Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy # 00084
Original Effective Date: 03/25/2002
Current Effective Date: 12/17/2016

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 of the policy statements refer to performing magnetic resonance imaging (MRI) of the breast with a breast coil. MRI of the breast without the use of a breast coil, regardless of the clinical indication, is considered investigational.*

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 for breast cancer in high risk patients **Note: There is no standardized method for determining a woman’s risk of breast cancer that incorporates all possible risk factors. There are validated risk prediction models, but they are based primarily on family history.**
  - The following list includes individual risk factors known to indicate a high risk of breast cancer by themselves:
    - lobular carcinoma in situ
    - a known BRCA1 or BRCA2 mutation
    - another gene mutation associated with high risk, eg, TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), CDH1, and STK11, ATM, CHEK2, and PALB2
    - high risk (lifetime risk about ≥20%) of developing breast cancer as identified by models that are largely defined by family history
    - received radiotherapy to the chest between 10 and 30 years of age
  - Detection of a suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma
  - A new diagnosis of breast cancer to evaluate the contralateral breast when clinical and mammographic findings are normal
  - 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
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- 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

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:
- 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)
- 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
- to determine response during neoadjuvant chemotherapy in patients with locally advanced breast cancer
- for evaluation of residual tumor in patients with positive margins after lumpectomy

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
(National Cancer Care Network, www.nccn.org)
A number of other factors may increase the risk of breast cancer but do not by themselves indicate high risk. It is possible that combinations of these factors may be indicative of high risk, but it is not possible to give quantitative estimates of risk. As a result, it may be necessary to individualize the estimate of risk taking into account 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).
National Comprehensive Cancer Network guidelines state there is insufficient evidence for any recommendations for breast MRI for patients with the following mutations: BARD1, FANCC, MRE11A, MUTYH, NF1, NBN, RAD50, SMARCA, or XRCC2. Moreover, there are conflicting data on risks associated with a MLH1, MSH2, MSH6, PMS2, and EPCAM gene deletion (https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf).

**Background/Overview**

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

**Screening Uses**

Screening uses include detection of breast cancer in patients who are at high genetic risk for breast cancer and detection of breast cancer in patients who have breast characteristics limiting the sensitivity of 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 \textit{BRCA1} or \textit{BRCA2} genetic mutations 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 mammographic screening. These characteristics are dense breast tissue, breast implants, or scarring after breast-conserving therapy (BCT). BCT consists of breast-conserving surgery (BCS) followed by radiotherapy (RT).

**Detection Uses**

Detection of a 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.

Detection of 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.

**Diagnostic Uses**

- Diagnosis of low-suspicion findings on conventional testing not indicated for immediate biopsy but referred for short-interval follow-up
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- Diagnosis of a suspicious breast lesion to avoid biopsy
- Preoperative tumor mapping (e.g., detection of multicentric disease) in patients with clinically localized breast cancer who are considered candidates for breast-conserving surgery followed by radiation therapy
- 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. Those 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 a period of two years to demonstrate stability of benign findings or to detect progression, indicating 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 considered suspicious that are detected by clinical exam or mammography are frequently referred for biopsy; however, only a minority of such biopsies reveal breast cancer due to the relative 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 seen on only one mammographic view that is recommended for biopsy; however, the lesion cannot be seen in other views or on ultrasound, so percutaneous biopsy localization cannot be performed. MRI would be used, in this situation, to localize the suspicious lesion and permit biopsy and would presumably lead to earlier diagnosis of breast cancer compared to waiting until the lesion was visible on two mammographic views or ultrasound. This is an infrequent occurrence so the evidence base addressing this use is mainly anecdotal, but the rationale supporting this use is good.

Patients with localized breast cancer are considered candidates for BCS followed by radiation therapy. However, mastectomy may be considered in patients with multicentric disease. MRI has been investigated as a technique to assess the extent of tumor in the breast and specifically to detect multicentric disease as an aid to surgical planning.

Patients with locally advanced breast cancer are generally offered neoadjuvant chemotherapy in the hopes of reducing tumor size to permit BCT. Evaluation of tumor size and extent with conventional techniques (i.e., mammography, clinical exam, ultrasound) is suboptimal, and breast MRI has been proposed as a more accurate means of determining tumor size for surgical planning. Tumors that respond to chemotherapy get smaller and may even disappear; however, actual reduction in size is a delayed finding.
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and earlier changes in vascularity in tumors responsive to chemotherapy have been observed. Reduction in the degree of contrast enhancement on MRI has been noted in tumors relatively early in the course of chemotherapy, and the role of this MRI finding as an early predictor of tumor response has been explored as a means to optimize choice of chemotherapeutic agents (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 the chest wall tissues. Typically, modified radical mastectomy removes only the fascia of the pectoralis muscle; however, tumor involvement of the muscle would necessitate removal of the muscle (or a portion of it) as well. In smaller tumors, potentially eligible for BCT, it is necessary to determine how closely the tumor abuts the pectoralis muscle and whether it invades the muscle to know preoperatively if 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.

Breast conserving therapy includes complete removal of the primary tumor along with a rim of normal surrounding tissues. Pathological assessment of surgical margins is performed on excisional specimens to determine whether tumor extends to the margins of resection. Surgical specimens are generally oriented and marked to direct re-excision if margins are shown to contain tumor; however, when tumor is not grossly visible, the extent of residual tumor within the breast can only be determined through repeat excision and pathological assessment. MRI has been proposed to evaluate the presence and extent of 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)

Magnetic resonance imaging of the breast can be performed using commercially available magnetic resonance (MR) scanners and intravenous MR contrast agents. Specialized breast coils such as the Access Breast Coil 4/SMS (Confirma, Kirkland, WA) and MR-compatible equipment for performing biopsy have been developed and cleared for marketing by the U.S. FDA through the 510(k) process. FDA determined that these devices are substantially equivalent to predicate devices for use “in conjunction with a MR imager to produce diagnostic and interventional images of the breast, chest wall and axillary tissues that can be interpreted by a trained physician” (Access Breast Coil 4/SMS 510[k] notification letter dated March 29, 2006).

**Rationale/Source**

**Screening Uses**

**Magnetic Resonance Imaging to Screen for High-Risk Breast Cancer**

The original evidence review was based on a 2003 TEC Assessment. This Assessment concluded that for high-risk women, the evidence appeared to show at least equivalent 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 and mammography detected 33%. Abstracts showed findings consistent with superior sensitivity of MRI and either equivalent or slightly inferior specificity.
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Other studies since the 2003 TEC Assessment have corroborated the improved sensitivity of MRI compared with mammography in high-risk women. In addition, Chiarelli et al found higher diagnostic accuracy for detecting breast cancer in high-risk women with MRI plus mammography compared with mammography alone.

To evaluate sensitivity and specificity of screening MRI in women ages 50 years or older with high breast cancer risk, Phi et al (2015) conducted an individual patient data meta-analysis of 6 trials in women with BRCA1 and BRCA2 mutations (N=1951; 22% >age 50 years). Literature was searched in April 2013. Screening examinations were obtained annually in all 6 trials. Sensitivity of mammography, MRI, and the combination was similar in women regardless of age. However, specificity of all 3 imaging modalities was statistically superior in women age 50 years or older compared with women younger than 50 years; specificity of MRI in older versus younger women was 89% (95% confidence interval [CI], 84% to 92%) versus 84% (95% CI, 78% to 88%), respectively. Sensitivity and specificity of combination MRI plus mammography were similar to those of MRI alone in both age groups.

Sensitivity of MRI for detecting breast cancer may vary by type of lesion. Kuhl et al (2007) reported results for the diagnosis of ductal carcinoma from a prospective series in a single, specialized referral center. Over a 5-year period, 7319 women who were referred to this center received MRI in addition to mammography for diagnostic assessment and screening. A total of 193 (2.6%) women received a final surgical pathology diagnosis of pure DCIS. Of those, 167 (87%) had undergone both imaging tests preoperatively; 93 (56%) of these cases were diagnosed by mammography and 153 (92%) by MRI (p<0.001). Of 89 high-grade DCIS lesions, 43 (48%) were missed by mammography but detected by MRI; 2 lesions (2%) were missed by MRI but detected by mammography. MRI was significantly more sensitive than mammography in detecting high-grade DCIS (80% vs 61%, p=0.13). The authors noted that their results were not representative of the typical screening setting. They also indicated that a multi-institutional trial would be needed to further investigate the role of MRI for diagnosing DCIS in a screening population and to determine the impact of MRI screening on important outcomes such as recurrence rates and mortality. It should be noted that in 2010, the Society of Breast Imaging and the American College of Radiology (ACR) jointly recommended annual screening with both MRI and mammography for high-risk women.

King et al (2013) et al retrospectively reviewed the clinical course of 776 women at a single institution who were diagnosed with lobular carcinoma in situ and offered screening by annual mammography alone (n=321) or mammography plus MRI (n=455). At a median follow-up of 58 months, detection of incident cancers was similar between screening groups (13% each). The proportion of DCIS detected compared with invasive cancers detected also was similar between groups (p=0.69). In patients with lobular carcinoma in situ at increased risk for breast cancer, screening with MRI and mammography did not increase the detection of incident cancers compared with mammography alone.

Section Summary: Magnetic Resonance Imaging to Screen for High Risk of Breast Cancer
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 more unnecessary workups and biopsies due to false-positive results.

MRI to Screen for Average Risk of Breast Cancer
In a systematic review of literature conducted for the 2016 U.S. Preventive Services Task Force breast cancer screening recommendation update, no randomized controlled trials (RCTs) or nonrandomized observational studies identified evaluated MRI for screening average-risk women for breast cancer. Thus, there is a lack of published evidence on MRI screening of average-risk women. Because the prevalence of breast cancer is extremely low in average-risk young women, screening with a test such as MRI that has inferior 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 MRI screening applied to young, average-risk women.

Section Summary: MRI to Screen for Average Risk of Breast Cancer
There is a lack of evidence on MRI screening for average-risk women; a recent systematic review did not identify any RCTs or nonrandomized comparative studies. Moreover, 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.

MRI to Screen for Breast Cancer When Breast Characteristics Limit the Sensitivity of Mammography
Evidence for on limited sensitivity to mammography is based on a 2004 TEC Assessment and a number of more recent articles. The sensitivity of mammography is limited in patients after BCT; therefore, there is the potential for improved sensitivity with MRI. However, additional prospective studies are needed to confirm this and to identify patient subsets most likely to benefit from MRI evaluation given the relatively low incidence of recurrence.

Discussion continues on the possible use of MRI to screen women with 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 1 other breast cancer risk factor. Half (54%) of women had a personal history of breast cancer. In a substudy, 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 the substudy, and 612 (98%) completed the needed tests; 16 cancers were found 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.

In a 2009 retrospective study, MRI accuracy was evaluated in patients who had dense breasts and suspected breast cancer or inconclusive evaluations at a single institution in Italy. The criterion standard was histology at 6- and/or 18-month follow-up. MRI was compared with mammography or ultrasound. About half of women were found to have breast cancer. Of 238 patients, 97 (41%) had all 3 imaging tests.
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Sensitivity and specificity were 98% and 95%, respectively, for MRI; 73% and 45%, respectively, for mammography; and 86% and 41%, respectively, for ultrasound. In this study, MRI was used to evaluate patients suspected of having breast cancer or with equivocal results from other modalities, including clinical examination. Although specificity was relatively high and the negative predictive value (NPV) in this selected population was 98%, this study does not provide sufficient evidence that MRI can be used as a substitute for biopsy in these patients.

Section Summary
There is a lack of prospective studies on the diagnostic accuracy of MRI versus mammography in patients who have had BCT. There are several studies of MRI in women with dense breasts, but, in these studies, women also had suspected breast cancer or other breast cancer risk factors. Evidence is lacking on MRI screening of women with breast characteristics limiting the sensitivity of mammography but who are not otherwise at high risk of breast cancer.

Other Detection Uses
MRI to Detect Suspected Occult Breast Primary Tumor With Axillary Nodal Adenocarcinoma With a Negative Mammography and Physical Exam
Evidence on detection of suspected occult breast cancer is based on a 2004 TEC Assessment 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%.

A 2010 systematic review of studies on the use of MRI in patients with mammographically occult breast cancer and an axillary metastasis evaluated 8 retrospective studies (total N=220 patients). 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%).

Section Summary
The use of MRI to guide BCS rather than presumptive mastectomy appears to offer the substantial benefit of breast conservation for those patients in whom MRI detects the primary tumor.

MRI to Detect Breast Cancer in the Contralateral Breast With Established Breast Cancer
In 2007, Lehman et al reported results of the ACRIN-A6667 trial. They reported that 30 (3%) of 969 women with a recent diagnosis of unilateral breast cancer were found to have 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 DCIS. In this study, 121 (12.5%) patients had biopsies, with a positive biopsy rate of 24.8%. With 1-year follow-up, sensitivity of MRI was 91% and specificity was 88%. Results of this study 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...
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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.

Section Summary
The available evidence suggests that 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 of 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.

MRI to Detect Low-Suspicion Findings on Conventional Testing That Are Not Indicated for Immediate Biopsy
Evidence on low-suspicion findings is based on a 2004 TEC Assessment. 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.

Section Summary
A TEC Assessment found insufficient evidence on the use of MRI to diagnose low-suspicion findings on conventional testing that are not indicated for immediate biopsy. Well-designed prospective confirmatory studies would be necessary to permit conclusions on the effect this adjunctive use of breast MRI has on health outcomes.

Diagnostic Uses
MRI to Further Characterize Suspicious Breast Lesions
Evidence on further characterization based on TEC Assessments from 2000, 2001, and 2004. Studies addressed a group of patients who have breast lesions of sufficient suspicion to warrant recommendation to undergo biopsy for diagnosis. Therefore, MRI results are assumed to have an impact on the decision whether to undergo definitive biopsy, considered the criterion standard.

Available evidence did not show that 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. The TEC Assessment concluded that potential benefits of sparing a fraction of patients from unnecessary biopsy does not outweigh potential harms considering the current level of diagnostic performance of breast MRI.
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A fairly large study by Bluemke et al (2004) addressing this patient population was released after the 2004 TEC Assessment but did not change conclusions. Based on MRI results from 821 patients, sensitivity was 88.1% and specificity was 67.7%.

A systematic review published in 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 pooled negative likelihood ratio was 0.12 (95% CI, 0.09 to 0.15). For breast cancer or high-risk lesions versus benign lesions, the area under the curve (AUC) for MRI was 0.91.

Two single-institution, prospective cohort studies examined the diagnostic accuracy of breast MRI for lesions identified on mammography or ultrasound. Strobel et al (2015) in Germany included lesions characterized as Breast Imaging Reporting and Data System (BI-RADS) 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 BI-RADS categories 1, 2, or 3 on MRI were followed-up with imaging for 18 months, except for pure clustered microcalcifications (without accompanying mass), which was biopsied or was followed-up 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. PPV of MRI was 73% compared with 19% for conventional imaging. 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 BI-RADS 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). Incidence of malignancy including DCIS was 46%. PPV of MRI was 87% compared with 60% for mammography. NPV of MRI was 91%.

**Section Summary: MRI to Further Characterize 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 NPV is sufficient to preclude the need for biopsy. Although 2 recent studies 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.
MRI as a Preoperative Mapping Technique to Identify Multicentric Disease With Clinically Localized Breast Cancer

Evidence on preoperative mapping was based on a 2004 TEC Assessment. 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. As a result of these findings, there was controversy regarding the use of MRI preoperatively for patients diagnosed with breast cancer. Although these studies were not sufficient to determine the effect on health outcomes, they suggested a mechanism by which outcomes may be improved. If additional disease is detected, then the use of MRI may lead to improved surgical decision making and a reduction in re-excisions due to foci of malignancy missed at the initial evaluation.

A 2008 meta-analysis of 19 observational studies (total N=2610 patients) reported quantitative estimates of incremental findings on MRI and incidences of resulting changes in clinical management. Median prevalence of additional ipsilateral cancer foci detected by preoperative MRI was 16% (interquartile range [IQR], 11%-24%). Conversion from BCT to mastectomy occurred in 8.1% (95% CI, 5.9% to 11.3%) of patients, and change to a more extensive local surgery occurred in 11.3% (95% CI, 6.8% to 18.3%). Of additional mastectomies, 1.1% may have been clinically inappropriate, as judged by lack of extensive disease on histopathology. The rate of possibly inappropriate change to a wider local excision was estimated to be 5.5%.

In 2012, Plana et al published systematic review and meta-analysis of 50 publications reporting on 10,811 women. In this analysis, additional disease was detected in the ipsilateral breast in 20% of women and in the contralateral breast in 6%. Of the additional lesions detected, approximately two-thirds were malignant and one-third were benign by final histopathology, for a PPV of 66%. Based on MRI findings, 8% of women were appropriately referred for mastectomy rather than BCT, and 2% were inappropriately referred for mastectomy.

A 2013 meta-analysis included 2 RCTs and 7 studies that compared preoperative MRI with standard preoperative assessment in 3738 women with newly diagnosed breast cancer. Results were reported separately for 6 studies that included patients with breast cancers of any type (n=3112) and 3 studies that included patients with invasive lobular histology only (n=626). The proportion of patients who had mastectomy was significantly greater in preoperative MRI groups, both for patients with any type of breast cancer (26% vs 18%; adjusted odds ratio [OR], 1.51; 95% CI, 1.21 to 1.89; p<0.001) and for patients with invasive lobular cancer only (43% vs 40%; adjusted OR=1.64; 95% CI, 1.04 to 2.59; p=0.034). This increase was due to increased initial mastectomy because the odds of conversion from BCS to mastectomy did not differ significantly between MRI and no-MRI groups. Similarly, the odds of having re-excision surgery after initial BCS did not differ statistically between groups, both for patients with any type of breast cancer and for those with invasive lobular cancer only. Statistical measures of between-study heterogeneity were not reported. In unadjusted analysis, the odds of re-excision surgery after initial BCS were significantly greater in patients with invasive lobular cancer who did not have preoperative MRI (11% vs 18%);
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unadjusted OR=0.56; 95% CI, 0.33 to 0.95; p=0.031); however, because the odds ratio was not statistically significant in adjusted analysis, this result is not considered definitive.

A 2016 study by Parvaiz et al evaluated change in surgical planning after MRI in 72 patients newly diagnosed with lobular carcinoma, and had relatively long-term findings. The study focused on patients offered BCS only if the MRI confirmed the presence of unifocal small cancers seen on mammography and ultrasound. Patients whose intention before MRI was to undergo mastectomy were excluded from the study. Nineteen (26%) of 72 patients had a change in proposed intervention based on MRI findings. This included 7 women with identified multifocal disease and 10 women with larger lesions than found on other imaging studies. The other 2 patients were found on MRI to have contralateral breast cancer needing bilateral intervention. After MRI, management of these 19 patients changed from simple BCS to mastectomy in 15, double wire-guided BCS in 1, therapeutic mammoplasty in 1, and bilateral surgery in 2. Over a median follow-up of 44 months, the 72 patients had a 95.8% disease-free survival rate and a 98.6% overall survival rate. This study lacked a comparison group of patients who did not have MRI.

Reoperation Rates
Several RCTs evaluated the short-term benefit of preoperative MRI in women with localized breast cancer. A multicenter RCT from the U.K. (COMICE trial) examined the impact of presurgical MRI on the need for additional treatment within 6 months.38 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 quality of life between the 2 groups.

This RCT and 3 other comparative studies were included in a 2014 meta-analysis of individual patient data (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 (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.

A second RCT, the MONET trial, was published by Peters et al in 2011. This study randomized 463 patients with suspicious, nonpalpable breast lesions identified on 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=NS), as was the incidence of BCS (68% vs 66%). The incidence of re-excisions due to positive tumor margins was unexpectedly greater in the MRI group (34%) compared with the control group (12%; p=0.008).
In a 2014 RCT by Gonzalez et al in Sweden, 440 women 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). Ipsilateral reoperation rate was 5% in the MRI group versus 15% in the control group (p<0.001). Reoperation rates among those initially planned for BCS were 5% and 22%, respectively (p<0.001).

In addition to the RCTs, 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**

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. Detection of additional disease can lead to changes in surgical treatment, most importantly a change from BCS to mastectomy. Because of the high false-positive rate, current recommendations state that a biopsy of MRI-identified lesions should be undertaken before a decision on the type of surgery is made, to reduce the number of inappropriate mastectomies. If conversions to mastectomy are appropriate based on extent of disease, then patients in the MRI group would be expected to show lower rates of local recurrence and reoperations. Two RCTs evaluated short-term outcomes of a preoperative MRI versus no MRI and did not show lower short-term reoperation rates in the MRI group. A third RCT Sweden did find a reduction in reoperation rate with preoperative MRI. Further intermediate-to long-term studies are needed to determine whether outcomes are improved by preoperative MRI scanning. A large study of over 20,000 cases found that preoperative breast MRI was associated with lower odds of reoperation in patients with invasive lobular carcinoma, but not with other histologic types.

**MRI to Guide Surgical Decisions After Neoadjuvant Chemotherapy**

Evidence on guiding surgical decisions is based on a 2004 TEC Assessment 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 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 of 0.72 to 0.98; however, MRI is not intended as a replacement for histopathologic assessment.

Several systematic reviews were published after the 2004 TEC Assessment. Most recently, in 2015, Marinovich et al 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) 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% confidence interval was wider (-0.3 to 0.4 cm). In 5 studies (n=123) 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) comparing clinical examination and pathology (pooled MD = -0.8 cm; 95% CI, -1.5 to -0.1 cm).

Previously, Lobbes et al (2013) reported 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 1, 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
Studies, including a 2015 meta-analysis, found that MRI results were 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 versus mastectomy after neoadjuvant chemotherapy would be at least as beneficial and may lead more frequently to appropriate surgical treatment.

MRI to Evaluate Response to Neoadjuvant Chemotherapy With Locally Advanced Breast Cancer
Evidence for this question is based on a 2004 TEC Assessment, subsequent studies, and an ACRIN trial. 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.

The ACRIN 6657/I-SPY trial 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. MRIs were 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 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 (AUC ROC) of 0.09; corresponding AUC ROC values after the third and fourth MRIs were 0.07 and 0.05. Similar
findings were reported for predicting pathologic complete response (pCR). However, implications of these findings for treatment and outcomes are uncertain and were not addressed in this study.

The 2004 TEC Assessment reported a total of 6 studies (total N=206 patients) that performed breast MRI during the course of chemotherapy. MRI outcomes for response to chemotherapy were based on either 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.

A 2005 study examined whether MRI measurements of tumor volume and diameter predicted response to neoadjuvant chemotherapy and recurrence-free survival (RFS), but results did not change the conclusions reached in the 2004 Assessment. The authors found that initial (prechemotherapy) and final volumes were the strongest predictors of RFS. Early changes in MRI volume or diameter only showed a trend of association (p=0.7 or 0.8) with RFS. However, of 62 enrolled patients, only 32 (52%) were included in the analysis of early response. Several other studies on the ability of MRI to gauge response to neoadjuvant chemotherapy did not include MRIs during chemotherapy, when changes in therapy might be considered.

A 2011 study of 188 women who underwent MRI scans before and during neoadjuvant chemotherapy compared the ability of MRI to detect response to treatment by breast cancer subtype. The authors concluded that change in the largest diameter of enhancement on MRI was associated with tumor response among patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors but not among patients with more common estrogen receptor-positive/HER2-negative tumors.

Marinovich et al (2012) reviewed the literature on this topic to February 2011. Thirteen studies were included. They were heterogeneous in MRI parameters used, thresholds for identifying response, and definitions of pathologic response. The authors could not reach definitive conclusions because of limitations in study design and data reporting. This group conducted a subsequent systematic review with meta-analysis in 2013. Literature was searched to February 2011, and 44 studies (total N=2949 patients) assessing the ability of MRI to discriminate residual breast tumor after neoadjuvant chemotherapy from pCR were identified. 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 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 equal to or less than normal breast tissue) was used rather than an absolute threshold (complete absence of MRI enhancement) with little decrement to sensitivity. Pooled AUC ROC was 0.88, and 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% confidence intervals for pooled analyses were very large, rendering conclusions uncertain.

In the 2013 systematic review by Lobbes et al (just discussed), 8 studies reported measures of diagnostic accuracy. Median sensitivity, defined as the proportion of patients with pCR correctly classified by MRI, was
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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.

De Los Santos et al (2013) conducted a retrospective review of 746 women who received neoadjuvant chemotherapy and preoperative MRI. Incidence of pCR was 24%. Sensitivity, specificity, PPV, and NPV of MRI for detecting pCR were 83%, 47%, 47%, and 83%, respectively. Accuracy, defined as the correct proportion of all MRI results (true positive plus true negative, divided by the number of MRI scans performed), was 80%.

In a retrospective review of patients with HER2-negative breast cancer, Charehbili et al (2014) assessed diagnostic accuracy of contrast-enhanced MRI for detecting pathologic response to neoadjuvant chemotherapy. All patients had participated in an RCT that evaluated neoadjuvant chemotherapy (docetaxel, adriamycin, and cyclophosphamide [TAC]) with and without zoledronic acid. Of 250 randomized patients, 194 (78%) were included in the diagnostic accuracy study. Incidence of pCR was 21%. At the completion of neoadjuvant chemotherapy (6 cycles), AUC was 0.63 (95% CI, 0.52 to 0.74), and sensitivity, specificity, PPV, and NPV were 43%, 84%, 37%, and 87%, respectively. Accuracy for pCR was 76%.

Section Summary
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 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.

MRI to Diagnose 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 reported on 4 cases in which MRI was able to determine involvement of the chest wall with 100% accuracy.

Section Summary
Given the high level of diagnostic accuracy for MRI compared with criterion standard and conventional alternative techniques, the evidence is considered sufficient to conclude that breast MRI improves net health outcome.
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**MRI to Evaluate Residual Tumor After Lumpectomy With Positive Surgical Margins**
Evidence on evaluating residual tumor comprises several observational studies, most of which are retrospective. Seven studies evaluated the diagnostic performance of MRI to detect residual disease after previous biopsy or lumpectomy. Histopathologic examination on re-excision was used as the criterion standard. Most studies, including 1 prospective study, reported poor sensitivity and specificity of MRI for detection of residual disease. Two studies reporting more favorable results had methodologic issues that limited the influence of reported results. Three studies were conducted at the same institution and accrued patients during similar time periods, so overlap reporting may exist.

Lee et al (2004) prospectively studied 80 patients eligible for BCT who had close or positive margins on lumpectomy and were scheduled for re-excision lumpectomy. In this study, MRI was 61% sensitive and 70% specific for detection of residual tumor. The finding of extensive tumor on MRI led to mastectomy in 6 (7.5%) patients, but it is difficult to determine from the publication what proportion of these cases had false-positive MRI results. Bedrosian et al (2003) retrospectively studied 70 patients before re-excision and found that MRI had 57% sensitivity and 60% specificity. MRI prompted wider than initially planned surgical excision in 11 cases, 10 (91%) of which turned out to be false-positive MRI results. Kawashima et al (2001) studied 50 patients and reported 66% sensitivity and 81% specificity. Orel et al (1997) included 47 patients with questionable or positive margins after biopsy and found that MRI had 54% sensitivity and 62% specificity for residual tumor at the biopsy site. Similarly, sensitivity and specificity were low for identification of residual tumor anywhere in the breast (64% and 58%, respectively). Weinstein et al (2001) reviewed 14 cases of invasive lobular carcinoma that had prior excisional biopsy and found that MRI had 57% sensitivity and 0% specificity for identifying residual disease.

Frei et al (2000) retrospectively studied 68 patients with positive margins and examined the relationship between when MRI was performed after initial surgery and diagnostic performance of MRI for residual disease. This study excluded 3 patients with technically inadequate MRI studies and had publication discrepancies in reported results. Sensitivity of MRI ranged from 89% to 95%, with slight improvements noted with longer time intervals after initial surgery. Specificity was initially 52% for MRI performed at least 7 days after lumpectomy; when analysis was restricted to MRI conducted at least 28 days after lumpectomy, the specificity of MRI increased to 75%. Soderstrom et al (1997) retrospectively examined 19 patients with various indications for MRI, including 11 patients with close or positive margins after surgery, and found MRI was 100% sensitive and 71% specific for identification of residual tumor. The authors noted that MRI overestimated the extent of tumor in 1 patient who was counted as a true positive.

**Section Summary**
Available evidence is not sufficient to permit conclusions whether MRI improves net health outcomes when used to identify the presence and/or extent of residual disease after lumpectomy and before re-excision.

**MRI to Evaluate the Lesion 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.
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
Although the evidence base addressing this use is mainly anecdotal, the rationale supporting use of MRI 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Promoting Breast Cancer Screening in Women Who Survived Childhood Cancer</td>
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<td>Jul 2017</td>
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<td>A Study to Evaluate the Use of Supine MRI Images in Breast Conserving Surgery</td>
<td>136</td>
<td>Nov 2017</td>
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<td>NCT02244593</td>
<td>FAST MRI Study in Breast Cancer Survivors</td>
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<td>NCT01805076</td>
<td>MRI and Mammography Before Surgery in Patients With Stage I-II Breast Cancer</td>
<td>536</td>
<td>Sep 2019</td>
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</table>

NCT: national clinical trial.

For individuals who are asymptomatic with high risk of breast cancer who receive MRI to screen for breast cancer, the evidence includes a systematic review (TEC Assessment) and subsequent 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.
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For individuals who are asymptomatic with average risk of breast cancer who receive MRI to screen for breast cancer, the evidence includes a systematic review. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The recent systematic review did not identify any RCTs or nonrandomized comparative studies evaluating MRI for screening average-risk women. Moreover, 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 accuracy of mammography (eg, dense breasts) who receive MRI to screen for breast cancer, the evidence includes a systematic review (TEC Assessment) and subsequent diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. There is a lack of prospective studies on the diagnostic accuracy of MRI versus mammography in patients who have had BCT. There are several studies of MRI in women with dense breasts, but, in these studies, women also had suspected breast cancer or other breast cancer risk factors. Evidence is lacking on MRI screening of women with breast characteristics limiting the sensitivity of mammography, but who are not otherwise at high risk of breast cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected occult breast primary tumor with axillary nodal adenocarcinoma with negative mammography who receive MRI to detect breast cancer, the evidence includes a systematic review (TEC Assessment) and subsequent 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 BCS rather than presumptive mastectomy allowed a substantial portion of patients to avoid the morbidity of mastectomy. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have breast cancer who receive 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 as a result of these findings, which 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. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have low-suspicion findings on conventional breast detection tests who receive MRI to detect breast cancer, the evidence includes a systematic review (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. The evidence is insufficient to determine the effects of the technology on health outcomes.
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For individuals who have suspicious breast lesions who receive MRI to further characterize lesions, the evidence includes a systematic review (TEC Assessment) and subsequent 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 NPV is sufficient to preclude the need for biopsy. Although 2 recent studies have reported NPVs 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.

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. Detection of additional disease can lead to changes in surgical treatment, most importantly a change from BCS to mastectomy. Because of the high false-positive rate, current recommendations state that a biopsy of MRI-identified lesions should be undertaken before a decision on the type of surgery is made, to reduce the number of inappropriate mastectomies. If conversions to mastectomy are appropriate based on extent of disease, then patients in the MRI group would be expected to showed lower rates of local recurrence and reoperations. Study results were mixed, but some studies suggest a lower reoperation rate in patients with preoperative MRI scanning. The evidence is sufficient to determine qualitatively 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 and meta-analysis found that MRI results were well-correlated with pathologic assessment for measuring residual tumor size after neoadjuvant chemotherapy. The 2015 meta-analysis also found that MRI performed better than conventional methods. Using breast MRI instead of conventional methods to guide surgical decisions on BCT versus mastectomy after neoadjuvant chemotherapy would be at least as beneficial and may lead more frequently to appropriate surgical treatment. The evidence is sufficient to determine qualitatively 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
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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 (eg, 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 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 available, but MRI was 100% accurate for identifying chest wall involvement compared with the criterion standard. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have positive surgical margins after breast lumpectomy 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, generally reported poor sensitivity and specificity with MRI for detection of residual disease compared to the criterion standard. The studies with the most favorable findings had methodologic issues that limited the influence of reported results. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a suspicious breast lesion recommended for biopsy but not localizable by imaging tests who receive MRI to evaluate 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 in 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 in this situation where other good options are not available. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

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17. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). 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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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
06/28/2004  Managed Care Advisory Council approval
10/05/2004  Medical Director review
11/29/2004  Managed Care Advisory Council approval
10/05/2005  Medical Director review
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:
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- 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
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

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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:  12/17/2016

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
Next Scheduled Review Date:  11/2017

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<tr>
<td>CPT</td>
<td>0159T, 77058, 77059</td>
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<td>ICD-10 Diagnosis</td>
<td>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, C50.811-C50.829, 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</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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:

1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
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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.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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