Molina Clinical Policy
Epithelial Cell Cytology in Breast Cancer Risk Assessment
Policy Number: G2059

POLICY SECTIONS

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, 2020).

RELATED POLICIES

Policy No.	Policy Title
G2124	Serum Tumor Markers for Malignancies
M2126	Use of Common Genetic Variants (Single Nucleotide Polymorphisms) to Predict Risk of Non-Familial Breast Cancer

INDICATIONS and/or LIMITATIONS OF COVERAGE

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

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 a patient's illness.

1. Cytologic analysis of epithelial cells from nipple aspirations as a technique to assess breast cancer risk and manage patients at high risk of breast cancer DOES NOT MEET COVERAGE CRITERIA. Techniques of collecting nipple aspiration fluid, include, but are not limited to, ductal lavage and suction.

SCIENTIFIC BACKGROUND

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women in the United States. Approximately 1 in 8 women will develop breast cancer in their lifetime and breast cancer alone makes up 30% of female cancers (Siegel, Miller, Fuchs, & Jemal, 2021; Siegel, Miller, & Jemal, 2019). 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 5-15 percent of pathologic nipple discharge cases, cancer is identified (Golshan, 2018, 2020).

Breast cancer originates in breast epithelium and is associated with progressive molecular and morphologic changes. Women 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, Patuleia, van Gils, van der Wall, & van Diest, 2019).

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, Wauters, van de Ven, & Strobbe, 2009).

Clinical Utility and Validity

Hornberger, Chen, Li, Kakad, and Quay (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).

GUIDELINES AND RECOMMENDATIONS

American Society of Breast Surgeons (ASBS) (ASBS, 2016, 2019)

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) (NCCN, 2021)

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, breast cancer screening and diagnosis guidelines (NCCN, 2019, 2021) state that "current evidence does not support the routine use of ductal lavage as a screening procedure," and that "ductal lavage is not recommended by the NCCN for breast cancer screening or diagnosis."

Food and Drug Administration (FDA) (FDA, 2017)

In 2017 the FDA issued a safety warning (FDA, 2017) 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."

American College of Radiology (ACR) (Lee et al., 2017)

In 2017, the ACR published appropriateness criteria for the evaluation of nipple discharge. These criteria state that "Cytologic examination of nipple discharge has not proven to be effective in differentiating benign from malignant lesions" (Lee et al., 2017).

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. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A search for "ductal lavage" and "nipple aspirate" on the FDA website is limited to a consumer update titled "Nipple

Aspirate Test is No Substitute for Mammogram." Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

APPLICABLE CPT / HCPCS PROCEDURE CODES

CPT	Code Description
88108	Cytopathology, concentration technique, smears and interpretation (e.g., Saccomanno technique)
88112	Cytopathology, selective cellular enhancement technique with interpretation (e.g., liquid based slide preparation method), except cervical or vaginal

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

Approval History

Type	Date	Action
Effective Date	7/1/2022	New Policy
Revision Date		

EVIDENCE-BASED SCIENTIFIC REFERENCES

ASBS. (2016). Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions. Retrieved from ASBS.

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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). doi:10.3390/ijms20225814

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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. doi:10.1186/s12014-017-9179-4

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2021). Cancer Statistics, 2021. CA Cancer J Clin, 71(1), 7-33. doi:10.3322/caac.21654

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. CA Cancer J Clin, 69(1), 7-34. doi:10.3322/caac.21551

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*