Breast Transillumination, Electrical Impedance Scanning (EIS), and Elastography

Number: 0386

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers transillumination (optical imaging, light scanning or diaphanography) of the breast experimental and investigational because this technique has not been established by the peer-reviewed medical literature to be an acceptable alternative to conventional mammography in detecting breast cancer.

II. Aetna considers electrical impedance scanning (EIS) of the breast to be experimental and investigational because there is inadequate evidence in the peer-reviewed published medical literature of the ability of this method to distinguish benign from malignant breast lesions or the effectiveness of EIS of the breast in improving clinical outcomes.

III. Aetna considers breast elastography by any method (i.e., ultrasound or magnetic resonance) experimental and investigational because there is insufficient evidence of its effectiveness in improving clinical outcomes.

Policy History

Last Review 04/13/2017
Effective: 02/02/2000
Next Review: 04/12/2018

Additional Information

Clinical Policy Bulletin Notes
IV. Aetna considers optical coherence micro-elastography for identifying malignant tissue and lymph node involvement during breast-conserving surgery experimental and investigational because the effectiveness of this approach has not been established (see CPB 886 - Optical Coherence Tomography/Microelastography in Breast Cancer).

See also CPB 0105 - Magnetic Resonance Imaging (MRI) of the Breast (.../100_199/0105.html); CPB 0269 - Breast Biopsy Procedures (.../200_299/0269.html); CPB 0337 - BreastAlert Differential Temperature Sensor (0337.html); CPB 0517 - Breast Ductal Lavage and Fiberoptic Ductoscopy (.../500_599/0517.html); and CPB 0584 - Mammography (.../500_599/0584.html).

Background
Mammography remains the generally accepted standard for breast cancer screening and diagnosis. However, efforts to provide new insights regarding the origins of breast disease and to find different approaches for addressing several key challenges in breast cancer, including detecting disease in mammographically dense tissue, distinguishing between malignant and benign lesions, and understanding the impact of neoadjuvant chemotherapies, has lead to the investigation of several novel methods of breast imaging for breast cancer management.

Breast Transillumination:

Optical imaging involves passing light through the breast, or reflecting light off of the breast, and then measuring the light that returns. It is purportedly useful in the detection of tumors or the blood vessels that supply them. Breast transillumination (also known as light scanning, diaphanography, optical imaging, optical mammography, dynamic optical breast imaging (DOBI), optical transillumination spectroscopy, diffuse optical spectroscopy (DOS), and transillumination breast spectroscopy) is based on the theory that normal and abnormal tissues reflect different light intensities. Various transilluminators have been created to screen and diagnose cancers of the breast. One such device, the
Computed Tomography Laser Mammography (CTLM) (Imaging Diagnostic Systems Inc., Fort Lauderdale, FL), is a near-infrared (NIR) laser breast imaging system that measures the absorption of NIR light by hemoglobin. Another method currently under investigation is opto-acoustic tomography (OAT) imaging. This hybrid imaging technique combines optic and acoustic imaging to map the distribution of optical absorption within biological tissues by means of laser-induced ultrasonic signals.

Breast transilluminators have not been proven to be an acceptable alternative to conventional mammography. The U.S. Food and Drug Administration (FDA)'s Obstetrics and Gynecology Devices Advisory Panel (1991) considered the clinical utility of breast transilluminators and concluded that "[e]xcept in investigational settings, the devices do not provide meaningful clinical information and should not be used in the clinical evaluation of breast tissue, neither alone nor in conjunction with other techniques." An Agency for Healthcare Research and Quality Clinical Practice Guideline (Bassett et al, 1994) concluded that “[l]ight scanning (diaphanography and transillumination) should not be used for screening or diagnostic evaluation of the breast”. The British Columbia Cancer Agency (2001) has concluded that “[a]t the present state of development, transillumination is not an appropriate imaging device for breast cancer screening.” The American Cancer Society (2009) stated that these experimental imaging tests are still in the earliest stages of research.

**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. Some evidence has been found that malignant breast tumors have lower electrical impedance than surrounding normal tissues. This observation has led to the proposal that electrical impedance could be used as an indicator for breast cancer detection. However, the separation of malignant tumors from benign lesions based on impedance measurements needs
further investigation.

Electrical impedance scanning (EIS) involves continuous transmission of electricity into the body via an electrical patch on the arm or a handheld device. As the current travels through the breast, it is measured by a probe on the surface of the skin. Cancerous and normal tissue conduct electricity differently, and cancerous images purportedly appear as bright white areas.

There are no prospective clinical studies demonstrating the clinical utility of electrical impedance scanning (EIS) in distinguishing benign from malignant breast lesions, either in place of or as an adjunct to mammography or magnetic resonance imaging. An assessment of technologies for breast cancer screening and diagnosis conducted by the Institute of Medicine of the National Academy of Sciences (2001) concluded that “[c]linical data suggest the technology [EIS] could play a role in breast cancer detection, but more study is needed to define a role in relation to existing technologies.”

Stojadinovic et al (2005) presented preliminary results on the use of EIS for the early detection of breast cancer in young women. They stated that EIS appears promising for early detection of breast cancer, and identification of young women at increased risk for having the disease at time of screening. Positive EIS-associated breast cancer risk compares favorably with relative risks of conditions commonly used to justify early breast cancer screening. The authors also noted that more data are needed to ascertain more accurately the actual sensitivity. These investigators also believe that EIS has promise as a breast cancer screening modality for a group of women for whom no effective screening modality currently exists. Electrical impedance scanning seems to identify a population at increased risk for having breast cancer for whom further imaging examinations may be warranted.

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: (i) 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), (ii) a lack of ethnicity data, and (iii) a "high" false-positive rate (Taulbee, 2006).

Blackmore et al (2007) stated that risk assessment by parenchymal density pattern, a strong physical indicator of future breast cancer risk, is available with the onset of mammographic screening programmes. However, due to the use of ionizing radiation, mammography is not recommended for use in younger women, thereby rendering risk assessment unattainable at an earlier age. These investigators reported on the use of visible and near infra-red light on 292 women with radiologically normal mammograms to determine if transillumination breast spectroscopy (TIBS) can identify women with a high parenchymal density pattern as an intermediate indicator of breast cancer risk. Principal component analysis was used to reduce the spectral data and generate density scores for each woman. To assess the accuracy of TIBS, logistic regression was used to calculate crude and adjusted odds ratios (OR) and 95 % confidence intervals (CI) for each score. Receiver operator characteristic curves and area under the curve (AUC) were also calculated for the crude and adjusted logistic models. Optical information relating to tissue chromophores, such as water, lipid and hemoglobin content, was sufficient to identify women with high parenchymal density. The resulting AUC for the final and most parsimonious multi-variate logistic model was 0.922 (95 % CI: 0.878 to 0.967). The authors concluded that TIBS provides information correlating to high parenchymal density and is a promising tool for risk assessment,
particularly for younger women. Furthermore, Blackmore and colleagues (2008) also reported that TIBS scores may prove useful as intermediate markers in studies of breast cancer etiology and prevention.

In a prospective, two-cohort trial of pre-menopausal women, Stojadinovic et al (2008) estimated the relative probability of breast cancer in T-Scan+ women compared to randomly selected young women. The Specificity (S(p))-Cohort evaluated T-Scan specificity in 1,751 asymptomatic women aged 30 to 39. The Sensitivity (S(n))-Cohort evaluated T-Scan sensitivity in 390 women aged 45 to 30 scheduled for biopsy. Specificity, sensitivity, and conservative estimate of disease prevalence were used to calculate relative probability. In the S(p)-Cohort, 93 of 1,751 women were T-Scan+ (S(p) = 94.7 %; 95 % CI: 93.7 to 95.7 %). In the S(n)-Cohort, 23 of 87 biopsy-proven cancers were T-Scan+ (S(n) = 26.4 %; 95 % CI: 17.4 to 35.4 %). Given S(p) = 94.7 %, S(n) = 26.4 % and prevalence of 1.5 cancers/1,000 women (aged 30 to 39), the relative probability of a T-Scan+ woman having Br-Ca is 4.95: (95 % CI: 3.16 to 7.14). The authors concluded that EIS can identify a subset of young women with a relative probability of breast cancer almost 5 times greater than in the population of young women at-large. The drawbacks of this study were discussed by the afore-mentioned FDA panel.

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 (n = 583) aged 45 years and under scheduled for mammary biopsy. Of the 583 cases, 143 were diagnosed with breast cancer. The sensitivities of EIS, ultrasound and the combination method were 86.7 % (124/143), 72 % (103/143), and 93.7 % (134/143) and the specificities were 72.9 % (321/440), 82.5 % (363/440), and 64.1 % (282/440), respectively. The relative possibilities of breast cancer for the positive young women detected by EIS, ultrasound, and the combination method were 8.67, 5.77, and 14.84, respectively. The authors concluded that the combination of EIS and ultrasound is likely to become an applicable method for early detection of breast cancer in young women.
Elastography:

Elastography refers to the measurement of elastic properties of tissues and is based on the principle that malignant tissue is harder than benign tissue. Manual palpation in the detection of breast cancer suggests that breast elastography could potentially provide a diagnostic tool for detecting cancerous lesions deeper within the breast. The technique is typically performed with ultrasound (US), but research with magnetic resonance (MR) is also under way. Advantages of the US elastography are ubiquitous applicability and cost-effectiveness. Magnetic resonance elastography (MRE) offers improved reconstruction and the possibility to assess potential anisotropic properties.

There are 3 main types of US elasticity imaging: (i) elastography that tracks tissue movement during compression to obtain an estimate of strain, (ii) sonoelastography that uses color Doppler to generate an image of tissue movement in response to external vibrations, and (iii) tracking of shear wave propagation through tissue to obtain the elastic modulus.

The SonixTouch Ultrasound Imaging System received 510(k) marketing clearance by the FDA in October, 2008. The device includes an elastography imaging mode. Mechanical pressure with the hand on the transducer produces an imaging sequence similar to the B-mode sequence except the system will acquire the radio-frequency signal instead of acquiring B mode data. The algorithm extracts a strain value information for every point on the image. The elastography image then color-codes the stiff versus softer structures.

Magnetic resonance elastography is a phase-contrast-based magnetic resonance imaging (MRI) technique that can directly visualize and quantitatively measure propagating acoustic strain waves in tissue subjected to harmonic mechanical excitation. The data acquired allows the calculation of local quantitative values of shear modulus and the generation of images that depict tissue elasticity or stiffness.

Garra et al (1997) examined the feasibility of elastography to
determine the appearance of various breast lesions and the potential of elastography to diagnosis breast lesions. A total of 46 breast lesions were examined with elastography. Patients underwent biopsy or aspiration of all lesions, revealing 15 fibroadenomas, 12 carcinomas, 6 fibrocystic nodules, and 13 other lesions. The elastogram was generated from radio-frequency data collected with use of a 5-MHz linear-array transducer. The elastogram and corresponding sonogram were evaluated by a single observer for lesion visualization, relative brightness, and margin definition and regularity. The sizes of the lesions at each imaging examination and at biopsy were recorded and compared. Softer tissues such as fat appeared as bright areas on elastograms. Firm tissues, including parenchyma, cancers, and other masses, appeared darker. The cancers were statistically significantly darker than fibroadenomas (p < 0.005) and substantially larger on the elastogram than on the sonogram. A total of 73% of fibroadenomas and 56% of solid benign lesions could be distinguished from cancers by using lesion brightness and size difference. Some cancers that appeared as areas of shadowing on sonograms appeared as discrete masses on elastograms. The authors concluded that elastography has the potential to be useful in the evaluation of areas of shadowing on the sonogram and that it may be helpful in the distinction of benign from malignant masses.

Lorenzen et al (2002) explored the potential of elasticity as a parameter for the diagnosis of breast lesions using MRE in 15 female patients with malignant tumors of the breast, 5 patients with benign breast tumors, and 15 healthy volunteers. Malignant invasive breast tumors documented the highest values of elasticity with a median of 15.9 kPa and a wide range of stiffnesses between 8 and 28 kPa. In contrast, benign breast lesions represented low values of elasticity, which were significantly different from malignant breast tumors (median elasticity: 7.0 kPa; p = 0.0012). This was comparable to the stiffest tissue areas in healthy volunteers (median elasticity 7.0 kPa), whereas breast parenchyma (median: 2.5 kPa) and fatty breast tissue (median: 1.7 kPa) showed the lowest values of elasticity. Two invasive ductal carcinomas had elasticity values of 8 kPa and two stiff parenchyma areas in healthy volunteers had
elastici ties of 13 and 15 kPa. These lesions could not be differentiated by their elasticity. The authors concluded that MRE is a promising new imaging modality with the capability to assess the viscoelastic properties of breast tumors and the surrounding tissues; however, there is an overlap in the elasticity ranges of soft malignant tumors and stiff benign lesions.

Sinkus et al (2005) examined the viscoelastic shear properties of breast lesions measured by MRE applied in the course of standard MR mammography to 15 patients with different pathologies (6 breast cancer cases, 6 fibroadenoma cases and 3 mastopathy cases). Breast cancer appeared on average 2.2 (p < 0.001) times stiffer. All breast cancer cases showed a good delineation to the surrounding breast tissue with an average elevation of a factor of 3.3 (p < 1.4 x 10(-6)). However, the results were not found to be useful for separating benign from malignant lesions.

Giuseppeetti et al (2005) assessed the diagnostic accuracy of elastography in characterizing nodular breast lesions. A total of 82 patients who received mammographic, US and elastographic evaluation in a single session at two Italian centers between January and August 2004 according to identical protocols exhibited 91 nodules that were subjected to cytological/histological examination. Lesions were classified and scored and the sensitivity and specificity of elastography calculated. Overall sensitivity and specificity were 79 % and 89 %, respectively. However, sensitivity was 86 % and 65 % and specificity 100 % and 62 % for lesions less than 2 cm and greater than 2 cm in diameter, respectively. The authors concluded that larger studies are needed to establish semiological patterns.

Itoh et al (2006) evaluated the diagnostic performance of real-time elastography (RTE) by using the extended combined autocorrelation method (CAM) to differentiate benign from malignant breast lesions, with pathologic diagnosis as the reference standard. Conventional US and RTE with CAM were performed in 111 women (mean age of 49.4 years; age range of 27 to 91 years) who had breast lesions (59 benign, 52 malignant). Elasticity images were assigned an elasticity score according to the degree and distribution of strain induced by light
compression. The area under the curve and cut-off point, both of which were obtained by using a receiver operating characteristic curve analysis, were used to assess diagnostic performance. Mean scores were examined by using a Student t test. Sensitivity, specificity, and accuracy were compared by using the standard proportion difference test or the Delta-equivalent test. For elasticity score, the mean +/- standard deviation was 4.2 +/- 0.9 for malignant lesions and 2.1 +/- 1.0 for benign lesions (p < 0.001). When a cut-off point of between 3 and 4 was used, elastography had 86.5 % sensitivity, 89.8 % specificity, and 88.3 % accuracy. When a best cut-off point of between 4 and 5 was used, conventional US had 71.2 % sensitivity, 96.6 % specificity, and 84.7 % accuracy. Elastography had higher sensitivity than conventional US (p < 0.05). By using equivalence bands for non-inferiority or equivalence, it was shown that the specificity of elastography was not inferior to that of conventional US and that the accuracy of elastography was equivalent to that of conventional US. The authors concluded that US elastography with the proposed imaging classification had almost the same diagnostic performance as conventional US.

Thomas et al (2006) compared the sensitivity and specificity of elastography with that of B-mode US and mammography in 300 patients with histologically confirmed breast lesions (168 benign, 132 malignant). Evaluation was by means of the 3-dimensional (3-D) finite-element method. The data were color-coded and superimposed on the B-mode US scan. The images were evaluated by two independent readers. The results were compared with mammography, histology, and the data obtained by previous US investigations. Sensitivity and specificity in the differentiation of benign and malignant lesions were 87 % and 85 %, respectively, for mammography and 94 % and 83 % for B-mode US. The 2 examiners were in very good agreement in their evaluation of the elastograms (kappa: 0.86). Elastography had a sensitivity of 82 % and a specificity of 87 %. Elastography was superior to B-mode US in diagnosing Breast Imaging Reporting and Data System (BI-RADS) 3 lesions (92 % versus 82 % specificity) and in lipomatous involution (80 % versus 69 % specificity).

Zhang et al (2006) investigated the clinical value of RTE in the
The diagnosis of breast cancer in 120 patients with breast lumps (135 lesions). Patients were examined with B-mode imaging, color Doppler flowing imaging (CDFI) and RTE. The elastogram was graded using a 5-score evaluating method. The post-operative pathological diagnosis was used as the gold standard, and the sensitivity, specificity and accuracy of RTE and 2-D US combined with RTE in diagnosis of breast cancer were calculated. When the score greater than 4 was set for cut-off criteria of malignancy, the sensitivity, specificity and accuracy of RTE was 85.45 %, 83.75 % and 84.4 %, respectively. When 2-D US combined with RTE was used, the sensitivity, specificity and accuracy increased up to 100 %, 95 % and 97 %, respectively.

Thomas et al (2006) evaluated whether RTE could improve the differentiation and characterization of benign and malignant breast lesions. Real-time elastography was carried out in 108 potential breast tumor patients with cytologically/histologically confirmed focal breast lesions (59 benign, 49 malignant; median age, 53.9 years; range of 16 to 84 years). Tumor and healthy tissue were differentiated by measurement of elasticity based on the correlation between tissue properties and elasticity modulus. Evaluation was performed using the 3-D finite element method, in which the information is color-coded and superimposed on the B-mode US image. A second observer evaluated the elastography images, in order to improve the objectivity of the method. The results of B-mode scan and elastography were compared with those of histology and previous sonographic findings.

Sensitivities and specificities were calculated, using histology as the gold standard. B-mode US had a sensitivity of 91.8 % and a specificity of 78 %, compared with sensitivities of 77.6 % and 79.6 % and specificities of 91.5 % and 84.7 %, respectively, for the two observers evaluating elastography. Agreement between B-mode US and elastography was good, yielding a weighted kappa of 0.67. The authors concluded that RTE improves the specificity of breast lesion diagnosis and is a promising new approach for the diagnosis of breast cancer.

from 232 consecutive patients were diagnosed as benign or malignant by mammography and sonography and further analyzed with US elastography. The diagnostic results were compared with histopathologic findings. The sensitivity, specificity, accuracy, positive and negative predictive values, and false-positive and -negative rates were calculated for each modality and the combination of US elastography and sonography. Of 296 lesions, 87 were histologically malignant, and 209 were benign. Ultrasound elastography was the most specific (95.7 %) and had the lowest false-positive rate (4.3 %) of the 3 modalities. The accuracy (88.2 %) and positive predictive value (PPV) (87.1 %) of US elastography were higher than those of sonography (72.6 % and 52.5 %, respectively). The sensitivity values, negative predictive values (NPV), and false negative rates of the 3 modalities had no differences. A combination of US elastography and sonography had the best sensitivity (89.7 %) and accuracy (93.9 %) and the lowest false-negative rate (9.2 %). The specificity (95.7 %) and PPV (89.7 %) of the combination were better, and the false-positive rate (4.3 %) of the combination was lower than those of mammography and sonography. The authors concluded that US elastography is a promising technique for evaluating breast lesions.

Tardivon et al (2007) evaluated elastography in the characterization of breast nodules in 122 lesions. Elastography (Hitachi, 7.5- to 13-MHz probe; Ueno classification, scores 1-3 = benign, 4-5 = malignant) was evaluated in 125 sub-clinical lesions in 114 patients. The results were compared to those of the American College of Radiology's BI-RADS sonography categories (benign = 2 and 3, malignant = 4 and 5) and to the results of the percutaneous samples taken and/or surgery (122 lesions evaluated, 59 % less than 10 mm, 61 cancers, 61 benign lesions). There were 3 technical failures (2.4 %). The elastography was in agreement with histology for 101 lesions, with 13 false-negative results and 8 false-positive results (sensitivity, 78.7 %; specificity, 86.9 %; PPV, 85.7 %; NPV, 80.3 %); versus agreement with the BI-RADS classification for 98 lesions with one false-negative result and 23 false-positive results (sensitivity, 98.4 %; specificity, 47.5 %; PPV, 65.2 %; NPV, 96.7 %).
Cho et al (2008) compared the diagnostic performances of conventional US and US elastography for the differentiation of non-palpable breast masses, and to evaluate whether elastography is helpful at reducing the number of benign biopsies, using histological analysis as a reference standard. Conventional US and RTE images were obtained for 100 women who had been scheduled for a US-guided core biopsy of 100 non-palpable breast masses (83 benign, 17 malignant). Two experienced radiologists unaware of the biopsy and clinical findings analyzed conventional US and elastographic images by consensus, and classified lesions based on degree of suspicion regarding the probability of malignancy. Results were evaluated by receiver operating characteristic (ROC) curve analysis. In addition, the authors investigated whether a subset of lesions were categorized as suspicious by conventional US, but as benign by elastography. Areas under the ROC curves (Az values) were 0.901 for conventional US and 0.916 for elastography (p = 0.808). For BI-RADS category 4a lesions, 44% (22 of 50) had an elasticity score of 1 and all were found to be benign. The authors concluded that elastography had a diagnostic performance comparable to that of conventional US for the differentiation of non-palpable breast masses.

Researchers have tested the feasibility of breast elastography and the results confirm the hypothesis that breast elastography can quantitatively depict the elastic properties of breast tissues and reveal high shear elasticity in known breast tumors. However, the clinical benefits of elastography imaging are still under evaluation and no clinical diagnosis can be made other than being able to tell whether or not a structure inside the patient is stiffer than another one. Further research is needed to evaluate the potential clinical applications of breast elastography, such as detecting breast carcinoma and characterizing suspicious breast lesions.

Kumm and Szabunio (2010) evaluated the application and diagnostic performance of elastography for the characterization of breast lesions in patients referred for biopsy. Subjects referred for ultrasound-guided biopsy of sonographically apparent breast lesions were included in this study. The Hitachi Hi-Vision 900
ultrasound was used to generate index test results for elastography scoring (ES) and for strain ratio (SR) measurement. Sensitivity, specificity, PPV and NPV were determined using pathologic results from 14-gauge core needle biopsy as the reference standard. A total of 310 lesions in 288 patients were included in this series. Of these 310 lesions, 223 (72%) were benign and 87 (28%) were malignant. Sensitivity was 0.76 for ES and 0.79 for SR. Specificity was 0.81 for ES and 0.76 for SR. The PPV was 0.60 for ES and 0.57 for SR; the NPV was 0.90 for ES and 0.90 for SR. Strain ratio values for malignant lesions were significantly higher (median ratios of 10.5 and 2.7, respectively, p < 0.001). The authors concluded that while the initial clinical performance of elastography imaging shows potential to reduce biopsy of low-risk lesions, a large-scale trial addressing appropriate patient selection, diagnostic parameters, and practical application of this technique is needed before widespread clinical use.

Siegmann et al (2010) assessed the additional value of MRE to contrast-enhanced (ce) MRI for breast lesion characterisation. A total of 57 suspected breast lesions in 57 patients (mean age of 52.4 years) were examined by ce MRI and MRE. All lesions were classified into BI-RADS categories. Viscoelastic parameters, e.g., alpha0 as an indicator of tissue stiffness, were calculated. Histology of the lesions was correlated with BI-RADS and viscoelastic properties. The PPV for malignancy, and the sensitivity and specificity of ce MRI were calculated. The ROC curves were separately calculated for both ce MRI and viscoelastic properties and conjoined to analyse the accuracy of diagnostic performance. The lesions (mean size of 27.6 mm) were malignant in 64.9% (n = 37) of cases. The PPV for malignancy was significantly (p < 0.0001) dependent on BI-RADS classification. The sensitivity of ce MRI for breast cancer detection was 97.3% (36/37), whereas specificity was 55% (11/20). If ce MRI was combined with alpha0, the diagnostic accuracy could be significantly increased (p < 0.05; AUC(ce MRI) = 0.93, AUC(combined) = 0.96). The authors concluded that the combination of MRE and ce MRI could increase the diagnostic performance of breast MRI. Moreover, they stated that further investigations of larger cohorts and smaller lesions (in particular
those only visible on MRI) are needed to validate these findings.

Yi et al (2012) evaluated the diagnostic value of sonoelastography by correlation with histopathology compared with conventional ultrasound on the decision to biopsy. Prospectively determined BI-RADS categories of conventional ultrasound and elasticity scores from strain sonoelastography of 1,786 non-palpable breast masses (1,523 benign and 263 malignant) in 1,538 women were correlated with histopathology. The sensitivity and specificity of 2 imaging techniques were compared regarding the decision to biopsy. These researchers also investigated whether there was a subset of benign masses that were recommended for biopsy by B-mode ultrasound but that had a less than 2 % malignancy rate with the addition of sonoelastography. The mean elasticity score of malignant lesions was higher than that of benign lesions (2.94 +/- 1.10 versus 1.78 +/- 0.81) (p < 0.001). In the decision to biopsy, B-mode ultrasound had higher sensitivity than sonoelastography (98.5 % versus 93.2 %) (p < 0.001), whereas sonoelastography had higher specificity than B-mode ultrasound (42.6 % versus 16.3 %) (p < 0.001). BI-RADS category 4a lesions with an elasticity score of 1 had a malignancy rate of 0.8 %. The authors concluded that sonoelastography has higher specificity than B-mode ultrasound in the differentiation between benign and malignant masses and has the potential to reduce biopsies with benign results.

Landoni and colleagues (2012) developed a quantitative method for breast cancer diagnosis based on elastosonography images in order to reduce whenever possible unnecessary biopsies. The proposed method was validated by correlating the results of quantitative analysis with the diagnosis assessed by histopathologic examination. A total of 109 images of breast lesions (50 benign and 59 malignant) were acquired with the traditional B-mode technique and with elastographic modality. Images in Digital Imaging and COmmunications in Medicine format (DICOM) were exported into a software, written in Visual Basic, especially developed to perform this study. The lesion was contoured and the mean grey value and softness inside the region of interest (ROI) were calculated. The correlations between variables were investigated and receiver operating
characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of the proposed method. Pathologic results were used as standard reference. Both the mean grey value and the softness inside the ROI resulted statistically different at the t-test for the 2 populations of lesions (i.e., benign versus malignant): p <0.0001. The area under the curve (AUC) was 0.924 (0.834 to 0.973) and 0.917 (0.826 to 0.970) for the mean grey value and for the softness respectively. The authors concluded that quantitative elastosonography is a promising ultrasound technique in the detection of breast cancer; but large prospective trials are needed to determine if quantitative analysis of images can help to overcome some pitfalls of this method.

In a meta-analysis, Sadigh et al (2012) reviewed evidence on diagnostic performance of strain ratio and length ratio, 2 different strain measurements in ultrasound elastography (USE), for differentiating benign and malignant breast masses. A literature search of PubMed and other medical and general purpose databases from inception through January 2012 was conducted. Published studies that evaluated the diagnostic performance of USE alone reporting either strain ratio or length ratio for characterization of focal breast lesions and using cytology (fine needle aspiration) or histology (core biopsy) as a reference standard were included. Summary diagnostic performance measures were assessed using bi-variate generalized linear mixed modeling. A total of 9 studies reported strain ratio for 2,087 breast masses (667 cancers, 1,420 benign lesions). Summary sensitivity and specificity were 88 % (95 % CI: 84 to 91 %), and 83 % (95 % CI: 78-88 %), respectively. The positive and negative likelihood ratios (LR) were 5.57 (95 % CI: 3.85 to 8.01) and 0.14 (95 % I: 0.09 to 0.20), respectively. The inconsistency index for heterogeneity was 6 % (95 % CI: 1 to 22 %) for sensitivity and 8 % (95 % CI: 3 to 24 %) for specificity. Analysis of 3 studies reporting length ratio for 450 breast masses demonstrated sensitivity and specificity of 98 % (95 % CI: 93 to 99 %) and 72 % (95 % CI: 31 to 96 %), respectively. Strain ratio and length ratio have good diagnostic performance for distinguishing benign from malignant breast masses. The authors concluded that although, this performance may not be incrementally superior to that of BI-RADS in B-mode ultrasound, the application of USE using strain
ratio or length ratio in combination with USB may have the potential to benefit the patients, and this requires further comparative effectiveness and cost-effectiveness analyses.

Vreugdenburg et al (2013) evaluated all the available evidence of safety, effectiveness and diagnostic accuracy for three emerging classes of technology promoted for breast cancer screening and diagnosis: Digital infrared thermal imaging (DITI), EIS and elastography. A systematic search of seven biomedical databases (EMBASE, PubMed, Web of Science, CRD, CINAHL, Cochrane Library, Current Contents Connect) was conducted through March 2011, along with a manual search of reference lists from relevant studies. The principal outcome measures were safety, effectiveness, and diagnostic accuracy. Data were extracted using a standardized form, and validated for accuracy by the secondary authors. Study quality was appraised using the quality assessment of diagnostic accuracy studies tool, while heterogeneity was assessed using forest plots, Cooks' distance and standardized residual scatter plots, and I (2) statistics. From 6,808 search results, a total of 267 full-text articles were assessed, of which 60 satisfied the inclusion criteria. No effectiveness studies were identified. Only 1 EIS screening accuracy study was identified, while all other studies involved symptomatic populations. Significant heterogeneity was present among all device classes, limiting the potential for meta-analyses. Sensitivity and specificity varied greatly for DITI (Sens = 0.25 to 0.97, Spec = 0.12 to 0.85), EIS (Sens = 0.26 to 0.98, Spec = 0.08-to 0.81) and ultrasound elastography (Sens = 0.35 to 1.00, Spec = 0.21 to 0.99). The authors concluded that there is currently insufficient evidence to recommend the use of these technologies for breast cancer screening. Moreover, the high level of heterogeneity among studies of symptomatic women limits inferences that may be drawn regarding their use as diagnostic tools. They stated that future research employing standardized imaging, research and reporting methods is needed.

Olgun and colleagues (2014) determined the correlations between the elasticity values of solid breast masses and histopathological findings to define cut-off elasticity values differentiating malignant from benign lesions. A total of 115 solid
breast lesions of 109 consecutive patients were evaluated prospectively using shear wave elastography (SWE). Two orthogonal elastographic images of each lesion were obtained. Minimum, mean, and maximum elasticity values were calculated in regions of interest placed over the stiffest areas on the 2 images; these researchers also calculated mass/fat elasticity ratios. Correlation of elastographic measurements with histopathological results were studied. A total of 83 benign and 32 malignant lesions were histopathologically diagnosed. The minimum, mean, and maximum elasticity values, and the mass/fat elasticity ratios of malignant lesions, were significantly higher than those of benign lesions. The cut-off value was 45.7 kPa for mean elasticity (sensitivity, 96 %; specificity, 95 %), 54.3 kPa for maximum elasticity (sensitivity, 95 %; specificity, 94 %), 37.1 kPa for minimum elasticity (sensitivity, 96 %; specificity, 95 %), and 4.6 for the mass/fat elasticity ratio (sensitivity, 97 %; specificity, 95 %). The authors concluded that WE yielded additional valuable quantitative data to ultrasonographic examination on solid breast lesions; and SWE may serve as a complementary tool for diagnosis of breast lesions. Moreover, they stated that long-term clinical studies are needed to accurately select lesions requiring biopsy.

In a meta-analysis, Chen and colleagues (2014) examined the performance of SWE for the differentiation of benign and malignant breast lesions. PubMed, Embase and the Cochrane library were searched for studies published up to January 2014. The references of retrieved relevant articles were reviewed to identify potential publications. Random-effect meta-analysis was conducted to assess the overall sensitivity and specificity of SWE in the differentiation of breast lesions. A total of 11 articles, including 2,424 patients, were included in the present meta-analysis. The summarized sensitivity and specificity of the SWE performance based on maximum elasticity were 0.93 (95 % CI: 0.9 to 0.95) and 0.81 (95 % CI: 0.78 to 0.83), respectively. For the mean elasticity, the summarized sensitivity and specificity were 0.94 (95 % CI: 0.92 to 0.96) and 0.71 (95 % CI: 0.69 to 0.74), respectively. The summarized sensitivity and specificity were 0.77 (95 % CI: 0.70 to 0.83) and 0.88 (95 % CI: 0.84 to 0.91) for the SD of elasticity. The authors concluded that SWE has a high
sensitivity and specificity in the differentiation of benign and malignant breast lesions. However, they stated that more large and prospective studies are needed to further examine the performance of SWE.

Chamming's et al (2015) evaluated imaging performances for the detection, characterization and biopsy of breast micro-calculifications and made recommendations. French and English publications were searched using PubMed, Cochrane Library and international learned societies recommendations. Digital mammography (DR [Direct Radiography] and CR [Computed Radiography]) and screen-film mammography demonstrated good performances for the detection and the characterization of breast micro-calculifications. Systematic use of the 2013 edition of the BI-RADS lexicon was recommended for description and characterization of micro-calculations. Faced with BI-RADS 4 or 5 micro-calculations, breast ultrasound is recommended but a normal result does not eliminate the diagnosis of cancer and other examination should be performed. Literature review does not allow recommending digital breast tomosynthesis, elastography or MRI to analyze micro-calculations. In case of probably benign micro-calculations (BI-RADS 3), 6 months, 1 year and at least 2 years follow-up are recommended. In case a biopsy is indicated, it is recommended to use a vacuum-assisted macro-biopsy system with 11-G needles or bigger. If no calcification is visible on the radiography of the specimen, it is recommended to obtain additional samples.

In a meta-analysis, Liu et al (2016) estimated the diagnostic performance of SWE in differentiating malignant from benign breast lesions. A literature search of PubMed, Web of Science and Scopus up to November 2014 was conducted. A summary receiver operating characteristic curve was constructed, and pooled weighted estimates of sensitivity and specificity were calculated using a bi-variate mixed-effects regression model. A total of 33 studies, which included a total of 5,838 lesions (2,093 malignant, 3,745 benign) from 5,397 patients, were finally analyzed. Summary sensitivity and specificity were 0.886 (95 % CI: 0.858 to 0.909) and 0.866 (95 % CI: 0.833 to 0.894), respectively. The pooled diagnostic OR was 50.41 (95 % CI:
34.972 to 72.664). And the area under the receiver operating characteristic curve of SWE was 0.94 (95 % CI: 0.91 to 0.96). No publication bias existed among these studies (p = 0.245). In the subgroup analysis, sensitivity and specificity were 0.862 (95 % CI: 0.811 to 0.901) and 0.875 (95 % CI: 0.793 to 0.928) among 1,552 lesions from 1,429 patients in the 12 studies using acoustic radiation force impulse imaging and 0.897 (95 % CI: 0.863 to 0.923) and 0.863 (95 % CI: 0.831 to 0.889) among another 4,436 lesions from 4,097 patients in the 21 studies using supersonic shear imaging. When analysis confined to 9 studies evaluated the diagnostic performance of combination SWE and conventional ultrasound, the area under the curve was 0.96 (95 % CI: 0.94 to 0.97), yielding a sensitivity of 0.971 (95 % CI: 0.941 to 0.986) and specificity of 0.801 (95 % CI: 0.733 to 0.856). The authors concluded that SWE appeared to be a good quantitative method for differentiating breast lesions, with promise for integration into routine imaging protocols.

In a retrospective study, Chung and associates (2016) evaluated the diagnostic performance of SWE for the differential diagnosis of breast papillary lesions. A total of 79 breast papillary lesions in 71 consecutive women underwent ultrasound and SWE prior to biopsy. Ultrasound features and quantitative SWE parameters were recorded for each lesion. All lesions were surgically excised or excised using an ultrasound-guided vacuum-assisted method. The diagnostic performances of the quantitative SWE parameters were compared using the AUC. Of the 79 lesions, 6 (7.6 %) were malignant and 12 (15.2 %) were atypical. Orientation, margin, and the final BI-RADS ultrasound assessments were significantly different for the papillary lesions (p < 0.05). All qualitative SWE parameters were significantly different (p < 0.05). The AUC values for SWE parameters of benign and atypical or malignant papillary lesions ranged from 0.707 to 0.757 (sensitivity, 44.4 to 94.4 %; specificity, 42.6 to 88.5 %). The maximum elasticity and the mean elasticity showed the highest AUC (0.757) to differentiate papillary lesions. The authors concluded that SWE provided additional information for the differential diagnosis of breast papillary lesions; quantitative SWE features were helpful to differentiate breast papillary lesions. Moreover, they stated that further study about breast papillary lesions using larger ROI size
may be necessary.

This study had several drawbacks; (i) small sample size (n = 71). Of 217 papillary lesions diagnosed by US-guided CNB, only 79 (36.4 %) were finally included due to the lack of a SWE image or no excision. Thus, large numbers and multi-center studies are needed in the future, (ii) the authors did not compare their results with those of conventional US or assess combined diagnostic performance; further studies combining SWE and conventional US in are needed to differentiate papillary lesions, (iii) these researchers used a 2x2-mm sized ROI. Larger ROI might be more accurate for the assessment of the breast masses by providing both maximum stiffness and heterogeneity of breast lesions.

In a systematic review and meta-analysis, Blank and colleagues (2017) reported measured elasticity of benign and malignant breast pathologies from SWE, quantitatively confirmed the effect of the selected ROI on these measures and tested the hypothesis that a metric of heterogeneity based on the mean and maximum elasticity can improve specificity of diagnosis. The elasticity of benign, malignant and specific pathologic states were reported from 22 publications encompassing 2,989 patients, identified from a structured search of the literature from May to September 2015. A total of 12 articles were included in a meta-analysis that grouped results by the method of ROI selection to discriminate between different pathologies. These researchers observed a significant correlation between the method of selection of ROI for malignant mean (p < 0.001) and maximum (p = 0.027) elasticity, but no correlation with benign measures. They defined a quantitative heterogeneity parameter, the "stiffness gradient", computed from the mean and maximum measured elasticity. The stiffness gradient out-performed the current standard maximum elasticity metric in stratifying malignancy risk by a margin of 15 % for the partial ROI, and 42 % for the maximized ROI. An anecdotal example of improved differentiation using the stiffness gradient on pathology-specific lesions was also provided. The authors concluded that these results quantitatively indicated that the method of ROI selection in SWE not only has a significant impact on the resulting mean reported elasticity of a lesion, but may
provide some insight into lesion heterogeneity. They stated that these findings suggested that further exploration of quantitative heterogeneity is needed to improve the specificity of diagnosis.

In a prospective study, Ma and co-workers (2016) evaluated SWE and SWE combined with the Ki-67 index as novel predictive modalities for the pathological response of invasive breast cancer to neoadjuvant chemotherapy (NAC). This study recruited 66 eligible patients from July 2014 to November 2015. Tumor stiffness, which corresponds with tumor progression and invasiveness, was assessed by quantitative SWE 1 day before biopsy (time-point t0, elasticity E0), 1 day before next NAC cycle (t1-t5, E1-E5), and 1 day before surgery (t6, E6). The relative changes in SWE parameters after the 1st and 2nd NAC cycles were considered as the variables [ΔE (t1), ΔE (t2)]. The pathological response was classified according to the residual cancer burden (RCB) protocol. Correlations between RCB scores and variables were evaluated. The predictive diagnostic performances of SWE parameters, Ki-67 index, and the predictive RCB (predRCB) score determined by a linear regression model were compared. Some immunohistochemical and molecular factors and SWE parameters were significantly different among the 3 RCB groups. The ΔEmean (t2) and Ki-67 had significantly better diagnostic performance than other parameters regarding predicting the pathological response (the RCB-I response and RCB-III resistance). However, the correlation between ΔEmean (t2) and Ki-67 index was significantly weaker as a diagnostic predictor (r = 0.29). These researchers generated a new predictive modality, predRCB, which is a multi-variable linear regression model that combines ΔEmean (t2) and the Ki-67 index. The predRCB modality showed better diagnostic performance than SWE parameters and Ki-67 index alone. The authors concluded that these findings highlighted the potential utility for adding the Ki-67 index to the SWE results, which may improve the predictive power of SWE and facilitate personalizing the treatment regimes of patients with breast cancer. Moreover, they stated that these results should be validated in the future by performing a multi-center prospective study with a larger cohort.

Wang and co-workers (2016) identified the automated breast
volume scanning (ABVS) and shear wave velocity (SWV) characteristics of different pathological types of breast carcinoma. These researchers performed a retrospective review of both ABVS and SWV imaging of 118 consecutive breast masses. The imaging features of both techniques were assessed with reference to histopathological results. Echo heterogeneity with a smooth and lobulated margin was a significant feature more frequently found in mucinous carcinoma groups (100 %, p < 0.05). Between different stages of ductal carcinoma, echo homogeneity was more likely in high-grade ductal carcinomas (p < 0.05); SWV differences existed between inside tumor areas and either tumor boundary or tissues outside the tumors (p < 0.05), and values differed between different breast carcinoma stages. The central and tumor margin areas of ductal carcinomas were much harder than in tubular carcinoma and micro-carcinoma, respectively (p < 0.05); SWV ROC curve analyses yielded a cut-off value of 3.015 m/s between ductal carcinoma in-situ (DCIS) and invasive ductal carcinoma in the central part of lesions, with 83.5 % sensitivity and 80 % specificity for T0 versus T1-3 staging. The authors concluded that since some features were associated with different breast carcinoma types and stages, ABVS and SWV imaging has the potential to give clues about breast carcinoma differentiation in a non-invasive manner.

Optical Coherence Micro-Elastography for Intraoperative Assessment of Breast Cancer Margins and Lymph Node Involvement:

Allen and colleagues (2016) noted that incomplete excision of malignant tissue is a major issue in breast-conserving surgery, with typically 20 to 30 % of cases requiring a second surgical procedure arising from post-operative detection of an involved margin. These investigators reported advances in the development of a new intra-operative tool, optical coherence micro-elastography (OCME), for the assessment of tumor margins on the micro-scale. They demonstrated an important step by conducting whole specimen imaging in intra-operative time frames with a wide-field scanning system acquiring mosaicked elastograms with overall dimensions of approximately 50 × 50 mm, large enough to image an entire face of most lumpectomy
specimens. This capability was enabled by a wide-aperture annular actuator with an internal diameter of 65 mm. The authors demonstrated feasibility by presenting elastograms recorded from freshly excised human breast tissue, including from a mastectomy, lumpectomies and a cavity shaving. These researchers stated that they will incorporate further reductions in acquisition and processing time and determine the diagnostic accuracy of compression OCME in identifying malignant tissue during breast-conserving surgery.

Kennedy and associates (2016) noted that evaluation of lymph node involvement is an important factor in detecting metastasis and deciding whether to perform axillary lymph node dissection (ALND) in breast cancer surgery. As ALND is associated with potentially severe long-term morbidity, the accuracy of lymph node assessment is imperative in avoiding unnecessary ALND. The mechanical properties of malignant lymph nodes are often distinct from those of normal nodes. A method to image the micro-scale mechanical properties of lymph nodes could, therefore, provide diagnostic information to assist in the evaluation of lymph node involvement in metastatic cancer. In this study, these investigators scanned axillary lymph nodes, freshly excised from breast cancer patients, with OCME, a method of imaging micro-scale mechanical strain, to assess its potential for the intra-operative assessment of lymph node involvement. A total of 26 fresh, unstained lymph nodes were imaged from 15 patients undergoing mastectomy or breast-conserving surgery with axillary clearance. Lymph node specimens were bisected to allow imaging of the internal face of each node. Co-located OCME and optical coherence tomography (OCT) scans were taken of each sample, and the results compared to standard post-operative hematoxylin-and-eosin-stained histology. The optical back-scattering signal provided by OCT alone may not provide reliable differentiation by inspection between benign and malignant lymphoid tissue. Alternatively, OCME highlighted local changes in tissue strain that corresponded to malignancy and were distinct from strain patterns in benign lymphoid tissue. The mechanical contrast provided by OCME complemented the optical contrast provided by OCT and aided in the differentiation of malignant tumor from
uninvolved lymphoid tissue. The authors concluded that the combination of OCME and OCT images represents a promising method for the identification of malignant lymphoid tissue. They noted that this method shows potential to provide intra-operative assessment of lymph node involvement, thus, preventing unnecessary removal of uninvolved tissues and improving patient outcomes.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".

CPT codes not covered for indications listed in the CPB:

There is no specific CPT code for breast transillumination

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0346T</td>
<td>Ultrasound, elastography (List separately in addition to code for primary procedure)</td>
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Other CPT codes related to the CPB:

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<th>Code</th>
<th>Description</th>
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<td>77065-77067</td>
<td>Screening mammography</td>
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ICD-10 codes not covered for indications listed in the CPB:

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<th>Code</th>
<th>Description</th>
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<tr>
<td>C50.011 - C50.929</td>
<td>Malignant neoplasm of breast</td>
</tr>
<tr>
<td>C79.81</td>
<td>Secondary malignant neoplasm of the breast</td>
</tr>
<tr>
<td>D05.00 - D05.92</td>
<td>Carcinoma in situ of breast</td>
</tr>
<tr>
<td>D24.1 - D24.9</td>
<td>Benign neoplasm of breast</td>
</tr>
<tr>
<td>N60.01 - N65.1</td>
<td>Disorders of breast</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

1. National Coverage Determination (NCD) for Transillumination Light Scanning or Diaphanography (30.9).
2. Sabel M, Aichinger H. Recent developments in breast


47. Manduca A, Oliphant TE, Dresner MA, et al. Magnetic resonance elastography: Non-invasive mapping of tissue


90. Ma Y, Zhang S, Zang L, et al. Combination of shear wave


Amendment to
Aetna Clinical Policy Bulletin Number:
0386 Breast Transillumination, Electrical Impedance Scanning (EIS), and Elastography

There are no amendments for Medicaid.