotherapy. To be eligible for inclusion, studies had to evaluate at least 15 patients undergoing neoadjuvant chemotherapy who were evaluated with MRI and at least 1 other test (ie, mammography, ultrasound, clinical examination) after surgery. Studies also had to report residual tumor size (ie, longest diameter). Twenty-four studies met inclusion criteria, and individual patient data were available for 8 of these studies (n=300 patients). The pooled mean difference (MD) in size estimates between MRI and pathology (8 studies, n=243 patients) was 0.0 cm; 95% CI, -0.1 to 0.2 cm). In 4 studies comparing size estimates of mammography and pathology, the MD was 0.0 cm, but the 95% CI was wider (-0.3 to 0.4 cm). In 5 studies (n=123 patients) reporting on the MD between ultrasound and pathology, the pooled estimate was -0.3 cm (95% CI, -0.6 to 0.1 cm). The largest size variance was for studies (3 studies, n=107 patients) comparing clinical examination with pathology (pooled MD = -0.8 cm; 95% CI, -1.5 to -0.1 cm).

Previously, Lobbes et al (2013) reported on a systematic review of 35 studies (total N=2359 patients) reporting on the ability of MRI to predict tumor size after neoadjuvant chemotherapy. Literature was searched to July 2012. Median correlation coefficient was 0.70 (range, 0.21-0.98). Variation in size between MRI and pathology ranged from -1.4 to +2.0 cm.

Section Summary: Guiding Surgical Decisions After Neoadjuvant Chemotherapy

Studies, including a 2015 meta-analysis, have found that MRI results are well-correlated with pathologic assessment for measuring residual tumor size after neoadjuvant chemotherapy and that MRI performed better than conventional methods. Using breast MRI instead of conventional methods to guide surgical decisions regarding BCT vs mastectomy after neoadjuvant chemotherapy would be at least as beneficial and might lead more frequently to appropriate surgical treatment.

Evaluating Suspected Chest Wall Involvement

Morris et al (2000) prospectively studied 19 patients with posteriorly located breast tumors suspected to involve the pectoralis major muscle based on either mammography or clinical exam. Thirteen tumors were thought to be fixed to the chest wall on clinical exam, and 12 appeared to have pectoral muscle involvement on mammography. MRI results were compared with surgical and pathologic findings. The presence of abnormal enhancement within the pectoralis major muscle on MRI was 100% sensitive and 100% specific for identifying 5 tumors that actually involved the pectoralis major muscle.

Two other retrospective studies have reported on 4 cases in which MRI was able to determine the involvement of the chest wall with 100% accuracy.
Evaluating and Localizing Lesions Prior to Biopsy

Use of MRI to evaluate lesions prior to biopsy is infrequent. MRI is used in this situation to permit biopsy and breast cancer diagnosis sooner than waiting until the lesion is visible on 2 mammographic views or on ultrasound or becomes palpable. The evidence base addressing this use is mainly anecdotal.

De Lima Docema et al (2014) used contrast-enhanced MRI to locate occult tumors in 25 patients selected from a group who had undergone breast MRI for suspicious incidental MRI findings at a single institution in Brazil. Sentinel lymph node mapping and tumor resection was done simultaneously. Malignant tumors were confirmed in 15 (60%) patients, including 4 patients with DCIS. Survival outcomes were not reported.

Section Summary: Evaluating and Localizing Lesions Prior to Biopsy

Although the evidence base addressing this use of MRI is mainly anecdotal, the rationale supporting its use is good. Improved health outcomes are expected by enabling earlier diagnosis of breast cancer. A small cohort study in Brazil identified malignant tumors in 60% of patients with MRI-detected occult lesions using contrast-enhanced MRI.

Evaluating Response to Neoadjuvant Chemotherapy With Locally Advanced Breast Cancer

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy # 00084
Original Effective Date: 03/25/2002
Current Effective Date: 06/01/2019

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Evidence on the use of MRI to assess response to chemotherapy is based on a TEC Assessment (2004) and subsequent studies.

The TEC Assessment reported on 6 studies (total N=206 patients) that performed breast MRI during the course of chemotherapy. MRI outcomes for response to chemotherapy were based on a reduction in tumor size or reduction in contrast enhancement. Three studies reported NPV results of 38%, 83%, and 100%, respectively; however, the 2 lower estimates were from prospective studies, and the highest estimate was from a retrospective study.

Three systematic reviews of MRI to evaluate response to neoadjuvant chemotherapy have been published. Characteristics of the reviews are shown in Table 11 and described briefly in the following paragraphs. Li et al (2018) compared the performance of MRI with positron emission tomography (PET) plus computer tomography (CT).

Table 11. Characteristics of Systematic Reviews Assessing MRI to Evaluate Response to NAC

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Studies</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2018)</td>
<td>Up to</td>
<td>13</td>
<td>Had both PET/CT and MRI after preoperative NAC with at least 10 patients</td>
<td>MRI: 575 (16-142) PET/CT: 618 (16-142)</td>
<td>Observational (prospective, retrospective)</td>
<td>Postoperative pathologic result (pCR vs non-pCR)</td>
</tr>
<tr>
<td>Marinovich et al (2013)</td>
<td>Up to</td>
<td>44</td>
<td>Newly diagnosed breast cancer undergoing NAC, with MRI undertaken after NAC</td>
<td>2949 (14-869)</td>
<td>Observational (prospective, retrospective)</td>
<td>Pathologic response based on surgical excision preferred; other references standards allowed</td>
</tr>
<tr>
<td>Lobbes et al (2013)</td>
<td>Up to</td>
<td>8</td>
<td>Newly diagnosed breast cancer for whom breast MRI was not performed at baseline or prior to surgery but after completion of NAC with at least 25 patients</td>
<td>560 (31-195)</td>
<td>Observational (prospective, retrospective)</td>
<td>NR</td>
</tr>
</tbody>
</table>

CT: computed tomography; MRI: magnetic resonance imaging; NAC: neoadjuvant chemotherapy; NR: not reported; pCR: pathologic complete response; PET: positron emission tomography.

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Results of the systematic reviews are shown in Table 12. Li et al (2018) reported on a systematic review comparing MRI with PET/CT to evaluate pathologic response to neoadjuvant chemotherapy and included studies in which patients underwent both PET/CT and MRI after preoperative neoadjuvant chemotherapy, postoperative complete pathologic response (pCR vs non-pCR) was used as the reference standard, and the study included at least 10 patients. Methodologic quality was assessed using QUADAS-2. Most domains were rated as low risk of bias in all studies; however, only 2 studies enrolled consecutive or random samples and in only 3 studies were the reference standard results interpreted without knowledge of the results of the index tests. There was a high level of heterogeneity in the pooled estimate of both sensitivity (88%; 95% CI, 78 to 94; $I^2=83$%) and specificity (69%; 95% CI, 51 to 83; $I^2=72$%) for MRI.

Marinovich et al (2013) conducted a systematic review with meta-analysis. Forty-four studies (total N=2949 patients) assessing the ability of MRI to discriminate residual breast tumor after neoadjuvant chemotherapy from pCR were identified. Studies were heterogeneous in MRI parameters used, thresholds for identifying a response, and definitions of pathologic response. Median MRI sensitivity, defined as the proportion of patients with residual tumor correctly classified by MRI, and specificity, defined as the proportion of patients with pCR classified by MRI as the absence of residual tumor, were 0.92 (IQR, 0.85-0.97) and 0.60 (IQR, 0.39-0.96), respectively. Specificity increased when a relative threshold for defining negative MRI (ie, contrast enhancement was less than or equal to normal breast tissue) was used rather than an absolute threshold (complete absence of MRI enhancement) with little decrement to sensitivity. The pooled area under the receiver operating characteristic curve was 0.88, and the diagnostic odds ratio was 17.9 (95% CI, 11.5 to 28.0). (A diagnostic odds ratio of 1 indicates no discriminatory ability; higher values indicate better test performance.) Accuracy decreased when residual DCIS was included in the definition of pCR. Statistical measures of between-study heterogeneity were not reported. A subset of studies compared MRI with other imaging modalities (mammography, ultrasound) and clinical exam; however, 95% CIs for pooled analyses were very large, rendering conclusions uncertain.

In the systematic review by Lobbes et al (2013), 8 studies reported on measures of diagnostic accuracy. Median sensitivity, defined as the proportion of patients with pCR correctly classified by MRI, was 42% (range, 25%-92%). Median specificity, defined as the proportion of patients without pCR correctly classified by MRI, was 89% (range, 50%-97%). Median (range) PPV and NPV were 64% (50%-73%) and 87% (71%-96%), respectively.

Table 12. Results of Systematic Reviews Assessing MRI to Evaluate Response to NAC

<table>
<thead>
<tr>
<th>Study</th>
<th>MRI Sensitivity, %</th>
<th>MRI Specificity, %</th>
<th>Mammography Sensitivity, %</th>
<th>Mammography Specificity, %</th>
<th>PET/CT Sensitivity, %</th>
<th>PET/CT Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2018)</td>
<td>575</td>
<td>575</td>
<td>618</td>
<td>618</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>575</td>
<td>575</td>
<td>618</td>
<td>618</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE (95% CI)</td>
<td>88 (78 to 94)</td>
<td>69 (51 to 83)</td>
<td>NR</td>
<td>NR</td>
<td>77 (58 to 90)</td>
<td>78 (63 to 88)</td>
</tr>
<tr>
<td>Marinovich et al (2013)</td>
<td>2949</td>
<td>2949</td>
<td>2949</td>
<td>2949</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy # 00084
Original Effective Date: 03/25/2002
Current Effective Date: 06/01/2019

<table>
<thead>
<tr>
<th>Study</th>
<th>MRI Median (IQR)</th>
<th>Mammography Median</th>
<th>PET/CT Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>560</td>
<td>560</td>
<td>NR</td>
</tr>
<tr>
<td>Median (range)</td>
<td>42 (25-92)</td>
<td>89 (50-97)</td>
<td>NR</td>
</tr>
</tbody>
</table>

CT: computed tomography; IQR: interquartile range; MRI: magnetic resonance imaging; NAC: neoadjuvant chemotherapy; PE: pooled estimate; NR: not reported; PET: positron emission tomography.

Observational Studies
The ACRIN 6657/I-SPY trial (2012) enrolled 206 women ages 26 to 68 years with invasive breast cancer 3 cm or larger who were receiving anthracycline-based neoadjuvant chemotherapy, with or without a taxane. MRI was performed at 4 time points: before chemotherapy, after 1 cycle of chemotherapy, between the anthracycline-based regimen and the taxane, and after all chemotherapy but before surgery. Various MRI parameters were evaluated for their ability to predict the pathologic outcome. Results were reported as the difference in predictive ability for residual cancer burden, a composite pathologic index, between MRI parameters and clinical size predictors at the same time points. MRI findings were a stronger predictor of pathologic outcomes than clinical assessment, with the largest difference being tumor volume after the first chemotherapy cycle and a difference in the area under the receiver operating characteristic curve of 0.09; corresponding area under the receiver operating characteristic curve values after the third and fourth MRIs were 0.07 and 0.05. Similar findings were reported for predicting pCR.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The most important use of MRI would be to reliably identify patients whose tumors are not responding to neoadjuvant chemotherapy (high NPV) to avoid added morbidity associated with continued ineffective chemotherapy. Such chemotherapy may be discontinued or changed to an alternative and potentially effective regimen. MRI is harmful if it falsely suggests a lack of response (low specificity) and leads to premature discontinuation of effective chemotherapy.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing breast MRI to identify patients whose tumors are not responding to neoadjuvant chemotherapy to guide subsequent systemic therapy were identified.
Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Given the lack of published evidence comparing MRI with other methods for assessing response and heterogeneity in existing evidence, evaluations of incremental clinical validity are not possible. Furthermore, it is not clear that any resulting change in patient management (eg, discontinuation of chemotherapy or change to a different regimen) would improve outcomes.

Section Summary: Evaluating Response to Neoadjuvant Chemotherapy With Locally Advanced Breast Cancer
Studies, including systematic reviews, have not found sufficient evidence to determine whether breast MRI can reliably predict lack of response to neoadjuvant chemotherapy. There is a large amount of variability in reported performance characteristics of MRI in published studies, leaving uncertain the true accuracy of MRI for this purpose. Furthermore, evidence would need to show that any resulting change in patient management (eg, discontinuation of chemotherapy or change to a different regimen) would improve outcomes.

Evaluating Residual Tumor After Lumpectomy or Breast Conservation Surgery

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Evidence on evaluating residual tumor includes several observational studies, most of which are retrospective. Histopathologic examination on re-excision was used as the criterion standard. Three studies were conducted at the same institution and accrued patients during similar time periods, so overlap reporting may exist. Most of the studies were published before 2005 and are not discussed further. Characteristics of studies published since 2015 are shown in Table 13 and described briefly in the following paragraphs.

Table 13. Characteristics of Clinical Validity Studies Assessing MRI to Evaluate Residual Tumor After Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Timing of Reference Assessors</th>
<th>Blinding of Assessors</th>
<th>Comment</th>
</tr>
</thead>
</table>

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RESULTS

Lee et al (2018) reported on the results of a study comparing breast MRI with ultrasonography for detecting remnant lobular carcinoma in situ (LCIS) lesions after initial excision. Twenty-nine patients with LCIS were enrolled between 2011 and 2015. Methods are poorly described. Residual lesions were identified by pathology in 12 (41%) cases. The sensitivity of ultrasonography was 58% compared with 83% for breast MRI; precision estimates were not reported. Specificity was 100% for both modalities.

Krammer et al (2017) published a retrospective study evaluating breast MRI to assess residual disease in 175 patients who had been candidates for BCS and had positive surgical margins. MRIs were read independently by 2 radiologists, both of whom had access to the pathology report from the initial surgery and any prior breast imaging. Pathology findings served as the criterion standard. For reader 1, the sensitivity and specificity of detecting residual disease was 63% and 75%, respectively. For reader 2, sensitivity and specificity were 83% and 64%, respectively. The interobserver agreement was moderate (κ=0.56).

LCIS: lobular carcinoma in situ; MRI: magnetic resonance imaging; NR: not reported; Retro: retrospective.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients in Taiwan with LCIS who had initial excision from 2011 to 2015</th>
<th>Unclear</th>
<th>Histopathology</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
<th>Few details on study design or conduct provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2018)</td>
<td>Women with positive margins after initial surgery for breast cancer, from 2004 to 2013</td>
<td>Retro</td>
<td>Histopathology</td>
<td>• Read independently by 2 radiologists • Criteria for suspected residual disease: asymmetric thickening or nodular enhancement with irregular or spiculated margins or extensive focal non-mass enhancement</td>
<td>NR</td>
<td>Radiologists had access to other imaging results, when available</td>
<td></td>
</tr>
</tbody>
</table>

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Table 14. Results of Clinical Validity Studies Assessing MRI to Evaluate Residual Tumor After Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Condition, %</th>
<th>Clinical Validity Confidence Interval, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2018)</td>
<td>NR</td>
<td>29</td>
<td>Any invasive focus or other malignancy</td>
<td>41</td>
<td>Sens: NR Spec: NR PPV: NR NPV: NR</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td>83% (NR)</td>
<td>Sens: 100% Spec: 100% PPV: NR NPV: NR</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td></td>
<td></td>
<td></td>
<td>58% (NR)</td>
<td>Sens: 100% Spec: 100% PPV: NR NPV: NR</td>
</tr>
<tr>
<td>Krammer et al (2017)</td>
<td>180</td>
<td>175</td>
<td>Received chemo prior to postop MRI (n=4), poor MR image quality (n=1)</td>
<td>79</td>
<td>Sens: 73% Spec: 72% PPV: 91% NPV: 45%</td>
</tr>
</tbody>
</table>

Table 15 and 16 display notable gaps identified in each study.

Table 15. Relevance Gaps of Clinical Validity Studies of MRI to Evaluate Residual Tumor After Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesa</th>
<th>Duration of Follow-Upa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2018)</td>
<td>1.2. No description provided</td>
<td>1. No description provided</td>
<td>1. Health outcomes not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

MRI: magnetic resonance imaging.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

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Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

### Table 16. Study Design and Conduct Gaps of Clinical Validity Studies Assessing MRI to Evaluate Residual Tumor After Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2018)</td>
<td>1. Not described</td>
<td>1,3,4. Not described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krammer et al (2017)</td>
<td>1. Not blinded to other imaging results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. MRI: magnetic resonance imaging.

| a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience). |
| b Blinding key: 1. Not blinded to results of reference or other comparator tests. |
| c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described. |
| e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data. |
| f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported. |

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The most important use of MRI would be to reliably identify patients with residual tumor following initial surgery to guide the selection of second surgical procedures in women with positive margins.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.
No RCTs assessing breast MRI to identify patients with a residual tumor to guide subsequent surgery were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Given the low quality of existing evidence, evaluations of incremental clinical validity are not possible. Furthermore, it is not clear that any resulting change in a patient would improve outcomes.

Section Summary: Evaluating Residual Tumor After Lumpectomy or Breast Conservation Surgery

Available evidence is not sufficient to permit conclusions whether the use of MRI identifies the presence and/or extent of residual disease after lumpectomy or BCS and before re-excision. Most studies were retrospective, and most reported moderate sensitivity and specificity of MRI for detection of residual disease. One study published after 2015 reported the sensitivity and specificity of MRI to be over 70%. The other study published after 2015 reported a sensitivity of 83% and a specificity of 100% but offered very few details on methods, so study quality cannot be assessed.

SUMMARY OF EVIDENCE

Screening Uses

For individuals who are asymptomatic with high risk of breast cancer who receive MRI as an adjunct to screen for breast cancer, the evidence includes systematic reviews (including a TEC Assessment) and diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Studies have found that MRI is more sensitive than mammography or ultrasonography in detecting malignancy. Because of the high likelihood of malignancy among women at high risk for breast cancer, the benefits of detecting cancer earlier with MRI outweigh the disadvantages of incurring unnecessary workups and biopsies due to false-positive results. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with average risk of breast cancer who receive MRI as an adjunct to screen for breast cancer, the evidence includes systematic reviews and clinical validity studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The systematic reviews did not identify any RCTs or nonrandomized comparative studies evaluating MRI for screening average-risk women. One comparative observational study has been published since the systematic reviews. The diagnostic accuracy of screening tests would likely be lower in this lower prevalence population, and there would be higher false-positive rates, morbidity, and anxiety. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with characteristics limiting the accuracy of mammography (eg, dense breasts) who receive MRI as an adjunct to screen for breast cancer, the evidence includes a systematic review (TEC
Assessment) and diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. There are limited data on the diagnostic accuracy of MRI vs mammography in patients who have had breast-conserving therapy or who have dense breasts. The evidence is insufficient to determine the effects of the technology on health outcomes.

Detection Uses
For individuals who have suspected occult breast primary tumor with axillary nodal adenocarcinoma with negative mammography who receive MRI as an adjunct to detect breast cancer eligible for breast-conserving therapy, the evidence includes a systematic review (TEC Assessment) and meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The studies found that adjunctive use of breast MRI to guide breast-conserving surgery rather than preemptive mastectomy allowed a substantial portion of patients to avoid the morbidity of mastectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have breast cancer who receive adjunctive MRI of the contralateral breast, the evidence includes cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. A study of nearly 1000 patients found that MRI could detect contralateral breast cancer with a high degree of accuracy. Although long-term outcomes of these contralateral breast cancers are not fully known, important changes in management will occur (eg, simultaneous treatment of synchronous cancers) as a result of these findings, which should lead to improved outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have low-suspicion findings on conventional mammography who receive MRI as an adjunct to detect breast cancer, the evidence includes a systematic review (including a TEC Assessment). Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The TEC Assessment concluded that, although the available studies suggested reasonably high diagnostic accuracy, none of the studies used prospective methods in appropriate study populations or appropriate comparison interventions such as short-interval mammographic follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspicious breast lesions who receive MRI as an adjunct to further characterize lesions, the evidence includes systematic reviews (including a TEC Assessment) and cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Studies have found that MRI for evaluation of suspicious breast lesions has a relatively high sensitivity and a moderately high specificity. However, it has not yet been established that the negative predictive value is sufficient to preclude the need for biopsy. Although 2 recent studies have reported negative predictive values greater than 90% in certain types of breast lesions, these were non-U.S., single-institution studies that require replication in larger, multicenter trials. Therefore, the use of MRI to further characterize suspicious lesions is currently unlikely to alter clinical management. In addition, the moderately
high rate of false-positives will lead to substantial numbers of unnecessary biopsies. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Treatment-Related Uses**

For individuals who have clinically localized breast cancer who receive MRI for preoperative mapping to identify multicentric disease, the evidence includes RCTs, systematic reviews, and prospective cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Studies have found that, for patients with clinically localized breast cancer, MRI can detect additional areas of disease in the ipsilateral or contralateral breast beyond that detected by standard imaging; further, MRI is associated with a higher rate of mastectomy. Follow-up studies have reported mixed results including no significant reduction in reoperations rates after MRI while other studies have reported lower odds of reoperation in patients with invasive lobular carcinoma. No significant differences in ipsilateral local or distant recurrence-free survival after MRI-guided treatment were found in meta-analyses. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have locally advanced breast cancer undergoing neoadjuvant chemotherapy who receive MRI to guide surgical decisions after neoadjuvant chemotherapy, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Both a 2004 TEC Assessment and a 2015 systematic review found that MRI results were well-correlated with pathologic assessment for measuring residual tumor size after neoadjuvant chemotherapy. The 2015 systematic review also found that MRI performed better than conventional methods. Using breast MRI instead of conventional methods to guide surgical decisions on breast-conserving therapy vs mastectomy after neoadjuvant chemotherapy would be at least as beneficial and may lead to appropriate surgical treatment more often. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have posteriorly located breast tumors who receive MRI to diagnose chest wall involvement, the evidence includes cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Only a few small studies were identified, but MRI was 100% accurate in identifying chest wall involvement compared with the criterion standard. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a suspicious breast lesion recommended for biopsy but not localizable by mammography or ultrasonography who receive MRI to evaluate and localize the lesion prior to biopsy, the evidence includes a cohort study. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. A small cohort study from Brazil identified malignant tumors in 60% of patients with MRI-detected occult lesions using contrast-enhanced MRI. Although there is little published evidence supporting this indication, improved health outcomes are expected by enabling earlier
diagnosis of breast cancer for suspicious lesions where other good options are not available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. For individuals who have locally advanced breast cancer undergoing neoadjuvant chemotherapy who receive MRI to evaluate response to chemotherapy, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Studies, including systematic reviews, have not found that there is sufficient evidence to determine whether breast MRI can reliably predict lack of response to neoadjuvant chemotherapy. There is a large amount of variability in reported performance characteristics of MRI in published studies, leaving uncertainty about the true accuracy of MRI for this purpose. Furthermore, evidence would need to show that any resulting change in patient management (e.g., discontinuation of chemotherapy, change to a different regimen) would improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have positive surgical margins after lumpectomy or breast conservation surgery who receive MRI to evaluate residual tumor, the evidence includes cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The studies, most of which were retrospective and published before 2005, generally reported moderate sensitivity and specificity with MRI for detection of residual disease compared with the criterion standard. Two retrospective studies published since 2015 have uncertain or high risk of bias and therefore performance characteristics are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Magnetic resonance imaging of the breast in screening women considered to be at high genetic risk of breast cancer. TEC Assessments 2003;Volume 18:Tab 15.

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19. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Breast magnetic resonance imaging (MRI) for detection or diagnosis of primary or recurrent breast cancer TEC Assessments. 2004;Volume 19:Tab 1.

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82. Cho N, Han W, Han BK, et al. Breast cancer screening with mammography plus ultrasonography or magnetic resonance imaging in women 50 years or younger at diagnosis and treated with breast conservation therapy. *JAMA Oncol.* Nov 1 2017;3(11):1495-1502. PMID 28655029


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**Policy History**

**Original Effective Date:** 03/25/2002

**Current Effective Date:** 06/01/2019

**03/06/2002** Medical Director review

**03/21/2002** Medical Policy Committee review

**03/25/2002** Managed Care Advisory Council approval

**06/24/2002** Format revision. No substance change to policy

**05/07/2004** Medical Director review

**05/18/2004** Medical Policy Committee review. Format revision. Clinical criteria revision.

**06/28/2004** Managed Care Advisory Council approval

**10/05/2004** Medical Director review

**11/16/2004** Medical Policy Committee review. Format revision. Policy revised to include statement requiring use of a breast coil. Coverage Eligibility Revision. Added coverage eligibility for presurgical planning in patients with locally advanced breast cancer, and to determine presence of pectoralis major muscle/ chest wall invasion. Added investigational status for screening technique of the contralateral breast and average risk patients, preoperative tumor mapping, to determine response to neoadjuvant chemotherapy and evaluation of residual tumor.

**11/29/2004** Managed Care Advisory Council approval

**10/05/2005** Medical Director review

**10/18/2005** Medical Policy Committee review. Format revision. FDA approval information added. Coverage eligibility unchanged.

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10/27/2005  Quality Care Advisory Council approval
07/07/2006  Format revision; addition of FDA and/or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006  Medical Director review
08/09/2006  Medical Policy Committee approval. MRI of the breast for preoperative tumor mapping to evaluate the presence of multicentric disease in patients with clinically localized breast cancer who are candidates for breast-conservation therapy was changed from investigational to eligible for coverage.
12/06/2006  Medical Director review
12/20/2006  Medical Policy Committee approval. Coverage eligibility changed to allow coverage for the following indications:
• To assess response during neoadjuvant chemotherapy: magnetic resonance mammography may be performed before, during and after chemotherapy, to assess response to treatment and extent of residual disease, prior to surgery.
• To evaluate multi-centric disease in newly diagnosed breast carcinomas - in the contralateral breast, to interrogate for lesions not suspected by mammography and physical exam.
• To evaluate lesion, when primary screening test results (mammography, breast ultrasound, biopsy) and physical examination are inconclusive for breast carcinoma or when these studies cannot be performed.
• To detect residual disease post-lumpectomy with close or positive pathological margins, particularly when breast conservation and local re-excision are planned.
• To detect local recurrence of breast carcinoma post-mastectomy breast reconstruction, with implant or tissue transfer flap.
• To detect breast cancer in patients with personal history of infiltrating ductal carcinoma, particularly among candidates for breast conservation.
• To assess the extent and multicentricity of disease in invasive lobular carcinoma, particularly when primary screening tests are inconclusive or when breast conservation is considered.
• To differentiate palpable mass(es) from surgical scar tissue following breast surgery, breast reconstruction or radiation therapy.
12/05/2007  Medical Director review
12/19/2007  Policy Committee approval. Coverage eligibility unchanged.
12/03/2008  Medical Director review
12/17/2008  Policy Committee approval. Added the phrase “with a breast coil” for clarity of coverage statement.
12/04/2009  Medical Policy Committee approval
08/05/2010  Medical Policy Committee approval
08/18/2010  Medical Policy Implementation Committee approval. Added a Patient Selection Criteria bullet indicating that the use of MRI of the breast with a breast coil may be considered eligible for coverage to detect breast cancer in an individual with a personal history of breast cancer.
11/04/2010  Medical Policy Committee review

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11/16/2010  Medical Policy Implementation Committee approval. Defined high-risk in the Background/Overview section. Deleted the following statement from the first bullet in the coverage section: “(Genetic counseling in hereditary breast cancer should precede surveillance for breast carcinoma with MRI mammography)”.

11/03/2011  Medical Policy Committee approval
11/16/2011  Medical Policy Implementation Committee approval. No change to coverage.
11/01/2012  Medical Policy Committee review
11/07/2013  Medical Policy Committee review
11/06/2014  Medical Policy Committee review
11/21/2014  Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015  Medical Policy Committee review
11/16/2015  Medical Policy Implementation Committee approval. No change to coverage.
11/03/2016  Medical Policy Committee review
11/16/2016  Medical Policy Implementation Committee approval. Modification of coverage indications, high risk definition modified and moved from Background section to policy statements. Guidelines section added.

01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017  Medical Policy Committee review
08/09/2018  Medical Policy Committee review
08/15/2018  Medical Policy Implementation Committee approval. Added “Screening for breast cancer in any person previously diagnosed with breast cancer who has completed treatment, including a bilateral mastectomy, and was subsequently determined to be cancer free” as eligible under the Screening uses section.

01/10/2019  Medical Policy Committee review
01/23/2019  Medical Policy Implementation Committee approval. Screening uses criteria revised. Removed ATM and CHEK2 genes from covered criteria.

Next Scheduled Review Date:  01/2020

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<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
</table>
| CPT       | Codes deleted eff 1/1/19: 0159T, 77058, 77059  
            Codes added eff 1/1/19: 77046, 77047, 77048, 77049 |
| HCPCS     | C8903, C8905, C8906, C8907, C8908 |
| ICD-10 Diagnosis | C50.011-C50.029, C50.111-C50.129, C50.211-C50.229, C50.311-C50.329  
            C50.411-C50.429, C50.511-C50.529, C50.611-C50.629, C50.711-C50.729  
            C50.911-C50.929, C79.81, D05.00-D05.02, D05.10-D05.12  
            D05.80-D05.82, D05.90-D05.92, N63, Z15.01  
            Z80.3, Z85.3 |

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.
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