

**American College of Radiology  
ACR Appropriateness Criteria®  
Evaluation of Nipple Discharge**

**Variant 1:**                    **Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male).  
Physiologic nipple discharge. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Not Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Mammography diagnostic	Usually Not Appropriate	☼☼
Image-guided core biopsy breast	Usually Not Appropriate	Varies
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

**Variant 2:**                    **Adult male or female 40 years of age or older. Pathologic nipple discharge. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Image-guided core biopsy breast	Usually Not Appropriate	Varies
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

**Variant 3: Adult male or female 30 to 39 years of age. Pathologic nipple discharge. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

**Variant 4: Adult male younger than 30 years of age. Pathologic nipple discharge. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Image-guided core biopsy breast	Usually Not Appropriate	Varies
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

**Variant 5: Adult female younger than 30 years of age. Pathologic nipple discharge. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Not Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Mammography diagnostic	Usually Not Appropriate	☼☼
Image-guided core biopsy breast	Usually Not Appropriate	Varies
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

**Variant 6:** Adult transfeminine (male-to-female) patient 30 years of age or older. Pathologic nipple discharge. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Image-guided core biopsy breast	Usually Not Appropriate	Varies
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

**Variant 7:** Adult transfeminine (male-to-female) patient younger than 30 years of age. Pathologic nipple discharge. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	○
Digital breast tomosynthesis diagnostic	Usually Appropriate	☼☼
Mammography diagnostic	Usually Appropriate	☼☼
Ductography	Usually Not Appropriate	☼☼
Image-guided core biopsy breast	Usually Not Appropriate	Varies
Image-guided fine needle aspiration breast	Usually Not Appropriate	Varies
MRI breast without and with IV contrast	Usually Not Appropriate	○
MRI breast without IV contrast	Usually Not Appropriate	○
Sestamibi MBI	Usually Not Appropriate	☼☼☼
FDG-PET breast dedicated	Usually Not Appropriate	☼☼☼

## EVALUATION OF NIPPLE DISCHARGE

Expert Panel on Breast Imaging: Matthew F. Sanford, MD<sup>a</sup>; Priscilla J. Slanetz, MD, MPH<sup>b</sup>; Alana A. Lewin, MD<sup>c</sup>; Arnold M. Baskies, MD<sup>d</sup>; Laura Bozzuto, MD<sup>e</sup>; Susan A. Branton, MD<sup>f</sup>; Jessica H. Hayward, MD<sup>g</sup>; Huong T. Le-Petross, MD<sup>h</sup>; Mary S. Newell, MD<sup>i</sup>; John R. Scheel, MD, PhD, MPH<sup>j</sup>; Richard E. Sharpe Jr., MD, MBA<sup>k</sup>; Gary A. Ulaner, MD, PhD<sup>l</sup>; Susan P. Weinstein, MD<sup>m</sup>; Linda Moy, MD.<sup>n</sup>

### **Summary of Literature Review**

#### **Introduction/Background**

Nipple discharge is common with a prevalence of 4.8% to 7.4%, with 50% to 80% of reproductive age women experiencing at least one episode during their lifetime [1-3]. Nipple discharge is the third most common breast complaint after pain and a lump. It is reported by 5% to 10% of women at the time of routine medical examinations [4-7]. Nipple discharge can be characterized as physiologic or pathologic. Physiologic discharge is often provoked, originates from multiple duct orifices, is bilateral and white, green, or yellow in color [2]. In a study of 13,443 women with nipple discharge, 316 (2.3%) had nonspontaneous discharge, only 1 (0.3%) of whom had carcinoma [8]. Similarly, a retrospective review of 273 women who underwent diagnostic and therapeutic surgery for nipple discharge found no malignancies in those presenting with physiologic nipple discharge [9]. Pathologic nipple discharge demonstrates at least one of the following features: spontaneous from a single-duct orifice, unilateral, serous, or bloodstained. The most common causes of pathologic nipple discharge are benign, such as intraductal papilloma/papillomatosis (35%–48%) and duct ectasia (17%–36%) [5,6,10]. Most nipple discharge is not associated with an underlying breast malignancy but may provoke concern by the patient and their provider [5,6,10]. The rate of malignancy associated with pathologic nipple discharge varies widely from 3% to 29% depending on the type of discharge, patient population studied, the intervention undertaken, and histopathologic classification [5,11]. Larger studies estimate the rate of malignancy or high-risk histopathologic lesions to be closer to 11% to 16% of patients with pathologic nipple discharge [5,6,12-18]. Even though nipple discharge in males is rare, it has a strong association with an underlying malignancy based on a recent study of 430 consecutive men with nipple discharge revealing malignancy in 57% [19]. In men with a palpable mass and nipple discharge, the rate of breast cancer has been reported to be as high as 75% [20,21]. Of the approximately 8 to 25 million persons worldwide identifying as transgender [22], it is unknown how many will develop nipple discharge, and there are no specific studies addressing the imaging of this population.

The standard evaluation for nipple discharge includes a detailed clinical history and physical examination that directs the need for and type of breast imaging [11]. In patients with inconclusive breast imaging, the patient and provider may elect for surgical consultation. Historically, major duct excision has been the reference standard for defining the causative lesion of the nipple discharge and eliminating symptoms. However, this approach may not be optimal for all, because the lesion may not be identifiable on pathology, the procedure may impair a patient's ability to breast feed, and peripheral breast lesions may not be amenable to excision [17,23,24]. If a target is identified by imaging, excision by diagnostic vacuum-assisted percutaneous core needle biopsy (CNB) may offer an alternative to surgery.

#### **Special Imaging Considerations**

In 2018, Schulz-Wendtland et al [25] first described a technique combining digital breast tomosynthesis (DBT) and ductography and evaluated 5 women with pathologic nipple discharge. They found that DBT-ductography performed comparably to high-resolution ultrasound (US) in identifying suspicious imaging lesions. In 2020 Moschetta et al [26] used this nascent technique on 49 consecutive patients with spontaneous, unilateral, single-pore discharge and inconclusive conventional digital mammography and US. In this series, they compared DBT-

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ductography with conventional full-field galactography and found improved sensitivity (95% versus 77%) and accuracy (96% versus 80%) with identical specificity (80%).

### **Initial Imaging Definition**

Initial imaging is defined as imaging at the beginning of the care episode for the medical condition defined by the variant. More than one procedure can be considered usually appropriate in the initial imaging evaluation when:

- There are procedures that are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care)

OR

- There are complementary procedures (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

### **Discussion of Procedures by Variant**

#### **Variant 1: Adult female or male or transfeminine (male-to-female) or transmasculine (female-to-male). Physiologic nipple discharge. Initial imaging.**

Physiologic nipple discharge is defined as bilateral, originating from multiple ducts, white/green/yellow in color, or milky in appearance [27]. It tends to occur only when provoked [8]. Many studies have shown physiologic nipple discharge to be benign, with no association *with* *in situ* or invasive carcinoma [9,28,29].

#### **Mammography Diagnostic**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

#### **Digital Breast Tomosynthesis Diagnostic**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

#### **US Breast**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

#### **Ductography**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

#### **MRI Breast**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

#### **FDG-PET Breast Dedicated**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

#### **Image-guided Core Biopsy Breast**

Image-guided core biopsy is not required for the evaluation of physiologic nipple discharge in the female patient.

#### **Image-Guided Fine Needle Aspiration Breast**

Image-guided fine-needle aspiration (FNA) is not required for the evaluation of physiologic nipple discharge in the female patient.

#### **Sestamibi MBI**

If patient history and physical examination demonstrate physiologic nipple discharge and routine screening mammography is up to date, no further radiologic investigation is needed [28,29].

Therefore, if the clinical findings are consistent with physiologic nipple discharge and a women's health maintenance, including screening mammography, is current, diagnostic breast imaging is likely unnecessary [6,7].

## **Variant 2: Adult male or female 40 years of age or older. Pathologic nipple discharge. Initial imaging.**

### **Mammography Diagnostic**

Mammography is the first-line imaging modality for evaluation of pathologic nipple discharge in male and female patients in this age group [30]. Although 3% to 29% of pathologic nipple discharge is due to an underlying breast cancer, full-field mammography often does not demonstrate these lesions because they may be very small, contain no calcifications, or are completely intraductal [1-3]. To better evaluate the subareolar breast in patients with an asymmetry/focal asymmetry or suspicious microcalcifications, additional mammographic views with spot compression and magnification may be needed [31].

Most cases of pathologic nipple discharge are due to a benign intraductal papilloma [32]. When visible on mammography, imaging findings of papilloma include asymmetrically dilated ducts, a circumscribed benign-appearing subareolar mass, or grouped microcalcifications [1]. Up to 12% of patients with ductal carcinoma in situ (DCIS) present with nipple discharge [33]. DCIS is usually detected mammographically as fine, linear, discontinuous, and branching microcalcifications in linear, ductal, or segmental distribution and less often as a mass, asymmetry/focal asymmetry, or architectural distortion on mammography [11]. The mammographic features of invasive carcinomas are well known, including a mass of various margin characteristics with or without microcalcifications or an asymmetry, focal asymmetry, or architectural distortion [34].

For detection of malignancy (DCIS and invasive cancer), the reported sensitivity of mammography varies widely between 15% and 68%, with a specificity between 38% and 98% [3,9,23,28]. In one study, the positive predictive value (PPV) was 42%, and the negative predictive value (NPV) was 90% [23]. Malignant and high-risk lesions are identified by mammography with a reported sensitivity of 10% to 26%, specificity of 94% to 95%, PPV of 18%, and NPV of 88% [3,16]. The possible causes of the wide variation in reported sensitivity include differences in imaging technology (digital versus film-screen mammography) and varied breast density among different cohorts of patients.

In a study of 106 patients >30 years of age with pathologic nipple discharge, Gray et al [28] showed the risk of carcinoma to be 3% with a negative mammogram and 0% when both mammogram and subareolar US were negative. Although low in sensitivity and PPV, mammography remains useful in the evaluation of pathologic nipple discharge because of its high specificity and high NPV.

### **Digital Breast Tomosynthesis Diagnostic**

Although there is no relevant literature to support the use of DBT alone in assessing nipple discharge, mammography is useful for evaluating pathologic nipple discharge in male and female patients in this age group [30]. Early studies with DBT demonstrate promise in assessing the symptomatic breast [35,36].

### **US Breast**

US is useful in identifying invasive cancer and assessing extent of disease but has a diminished sensitivity for detecting DCIS [9,12,37,38]. In patients with pathologic nipple discharge, US identifies lesions not visible on mammography 63% to 69% of the time [30,39]. US adds specificity for some lesions when compared with mammography if it identifies the mammographic finding as a simple cyst or duct ectasia. US expands on ductography in its ability to visualize and detect abnormalities in multiple rather than single ducts [24].

US alone has a reported sensitivity (56%–80%), specificity (61%–75%), PPV (29%–39%), and NPV (90%–91%) for detection of underlying malignancy in patients with pathologic nipple discharge [3,9,23]. The wide variation in reported performance can be explained by differences in the definition of pathologic nipple discharge and variation in US technique [9].

Although more sensitive than mammography, US suffers from lower specificity in differentiating benign versus malignant lesions [9]. False-positive US results may be due to volume averaging with the ductal wall in a tortuous duct, intraductal and periductal fibrosis, adherent blood clots, or inspissated debris [31]. Previous studies have also reported mammography and US to be unreliable in predicting histology in patients with pathologic nipple discharge, which underscores the necessity of histological diagnosis [17,23]. In male and female patients, US is useful in identifying and assessing lesions and for biopsy guidance [40].

### **Ductography**

Ductography may demonstrate small lesions and localize the duct responsible for the nipple discharge. Ductography is minimally invasive, may be uncomfortable, and can be time-consuming. The procedure is technically challenging with 10% to 15% of cases resulting in inadequate or incomplete results [41,42]. The discharge must be present on

the day of ductography so that a cannula can be placed in the appropriate duct. Failure to cannulate the discharging duct may lead to a false negative [43]. Ductography is not recommended in lactating women or patients with active mastitis. Known hypersensitivity to iodinated contrast agents is a relative contraindication. Findings on ductography suggestive of malignant or papillary lesions include intraductal filling defect, partial or complete obstruction of a duct, duct expansion or distortion, and duct wall irregularity [1].

In patients with pathologic nipple discharge and a negative mammogram and US, Morrogh et al [44] reported the PPV and NPV of ductography for detection of cancer and high-risk lesions to be 19% and 63%, respectively. In the setting of negative standard evaluations, ductography localized 76% of otherwise occult malignant/high-risk lesions and 91% of benign lesions [39]. When the standard evaluation is positive, ductography facilitated preoperative localization of the causative lesion in 78% of cases [39]. For detection of cancer in patients with pathologic nipple discharge, 2 studies showed the sensitivity, specificity, PPV, and NPV of ductography to be 75% to 100%, 6% to 49%, 16% to 18%, and 93% to 100%, respectively [16,23]. For detection of high-risk lesions, Adepoju et al [16] reported the sensitivity, specificity, PPV, and NPV of ductography to be 75%, 53%, 22%, and 92%, respectively.

Ductography is more sensitive than mammography and US but has lower specificity than both modalities. A negative ductogram does not reliably exclude an underlying cancer or high-risk lesion, with the false-negative rate reported to be as high as 20% to 30% [44]. As such, the primary value of ductography is to localize intraductal lesions and assist in surgery [45]. A study found that patients who underwent ductography-guided operations or any other surgical procedure with image guidance of the lesion were significantly more likely to have a specific underlying lesion identified than patients who underwent central duct excision alone [23,42].

### **MRI Breast**

The sensitivity of breast MRI for detecting invasive breast cancer is high, ranging from 93% to 100%. Breast MRI specificity ranges from 37% to 97% and relies on analysis of a lesion's morphology and enhancement kinetics [46]. Malignant lesions may appear as a mass or nonmass enhancement in a ductal or segmental distribution on MRI. Noncontrast MRI, although useful for evaluation of implant integrity, has little value in the detection of malignant or high-risk lesions in patients with nipple discharge [47].

Contrast-enhanced breast MRI has high sensitivity for detecting benign papillary lesions as well as in situ and invasive carcinoma [3]. Furthermore, MRI allows identification of index lesions in peripheral ducts that are beyond the area normally encompassed by terminal duct excision, ductography, or targeted US [44]. Index or synchronous lesions found on MRI alone can be percutaneously biopsied with MRI guidance to allow for single-stage definitive surgical management (if malignant) or potentially to avoid unnecessary surgical excision for some benign lesions.

In general, MRI may be considered in cases in which mammography and US have failed to identify an underlying cause of pathologic nipple discharge [3,44,48-50]. The sensitivities of breast MRI for detecting the cause of the pathologic nipple discharge are 86% to 100% for invasive cancer and 40% to 100% for noninvasive disease [3,12,44,49,51,52]. Bahl et al [52] reported the sensitivity, specificity, PPV, and NPV of MRI for detecting malignancy in patients with pathologic nipple discharge to be 100%, 68%, 37%, and 100%, respectively. Several studies have shown that MRI has higher sensitivity and specificity than US and ductography for lesion detection and may be an alternative to ductography [12,32,48,49]. However, a study by van Gelder et al [51] asserted that MRI has limited added value in patients with unilateral bloody nipple discharge who showed no signs of a malignancy on conventional diagnostic examinations, because malignancy was demonstrated in <2% of their cases. Despite the high sensitivity of breast MRI, it is not indicated as initial imaging in a patient with pathologic nipple discharge.

### **FDG-PET Breast Dedicated**

High-resolution cameras specifically designed for breast imaging have improved detection of small and noninvasive carcinomas. However, specific research evaluating women with nipple discharge is lacking [41,53]. Currently, there is no relevant literature for the use of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET in the evaluation of a male or female patient with pathologic nipple discharge.

### **Image-Guided Core Biopsy Breast**

Previous studies showed that mammography, US, and ductography are unreliable in predicting histology in patients with pathologic nipple discharge [17,23,44], which underscores the importance of histological diagnosis of lesions identified on imaging. The biopsy procedures may be guided by stereotactic mammography, US, ductography, or MRI, depending on the imaging modality that best depicts the lesion. CNB is preferred over FNA because the larger gauge needle improves sampling [54,55]. Placement of a tissue marker at the end of the biopsy allows for needle



localization and excision if the biopsied lesion yields malignant or high-risk histology. Vacuum-assisted CNB is particularly useful in assuring complete sampling of small intraductal papillary lesions [24]. Although biopsy is a diagnostic procedure, the process of removing enough of the intraductal papillary lesion during vacuum-assisted core biopsy may be therapeutic and will lead to permanent cessation of nipple discharge in 90% to 97.2% of patients [24,56]. However, Reiner et al [57] cautioned that ductography-guided 11-gauge vacuum-assisted stereotactic biopsy should not be used as a substitute for surgical duct excision in cases of pathologic nipple discharge with abnormalities on ductography because of the high underestimation rate (50%) for high-risk lesions and DCIS, false-negative rate (7%), and histopathological detection of lesion remnants in every case.

Papillomas are historically considered high-risk lesions, with reported rates of upgrade to malignancy between 3% and 14% [58,59]. The management of papillomas diagnosed on CNB is controversial and varies by institution [60]. Because papillomas diagnosed on CNB are often excised, excisional biopsy instead of CNB may be useful when a papillary lesion is anticipated based on imaging findings. A recent study suggests that patients with nonbloody pathologic nipple discharge, a benign CNB, or normal imaging (cancer risk <2%) may be considered for nonoperative management if they do not have risk factors such as prior ipsilateral breast cancer, BRCA mutation, or atypia on CNB [61].

According to the surgical literature, major duct excision remains the reference standard to exclude malignancy in patients with unremarkable imaging, when even a negative ductogram (NPV 63%–82%) [17,30] or MRI (NPV 87%–100%) [44,52] does not exclude an underlying cancer or high-risk lesion [13,39,44].

In addition, US does not reliably distinguish between benign and malignant small intraductal lesions [9]. Therefore, the decision to perform percutaneous biopsy versus major duct excision should involve the patient and their health care provider.

Image-guided CNB is equally useful in male patients for obtaining tissue diagnosis and assisting in patient management [40]. Image-guided CNB is not indicated as the initial examination to evaluate pathologic nipple discharge.

### **Image-Guided Fine Needle Aspiration Breast**

Once a suspicious lesion that is likely responsible for the pathologic nipple discharge is identified on imaging, image-guided FNA or CNB can be performed for histological diagnosis. 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 histological grading of a lesion [54,55]. Image-guided FNA is not indicated as the initial examination to evaluate pathologic nipple discharge.

### **Sestamibi MBI**

There is no relevant literature to support the use of molecular breast imaging (MBI) in the evaluation of a male or female patient with pathologic nipple discharge.

### **Variant 3: Adult male or female 30 to 39 years of age. Pathologic nipple discharge. Initial imaging.**

The risk of breast cancer is relatively low ( $\leq 1.4\%$ ) for women in their fourth decade [62]. There are scant data on the risk of breast cancer in women 30 to 39 years of age presenting with pathologic nipple discharge. In one study, no malignancy was recorded among patients 30 to 39 years of age with pathologic nipple discharge and no palpable mass [9]. However, a study of 19 patients <40 years of age with pathologic nipple discharge [23] found 2 cancers. There is no other relevant literature that addresses the appropriateness of imaging in women 30 to 39 years of age with the specific symptom of pathologic nipple discharge.

### **Mammography Diagnostic**

The sensitivity of US for palpable or nonpalpable breast cancer is higher than that of mammography (95.7% versus 60.9%) for women 30 to 39 years of age [63,64]. Either mammography or US may be used as the initial imaging modality, on the basis of institutional preference and case-by-case consideration. However, mammography has its value in detecting suspicious microcalcifications, given the high incidence of patients with DCIS presenting with nipple discharge.

Because of the high incidence (23%–57%) of breast cancer in male patients with nipple discharge [19,65], imaging with mammography is indicated as an initial study per the ACR Appropriateness Criteria<sup>®</sup> topic on “[Evaluation of the Symptomatic Male Breast](#)” [40].



### **Digital Breast Tomosynthesis Diagnostic**

Although there is no relevant literature to support the use of DBT alone in assessing nipple discharge, mammography is useful for evaluating pathologic nipple discharge in male and female patients in this age group [30]. Early studies with DBT demonstrate promise in assessing the symptomatic breast [35,36].

### **US Breast**

The sensitivity of US for palpable or nonpalpable breast cancer is higher than that of mammography (95.7% versus 60.9%) for women 30 to 39 years of age [63,64]. Hence, US may be useful as the initial imaging modality, with mammography added when necessary.

### **Ductography**

Ductography may demonstrate small lesions and localize the duct responsible for the nipple discharge. Ductography is minimally invasive, may be uncomfortable, and can be time-consuming. The procedure is technically challenging with 10% to 15% of cases resulting in inadequate or incomplete results [41,42]. The discharge must be present on the day of ductography so that a cannula can be placed in the appropriate duct. Failure to cannulate the discharging duct may lead to a false negative [43]. Ductography is not recommended in lactating women or patients with active mastitis. Known hypersensitivity to iodinated contrast agents is a relative contraindication. Findings on ductography suggestive of malignant or papillary lesions include intraductal filling defect, partial or complete obstruction of a duct, duct expansion or distortion, and duct wall irregularity [1].

In patients with pathologic nipple discharge and a negative mammogram and US, Morrogh et al [44] reported the PPV and NPV of ductography for the detection of cancer and high-risk lesions to be 19% and 63%, respectively. In the setting of negative standard evaluations, ductography localized 76% of otherwise occult malignant/high-risk lesions and 91% of benign lesions [39]. When the standard evaluation is positive, ductography facilitated preoperative localization of the causative lesion in 78% of cases [39]. For detection of cancer in patients with pathologic nipple discharge, 2 studies showed the sensitivity, specificity, PPV, and NPV of ductography to be 75% to 100%, 6% to 49%, 16% to 18%, and 93% to 100%, respectively [16,23]. For detection of high-risk lesions, Adepoju et al [16] reported the sensitivity, specificity, PPV, and NPV of ductography to be 75%, 53%, 22%, and 92%, respectively.

Ductography is more sensitive than mammography and US but has a lower specificity than both modalities. A negative ductogram does not reliably exclude an underlying cancer or high-risk lesion, with the false-negative rate reported to be as high as 20% to 30% [44]. As such, the primary value of ductography is to localize intraductal lesions and assist in surgery [45]. A study found that patients who underwent ductography-guided operations or any other surgical procedure with image guidance of the lesion were significantly more likely to have a specific underlying lesion identified than patients who underwent central duct excision alone [23,42].

At this time, there is no relevant literature available for use of ductography for evaluation of a male patient with nipple discharge.

### **MRI Breast**

The sensitivity of breast MRI for detecting invasive breast cancer is high, ranging from 93% to 100%. Breast MRI specificity ranges from 37% to 97% and relies on analysis of a lesion's morphology and enhancement kinetics [46]. Malignant lesions may appear as a mass or nonmass enhancement in a ductal or segmental distribution on MRI. Noncontrast MRI, although useful for evaluation of implant integrity, has little value in the detection of malignant or high-risk lesions in patients with nipple discharge [47].

Contrast-enhanced breast MRI has a high sensitivity for detecting benign papillary lesions as well as in situ and invasive carcinoma [3]. Furthermore, MRI allows for the identification of index lesions in peripheral ducts that are beyond the area normally encompassed by terminal duct excision, ductography, or targeted US [44]. Index or synchronous lesions found on MRI alone can be percutaneously biopsied with MRI guidance to allow for single-stage definitive surgical management (if malignant) or potentially to avoid unnecessary surgical excision for some benign lesions.

In general, MRI should be considered in cases in which mammography and US have failed to identify an underlying cause of pathologic nipple discharge [3,44,48-50]. The sensitivities of breast MRI for detecting the cause of the pathologic nipple discharge are 86% to 100% for invasive cancer and 40% to 100% for noninvasive disease [3,12,44,49,51,52]. Bahl et al [52] reported the sensitivity, specificity, PPV, and NPV of MRI for detecting malignancy in patients with pathologic nipple discharge to be 100%, 68%, 37%, and 100%, respectively. Several

studies have shown that MRI has a higher sensitivity and specificity than US and ductography for lesion detection and may be an alternative to ductography [12,32,48,49]. However, a study by van Gelder et al [51] asserted that MRI has limited added value in patients with unilateral bloody nipple discharge who showed no signs of a malignancy on conventional diagnostic examinations, because malignancy was demonstrated in <2% of their cases.

At this time, there is no relevant literature available for use of MRI for evaluation of a male patient with nipple discharge.

### **FDG-PET Breast Dedicated**

High-resolution cameras specifically designed for breast imaging have improved detection of small and noninvasive carcinomas. However, specific research evaluating women with nipple discharge is lacking [41,53]. Currently, there is no relevant literature for the use of FDG-PET in the evaluation of a male or female patient with pathologic nipple discharge.

### **Image-Guided Core Biopsy Breast**

Previous studies showed that mammography, US, and ductography are unreliable in predicting histology in patients with pathologic nipple discharge [17,23,44], which underscores the importance of histological diagnosis of lesions identified on imaging. The biopsy procedures may be guided by stereotactic mammography, US, ductography, or MRI, depending on the imaging modality that best depicts the lesion. CNB is preferred over FNA because the larger gauge needle improves sampling [54,55]. Placement of a tissue marker at the end of the biopsy allows for needle localization and excision if the biopsied lesion yields malignant or high-risk histology. Vacuum-assisted CNB is particularly useful in assuring complete sampling of small intraductal papillary lesions [24]. Although biopsy is a diagnostic procedure, the process of removing enough of the intraductal papillary lesion during vacuum-assisted core biopsy may be therapeutic and will lead to permanent cessation of nipple discharge in 90% to 97.2% of patients [24,56]. However, Reiner et al [57] cautioned that ductography-guided 11-gauge vacuum-assisted stereotactic biopsy should not be used as a substitute for surgical duct excision in cases of pathologic nipple discharge with abnormalities on ductography because of the high underestimation rate (50%) for high-risk lesions and DCIS, false-negative rate (7%), and histopathological detection of lesion remnants in every case.

Papillomas are historically considered high-risk lesions, with reported rates of upgrade to malignancy between 3% and 14% [58,59]. The management of papillomas diagnosed on CNB is controversial and varies by institution [60]. Because papillomas diagnosed on CNB are often excised, excisional biopsy instead of CNB may be useful when a papillary lesion is anticipated based on imaging findings. A recent study suggests that patients with nonbloody pathologic nipple discharge, a benign CNB, or normal imaging (cancer risk <2%) may be considered for nonoperative management if they do not have risk factors such as prior ipsilateral breast cancer, BRCA mutation, or atypia on CNB [61].

According to the surgical literature, major duct excision remains the reference standard to exclude malignancy in patients with unremarkable imaging, when even a negative ductogram (NPV 63%–82%) [17,30] or MRI (NPV 87%–100%) [44,52] does not exclude an underlying cancer or high-risk lesion [13,39,44].

In addition, US does not reliably distinguish between benign and malignant small intraductal lesions [9]. Therefore, the decision to perform percutaneous biopsy versus major duct excision should involve the patient and their health care provider.

Image-guided CNB is equally useful in male patients for obtaining tissue diagnosis and assisting in patient management [40]. Image-guided CNB is not indicated as the initial examination to evaluate pathological nipple discharge.

### **Image-Guided Fine Needle Aspiration Breast**

Once a suspicious lesion that is likely responsible for the pathologic nipple discharge is identified on imaging, image-guided FNA or CNB can be performed for histological diagnosis. 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 histological grading of a lesion [54,55]. Image-guided FNA is not indicated as the initial examination to evaluate pathological nipple discharge.

### **Sestamibi MBI**

There is no relevant literature to support the use of MBI in the evaluation of a male or female patient with pathologic nipple discharge.

**Variant 4: Adult male younger than 30 years of age. Pathologic nipple discharge. Initial imaging.**

For male patients presenting with nipple discharge, the incidence of cancer is high (23%–57%) [19,65]. Given the high pretest probability, imaging is appropriate for male patients <30 years of age.

**Mammography Diagnostic**

Diagnostic mammography is useful in distinguishing malignancy from benign breast conditions in symptomatic male patients with nipple discharge [1,2]. Please refer to the ACR Appropriateness Criteria® topic on “[Evaluation of the Symptomatic Male Breast](#)” [40] for additional details.

**Digital Breast Tomosynthesis Diagnostic**

Although there is no relevant literature to support the use of DBT alone in assessing nipple discharge, mammography is useful for evaluating pathologic nipple discharge in male and female patients in this age group [30]. Early studies with DBT demonstrate promise in assessing the symptomatic breast [35,36].

**US Breast**

In conjunction with mammography or DBT, US is often useful in assisting with management decisions and to facilitate US core biopsy [3]. Please refer to the ACR Appropriateness Criteria® topic on “[Evaluation of the Symptomatic Male Breast](#)” [40] for additional details.

**Ductography**

There is no relevant literature to support the use of ductography for the evaluation of male patients with nipple discharge.

**MRI Breast**

There is no relevant literature to support the use of MRI for the evaluation of male patients with nipple discharge.

**FDG-PET Breast Dedicated**

There is no relevant literature to support the use of FDG-PET for the evaluation of male patients with nipple discharge.

**Image-guided Core Biopsy Breast**

There is no relevant literature to support the use of core biopsy for the evaluation of male patients with nipple discharge. However, if an imaging abnormality is identified, US may be used to direct biopsy.

**Image-Guided Fine Needle Aspiration Breast**

There is no relevant literature to support the use of image-guided FNA for the evaluation of male patients with nipple discharge.

**Sestamibi MBI**

There is no relevant literature to support the use of MBI for the evaluation of male patients with nipple discharge.

**Variant 5: Adult female younger than 30 years of age. Pathologic nipple discharge. Initial imaging.**

The probability of a woman developing breast cancer over the next decade increases with age; the risk is 1 in 1,681 at 20 years of age, 1 in 232 at 30 years of age, and 1 in 69 at 40 years of age [62]. Breast cancer is rare in women <30 years of age, with the exception of those with a genetic predisposition or prior mantle radiation to the chest. In a study by Seltzer et al [66] on the significance of age in patients with nipple discharge, malignancy was found in 1 of 10 patients <30 years of age. However, caution should be exercised interpreting these results given a very small sample size and the possible inclusion of high-risk patients.

**Mammography Diagnostic**

Most breast lesions in young women are not visualized on mammography [67,68] because of the low incidence of breast cancer (0.4% or lower) in women <30 years of age. US is most useful for initial imaging in this population; however, diagnostic mammography may be useful when US shows a suspicious finding.

**Digital Breast Tomosynthesis Diagnostic**

Although there is no relevant literature to support the use of DBT alone in assessing nipple discharge, mammography is useful for evaluating pathologic nipple discharge in male and female patients in this age group [30]. Early studies with DBT demonstrate promise in assessing the symptomatic breast [35,36].

## **US Breast**

Yue et al [69] studied 955 women <25 years of age who presented with breast symptoms including palpable mass, pain, and nipple discharge. US was performed in 692 patients and was normal/negative in 671 patients and indeterminate in 21 patients. No cancer was found in this group via biopsy or clinical follow-up. However, it is unknown how many of these patients had pathologic or physiologic discharge.

## **Ductography**

There is no relevant literature to support the use of ductography in women <30 years of age with symptoms of pathologic nipple discharge.

## **MRI Breast**

There is no relevant literature to support the use of MRI in women <30 years of age with symptoms of pathologic nipple discharge.

## **FDG-PET Breast Dedicated**

There is no relevant literature to support the use of FDG-PET in women <30 years of age with symptoms of pathologic nipple discharge.

## **Image-guided Core Biopsy Breast**

There is no relevant literature to support the use of image-guided core biopsy in women <30 years of age with symptoms of pathologic nipple discharge. However, if an imaging abnormality is identified, US may be used to direct biopsy.

## **Image-Guided Fine Needle Aspiration Breast**

There is no relevant literature to support the use of image-guided FNA in women <30 years of age with symptoms of pathologic nipple discharge.

## **Sestamibi MBI**

There is no relevant literature to support the use of MBI in women <30 years of age with symptoms of pathologic nipple discharge.

## **Variant 6: Adult transfeminine (male-to-female) patient 30 years of age or older. Pathologic nipple discharge. Initial imaging.**

In cisgender men presenting with nipple discharge, the incidence of cancer is high (23%–57%) [19,65]. Therefore, given the high pretest probability, imaging is appropriate in transgender women  $\geq 30$  years of age. Transgender women who are taking gender-affirming hormone therapy are at an increased risk for breast cancer [70]. Endogenous or exogenous exposure to estrogen results in an increase in the lobules, ducts, and acini identical to the natal female breast. As such, imaging maybe be considered regardless of the duration of hormone therapy.

## **Mammography Diagnostic**

Diagnostic mammography is useful in distinguishing malignancy from benign breast conditions in symptomatic transfeminine patients [1,2]. Please refer to the ACR Appropriateness Criteria® topic on “[Evaluation of the Symptomatic Male Breast](#)” [40] for additional details.

## **Digital Breast Tomosynthesis Diagnostic**

Although there is no relevant literature to support the use of DBT alone in assessing nipple discharge, mammography is useful for evaluating pathologic nipple discharge in male and female patients in this age group [30]. Early studies with DBT demonstrate promise in assessing the symptomatic breast [35,36].

## **US Breast**

In conjunction with mammography or DBT, US is often useful in assisting with management decisions and to facilitate US core biopsy [3]. Please refer to the ACR Appropriateness Criteria® topic on “[Evaluation of the Symptomatic Male Breast](#)” [40] for additional details.

## **Ductography**

There is no relevant literature to support the use of ductography for evaluation of transgender patients with nipple discharge.

## **MRI Breast**

There is no relevant literature to support the use of MRI for evaluation of transgender patients with nipple discharge.

### **FDG-PET Breast Dedicated**

There is no relevant literature to support the use of FDG-PET for evaluation of transgender patients with nipple discharge.

### **Image-guided Core Biopsy Breast**

There is no relevant literature to support the use of image-guided core biopsy for evaluation of transgender patients with nipple discharge. However, if an imaging abnormality is identified, US may be used to direct biopsy.

### **Image-Guided Fine Needle Aspiration Breast**

There is no relevant literature to support the use of image-guided FNA for evaluation of transgender patients with nipple discharge.

### **Sestamibi MBI**

There is no relevant literature to support the use of MBI for evaluation of transgender patients with nipple discharge.

### **Variant 7: Adult transfeminine (male-to-female) patient younger than 30 years of age. Pathologic nipple discharge. Initial imaging.**

In cisgender males presenting with nipple discharge, the incidence of cancer is high (23%–57%) [19,65]. Therefore, given the high pretest probability, imaging is appropriate in transgender women <30 years of age. Transgender women who are taking gender-affirming hormone therapy are at an increased risk for breast cancer [70]. Endogenous or exogenous exposure to estrogen results in an increase in the lobules, ducts, and acini identical to the natal female breast. As such, imaging maybe be considered regardless of the duration of hormone therapy.

### **Mammography Diagnostic**

Diagnostic mammography is useful in distinguishing malignancy from benign breast conditions in symptomatic transfeminine patients with nipple discharge [1,2]. Please refer to the ACR Appropriateness Criteria® topic on “[Evaluation of the Symptomatic Male Breast](#)” [40] for additional details.

### **Digital Breast Tomosynthesis Diagnostic**

Although there is no relevant literature to support the use of DBT alone in assessing nipple discharge, mammography is useful for evaluating pathologic nipple discharge in male and female patients in this age group [30]. Early studies with DBT demonstrate promise is assessing the symptomatic breast [35,36].

### **US Breast**

In conjunction with mammography or DBT, US is often useful in assisting with management decisions and to facilitate US core biopsy [3]. Please refer to the ACR Appropriateness Criteria® topic on “[Evaluation of the Symptomatic Male Breast](#)” [40] for additional details.

### **Ductography**

There is no relevant literature to support the use of ductography for evaluation of transgender patients with nipple discharge.

### **MRI Breast**

There is no relevant literature to support the use of MRI for evaluation of transgender patients with nipple discharge.

### **FDG-PET Breast Dedicated**

There is no relevant literature to support the use of FDG-PET for evaluation of transgender patients with nipple discharge.

### **Image-guided Core Biopsy Breast**

There is no relevant literature to support the use of core biopsy for evaluation of transgender patients with nipple discharge. However, if an imaging abnormality is identified, US may be used to direct biopsy.

### **Image-Guided Fine Needle Aspiration Breast**

There is no relevant literature to support the use of image-guided FNA for evaluation of transgender patients with nipple discharge.

### **Sestamibi MBI**

There is no relevant literature to support the use of MBI for evaluation of transgender patients with nipple discharge.

## Summary of Recommendations

- **Variation 1:** Diagnostic imaging is usually not appropriate for assessing physiologic nipple discharge in adult female, male, transfeminine (male-to-female), or transmasculine (female-to-male) patients.
- **Variation 2:** DBT or diagnostic mammography is usually appropriate for the initial imaging of pathologic nipple discharge in adult male or female patients 40 years of age or older. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Breast US is complementary to DBT and diagnostic mammography and may be performed during the same patient encounter or in close approximation to one another to better characterize the disease process.
- **Variation 3:** DBT or diagnostic mammography is usually appropriate for the initial imaging of pathologic nipple discharge in adult male or female patients 30 to 39 years of age. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Breast US is complementary to DBT and diagnostic mammography and may be performed during the same patient encounter or in close approximation to one another to better characterize the disease process.
- **Variation 4:** DBT or diagnostic mammography is usually appropriate for the initial imaging of pathologic nipple discharge in adult male patients younger than 30 years of age. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Breast US is complementary to DBT and diagnostic mammography and may be performed during the same patient encounter or in close approximation to one another to better characterize the disease process.
- **Variation 5:** Breast US is usually appropriate as the initial imaging of pathologic discharge in adult female patients younger than 30 years of age.
- **Variation 6:** DBT or diagnostic mammography is usually appropriate for the initial imaging of pathologic nipple discharge in transfeminine (male-to-female) patients 30 years of age or older. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Breast US is complementary to DBT and diagnostic mammography and may be performed during the same patient encounter or in close approximation to one another to better characterize the disease process.
- **Variation 7:** DBT or diagnostic mammography is usually appropriate for the initial imaging of pathologic nipple discharge in adult transfeminine (male-to-female) patients younger than 30 years of age. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Breast US is complementary to DBT and diagnostic mammography and may be performed during the same patient encounter or in close approximation to one another to better characterize the disease process.

## Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

## Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

## Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document [71].

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
⊕	<0.1 mSv	<0.03 mSv
⊕⊕	0.1-1 mSv	0.03-0.3 mSv
⊕⊕⊕	1-10 mSv	0.3-3 mSv
⊕⊕⊕⊕	10-30 mSv	3-10 mSv
⊕⊕⊕⊕⊕	30-100 mSv	10-30 mSv

\*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.