



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Mammary Duct Aspiration and Lavage**

**Effective Date ..... 2/15/2011**  
**Next Review Date..... 2/15/2012**  
**Coverage Policy Number ..... 0038**

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## INSTRUCTIONS FOR USE

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## Coverage Policy

**CIGNA does not cover ductal lavage of the mammary ducts for any indication, because it is considered experimental, investigational or unproven.**

**CIGNA does not cover automated mammary duct aspiration by non-invasive collection devices (e.g., HALO™ Breast Pap Test ) for any indication, because they are considered experimental, investigational or unproven.**

## 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 (American Cancer Society [ACS], 2010). 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% (National Cancer Institute [NCI], 2010). 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). The use of MRI in combination with mammography provides a highly sensitive screening strategy (i.e. sensitivity 93%–100%) (Lord, 2007).

Approximately 85% of breast cancer originates in the epithelial cells lining the milk ducts. 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 (Domchek, 2002; West, 2004; Beuhning, 2006; Baltzell, 2008). According to the ACS (2010), 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):** To perform DL, a small amount of anesthetic cream is applied to the nipple area, and a breast pump is used to apply mild suction to the nipple to draw out fluid from the milk ducts. A microcatheter is then inserted into the opening of any fluid-yielding duct(s); saline solution is introduced, and fluid containing cells from the duct(s) is collected (Gemignani, 2008).

DL has been investigated as a method to improve the sensitivity of standard screening mammography. It 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. 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). Scarce data are available regarding the sensitivity, specificity, and positive predictive value (PPV) of aspirate fluid obtained by DL.

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).

DL may be feasible for retrieving epithelial cells; however, 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.

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.

## Literature Review

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.

- **Breast Cancer Screening:** To determine if 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. Eleven percent of lavages yielded atypical or papillary-type cells. 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  $\geq 1.7\%$  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. DL cytology was interpreted as atypical in 18% of ducts; mild and marked atypia was diagnosed in 11% and 6.6% of ducts, respectively. 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. The number of matched ducts that had  $\geq 100$  total epithelial cells yielded at both time points was 49%. There was a decrease in cell yield between the baseline and six-month DL procedures, with a subsequent increase in insufficient cells for morphologic diagnosis. Overall concordant cytologic diagnosis was present in 43%. Of the 187 ducts cannulated at baseline. In the 65 women who chose observation and returned for the six-month lavage, 83% of ducts from 63 women were successfully recannulated. When analyzed by matched duct, 56% of matched ducts with mild atypia at baseline yielded benign cells at six months, while 14% of matched ducts with benign cytology at baseline showed mild atypia at six months; one duct (1%) showed severe atypia. 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. They also noted that cytologic diagnosis of cells obtained by ductal lavage (DL) is 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:** 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.,  $\geq 10$  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 cell count for DL was an average of 5215 cells per subject; for RPFNA, the average sample size was 10,614 cells per subject. 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 NAF and DL at two time points six months apart in 69 women with increased risk of breast cancer. At baseline, 65% of premenopausal and 41% of postmenopausal women produced NAF ( $p=0.05$ ); 72% had successful lavage of at least one duct. 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. Twelve adequate cellular DL samples were obtained. Six cytology results were concordant with the histological findings, six were not. 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. Study participants had diagnoses of invasive breast cancer, associated ductal carcinoma in situ that was too large to allow breast conservation, multicentric disease, or were undergoing a prophylactic mastectomy due to high risk. 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.

#### **Automated Non-Invasive Mammary Duct Aspiration Collection Devices (e.g., HALO™ Breast Pap Test):**

The use of an automated device (e.g., the HALO™ Breast Pap Test) to perform aspiration has been proposed to obtain nipple aspirate fluid for cytological analysis. According to the manufacturer, HALO combines warmth, massage and suction to bring nipple aspirate fluid (NAF) to the surface. Using gentle compression, heat, and suction, it uses adjustable breast cups to collect NAF which can be sent for analysis for the presence of normal, premalignant, and malignant cells.

Based upon the description of the provided by the manufacturer (NeoMatrix, LLC., Irvine, CA), and the U.S. Food and Drug Administration (FDA) approval (2002), the HALO™ Breast Pap Test is a noninvasive nipple aspirate fluid (NAF) collection system designed for use in a primary care setting. It is specifically approved to collect nipple aspirate fluid (NAF) for subsequent cytology testing. 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 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 such as mammography, clinical breast exam, and self breast examination."

The clinical utility of this intervention 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 automated nipple aspirate fluid collection devices, such as the HALO™ Breast Pap Test, 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 this device to assess breast cancer risk is unknown.

#### **Literature Review**

Data are scarce in the published peer-reviewed scientific literature regarding the effectiveness of automated 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.

### **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.

### **Professional Societies/Organizations**

**American Cancer Society (ACS, 2010):** 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 breast cancer. 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.”

**American Society of Breast Surgeons (ASBS, 2007):** The ASBS notes “The cytologic interpretation of breast epithelial cells must be standardized to ensure accurate risk assessment. Ductal lavage is not a cancer detection technique and should not replace standard cancer screening methods. Long-term studies are necessary to better define the risk assessment contribution of cytologic atypia detected via these and other methods. The ASBS encourages participation in such trials.

**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 (2010) notes “Current evidence does not support the use of ductal lavage as a screening procedure.”

### **Summary**

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 automated 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.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Experimental, investigational, unproven, and not covered when used to report ductal lavage of the mammary ducts or automated non-invasive mammary aspiration collection devices (e.g., HALO™ Breast Pap Test):**

CPT* Codes	Description
19499	Unlisted procedure, breast

ICD-9-CM Diagnosis Codes	Description
V16.3	Family history of malignant neoplasm; breast
V84.01	Genetic susceptibility to malignant neoplasm of breast
	All codes

**\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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## Policy History

<b><u>Pre-Merger Organizations</u></b>	<b><u>Last Review Date</u></b>	<b><u>Policy Number</u></b>	<b><u>Title</u></b>
CIGNA HealthCare	2/15/2008	0038	Mammary Ductal Lavage (DL)

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