

**Evaluation of Nipple Discharge
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Onstad M, Stuckey A. Benign breast disorders. <i>Obstet Gynecol Clin North Am.</i> 2013;40(3):459-473.	Review/Other-Dx	N/A	To review common benign breast problems in the manner whereby they are most likely to be presented to the clinician. A discussion of common breast symptoms is followed by a review of benign breast processes found incidentally on imaging and biopsies.	Benign breast lesions are much more common than malignant lesions. Women may present with specific complaints related to their breasts, or may have abnormal screening mammograms that lead to the diagnosis of benign breast disease. Evaluation should include obtaining a relevant history, performing a physical examination, ordering imaging studies as appropriate, and obtaining a tissue diagnosis when indicated. Some benign breast diseases have been associated with an increased risk for developing breast cancer.	4
2. Alcock C, Layer GT. Predicting occult malignancy in nipple discharge. <i>ANZ J Surg.</i> 2010;80(9):646-649.	Observational-Dx	49 patients	To determine which investigations and patient factors could help predict which patients with pathological nipple discharge would later be found to have an underlying malignancy.	Of the 49 patients undergoing surgery for nipple discharge, 21 were diagnosed with intraductal papilloma, 19 with duct ectasia, 6 with carcinoma, 2 with benign breast disease and 1 with lobular carcinoma in situ. In all of the patients determined to have malignancy, none demonstrated malignant changes on mammography or US. Only 2 of the 6 patients with malignancy were found to have atypical cells on cytological analysis. The sensitivity of blood detected in nipple discharge at predicting malignancy was 0.83, specificity of 0.53, PPV of 0.20 and NPV 0.96.	3

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3. Lorenzon M, Zuiani C, Linda A, Londero V, Girometti R, Bazzocchi M. Magnetic resonance imaging in patients with nipple discharge: should we recommend it? <i>Eur Radiol.</i> 2011;21(5):899-907.	Observational-Dx	38 women	To compare the sensitivity of CE-MRI, mammography and US in patients with nipple discharge.	5/38 malignancies (13.2%; 3 invasive, 2 intraductal; 4 ipsilateral, 1 contralateral to nipple discharge), and 14/38 HRL (36.8%; 11 intraductal papillomas, 1 papilloma with LCIS, 1 sclerosing papilloma and 1 atypical intraductal hyperplasia, all ipsilateral) were found. CE-MRI identified 5/5 cancers and 13/14 HRL (overall sensitivity = 94.7%; overall specificity = 78.9%). 3/5 cancers (1 invasive, 1 in-situ; 1 invasive contralateral) and 2/14 HRL were detected by CE-MRI only. Mammography found 2/5 cancer and 3/14 HRL (overall sensitivity = 26.3%; overall specificity = 94.7%). US identified 1/5 cancer and 11/14 HRL (overall sensitivity = 63.2%; overall specificity = 84.2%). 1/14 HRL was detected by US only. Compared with mammography and US, CE-MRI showed statistically significantly higher overall sensitivity values ($P < 0.0001$, $P = 0.042$ respectively).	3

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<p>4. Goksel HA, Yagmurdu MC, Demirhan B, et al. Management strategies for patients with nipple discharge. <i>Langenbecks Arch Surg.</i> 2005;390(1):52-58.</p>	<p>Observational-Dx</p>	<p>13,443 patients</p>	<p>To assess management strategies for patients with nipple discharge.</p>	<p>Nipple discharge was the presenting symptom in 603 (4.5%) of the cases. 287 (48%) of the 603 patients showed spontaneous nipple discharge and the other 316 (52%) showed provoked nipple discharge. In the spontaneous nipple discharge group, 124 (43%) tissue specimens were obtained by either biopsy or sub-areolar exploration. Histopathological examination revealed that the most frequent causes of nipple discharge in these cases were intraductal papilloma (49 patients; 40%), intraductal carcinoma (35 patients; 28%), and cystic disease (15 patients; 12%). 20 tissue specimens were obtained from the group with provoked nipple discharge. In these cases, the most frequently identified causes of nipple discharge were cystic disease (7 patients; 35%), intraductal papilloma (6 patients; 30%), ductal ectasia (2 patients; 10%), and carcinoma (1 patient; 5%). The spontaneous nipple discharge and provoked nipple discharge groups differed significantly with respect to age ($P=0.001$) and duration of nipple discharge ($P=0.008$). The incidence of cancer was higher in the spontaneous nipple discharge specimens than in the provoked nipple discharge specimens (28% vs 5%, respectively; $P=0.01$). The number of pregnancies was significantly higher and the duration of lactation was significantly longer in the spontaneous nipple discharge group ($P=0.03$ and $P=0.02$, respectively).</p>	<p>4</p>

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5. Bahl M, Baker JA, Greenup RA, Ghate SV. Diagnostic Value of Ultrasound in Female Patients With Nipple Discharge. <i>AJR Am J Roentgenol.</i> 2015;205(1):203-208.	Observational-Dx	327 female patients	To assess the contribution of US to the evaluation of patients with pathologic nipple discharge at a large academic institution.	Over a 3-year period, 327 females (mean age, 48 years; range, 13–88 years) presented with nipple discharge. Among these patients, 273 (83%) underwent surgical excision or clinical or radiographic follow-up at least 2 years after presentation and composed the study population. Among the 273 patients, 262 (96%) underwent mammography and 246 (90%) underwent US. Among 252 patients who had at least 1 pathologic feature of nipple discharge and underwent surgical excision or at least 2 years of follow-up, a total of 20 (8%) cases of DCIS or invasive adenocarcinoma were diagnosed. DCIS or invasive adenocarcinoma was diagnosed in 8 patients with normal US findings. For the detection of DCIS and invasive adenocarcinoma, the sensitivity and specificity of US were 56% (10/18) and 75% (170/228); the sensitivity and specificity of mammography were 15% (3/20) and 98% (237/242).	3
6. Gray RJ, Pockaj BA, Karstaedt PJ. Navigating murky waters: a modern treatment algorithm for nipple discharge. <i>Am J Surg.</i> 2007;194(6):850-854; discussion 854-855.	Observational-Dx	204 patients	To define the risk of carcinoma among patients with defined clinical and imaging findings to create an evidence-based treatment algorithm.	Nipple discharge was present in 204 patients. Carcinoma was identified in 7 patients (3% of all, 9% of those undergoing biopsy). Age ≥50 years, abnormal mammography, and abnormal US were the only significant predictors of carcinoma. Among patients with unilateral, spontaneous, bloody, or serous discharge with a negative mammogram, the carcinoma risk was 3%. Among patients with unilateral, spontaneous, bloody, or serous discharge with a negative mammogram and subareolar US, the carcinoma risk was 0%.	3

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7. Gulay H, Bora S, Kilicturgay S, Hamaloglu E, Goksel HA. Management of nipple discharge. <i>J Am Coll Surg.</i> 1994;178(5):471-474.	Review/Other-Dx	448 patients	To compile the clinical findings and course of patients with nipple discharge seen by 1 of the authors between 1959 and 1991.	Nipple discharge was the presenting symptom in 448 (4.8%) of 9,312 women who consulted 1 of the authors with a complaint of disease of the breast. Nipple discharge was spontaneous in 243 (2.6%) and provoked in 205 (2.2%) of the patients. The ages of the patients ranged from 13 to 75 years (mean of 42.5 years) in the spontaneous and 16 to 70 years (mean of 37.8 years) in the provoked discharge group. When a palpable mass was found, biopsy was undertaken, while in instances of nipple discharge only, subareolar exploration was performed. Of the 115 patients in the spontaneous and 25 patients in the provoked groups who underwent biopsy, the most frequent cause of nipple discharge was intraductal papilloma (47.8%). Nipple discharge was the result of carcinoma in 35 patients (14.4%) in the spontaneous and 6 patients (2.9%) in the provoked group, respectively. In patients with a palpable mass, the incidence of carcinoma was 61.5% compared with 6.1% in patients with nipple discharge only.	4
8. Orel SG, Dougherty CS, Reynolds C, Czerniecki BJ, Siegelman ES, Schnall MD. MR imaging in patients with nipple discharge: initial experience. <i>Radiology.</i> 2000;216(1):248-254.	Observational-Dx	23 patients	To investigate the potential of contrast MRI in patients with nipple discharge.	In 11/15 (73%) patients who underwent excisional biopsy, MRI findings correlated with histopathologic findings. MRI demonstrated 4 of 6 benign papillomas and 1 of 2 fibroadenomas as circumscribed, enhancing subareolar masses. Findings of 1 MRI examination were negative, and benign tissue was found at excisional biopsy. MRI findings were suspicious in 6 of the 7 patients with excisional biopsy findings of malignancy (regional enhancement [n = 2], ductal enhancement [n = 2], peripherally enhancing mass [n = 1], and spiculated mass [n = 1]). In 1 of the 7 patients, a benign-appearing intraductal mass was identified at MRI; excisional biopsy revealed a benign papilloma with an adjacent focus of DCIS.	3

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<p>9. Seltzer MH, Perloff LJ, Kelley RI, Fitts WT, Jr. The significance of age in patients with nipple discharge. <i>Surg Gynecol Obstet.</i> 1970;131(3):519-522.</p>	<p>Review/Other-Dx</p>	<p>336 patients</p>	<p>To determine if age of the patient has significant bearing on management, since patients in the older age groups with nipple discharge and no palpable mass had a high incidence of carcinoma of the breast.</p>	<p>Among our total group of 3,787 patients, 336, or slightly less than 10%, had a history of nipple discharge. 136 patients, 40% of those with nipple discharge, had no palpable mass. In this group, there were 16 instances of carcinoma, an incidence of 11.8%. Over the age of 60 years, 9 out of the 28 patients with nipple discharge and no associated mass had carcinoma, an incidence of 32%. There were 62 additional instances of carcinoma in the 200 patients with both nipple discharge and a palpable mass. This represents a carcinoma incidence in this group of 31%, and results in an incidence of carcinoma for all patients with discharge of 23% or 78 out of 336. Of all patients with bloody discharge, 25% had carcinoma, while 21% of those with serous discharge had carcinoma. Patients over the age of 60 years are of interest in that 46% of those with bloody discharge had carcinoma while 56% of those with serous discharge had carcinoma. Cytologic examination of nipple discharge in our experience has not proved helpful in differentiating benign from malignant breast lesions.</p>	<p>4</p>

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10. Cabioglu N, Hunt KK, Singletary SE, et al. Surgical decision making and factors determining a diagnosis of breast carcinoma in women presenting with nipple discharge. <i>J Am Coll Surg.</i> 2003;196(3):354-364.	Observational-Dx	146 patients	To identify patient and nipple-discharge characteristics associated with the diagnosis of breast cancer and to determine the utility of mammography, US, ductography, and cytology in surgical decision making in patients presenting with pathologic nipple discharge.	A total of 146 patients presented at our institution with nipple discharge during the study period. Of these, 52 had clinically benign discharge and were managed without surgical intervention; 94 patients had pathologic discharge and underwent a biopsy procedure for histologic diagnosis, treatment, or both. Logistic regression analysis identified mammographic (relative risk = 10.47, 95% CI, 2.36 to 46.39, $P=0.0002$) and US (RR = 5.54, 95% CI, 1.27 to 25.40, $P=0.028$) abnormalities as independent factors associated with a malignant diagnosis. 19 cancers, 62 papillomas, and 13 other benign lesions were identified among the patients with pathologic discharge. In 3 patients with cancer (15.8%) and 30 patients with a papilloma (48.4%), ductography was the only means of identifying lesions to be resected. Patients who underwent ductography-guided operation (n = 42, 50%) or any surgical procedure including a localization study (n = 66, 78.6%) were significantly more likely than patients who underwent central duct excision alone to have a specific underlying lesion identified ($P=0.045$ and $P=0.033$, respectively).	3
11. Kalu ON, Chow C, Wheeler A, Kong C, Wapnir I. The diagnostic value of nipple discharge cytology: breast imaging complements predictive value of nipple discharge cytology. <i>J Surg Oncol.</i> 2012;106(4):381-385.	Observational-Dx	89 patients	To determine the predictive value of nipple discharge cytology in conjunction with breast imaging.	89 patients identified. 65 had positive cytology, with a false positive rate of 32.3%. They were associated with papillomas in 52%, benign non-papillary in 33% and malignant lesions in 9% of cases. Nipple discharge cytology was positive in 69.6% of papillomas and 92% of atypical/malignant lesions; 30% had abnormal breast imaging and positive cytology. Nipple discharge cytology had a sensitivity of 74.5%, specificity of 30%, and PPV of 68%. The PPV increased to 85% with associated abnormal breast imaging.	3

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12. Morrogh M, Park A, Elkin EB, King TA. Lessons learned from 416 cases of nipple discharge of the breast. <i>Am J Surg.</i> 2010;200(1):73-80.	Observational-Dx	475 patients	To define clinical predictors of malignancy and examine the utility of common preoperative studies.	Following standard evaluation (clinical breast examination/mammogram/US), 129/416 (31%) were considered to have physiological nipple discharge and were managed expectantly, whereas 287/416 (69%) underwent further evaluation (cytology/ductography/MRI) followed by biopsy +/- surgery. Clinical features associated with pathological nipple discharge included bloody nipple discharge (adjusted odds ratio 3.7) and spontaneous nipple discharge (adjusted odds ratio 3.2). Biopsy/surgery identified a causative lesion in 259/287 (90%), of which 37% were either malignant (n = 65) or high-risk (n = 30) lesions. The sole clinical predictor of malignant/HRL was a palpable mass (adjusted odds ratio 4.3). Preoperative evaluation identified 76/95 (80%) malignant/HRLs, whereas 19/95 (20%) were identified by duct excision alone.	3
13. Adepoju LJ, Chun J, El-Tamer M, Ditkoff BA, Schnabel F, Joseph KA. The value of clinical characteristics and breast-imaging studies in predicting a histopathologic diagnosis of cancer or high-risk lesion in patients with spontaneous nipple discharge. <i>Am J Surg.</i> 2005;190(4):644-646.	Observational-Dx	168 cases	To determine the utility of breast-imaging studies in identifying cancer and HRLs among patients with spontaneous, single-duct, nipple discharge.	The sensitivity of mammography was 10%, the specificity 94%, the NPV 88%, and the PPV 18%. US had a sensitivity of 36%, specificity of 68%, PPV of 14%, and NPV of 89%. Ductography had a sensitivity of 75%, specificity of 49%, and NPV and PPV of 93% and 18%, respectively.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
<p>14. Morrogh M, King TA. The significance of nipple discharge of the male breast. <i>Breast J.</i> 2009;15(6):632-638.</p>	<p>Review/Other-Dx</p>	<p>24 male patients</p>	<p>The authors present their experience with male patients presenting with a chief complaint of nipple discharge.</p>	<p>Among 24 male patients presenting for evaluation, 14 (58%) presented with a chief complaint of nipple discharge, while the remaining 10 (42%) presented for evaluation of a palpable mass in the absence of nipple discharge. Among 14 patients presenting with nipple discharge, subsequent clinical breast examination identified a breast mass +/- nipple changes in 7/14 patients. In total, 8/14 (57%) patients had an underlying malignancy; 2/7 patients with nipple discharge alone had DCIS (median interval from onset of nipple discharge to presentation 3 weeks, range 2-4 weeks), and 6/7 patients with nipple discharge and a palpable mass had invasive disease (median interval between onset of nipple discharge and presentation 16 weeks, range 2-52). The remaining 10/24 patients presented with a painless palpable mass of whom 8 (80%) were found to have underlying invasive disease (median interval between onset of mass, and presentation was 4 weeks, range 2-20 weeks). All patients with invasive disease were node-positive. At 23.7 months median follow-up (range, 7.7-88.3 months), 14/16 cancer patients remain free of disease and 2 have died as a direct result of metastatic disease. The incidence of cancer among males presenting with nipple discharge was 57%.</p>	<p>4</p>

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15. Munoz Carrasco R, Alvarez Benito M, Rivin del Campo E. Value of mammography and breast ultrasound in male patients with nipple discharge. <i>Eur J Radiol.</i> 2013;82(3):478-484.	Observational-Dx	26 men with 21 mammograms and 19 USs	To assess the contribution of mammography and US in men with nipple discharge.	The final diagnoses were: 6 carcinomas (23.1%), 10 gynecomastias, 2 pseudogynecomastias and 8 normal breast tissues. Mammograms and USs performed on all 5 patients with infiltrating carcinoma showed a mass (categories 4 and 5). In all these patients except 1, a breast mass was also noted and the physical examination was positive or suspected malignancy. In the patient with carcinoma in situ, the only conspicuous clinical sign was bloody nipple discharge and the mammography showed calcifications (category 4) that were not visible on US. Radiological findings of all patients without malignancy were classified as categories 1 and 2. The diagnostic performance of physical examination was lower than mammography and US ($P>0.05$). Mammography was more sensitive than US (100% vs 83.3%). Both techniques showed the same specificity (100%).	3
16. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. <i>Lancet.</i> 2006;367(9510):595-604.	Review/Other-Tx	N/A	Review management of male breast cancer.	Surgery is usually mastectomy with axillary clearance or sentinel node biopsy. Indications for radiotherapy, by stage, are similar to female breast cancer. Because 90% of tumors are estrogen-receptor-positive, tamoxifen is standard adjuvant therapy, but some individuals could also benefit from chemotherapy. Hormonal therapy is the main treatment for metastatic disease, but chemotherapy can also provide palliation. National initiatives are increasingly needed to improve information and support for male breast cancer patients.	4
17. Mainiero MB, Lourenco AP, Barke LD, et al. ACR Appropriateness Criteria Evaluation of the Symptomatic Male Breast. <i>J Am Coll Radiol.</i> 2015;12(7):678-682.	Review/Other-Dx	N/A	To evaluate the appropriateness of imaging modalities for the assessment of male patients with breast symptoms	No results stated in abstract.	4

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18. Dinkel HP, Trusen A, Gassel AM, et al. Predictive value of galactographic patterns for benign and malignant neoplasms of the breast in patients with nipple discharge. <i>Br J Radiol.</i> 2000;73(871):706-714.	Observational-Dx	351 galactograms	To identify features of malignant and nonmalignant neoplastic breast disease on galactography and to estimate their predictive value.	Extravasation or incomplete filling precluded reading in 9.5% of examinations. Among the remaining 143 examinations there were 11 cancers (7.7%), 56 papillomas (39.2%), 19 cases of intraductal papillomatous proliferation (13.3%), 55 cases of fibrocystic or secretory disease (38.5%) and 2 normals. A “filling defect/cut-off” pattern (n = 90) was found in 6 cancers (6.7%) and 58 cases of papilloma or papillomatous proliferation (64.4%). A “leafless tree” pattern was found only in benign cases (n = 12; 8.4%). In 32/143 cases (22.4%) a “ductal ectasia” pattern was present, in 1 case of which (3.1%) cancer was found. Cancer was identified in 2 of 4 cases with an “architectural distortion” pattern.	3
19. Van Zee KJ, Ortega Perez G, Minnard E, Cohen MA. Preoperative galactography increases the diagnostic yield of major duct excision for nipple discharge. <i>Cancer.</i> 1998;82(10):1874-1880.	Review/Other-Dx	46 cases	To investigate the utility of preoperative galactography in targeting the causative lesion.	Preoperative galactography was obtained in 7/31 patients (23%) with bloody nipple discharge and 9/15 patients (60%) with guaiac negative discharge. All patients undergoing preoperative galactography were found to have either a filling defect and/or duct cutoff (n = 13) or duct ectasia (n = 3). All patients with a filling defect and/or duct cutoff on galactogram were found to have a carcinoma or papilloma at surgery. In the 3 patients with duct ectasia observed on galactogram, the diagnosis was confirmed at surgery. All patients who underwent preoperative galactography were found to have specific pathology that accounted for the nipple discharge vs 20/30 patients (67%) who did not undergo preoperative galactography (P=0.009).	4

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20. Moriarty AT, Schwartz MR, Laucirica R, et al. Cytology of spontaneous nipple discharge--is it worth it? Performance of nipple discharge preparations in the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytopathology. <i>Arch Pathol Lab Med.</i> 2013;137(8):1039-1042.	Observational-Dx	2506 responses	To evaluate participant responses in the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytopathology to assess the accuracy of cytologic interpretation of nipple discharge preparation.	Of 2506 responses, 1280 (51%) were malignant, 171 (7%) were papillary, and 1055 (42%) were benign. There were 222 discordant general category responses with a false-positive/suspicious rate of 12.8% and a false-negative rate of 3.4%. The most common false-negative diagnosis was mastitis/abscess (125/1272 responses; 9.8%). The most common false-positive response was papillary lesion (26/457 responses; 5.7%). There were no differences between stains or years. Cytotechnologists performed better than pathologists; pathologists had a higher false-negative rate than cytotechnologists (15.3% vs 7.9%, $P<.001$).	3
21. Dooley WC. Breast ductoscopy and the evolution of the intra-ductal approach to breast cancer. <i>Breast J.</i> 2009;15 Suppl 1:S90-94.	Review/Other-Dx	N/A	To discuss breast ductoscopy and the evolution of the intra-ductal approach to breast cancer	The early techniques using a single microfiber scope without ductal distension was successful in navigating only the first 1-3 cm of the ducts and fraught with technical problems such as scope breakage and poor image quality. In spite of these barriers there has been increasing use of this technology in Japan and more widespread acceptance as the technology of scope design improved. Dooley and others tested a new method of obtaining a rich cytologic specimen from the ducts of high-risk women known as ductal lavage recently. The success of this procedure was that it detected severe cytologic and malignant atypia in clinically and radiographically normal breasts. Reproducibly, the same breast duct could be cannulated and severely atypical cytology obtained. The problem arose in identifying the lesion within the breast, which was the source for the atypia. New American multi-fiber microendoscopes were applied to solve this problem in an initial series of patients with abnormal cytology to identify the lesions.	4

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22. Kapenhas-Valdes E, Feldman SM, Boolbol SK. The role of mammary ductoscopy in breast cancer: a review of the literature. <i>Ann Surg Oncol</i> . 2008;15(12):3350-3360.	Review/Other-Dx	N/A	To review the literature for the role of mammary ductoscopy.	No results listed in abstract.	4
23. Lubina N, Schedelbeck U, Roth A, et al. 3.0 Tesla breast magnetic resonance imaging in patients with nipple discharge when mammography and ultrasound fail. <i>Eur Radiol</i> . 2015;25(5):1285-1293.	Observational-Dx	50 patients, 56 breasts	To compare 3.0 T breast MRI with galactography for detection of benign and malignant causes of nipple discharge in patients with negative mammography and US.	Sensitivity and specificity of MRI vs galactography for detecting pathologic findings were 95.7% vs 85.7% and 69.7% vs 33.3%, respectively. For the supposed concrete pathology based on MRI findings, the specificity was 67.6% and the sensitivity 77.3% (PPV 60.7%, NPV 82.1%). 8 malignant lesions were detected (14.8%). The estimated size at breast MRI showed excellent correlation with the size at histopathology (Pearson's correlation coefficient 0.95, $P < 0.0001$).	2
24. Morrogh M, Morris EA, Liberman L, Borgen PI, King TA. The predictive value of ductography and magnetic resonance imaging in the management of nipple discharge. <i>Ann Surg Oncol</i> . 2007;14(12):3369-3377.	Observational-Dx	306 patients	To determine the predictive value of ductography and MRI in this setting.	Among 306 patients, 186 (61%) underwent further evaluation with ductography (n = 163) and/or MRI (n = 52), 35 (11%) underwent major duct excision alone, and 85 (28%) were followed clinically. Ultimately, 182/306 (59%) patients underwent surgery and/or biopsy. Overall incidence of malignant or high-risk pathology was 15% (46/306). Ductography was completed in 139/163 (85%) studies and detected 12 cancers and 7 HRLs, but failed to identify 4 cancers and 2 HRL (PPV 19%, NPV 63%). MRI detected 7 cancers and 3 HRL, but failed to identify 1 cancer and 1 HRL (PPV 56%, NPV 87%). Major duct excision alone (n = 35) detected 5 cancers and 3 HRL. Of all patients not having surgery, (142/306, 41%), 1 (0.01%) presented with an invasive cancer at 102 months (median follow-up, 6.3 months; range, 0–124 months).	3

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25. Sarica O, Zeybek E, Ozturk E. Evaluation of nipple-areola complex with ultrasonography and magnetic resonance imaging. <i>J Comput Assist Tomogr.</i> 2010;34(4):575-586.	Review/Other-Dx	N/A	To evaluate nipple-areola complex with US and MRI	Because both benign and malignant nipple periareolar region lesions may present with similar clinical findings such as nipple discharge and retraction, they require a diagnostically specific imaging workup. Despite multidisciplinary clinical approaches, malignancy cannot be excluded without diagnostic modalities. Because of the intricacy of the anatomical structures and their superficial position, the diagnostic techniques routinely used to evaluate the different sides of the breast may often be inadequate. Adjunct use of multiple imaging modalities is necessary to evaluate this region.	4
26. Brandt KR, Craig DA, Hoskins TL, et al. Can digital breast tomosynthesis replace conventional diagnostic mammography views for screening recalls without calcifications? A comparison study in a simulated clinical setting. <i>AJR Am J Roentgenol.</i> 2013;200(2):291-298.	Observational-Dx	146 women	To evaluate DBT as an alternative to conventional diagnostic mammography in the workup of noncalcified findings recalled from screening mammography in a simulated clinical setting that incorporated comparison mammograms and breast US results.	Agreement between DBT and diagnostic mammography BI-RADS categories was excellent for readers 1 and 2 (kappa = 0.91 and kappa = 0.84) and good for reader 3 (kappa = 0.68). For readers 1, 2, and 3, sensitivity and specificity of DBT for breast abnormalities were 100%, 100%, and 88% and 94%, 93%, and 89%, respectively. The clinical workup averaged 3 diagnostic views per abnormality and US was requested in 49% of the cases. DBT was adequate mammographic evaluation for 93%–99% of the findings and US was requested in 33%–55% of the cases.	2
27. Gennaro G, Hendrick RE, Toledano A, et al. Combination of one-view digital breast tomosynthesis with one-view digital mammography versus standard two-view digital mammography: per lesion analysis. <i>Eur Radiol.</i> 2013;23(8):2087-2094.	Observational-Dx	463 breasts of 250 patients	To evaluate the clinical value of combining one-view mammography (cranio-caudal) with the complementary view tomosynthesis (mediolateral-oblique) in comparison to standard two-view mammography in terms of both lesion detection and characterization.	The 463 cases (breasts) reviewed included 258 with 1 to 3 lesions each, and 205 with no lesions. The 258 cases with lesions included 77 cancers in 68 breasts and 271 benign lesions to give a total of 348 proven lesions. The combination, DBT (mediolateral-oblique)+ two-view mammography (cranio-caudal), was superior to two-view mammography (cranio-caudal + mediolateral-oblique) in both lesion detection and lesion characterization overall and for benign lesions. DBT (mediolateral-oblique)+ two-view mammography (cranio-caudal) was noninferior to two-view mammography for malignant lesions.	2

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28. Waldherr C, Cerny P, Altermatt HJ, et al. Value of one-view breast tomosynthesis versus two-view mammography in diagnostic workup of women with clinical signs and symptoms and in women recalled from screening. <i>AJR Am J Roentgenol.</i> 2013;200(1):226-231.	Observational-Dx	144 women	To compare the diagnostic value of one-view DBT vs two-view FFDM alone, vs a combined reading of both modalities.	86 of the 144 patients were found to have breast cancer. The BI-RADS categories for one-view DBT were significantly better than those for two-view FFDM ($P<0.001$) and were equal to those of the combined reading in both women admitted for diagnostic workup and women recalled from screening. The sensitivity and NPVs of DBT were superior to those of FFDM in fatty and dense breasts overall and in women admitted for diagnostic workup and in women recalled from screening. Only 11% of DBT examinations required additional imaging, compared with 23% of FFDMs.	3
29. Yang TL, Liang HL, Chou CP, Huang JS, Pan HB. The adjunctive digital breast tomosynthesis in diagnosis of breast cancer. <i>Biomed Res Int.</i> 2013;2013:597253.	Observational-Dx	59 breasts of 57 patients	To compare the diagnostic performance of DBT and DM for breast cancers.	A total of 59 breast cancers were reviewed, including 17 (28.8%) mass lesions, 12 (20.3%) focal asymmetry/density, 6 (10.2%) architecture distortion, 23 (39.0%) calcifications, and 1 (1.7%) intracystic tumor. Combo DBT was perceived to be more informative in 58.8% mass lesions, 83.3% density, 94.4% architecture distortion, and only 11.6% calcifications. As to the forced BIRADS score, 84.4% BIRADS 0 on DM was upgraded to BIRADS 4 or 5 on DBT, whereas only 27.3% BIRADS 4A on DM was upgraded on DBT, as BIRADS 4A lesions were mostly calcifications. A significant P value (<0.001) between the BIRADS category and index lesions was noted.	3
30. Stavros AT. Breast anatomy: the basis for understanding sonography. In: Stavros AT, ed. <i>Breast ultrasound.</i> Philadelphia, PA: Lippincott Williams & Wilkins; 2004: 56–108.	Review/Other-Dx	N/A	Book chapter.	N/A	4
31. Stavros AT. Ultrasound indication and interpretation. In: Bassett LW, Mahoney MC, Apple SK, D'Orsi CJ, eds. <i>Breast imaging.</i> Philadelphia, PA: Elsevier Saunders; 2011.	Review/Other-Dx	N/A	Book chapter.	N/A	4

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Cardenosa G, Eklund GW. Benign papillary neoplasms of the breast: mammographic findings. <i>Radiology</i> . 1991;181(3):751-755.	Observational-Dx	77 patients	To evaluate the mammographic findings of benign papillary neoplasms of the breast	51 patients (66%) had solitary papillomas. 37 of these patients were symptomatic; 36 had spontaneous nipple discharge, and 1 had a palpable mass. Ductography was positive in 32 of the 35 patients who underwent the procedure. In the 14 asymptomatic patients, subareolar (n = 10) and peripheral (n = 4) mammographic abnormalities prompted biopsy. 14 patients (18%) had multiple peripheral papillomas, and 1 patient also had bilateral central solitary papillomas. 11 of these patients were asymptomatic, while 2 presented with palpable abnormalities and 1 with spontaneous bilateral discharge. Mammographic findings included microcalcifications (n = 5) and clustering nodules (n = 2). Associated atypical ductal hyperplasia was found in 6 (43%) of the 14 patients with multiple peripheral papillomas. Some of these patients also had lobular carcinoma in situ and radial scars. 12 patients had multiple central papillomas; all presented with spontaneous nipple discharge and had positive ductograms.	4
33. Sickles EA. Galactography and other imaging investigations of nipple discharge. <i>Lancet</i> . 2000;356(9242):1622-1623.	Review/Other-Dx	N/A	No abstract available.	No abstract available.	4
34. Koskela A, Berg M, Pietilainen T, Mustonen P, Vanninen R. Breast lesions causing nipple discharge: preoperative galactography-aided stereotactic wire localization. <i>AJR Am J Roentgenol</i> . 2005;184(6):1795-1798.	Review/Other-Dx	9 patients	To assess the feasibility and diagnostic performance of these techniques in patients with spontaneous unilateral nipple discharge.	No results stated in the abstract.	4

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Ballesio L, Maggi C, Savelli S, et al. Role of breast magnetic resonance imaging (MRI) in patients with unilateral nipple discharge: preliminary study. <i>Radiol Med.</i> 2008;113(2):249-264.	Review/Other-Dx	44 patients	To assess the role of MRI in patients with unilateral nipple discharge.	MRI identified 25 enhancing lesions Breast Imaging Reporting and Data Systems (BI-RADS) 3 or 4) and confirmed the galactographic findings (ductal ectasia, intraluminal filling defects). 5 papillomatoses appeared as patchy, homogeneous enhancing areas, 15 intraductal papillomas as areas with well-defined margins and type II time-intensity curves, and 2 atypical ductal hyperplasias as diffuse nodular enhancement. One micropapillary DCIS, 1 papillary carcinoma and 1 infiltrating ductal carcinoma were visualized as 2 segmental areas of enhancement and 1 mass-like enhancement with poorly defined margins (BI-RADS 4). The follow-up was negative, showing no pathological enhancement (BI-RADS 1) in 12 patients and benign enhancement (BI-RADS 2) in 7.	4
36. Mathieu I, Mazy S, Willemart B, Destine M, Mazy G, Lonneux M. Inconclusive triple diagnosis in breast cancer imaging: is there a place for scintimammography? <i>J Nucl Med.</i> 2005;46(10):1574-1581.	Observational-Dx	104 patients; 118 procedures	Retrospective study to evaluate impact of SM in patients with doubtful or discordant triple diagnosis—that is mammography, US, and FNAC.	Breast cancer was proven in 69 cases. SM-SPECT had a sensitivity of 88.4% and a specificity of 67%. 11 cancers were detected by SPECT, although planar images were negative. SM-SPECT was more sensitive in patients scanned at initial presentation (95%) than in those with suspected recurrence (81%). SM-SPECT correctly evaluated multicentricity or bilaterality in 8/11 patients and resulted in an increased tumor size in 8 patients. Overall, SM-SPECT modified the patient management in 58/118 cases (49%): SM made the diagnosis of cancer in 30 cases with doubtful or discordant triple diagnosis and ruled out malignancy in 28 cases. SM-SPECT had a sensitivity of 88.4% and a specificity of 67%. Overall, SM-SPECT modified patient management in 58/118 cases (49%).	3

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Yutani K, Shiba E, Kusuoka H, et al. Comparison of FDG-PET with MIBI-SPECT in the detection of breast cancer and axillary lymph node metastasis. <i>J Comput Assist Tomogr.</i> 2000;24(2):274-280.	Observational-Dx	40 patients	Compare FDG-PET to MIBI-SPECT for breast cancer diagnosis and axillary lymph node metastasis in the same patients.	38 patients had breast cancer, and the remaining 2 had benign breast lesions. The sensitivities of FDG-PET and MIBI-SPECT were 78.9% and 76.3% for breast cancer and 50.0% and 37.5% for axillary lymph node metastasis, respectively. MIBI-SPECT is comparable with FDG-PET in detecting breast cancer. Neither FDG-PET nor MIBI-SPECT is sufficiently sensitive to rule out axillary lymph node metastasis. Results indicate that MIBI-SPECT is comparable with FDG-PET in detecting breast cancer. Neither FDG-PET nor MIBI-SPECT is sufficiently sensitive to rule out axillary lymph node metastasis.	2
38. Berg WA, Weinberg IN, Narayanan D, et al. High-resolution fluorodeoxyglucose positron emission tomography with compression ("positron emission mammography") is highly accurate in depicting primary breast cancer. <i>Breast J.</i> 2006;12(4):309-323.	Observational-Dx	92 lesions in 77 women	To prospectively assess the diagnostic performance of a high-resolution PET scanner using mild breast compression (positron emission mammography).	Of 48 cancers, 16 (33%) were clinically evident; 11 (23%) were DCIS, and 37 (77%) were invasive (30 ductal, 4 lobular, and 3 mixed; median size 21 mm). Positron emission mammography depicted 10/11 (91%) DCIS and 33/37 (89%) invasive cancers. Positron emission mammography was positive in 1 of 2 T1a tumors, 4 of 6 T1b tumors, 7 of 7 T1c tumors, and 4 of 4 cases where tumor size was not available (eg, no surgical follow-up). Positron emission mammography sensitivity for detecting cancer was 90%, specificity 86%, PPV 88%, NPV 88%, accuracy 88%, and AUC 0.918. In 3 patients, cancer foci were identified only on positron emission mammography, significantly changing patient management. Excluding 8 diabetic subjects and 8 subjects whose lesions were characterized as clearly benign with conventional imaging, positron emission mammography sensitivity was 91%, specificity 93%, PPV 95%, NPV 88%, accuracy 92%, and AUC 0.949 when interpreted with mammographic and clinical findings. FDG-positron emission mammography has high diagnostic accuracy for breast lesions, including DCIS.	2

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Brem RF, Fishman M, Rapelyea JA. Detection of ductal carcinoma in situ with mammography, breast specific gamma imaging, and magnetic resonance imaging: a comparative study. <i>Acad Radiol.</i> 2007;14(8):945-950.	Observational-Dx	20 women with 22 biopsy-proven DCIS	To evaluate the sensitivity of high-resolution BSGI for the detection of DCIS based on histopathology and to compare the sensitivity of BSGI with mammography and MRI for the detection of DCIS.	Pathologic tumor size of the DCIS ranged from 2 to 21 mm (mean 9.9 mm). Of 22 cases of biopsy-proven DCIS in 20 women, 91% were detected with BSGI, 82% were detected with mammography, and 88% were detected with MRI. BSGI had the highest sensitivity for the detection of DCIS, although this small sample size did not demonstrate a statistically significant difference. 2 cases of DCIS (9%) were diagnosed only after BSGI demonstrated an occult focus of radiotracer uptake in the contralateral breast, previously undetected by mammography. There were 2 false-negative BSGI studies. BSGI has higher sensitivity for the detection of DCIS than mammography or MRI and can reliably detect small, subcentimeter lesions.	3
40. Garg S, Mohan H, Bal A, Attri AK, Kochhar S. A comparative analysis of core needle biopsy and fine-needle aspiration cytology in the evaluation of palpable and mammographically detected suspicious breast lesions. <i>Diagn Cytopathol.</i> 2007;35(11):681-689.	Observational-Dx	50 patients	To compare value of CNB and FNAC in the evaluation of palpable and mammographically detected suspicious breast lesions.	Sensitivity and specificity of mammography for malignant diagnosis was 84.37% and 83.33%, respectively. Sensitivity and specificity of FNAC for malignant diagnosis was 78.15% and 94.44%, respectively, and of CNB was 96.5% and 100%, respectively. CNB is superior to FNAC in the diagnosis of breast lesions in terms of sensitivity, specificity, correct histological categorization of the lesions and tumor grading.	3
41. Homesh NA, Issa MA, El-Sofiani HA. The diagnostic accuracy of fine needle aspiration cytology versus core needle biopsy for palpable breast lump(s). <i>Saudi Med J.</i> 2005;26(1):42-46.	Experimental-Dx	296 patients	Prospective randomized controlled clinical trial to compare the accuracy of FNAC and CNB in patients with palpable breast masses.	FNAC had sensitivity of 66.66%, specificity of 81.8% accuracy of 75.7%, PPV of 100% and NPV of 90%. CNB had sensitivity of 92.3%, specificity of 94.8%, and accuracy of 93.4%, PPV of 100% and NPV 100%. CNB is more accurate than FNAC. Both procedures are simple, easy, safe, cheap and reliable, but CNB is more accurate than the FNAC.	1

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Barreau B, de Mascarel I, Feuga C, et al. Mammography of ductal carcinoma in situ of the breast: review of 909 cases with radiographic-pathologic correlations. <i>Eur J Radiol.</i> 2005;54(1):55-61.	Observational-Dx	909 cases	To analyze radiologic signs of DCIS to appreciate the extension and there possible “aggressivity”.	We retrospectively analyzed mammographies of 909 DCIS (1980–1999) and compared our results to those of literature. Microcalcifications were present in 75% of the cases, and soft-tissue abnormalities in 27% cases with association with calcifications in 14% of cases. Palpable masses were found in 12% of the cases and nipple discharge was present in 12% of the cases. The radiographic–pathologic correlation allowed to suspect the DCIS “aggressiveness” on radiologic signs. Granular, linear, branching and/or galactophoric topography of the microcalcifications were correlated with necrosis, grade 3, comedocarcinoma type. A number of microcalcifications higher than 20 was correlated with necrosis and grade 3. Mammographic size was correlated to histologic size. Masses were correlated with grade 1. A diagnosis strategy can be proposed with a multidisciplinary approach.	4
43. Apple SK, Overstreet JMJ, Bassett LW. Ductal carcinoma in situ and Paget's disease. In: Bassett LW, Mahoney MC, Apple SK, D'Orsi CJ, eds. <i>Breast imaging.</i> Philadelphia, PA: Elsevier Saunders; 2011.	Review/Other-Dx	N/A	Book chapter.	N/A	4

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Harvey JA, Nicholson BT, Cohen MA. Finding early invasive breast cancers: a practical approach. <i>Radiology</i> . 2008;248(1):61-76.	Review/Other-Dx	N/A	To provide a practical approach to the detection and management of breast masses and focal asymmetries.	Invasive breast cancers typically manifest mammographically as focal asymmetries or masses. Strategies for detecting focal asymmetries and masses on screening mammograms include side-by-side comparison, looking for parenchymal contour deformity, close inspection of the retromammary fat, identifying the presence of associated findings, and comparison with prior mammograms. Focal asymmetries are often normal but are concerning when there is distortion of the normal breast architecture. Masses and focal asymmetries are best evaluated in the diagnostic setting by using spot compression and true lateral views and, frequently, US. Management of a lesion depends on the worst imaging feature. Indications for an assessment of probably benign findings are very specific but are often misapplied.	4
45. Berg WA, Gilbreath PL. Multicentric and multifocal cancer: whole-breast US in preoperative evaluation. <i>Radiology</i> . 2000;214(1):59-66.	Observational-Dx	40 patients	To evaluate preoperative whole-breast US in the management of breast cancer.	US depicted 45 (94%) of 48 invasive tumor foci and 7 (44%) of 16 foci of DCIS. Mammography depicted 39 (81%) of 48 invasive tumor foci and 14 (88%) of 16 foci of DCIS. The 9 (14%) of 64 malignant foci seen only at US included 3 infiltrating ductal carcinomas, 2 mixed infiltrating and intraductal carcinomas, 2 infiltrating lobular carcinomas, and 2 foci of DCIS. 2 (18%) of 11 foci of infiltrating lobular carcinoma were missed at both US and mammography. Of 20 patients mammographically suspected of having unifocal disease, 3 (15%) required wider excision on the basis of US findings. 2 additional foci were depicted only at US in 1 of 16 patients mammographically suspected of having multicentric or multifocal disease. Of 4 patients with mammographically occult disease, US correctly depicted the diffuse (n = 2) or unifocal (n = 2) extent of the cancer.	3

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Nakahara H, Namba K, Watanabe R, et al. A comparison of MR imaging, galactography and ultrasonography in patients with nipple discharge. <i>Breast Cancer</i> . 2003;10(4):320-329.	Observational-Dx	55 patients	To assess the usefulness of 3D CE-MRI compared with galactography and US.	CE-MRI demonstrated all malignant lesions including DCIS. 4 cases of DCIS were not visualized by US and 3 malignant lesions were missed by galactography. In the MR study, segmental clumped enhancement (PPV =100%), and focal mass with smooth border (NPV =87.5%) were the statistically significant predictive factors.	3
47. Skaane P, Sauer T. Ultrasonography of malignant breast neoplasms. Analysis of carcinomas missed as tumor. <i>Acta Radiol</i> . 1999;40(4):376-382.	Observational-Dx	2,985 patients	To analyze the clinical and pathological features of breast malignancies missed as tumor on US in a large consecutive series of patients and in a subpopulation manifesting with no suspicious microcalcifications on mammography.	42 (11.8%) of the 355 malignant neoplasms were missed as tumor on US, including 6 (2.5%) of the 243 palpable and 36 (32.1%) of the 112 nonpalpable malignancies. Most of the missed tumors were DCIS and microinvasive ductal carcinomas dominated by DCIS. In the subpopulation, 14 (5.7%) of the 245 malignancies were missed as tumor on US, including 4 (2.2%) of the 180 palpable and 10 (15.4%) of the 65 nonpalpable lesions. Of the 245 malignancies, 6 (2.4%) had a normal US finding, including 2 palpable retropapillary tumors and 4 incidental findings at histology.	3
48. Rissanen T, Reinikainen H, Apaja-Sarkkinen M. Breast sonography in localizing the cause of nipple discharge: comparison with galactography in 52 patients. <i>J Ultrasound Med</i> . 2007;26(8):1031-1039.	Observational-Dx	52 patients	To evaluate breast US in localizing abnormalities in the discharging duct in patients with spontaneous nipple discharge.	The final diagnosis was benign in 47 cases (90%) and malignant in 5 cases (10%). US visualized an echogenic intraductal tumor in 36 (69%) of 52 cases, dilated duct(s) without an intraductal tumor in 6 cases (12%), and no abnormality in 10 cases (19%). 80% of papillomatous lesions, 58% of other benign lesions, and 20% of malignant lesions were sonographically positive. The abnormal duct was surgically removed after methylene blue staining in 38 cases, after sonographically guided wire localization in 11 cases, after both wire localization and methylene blue staining in 1 case, and with review of the diagnostic galactographic images in 2 cases.	3

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Simmons R, Adamovich T, Brennan M, et al. Nonsurgical evaluation of pathologic nipple discharge. <i>Ann Surg Oncol</i> . 2003;10(2):113-116.	Observational-Dx	108 patients	To evaluate the sensitivity and specificity of using mammography, ductography, cytology, and Hemocult staining to detect malignant lesions causing pathologic nipple discharge.	Of the 108 surgical histopathology specimens, 90/108 patients were benign, 5/108 patients were atypical, and 13/108 patients were malignant. The sensitivity of mammography was 57.1%, specificity was 61.5%, PPV was 16.7%, and NPV was 91.4%. Hemocult sensitivity was 50%, specificity was 0%, PPV was 20%, and NPV was 0%. The sensitivity of ductography was 0%, specificity was 90%, PPV was 0%, and NPV was 81.8%. The sensitivity of cytology was 11.1%, specificity was 96.3%, PPV was 50%, and NPV was 76.5%.	3
50. Mahoney MC, Jackson VP, Bassett LW. Galactography. In: Bassett LW, Mahoney MC, Apple SK, D'Orsi CJ, eds. <i>Breast imaging</i> . Philadelphia, PA: Elsevier Saunders; 2011.	Review/Other-Dx	N/A	Book chapter.	N/A	4
51. Comstock CE, Sung JS. Computer-aided detection for breast MRI. In: Molleran VM, Mahoney MC, eds. <i>Breast MRI</i> . Philadelphia, PA: Elsevier Saunders; 2014.	Review/Other-Dx	N/A	Book chapter.	N/A	4
52. Kleimeyer AE, Mahoney MC. MRI for breast implant evaluation. In: Molleran VM, Mahoney MC, eds. <i>Breast MRI</i> . Philadelphia, PA: Elsevier Saunders; 2014.	Review/Other-Dx	N/A	Book chapter.	N/A	4
53. Manganaro L, D'Ambrosio I, Gigli S, et al. Breast MRI in patients with unilateral bloody and serous-bloody nipple discharge: a comparison with galactography. <i>Biomed Res Int</i> . 2015;2015:806368.	Observational-Dx	53 patients	To assess the role of breast MRI compared to galactography in patients with unilateral bloody or serous-bloody nipple discharge.	After surgery and follow-up, 8 patients had no disease (15%), 23 papilloma (43%), 11 papillomatosis (21%), 5 DCIS (10%), and 6 papillary carcinoma (11%) diagnoses. Both techniques presented 100% specificity; MRI sensitivity was 98% vs 49% of galactography. Considering MRI, we found a statistical association between mass enhancement and papilloma ($P<0.001$; AUC 0.957; CI 0.888–1.025), ductal enhancement and papillomatosis ($P<0.001$; AUC 0.790; CI 0.623–0.958), segmental enhancement and ductal cancer in situ ($P=0.007$; AUC 0.750; CI 0.429–1.071), and linear enhancement and papillary cancer ($P=0.011$).	2

* See Last Page for Key

**Evaluation of Nipple Discharge
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. Mortellaro VE, Marshall J, Harms SE, Hochwald SN, Copeland EM, 3rd, Grobmyer SR. Breast MR for the evaluation of occult nipple discharge. <i>Am Surg.</i> 2008;74(8):739-742.	Review/Other-Dx	2 case reports	To document the capacity of MR to identify areas of associated pathology in patients with pathologic nipple discharge that could not otherwise be detected by conventional workup.	Breast MR should be considered in the toolbox evaluation of occult nipple discharge when other available strategies have failed to demonstrate an underlying etiology for the pathologic discharge. The use of breast MR in this setting may permit directed evaluation and management of potentially malignant lesions.	4
55. van Gelder L, Bisschops RH, Menke-Pluymers MB, Westenend PJ, Plaisier PW. Magnetic resonance imaging in patients with unilateral bloody nipple discharge; useful when conventional diagnostics are negative? <i>World J Surg.</i> 2015;39(1):184-186.	Observational-Dx	111 women	To evaluate the diagnostic value of breast MRI in patients with unilateral bloody nipple discharge in the absence of a palpable mass, with negative findings on mammography combined with US.	A total of 111 women (mean age 52 years; range 23–80) were included. In 9 (8%) patients, malignancy was suspected on MRI while conventional imaging was normal. In 8 (89%) of these patients, histology was obtained, 2 by core biopsy and 6 by terminal duct excision. Benign conditions were found in 6 patients (86%) and a (pre-) malignant lesion in 2 patients. In both cases, it concerned a DCIS, which was treated with breast-conserving therapy. Moreover, in 2 cases of (pre)malignancy, the MRI was interpreted as negative. In patients with unilateral bloody nipple discharge who show no signs of a malignancy on conventional diagnostic examinations, the added value of a breast MRI is limited, since a malignancy can be demonstrated in 2%.	3

**Evaluation of Nipple Discharge
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Bahl M, Baker JA, Greenup RA, Ghate SV. Evaluation of Pathologic Nipple Discharge: What is the Added Diagnostic Value of MRI? <i>Ann Surg Oncol</i> . 2015;22 Suppl 3:S435-441.	Observational-Dx	103 women	To determine the diagnostic value of MRI for the evaluation of patients with pathologic nipple discharge.	Over a 10-year period, 103 women (mean age 46 years, range 25-72 years) underwent MRI for evaluation of nipple discharge. 91 patients (88 %) underwent surgical excision or had clinical and/or radiographic follow-up at least 2 years after presentation and thus comprise the study population. 11 (30 %) of 37 patients with MRIs coded as BI-RADS 4 of 5 were diagnosed with DCIS (n = 6) or invasive adenocarcinoma (n = 5). 7 (64 %) of 11 patients diagnosed with malignancy had a negative mammographic and sonographic workup. None of the patients with MRIs coded as BI-RADS 1, 2, or 3 was diagnosed with malignancy immediately after presentation or during the 2-year follow-up period. The sensitivity and specificity of MRI for the detection of malignancy were 100% (11 of 11) and 68% (54 of 80), respectively. The PPV and NPV were 37% and 100%, respectively.	3
57. Hirose M, Nobusawa H, Gokan T. MR ductography: comparison with conventional ductography as a diagnostic method in patients with nipple discharge. <i>Radiographics</i> . 2007;27 Suppl 1:S183-196.	Review/Other-Dx	N/A	To review the causes of pathologic nipple discharge and discuss the diagnostic strategy; to demonstrate and explain the findings at conventional ductography, MR ductography, and fusion imaging with MR ductography and MR mammography in patients with pathologic nipple discharge; and to discuss the advantages and disadvantages of conventional ductography and MR ductography.	No results stated in abstract.	4
58. Dennis MA, Parker S, Kaske TI, Stavros AT, Camp J. Incidental treatment of nipple discharge caused by benign intraductal papilloma through diagnostic Mammotome biopsy. <i>AJR Am J Roentgenol</i> . 2000;174(5):1263-1268.	Observational-Tx	49 women	To evaluate imaging-guided vacuum-assisted mammotome biopsy as a minimally invasive method of obtaining a satisfactory diagnosis and eliminating the bothersome symptoms in patients presenting with nipple discharge.	In all biopsied patients, satisfactory tissue for diagnosis was obtained. In patients biopsied with the mammotome probe, follow-up at a mean time of 13 months revealed resolution of the presenting problematic discharge in 97.2% of patients. Complications were mild and infrequent. Only 1 of 50 percutaneously biopsied lesions was not benign and required subsequent surgery.	2

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
59. Reiner CS, Helbich TH, Rudas M, et al. Can galactography-guided stereotactic, 11-gauge, vacuum-assisted breast biopsy of intraductal lesions serve as an alternative to surgical biopsy? <i>Eur Radiol.</i> 2009;19(12):2878-2885.	Observational-Dx	18 patients	To determine the value of galactography-guided, stereotactic, vacuum-assisted breast biopsy for the assessment of intraductal breast lesions and its potential as a therapeutic tool that could eliminate the need for surgical excision.	After vacuum-assisted breast biopsy, histopathology revealed invasive ductal carcinoma in 3 (17%), DCIS in 6 (33%), HRLs in 6 (33%) and benign lesions in 3 (17%) cases. After surgical biopsy, histopathology confirmed the previously established diagnosis in 11 lesions (61%). The underestimation rate for HRLs and DCIS was 50% (6/12). The false-negative rate was 7% (1/14). Histopathology examination after surgery showed that not a single lesion had been completely removed at vacuum-assisted breast biopsy.	3
60. Liberman L, Tomos C, Huzjan R, Bartella L, Morris EA, Dershaw DD. Is surgical excision warranted after benign, concordant diagnosis of papilloma at percutaneous breast biopsy? <i>AJR Am J Roentgenol.</i> 2006;186(5):1328-1334.	Observational-Dx	3864 lesions	To determine the cancer frequency in lesions yielding a benign, concordant diagnosis of papilloma at percutaneous breast biopsy.	Cancer was found in 5 (14%) of the 35 lesions yielding a benign, concordant diagnosis of papilloma at percutaneous biopsy. Cancer histology was DCIS in 4 (80%) and node-negative invasive cancer in 1. 4 (80%) of 5 cancers were identified due to interval change at follow-up (median, 22 months; range, 7-25 months). In 6 (17%) of 35 lesions, surgery revealed HRLs including atypical ductal hyperplasia (n = 3), radial scar (n = 2), and lobular carcinoma in situ (n = 1). There was a significantly ($P=0.02$) higher frequency of cancer or HRL in women with multiple vs solitary papillomas and a trend ($P=0.09$) toward a higher cancer rate in women with vs without a family history of breast cancer. Breast cancer history, menopausal status, mammographic pattern, biopsy method, and removal of imaging target had no significant impact on cancer rate.	3

**Evaluation of Nipple Discharge
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Sydnor MK, Wilson JD, Hijaz TA, Massey HD, Shaw de Paredes ES. Underestimation of the presence of breast carcinoma in papillary lesions initially diagnosed at core-needle biopsy. <i>Radiology</i> . 2007;242(1):58-62.	Observational-Dx	57 women	To retrospectively determine the degree of underestimation of breast carcinoma diagnosis in papillary lesions initially diagnosed at CNB.	In 38/63 lesions, surgical excision was performed; in 25 additional lesions (considered benign), follow-up mammography (24-month minimum) was performed, with no interval change. In 15 lesions, 14-gauge core needle was used; in 48, vacuum assistance (mean cores per lesion, 8.7). Carcinoma was found at excision in 14/38 lesions. Core pathologic findings associated with malignancy were benign papilloma (n=1), sclerotic papilloma (n=1), micropapilloma (n=2), and atypical papilloma (n=10). Frequency of malignancy was 1 (3%) of 38 benign papillomas, 10 (67%) of 15 atypical papillomas, 2 (50%) of 4 micropapillomas, and 1 (17%) of 6 sclerotic papillomas. Excisional findings included lobular carcinoma in situ (n=2), DCIS (n=7), papillary carcinoma (n=2), and invasive ductal carcinoma (n=3). Low-risk group (micropapillomas and sclerotic and benign papillomas) was compared with high-risk atypical papilloma group. Core findings were associated with malignancy at excision for atypical papilloma ($P=.006$). Lesion location, mammographic finding, core number, or needle type were not associated ($P>.05$) with underestimation of malignancy at excision.	3
62. Georgian-Smith D, Lawton TJ. Controversies on the management of high-risk lesions at core biopsy from a radiology/pathology perspective. <i>Radiol Clin North Am</i> . 2010;48(5):999-1012.	Review/Other-Dx	N/A	To discuss the controversies on the management of HRLs at core biopsy from a radiology/pathology perspective.	No results listed in abstract.	4

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Dupont SC, Boughey JC, Jimenez RE, Hoskin TL, Hieken TJ. Frequency of diagnosis of cancer or high-risk lesion at operation for pathologic nipple discharge. <i>Surgery</i> . 2015;158(4):988-994; discussion 994-985.	Observational-Dx	311 subareolar duct excisions cases	To stratify patients into groups most likely to benefit from operation as well as to reliably identify a group of patients for whom operation might be avoided.	In 27 cases, cancer was diagnosed preoperatively. Among the remaining 284, 26 (9%) were diagnosed with cancer and 8 (3%) with atypia at operation. At greatest risk of upstage to cancer were patients with prior ipsilateral breast cancer (3/8; 38%), BRCA mutation (2/3; 67%) or atypia on CNB (3/8; 38%). Excluding these patients lowered cancer and atypia upstages (7% [18/265] and 3% [7/265]), with bloody (vs serous) discharge ($P=.001$), and focal imaging abnormality ($P=.02$), the strongest risk factors. Serous discharge and either normal imaging or a benign CNB had a 1.3% cancer upstage rate.	3
64. Dawes LG, Bowen C, Venta LA, Morrow M. Ductography for nipple discharge: no replacement for ductal excision. <i>Surgery</i> . 1998;124(4):685-691.	Observational-Dx	91 patients	To investigate whether ductography supplied additional information in the decision for surgery and/or the localization of pathologic lesion.	Of 91 patients with nipple discharge, 49 met the criteria for physiologic discharge and 42 had pathologic discharge. 11 with physiologic discharge had ductograms; none were abnormal. 4 of 20 preoperative ductograms were normal but showed intraductal papillomas at the time of surgery; 6 of 20 (30%) had multiple lesions. 4 lesions on ductograms did not demonstrate corresponding lesions in the surgical specimen. It is uncertain whether this is due to a missed lesion or a false-positive ductogram.	3
65. American Cancer Society. Cancer Facts and Figures 2012: Atlanta: American Cancer Society. 2012; Available at: http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-030975.pdf .	Review/Other-Dx	N/A	Presents breast cancer facts and figures for 2012.	N/A	4

**Evaluation of Nipple Discharge
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Lehman CD, Lee CI, Loving VA, Portillo MS, Peacock S, DeMartini WB. Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30-39 years of age. <i>AJR Am J Roentgenol.</i> 2012;199(5):1169-1177.	Observational-Dx	1208 cases in 954 patients	To determine the accuracy and value of breast US for primary imaging evaluation of women 30–39 years of age who present with focal breast signs or symptoms.	Outcomes were benign in 1185/1208 (98.1%) and malignant in 23/1208 (1.9%) cases. Sensitivities for US and mammography were 95.7% and 60.9%, respectively. Specificities for US and mammography were 89.2% and 94.4%, respectively. NPV was 99.9% for US and 99.2% for mammography. PPV was 13.2% for US and 18.4% for mammography. Mammography detected 1 additional malignancy in an asymptomatic area in a 32-year-old woman who was subsequently found to have a BRCA2 gene mutation.	3
67. Osako T, Iwase T, Takahashi K, et al. Diagnostic mammography and ultrasonography for palpable and nonpalpable breast cancer in women aged 30 to 39 years. <i>Breast Cancer.</i> 2007;14(3):255-259.	Observational-Dx	165 patients	To investigate the relationship between the tumor size of breast cancer by palpation and the sensitivity of mammography and US, and which modality can detect nonpalpable breast cancer in women aged 30 to 39 years.	Of 165 patients, 147 patients (89%) showed mammographically dense breasts. Of 165 cancers, 14 (8%) were Tnp, 40 (24%) were T1p, 82 (50%) were T2p, and 29 (18%) were T3p. The sensitivity of mammography was 57% (8/14) for Tnp, 78% (31/40) for T1p, 90% (74/82) for T2p, and 97% (28/29) for T3p. The sensitivity of US was 43% (6/14) for Tnp and 100% for palpable cancers. Of 14 nonpalpable cancers, 4 (29%), 4 (29%), and 2 (14%) could be detected by only mammography, bloody nipple discharge, and US, respectively. The sensitivity of mammography depends on the tumor size and on palpation in this age range. Mammography fails to detect relatively large palpable cancers. On the other hand, US can detect all palpable cancers. However, the sensitivity of US declines for nonpalpable cancers. For the detection of nonpalpable cancers, mammography, US, and nipple discharge are complementary modalities.	4
68. Ciatto S, Bravetti P, Bonardi R, Rosselli del Turco M. The role of mammography in women under 30. <i>Radiol Med.</i> 1990;80(5):676-678.	Observational-Dx	305 patients	To determine the appropriate use of mammography in younger women with a solid palpable mass.	Mammography missed 5/18 cancers (28%) and is not recommended in women under 30 except for preoperative cases with a strong suspicion of cancer.	3

**Evaluation of Nipple Discharge
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. Williams SM, Kaplan PA, Petersen JC, Lieberman RP. Mammography in women under age 30: is there clinical benefit? <i>Radiology</i> . 1986;161(1):49-51.	Observational-Dx	76 patients; 2 observers	Retrospective study to determine the utility of mammography in women less than 30 years of age referred for mammography.	55% had a palpable mass. In this group, no mass seen by mammography in 74%. But 14% had a definite lesion found by other means. No cancers were found. US may be best initial approach with mammography reserved for preoperative cases.	4
70. Yue D, Swinson C, Ravichandran D. Triple assessment is not necessary in most young women referred with breast symptoms. <i>Ann R Coll Surg Engl</i> . 2015;97(6):466-468.	Observational-Dx	955 females aged under 25 years	To see whether CNB/FNA could be avoided in young women with benign findings on clinical examination and imaging.	The most common presenting complaint was a lump, followed by pain and nipple discharge. Clinical examination was normal or revealed benign findings in all except 15 patients, in whom it was indeterminate. US was performed in 692 patients (72%) and was normal (n=289) or benign (n=382) in all except 21 patients, in whom it was indeterminate. In 6 patients, both were indeterminate. A total of 317 patients (35%) had triple assessment: FNA in 106, CNB in 239 and both in 9 cases. No cancers were diagnosed.	3
71. Ashfaq A, Senior D, Pockaj BA, et al. Validation study of a modern treatment algorithm for nipple discharge. <i>Am J Surg</i> . 2014;208(2):222-227.	Observational-Dx	192 patients	To validate the proposed treatment algorithm after its implementation in our practice.	A total of 192 patients, mean age 56 years, were studied. Risk of carcinoma among the entire cohort was 5%. Breast surgeon was consulted for 142 (74%) patients: 48 (34%) underwent initial subareolar excision and 94 (66%) were clinically followed. The rate of carcinoma was 17% (8/48) after initial subareolar excision, 0% (0/13) for those without imaging abnormalities, 23% (8/35) with imaging abnormalities, and 1% (1/94) with clinical follow-up. Of patients who underwent follow-up, 21% (n = 20) underwent subareolar excision because of imaging abnormality (n = 1, 1%) or persistent discharge (n = 19, 20%). Most patients had DCIS (n = 5, 56%).	3

Evaluation of Nipple Discharge
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Skaane P, Bandos AI, Eben EB, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. <i>Radiology</i> . 2014;271(3):655-663.	Experimental-Dx	24,901 examinations	To compare the performance of 2 versions of reconstructed 2D images in combination with DBT vs the performance of standard FFDM plus DBT.	Cancer detection rates were 8.0, 7.4, 7.8, and 7.7 per 1000 screening examinations for FFDM plus DBT in period 1, initial reconstructed 2D images plus DBT in period 1, FFDM plus DBT in period 2, and current reconstructed 2D images plus DBT in period 2, respectively. False-positive scores were 5.3%, 4.6%, 4.6%, and 4.5%, respectively. Corresponding reader-adjusted paired comparisons of false-positive scores revealed significant differences for period 1 ($P=.012$) but not for period 2 (ratio = 0.99; 95% CI: 0.88, 1.11; $P=.85$).	1
73. Zuley ML, Guo B, Catullo VJ, et al. Comparison of two-dimensional synthesized mammograms versus original digital mammograms alone and in combination with tomosynthesis images. <i>Radiology</i> . 2014;271(3):664-671.	Observational-Dx	123 patients	To assess interpretation performance and radiation dose when 2D synthesized mammography images vs standard FFDM images are used alone or in combination with DBT images.	Probability of malignancy-based mean AUCs for synthesized mammography and FFDM images alone was 0.894 and 0.889, respectively (difference, -0.005; 95% CI: -0.062, 0.054; $P=.85$). Mean AUC for synthesized mammography with tomosynthesis and FFDM with tomosynthesis was 0.916 and 0.939, respectively (difference, 0.023; 95% CI: -0.011, 0.057; $P=.19$). In terms of the reader-specific AUCs, 5 readers performed better with synthesized mammography alone vs FFDM alone, and all 8 readers performed better with combined FFDM and tomosynthesis (absolute differences from 0.003 to 0.052). Similar results were obtained by using a nonparametric analysis of forced BI-RADS ratings.	3

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
 - a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
 - b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
 - c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

AUC = Area under the receiver operating characteristic curve

BSGI = Breast-specific gamma imaging

CE-MRI = Contrast-enhanced magnetic resonance imaging

CI = Confidence interval

CNB = Core needle biopsy

DBT = Digital breast tomosynthesis

DCIS = Ductal carcinoma in situ

DM = Digital mammography

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

FFDM = Full-field digital mammography

FNAC = Fine-needle aspiration cytology

HRL = High-risk lesion

MIBI = Tc-99m methoxyisobutylisonitrile

MRI = Magnetic resonance imaging

NPV = Negative predictive value

PPV = Positive predictive value

SM = Scintimammography

SPECT = Single-photon-emission computed tomography

US = Ultrasound