Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis

Policy Number: CS029.T
Effective Date: August 1, 2025

Instructions for Use

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Related Community Plan Policy

- Genetic Testing for Hereditary Cancer

Commercial Policy

- Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis

Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Idaho	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Idaho Only)
Indiana	None
Kansas	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Kansas Only)
Kentucky	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Kentucky Only)
Nebraska	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Nebraska Only)
New Jersey	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for New Jersey Only)
New Mexico	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for New Mexico Only)
North Carolina	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for North Carolina Only)
Ohio	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Ohio Only)
Pennsylvania	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Pennsylvania Only)
Tennessee	Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Tennessee Only)

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 federal, state, or contractual requirements 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

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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 performed 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)

Results of studies evaluating the use of DL for breast cancer screening, breast cancer diagnosis, or as an alternative tool to guide surgery do not provide sufficient evidence to conclude benefit. Abnormal ductal lavage findings do not reliably predict the development of breast cancer. The intervention has low sensitivity, as well as a high percentage of inconclusive results. There is no evidence that breast cancer mortality improves with DL when added to standard screening and it is not recommended by practice guidelines. Further longitudinal studies would be required to validate its clinical utility and oncologic outcomes.

Do Conto et al. (2016) performed micro ribonucleic acid (microRNA) analysis of breast ductal fluid in women with unilateral breast cancer (n = 22). Samples were obtained by using DL. Seventeen differentially expressed microRNAs between tumor and paired normal samples from participants with ductal breast carcinoma were identified. A systems biology analysis of these differentially expressed microRNAs pointed to possible pathways and cellular processes that have been previously described as having an important role in breast cancer, including the Wnt, ErbB, MAPK, TGF-β, mTOR, PI3K-Akt, and p53 signaling pathways. The most significant top two pathways were Wnt and ErbB ($p < 0.0001$). The authors concluded that the results suggested microRNA analysis of breast ductal fluid is feasible and potentially very useful for the detection of breast cancer. Limitations of the study include the single-center design. The authors also noted there was limited size in various strata, which would need to 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 participants, ≥ 35 years, at high risk for developing breast cancer. The study included 102 participants. All participants underwent DL. Participants found to have atypia underwent ductoscopy-directed duct excision (group 1). Participants 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%) participants had atypical lavage cytology (group 1), and 75 (74%) participants had benign cytology (group 2). Subsequent duct excision in group 1 revealed benign histology in 11 (44%) participants, papillomas in 9 (36%) participants, atypical hyperplasia in 4 participants (16%), and ductal carcinoma in situ (DCIS) in one (4%) participant. At follow-up, three participants developed breast cancer, including one group 1 participant and two group 2 participants. The authors concluded that although 20% of high-risk participants with DL atypia developed atypical hyperplasia or malignancy on subsequent excision, the majority did not. Even in this high-risk population, atypia identified by DL was not associated with a higher risk of developing subsequent breast cancer. Limitations of the study include the single-center design.

In a cohort study, Carruthers et al. (2007) evaluated if DL could predict the occurrence of breast cancer as well as further stratify participants at high risk for developing breast cancer. DL was performed in 116 high-risk participants. High risk was defined as 5-year Gail Risk score ≥ 1.7%; personal history of breast cancer; strong family history of breast cancer despite having a Gail Risk score < 1.7%; or previous suspicious biopsy specimen revealing atypical ductal hyperplasia,

atypical lobular hyperplasia, or lobular carcinoma in situ. If atypia or papillary cells were identified, a standard protocol of evaluation was initiated. Two hundred twenty-three lavages were performed on 116 participants. Twenty-seven lavages in 25 participants yielded atypical or papillary-like cells. The 15 participants who underwent further evaluation for atypia had no evidence of cancerous or precancerous lesions. During this follow-up period (range 1-4 years), two participants developed breast cancer. Both of these participants had a normal previous lavage. No participants with an abnormal lavage developed cancer during follow-up. The authors concluded DL was of limited value in the screening of high-risk participants. Limitations of the study include the single-center design and short follow-up period.

Francescatti et al. (2005) evaluated the results of attempted DL for 120 individuals at high risk for breast cancer in a single-surgeon clinical practice. High risk was based on Gail risk score, a previous breast carcinoma, or nipple discharge. Thirty-two individuals did not undergo DL due to no fluid or unsuccessful cannulation. Of the remaining 88 individuals, 15 (17%) had insufficient epithelial content for diagnosis, 51 (58%) had benign cytologic results, and 22 (25%) had abnormal cells. Of the 25%, 20 individuals had mild atypia, one had marked atypia, and one had malignant changes. The authors concluded DL can be done in a surgical practice and can stratify individual risk. Additionally, formulating a treatment plan based on objective cytologic criteria is important to both the individual and the surgeon. Limitations of the study include the single-center design.

Khan et al. (2004) studied the association between DL cytologic findings and histologic findings in participants with known breast cancer. DL was performed on 44 breasts in 32 participants with known cancer and on eight breasts in seven participants 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 DL 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 DL appeared to have low sensitivity and high specificity for cancer detection. Limitations of the study include the single-center design and small sample size.

In a pilot study, Hartman et al. (2004) evaluated the efficacy of DL and magnetic resonance imaging (MRI) versus mammography and clinical breast exam to identify early malignancy and high-risk lesions in participants at increased genetic risk of breast carcinoma. The study included 41 participants with inherited BRCA1 or BRCA2 mutation or 10% risk of developing breast cancer within 10 years according to the Claus model. Participants underwent biannual clinical breast exam and annual mammography, breast MRI, and DL. DL detected atypia in specimens from seven (23%) participants, including a high-grade atypia in one participant with a normal mammogram and normal MRI results. Six other participants who had atypia on DL had normal mammographic results. The data suggested 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 outcomes. Limitations of the study include the single-center design, small sample size, and short follow-up period.

In a small cross-sectional study, Brogi et al. (2003) evaluated the findings of DL performed in individuals with known mammary carcinoma and correlated the results with the features of carcinoma in situ in mastectomy specimens. The study included 30 individuals undergoing mastectomy for mammary carcinoma (n = 26) or risk-reducing mastectomy (n = 4). DL was performed on all affected breasts before and after mastectomy. Twenty-nine DL samples were satisfactory for cytological examination. While no DL sample was clearly malignant, four (14%) showed marked atypia, 10 (34%) showed mild atypia, and 15 (52%) were benign. Interobserver agreement was reported (average kappa = 0.52). Of the 29 DL samples satisfactory for cytological examination, 27 were obtained from 24 breasts containing carcinoma in situ. (Carcinoma in situ was not identified in two mastectomy specimens.) Specimens from these 24 breasts were evaluated for cytohistologic correlation. Invasive carcinoma was found in 20 samples. Two DL samples from breasts with extensive lobular carcinoma in situ showed mild atypia. The authors concluded DL had low sensitivity for breasts with carcinoma in situ that also contained invasive carcinoma. Thus, DL remains investigational. Close follow-up should be continued for all individuals undergoing DL, including those with benign diagnoses. Limitations of the study include the small sample size.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines on breast cancer screening and diagnosis state that DL is not recommended. Additionally, nipple smear cytology is not routinely recommended for patients with nipple discharge, but no palpable symptom (NCCN, 2025).

Nipple Aspirate Fluid (NAF)

Results of studies evaluating the use of NAF for use in breast cancer screening, breast cancer diagnosis, or screening as alternative tools to guide surgery do not provide sufficient evidence to conclude benefit. Limitations in diagnostic accuracy,

sample adequacy, and impact on clinical outcomes preclude the routine use of NAF. Further clinical validation is needed to determine if NAF collection leads to earlier detection of breast cancer or improved survival.

Jiwa et al. (2021) performed a systematic review and meta-analysis to determine the diagnostic accuracy of NAF cytology in asymptomatic individuals, as a screening tool for breast cancer, or as a predictor of future cancer risk. The systematic review included 19 studies, 9,308 individuals, and cytology results from 10,147 breasts. The results of the meta-analysis revealed that the sensitivity of NAF cytology for cancer detection in asymptomatic women is poor (0.64) (95% confidence interval [CI] 0.62-0.66), but the specificity is extremely high (0.97) (95% CI 0.97-0.98). The study also found that a mean of 38.9% of NAF samples were deemed inadequate for analysis, and determined this to be one of the greatest limitations of nipple fluid cytology. Additionally, the authors 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 be accurately evaluated is limited. This could result in not diagnosing a proportion of breast cancers. The authors concluded that the diagnostic accuracy of NAF cytology is limited because of poor sensitivity. Emerging techniques for surveillance and screening will need to have a personalized approach and surpass the present diagnostic accuracy of cytology, reproducibility of results, user dependency, and laboratory turn-around time. (Loud et al. 2009 and Dooley et al. 2001, 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 of using NAF for liquid biopsies. NAF samples were collected from two groups, participants who were breast cancer-free and participants with breast cancer. From a bank of 112 NAF samples (55 pairs and 57 single samples), matched pairs (n = 15) were characterized for physicochemical properties and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Four pairs were selected for semiquantitative proteomic profiling. Trypsin-digested peptides were analyzed using a mass spectrometer. The resulting data were subject to bioinformatics analysis and statistical evaluation for functional significance. A total of 1,990 unique proteins were identified, many of which were determined to be established cancer-associated markers. Matched pairs shared the greatest similarity (average Pearson correlation coefficient of 0.94). Though, significant variations between participants were observed. The high level of milk proteins in participants who were breast cancer-free compared to participants with breast cancer was associated with galactorrhea. The authors concluded that using matched pairs increased confidence in participant-specific protein levels. However, changes relating to cancer stage require investigation of a larger cohort. Limitations of the study include the single-center design and small sample size.

Using gene amplicon sequencing, Chan et al. (2016) compared the NAF microbiome of participants with a history of breast cancer and healthy control participants. The study included 48 participants, 25 with a history of breast cancer and 23 healthy control participants. The study results revealed that the NAF microbiome showed significant differences in community composition between the two groups. Two operational taxonomic units also showed differences in the relative abundances of NAF. NAF from participants with a history of breast cancer exhibited a relatively higher incidence of the genus *Alistipes.* While NAF from healthy control participants was relatively more abundant in an unclassified genus from the family Sphingomonadaceae. There were no differences in areolar skin samples between the two groups. The microbes associated with breast cancer were noted to share an enzymatic activity, previously implicated as promoting breast cancer, Beta-Glucuronidase. The authors concluded this study demonstrated the presence of microbes in NAF and that the microbiome from participants with a history of breast cancer and healthy control participants were significantly different. The study also identified organisms that are differentially present between the two groups. Additionally, the study provided metabolic insight into possible mechanisms for the association between breast microflora and malignancy. Limitations of the study include the small sample size. The authors also noted that treatment information for all participants with a history of breast cancer was not available. It is possible that another common factor, such as radiation or other therapy, could have contributed to the study findings. Further studies were recommended to explore how bacteria are associated with breast cancer.

Shidfar et al. (2016) evaluated endocrine levels in NAF to determine whether a relationship existed for protein biomarkers previously implicated as a risk for breast cancer. NAF and blood samples were obtained simultaneously from 54 healthy participants and from the contralateral unaffected breast of 60 participants with breast cancer. The abundance of five proteins and basic fibroblast growth factor in NAF was measured using enzyme-linked immunosorbent assay (ELISA). The NAF and serum concentrations of estradiol, estrone, progesterone, androstenedione, testosterone, and dehydroepiandrostrerone (DHEA) were measured using ELISA or radioimmunoassay. NAF proteins were found to be more strongly related to local hormone levels than to systemic hormone levels. Some proteins were specifically correlated with different NAF steroids. This finding suggesting that these steroids may contribute to breast cancer risk through different mechanisms. The authors concluded that NAF proteins, previously implicated as breast cancer risk markers, showed stronger correlations with NAF hormone levels than with serum hormone levels. These results indicated that local breast steroid hormone levels may determine the level of expression of these proteins in the breast. Additionally, these hormone-responsive proteins were found responsive to the abundant androgenic steroids found in NAF. While no case-

control differences in these NAF proteins were observed, the results provided insights into the regulation of these proteins by androgens signaling pathway that may affect breast cancer risk. Limitations of the study include the single-center design and small sample size. The authors also noted that studies examining the abundance of target proteins in breast tissues using immunohistochemistry are necessary to evaluate the overall expression of the target proteins and correlation with NAF hormone.

Chatterton et al. (2016) evaluated NAF hormone concentrations and breast cancer risk. There were 160 cases of cancer and 157 controls in the main study (two premenopausal participants did not have menstrual data and were unavailable for this comparison). Participants 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 analysis of covariance, adjusted for batch. The authors found no association between NAF estradiol and breast cancer risk based on contralateral unaffected breasts in the cases of cancer versus controls. Though, a positive association of NAF DHEA with estrogen receptor (ER)-positive cancer was observed. The lack of association of serum DHEA with risk indicated a closer association of NAF than serum DHEA with breast cancer risk. Although estrogen levels were not significantly associated with cancer risk in the reported data, the high correlation of estrogens and androgens within the tissue provided evidence for greater availability of estrogen in the unaffected, high-risk breast. The authors noted that 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. Limitations of the study include the single-center design.

Sauter et al. (2010) prospectively performed cytologic assessment and image analysis on matched NAF and mammary ductoscopy (MD) specimens to determine accuracy in cancer detection and whether the two collection methods provided complementary information. NAF and MD specimens were collected in the operating theater from 84 breasts of 75 participants prior to planned surgical procedure to remove a lesion that was palpable, suspicious for cancer by imaging criteria, or a breast with pathologic nipple discharge (PND). The study results revealed that cytologic evaluation proved more accurate in participants without PND. This was mainly attributed to the potential for a false positive diagnosis in those with PND. The sensitivity of NAF and MD cytology was low (10% and 14%, respectively). However, both were 100% specific in cancer detection in the non-PND cohort. Combining NAF and MD cytology improved sensitivity (24%) without sacrificing specificity (100%). Combining NAF and MD cytology with aneuploid image analysis improved the sensitivity (45%) while maintaining high specificity (100%). The best predictive model was positive NAF cytology and/or MD cytology combined with image analysis aneuploidy. This model resulted in 55% sensitivity and 100% specificity for breast cancer detection. The authors concluded cytologic evaluation and image analysis of NAF and MD specimens are complementary. However, the presence of atypical cells arising from an intraductal papilloma in ductoscopic specimens is a potential source of false positives in participants with nipple discharge. Limitations of the study include the small sample size and uncontrolled 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. This invasive procedure is technically challenging, can be uncomfortable, and has a steep learning curve, limiting widespread use. Only a small portion of the breast ductal system can be examined, and peripheral lesions are often inaccessible. There is no high-quality evidence that ductoscopy improves breast cancer detection rates, earlier stage of diagnosis, or breast cancer mortality. Further studies are needed to substantiate outcome benefits.

Zhang et al. (2025) conducted a retrospective study to investigate the value of FDS and the feasibility of immediate methylene blue injection to identify discharging ducts and intraductal lesions without overflow during surgery. The study included 164 patients with PND who underwent FDS followed by surgery. Methylene blue was injected into the discharging ducts of patients immediately after FDS, but before selective ductectomy. The overall malignancy detection rate was 14.0%. Both ultrasound and mammography were negative in 48.8% of patients. Pathology revealed breast cancers in 12.5% of participants. Older, menopausal patients, with positive mammography and bloody discharge had a higher propensity for malignancy ($p < 0.05$). Ductoscopic features, including multiple and distal lesions, irregular morphology and hemorrhage of the lesions, and roughness and stiffness of the ductal walls were also associated with malignancy ($p < 0.05$). Surgery 12-24 hours after methylene blue injection resulted in optimal dyeing without overflow during surgery. FDS diagnosis was also compared with pathology. The sensitivity, specificity, positive predictive rate (PPV) and negative predictive rate (NPV) of FDS were 85.6%, 52.7%, 68.8%, 75.0% for single intraductal papilloma (Kappa concordance index = 0.393, $p < 0.001$), 8.3%, 94.7%, 11.1%, 92.9% for intraductal papillomatosis (Kappa concordance index = 0.035, $p > 0.05$) and 65.2%, 94.3%, 65.2%, 94.3% for breast cancer (Kappa concordance index = 0.595, $p < 0.001$), separately. The authors concluded that FDS can detect intraductal lesions and provide a certain predictive value for patients with PND and a negative ultrasound or mammography. Additionally, the immediate injection of methylene blue after FDS in selective ductectomy allows the direct visualization of the discharging mammary ducts and

intraductal lesions, especially for multiple, non-elevated, and peripheral branches, without overflow. This technique may play an important role in detecting early breast cancer. Limitations of the study include the single-center, retrospective design. The authors also noted larger samples and statistical data analysis are required to support the optimal timing of methylene blue injection.

Yuan et al. (2022) conducted a retrospective study aimed to compare the diagnostic accuracy of high-frequency ultrasound (HFUS) and FDS for PND. The study excluded cases of PND during pregnancy and lactation. All participants were female, with a mean age of 48.0 ±4.6 years (16-72 years). HFUS and FDS were conducted in 210 participants 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 ($\chi_2 = 0.80$, $p > 0.05$). The accuracy of HFUS combined with FDS was 93.14% (231/248), showing statistical differences ($\chi^2 = 10.91$, $p > 0.05$). The authors concluded both HFUS and FDS demonstrated high diagnostic values for PND. HFUS has the advantage of being noninvasive for PND with duct ectasia and exhibited good qualitative and localization diagnostic values. The authors stated HFUS of the breast is the preferred evaluation method for PND. 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 participants whose lesions cannot be revealed by HFUS, combining HFUS with FDS can significantly increase the diagnostic accuracy. The study is limited by the single-center design and 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, observational, consecutive, cohort study to evaluate ductoscopy as an alternative to surgery in 244 patients with negative conventional imaging. Depending on the results of the ductoscopy, patients were scheduled for surgery or follow-up. The mean follow-up was 14.5 months (range: 3 months to 44.6 months). Twenty-eight patients were lost to follow up, leaving 215 to be included in the data analysis. Prior to the ductoscopy, 60 of the 215 participants had undergone biopsy and 103 had undergone PND cytology. Histology revealed that 54.2% of patients had papilloma, 40.7% had normal or benign tissue, 1.7% had atypical morphology, and 3.4% had an infection. Cytology revealed that 51.5% of patients had no abnormalities or PND was benign, 29.1% had papilloma, 10.7% showed atypical cells, 6.8% had inflammatory cells, and in 1.9% the analysis was inconclusive, but with no signs of malignancy. Ductoscopy was successful in 151 participants. However, the procedure was unsuccessful in 64 patients (30%) due to perforation of the ductal wall, attempts in spite of contraindications (retracted nipple or previous procedure), narrow ducts, or due to total occlusion from an obstructive lesion. Of note, PND stopped in 18 cases, even after an unsuccessful ductoscopy. This was attributed to the self-limiting nature of PND and the possible effect of DL in some patients, especially in duct ectasia and/or ductitis, or in the absence of a true intraductal lesion. Mild post procedure complications, including pain (14.8%) and mastitis (2.3%) were reported in 37 patients. Only one major complication, a granulomatous mastitis, occurred. Ductoscopy revealed a sensitivity of 71.4% for detecting malignancy (95% CI, 29.0%-96.3%), a specificity of 97.9% (95% CI, 94.0%-99.6%), and an NPV of 98.6% (95% CI, 95.6%-99.6%). The authors concluded ductoscopy can be safely used as an alternative for surgery in the workup for PND. Ductoscopy had a high specificity and NPV when used to detect malignancy. It also had the therapeutic potential to stop PND in some cases. Limitations of the study include the single-center, retrospective design, and short follow-up period.

Zhang et al. (2020) conducted a retrospective study to investigate the value of FDS for the diagnosis and locating of intraductal lesions in cases with PND. The study included 3,696 cases in China that initially presented with PND. A total of 4,456 FDSs were performed. 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 identified with FDS, there were 1,933 cases of intraductal papilloma, 584 cases of intraductal papillomatosis, and 299 cases of intraductal carcinoma. Pathological examination confirmed 2,816 cases of elevated lesions, including 1,942 cases of intraductal papilloma, 578 cases of intraductal papillomatosis, and 296 cases of intraductal carcinoma. A comparison of FDS and pathological diagnoses found that for elevated intraductal lesions, FDS correctly confirmed 97.52%, 90.07%, and 94.31% of the cases of intraductal papilloma, intraductal papillomatosis, and intraductal carcinoma, respectively. The kappa concordance indexes were 0.913, 0.881, and 0.942, respectively (all $p < 0.001$). Among the 880 cases of non-elevated lesions identified with FDS, there were 380 cases of duct dilation, 350 cases of duct inflammation, 136 cases of duct dilation and inflammation,

and 14 cases of DCIS. Pathological examination confirmed 880 cases of non-elevated lesions, including 379 cases of duct dilatation, 351 cases of duct inflammation, 136 cases of duct dilation and inflammation, and 14 cases of DCIS. A comparison of FDS and pathological diagnoses found that for non-elevated intraductal lesions, FDS correctly confirmed 98.95%, 99.43%, 97.79%, and 92.86% of the cases of duct dilation, duct inflammation, duct dilation and inflammation, and DCIS, respectively. The kappa concordance indexes were 0.984, 0.988, 0.974, and 0.927, respectively (all $p < 0.001$). Follow-up was 3 months to 12 years (averaging 53 months). There were 241 cases of DCIS: eight cases had local recurrence, and two cases had metastasis. There were 41 cases of invasive ductal carcinoma: three cases had recurrence, three had metastases, and there was one death. There were 23 cases of invasive lobular carcinoma: two cases of recurrence and one case of metastasis. The authors concluded FDS had a high PPV and correlated well with the results of the pathological examination, showing the value of FDS for patients with PND. FDS was able to observe the lesions and increase the detection rate of early-stage breast cancer. FDS was simple to operate, low in cost, required no appointment, and was appropriate for Chinese conditions. Additionally, patients with intraductal inflammation or hyperplasia no longer need to undergo surgery. Surgery can be reduced in patients with benign intraductal lesions. Patients with early-stage malignant tumors may be diagnosed and treated promptly, improving the chance of breast-preserving radical mastectomy, helping to reduce patient discomfort, and preserve breast appearance. Limitations of the study include the single-center, retrospective design.

A randomized controlled trial completed by Gui et al. (2018) evaluated the accuracy and effectiveness of intraoperative duct endoscopy in PND. Participants 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 participants 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 participants. 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%, PPV of 71%, and NPV 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 PND. Duct endoscopy did not influence the pathological yield of benign or malignant diagnoses nor surgical resection volumes. Limitations of the study include the single-center design and small sample size. Additionally, 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 for individuals with PND. The systematic review included 20 studies. Ten studies were prospective cohort studies and six were retrospective cohort studies. The study design of four studies was not mentioned. Malignancy rates varied from 0% to 27%. Twelve studies of 1,994 individuals were eligible for meta-analysis. Two different definitions were used to classify ductoscopic findings. DS_{any} described any visualized finding at ductoscopy classified as positive and normal ducts in ductoscopy classified as negative. DS_{susp} described any ductoscopically suspicious findings classified as positive. Pooled sensitivity and specificity of DS_{any} were 94% (95% CI 88-97) and 47% (44-49), respectively. Pooled sensitivity and specificity of DS_{susp} were 50% (36-64) and 83% (81-86), respectively. Heterogeneity between studies was moderate to large for sensitivity (DS_{any}: $I2 = 17.5\%$; DS_{susp}: $I2 = 37.9\%$) and very large for specificity (DS_{any}: $I2 = 96.8\%$; DS_{susp}: $I2 = 92.6\%$). The authors concluded that ductoscopy detects about 94% of all underlying malignancies for individuals with PND. However, ductoscopy does not permit reliable discrimination between malignant and benign findings. The authors noted the study was limited due to the heterogeneity in interpretation of the index test (ductoscopy) between the different studies. Additionally, there was poorly reported information on inclusion methods, previous diagnostic investigations, and patient characteristics. This raised concerns regarding applicability, and hampered quality assessment and data extraction. (Dooley, 2002, which was previously cited in this policy, is included in this systematic review.)

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 April 15, 2025)

The FDA noted in a Consumer Update, “Mammography: What You Need to Know,” that nipple aspirate tests are not substitutes for mammograms (October 26, 2023). Additional information is available at: https://www.fda.gov/consumers/consumer-updates/mammography-what-you-need-know. (Accessed April 15, 2025)

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Policy History/Revision Information

Date	Summary of Changes
04/01/2026	**Template Update** • Removed content/language pertaining to the state of Louisiana
11/01/2025	**Application** ***Nebraska*** and ***North Carolina*** • Added language to indicate this Medical Policy does not apply to the states of **Nebraska** and **North Carolina**; refer to the state-specific policy versions
08/01/2025	**Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS029.S

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. 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.

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