Cytological Examination of Breast Fluids for Cancer Screening or Diagnosis (for Louisiana Only)

Policy Number: CS029LA.O~~N~~
Effective Date: ~~August 1, 2020~~**TBD**

➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

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

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 **or the ForeCYTE Breast Health Test**. HALO **and ForeCYTE are** ~~is an~~ automated systems 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)

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer screening and diagnosis state that current evidence does not support the routine use of DL as a screening procedure for breast cancer (NCCN, 2019). 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, 20~~19~~**21**).

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.

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). An updated consensus statement (2019) does not mention ductal lavage.

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 ~~NAF~~ **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.

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 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).

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).

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.

In a systematic review, Shaheed et al. (2018) evaluated the use of NAF as a diagnostic tool in the early detection of breast cancer. They observed that NAF collection has been achieved with varying degrees of success dependent on the method and the practitioner and, in some cases, has deterred researchers from further investigation. A wider study of a panel of biomarkers will, in the authors' opinion, provide increased specificity and would enable development of a clinical assay. They concluded that identifying biomarkers indicative of the earliest stages of malignancy has great potential through NAF, but so far it has not been fully explored.

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 galactorrhoea. 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.

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.

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-hyperplasic ductal epithelial cells, 10% (18/187) had benign hyperplasic 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.

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.

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.

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 percent). The authors concluded that ductoscopy detects about 94 per–cent of all underlying malignancies in patients with PND but does not permit reliable discrimination between malignant and benign findings.

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).

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).

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).

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 **May 2, 2022**~~June 16, 2020~~)**.**

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~~.~~ (Accessed **May 2, 2022**~~June 16, 2020~~)**.**

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. Additionally, the nipple aspirate test may produce false positive or false negative results, as aspirate fluid containing few cells, or no cells at all may miss cancers and give women "dangerously false reassurance". 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. After being "falsely described" as substitutes for mammograms, and resultant FDA initiated regulatory action, the manufacturers have voluntarily removed the HALO® Breast Pap Test system and ForeCYTE Breast Health Test from the market. https://www.fda.gov/consumers/consumer-updates/nipple-aspirate-test-no-substitute-mammogram (Accessed May 3, 2022).**

On October 27, 2017, the FDA confirmed this stance in a consumer update "Nipple Aspirate Test Is No Substitute for Mammogram". This update states that the FDA knows of no valid scientific data demonstrating that this test, alone, is an effective screening tool for detecting breast cancer or other breast disease. Additional information available at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm378257.htm (Accessed May 2, 2022).

The FDA also noted in their Consumer Update, "Mammography: What you need to know" published on January 13, 2021 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 May 2, 2022).

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Policy History/Revision Information

Date	Summary of Changes
TBD	Supporting Information • Updated *Description of Services, Clinical Evidence, FDA, and References* sections to reflect the most current information • Archived previous policy version CS029LA.N

Instructions for Use

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