CYTOLOGICAL EXAMINATION OF BREAST FLUIDS FOR CANCER SCREENING

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INSTRUCTIONS FOR USE
This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

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

COMMERCIAL, MEDICARE & MEDICAID COVERAGE RATIONALE

Breast ductal lavage is not medically necessary for use in breast cancer screening of either low-risk or high-risk women. There is inadequate clinical evidence that breast ductal lavage either allows for better clinical decision-making or reduces breast cancer mortality. Further studies are necessary to determine the efficacy of cytological examination of ductal fluid in detecting atypical cells to identify women at increased risk of breast cancer as well as comparing the results to established methods of detecting and diagnosing breast cancer. Ductal lavage is intended for use in high-risk women but no definite patient selection criteria for ductal lavage of the breast have been established.

Breast ductal fluid aspiration and cytology is not medically necessary for use in breast cancer screening of either low-risk or high-risk women. There is inadequate clinical evidence that automated nipple aspiration either allows for better clinical decision-making or reduces breast cancer mortality. Further studies are necessary to determine the efficacy of cytological examination of ductal fluid.
fluid in detecting atypical cells to identify women at increased risk of breast cancer as well as comparing the results to established methods of detecting and diagnosing breast cancer.

**Fiberoptic ductoscopy, with or without ductal lavage, is not medically necessary for use in breast cancer diagnosis or screening or as an intraoperative tool to guide surgery.** There is insufficient clinical evidence demonstrating that fiberoptic ductoscopy allows for better clinical decision-making, reduces breast cancer mortality or serves as a useful adjunct to or replacement of open surgical excision.

Medicare does not have a National Coverage Determination (NCD) that addresses breast ductal lavage (DL), breast ductal fluid aspiration and cytology or for fiberoptic ductoscopy, with or without ductal lavage. Local Coverage Determinations (LCDs) for Nevada do not exist at this time (Accessed April 2017).

**For Medicare and Medicaid Determinations Related to States Outside of Nevada:**
Please review Local Coverage Determinations that apply to other states outside of Nevada. [http://www.cms.hhs.gov/mcd/search](http://www.cms.hhs.gov/mcd/search)

**Important Note:** Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

### DESCRIPTION OF SERVICES

In addition to looking for more effective treatments for breast cancer, research is aimed at reducing mortality through earlier detection. Cytological examination of epithelial cells found in breast ductal fluids has been studied as an early indicator of breast cancer. Ductal fluids can be obtained by ductal lavage or nipple aspiration.

Ductal lavage is an invasive procedure that removes ductal fluid by inserting a microcatheter into the breast ducts via the nipple. Nipple aspiration can also be done using fine needle aspiration or, noninvasively, using the HALO Breast Pap Test system. HALO is an automated system that collects nipple aspirate fluid (NAF) using a combination of heat, massage and suction.

Ductal fluid may also be obtained using fiberoptic ductoscopy which allows direct visualization of breast ducts using a very thin endoscope. Fiberoptic ductoscopy allows for evaluation of abnormal nipple discharge in conjunction with aspiration cytology, biopsy or surgical excision.

### CLINICAL EVIDENCE

**Ductal Lavage (DL)**
A National Cancer Institute (NCI) report states that because ductal lavage screening has not been compared to mammography, and there is no evidence of efficacy or mortality reduction, its use as a screening or diagnostic tool remains investigational (NCI, 2016).

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer screening and diagnosis state that current evidence does not support the routine use of ductal lavage as a screening
modality for breast cancer (NCCN, 2015). NCCN guidelines on breast cancer risk reduction state that the clinical utility and role of nipple aspiration or ductal lavage are still being evaluated and should only be used in the context of a clinical trial (NCCN, 2016).

Cyr et al. (2011) conducted a prospective, single-center study to determine which histological lesions produce cellular atypia in lavage specimens and whether ductoscopy adds useful information for the evaluation of high-risk patients with atypical lavage cytology. A total of 102 women, ≥35 years, at high risk for developing breast cancer were enrolled. All underwent ductal lavage. Women found to have atypia underwent ductoscopy-directed duct excision (group 1). Women without atypia were observed (group 2). The median age was 49 (range 34-73) years with a median follow-up of 80 (range 5-90) months. Overall, 27 (26%) had atypical lavage cytology (group 1), and 75 (74%) had benign cytology (group 2). Subsequent duct excision in group 1 revealed benign histology in 11 (44%), papillomas in 9 (36%), atypical hyperplasia (AH) in 4 (16%) and ductal carcinoma in situ (DCIS) in 1 (4%). At follow-up, three patients developed breast cancer, including one group 1 patient and two group 2 patients. Although 20% of high-risk women with ductal lavage atypia have AH or malignancy on subsequent excision, the majority do not. The authors concluded that atypia identified by ductal lavage is not associated with a higher risk of developing subsequent breast cancer, even in this high-risk population.

One large, manufacturer-sponsored, multi-center, prospective clinical trial compared the efficacy of breast DL with nipple aspiration for the collection and cytological detection of cellular atypia in 507 women (700 breasts) at high risk for breast cancer. DL was significantly more likely than nipple aspiration to provide sufficient cells for cytological diagnosis (78% versus 27% of patients), resulted in the collection of a greater number of cells per breast, and resulted in significantly more diagnoses of cellular atypia or breast cancer (17% versus 4% for paired samples and 24% versus 10% for paired and unpaired samples combined). The number of epithelial cells per breast duct obtained during DL correlated significantly with the severity of the cytopathological changes found. The median numbers of cells collected per duct were as follows: benign, 4000; mild atypia, 13,400; marked atypia, 40,000; and malignant, 83,000. DCIS was diagnosed by histopathological examination in 4 of 11 (36%) patients with cellular abnormalities on DL that had imaging and surgery; however, no data are available on the 7 remaining patients. Interpretation of the data from this study is hampered by weaknesses in study design and execution such as the lack of follow-up and histopathological confirmation of the findings for all patients as well as a lack of information on how the test results influenced health outcomes (Dooley et al., 2001).

In a cohort study, Carruthers et al. (2007) evaluated if ductal lavage 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 > or = 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. Two hundred twenty-three 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 precancerous 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 ductal lavage to be of limited value in the screening of high-risk patients.
In a small cross-sectional study, Brogi et al. (2003) evaluated the correlation between cytological diagnoses obtained by DL and histopathological findings in 30 mastectomy specimens from 26 breast cancer patients and 4 patients undergoing prophylactic mastectomy. Twenty-nine DL samples were satisfactory for cytological examination. Of these, 27 were obtained from 24 breasts with CIS; 20 samples showed invasive breast cancer. Among the 29 satisfactory DL samples, 10 (34%) showed mild atypia, 4 (14%) showed marked atypia, 15 (52%) were benign, and 0 (0%) showed cancer cells. While interobserver agreement was fair (kappa value = 0.52), the authors concluded that DL lacks sufficient sensitivity for the diagnosis of breast cancer.

In a pilot study, Hartman et al. (2004) evaluated the efficacy of DL and magnetic resonance imaging (MRI) versus mammography and clinical breast exam (CBE) for breast cancer detection in women at high risk for the disease who were BRCA mutation carriers or who had a > 10% risk of developing breast cancer within 10 years according to the Claus model. DL detected atypia in specimens from 7 (23%) patients including a high-grade atypia in 1 patient with a normal mammogram and normal MRI results. Six other patients who had atypia on DL had normal mammographic results. The data suggest that DL might detect lesions that are otherwise missed; however, longer-term follow-up is needed to determine if the detection of cellular atypia on DL accurately predicts the risk of breast cancer and affects patient outcomes.

Francescatti et al. (2005) evaluated the results of attempted ductal lavage in 120 patients at high-risk for breast cancer. Thirty-two patients were excluded because 29 patients did not produce nipple aspirate fluid and the surgeon was unable to cannulate the effluent-producing duct in 3 patients. Of the remaining 88 patients, 15 (17%) had insufficient epithelial content for diagnosis, 51 (58%) had benign cytologic results, and 22 (25%) had abnormal cells. Of the 25%, 20 patients had mild atypia, 1 had marked atypia and 1 had malignant changes.

Khan et al. (2004) studied the association between ductal lavage cytologic findings and histologic findings in women with known breast cancer. Ductal lavage was performed on 44 breasts in 32 women with known cancer and on 8 breasts in 7 women undergoing prophylactic mastectomy, two with occult malignancy. In 39 ducts with complete cytologic and histologic data and when marked atypia or malignant cells defined a positive cytologic test, sensitivity of ductal lavage was 43%, specificity was 96%, and accuracy was 77%. When mild or marked atypia or malignant cells defined a positive cytologic test, sensitivity was 79%, specificity was 64%, and accuracy was 69%. Analysis of all 31 cytologically evaluable breasts showed sensitivity was 17%, specificity was 100%, and accuracy was 19%. The investigators concluded that ductal lavage appears to have low sensitivity and high specificity for cancer detection.

Specimens obtained by DL might be suitable for evaluation by techniques such as fluorescent in situ hybridization (FISH) or cytogenetic analysis. Preliminary studies have demonstrated the feasibility of analyzing ductal epithelial cells for chromosomal abnormalities, which could potentially assist in the definitive diagnosis of breast cancer. However, these diagnostic techniques are in the preliminary stages of development and it remains unclear how they would impact the diagnostic accuracy of DL or its role in risk stratification (Yamamoto et al., 2003; Evron et al., 2001; King et al., 2003). Overall, the published evidence regarding DL suggests that the procedure is feasible and well tolerated, is less invasive and yields a greater number of breast duct epithelial cells for cytological analysis than FNA, and is capable of detecting abnormal cells in NAF specimens from individual breast ducts.
However, there are minimal data on the diagnostic sensitivity or specificity of DL, on the clinical significance of the presence of atypical cells in DL specimens, on whether the demonstration of no atypical or malignant cells correlates with a decreased risk for breast cancer, or on the use of either positive or negative test results in patient management or outcomes. Furthermore, there is speculation that breast cancer is not a field defect throughout the breast but can occur in one ductal system, thus if that ductal system is not lavaged, a false negative would be yielded (Lindsey, 2004).

In a consensus statement on Screening Mammography, The American Society of Breast Surgeons addressed ductal lavage, stating that its use for the screening of average risk women is not supported outside of clinical trials. (2015)

**Nipple Aspirate Fluid (NAF)**

Hornberger et al. (2015) performed a systematic review to evaluate the association of proliferative epithelial disease found in nipple aspirate fluid (PED-NAF) and the risk of developing breast cancer. Sixteen studies were analyzed, containing data on 20,808 unique aspirations from over 17,378 subjects. Among aspirations from women free of breast cancer, 51.5% contained fluid, in which over 27.7% had PED on cytology. In the two prospective studies of 7850 cancer-free women, abnormal cytology by NAF carried a 2.1-fold higher risk of developing breast cancer, compared with women from whom no fluid could be obtained. The authors concluded that PED-NAF among women free of breast cancer, compared with no fluid being obtained, had an independent risk of developing breast cancer comparable to the risk of a woman with a positive family history of breast cancer. It was noted that heterogeneity across studies may have influenced the results. The limited literature calls for prospective studies on asymptomatic women with long-term follow-up.

Only one study on the use of the HALO NAF Collection System for testing nipple aspirate fluid was identified in the published, peer-reviewed medical literature. Proctor et al. (2005) conducted a multi-center prospective observational clinical trial involving 500 asymptomatic women for the purpose of assessing fluid production, adequacy, safety and patient acceptance of the HALO NAF Collection System. Thirty-eight percent (190/500) produced fluid and 187 were available for cytologic analysis. Cytologic classification showed 50% (93/187) had insufficient cellular material, 38% (71/187) had benign non-hyperplastic ductal epithelial cells, 10% (18/187) had benign hyperplastic ductal epithelial cells, 3% (5/187) had atypical ductal epithelial cells and there were no cells of unequivocal malignancy. Overall, 19% of the subjects produced NAF with adequate cellularity and 1% were found to have cytologic atypia. Although this study had a fairly large sample, the number of subjects who were able to produce NAF with cellularity and the yield of cytologic atypia found in that population does not support the efficacy of this method of screening for breast cancer.

Sauter et al. (2010) prospectively performed cytologic assessment and image analysis (IA) on matched nipple aspirate fluid (NAF) and mammary ductoscopy (MD) specimens to determine (1) the accuracy of these methods in cancer detection and (2) whether the two collection methods provide complementary information. NAF and MD specimens were collected from 84 breasts from 75 women who underwent breast surgery. The NAF cytology had a limited ability to detect women with cancer (identified only 10%) but was 100% accurate in identifying women who did not have cancer. In women with spontaneous nipple discharge, the test had many false positives. Combining NAF and MD cytology information improved sensitivity (24%) without sacrificing specificity. However, the significance of these conclusions is limited by small sample size and an uncontrolled study design.
The clinical evidence was reviewed on May 12, 2016 with no additional information identified that would change the not medically necessary conclusion.

**Fiberoptic Ductoscopy (FDS)**
Most of the published evidence on FDS is limited to preliminary cross-sectional studies evaluating the technical success of intraductal visualization and the diagnostic accuracy of the technique or the feasibility of intraoperative breast endoscopy.

Shen et al. (2001) studied the role of FDS in 415 women with abnormal nipple discharge. FDS identified an intraductal papilloma (IDP) in 166 patients (40%) including 10 with atypical papillomas and 156 with typical papillomas. DCIS was confirmed by histopathological examination in 11 patients with IDPs; 6 (55%) of these patients had normal findings on mammography and CBE. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for FDS were 73%, 99%, 80%, and 98%, respectively. For FDS and DL together, the corresponding figures were 64%, 100%, 100% and 97%. The results suggest that FDS can diagnose precancerous lesions of the breast that are not detected by conventional means. It was unclear how or whether patients with normal findings by FDS were followed up to confirm the absence of disease (to confirm the specificity and NPV values), or how the test results impacted clinical decision-making.

In a study of 65 patients with abnormal nipple discharge, FDS identified intraductal abnormalities in 38 patients; the results of histopathological examination were positive in 37 of 38 (97.4%). The PPV of FDS was 97.4% versus a PPV of 89.2% for ductography, a statistically significant difference. The sensitivity, specificity, and accuracy of DL were 50%, 94.3%, and 89.7%, respectively. The authors concluded that FDS had good PPV for detection of intraductal lesions; however, the sensitivity of DL was low for the diagnosis of breast cancer in this population (Yamamoto et al., 2001).

A small clinical study evaluated the efficacy of intraoperative FDS for the management of symptomatic bloody nipple discharge in 27 patients with normal mammographic findings within 3 months before surgery. Breast endoscopy was technically successful in 26 patients, and allowed for visualization of all of the proximal ducts. A lesion associated with the bleeding was identified in 26 of the 26 (100%) patients who were cannulated, with 19 (70%) having multiple intraluminal lesions. In 2 patients, DCIS was located 2 to 4 cm deeper than large retroareolar papillomas within the duct. Breast cancer was detected in 2 (7.4%) patients, and in both there was a more proximal papilloma within the same ductal system. One breast cancer found by FDS was not visible on a mammogram or ultrasound image. Atypical ductal hyperplasia (ADH) was the cause of bleeding in 33% of the patients with benign lesions. Since FDS identified a relatively high incidence of multiple lesions that might otherwise have been missed, the authors concluded that standard surgery to treat patients with bloody nipple discharge, i.e., blind resection of the first 2 to 3 cm of the duct, might miss DCIS or ADH located deeper within the breast duct that are the true bleeding source. Further research is needed to determine whether there are situations in which FDS-guided resection would serve as a useful adjunct to or if it could replace open surgical excision (Dooley, 2002).

In a small preliminary study of 49 patients, FDS identified intraductal lesions that were not observed on ductography or mammography in 8 (16%) of the 49 patients with nipple discharge or suspected breast cancer (the reasons for suspicion of breast cancer were not provided). Intraductal papillomas in 2 patients and DCIS in 6 patients that were detected by FDS and DL were confirmed by
histopathology, as the 8 patients proceeded to have surgery. The authors noted that the test results aided in surgical planning but added that additional studies are needed to determine the optimal role of FDS and DL in treatment decision-making (Hunerbein et al., 2003).

Some researchers have challenged the utility of FDS and DL for the detection and diagnosis of breast cancer. In a retrospective analysis of the presence and type of involvement of the nipple and central duct area in 801 mastectomy specimens performed for invasive breast cancer, DCIS, or both, 17% of the invasive cancers had no demonstrable intraductal component defined as atypical proliferation or atypical cells. Furthermore, only 22% of cases showed nipple and central duct involvement. These findings lead to questions regarding the adequacy of these methods for breast cancer detection since their accuracy depends upon the presence and accessibility of precursor lesions such as ADH or intraductal carcinomas. Since FDS and DL examine only 1 or 2 ducts among a total of 15 to 20 breast ducts that open at the nipple, these techniques might also miss focal abnormalities or those occurring in ducts that are not examined (Badve, 2004; Badve et al., 2003).

The clinical evidence was reviewed on May 12, 2016 with no additional information identified that would change the not medically necessary conclusion.

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


The HALO® Breast Pap Test (HALO Healthcare) was approved for marketing by the FDA on September 23, 2002. The device is intended to non-invasively extract samples of breast duct fluid for breast cancer screening, providing a sample for a "Pap smear" for the breast. Available at: [http://www.accessdata.fda.gov/cdrh_docs/pdf2/K020848.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf2/K020848.pdf). (Accessed April 2017)

According to the FDA, breast ductoscopes are considered unclassified devices.

On December 12, 2013, the FDA issued a Safety Alert regarding nipple aspirate testing. The alert states that a nipple aspirate test is not a replacement for mammography, other breast imaging tests or breast biopsy, and should not be used by itself to screen for or diagnose breast cancer. The FDA is not aware of any valid scientific data to show that a nipple aspirate test by itself is an effective screening tool for any medical condition including the early detection of breast cancer or other breast disease. Additional information available at: [http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm378489.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm378489.htm). (Accessed April 2017)

**APPLICABLE CODES**

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

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<th>CPT® Code</th>
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<td>19499</td>
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REFERENCES


HALO Healthcare, Inc. website.


The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.