6.01.29	Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer		
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Section:	6.0 Radiology	**Page:**	Page 1 of 44

Policy Statement

MRI for Screening Uses

MRI of the breast may be considered **medically necessary** for breast cancer screening in patients with **any** of the following conditions*:

- Lobular carcinoma in situ
- A known *BRCA1* or *BRCA2* variant
- High risk of BRCA1 or BRCA2 variant due to a known presence of the variant in relatives
- Another gene variant associated with high risk, e.g., *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, and *STK11, ATM, CHEK2*, and *PALB2* or who have a first-degree relative with one of these syndromes
- High risk (lifetime risk about greater than or equal to 20% or 5-year risk of greater than or equal to 3%) 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

*(National Cancer Care Network [NCCN], https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf)

MRI for Detection Uses

MRI of the breast may be considered **medically necessary** for detection of a suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma (i.e., negative mammography and physical exam).

MRI of the breast may be considered **medically necessary** in patients with a new diagnosis of breast cancer to evaluate the contralateral breast when clinical and mammographic findings are normal.

MRI for Treatment-Related Uses

MRI of the breast may be considered **medically necessary** for **any** of the following indications:

- 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 (see Policy Guidelines section)
- Presurgical 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

MRI of the breast is considered **investigational** for **all** of the following indications:

- As a screening technique in average-risk patients
- As a screening technique for the detection of breast cancer when the sensitivity of mammography (i.e., mammography using low-dose x-rays for imaging) is limited (i.e., dense breasts, breast implants, scarring after breast cancer treatment)
- For the diagnosis of low-suspicion findings on conventional testing not indicated for immediate biopsy and referred for short-interval follow-up
- For the 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 the evaluation of residual tumor in patients with positive margins after initial lumpectomy or breast conservation surgery

Policy Guidelines

High-Risk Considerations
There is no standardized method for determining a woman's risk of breast cancer that incorporates all possible risk factors. Clinical practice guidelines offer guidance on factors known to individually indicate a high risk of breast cancer (see the Supplemental Information section).

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

General
A first-degree relative is defined as the parents, brothers, sisters, or children of an individual.

Considerations for Performing Magnetic Resonance Imaging
Breast magnetic resonance imaging (MRI) exams should be performed and interpreted by an expert breast imaging team working with the multidisciplinary oncology treatment team.

Breast MRI exams require a dedicated breast coil and the use of contrast agents 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. Since these are standard, documentation is not needed for approval (unless something unusual is noted that is of concern). CPT codes 77048 (unilateral) or 77049 (bilateral) would be used for cancer detection.

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.

Consideration of *BRCA1* and *BRCA2* gene mutation testing should be given for women who have a family history suspected of having the BRCA1 or BRCA2 mutation, which has not been identified. (For further reference see Blue Shield of California Medical Policy: Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome [BRCA1 or BRCA2]).

Risk Assessment Tools
If a risk assessment model value is not documented; Blue Shield of California (BSC) will use the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool[73] available at: *https://bcrisktool.cancer.gov/.

A number of risk assessment tools based mainly on family history can assist practitioners in estimating breast cancer risk and include the Claus (1), modified Gail (2), Tyrer-Cuzick (3), and BRCAPRO (4) models.

***Note**: The tool should not be used to calculate breast cancer risk for women who have already had a diagnosis of breast cancer, lobular carcinoma in situ (LCIS), or ductal carcinoma in situ (DCIS).*

The member information required to calculate risk of breast cancer includes:

- Age
- Age at time of first menstrual period
- Age at time of her first live birth
- First degree relatives with a history of breast cancer
- History and number of breast biopsies performed
- Diagnosis of atypical hyperplasia with at least one breast biopsy
- Ethnicity/Race

The Breast Imaging Reporting and Data System (BI-RADS) Classification
The Breast Imaging Reporting and Data System (BI-RADS) provides a standardized classification system for mammograms[74]:

BI-RADS Category	Assessment	Clinical Management Recommendation(s)
0	Incomplete	Additional imaging evaluation needed before final assessment
1	Negative	No lesion found (routine follow-up)
2	Benign finding	No malignant features; e.g. cyst (routine follow-up for age, clinical management)
3	Probably benign finding	Malignancy is highly unlikely, e.g. fibroadenoma (initial short interval follow-up)
4	Suspicious abnormality	Low to moderate probability of cancer, biopsy should be considered
5	Highly suggestive of malignancy	Almost certainly cancer, appropriate action should be taken
6	Known cancer	Biopsy proven malignancy, prior to institution of therapy

Coding
Effective January 1, 2019, the following CPT codes describing magnetic resonance imaging of the breast **replaced codes 77058 and 77059**:

- **77046**: Magnetic resonance imaging, breast, without contrast material; unilateral
- **77047**: Magnetic resonance imaging, breast, without contrast material; bilateral
- **77048**: Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; unilateral
- **77049**: Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; bilateral

Description

Magnetic resonance imaging (MRI) of the breast is performed using scanners and intravenous imaging contrast agents in combination with specialized breast coils. This evidence review only addresses the use of breast MRI for clinical indications related to detection or diagnosis of breast cancer.

Note: This policy only addresses the use of breast MRI for clinical indications related to detection, and diagnosis of breast cancer. The use of MRI to monitor silicone gel-filled breast implants for leaks or ruptures, which may be done without contrast enhancement, is addressed

in Blue Shield of California Medical Policy: Magnetic Resonance Imaging to Monitor the Integrity of Silicone-Gel-Filled Breast Implants.

Related Policies

- Computer-Aided Evaluation of Malignancy with Magnetic Resonance Imaging of the Breast
- Digital Breast Tomosynthesis
- Magnetic Resonance Imaging to Monitor the Integrity of Silicone Gel-Filled Breast Implants

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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) and magnetic resonance–compatible equipment for performing biopsy have been developed and cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. The Food and Drug Administration determined that these devices are substantially equivalent to predicate devices for use "in conjunction with a magnetic resonance imager (MRI) to produce diagnostic and interventional images of the breast, chest wall and axillary tissues that can be interpreted by a trained physician."[1]

Rationale

Background

Magnetic Resonance Imaging

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 as an additional imaging test alone, or in combination with other imaging modalities. Each potential use 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 is an example of how to detect suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma and negative mammography and clinical breast exam:

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

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

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

The following are examples of how to detect breast cancer in the case of:

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

Treatment-Related Uses

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

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

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

Literature Review

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

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

Screening Uses

Clinical Context and Test Purpose

The question addressed in this portion of the evidence review is whether the use of magnetic resonance imaging (MRI) as an adjunct to screen for breast cancer improves the net health outcome compared with standard mammographic techniques.

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

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

Patients

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

Interventions

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

Comparators

The following test is currently being used to make decisions about managing breast cancer: mammography alone.

Outcomes

The outcomes of interest for diagnostic accuracy include test accuracy and test validity (i.e., 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 (e.g., need for additional testing or procedures).

Timing

MRI would be performed as an adjunct to routine screening; timing can be guided by national guidelines on breast cancer screening.

Setting

Breast MRI is administered in an outpatient imaging setting.

Study Selection Criteria

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

Technically Reliable

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

Screening Individuals at High Risk of Breast Cancer

Clinically Valid

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

Systematic Reviews

The original evidence review was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2003).[2] 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.[3,4] In both studies, MRI detected 100% of cancer cases; mammography detected 33%.

Three systematic reviews identified have included women at high risk of developing breast cancer. Warner et al (2008) review included 11 studies published through 2008.[5] Two reviews by Phi et al (2015, 2017) reported 2 individual patient data meta-analyses from the same 6 studies published between 2010 and 2013.[6,7] Phi et al (2015) included the women with *BRCA1* or *BRCA2* variants and Phi et al (2017) included the women with a strong family history of breast without a known variant. Characteristics of the systematic reviews are shown in Table 1.

Table 1. Characteristics of Systematic Reviews Assessing MRI Screening in High-Risk Women

Study	Dates	Studies	Participants	N (Range)	Design	Reference Standard
Phi et al (2017)[7]	2010-2013	6	Women with a family history of breast cancer without a known genetic variant	2226	Prospective	Biopsy-confirmed cancer for positive; at least 1 y follow-up for negative
Phi et al (2015)[6]	2010-2013	6	Women with *BRCA1* or *BRCA2* variants	2033	Prospective	Biopsy-confirmed cancer for positive; at least 1 y follow-up for negative
Warner et al (2008)[5]	1995-2008	11	Women at very high risk of breast cancer (*BRCA1* or *BRCA2* or other variants or a family history consistent with hereditary breast cancer)	4983 (41-1909)	Prospective	Biopsy-confirmed cancer

MRI: magnetic resonance imaging.

Results of the systematic reviews are shown in Table 2. The reviews concluded that screening breast MRI is more sensitive but less specific than mammography for the detection of invasive cancers in high-risk women. The sensitivity of combined MRI and mammography was approximately 93% or higher in the reviews while the sensitivity of mammography alone was between approximately 40% and 55%. The Warner (2008) review did not present a risk of bias or quality assessment of included studies. Phi (2015) assessed quality using the QUADAS-2 tool. All included studies were considered good quality.

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

Study	MRI		Mammogram		MRI Plus Mammogram	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Phi et al (2017)[7]						
Total N	2226	2226	2226	2226	2226	2226
PE (95% CI)	89 (76 to 96)	83 (77 to 88)	55 (41 to 69)	94 (90 to 96)	98 (86 to 100)	79 (73 to 84)
Phi et al (2015)[6]						
Total N	1951	1951	1951	1951	1951	1951
PE (95% CI)	85 (69 to 94)	85 (79 to 89)	40 (30 to 50)	94 (89 to 97)	93 (80 to 98)	80 (73 to 86)
Warner et al (2008)[5]						

Study	MRI		Mammogram		MRI Plus Mammogram	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Total N	15576	15576	15496	15496	6781	6781
PE (95% CI)	77 (70 to 84)	86 (81 to 92)	39 (37 to 41)	95 (93 to 97)	94 (90 to 97)	77 (75 to 80)

CI: confidence interval; MRI: magnetic resonance imaging; PE: pooled estimate.

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

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

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

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

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

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

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

Systematic Reviews
In a systematic review of literature conducted by Nelson et al (2016) for the U.S. Preventive Services Task Force breast cancer screening recommendation update, no RCTs or nonrandomized observational studies identified evaluated adjunctive MRI for screening average-risk women for breast cancer.[8] 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.

Health Quality Ontario (2016) published a systematic review of MRI as an adjunct to mammography for women not at high risk of breast cancer.[9] 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 (e.g., mortality, health-related quality of life, screening-related harms) and diagnostic outcomes (e.g., sensitivity, specificity), and biopsy and recall rates. Reviewers did not find any studies that met eligibility criteria. They concluded that there was a lack of evidence to inform the questions of the diagnostic accuracy of MRI plus mammography vs MRI alone and the impact of adjunct screening MRI on health outcomes in patients at less than high risk of breast cancer.

Observational Studies

One comparative observational study was published following the preceding systematic reviews. Kuhl et al (2017) reported results of a prospective study of supplemental MRI screening in addition to screening mammography with or without screening ultrasonography in women at average risk of breast cancer.[10] Characteristics of the study are shown in Table 3.

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

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Tests	Blinding of Assessors
Kuhl et al (2017)[10]	Women 40-70 y without breast cancer–associated risk factors (lifetime risk <15%) evaluated in Germany between 2005 and 2013	Prospective	• Pathology for positive finding • 2-y FU for negative finding	Read by 9 breast radiologists with 5-18 y of experience; BIRADS category 4 or 5 referred for biopsy	Imaging completed within 4 wk of each other	Yes

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

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

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

Study	Initial N	Final N	Excluded Samples	Prevalence of Condition	Clinical Validity (95% Confidence Interval), %			
					Sensitivity	Specificity	PPV	NPV
Kuhl et al (2017)[10]	2181	2120	Excluded if insufficient FU	0.029				
MRI					100 (75 to 100)	97 (97 to 98)	36 (29 to 43)	NR
Mammography					8 (0.2 to 36)	NR	NR	NR
Ultrasonography					8 (0.2 to 41)	NR	NR	NR

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

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

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kuhl et al (2017)[10]				1. Health outcomes not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
MRI: magnetic resonance imaging.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 6. Study Design and Conduct Gaps of Clinical Validity Studies of MRI Screening in Average-Risk Women

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Kuhl et al (2017)[10]						2. Only sensitivity comparisons provided

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
MRI: magnetic resonance imaging.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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

Clinically Useful

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

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

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

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

Given the limited published evidence on MRI screening of average-risk women, evaluations of clinical validity and clinical utility are not possible.

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

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

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

Systematic Reviews
Evidence for individuals with a limited sensitivity of mammography was informed by a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment (2004).[11] No systematic reviews were identified.

Observational Studies: Dense Breasts
In the 2012 ACRIN (American College of Radiology Imaging Network) 6666 trial, mammography alone was compared with mammography plus ultrasound in women 25 years or older with at least heterogeneously dense breast tissue and at least 1 other breast cancer risk factor.[12] Half (54%) of women had a personal history of breast cancer. In an MRI subanalysis, women who completed 3 rounds of screening and did not have contraindications or renal impairment were asked to undergo contrast-enhanced MRI within 8 weeks of the last screening mammography. Six hundred twenty-seven women consented and were eligible for this subanalysis, and 612 (98%) completed the needed tests; 16 cancers were detected in these women. Sensitivity increased from 44% (95% CI, 20% to 70%) for mammography plus ultrasound to 100% (95% CI, 79% to 100%; p=0.004) when MRI was added. Specificity declined from 84% (95% CI, 81% to 87%) for mammography plus ultrasound to 65% (95% CI, 61% to 69%; p<0.001) for all 3 tests. Over the 3-year study period, another 9 cancers were identified between screening tests, and 2 additional cancers were identified off-study.

Observational Studies: Following Breast-Conserving Therapy
Two prospective studies have reported on the performance of surveillance breast MRI following breast-conserving therapy (BCT).[13,14] Study characteristics are shown in Table 7. Both studies were performed in Korea and it is unclear whether the populations overlapped.

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

Study	Study Population	Design[a]	Reference Standard	Identification of Positive MRI Test	Timing of Tests	Blinding of Assessors	Comment
Kim et al (2017)[14]	Women in Korea undergoing surveillance breast MRI following BCT from 2014 to 2016	Prospective observational	• Pathology for positive results • Cancer not confirmed at 1-y surveillance imaging for negative results	Assessed as BIRADS category 4 or 5 by 1 radiologist with 10+ y of experience in breast MRI	MRI within 4 wk of screening mammo and breast US	No (readers knew results of prior imaging studies)	Funded by Bayer Korea
Cho et al (2017)[13]	Women aged ≤50 y in Korea undergoing surveillance breast MRI following BCT from 2010 to 2016	Prospective observational	• Pathology for positive results • Cancer not confirmed at 1-y surveillance imaging for negative results	Assessed as BIRADS category 3+ by 1 radiologist with 5+ y of experience in breast MRI	MRI within 2 mo of screening mammo and breast US	Yes	• Funded by Bayer Korea • Overlap with Kim (2017) unclear

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

Results of the clinical validity studies for surveillance of breast MRI following BCT are shown in Table 8. The sensitivity of MRI was higher than mammography and ultrasound with overlapping confidence intervals in both studies. Specificity of MRI was lower than mammography and ultrasound. The combination of mammography and MRI was 100% sensitive and 87%specific. The review by Cho et al (2017) reported that the recall rate was significantly higher for mammography plus MRI (13.8%; 95% CI, 12.0% to 15.5%) compared with mammography (4.4%; 95% CI, 3.3% to 5.5%), as was the biopsy rate (2.7% [95% CI, 2.0% to 3.4%] vs 0.5 [95% CI, 0.2% to 0.8%]). The yield per 1000 examinations was 8.2 (95% CI, 4.3 to 12.2) for mammography plus MRI vs 4.4 (95% CI, 1.5 to 7.2) for mammography.[13]

Table 8. Results of Clinical Validity Studies Assessing Surveillance Breast MRI after BCT

Study	Initial N	Final N	Excluded Images	Recurrence Rate, %	Clinical Validity (95% Confidence Interval),%			
					Sens	Spec	PPV	NPV
Kim et al (2017)[14]	421 women (429 breast MRIs)	414 women (422 breast MRIs)	Initial diagnosis of malignant phyllodes tumor, lobular carcinoma in situ (n=6), or developed supraclavicular lymph node metastasis within 12 mo (n=1)	2.6				
MRI					82 (48 to 98)	95 (92 to 97)	31 (15 to 51)	99 (98 to 100)

Study	Initial N	Final N	Excluded Images	Recurrence Rate, %	Clinical Validity (95% Confidence Interval),%			
US					18 (2 to 52)	98 (96 to 99)	20 (3 to 56)	98 (96 to 99)
Mammography					18 (2 to 52)	99 (98 to 100)	40 (5 to 85)	98 (96 to 99)
Cho et al (2017)[13]	801	754	Withdrew consent (n=39) or had systemic metastasis (n=7); unclear (n=1)	2.3				
MRI					88 (66 to 97)	90 (88 to 91)	24 (14 to 37)	NR
US					65 (41 to 83)	90 (89 to 92)	35 (19 to 55)	NR
Mammography					53 (31 to 74)	96 (95 to 97)	73 (43 to 90)	NR
Mammography plus MRI					100 (82 to 100)	87 (85 to 89)	29 (18 to 42)	NR

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

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

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kim et al (2017)[14]				1. Health outcomes not reported	
Cho et al (2017)[13]				1. Health outcomes not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
BCT: breast-conserving therapy; MRI: magnetic resonance imaging.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

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

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Kim et al (2017)[14]		1. Not blinded to results of mammography, US, or PET/CT				
Cho et al (2017)[13]						

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
BCT: breast-conserving therapy; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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

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

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

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

Given the limited published evidence on MRI screening in individuals who have breast characteristics that limit the sensitivity of mammography, evaluations of clinical validity and clinical utility are not possible.

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

Detection Uses

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

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

Comparators

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

Outcomes

The outcomes of interest for diagnostic accuracy include test accuracy and test validity (i.e., sensitivity, specificity). Primary outcomes of interest for clinical utility are the avoidance of invasive procedures (e.g., 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

Breast MRI is administered in an imaging setting.

Study Selection Criteria

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

Technically Reliable

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

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

Clinically Valid

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

De Besser et al (2010) evaluated 8 retrospective studies in a systematic review of studies on the use of MRI in patients (total N=220 patients) with mammographically occult breast cancer and

an axillary metastasis.[15] In 7 studies, a potential primary lesion was detected in a mean of 72% of cases (range, 36%-86%). Pooling individual patient data yielded a sensitivity of 90% (range, 85%-100%) in detecting an actual malignant tumor. Specificity, however, was 31% (range, 22%-50%).

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

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

Evidence on detection of suspected occult breast cancer is based on a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment (2004)[11] and a subsequent meta-analysis. The Assessment concluded that, in this small subgroup of patients, adjunctive use of breast MRI allowed a substantial portion of patients (25%-61%) to avoid the morbidity of mastectomy; risk of unnecessary biopsy was estimated to be 8%.

Section Summary: Detecting Suspected Occult Breast Primary Tumor With Axillary Nodal Adenocarcinoma With a Negative Mammography and Physical Exam
The use of MRI to guide breast-conserving surgery (BCS) rather than presumptive mastectomy appears to offer the substantial benefit of breast conservation for those patients in whom MRI detects the primary tumor.

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

Lehman et al (2007) reported on the results of the ACRIN-A6667 trial.[16] They found that 30 (3%) of 969 women with a recent diagnosis of unilateral breast cancer had contralateral cancer at the time of initial diagnosis using MRI. Contralateral lesions were not detected by mammography or physical exam. Eighteen (60%) of the 30 cancers were invasive and 12 (40%) were ductal carcinoma in situ (DCIS). In this study, 121 (12.5%) patients had biopsies, with a positive biopsy rate of 24.8%. With 1-year follow-up, the sensitivity of MRI was 91% and specificity was 88%. Results of this trial in a diverse group of patients were similar to the findings of others.

Liberman et al (2003) reported on 212 women who had negative mammograms of the asymptomatic contralateral breast and found 12 cancers (prevalence, 5%) on MRI, including 6 DCIS and 6 infiltrating carcinomas.[17] 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.[18]

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

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

No RCTs assessing diagnostic breast MRI in individuals with suspected contralateral breast cancer after established breast cancer were identified.

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

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

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

Detecting Breast Cancer in the Case of Low-Suspicion Findings on Conventional Mammography
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the Clinically Useful section for discussion.

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

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

Evidence on low-suspicion findings is based on a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment (2004).[11] Available evidence has suggested that adjunctive MRI may be very sensitive and specific in patients with low-suspicion findings on conventional testing and may provide a useful method to select patients for biopsy or to avoid prolonged short-interval follow-up. However, none of the available studies used prospective methods appropriate to patient populations to directly compare the sensitivity and specificity of short-interval mammographic follow-up with MRI and to determine the effects of adjunctive MRI on cancer detection rate and biopsy rate.

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

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

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

Detecting Breast Cancer by Further Characterizing Suspicious Breast Lesions
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews
Evidence on further characterization of suspicious breast lesions was summarized in 3 Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessments (2000, 2001, 2004).[11,19,20] Studies addressed a group of patients who have breast lesions of sufficient suspicion to warrant a recommendation to undergo biopsy for diagnosis. Therefore, MRI results were assumed to have an impact on the decision whether to undergo definitive biopsy, considered the criterion standard.

A systematic review published by Medeiros et al (2011) analyzed 69 studies including 9298 women.[21] Pooled sensitivity was 90% (95% CI, 88% to 92%), and pooled specificity was 75% (95% CI, 70% to 79%). The pooled positive likelihood ratio of an abnormal MRI for malignancy was 3.6 (95% CI, 3.0 to 4.2) and the pooled negative likelihood ratio was 0.12 (95% CI, 0.09 to 0.15). For breast cancer or high risk lesions vs benign lesions, the area under the curve for MRI was 0.91.

Observational Studies
Two single-institution, prospective cohort studies examined the diagnostic accuracy of breast MRI for lesions identified by mammography or ultrasound. Strobel et al (2015) in Germany included lesions characterized as Breast Imaging Reporting and Data System (BIRADS) category 4 by conventional workup in 340 women.[22] Most women were postmenopausal (61%), had no previous breast biopsy (64%), or family history of breast cancer (62%), and underwent initial evaluation for routine screening (88%). Of 353 lesions, 135 (38%) were biopsied; lesions down-graded to BIRADS categories 1, 2, or 3 on MRI were followed with imaging for 18 months, except for pure clustered microcalcifications (without accompanying mass), which were biopsied or followed with imaging for 24 months at patient discretion; none of the lesions monitored progressed during follow-up. Overall incidence of malignancy including DCIS was 20% (n=69). MRI down-graded 256 (28%) of 353 lesions, confirmed 37 (11%) lesions, and upgraded 50 (14%) lesions. The PPV of MRI was 73% compared with 19% for conventional imaging. The negative predictive value (NPV) of MRI was 99% (and could not be calculated for conventional imaging). For pure clustered microcalcifications, sensitivity was 89% (25/28 lesions) and the false-negative rate was 12% (3/28 lesions). False-positive MRI findings resulted in biopsy for 5 (1.5%) of 340 women.

In a similar study, Li et al (2014) in China included 84 women with BIRADS categories 3, 4, or 5 microcalcifications on mammography.[23] Most patients were premenopausal (81%), had no family history of breast cancer (83%), and underwent initial evaluation for routine screening (56%). All lesions were biopsied surgically (n=91). The incidence of malignancy including DCIS was 46%. The PPV of MRI was 87% compared with 60% for mammography. The NPV of MRI was 91%.

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

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

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

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

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

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

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

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the

intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

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

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

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

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

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

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

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

Setting
Breast MRI is administered in an outpatient imaging setting.

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

Preoperative Mapping to Identify Multicentric Disease with Clinically Localized Breast Cancer

Systematic Reviews

Evidence on preoperative mapping was based on a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment (2004).[24] The Blue Cross Blue Shield Association Technology Evaluation Center 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.[25-29] The most recent and comprehensive meta-analysis was published by Houssami et al (2017).[27] Studies included in the review were comparative (randomized or nonrandomized), evaluated preoperative MRI vs an alternative approach that did not include MRI, and reported quantitative data on surgical outcomes. The primary end point for the meta-analysis was whether patients underwent mastectomy as surgical treatment. Secondary end points were re-excision rates after BCS, positive margins after BCS, and receipt of contralateral prophylactic mastectomy.

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

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

One meta-analysis has addressed breast cancer recurrence rates. This meta-analysis, by Houssami et al (2014), analyzed individual patient data from 4 studies—1 RCTs and 3 nonrandomized comparative studies (total N=3180 patients).[29] Most patients (62%-93%) had localized, invasive disease and received BCT and systemic chemotherapy. After a median follow-up of 2.9 years (interquartile range [IQR], 1.6-4.5 years), there was no difference in estimated 8-year ipsilateral local (adjusted hazard ratio [HR], 0.88; 95% CI, 0.52 to 1.51; p=0.65) or distant (adjusted HR=1.18; 95% CI, 0.76 to 2.27; p=0.48) recurrence-free survival overall or in patients who received BCT only.

Randomized Controlled Trials

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

The RCT by Gonzalez et al (2014) in Sweden assessed 440 women who underwent surgical treatment of invasive breast cancer with or without presurgical breast MRI.[30] Breast MRI provided incremental information that altered treatment plan in 40 (18%) of 220 patients in the MRI group. Conversion from planned BCS to mastectomy occurred more often in the MRI group (20%) than in the control group (10%; p=0.024). However, more patients in the MRI group had planned BCS at baseline (70%) than in the control group (60%; p=0.036). The ipsilateral reoperation rate was

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

A second RCT, the MONET trial, was reported by Peters et al (2011).[31] It randomized 463 patients with suspicious, nonpalpable breast lesions identified by mammography or ultrasound to prebiopsy MRI or usual care. Of 207 evaluable patients in the MRI group, 11 additional suspicious lesions were identified on MRI and were occult on other imaging studies. All 11 additional lesions underwent biopsy, with 2 (18%) positive for malignancy. The incidence of mastectomy was similar between groups (32% vs 34%, p=0.776), as was the incidence of BCS (68% vs 66%). The incidence of re-excisions due to positive tumor margins was significantly greater in the MRI group (34%) than in the control group (12%; p=0.008).

A multicenter RCT from the U.K. (COMICE trial), reported ty Turnbull et al (2010), examined the impact of presurgical MRI on the need for additional treatment within 6 months.[32] This study was an open, parallel-group trial conducted at 45 centers in the U.K. and enrolled 1623 women with biopsy-proven breast cancer who were scheduled for wide local excision BCT. Of 816 patients in the MRI group, 58 (7%) underwent mastectomy as a result of MRI findings and/or patient choice, compared with 10 (1%) patients in the no-MRI group who underwent mastectomy by patient choice. There was no statistically significant reduction in reoperation rates in those who received MRI scans (19% in both groups; OR=0.96; 95% CI, 0.75 to 1.24; p=0.77). In the MRI group, 19 (2%) patients had a "pathologically avoidable" mastectomy, defined as a mastectomy based on MRI results showing more extensive disease, but histopathology showing only localized disease. Twelve months after surgery, there was no statistically significant difference in the quality of life between groups.

Since the publication of the Houssami meta-analysis, Bruck et al (2018) reported on the results of an RCT to evaluate the diagnostic value of preoperative MRI in 100 patients with newly diagnosed unifocal stage I invasive ductal carcinoma.[33] Patients were randomized in a 1:1 ratio to preoperative breast MR or surgery without MRI. Breast MRI detected an additional finding in 14 patients (28%) and MRI detected lesions in 7 (14%) of patients undergoing MRI were confirmed to be malignant. Seven (14%) patients underwent breast reoperation in the MRI group compared with 12 (24%) patients in the control group (p=0.20). Definitive mastectomy was performed in 6 (12%) patients in the MRI group compared with 2 (4%) in the control group (p=0.14).

Observational Studies

In addition to the RCTs, Onega et al (2018) reported on the association between preoperative MRI and all-cause mortality in 5 registries (total N=4454 patients) of the National Cancer Institute-sponsored Breast Cancer Surveillance Consortium.[34] Data from the Breast Cancer Surveillance Consortium registries were linked to Medicare claims data or electronic health records; women ages 66 and older with an initial nonmetastatic breast cancer (stage I–III) diagnosed from 2005 to 2010 were included with follow-up continuing through 2014. Nine hundred seventeen (21%) women underwent preoperative MRI. The unadjusted 5-year cumulative probability of death was 0.12 for women with MRI and 0.17 for those without (HR=0.67; 95% CI, 0.54 to 0.82). However, after adjustment for age, sociodemographic, and clinical factors, the association was attenuated (HR=0.90; 95% CI, 0.72 to 1.12).

Fortune-Greeley et al (2014) retrospectively examined case records of 20,332 women with invasive breast cancer in the Surveillance Epidemiology and End Results–Medicare-linked dataset.[35] Twelve percent of patients had a preoperative MRI. Among patients with invasive lobular carcinoma, but not other histologic types, preoperative breast MRI was associated with lower odds of reoperation after initial partial mastectomy (adjusted OR=0.59; 95% CI, 0.40 to 0.86).

Section Summary: Preoperative Mapping to Identify Multicentric Disease with Clinically Localized Breast Cancer

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

Guiding Surgical Decisions After Neoadjuvant Chemotherapy

Systematic Reviews

Evidence on guiding surgical decisions is based on a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment (2004)[36] and more recent publications. Compared with conventional methods of evaluating tumor size and extent (i.e., 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.[37] 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.[38] MRI results were well-correlated with results of histopathologic assessment (criterion standard) with correlation coefficients ranging from 0.72 to 0.98; however, MRI is not intended as a replacement for histopathologic assessment.

Several systematic reviews have been published since the 2004 Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment. Most recently, Marinovich et al (2015) published an individual patient data meta-analysis of agreement between MRI and pathologic tumor size and other evaluation methods after neoadjuvant chemotherapy.[39] 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 (i.e., mammography, ultrasound, clinical examination) after surgery. Studies also had to report residual tumor size (i.e., 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.[40] Literature was searched to July 2012. Median correlation coefficient was 0.70 (range, 0.21-0.98). Variation in size between MRI and pathology ranged from -1.4 to +2.0 cm.

Section Summary: Guiding Surgical Decisions after Neoadjuvant Chemotherapy

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

Evaluating Suspected Chest Wall Involvement

Morris et al (2000) prospectively studied 19 patients with posteriorly located breast tumors suspected to involve the pectoralis major muscle based on either mammography or clinical exam.[41] Thirteen tumors were thought to be fixed to the chest wall on clinical exam, and 12 appeared to have pectoral muscle involvement on mammography. MRI results were compared with surgical and pathologic findings. The presence of abnormal enhancement within the pectoralis major muscle on MRI was 100% sensitive and 100% specific for identifying 5 tumors that actually involved the pectoralis major muscle.

Two other retrospective studies have reported on 4 cases in which MRI was able to determine the involvement of the chest wall with 100% accuracy.[42,43]

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 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.[44] Sentinel lymph node mapping and tumor resection was done simultaneously. Malignant tumors were confirmed in 15 (60%) patients, including 4 patients with DCIS. Survival outcomes were not reported.

Section Summary: Evaluating and Localizing Lesions Prior to Biopsy

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

Evaluating Response to Neoadjuvant Chemotherapy with Locally Advanced Breast Cancer

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

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

Technically Reliable

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

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

Systematic Reviews
Evidence on the use of MRI to assess response to chemotherapy is based on a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment (2004)[36] and subsequent studies.

The Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment reported on 6 studies (total N=206 patients) that performed breast MRI during the course of chemotherapy.[36] MRI outcomes for response to chemotherapy were based on a reduction in tumor size or reduction in contrast enhancement. Three studies[45-47] reported NPV results of 38%, 83%, and 100%, respectively; however, the 2 lower estimates were from prospective studies, and the highest estimate was from a retrospective study.

Three systematic reviews of MRI to evaluate response to neoadjuvant chemotherapy have been published.[40,48,49] Characteristics of the reviews are shown in Table 11 and described briefly in the following paragraphs. Li et al (2018) compared the performance of MRI with positron emission tomography (PET) plus computer tomography (CT).[49]

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

Study	Dates	Studies	Participants	N (Range)	Design	Reference Standard
Li et al (2018)[49]	Up to 2017	13	Had both PET/CT and MRI after preoperative NAC with at least 10 patients	• MRI: 575 (16- 142) • PET/CT: 618 (16-142)	Observational (prospective, retrospective)	Postoperative pathologic result (pCR vs non-pCR)
Marinovich et al (2013)[48]	Up to 2011	44	Newly diagnosed breast cancer undergoing NAC, with MRI undertaken after NAC	2949 (14-869)	Observational (prospective, retrospective)	Pathologic response based on surgical excision preferred; other references standards allowed
Lobbes et al (2013)[40]	Up to 2012	8	Newly diagnosed breast cancer for whom breast MRI was not performed at baseline or prior to surgery but after completion of NAC with at least 25 patients	560 (31-195)	Observational (prospective, retrospective)	NR

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

Results of the systematic reviews are shown in Table 12. Li et al (2018) reported on a systematic review comparing MRI with PET/CT to evaluate pathologic response to neoadjuvant chemotherapy and included studies in which patients underwent both PET/CT and MRI after preoperative neoadjuvant chemotherapy, postoperative complete pathologic response (pCR vs non-pCR) was used as the reference standard, and the study included at least 10 patients. Methodologic quality was assessed using QUADAS-2. Most domains were rated as low risk of bias in all studies; however, only 2 studies enrolled consecutive or random samples and in only 3 studies were the reference standard results interpreted without knowledge of the results of the

index tests. There was a high level of heterogeneity in the pooled estimate of both sensitivity (88%; 95% CI, 78 to 94; I^2=83%) and specificity (69%; 95% CI, 51 to 83; I^2=72%) for MRI.

Marinovich et al (2013) conducted a systematic review with meta-analysis.[48] Forty-four studies (total N=2949 patients) assessing the ability of MRI to discriminate residual breast tumor after neoadjuvant chemotherapy from pCR were identified. Studies were heterogeneous in MRI parameters used, thresholds for identifying a response, and definitions of pathologic response. Median MRI sensitivity, defined as the proportion of patients with residual tumor correctly classified by MRI, and specificity, defined as the proportion of patients with pCR classified by MRI as the absence of residual tumor, were 0.92 (IQR, 0.85-0.97) and 0.60 (IQR, 0.39-0.96), respectively. Specificity increased when a *relative* threshold for defining negative MRI (i.e., contrast enhancement was less than or equal to normal breast tissue) was used rather than an *absolute* threshold (complete absence of MRI enhancement) with little decrement to sensitivity. The pooled area under the receiver operating characteristic curve was 0.88, and the diagnostic odds ratio was 17.9 (95% CI, 11.5 to 28.0). (A diagnostic odds ratio of 1 indicates no discriminatory ability; higher values indicate better test performance.) Accuracy decreased when residual DCIS was included in the definition of pCR. Statistical measures of between-study heterogeneity were not reported. A subset of studies compared MRI with other imaging modalities (mammography, ultrasound) and clinical exam; however, 95% CIs for pooled analyses were very large, rendering conclusions uncertain.

In the systematic review by Lobbes et al (2013), 8 studies reported on measures of diagnostic accuracy.[40] Median sensitivity, defined as the proportion of patients with pCR correctly classified by MRI, was 42% (range, 25%-92%). Median specificity, defined as the proportion of patients without pCR correctly classified by MRI, was 89% (range, 50%-97%). Median (range) PPV and NPV were 64% (50%-73%) and 87% (71%-96%), respectively.

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

Study	MRI		Mammography		PET/CT	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Li et al (2018)[49]						
Total N	575	575			618	618
PE (95% CI)	88 (78 to 94)	69 (51 to 83)	NR	NR	77 (58 to 90)	78 (63 to 88)
Marinovich et al (2013)[48]						
Total N	2949	2949				
Median (IQR)	92 (85-97)	60 (39-96)	NR	NR	NR	NR
Lobbes et al (2013)[40]						
Total N	560	560				
Median (range)	42 (25-92)	89 (50-97)	NR	NR	NR	NR

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

Observational Studies

The ACRIN 6657/I-SPY trial (2012) enrolled 206 women ages 26 to 68 years with invasive breast cancer 3 cm or larger who were receiving anthracycline-based neoadjuvant chemotherapy, with or without a taxane.[50] MRI was performed at 4 time points: before chemotherapy, after 1 cycle of chemotherapy, between the anthracycline-based regimen and the taxane, and after all chemotherapy but before surgery. Various MRI parameters were evaluated for their ability to predict the pathologic outcome. Results were reported as the difference in predictive ability for residual cancer burden, a composite pathologic index, between MRI parameters and clinical size predictors at the same time points. MRI findings were a stronger predictor of pathologic outcomes than clinical assessment, with the largest difference being tumor volume after the first chemotherapy cycle and a difference in the area under the receiver operating characteristic curve of 0.09; corresponding area under the receiver operating characteristic curve values after the third and fourth MRIs were 0.07 and 0.05. Similar findings were reported for predicting pCR.

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

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

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

No RCTs assessing breast MRI to identify patients whose tumors are not responding to neoadjuvant chemotherapy to guide subsequent systemic therapy were identified.

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

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

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

Evaluating Residual Tumor after Lumpectomy or Breast Conservation Surgery
Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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

Evidence on evaluating residual tumor includes several observational studies, most of which are retrospective.[51-59] Histopathologic examination on re-excision was used as the criterion standard. Three studies were conducted at the same institution and accrued patients during similar time periods, so overlap reporting may exist.[52,54,55] Most of the studies were published before 2005 and

are not discussed further. Characteristics of studies published since 2015 are shown in Table 13 and described briefly in the following paragraphs.[56,57]

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

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Lee et al (2018)[57]	Patients in Taiwan with LCIS who had initial excision from 2011 to 2015	Unclear	Histopathology	NR	NR	NR	Few details on study design or conduct provided
Krammer et al (2017)[56]	Women with positive margins after initial surgery for breast cancer, from 2004 to 2013	Retro	Histopathology	• Read independently by 2 radiologists • Criteria for suspected residual disease: asymmetric thickening or nodular enhancement with irregular or spiculated margins or extensive focal non-mass enhancement	NR	Radiologists had access to other imaging results, when available	

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

Results of the clinical validity studies published after 2015 are shown in Table 14. Lee et al (2018) reported on the results of a study comparing breast MRI with ultrasonography for detecting remnant lobular carcinoma in situ (LCIS) lesions after initial excision.[57] Twenty-nine patients with LCIS were enrolled between 2011 and 2015. Methods are poorly described. Residual lesions were identified by pathology in 12 (41%) cases. The sensitivity of ultrasonography was 58% compared with 83% for breast MRI; precision estimates were not reported. Specificity was 100% for both modalities.

Krammer et al (2017) published a retrospective study evaluating breast MRI to assess residual disease in 175 patients who had been candidates for BCS and had positive surgical margins.[56] MRIs were read independently by 2 radiologists, both of whom had access to the pathology report from the initial surgery and any prior breast imaging. Pathology findings served as the criterion standard. For reader 1, the sensitivity and specificity of detecting residual disease was 63% and 75%, respectively. For reader 2, sensitivity and specificity were 83% and 64%, respectively. The interobserver agreement was moderate (κ=0.56).

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

Study	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% Confidence Interval), %			
					Sens	Spec	PPV	NPV
Lee et al (2018)[57]	NR	29	Any invasive focus or other malignancy	41				
MRI					83% (NR)	100% (NR)	NR	NR

Study	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% Confidence Interval), %			
Ultrasonography					58% (NR)	100% (NR)	NR	NR
Krammer et al (2017)[56]	180	175	Received chemo prior to postop MRI (n=4), poor MR image quality (n=1)	79				
MRI					73% (NR)	72% (NR)	91% (NR)	45% (NR)

chemo: chemotherapy; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; postop: postoperative; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

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

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Lee et al (2018)[57]		1,2. No description provided	1. No description provided	1. Health outcomes not reported	
Krammer et al (2017)[56]			3. No comparator	1. Health outcomes not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
MRI: magnetic resonance imaging.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

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

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Lee et al (2018)[57]		1. Not described	1,3,4. Not described			1. No precision estimates provided 2. No statistical comparison to other methods
Krammer et al (2017)[56]		1. Not blinded to other imaging results				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
MRI: magnetic resonance imaging.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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

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

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

No RCTs assessing breast MRI to identify patients with a residual tumor to guide subsequent surgery were identified.

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

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

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

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

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

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

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

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

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

For individuals who have suspicious breast lesions who receive MRI as an adjunct to further characterize lesions, the evidence includes systematic reviews (including a Blue Cross Blue Shield Association Technology Evaluation Center TEC Assessment) and cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. Studies have found that MRI for evaluation of suspicious breast lesions has a relatively

high sensitivity and a moderately high specificity. However, it has not yet been established that the negative predictive value is sufficient to preclude the need for biopsy. Although 2 recent studies have reported negative predictive values greater than 90% in certain types of breast lesions, these were non-U.S., single-institution studies that require replication in larger, multicenter trials. Therefore, the use of MRI to further characterize suspicious lesions is currently unlikely to alter clinical management. In addition, the moderately high rate of false-positives will lead to substantial numbers of unnecessary biopsies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

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

For individuals who have a suspicious breast lesion recommended for biopsy but not localizable by mammography or ultrasonography who receive MRI to evaluate and localize the lesion prior to biopsy, the evidence includes a cohort study. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and resource utilization. A small cohort study from Brazil identified malignant tumors in 60% of patients with MRI-detected occult lesions using contrast-enhanced MRI. Although there is little published evidence supporting this indication, improved health outcomes are expected by enabling earlier diagnosis of breast cancer for suspicious lesions where other good options are not available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have locally advanced breast cancer undergoing neoadjuvant chemotherapy who receive MRI to evaluate response to chemotherapy, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are overall survival,

disease-specific survival, test accuracy and validity, and resource utilization. Studies, including systematic reviews, have not found that there is sufficient evidence to determine whether breast MRI can reliably predict lack of response to neoadjuvant chemotherapy. There is a large amount of variability in reported performance characteristics of MRI in published studies, leaving uncertainty about the true accuracy of MRI for this purpose. Furthermore, evidence would need to show that any resulting change in patient management (e.g., discontinuation of chemotherapy, change to a different regimen) would improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (v.1.2018),[60] breast cancer screening and diagnosis (v.2.2018),[61] and genetic assessment of those at high risk of breast and/or ovarian cancer (v.1.2019)[62] list the following indications for breast magnetic resonance imaging (MRI).

Screening (as an adjunct to mammography):

Recommend Annual MRI Screening (Based on Evidence)

- First-degree relative of *BRCA* carrier, but untested: commence at age 25-29 y
- Lifetime risk 20% or greater, as defined by models that are largely dependent on family history, commence 10 years prior to youngest family member but not prior to age 25 y

Recommend Annual MRI Screening (Based on Expert Consensus Opinion):

- Radiation to chest between 10 and 30 years

Consider MRI screening for LCIS [lobular carcinoma in situ] and ALH [atypical lobular hyperplasia]/ADH [atypical ductal hyperplasia] based on emerging evidence if lifetime risk ≥20%.

Insufficient evidence to Recommend for or Against MRI Screening:

- Lifetime risk 15%-20%, as defined by models that are largely dependent on family history
- Heterogeneously or extremely dense breast on mammography
- Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)

Recommend Against MRI Screening (Based on Expert Consensus Opinion):

- Women at <15% lifetime risk[61]

NCCN guidelines state that women at "increased risk" of breast cancer includes the following groups:

- Women with a prior history of breast cancer
- Women ≥ 35 years of age with a 5-year risk of invasive breast cancer ≥ 1.7% (per Gail Model)
- Women who have a lifetime risk >20% based on history of LCIS or ADH/ALH

- Women who have a lifetime risk >20% as defined by models that are largely dependent on family history
- Women between the ages of 10 and 30 years with prior thoracic RT [radiotherapy]
- Women with a pedigree suggestive of or known genetic predisposition[61]

NCCN guidelines recommend MRI for patients with *BRCA* pathogenic or likely pathogenic variants starting at age 25 and state that MRI can be considered for patients with the following genetic variants:

- *ATM, CHEK2,* and *NBN*, starting at age 40
- *CDH1* and *PALB2*, starting at age 30
- *NF1*, from ages 30 to 50[62]

NCCN guidelines also state there is insufficient evidence for any recommendations for use of breast MRI for patients with the following genetic variants: *BARD1*, *FANCC*, *MRE11A*, *MUTYH*, *RECQL4*, *RAD50*, *RINT1*, *SLX4*, *SMARCA*, or *XRCC2*. Moreover, there are conflicting data on risks associated with a *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* gene deletion.[62]

Diagnosis[60]:

- Optional MRI for women with nipple discharge, no palpable mass and a BI-RADS rating of 1-3
- To consider MRI for women with skin changes with a suspicion of inflammatory breast cancer or Paget's disease with BI-RADS 1-3 on mammogram ± ultrasound and a benign punch biopsy of the skin or nipple

Pretreatment evaluation[60]:

- To define extent of cancer of presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis (category 2B). There are no high-level data demonstrating that use of MRI to guide choice of local therapy improves outcomes (local recurrence or survival).
- May be useful to identify primary cancer in women with axillary nodal adenocarcinoma or with Paget disease of the nipple with negative mammography, ultrasound, or clinical breast exam

Treatment[60]:

- Before and after preoperative systemic therapy to evaluate extent of disease, response to treatment, and potential for breast-conserving therapy

Surveillance[60]:

- Utility of follow-up screening in women with prior breast cancer is undefined. Generally, should only be considered for women with 20% lifetime risk of breast cancer.

American Cancer Society

The American Cancer Society guide on early detection of breast cancer, last revised in 2017, has recommended the following on MRI[63]:

> A breast MRI is mainly used for women who have been diagnosed with breast cancer, to help measure the size of the cancer, look for other tumors in the breast, and to check for tumors in the opposite breast. For certain women at high risk for breast cancer, a screening MRI is recommended along with a yearly mammogram. MRI is not recommended as a screening tool by itself because it can miss some cancers that a mammogram would find.
>
> Although MRI can find some cancers not seen on a mammogram, it's also more likely to find something that turns out not to be cancer (called a false positive). False-positive findings have to be checked out to know that cancer isn't present. This means more tests and/or biopsies. This is why MRI is not recommended as a screening test for women at average risk of breast cancer, because it would mean unneeded biopsies and other tests for many of these women.

American College of Radiology

The American College of Radiology has appropriateness criteria for breast imaging, which were developed in 2012 and revised in 2017[64]; palpable breast masses,[65] revised in 2016; initial workup and surveillance for stage I breast cancer, reviewed in 2016[66]; and monitoring response to neoadjuvant therapy, 2017[67] (see Table 17).

Table 17. MRI-Related to Criteria for Breast Cancer Screening, Diagnosis, and Monitoring Response

Specific Indications	MRI Rating
High risk women: women with a *BRCA* gene variant and their untested first-degree relatives, women with a history of chest irradiation between the ages of 10 and 30 years, women with 20% or greater lifetime risk of breast cancer	Usually appropriate with and without contrast (with mammography)
Intermediate-risk women: women with personal history of breast cancer, lobular neoplasia, atypical ductal hyperplasia, or 15%-20% lifetime risk of breast cancer	May be appropriate with and without contrast (with mammography)
Average-risk women: women with <15% lifetime risk of breast cancer, breasts not dense	Usually not appropriate with and without contrast
Evaluating palpable breast mass. All indications reviewed	Usually not appropriate with and without contrast
Initial determination of tumor size and extent within the breast prior to neoadjuvant chemotherapy.	Usually appropriate without and with contrast
Imaging of the breast after initiation or completion of neoadjuvant chemotherapy [if a prechemotherapy MRI was performed].	Usually appropriate without and with contrast
Axillary evaluation prior to neoadjuvant chemotherapy.	May be appropriate without and with contrast
Known breast cancer. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla not previously evaluated.	May be appropriate without and with contrast
Surveillance. Rule out local recurrence.	May be appropriate without and with contrast

MRI: magnetic resonance imaging.

The College (2018) issued recommendations for breast cancer screening in women at higher-than-average risk.[68] The recommendations for MRI are as follows:

- For women with genetics-based increased risk (and their untested first-degree relatives), history of chest radiation, calculated lifetime risk of 20% or more, breast MRI should be performed annually beginning at age 25 to 30
- For women with personal histories of breast cancer and dense breast tissue, or those diagnosed before age 50, annual surveillance with breast MRI is recommended
- For women with personal histories of breast cancer not included in the above, or with LCIS or atypia on prior biopsy, MRI should be considered, especially if other risk factors are present

American Society of Clinical Oncology

The American Society of Clinical Oncology (2006) has published guidelines for follow-up and management after primary treatment of breast cancer.[69] In 2013, the guidelines were updated with a systematic review of the literature through March 2012, and no revisions were made.[70] The guidelines recommended against the use of breast MRI "for routine follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination."[70] Furthermore, "The decision to use breast MRI in high risk patients should be made on an individual basis depending on the complexity of the clinical scenario."[69]

International Late Effects of Childhood Cancer Guideline Harmonization Group

The International Late Effects of Childhood Cancer Guideline Harmonization Group from 9 countries (2013) published evidence-based recommendations for breast cancer surveillance in female survivors of childhood, adolescent, and young adult cancer who received chest irradiation before age 30 years and have no genetic predisposition to breast cancer.[71] The

authors found concordance among previous guidelines to initiate annual breast MRI exams beginning at age 25 or 8 years after radiation. Based on systematic review of the literature to August 2011 and expert consensus, the authors recommended mammography, breast MRI, or both for surveillance (strong recommendation based on high-quality evidence with a low degree of uncertainty). The authors acknowledged that "no prospective studies have assessed the use of MRI screening in this population." The recommendation was therefore based on extrapolation of evidence from patients with hereditary risk for breast cancer.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2016) updated its recommendations on breast cancer screening. The Task Force concluded the following on breast MRI[72]:

> "… the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, magnetic resonance imaging, DBT [digital breast tomosynthesis], or other methods in women identified to have dense breasts on an otherwise negative screening mammogram."

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01929395	A Study to Evaluate the Use of Supine MRI Images in Breast Conserving Surgery	138	Jul 2018
NCT02933489	Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts	1450	Dec 2018
NCT02244593	FAST MRI Study in Breast Cancer Survivors	300	May 2020
NCT01716247	Comparison of Contrast Enhanced Mammography to Breast MRI in Screening Patients at Increased Risk for Breast Cancer	1000	Jun 2018
NCT01805076	MRI and Mammography Before Surgery in Patients with Stage I-II Breast Cancer	536	Sep 2019
Unpublished			
NCT02798796	Brazilian Randomized Study - Impact of MRI for Breast Cancer (BREAST-MRI)	372	Nov 2016 (unknown)

NCT: national clinical trial.

References

1. Food and Drug Administration (FDA). 510(k) Summary of Safety and Effectiveness: Access Breast Coil 4/SMS. 2006; https://www.accessdata.fda.gov/cdrh_docs/pdf6/K060547.pdf. Accessed August 21, 2018.
2. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Magnetic resonance imaging of the breast in screening women considered to be at high genetic risk of breast cancer. TEC Assessments 2003;Volume 18:Tab 15.
3. Kuhl CK, Schmutzler RK, Leutner CC, et al. Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology. Apr 2000;215(1):267-279. PMID 10751498
4. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol. Aug 1 2001;19(15):3524-3531. PMID 11481359

5. Warner E, Messersmith H, Causer P, et al. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. May 6 2008;148(9):671-679. PMID 18458280
6. Phi XA, Houssami N, Obdeijn IM, et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age >/= 50 years: evidence from an individual patient data meta-analysis. J Clin Oncol. Feb 1 2015;33(4):349-356. PMID 25534390
7. Phi XA, Houssami N, Hooning MJ, et al. Accuracy of screening women at familial risk of breast cancer without a known gene mutation: Individual patient data meta-analysis. Eur J Cancer. Nov 2017;85:31-38. PMID 28886475
8. Nelson HD, Fu R, Cantor A, et al. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. Feb 16 2016;164(4):244-255. PMID 26756588
9. Health Quality Ontario. Magnetic resonance imaging as an adjunct to mammography for breast cancer screening in women at less than high risk for breast cancer: a health technology assessment. Ont Health Technol Assess Ser. Dec 2016;16(20):1-30. PMID 27990198
10. Kuhl CK, Strobel K, Bieling H, et al. Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. Radiology. May 2017;283(2):361-370. PMID 28221097
11. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Breast magnetic resonance imaging (MRI) for detection or diagnosis of primary or recurrent breast cancer TEC Assessments. 2004;Volume 19:Tab 1.
12. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA. Apr 4 2012;307(13):1394-1404. PMID 22474203
13. Cho N, Han W, Han BK, et al. Breast cancer screening with mammography plus ultrasonography or magnetic resonance imaging in women 50 years or younger at diagnosis and treated with breast conservation therapy. JAMA Oncol. Nov 1 2017;3(11):1495-1502. PMID 28655029
14. Kim EJ, Kang BJ, Kim SH, et al. Diagnostic performance of and breast tissue changes at early breast MR imaging surveillance in women after breast conservation therapy. Radiology. Sep 2017;284(3):656-666. PMID 28419815
15. de Bresser J, de Vos B, van der Ent F, et al. Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review. Eur J Surg Oncol. Feb 2010;36(2):114-119. PMID 19822403
16. Lehman CD, Gatsonis C, Kuhl CK, et al. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med. Mar 29 2007;356(13):1295-1303. PMID 17392300
17. Liberman L, Morris EA, Kim CM, et al. MR imaging findings in the contralateral breast of women with recently diagnosed breast cancer. AJR Am J Roentgenol. Feb 2003;180(2):333-341. PMID 12540428
18. Lehman CD, Blume JD, Thickman D, et al. Added cancer yield of MRI in screening the contralateral breast of women recently diagnosed with breast cancer: results from the International Breast Magnetic Resonance Consortium (IBMC) trial. J Surg Oncol. Oct 1 2005;92(1):9-15; discussion 15-16. PMID 16180217
19. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Magnetic resonance imaging of the breast: differential diagnosis of a breast lesion. TEC Assessments. 2000;Volume 15:Tab 10.
20. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Magnetic resonance imaging of the breast: differential diagnosis of a breast lesion to avoid biopsy. TEC Assessments. 2001;Volume 16:Tab 15.
21. Medeiros LR, Duarte CS, Rosa DD, et al. Accuracy of magnetic resonance in suspicious breast lesions: a systematic quantitative review and meta-analysis. Breast Cancer Res Treat. Apr 2011;126(2):273-285. PMID 21221772

22. Strobel K, Schrading S, Hansen NL, et al. Assessment of BI-RADS Category 4 lesions detected with screening mammography and screening US: utility of MR imaging. Radiology. Feb 2015;274(2):343-351. PMID 25271857
23. Li E, Li J, Song Y, et al. A comparative study of the diagnostic value of contrast-enhanced breast MR imaging and mammography on patients with BI-RADS 3-5 microcalcifications. PLoS One. Nov 2014;9(11):e111217. PMID 25365327
24. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Magnetic resonance imaging of the breast for preoperative evaluation in patients with localized breast cancer. TEC Assessments. 2004;Volume 19:Tab 8.
25. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. Jul 1 2008;26(19):3248-3258. PMID 18474876
26. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg. Feb 2013;257(2):249-255. PMID 23187751
27. Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat. Sep 2017;165(2):273-283. PMID 28589366
28. Plana MN, Carreira C, Muriel A, et al. Magnetic resonance imaging in the preoperative assessment of patients with primary breast cancer: systematic review of diagnostic accuracy and meta-analysis. Eur Radiol. Jan 2012;22(1):26-38. PMID 21847541
29. Houssami N, Turner R, Macaskill P, et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. J Clin Oncol. Feb 10 2014;32(5):392-401. PMID 24395846
30. Gonzalez V, Sandelin K, Karlsson A, et al. Preoperative MRI of the breast (POMB) influences primary treatment in breast cancer: a prospective, randomized, multicenter study. World J Surg. Jul 2014;38(7):1685-1693. PMID 24817517
31. Peters NH, van Esser S, van den Bosch MA, et al. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. Eur J Cancer. Apr 2011;47(6):879-886. PMID 21195605
32. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. Feb 13 2010;375(9714):563-571. PMID 20159292
33. Bruck N, Koskivuo I, Bostrom P, et al. Preoperative magnetic resonance imaging in patients with stage I invasive ductal breast cancer: a prospective randomized study. Scand J Surg. Mar 2018;107(1):14-22. PMID 28401771
34. Onega T, Zhu W, Weiss JE, et al. Preoperative breast MRI and mortality in older women with breast cancer. Breast Cancer Res Treat. Jul 2018;170(1):149-157. PMID 29516372
35. Fortune-Greeley AK, Wheeler SB, Meyer AM, et al. Preoperative breast MRI and surgical outcomes in elderly women with invasive ductal and lobular carcinoma: a population-based study. Breast Cancer Res Treat. Jan 2014;143(1):203-212. PMID 24305978
36. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Breast MRI for management of patients with locally advanced breast cancer who are being referred for neoadjuvant chemotherapy. TEC Assessments. 2004;Volume19:Tab 7.
37. Drew PJ, Kerin MJ, Mahapatra T, et al. Evaluation of response to neoadjuvant chemoradiotherapy for locally advanced breast cancer with dynamic contrast-enhanced MRI of the breast. Eur J Surg Oncol. Nov 2001;27(7):617-620. PMID 11669587
38. Partridge SC, Gibbs JE, Lu Y, et al. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. AJR Am J Roentgenol. Nov 2002;179(5):1193-1199. PMID 12388497
39. Marinovich ML, Macaskill P, Irwig L, et al. Agreement between MRI and pathologic breast tumor size after neoadjuvant chemotherapy, and comparison with alternative tests: individual patient data meta-analysis. BMC Cancer. Oct 08 2015;15:662. PMID 26449630
40. Lobbes MB, Prevos R, Smidt M, et al. The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving

neoadjuvant chemotherapy: a systematic review. Insights Imaging. Apr 2013;4(2):163-175. PMID 23359240
41. Morris EA, Schwartz LH, Drotman MB, et al. Evaluation of pectoralis major muscle in patients with posterior breast tumors on breast MR images: early experience. Radiology. Jan 2000;214(1):67-72. PMID 10644103
42. Kerslake RW, Carleton PJ, Fox JN, et al. Dynamic gradient-echo and fat-suppressed spin-echo contrast-enhanced MRI of the breast. Clin Radiol. Jul 1995;50(7):440-454. PMID 7614789
43. Rodenko GN, Harms SE, Pruneda JM, et al. MR imaging in the management before surgery of lobular carcinoma of the breast: correlation with pathology. AJR Am J Roentgenol. Dec 1996;167(6):1415-1419. PMID 8956569
44. de Lima Docema MF, Costa PA, de Andrade FE, et al. Magnetic resonance imaging-guided occult breast lesion localization and simultaneous sentinel lymph node mapping. World J Surg Oncol. Oct 23 2014;12:320. PMID 25341393
45. Balu-Maestro C, Chapellier C, Bleuse A, et al. Imaging in evaluation of response to neoadjuvant breast cancer treatment benefits of MRI. Breast Cancer Res Treat. Mar 2002;72(2):145-152. PMID 12038705
46. Cheung YC, Chen SC, Su MY, et al. Monitoring the size and response of locally advanced breast cancers to neoadjuvant chemotherapy (weekly paclitaxel and epirubicin) with serial enhanced MRI. Breast Cancer Res Treat. Mar 2003;78(1):51-58. PMID 12611457
47. Rieber A, Brambs HJ, Gabelmann A, et al. Breast MRI for monitoring response of primary breast cancer to neo-adjuvant chemotherapy. Eur Radiol. Jul 2002;12(7):1711-1719. PMID 12111062
48. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. J Natl Cancer Inst. Mar 6 2013;105(5):321-333. PMID 23297042
49. Li H, Yao L, Jin P, et al. MRI and PET/CT for evaluation of the pathological response to neoadjuvant chemotherapy in breast cancer: A systematic review and meta-analysis. Breast. May 11 2018;40:106-115. PMID 29758503
50. Hylton NM, Blume JD, Bernreuter WK, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY Trial. Radiology. Jun 2012;263(3):663-672. PMID 22623692
51. Lee JM, Orel SG, Czerniecki BJ, et al. MRI before reexcision surgery in patients with breast cancer. AJR Am J Roentgenol. Feb 2004;182(2):473-480. PMID 14736685
52. Bedrosian I, Mick R, Orel SG, et al. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer. Aug 1 2003;98(3):468-473. PMID 12879462
53. Kawashima H, Tawara M, Suzuki M, et al. Effectiveness of dynamic MRI for diagnosing pericicatricial minimal residual breast cancer following excisional biopsy. Eur J Radiol. Oct 2001;40(1):2-9. PMID 11673001
54. Orel SG, Reynolds C, Schnall MD, et al. Breast carcinoma: MR imaging before re-excisional biopsy. Radiology. Nov 1997;205(2):429-436. PMID 9356624
55. Weinstein SP, Orel SG, Heller R, et al. MR imaging of the breast in patients with invasive lobular carcinoma. AJR Am J Roentgenol. Feb 2001;176(2):399-406. PMID 11159081
56. Krammer J, Price ER, Jochelson MS, et al. Breast MR imaging for the assessment of residual disease following initial surgery for breast cancer with positive margins. Eur Radiol. May 31 2017;27(11):4812-4818. PMID 28567547
57. Lee RK, Kim HJ, Lee J. Role of breast magnetic resonance imaging in predicting residual lobular carcinoma in situ after initial excision. Asian J Surg. May 2018;41(3):279-284. PMID 28286021
58. Frei KA, Kinkel K, Bonel HM, et al. MR imaging of the breast in patients with positive margins after lumpectomy: influence of the time interval between lumpectomy and MR imaging. AJR Am J Roentgenol. Dec 2000;175(6):1577-1584. PMID 11090379
59. Soderstrom CE, Harms SE, Farrell RS, Jr., et al. Detection with MR imaging of residual tumor in the breast soon after surgery. AJR Am J Roentgenol. Feb 1997;168(2):485-488. PMID 9016232

60. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: breast cancer. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 11, 2018.
61. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. Version 2.2018. https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed July 11, 2018.
62. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast and ovarian. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed July 11, 2018.
63. American Cancer Society. Breast MRI Scans. 2017; https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/breast-MRI-scans.html. Accessed August 21, 2018.
64. American College of Radiology. Appropriateness criteria - breast cancer screening, revised 2017. https://acsearch.acr.org/docs/70910/Narrative/. Accessed July 11, 2018.
65. American College of Radiology. Appropriateness criteria - Palpable Breast Masses, revised 2016. https://acsearch.acr.org/docs/69495/Narrative/. Accessed July 11, 2018.
66. American College of Radiology. Appropriateness criteria - Stage I Breast Cancer: Initial Workup and Surveillance for Local Recurrence and Distant Metastases in Asymptomatic Women, reviewed 2016. https://acsearch.acr.org/docs/69496/Narrative/. Accessed July 11, 2018.
67. American College of Radiology. Appropriateness criteria - Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer, 2017. https://acsearch.acr.org/docs/3099208/Narrative/. Accessed July 11, 2018.
68. Monticciolo DL, Newell MS, Moy L, et al. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. J Am Coll Radiol. Mar 2018;15(3 Pt A):408-414. PMID 29371086
69. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. Nov 1 2006;24(31):5091-5097. PMID 17033037
70. Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. Mar 1 2013;31(7):961-965. PMID 23129741
71. Mulder RL, Kremer LC, Hudson MM, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. Dec 2013;14(13):e621-629. PMID 24275135
72. U.S. Preventive Services Task Force. Final Recommendation Statement. Breast Cancer: Screening. 2016; https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening1. Accessed July 21, 2018.
73. National Cancer Institute (NCI). Breast Cancer Risk Assessment Tool, 2008. Accessed on November 2, 2016 from http://www.cancer.gov/bcrisktool/.
74. American College of Radiology (ACR). ACR BI-RADS® – US Lexicon Classification Form, 2014. ACR BI-RADS® Atlas 5. Accessed on November 2, 2016 from http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/BIRADS/USLexiconClass.pdf.
75. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 6.01.29 (September 2018).

Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:

  - Age
  - Age at time of first live birth, if applicable
  - Age at time of first menstrual period
  - History and number of breast biopsies and pathology results
  - History of radiation therapy and at what age, if applicable
  - Reason for MRI
  - Relatives with a history of breast cancer
- Genetic testing reports (e.g., *BRCA1* or *BRCA2* testing), if applicable
- Pathology report(s), if applicable
- Radiology report(s) (e.g., mammogram, breast ultrasound)

Post Service
- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	77046	Magnetic resonance imaging, breast, without contrast material; unilateral ***(Code effective 1/1/2019)***
	77047	Magnetic resonance imaging, breast, without contrast material; bilateral ***(Code effective 1/1/2019)***
	77048	Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; unilateral ***(Code effective 1/1/2019)***
	77049	Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; bilateral ***(Code effective 1/1/2019)***
	77058	Magnetic resonance imaging, breast, without and/or with contrast material(s); unilateral ***(Deleted code effective 1/1/2019)***
	77059	Magnetic resonance imaging, breast, without and/or with contrast material(s); bilateral ***(Deleted code effective 1/1/2019)***
HCPCS	C8903	Magnetic resonance imaging with contrast, breast; unilateral
	C8904	Magnetic resonance imaging without contrast, breast; unilateral ***(Deleted code effective 1/1/2019)***
	C8905	Magnetic resonance imaging without contrast followed by with contrast, breast; unilateral
	C8906	Magnetic resonance imaging with contrast, breast; bilateral
	C8907	Magnetic resonance imaging without contrast, breast; bilateral ***(Deleted code effective 1/1/2019)***

Type	Code	Description
	C8908	Magnetic resonance imaging without contrast followed by with contrast, breast; bilateral
ICD-10 Procedure	BH30Y0Z	Magnetic Resonance Imaging (MRI) of Right Breast using Other Contrast, Unenhanced and Enhanced
	BH30YZZ	Magnetic Resonance Imaging (MRI) of Right Breast using Other Contrast
	BH31Y0Z	Magnetic Resonance Imaging (MRI) of Left Breast using Other Contrast, Unenhanced and Enhanced
	BH31YZZ	Magnetic Resonance Imaging (MRI) of Left Breast using Other Contrast
	BH32Y0Z	Magnetic Resonance Imaging (MRI) of Bilateral Breasts using Other Contrast, Unenhanced and Enhanced
	BH32YZZ	Magnetic Resonance Imaging (MRI) of Bilateral Breasts using Other Contrast

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/12/1994	New Policy Adoption	Medical Policy Committee
04/28/1998	No change	External Review
06/13/2001	BCBSA Medical Policy adoption	Medical Policy Committee
02/13/2002	Adopted BCBSA TEC for differential diagnosis of a breast lesion to avoid biopsy	Medical Policy Committee
06/01/2003	Policy Review	Medical Policy Committee
06/01/2004	Adopted BCBSA TEC December 2003; Vol.18, No.15 as CTAF June 2004 consent agenda. Policy updated.	Medical Policy Committee
12/01/2004	Adopted BCBSA TEC September 2004; Vol.19, No.7. CTAF June 2004 consent agenda. Policy updated.	Medical Policy Committee
06/01/2005	Administrative Review	Administrative Review
06/28/2007	Policy Revision	Medical Policy Committee
07/02/2007	Policy published	Administrative Review
01/11/2008	Language clarification. Used NCI guidelines to determine risk. Position unchanged.	Medical Policy Committee
05/16/2008	BCBSA Medical Policy Adoption. Revised ACS guidelines and lifetime risk figure	Medical Policy Committee
09/25/2009	Policy Revision Criteria Revised Combined Policies MRI of the Breast and Computer-Aided Detection with MRI of the Breast	Medical Policy Committee
09/27/2013	Policy revision with position change	Medical Policy Committee
08/29/2014	Policy title change from MRI of the Breast Policy revision with position change	Medical Policy Committee
09/30/2015	Policy revision without position change	Medical Policy Committee
12/01/2016	Policy title change from Magnetic Resonance Imaging of the Breast Policy revision without position change	Medical Policy Committee
07/01/2017	Coding update	Administrative Review
12/01/2017	Policy revision without position change	Medical Policy Committee

Effective Date	Action	Reason
11/01/2018	Policy revision without position change	Medical Policy Committee
01/01/2019	Coding update	Administrative Review
03/01/2019	Administrative Update	Administrative Review

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.