INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Refer to Coverage Determination Guideline (CDG) titled Preventive Care Services for screening mammography.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee specific benefit document to determine benefit coverage.

The federal Patient Protection and Affordable Care Act (PPACA) follows the Grade B recommendation of the US Preventive Services Task Force, and requires preventive benefit coverage for screening mammography for women over age 40.
Breast Imaging as an Adjunct to Mammography
Digital mammography is proven and medically necessary for patients with dense breast tissue.

Breast Magnetic Resonance Imaging (MRI)
Breast magnetic resonance imaging (MRI) is proven and medically necessary for patients at high risk for breast cancer as defined as having any of the following:
- Personal history of atypical breast histologies
- Family history or genetic predisposition for breast cancer
- Prior therapeutic thoracic radiation therapy
- Dense breast tissue with any one of the following risk factors:
  - Lifetime risk of breast cancer of ≥20%, according to risk assessment tools based on family history
  - Personal history of BRCA1 or BRCA 2 gene mutations
  - First-degree relative with a BRCA 1 or BRCA 2 gene mutation but not having had genetic testing themselves
  - Prior therapeutic thoracic radiation therapy between ages of 10-30
  - Personal history of Li Fraumeni Syndrome, Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes.

Breast magnetic resonance imaging (MRI) is unproven and not medically necessary for patients with dense breast tissue not accompanied by defined risk factors as described above.

Digital Breast Tomosynthesis (3-D Mammography)
Digital tomosynthesis is unproven and not medically necessary for the screening and diagnosis of breast cancer.
There is insufficient evidence to conclude that digital tomosynthesis of the breast is effective for the screening or diagnosis of breast cancer. Clinical evidence has not yet demonstrated that digital breast tomosynthesis used as an adjunct to standard mammography reduces the mortality rate from breast cancer.

Magnetic Resonance Elastography of the Breast
Magnetic resonance elastography (MRE) is unproven and not medically necessary for breast cancer screening or diagnosis.
There is insufficient evidence to conclude that MRE of the breast is effective for the screening or diagnosis of breast cancer. While data from small feasibility studies indicate that MRE may have some ability to discriminate between cancerous tissue and normal breast tissue or benign lesions based on tissue stiffness, there was overlap in values, and the diagnostic accuracy of MRE for detection of breast cancer remains to be determined. There are no definitive patient selection criteria for MRE for breast cancer detection.

Breast Specific Gamma Imaging (Scintimammography)
Scintimammography is unproven and not medically necessary for breast cancer screening or diagnosis.
There is insufficient evidence that this diagnostic modality can differentiate benign from malignant breast lesions. Based on the evidence, the role of scintimammography remains unclear since this technology has not been shown to be accurate enough to screen for breast cancer or allow a confident decision to defer biopsy.

Electrical Impedance Scanning (EIS)
Electrical impedance scanning (EIS) is unproven and not medically necessary for the detection of breast cancer.
There is insufficient evidence that EIS is effective in detecting malignant breast tissue. Evaluation of sensitivity and negative predictive value for EIS is inconsistent. Well-designed studies are needed to determine whether or not EIS is effective as an adjunct to mammography or provides a positive clinical benefit.

Computer Aided Detection for MRI of the Breast
Computer aided detection (CAD) is unproven and not medically necessary as an aid for radiologists to interpret contrast-enhanced magnetic resonance imaging (MRI) of the breast.
Clinical evidence has not yet demonstrated that CAD improves patient outcomes or reduces breast cancer mortality when added to contrast-enhanced MRI. 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. Prospective, well-designed and executed studies are needed to determine whether or not the use of CAD provides a positive clinical benefit.

Breast Ultrasound
Breast ultrasound is unproven and not medically necessary for routine breast cancer screening including patients with dense breast tissue.
Clinical evidence has not yet demonstrated that routine use of ultrasonography as an adjunct to screening mammography reduces the mortality rate from breast cancer.

**Breast ultrasound is proven and medically necessary as an aid for radiologists to localize breast lesions and in guiding placement of instruments for cyst aspiration and percutaneous breast biopsies.**

**Computer Aided Detection for Ultrasound**

Computer-aided detection (CAD) is unproven and not medically necessary as an aid for radiologists to detect breast cancer during ultrasound.

Clinical evidence has not yet demonstrated that CAD improves patient outcomes or reduces breast cancer mortality when added to ultrasonography. Future research should include better-designed studies, including prospective studies and randomized controlled trials evaluating this technology in large numbers of screening ultrasounds.

**Computer Aided Tactile Breast Imaging**

Computer-aided tactile breast imaging is unproven and not medically necessary.

Clinical evidence is insufficient to determine whether tactile breast imaging improves outcomes for the screening or diagnosis of breast cancer. Future research should include better-designed studies, including comparative, prospective and randomized controlled trials evaluating this technology.

**Automated Breast Ultrasound**

Automated breast ultrasound is unproven and not medically necessary.

Clinical evidence is insufficient to determine whether automated breast ultrasound improves the detection rate of breast cancer compared to screening mammography. Future research should include better-designed studies, including prospective studies and randomized controlled trials evaluating this technology.

Refer to the Evidence-Based Clinical Guidelines – Imaging for:
- Magnetic resonance imaging (MRI) of the breast
- 3D rendering of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modalities

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0159T</td>
<td>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</td>
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<tr>
<td>0346T</td>
<td>Ultrasound, elastography (List separately in addition to code for primary procedure)</td>
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<tr>
<td>0422T</td>
<td>Tactile breast imaging by computer-aided tactile sensors, unilateral or bilateral</td>
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<tr>
<td>76377</td>
<td>3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality; requiring image post-processing on an independent workstation</td>
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<td>76498</td>
<td>Unlisted magnetic resonance procedure (eg, diagnostic, interventional)</td>
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<tr>
<td>76499</td>
<td>Unlisted diagnostic radiographic procedure</td>
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<td>76641</td>
<td>Ultrasound, breast, unilateral, real time with image documentation, including axilla when performed; complete</td>
</tr>
<tr>
<td>76642</td>
<td>Ultrasound, breast, unilateral, real time with image documentation, including axilla when performed; limited</td>
</tr>
<tr>
<td>77051</td>
<td>Computer-aided detection (computer algorithm analysis of digital image data for lesion detection) with further review for interpretation, with or without digitization of film radiographic images; diagnostic mammography (List separately in addition to code for primary procedure)</td>
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<tr>
<td>77052</td>
<td>Computer-aided detection (computer algorithm analysis of digital image data for lesion detection) with further review for interpretation, with or without digitization of film radiographic images; screening mammography (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>77055</td>
<td>Mammography; unilateral</td>
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Mammography is a specific type of imaging that uses a low-dose x-ray system for examination of the breasts. This is considered the best available method for early detection of breast cancer, particularly in the case of small or nonpalpable lesions. An abnormal screening mammogram requires a diagnostic test to confirm whether cancer is present. Lesions that are suggestive of cancer are evaluated with tissue biopsy. If a noninvasive diagnostic test is available that can accurately exclude cancer; many women with an abnormal mammogram could avoid biopsy. Therefore, efforts to develop adjuvant imaging procedures continue. This policy will focus on digital tomosynthesis, magnetic resonance elastography, scintimammography, electrical impedance scanning and computer-aided detection for MRI, automated breast ultrasound and ultrasound for breast cancer screening and the diagnosis of breast cancer.

The National Cancer Institute estimates that about 40 percent of women undergoing screening mammography have dense breasts. These women have an increased risk of breast cancer, with detection usually at a more advanced and difficult to treat stage.

Mammography is a low-dose X-ray imaging method of the breast. However, mammograms of dense breasts can be difficult to interpret. Fibroglandular breast tissue and tumors both appear as solid white areas on mammograms. As a result, dense breast tissue may obscure smaller tumors, potentially delaying detection of breast cancer.

Digital Tomosynthesis Systems: Digital tomosynthesis systems are being studied as an adjunct and alternative to x-ray mammography for the screening and diagnosis of breast cancer. Digital tomosynthesis is a three-dimensional (3-D) breast imaging technique based on full-field digital mammography. During digital tomosynthesis, multiple image slices of approximately one milliliter or less are obtained, processed by a computer and displayed as a high-resolution, 3-D image on a workstation.

Magnetic Resonance Elastography (MRE) of the Breast: MRE of the breast is a phase-contrast-based MRI technique that is based upon quantitative differences in the mechanical properties of normal and malignant tissues. Specifically, the elastic modulus of breast cancer tissue is approximately 5- to 20-fold higher than that of the surrounding fibroglandular tissue, i.e., breast cancers are usually harder than normal tissues. This difference can be measured by applying a known stressor and measuring the resulting deformation. MRE is performed by a radiologist in an MRI suite equipped with the electromechanical driver and integrated radiofrequency coil unit.

Breast specific gamma imaging (BSGI): BSGI, also known as scintimammography (SMM) or molecular breast imaging (MBI) is a noninvasive diagnostic technology that detects tissues within the breast that accumulate higher levels of a radioactive tracer that emit gamma radiation. The test is performed with a gamma camera after intravenous administration of radioactive tracers. Scintimammography has been proposed primarily as an adjunct to mammography and physical examination to improve selection for biopsy in patients who have palpable masses or suspicious mammograms.

Electrical Impedance Scanning (EIS): EIS was developed as a confirmatory test to be used in conjunction with mammography. The device detects abnormal breast tissue using small electrical currents. Since malignant tissue

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<td>77057</td>
<td>Screening mammography, bilateral (2-view study of each breast)</td>
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<tr>
<td>77058</td>
<td>Magnetic resonance imaging, breast, without and/or with contrast material(s); unilateral</td>
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<tr>
<td>77059</td>
<td>Magnetic resonance imaging, breast, without and/or with contrast material(s); bilateral</td>
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<tr>
<td>77061</td>
<td>Digital breast tomosynthesis; unilateral</td>
</tr>
<tr>
<td>77062</td>
<td>Digital breast tomosynthesis; bilateral</td>
</tr>
<tr>
<td>77063</td>
<td>Screening digital breast tomosynthesis, bilateral (List separately in addition to code for primary procedure)</td>
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<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>G0202</td>
<td>Screening mammography, producing direct digital image, bilateral, all views</td>
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<tr>
<td>G0204</td>
<td>Diagnostic mammography, producing direct digital image, bilateral, all views</td>
</tr>
<tr>
<td>G0206</td>
<td>Diagnostic mammography, producing direct digital image, unilateral, all views</td>
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<td>G0279</td>
<td>Diagnostic digital breast tomosynthesis, unilateral or bilateral (List separately in addition to G0204 or G0206)</td>
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<td>S8080</td>
<td>Scintimammography (radioimmunoscintigraphy of the breast), unilateral, including supply of radiopharmaceutical</td>
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| Description of Services |

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Breast Imaging For Screening And Diagnosing Cancer
UnitedHealthcare Commercial Medical Policy

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tends to conduct more electricity than normal tissue, the electrical current produced creates a conductivity map of the breast which automatically identifies sites that appear suspicious. The transmission of electricity into the body is via an electrical patch on the arm or a handheld device which travels to the breast. This is measured by a probe on the surface of the skin.

**Computer Aided Detection with MRI of the Breast:** In contrast to CAD systems used with mammography, CAD analysis with MRI creates a 2- or 3-dimensional (2-D, 3-D) color-coded image that is overlaid on the MRI image to mark potentially malignant areas of the breast which allows the radiologist to compare the enhanced image to the original MRI.

**Breast Ultrasound:** Ultrasound, also known as sonography, is an imaging method using sound waves rather than ionizing radiation to a part of the body. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is often first lubricated with ultrasound gel). It emits sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image on a computer screen. Ultrasound is useful for evaluating some breast masses and is the only way to tell if a suspicious area is a cyst (fluid-filled sac) without placing a needle into it to aspirate (draw out) fluid. Cysts cannot accurately be diagnosed by physical exam alone. Breast ultrasound may also be used to help doctors guide a biopsy needle into some breast lesions.

**Computer-Aided Detection (CAD) for Ultrasound:** CAD systems for ultrasound use pattern recognition methods to help radiologists analyze images and automate the reporting process. These systems have been developed to promote standardized breast ultrasound reporting.

**Computer Aided Tactile Breast Imaging:** Tactile breast imaging includes placing a tactile array sensor in contact with a portion of the patient’s body, to generate data signals corresponding to pressure gradients encountered by portions of the tactile array sensor. As the clinician gently moves the hand-held sensor across the breast and underarm area, data signals are then processed into multi-dimensional color images that instantly appear on a computer screen in real-time, allowing the clinician to view the size, shape, hardness and location of suspicious masses immediately.

**Automated Breast Ultrasound:** Automated Breast Ultrasound is the first and only ultrasound system developed and US Food and Drug Administration (FDA) approved specifically for breast cancer screening in women with dense breast tissue who have not had previous breast biopsies or surgeries. It is used as an adjunct to mammography. The high center-frequency significantly sharpens detail resolution while the ultra-broadband performance simultaneously delivers distinct contrast differentiation.

### CLINICAL EVIDENCE

**Digital Mammography**

**Professional Societies/Organizations**

**American College of Obstetricians and Gynecologists (ACOG, 2015)**

The American College of Obstetricians and Gynecologists (ACOG, 2015) practice for management of women with dense breasts diagnosed by mammography recommends routine screening with use of digital mammography for women diagnosed with dense breasts. They do not recommend routine use of alternative or adjunctive tests to screening mammography in women with dense breasts who are asymptomatic and have no additional risk factors.

**Digital Breast Tomosynthesis (3-D Mammography)**

An updated Hayes (2015) conducted a review of literature of studies of tomosynthesis alone versus conventional diagnostic mammography (DM). They concluded for breast cancer detection, tomosynthesis is not consistently better than conventional digital mammography (DM) unless it is combined with conventional DM. These imaging methods differ in that tomosynthesis combines multiple low- radiation dosage images while DM captures a single higher-dosage image. These differing image collection techniques may be complementary, allowing the combination of the 2 techniques to provide better breast imaging than either technique alone. However, additional studies are needed to confirm this conclusion and to determine whether the apparent benefits of combining tomosynthesis and conventional DM offset the increase in radiation dosage and additional time needed to collect and interpret the results of tomosynthesis and DM imaging. A particular concern is that most of the studies did not compare tomosynthesis with conventional DM that included spot compression and magnified and angled views.

Friedewald and colleagues (2014) reported a retrospective analysis in the June 2014 Journal of American Medical Association. Screening performance metrics from 13 academic and nonacademic breast centers were evaluated to determine if mammography combined with tomosynthesis is associated with better performance of breast screening programs in the United States. A total of 454,850 examinations were evaluated. 281,187 digital mammography and 173,663 digital mammography plus tomosynthesis. With digital mammography 29,726 patients were recalled and
5056 biopsies resulted in cancer diagnosis in 1207 patients. With digital mammography plus tomosynthesis, 15,541 patients were recalled and 3285 biopsies resulted in cancer diagnosis in 950 patients. Adding tomosynthesis was associated with an increase in the positive predictive value for recall. This study had several limitations. First, lack of a randomized cohort trial design. Another limitation of this study is that only population-level statistics were available from each site. Therefore, the authors were not able to evaluate the number of repeat examinations and, as a consequence, avoided statistical assumptions of independent observations. And finally, while implementation of tomosynthesis in this study was associated with a reduction in recall rate from screening, follow-up data was not available that would allow evaluation of false-negative result rates. The authors stated that since study did not assess clinical outcomes so whether the increase in cancer detection rates and its benefit is not known. Further studies are needed to assess the relationship to clinical outcomes.

Skaane and colleagues (2013) reported a preplanned interim analysis of two arms of a four-arm study comparing Digital Mammography (DM) and Digital Breast Tomosynthesis (DBT) in a side-by-side feature analysis for cancer detection. This single institution, prospective screening trial, was sponsored by the manufacturer of the DBT equipment (Hologic, Inc.). Cancer detection rates, false-positive rates before arbitration, positive predictive values for women recalled after arbitration, and the type of cancers detected with use of digital mammography alone and combined with tomosynthesis were reported.

Of the 29,652 women invited to participate in the study, 17,960 attended the screening program, with 12,631 consenting to participate in the study. The authors performed a preplanned interim analysis of results from 12,631 examinations interpreted by using mammography alone and mammography plus tomosynthesis from November 22, 2010, to December 31, 2011. Analyses were based on marginal log-linear models for binary data, accounting for correlated interpretations and adjusting for reader-specific performance levels by using a two-sided significance level of .0294. Detection rates, including those for invasive and in situ cancers, were 6.1 per 1000 examinations for mammography alone and 8.0 per 1000 examinations for mammography plus tomosynthesis. False-positive rates before arbitration were 61.1 per 1000 examinations with mammography alone and 53.1 per 1000 examinations with mammography plus tomosynthesis. After arbitration, positive predictive values for recalled patients with cancers verified later were comparable (29.1% and 28.5%, respectively, with mammography alone and mammography plus tomosynthesis). Twenty-five additional invasive cancers were detected with mammography plus tomosynthesis.

The Society of Breast Imaging (SBI) and the American College of Radiology (ACR) statement on Tomosynthesis Breast Cancer Screening Study (Skaane et al.) states the following:
While the study results are promising, they do not provide adequate information to define the role of tomosynthesis in clinical practice... Although the cancer detection rate was higher when tomosynthesis was added to mammography alone, it is not known if an equal incremental benefit will be realized in a second screening round. This small study does not supply statistical information regarding subgroups of women that might benefit, or might not benefit from adding tomosynthesis. How the technology will affect screening accuracy among women of different ages, risk profiles and parenchymal density is uncertain. In addition, how this technology would affect reader performance among U.S. radiologists with varying practice patterns and expertise is also uncertain. Other questions include whether computer aided detection will provide any further benefit, and if reconstructed images can be used, in lieu of standard full field digital images, to reduce radiation dose (ACR, 2014).

An updated 2015 Blue Cross Blue Shield TEC Assessment, "Use of digital breast tomosynthesis with mammography for breast cancer screening or diagnosis" concluded that current evidence on use of breast tomosynthesis plus mammography versus mammography alone for screening is insufficient to permit conclusions regarding the effect on health outcomes of adding breast tomosynthesis. Most available studies are retrospective and many did not use adequate reference standards. Also, most subjects did not serve as their own controls. The risk of bias for most of the studies was high. Studies with longer follow-up are needed. Adding tomosynthesis to mammography may also increase over detection and entails greater radiation exposure.
A 2015 ECRi Health Technology Forecast for Digital Breast Tomosynthesis for Screening and Diagnosis of Breast Cancer found that some studies suggest the digital breast tomosynthesis might reduce recalls and improve breast cancer detection. They also reported that digital mammography produces two-dimensional images that can mask some small lesions or mistakenly identify dense breast tissue as tumors, potentially missing some cancers or increasing false positives. However, few studies have yet demonstrated whether this add-on technology reduces breast cancer survival.

Rafferty and colleagues (2013) compared the diagnostic accuracy and recall rates for radiologists using breast tomosynthesis combined with digital mammography versus digital mammography alone. One thousand one hundred and ninety-two (1192) participants provided mediolateral oblique and craniocaudal digital mammographic and tomosynthesis images of both breasts. At each accruing site, a breast imager read the digital mammographic images and a second breast imager trained in tomosynthesis interpretation read the tomosynthesis images for each participant presenting for screening. The breast imager was blinded to the results of the other modality and the investigational examination images of the participants presenting for biopsy were not interpreted prospectively.
Diagnostic accuracy was compared with receiver operating characteristic analysis. Recall rates of noncancer cases, sensitivity, specificity, and positive and negative predictive values determined by analyzing Breast Imaging Reporting and Data System scores were compared for the two methods. The authors concluded that the addition of tomosynthesis to digital mammography provides the dual benefit of significantly increased diagnostic accuracy and significantly reduced recall rates for noncancerous cases. Some of the limitations of the study, which were acknowledged by the authors, include the fact that the reader studies were enriched, and the results in true screening populations may differ. The authors also acknowledge that there was an inherent inclusion bias against tomosynthesis with regards to cancer detection in a screening population. Almost all of the cancers were acquired in participants who were scheduled for biopsy and had been detected on conventional mammograms as part of standard screening evaluation. Therefore, it is likely that the study results underestimate the potential gains in sensitivity that might occur in clinical practice. Additional studies done in the clinical environment are needed to confirm the performance of tomosynthesis combined with digital mammography versus digital mammography alone.

Researchers (Ciatto, 2013) published the results of the Screening with Tomosynthesis OR standard Mammography (STORM) trial. The prospective comparison study examined the effect of integrated 2D and 3D mammography in population breast-cancer screening. A total of 7292 women (median age 58 years) were screened. The cancer detection rate using 2D only was 5.3 cancers per 1000 while the detection rate using 2D and 3D screening was 8.1 cancers per 1000 screens. The incremental cancer detection rate ascribed to integrated 2D and 3D mammography was 2.7 cancers per 1000 screens. There was a 17% reduction in the recall rate when DBT was performed in addition to conventional screening mammography. The authors acknowledged that randomized controlled trials are needed to compare integrated 2D and 3D mammography with 2D mammography for breast cancer screening. Prospective comparative data (accuracy, clinical utility) for digital tomosynthesis versus other breast imaging modalities are lacking. The published preliminary studies do not clarify what role digital tomosynthesis should provide in lieu of or in conjunction with other breast imaging modalities. The studies utilize different mechanisms, algorithms and devices for creating digital two-dimensional (2D) or three-dimensional (3D) images. There is insufficient evidence in the published peer-reviewed scientific literature supporting the accuracy and clinical utility of 2D and 3D digital tomosynthesis for breast imaging (Hass et al., 2013, Zuley et al., 2013, Mitchell et al., 2012; Bernardi et al., 2012; Fornvik et al., 2010; Gennaro et al., 2010).

Teertstra et al (2010) assessed mammography and digital breast tomosynthesis (DBT) in 513 women with an abnormal screening mammogram or with clinical symptoms. The ACR BI-RADS criteria were used to classify the cases. In 112 newly detected cancers, DBT and mammography were each false-negative in 8 cases (7%). In three cases, both mammography and DBT failed to detect the carcinoma. The sensitivity of both techniques for the detection of breast cancer was 92.9%, and the specificity of mammography was 86.1% and 84.4% for DBT. The authors concluded that DBT can be used as an additional technique to mammography in individuals referred with an abnormal screening mammogram or with clinical symptoms. They also acknowledged that the additional lesions detected by DBT are also likely to be detected by other techniques used in the clinical work-up of these individuals.

Chen et al. (2007) conducted a pilot study of 13 women to assess the clinical feasibility of contrast enhanced (CE) digital breast tomosynthesis (DBT) as an adjunct to digital mammography, and to correlate lesion enhancement characteristics and morphology obtained with CE-DBT to digital mammography, ultrasound, and magnetic resonance (MR). Eleven of 13 patients had breast cancer (6 invasive ductal carcinoma, 4 ductal carcinoma in situ and 1 invasive lobular carcinoma). Suspicious enhancing lesions were demonstrated with CE-DBT in 10 of 11 cases of proven breast cancer. The authors concluded that CE-DBT, as an adjunct to digital mammography, may be a potential alternative tool for breast lesion morphologic and vascular characterization. The study is limited by small sample size.

Gur et al. (2009) compared the diagnostic performance of full-field digital mammography (FFDM) with digital breast tomosynthesis in a retrospective study including 125 women, of whom 35 had verified findings of cancer and 90 showed no evidence of cancer. Use of the combination of digital breast tomosynthesis and FFDM was associated with 30% reduction in recall rate for cancer-free examinations that would have led to recall if FFDM had been used alone. Use of digital breast tomosynthesis alone also tended to reduce recall rates, an average of 10%, although the observed decrease was not statistically significant. There was no convincing evidence that use of digital breast tomosynthesis alone or in combination with FFDM results in a substantial improvement in sensitivity.

A retrospective study by Spangler et al. (2011) compared the ability of digital breast tomosynthesis and full field digital mammography (FFDM) to detect and characterize calcifications in 100 paired examinations. There were 20 biopsy-proven cancers, 40 biopsy-proven benign calcifications and 40 randomly selected negative screening studies reviewed. Overall calcification detection sensitivity was higher for FFDM (84%) than for digital breast tomosynthesis (75%). Of the calcifications accurately detected using FFDM, 14 cancers and 38 benign calcifications were not detected with digital breast tomosynthesis. Of the calcifications accurately detected using digital breast tomosynthesis, 4 cancers and 13 benign calcifications were not detected with FFDM. The authors concluded that FFDM appears to be slightly more sensitive than digital breast tomosynthesis for the detection of calcification. This study is limited by retrospective design and a small study sample.
A study by Poplack et al. (2007) compared the image quality of tomosynthesis with that of conventional mammography and to estimate the recall rate of screening when tomosynthesis is used in addition to mammography. There were 99 digital screening recalls in 98 women. The image quality of tomosynthesis was equivalent (n = 51) or superior (n = 37) to diagnostic mammography in 89%. Rate of recall was 52%. The authors found that when used adjunctively with digital screening, tomosynthesis would have decreased the recall rate by nearly half. This was mostly due to recognition of tissue overlap, because no abnormality was seen with tomosynthesis in those cases. The authors concluded that tomosynthesis has comparable or superior image quality to that of film-screen mammography in the diagnostic setting, and it has the potential to decrease the recall rate when used adjunctively with digital screening mammography. However, the study is limited by small sample size.

Andersson et al. (2008) conducted an unblinded study of 36 women to compare breast cancer visibility in one-view breast tomosynthesis (BT) to cancer visibility in one- or two-view digital mammography (DM). Forty breast cancers were found in 37 breasts. The authors found that cancer visibility on breast tomosynthesis was greater in 22 of 40 cancers found compared to single view digital mammography. Thirteen of the remaining 18 cancers were equally visible/clearly visible on single view digital mammography and breast tomosynthesis. While it appears that breast tomosynthesis identifies some cases of breast cancer, in over half of the patients accuracy of diagnosis was not increased and therefore it cannot be concluded what type of patient should have breast tomosynthesis and at what stage in the screening process this should occur. The study is also limited by small sample size and non-blinded study design.

Tomosynthesis units are in limited clinical use; among the largest manufacturers: the Hologic Selenia Dimensions was recently approved for clinical use in the United States; the Siemens Mammatom Inspiration is available for use in Europe (approved for FFDM only in the United States); and the GE tomosynthesis system is undergoing testing for eventual submission for clinical approval. At the present time, no CAD products for breast tomosynthesis are commercially available in the United States. (Baker and Lo, 2011)

There are currently 6 ongoing clinical studies for digital tomosynthesis identified by our search of the National Clinical Trials database.

Professional Societies/Organizations/Position Statements

American Cancer Society (ACS)

On its website, the ACS (2015) states that although digital breast tomosynthesis units are steadily being introduced in mammography facilities, at the time the protocol for the evidence review was developed, there was too little data on digital breast tomosynthesis to include comparisons to 2D mammography. The issue will continue to be revisited and will be updated as evidence emerges.

American College of Obstetricians and Gynecologists (ACOG)

Guidelines on breast cancer screening from the American College of Obstetricians and Gynecologists (ACOG, 2014) concluded that digital breast tomosynthesis current evidence is insufficient to assess the benefits and harms of tomosynthesis (3-D mammography) as a screening modality for breast cancer. Further study will be necessary to confirm whether digital mammography with tomosynthesis is a cost-effective approach capable of replacing digital mammography alone as the first-line screening modality of choice for breast cancer screening.

The 2015 committee opinion published by ACOG does not support the use of DBT at this time and states:

Current published evidence does not demonstrate meaningful outcome benefits (eg, reduction in breast cancer mortality) with supplemental tests (eg, ultrasonography and magnetic resonance imaging) to screening mammography or with alternative screening modalities (eg, breast tomosynthesis or thermography) in women with dense breasts who do not have additional risk factors. Evidence is lacking to advocate for additional testing until there are clinically validated data that indicate improved screening outcomes.

The American College of Radiology (ACR)

The 2014 position statement for new digital technology, breast tomosynthesis states that, “breast tomosynthesis has shown to be an advance over digital mammography, with higher cancer detection rates and fewer patient recalls for additional testing. As this technology is used in clinical practice, we anticipate that further studies will clarify its impact on long-term clinical outcomes, including reduced mortality. We therefore recommend use of tomosynthesis as it has been shown to improve key screening parameters compared to digital mammography.”

The National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) (2015) guidelines state early studies show promise for tomosynthesis mammography. Two large trials showing a combined use of digital mammography and tomosynthesis
resulted in improved cancer detection and decreased call back rates; of note this is double the dose of radiation and is a factor in recommending this modality. Definitive studies are still pending. There is evidence to suggest that use of mammography in addition to DBT may increase the number of cancers detected, which would then translate into a decrease in the number who undergo unnecessary recalls. However, the published feasibility and experimental studies are unclear if DBT should be utilized for diagnostic, screening or surveillance purposes, or if it should be used in lieu of or in conjunction with other imaging technologies.

The National Cancer Institute

The National Cancer Institute (2014) states that for three-dimensional (3D) mammography, also known as breast tomosynthesis, accuracy has not been established compared with that of 2D mammography in randomized studies. Therefore, researchers do not know whether 3D mammography is better or worse than standard mammography at avoiding false-positive results and identifying early cancers.

Automated Breast Ultrasound System (ABUS)

A 2013 Hayes report evaluating automated breast ultrasound system (ABUS), found that the results presented in the majority of the study abstracts report overall favorable results when using three-dimensional automated breast ultrasound. Further review is required to confirm abstract content and, therefore, conclusions about the safety and effectiveness of this technology cannot be made until a full assessment has been completed.

A Prospective Multicenter Matched-pair Clinical Study to Evaluate the Sensitivity and Specificity of ABUS and Digital X-Ray Mammography (XRM) Together as a Breast Cancer Screening Method Compared to XRM Alone in Women With >50% Parenchymal Density, was noted to have completed in December 2014. Study results are not yet ready for review.

Prosch et al. (2011) conducted a prospective diagnostic study. The study examined 148 breasts of 76 patients with handheld ultrasound (US) and ABUS. The ABUS data were evaluated separately by two investigators. The inter-observer agreement for the breast imaging reporting and data system (BI-RADS) classification among the two observers using ABUS was high, the agreement with handheld US was moderate. The sensitivity in the detection of breast cancer was 87.5% for handheld US and 75% for the ABUS evaluation by observer 1. The sensitivity was 87.5% for the ABUS evaluation and 83% for mammography by observer 2. The authors concluded that ABUS examinations focusing on the BI-RADS classification have low inter-observer variability, compared to handheld US.

An extensive literature search was conducted. All of the studies found were small sample size, case, comparative, and retrospective in nature. The results presented in the majority of the study abstracts report overall favorable results when using three-dimensional automated breast ultrasound. The main limitation in the studies that have been conducted is that they included a higher proportion of malignant lesions or breast masses than would be found in the screening population. Larger scale research will be needed to be conducted to determine its role in breast cancer screening.

Magnetic Resonance Elastography of the Breast

Although there are ongoing studies and clinical trials, there continues to be inadequate evidence in the peer-reviewed medical literature to support safety and efficacy of MRE. When used in conjunction with conventional ultrasound, breast elastography appears to be promising in assisting to differentiate potentially benign from malignant lesions, however, large prospective clinical trials addressing appropriate patient selection, diagnostic parameters, and practical application of this technique are necessary prior to widespread clinical use.

A prospective study by Siegmann et al. (2010) evaluated the value of adding magnetic resonance elastography (MRE) to contrast-enhanced MR imaging (MRI) for evaluating breast lesions in 57 patients. The sensitivity of MRI was 97.3% whereas specificity was 55%. If contrast-enhanced MRI was combined with c0 (indicator of tissue stiffness), the diagnostic accuracy could be significantly increased. The authors concluded that combining MRE with MRI increase the diagnostic performance of breast MRI; however, larger studies are needed to validate the results and to identify the patients best suited for a combined procedure.

McKnight et al. (2002) and Lorenzen et al. (2002) evaluated small feasibility studies on the ability of MRE to differentiate breast cancers from normal breast tissue and benign tumors in mastectomy specimens, breast cancer patients and healthy women. Although the MRE results showed that some breast cancers display increased tissue stiffness compared with benign tumors or normal breast tissue, there was overlap in values, and the accuracy of MRE for detection of breast cancer remains in question.

Fifteen patients with breast lesions underwent MRE and all breast cancer cases showed a good delineation to the surrounding breast tissue. The results for shear viscosity did not indicate that MRE was useful for differentiating benign from malignant lesions. (Sinkus et al., 2005)
Breast Imaging For Screening And Diagnosing Cancer
UnitedHealthcare Commercial Medical Policy

**Professional Societies/Organizations**

**American Cancer Society (ACS)**

The ACS guidelines assign an evidence level of C for breast cancer screening with magnetic resonance elastography (preclinical data suggest possible promise, but clinical data are sparse or nonexistent; more study is needed). (Smith et al., 2003) (Saslow, et al., 2007)

**Breast Specific Gamma Imaging (BSGI) (also known as Scintimammography)**

An Updated 2013 ECRI Health Technology Assessment Evidence Report found that the evidence is insufficient to evaluate the accuracy and utility of BSGI for any other breast applications.

A 2014 Hayes report evaluating breast-specific gamma imaging (BSGI) found that the available evidence does not provide conclusive evidence that breast-specific gamma imaging can be relied on rather than biopsy, US, or MRI in women who have suspicious breast lesions on mammograms. In several of the reviewed studies, BSGI detected some cancerous lesions that were not detected by mammography; however, these studies did not report whether the increased detection corresponded to a statistically significant increase in the sensitivity of BSGI compared with mammography. In the studies that provided data on patient management, BSGI was not rigorously compared with MRI or US to determine whether it was more effective. Only two studies reported the statistical significance of results, both of which indicated that BSGI was more specific than MRI. Although further studies may indicate that breast-specific gamma imaging has greater sensitivity than ultrasonography and MRI, breast-specific gamma imaging has the disadvantage that it exposes the patient to radiation. In addition, unlike biopsy, breast-specific gamma imaging does not provide a definitive diagnosis since it incorrectly indicates that 15% to 40% of benign lesions are cancerous. The quality of the evidence is low due to the predominately retrospective study design, small sample sizes, and, in some cases, lack of statistical analysis of results. Additional studies are needed to determine the place in therapy of BSGI versus the alternatives.

Weigert et al reported data from a retrospective multicenter patient registry. This study analyzed 1042 patients drawn from 2004 patients in the registry. Women included in the study had BSGI imaging, pathologic diagnosis by biopsy, and at least six months follow-up. BSGI had been recommended for patients with at least two of the following indications: equivocal or negative mammogram/ultrasound and an unresolved clinical concern; personal history of breast cancer or current cancer diagnosis; palpable masses negative on mammogram or ultrasound; radiodense breast tissue; or high risk for breast cancer. In this population, BSGI had a reported sensitivity of 91%, specificity of 77%, positive predictive value of 57%, and NPV of 96%. In 139 patients who had a suspicious lesion on mammography, BSGI imaging was negative in 21 cases, 13 of which were true negatives and eight of which were false negatives. The mix of indications in this study makes it difficult to generalize the results or to determine whether the performance of BSGI varies by indication.

Kim (2012) evaluated the adjunctive benefits of BSGI versus MRI in breast cancer patients with dense breasts. This study included a total of 66 patients with dense breasts (breast density greater than 50%) and already biopsy-confirmed breast cancer. All of the patients underwent BSGI and MRI as part of an adjunct modality before the initial therapy. Of 66 patients, the 97 undetermined breast lesions were newly detected and correlated with the biopsy results. Twenty-six of the 97 breast lesions proved to be malignant tumors; the remaining 71 lesions were diagnosed as benign tumors. The sensitivity and specificity of BSGI were 88.8% and 90.1% respectively, while the sensitivity and specificity of MRI were 92.3% and 39.4%, respectively. MRI detected 43 false-positive breast lesions, 37 (86.0%) of which were correctly diagnosed as benign lesions using BSGI. In 12 malignant lesions less than 1 cm, the sensitivities of BSGI and MR imaging were 83.3% and 91.7% respectively. The author concluded that BSGI showed an equivocal sensitivity and a high specificity compared to MRI in the diagnosis of breast lesions. In addition, BSGI had a good sensitivity in discriminating breast cancers less than or equal to 1 cm. The results of this study suggested that BSGI could play a crucial role as an adjunctive imaging modality which can be used to evaluate breast cancer patients with dense breasts. The study was limited by small sample size, larger prospective studies are needed to determine the true sensitivity and specificity of BSGI.

Based on 44 studies of scintimammography, an analysis found that for non-palpable lesions, the specificity of scintimammography was 39.2% (at a fixed 95% sensitivity). At the mean threshold of the included studies, the sensitivity was 68.7% and specificity was 84.8%. The analysis also found that in women with non-palpable lesions, the negative likelihood ratio of scintimammography was 0.41 (i.e., if a woman with a non-palpable lesion is diagnosed as having no cancer by scintimammography, her chance of having breast cancer drops from 20% to 9.3%). (AHRQ, 2006)

A meta-analysis of scintimammography included 5,473 patients from studies performed since 1997. The overall sensitivity was 85% and the specificity was 84% for single-site trial studies, and for multi-center trial studies the overall sensitivity was 85% and the specificity was 83%. (Hussain and Buscombe, 2006) Another meta-analysis evaluating scintimammography included 5,340 patients from studies published between January 1967 and December
A retrospective study by Brem et al. (2008) evaluated the sensitivity and specificity of breast-specific gamma imaging (BSGI) in 146 patients (167 lesions) for the detection of breast cancer. Breast biopsy identified 83 cancers (16 ductal carcinoma in situ [DCIS] and 67 invasive cancers). BSGI helped detect cancer in 80 of 83 malignant lesions with a sensitivity of 96.4% and correctly identified 50 of 84 nonmalignant lesions as negative for cancer with a specificity of 59.5%. The positive predictive value for 80 of 114 malignant lesions with a BSGI examination with findings positive for cancer was 68.8% and the negative predictive value for 50 of 53 nonmalignant lesions was 94.3%. BSGI helped detect occult cancer not visualized at mammography or ultrasonography in 6 patients. The authors concluded that with a sensitivity of 96.4% and 59.5% specificity, BSGI is promising for detecting breast cancers; however the authors note that larger studies are needed to support the findings. The study is manufacturer sponsored.

Brem et al. (2009) conducted a multi-centered retrospective review of 26 women (28 carcinomas) to compare the sensitivity of mammography, sonography, MRI, and breast-specific gamma imaging (BSGI) in the detection of invasive lobular carcinoma. Mammograms were negative in 6 of 28 (21%), yielding a sensitivity of 79%. In the 25 patients who underwent sonography, 17 had focal hypoechoic areas, yielding a sensitivity of 68%. In the 12 patients who underwent MRI, the sensitivity was 83%. BSGI had a sensitivity of 93%. There was no statistically significant difference in the sensitivity of BSGI, MRI, sonography, or mammography; however there was a non-significant trend toward improved detection with BSGI. Based on the sensitivity ratings, the authors concluded that BSGI is an effective technique that should be used to evaluate patients with suspected cancer and has a promising role in the diagnosis of invasive lobular carcinoma. The study is limited by small sample size however invasive lobular carcinoma is a rarer form of breast cancer. Larger studies are needed to validate the results and evaluate the utility in diagnosing lobular cancer.

Another retrospective review by Brem et al. (2007) compared BSGI and magnetic resonance for detecting ductal carcinoma in situ (DCIS) in 20 women (22 lesions). Of the 22 lesions, 91% were detected with BSGI, 82% were detected with mammography, and 88% were detected with magnetic resonance imaging. While BSGI appeared to have the highest sensitivity for the detection of DCIS, the sample size was small which did not demonstrate a statistically significant difference.

Gommans et al. (2007) evaluated 103 women with non-palpable breast lesions detected by mammogram that underwent scintimammography before biopsy. Scintimammography had a specificity of 92.8%, a sensitivity of 82.2%, a positive predictive value of 90.2%, and a negative predictive value of 86.6%.

Ninety women with lesions smaller than 2 cm were examined by scintimammography before biopsy. Sensitivity was 29% for lesions less than 5 mm and 97% for lesions 11 mm or greater. The overall sensitivity was 85%. Scintimammography detected 8 additional mammographically occult tumors in 7 patients. (O'Connor et al., 2007)

Overall, the evidence to date does not provide sufficient support for the studies above. Limited evidence on the diagnostic accuracy of BSGI reports that the test has a relatively high sensitivity and specificity for detecting malignancy. However, the evidence does not establish that BSGI improves outcomes when used as an adjunct to mammography for breast cancer screening. In the available studies, the negative predictive value of BSGI has not been high enough to preclude biopsy in patients with inconclusive mammograms. In addition, the evidence is not sufficient to conclude that BSGI is better than MRI for this purpose. Larger, higher-quality studies are required to determine whether BSGI has a useful role as an adjunct to mammography.

**Professional Societies/Organizations**

**The Society of Nuclear Medicine (SNM)**

SNM published guidelines in 2004 for breast scintigraphy that indicate that further study is needed to determine the population that is most likely to benefit from this procedure. The guideline also states that the usefulness of scintigraphy requires further study.

Another guideline on Breast Scintigraphy with Breast-Specific Gamma Cameras published by SNM in 2010 indicates that breast-specific gamma imaging may be useful for:

- patients with recently detected breast malignancy
- patients at high risk for breast malignancy
- patients with indeterminate breast abnormalities and remaining diagnostic concerns
- patients with technically difficult breast imaging
- patients for whom Breast MRI would be indicated
- monitor neoadjuvant tumor response in patients undergoing preoperative chemotherapy

1999. The aggregated summary estimates of sensitivity and specificity for scintimammography were 85.2% and 86.6% respectively. The authors concluded that scintimammography may be used effectively as an adjunct to mammography when additional information is required to reach a definitive diagnosis. The authors also indicated that the role of scintimammography should be assessed on the basis of large, multi-center studies. (Liberman et al., 2003)
American Cancer Society (ACS)
According to ACS guidelines, breast cancer screening with scintimammography is not recommended. (evidence level of C - preclinical data suggests possible promise, but clinical data are sparse or nonexistent; more study is needed). (Smith et al., 2003) On its Website, the ACS (2014) states that scintimammography is not used commonly and its usefulness is still being evaluated. Current research is aimed at improving the technology and evaluating its use in specific situations, such as in women with dense breasts.

Agency for Healthcare Research and Quality (AHRQ)
In 2006, a report by the AHRQ concluded that for every 1,000 women who had a negative scintimammography, approximately 907 women would have avoided an unnecessary biopsy, but 93 women would have missed cancers. These numbers were for women with nonpalpable breast lesions only.

National Comprehensive Cancer Network® (NCCN)
According to the National Comprehensive Cancer Network's (NCCN®) clinical practice guideline for breast cancer screening and diagnosis (NCCN, 2015), early studies show promise for digital breast tomosynthesis. Two large trials showing a combined use of digital mammography and tomosynthesis resulted in improved cancer detection and decreased call back rates; of note, this is double the dose of radiation and is a factor in recommending this modality. Definitive studies are still pending.

The NCCN Breast Cancer Screening and Diagnosing Guidelines (v.1.2015) states:
If the physical examination is negative in an asymptomatic woman, the next decision point is based on risk stratification. Women can be stratified into two basic categories for the purpose of screening recommendations: those at normal risk and those at increased risk. For screening women at normal risk, NCCN panel recommends annual mammogram for normal-risk women age 40 and older, with breast awareness encouraged.

The NCCN panel recommends for men positive for BRCA 1/2 mutation include breast awareness and a clinical breast exam every 6 – 12 months. Baseline mammography should be considered at age 40 years, followed by annual mammography for those men with gynecomastia or parenchymal/glandular breast density on baseline study.

National Cancer Institute (NCI)
According to NCI (2010), the theoretical advantage of scintimammography is the potential to obtain staging information, but only small clinical series have been published.

American College of Radiology (ACR)
According to 2015 ACR practice guidelines for breast specific gamma imaging scintigraphy: There is insufficient evidence to support the use of breast specific gamma imaging (BSGI) for breast cancer screening, and is not indicated for screening in their present form.

The American College of Radiology (ACR) practice guideline for the performance of tumor scintigraphy (with gamma cameras) (2015) stated that "more recently, breast-specific gamma imaging (BSGI) which uses a high-resolution, small-field-of-view gamma camera optimized to image breast tumors has been developed. Areas of active investigation concerning potential indications include determination of extent of disease in women with newly diagnosed breast cancer, and evaluation of patients with dense breasts. Additional clinical evidence is needed to assess where BSGI will fit in the imaging algorithm of breast cancer. When BSGI is performed, the ability to correlate BSGI findings with other breast imaging techniques and a defined protocol for evaluation of abnormalities seen only on BSGI should be in place

Electrical Impedance Scanning (EIS)
Experimental studies have shown that significant changes occur in the electrical properties of breast cancer tissue compared to the surrounding normal tissue. This phenomenon motivated studies on cancer detection using electrical impedance techniques. However, the separation of malignant tumors from benign lesions based on impedance measurements needs further investigation. There is insufficient evidence in the published peer-reviewed scientific literature to support the diagnostic utility of electrical impedance scanning (EIS) of the breast of the breast. The incremental diagnostic value of these alternative breast imaging procedures as an adjunct to mammography has not yet been established, and the impact of the use of these systems on meaningful health outcomes remains unknown.

In a prospective, multi-center study, Wang et al (2010) reported the sensitivity and specificity for the combination of EIS and ultrasound in identifying breast cancer and calculated the relative risk of breast cancer in young women. The young women (583 cases) scheduled for mammary biopsy underwent EIS and ultrasound, respectively. EIS and ultrasound results were compared with final histopathology results. Of the 583 cases, 143 were diagnosed with breast cancer. The relative probability of breast cancer for the young women was detected by EIS, ultrasound, and the
A prospective, multicenter clinical trial by Stojadinovic et al. (2005) evaluated EIS in 1,103 women. Twenty-nine cancers with a mean tumor size 1.7 cm were confirmed thru biopsy. Electrical impedance scanning had 17% sensitivity, 90% specificity, and a negative predictive value (NPV) of 98%. Statistically significant increases in specificity were observed for women who were premenopausal and women who were not using hormone replacement therapy. False-positive rates were increased in postmenopausal women and those taking exogenous hormones. While the authors concluded that EIS appears promising for early detection of breast cancer, the increased false positive rates in postmenopausal women and those taking exogenous hormones is concerning.

In contrast, Szabo et al. (2005) evaluated the diagnostic accuracy of targeted electrical impedance imaging in 137 women with 145 lesions. The specificity of electrical impedance imaging, using the TS2000 was significantly lower compared to mammography (49% compared to 97%) and ultrasound (100%). Sensitivity, after adding TS2000, was not impacted, but specificity was decreased to 46%. The authors concluded that targeted electrical impedance imaging as an adjunct to mammography and ultrasonography in the diagnosis of breast lesions is not justified.

A prospective case series by Fuchsjaeger et al. (2005) compared ultrasonography with EIS in 121 women with 128 BI-RADS category IV lesions. Upon biopsy, 37 lesions were found to be malignant with 16 being invasive ductal cancers and 11 being ductal carcinomas in situ. Of 91 benign lesions, the most common types were fibroadenomas (n=33) and fibrocystic changes (n=28). Mean lesion size was 1.6 ± 1.3 cm for the malignant lesions and 1.6 ± 0.7 cm for the benign lesions. For the malignant and the benign lesions, mean lesion depth was 0.9 ± 0.5 cm. EIS had 95% sensitivity, 75% specificity, and 97% negative predictive value (NPV) for detection of malignancies, whereas ultrasonography had 91% sensitivity, 34% specificity, and 92% NPV. EIS provided results in all patients, including those who had microcalcifications. Although EIS performed better for smaller lesions and lesions that were closer to the skin, it was not reported whether these improvements were statistically significant.

This test is FDA-approved as a diagnostic aid in helping classify tumors found on mammogram. However, this technology has not had sufficient clinical testing to be used in breast cancer screening. The incremental diagnostic value of this technology as an adjunct to mammography has not yet been established (American Cancer Society [ACS], 2012).

Professional Societies/Organizations

Society of Breast Imaging (SBI)

The SBI Position Statement 'Use of Alternative Imaging Approaches to Detection of Breast Cancer' states that "often predicated on the increased vascularity associated with cancer, techniques to detect increased heat production, oxygen consumption, electrical impedance, light absorption, microwave transmission, and nitrous oxide production have indicated changes in the breast containing cancer that may assist in detection or diagnosis. While many of these approaches have received FDA approval for safety, such techniques remain either experimental or investigational, given the lack of standard techniques that can be uniformly applied and paucity of sufficient research to substantiate reliability of results. None of these tests have been shown to reduce mortality among tested women in randomized controlled trials."

Computer-Aided Detection with MRI of the Breast

Computer-aided detection has been used to aid radiologists’ interpretation of contrast-enhanced MRI of the breast, which 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 in whom mammography is less accurate (e.g., younger women and those with denser breasts). The use of CAD may also reduce the time needed to interpret breast MRI images, which currently takes much longer than reading mammograms.

The published evidence on CAD MRI consists of 2 small clinical studies (Demartini et al., 2005; Lehman et al., 2006) performed with the CADStream and a few studies that reported on the development and validation of 3TP. (Hauth et al., 2006; Kelcz et al., 2002) and non-commercial CAD systems (Deurloo et al., 2005; Pediconi et al., 2005; Meinel et al., 2007)

DeMartini et al. (2005) performed a study to determine the utility of CADStream applied to breast MRI in 15 newly diagnosed breast cancer patients (16 lesions) undergoing neoadjuvant chemotherapy. Prior to chemotherapy, all tumors demonstrated CAD-assessed significant enhancement. Following chemotherapy, 7/16 tumors showed no residual significant enhancement, but all had residual disease at pathology. The authors concluded that CAD may be helpful in assessing changes in MRI enhancement profiles of tumors following chemotherapy. However, CAD-assessed significant enhancement following chemotherapy can be falsely negative for residual malignancy, and CAD tumor sizes are less accurate than those measured by the radiologist in predicting size of residual malignancy. CAD may complement but should not replace the radiologist’s assessment of tumors in this patient population.
Lehman et al. (2006) compared the accuracy of breast MRI interpretations of 33 consecutive lesions seen only on MRI (9 malignant, 24 benign) with and without CADstream. For benign lesions, the false-positive rate was reduced by 25% to 50%, depending on the enhancement thresholds used for the analysis. The authors concluded that CADstream accurately showed significant enhancement in all the malignant lesions while depicting 12 of 24 benign lesions as showing insignificant enhancement. The authors further stated if these results are validated by a larger study, the number of unnecessary biopsies of MR lesions could be reduced without a concomitant decrease in cancer detection.

Currently, there are a few retrospectively designed studies which do not establish the accuracy or clinical utility of CAD systems. Additional well-designed prospective trials are needed to establish what if any impact CAD systems may have on long-term breast cancer survival rates.

The Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) completed a technology assessment in 2006 for CAD with MRI and concluded that 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 (BCBSA, 2006c)

**Computer-Aided Detection for Ultrasound**

Only one retrospective study with a small sample size evaluated CAD for detection and diagnosis of breast cancer. Additional prospective studies are needed to confirm that CAD systems improve diagnostic performance for radiologists interpreting breast ultrasound images, and that any improvement in diagnostic performance results in a clinical benefit, such as appropriately selecting patients for biopsy or for clinical follow-up.

A retrospective study by Sahiner et al. (2007) evaluated ultrasound images with or without the use of CAD in 101 women. When a 2% likelihood of malignancy was used as the threshold for biopsy recommendation, the average sensitivity of radiologists increased from 96% to 98% with CAD, while the average data set decreased form 22% to 19%. The investigators concluded that use of a computer algorithm may improve accuracy in identifying malignant from benign breast masses. The results of several uncontrolled studies suggest that CAD systems for ultrasounds may be useful for evaluating breast masses. (Huang et al., 2005; Chang et al., 2005; Joo et al., 2004; Chen et al., 2003) However, published evidence has not yet demonstrated that CAD improves patient outcomes or reduces breast cancer mortality when added to ultrasonography.

**Professional Societies**

**American College of Radiology (ACR)**

The ACR Practice Guideline for the performance of screening and diagnostic mammography (2014) states “Double reading and computer-aided detection (CAD) may slightly increase the sensitivity of mammographic interpretation, and may be used. However, this sensitivity is at the expense of decreased specificity with increased recall and biopsy rates.

**Computer Aided Tactile Breast Imaging**

Comprehensive literature review of Hayes, ECRI, AHRQ, MCG, NICE, and Cochrane did not produce detailed comprehensive information regarding this technology. Controlled trials are needed to demonstrate that use of computer aided tactile breast imaging results in improved clinical outcomes.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Mammographic x-ray systems are classified as Class II devices. The FDA regulates the marketing of mammography devices and regulates the use of such devices via the Mammography Quality Standards Act (MQSA). The FDA has granted pre-market approval to several digital mammography systems (product code MUE) for breast cancer screening and diagnosis.

**Digital Breast Tomosynthesis (DBT):** DBT systems require approval through the U.S. Food and Drug Administration (FDA) premarket approval (PMA) application process. DBT systems are subject to Mammography Quality Standards Act accreditation.

In February 2011, the Center for Devices and Radiological Health of the U.S. Food and Drug Administration (FDA) granted premarket approval for the Selenia Dimensions 3D system (Hologic, Inc). According to the premarket approval letter (P080003), "the device is indicated to generate digital mammographic images that can be used for screening and diagnosis of breast cancer." The FDA approval letter also states that the Selenia Dimensions (2D or 3D) system is intended for use in the same clinical applications as 2D mammography systems for screening mammograms and may be used for additional diagnostic workup of the breast.
As part of the premarket approval process, the FDA reviewed results from two studies where board-certified radiologists were asked to review 2-D and 3-D images from more than 300 mammography exams. In both studies, radiologists viewing the 2-D images in conjunction with the 3-D images obtained a seven percent improvement in their ability to distinguish between cancerous and non-cancerous cases versus viewing the 2-D images alone. While the combination of the Selenia’s 2-D and 3-D images approximately doubled the amount of radiation the individual was exposed to, it improved the accuracy with which radiologists detected cancers, decreasing the number of women recalled for a diagnostic workup. The Selenia Dimensions System is marketed by Hologic Inc., located in Bedford, Massachusetts.

In May 2013, the FDA expanded the scope of the premarket approval for Hologic Inc. Selenia Dimensions System to include the C-View software, which generates a synthetic 2D image using information obtained from the multiple 3D views of the breast. With the expanded application, "each screening examination may consist of: a 2D FFDM image set; or a 2D and 3D image set, where the 2D image can be either a FFDM or a 2D image generated from the 3D image set."

In August 2014, FDA granted PMA for SenoClaire (GE Healthcare) for 3-D Breast Tomosynthesis.

SenoClaire acquires 2D images and also acquires multiple projection views to produce 3D DBT images suitable for screening and diagnosis of breast cancer. SenoClaire can be used for the same clinical applications as traditional mammographic systems for screening mammograms. A screening examination will consist of a 2D image set consisting of a craniocaudal view and a mediolateral oblique view or a 2D craniocaudal view and 3D DBT mediolateral oblique image set. The SenoClaire Digital Breast Tomosynthesis option for the Senographe Essential FFDM system may also be used for additional diagnostic workup of the breast.

The third digital breast tomosynthesis (DBT) system to become available on the U.S. market was cleared on April 23, 2015, by the U.S. Food and Drug Administration (FDA). The Mammmomat Inspiration with Tomosynthesis Option, the DBT add-on for Siemens Healthcare's Mammmomat Inspiration digital mammography platform (Siemens AG, Munich, Germany) offers another three-dimensional (3-D) option to supplement traditional two-dimensional (2-D) digital mammography.

**Magnetic Resonance Elastography of the Breast:** The GE Signa(TM) 1.5T Infinity TwinSpeed(TM) Magnetic Resonance System received 510(k) approval on August 3, 2001 as a whole body scanner to obtain images of the head and body.

**Breast Specific Gamma Imaging (BSGI):** BSGI for diagnosing breast cancer is a procedure and, therefore, is not subject to FDA regulation. However, the equipment used to conduct BSGI is subject to FDA regulation. The cameras used during BSGI are considered Class I radiologic devices. A scintillation (gamma) camera is a device intended to image the distribution of radionuclides in the body by means of a photon radiation detector. The Dilon 6800 camera (K984466) received 510(k) clearance in 1999.

**Automated Breast Ultrasound System (ABUS):** Automated breast (or whole breast) ultrasound devices are regulated by the FDA as Class III devices. A search of the FDA website for “automated breast ultrasound” and “automated whole breast ultrasound” retrieved only 1 device with premarket approval (PMA) (somo•v Automated Breast Ultrasound System [ABUS]; U-Systems Inc.) and 3 devices with 510(k) clearance (Automated Breast Ultrasound System [ABUS], U-Systems Inc.; the SonoCiné Adjunctive Breast Ultrasound System [ABU], Model 100, SonoCiné Inc.; and the ACUSON S2000 ABVS Ultrasound System).

The somo•v Automated Breast Ultrasound System (ABUS) (U-Systems Inc.) received PMA approval (P110006) on September 18, 2012. It should be noted that the acronym “ABUS” is a trademark of U-Systems Inc. (a division of GE Healthcare Company). The somo•v Automated Breast Ultrasound System may be used to produce ultrasound images of the breast for breast cancer screening following a negative mammogram. The ABUS scans the entire breast. It has a workstation that allows physicians to review ultrasound images from different angles producing several images for review. The ultrasound imaging technology can help reveal hidden tumors in the dense breast tissue. The ABUS is intended for use in women with dense breasts who have negative X-ray mammography results and have not had previous invasive procedures, such as breast surgeries or biopsies.

**Electrical Impedance Scanning:** Several electrical impedance breast imagers have received premarket approval (PMA). Approved devices include:
- T-Scan 2000™ (P970033) which received PMA approval on April 16, 1999
- TS2000™ (P970033 S001) which received PMA approval on November 15, 1999
- TranScan T-Scan 2000™ (P970033 S002), which received PMA approval on May 3, 2000.
On August 29, 2006, the FDA's Obstetrics and Gynecology Devices Panel voted unanimously not to recommend approval of Mirabel Medical Systems' T-Scan 2000 ED bioimpedance device, which is designed to evaluate the risk of breast cancer in asymptomatic women aged 30 to 39 years with no family history of breast cancer and no other known risk factors. The device would be employed in combination with clinical breast examination for this age group whose annual examination does not usually entail mammography.

The FDA panel decided that the data did not provide a reasonable assurance of the effectiveness to support the device's proposed indication. Furthermore, some panel members were concerned with other aspects of the clinical trial: the apparent differences in the characteristics of the 2 trial populations (1,751 women aged 30 to 39 years in the study arm designed to measure specificity and 390 women aged 30 to 45 years in the study arm measuring sensitivity), lack of ethnicity data, and a "high" false-positive rate.

These devices are approved as an adjunct to mammography in patients whose lesions are American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS) category III (probably benign) or IV (suspicious abnormality), based on mammography.

**Computer Aided Detection for MRI of the Breast:** The 3TP Software Option was approved on June 23, 2003 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.

CADstream Version 2.0 was approved on July 30, 2003, followed by Version 3.0 in 2004 and Version 4.0 in 2005. CADstream is intended for use in analyzing MRI studies.

DynaCAD™ was approved on July 21, 2004 as a post-processing software package intended for use in viewing and analyzing magnetic resonance imaging (MRI) studies. DynaCAD also provides an intervention planning tool (DynaLOC) which assists with MRI guidance of percutaneous interventional procedures.

**Computer-Aided Detection for Ultrasound:** The FDA has approved several computer-aided detection systems for ultrasonography. In May 2005, the FDA granted approval of a B-CAD System.


**Computer Aided Tactile Breast Imaging:** On August 14, 2014 the Food and Drug Administration (FDA) issued a draft guidance document. The draft provides guidance on a streamlined process for submitting requests to the FDA to down-classify certain low-to-moderate-risk devices that have been automatically classified as Class III. The de novo process is an important premarket pathway option for companies that intend to market novel device technologies that the FDA has not previously reviewed or classified, such as novel health IT or laboratory diagnostic technologies.

The draft guidance clarifies that the FDA will consider requests for de novo classification only if the following criteria are met:

- There is no identifiable predicate device.
- The device is of low to moderate risk, and general controls or general and special controls would provide reasonable assurance of the device's safety and effectiveness.
- The known risks and benefits of the device can be explained, the known risks can be effectively mitigated, and the device's effectiveness can be assured through application of general controls or general and special controls.

See the following website for more information: Guidance document [http://www.fda.gov/RegulatoryInformation/Guidances/ucm072678.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm072678.htm)

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare covers screening and diagnostic mammography when criteria are met. See the [NCD for Mammograms (220.4)](http://www.fda.gov/RegulatoryInformation/Guidances/ucm072678.htm). Medicare does not have NCDs for the following: Digital Mammography, Breast Magnetic Resonance Imaging (MRI), Digital Breast Tomosynthesis (3-D Mammography), Magnetic Resonance Elastography of the Breast, Breast Specific Gamma Imaging (Scintimammography), Electrical Impedance Scanning (EIS), Computer Aided Detection for MRI of the Breast, Breast Ultrasound, Computer Aided Detection for Ultrasound, Computer Aided Tactile Breast Imaging and Automated Breast Ultrasound.

Local Coverage Determinations (LCDs) do exist. Refer to the following LCDs: [Breast Imaging: Breast Echography (Sonography)/Breast MRI/Ductography](http://www.fda.gov/RegulatoryInformation/Guidances/ucm072678.htm), [Breast Imaging Mammography/Breast Echography (Sonography)/Breast](http://www.fda.gov/RegulatoryInformation/Guidances/ucm072678.htm).
REFERENCES

20. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Breast-specific gamma imaging (BSGI), molecular breast imaging (MBI), or scintimammography with breast-specific gamma camera. TEC Assessments 2013; Volume 28
22. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Use of digital breast tomosynthesis with mammography for breast cancer screening or diagnosis. TEC Assessment Program. 2015
23. Digital Breast Tomosynthesis with Mammography for Breast Cancer Screening or Diagnosis. TEC Assessments 2014:
38. ECRI Institute Target Database. Computer-assisted detection with magnetic resonance imaging (MRI) to detect breast cancer. October 2007.


... (Continued with more references)


POLICY HISTORY/REVISION INFORMATION

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<tr>
<td>06/01/2016</td>
<td>Reformatted and reorganized policy; transferred content to new template</td>
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<td>Updated supporting information to reflect the most current clinical evidence, FDA</td>
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