

## Medical Policy



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### **Title: Computer-Aided Evaluation of Malignancy with Magnetic Resonance Imaging of the Breast**

#### **Professional**

Original Effective Date: October 5, 2006

Revision Date(s): April 19, 2007;

November 2, 2009

Current Effective Date: November 2, 2009

#### **Institutional**

Original Effective Date: November 2, 2009

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#### **DESCRIPTION**

The use of computer-aided evaluation (CAE), also known as computer-aided detection (CAD), 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 of the difficulty in distinguishing between benign and malignant lesions. MRI may be used to screen women at high genetic 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 gauge the impact of cancer treatment. The CAE systems reviewed in this policy are intended to improve the specificity of MRI in detecting or measuring malignant tissue, while maintaining the generally high sensitivity of MRI. This could potentially reduce biopsy rates if it improves the ability to identify which MRI-detected lesions are almost certainly benign. There is anecdotal information that MRI may also be used in an effort to reduce re-operation rates among patients undergoing breast-conserving surgery by more clearly identifying the tissue that should be removed. The use of CAE may also shorten the time needed to interpret breast MRI images, which currently takes longer than reading mammograms.

CAE systems for MRI essentially provide easier ways of interpreting the patterns of contrast enhancement and washout across a series of images, which in turn may help identify lesions and their likelihood of being malignant. In contrast to computer-aided detection (CAD) systems used with mammography, CAE for MRI is not aimed primarily at identifying 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 are 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 they can 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 patterns of enhancement for each pixel in the breast image, thereby allowing the radiologist to analyze the enhancement patterns systematically.

CAE systems for MRI of the breast were initially called CAD systems, the same terminology used for mammography. However, the focus with MRI of the breast is on improving specificity (distinguishing malignant from benign) rather than increasing sensitivity (i.e., detection), as in mammography. The authors of 2 recent studies refer to CADStream as a computer-aided evaluation (CAE) program, and that terminology has been adopted in this policy.

Several CAE systems for use with MRI of the breast have 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA). The 3TP Software Option, manufactured by 3TP LLC (now called CAD Sciences, White Plains, NY), was cleared on June 23, 2003. iCAD acquired CAD Sciences in 2008 and is now marketing a system called SpectraLook™ with CADVue™. CADstream™, which is manufactured by Confirma, Inc. (Kirkland, WA), was cleared on July 30, 2003. A third system called Aegis (Sentinelle Medical Inc, Toronto, Ontario, Canada) received 510(k) marketing clearance from the FDA on February 9, 2007, as substantially equivalent to CADStream Version 4.0. However, in the 510(k) documents, the manufacturer states that the primary goal of Aegis is “to identify where and how deep a biopsy or localization needle should be inserted into an imaged breast.” Additional products include DynaCAD (MRI Devices Corporation, Waukesha, WI; now apparently from Invivo Corp, Orlando, FL), which was cleared July 21, 2004; and Z3D Contrast Acuity Software (Clario Medical Imaging, Inc., Seattle, WA), which was cleared September 5, 2008, and is apparently used in conjunction with CAE for MRI systems. Some of these systems may have broader uses beyond breast MRI. There also may be some overlap in the functions performed by these devices and other image-processing systems.

According to documents filed with the FDA, the 3TP Software Option is “intended to be used as a post-processing software package designed to provide a reliable means for visualizing the presence and pattern of contrast-induced enhancement on MR datasets.” It provides a color-coded image that indicates the likelihood that each pixel shows malignant or benign tissue based on the changes in enhancement at 3 points in time, which are defined by the software program. CADstream is described as a “Computer Aided Detection (CAD) system intended for use in analyzing magnetic resonance imaging (MRI) studies. CADstream automatically registers serial patient image acquisitions to minimize the impact of patient motion, segments and labels tissue types based on enhancement characteristics (parametric image maps), and performs other user-defined post-processing functions (image subtractions, multiplanar reformats, maximum intensity projections). When interpreted by a skilled physician, this device provides information

that may be useful in screening and diagnosis...Patient management should not be based solely on the results of the CADstream analysis." It also provides automated determination of volumes of interest. In addition, CADstream can be used during MRI-guided biopsies.

### **POLICY**

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

### **RATIONALE**

This policy regarding computer-aided evaluation (CAE) for magnetic resonance imaging (MRI) of the breast is based on a 2006 TEC Assessment (1) and updated with a literature search through March 2009. Key aspects of that assessment are reviewed and summarized in this section.

The TEC Assessment summarized 4 published articles and 4 abstracts that met the search criteria. (To meet search criteria, articles had to compare the sensitivity and specificity of MRI of the breast interpreted with and without the use of CAE systems. While the search focused on commercially available CAE systems, some articles on other systems were included. In addition, studies had to report on cancer detection based on histological 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 (2) provided information on one of the non-commercial systems used to evaluate women with cancer who were eligible for breast-conserving therapy (BCT). (Note: Policy No. 6.01.29, "MRI of the Breast," lists this use as investigational.) Additional findings (other lesions or larger lesions) were found in 48 of the 116 (41%) women; about 80% of these women had further workup; and in 27 of these women the findings were malignant. The area under the ROC curve was 0.91+0.04 for the radiologist reading and 0.98+0.04 for the combined radiologist and computerized reading ( $p=0.03$ ). However, the ability to generalize these results and the clinical impact of the findings is uncertain.

Four abstracts of studies were included in the TEC Assessment because of the small number of studies identified. However, the need to exercise caution in using results from abstracts must be kept in mind as these results are reviewed. Of the 4 abstracts, 2 used CADstream, 1 did not report the system used, and 1 was an excerpt from an article that summarized the results of 3 earlier abstracts on the 3TP system. It is not clear whether the current 3TP system has been modified substantially from the version used in these studies. Once again, these abstracts report on the results of CAE with MRI among women with known lesions.

Finally, DeMartini reported on the use of CAE with MRI in 15 patients to assess the impact of chemotherapy. (3) This small study found there were a substantial number of false negative results for residual malignancy using CAE—a different type of problem than found with most other uses of MRI, i.e., too many false positive results.

Unfortunately, the literature on the use of CAE with MRI of the breast was sparse overall, and few studies addressed the specific situations in which CAE with MRI is used in a clinical setting. Many of the few articles and abstracts calculated test characteristics on the basis of 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 (DCIS), the mix of DCIS versus masses would affect the calculations of sensitivity and specificity and might affect the impact of the CAE system.

Prospective, well-designed and executed studies that look specifically at the addition of CAE with MRI for the specific uses of interest are needed to determine whether or not the use of CAE provides a positive clinical benefit to these patients.

In summary, there are no high-quality, published studies of the impact of commercially available CAE systems on the sensitivity and specificity of MRI of the breast. The few studies and abstracts available focus primarily on the development of a CAE system or they include samples of women that are highly selective and usually have far more cases of cancer than would be encountered in a screening population.

### **2008 Update**

Two articles were published, apparently based on the retrospective study presented in an abstract mentioned previously. The first article, published in 2006, reported on 33 consecutive lesions biopsied under MRI guidance at a single institution. (4) The second article, published in 2007, reported on 155 consecutive lesions that appeared to subsume the 33 lesions included in the 2006 study; the later article is therefore summarized here. (5) The lesions were not palpable or visible on mammography or sonography and were assessed with and without CAE. (4) All of these lesions were rated BIRADS 4 or 5, i.e., suspicious or highly suggestive of malignancy. Of these lesions, 64% were in recently diagnosed breast cancer patients, 14% were in high-risk patients being screened, and 14% were for problem solving. Three different MRI imaging protocols were used. CADStream was then retrospectively applied for this study. Each pixel in the image was color coded based on, first, whether it reaches a threshold level of enhancement in the first post-contrast image, and, second, whether the enhancement increases, plateaus, or decreases in subsequent post-contrast images. The threshold level of enhancement for the first post-contrast image varied from 50% to 100%. One lesion was excluded for a technical issue with the initial MRI. As expected, increasing the level of enhancement required (to 100%) lowered the number of false positive results. Thirty-eight of 41 (93%) malignant lesions enhanced at both thresholds [1]; while enhancement was absent in 23% of benign lesions. Two of the 3 false negative lesions exhibited

enhancement when the cursor was manually placed over the lesion. At the 50% enhancement level, no statistically significant difference was found in the positive predictive value between the initial reading and the subsequent application of CAE; at the 100% enhancement level, however, the positive predictive value was significantly higher with CAE than without (30.4% vs. 26.6%,  $p=0.02$ ). Because the radiologists who read each set of images with and without CAE were not necessarily the same, it is possible that some of this difference might be due to a variation across readers rather than to the addition of CAE. There was no significant difference in subsequent enhancement patterns (i.e., washout, persistent, or plateau) between benign and malignant lesions; and many lesions included diverse enhancement patterns.

In the first report (4), the authors highlighted the possibility of using the CAE results to identify lesions that do not need to be biopsied, in other words, to identify a subset of the false positive findings that could safely avoid biopsy. However, the sample was highly selective and not representative of the full spectrum of findings likely to be encountered in practice. In the second report (5), not all of the lesions identified as benign with CAE were in fact benign, i.e., there were false negative findings. The risk of missing cancers and delaying treatment has to be weighed against the opportunity for reducing the number of unnecessary biopsies. The magnitude of this risk cannot be estimated reliably from a single study.

Further research is needed that focuses on the incremental value of CAE in larger samples and a variety of settings.

### **2009 Update**

The policy was updated with a literature search conducted in March 2009; no new relevant studies were found.

### **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.**

#### **CPT/HCPCS**

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

**REVISIONS**

04-19-2007	Policy added to the bcbsks.com web site.
11-02-2009	Title: <ul style="list-style-type: none"> <li>▪ Title changed From "Magnetic Resonance Imaging (MRI) and Computer Assisted Detection (CAD)" To " Computer-Aided Evaluation of Malignancy with Magnetic Resonance Imaging of the Breast"</li> </ul>
	Description section updated.
	Rationale section added.
	References section updated.

**REFERENCES**

1. 2006 TEC Assessment; Tab 4.
2. Deurloo EE, Peterse JL, Rutgers EJ et al. Additional breast lesions in patients eligible for breast-conserving therapy by MRI: impact on preoperative management and potential benefit of computerized analysis. *Eur J Cancer* 2005; 41(10):1393-401.
3. DeMartini WB, Lehman CD, Peacock S et al. Computer-aided detection applied to breast MRI: assessment of CAD-generated enhancement and tumor size in breast cancers before and after neoadjuvant chemotherapy. *Acad Radiol* 2005; 12(7):806-14.
4. Lehman CD, Peacock S, DeMartini WB, Chen X. A new automated software system to evaluate breast MR examinations: Improved specificity without decreased sensitivity. *AJR* 2006; 187:51-6.
5. Williams TC, DeMartini WB, Partridge SC, Peacock S, Lehman CD. Breast MR imaging: Computer-aided evaluation program for discriminating benign from malignant lesions. *Radiology* 2007; 244(1):94-103.