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Epithelial Cell Cytology in Breast Cancer Risk Assessment

Policy Number: AHS – G2059 – Epithelial Cell Cytology in Breast Cancer Risk Assessment	Prior Policy Name and Number, as applicable:
Initial Presentation Date: 09/18/2015 Original Presbyterian Effective Date: 07/01/2024 Revision Date: 09/04/2024 Revision Effective Date: 01/01/2025	

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).

II. Related Policies

Policy Number	Policy Title
AHS-G2124	Serum Tumor Markers for Malignancies
AHS-M2126	Use Of Common Genetic Variants (Single Nucleotide Polymorphisms) To Predict Risk of Non-Familial Breast Cancer

III. 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**.

IV. Table of Terminology

Term	Definition
ACR	American College of Radiology
ASBS	American Society of Breast Surgeons
CMS	Centers for Medicare and Medicaid Services
DHEA	Dehydroepiandrosterone
FDA	Food and Drug Administration
FNA	Fine needle aspiration
LDT	Laboratory developed Tests
NAF	Nipple aspirate fluid
NCCN	National Comprehensive Cancer Network
PED	Proliferative epithelial disease

V. 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" (Kamalı & Kamalı, 2022).

VI. 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).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, please visit the New Mexico Medicaid website: https://www.hsd.state.nm.us/providers/rules-nm-administrative-code/.

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.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
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)

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

IX. Evidence-based Scientific References

ASBS. (2016). *Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions*. https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Concordance-Assessment-of-Image-Guided-Breast-Biopsies.pdf

ASBS. (2019). *Screening Mammography*. https://www.breastsurgeons.org/docs/statements/Position-Statement-on-Screening-Mammography.pdf

Breast Cancer Sourcebook. (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. *Horm Cancer*, *7*(2), 127-136. https://doi.org/10.1007/s12672-016-0252-7

FDA. (2023). *Mammography: What You Need to Know*. https://www.fda.gov/consumers/consumer-updates/mammography-what-you-need-know

Golshan, M. (2024, 02/12/2024). *Nipple discharge*. 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. *Curr Med Res Opin*, *31*(2), 253-262. https://doi.org/10.1185/03007995.2014.988209

Joe, B., & Esserman, L. (2024, May 3). *Breast biopsy*. https://www.uptodate.com/contents/breast-biopsy

Kamalı, G. H., & Kamalı, S. (2022). The Role of Ductal Lavage Cytology in the Diagnosis of Breast Cancer. *Archives of Iranian Medicine (AIM)*, *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. *Eur J Surg Oncol*, *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. *Int J Mol Sci*, *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

X. Revision History

Revision Date	Summary of Changes
09/04/2024 Revision Effective Date: 01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
Original Presbyterian Effective Date: 07/01/2024	Policy was adopted by Presbyterian Health Plan for all lines of business.