Epithelial Cell Cytology in Breast Cancer Risk Assessment and High-Risk Patient Management: Ductal Lavage and Fiberoptic Ductoscopy

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Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers ductal lavage or fiberoptic ductoscopy of the mammary ducts to be investigational.*

Background/Overview

Ductal Lavage
Ductal lavage (DL) of the mammary ducts describes a technique for collecting epithelial cells from individual mammary ducts for subsequent cytologic analysis. Ductal lavage has been investigated as a diagnostic and risk assessment tool in patients at high risk of breast cancer but without clinical or mammographic findings. For example, the finding of atypical hyperplasia may be associated with an increased risk of breast cancer. Malignant cells may also be identified in rare cases.

Ductal lavage involves several steps. First, fluid-yielding mammary ducts are identified using nipple aspiration. Next a micro catheter is inserted into the natural nipple opening of the individual mammary ducts. Saline is then infused and ductal fluid withdrawn. The fluid is then analyzed microscopically for cytologic abnormalities.

Fiberoptic Ductoscopy
Fiberoptic ductoscopy (FDS), the direct visualization of the breast duct lining using a very thin fiberoptic scope, has been employed to identify the source of atypical cells found on DL, as well as for evaluation of abnormal nipple discharge in conjunction with aspiration cytology, biopsy or surgical excision. Fiberoptic ductoscopy systems have micro endoscopes with an outer air channel on the fiberscope which permits instillation and re-collection of saline to retrieve cells from the breast ductal system.
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FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The FirstCyte Breast Test (Cytyc) is a device used for ductal lavage that has been cleared for marketing by the U.S. FDA.

A suction collection system, the HALO NAF collection system (Neomatrix) has also received FDA clearance as a technique to collect ductal epithelial cells. In this system, small breast cups are placed on the woman's breast and adjusted to fit. The system is then engaged and automatically warms the breast and applies light suction to bring nipple aspirate fluid to the surface. Similar to ductal lavage, the fluid is then analyzed microscopically for cytologic abnormalities.

Centers for Medicare & Medicaid Services (CMS)
CMS have no national coverage policy on the use of DL or FDS.

Rationale/Source
Validation of a diagnostic technology requires data regarding its technical performance, diagnostic performance (i.e., sensitivity, specificity and positive and negative predictive value) compared to a gold standard and data regarding how the diagnostic information will be used in the management of the patient and whether beneficial health outcomes result.

1. Technical Performance
   Nipple aspiration alone can be used to collect epithelial cells for cytologic analysis; DL is designed to harvest an increased number of cells for analysis. In a multicenter clinical trial of 507 women who underwent nipple aspiration followed by DL, nipple aspiration produced an adequate sample in 27% of women while DL produced an adequate sample in 78% of women. A median of 13,500 cells per duct was collected by DL compared to a median of 120 epithelial cells per breast collected by nipple aspiration.

2. Diagnostic Performance
   Dooley and colleagues reported on a multicenter clinical trial of 507 women who underwent DL. A total of 57% of women had a prior history of breast cancer and 39% had a 5-year Gail risk for breast cancer of 1.7% or more. ([It should be noted the patient selection criteria for this study are similar to those used in the large randomized trial of tamoxifen as a breast cancer chemoprevention therapy. Using a Gail index of =1.7, all women over the age of 60 years would be considered at high risk.) For DL, 24% of women had abnormal cells that were mildly (17%) or markedly atypical (6%) or malignant (<1%). Ductal lavage detected abnormal cells 3.2 times more often than nipple aspiration. However, whether or not
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this increased sensitivity is accompanied by decreased specificity and thus a decreased overall risk of cancer using DL is unknown.

It is difficult to identify a gold standard test to validate the diagnostic performance of DL. For example, since DL is performed in patients without mammographic abnormalities, there is no obvious target for diagnostic confirmation with a tissue sample. In cases in which cells suspicious for malignancy have been reported, some patients may have undergone either surgical resection of the involved duct or a broader surgical resection. However, there have been no studies published regarding the diagnostic performance in this setting. No studies have been reported on the results of DL in patients with mammographic abnormalities who are scheduled to undergo biopsy.

3. How Diagnostic Information will be used to Benefit the Management of Patients.

Results of DL cytology can be broadly subdivided into those with an insufficient sample, those with malignant cells, those with hyperplasia, including atypical hyperplasia or those with benign cells. Currently, no published studies focus on how the results of DL would be used in any of these categories.

The following discussion suggests some potential applications:

- **Insufficient Sample**
  There would be presumably no impact on the management of the patient when an insufficient sample was produced. Based on the preliminary results published, this would occur in about 22% of the patients.

- **Hyperplasia without Atypia**
  Hyperplasia is relatively common among high-risk women (31%–42%) and, to a somewhat lesser extent, among various populations of women not specifically selected to be at high risk (12%–37%). Although hyperplasia without atypia is associated with increased cancer risk in some studies, its relatively high prevalence in both high- and low-risk populations decreases its utility as a risk marker.

- **Hyperplasia with Atypia**
  The association between histologic atypical hyperplasia and an increased risk of breast cancer has been most frequently studied in the setting of patients with mammographic abnormalities. The natural history of atypical hyperplasia may be different in women without mammographic abnormalities, potentially representing a spontaneously resolving cytologic abnormality. Two studies offer related data. Wrensch and colleagues reported on a prospective study of 2,701 white women at average risk of breast cancer who underwent nipple aspiration and then were followed up for an average of 12 years. The relative risk of cancer in women with cytologic atypia was 4.9 compared to non-yielders of nipple fluid or 2.8 compared to women with normal cytology. In women
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with cytologic atypia and a family history, the relative risk was 18.1 compared to non-yielders of fluid without family history. After 21 years of follow-up, the relative risks were lower, suggesting that risk decreased over time.

More recently, Fabian and colleagues reported on a group of 480 women without mammographic abnormalities who were considered at high risk of breast cancer and who underwent 2 random periareolar fine-needle aspirations at 6-month intervals. Risk factors included a family history of breast cancer, a prior history of a precancerous lesion (i.e., atypical hyperplasia or carcinoma in situ) or a prior history of breast cancer. In 21% of patients, results of the fine-needle aspiration revealed atypical hyperplasia. After follow-up of 45 months, the relative risk of cancer in women with cytologic atypia was 5.0 compared to women without atypical results. The two strongest predictors of cancer development were risk assessment based on the Gail model and the presence of atypical hyperplasia on fine-needle aspiration.

The relative risk results for nipple aspiration or fine needle aspiration cytology have been equated with a relative risk of 5.3 in women with histologic atypia compared to women without proliferative disease on biopsy of a lesion, reported in a retrospective study. However, due to the different follow-up intervals, different baseline risk populations studied and different referent populations, these results cannot be quantitatively compared. Thus, it is not known whether cancer risk associated with cytologic atypia is of the same magnitude as cancer risk associated with histologic atypia on biopsy of a lesion.

Cytologic hyperplasia with atypia alone in low- to moderate-risk populations had poor sensitivity (4.2%) and low positive predictive value (13.8%). Thus, this procedure has poor utility for general population screening to identify those at increased risk.

For women already at high risk of breast cancer by Gail model analysis, the following treatment options are available: increased surveillance (i.e., an increased frequency of breast self-examination or clinical exam or an increased frequency of mammography), a prophylactic mastectomy or chemoprevention with tamoxifen. Increased surveillance is recommended for all, and prophylactic mastectomy is considered only by relatively few women who have other strong risk factors (i.e., BRCA1 or BRCA2 mutation). The net benefits of tamoxifen, taking into account possible adverse events, are greatest for women of younger age with greater Gail risk, yet patients are reluctant to select chemoprevention. For high-risk women with no history of histologic atypical hyperplasia of a biopsied lesion, it has been proposed that findings of cytologic atypia on DL may revise the risk estimate upward, increase the likelihood of choosing chemoprevention and decrease cancer incidence. However, no studies have specifically explored decision making or outcomes regarding these treatment alternatives in mammographically normal women with atypical hyperplasia by cytologic analysis.
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Indirect evidence exists in the form of the National Surgical Adjuvant Breast and Bowel Project P-1 trial, which randomized 13,388 high-risk patients (i.e., Gail risk greater than 1.7%) to receive either chemoprevention with tamoxifen or placebo. The principal outcomes were the subsequent incidence of in situ or invasive cancer over the next five years. This trial reported that overall, tamoxifen was associated with a 49% reduction in incidence of invasive breast cancer. When a history of atypical hyperplasia was present, tamoxifen was associated with an 86% reduction in the incidence of subsequent breast cancer. However, in this trial, atypical hyperplasia was presumably diagnosed in patients with mammographic abnormalities. Whether or not women with cytologic atypia by DL benefit to the same extent is unknown. It is possible that knowledge of added risk as a result of cytologic analysis may influence choosing tamoxifen therapy by those at greatest risk and most likely to benefit. It is also possible that knowledge of a negative cytologic analysis result would influence patients to avoid tamoxifen when they might otherwise benefit. No evidence exists to evaluate potential net benefit or harm in decision making or, ultimately, in patient outcomes.

The role of atypical hyperplasia as part of the decision making for prophylactic mastectomy is based on the hypothesis that atypia precedes the development of cancer. However, any patient with a BRCA1 or BRCA2 mutation may be considered a candidate for prophylactic mastectomy. The emergence of atypia may suggest a more immediate need for prophylactic mastectomy and thus may affect the timing of the surgery. However, this strategy has not been formally tested.

4. Malignant cells
   The results of the multi-institutional trial, currently summarized on the manufacturer’s web site but not published in the peer-reviewed literature, report that malignant cells were identified in only 2 of 383 (0.5%). Therefore, it is unlikely that DL will be routinely used to diagnose malignancy. In the rare event of malignant cells, imaging, ductogram or ductoscopy are possible follow-up procedures, but a negative imaging result or ductogram does not exclude significant pathology and the overall sensitivity of ductography is unknown. The value of terminal duct excision is also unknown. Prophylactic mastectomy on the basis of a malignant lavage is not encouraged.

5. Benign cells
   Without an understanding of the sensitivity of DL, it is not possible to interpret a finding of benign cells, as this could represent a false-negative result.

The above conclusions are supported by a 2002 TEC Assessment that offered the following observations and conclusions:

- No studies directly compare routine surveillance versus routine surveillance plus epithelial cell cytology analysis in the follow-up of high-risk women for the detection of long-term outcomes. No
studies compared the outcomes of patients whose management was determined by the results of routine surveillance vs. routine surveillance plus epithelial cell cytology analysis. No studies have used DL, nipple aspiration, or random perioareolar fine-needle aspiration to influence patient management in the population of interest.

- There is some indirect evidence from the NSABP Breast Cancer Prevention Trial (P-1), which enrolled women at high risk and randomly assigned them to placebo or tamoxifen for five years. Women with a history of atypical hyperplasia who received tamoxifen had a risk ratio for subsequent breast cancer of 0.14 compared to those who received placebo over a median follow-up time of 54.6 months. Thus, high-risk women with a history of atypical hyperplasia benefited to a greater degree than the study population as a whole. It was noted, however, that the number of women in this subgroup was small and that this was only 1 of 5 subgroups examined. Women without a history of atypical hyperplasia who received tamoxifen also benefited with a risk ratio of 0.56. Thus, the lack of a history of atypical hyperplasia does not preclude improved outcomes with tamoxifen treatment.

- The results of the P-1 trial cannot address whether or not participants, particularly those with a negative history, had cytologic evidence of hyperplasia or atypical hyperplasia at the time of enrollment. It is possible that some of the women who were negative for a history of atypical hyperplasia would have been positive at study entry by random cytology and may have accounted for at least part of the benefit in this subgroup. Nevertheless, it cannot be ruled out that women with no detectable atypical hyperplasia may still benefit from tamoxifen treatment.

- Considering the above, the Assessment concluded that the evidence was insufficient to support the use of cytologic hyperplasia with atypia as a clinically useful intermediate biomarker outside of clinical trials at this time. The existing evidence is of high clinical interest, but further follow-up studies of risk and trials of intervention in women with this marker are needed.

A review article and a commentary were identified, that discussed potential applications of DL. Both of these articles cite the same studies as discussed in the TEC Assessment, however, to date there are no controlled trials that formally investigate the proposed applications of DL.

In 2003, the American Society of Breast Surgeons issued an “official statement” regarding DL, which reads in part:

“Ductal lavage is a minimally invasive method of collecting breast epithelial cells for cytological examination. Because most breast cancer originates from the same layer of epithelial cells that line the milk ducts, it appears that atypical changes in breast epithelial cells will confer similar relative risk increases regardless of the method of collection. There is no reason to believe that the long-term risk
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associated with atypia diagnosed by DL will be different from other methods of determining cytologic atypia.

The American Society of Breast Surgeons supports the use of DL as a cell-based risk assessment tool in high-risk and borderline-risk women to assist them in making more informed decisions regarding risk reduction and management options. This information can help to guide consideration of a variety of management options, ranging from risk-reduction therapy (tamoxifen or enrollment in the STAR trial) to closer surveillance or even prophylactic mastectomy. Long-term studies are necessary to better define the risk-assessment contribution of cytologic atypia detected via these and other methods. The American Society of Breast Surgeons encourages participation in such trials.”

Evidence from the available studies suggests that FDS is feasible, it yields useful clinical information on intraductal disease and it allows for the performance and cytological examination of DL washings for detection of cellular atypia. However, there is minimal evidence on how this technique would be used in the management of the patient, i.e., either in determining the need for other diagnostic tests, such as mammography or ductography, in assessing the need for surgical biopsy or excision or in planning the extent of surgical excision.

While this procedure yields some potentially useful information, no studies have evaluated how the test results would influence clinical decision making whether FDS has a positive impact on patient management or health outcomes or whether it reduces breast cancer morbidity and mortality. Definitive conclusions regarding the roles of FDS in the diagnosis and management of breast cancers and precancers require data from well-designed clinical trials employing strict patient inclusion criteria and long-term follow-up and through the refinement of risk-assessment models incorporating DL results.

Hayes performed and updated search in November 2006 retrieved 16 abstracts, including a multi-center study, case-series studies and review articles. Efficacy, patient selection criteria, safety issues and Hayes rating remain unchanged from the 2004 Directory Report.

A literature review from June 2006 through June 2007 was conducted and none of the publications identified would prompt a change in the coverage statement. In particular, no results have been published from controlled trials that investigate the proposed applications of DL. A recent article also raised questions that the low intrarater and interrater cytologic consistency may compromise the interpretation of clinical studies of DL.

A number of publications were identified that questioned the technical and diagnostic performance of DL. One study assessed the reproducibility of repeated DL in 65 high-risk women. Lavage was conducted in
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162 (87%) matched ducts from 63 (97%) women at baseline and 6 months. Over half of the matched ducts (51%) from 17 (27%) women were categorized as having an inadequate number of cells (<100) for morphologic diagnosis. When analyzed either per woman or per duct, there was poor agreement (kappa index from 0.14 to 0.30) between baseline and 6-month follow-up for cell yield and cytologic diagnosis. The authors concluded that DL has limited utility for the serial monitoring of breast epithelium. Another study compared breast tissue acquisition by DL with random periareolar fine-needle aspiration (immediately following lavage) in 86 women at high risk for breast cancer. Sample retrieval was successful in 100% of the women by needle aspiration, and 97% had adequate samples (10 or more epithelial cells). In contrast, samples were retrieved in only 51% of subjects using DL; the sample was considered adequate in 71% of these, resulting in a total yield of 31%. The authors concluded that fine-needle aspiration is a more practical option for clinical trials. A third study performed DL on 150 women (irrespective of the calculated risk level); 67 were patients with breast cancer. Adequate samples (10 cells or more) for diagnosis were obtained from 90% of women but only 67% of ducts. Of 83 women without breast cancer, atypia was diagnosed in 34% of 44 women with a 5-year Gail risk of <1.7% and 28% of 39 women who had a 5-year Gail risk of 1.7% or greater.

A number of recent studies suggest poor technical and diagnostic performance of DL. This technology has not been shown to improve the net health outcome. Therefore, the coverage statement is unchanged.

A search of the literature was performed through June 2009. The literature search did not identify any new high-quality clinical trials that would alter previous conclusions.

Visvanathan et al evaluated the reliability of nipple aspirate fluid (NAF) and DL at 2 time points 6 months apart in women (n=69) at increased risk for breast cancer. Eligible women had a 5-year Gail risk of 1.66% or higher or lifetime risk of >20%, and/or a family history or personal history of breast cancer. All ducts that produced NAF were cannulated. Participants (mean age, 47 years) were enrolled over 35 months. Forty-seven returned for a second visit. Of the women who returned for a second visit, 18 of 24 who produced NAF had at least 1 duct successfully cannulated. Twenty-four ducts in 14 women were lavaged twice. Among these ducts, cellular yield for the two time points was inconsistent and only fair cytologic agreement was observed. The authors concluded that the use of DL is limited by technical challenges in duct cannulation, inconsistent NAF production, a high rate of inadequate cellular material for diagnosis, fair cytologic reproducibility, and low participant return rates.

Khan et al reported on a proof-of-principle phase 2 study to assess the utility of DL to measure biomarkers of tamoxifen action. The authors’ conclusions are as follows: “…we observed the expected changes in tamoxifen-related biomarkers; however, poor reproducibility of biomarkers in the observation group, the
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53% attrition rate of subjects from recruitment to biomarker analyses, and the expense of ductal lavage are significant barriers to the use of this procedure for biomarker assessment over time.”

Summary

In summary, the available literature regarding DL and suction collection systems for breast cancer risk assessment are inadequate to draw clinical conclusions. The coverage statement remains unchanged. These procedures are investigational for the assessment of breast cancer risk given the insufficient evidence to evaluate the impact on net health outcome.

References

11. Blue Cross and Blue Shield Association, 2002 TEC Assessments; Tab 1.
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07/11/2007 Medical Director review

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07/22/2009  Medical Policy Committee approval. Coverage eligibility unchanged.
07/01/2010  Medical Policy Committee approval
07/07/2011  Medical Policy Committee review
06/28/2012  Medical Policy Committee review. Recommend archiving policy.
07/27/2012  Medical Policy Implementation Committee approval. Archived.

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