6.01.45	Computer-Aided Evaluation of Malignancy With Magnetic Resonance Imaging of the Breast		
Original Policy Date:	March 30, 2015	**Effective Date:**	November 1, 2017
Section:	6.0 Radiology	**Page:**	Page 1 of 9

Policy Statement

The use of computer-aided evaluation (CAE) for interpretation of magnetic resonance imaging (MRI) of the breast is considered **investigational**.

Policy Guidelines

There is an add-on CPT category III code for the use of computer-aided evaluation with magnetic resonance imaging (MRI) of the breast:

- **0159T:** Computer-aided detection, including computer algorithm analysis of MRI image data for lesion detection/characterization, pharmacokinetic analysis, with further physician review for interpretation, breast MRI (List separately in addition to code for primary procedure)

This code would be used with the CPT code for breast MRI (77058-77059).

Description

The use of computer-aided evaluation (CAE) is proposed to assist radiologists' interpretation of contrast-enhanced magnetic resonance imaging (MRI) of the breast and to improve the accuracy of diagnosis of malignancy.

Related Policies

- Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Benefit Application

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

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

Regulatory Status

Several CAE systems for use with MRI of the breast have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process, some systems of which may have broader uses beyond breast MRI. Examples of FDA-cleared devices include:

- SpectraLook ®, part of iCAD's VersaVue® Enterprise Suite (iCAD, Nashua, NH), was cleared for marketing by the FDA through the 510(k) process in 2012. The VersaVue® Enterprise Suite is intended for postprocessing of magnetic resonance images as a means for visualizing these images. A previous version of this device, 3TP (3Time Point), was cleared in 2008.

- CADstream® (Merge Healthcare, Milwaukee, WI) was cleared for marketing by the FDA through the 510(k) process in 2003, at which time it was distributed by Confirma (Kirkland, WA).
- Aegis™ Breast (Hologic, Marlborough, MA; previously owned by Sentinelle Medical) was cleared for marketing by the FDA through the 510(k) process in 2007. However, in the 510(k) documents, the manufacturer stated that the primary goal of the technology is "to identify where and how deep a biopsy or localization needle should be inserted into an imaged breast."
- DynaCAD for Breast (MRI Devices, Waukesha, WI; now from Invivo, Gainesville, FL) was cleared for marketing by the FDA through the 510(k) process in 2004.

Rationale

Background

The use of computer-aided evaluation (CAE) is proposed to assist radiologists' interpretation of contrast-enhanced magnetic resonance imaging (MRI) of the breast. MRI of the breast is suggested as an alternative or adjunct to mammography or other screening and diagnostic tests because of its high sensitivity in detecting breast lesions. However, it has a high false-positive rate because it is difficult to distinguish between benign and malignant lesions. MRI may be used to screen women at high risk of breast cancer or to look for more extensive disease in women diagnosed with breast cancer who are eligible for breast-conserving surgery; it is also being studied to gage the impact of cancer treatment.

CAE systems reviewed here are intended to improve the specificity of MRI in detecting or measuring malignant tissue while maintaining the generally high sensitivity of MRI. Improved ability to identify MRI-detected lesions that are almost certainly benign could potentially reduce biopsy rates. There is anecdotal evidence that MRI also may reduce reoperation rates among patients undergoing breast-conserving surgery by more clearly identifying tissue that should be removed. CAE also may reduce the time needed to interpret breast MRI images, which currently takes longer than reading mammograms.

CAE systems for MRI provide an easier way to interpret patterns of contrast enhancement across a series of images, which in turn may help identify lesions and their likelihood of being malignant. Two key aspects of enhancement (also called kinetics) are examined: (1) Within the first minute or so, how quickly does the lesion enhance up to a certain threshold (e.g., 50% or 100% of the initial value; rapid enhancement [>90% in 90 seconds] suggests malignancy)? (2) What is the subsequent pattern of enhancement (i.e., continues to increase [persistently ascending], plateaus, or declines [called washout, which is associated with malignancy])?[1]

In contrast to computer-aided detection systems used with mammography, CAE for MRI is not primarily intended to identify lesions for consideration by a radiologist. Unlike the subtle appearance of lesions on mammography, most cancers enhance on MRI. The challenge is determining which lesions are benign and which malignant. A large number of images are produced during MRI of the breast: images are taken at varying "depths" throughout each breast multiplied by the number of times the breast is imaged to capture different time points in the enhancement process; this can produce hundreds of images. Radiologists view the images to detect suspicious areas, and then pick a region of interest and look at the enhancement pattern. However, there may be variations across radiologists in the regions of interest selected and in the precise definition of the region of interest. CAE systems, in contrast, use color-coding and differences in hue to indicate the pattern of enhancement for each pixel in the breast image, thereby allowing radiologists to analyze enhancement patterns systematically.

Literature Review

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) its technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and

(3) clinical utility demonstrating that the diagnostic information can be used to improve patient outcomes.

Computer-Aided Evaluation of Breast Cancer with Standard Magnetic Resonance Imaging vs Standard MRI Alone

Clinical Validity
To demonstrate the impact of computer-aided evaluation (CAE) in the diagnosis of breast cancer, studies that compare the sensitivity and specificity of magnetic resonance imaging (MRI) with and without the use of CAE systems are needed. Such studies can demonstrate the incremental diagnostic accuracy of CAE compared with no CAE. Ideally, these studies should be prospective and evaluate a population of patients similar to that presenting for breast cancer screening or diagnosis in a clinical setting.

Systematic Reviews
This evidence review was originally informed by a 2006 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment on computer-aided detection of malignancy, which summarized 4 published articles and 4 abstracts that compared the accuracy of MRI with and without CAE.[2] The reviewed studies focused on commercially available CAE systems, but articles on other systems were included. Also, studies had to report on cancer detection based on histologic results. Three of the articles reported on development and validation of CAE systems aimed at distinguishing between malignant and benign lesions, and they used information on women with known lesions. The fourth article provided information on one of the noncommercial systems used to evaluate women with cancer who were eligible for breast-conserving therapy.[3] Conclusions of the TEC Assessment were that the literature on CAE with MRI of the breast was sparse overall and that few studies addressed specific situations in which CAE with MRI is used in a clinical setting. The articles and abstracts calculated test characteristics by lesions and not the number of women or breasts. In a screening population, many women would not have any lesions; including these women might alter the results. Given MRI's lower sensitivity in detecting ductal carcinoma in situ, the mix of ductal carcinoma in situ vs invasive masses would affect the calculations of sensitivity and specificity and might affect the impact of the CAE system.

A more recent systematic review of the literature on CAE with MRI for breast cancer diagnosis was published in 2011 by Dorrius et al.[4] Reviewers identified 10 CAE studies in women with benign and/or malignant breast lesions (Breast Imaging Reporting and Data System [BI-RADS] category ≥2). In a meta-analyses of 3 studies (211 lesions, 55% malignant), one of which used 3.0-Tesla (T) MRI, sensitivity of experienced radiologists' blinded readings was 89% both with and without CAE, but the specificity decreased from 86% (95% confidence interval [CI], 79% to 91%) without CAE to 82% (95% CI, 76% to 87%) with CAE, a statistically nonsignificant difference. Reviewers attributed the decrease to a greater reliance by radiologists on the contrast enhancement pattern provided by CAE in the absence of morphology data, which CAE does not provide. For residents with limited breast MRI experience, the specificity was approximately 78% with or without CAE, but the sensitivity increased from 72% (95% CI, 62% to 81%) without CAE to 89% (95% CI, 80% to 94%) with CAE, a statistically nonsignificant difference. Statistical heterogeneity was moderate to substantial (I^2 range, 56%-83%) for all results except for the specificity of residents' readings both with and without CAE, which had low-to-moderate statistical heterogeneity (I^2 range, 24%-33%).

Retrospective Diagnostic Accuracy Studies
Larger representative diagnostic accuracy studies published after the 2011 systematic review are described next. All studies are retrospective analyses that included populations of patients not reflective of those seen in clinical care. Most were conducted in Asia where protocols may differ from those used in the United States.

Yun et al (2016) in South Korea retrospectively studied 124 patients newly diagnosed with breast cancer.[5] Patients underwent conventional MRI and MRI plus CAE as part of a preoperative assessment of the extent of breast cancer. A commercially available CAE device (CADstream) was used. Images were evaluated by 2 experienced radiologists blinded to histopathology results and patient characteristics. Analysis focused on differences in CAE MRI parameters in axillary lymph node–positive patients (n=34 [26%]) and axillary lymph node–negative patients (n=90 [74%]). The diagnostic accuracy of conventional MRI for differentiating between benign and metastatic axillary lymph nodes was 84.7%, with a sensitivity of 82.4% and a specificity of 85.7%. When CAE with MRI was used, the sensitivity improved to 91.2%, and the specificity to 94.4%, though neither sensitivity (p=0.403) nor specificity (p=0.086) was statistically significant with CAE. However, overall accuracy (defined by the area under the receiver operating characteristic curve) increased from 83.7% without CAE to 93.5% with CAE.

Song et al (2015) in Korea retrospectively evaluated 86 patients with invasive breast cancer using MRI alone, MRI plus CAE, mammography, ultrasound computed tomography, and fluorodeoxyglucose with positron emission tomography.[6] Patients underwent all imaging procedures and did not have adjuvant chemotherapy or an excisional biopsy during the previous 6 months. For MRI plus CAE, the CADstream device was used, and pathologic analysis was used as the reference standard. Two experienced radiologists blinded to the pathology report independently evaluated each image and final decisions were reached by consensus. There were no significant differences among all 6 imaging methods for measuring tumor size (p=0.017). Also, there were no significant differences in measuring pathologic tumor size between MRI with and without CAE. For evaluation of lymph node status, there was no significant difference in the diagnostic accuracy of MRI alone and MRI plus CAE.

Liu et al (2014) retrospectively compared radiologists' readings of 3.0-T MRI images with readings by CAE (DynaCAD) in 78 consecutive patients with newly diagnosed breast lesions at a single institution in China.[7] Lesions less than 0.8 cm in long-axis diameter were excluded (sensitivity was not assessed). Diagnoses of 93 mass-like and non-mass-like lesions (e.g., ductal carcinoma in situ, invasive lobular carcinoma, papilloma) were confirmed by needle core biopsy (n=13) or surgical histology (n=80). Of 51 mass-like lesions, 29 were malignant; of 42 non-mass-like lesions, 23 were malignant. Three experienced radiologists blinded to histologic diagnosis performed MRI readings, and 3 radiologists performed CAE readings; it is unclear whether they were the same radiologists. Overall diagnostic accuracy was 74% for radiologists and 87% for CAE. For mass-like lesions, accuracy was similar between radiologists and CAE. For non-mass-like lesions, accuracy was 67% for radiologists and 86% for CAE. Limitations of this study included calculation of test characteristics based on the number of lesions rather than on the number of women or the number of breasts. Further, results may be applicable only to patients with lesions greater than 0.8 cm and possibly only to readings made by 3.0-T MRI.

Lehman et al (2013) reported on a U.S.-based multicenter, retrospective study of 9 experienced and 11 inexperienced radiologists who read a set of dynamic contrast-enhanced breast MRIs twice, once with and once without CADstream.[8] Of 70 MRIs in the set, 27 had a benign outcome, and 43 had a malignant outcome. Among experienced readers, sensitivity increased from 84% without CAE to 91% with CAE, a statistically significant difference of 7 percentage points (95% CI, 4 to 11). Among inexperienced readers, sensitivity increased from 77% to 83% with CAE, a difference of 6 percentage points (95% CI, 1 to 10). Specificity (BI-RADS category 3 [considered negative]) did not change with the addition of CAE for either group. Similarly, overall diagnostic accuracy did not change statistically for either group: For experienced readers, the area under the receiver operating characteristic curve was 0.80 without CAE and 0.83 with CAE (these values were reversed without subsequent correction in the narrative description of results). For inexperienced readers, the area under the receiver was 0.77 without CAE and 0.79 with CAE. There was no significant difference in overall time to assessment with or without CAE.

Section Summary: Clinical Validity
A 2006 TEC assessment found insufficient literature on CAE of malignancy with breast MRI, and a 2011 systematic review did not find statistically significant differences in diagnostic accuracy between CAE plus MRI and MRI alone. Several studies were published after the systematic review, and most did not find that CAE plus MRI resulted in statistically significant improvement in diagnostic accuracy. Studies were retrospective in nature and tended to include women already diagnosed with breast cancer.

Clinical Utility

To demonstrate clinical utility, prospective studies that evaluate whether incremental diagnostic accuracy leads to changes in management and improved outcomes are needed. Decisions for biopsies may be changed as a result of CAE; in particular, biopsies may be performed in areas of abnormality identified by CAE not seen on standard MRI. This might, in turn, improve the detection rate for malignancies. It is also possible that the number of false-positive biopsies might be increased when CAE is used.

There is no direct evidence (i.e., prospective studies) that evaluates the impact of CAE on health outcomes. There are also no relevant modeling studies that estimate the impact of CAE on outcomes. Because incremental changes in sensitivity and specificity with CAE are unknown, it is not possible to estimate the number of additional malignancies that would be detected by CAE, nor is it possible to determine the number of additional false-positive biopsies that would be performed. As a result, the clinical utility of CAE when added to standard MRI of the breast has yet to be determined.

Section Summary: Clinical Utility
No published comparative studies were available on the impact of CAE plus MRI on patient management and health outcomes compared with MRI alone. Furthermore, there is insufficient information to formulate a model of indirect evidence to support clinical utility. Thus, the utility of CAE plus MRI in clinical care cannot be determined from the literature.

Summary of Evidence

For individuals with risk of breast cancer, with suspected breast cancer, or diagnosed with breast cancer, who receive CAE of breast malignancy with MRI, the evidence includes diagnostic accuracy studies and systematic reviews. Relevant outcomes are disease-specific survival, test accuracy and validity, and resource utilization. The most recent systematic review (2011) did not find a statistically significant improvement in the sensitivity and specificity with MRI plus CAE vs MRI alone. Moreover, retrospective studies published in the last 5 years generally did not find that CAE resulted in statistically significant improvement in diagnostic accuracy compared with MRI alone. Studies were generally conducted in women already diagnosed with breast cancer; there is less literature on breast cancer detection. Also, there are no comparative studies evaluating the impact of CAE with MRI on patient management decisions or health outcomes compared with MRI alone. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current breast cancer guidelines from the National Comprehensive Cancer Network do not address the use of computer-aided evaluation (CAE) for contrast-enhanced magnetic resonance imaging (MRI). These guidelines include those on breast cancer (v.2.2017),[9] breast cancer risk reduction (v.1.2017),[10] breast cancer screening and diagnosis (v.1.2017),[11] and genetic/familial high risk assessment for breast and ovarian (v.2.2017).[12]

American College of Radiology

In 2016, the American College of Radiology amended its 2011 practice parameter on the use of MRI-guided breast interventional procedures. There were no recommendations on use of CAE with breast MRI.[13]

European Society of Breast Cancer Specialists

The European Society of Breast Cancer Specialists issued consensus recommendations for MRI of the breast in 2010, which indicated that the evidence on the use of software for breast computer-aided diagnosis MRI is insufficient to recommend routine use.[14]

In 2012, the Society published a consensus document to define the management of young women with breast cancer.[15] The international recommendations were based on literature reviews using the U.S. Agency for Healthcare Research and Quality methodology. Pertinent to our evidence review, the Society did not include the use of software for breast computer-aided diagnosis MRI.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for CAE of malignancy with breast MRI have been identified.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

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12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed August 24, 2017.
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15. Cardoso F, Loibl S, Pagani O, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. Dec 2012;48(18):3355-3377. PMID 23116682
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Documentation for Clinical Review

- No records required

Coding

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

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	0159T	Computer-aided detection, including computer algorithm analysis of MRI image data for lesion detection/characterization, pharmacokinetic analysis, with further physician review for interpretation, breast MRI (List separately in addition to code for primary procedure)
HCPCS	None	
ICD-10 Procedure	BH30Y0Z	Magnetic Resonance Imaging (MRI) of Right Breast using Other Contrast, Unenhanced and Enhanced
	BH30YZZ	Magnetic Resonance Imaging (MRI) of Right Breast using Other Contrast
	BH30ZZZ	Magnetic Resonance Imaging (MRI) of Right Breast
	BH31Y0Z	Magnetic Resonance Imaging (MRI) of Left Breast using Other Contrast, Unenhanced and Enhanced

Type	Code	Description
	BH31YZZ	Magnetic Resonance Imaging (MRI) of Left Breast using Other Contrast
	BH31ZZZ	Magnetic Resonance Imaging (MRI) of Left Breast
	BH32Y0Z	Magnetic Resonance Imaging (MRI) of Bilateral Breasts using Other Contrast, Unenhanced and Enhanced
	BH32YZZ	Magnetic Resonance Imaging (MRI) of Bilateral Breasts using Other Contrast
	BH32ZZZ	Magnetic Resonance Imaging (MRI) of Bilateral Breasts
ICD-10 Diagnosis	All Diagnoses	

Policy History

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

Effective Date	Action	Reason
08/29/2014	BCBSA Medical Policy adoption	Medical Policy Committee
03/30/2015	Policy revision without position change	Medical Policy Committee
11/01/2016	Policy revision without position change	Medical Policy Committee
11/01/2017	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements (as applicable to your plan)

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

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

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national

guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.