

Computer-Aided Detection of Malignancy with Magnetic Resonance Imaging of the Breast



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Executive Summary

Background

The use of computer-aided detection (CAD) is proposed to supplement radiologists' interpretation of contrast-enhanced magnetic resonance imaging (MRI) of the breast. MRI of the breast is sometimes used as an alternative to mammography or other screening and diagnostic tests because of its high sensitivity in detecting breast lesions, even among those women—for example, younger women and those with denser breasts—in whom mammography is less accurate. However, MRI has a high false-positive rate because of the difficulty in distinguishing between benign and malignant lesions. It is also used to look for more extensive disease in women diagnosed with breast cancer and to gauge the impact of treatment. The CAD systems reviewed in this Assessment are intended to improve the specificity of MRI in detecting or measuring malignant tissue, while maintaining the generally high sensitivity of MRI. The use of CAD may also shorten the time needed to interpret breast MRI images, which currently takes much longer than reading mammograms.

Objective

To assess the evidence on the use of CAD with MRI of the breast by comparing the sensitivity, specificity, and recall rate¹ of MRI with and without the use of commercially available CAD systems in detecting malignant lesions, evaluating the extent of disease in women with cancer, or gauging the impact of treatment.

Search Strategy

MEDLINE search through March 2006, as well as reviewing reference lists and querying experts in the field.

Selection Criteria

Articles had to compare the sensitivity and specificity of MRI of the breast read with and without the use of CAD systems. The primary focus is on commercially available CAD systems, although some articles on other systems were included if they provided useful information on the potential impact of CAD systems. Additionally, studies had to report on cancer detection based on histological results for at least some of the patients in the sample. Articles on CAD development that did not include independent testing sets or that had fewer than 20 cases were excluded. Selected abstracts were included, but their results should be interpreted with caution.



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¹ The recall rate is the percentage of patients asked to come back for further evaluation.

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Main Results

Many of the studies on the use of CAD with MRI of the breast primarily report on the development of CAD systems or testing new CAD approaches. Few of them evaluate commercially available CAD systems. Several of those that do, report on the development and testing of approaches that underlie one of the commercially available systems (3TP); it is not clear to what degree the current 3TP system has or has not been modified compared to these earlier approaches. Although the studies had to have separate testing data sets to be included in this Assessment, these data sets often were enriched with more cancer cases or consisted exclusively of cases in which lesions had been found. As a result, the range of sensitivities and specificities cannot be applied to the populations usually found in a clinical setting. In addition, because many of the studies are retrospective and report primarily on the development and testing of a CAD system, they lack the rigor and generalizability of a large, prospective, well-designed study.

Author's Conclusions and Comments

Unfortunately, the literature on the use of CAD with MRI of the breast was sparse overall, and few studies addressed the specific situations in which CAD 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 CAD system. There is one article looking at the use of a non-commercial CAD system with MRI among women scheduled for breast-conserving therapy (BCT). About 41% of these women had additional findings (larger or additional lesions), 56% of which were malignant. The results led to changes in treatment when more extensive disease was found. 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 ($p=0.03$).

The literature as a whole is not clear on how the CAD system is to be used. In the case of CAD with mammography, the radiologist reads the original films first, makes a diagnosis, and then reviews the CAD results. Because CAD is not 100% sensitive, lesions detected both before the use of CAD and after viewing the CAD results may be worked up. In this way, CAD can add to the sensitivity of mammography, but not its specificity. With MRI of the breast, the sensitivity is already high, and the focus is primarily on increasing the specificity. In some articles, it appears that CAD is intended as an adjunct to the initial MRI reading, just as with CAD and mammography. In other articles, it is proposed as a way of speeding up the MRI reading process, and the precise protocol to be followed in reading the MRI images is not clear. Furthermore, unlike in the case of CAD with mammography, in the documents regarding the FDA clearance it does not specify that CAD must be added only after an initial reading of the images alone, although it does say for one system that "Patient management decisions should not be made based solely on the results of the CADstream analysis." Obviously, the impact of CAD on the accuracy of MRI of the breast may depend in part on how the CAD results are incorporated into the reading and diagnostic process.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the computer-aided detection of malignancy with MRI of the breast meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Two CAD systems for use with MRI of the breast have 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA).

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

There are no high quality, current published studies of the impact of commercially available CAD systems on the sensitivity and specificity of MRI of the breast. The few studies and abstracts available focus primarily on the development of the CAD 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.

**3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.**

There is insufficient evidence to assess whether the use of CAD systems would maintain or increase the sensitivity, specificity, and recall rates of MRI of the breast. Given the inability to evaluate these intermediate outcomes, it is not possible to assess the impact of CAD on health outcomes such as treatment success among breast cancer patients or survival.

5. The improvement must be attainable outside the investigational settings.

Whether the use of CAD with MRI of the breast improves outcomes has not been established in the investigational setting.

For the above reasons, computer-aided detection of malignancy with MRI of the breast does not meet the TEC criteria.

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TEC Staff Contributors

Author—Barbara M. Rothenberg, Ph.D.; **TEC Executive Director**—Naomi Aronson, Ph.D.; **Managing Scientific Editor**—Kathleen M. Ziegler, Pharm.D.; **Research/Editorial Staff**—Claudia J. Bonnell, B.S.N., M.L.S.; Maxine A. Gere, M.S.

Blue Cross and Blue Shield Association Medical Advisory Panel

Allan M. Korn, M.D., F.A.C.P.—Chairman, *Senior Vice President, Clinical Affairs/Medical Director, Blue Cross and Blue Shield Association*; **Alan M. Garber, M.D., Ph.D.**—Scientific Advisor, *Staff Physician, U.S. Department of Veterans Affairs*; **Henry J. Kaiser, Jr., Professor, and Professor of Medicine, Economics, and Health Research and Policy, Stanford University**; **Steven N. Goodman, M.D., M.H.S., Ph.D.**—Scientific Advisor, *Associate Professor, Johns Hopkins School of Medicine, Department of Oncology, Division of Biostatistics (joint appointments in Epidemiology, Biostatistics, and Pediatrics)*—American Academy of Pediatrics Appointee. ■ **Panel Members** **Peter C. Albertsen, M.D.**, *Professor, Chief of Urology, and Residency Program Director, University of Connecticut Health Center*; **Edgar Black, M.D.**, *Vice President, Chief Medical Officer, BlueCross BlueShield of the Rochester Area*; **Sarah T. Corley, M.D.**, *Physician Consultant, NexGen Healthcare Information Systems, Inc.*—American College of Physicians Appointee; **Helen Darling, M.A.**, *President, National Business Group on Health*; **Josef E. Fischer, M.D., F.A.C.S.**, *Mallinckrodt Professor of Surgery, Harvard Medical School and Chair, Department of Surgery, Beth Israel Deaconess Medical Center*—American College of Surgeons Appointee; **Willard K. Harms, M.D., M.M.**, *Medical Director, Medical Policy and Adjudication, Blue Cross Blue Shield of Illinois*; **I. Craig Henderson, M.D.**, *Adjunct Professor of Medicine, University of California, San Francisco*; **Mark A. Hlatky, M.D.**, *Professor of Health Research and Policy and of Medicine (Cardiovascular Medicine), Stanford University School of Medicine*; **Bernard Lo, M.D.**, *Professor of Medicine and Director, Program in Medical Ethics, University of California, San Francisco*; **Barbara J. McNeil, M.D., Ph.D.**, *Ridley Watts Professor and Head of Health Care Policy, Harvard Medical School, Professor of Radiology, Brigham and Women's Hospital*; **Brent O'Connell, M.D., M.H.S.A.**, *Vice President and Medical Director, Pennsylvania Blue Shield/Highmark, Inc.*; **William R. Phillips, M.D., M.P.H.**, *Clinical Professor of Family Medicine, University of Washington*—American Academy of Family Physicians Appointee; **Maren T. Scheuner, M.D., M.P.H.**, *Visiting Associate Professor, Department of Health Services, UCLA School of Public Health*—American College of Medical Genetics Appointee; **J. Sanford Schwartz, M.D.**, *Professor of Medicine, Department of Medicine, University of Pennsylvania School of Medicine and Professor, Health Care Systems, Health Management & Economics, The Wharton School*; **Earl P. Steinberg, M.D., M.P.P.**, *President, Resolution Health, Inc.*; **A. Eugene Washington, M.D., M.Sc.**, *Executive Vice Chancellor, University of California, San Francisco*; **Jed Weissberg, M.D.**, *Associate Executive Director for Quality and Performance Improvement, The Permanente Federation.*

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Assessment Objective

This Assessment will review the evidence on the use of computer-aided detection (CAD) with magnetic resonance imaging (MRI) of the breast by comparing the sensitivity, specificity, and recall rate of MRI for the specific indications described, with and without the use of commercially available CAD systems. The primary focus is on determining whether the use of CAD would increase the specificity of MRI and thereby reduce the large number of false-positive results, without adversely affecting the high sensitivity of MRI of the breast. The indications covered in this Assessment include the use of MRI of the breast for screening women at high genetic risk of breast cancer, for gauging tumor size, for detecting multifocal or multicentric disease, and for measuring the impact of chemotherapy.

Background

Summary of Prior Assessments on Use of MRI of the Breast

The Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) has released 4 Assessments on the use of MRI of the breast since late 2003, which look at the available evidence on a number of possible uses of this technology. The results are summarized in Table 1. Additional details can be found in the Assessments (TEC 2003, 2004a-c).

In late 2005, TEC staff conducted a literature search on the use of MRI of the breast for indications that currently do not meet TEC criteria. Although additional studies have been published since the Assessments described in Table 1 were released, they were not sufficient to stimulate a reassessment.

There are also several other potential uses of MRI that are not covered in the Assessments. They include the use of MRI to determine the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumor and to screen the contralateral breast in patients who have breast cancer.

A number of clinical trials are underway on the use of MRI of the breast, including several by the American College of Radiology Imaging Network (ACRIN), including the ACRIN-A6667 trial, "MRI Evaluation of the Contralateral Breast in Women with a Recent Diagnosis of

Breast Cancer." It completed enrollment of 1,000 subjects as of June 2004; monitoring is continuing through December 2006. Another ongoing trial is ACRIN Protocol A6657, called "Contrast-Enhanced Breast MRI for Evaluation of Patients Undergoing Neoadjuvant Treatment for Locally-Advanced Breast Cancer." As of November 11, 2005, 214 of the desired 244 subjects had been enrolled. For more information on these trials, see www.acrin.org/current_protocols.html.

Additional studies on optimal strategies for screening women at high genetic risk of breast cancer are underway, including at the National Institutes of Health (Protocol Number 01-C-0009, "Breast Imaging Studies in Women at High Genetic Risk of Breast Cancer: Annual Follow-up Study") and at Stanford University (NCT00255060, "Comprehensive Screening for Women at High Genetic Risk of Breast Cancer"). It does not appear from the limited information available on these studies at www.clinicaltrials.gov that they will look at the impact of CAD systems on the accuracy of MRI. Many other trials on the use of MRI of the breast are also listed on that site, and none of them mentions CAD in the brief descriptions available.

The current Assessment on the use of CAD with MRI of the breast will look for evidence that 1) CAD improves the accuracy of MRI for those indications in which MRI has been shown to produce equal or better outcomes than the alternative approach or 2) CAD sufficiently improves the accuracy of MRI that indications currently not known to produce equal or better outcomes may cross that threshold with the addition of CAD.

Breast MRI

Over the past decade, MRI of the breast has been studied in a variety of clinical settings, including both benign and malignant conditions of the breast. MRI has shown clinical utility in evaluating silicone breast implants for rupture. Controversy remains, however, regarding the role MRI should play in the evaluation of patients with known or suspected breast cancer. While MRI has a very high sensitivity for detecting lesions, its specificity is variable and often quite low because of the difficulty in distinguishing between benign and malignant lesions. The sensitivity for detection of invasive carcinoma overall is above 90%, while specificities between 37% and 90% have been reported (Deurloo et al. 2005a). The low specificity is

Table 1. Summary of TEC Assessments on MRI of the Breast

Indication	Meets TEC Criteria?*	Conclusions	Source
Screening women at high genetic risk of breast cancer	Yes	MRI is at least as sensitive as mammography in detecting breast cancer in this population. It may be more sensitive with equivalent or slightly inferior specificity.	TEC 2003
MRI used to detect breast cancer in patients with breast characteristics that limit the sensitivity of mammography, e.g., dense breasts, implants, scarring after treatment for breast cancer	No	For women with no prior breast cancer among these groups, there is insufficient evidence on the performance of MRI. The preliminary results for women with prior cancer suggest possibly higher sensitivity and similar or better specificity, but they need to be confirmed in additional prospective studies, which also identify the subsets of patients where MRI is most useful.	TEC 2004a
MRI used to detect a suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma and negative mammography and clinical breast exam	Yes	Combining the available studies, the sensitivity of MRI for this use is about 94%, while the PPV was generally 90% or greater. The use of positive MRI findings to guide BCT instead of presumptive mastectomy appears to offer substantial benefit with relatively little harm associated with unnecessary biopsy.	TEC 2004a
MRI used to diagnose low-suspicion findings on conventional testing among women who have been referred for short-interval follow-up rather than immediate biopsy	No	The available evidence is not of sufficient quality or quantity to permit conclusions concerning the effect of MRI as an adjunctive diagnostic test on health outcomes.	TEC 2004a
MRI used to diagnose a suspicious breast lesion to avoid biopsy	No	While MRI would identify a number of patients who could safely avoid biopsy, it would incorrectly identify some cancers as benign. The potential benefit of sparing patients from unnecessary biopsy does not outweigh the potential harm of a missed or delayed diagnosis of breast cancer.***	TEC 2004a
MRI performed before and after completion of neoadjuvant chemotherapy for presurgical planning	Yes	MRI appears to provide a more accurate preoperative assessment of residual tumor after neoadjuvant chemotherapy. This can be used to more accurately identify candidates for breast-conserving therapy and to avoid the need for re-excision surgery when BCT is not appropriate.	TEC 2004b

Table 1. Summary of TEC Assessments on MRI of the Breast (cont'd)

Indication	Meets TEC Criteria?*	Conclusions	Source
MRI performed before and during neoadjuvant chemotherapy to provide an early prediction of response to chemotherapy	No	There is insufficient evidence to determine whether breast MRI can reliably predict response to neoadjuvant chemotherapy.	TEC 2004b
Preoperative evaluation in women with localized breast cancer, primarily to look for multicentric disease	No	MRI is more sensitive than the current presurgical evaluation in identifying multicentric breast tumors, although presurgical biopsy is needed to weed out false positive results. However, there is insufficient evidence to show that using these findings to change treatment from BCT to mastectomy leads to better outcomes, given the use of radiation therapy following surgery. Therefore, the value of identifying the multicentric lesions is unclear.	TEC 2004c
Preoperative evaluation in women with localized breast cancer, primarily to look for multifocal disease	NA**	MRI is more sensitive at identifying multifocal disease, although the findings on its specificity vary. There is insufficient information to determine whether the use of MRI to guide BCT would increase the likelihood of obtaining negative margins and reduce the need for re-excision surgery.	TEC 2004c
Preoperative evaluation of primary tumor size	NA**	It does appear that MRI measurements of tumor size are better correlated with pathological measurements than mammography is. But again, the impact on outcomes has not been demonstrated.	TEC 2004c

* The TEC criteria are as follows: (1) The technology must have final approval from the appropriate governmental regulatory bodies. (2) The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes. (3) The technology must improve the net health outcome. (4) The technology must be as beneficial as any established alternatives. (5) The improvement must be attainable outside the investigational setting.

** Several indications did not undergo a full assessment but were discussed in an appendix to Vol. 18, No. 8 (TEC 2004c).

*** This conclusion was supported by a recent comparative effectiveness report from the federal Agency on Healthcare Research and Quality on the accuracy of noninvasive diagnostic tests in women presenting with breast abnormalities (either by mammography or physical examination). The report specifically compared ultrasound (US), positron emission tomography (PET), scintimammography, and magnetic resonance imaging (MRI) (Bruening et al. 2006). It recommends against using MRI or any of the other tests to identify women with suspicious mammograms who do not need to go on for biopsy. Considering women at an average risk of breast cancer following an abnormal mammogram (20%), for every 1,000 women who had a negative MRI, 38 cases of cancer would be missed in return for avoiding 962 unnecessary biopsies.

particularly challenging in younger women, who are more likely to have enhancing benign lesions (Gilhuijs et al. 2002). Considerable work has been done to develop algorithms that distinguish between benign and malignant lesions, usually relying on a combination of morphologic and temporal characteristics (the latter refers to the distinctive enhancement and washout patterns following the administration of contrast).

Breast MRI is performed using commercially available MRI machines, but technical approaches to MRI of the breast vary (Orel and Schnall 2001; Liberman 2004). Breast tissues generally have similar signal intensities as tumor tissue on routine MRI sequences. However, malignant breast lesions typically demonstrate significant enhancement following the intravenous administration of contrast agents containing gadolinium chelates. Tumor enhancement relates to increased angiogenesis in tumor tissues and increased vascular permeability (Knopp et al. 1999). While the vast majority of malignant breast lesions exhibit contrast enhancement, some malignancies may not (e.g., lobular carcinoma, ductal carcinoma in situ [DCIS]), producing false-negative results; and some benign breast conditions may demonstrate marked contrast enhancement (e.g., fibroadenoma, inflammatory conditions). Normal breast tissues may demonstrate diffuse enhancement that relates to hormonal influences. Thus, performing MRI during the first 2 weeks of the menstrual cycle has been recommended to reduce this phenomenon (Rieber et al. 1999).

The observation that contrast enhancement of a breast lesion is a nonspecific feature has led investigators to explore whether patterns of lesion enhancement on dynamic imaging after contrast bolus might provide a greater degree of specificity in diagnosing malignancy. Typically, malignant lesions reach peak enhancement early and then wash out more quickly. Benign lesions that show enhancement (such as fibroadenoma) generally demonstrate a less rapid initial increase in enhancement and continue to enhance over time; however, there is variability and overlap in these patterns, and time-enhancement patterns alone do not provide an accurate diagnosis in all cases (Kuhl et al. 1999; Orel 1999; Shepardson and Listinsky 2005).

Some investigators have incorporated additional criteria into the determination of MRI results in an attempt to increase the specificity without compromising sensitivity (Liberman 2004; Nunes et al. 1997b, 2001). Descriptive features of lesion morphology such as those used in X-ray mammography may be helpful in this regard. For example, lesions with irregular or spiculated margins are characteristically malignant, while lesions with smooth, regular margins are usually benign (Nunes et al. 1997a). Others have studied the distribution pattern of contrast enhancement within a lesion, noting whether there is uniform or heterogeneous enhancement. One study of 79 enhancing lesions in 49 women noted that rapid washout of contrast enhancement from the periphery of the lesion was 100% specific in identifying malignancy, although this feature was only seen in about half of the malignant lesions studied (Sherif et al. 1997). Another study of 94 lesions in 91 women also found 100% specificity of a peripheral enhancement pattern, but only 34% of malignancies could be detected by using this feature alone (Mussurakis et al. 1998).

MRI scanning is performed both before contrast administration (pre-contrast) and after contrast administration (post-contrast), but there are several technical methods employed by different investigators. Post-contrast images maximizing spatial resolution (better detail in images) may be obtained using high-resolution MRI sequences, or images maximizing temporal resolution may be acquired using dynamic imaging. High-resolution MRI generally requires several minutes to acquire the data, and thus only 1 or 2 sets of post-contrast images may be obtained during the 5-minute period of enhancement after contrast injection. Dynamic imaging sequences sacrifice some spatial resolution and are each acquired within seconds, so that imaging may be rapidly repeated during the enhancement period. High-resolution imaging demonstrates the presence of enhancing lesions, but does not provide dynamic information on the variation of enhancement levels over time.

The magnetic field strength of the MRI machine employed varies in the literature. Most studies use a general-purpose high-field MRI system (1.0–1.5 Tesla) for imaging, although low-field MR systems (approximately 0.5 Tesla) have been studied as well. Low-field strengths

have inherent limitations in sensitivity for detecting gadolinium enhancement and lower signal-to-noise ratios compared to high-field imaging, and they may require longer data acquisition times. Possible advantages of low-field systems are lower cost and the potential for “open-access” designs, permitting access to the patient for MRI-guided biopsy.

MRI of the breast is typically performed with the patient in a prone position with the breasts hanging through a cutout in the table. The use of a dedicated breast coil is recommended. Some studies have explored using breast compression. When MRI-guided biopsy of a lesion is planned, the patient may be positioned on her side to permit easier access to the breast for biopsy. Biopsy of breast lesions identified on MRI has been accomplished using MRI-compatible needles and localization equipment (Morris et al. 2002; Kuhl et al. 2001; Helbich 2001; Orel et al. 1994; deSouza et al. 1995).

There are several limitations with MRI of the breast, including the lower specificity, higher cost, and longer time to interpret. The question is whether CAD can address some of these issues.

Computer-Aided Detection (CAD) Systems.

CAD 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 CAD systems used with mammography, CAD 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. CAD systems, in contrast, use

color-coding and differences in hue to indicate the patterns of enhancement for each pixel in the breast image. It thereby may allow the radiologist to analyze the enhancement patterns systematically, although there is some question about how effective it is in reducing interobserver variability (Gabriel et al. 2005). Some CAD programs apparently incorporate morphological characteristics as well to estimate a probability of malignancy.

This Assessment focuses on CAD systems that are commercially available. However, because of the paucity of literature assessing the performance of these systems, research on several other CAD systems is also presented to provide context.

There are 2 CAD systems for use with MRI that are commercially available: 3TP Software Option (CAD Sciences, White Plains, NY) and CADstream™ (Confirma, Inc., Kirkland, WA). According to documents filed with the U.S. Food and Drug Administration (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.

One researcher described the CADstream system as follows:

The CAD software is designed to automate many image-processing and analysis functions currently performed manually by the MRI technologist and radiologist. The system produces color overlay maps over lesions found to have enhancement meeting a user-specified minimum threshold. In addition, it provides an automated interactive display of kinetic enhancement curves and details of all regions meeting the specified threshold of enhancement. (DeMartini et al. 2005a)

FDA Status. Two CAD 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. CADstream™, which is manufactured by Confirma, Inc. (Kirkland, WA), was cleared on July 30, 2003.

Methods

Search Methods

A literature search of MEDLINE was conducted using the following search strategy through March 2006: textword searches using (“magnetic resonance” OR MRI) AND breast AND various other terms: computer aided, computer assisted, CAD, pharmacokinetic analysis, neural network, etc. Articles were restricted to those in the English language and reporting on human subjects. Other articles were identified from reference lists and consultation with experts. In all, 70 articles and 8 abstracts were reviewed to identify those that examined the incremental impact of CAD systems on the sensitivity, specificity, and/or recall rate of MRI of the breast for its various uses. Only articles that looked at commercially available CAD systems were included in the formal Assessment; articles examining other CAD systems were used to provide context.

Study Selection

Articles had to compare the sensitivity and specificity of MRI of the breast read with and without the use of CAD systems. The primary focus is on commercially available CAD systems, although some articles on other systems were included if they provided useful information on the potential impact of CAD

systems. Additionally, studies had to report on cancer detection based on histological results for at least some of the patients in the sample. Articles on CAD development that did not include independent testing sets or that had fewer than 20 cases were excluded.

Because of the paucity of literature on the use of CAD with MRI of the breast, 8 abstracts were also reviewed. Results from abstracts, while suggestive, should be viewed with caution. First, there is insufficient detail to assess the validity and generalizability of the results. Second, studies have found differences in the specific results reported in abstracts and in the peer-reviewed articles that are subsequently published, in part because abstracts may contain only preliminary results. For example, in 1 study of 148 randomized controlled trials presented at the American College of Cardiology scientific meetings that were subsequently published, 60 (41%) reported efficacy estimates in the published article that differed from the abstract (Toma et al. 2006).

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association’s Medical Advisory Panel (MAP) on February 23, 2006. To maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the text where appropriate. There were no studies that would change the conclusions of the Assessment.

Formulation of the Assessment

Patient Indications

There are a variety of patient indications for MRI of the breast because of its varied uses. Generally, the uses fall into 2 categories: a) screening and b) evaluation of patients diagnosed with breast cancer. The primary screening use is probably among women considered to be at high risk of breast cancer and possibly among women with certain types of breasts (e.g., dense) where mammography may not perform well. Screening of other women at average risk is not recommended because of the high false positive rate. When used among women diagnosed with breast cancer, MRI is

used to identify additional lesions, gauge the size of the lesion, and track the impact of treatment.

Technologies to be Compared

MRI of the breast supplemented by the use of a CAD system will be compared with MRI of the breast without CAD.

Health Outcomes

Benefits. The potential benefits of CAD with MRI vary with its uses. When used for screening selected populations (e.g., those at high risk of cancer), the improved sensitivity of MRI compared to mammography comes at the cost of lower specificity. If CAD improves the specificity of MRI, it would reduce the number of unnecessary biopsies or further work-ups. CAD systems are also potentially helpful in bringing the accuracy of less-skilled readers up to those of expert readers. Improving the sensitivity of MRI would lead to earlier treatment of women with cancer and, it is hoped, lower recurrence rates and increased survival. Improving the specificity would reduce unnecessary diagnostic tests and biopsies, with the accompanying psychological distress, discomfort, and cost. It might also reduce the potential for lower compliance with screening recommendations in the future, if false-negative results have an adverse impact on compliance with screening.

If CAD improves the accuracy of MRI in women with breast cancer, it could potentially lead to better decisions regarding the use of breast-conserving therapy versus mastectomy as well as help guide decisions on the use of different chemotherapy agents. Many women would prefer breast-conserving therapy if it would not worsen their outcomes, and CAD with MRI could improve the ability to identify appropriate candidates for this procedure. If CAD improved MRI's ability to identify patients who were not responding to chemotherapy, a change in treatment could be made that might increase the likelihood of a good outcome while reducing the adverse effects associated with an ineffective treatment.

If the addition of CAD improves the accuracy of MRI of the breast, it may allow for broader uses of MRI, which has the advantage that it requires no radiation, is non-invasive (except for the use of contrast), provides three-dimensional images, and may be more comfortable for women because it does not use breast compression, as mammography does.

Harms. If the use of CAD increases the number of recalls and biopsies without an appreciable increase in the number of cancers detected, then it may increase the burden of screening for women. If it increases the false-positive rate and the number of negative biopsies, it produces anxiety and possibly physical discomfort without any commensurate benefit. There has been a concern that compliance with mammography screening may decline after a person has a false-positive result, although this has not always been borne out (Chiarelli et al. 2003, Currence et al. 2005). Unnecessary testing is also costly.

If the use of CAD with MRI increases its sensitivity and/or its specificity in detecting multifocal or multicentric disease, it may lead to an increase in the use of mastectomies versus breast-conserving therapy. The difficulty is that there is no current evidence that mastectomies in these cases would produce better outcomes than breast-conserving therapy followed by radiation. (For a more detailed discussion of this issue, see TEC 2004c). Similarly, if changes in chemotherapy are made as a result of the MRI plus CAD results, outcomes could be worsened rather than improved.

Specific Assessment Question

- When performing MRI of the breast, how does adding a review of CAD results to the reading process affect the sensitivity and specificity of MRI, and a) the number of unnecessary additional tests or biopsies or b) treatment outcomes?

Review of Evidence

To assess the impact of the addition of CAD to the reading of MRI of the breast, it is important to have studies that look at the performance of MRI with and without CAD in the specific populations of interest. Ideally, these studies would be prospective, would include multiple readers, would recruit a consecutive list of patients (to reduce bias), and would otherwise be well-designed, executed, and reported. It is important to examine the impact of CAD on both sensitivity and specificity and ensure that CAD systems do not reduce sensitivity while potentially increasing specificity.

Table 2 summarizes the 4 published articles and 4 abstracts that met the search criteria. Three of the articles reported on development

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Articles in Peer-Reviewed Journals							
Deurloo et al. 2005a; distinguishing between benign and malignant lesions	Mixed: Some prospective and some retrospective cases	The description of the various data sets used in this analysis was sometimes difficult to follow. All lesions depicted on MRI at their clinic during a specified period were eligible for inclusion, including focal masses and areas of non-mass-related enhancement. Lesions were <i>consecutively</i> included if they were pathologically proven or showed transient enhancement. Lesions that were not pathologically proven were included only if there were areas of transient enhancement. The volume of the lesion had to be smaller than 4 cm ³ . Lesions in patients undergoing core biopsy prior to MRI were excluded. There were apparently 3 data sets: (1) Training data set of first 50 benign and first 50 malignant lesions; 44 of the 100 lesions were symptomatic. This data set is not discussed further in this table. (2) Test set of "remaining" 136 lesions (84 malignant; 64 symptomatic) that were selected along with the test set above. (3) Independent set of 72 <i>consecutive</i> clinically and mammographically occult lesions that also met above criteria.	Histopathologic proof or transient enhancement as an indicator of benign lesions	Developed their own system (described in Gilhuijs et al. 2002).	A radiologist read the original images and selected possible lesions. The CAD system then provided information, including the probability of malignancy, on these areas.	Calculated per lesion, not per patient: (1) Data set 2 (n=136): Area under the ROC curve (A_z) with CAD = 0.91±0.02. Value without CAD not reported. (2) Data set 3 (n=72): A_z with CAD= 0.85±0.05; A_z without CAD= 0.86±0.05 (p=0.99) but A_z with model that combines first reading and CAD results=0.91±0.03 and is significantly larger than A_z without CAD (p=0.03).	<ul style="list-style-type: none"> - This is not a commercially available CAD system. - The article also reports on retraining the CAD system with additional cases. - The accuracy of MRI from a single reading can be improved by adding this CAD system when more weight is given to the CAD results for lesions that the radiologists rate suspicious or indeterminate.

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Articles in Peer-Reviewed Journals (cont'd)							
Deurloo et al. 2005b; assess the incidence and impact of additional findings from MRI on the workup of patients eligible for BCT	Prospective	116 patients (118 lesions) with pathology-proven cancer scheduled for BCT (2 had bilateral cancer)	Pathology	Developed their own system (described in Gilhuijs et al. 2002).	A radiologist read the original images and selected possible lesions. The CAD system then provided information, including the probability of malignancy, on these areas	Additional findings (other lesions or larger lesions) were found by MRI in 48 (41%) patients; about 80% of these women had further workup. In 27 the findings were malignant, causing a change in treatment. 18 of the women changed to mastectomy, 7 had a wider excision, and 2 had additional contralateral surgery. 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).	<ul style="list-style-type: none"> – This is not a commercially available CAD system. – The value of screening for contralateral malignant lesions is the focus of a clinical trial currently being conducted by ACRIN.

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Articles in Peer-Reviewed Journals (cont'd)							
Kelcz et al. 2002; distinguishing between benign and malignant lesions	Prospective	62 women randomly selected from patients seen in their radiology practice (12,000 mammograms/yr) for palpable masses, or mammographic or sonographic abnormalities thought by the radiologist and surgeon to require biopsy. They have 68 lesions; 31 are malignant. Excluded women with a high probability of a cyst. Five cases were dropped because the patient elected follow-up rather than biopsy (3), there was incomplete correlation with the biopsy specimen (1), and there was motion (1).	Pathology	3TP*	Original MRI images read first by radiologist, then sent for application of CAD algorithm and followed by a separate reading.	<p>Calculated per lesion, not per patient:</p> <p>Without CAD: Sens=93% Spec=82%</p> <p>With CAD: Sens=87% Spec=84%</p> <p>The sensitivity is higher for solid masses (96%) than microcalcifications (63%); specificity similar.</p>	<ul style="list-style-type: none"> - Article focuses primarily on CAD development. - The authors recommend some modifications to the program; it is not known whether these have been incorporated into the current version of 3TP. - Because the sensitivity is substantially higher for masses than for microcalcifications, the overall sensitivity for a given sample will depend substantially on the mix of lesions in the sample. - Also, it is not completely clear which images the radiologist reviewed for the reading without CAD; we are assuming that all of the data in the column to the left are based on the same images.

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Articles in Peer-Reviewed Journals (cont'd)							
Pediconi et al. 2005; distinguishing between benign and malignant lesions	Prospective	36 consecutive women with suspected breast cancer on mammography or sonography. They had 68 lesions; 54 were malignant. Patients were excluded who were under 18, pregnant or lactating, had received any other contrast agent during the 48 hours before contrast agent administration, were undergoing radiation therapy, chemotherapy, or anticancer radiation therapy prior to contrast administration, had a history of hypersensitivity to gadolinium chelates or were otherwise contraindicated for MR imaging, or had any medical condition or other circumstances that would significantly decrease the chances of obtaining reliable data.	Histology	Developed their own system.	Blinded reading of original films by two readers followed by reading with CAD at least 2 weeks later.	<p>Calculated per lesion, not per patient:</p> <p>Without CAD: Sens=90.7% (95% CI: 79.7–96.9) Spec=92.9 (95% CI: 66.1–99.8)</p> <p>With CAD: Sens=92.6% (95% CI: 82.1–97.9) Spec=85.7 (95% CI: 57.2–98.2)</p> <p>No difference in sens or spec with and without CAD, but readers expressed more confidence in diagnoses based on reading with CAD.</p>	CAD development paper. Authors note that high specificity might be overestimated due to small number of lesions, high proportion of malignant lesions, and the low number of benign lesions. They also argue that CAD may produce more operator independent assessments and save time.

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Articles in Peer-Reviewed Journals (cont'd)							
Szabó et al. 2004; distinguishing between benign and malignant lesions	Prospective	Study used sample of 93 consecutive women with 114 lesions detected by physical examination or mammography who were referred for surgery. <i>9 lesions with nonenhancing and nonmass contrast enhancement patterns were excluded</i> , leaving 89 patients with 105 lesions (75 malignant). Half of this sample was randomly selected for use as the verification set, resulting in 46 lesions, 29 of which were malignant. Four additional lesions were revealed incidentally by MRI; whether they were in the training or verification set was not reported.	Histopathology	Developed their own system based on artificial neural networks.	Original images read by 3 experienced radiologists, and a consensus rating was produced.	Calculated per enhancing lesion, not per patient: Area under the ROC curve = 0.799 (0.076) for the expert radiologist and 0.678 (0.086) to 0.771 (0.080) for the various CAD models tested. (The values in parentheses above are the standard errors.)	

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Abstracts (Limited Information on Patient Selection, etc.)							
Vilanova et al. 2005; distinguishing between benign and malignant lesions	Retrospective	51 breast MRI from women with histology proven breast carcinoma. 66 lesions evaluated; 57 were malignant. Selection: NR.	Histology	NR	NR	Calculated per lesion, not per patient: Without CAD: Sens=89% Spec=66% With CAD: Sens=95% Spec=66%	The mean analysis time was 5 min. with CAD; 17 min. without CAD.
DeMartini et al. 2005b; distinguishing between benign and malignant lesions	NR	154 consecutive suspicious breast lesions detectable only on MRI; 41 were malignant.	Histology based on MRI-guided biopsy	CADstream	NR	Only reports changes in specificity with use of CAD at 2 thresholds: 50% and 100% of minimum enhancement. Reports that false positive rates are reduced by 8.8% at the 50% threshold (NS) and by 23.0% at the 100% threshold (p=0.02). Reports sensitivity of 93% with CAD; NR without CAD.	Reports that "There were no significant differences between enhancement patterns of benign and malignant lesions, with all lesions demonstrating a wide range of signal intensity peaks and a wide range of washout, plateau, and persistent patterns of enhancement." If this is the case, it is not clear how use of the CAD system, which provided "automated assessment of enhancement parameters" improved the accuracy of MRI.

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Abstracts (Limited Information on Patient Selection, etc.) (cont'd)							
Lehman et al. 2003; distinguishing between benign and malignant lesions and identifying lesions not needing biopsy	Apparently prospective	<i>33 consecutive lesions seen only on MRI (9 malignant).</i>	Histology	CADstream	Did not compare radiologist reading of original films to reading with CAD. Did compare CAD results using 3 different enhancement thresholds (50%, 80%, 100%).	Calculated per lesion, not per patient: 100% threshold: Sens=100%; FR rate reduced by 50% (p<0.01) 80% threshold: Sens=100%; FP rate reduced by 33% (p=0.05) 50% threshold: Sens=100%; FP rate reduced by 25% (NS) The baseline FP rate is not reported, only the percentage reductions in it at each CAD threshold.	The authors note that there was no distinctive pattern for malignant vs. benign lesions in terms of washout, persistence, and plateau patterns of enhancement.

Table 2. Summary of Studies on the Use of Computer-Aided Detection with MRI of the Breast (cont'd)

Citation and Major Objective	Study Type	Population and Selection Process	Gold Standard	CAD System	Reading Protocol	Results	Comments
Abstracts (Limited Information on Patient Selection, etc.) (cont'd)							
Furman-Haran & Degani 2002; distinguishing between benign and malignant lesions	Prospective	122 lesions at two hospitals/clinics; 46 malignant.	NR	3TP	Reading of original image at hospital/ clinic, with application of CAD and interpretation at research site.	Calculated per lesion, not per patient: Without CAD: NR With CAD: Sens=85%; Spec=86%; Sens of detecting masses=95%; Area under the ROC curve=0.93±0.02	This is a summary of 3 abstracts from 1999 to 2001.

*The algorithm codes the SI [signal intensity] changes among the three time points using color intensity and color hue as follows: First, color intensity codes the rate at which the SI changes between the first and second time points, with a resolution of 256 intensities in which dark color signifies slow change and bright colors signify rapid change. Second, color hue is a measure of contrast agent washout and is coded depending on the SI change between the images recorded at the second and third time points. If the SI increases from the second to the third time point, that location is coded blue; if it stays constant ($\pm 10\%$), it is coded green; and if it decreases, it is coded red.

FP: false positive; NR: not reported; ROC curve: receiver operating characteristic curve; Sens: sensitivity; Spec: specificity

and validation of other CAD systems and used information on women with known lesions. The fourth article provided additional information on one of these non-commercial systems used to evaluate women with cancer who were eligible for breast-conserving therapy (BCT). Additional findings (other lesions or larger lesions) were found in 48 of 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 ($p=0.03$).

The need to exercise caution in using results from abstracts has been explained previously and should be kept in mind as these results are reviewed. Of the 4 abstracts, 2 used CADstream, one did not report the system used, and one 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 CAD with MRI among women with known lesions.

In addition, because many of the studies were retrospective and reported primarily on the development and testing of a CAD system, they lack the rigor and generalizability of a large, prospective, well-designed study.

There is also an article on the use of CAD with MRI to assess the impact of chemotherapy (DeMartini et al. 2005a). It was not included in the table, because it has a sample size of only 15. It found that there were a substantial number of false-negative results for residual malignancy using CAD—a different type of problem than found with most other uses of MRI (i.e., too many false-positive results).

Conclusions

Unfortunately, the literature on the use of CAD with MRI of the breast was sparse overall, and few addressed the specific situations in which CAD with MRI is used in a clinical setting. 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 CAD system. There is one article looking at the use of a non-commercial CAD system with MRI among women scheduled for breast-conserving therapy. About 41% of these women had additional findings (larger or additional lesions), 56% of which were malignant. The results led to changes in treatment when more extensive disease was found. 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 ($p=0.03$).

Many of the studies and abstracts used highly selected sample populations, used the lesion rather than the patient or even the breast as the unit of analysis, reported on small number of patients and/or readers, or focused on CAD systems that do not appear to be available commercially in the United States. In a number of the studies, there is no statistically significant difference in sensitivity, specificity, etc., between MRI alone and MRI with CAD, although caution should be used in interpreting the data provided as true estimates of sensitivity or specificity, given the limitations of the studies. Prospective, well-designed and executed studies that look specifically at the addition of CAD with MRI for the specific uses of interest are needed to determine whether or not the use of CAD provides a positive clinical benefit to these patients.

Furthermore, the literature as a whole is not clear on how the CAD system is to be used. In the case of CAD with mammography, the radiologist reads the original films first, makes a diagnosis, and then reviews the CAD results. In some articles, it appears that CAD is intended as an adjunct to the initial MRI reading, just as with CAD and mammography. In other articles, it appears to be proposed as a way of speeding up the MRI reading process, and the precise protocol to be followed in reading the MRI is not clear. Furthermore, unlike in the case of CAD with mammography, in the documents regarding FDA clearance, it does not specify that CAD must be added only after an initial reading of the images alone, although it does say for one system that "Patient management decisions should not be made based solely on the results of the CADstream analysis." Obviously, the impact of CAD on the accuracy of MRI of the breast may depend in part on how the CAD results are incorporated into the reading and diagnostic process.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the computer-aided detection of malignancy with MRI of the breast meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Two CAD systems for use with MRI of the breast have 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA).

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

There are no high quality, current published studies of the impact of commercially available CAD systems on the sensitivity and specificity of MRI of the breast. The few studies and abstracts available focus primarily on the development of the CAD 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.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

There is insufficient evidence to assess whether the use of CAD systems would maintain or increase the sensitivity, specificity, and recall rates of MRI of the breast. Given the inability to evaluate these intermediate outcomes, it is not possible to assess the impact of CAD on health outcomes such as treatment success among breast cancer patients or survival.

5. The improvement must be attainable outside the investigational settings.

Whether the use of CAD with MRI of the breast improves outcomes has not been established in the investigational setting.

For the above reasons, computer-aided detection of malignancy with MRI of the breast does not meet the TEC criteria.

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**Blue Cross and
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225 North Michigan Avenue
Chicago, Illinois 60601-7680
www.bcbs.com/tec