# Cigna Medical Coverage Policy

**Subject** **Mammary Ductoscopy, Aspiration and Lavage**

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## Coverage Policy

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## General Background

The goal of screening exams for early breast cancer detection is to find cancers before they start to cause symptoms. Standard methods of early breast cancer detection are screening mammography, clinical breast examination (CBE), and monthly self-breast exam. Overall sensitivity of mammography is 75%; specificity is >90%. The positive predictive value (PPV) of a screening mammogram ranges between 6.3%– 8%, depending upon age. Overall sensitivity of clinical breast exam is 40%–69%. In women ages 50–59 years, specificity for

clinical breast exam ranges from 88%–96%, while the PPV is 3%–4% (American Cancer Society [ACS], 2012; National Cancer Institute [NCI], 2012; National Comprehensive Cancer Network® [NCCN], 2012 ).

If breast abnormalities are found on screening or are present on physical exam, standard methods used for further testing may include diagnostic mammography films, ultrasound, and/or magnetic resonance imaging (MRI), fine needle aspiration (FNA), core-needle or incisional breast biopsy. The use of MRI in combination with mammography provides a highly sensitive screening strategy (i.e. sensitivity 93%–100%) In select cases, ductography (i.e., sensitivity 19%, negative predictive value [NPV] 63%) also known as galactography may be used to evaluate spontaneous nipple discharge (Inglehart, 2008; Lord, 2007; Morrogh, 2007).

Mammary ductoscopy (MD) has been proposed as a diagnostic tool for screening individuals at high-risk of breast cancer, investigation of pathologic nipple discharge, and intraoperative use to guide duct excision in breast conserving surgery. Ductal lavage has been proposed as a means of extracting nipple aspirate fluid to screen for breast cancer, and for use in risk assessment and stratification.

**Mammary Ductoscopy**
Mammary ductoscopy, also referred to as fiberoptic ductoscopy or breast duct endoscopy, involves the direct visualization of the mammary ducts and the use of a rigid camera or ductoscope. Researchers have proposed the use of direct visualization of the mammary ducts through rigid and fiberoptic scopes in an attempt to increase the sensitivity of early recognition of cellular changes in the mammary duct lining. The rationale is that direct visualization may assist in confirming the presence of cancer when a diagnosis cannot be confirmed using standard imaging techniques such as mammography, ultrasound or magnetic resonance imaging (MRI). However, the capacity of MD for the direct observation of lesions in smaller caliber peripheral ducts and the terminal duct-lobular units where premalignant and malignant lesions often originate is limited by the outer diameter of the scope and the complex branching pattern of the mammary ducts (Periera, 2005). The use of MD allows the visualization of only a few of the ducts that open to the nipple, leaving the other 13–18 ducts that open at or just below the nipple surface unexamined (Al Sarakbi, 2006). As technologies have evolved, the addition of fiberoptics has expanded the visual fields that may be examined during this procedure. Currently available ductoscopes have limited ability to biopsy lesions. At this time its limited biopsy facility and inability to visualize all of the ductal system limit its usefulness in the screening of breast cancer (Hung, 2009; Kapenhaus-Valdes, 2008).

**U.S. Food and Drug Administration (FDA)**
Several ductoscopes have been approved for use by the FDA. Although they were originally classified as 510(k) devices, they are now considered unclassified by the FDA. According to the FDA, a ductoscope is a device intended for use in viewing an interior cavity of the human body through either a natural opening or an incision. Examples of these devices include the ViaDuct™ Miniscope (Acueity Inc., Palo Alto, CA) which received 510(k) approval in May 2004, and the Mastascope™ (Lifeline Biotechnologies, Pompano Beach, FL), approved in June 2004.

**Literature Review**
**Breast Cancer Screening:** Randomized controlled clinical trial data evaluating the effectiveness of mammary ductoscopy for breast cancer screening are lacking.

As part of an ongoing long-term research project aimed at exploring the potential clinical applications of mammary ductoscopy, Sarakbi and colleagues (2006) conducted a prospective study of 26 women to assess its technical feasibility, its role in guiding ductal excisional surgery, and its use in the identification of malignancy. Study participants were divided into two groups with Group A (n=13) undergoing mastectomy or lumpectomy for ductal carcinoma, and Group B (n=13) presenting with pathological nipple discharge (PND). MD was performed using the Mastascope™ (Lifeline Biotechnologies, Pompano Beach, FL). Intraductal pathology was visualized in (80%of patients, but ductal cytology was positive for malignancy in only two cases with sensitivity of 16% and specificity of 100%. In Group B, seven patients underwent ductoscopy-guided duct excision, which revealed ductal carcinoma in situ (DCIS) in one, papilloma in four, and benign disease in two patients. The authors concluded that, although MD is feasible, its cytological yield is not sufficient for the diagnosis of malignancy, and the development of a biopsy tool that obtains tissue under direct visualization is required.

Badve et al. (2003) conducted a retrospective analysis evaluating the efficacy of fiberoptic ductoscopy as a screening tool for detecting cancer, using the frequency of involvement of the nipple and central duct area in

mastectomy specimens as surrogate markers to estimate the utility of ductoscopy in breast cancer patients. The review of 801 mastectomy specimens showed nipple and central duct involvement in only 22% of the cases. These findings suggest fiberoptic ductoscopy is not a good method for detecting most forms of breast cancer, as ductoscopy yielded a low diagnostic accuracy. This study is limited by the lack of statistical analysis including the comparison between fiberoptic ductoscopy and standard screening tools, and the lack of specific clinical outcomes data.

**Evaluation of Nipple Discharge:** Randomized controlled clinical trial data evaluating the effectiveness of mammary ductoscopy for evaluation of nipple discharge are lacking. Evidence consists primarily of uncontrolled case series.

In a prospective case series by Sauter et al. (2009), the sensitivity and specificity of MD were reported to be 13% and 18%, respectively, for cytology in breasts with pathological nipple discharge (PND). In breasts without PND, sensitivity and specificity were 14% and 100%, respectively. Study limitations include uncontrolled design and lack of comparison with standard therapies.

Simpson et al. (2009) reported experience with mammary ductoscopy as the first center in Canada to apply this technology to surgical practice. Between 2004 and 2008, 65 women with pathologic nipple discharge received ductoscopy prior to surgical duct excision under general anesthesia. Data regarding cannulation and complication rates, procedure length and lesion visualization rate compared to preoperative ductography (if performed) were prospectively collected. Cannulation was achieved in 63 of 66 breast ducts (95%) and a lesion was visualized in 52 of 63 breast ducts (883%). The mean procedure length was 5.1 minutes, and there were no complications. Lesions seen during ductography were seen endoscopically (i.e., during ductoscopy) 30 of 33 times (91%). All three malignancies were seen during ductoscopy; invasive carcinoma in one patient, and in situ disease in two. Ductoscopy was helpful in defining the extent of duct excision. There was poor correlation, however, between endoscopic classification and final pathology. The authors concluded that ductoscopy is feasible, safe and practical, and is now used routinely to identify the location and extent of the excision without ordering preoperative ductography. Identifying pathology based on the endoscopic appearance is unreliable unless the lesion is solitary and polypoid.

Liu et al. (2008) reported findings on 1048 women (1093 breasts) with spontaneous nipple discharge who underwent fiberoptic ductoscopy. Intraductal abnormalities were visualized in 54.3% of this cohort. Sensitivity for breast cancer associated with nipple discharge was 94.2% in this cohort and 94.4% for nonpalpable disease. Mammography, high-frequency sonography, and mammography plus sonography were also performed as preoperative assessment and to guide subsequent biopsy. Sensitivity for these tools was reported as 56.8%, 48.6%, and 36.4%, respectively ($p<0.001$) for breast cancer associated with nipple disease and 42.3%, 38.5%, and 10.3% for nonpalpable disease. Limitations include uncontrolled study design and lack of data regarding specificity and the positive and negative predictive value of fiberoptic ductoscopy.

**Guided Duct Incision/Breast Conserving Surgery:** Randomized controlled clinical trial data to evaluate the effectiveness of mammary ductoscopy to guide duct incision during breast conserving surgery are lacking. Uncontrolled study design, small patient populations, and a lack of long-term outcomes limit the ability to extrapolate results to the general population.

A retrospective review conducted by Vaughan et al. (2009) evaluated ductoscopy-directed duct excision and collection of ductal washings in patients with pathological discharge presenting to the Cleveland Clinic Foundation breast center between 1999 and 2001 (n=89). The rate of abnormal pathology was 88%. Most abnormalities were benign (71% papillomas) but the atypia rate for this group was 62%. The combination of visualization and pathologic analysis of washings provided the highest predictive value for the diagnosis of papilloma. The authors stated that mammary ductoscopy offers the advantage of high lesion localization rates with intraoperative guidance. Ductal washings taken at the time of operation are not useful for that operation, however, which is why preoperative ductoscopy has become popular among physicians using this technique. Preoperative ductoscopy is less useful than intraoperative ductoscopy in guiding the surgical excision however. Since the vast majority of patients undergoing ductoscopy-guided duct excision in this study had identifiable lesions on ductoscopy and pathology, the use of routine ductography or preoperative office ductoscopy to select operative candidates is not necessary since nearly all patients require surgical excision. The authors stated that until a test is available that can definitively differentiate between benign and malignant lesions, duct excision for

pathologic nipple discharge is necessary. Intraoperative ductoscopy identifies the lesion and helps guide the dissection in most cases, allowing greater conservation of normal breast tissue.

Tekin et al. (2009) conducted a case series to investigate the reliability of intra-operative breast ductoscopy n patients with pathologic nipple discharge that could not be identified using mammography or ultrasound (n=34). Discharge was considered pathologic if it was spontaneous, bloody, serous, and persisting more than two months. The ductoscope was successfully introduced into the external orifice of the ducts at the nipple and proximal breast ducts were successfully visualized in 30 of 34 patients (88%). Ductoscopy revealed intraductal lesions in 20 patients (66%), including papilloma (9), signs of either acute inflammation (bleeding, erythema) or previous inflammation with healing (adhesions and blocked ducts.). Invasive breast carcinoma was identified in two patients, one with ductal carcinoma in situ with minimal invasion, and one with invasive breast carcinoma. The authors concluded that breast ductoscopy is a useful diagnostic modality in patients with pathologic nipple discharge, and that there is an obvious need to design prospective clinical trials that evaluate the potential role in breast cancer screening, guiding risk reducing strategies, and addressing this technique as an adjunct to breast conservation surgery.

MD has been investigated as a surgical guide to assist the clinician in minimizing the extent of breast tissue excised during breast conserving surgery while ensuring clear histopathological margins. Although MD may identify intraductal abnormalities they may be benign or within the standard field of resection therefore adding no benefit to the patient (Khan, 2006; Kappenhaus-Valdes, 2008).

Kapenhaus-Valdes et al. (2008) reviewed outcomes of the use of MD in 110 ducts of 93 women with nipple discharge. A subset of patients (n=67) underwent ductoscopically-guided duct incision of 77 ducts. No statistical comparison of outcomes between the use of MD and other technologies was reported. This review also lacks data regarding the PPV, sensitivity and specificity of this technology. No conclusion regarding how this technology compares to standard diagnostic methods in the diagnosis of nipple discharge can be made.

Grunwald et al. (2007) performed a retrospective analysis of 71 MDs that were preoperatively undertaken in 64 patients in which an open biopsy with targeted excision was indicated. Indications for open biopsy were based on results obtained from cytological, histological or image findings from mammography, galactography or sonography of the breast. Additionally, magnetic resonance imaging (MRI), nipple smear, fine needle aspiration cytology, and high-speed core biopsy were performed in some patients according to indications and to examine the performance of the individual diagnostic methods. In 71 mammary ductoscopies (MD), this procedure showed a sensitivity and specificity of 55.2% and 61.5%, respectively, compared to nipple smear (n=58, 36.7%, 92.3%); mammography (n=71, 37.9%, 92.3%); galactoscopy (n=19, 56.3%, 100%); duct sonography (n=71, 67.3%, 61.5%); MRI (n=27, 65.2%, 25.0%); FNAC (n=34, 51.9%, 100%); and core biopsy (n=11, 42.9%, 100%), respectively. Positive predictive value (PPV) was 100% for all procedures. The authors noted that a prospective, multicenter trial has been initiated in order to make conclusive statements about ductoscopy, especially to precisely define the indications for this method.

Kim et al. (2004) performed a case series study (n=30) reporting the results of 19 patients with a preoperative histologic diagnosis of in situ or invasive breast cancer who underwent intraoperative MD immediately preceding therapeutic partial mastectomy. Only 19 of 30 patients were able to produce nipple aspirate fluid. An intraductal abnormality was visualized in 15 of 19 patients; however, 10 of these intraductal abnormalities were intramural or adjacent to the standard partial mastectomy resection field and histology was negative for carcinoma. The authors noted that MD did not add value to patient care or alter the surgical intervention that the patients were undergoing. This study was also limited by lack of randomization, small patient numbers, and lack of statistical analysis of the PPV, sensitivity, or specificity of this technology as well as a lack of statistical comparison between this technology and partial mastectomy outcomes.

Dooley (2003) prospectively studied the use of operative breast endoscopy to assist the surgeon in the determination of intraoperative margin assessment, and to define the ductal anatomy in order to best position the lumpectomy to achieve clear margins at first excision of abnormal or malignant breast tissue. The surgeon was able to successfully perform mammary ductoscopy (MD) on 150 of 201 patients. Notably, the positive margin rate of the 150 patients was 5.0%. Additionally, MD identified 83 cases that showed additional intraluminal lesions outside the margin anticipated based on clinical and preoperative imaging. This study is limited by the lack of statistical analysis, randomization, or long-term patient outcomes.

**Professional Societies/Organizations**
The American Cancer Society, American College of Obstetricians and Gynecologists, American Society of Breast Surgeons, and the National Cancer Institute do not address the use of MD for the screening, diagnosis, or treatment of breast cancer.

The National Comprehensive Cancer Network guideline, Breast Cancer Screening and Diagnosis Version 2.2013, includes the following in a section discussing nipple discharge without a palpable mass:

Mammary ductoscopy is useful in evaluating patients who have nipple discharge, for accurate visualization, analysis, and excision of intraductal abnormalities. Magnetic resonance imaging (MRI) may play an adjunctive role, aiding in the differentiation of benign ductal abnormalities from malignant ones Preliminary studies have shown that breast MRI aids in the diagnosis of suspected ductal disease and is an alternative to ductoscopy when the latter cannot be used.

Ductoscopy is not included in the accompanying diagnostic follow-up algorithm, however

**Summary for MD:** Prospective randomized controlled studies are required to determine the benefits of MD over conventional diagnostic and surgical methods. While MD appears to be technically feasible, issues that have yet to be determined concerning the use of MD include:

- how the use of mammary ductoscopy (MD) will translate into possible increased surveillance of at-risk patients of all ages
- whether unwarranted chemotherapeutic or surgical prophylactic treatment may be initiated because of false-positive results
- how findings from MD may be used to modify ongoing chemotherapeutic regimens
- whether validation by MD that no atypia exists in a known high-risk patient warrants additional studies, other than repeat mammography, CBE, ultrasound or MRI (Newman, 2004)

The role of MD in breast cancer screening and breast conservation surgery has yet to be fully defined (Tang, 2010). Randomized controlled clinical trials published in the peer-reviewed scientific literature evaluating the use of MD in the screening of breast cancer, for the evaluation and management of nipple discharge, and for its role in breast-conserving surgery are lacking; studies are limited to uncontrolled case series and case reports. There is also a lack of comparison of long-term clinical outcomes of MD compared with conventional technologies or used as an adjunct to conventional technologies. At this time MD is not considered a standard diagnostic tool for any indication.

**Mammary Duct Aspiration and Lavage**
Nipple aspirate fluid (NAF) has been investigated as a risk assessment tool for patients who produce discharge. Uncontrolled studies have demonstrated an increased relative risk (RR=1.9–5) of breast cancer in women with abnormal cytology or epithelial cells in NAF when compared to women from whom NAF was attempted but not obtained (West, 2004; Beuhring, 2006; Baltzell, 2008). According to the ACS (2011), nipple aspiration may be useful as a test of cancer risk but is not appropriate as a screening test for cancer and has not been shown to detect cancer early.

Several methods of mammary duct aspiration have been proposed as means of extracting nipple aspirate fluid. These include invasive (e.g., ductal lavage) and non-invasive methods (e.g., automated mammary aspiration collection devices). Prospective randomized studies are required to determine the benefits of these methods over conventional diagnostic and surgical methods. Several randomized clinical trials investigating the diagnostic utility of using nipple aspirate fluid and ductal lavage as potential screening tools for women at moderate-to-high risk of developing breast cancer are in progress.

**Ductal Lavage (DL):** DL has been investigated as a method to improve the sensitivity of standard screening mammography. For its use in the identification of intraductal abnormalities, published data on the sensitivity and specificity of DL reflect ranges of 17%–83.8% and 64%–100%, respectively (Lang, 2007; Dua, 2006; Khan, 2004). DL has also been suggested as a way to improve the stratification of women with clinical evidence of increased breast cancer risk by the detection of atypia within the cells of the mammary ducts. It is proposed that

analysis of ductal lavage fluid containing atypical cells may indicate that a patient is at increased risk of developing breast cancer. Scarce data are available regarding the sensitivity, specificity, and positive predictive value (PPV) of aspirate fluid obtained by DL.

While DL may be feasible for retrieving epithelial cells, the relationship between the various degrees of cellular atypia and the underlying process of tumorigenesis is unknown. DL allows duct-specific sampling but is more invasive than standard imaging techniques recommended for breast cancer screening. Additionally, the use of saline irrigation may dilute the nipple aspirate fluid and complicate quantitative analysis of biomarkers (Locke, 2004). On the basis of cytologic interpretation of DL nipple aspiration samples compared with mammography results the sensitivity specificity and PPV of DL are unknown. Data are limited and do not suggest that DL is an effective screening tool for breast cancer.

Although promising as a method of sampling breast epithelium, several issues concern the diagnostic utility of DL. These include how the use of DL findings will translate into possible increased surveillance of at-risk patients of all ages, whether unwarranted chemotherapeutic or surgical prophylactic treatment may be initiated because of false-positive results, and how findings from DL may modify ongoing chemotherapeutic regimens. Additionally, it is unknown whether validation by ductal lavage (DL) that no atypia exists in a known high-risk patient warrants additional studies, other than repeat mammography, clinical breast exam, ultrasound or magnetic resonance imaging (MRI) (Masood, 2005; Newman, 2004).

**Literature Review**

**Breast Cancer Screening:** Loud et al. (2009) evaluated patient characteristics of a cohort of women from BRCA families (n=171) by obtaining NAF and adequate cell counts of DL specimens. 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.

To determine if ductal lavage (DL) could predict the occurrence of breast cancer as well as stratify patients at high risk of developing breast cancer, Carruthers et al. (2007) performed 223 DL procedures in 116 high-risk patients. Sixty-two percent had sufficient cells for evaluation. In 15 patients who underwent further evaluation for atypia, no evidence of cancerous or precancerous lesions was found. All patients received follow-up ranging from one to four years; two patients with previous normal lavage developed breast cancer. No patient with abnormal lavage developed cancer during follow-up. The authors noted that DL was of limited value in the screening of high-risk patients and removed it from their treatment algorithm. Data suggest that abnormal lavage did not correlate with premalignant or malignant pathology in the breast at the time of lavage and did not correlate with an increased risk of development of breast carcinoma during the study period.

In order to determine if a five-year Gail risk ≥ 1.7% or the presence of nipple aspirate fluid (NAF) predicts atypia, Bushnaq et al. (2007) reported the results of 150 women who were unselected for breast cancer risk and who underwent nipple ductal lavage (DL) with cannulation of all NAF-producing ducts, producing 516 lavage samples. Of these, 33% were classified as insufficient cellular material for diagnosis (ICMD). Samples were adequate for cytologic diagnosis in 89.9% of patients. Neither NAF by ductal lavage nor Gail risk predicted lavage atypia.

To assess the reproducibility of cannulation, cell yield and cytologic diagnosis from DL from the same duct at two time points, Patil et al. (2007) conducted a phase II clinical trial of women at high risk of breast cancer. One hundred eighty-two women were recruited to the study; 161 received a successful baseline DL. Sixty-three patients with 162 ducts underwent successful DL on follow-up at three months; matched ducts yielding ≥ 100 total epithelial cells was 49%. Reproducible atypia was seen in 42% women and 20% of matched ducts with atypical cytology at baseline. The authors noted that trials that require assessments of duct cannulation-related biomarkers at two time points need to build a significant attrition of the study population into the design. In this study cytologic diagnosis of cells obtained by ductal lavage (DL) was not reproducible over time, even in the absence of a risk-reducing intervention, and does not appear to be a useful biomarker.

**Risk Assessment and Stratification:** According to Cyr (2011) a prospective trial of 102 women who underwent DL demonstrated poor concordance with histology and the addition of ductoscopy added little to the evaluation in asymptomatic, high-risk patients. Ductal lavage and ductoscopy identified histologic atypia or malignancy in only 5% high-risk women although cytologic atypia was identified in 26%. There was no apparent difference in

the risk of future breast cancer development between those with atypia on ductal lavage and those without at six years of follow-up. Cytologic evaluation of ductal lavage and ductoscopy specimens appears to be of limited utility for stratifying or monitoring women at high risk of developing breast cancer.

Khan et al. (2009) reported results of a study evaluating the effectiveness of DL for biomarker assessment. One hundred fifteen women received an initial DL with repeat DL at six months. The authors noted although expected changes in tamoxifen-related biomarkers were noted, "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."

Arun et al. (2007) compared random periaerolar fine needle aspiration (RPFNA) and DL as breast tissue acquisition methods by evaluating sample adequacy and tolerability in participants in two prospective Phase II breast cancer prevention trials. Eighty-six women considered high risk for breast cancer underwent these procedures on the same day to establish a baseline. Retrieval rate for RPFNA was 100%; 96% of these were adequate samples (i.e., ≥ 10 epithelial cells). Breast fluid samples were retrieved via DL in 73% of the patients; 71% were also considered adequate samples. When the entire cohort was considered, adequate samples via DL were retrieved in only 31% of patients. The authors noted that the cytology of the DL and RPFNA slides from the same subject were not different. In the DL samples, identification of atypical hyperplasia (AH) and hyperplasia was 3.7% and 11.1%, respectively, compared with 12.9% and 24.7%, respectively for RPFNA.

Visvanathan et al. (2007) evaluated the reliability of nipple aspirate fluid (NAF) and DL at two time points six months apart in 69 women with increased risk of breast cancer. Of the 47 women returning for a second visit, 24 produced NAF and 18 were successfully recannulated. Cellular yield between the two time points was inconsistent, and only fair cytologic agreement was reached. The use of ductal lavage is limited by technical challenges in cannulation, inconsistent NAF production, a high rate of inadequate cellular material for analysis, fair cytologic reproducibility, and low participant return rates.

To determine the accurate correlation of nipple aspirate, ductal lavage cytology and histopathological findings, West et al. (2006) conducted a prospective correlative study of 22 patients scheduled to undergo core needle or surgical breast biopsy. Overall specificity of cytology versus histopathological findings was 83.4%; however, cytologic-histologic correlation was discordant in 50% of the findings. West and colleagues noted that the use of ductal lavage (DL) in screening for intraepithelial neoplasias or early invasive cancers requires further investigation with perhaps a larger multicenter trial and that currently the procedure should not be recommended outside of the context of a scientific study.

Khan et al. (2004) conducted a consecutive case study of 39 women to determine the association between histopathological mastectomy findings versus the cytologic findings from ductal lavage; to establish the sensitivity and specificity of ductal lavage in the presence of known breast cancer; and to estimate the frequency with which cancer was found in breast ducts that failed to yield fluid. Ductal lavage (DL) was performed on 44 cancerous breasts and eight noncancerous breasts. When the lavage samples were analyzed for marked atypia or malignant cytology, only five ductal samples confirmed the diagnosis of breast cancer (sensitivity, 43%; specificity, 96%; accuracy, 77%). Sensitivity, specificity and accuracy decreased when the lavage samples were analyzed for mild, marked atypia or malignant cells (sensitivity, 79%; specificity, 64%; accuracy, 69%). Total study sensitivity, specificity, and accuracy were 17%, 100%, and 19%, respectively. It could not be determined if these findings resulted from cancer-containing ducts failing to yield fluid or if they had benign or mildly atypical cytology. This study failed to show that DL could be used as a reliable screening or diagnostic tool for breast cancer patients or patients with known high risk for breast cancer.

**Professional Societies/Organizations**

**American Cancer Society (ACS, 2012):** The ACS notes "Ductal lavage is an experimental test developed for women who have no symptoms of breast cancer, but are at very high risk for the disease. It is not a test to screen for or diagnose breast cancer, but it may help give a better picture of a woman's risk of developing it." "Ductal lavage is not considered appropriate for women who are not at high risk for breast cancer. It is not clear if it will ever be ~~a~~ useful ~~tool.~~ The test has not been shown to detect cancer early. It is more likely to be useful as a test of cancer risk rather than as a screening test for cancer. More studies are needed to better define the usefulness of this test."

Regarding nipple aspiration, the ACS notes, “As with ductal lavage, the procedure may be useful as a test of cancer risk but is not appropriate as a screening test for cancer. The test has not been shown to detect cancer early.”

**National Cancer Institute (NCI, 2011):** Regarding ductal lavage the NCI notes “Whether this procedure led to the detection of any cancers earlier than mammography alone would have done is not known, and no data are available to determine the efficacy or mortality reduction of ductal lavage use as a screening or diagnostic tool. Therefore, the use of this procedure as a screening tool remains investigational. “

**National Comprehensive Cancer Network™ (NCCN™):** NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis (version 2.2013) states that current evidence does not support the routine use of ductal lavage as a screening procedure.

**Summary for Ductal Lavage:** At this time, there is insufficient evidence that DL has clinical utility compared with established methods of detecting and diagnosing breast cancer or that this diagnostic technique improves health outcomes. No definitive patient selection criteria for ductal lavage of the breast have been established. Additional limitations in the peer-reviewed, published literature include significant methodological and study design problems, as well as lack of standardization of risk assessment protocols. The role of ductal lavage has not yet been established.

Data regarding the sensitivity and specificity of DL in detecting breast cancer, its usefulness in risk stratification, and the significance of mild atypia as detected by DL are limited. Well-designed systematic evaluation of the impact of DL on risk assessment, treatment determination and long-term outcomes is lacking. The published peer-reviewed scientific literature consists of uncontrolled case series and case reports.

**Non-Invasive Mammary Duct Aspiration Collection Devices:** The use of a collection device to perform mammary duct aspiration has been proposed to obtain nipple aspirate fluid for cytological analysis

**U.S. Food and Drug Administration (FDA)**
The Halo™ Breast Pap Test system (NAFD 100, NeoMatrix, LLC, Irvine, CA) received a 510K approval in September 2002. The device is indicated for the collection of nipple aspirate fluid for cytological evaluations.

Based upon the description of the device provided by the manufacturer website (NeoMatrix, LLC., Irvine, CA), “The HALO™ Breast Pap Test is a noninvasive nipple aspirate fluid (NAF) collection system designed for use in a primary care setting. It is approved for the collection of nipple aspirate fluid for cytological evaluation. The collected fluid can be used in the determination and/or differentiation of normal versus premalignant versus malignant cells.” The device is marketed as a screening method to assess breast cancer risk and is proposed as a method for early detection of a women’s risk of developing breast cancer. The manufacturer website notes “HALO is not a diagnostic test and cannot be used to exclude breast cancer. Patients should continue to undergo other clinical breast screening procedures (mammography, clinical breast exam, self breast examination) as determined by and with their physicians.”

The Mammary Aspiration Specimen Cytology Test (MASCT) System received 510(k) approval in 2001 and 2003 (Nastech Pharmaceutical, Inc., Hauppauge, NY, currently offered by Atossa Genetics, Inc., Seattle, WA). The FDA issued a substantial equivalence determination. According to the FDA (2003), “The MASCT device is intended for use in the collection of nipple aspirate fluid for laboratory cytological testing. The collected fluid can be used in the determination and/or differentiation of normal versus premalignant versus malignant cells.”

According to the Atossa Genetics website, “The MASCT System (Atossa Genetics, Inc., Seattle, WA) uses a hydrophilic (“water seeking”) membrane in contact with the nipple to “wick” fluid from the orifice of the ducts by capillary action during the cycles of negative pressure.” The website 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 exam.” The website notes “A clinical trial of the MASCT system was performed at the State University of New York, Stony Brook NY to test the efficiency of nipple aspirate fluid (NAF) collection in normal volunteer women. Of the 31 subjects, 30 (97%) had measurable NAF; 24 bilaterally and 6 unilaterally. NAF samples ranged from 1 to 37 µL with an average of 7 µL and all samples collected were deemed to be clinically useful. Fifty-eight of sixty NAF samples were reported as cytology Class I, and 2 of 60 were reported as cytology Class IIa. No adverse events were reported.”

On October 4, 2013, Atossa Genetics Inc. initiated a voluntary recall to remove the ForeCYTE Breast Health Test and the MASCT device from the market in order to address concerns raised by the U.S. FDA in a warning letter received in February 2013. The FDA raised concerns about the current instructions for use, certain promotional claims used to market these devices, and the need for FDA clearance for certain changes made to the specimen collection process.

**Literature Review**
Data are scarce in the published peer-reviewed scientific literature regarding the effectiveness of collection devices for the screening of breast cancer. There is a lack of well-designed controlled studies, and long-term outcomes. Randomized controlled studies are required to determine the clinical utility of these devices compared with standard methods of breast cancer screening.

Proctor et al. (2005) reported results of a prospective, multi-center, observational clinical study sponsored by the device manufacturer involving 500 asymptomatic, nonpregnant, non-lactating women with no history of breast cancer, breast surgery (e.g. breast augmentation or breast reduction), or nipple piercing. Fluid production, adequacy, safety and patient acceptance of the Halo NAF Collection System were assessed. Thirty-eight percent of patients produced fluid; 187 were available for cytologic analysis. Cytologic classification of fluid producers showed 50% with insufficient cellular material, 38% with benign nonhyperplastic ductal epithelial cells, 10% with benign hyperplastic ductal epithelial cells, 3% with atypical ductal epithelial cells, none were unequivocal malignancy. Overall, 19% of the subjects produced NAF with adequate cellularity and 1% were found to have cytologic atypia. Gail five-year risk profiles were obtained for the participants over the age of 35. Overall, no statistical difference was seen with regards to fluid production and calculated Gail profile result ($p = 0.2$). Comparison of Gail risk (>1.7% versus <1.7%) and cytology category results, for the 190 women assessed, showed no significant difference ($p = 0.68$). The study is limited by study design, and long-term follow-up is needed to determine the clinical significance of study outcomes.

**Professional Societies/Organizations**
The American Cancer Society, American College of Obstetricians and Gynecologists, American Society of Breast Surgeons, National Cancer Institute, and National Comprehensive Cancer Network do not address the use of non-invasive mammary duct aspiration collection devices for the screening, diagnosis or treatment of breast cancer.

**Summary for Non-Invasive Mammary Duct Aspiration Collection Devices:** The clinical utility of a nipple aspirate collection system has not been demonstrated compared with standard breast cancer screening procedures. There is a lack of evidence in the published peer-reviewed scientific literature regarding the ability of nipple aspirate fluid collection devices to obtain sufficient nipple aspirate yields, and to determine the contribution of these yields to risk assessment. Additionally, the sensitivity, specificity, or predictive value of non-invasive mammary duct collection devices to assess breast cancer risk is unknown.

**Use Outside the U.S.**
European Society of Medical Oncology (ESMO) clinical practice guidelines for the diagnosis, treatment and follow-up do not mention mammary ductoscopy, aspiration, or lavage (Senkus et al. on behalf of the ESMO Guidelines Working Group, 2013). These guidelines are endorsed by the Japanese Society of Medical Oncology.

**Summary**
Mammary ductoscopy (MD) has been proposed as a diagnostic tool for use in screening for breast cancer, for the evaluation of nipple discharge and as a surgical guide to assist in breast conserving surgery. Published studies are limited by a lack of randomized controlled trials evaluating the safety and effectiveness of this technology. Additionally, long-term clinical outcomes regarding MD compared with conventional technologies such as mammography, ultrasound, or magnetic resonance imaging are lacking. The effectiveness and clinical utility of mammary ductoscopy has not yet been established for any indication.

There is insufficient evidence to support the diagnostic utility of ductal lavage (DL) of the mammary ducts for any indication. The results of ongoing well-designed large population, multicenter, randomized controlled clinical trials with long-term follow-up are needed before the role of DL in the screening, diagnosis and management of breast cancer or any other condition can be established.

There is insufficient evidence in the published peer-reviewed scientific literature to support the diagnostic utility of mammary duct aspiration collection devices for any indication. The role of these devices in breast cancer screening, diagnosis, and management has not yet been established.

Clinical trials are in progress to determine the diagnostic utility of using nipple aspirate fluid, ductal lavage and MD as potential screening tools for women at moderate-to-high risk of developing breast cancer. Ongoing studies will also analyze the extent to which nipple aspiration, ductal lavage, and duct endoscopy may assess cancer cells in women who are undergoing surgery for breast cancer.

## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Experimental/Investigational/Unproven/Not Covered when used to report mammary ductoscopy, lavage or aspiration by a non-invasive collection device:**

| CPT®* Codes | Description |
|---|---|
| 19499 | Unlisted procedure, breast |

***Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.**

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