Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Magnetic Resonance Imaging for Breast Cancer

Description/Background

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) of the breast can be used to screen, detect, and/or diagnose and manage breast cancer. However, mammogram is the recommended screening modality for breast cancer.

An MRI can be used as a replacement for mammography screening, or as an additional imaging test alone, or in combination with other imaging modalities.

Health Disparities in Breast Cancer

Based on data from 2014 through 2018, age-adjusted breast cancer mortality is approximately 40% higher among Black women compared to non-Hispanic White women in the United States (27.7 vs 20.0 deaths per 100,000 women), despite a lower overall incidence of breast cancer among Black women (125.8 vs 139.2 cases per 100,000 women).[1] Experts postulate that this divergence in mortality may be related to access issues; Black women are more likely than White women to lack health insurance limiting their access to screening and appropriate therapies. Socioeconomic status is also a driver in health and health outcome disparities related to breast cancer.[2] Women with low incomes have significantly lower rates of breast cancer screening, a higher probability of later-stage diagnosis, and are less likely to receive high quality care, resulting in higher mortality from breast cancer.

Regulatory Status:

An 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."[3]

Medical Policy Statement

Magnetic resonance imaging of the breast is **established**. It is considered a useful option for individuals meeting criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Note: All the following policy statements refer to performing MRI of the breast with a breast coil and the use of contrast. MRI of the breast without the use of a breast coil, regardless of the clinical indication, is considered experimental/investigational.

A. Annual MRI of the breast may be considered established for **screening** (as an adjunct to mammography) for breast cancer in individuals at high risk of breast cancer.

High-Risk Considerations
There is no standardized method for determining a woman's risk of breast cancer that incorporates all possible risk factors. There are validated risk prediction models, but they are based primarily on family history.

The following list includes individual factors known to indicate a high risk of breast cancer:

- An individual diagnosed with lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH) or atypical ductal hyperplasia (ADH)
- An individual with a genetic predisposition to breast cancer, in themselves or a first degree relative, that includes **any** of the following**:**
  - Bannayan-Riley-Ruvalcaba syndrome
  - BRCA1 and BRCA2 mutations
  - Cowden syndrome (PTEN)
  - Li-Fraumeni syndrome (TP53)
- An individual with **any** of the following gene mutations: *ATM, BARD 1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*
- An individual with a lifetime risk of 20% or greater of developing breast cancer identified by models that are largely defined by family history (eg: BOADICEA/CanRisk, BRCAPRO, Tyrer-Cuzick).

- An individual who received radiation therapy (RT) with exposure to the breast tissue between 10 and 30 years of age

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

B. MRI of the breast is considered established for the following indications:
Suspected cancer:
- Single follow-up MRI at 6 months following a breast MRI with BI-RADS category 3 findings
- Differentiation of palpable mass from surgical scar tissue
- Lesion/abnormality characterization when other imaging (i.e., ultrasound, mammography) are inadequate to localize the lesion for biopsy
- Metastatic cancer of unknown primary and suspected to be of breast origin and/or malignant axillary lymph node (breast origin) and no mammographic findings of primary breast carcinoma
- Evaluation of pathologic nipple** discharge after nondiagnostic mammography and ultrasound
- Suspected breast implant-associated anaplastic large cell lymphoma in individuals with textured implants when ultrasound is nondiagnostic

***Pathologic nipple discharge: persistent and reproducible on exam, spontaneous, unilateral, single duct, and clear or bloody*

Diagnostic Workup and Management:
When **one** of the following criteria are met:
- To determine the extent of disease in biopsy-proven breast cancer in **either** of the following:
  - Ductal carcinoma in situ (DCIS) when the lesion is greater than 2 cm: **or**
  - Invasive breast carcinoma
- To define the relationship of the tumor to the fascia and its extension into the pectoralis major, serratus anterior, and/or intercostal muscles prior to surgery
- Preoperative tumor mapping of the involved breast to evaluate the presence of multicentric disease in individuals with clinically localized breast cancer with the exception of DCIS, (see criteria for DCIS above), who are candidates for breast-conservation therapy
- Presurgical planning in individuals with locally advanced breast cancer (before and after completion of neoadjuvant chemotherapy) to permit tumor localization and characterization
- Suspected recurrence in individuals with tissue transfer flaps (rectus, latissimus dorsi and gluteal) post-reconstruction
- Suspected recurrence of breast cancer in individuals when clinical, mammographic, and/or sonographic findings are inconclusive
- Post-lumpectomy with close or positive margins to evaluate for residual disease

- Malignant axillary lymph node (breast origin) and no breast mass on physical exam, mammogram or on ultrasound.

Surveillance

Annual surveillance in individuals with a personal history of breast cancer after breast conserving therapy or unilateral mastectomy is recommended in **ANY** of the following scenarios:

- Heterogeneously or extremely dense breasts
- Those diagnosed with breast cancer before the age of 50
- Those who meet criteria for MRI breast screening (see inclusion A above)

Exclusions:

- Screening technique, either alone or as an adjunct to mammography, in average-risk individuals
- Screening technique, either alone or as an adjunct to mammography, for the detection of breast cancer when the sensitivity of mammography is limited (i.e., dense breasts)
- Diagnosis of low-suspicion findings on conventional testing, immediate biopsy is not indicated, and the patient is referred for short-interval follow-up
- Diagnosis of a suspicious breast lesion to avoid biopsy

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

77046 77047 77048 77049

Other codes (investigational, not medically necessary, etc.):

N/A

Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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

Screening Individuals at High-Risk of Breast Cancer

Clinical Context and Test Purpose

Screening uses include screening for breast cancer in individuals who are at high genetic risk for breast cancer. MRI of the breast has been investigated as a screening tool in specific higher-risk subgroups of individuals. First, it has been studied in individuals 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 individuals, and mammography is considered less sensitive in younger individuals due to the prevalence of dense breast tissue.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals at high-risk of developing breast cancer.

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 (eg, need for additional testing or procedures).

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

Study Selection Criteria

This evidence review focuses on systematic reviews. For the evaluation of the clinical validity of MRI as an adjunct to screening with mammography, we sought systematic reviews that focused on studies meeting the following eligibility criteria:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

REVIEW OF EVIDENCE

Systematic Reviews

Three systematic reviews identified have included women at high-risk of developing breast cancer. Warner et al (2008) reviewed 11 studies published through 2008.[4] 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.[5,6] Phi et al (2015) included women with *BRCA1* or *BRCA2* variants and Phi et al (2017) included the women with a strong family history of breast cancer without a known variant. Ding et al (2023) included women with *BRCA1* or *BRCA2* variants, personal or family history of breast or ovarian cancer, or history of prior chest irradiation.[7] Characteristics of the systematic reviews are shown in Table 1.

Table 1. Characteristics of Systematic Reviews Assessing Magnetic Resonance Imaging Screening in High-Risk Women

Study	Dates	Studies	Participants	N (Range)	Design	Reference Standard
Ding et al (2023)[7]	2000-2021	18	Women with *BRCA1* or *BRCA2* variants, family or personal history of breast or ovarian cancer, history of chest irradiation	1799 (NR)	Prospective and retrospective	Pathological examination
Phi et al (2017)[6]	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)[5]	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)[4]	1995-2008	11	Women at very high-risk of breast cancer (*BRCA1* or *BRCA2* or other variants or family history consistent with hereditary breast cancer)	4983 (41-1909)	Prospective	Biopsy-confirmed cancer

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 et al (2008) review did not present a risk of bias or quality assessment of included studies. Phi et al (2015) assessed quality using the QUADAS-2 tool. All included studies were considered good quality.

Table 2. Results of Systematic Reviews Assessing Magnetic Resonance Imaging Screening in High-Risk Women

Study	MRI		Mammogram		MRI Plus Mammogram	
	Sensitivity, %	***Specificity, %***	***Sensitivity, %***	***Specificity, %***	***Sensitivity, %***	***Specificity, %***
Ding et al (2023)[7]						
Mean cancer detection rate	15.4	NR	7.0	NR	16.7	NR

Phi et al (2017)[6]						
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)[5]						
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)[4]						
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; NR: not reported;
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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary or testing.

The clinical usefulness of MRI as an adjunct to mammography for screening individuals at high risk of breast cancer is supported by an indirect chain of evidence. 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, 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

Clinical Context and Test Purpose

Screening uses include screening for breast cancer in individuals who are at average genetic risk for breast cancer.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals at average-risk of developing breast cancer.

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 (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility are overall mortality and breast cancer-specific mortality. Another outcome of interest for clinical utility is resource utilization (eg, need for additional testing or procedures).

Breast MRI is performed as an adjunct to routine screening; timing can be guided by national guidelines on breast cancer screening (see Supplemental Information section).

Study Selection Criteria
For the evaluation of the clinical validity of MRI as an adjunct to screening with mammography, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

REVIEW OF EVIDENCE

Systematic Reviews
In a systematic review of literature conducted by Nelson et al (2016) for the 2016 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 (eg, mortality, health-related quality of life, screening-related harms) and diagnostic outcomes (eg, sensitivity, specificity), and biopsy and recall rates. Reviewers did not find any studies that met eligibility criteria. They concluded that there was a lack of evidence to inform the questions of the diagnostic accuracy of MRI plus mammography versus MRI alone and the

impact of adjunct screening MRI on health outcomes in individual at less than high-risk of breast cancer.

Section Summary: Screening of Individuals at Average-Risk of Breast Cancer
The 2016 U.S. Preventative Services Task Force systematic review and guideline concluded that because the prevalence of breast cancer is low in average risk young women, screening with MRI, which has lower specificity would result in a lower PPV and many more false positive results. A systematic review by Health Quality Ontario concluded that there was lack of evidence on the impact of MRI on health outcomes of individuals at less than high risk of breast cancer.

Screening When Breast Characteristics Limit the Sensitivity of Mammography

Clinical Context and Test Purpose
Screening MRI has been suggested for individuals who may or may not be at increased risk but who have breast tissue characteristics that limit the sensitivity of mammographic screening (these characteristics are dense breast tissue, breast implants, or scarring after breast-conserving therapy [BCT]). BCT consists of breast-conserving surgery (BCS) followed by radiotherapy.

The following PICO was used to select literature to inform this review.

Populations
The population of interest are individuals with breast characteristics that limit the sensitivity of mammography. For example, individuals who have dense breasts or prior BCT.

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 (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility are overall mortality and breast cancer-specific mortality. Another outcome of interest for clinical utility is resource utilization (eg, need for additional testing or procedures).

MRI is performed as an adjunct to routine screening; timing can be guided by national guidelines on breast cancer screening (see the Supplemental Information section).

Study Selection Criteria
The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

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).

REVIEW OF EVIDENCE

Systematic Reviews

In a systematic review of literature conducted by Henderson et al (2024) for the 2023 U.S. Preventive Services Task Force breast cancer screening recommendation update, the authors identified 1 RCT evaluating supplemental screening with MRI in patients with dense breasts (see Bakker et al [2019].[10,] Although there was reduced interval cancer risk with supplemental screening, there was also increased false-positive recalls and biopsies. The authors considered the evidence insufficient to support supplemental screening with MRI in patients with dense breasts.

A systematic review with meta-analysis by Faheem et al (2024) identified 18 publications evaluating supplemental MRI screening in patients with increased or average risk of breast cancer.[11,] The majority of the data was observational, but 4 reports were RCTs. The sensitivity of supplemental MRI was estimated to be 98.4% (95% CI, 96.7% to 99.5%). The positive predictive value was actually lower in patients at increased risk compared with those at average risk (6.9% vs 19.2%), which is unexpected due to the anticipated higher disease prevalence in higher risk patients. The analysis is limited by high heterogeneity and lack of morbidity and mortality information.

Randomized Controlled and Single Arm Studies: Dense Breasts

One RCT and a prospective observational study were identified that evaluated the use of supplemental MRI in individuals who received screening mammography and/or ultrasound. Characteristics of the studies are shown in Table 3.

Table 3. Characteristics of Clinical Validity Studies Assessing Supplemental Breast Magnetic Resonance Imaging for Routine Screening in Women

Study	Study Population	Design	Reference Standard	Identification of Positive MRI Test	Timing of Tests	Blinding of Assessors	Comment
Bakker et al (2019)[12]DENSE	Women aged 50 to 75 y in the Netherlands with extremely dense breast tissue with negative results on screening mammography: socioeconomic status was recorded at baseline: 36.1% of women were in the highest status quartile (quartile 1), 23.6% in quartile 3, 22.7% in quartile 2, and 17.4% were in the lowest status quartile 4	RCT	Incidence of Interval cancers (positive MRI result that was confirmed histologically) during 2-year screening period	Assessed as BI-RADS category 4 or 5 by 1 radiologist with 5+y of experience in breast MRI; Patients with BI-RADS category of 3 received follow-up MRI after 6 months	Mammography screening with or without MRI every 2 y	NR	Funded by the University Medical Center Utrecht, the Netherlands Organization for Health Research and Development, the Dutch Cancer Society, the Dutch Pink Ribbon-A Sister's Hope organization, Stichting Kankerpreventie Midden-West, Bayer Pharmaceuticals, and Volpara Health Technologies
Berg et al (2012)[13]	Women aged 25 years and older with	Prospective trial	Most severe biopsy result within 365 days	Assessed as BI-RADS	MRI within 8 weeks of last	Yes (Interpretation was blinded to	Funded by the Avon Foundation and National

	heterogeneously dense or extremely dense breast tissue with at least 1 risk factor for breast cancer. Women had undergone 3 negative screenings of mammography and supplemental ultrasound 93% of women in the study were White; the remainder of women were Hispanic or Latino, Black, Native Hawiaiian or Pacific Islander, Asian, or American Indian or Alaskan Native.		of mammographic screening and/or clinical follow-up at 1year	score of 3, 4 or 5	screening mammography	other test results)	Institutes of Health grants

BI-RADS: Breast Imaging Reporting and Data System; MRI: magnetic resonance imaging; NR: not reported.

Results of the clinical validity studies are shown in Table 4. Bakker et al (2019) conducted a multicenter RCT (DENSE) with 40,373 women with extremely dense breast tissue and normal mammography results who were assigned to an optional supplemental MRI or mammography-only screening.[12] There were 8061 patients invited to undergo MRI (MRI-invitation group); however, 4783 patients participated in supplemental MRI screening and 3278 chose not to participate. There were 32,312 patients who only received mammography (mammography-only group). The interval-cancer rate was 2.5 per 1000 screenings in the MRI-invitation group compared to 5.0 per 1000 screenings in the mammography-only group (rate difference, 2.5; 95% confidence interval [CI], 1.0 to 3.7;p<0.001). Of note, among the 20 interval cancers diagnosed in the MRI-invitation group, 16 were diagnosed in patients who did not accept the supplemental MRI invitation (4.9 per 1000 screenings), while 4 were diagnosed in patients who underwent MRI screening(0.8 per 1000 screenings). The MRI cancer-detection rate among the women who actually underwent MRI screening was 16.5 per 1000 screenings (95% CI, 13.3 to 20.5). Women who completed the first screening MRI were eligible for a second MRI round if they had a negative screening result and responded to their next invitation from the regular mammography screening program.[14,] A total of 3436 women participated in the second round. The cancer detection rate in the second round was 5.8 per 1000 screening examinations (95% CI, 3.8 to 9.0). The specificity of second-round MRI was 97%, and the positive predictive value of recall for additional testing was 18.2% and was 24% for biopsy.

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.[13] Half (54%) of women had a personal history of breast cancer. In a 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=.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<.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.

Table 4. Results of Clinical Validity Studies Assessing Supplemental Breast Magnetic Resonance Imaging for Routine Screening in Women

Study	Initial N	Final N	Excluded Images	Cancer Rate	Clinical Validity, % (95% CI)			
					Sensitivity	Specificity	PPV	NPV
Bakker et al (2019)[12]DENSE	40,373 (8061 were invited to undergo MRI screening)	40,373 (Of 8061 who were invited to undergo MRI screening, 4783 underwent screening)	11 died, 3 moved abroad	*Interval Cancer Rate*				
MRI invitation + mammography				2.5 per 1000 screenings (95% CI, 1.6 to 3.8)	95.2 (88.1 to 98.7)	92 (NR)	Recall for additional testing: 17.4 (14.2 to 21.2) Biopsy: 26.3 (21.7 to 31.6)	NR
Mammography alone				5.0 per 1000 screenings (95% CI, 4.3 to 5.8)	NR	NR	NR	NR
Berg et al (2012)[13]	627 women were screened for the MRI sub study	612 MRI participants	15 were excluded because there was no reference standard	*Cancer diagnosis*				
Supplemental MRI				16 (2.6%) participants	100 (79 to 100)	65 (61 to 69)	19 (11 to 29)	NR
Mammography and ultrasound				NA	44 (20 to 70)	84 (81 to 87)	18 (8 to 34)	NR

NA: not applicable; CI: confidence interval; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

Tables 5 and 6 discuss relevant limitations of the studies.

Table 5. Study Relevance Limitations of Clinical Validity Studies of Supplemental Breast Magnetic Resonance Imaging for Routine Screening in Women

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Bakker et al (2019)[12]DENSE				1. Health outcomes not reported	

Berg et al (2012)[13]				1. Health outcomes not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a]Population key: 1. Intended use population unclear,2. Study population is unclear,3. Study population not representative of intended use, 4. Enrolled populations do not reflect relevant diversity, 5. Other.
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 Limitations of Clinical Validity Studies of Supplemental Breast Magnetic Resonance Imaging for Routine Screening in Women

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Bakker et al (2019)[12]		1. Not blinded to test groups				
Berg et al (2012)[13]			4. Expertise of evaluators not described.			2. Comparison with other tests not reported.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
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 with other tests not reported.

Observational Studies: Following Breast-Conserving Therapy

Two prospective studies have reported on the performance of surveillance breast MRI following BCT.[15,16] 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)[16]	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 BI-RADS 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)[15]	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 BI-RADS 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; BI-RADS: 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 CIs 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 versus 4.4 (95% CI, 1.5 to 7.2) for mammography.[15]

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)[16]	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)
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)[15]	801	754	Withdrew consent (n=39) or had systemic metastasis (n=7); unclear (n=1)	2.3				

Study	Initial N	Final N	Excluded Images	Recurrence Rate, %	Clinical Validity (95% Confidence Interval),%			
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

MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; US: ultrasound.

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

Table 9. Relevance Limitations of Clinical Validity Studies of Surveillance Breast Magnetic Resonance Imaging After Breast-Conserving Therapy

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kim et al (2017)[16]				1. Health outcomes not reported	
Cho et al (2017)[15]				1. Health outcomes not reported	

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

[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 Limitations of Clinical Validity Studies of Surveillance Breast Magnetic Resonance Imaging After Breast-Conserving Therapy

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]

Kim et al (2017)[16]		1. Not blinded to results of mammography, US, or PET/CT				
Cho et al (2017)[15]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
BCT: breast-conserving therapy; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[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 with other tests not reported.

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

The RCT from the Netherlands (Bakker 2019) found that among women with dense breasts, the use of MRI increased the cancer detection rate and decreased the interval cancer rate compared to mammography. However, the false positive rate was 79.8 per 1000 screenings. The trial is continuing in order to assess the effects over time of adjunctive screening with MRI. The prospective cohort trial by the American College of Radiology Imaging Network (ACRIN 6666; Berg 2012) found that the addition of MRI resulted in high cancer detection, but with increased false positive findings. The evidence is insufficient to show that the use of adjunctive MRI to screen average risk individuals who have dense breasts improves the net health outcome.

Two studies assessed the addition of MRI to mammography for surveillance of women who had been treated for cancer with BCT. The sensitivity of adjunct MRI was greater than mammography alone, but with overlapping confidence intervals. The companion study of women under 50 years showed higher cancer detection rates with adjunct MRI but lower specificity than mammography alone; the authors suggested that adjunctive mammography improves detection of early stage but biologically aggressive cancer in the population of younger women. However, to the extent that younger women may constitute a higher risk population, the delineation of MRI for screening high risk individuals is addressed in high-risk screening section of this policy. The evidence is insufficient to demonstrate that adjunctive MRI for screening improves the net health outcome when breast characteristics limit the sensitivity of mammography.

DETECTION USES

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

Clinical Context and Test Purpose
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 primary breast tumor might permit BCT instead of presumptive mastectomy.

The questions addressed in this portion of the evidence review:

- Does the use of MRI as an adjunct to detect breast cancer eligible for BCT improve the net health outcome compared to standard techniques in individuals with suspected occult breast primary tumor with axillary nodal adenocarcinoma and negative mammography?
- Is this degree of increased accuracy likely to improve net health outcomes via the earlier diagnosis, better patient management decisions, and more appropriate treatment?

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with suspected occult breast primary tumor with axillary nodal adenocarcinoma and negative mammography.

Interventions

The intervention of interest is MRI examination as an adjunct to detect breast cancer eligible for BCT.

Comparators

The comparator of interest is a preemptive mastectomy.

Outcomes

The outcomes of interest for diagnostic accuracy include test accuracy and test validity (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility are the avoidance of invasive procedures (eg, biopsy, mastectomy), the ability to detect cancer that would require additional or earlier treatment, and overall mortality and breast cancer-specific mortality rates.

Breast MRI is performed after a positive breast cancer screening or diagnostic examination.

Study Selection Criteria

For the evaluation of the clinical validity of MRI as an adjunct to detect breast cancer eligible for BCT, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence

Systematic Reviews

De Besser et al (2010) evaluated 8 retrospective studies in a systematic review of studies on the use of MRI in patients (N=220) with mammographically occult breast cancer and an axillary metastasis.[17] 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 individuals 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 individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Evidence on detection of suspected occult breast cancer is based on a TEC Assessment (2004)[18] and a subsequent meta-analysis, which appear to be the only direct evidence available for this indication. 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 the 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 individuals in whom MRI detects the primary tumor.

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

Clinical Context and Test Purpose
Individuals with abnormal findings on mammography are categorized according to the level of suspicion of the findings. Individuals with low-suspicion findings are often recommended to undergo short-interval follow-up after three to six months (instead of immediate biopsy). This follow-up may continue for two 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 more sensitive technique to further characterize low-suspicion breast lesions, so that individuals 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.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with low-suspicion findings on conventional mammography.

Interventions
The intervention of interest is MRI examination as an adjunct to standard care with short-interval mammographic follow-up.

Comparators
The comparator of interest is standard care and short-interval mammographic follow-up.

Outcomes
The outcomes of interest for diagnostic accuracy include test accuracy and test validity (ie, sensitivity, specificity). Primary outcomes of interest for clinical utility are the avoidance of invasive procedures (eg, biopsy, mastectomy), the ability to detect cancer that would require additional or earlier treatment, and overall mortality and breast cancer-specific mortality rates.

Breast MRI is performed after a positive breast cancer screening or diagnostic examination.

Study Selection Criteria
The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

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).

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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

REVIEW OF EVIDENCE

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. Currently, there is a lack of direct evidence supporting use.

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
Currently, there is a lack of direct evidence supporting use for this indication. 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

Clinical Context and Test Purpose

Breast lesions detected by clinical exam or mammography that are considered suspicious are frequently 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 individuals 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 individuals who have a suspicious lesion that can only be seen on one mammographic view (ie, the lesion cannot be seen in other views or on an ultrasound). Individuals 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 two 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.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with suspicious breast lesions.

Interventions
The intervention of interest is MRI examination as an adjunct to mammography and clinical assessment.

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

Study Selection Criteria
The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

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).

REVIEW OF EVIDENCE

Systematic Reviews

A systematic review published by Medeiros et al (2011) analyzed 69 studies including 9298 women.[19] 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.

A systematic review published by Zhang et al (2022) included 29 studies with 2976 patients and 3365 suspicious breast lesions.[20] The sensitivity and specificity of MRI features in differentiating malignant from benign breast lesions ranged from 73.8% to 91.9% and from 33.9% to 85.4%, respectively. The enrolled studies showed high heterogeneity. For differentiating malignant from benign breast lesions, the area under the curve values of MRI features; irregular shape, noncircumscribed margin, mass enhancement, heterogeneous internal enhancement, and type II or III time intensity curve patterns were 0.79, 0.87, 0.63, 0.82, and 0.89, respectively.

Single Arm 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 (BI-RADS) category 4 by conventional workup in 340 women.[21] Most women were postmenopausal (61%), had no previous breast biopsy (64%), or family history of breast cancer (62%), and underwent initial evaluation for routine screening (88%). Of 353 lesions, 135 (38%) were biopsied; lesions down-graded to BI-RADS categories 1, 2, or 3 on MRI were followed 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. The 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 a biopsy for 5 (1.5%) of 340 women.

In a similar study, Li et al (2014) in China included 84 women with BI-RADS categories 3, 4, or 5 microcalcifications on mammography.[22] 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 the MRI was 91%.

de Oliveira Pereira et al (2020) performed a cross-sectional study in Brazil of 32 women with suspected breast tumor based on findings from mammography, ultrasonography, or MRI.[23] The mean age of patients was 54.6 years, and the mean breast lump size was 1.6 cm. The sensitivity, specificity, PPV, and NPV were 100%, 50%, 66.7%, and 100%, respectively, for MRI; 56.2%, 87.5%, 81.8%, and 66.7% for mammography; and 75%, 18.8%, 48%, and 42.8% for ultrasonography.

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 individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

REVIEW OF EVIDENCE

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.

Section Summary: Detecting Breast Cancer by Further Characterizing Suspicious Breast Lesions
Use of MRI for evaluation of suspicious breast lesions has 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 3 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
Treatment-related uses addressed here are surgical planning, evaluating tumor response to neoadjuvant therapy, and evaluating residual tumor after BCT. Preoperative planning includes identification of multicentric disease in clinically localized breast cancer; surgical decisions after neoadjuvant chemotherapy; evaluation of suspected chest wall involvement, and localizing lesions prior to biopsy.

For each of these indications, study selection prioritized systematic reviews focusing on the relevant patient population and purpose. Systematic reviews were supplemented by studies of clinical validity. For the evaluation of clinical validity of MRI examination for the proposed purpose, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

In addition, studies of clinical usefulness were sought. These are studies that report the outcomes of using MRI for the proposed purpose, with preference for RCTs.

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

The sections on surgical planning address 4 specific indications (1) identification of multicentric disease in clinically localized breast cancer; (2) surgical decisions after neoadjuvant chemotherapy; (3) evaluation of suspected chest wall involvement; and (4) localizing lesions prior to biopsy.

Preoperative Mapping to Identify Multicentric Disease With Clinically Localized Breast Cancer

Clinical Context and Test Purpose
Individuals with clinically localized breast cancer are considered candidates for BCS followed by radiotherapy. However, mastectomy may be considered in individuals with the multicentric disease (in a separate quadrant of the breast). MRI has been investigated as a technique to assess the extent of the tumor in the breast, specifically to detect the multicentric disease as an aid to surgical planning.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with clinically localized 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 without MRI.

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

Breast MRI is performed after identification of suspicious breast lesions, or before or after treatment for breast cancer.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach' within each category of study design, studies with larger sample sizes and longer duration were preferred.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

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.[24,25,26,27,28,29,30]

Eisen et al (2024) conducted a systematic review and meta-analysis of 51 studies (8 RCTs) evaluating preoperative MRI in patients with newly diagnosed breast cancer.[30] This review continues to indicate improved outcomes with the the use of MRI in terms of decreased reoperation (OR, 0.73; 95% CI, 0.63 to 0.85), re-excisions (OR, 0.63; 95% CI, 0.45 to 0.89), and recurrence (HR, 0.77; 95% CI, 0.65 to 0.90). However, the results for recurrence-free survival (HR, 0.77; 95% CI, 0.53 to 1.12) and OS (HR, 0.89; 95% Ci, 0.74 to 1.07) were not significantly improved with MRI.

Li et al (2022) conducted a systematic review of 19 studies (4 RCTs, 15 observational) that evaluated the efficacy of preoperative MRI in patients with invasive breast cancer.[29] All breast cancer types were included but patients had to be undergoing curative surgery (eg, excision or BCS). All studies included a control group. The primary outcome, mastectomy rate, was significantly increased with preoperative MRI (odds ratio [OR], 1.36; 95% CI, 1.13 to 1.64; p=.001; I^2=91%) based on data from 16 studies (n=86,075). Preoperative MRI significantly reduced the rate of reoperation (OR, 0.77; 95% CI, 0.62 to 0.97; p=.02; I^2=71%). Other outcomes, including primary BCS, secondary mastectomy, and the rate of positive margins, were not significantly different between groups. An analysis of 3 studies in patients with invasive lobular carcinoma found similar results for all outcomes among patients who did and did not receive preoperative MRI.

The most recent meta-analysis published by Houssami et al (2017).[26] 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 endpoint for the meta-analysis was whether patients underwent mastectomy as surgical treatment. Secondary endpoints 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 endpoint, a pooled analysis of 15 studies (N=85,975) found significantly greater odds of receiving a mastectomy after preoperative MRI than after no MRI ([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=.988) or the odds of re-excision (5 studies: OR=0.65;

95% CI, 0.35 to 1.24; p=.192). Among the secondary outcomes, a pooled analysis of 3 studies found a significantly higher odds of contralateral prophylactic mastectomy after MRI (OR=1.91; 95% CI, 1.25 to 2.91). There were no significant differences between groups on other secondary outcomes (ie, re-excision rates, positive margins, reoperation rates).

One meta-analysis has addressed breast cancer recurrence rates. This meta-analysis, by Houssami et al (2014), analyzed individual patient data from 4 studies-1 RCTs and 3 nonrandomized comparative studies (total n=3180).[28] 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=.65) or distant (adjusted HR=1.18; 95% CI, 0.76 to 2.27; p=.48) recurrence-free survival overall or in patients who received BCT only.

Randomized Controlled Trials

Since the publication of the Houssami et al (2017)[26] meta-analysis, Bruck et al (2018)[31] reported on the results of an RCT to evaluate the diagnostic value of preoperative MRI in 100 patients with newly diagnosed unifocal stage I invasive ductal carcinoma. Patients were randomized in a 1:1 ratio to preoperative breast MR or surgery without MRI. Breast MRI detected an additional finding in 14 patients (28%) and MRI detected lesions in 7 (14%) patients, that 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=.20). Definitive mastectomy was performed in 6 (12%) patients in the MRI group compared with 2 (4%) in the control group (p=.14).

Mota et al (2023) conducted a single-center, open-label RCT (BREAST-MRI) in patients with breast cancer undergoing breast conserving surgery.[32] Two hundred fifty-seven patients received preoperative MRI and 267 patients served as controls. Local relapse-free survival (p=.7), overall survival (p=.8), and reoperation rates (p=.85) were similar between groups; however, 21 patients underwent mastectomy in the MRI group compared to 1 patient in the control group.

A discussion of the 3 RCTs included in the Houssami et al (2017) 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.[33] Breast MRI provided incremental information that altered the 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=.024). However, more patients in the MRI group had planned BCS at baseline (70%) than in the control group (60%; p=.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 preoperative MRI and surgical management in patients with nonpalpable breast cancer trial, was reported by Peters et al (2011).[34] 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=.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=.008).

A multicenter RCT from the U.K., Comparative effectiveness of MRI in breast cancer trial, reported ty Turnbull et al (2010), examined the impact of presurgical MRI on the need for additional treatment within 6 months.[35] 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=.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.

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 (N=4454) of the National Cancer Institute-sponsored Breast Cancer Surveillance Consortium.[36] Data from the Breast Cancer Surveillance Consortium registries were linked to Medicare claims data or electronic health records; women ages 66 and older with 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 20332 women with invasive breast cancer in the Surveillance Epidemiology and End Results-Medicare-linked dataset.[37] Twelve percent of patients had a preoperative MRI. Among patients with invasive lobular carcinoma, but no 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).

Zeng et al (2020) performed a retrospective analysis of 512 women age ≤50 years undergoing BCT.[38] Preoperative MRI was performed in 64.5% of women. In patients who did versus did not receive preoperative MRI, mean age was 43.4 and 43.6 years, and tumor size was 1.64 and 1.80 cm, respectively. In those who received MRI versus no MRI, local recurrence occurred in 7.9% versus 8.2% of patients, respectively (adjusted HR with MRI vs no MRI, 1.03; 95% CI, 0.53 to 1.99), and was associated with distant recurrence in 6.4% versus 6.6% of patients (adjusted HR with MRI vs no MRI, 0.89; 95% CI, 0.43 to 1.84).

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 individuals with invasive lobular carcinoma. No significant differences in ipsilateral local or distant recurrence-free survival after MRI-guided treatment were found in meta-analyses. While there is limited evidence that use of MRI to identify multicentric disease improves recurrence free survival or reduces operations in the overall population, benefit might accrue to sub populations, particularly high risk individuals.

Guiding Surgical Decisions After Neoadjuvant Chemotherapy

Clinical Context and Test Purpose
Individuals with locally advanced breast cancer are usually offered neoadjuvant chemotherapy to reduce tumor size and permit BCT. Evaluation of tumor size and extent using conventional techniques (ie, mammography, clinical examination, ultrasonography) is suboptimal, and breast MRI has been proposed as a means to more accurately determine tumor size for surgical planning. MRI before chemotherapy is used to document tumor location so that the tumor can be optimally evaluated after chemotherapy, especially if the size and degree of contrast enhancement are greatly reduced. Tumors that respond to chemotherapy get smaller and may even disappear; however, 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 the chemotherapeutic agent (eg, to alter chemotherapy regimen if the tumor appears unresponsive).

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with locally advanced breast cancer undergoing neoadjuvant chemotherapy.

Interventions
The intervention of interest is MRI to guide surgical decisions after neoadjuvant chemotherapy.

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

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

Breast MRI is performed after identification of suspicious breast lesions, or before or after treatment for breast cancer.

Study Selection Criteria
The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

REVIEW OF EVIDENCE

Systematic Reviews
Compared with conventional methods of evaluating tumor size and extent (ie, mammography, clinical exam, ultrasound), MRI of the breast provides an estimation of tumor size and extent that is at least as good as or better than that based on alternatives. Drew et al (2001) found MRI to be 100% sensitive and specific for defining residual tumor after chemotherapy.[39] Conversely, mammography achieved 90% sensitivity and 57% specificity (mammography results considered equivocal), and the 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 a clinical exam.[40] The MRI results were well-correlated with results of the 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.

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.[41] To be eligible for inclusion, studies had to evaluate at least 15 patients undergoing neoadjuvant chemotherapy who were evaluated with MRI and at least 1 other test (ie, mammography, ultrasound, clinical examination) after surgery. Studies also had to report residual tumor size (ie, longest diameter). Twenty-four studies met inclusion criteria, and individual patient data were available for 8 of these studies (n=300). The pooled mean difference (MD) in size estimates between MRI and pathology (8 studies, n=243) was 0.0 cm; 95% CI, -0.1 to 0.2 cm). In 4 studies comparing size estimates of mammography and pathology, the MD was 0.0 cm but the 95% CI was wider (-0.3 to 0.4 cm). In 5 studies (n=123) reporting on the MD between ultrasound and pathology, the pooled estimate was -0.3 cm (95% CI, -0.6 to 0.1 cm). The largest size variance was for studies (3 studies, n=107) comparing clinical examination 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) reporting on the ability of MRI to predict tumor size after neoadjuvant chemotherapy.[42] 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

Clinical Context and Test Purpose

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 the 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.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with posteriorly located breast tumors.

Interventions

The intervention of interest is MRI to diagnose chest wall involvement.

Comparators

The following tests and practices are currently being used to make decisions about managing breast cancer: mammography.

Outcomes

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

Breast MRI is performed after identification of suspicious breast lesions, or before or after treatment for breast cancer.

REVIEW OF EVIDENCE

Observational Studies

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.[43] 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.[44,45]

Section Summary: Evaluating Suspected Chest Wall Involvement

Evidence on MRI for evaluating suspected chest wall involvement with posteriorly located tumors is based on prospective and retrospective observational studies. All studies found that MRI was able to detect chest wall involvement with 100% accuracy. 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

Clinical Context and Test Purpose

An 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 following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with a suspicious breast lesion recommended for biopsy but not localizable by mammography or ultrasonography.

Interventions
The intervention of interest is MRI to evaluate and localize breast lesion prior to biopsy.

Comparators
The following tests and practices are currently being used to make decisions about managing breast cancer: waiting until lesion becomes palpable or visible on mammography or ultrasonography.

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

MRI is performed after identification of suspicious breast lesions recommended for biopsy.

Study Selection Criteria
The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

REVIEW OF EVIDENCE

Observational Study
Use of MRI to evaluate lesions prior to biopsy is infrequent. The evidence base addressing this use is mainly anecdotal.

Xie et al (2023) retrospectively evaluated the value of breast MRI to downgrade suspicious lesions (BI-RADS 4A or 4B) found on ultrasound in 167 patients with 186 lesions.[46] Compared to pathology and imaging findings over the subsequent 12 months, MRI had 100% sensitivity, 92.6% specificity, 87.8% PPV, and 100% NPV. Four additional suspicious lesions were detected by MRI, of which 3 (75%) were malignant. Survival was not mentioned. The authors concluded that MRI could allow suspicious lesions to be downgraded and prevent unneeded biopsies.

De Lima Docema et al (2014)[47] 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 were 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
A small cohort study in Brazil identified malignant tumors in 60% of patients with MRI-detected occult lesions using contrast-enhanced MRI. A retrospective study of patients with suspicious lesions on ultrasound reported high sensitivity, specificity, PPV, and NPV of MRI to downgrade lesion status and prevent biopsies.

Evaluating Response to Neoadjuvant Chemotherapy With Locally Advanced Breast Cancer

Clinical Context and Test Purpose

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with locally advanced breast cancer undergoing neoadjuvant chemotherapy.

Interventions
The intervention of interest is MRI to evaluate the response to chemotherapy.

Comparators
The comparator of interest is clinical assessment alone.

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

Breast MRI is performed after a period of undergoing neoadjuvant chemotherapy.

Study Selection Criteria
The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

REVIEW OF EVIDENCE

Systematic Reviews

Three systematic reviews of MRI to evaluate response to neoadjuvant chemotherapy have been published.[42,48,49,50] 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 computed tomography (CT).[45]

Table 11. Characteristics of Systematic Reviews Assessing Magnetic Resonance Imaging to Evaluate Response to Neoadjuvant Chemotherapy

Study	Dates	Studies	Participants	N (Range)	Design	Reference Standard
Janssen et al (2022)[50]	2000 to 2019	26	Patients with early-stage breast cancer who received MRI after NAC	4497 (NR)	Observational (prospective, retrospective)	Pathologic response
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)[42]	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. Janssen et al (2022) reported the results of a systematic review that evaluated the accuracy of MRI for detecting pCR after neoadjuvant chemotherapy.[50] Risk of bias was assessed using the QUADAS-2 tool. Sensitivity was highest for hormone receptor (HR)-negative/*HER2*-negative cancer (0.67), followed by HR-negative/*HER2*-positive (0.65), HR-positive/*HER2*-positive (0.60), and HR-positive/HER2-negative (0.55). None of the differences in sensitivity were significant between groups. Specificity results were 0.85, 0.81, 0.74, and 0.88, respectively. Specificity was significantly different between the HR-negative/*HER2*-positive and R-positive/HER2-negative groups (p=.046).

Li et al (2018)[49] 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

pathologic complete 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 two studies enrolled consecutive or random samples and in only three 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.[41] Forty-four studies (total n=2949) 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, was 0.92 (IQR, 0.85-0.97) and 0.60 (IQR, 0.39-0.96), respectively. Specificity increased when a *relative* threshold for defining negative MRI (ie, contrast enhancement was less than or equal to normal breast tissue) was used rather than an *absolute* threshold (complete absence of MRI enhancement) with little decrement to sensitivity. The pooled area under the receiver operating characteristic curve was 0.88, and the diagnostic odds ratio was 17.9 (95% CI, 11.5 to 28.0). (A diagnostic odds ratio of one 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.[42] 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 Magnetic Resonance Imaging to Evaluate Response to Neoadjuvant Chemotherapy

Study	MRI		Mammography		PET/CT	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Janssen et al (2022) [50]						
HR-/*HER2*- (n=1646), PE (95% CI)	0.67 (0.58 to 0.74)	0.85 (0.81 to 0.88)	NR	NR	NR	NR
HR-/*HER2*+ (n=1013), PE (95% CI)	0.65 (0.56 to 0.73)	0.81 (0.74 to 0.86)	NR	NR	NR	NR
HR+/*HER2*- (n=2273), PE (95% CI)	0.55 (0.45 to 0.64)	0.88 (0.84 to 0.91)	NR	NR	NR	NR
HR+/*HER2*+ (n=1144), PE (95% CI)	0.60 (0.50 to 0.70)	0.74 (0.63 to 0.83)	NR	NR	NR	NR
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 to 97)	60 (39 to 96)	NR	NR	NR	NR
Lobbes et al (2013)[42]						
Total N	560	560				
Median (range)	42 (25 to 92)	89 (50 to 97)	NR	NR	NR	NR

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

Nonrandomized Trials

TRAIN-3, a multicenter, single-arm study is an ongoing phase 2 study evaluating MRI-guided optimization of neoadjuvant chemotherapy in stage II to III HER2-positive breast cancer.[51] A total of 467 patients were enrolled between 2019 and 2021 at 43 hospitals in the Netherlands. Patients received neoadjuvant chemotherapy with MRI and lymph node biopsy administered every 3 cycles. Surgery was performed when patients had a complete radiological response or after a maximum of 9 chemotherapy cycles. Results for the primary outcome of 3-year event-free survival have not yet been published; however, van der Voort et al (2024) reported results for secondary endpoints. Patients with hormone receptor-negative disease had 26.4 months median follow-up with a radiological CR of 36% (95% CI, 30% to 43%) after 1 to 3 cycles, 60% (95% CI, 53% to 66%) after 1 to 6 cycles, and 73% (95% CI, 66% to 78%) after 1 to 9 cycles. Patients with hormone receptor-positive disease had 31.6 months median follow-up with a radiological CR of 29% (95% CI, 24% to 36%) after 1 to 3 cycles, 51% (95% CI, 44% to 57%) after 1 to 6 cycles, and 59% (95% CI, 53% to 66%) after 1 to 9 cycles. Among patients with a radiological CR after 1 to 9 cycles, a pCR was observed in 87% (95% CI, 81% to 92%) of patients with hormone receptor-negative tumors and in 53% (95% CI, 44% to 61%) of patients with hormone receptor-positive tumors. Results from the primary outcome are needed to support MRI in these patients.

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.[52] Of the patients included in the study, 74.4% were White, 19.2% were Black, 4% were Asian, and 2.4% were more than one race or unknown race; 4.2% of patients were Hispanic or Latino. The MRI was performed at four time points: before chemotherapy, after one 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 the 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; the 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.

Section Summary: Evaluating Response to Neoadjuvant Chemotherapy With Locally Advanced Breast Cancer

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

Evaluating Residual Tumor After Lumpectomy or Breast Conservation Surgery

Clinical Context and Test Purpose

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 a 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.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with positive surgical margins after lumpectomy or BCT.

Interventions

The intervention of interest is MRI to evaluate the residual tumor.

Comparators

The comparator of interest is pathologic inspection.

Outcomes

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

Breast MRI is performed after lumpectomy or BCT.

Study Selection Criteria

The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

REVIEW OF EVIDENCE

Observational Studies

Evidence on evaluating residual tumor includes several observational studies, most of which are retrospective. [53,54,55,56,58,59,60,61] 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.[54,56,57] 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.[58,59]

Table 13. Characteristics of Clinical Validity Studies Assessing Magnetic Resonance Imaging 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)[59]	Patients in Taiwan with LCIS who had initial excision from 2011 to 2015; race or ethnicity were not described	Unclear	Histopathology	NR	NR	NR	Few details on study design or conduct provided
Krammer et al (2017)[58]	Women with positive margins after initial surgery for breast cancer, from 2004 to 2013; race or ethnicity were not described	Retrospective	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 lesions after initial excision.[59] Twenty-nine patients with lobular carcinoma in situ 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.[58] MRIs were read independently by two 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), %			
					Sensitivity	Specificity	PPV	NPV

Lee et al (2018)[59]	NR	29	Any invasive focus or other malignancy	41				
MRI					83% (NR)	100% (NR)	NR	NR
Ultrasonography					58% (NR)	100% (NR)	NR	NR
Krammer et al (2017)[58]	180	175	Received chemo prior to postoperative MRI (n=4), poor MRI image quality (n=1)	79				
MRI					73% (NR)	72% (NR)	91% (NR)	45% (NR)

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 limitations identified in each study.

Table 15. Relevance Limitations of Clinical Validity Studies of Magnetic Resonance Imaging to Evaluate Residual Tumor After Surgery

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Lee et al (2018[59]	2. Study Population is unclear	1,2. No description provided	1. No description provided	1. Health outcomes not reported	
Krammer et al (2017)[58]	2. Study Population is unclear		3. No comparator	1. Health outcomes not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
MRI: magnetic resonance imaging.
aPopulation key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[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 Limitations of Clinical Validity Studies Assessing Magnetic Resonance Imaging 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)[59]		1. Not described	1,3,4. Not described			1. No precision estimates provided 2. No statistical comparison to other methods
Krammer et al (2017)[58]		1. Not blinded to other imaging results				

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

[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b]Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c]Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[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 with other tests not reported.

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

The 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 magnetic resonance imaging (MRI) as an adjunct to screening for breast cancer, the evidence includes systematic reviews and diagnostic accuracy studies. Relevant outcomes are overall survival (OS), 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 an improvement in the net health outcome.

For individuals who are asymptomatic with average-risk of breast cancer who receive MRI as an adjunct to screening for breast cancer, the evidence includes systematic reviews. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. The systematic reviews did not identify any randomized controlled trials (RCTs) or nonrandomized comparative studies evaluating MRI for screening average-risk women. 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 that the technology results in an improvement in the net health outcome.

For individuals with characteristics limiting the accuracy of mammography (eg, dense breasts) who receive MRI as an adjunct to screening for breast cancer, the evidence includes a RCT, and diagnostic accuracy studies. Relevant outcomes are OS, 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 (BCT) or who have dense breasts. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 BCT, the evidence includes a systematic review (TEC Assessment) and meta-analysis. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. The studies found that adjunctive use of breast MRI to guide BCS 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 an 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, current direct evidence is lacking. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. Well-designed prospective studies would be necessary to permit conclusions about the effect of this adjunctive use of breast MRI on health outcomes

The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspicious breast lesions who receive MRI as an adjunct to further characterize lesions, the evidence includes systematic reviews and cohort studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. Studies have found that MRI for evaluation of suspicious breast lesions has relatively high sensitivity and a moderately high specificity. However, it has not yet been established that the NPV is sufficient to preclude the need for biopsy. Although 3 recent studies have reported NPVs greater than 90% in certain types of breast lesions, these were non-U.S., single-institution studies that require replication in larger, multicenter trials. Therefore, the use of MRI to further characterize suspicious lesions is currently unlikely to alter clinical management. In addition, the moderately high rate of false-positives will lead to substantial numbers of unnecessary biopsies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, 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 an improvement in the net health outcome.

For individuals who have locally advanced breast cancer undergoing neoadjuvant chemotherapy who receive an MRI to guide surgical decisions after neoadjuvant chemotherapy, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and

resource utilization. 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 BCT versus 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 an improvement in the net health outcome.

For individuals who have posteriorly located breast tumors who receive an MRI to diagnose chest wall involvement, the evidence includes cohort studies. Relevant outcomes are OS, 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 an 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 OS, 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. A retrospective study found that MRI could reduce the need for unnecessary biopsy. 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 an improvement in the net health outcome.

For individuals who have locally advanced breast cancer undergoing neoadjuvant chemotherapy who receive an MRI to evaluate response to chemotherapy, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. Studies, including systematic reviews, have not found that there is sufficient evidence to determine whether breast MRI can reliably predict lack of response to neoadjuvant chemotherapy. There is a large amount of variability in reported performance characteristics of MRI in published studies, leaving uncertainty about the true accuracy of MRI for this purpose. Furthermore, evidence would need to show that any resulting change in patient management (eg, discontinuation of chemotherapy, change to a different regimen) would improve outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have positive surgical margins after lumpectomy or BCS who receive MRI to evaluate residual tumor, the evidence includes cohort studies. Relevant outcomes are OS, 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 an uncertain or high-risk of bias and therefore performance characteristics are unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Breast Cancer (v. 4.2024)[62] Breast Cancer Screening and Diagnosis (v.2.2024),[63] and Genetic Assessment Of Those At High-Risk Of Breast, Ovarian, and Pancreatic Cancer (v.2.2024)[64] list the following indications for breast magnetic resonance imaging (MRI).

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v.1.2025)[64]
The guidelines state that a carrier of a BRCA1/2 pathogenic or likely pathogenic variant should have annual breast MRI screening with contrast beginning between the ages of 25 and 29 years,

Also: "There is now strong evidence that genes beyond *BRCA1/2* confer markedly increased risk of breast and/or ovarian cancers. These genes include *ATM, BARD1, BRIP1, CDH1, CHEK2, PALB2, PTEN,* and *TP53*.

The NCCN guidelines for genetic or familial high-risk assessment for breast cancer recommend MRI screening with and without contrast for patients with *BRCA* pathogenic or likely pathogenic variants starting at age 25 to 29 years or individualized if the family had breast cancer diagnosis before age 30. The guidelines further state that MRI with and without contrast can be considered for patients with the following genetic variants:[64]

- *ATM,* and *CHEK2* starting at age 30 to 35 years
- *CDH1,STK11* and *PALB2*, starting at age 30 years
- *NF1*, from ages 30 to 50 years
- *TP53* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, starting at age 20 to 29 years
- *BARD1,RAD51C* and *RAD51D*, starting at age 40 years
- *PTEN* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, starting at age 30 years or 10 years before
- the earliest breast cancer in the family (whichever comes first)

The NCCN guidelines for genetic or familial high-risk assessment for breast cancer also state there is insufficient evidence for any recommendations for use of breast MRI for patients with the following genetic
variants: *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM, FANCC*, *MRE11A*, *MUTYH* heterozygotes, *NBN*, *RECQL*, *RAD50*, *RINT1*, *SLX4*, *SMARCA4*, or *XRCC2*.

Breast Cancer Screening and Diagnosis (v.2.2024)[63]
Screening

Screening (as an adjunct to mammography):[63]

"Recommend Annual MRI Screening:
- For individuals with a genetic mutation, or an untested first-degree relative of gene mutation carrier

- For individuals who received thoracic radiotherapy (RT) between the ages of 10 and 30 years
- For those with a lifetime risk ≥20% as defined by models that are largely dependent on family history
- Consider annual MRI screening for individuals with lobular neoplasia (LCIS/ALH) or ADH and ≥20% lifetime risk

Consideration of supplemental screening is recommended (category 2A):

- "For individuals in all breast density and risk categories, the panel recommends shared decision-making with counseling on the risks and benefits of supplemental screening following evaluation of the individual's breast density and other risk factors."
- "Individuals with a residual lifetime risk of breast cancer of 15% to 20% may be considered for supplemental screening on an individual basis, depending on risk factors.

The NCCN guidelines for breast cancer screening and diagnosis also state that individuals assigned female at birth at "increased risk" of breast cancer include the following groups: [63]

- those ≥ 35 years of age with a 5-year risk of invasive breast r carcinoma ≥1.7% (per the Modified Gail Model);
- those who have a lifetime risk 20% based on history of LCIS or ADH/ALH;
- those who have a lifetime risk ≥20% as defined by models that are largely dependent on family history;
- those who received prior thoracic irradiation between the ages of 10 and 30 years with prior thoracic RT
- those with a pedigree suggestive of or with a known genetic predisposition"

Guidelines on breast cancer screening and diagnosis make the following recommendations on diagnosis: [63]

- Optional MRI for women with nipple discharge, no palpable mass, and a Breast Imaging Reporting and Data System (BI-RADS) rating of 1 to 3.
- For patients with skin changes consistent with serious breast disease, consideration of breast MRI is included in the guidelines for those with benign biopsy of skin or nipple following BI-RADS category 1 to 3 assessment. Since a benign skin punch biopsy in a patient with clinical suspicion of inflammatory breast cancer (IBC) does not rule out malignancy, further evaluation is recommended…[and] MRI may be used for suspicious nipple discharge when mammography and ultrasound are not diagnostic.

Breast Cancer (v.6.2024)[62]
Principles of Dedicated Breast MRI Testing

Guidelines on breast cancer make the following recommendations on pretreatment evaluation with breast MRI: [62]

- "May be useful in identifying otherwise clinically occult disease in patients presenting with axillary nodal metastases (cT0, cN+), with Paget disease, or with invasive lobular carcinoma poorly (or inadequately) defined on mammography, ultrasound, or physical examination."

- "May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis."

Guidelines on breast cancer make the following recommendations related to MRI surrounding treatment: [62]

- “May be helpful for breast cancer evaluation before and after preoperative systemic therapy to define extent of disease, response to treatment, and potential for breast-conservation therapy."
- “False-positive findings on breast MRI are common. Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended.”

Guidelines on breast cancer make the following recommendations on MRI related to surveillance:[62]

- The utility of MRI in follow-up screening of patients with prior breast cancer is undefined and annual MRI is recommended in patients with dense breasts those diagnosed at 50 years of age or younger.

The recommended workup and staging of ductal carcinoma in situ includes MRI as indicated.
For the workup of invasive breast cancer, use of MRI is optional.
The use of breast MRI in follow-up of women with prior breast cancer is undefined. It may be considered as an option in women with high lifetime risk (greater than 20% based on models largely dependent on family history) of developing a second primary breast cancer.

American Cancer Society
The American Cancer Society recommendations for the early detection of breast cancer, most recently updated in 2022, recommended the following on MRI:[65]

"Women who are high risk for breast cancer based on certain factors should get a breast MRI and a mammogram every year, typically starting at age 30. This includes women who:

- Have a lifetime risk of breast cancer of about 20% to 25% or greater, according to risk assessment tools that are based mainly on family history
- Have a known *BRCA1* or *BRCA2* gene mutation (based on having had genetic testing)
- Have a first-degree relative (parent, brother, sister, or child) with a BRCA1 or BRCA2 gene mutation, and have not had genetic testing themselves
- Had radiation therapy to the chest when they were between the ages of 10 and 30 years
- Have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have first-degree relatives with one of these syndromes

The American Cancer Society recommends against MRI screening for women whose lifetime risk of breast cancer is less than 15%.
There's not enough evidence to make a recommendation for or against yearly MRI screening for women who have a higher lifetime risk based on certain factors, such as:

- Having a personal history of breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH)

- Having 'extremely' or 'heterogeneously' dense breasts as seen on a mammogram

If MRI is used, it should be in addition to, not instead of, a screening mammogram. This is because although an MRI is more likely to find cancer than a mammogram, it may still miss some cancers that a mammogram would find.

Most women at high risk should begin screening with MRI and mammograms when they are 30 and continue for as long as they are in good health. But this is a decision that should be made with a woman's health care providers, taking into account her personal circumstances and preferences."

American College of Radiology

The American College of Radiology has appropriateness criteria for breast cancer screening, which were developed in 2012 and most recently revised in 2023;[66] palpable breast masses,[66] revised in 2022;initial workup and surveillance for stage I breast cancer, reviewed in 2019[67]; monitoring response to neoadjuvant therapy, 2022[69], transgender breast cancer screening, 2021[70]; and supplemental breast cancer screening based on breast density,2021[71] (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 certain gene variants (e.g., BRCA1, BRCA2, p53, ATM, CHEK2, PALB2) and their untested first-degree relatives, women with a history of thoracic or upper abdominal radiation therapy before 30 years of age, women with >20% to 25% lifetime risk of breast cancer, and some women with a personal history of breast cancer.	Usually appropriate with and without contrast (with mammography)
Intermediate-risk women: some 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	May be appropriate with and without contrast (with mammography)
Evaluating palpable breast mass. All indications reviewed	Usually not appropriate with and without contrast
Known breast cancer. Initial determination of tumor size and extent within the breast prior to neoadjuvant chemotherapy.	Usually appropriate without and with contrast
Known breast cancer. Imaging of the breast after initiation or completion of neoadjuvant chemotherapy	Usually appropriate without and with contrast
Known breast cancer, clinically node-negative.Axillary evaluation prior to neoadjuvant chemotherapy.	Usually not appropriate
Known breast cancer Clinically node-negative. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla not previously evaluated.	Usually not appropriate
Known breast cancer, clinical suspicion of metastatic disease. Staging or assessment of response to neoadjuvant chemotherapy.	Usually not appropriate
Known axillary lymph node-positive breast cancer on prior mammography, ultrasound, or MRI. Axillary evaluation after completion of neoadjuvant chemotherapy, axilla previously evaluated.	Usually not appropriate
Known breast cancer. Axillary imaging suspicious for metastatic disease on mammography, ultrasound, or MRI during initial evaluation.	Usually not appropriate
Surveillance. Rule out local recurrence.	May be appropriate without and with contrast

Transfeminine (male-to-female) patient, 40 years of age or older with past or current hormone use ≥5 years; average risk patient.	Usually not appropriate without and with contrast
Transfeminine (male-to-female) patient, 25 to 30 years of age or older with past or current hormone use ≥5 years; higher-than-average risk.	Usually not appropriate without and with contrast
Transfeminine (male-to-female) patient with no hormone use (or hormone use <5 years) at any age; average-risk patient	Usually not appropriate without and with contrast
Transfeminine (male-to-female) patient, 25 to 30 years of age or older with no hormone use (or hormone use <5 years); higher-than-average risk.	Usually not appropriate without and with contrast
Transmasculine (female-to-male) patient with bilateral mastectomies ("top surgery") at any age and any risk.	Usually not appropriate without and with contrast
Transmasculine (female-to-male) patient with reduction mammoplasty or no chest surgery, 40 years of age or older; average-risk patient (less than 15% lifetime risk of breast cancer).	Usually not appropriate without and with contrast
Transmasculine (female-to-male) patient with reduction mammoplasty or no chest surgery, ≥30 years of age. Intermediate risk (patient with personal history of breast cancer, lobular neoplasia, atypical ductal hyperplasia, or 15% to 20% lifetime risk of breast cancer).	May be appropriate without and with contrast; usually not appropriate without contrast
Transmasculine (female-to-male) patient with reduction mammoplasty or no chest surgery, 25 to 30 years of age or older. High risk (with genetic predisposition to breast cancer or untested patient with a first-degree relative with genetic predisposition to breast cancer, patient with a history of chest irradiation between 10 to 30 years of age, patient with 20% or greater lifetime risk of breast cancer).	Usually appropriate without and with contrast; usually not appropriate without contrast
Average-risk females with nondense breasts	Usually not appropriate without and with contrast
Intermediate-risk females with nondense breasts	Usually not appropriate without and with contrast
High-risk females with nondense breasts	Usually not appropriate without and with contrast
Average-risk females with dense breasts	May be appropriate without and with contrast; usually not appropriate without contrast
Intermediate-risk females with dense breasts	May be appropriate without and with contrast; usually not appropriate without contrast
High-risk females with dense breasts	Usually appropriate without and with contrast; usually not appropriate without contrast

MRI: magnetic resonance imaging

American Society of Clinical Oncology

The American Society of Clinical Oncology (2006) published guidelines for follow-up and management after primary treatment of breast cancer.[72] In 2013, the guidelines were updated with systematic review of the literature through March 2012, and no revisions were made.[73] 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."[73] 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."[72]

International Late Effects of Childhood Cancer Guideline Harmonization Group

The International Guideline Harmonization Group (2023) 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.[74] The guideline recommends to

initiate annual breast MRI exams beginning at age 25 or 8 years after radiation. Based on a systematic review of the literature to June 2019, the authors recommended mammography and breast MRI for surveillance (strong recommendation based on high-quality evidence with a low degree of uncertainty). The authors acknowledged that "there are no studies of survivors of [childhood, adolescent, and young adult] cancer that investigated whether early detection by MRI or mammography results in better prognosis." However, the panel concluded that the benefits of initiating early annual mammography and MRI are expected to outweigh the harms.

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (2024) updated its recommendations on breast cancer screening. The task force concluded the following on breast MRI;[75,76]

"… the current evidence is insufficient to assess the balance of benefits and harms of supplemental screening for breast cancer using breast ultrasonography or magnetic resonance imaging in women identified to have dense breasts on an otherwise negative screening mammogram."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and 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			
NCT03820063	Image-guided De-escalation of Neo-adjuvant Chemotherapy in HER2-positive Breast Cancer: the TRAIN-3 Study	462	May 2032
NCT06445738	A Two-arm, Non-randomised, Prospective, Multicentre Study Using Magnetic Resonance Imaging (MRI) Findings and Pathology Features to Select Patients With Early Breast Cancer for Omission of Post-operative Radiotherapy	1400	Jan 2039
NCT06127797	Surveillance MRI Registry for Patients Who Had Breast Cancer With Dense Breast Tissue	1000	Aug 2029
NCT05968157	MIRAI-MRI: Comparing Screening MRI for Patients at High Risk for Breast Cancer Identified by Mirai and Tyrer-Cuzick	500	Jan 2025
NCT05797545	Comparison of Ultrasound and Breast MRI for Breast Cancer Detection Among Women With Dense Breasts and a Personal History of Breast Cancer	1464	May 2028
NCT05704062	Multi-Functional Magnetic Resonance Imaging Modalities for Assessment of Breast Cancer Response to Neoadjuvant Chemotherapy	135	Nov 2026
NCT05825768	Preoperative Magnetic Resonance Imaging to Obtain Adequate Resection Margins (PRIMAR) Trial	440	Aug 2026
NCT01805076	Effect of Preoperative Breast MRI on Surgical Outcomes, Costs and Quality of Life of Women With Breast Cancer	317	Feb 2025

NCT01035112	Magnetic Resonance Imaging of Breast Cancer	445	May 2027
Unpublished			
NCT00474604	MRI Evaluation of Breast Tumor Growth and Treatment Response	209 (actual)	Apr 2023
NCT01716247	Comparison of Contrast Enhanced Mammography to Breast MRI in Screening Patients at Increased Risk for Breast Cancer	1000	Jun 2018

NCT: national clinical trial

Government Regulations

National:

Medicare does not have a specific policy addressing MRI of the breast.

National Coverage Determination (NCD) for Magnetic Resonance Imaging (220.2)
Effective date: 4/10/2018,
Implementation date: 12/10/2018

All other uses of MRI or MRA for which CMS has not specifically indicated coverage or non-coverage continue to be eligible for coverage through individual local MAC discretion.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Computer-Aided Detection Mammography (Retired)
- Computer-Aided Evaluation of Malignancy as an Adjunct to Magnetic Resonance Imaging of the Breast (retired)
- Digital Mammography (Retired)
- Digital Breast Tomosynthesis (3-D Mammography)
- Fiberoptic Ductoscopy of the Breast (Retired)
- Magnetic Resonance Imaging to Monitor Integrity of Silicone-Gel-Filled Breast Implants
- Scintimammography and Gamma Imaging of the Breast and Axilla
- Ultrasound for Breast Cancer Screening

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/27/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/31/02	7/31/02	7/19/02	Joint policy established
1/27/04	1/27/04	3/1/04	Routine maintenance
6/6/05	6/6/05	5/9/05	Routine maintenance
3/8/06	3/8/06	3/10/06	Routine maintenance
1/1/07	10/31/06	11/13/06	Routine maintenance
3/1/08	2/18/08	1/2/08	Maintenance – change in criteria
3/1/09	12/9/09	12/8/08	Maintenance – examples and clarification of criteria
5/1/10	2/16/10	2/16/10	Routine Maintenance. Policy title changed to “Magnetic Resonance Imaging of the Breast”. Previous title: “Magnetic Resonance Imaging of the Breast for Cancer”.
9/1/13	6/18/13	6/26/13	Routine maintenance. Policy reformatted to mirror BCBSA. Created separate policy for MRI used to monitor rupture of silicone breast implants. See “Magnetic Resonance Imaging to Monitor Integrity of Silicone-Gel-Filled Breast Implants.”
11/1/14	8/21/14	8/25/14	Routine maintenance
3/1/16	12/10/15	12/10/15	Routine maintenance
3/1/17	12/13/16	12/13/16	Routine maintenance Title changed to “Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer.” Previous title – “Magnetic Resonance Imaging of the Breast.” Revised inclusion addressing screening for high risk of breast cancer to incorporate new NCCN criteria.

3/1/18	12/12/17	12/12/17	Routine maintenance Exclusions updated: Second bullet edited: removed "breast implants, scarring after treatment for breast cancer." Deleted fifth bullet: "Determination of a response during neoadjuvant chemotherapy…" Deleted sixth bullet: "Evaluation of residual tumor…"
3/1/19	12/11/18		Routine maintenance. Codes 77046, 77047 added. Update includes minor changes to inclusions.
5/1/19	2/19/19		Code update: codes 77058, 77059 deleted as of 12/31/18.
3/1/20	1/9/20		Routine maintenance, reference #50 added. Added codes 77048, 77049.
3/1/21	12/15/20		Routine maintenance
3/1/22	12/14/21		Routine maintenance. Ref 22,35,65,66 added AIM criteria added to inclusions
3/1/23	12/20/22		Routine maintenance (jf) Ref (1, 2) • Vendor: AIM criteria added to inclusions Post-lumpectomy with close or positive margins to evaluate for residual disease (under work up and management section) • NCCN guidelines updated gene under inclusion criteria. Added Genes from NCCN guidelines: RAD 21 C and RAD 51 D, BARD 1, and STK 11 and NBN was deleted Vendor: Yes, AIM: To align with AIM 2022 criteria, we added under management and diagnostic section on pg 4. post-lumpectomy with close or positive margins to evaluate for residual disease.

			Removal of 3rd bullet • Evaluation of the contralateral breast in those patients with a new diagnosis of breast cancer when clinical and mammographic findings are normal Added the following sentence in the MRI section. However, mammogram is the recommended screening modality for of breast cancer.
3/1/24	12/19/23		Routine maintenance (jf) Vendor: Carelon -Added updated genes per NCCN in supplemental section of policy RAD51C and RAD51D, starting at age 40 years, *STK11* starting at 30 years, modified years 30-35 for *ATM, BARD1, and CHEK2. The genes are a*lready as EST in inclusions. Added Ref: 8,29,31,45,49 - Edit to Inclusions under Diagnostic Workup and Management to align with Carelon guidelines. -Edit to inclusions include: • Added under Diagnostic Workup and Management inclusions Malignant axillary lymph node (breast origin) and no breast mass on physical exam, mammogram or on ultrasound. • Added to inclusions of high-risk consideration added eg: of models: (eg: BOADICEA/CanRisk, BRCAPRO, Tyrer-Cuzick). Per NCCN guidelines Invasive Breast Cancer 4.2023 added inclusions under surveillance • Patients with dense breasts treated with Breast

			Conserving Surgery + Radiation Therapy • Those diagnosed with breast cancer before the age of 50. Removed PICO: Detecting contralateral breast cancer after established Breast Cancer PICO based on removal of 3rd bullet in 2022. Evaluation of the contralateral breast in those patients with a new diagnosis of breast cancer when clinical and mammographic findings are normal. Removed references 16,17 and 18. Edit to the title: removal of "detection and diagnosis of" original title, Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer.
3/1/25	12/17/24		Routine maintenance (jf) Vendor: Carelon Oncologic guidelines 2025 draft. MPS- Removed "The safety and effectiveness of" Added Ref: 10,11,14,30,51,76 Ref 72 removed Monticciolo 2018 Am College of Radiology per BCBSA Patients replaced with individuals o Edits to the inclusions and exclusions section. o Added under suspected cancer pathologic nipple** o **Pathologic nipple discharge: persistent and reproducible on exam, spontaneous, unilateral, single duct, and clear or bloody o Under Surveillance: Removal of dense breast treated with breast conserving surgery + radiation therapy.

			○ Under Surveillance: Added Heterogeneously or extremely dense breasts ○ Under Exclusions: Added either alone or as an adjunct to mammography ○ Removal of safety and effectiveness from MPS

Next Review Date: 4rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MAGNETIC RESONANCE IMAGING FOR BREAST CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy guidelines apply
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.