Prior Authorization Review Panel  
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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Type of Submission – Check all that apply:

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0517 Breast Ductal Lavage and Fiberoptic Ductoscopy**

This CPB has been revised to state that breast ductal lavage is considered experimental and investigational for non-lactational mastitis.

Name of Authorized Individual (Please type or print):  
Signature of Authorized Individual:
Breast Ductal Lavage and Fiberoptic Ductoscopy

Number: 0517

Policy

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

I. Breast Ductal Lavage

A. Aetna considers breast ductal lavage a medically necessary appropriate alternative to aspiration to diagnose members with non-lactational sporadic nipple discharge where the yield of cellular material from a direct nipple aspirate is too low to permit adequate cytological analysis.

B. Aetna considers breast ductal endoscopy combined with ductal lavage experimental and investigational for the evaluation of contralateral breast in women with ipsilateral breast cancer because the clinical value of this approach has not been established.

C. Aetna considers breast ductal lavage (e.g., Pro-Duct Catheter (Pro-Duct Health, Inc., Menlo Park, CA), the ForeCYTE Breast Health test, the Mammary Aspirate Specimen Cytology Test [MASCT] System, and the Halo Breast Pap Test system (NeoMatrix, LLC, Irvine, CA)) experimental and investigational for breast cancer screening, breast cancer risk assessment, and for all other indications (e.g., treatment of non-lactational mastitis) because of insufficient evidence in the peer-reviewed literature.
D. Aetna considers assessment of genetic methylation patterns in ductal lavage samples for prediction of breast cancer risk experimental and investigational because of insufficient evidence in the peer-reviewed literature.

E. Aetna considers miRNA analysis of breast ductal fluid for the detection of breast cancer experimental and investigational because its effectiveness has not been established.


also Oophorectomy (../200_299/0227.html).

II. Fiberoptic Ductoscopy

A. Aetna considers fiberoptic ductoscopy (Acueity System, Acueity, Inc., Larkspur, CA) experimental and investigational for breast cancer screening because of insufficient evidence in the peer-reviewed literature.

B. Aetna considers fiberoptic ductoscopy combined with cytology testing medically necessary for diagnosing intra-ductal lesions in women with non-lactational sporadic nipple discharge accompanied by documented positive cytology.

C. Aetna considers fiberoptic ductoscopy medically necessary as a guide for resection of known breast intra-ductal cancer.

Background

Cytological screening studies the epithelial cells from fluid samplings taken from the ducts of the breast. Cytological screening can be conducted using nipple aspirate fluid (NAF) or by ductal lavage.

Breast Ductal Lavage

Breast ductal lavage is a procedure in which epithelial cells are collected from individual breast ducts for cytological examination to determine if abnormal cells are present. Following the application of an anesthetic cream to the nipple area, a
breast pump is utilized to apply light suction to the nipple to draw out small amounts of ductal fluid. Once the natural duct openings are found, an anesthetic is inserted into the duct, followed by catheter insertion. Saline is infused into the catheter to wash the duct and collect cells that are sent to the laboratory for analysis.

Breast ductal lavage (DL) has been promoted as a means of screening women with negative physical examinations and mammograms who are at high risk for breast cancer. Most breast cancer begins in the epithelial cells lining the interior of the breast milk ducts, and the Pro-Duct Catheter has been used to collect breast duct epithelial cells for cytological evaluation. The collected fluid has been used in the differentiation of normal, atypical (pre-malignant), and malignant breast duct cells.

To perform DL, ductal orifices are located, and a flexible microcatheter is threaded through the nipple into each duct. Saline is infused into the ducts, and the breast is massaged to dislodge cellular material from the ducts' internal lining. Saline and cellular material is then collected from the breast through the microcatheter. Cells are separated from saline and analyzed cytologically to identify those that are atypical or malignant.

The Pro-Duct Catheter was cleared by the Food and Drug Administration (FDA) based on a 510(k) application. Thus, the manufacturer was not required by the FDA to produce evidence of the Pro-Duct catheter's effectiveness prior to marketing.

There are no prospective clinical studies in the published peer-reviewed medical literature on the effectiveness of breast DL as a screening test for women at high-risk for breast cancer. Dooley et al (2001) presented cross-sectional data on 507 women at high-risk of breast cancer (Gail Index greater than 1.7), with no suspicion of malignancy on mammogram or physical examination, and compared the relative yields of atypical cells from DL and nipple aspirate. Of the 507 women, 383 women had DL specimens sent for cytology, and 417 had nipple aspirate fluid samples sent for cytology. Mildly atypical cells were detected in 17 % of women who underwent DL, and markedly atypical or malignant cells were detected in an additional 6 and less than 1 % of these women, respectively. For women who underwent nipple aspiration, mildly atypical cells were found in 6 %, markedly atypical cells in 3 %, and malignant cells in less than 1 %. The authors concluded that these data
suggest that DL may be more sensitive at detecting ductal atypia than nipple aspirate, based on the larger yield of abnormal ductal cells. Subjects with suspicious/malignant cytology are currently undergoing follow-up.

To date, no Federal public health agencies or leading professional medical organizations have recommended DL as a screening test for women at high-risk for breast cancer. The FDA (2013) has stated that they are unaware of any valid scientific data to show that nipple aspirate tests, when used on their own, are an effective screening tool for any medical condition, including the detection of breast cancer or other breast disease. Evidence-based guidelines from the American Cancer Society (Smith et al, 2003) concluded, "[t]here are currently insufficient data to recommend the use of ductal lavage either as an independent screening modality or in combination with screening mammography." A report by the Institute of Medicine of the National Academy of Sciences (2004) has stated that the use of DL "is still mainly limited to clinical trials to determine the sensitivity, specificity, and appropriate application in clinical use." An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2002) concluded that "the evidence is insufficient to support the use of cytologic hyperplasia with atypia as a clinically useful intermediate biomarker outside of clinical trials at this time. The existing evidence is of high clinical interest but further follow-up studies of risk and trials of intervention in women with this marker are needed." An assessment by the California Technology Assessment Forum (Feldman, 2003) concluded that DL does not meet CTAF’s assessment criteria. Data from clinical trials are needed to define the sensitivity, specificity, and predictive values of breast DL as a screening test for breast cancer. In addition, prospective controlled clinical trials are needed on the impact of screening DL on health outcomes of women at high-risk for breast cancer. The National Comprehensive Cancer Network (NCCN) 2013 guidelines state that the clinical utility of nipple aspiration is still being evaluated and that it should not be used as a breast cancer screening technique.

The findings of Khan et al (2004) indicated that DL is not an effective diagnostic test for breast cancer. These researchers investigated the association between DL cytologic findings and histologic findings in women with known breast cancer undergoing mastectomy. Ductal lavage was performed in the operating room before mastectomy on 44 breasts from 32 women with known cancer and on 8 breasts from 7 women undergoing prophylactic mastectomy, 2 with occult malignancy. If the DL sample from one or more ducts contained enough epithelial cells for a cytologic diagnosis, lavaged ducts were injected with a mixture of colored
dye, gelatin, and a radiographic contrast compound after mastectomy, and breast tissue was radiographed and sectioned. Histologic findings in ducts with and without dye were recorded. Associations between cytologic results and histologic results were examined by uni-variate and multi-variable analyses. These investigators concluded that in breasts with cancer, DL appears to have low sensitivity and high specificity for cancer detection, possibly because cancer-containing ducts fail to yield fluid or have benign or mildly atypical cytology.

Carruthers et al (2007) examined if DL could predict the occurrence of breast cancer as well as further stratify patients at high-risk for developing breast cancer. Ductal lavage was performed in 116 high-risk patients (Gail Risk score greater than or equal to 1.7 %, previous breast cancer, strong family history, previous suspicious biopsy specimen). If atypia or papillary cells were identified, a standard protocol of evaluation was initiated. A total of 223 lavages were performed on 116 patients. Twenty-seven lavages in 25 patients yielded atypical or papillary-like cells. The 15 patients who underwent further evaluation for atypia had no evidence of cancerous or pre-cancerous lesions. All patients were followed-up: 2 developed breast cancer, both of whom had had normal previous lavage. No patient with abnormal lavage developed cancer during follow-up. The authors concluded that DL is of limited value in the screening of high-risk patients and have removed it from their treatment algorithm.

Nipple aspiration uses gentle suction to collect fluid from the nipple. The device utilizes warmth, compression and vacuum. Examples of this device include, but may not be limited to, HALO NAF Collection System and ForeCYTE Breast Health test. Typically, only a tiny amount of fluid and a few cells can be obtained by this method, limiting the types of studies that can be done.

The Halo Breast Pap Test system (NeoMatrix, LLC, Irvine, CA) was cleared by the FDA based on a 510(k) application for collection of nipple aspirate fluid (NAF) for cytological evaluation. According to the manufacturer, the Halo Breast Pap Test system, an office-based, automatic, non-invasive test, is designed to detect abnormal cells in the breast (often a precursor to cancer) up to 8 years earlier than a lesion might be found on a mammogram or a self examination. Using gentle suction like a breast pump, the Halo device utilizes adjustable breast cups to collect NAF for cytological evaluation. During the 5-min cycle, the Halo device generates mild compression on both breasts while applying heat simultaneously. At the end
of the cycle, the Halo system initiates gentle suction to retrieve any fluid from the ducts. The collected fluid can be analyzed for the presence of normal, pre-malignant, and malignant cells.

At the present time, only 1 clinical trial has been identified addressing the Halo device. In a prospective, multi-center, observational clinical study involving asymptomatic women, Proctor and colleagues (2005) evaluated fluid production, adequacy, safety and patient acceptance of the Halo NAF Collection System. Cytological evaluation of all NAF samples was performed using previously described classification categories. Of the 500 healthy subjects, 38 % (190/500) produced fluid and 187 were available for cytological analysis. Cytological classification of fluid producers showed 50 % (93/187) category 0 (insufficient cellular material), 38 % (71/187) category I (benign non-hyperplastic ductal epithelial cells), 10 % (18/187) category II (benign hyperplastic ductal epithelial cells), 3 % (5/187) category III (atypical ductal epithelial cells) and none were category IV (unequivocal malignancy). Overall, 19 % of the subjects produced NAF with adequate cellularity and 1 % were found to have cytological atypia. The authors concluded that the Halo system is a simple, safe, rapid, automated method for standardized collection of NAF which is acceptable to patients. Cytological assessment of Halo-collected NAF showed the ability to detect benign and pre-neoplastic ductal epithelial cells from asymptomatic volunteers. However, well-designed studies with long-term follow-up are needed to ascertain the clinical significance of insufficient samples, NAF producers versus non-producers, as well as other cytological categories found on NAF samples collected with the Halo device.

The introduction of the Halo Breast Pap Test has been compared to the introduction of the cervical pap test in the 1950s, which has been credited with lowering cervical cancer mortality by more than 70 % through the identification of abnormal cells in the cervix. However, whether the same can be said for the Halo Breast Pap Test remains to be seen. The clinical value of the Halo Breast Pap Test system has yet to be established by further prospective, randomized controlled studies.

The FDA (2013) has stated that the cervical Pap smear has a known clinical benefit supported by extensive clinical studies over many years, and that its scientific ability to screen for cervical cancer is unquestioned. The nipple aspiration test has no such evidence supporting it. In addition, if a Pap smear shows abnormal cells of
the cervix, there are follow-up procedures that can be done to try to identify the location of those cells, after which a biopsy of the area is possible. With a breast nipple aspirate, if there are abnormal cells, the test does not target where those cells are coming from, so a biopsy may not be possible (FDA, 2013). Moreover, while the risk of abnormal cervical cells progressing to cancer is known, the risk of abnormal breast cells progressing to cancer is not. The nipple aspiration test may produce results that are falsely positive or falsely negative. False positives are possible because cells can be damaged in the aspiration process and appear abnormal. False negatives are also possible. Companies acknowledge that over 90% of their fluid samples may contain either very scant cells or no cells at all (FDA, 2013). Yet the companies call such results "diagnostically useful" and even conclude that a patient is healthy based on a cell-free sample (FDA, 2013). However, the nipple aspiration test may be missing cancers and giving women dangerous false assurance.

Danforth and colleagues (2006) studied the feasibility of combining breast ductal endoscopy with ductal lavage in the high-risk contralateral breast of women with ipsilateral breast cancer for the evaluation of high-risk ducts and acquisition of ductal epithelial cells for analysis. Breast ducts were studied by DL and ductal endoscopy, and epithelial cell content studied cytologically and quantitatively. A total of 25 patients and 44 ducts, including 22 (50.0%) which did not produce nipple aspirate fluid, were studied. Cellular atypia was present in 5 patients. Ductal endoscopy was performed on 1 or more ducts in 24 subjects. Structural changes were noted in 63.6% of the ducts, most commonly fibrous stranding or bridging. Ductal sampling with endoscopic brush and coil sampling devices provided additional cellular samples of relatively pure ductal epithelial content (greater than or equal to 91% purity) in 8/11 subjects. The authors concluded that breast ductal endoscopy combined with DL represents a feasible approach for characterizing the ducts and ductal epithelium of the high-risk breast, especially in a research setting.

Ductal lavage has potential use in risk assessment and biomarker evaluation among women at increased risk for breast cancer. However, little is known about the reliability of the procedure. Visvanathan and colleagues (2007) evaluated the reliability of NAF and DL at 2 time-points 6 months apart in women at increased risk for breast cancer. Eligible women had a 5-year Gail risk greater than or equal to 1.66% or lifetime risk of greater than 20%, and/or a family history or personal history of breast cancer. All ducts that produced NAF were cannulated. The kappa statistic was used to evaluate reliability of NAF production, cellular yield, and
cytologic diagnosis. A total of 69 women (mean age of 47 years) were enrolled over 35 months. Forty-seven returned for a second visit. At baseline, 65 % of pre-menopausal and 41 % of post-menopausal women produced NAF (p = 0.05), of which 72 % underwent successful lavage of at least 1 duct. Samples of inadequate cellular material for diagnosis were significantly more likely in post-menopausal women than in pre-menopausal women (p = 0.04). Of the women who returned for a second visit, 18 of 24 who produced NAF had at least 1 duct successfully cannulated. Twenty-four ducts in 14 women were lavaged twice. Among these ducts, cellular yield for the 2 time-points was inconsistent (kappa = 0.33 +/- 0.13), and only fair cytologic agreement was observed (kappa = 0.32 +/- 0.15). Ductal lavage was associated with moderate discomfort. The authors concluded that the use of DL is limited by technical challenges in duct cannulation, inconsistent NAF production, a high rate of inadequate cellular material for diagnosis, fair cytologic reproducibility, and low participant return rates.

Patil et al (2008) performed a phase II trial, wherein high-risk women chose tamoxifen treatment or observation following an entry DL procedure. These researchers presented data from the non-intervention arm of the study to assess the reproducibility of cannulation, cell yield, and cytologic diagnosis from DL of the same duct at 2 time-points. Inter-observer variability was evaluated by a blinded review of Papanicoloau-stained slides by 2 cytopathologists. A total of 65 women had a successful lavage of 187 ducts at baseline and chose observation; 63/65 (97 %) had a successful lavage 6 months later. Successful re-cannulation of the same duct was accomplished in 63 women (97 %) and 162 ducts (87 %). Total epithelial cell yields greater than or equal to 100 were obtained from 57/65 women (88 %) and 129/187 ducts (69 %) at baseline, and 46/63 women (73 %) and 80/162 ducts (49 %) at both time-points. Cytologic diagnosis was reproducible in 27/63 (43 %) women and 77/162 (48 %) ducts. Inter-observer variability for cytologic diagnosis between 2 observers showed good agreement (kappa = 0.62). The authors concluded that re-cannulation and lavage of the same duct after a 6-month interval can be achieved with high frequency; however, reproducibility of cell yield and cytologic findings from the same duct is sub-optimal, leading to significant attrition of evaluable subjects. The utility of DL for the serial monitoring of breast epithelium is therefore limited.

Khan and associates (2009) reported a proof-of-principle phase II study to assess the utility of DL to measure biomarkers of tamoxifen action. These investigators enrolled women with a 5-year breast cancer risk estimate greater than 1.6 % or the
unaffected breast of women with T1a or T1b breast cancer. After entry DL, subjects chose tamoxifen or observation and underwent repeat DL 6 months later. Samples were processed for cytology and immunohistochemistry for estrogen receptor alpha, Ki-67, and cyclooxygenase-2. Of 182 women recruited, 115 (63 %) underwent entry and repeat DL; 85 (47 %) had sufficient cells for analysis from greater than or equal to 1 duct at both time-points; in 78 (43 %), cells were sufficient from greater than or equal to 1 matched ducts. Forty-six women chose observation and 39 chose tamoxifen. These researchers observed greater reductions in the tamoxifen group than in the observation group for Ki-67 (adjusted p = 0.03) and estrogen receptor alpha (adjusted p = 0.07), but not in cyclooxygenase-2 (adjusted p = 0.4) labeling. Cytologic findings showed a trend toward improvement in the tamoxifen group compared with the observation group. Inter-observer variability for cytologic diagnosis between 2 observers showed good agreement (kappa = 0.44). Using DL, the authors observed the expected changes in tamoxifen-related biomarkers; however, poor reproducibility of biomarkers in the observation group, the 53 % attrition rate of subjects from recruitment to biomarker analyses, and the expense of DL are significant barriers to the use of this procedure for biomarker assessment over time.

Wood et al (2009) evaluated DL performance in women with known breast cancer and assessed cell yield from contralateral high-risk breasts. Women with newly diagnosed breast cancer were offered study participation. They underwent bilateral nipple aspiration, followed by DL of those ducts demonstrating NAF production. The procedures were conducted in the operating room prior to definitive surgery. Samples were interpreted masked as to which breast was malignant, and the interpretation used a 5-category scheme: (i) insufficient, (ii) benign, (iii) mildly atypical, (iv) markedly atypical or (v) malignant. A total of 23 women with 24 cancers were enrolled, ranging in age from 32 to 76. One had ductal carcinoma in situ; there were 13 T1, 6 T2 and 4 T3 lesions. Nipple aspiration fluid was identified in 72 % of breasts, more commonly in cancerous than unaffected breasts. Ductal lavage was performed on 33 breasts; of these, 55 % were adequate. Only 16.6 % of samples from malignant breasts contained abnormality, marked atypia in 1 and malignancy in 3. No samples from unaffected breasts demonstrated cellular abnormalities. The authors concluded that the low sensitivity of DL performed on malignant breasts to identify abnormal cells adds to the growing body of evidence that this is not an effective tool in identifying existing breast cancer. Numbers are small, but the ability of DL to identify atypia in unaffected high-risk breasts may also
be sub-optimal. They stated that future efforts should focus on molecular markers of risk and on alternate means of cell or tissue retrieval.

Loud et al (2009) evaluated patient characteristics associated with obtaining NAF and adequate cell counts in DL specimens from the largest cohort of women from BRCA families yet studied (BRCA1/2 = 146, mutation-negative = 23, untested = 2). Fisher's exact test was used to evaluate categorical variables; Wilcoxon non-parametric test was used to evaluate continuous variables associated with NAF or DL cell count adequacy. Logistic regression was used to identify independent correlates of NAF and DL cell count adequacy. From 171 women, 45 (26 %) women had NAF and 70 (41 %) women had DL samples with greater than or equal to 10 cells. Post-menopausal women with intact ovaries compared with pre-menopausal women [odds ratio (OR), 4.8; p = 0.03] and women without a prior breast cancer history (OR, 5.2; p = 0.04) had an increased likelihood of yielding NAF. Having breast-fed (OR, 3.4; p = 0.001), the presence of NAF before DL (OR, 3.2; p = 0.003), and being pre-menopausal (OR, 3.0; p = 0.003) increased the likelihood of DL cell count adequacy. In known BRCA1/2 mutation carriers, only breast-feeding (OR, 2.5; p = 0.01) and the presence of NAF (OR, 3.0; p = 0.01) were independent correlates of DL cell count adequacy. The authors concluded that DL is unlikely to be useful in breast cancer screening among BRCA1/2 mutation carriers because the procedure fails to yield adequate specimens sufficient for reliable cytologic diagnosis or to support translational research activities.

Do Canto et al (2016) stated that identification of new biomarkers for breast cancer remains critical in order to enhance early detection of the disease and improve its prognosis. These researchers performed an untargeted metabolomic analysis of breast ductal fluid using an ultra-performance liquid chromatography coupled with a quadrupole time-of-light (UPLC-QTOF) mass spectrometer. They examined the metabolomic profiles of breast tumors using ductal fluid samples collected by ductal lavage (DL); and studied fluid from both the affected breasts and the unaffected contralateral breasts (as controls) from 43 women with confirmed unilateral breast cancer. Using this approach, these investigators identified 1,560 ions in the positive mode and 538 ions in the negative mode after preprocessing of the UPLC–QTOF data. Paired t-tests applied on these data matrices identified 209 ions (positive and negative modes combined) with significant change in intensity level between affected and unaffected control breasts (adjusted p-values < 0.05). Among these, 83 ions (39.7 %) showed a fold change (FC) greater than 1.2 and 66
ions (31.6 %) were identified with putative compound names. The metabolites that these researchers identified included endogenous metabolites such as amino acid derivatives (N-Acetyl-DL-tryptophan) or products of lipid metabolism such as N-linoleoyl taurine, trans-2-dodecenoylcarnitine, lysophosphatidylcholine LysoPC (18:2(9Z,12Z)), glycerophospholipids PG(18:0/0:0), and phosphatidylserine PS (20:4(5Z,8Z,11Z,14Z). Generalized LASSO regression further selected 21 metabolites when race, menopausal status, smoking, grade and TNM stage were adjusted for. A predictive conditional logistic regression model, using the LASSO selected 21 ions, provided diagnostic accuracy with the area under the curve of 0.956 (sensitivity/specitivity of 0.907/0.884). The authors concluded that this was the first study that showed the feasibility of conducting a comprehensive metabolomic profiling of breast tumors using breast ductal fluid to detect changes in the cellular microenvironment of the tumors and showed the potential for this approach to be used to improve detection of breast cancer.

Breast Ductal Lavage for Non-Lactational Mastitis

Chen and colleagues (2019) noted that surgery, steroids, and/or observations alone have been proposed for patients with non-lactational mastitis (NLM), but most of these studies were retrospective. The optimal treatment for these patients remains unclear. In a prospective, single-arm, proof-of-concept trial, these researchers examined the feasibility and safety of ductal lavage as a novel treatment for patients with NLM. Eligible patients with NLM received an intra-ductal infusion of corticosteroids and anti-microbial agents and returned the next day for a breast massage. This cycle was repeated for 2 weeks, and these investigators followed-up participants for 1 year. Patients did not receive surgery or steroids following ductal lavage. The primary end-point was the time to complete response (CR). This trial included 32 patients with a median (range) age of 32 (20 to 53) years. Skin erythema and tenderness were the major symptoms. The median (range) visual analog score (VAS) was 5 (0 to 9). There were 21 (65.6 %), 4 (12.5 %), and 7 (21.9 %) patients diagnosed as idiopathic granulomatous mastisitis, periductal mastisitis, and unspecific NLM, respectively. During the ductal lavage, the median (range) number of cannulated ducts at 1st attempt was 5 (3 to 8). Ductal lavage significantly reduced the VAS and mastitis score (M-score) (p < 0.01). Within a median follow-up of 15.6 months, 93.8 % (30/32) of patients achieved CR. The median (range) time to CR was 6 (0.5 to 21) months; 3 patients (10.0 %) relapsed. No adverse events (AEs) associated with ductal lavage were observed. The
authors concluded that ductal lavage for patients with NLM was feasible and safe, and a definitive randomized controlled trial (RCT) for further investigation is needed.

**Fiberoptic Ductoscopy**

Fiberoptic ductoscopy (may also be called mammary endoscopy) is a procedure in which a small fiberoptic scope is inserted into the ductal opening of the nipple. This is performed to visualize the ductal system of the breast to detect abnormalities. Cells are also collected using ductal lavage after examination of the ducts.

Fiberoptic ductoscopy (e.g., microendoscopic intraductal mammary visualization) with the Acueity System for the detection, diagnosis and treatment of breast cancer, is currently being used in research and clinical trial collaborations with a number of academic facilities, including the Cleveland Clinic and Johns Hopkins Medical Center. This research is aimed at demonstrating the value of this technology in the detection and management of early stage breast cancer and other forms of intra-ductal breast disease. Acueity’s optical system and ductoscope, about the size of a pencil tip, enable physicians to look through the nipple directly into the milk ducts where most breast cancer develops. The system projects large and sharp video images of ducts on screen, and detects lesions as small as 0.1 mm in diameter. The system is not designed to replace mammography, but to provide an early detection option for women at risk. However, the safety and effectiveness of the Acueity System for the detection, diagnosis and treatment of breast cancer has not been demonstrated by the publication of randomized well-controlled studies in the medical literature.

Moncrief and colleagues (2005) performed a retrospective review of the records of 117 consecutive women who underwent ductoscopy to guide ductal excision or received conventional terminal duct excision without ductoscopy. These investigators stated that ductoscopy identifies intra-ductal lesions in a high proportion of women with spontaneous nipple discharge and it may contribute to more accurate resection of these. However, a prospective study is needed to obtain an unbiased assessment of these possible advantages.

Hunerbein and colleagues (2006) stated that fiberoptic ductoscopy is increasingly used to assess pathological nipple discharge. A major limitation of this technique is the inability to obtain tissue samples from suspicious intra-ductal lesions. These
Researchers presented a novel technique for ductoscopic biopsy of intra-luminal tumors. From 2002 to 2005, ductoscopy was performed in 38 women with nipple discharge using a rigid gradient index microendoscope (diameter 0.7 mm) and a special needle for intra-ductal vacuum assisted biopsy. Results of pre-operative biopsy were correlated with the histology of the resection specimen. Cannulation of the discharging duct was successful in 37 of 38 patients (97%). Intra-ductal lesions were diagnosed in 29 women (78%). The sensitivity of ductoscopy and galactography in the detection of intra-ductal lesion was comparable (96% versus 89%). Ductoscopic biopsy of intra-ductal lesions was technically successful in all but 1 case. Generally, the quality of the biopsy samples was good. Diagnostic biopsy samples were obtained in 26 of 28 patients (93%). Two samples contained necrosis and were considered to be non-representative. Histological analysis of the biopsy specimens showed 22 papilloma, 2 in situ carcinoma and 2 invasive carcinoma. Histology of the resection specimens confirmed the diagnosis in all cases, but there was 1 case with additional carcinoma lobulare in situ. The authors concluded that ductoscopic vacuum assisted biopsy is a new technique for tissue sampling of intra-ductal breast lesions. They noted that this method may improve pre-operative evaluation of pathological nipple discharge in selected patients, but it should not be considered as a method for screening of early breast cancer.

Liu et al (2008) reported the outcomes of fiberoptic ductoscopy (FD) combined with cytology testing for diagnosing spontaneous nipple discharge. A total of 1,048 women (1,093 breasts total) underwent successful diagnostic FD. Discharge was unilateral (86.8%), single ductal (93.4%), and serous (57.9%) or bloody (36.0%). Among 437 (40.0%) of the FD-positive breasts, breast carcinomas was revealed in 49 cases (11.2%), central papillomas in 228 cases (52.2%), and atypical ductal hyperplasia in 5 cases (1.1%). Ten patients with positive cytology testing received microdochectomy in spite of having a negative FD, which revealed 2 additional ductal carcinomas in situ (DCIS), and 4 papillomas. About 489 breasts were negative for both FD and cytology testing and were subjected to follow-up. Approximately 77 (15.7%) of the breasts underwent tissue diagnosis within a median follow-up time span of 19 months, and 1 DCIS was detected. The sensitivity of FD for detection of malignant lesions was 94.2% and increased to 98.1% when combined with cytology testing. Nevertheless, it was less sensitive (p < 0.01) if these researchers used only cytology testing (58.3%), mammography (48.6%), high-frequency sonography (36.4%), or combination of mammography
and sonography (56.8\%) to detect these malignant lesions. The authors stated that these findings confirmed the value of FD combined with cytology testing as a diagnostic procedure in women with nipple discharge.

Wu and colleagues (2008) reported their experience of breast intra-ductal neoplasm resection under breast FD. The procedure was performed on 548 patients with nipple discharge. The clinical data of breast intra-ductal neoplasm found by FD in patients who underwent tumor resection were analyzed, and the breast intra-ductal neoplasm image characteristics, diagnosis, operative type and post-operative pathological results were analyzed. Of the 548 patients with nipple discharge, intra-ductal neoplasm was found in 187 cases (34.1\%), intra-ductal papilloma in 159 cases (29.0\%), intra-ductal papillomatosis in 12 cases (2.2\%), and breast carcinoma in 16 cases (2.9\%). A total of 135 patients were operated on; tumor resection or segmentectomy under the localization by FD were performed in 91 patients, and segmentectomy after breast duct infusion of methylene blue were performed in the remaining 44 subjects. The diagnostic rate under FD in the FD group (97.8\%) was higher than that in the breast duct infusion methylene group (86.4\%) (chi2 = 6.96, p = 0.008). The authors concluded that FD is not only accurate in diagnosing breast intra-ductal lesion, but also aids in localizing and removing the breast intra-ductal neoplasm.

Antill et al (2010) stated that genomic alterations (including gene hyper-methylation) are likely to precede the phenotypic changes associated with breast tumorigenesis. From a prospective collection of DL samples from women with a known mutation in BRCA1 or BRCA2, these investigators evaluated promoter methylation with a comparison of results with several variables, including breast cancer (BC) outcome. Hypermethylation of p16, RASSF1A, twist, and RARbeta was assessed using a qualitative, real-time, nested polymerase chain reaction (PCR) assay. Associations between methylation status and variables were tested using Fisher's exact test or logistic regression. Analyses were done at 3 levels: (i) a single breast, (ii) a single duct (both over time), and (iii) each DL sample in isolation. A total of 168 samples from 93 ducts in 54 breasts have been analyzed in 34 women (16 BRCA1 and 18 BRCA2 mutation carriers). A median of 2 DL was done (range of 1 to 5), with 7 women developing BC on study, 1 bilateral. Methylation of p16 was associated with a known BRCA1 mutation (p = 0.001, p < 0.001, and p < 0.001 for breast, duct, and sample levels, respectively) and women with a history of contralateral BC (p = 0.001 and p < 0.001 for duct and sample levels, respectively). An association was seen for women who developed BC on study and RASSF1A
methylation (p = 0.001 for sample level). The authors concluded that genetic methylation patterns could potentially be used to predict future BC risk. In addition, p16 methylation may be a predictor of BRCA1 mutation status. They stated that further research is needed to corroborate these findings.

According to Atossa Genetics (Seattle, WA), the ForeCYTE Breast Health test, a “Pap test for breast cancer,” is designed to collect nipple aspirate fluid (NAF), which contains cells from the lining of the milk ducts and the lobules, where approximately 99% of all breast cancers originate. Once collected, the NAF sample will undergo analysis in Atossa Genetics’ specially equipped pathology lab, known as the National Reference Laboratory for Breast Health, to determine whether the cells are normal, atypical (pre-malignant), or malignant, using a patented, multi-plex, immunohistochemical procedure. The ForeCYTE Breast Health test uses no radiation, is simple and painless, and takes less than 5 minutes in a doctor’s office or mammography center. The ForeCYTE Breast Health test is intended as an adjunct to mammography for women aged 50 to 73 years and for younger women aged 18 to 49 years for whom screening mammography is not recommended, due to mammography’s poor sensitivity in this age group and potential radiation safety issues.

According to the Atossa Genetics, the Mammary Aspirate Specimen Cytology Test [MASCT] System is used for the collection of NAF for cytological evaluation. The collected fluid can be used in the determination and/or differentiation of normal versus pre-malignant versus malignant cells. The MASCT System uses a hydrophilic membrane in contact with the nipple to “wick” fluid from the orifice of the ducts by capillary action during the cycles of negative pressure. Atossa Genetics also notes The MASCT System test cannot exclude breast cancer and is not a substitute for other clinical screening tests, such as mammography and clinical breast examination.

In February 2013 FDA issued a warning letter to Atossa Genetics, Inc. that, among other things, informed the company that their test was misbranded in that its labeling was false or misleading (FDA, 2013). The agency asked the firm to take prompt action to correct the violations addressed in the warning letter. In October 2013, Atossa initiated a voluntary recall to remove the ForeCYTE Breast Health Test from the market.
MicroRNA Analysis of Breast Ductal Fluid

Do Canto and colleagues (2016) noted that recent studies suggested that microRNAs show promise as biomarkers for breast cancer; however there is still a high degree of variability between studies making the findings difficult to interpret. In addition to blood, DL and nipple aspirate fluids represent an opportunity for biomarker detection because they can be obtained in a less invasive manner than biopsies and circumvent the limitations of evaluating blood biomarkers with regards to tissue of origin specificity. These researchers examined for the first time, through a real-time PCR array, the expression of 742 miRNAs in the DL fluid collected from 22 women with unilateral breast tumors. These investigators identified 17 differentially expressed miRNAs between tumor and paired normal samples from patients with ductal breast carcinoma. Most of these miRNAs have various roles in breast cancer tumorigenesis, invasion and metastasis, therapeutic response, or are associated with several clinical and pathological characteristics of breast tumors. Moreover, some miRNAs were also detected in other biological fluids of breast cancer patients such as serum (miR-23b, -133b, -181a, 338-3p, -625), plasma (miR-200a), and breast milk (miR-181a). An analysis of these differentially expressed miRNAs pointed out possible pathways and cellular processes previously described as having an important role in breast cancer (e.g., Wnt, ErbB, MAPK, TGF-β, mTOR, PI3K-Akt, p53 signaling pathways). These researchers also observed a difference in the miRNA expression with respect to the histological type of the tumors. The authors concluded that these findings suggested that miRNA analysis of breast ductal fluid is feasible and potentially very useful for the detection of breast cancer.

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 "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPT codes not covered for indications in the CPB:</td>
</tr>
<tr>
<td></td>
<td>Breast Ductal Lavage and Fiberoptic Ductoscopy:</td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td>ForeCYTE Breast Health test, Mammary Aspirate Specimen Cytology Test [MASCT]:</td>
</tr>
<tr>
<td></td>
<td>Other CPT codes related to the CPB:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>19030</td>
<td>Injection procedure only for mammary ductogram or galactogram</td>
</tr>
<tr>
<td>77053</td>
<td>Mammary ductogram or galactogram, single duct, radiological supervision and interpretation</td>
</tr>
<tr>
<td>77054</td>
<td>Mammary ductogram or galactogram, multiple ducts, radiological supervision and interpretation</td>
</tr>
<tr>
<td>88112</td>
<td>Cytopathology, selective cellular enhancement technique with interpretation (eg, liquid based slide preparation method), except cervical or vaginal</td>
</tr>
<tr>
<td>88161</td>
<td>Cytopathology smears, any other source; preparation, screening and interpretation</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- **C50.011** - Malignant neoplasm of breast [covered for known breast intraductal cancer when fiberoptic ductoscopy is used as a guide for resection only]
- **C50.929**
- **N64.52** - Nipple discharge [non-lactational sporadic nipple discharge]

ICD-10 codes not covered for indications listed in the CPB:

- **N61.0 - N61.1** - Inflammatory disorders of breast [non-lactational mastitis]
- **N63.0 - N63.42** - Unspecified lump in breast
- **N64.3 - N64.51, N64.53 - N64.9** - Other disorders of breast
- **T85.44x+** - Capsular contracture of breast implant
- **Z12.39** - Encounter for other screening for malignant neoplasm of breast
- **Z80.3** - Family history of malignant neoplasm of breast
- **Z85.3** - Personal history of malignant neoplasm of breast

The above policy is based on the following references:

1. Letter from Celia M. Witten, Ph.D., M.D., Director, Division of General and Restorative Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, Rockville, MD, to Angela B. Soito, Director, Regulatory and Quality Affairs, Pro-Duct Health, Inc., Menlo


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19. Klein PM, Lawrence JA. Lavage and nipple aspiration of breast ductal fluids: A 
source of biomarkers for environmental mutagenesis. Environ Mol Mutagen. 

20. Newman LA. Ductal lavage: What we know and what we don't. Oncology 

21. National Academy of Sciences, Institute of Medicine, Board on Science, 
Technology and Economic Policy, National Cancer Policy Board, Committee 
on New Approaches to Early Detection and Diagnosis of Breast Cancer, 
Saving Women's Lives: Strategies for Improving Breast Cancer Detection and 

22. Feldman MD. Nipple aspiration or ductal lavage cytology in risk assessment of 
breast cancer. Technology Assessment. San Francisco, CA: California 
Technology Assessment Forum; October 8, 2003.

23. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center 
(TEC). Use of epithelial cell cytology in breast cancer risk assessment and 
high-risk patient management. TEC Assessment Program. Chicago, IL: 
BCBSA; June 2002; 17(1).

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(20):1510-1517.

and conventional surgical excision in women with spontaneous nipple 

27. No authors listed. Ductal lavage not a good screening test for breast cancer. 


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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0517 Breast Ductal Lavage and Fiberoptic Ductoscopy

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania  revised 07/25/2019