Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis

Policy Number: 2025T0335GG
Effective Date: January 1, 2025

Instructions for Use

Table of Contents — **Page**

Related Commercial/Individual Exchange Policy
- Genetic Testing for Hereditary Cancer

Community Plan Policy
- Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

The following are unproven and not medically necessary for use in breast cancer screening, breast cancer diagnosis, or screening as alternative tools to guide surgery due to insufficient evidence of efficacy:
- Breast ductal lavage
- Breast ductal fluid aspiration and cytology
- Fiberoptic ductoscopy, with or without ductal lavage

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 Guidelines may apply.

CPT Code	Description
19499	Unlisted procedure, breast

CPT® is a registered trademark of the American Medical Association

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.

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)

The National Cancer Institute (NCI) states that while various methods to analyze breast tissue for malignancy have been proposed to screen for breast cancer, including fine needle aspiration, nipple aspirate, and ductal lavage, none are associated with a reduction in mortality (NCI, 2024).

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer screening and diagnosis state that DL is not recommended. Additionally, nipple smear cytology is rarely helpful and not recommended for patients with a nipple discharge but no palpable symptom (NCCN, 2024).

Do Conto et al. (2016) performed microRNA analysis of breast ductal fluid in unilateral breast cancer patients (n = 22), finding 17 differentially expressed miRNAs between tumor and paired normal samples from patients with ductal breast carcinoma. A systems biology analysis of these differentially expressed miRNAs points to possible pathways and cellular processes that have been described as having an important role in breast cancer. Among these, several pathways are hallmarks of cancer molecular signaling including for breast cancer, Wnt, ErbB, MAPK, TGF-β, mTOR, PI3K-Akt, and p53 signaling pathways (data not shown). The most significant top two pathways were Wnt and ErbB ($p < 0.0001$). The authors report that their results suggest miRNA analysis of breast ductal fluid is feasible and potentially very useful for the detection of breast cancer. A study limitation was sample size in various strata, which would be addressed by future larger studies.

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.

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.

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.

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.

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.

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).

Nipple Aspirate Fluid (NAF)

Jiwa et al. (2021) performed a systematic review and meta-analysis of 19 studies with 9308 participants to determine the diagnostic accuracy of nipple aspirate fluid (NAF) cytology in asymptomatic participants as a screening tool for breast cancer or as a predictor of future cancer risk. The results of the meta-analysis showed that the sensitivity of NAF cytology as a diagnostic tool is poor, although, the specificity is high. One of the major limitations with NAF cytology that the authors found in the review was that 38.9% of analyzed samples were deemed inadequate. They also noted that, since not all ducts drain to the nipple surface and that since most breast cancers arise from the epithelial lining of the terminal ducts, the proportion of ducts that can accurately be evaluated is limited which could result in not diagnosing a proportion of breast cancers. The authors concluded that the results of the systematic review and meta-analysis demonstrate that the diagnostic accuracy of NAF cytology is limited because of poor sensitivity and suggest that emerging techniques will need to have a personalized approach. (Publications by Dooley et al. 2001 and Loud et al. 2009, which were previously cited in this policy, are included in this systematic review).

In a pilot study, Shaheed et al. (2017) investigated the protein composition of nipple secretions and the implications for their use as liquid biopsies. Matched pairs of nipple discharge/NAF (n = 15) were characterized for physicochemical properties and SDS-PAGE. Four pairs were selected for semiquantitative proteomic profiling and trypsin-digested peptides analyzed using 2D-LC Orbitrap Fusion MS. The resulting data were subject to bioinformatics analysis and statistical evaluation for functional significance. A total of 1990 unique proteins were identified many of which are established cancer-associated markers. Matched pairs shared the greatest similarity (average Pearson correlation coefficient of 0.94), but significant variations between individuals were observed. The high level of milk proteins in healthy volunteer samples compared to the cancer patients was associated with galactorrhea. The authors concluded that using matched pairs increased confidence in patient-specific protein levels but changes relating to cancer stage require investigation of a larger cohort.

Chan et al. (2016) compared the NAF microbiome between women with a history of breast cancer (BC) and healthy control women (HC) using 16S rRNA gene amplicon sequencing. The NAF microbiome from BC and HC showed significant differences in community composition. Two Operational Taxonomic Units (OTUs) showed differences in relative abundances between NAF collected from BC and HC. In NAF collected from BC, there was relatively higher incidence of the genus Alistipes. By contrast, an unclassified genus from the Sphingomonadaceae family was relatively more abundant in NAF from HC. These findings reflect the ductal source DNA since there were no differences between areolar skin samples collected from BC and HC. Furthermore, the microbes associated with BC share an enzymatic activity, Beta-Glucuronidase, which in the author's opinion, may promote breast cancer. Further investigation of the ductal microbiome and its potential role in breast cancer are warranted.

Shidfar et al. (2016) evaluated endocrine levels in NAF to determine whether a relationship existed for protein biomarkers which have been suggested as a risk for breast cancer. NAF and blood samples were obtained simultaneously from 54 healthy women and from the contralateral unaffected breast of 60 breast cancer patients. The abundance of five proteins, superoxide dismutase (SOD1), C-reactive protein (CRP), chitinase-3-like protein 1 (YKL40), cathepsin D (CatD), and basic fibroblast growth factor (bFGF) in NAF was measured using ELISA. The NAF and serum concentrations of estradiol, estrone, progesterone, androstenedione, testosterone, and dehydroepiandrostrerone (DHEA) were measured using ELISA or RIA. In summary, NAF proteins were more strongly related to local hormone levels than to systematic hormone levels. Some proteins were specifically correlated with different NAF steroids, suggesting that these steroids may contribute to breast cancer risk through different mechanisms. Additional studies are needed to determine the role of NAF evaluation and breast cancer.

Chatterton et al. (2016) evaluated NAF hormone concentrations and breast cancer risk. There were 160 cases and 157 controls in the main study (two premenopausal women did not have menstrual data, and were unavailable for this comparison). Women with current or past endocrine disorders or taking exogenous hormones were excluded. The patterns of hormones in concomitant serum and NAF samples throughout the menstrual cycle were assessed by ANCOVA, adjusted for batch. The authors found no association between NAF estradiol and breast cancer risk based on contralateral unaffected breasts of cancer cases versus controls, but did observe a positive association of NAF DHEA with ER positive cancer. The lack of association of serum DHEA with risk indicates a closer association of NAF than serum DHEA with breast cancer risk in individuals. Although estrogen levels were not significantly associated with cancer risk in the reported data, the high correlation of estrogens and androgens within the tissue provide evidence for greater availability of estrogen in the unaffected, high risk breast. The negative association of NAF progesterone with ER negative cancer after adjustment for menopausal status must be considered preliminary, and may be explained by the small number of luteal phase ER negative cases.

Hornberger et al. (2015) performed a systematic review to evaluate the association of proliferative epithelial disease found in NAF (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. (Publications by Dooley et al. 2001 and Proctor et al. 2005, which were previously cited in this policy, are included in this systematic review).

Sauter et al. (2010) prospectively performed cytologic assessment and image analysis (IA) on matched 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.

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.

Yuan et al. (2022) conducted a retrospective study aimed to compare the diagnostic accuracy of high-frequency ultrasound (HFUS) and fiberoptic ductoscopy (FDS) for pathologic nipple discharge (PND) in a single hospital between July 2013 and May 2021, excluding cases of PND during pregnancy and lactation. All individuals were female, with a mean age of 48.0 ±4.6 years (16–72 years). High-frequency ultrasound and FDS were conducted in 210 patients with PND (248 lesions). The diagnostic accuracy of these two methods was compared using pathological diagnosis as the standard. Among 248 lesions, 16 and 15 of 16 malignant lesions were accurately diagnosed by HFUS and FDS, respectively. Of 232 benign lesions, 183 and 196 cases were accurately diagnosed by HFUS and FDS, respectively. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of HFUS in diagnosis of intraductal lesions were 84.36% (95% CI 79.26–88.39%), 60% (95% CI 23.07–92.89%), 96.03% (95% CI 96.55–99.83%), and 7.31% (95% CI 2.52–19.4%) respectively. The sensitivity, specificity, PPV, and NPV of FDS in diagnosis of intraductal lesions were 86.83% (95% CI 82.00–90.52%), 100% (95% CI 56.55–100%), 100% (95% CI 98.21–100%), and 13.51% (95% CI 5.91–27.98%) respectively. Diagnostic accuracy rates of HFUS and FDS were 83.87% (208/248) and 85.08% (211/248), respectively, exhibiting no statistical differences ($\chi2 = 0.80$, $p > 0.05$). The accuracy of HFUS combined with FDS was 93.14% (231/248), showing statistical differences ($\chi2 = 10.91$, $p > 0.05$). The authors concluded both HFUS and FDS demonstrated high diagnostic values for PND. HFUS has the advantage of being noninvasive for nipple discharge with duct ectasia and exhibited good qualitative and localization diagnostic values. The authors stated HFUS of the breast is a preferred evaluation method for patients with nipple discharge. If the cause of the disease, location of the lesion, and extent of the lesion can be established with HFUS, FDS examination is unnecessary. In this retrospective study, all malignant intraductal lesions were correctly diagnosed by HFUS because significant masses had already formed. Although FDS diagnosed 15 cases, it could only discover the presence of lesions. Indication of lesion extent and location in relation to surrounding tissues by FDS were inferior to those revealed by HFUS. For patients whose lesions cannot be revealed by HFUS, combining HFUS with FDS can significantly increase the diagnostic accuracy. The study is limited by its retrospective observations. Well designed, adequately powered, prospective, controlled clinical trials of FDS are needed to further describe safety and clinical outcomes (or efficacy).

Filipe et al. (2020) conducted a retrospective, single center, observational cohort study with 244 women with pathologic nipple discharge (PND) who underwent ductoscopy. The participants were followed at 2 weeks and at 3 months post-procedure. Depending on the results of the ductoscopy, the participants were scheduled for surgery or follow-up. Twenty-eight women were lost to follow up, leaving 215 of the participants' data to be included in the data analysis. Prior to the ductoscopy, sixty of the 215 women had undergone a biopsy and 103 had undergone cytology of the nipple discharge. The procedure was successful in 151 participants; however, it did not succeed in 64 women (30%) due to perforation of the ductal wall, attempts in spite of contraindications (retracted nipple or previous procedure), too narrow ducts or due to total occlusion from an obstructive lesion. Mild post procedure complications (pain 14.8%, and mastitis 2.3%) were noted in 37 women and only one major complication (a granulomatous mastitis) was noted in the 215 procedures The authors concluded that their study showed ductoscopy has a high specificity and negative predictive value when used to detect malignancy and that it has a therapeutic potential to stop PND itself. Limitations of the study include the small sample size, the retrospective approach to the review, short term follow up of 3 months and that the conclusions were drawn from experience at a single facility.

Zhang et al. (2020) conducted a retrospective analysis and 10-year follow-up on the use of fiberoductoscopy (FDS) for the management of pathological nipple discharge (PND) to investigate the value of FDS for the diagnosis and locating of intraductal lesions in cases with nipple discharge. A retrospective analysis and 10-year follow-up of 3,696 cases that initially presented with PND at a single center in China was performed. A total of 4,456 FDSs performed and the correlations between the FDS findings for distinct types of lesions and the pathological diagnosis were determined. Among the 2,816 cases of elevated lesions, FDS confirmed 1,933 cases of intraductal papilloma, 584 cases of intraductal papillomatosis, and 299 cases of intraductal carcinoma. Among the 880 cases of non-elevated lesions, FDS confirmed 380 cases of duct dilation, 350 cases of duct inflammation, 136 cases of duct dilation and inflammation, and 14 cases of ductal carcinoma in situ (DCIS). All patients followed up 3 months to 12 years. There were 241 DCIS in total, and 8 cases had local recurrence, 2 cases had metastasis. Invasive ductal carcinoma, 41 cases, 3 had recurrence and 3 had metastases, and 1 for death. Invasive lobular carcinoma 23 cases, recurrence 2 cases, metastasis 1 case. The authors concluded FDS has a high positive predictive rate and correlates with the results of the pathological examination, showing the value of FDS for patients with PND. The authors stated the advantage of FDS is that it can observe the lesions, increasing the detection rate of early-stage breast cancer. In addition, the authors stated patients with intraductal inflammation or hyperplasia no longer need to undergo surgery, and surgery can be reduced in patients with benign intraductal lesions. Patients with early-stage malignant tumors may be diagnosed and treated promptly, thus improving the chance of breast-preserving radical mastectomy, helping reduce patient discomfort and preserve breast appearance. The study is limited by its retrospective observations.

A randomized controlled trial (RCT) was completed by Gui et al. (2018) to evaluate the accuracy and effectiveness of intraoperative duct endoscopy in pathological nipple discharge. Patients requiring microdochectomy and/or major duct excision were randomized to duct endoscopy or no duct endoscopy before surgery. Primary endpoints were successful visualization of the pathological lesion in patients randomized to duct endoscopy, and a comparison of the causative pathology between the two groups. The secondary endpoint was to compare the specimen size between groups. A total of 68 breasts were studied in 66 patients; there were 31 breasts in the duct endoscopy group and 37 in the no-endoscopy group. Median age was 49 (range 19–81) years. Follow-up was 5.4 years in the duct endoscopy group and 5.7 years in no-endoscopy group. Duct endoscopy had a sensitivity of 80%, specificity of 71%, positive predictive value of 71% and negative predictive value of 80% in identifying any lesion. There was no difference in causative pathology between the groups. Median volume of the surgical resection specimen did not differ between groups. No serious adverse events were noted. The authors concluded that diagnostic duct endoscopy is useful for identifying causative lesions of nipple discharge. Duct endoscopy did not influence the pathological yield of benign or malignant diagnoses nor surgical resection volumes. Limitations include single-center study, a small sample size, and the numbers of breast cancer events were too small to evaluate test characteristic values for accuracy of duct endoscopy on identifying a malignant cause or predicting the extent of such disease. Further research is needed to determine the clinical relevance of these findings.

Waaijer et al. (2016) conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of ductoscopy in patients with pathological nipple discharge (PND). The search yielded 4642 original citations, of which 20 studies were included in the review. Malignancy rates varied from 0 to 27 per cent. Twelve studies, including 1994 patients, were eligible for meta-analysis. Pooled sensitivity and specificity of DSany were 94 (95 per cent c.i. 88 to 97) per cent and 47 (44 to 49) per cent respectively. Pooled sensitivity and specificity of DSsusp were 50 (36 to 64) and 83 (81 to 86) per cent respectively. Heterogeneity between studies was moderate to large for sensitivity (DSany: I2 = 17.5 per cent; DSsusp: I2 = 37.9 per cent) and very large for specificity (DSany: I2 = 96.8 per cent; DSsusp: I2 = 92.6 per cent). The authors concluded that ductoscopy detects about 94 percent of all underlying malignancies in patients with PND, but does not permit reliable discrimination between malignant and benign findings. (The publication by Dooley 2002, which was previously cited in this policy, is included in this systematic review).

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).

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).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Devices for collecting ductal fluid can be found at the following website using product code KNW: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed March 21, 2024)

The FDA noted in their Consumer Update, “Mammography: What you need to know,” October 26, 2023, that nipple aspirate tests are not substitutes for mammograms. Additional information is available at: https://www.fda.gov/consumers/consumer-updates/mammography-what-you-need-know. (Accessed March 19, 2024)

References

Badve S, Wiley E, Rodriguez N. Assessment of utility of ductal lavage and ductoscopy in breast cancer-a retrospective analysis of mastectomy specimens. Mod Pathol. 2003; 16(3):206-209.

Badve S. Ductal lavage and its histopathologic basis: a cautionary tale. Diagn Cytopathol. 2004; 30(3):166-171.

Brogi E, Robson M, Panageas KS, et al. Ductal lavage in patients undergoing mastectomy for mammary carcinoma: a correlative study. Cancer. 2003; 98(10):2170-2176.

Carruthers CD, Chapleskie LA, Flynn MB, et al. The use of ductal lavage as a screening tool in women at high risk for developing breast carcinoma. American Journal of Surgery 2007 Oct.194 (4):463-6.

Chan AA, Bashir M, Rivas MN, et al. Characterization of the microbiome of nipple aspirate fluid of breast cancer survivors. Sci Rep. 2016 Jun 21;6:28061.

Chatterton RT, Heinz RE, Fought AJ, et al. Nipple aspirate fluid hormone concentrations and breast cancer risk. Horm Cancer. 2016 April; 7(2):127–136.

Cyr AE, Margenthaler JA, Conway J, et al. Correlation of ductal lavage cytology with ductoscopy-directed duct excision histology in women at high risk for developing breast cancer: a prospective, single-institution trial. Ann Surg Oncol. 2011 Oct;18(11):3192-7.

Do Conto LM, Marian C, Willey S, et al. MicroRNA analysis of breast ductal fluid in breast cancer patients. Int J Oncol. 2016 May; 48(5): 2071–2078.

Dooley WC, Ljung BM, Veronesi U, et al. Ductal lavage for detection of cellular atypia in women at high risk for breast cancer. J Natl Cancer Inst. 2001; 93(21):1624-1632.

Dooley WC. Routine operative breast endoscopy for bloody nipple discharge. Ann Surg Oncol. 2002; 9(9):920-923.

Evron E, Dooley WC, Umbricht CB, et al. Detection of breast cancer cells in ductal lavage fluid by methylation-specific PCR. Lancet. 2001; 357(9265):1335-1336.

Filipe MD, Waaijer L, van der Pol C, et al. Interventional ductoscopy as an alternative for major duct excision or microdochectomy in women suffering pathologic nipple discharge: A single-center experience. Clinical Breast Cancer, 2020-06-01: 20(3); e334-e343.

Francescatti DS, Kluskens L, Shah L. Ductal lavage in the high-risk patient. The American Journal of Surgery 2005; 189:340-1.

Gui G, Agusti A, Twelves D, et al. INTEND II randomized clinical trial of intraoperative duct endoscopy in pathological nipple discharge. Br J Surg. 2018 Nov;105(12):1583-1590.

Hartman AR, Daniel BL, Kurian AW, et al. Breast magnetic resonance image screening and ductal lavage in women at high genetic risk for breast carcinoma. Cancer. 2004; 100(3):479-489.

Hornberger J, Chen SC, Li Q, et al. Proliferative epithelial disease identified in nipple aspirate fluid and risk of developing breast cancer: a systematic review. Curr Med Res Opin. 2015 Feb;31(2):253-62.

Jiwa N, Gandhewar R, Chauhan H, et al. Diagnostic accuracy of nipple aspirate fluid cytology in asymptomatic patients: A meta-analysis and systematic review of the literature. Ann Surg Oncol. 2021 Jul;28(7):3751-3760.

Khan SA, Wiley EL, Rodriguez N. Ductal lavage findings in women with known breast cancer undergoing mastectomy. J Natl Cancer Inst. 2004 Oct; 96(20):1510-7.

King BL, Tsai SC, Gryga ME, et al. Detection of chromosomal instability in paired breast surgery and ductal lavage specimens by interphase fluorescence in situ hybridization. Clin Cancer Res. 2003; 9(4):1509-1516.

Loud JT, Thiébaut AC, Abati AD, et al. Ductal lavage in women from BRCA1/2 families: is there a future for ductal lavage in women at increased genetic risk of breast cancer? Cancer Epidemiol Biomarkers Prev. 2009 Apr;18(4):1243-51.

National Cancer Institute (NCI). Breast cancer screening PDQ® Health Professional Version. Updated March 6, 2024. https://www.cancer.gov/types/breast/hp/breast-screening-pdq. Accessed March 21, 2024.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast cancer screening and diagnosis. Version 1.2024. March 29, 2024.

Proctor KA, Rowe LR, Bentz JS. Cytologic features of nipple aspirate fluid using an automated non-invasive collection device: a prospective observational study. BMC Women's Health. 2005 Aug 3;5:10.

Sauter ER, Klein-Szanto A, Macgibbon B, Ehya H. Nipple aspirate fluid and ductoscopy to detect breast cancer. Diagn Cytopathol. 2010 Apr;38(4):244-51.

Shaheed SU, Tait C, Kyriacou K, et al. Nipple aspirate fluid-A liquid biopsy for diagnosing breast health. Proteomics Clin Appl. 2017 Sep;11(9-10).

Shen KW, Wu J, Lu JS, et al. Fiberoptic ductoscopy for breast cancer patients with nipple discharge. Surg Endosc. 2001; 15(11):1340-1345.

Shidfar A, Fatokun T, Ivancic D, et al. Protein biomarkers for breast cancer risk are specifically correlated with local steroid hormones in nipple aspirate fluid. Horm Cancer. 2016 Aug;7(4):252-9.

Waaijer L, Simons JM, Borel Rinkes IH, et al. Systematic review and meta-analysis of the diagnostic accuracy of ductoscopy in patients with pathological nipple discharge. Br J Surg. 2016 May;103(6):632-643.

Yamamoto D, Senzaki H, Nakagawa H, et al. Detection of chromosomal aneusomy by fluorescence in situ hybridization for patients with nipple discharge. Cancer. 2003; 97(3):690-694.

Yamamoto D, Shoji T, Kawanishi H, et al. A utility of ductography and fiberoptic ductoscopy for patients with nipple discharge. Breast Cancer Res Treat. 2001; 70(2):103-108.

Yuan H, Tang X, Mou X, et al. A comparative analysis of diagnostic values of high-frequency ultrasound and fiberoptic ductoscopy for pathologic nipple discharge. BMC Med Imaging. 2022 Sep 2;22(1):155.

Zhang C, Li J, Jiang H, et al. Use of fiberoductoscopy for the management of pathological nipple discharge: ten years follow up of a single center in China. Gland Surg. 2020 Dec;9(6):2035-2043.

Policy History/Revision Information

Date	Summary of Changes
01/01/2025	**Template Update** • Created shared policy version to support application to UnitedHealthcare West plan membership **Supporting Information** • Archived previous policy versions 2024T0335FF and MMG031.S

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies 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.