



Louisiana

Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy # 00084

Original Effective Date: 03/25/2002

Current Effective Date: 01/02/2018

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

- Screening for breast cancer in high risk patients The following list includes individual risk factors known to indicate a high risk of breast cancer by themselves:
 - Lobular carcinoma in situ
 - Any other known BRCA1 or BRCA2 variant
 - Any other gene variant 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 $\geq 20\%$) 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 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

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Treatment-Related Uses

- Preoperative tumor mapping of the involved (ipsilateral) breast to evaluate the presence of multi-centric 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)

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

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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. There are validated risk prediction models, but they are based primarily on family history.

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, 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>).

National Comprehensive Cancer Network guidelines state there is insufficient evidence for any recommendations for breast MRI for patients with the following variants: *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 (NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast and ovarian. v.2.2017).

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.

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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.

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- Diagnosis of low-suspicion findings on conventional testing not indicated for immediate biopsy but referred for short-interval follow-up

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 (eg, 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 (ie, 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

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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

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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. Specifically, does the use of MRI improve 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.

Technical Reliability

The technical reliability of MRI devices is well-accepted.

Clinical Validity and Clinical Utility

Screening Individuals at High Risk of 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 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%. Further, abstracts in both studies revealed findings consistent with superior sensitivity of MRI and either equivalent or slightly inferior specificity.

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 (2014) 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* variants (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 of the two appeared 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 vs younger women was 89% (95% confidence interval [CI], 84% to 92%) vs 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 on 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 ductal carcinoma in situ (DCIS). Of those, 167 (87%) had undergone both imaging tests preoperatively; 93 (56%) of these cases were diagnosed by mammography and 153

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(92%) by MRI ($p < 0.001$). Of 89 high-grade DCIS lesions, 43 (48%) were missed by mammography but detected by MRI; 2 (2%) lesions were missed by MRI but detected by mammography. MRI was significantly more sensitive than mammography in detecting high- (98% vs 52%, $p < 0.001$) and intermediate-grade (91% vs 59%, $p = 0.013$) DCIS, but not for detecting low-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 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: 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

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 adjunctive 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 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.

In 2016, Health Quality Ontario published a systematic review on MRI as an adjunct to mammography for women who are 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

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met eligibility criteria. They concluded that there is 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.

Section Summary: Screening of Individuals at Average Risk of Breast Cancer

There is a lack of evidence on MRI screening for average-risk women; systematic reviews did not identify any RCTs or nonrandomized comparative studies. Moreover, 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

Evidence for individuals with limited sensitivity of 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 adjunctive MRI. However, additional prospective studies are needed to confirm this and to identify patient subsets most likely to benefit from adjunctive MRI evaluation given the relatively low incidence of recurrence.

Discussion continues on the possible use of adjunctive 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.

Section Summary: Screening When Breast Characteristics Limit the Sensitivity of Mammography

There is a lack of prospective studies on the diagnostic accuracy of MRI vs mammography in patients who have had BCT. For women who are not otherwise at high risk of breast cancer but have breast characteristics that limit the sensitivity of mammography, the evidence on MRI screening is lacking.

DETECTION 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 detect breast cancer in the ipsilateral or contralateral breast improves the net health outcome compared with standard techniques. Specifically, does MRI improve the diagnostic accuracy beyond standard evaluation

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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 comparators of interest are mammography and clinical assessment.

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.

Timing

MRI would be performed after a positive breast cancer screening or diagnostic examination.

Setting

The test would be performed in an imaging setting.

Technical Reliability

The technical reliability of MRI devices is well-accepted.

Clinical Validity and Clinical Utility

Detecting 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

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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: 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

In 2007, Lehman et al reported on 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.

Lieberman 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.

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

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.

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Louisiana

Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy # 00084

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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 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

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 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.

A fairly large study by Bluemke et al (2004) addressing this patient population with suspicious breast lesions 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%.

In a 2009 retrospective study, MRI accuracy was evaluated in patients who had dense breasts and suspected breast cancer or inconclusive evaluations from other modalities. 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. Sensitivity and specificity were 98% and 95%, respectively, for MRI; 73% and 45%, respectively, for mammography; and 86% and 41%, respectively, for ultrasound. 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.

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 vs benign lesions, the area under the curve (AUC) for MRI was 0.91.

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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: 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 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

Clinical Context and Test Purpose

The question addressed in this portion of the evidence review is whether use of MRI evaluation as an adjunct to guide treatment planning (eg, surgical approach) for patients with known or suspected breast cancer improves the net health outcome compared with standard techniques. Specifically, does 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.

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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 relevant comparators of interest are mammography, clinical assessment, and/or pathologic inspection.

Outcomes

The relevant outcomes of interest for diagnostic accuracy include test accuracy and test validity (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility include avoidance of invasive procedures (eg, 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

The test would be performed in an outpatient imaging setting.

Technical Reliability

The technical reliability of MRI devices is well-accepted.

Clinical Validity and Clinical Utility

Preoperative Mapping 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.

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

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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 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 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 2014 meta-analysis, published by Houssami et al in 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.

Reoperation Rates

A description of the 3 RCTs included in the 2017 Houssami meta-analysis (described above) is as follows.

A 2010 multicenter RCT from the U.K. (COMICE trial) 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 quality of life between groups.

A second RCT, the MONET trial, was published by Peters et al in 2011. It 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

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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%) 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 vs 15% in the control group ($p<0.001$). Reoperation rates among those initially planned for BCS were 5% and 22%, respectively ($p<0.001$).

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: 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 mastectomy after preoperative MRI vs no MRI in women with breast cancer. Follow-up studies reported mixed results, including no significant reduction in reoperations rates after MRI while other studies 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, there might have been insufficient power in the available data to detect differences in the overall population and further studies may help determine if particular subgroups derive greater benefit.

Guiding 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 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

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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 have been 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 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, 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 Response to Neoadjuvant Chemotherapy With Locally Advanced Breast Cancer

Evidence on the use of MRI to assess response to chemotherapy 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 (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. 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

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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 (AUROC) of 0.09; corresponding AUROC 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 trial.

The 2004 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 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, 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 recurrence-free survival. Early changes in MRI volume or diameter only showed a trend of association ($p=0.7$ or 0.8) with recurrence-free survival. 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 with 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. Reviewers 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

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enhancement) with little decrement to sensitivity. Pooled AUROC 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% CIs for pooled analyses were very large, rendering conclusions uncertain.

In the 2013 systematic review by Lobbes et al, 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.

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), area under the curve 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: 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 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

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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: Evaluating Suspected Chest Wall Involvement

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.

Evaluating Residual Tumor After Lumpectomy or Breast Conservation Surgery

Evidence on evaluating residual tumor comprises several observational studies, most of which were retrospective. Histopathologic examination on re-excision was used as the criterion standard. Most studies reported poor sensitivity and specificity of MRI for detection of residual disease. 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.

Two studies, published in or before 2000, that reported more favorable results had methodologic issues limiting the influence of reported results. Frei et al (2000) retrospectively studied 68 patients with positive margins and examined the relation 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

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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. In 2017, Krammer et al 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 ($\kappa=0.56$).

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

Available evidence is not sufficient to permit conclusions whether 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 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.

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.

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 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

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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 a systematic review. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. The systematic review did not identify any randomized control trials 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 as an adjunct 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 vs mammography in patients who have had breast-conserving therapy. For women who are not at high risk of breast cancer but whose breast characteristics might limit the sensitivity of mammography, the evidence on MRI screening is lacking. 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 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 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.

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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 (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 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 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 randomized controlled trials, 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 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 breast-conserving therapy vs mastectomy after neoadjuvant chemotherapy

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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 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 (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 identified, but MRI was 100% accurate for 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 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, generally reported poor sensitivity and specificity with MRI for detection of residual disease compared with 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 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 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 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.

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Policy History

Original Effective Date:	03/25/2002
Current Effective Date:	01/02/2018
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.
10/27/2005	Quality Care Advisory Council approval

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Louisiana

Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Policy # 00084

Original Effective Date: 03/25/2002

Current Effective Date: 01/02/2018

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: <ul style="list-style-type: none">• 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
12/16/2009	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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

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	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
11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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
11/15/2017	Medical Policy Implementation Committee approval. "Breast conservation surgery" added to policy statement on evaluation of residual tumor.
Next Scheduled Review Date:	11/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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

Code Type	Code
CPT	0159T, 77058, 77059
HCPCS	C8903, C8904, 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 C50.811-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

*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);
 - 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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