of Tennessee

Policy

Reimbursement Policy

Epithelial Cell Cytology in Breast Cancer Risk Assessment

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, 2020).

II. 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 Section VII 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 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.

III. 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
LDT	Laboratory developed Tests
NAF	Nipple aspirate fluid
NCCN	National Comprehensive Cancer Network
PED	Proliferative epithelial disease

IV. 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 et al., 2021; Siegel et al., 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, 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 et al., 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 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).

V. 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 (NCCN) Clinical Practice Guidelines in Oncology, breast cancer screening and diagnosis guidelines (NCCN, 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)

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)

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).

VI. 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, visit the applicable state Medicaid website.

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.

VII. 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

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