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

**Variant 1: Physiologic nipple discharge. Woman of any age. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
Mammography diagnostic	1	See references [2,4-7].	☼☼
Digital breast tomosynthesis diagnostic	1	See references [2,4-7].	☼☼
US breast	1	See references [2,4-7].	O
MRI breast without and with IV contrast	1	See references [2,4-7].	O
MRI breast without IV contrast	1	See references [2,4-7].	O
FDG-PEM	1	See references [2,4-7].	☼☼☼☼
Tc-99m sestamibi MBI	1	See references [2,4-7].	☼☼☼
Ductography	1	See references [2,4-7].	☼☼
Image-guided core biopsy breast	1	See references [2,4-7].	Varies
Image-guided fine needle aspiration breast	1		Varies
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 2: Pathologic nipple discharge. Man or woman 40 years of age or older. Initial imaging examination.**

Radiologic Procedure	Rating	Comments	RRL*
Mammography diagnostic	9	See references [3,6,8,10,13,14,16,25-29,32,34,42-44,71-73].	☼☼
Digital breast tomosynthesis diagnostic	9	See references [3,6,8,10,13,14,16,25-29,32,34,42-44,71-73].	☼☼
US breast	9	US is usually complementary to mammography. It can be an alternative to mammography if the patient had a recent mammogram or is pregnant. See references [3,5,10,12,13,16,25,30,31,45-49].	O
MRI breast without and with IV contrast	1	See references [3,8,23,24,35,46,51-55].	O
MRI breast without IV contrast	1	See references [51,52].	O
FDG-PEM	1	See reference [38].	☼☼☼☼
Tc-99m sestamibi MBI	1	See reference [39].	☼☼☼
Ductography	1	See references [10,12,13,18,24,32-34].	☼☼
Image-guided core biopsy breast	1	See references [5,10,12,24,31,40,41,49,58,59,63].	Varies
Image-guided fine needle aspiration breast	1		Varies
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 3:****Pathologic nipple discharge. Man or woman 30 to 39 years of age. Initial imaging examination.**

<b>Radiologic Procedure</b>	<b>Rating</b>	<b>Comments</b>	<b>RRL*</b>
Mammography diagnostic	9	See references [3,6,8,10,13,14,16,25-29,32,34,42-44,71-73] and references [9,10,53,66,67] for age-related issues.	☼☼
Digital breast tomosynthesis diagnostic	9	See references [3,6,8,10,13,14,16,25-29,32,34,42-44,71-73] and references [9,10,53,66,67] for age-related issues. See references [26-29] for tomosynthesis.	☼☼
US breast	9	US can be used as an initial examination in place of mammography in women in this age range. For men, it is complementary to mammography. See references [3,5,10,12,13,16,25,30,31,45-49] and references [9,66,67] for age-related issues.	O
MRI breast without and with IV contrast	1	See references [3,8,23,24,35,46,51-55].	O
MRI breast without IV contrast	1	See references [51,52].	O
FDG-PEM	1	See reference [38].	☼☼☼☼
Tc-99m sestamibi MBI	1	See reference [39].	☼☼☼
Ductography	1	See references [10,12,13,18,24,32-34].	☼☼
Image-guided core biopsy breast	1	See references [5,10,12,24,31,40,41,49,58,59,63].	Varies
Image-guided fine needle aspiration breast	1		Varies
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

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

<b>Radiologic Procedure</b>	<b>Rating</b>	<b>Comments</b>	<b>RRL*</b>
US breast	9	See references [9,65,68-70].	O
Mammography diagnostic	5	Mammography may be complementary when initial US shows a suspicious finding or the patient is BRCA positive or has another genetic mutation predisposing to breast cancer. See references [9,65,68-70].	☼☼
Digital breast tomosynthesis diagnostic	5	DBT may be complementary when initial US shows a suspicious finding or the patient is BRCA positive or has another genetic mutation predisposing to breast cancer. See references [9,26-29,65,68-70].	☼☼
MRI breast without and with IV contrast	1	See references [9,65,68-70].	O
MRI breast without IV contrast	1	See references [9,65,68-70].	O
FDG-PEM	1	See references [9,65,68-70].	☼☼☼☼
Tc-99m sestamibi MBI	1	See references [9,65,68-70].	☼☼☼
Ductography	1	See references [9,65,68-70].	☼☼
Image-guided core biopsy breast	1	See references [5,9,10,12,24,31,40,41,49,58,59,63,65,68-70].	Varies
Image-guided fine needle aspiration breast	1		Varies
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

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

<b>Radiologic Procedure</b>	<b>Rating</b>	<b>Comments</b>	<b>RRL*</b>
US breast	9	When the patient is <25 years old, US may be the initial examination, with mammography added as indicated. See references [9,14-17,65,68-70].	O
Mammography diagnostic	8	Mammography or DBT should be performed as the initial study in men >25 years old, given the high incidence of cancer in men with pathologic nipple discharge. See references [9,14-17,65,68-70].	☼☼
Digital breast tomosynthesis diagnostic	8	Mammography or DBT should be performed as the initial study in men >25 years old, given the high incidence of cancer in men with pathologic nipple discharge. See references [9,14-17,65,68-70].	☼☼
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☼☼☼☼
Tc-99m sestamibi MBI	1		☼☼☼
Ductography	1		☼☼
Image-guided core biopsy breast	1	See references [5,10,12,24,31,40,41,49,58,59,63].	Varies
Image-guided fine needle aspiration breast	1		Varies
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

## EVALUATION OF NIPPLE DISCHARGE

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### **Summary of Literature Review**

#### **Introduction/Background**

Nipple discharge is a common complaint that leads patients to breast imaging evaluation. At least 80% of women will experience at least 1 episode of nipple discharge during their reproductive years [1]. Nipple discharge is the third most common breast complaint after breast pain and breast mass, with a prevalence of 4.8% to 7.4%, and accounts for 5% of all breast symptoms [2,3]. It is categorized as physiologic or pathologic. Pathologic nipple discharge tends to be unilateral, from a single duct orifice, spontaneous, and serous or bloodstained. Nipple discharge that exhibits any one of these features may be considered pathologic. Physiologic nipple discharge tends to be bilateral, from multiple duct orifices, and white, green, or yellow in color [2]. In a study by Goskel et al [4], nonspontaneous nipple discharge, which was frequently colored or milky, was differentiated from spontaneous nipple discharge, which was considered pathologic. In this study, none of the patients with nonspontaneous nipple discharge developed cancer on follow-up examination. In another study by Bahl et al [5], no in situ or invasive cancers were found in patients whose nipple discharge did not exhibit any of the pathologic features. If patient history and physical examinations demonstrate physiologic nipple discharge and routine screening mammography is up to date, no radiologic investigation is needed [6,7].

Intraductal papilloma is the most common cause of pathologic nipple discharge, accounting for 35% to 48% of cases, followed by duct ectasia (17%–36%) [8]. However, an underlying malignancy can be found in 5% to 21% of patients with pathologic nipple discharge who undergo biopsy [3,5,8]. The risk of malignancy increases with age [9]. In a study by Seltzer et al [9] on the significance of age in patients with nipple discharge, malignancy was present in 3% of patients 40 years of age or younger with no palpable mass, 10% of patients 40 to 60 years of age, and 32% of those over 60 years. Excluding a malignant lesion is of primary importance in patients presenting with pathologic nipple discharge.

Several studies show that the rate of malignancy increases when radiologic or palpable abnormalities accompany nipple discharge [2,10-12]. Gülay et al [7] reported that the incidence of breast cancer in patients with spontaneous nipple discharge and a palpable finding was 61.5%, compared with 6.1% in patients with nipple discharge only. However, Adepoju et al [13] showed similar rates of breast cancer among patients with and without a positive physical examination (11% versus 13%) in their series.

Nipple discharge in the male breast is rare and thus imaging evaluation is not well documented. Two studies showed carcinoma in 23% to 57% of men presenting with nipple discharge [14,15]. In a study by Morrogh et al [14] of 430 patients presenting with nipple discharge at their institution during a 10-year period, 3% were male, of whom 57% were found to have underlying malignancy. This is in contrast to a 16% malignancy rate in their female cohort. Of the 91 male breast cancer patients treated at their institution over the study period, 9% presented with a chief complaint of nipple discharge. Although nipple discharge of the male breast is uncommon, it is a symptom that warrants further evaluation because of its strong association with underlying malignancy [14-16]. For a male patient presenting with suspicious nipple discharge, clinical suspicion of malignancy is often

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confirmed by breast examination. Imaging investigation such as mammography and sonography may assist in diagnosis, especially in the absence of a palpable mass [14,15,17]. Galactorrhea in males is secondary to endocrine or hormonal causes and requires a clinical rather than a radiologic workup.

In women with suspicious nipple discharge and negative conventional evaluation (physical examination, mammography, and sonography), the clinician may decide to proceed to major duct excision. A frequent criticism of this blind approach is that the pathologists may not always identify a discrete causative lesion for the discharge. Furthermore, major duct excision may be undesirable for a woman of childbearing age. Up to 20% of lesions associated with pathologic nipple discharge are >3 cm beyond the nipple and may not be excised by this procedure [10]. This finding highlights the benefit of thorough preoperative imaging evaluation, including ductogram and magnetic resonance imaging (MRI) when indicated. Lesion localization by imaging would ensure that the lesion is either biopsied or removed by major duct excision and can be identified in the specimen for pathologic evaluation [10,18,19].

Cytologic examination of nipple discharge has not proven to be effective in differentiating benign from malignant lesions [9,11,20]. Ductoscopy has been shown to be a valuable tool for working up patients with nipple discharge. However, it is available in only a few centers because of a lack of breast surgeons experienced in the technique and issues with cost and reimbursement [21,22].

### **Overview of Imaging Modalities**

The standard evaluation of all patients with pathologic nipple discharge includes history, physical examination, and imaging evaluation. Physical examination, when positive, has been reported to be associated with a significantly higher frequency of cancer [7]. Imaging evaluation usually begins with diagnostic mammography and ultrasound (US) [6,12]. Historically, ductograms have been performed for further evaluation of pathologic nipple discharge following negative mammography and sonography, as ductography may detect an underlying abnormality in 14% to 86% of cases [12,23,24]. As an alternative to ductography, breast MRI may be performed at the discretion of the radiologist, as MRI detects underlying causes of pathologic nipple discharge when mammography and US are negative in 19% to 96% of cases [23,24] and can potentially identify posterior lesions that are not routinely identified on ductography [24]. MRI has higher positive and negative predictive values than ductography in detection of high-risk lesions and cancers in patients with pathologic nipple discharge [24], leading some radiologists to prefer MRI over ductography in the evaluation of nipple discharge when mammography and sonography are negative.

#### *Mammography and digital breast tomosynthesis diagnostic*

Diagnostic mammography is the standard initial step in evaluation of a patient with pathologic nipple discharge, depending on age. The mammogram needs to include only the symptomatic breast if the patient has undergone recent bilateral screening mammography within the past 6 months. It usually consists of craniocaudal and mediolateral oblique views of the symptomatic breast, with additional views if indicated. [25].

Digital breast tomosynthesis (DBT) is a variant of standard digital mammography that allows for creation and viewing of thin-section reconstructed images that may decrease the lesion-masking effect of overlapping normal tissue and reveal the true nature of false-positive findings. Currently, there is no published literature that discusses the diagnostic accuracy of DBT compared with digital mammography in the specific setting of nipple discharge, and there is no literature on the role of DBT for the evaluation of nipple discharge. However, DBT can be useful in improving characterization of noncalcified lesions compared to conventional mammographic workup [26-29] and could therefore be useful in the setting of nipple discharge evaluation.

#### *Ultrasound*

US is a useful ancillary study for evaluation of pathologic nipple discharge, alone or combined with ductography. When mammography is negative, the retroareolar region of symptomatic breast is usually evaluated with US. A standoff pad or abundant warm US gel can improve detection of a retroareolar lesion by eliminating acoustic shadows caused by air trapped around the nipple and by bringing a superficial lesion into the focal zone. Special maneuvers described by Stavros [30] such as peripheral compression, 2-hand compression, and rolled-nipple techniques may be needed for successful imaging of the nipple and retroareolar region. US can guide biopsy if any suspicious US finding is demonstrated. When performed after a positive ductogram, US can show the extent of the lesion more accurately than can the ductogram, particularly when there is a duct cutoff sign [31].

### *Ductography (galactography)*

Ductography, also known as galactography, is a mammographic examination performed after cannulation and filling of the lactiferous duct or ducts that are secreting the suspicious discharge with iodinated contrast medium. It is historically the procedure of choice in identifying and localizing intraductal lesions in patients with pathologic nipple discharge [32,33]. Repeat ductography can be used to guide preoperative wire localization once a suspicious target lesion is identified [34].

### *Magnetic resonance imaging*

MRI may be useful in the management of pathologic nipple discharge, particularly in those with negative mammogram and sonogram [3]. MRI provides excellent visualization of dilated ducts and their contents without requiring duct cannulation, and it outlines enhancing pathology in good detail, thereby providing physiological information in addition to the morphological detail provided by mammography and US [35].

### *Nuclear medicine*

The use of nuclear medicine using a whole-body scanner has shown limited detection of small breast cancers [36,37]. The use of small high-resolution cameras specifically designed for breast imaging has improved detection of small and noninvasive carcinomas [38,39]. The breast dedicated imaging modalities available include Tc-99m sestamibi molecular breast imaging (MBI) and fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) positron emission mammography (PEM). At this time, there is no literature specific to the use of nuclear medicine techniques for evaluation of nipple discharge.

### *Image-guided fine-needle aspiration or core biopsy*

Once a suspicious lesion that is likely responsible for pathologic nipple discharge is identified on imaging, image-guided fine-needle aspiration (FNA) or core-needle biopsy (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 [40,41].

## **Discussion of Imaging Modalities by Variant**

### **Variant 1: Physiologic nipple discharge. Woman of any age. Initial imaging examination.**

Physiologic nipple discharges are those that are bilateral, originating from multiple ducts, white/green/yellow in color, or milky in appearance [2]. They tend to occur only when provoked [4]. Many studies have shown physiologic nipple discharge to be benign, with no association with in situ or invasive carcinoma [5-7].

### *Mammography or digital breast tomosynthesis diagnostic*

If patient history and physical examination demonstrate a physiologic nipple discharge and routine screening mammography is up to date, no radiologic investigation is needed [6,7].

### *Ultrasound*

If patient history and physical examination demonstrate a physiologic nipple discharge and routine screening mammography is up to date, no radiologic investigation is needed [6,7].

### *Ductography (galactography)*

If patient history and physical examination demonstrate a physiologic nipple discharge and routine screening mammography is up to date, no radiologic investigation is needed [6,7].

### *Magnetic resonance imaging*

If patient history and physical examination demonstrate a physiologic nipple discharge and routine screening mammography is up to date, no radiologic investigation is needed [6,7].

### *MBI and FDG-PEM*

If patient history and physical examination demonstrate a physiologic nipple discharge and routine screening mammography is up to date, no radiologic investigation is needed [6,7].

### *Image-guided fine-needle aspiration or core biopsy*

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



## **Variant 2: Pathologic nipple discharge. Man or woman 40 years of age or older. Initial imaging examination.**

### *Age- and sex-related issues*

Seltzer et al [9] studied 136 patients with pathologic nipple discharge and no palpable mass. The reported risk of cancer in this cohort was 10% in patients between the ages of 40 to 60 years and 32% after the age of 60 years. The high incidence of cancer in this age group justifies rigorous imaging evaluation.

There is a high incidence (23%–57%) of breast cancer in male patients with nipple discharge [14,15]. Imaging investigation such as mammography and sonography may assist in diagnosis and provide guidance for biopsy, especially in the absence of a palpable mass [14,15,17].

### *Mammography or digital breast tomosynthesis diagnostic*

Mammography is the first-line imaging modality for evaluation of pathologic nipple discharge in most practices. Although 5% to 21% of pathologic nipple discharge is due to an underlying breast cancer, full-field mammography often does not portray these lesions because they may be very small, contain no calcifications, or are completely intraductal [3,32,34]. To better evaluate the subareolar region in patients with asymmetry/focal asymmetry or suspicious microcalcifications, additional mammographic views with spot compression and magnification may be needed [25]. Currently, there is no published literature that discusses the diagnostic accuracy of DBT compared with digital mammography in the specific setting of nipple discharge, and there is no literature on the role of DBT for the evaluation of nipple discharge.

Most cases of pathologic nipple discharge are due to benign intraductal papilloma [8]. When visible on mammography, imaging findings of papilloma include asymmetrically dilated ducts, a circumscribed benign-appearing subareolar mass, or grouped microcalcifications [32]. Up to 12% of patients with ductal carcinoma in situ (DCIS) present with nipple discharge [42]. DCIS is usually detected 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 [43]. 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 [44].

For detection of malignancy (DCIS and invasive cancer), the reported sensitivity of mammography varied widely between 15% and 68%, with a specificity between 38% and 98% [3,5,6,10]. The positive predictive value (PPV) was 42% and negative predictive value (NPV) 90% in one report [10]. For identification of malignant and high-risk lesions combined, mammography has a reported sensitivity of 10% to 26%, specificity of 94% to 95%, PPV of 18%, and NPV of 88% [3,13]. The possible causes of the wide variation in reported sensitivity include difference in imaging technology (digital versus film-screen mammography) and varied breast density among different cohorts of patients.

In a study of 106 patients older than age 30 years with pathologic nipple discharge, Gray et al [6] 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.

For male and female patients in this age group, mammography is usually the initial imaging study [17].

### *Ultrasound*

US is very useful in identification of invasive cancer and estimation of its extent but has a lower sensitivity for detection of DCIS [5,45-47]. In evaluating pathologic nipple discharge, US can identify lesions not visible on mammography in 63% to 69% of cases [12,48]. To a certain degree, it can further evaluate mammographic findings to differentiate between benign and suspicious lesions. Compared to ductography, the advantage of US is its ability to visualize and detect abnormalities in multiple rather than single ducts [31].

The reported sensitivity, specificity, PPV, and NPV of US alone for detection of underlying malignancy in patients with pathologic nipple discharge are 56% to 80%, 61% to 75%, 29% to 39%, and 90% to 91%, respectively [3,5,10]. The wide variation in reported sensitivity can be explained by differences in the definition of pathologic nipple discharge and variation in US technique [5].

Although more sensitive than mammography, US suffers from lower specificity in differentiating benign versus malignant lesions [5]. False-positive US results may be caused by volume averaging with the ductal wall in a

tortuous duct, intraductal and periductal fibrosis, adherent blood clots, or inspissated secretions [25]. Previous studies have also reported mammography and US to be unreliable in predicting histological diagnosis in patients with pathologic nipple discharge [10,49]. This underscores the necessity of histological diagnosis of US-identified lesions. One important utility of US is to localize and guide CNB of image-detected lesions.

In male patients, US is as useful as in female patients in the identification and assessment of lesions and in guidance for biopsy [17].

#### *Ductography (galactography)*

Ductography has the ability to demonstrate very small lesions in the specific duct that is secreting the pathologic nipple discharge. However, it is invasive and may cause discomfort and pain. It can be time-consuming and technically challenging, with 10% of cases being technically inadequate [33]. The rate of incomplete ductography was reported to be as high as 15% on a series of 163 examinations [24]. 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 occur and contrast extravasation may render the ductogram nondiagnostic, necessitating a repeat attempt in 1 to 2 weeks [50]. Cannulation of the wrong duct may cause a false-negative ductogram while the pathologic nipple discharge persists. A repeat ductogram may be considered in this case. Ductography is not recommended in lactating women or patients with active mastitis. Known hypersensitivity to iodinated contrast agents is a relative contraindication. Findings on ductogram 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 [32].

In patients with pathologic nipple discharge and a negative standard evaluation, Morrogh et al [24] 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 [12]. When the standard evaluation is positive, additional ductography facilitated preoperative localization of the causative lesion in 78% of cases [12]. 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 [10,13]. For detection of high-risk lesions, Adepoju et al [13] reported the sensitivity, specificity, PPV, and NPV of ductography to be 75%, 53%, 22%, and 92%, respectively.

Although ductography is more sensitive than mammography and US, it has a lower specificity than these 2 modalities. The literature asserts the difficulty of distinguishing between malignant and benign lesions on a positive ductogram. Furthermore, 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% [24]. These results lead to the conclusion that the primary value of ductography is not to determine whether surgery is indicated but to locate the precise site of the intraductal lesions to aid in the choice of appropriate surgery [18]. 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 [10,19].

At this time, no literature is available in the use of ductography for evaluation of male patients with nipple discharge.

#### *Magnetic resonance imaging*

The sensitivity of breast MRI for detecting invasive breast cancer is high, within the range of 93% to 100%. The primary limitation of dynamic contrast-enhanced MRI is a relatively low specificity, reported to be between 37% and 97% [51]. Breast MRI specificity relies on analysis of a lesion's morphology and enhancement kinetics [51]. Malignant lesions may appear as a mass or nonmass enhancement in ductal or segmental distribution on MRI. Noncontrast MRI, although useful for evaluation of implant integrity, has no value in the detection of malignant or high-risk lesions in patients with nipple discharge [52].

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, ductogram, or targeted US [24]. Index or synchronous lesions found on MR alone can be percutaneously biopsied with MR 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 other approaches have failed to identify an underlying cause of pathologic nipple discharge [3,23,24,53,54]. The sensitivities of breast MRI for detection of underlying cause of pathologic nipple discharge are 86% to 100% for invasive cancer and 40% to 100% for noninvasive disease [3,24,46,53,55,56]. Bahl et al [56] reported a sensitivity, specificity, PPV, and NPV of MRI for detection of malignancy in patients with pathologic nipple discharge to be 100%, 68%, 37%, and 100%, respectively. Several studies showed that MRI has higher sensitivity and specificity than US and ductography for lesion detection and may be a useful alternative to ductography [8,23,46,53]. However, a study by van Gelder et al [55] 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, since malignancy can be demonstrated in <2% of their cases.

MR ductography has been advocated for evaluation of pathologic nipple discharge. It is performed with heavily T2-weighted sequences so that dilated ducts are depicted as tubular structures with high signal intensity. Similar to conventional ductography, intraductal lesions appear as a signal defect, duct wall irregularity, or ductal obstruction. It is noninvasive and requires no radiation or iodinated contrast media. When combined with contrast-enhanced MRI, the study can demonstrate the presence and extent of an intraductal lesion and its relationship with the dilated duct [57].

At this time, no literature is available in the use of MRI for evaluation of male patients with nipple discharge.

#### *MBI and FDG-PEM*

Although the use of small high-resolution cameras specifically designed for breast imaging has improved detection of small and noninvasive carcinomas, research specific to the evaluation of women with nipple discharge is lacking [38,39]. There is currently no known application for the use of MBI or FDG-PEM in the evaluation of a male or female patient with pathologic nipple discharge.

#### *Image-guided core biopsy*

Previous reports showed that mammography, US, and ductography are unreliable in predicting histological diagnosis in patients with pathologic nipple discharge [10,24,49]. This underscores the importance of histological diagnosis of lesions identified by imaging. The biopsy procedures may be guided by stereotactic mammography, US, ductography, or MRI, depending on the imaging modality that best demonstrated the lesion. CNB is preferred over FNA [40,41]. Placement of a tissue marker at the end of biopsy allows for needle localization and excision if the biopsied lesion has malignant or high-risk histology.

Vacuum-assisted CNB is particularly useful in assuring complete sampling of small intraductal papillary lesions [31]. 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 [31,58]. However, Reiner et al [59] cautioned that galactography-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 galactography abnormalities because of the high underestimation rate (50%) for high-risk lesions and DCIS, false-negative rate (7%), and histopathological detection of lesions' remnants in every case.

Papillomas are historically considered high-risk lesions, with reported rates of upgrade to malignancy between 3% and 14% [60,61]. The management of papillomas diagnosed on CNB is controversial and varies by institution [62]. Since papillomas diagnosed on CNB are often excised, excisional biopsy instead of CNB may be appropriate when a papillary lesion is anticipated based on imaging findings. A recent study suggests that patients with pathologic nipple discharge that is nonbloody, with 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 [63].

According to many reports in surgical literature, major duct excision remains the gold standard to exclude malignancy in patients with negative standard evaluation because a negative ductogram or MRI does not reliably exclude an underlying cancer or high-risk lesion [12,24,64]. In some cases, there is uncertainty whether the imaging-detected lesions are actually responsible for the nipple discharge. Although US can detect small intraductal lesions, it does not reliably distinguish between benign and malignant pathology [5]. Therefore, the decision to perform percutaneous biopsy versus major duct excision should involve the patient and her health care provider.

Image-guided CNB is equally useful in male patients for obtaining tissue diagnosis and assisting in patient management [17].

#### *Image-guided fine-needle aspiration*

Once a suspicious lesion that is likely responsible for 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 [40,41].

In male patients, image-guided FNA may be useful in obtaining cytological diagnosis.

#### **Variant 3: Pathologic nipple discharge. Man or woman 30 to 39 years of age. Initial imaging examination.**

The risk of breast cancer is relatively low (1.4% or less) for women in their fourth decade [65]. There are scant data on the risk of breast cancer in women 30 to 39 years of age presenting with pathologic nipple discharge. In the study by Seltzer et al [9], no malignancy was recorded among patients 30 to 39 years of age with pathologic nipple discharge and no palpable mass. However, a study by Cabioglu et al [10] found 2 cancers among 19 patients 40 years of age or younger (10.5%) presenting with pathologic nipple discharge. There is no other study in the literature that addresses the appropriateness of imaging in women 30 to 39 years of age with the specific symptoms of pathologic nipple discharge.

A study by Lehman et al [66] of 1208 cases in women 30 to 39 years of age with focal symptoms including palpable lump, thickening, or focal pain identified 23 malignant lesions (1.9%) with US. They concluded that breast imaging is warranted in women 30 to 39 years of age with focal signs and symptoms because of the small but real risk of malignancy. Since pathologic nipple discharge is associated with underlying malignancy in up to 21% of patients, it can be considered a symptom as significant as a palpable mass. Using the Lehman study as a parallel, one would conclude that breast imaging is also appropriate for patients with pathologic nipple discharge. The modalities discussed under Variant 2 for woman 40 years of age and over can be equally applied to patients in this age group, with some caveats.

#### *Mammography or digital breast tomosynthesis diagnostic*

The sensitivity of US for palpable or nonpalpable breast cancer is higher than that of mammography for women 30 to 39 years of age [66,67]. Hence, either mammography or US may be used as the initial imaging modality, based on 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 [14,15], imaging studies are also appropriate in male patients between the ages of 30 and 39 years. Following the recommendation of the ACR Appropriateness Criteria<sup>®</sup> “Evaluation of the Symptomatic Male Breast,” mammography should be the initial imaging study for these patients [17].

#### *Ultrasound*

The sensitivity of US for palpable or nonpalpable breast cancer is higher than that of mammography for women in this age group [66,67]. Hence, US may be used as the initial imaging modality, with mammography added when indicated.

Following the recommendation of the ACR Appropriateness Criteria<sup>®</sup> “Evaluation of the Symptomatic Male Breast,” mammography should be the initial imaging study for male patients with nipple discharge, and US is added to assist in diagnosis and guidance for biopsy [17].

#### *Ductography (galactography)*

Ductography has the ability to demonstrate very small lesions in the specific duct that is secreting the pathologic nipple discharge. However, it is invasive and may cause discomfort and pain. It can be time-consuming and technically challenging, with 10% of cases being technically inadequate [33]. The rate of incomplete ductography was reported to be as high as 15% on a series of 163 examinations [24]. 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 occur and contrast extravasation may render the ductogram nondiagnostic, necessitating a repeat attempt in 1 to 2 weeks [50]. Cannulation of the wrong duct may cause a false-negative ductogram while the pathologic nipple discharge persists. A repeat ductogram may be considered in this case. Ductography is not recommended in

lactating women or patients with active mastitis. Known hypersensitivity to iodinated contrast agents is a relative contraindication. Findings on ductogram 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 [32].

In patients with pathologic nipple discharge and a negative standard evaluation, Morrogh et al [24] 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 [12]. When the standard evaluation was positive, additional ductography facilitated preoperative localization of the causative lesion in 78% of cases [12]. 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 [10,13]. For detection of high-risk lesions, Adepoju et al [13] reported the sensitivity, specificity, PPV, and NPV of ductography to be 75%, 53%, 22%, and 92%, respectively.

Although ductography is more sensitive than mammography and US, it has a lower specificity than these 2 modalities. The literature asserts the difficulty of distinguishing between malignant and benign lesions on a positive ductogram. Furthermore, 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% [24]. These results lead to the conclusion that the primary value of ductography is not to determine whether surgery is indicated but to locate the precise site of the intraductal lesions to aid in the choice of appropriate surgery [18]. A study found that patients who underwent a ductography-guided operation 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 [10,19].

At this time, no literature is available in the use of ductography for evaluation of male patients with nipple discharge.

#### *Magnetic resonance imaging*

The sensitivity of breast MRI for detecting invasive breast cancer is high, within the range of 93% to 100%. The primary limitation of dynamic contrast-enhanced MRI is a relatively low specificity, reported to be between 37% and 97% [51]. Breast MRI specificity relies on analysis of a lesion's morphology and enhancement kinetics [51]. Malignant lesions may appear as a mass or nonmass enhancement in ductal or segmental distribution on MRI. Noncontrast MRI, although useful for evaluation of implant integrity, has no value in the detection of malignant or high-risk lesions in patients with nipple discharge [52].

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, ductogram, or targeted US [24]. Index or synchronous lesions found on MR alone can be percutaneously biopsied with MR 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 other approaches have failed to identify an underlying cause of pathologic nipple discharge [3,23,24,53-55]. The sensitivities of breast MRI for detection of underlying cause of pathologic nipple discharge are 86% to 100% for invasive cancer and 40% to 100% for noninvasive disease [3,24,46,53,55,56]. Bahl et al [56] reported the sensitivity, specificity, PPV, and NPV of MRI for detection of malignancy in patients with pathologic nipple discharge to be 100%, 68%, 37%, and 100%, respectively. Several studies showed that MRI has higher sensitivity and specificity than US and ductography for lesion detection and may be a useful alternative to ductography [8,23,46,53]. However, a study by van Gelder et al [55] 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, since malignancy can be demonstrated in <2% of their cases.

MR ductography has been advocated for evaluation of pathologic nipple discharge. It is performed with heavily T2-weighted sequences so that dilated ducts are depicted as tubular structures with high signal intensity. Similar to conventional ductography, intraductal lesions appear as a signal defect, duct wall irregularity, or ductal obstruction. It is noninvasive and requires no radiation or iodinated contrast media. When combined with contrast-enhanced MRI, the study can demonstrate the presence and extent of an intraductal lesion and its relationship with the dilated duct [57].

At this time, no literature is available in the use of MRI for evaluation of male patients with nipple discharge.

#### *MBI and FDG-PEM*

Although the use of small high-resolution cameras specifically designed for breast imaging has improved detection of small and noninvasive carcinomas, research specific to the evaluation of women with nipple discharge is lacking [38,39]. There is currently no known application for the use of MBI or FDG-PEM in the evaluation of a patient with pathologic nipple discharge.

At this time, no literature is available in the use of nuclear medicine for evaluation of male patients with nipple discharge.

#### *Image-guided core biopsy*

Previous reports showed that mammography, US, and ductography are unreliable in predicting histological diagnosis in patients with pathologic nipple discharge [10,24,49]. This underscores the importance of histological diagnosis of lesions identified by imaging. The biopsy procedures may be guided by stereotactic mammography, US, ductography, or MRI, depending on the imaging modality that best demonstrated the lesion. CNB is preferred over FNA [40,41]. Placement of a tissue marker at the end of biopsy allows for needle localization and excision if the biopsied lesion has malignant or high-risk histology.

Vacuum-assisted CNB is particularly useful in assuring complete sampling of small intraductal papillary lesions [31]. 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 [31,58]. However, Reiner et al [59] cautioned that galactography-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 galactography abnormalities because of the high underestimation rate (50%) for high-risk lesions and DCIS, false-negative rate (7%), and histopathological detection of lesions' remnants in every case.

Papillomas are historically considered high-risk lesions, with reported rates of upgrade to malignancy between 3% and 14% [60,61]. The management of papillomas diagnosed on CNB is controversial and varies by institution [62]. Since papillomas diagnosed on CNB are often excised, excisional biopsy instead of CNB may be appropriate when a papillary lesion is anticipated based on imaging findings. A recent study suggests that patients with pathologic nipple discharge that is nonbloody, with 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 [63].

According to many reports in surgical literature, major duct excision remains the gold standard to exclude malignancy in patients with negative standard evaluation because a negative ductogram or MRI does not reliably exclude an underlying cancer or high-risk lesion [12,24,64]. In some cases, there is uncertainty whether the imaging-detected lesions are actually responsible for the nipple discharge. Although US can detect small intraductal lesions, it does not reliably distinguish between benign and malignant pathology [5]. Therefore, the decision to perform percutaneous biopsy versus major duct excision should involve the patient and her health care provider.

Image-guided CNB is equally useful in male patients for obtaining tissue diagnosis and assisting in patient management [17].

#### *Image-guided fine-needle aspiration*

Once a suspicious lesion that is likely responsible for 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 [40,41].

In male patients, image-guided FNA may be useful in obtaining cytological diagnosis.

#### **Variant 4: Pathologic nipple discharge. Woman younger than 30 years of age. Initial imaging examination.**

The probability of a woman developing breast cancer over the next decade increases with age; the risk is 1 in 1681 at 20 years, 1 in 232 at 30 years, and 1 in 69 at 40 years of age [65]. Breast cancer is rare in women younger than 30 years, with the probable exception of those with a hereditary predisposition or prior mantle chest radiation. In a study by Seltzer et al [9] on the significance of age in patients with nipple discharge, malignancy

was found in 1 of 10 patients younger than 30 years. Although 10% seems a high percentage, the very small sample size makes it difficult to interpret. It is also unknown whether this was a high-risk patient.

#### *Mammography or digital breast tomosynthesis diagnostic*

Most breast lesions in young women are not visualized on mammography [68,69]. Because of the theoretically increased radiation risk of mammography and the low incidence of breast cancer (0.4% or lower) in women younger than 30 years, mammography does not appear appropriate for a patient of this age group. However, mammography may be indicated when the initial US shows a suspicious finding. US is also likely of very low yield.

#### *Ultrasound*

Yue et al [70] studied 955 women younger than 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 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 nipple discharge and whether the discharges were physiologic or pathologic.

#### *Ductography (galactography)*

There are currently no studies in the literature that address the appropriateness of ductography in women younger than 30 years with the specific symptoms of pathologic nipple discharge. Pertinent clinical factors such as family history and risk profile of the patient should be used to determine appropriate patient care.

#### *Magnetic resonance imaging*

There are currently no studies in the literature that address the appropriateness of MRI in women younger than 30 years with the specific symptoms of pathologic nipple discharge. Pertinent clinical factors such as family history and risk profile of the patient should be used to determine appropriate patient care.

#### *MBI and FDG-PEM*

There are currently no studies in the literature that address the appropriateness of MBI and FDG-PEM in women younger than 30 years with the specific symptoms of pathologic nipple discharge. Pertinent clinical factors such as family history and risk profile of the patient should be used to determine appropriate patient care.

#### *Image-guided fine-needle aspiration or core biopsy*

There are currently no studies in the literature that address the appropriateness of image-guided FNA or core biopsy in women younger than 30 years with the specific symptoms of pathologic nipple discharge. Pertinent clinical factors such as family history and risk profile of the patient should be used to determine appropriate patient care.

### **Variant 5: Pathologic nipple discharge. Man younger than 30 years of age. Initial imaging examination.**

For male patients presenting with nipple discharge, the incidence of cancer was high (23%–57%) [14,15]. Given the high pretest probability, imaging studies are appropriate even in male patient younger than 30 years of age.

#### *Mammography or digital breast tomosynthesis diagnostic*

Following the recommendation of the ACR Appropriateness Criteria® “Evaluation of the Symptomatic Male Breast,” mammography should be the initial imaging study for male patients with highly concerning physical examination findings such as nipple discharge, and US is useful in diagnosis and in guidance for biopsy. For male patients younger than 25 years of age, US may be the initial examination, with mammography added as indicated [17].

#### *Ultrasound*

Following the recommendation of the ACR Appropriateness Criteria® “Evaluation of the Symptomatic Male Breast,” mammography should be the initial imaging study for male patients with highly concerning physical examination findings such as nipple discharge, and US is useful in diagnosis and in guidance for biopsy. For male patients younger than 25 years of age, US may be the initial examination, with mammography added as indicated [17].

#### *Ductography (galactography)*

At this time, no literature is available in the use of ductography for evaluation of male patients with nipple discharge.

### *Magnetic resonance imaging*

At this time, no literature is available in the use of MRI for evaluation of male patients with nipple discharge.

### *MBI and FDG-PEM*

At this time, no literature is available in the use of MBI or FDG-PEM for evaluation of male patients with nipple discharge.

### *Image-guided fine-needle aspiration or core biopsy*

At this time, no literature is available in the use of image-guided FNA or core biopsy for evaluation of male patients with nipple discharge.

## **Summary of Recommendations**

- Imaging is not indicated for evaluation of physiologic nipple discharge.
- For men or women 40 years of age or older, mammography or DBT should be the initial examination. US is usually added as a complementary examination. Mammography should be repeated if the prior mammography was performed >6 months ago. US may be used as the initial examination if the patient had a recent mammography or is pregnant. Although MRI or ductography is usually not appropriate as an initial examination, it may be useful when the initial standard imaging evaluation is negative.
- For women 30 to 39 years of age, US can be used as an initial examination in place of mammography. Mammography/DBT should be performed as the initial study in men in this age range, given the high incidence of cancer in men with pathologic nipple discharge, with US serving as a complimentary examination. Although MRI or ductography is usually not appropriate as an initial examination, it may be useful when initial standard imaging evaluation is negative.
- For a women 30 years of age or younger, US should be the initial examination, even though the yield is low. Mammography or DBT may be complementary when the initial US shows suspicious findings or if the patient has a genetic mutation predisposing to breast cancer.
- For men 25 to 30 years of age, mammography or DBT should be performed initially, with US added as indicated, given the high incidence of breast cancer in men with pathologic nipple discharge. For men 25 years of age or younger, US may be the initial examination, with mammography added as indicated.

## **Summary of Evidence**

Of the 73 references cited in the *ACR Appropriateness Criteria<sup>®</sup> Evaluation of Nipple Discharge* document, 2 are categorized as therapeutic references, including 1 good-quality study. Additionally, 71 references are categorized as diagnostic references, including 2 well-designed studies, 6 good-quality studies, and 35 quality studies that may have design limitations. There are 29 references that may not be useful as primary evidence.

The 73 references cited in the *ACR Appropriateness Criteria<sup>®</sup> Evaluation of Nipple Discharge* document were published from 1970 through 2015.

Although there are references that report on studies with design limitations, 9 well-designed or good-quality studies provide good evidence.

## **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, both because of 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 to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the *ACR Appropriateness Criteria<sup>®</sup> [Radiation Dose Assessment Introduction](#)* document.



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”.

### Supporting Documents

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

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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.