

Subject:	Epithelial Cell Cytology in Breast Cancer Risk Assessment		
Policy Number:	PO-RE-032v3		
Effective Date:	02/01/2025	Last Approval Date:	12/16/2024

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I. Policy Description

Nipple aspiration and/or ductal lavage are non-invasive techniques to obtain epithelial cells for cytological examination to aid in the evaluation of nipple discharge for breast cancer risk (Golshan, 2024). Fine needle aspiration (FNA) is another approach that can be used in the initial diagnosis of a suspicious breast mass, although core biopsy is superior in sensitivity, specificity, and correct histological grading (Moy et al., 2017).

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual’s illness.

1. Cytologic analysis of epithelial cells to assess breast cancer risk and manage patients at high risk of breast cancer **DOES NOT MEET COVERAGE CRITERIA.**

Scientific Background

Breast cancer is the most frequently diagnosed cancer and is a leading cause of cancer death in the United States. Nipple discharge is a common breast complaint. Most nipple discharge is of benign origin; however, it is necessary to differentiate patients with benign nipple discharge from those who have an underlying pathology. In approximately five to 20 percent of pathologic nipple discharge cases, cancer is identified (Golshan, 2024).

Breast cancer originates in breast epithelium and is associated with progressive molecular and morphologic changes. Individuals with atypical breast ductal epithelial cells have an increased relative risk of breast cancer. Cytological evaluation of epithelial cells in nipple discharge has been used as a diagnostic aid. Due to the scant cellularity of specimens obtained by expression or aspiration of nipple discharge, ductal lavage was developed to enhance the ease and efficiency of collecting breast epithelial cells for cytologic analysis. The analysis of breast-specific liquid biopsies, such as nipple aspirate fluid, has potential to be used as a biomarker profiling technique for monitoring breast health (Shaheed et al., 2018). Researchers report that the measurement of nipple aspirate fluid, including miRNA, pathological nipple discharge, and breast ductal fluids, may help to improve early detection and management of breast cancer (Moelans et al., 2019).

Fine needle aspiration (FNA) is a biopsy option for a suspicious palpable breast mass. FNA is a rapid diagnosis technique, but it is not as accurate as core needle biopsy. FNA cannot differentiate in situ and invasive cancer and has higher rates of negative results and insufficient samples than core needle biopsy. The success of FNA results also varies with the operator and cytopathologist (Joe & Esserman, 2024).

Analytic Validity

In a retrospective study of 618 patients with nipple discharge over a 14-year period, the sensitivity and specificity of cytology were 17 and 66 percent, respectively; the authors concluded that “nipple discharge cytology has little complementary diagnostic value” (Kooistra et al., 2009).

Clinical Utility and Validity

Hornberger et al. (2015) performed a meta-analysis on the use of nipple aspirate fluid (NAF) in identifying breast cancer based on proliferative epithelial disease (PED). The authors reviewed 16 articles, 20808 unique aspirations, and 17378 subjects. Among cancer-free patients, 51.5% aspirations contained fluid, of which 27.7% showed a PED on cytology. Of the two prospective studies of 7850 women, patients with abnormal cytology showed a 2.1-fold higher risk of developing breast cancer compared to those without fluid (Hornberger et al., 2015).

Chatterton et al. (2016) measured sex steroid levels in nipple aspirate fluid; hormones were measured in samples from 160 breast cancer cases and 157 controls. Results showed a significantly higher concentration of dehydroepiandrosterone (DHEA) in the nipple aspirate fluid of patients with breast cancer compared to controls; further, DHEA levels were highly correlated with estradiol levels, indicating “a potentially important role of this steroid in breast cancer risk” (Chatterton et al., 2016).

Kamalı and Kamalı (2022) studied the usefulness of testing methods in surgical decision making. The study included 141 patients with pathological nipple discharge who were planning to undergo surgery. The diagnostic efficiency of ductal lavage cytology was compared to that of ultrasonography, mammography, magnetic resonance imaging, and ductography. The sensitivity of ductal lavage cytology was 70.5% and the specificity was 94.1%. The authors conclude that “negative cytology does

not exclude the possibility of malignancy, and positive results do not help in the differential diagnosis” (Kamali & Kamali, 2022).

Guidelines and Recommendations

American Society of Breast Surgeons (ASBS)

The Official Statement by the American Society of Breast Surgeons (ASBS, 2019) regarding Screening Mammography does not mention ductal lavage at all in their statement.

In 2016, the ASBS published a consensus guideline on the concordance assessment of image-guided breast biopsies and the management of borderline or high-risk lesions. These guideline state that “The decision to excise a papillary lesion without atypia needs to be individualized based on risk, including such criteria as size; symptomatology, including palpability and presence of nipple discharge; and breast cancer risk factors” (ASBS, 2016). This is the only mention of nipple discharge in the document.

National Comprehensive Cancer Network (NCCN)

National Comprehensive Cancer Network Clinical Practice Guidelines in breast cancer screening and diagnosis (NCCN, 2024) state that “thermography and ductal lavage are not recommended by the NCCN Panel for breast cancer screening or diagnosis.” The NCCN also notes that “the FDA has issued a safety alert stating that ductal lavage should not be a replacement for mammograms” (NCCN, 2024).

Food and Drug Administration (FDA)

In 2017 the FDA issued a safety warning stating that “...the FDA is unaware of any valid scientific data to show that a nipple aspirate test, when used on its own, is an effective screening tool for any medical condition, including the detection of breast cancer or other breast disease” (*Breast Cancer Sourcebook*, 2019). This was further affirmed with a safety warning published in 2023: “thermograms and nipple aspirate tests are not substitutes for mammograms” (FDA, 2023).

American College of Radiology (ACR)

The 2022 ACR appropriateness criteria for the evaluation of nipple discharge do not mention cytology. The ACR states that “image-guided FNA and core biopsy are not required for the evaluation of physiologic nipple discharge” but “image-guided FNA and core biopsy are not required for the evaluation of physiologic nipple discharge”. The ACR also notes “although some institutions demonstrate good results using FNA, larger series have shown that core biopsy is superior to FNA in terms of sensitivity, specificity, and correct histologic grading of a lesion” (Sanford et al., 2022).

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

II. Applicable Codes

Code	Description	Comment
88108	Cytopathology, concentration technique, smears and interpretation (eg, Saccomanno technique)	
88112	Cytopathology, selective cellular enhancement technique with interpretation (eg, liquid based slide preparation method), except cervical or vaginal	
88172	Cytopathology, evaluation of fine needle aspirate; immediate cytohistologic study to determine adequacy for diagnosis, first evaluation episode, each site	
88173	Cytopathology, evaluation of fine needle aspirate; interpretation and report	
88177	Cytopathology, evaluation of fine needle aspirate; immediate cytohistologic study to determine adequacy for diagnosis, each separate additional evaluation episode, same site (List separately in addition to code for primary procedure)	

III. Definitions

Term	Meaning
N/A	N/A

IV. Related Policies

Policy Number	Policy Description
PO-RE-041	Serum Tumor Markers for Malignancies
PO-RE-032	Use of Common Genetic Variants (Single Nucleotide Polymorphisms) To Predict Risk of Non-Familial Breast Cancer

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Procedure codes appearing in Reimbursement Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

V. Reference Materials

ASBS. (2016). <i>Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions</i> . https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Concordance-Assessment-of-Image-Guided-Breast-Biopsies.pdf
ASBS. (2019). <i>Screening Mammography</i> . https://www.breastsurgeons.org/docs/statements/Position-Statement-on-Screening-Mammography.pdf
<i>Breast Cancer Sourcebook</i> . (2019). (Sixth ed.). Omnigraphics Inc.
Chatterton, R. T., Heinz, R. E., Fought, A. J., Ivancic, D., Shappell, C., Allu, S., Gapstur, S., Scholtens, D. M., Gann, P. H., & Khan, S. A. (2016). Nipple Aspirate Fluid Hormone Concentrations and Breast Cancer Risk. <i>Horm Cancer</i> , 7(2), 127-136. https://doi.org/10.1007/s12672-016-0252-7
FDA. (2023). <i>Mammography: What You Need to Know</i> . https://www.fda.gov/consumers/consumer-updates/mammography-what-you-need-know
Golshan, M. (2024, 02/12/2024). <i>Nipple discharge</i> . https://www.uptodate.com/contents/nipple-discharge
Hornberger, J., Chen, S. C., Li, Q., Kakad, P., & Quay, S. C. (2015). Proliferative epithelial disease identified in nipple aspirate fluid and risk of developing breast cancer: a systematic review. <i>Curr Med Res Opin</i> , 31(2), 253-262. https://doi.org/10.1185/03007995.2014.988209
Joe, B., & Esserman, L. (2024, May 3). <i>Breast biopsy</i> . https://www.uptodate.com/contents/breast-biopsy
Kamali, G. H., & Kamali, S. (2022). The Role of Ductal Lavage Cytology in the Diagnosis of Breast Cancer. <i>Archives of Iranian Medicine (AIM)</i> , 25(11).
Kooistra, B. W., Wauters, C., van de Ven, S., & Strobbe, L. (2009). The diagnostic value of nipple discharge cytology in 618 consecutive patients. <i>Eur J Surg Oncol</i> , 35(6), 573-577. https://doi.org/10.1016/j.ejso.2008.09.009
Moelans, C. B., Patuleia, S. I. S., van Gils, C. H., van der Wall, E., & van Diest, P. J. (2019). Application of Nipple Aspirate Fluid miRNA Profiles for Early Breast Cancer Detection and Management. <i>Int J Mol Sci</i> , 20(22). https://doi.org/10.3390/ijms20225814
Moy, L., Heller, S. L., Bailey, L., D'Orsi, C., DiFlorio, R. M., Green, E. D., Holbrook, A. I., Lee, S. J., Lourenco, A. P., Mainiero, M. B., Sepulveda, K. A., Slanetz, P. J., Trikha, S., Yepes, M. M., & Newell,

M. S. (2017). ACR Appropriateness Criteria(®) Palpable Breast Masses. *J Am Coll Radiol*, 14(5s), S203-s224. <https://doi.org/10.1016/j.jacr.2017.02.033>

NCCN. (2024, June 19). *NCCN Clinical Practice Guidelines in Oncology; Breast Cancer Screening and Diagnosis V2.2024*. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf

Sanford, M. F., Slanetz, P. J., Lewin, A. A., Baskies, A. M., Bozzuto, L., Branton, S. A., Hayward, J. H., Le-Petross, H. T., Newell, M. S., Scheel, J. R., Sharpe, R. E., Jr., Ulaner, G. A., Weinstein, S. P., & Moy, L. (2022). ACR Appropriateness Criteria® Evaluation of Nipple Discharge: 2022 Update. *J Am Coll Radiol*, 19(11s), S304-s318. <https://doi.org/10.1016/j.jacr.2022.09.020>

Shaheed, S. U., Tait, C., Kyriacou, K., Linforth, R., Salhab, M., & Sutton, C. (2018). Evaluation of nipple aspirate fluid as a diagnostic tool for early detection of breast cancer. *Clin Proteomics*, 15, 3. <https://doi.org/10.1186/s12014-017-9179-4>

VI. Revision History

Revision Date	Summary of Changes
09/04/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
09/06/2023	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria: CC1 updated to reflect that all cytological analysis for breast cancer diagnosis DNMCC, as biopsy should be used to diagnose. CC now reads: "1) Cytologic analysis of epithelial cells to assess breast cancer risk and manage patients at high risk of breast cancer DOES NOT MEET COVERAGE CRITERIA." Added CPT code 88172, 88173, 88177

Disclaimer

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This policy is intended to serve as a resource for providers to use in understanding reimbursement guidelines for professional and institutional claims. This information is accurate and current as of the date of publication. It provides information from industry sources about proper coding practice. However, this document does not represent or guarantee that Healthfirst will cover and/or pay for services outlined. Reimbursement decisions are based on the terms of the applicable evidence of coverage, state and federal requirements or mandates, and the provider's participation agreement. This includes the determination of any amounts that Healthfirst or the member owes the provider.