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INVITED REVIEW

ESR Essentials: diagnostic work-up in patients with symptomatic breast disease—practice recommendations by the European Society of Breast Imaging

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Abstract

Breast complaints are frequent reasons for consultations in primary care or breast clinics. Breast pain, breast lumps, and nipple discharge are the most common complaints. Less common symptoms such as skin changes and axillary abnormalities also require specific diagnostic approaches. Imaging the symptomatic breast should be performed by appropriately trained breast radiologists following the best practice guidelines and quality standards. Full-field digital mammography (FFDM), digital breast tomosynthesis (DBT), and breast ultrasound (US) are the main modalities used in this primary setting. The choice depends on the patient's age and symptoms. Women younger than 30-years-old are first imaged by US, whereas women over 40-years-old usually require both FFDM or DBT and US. For women between 30-years-old and 40-years-old, the US is the modality of choice, whereas FFDM or DBT might also be performed if needed. Pregnant or lactating women with palpable lesions or nipple discharge are imaged with US as the first method; FFDM or DBT can also be performed depending on the degree of suspicion as the dose to the fetus is minimal, and shielding may even further reduce the dose. More advanced techniques such as breast magnetic resonance imaging or contrast-enhanced mammography are not indicated in this first diagnostic setting and are reserved for cases of established malignancy (local staging) or rare cases of equivocal findings not otherwise resolved or inflammatory breast cancer. Last, but not least, male breast symptoms should also be addressed with US and/or FFDM.

Clinical relevance statement It is equally important to correctly diagnose an underlying malignancy and to avoid false positives that would lead to unnecessary biopsies, increased costs, and anxiety for the patient. Proper use of imaging modalities ensures optimal diagnostic approach and minimizes false negatives.

Key Points

- *Ultrasound, full-field digital mammography, or digital breast tomosynthesis are the main imaging modalities in the diagnostic setting, while MRI or contrast-enhanced mammography should be reserved to selected cases.*
- *Initial imaging modality includes ultrasound combined with mammography or digital breast tomosynthesis depending on women's age and the presence (or not) of inconclusive findings.*
- *A negative imaging evaluation should not deter biopsy when a highly suspicious finding is found on physical examination.*

Keywords Breast neoplasms, Nipple discharge, Mammography, Ultrasonography

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Key recommendations

- Breast symptoms should prompt clinical consultation and an appropriate diagnostic imaging approach (level of recommendation: high).
- FFDM or DBT and US are the recommended imaging modalities used in this setting; for women < 40, US is the first imaging tool (level of recommendation: high).
- Contrast-based imaging (MRI or CEM) can be used in case of problem-solving or local staging (level of recommendation: moderate).

Introduction

Breast pain, breast lumps, and nipple discharge are the most common breast symptoms encountered in consultations. They account for 3% of family physician office visits and are experienced by as many as 16% of women over any 10-year period (22.8 presentations per 1000 person-years) [1]. In many cases, there is no underlying malignancy, though the likelihood of cancer is sufficiently high for these women presenting with focal, clinically suspicious, symptoms to be referred for appropriate diagnostic imaging. Focal palpable breast lumps are associated with a positive predictive value for cancer ranging from 8.1% to 24.6%, mostly depending on age [2, 3]. Nipple discharge is associated with underlying malignancy in between 5% and 12% of cases [4, 5], particularly when bloody or watery in nature. The reported risk of malignancy in the case of unilateral, isolated, non-cyclic focal breast pain is very low [6]; nevertheless, if new, focal, non-cyclic, unilateral breast pain is persistent or associated with other focal symptoms, it also warrants further diagnostic assessment. Skin changes such as erythema, "peau d'orange," as well as skin retraction (if not associated with previous surgery), and clinically suspicious axillary lymph nodes should, likewise, be appropriately investigated to exclude underlying malignancies. Male breast cancer, although rare and representing no more than 1% of breast cancers, presents with a palpable mass and as such, further assessment is mandatory [7].

Diagnostic assessment of patients with breast symptoms requires clinical examination, appropriate imaging, and needle biopsy. Imaging modalities used in each case are determined by the symptoms, clinical findings, and patient's age. This document provides general guidance to optimize procedures, generating a patient-based personalized approach to maximize resources and streamline workflows.

Breast pain

Breast pain accounts for up to 66% of physician visits for breast symptoms. Quality, duration, location, and radiation of pain, as well as recent trauma or aggravating activities, should be evaluated. Diffuse, cyclic pain is classically related to the menstrual cycle; it requires no further assessment [6]. It is worth noticing that oral contraceptives, hormone therapy, psychotropic drugs, and some cardiovascular agents have been associated with diffuse breast pain [1, 7, 8].

Noncyclic pain is not related to the menstrual cycle and may be unilateral or focal. Focal, persistent breast pain is potentially clinically significant and requires further assessment. To be defined as focal, it must involve < 25% of the breast and axillary tissue. US has a high negative predictive value (NPV), sensitivity, and specificity for the evaluation of breast pain, with a reported sensitivity of up to 100%, specificity of 92.5%, a positive predictive value of 13.6%, and NPV of 100% [9, 10]. Targeted ultrasonography (US) alone is the modality of choice to assess focal breast pain in women younger than 40 years or as an adjunct to full-field digital mammography (FFDM) or digital breast tomosynthesis (DBT) in women over 40. The Royal College of Radiologists indicates that mammography should be performed in patients aged 35–39 years with clinically and/or ultrasonically suspicious findings, preferably prior to biopsy [9]. The American College of Radiology also recommends consideration of FFDM or DBT, in addition to ultrasound (US), for women aged 30–39-years-old [10]. Cancer is a rare cause of focal, new, non-cyclic, clinically significant breast pain, ranging only from 0% to 3%. If the clinical findings and imaging results are normal, women can be reassured that the likelihood of malignancy is indeed very low [11–13]. Recently published data indicated that targeted US, when performed in conjunction with FFDM for the evaluation of focal breast pain in women with non-dense breasts, is of low utility when FFDM and clinical exams are negative [14, 15]. When focal breast pain is associated with other symptoms, for example, a palpable lump or nipple discharge, it should be considered a secondary symptom, and the diagnostic workup should focus on the primary complaint with a triple assessment undertaken.

Palpable breast lumps

Palpable breast lumps are also common breast complaints, second only to breast pain [16]. Breast lumps are not synonymous with breast cancer and are commonly associated with benign lesions such as cysts or fibroadenomas or even normal fibroglandular tissue; nevertheless, reported positive predictive values (meaning that the lump is caused by cancer) range from 8.1% to 24.6% depending on patient's age [2]. Breast cancer's most common clinical manifestation is indeed a breast mass. Palpable breast cancers are usually more aggressive and of poorer prognosis than those detected with screening, hence the need for optimal diagnostic assessment of all palpable abnormalities [17].

Characterization of breast masses by physical examination can be difficult; in general, malignant masses are

Table 1 EUSOBI recommendations for initial imaging in women with focal breast complaints

	US	FFDM/DBT	Biopsy
Women ≤ 40 years (level: moderate)	Yes	Usually not appropriate*	When indicated
Pregnant or lactating women (level: high)	Yes	Usually not appropriate*	When indicated
Women > 40 years (level: high)	Yes	Yes	When indicated

* Consider FFDM/DBT whenever the pre-test probability of malignancy is high, in women with inconclusive US findings or in case of proven malignancy (pre-test probability of malignancy refers to imaging and clinical findings)

firm and/or fixated, sometimes with associated skin or nipple retraction, whereas benign masses are typically mobile and soft. Imaging evaluation is necessary to adequately characterize a palpable breast lump. The radiologist should pay attention to establishing concordance between the clinical and imaging findings. The use of a skin marker on the area of clinical concern may be performed. The reported NPV of FFDM + US in this context ranges from 97.4% to 100% [18, 19]. Nevertheless, negative imaging evaluation should not deter biopsy when a highly suspicious finding is present on physical examination [19].

Imaging modalities of the first choice are FFDM or DBT and US. Stratification of the work-up is done according to most guidelines done by age [9, 10, 20–22] (Table 1).

FFDM and DBT are used here interchangeably, mainly depending on the availability of each system in local practices around Europe [23]. The use of FFDM or DBT, if both are available, is at the discretion of the breast radiologist performing the diagnostic work-up [21]. DBT can be acquired as additional imaging to the usual mammograms, or it can be acquired alone combined with a synthesized 2D mammographic view, created from the 3D tomosynthesis images. Due to multiple projections acquired during DBT, overlapping tissue can be further analyzed, thus obviating the need for spot compression mammographic views. Asymmetric densities and architectural distortions are better depicted. Mass lesion contours are better analyzed. Results of different studies comparing mammography alone with mammography with DBT demonstrated that DBT can significantly increase diagnostic performance and cancer detection by up to 30–40% [22, 23].

Women < 30 years of age

As a rule of thumb, US is considered the first imaging modality in young women < 30, as well as in pregnant and lactating women (Fig. 1) [9]. US can reliably detect breast cancers and characterize benign lesions such as cysts and fibroadenomas in this age group (Fig. 2). Due to the very low incidence of cancers in this group, there is no proven benefit of FFDM or DBT. Increased breast density in this age group resulting in reduced sensitivity of the techniques and radiation sensitivity issues are also to be considered, providing further reasons against the use of FFDM/DBT. However, if there are suspicious US findings, FFDM or DBT is recommended, in addition to breast

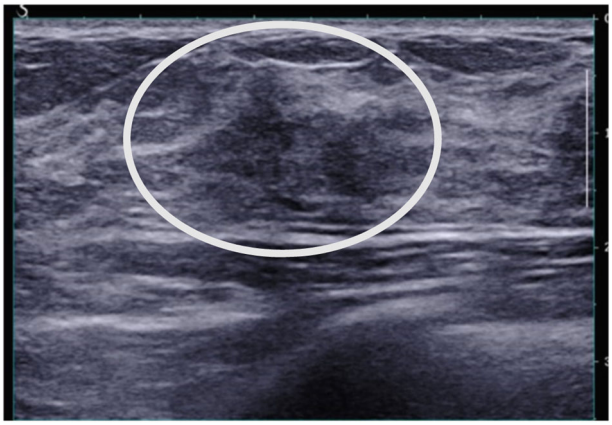


Fig. 1 Twenty-seven-year-old patient presenting with tender, focal breast lump in the upper outer quadrant of the right breast. US depicts a slightly hypoechoic mass with indistinct margins. A core biopsy confirmed a benign lesion related to focal adenosis. No further action or follow-up was needed

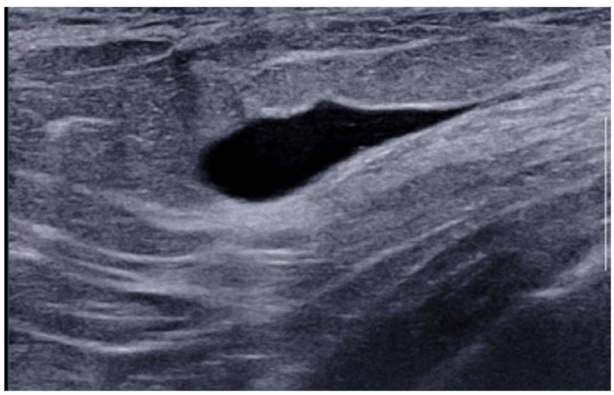


Fig. 2 Twenty-eight-year-old patient presenting with a soft, mobile, retroareolar lump of the right breast. US depicts an oval, purely anechoic mass with posterior enhancement, typical of a benign cyst. This is a BI-RADS 2 lesion, typically benign. No further action or follow-up was needed

biopsy. In women in this age group presenting with cancer, complete staging with DBT and contrast-enhanced mammography (CEM) or magnetic resonance imaging (MRI) is recommended.

Women in the age group 30–40 years of age

For patients in the age group 30–40 years, there is no universal consensus regarding the use of FFDM or DBT in the diagnostic setting of a palpable breast lump. In Europe, most national guidelines propose the US as the first imaging modality [20, 21]; if negative or showing clearly benign findings, no further assessment is required. If equivocal or showing suspicious findings, it should be completed with mammography or DBT. American and Canadian guidelines provide the option of starting either with targeted US or mammography; both approaches are considered reasonable evaluation modalities [8, 9]. EUSOBI recommends US as the first imaging modality in women < 40-years-old, whereas in women > 35-years-old, US can be complemented by FFDM or DBT if there are clinically and/or ultrasonographically unexplained findings.

Women > 40 years of age

For women over 40-years-old, diagnostic mammography or DBT and targeted US is the recommended approach [9, 10]. A radiopaque marker can be placed over the site of clinical concern and standard FFDM or DBT views (craniocaudal and mediolateral oblique) should be performed. Acquisitions might be repeated without markers if they obscure the lesion. DBT alleviates the need for additional spot views [22–25]; however, if not available, the diagnostic FFDM work-up should be completed with spot views. If the patient has undergone recent (≤ 6 months) bilateral mammography, only ipsilateral mammography is indicated [18]. If typically benign findings are present on FFDM that explain the complaints, such as a calcified fibroadenoma, hamartoma, or oil cyst, no further imaging is warranted. For all other mammographic findings, including masses with probably benign or suspicious features, further evaluation with targeted US is indicated.

Normal mammographic findings are not sufficient to rule out malignancy in a nonfatty breast (breast density ACR B, C, and D). If there is no mammographic finding at the site of the palpable lump, further workup with targeted US is also required irrespective of the breast density. Approximately 13% of women with palpable breast cancer have normal mammographic findings [26–28]. False reassurance from a normal mammogram can lead to a delay in cancer diagnosis (Fig. 3a–e).

It should be also noted that in older women with a palpable lump, targeted US performed by dedicated breast radiologists using high-end equipment has been shown to be the most effective imaging modality. Even in older women, it could therefore be envisioned to start the evaluation with US. Several studies support this approach, though it has not been embraced by guidelines and societies' recommendations. Nevertheless, literature data are worth noticing. In the prospective multicenter Breast US Trial BUST trial, Appelman et al evaluated targeted US as the first imaging modality in women presenting with focal breast symptoms (most commonly a palpable lump, 78% of cases). Seventy-three percent of patients were aged ≥ 40 years. All participants were evaluated with targeted US (and biopsy in case of BI-RADS 4 or 5 lesions) before DBT. Targeted US had 98.5% sensitivity (vs 87% for DBT), 90.8% specificity, and 90% overall accuracy. The Negative Predictive Value NPV for US was 99.8% [29]. Dodelzon and Katzen performed a literature review which confirms that US was superior to mammography across all included studies [30]. However, the highest NPVs are achieved by the combination of the two techniques, and it should be emphasized that the performance of DBT in women > 40 years also presents an opportunity to detect asymptomatic cancers, especially when no screening is offered yet. When mammography is not available or refused, an accurate diagnosis can often be obtained by US alone. It should be underlined that, in case of strong clinical suspicion, if imaging is negative, short-term clinical follow-up or the use of additional imaging techniques, such as MRI or CEM, is highly recommended [31].

In cases with a suspicious palpable area, targeted biopsy is essential even if imaging is negative. Triple assessment is considered the safest, most robust approach.

Pregnant and lactating women

Breast tissue changes during pregnancy and lactation, with the fibroglandular tissue becoming more abundant. Accordingly, most complaints in pregnant and lactating women are a direct result of these physiological changes. Targeted US is the primary imaging modality in these women and can usually accurately classify the pregnancy-related changes and associated benign lesions such as galactoceles and lactating adenomas [32]. On the other hand, it is essential to always be aware of the possibility of "pregnancy-associated breast cancer" (PABC). PABC is often diagnosed due to a persistent lump in the breast [33]. A negative US alleviates the need for additional mammographic evaluation (which is less sensitive due to the increased breast density). In a retrospective analysis by Chung et al over a period of 17 years, targeted US depicted all malignancies in lactating women with palpable masses. Adding mammography increased false-positive findings without any additional cancer diagnoses [32]. However, mammography is not absolutely contraindicated during pregnancy or in the lactation period and may be performed especially when there is

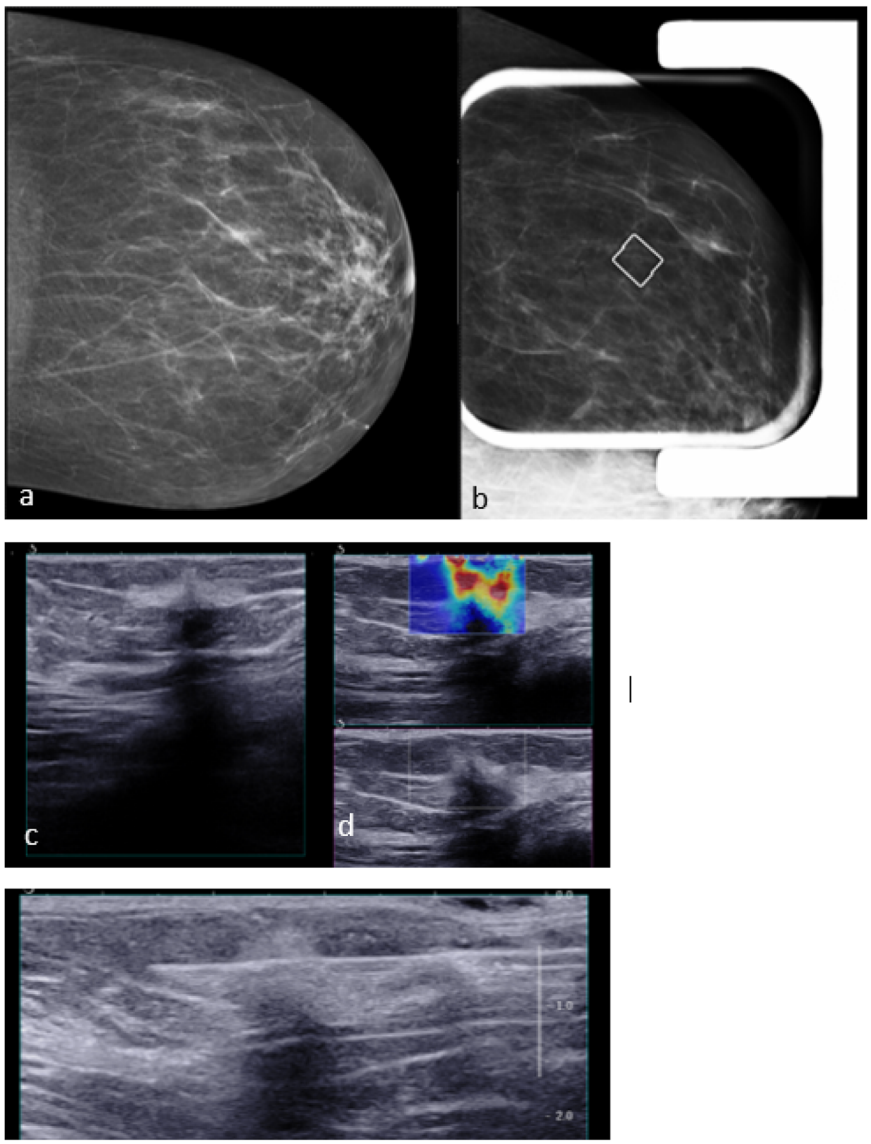


Fig. 3 Forty-eight-year-old patient presenting with a palpable lesion in the left breast at 3 o'clock. CC view (**a**) and spot view with marker (**b**) revealed no clear mammographic abnormality. Subsequent targeted US (**c**, **d**) revealed a hyperechoic ill-defined area with increased stiffness on the shear wave elastography. Core biopsy (**e**) was performed, and histology was in favor of invasive lobular cancer

strong clinical suspicion in women > 30 years. In pregnant women, FFDM or DBT only leads to a very minimal radiation dose to the fetus, which can be even further reduced by adequate shielding. In lactating women, before FFDM or DBT is performed, breastfeeding or pumping is recommended.

In the case of histopathologically proven PABC, further staging may be necessary. However, dynamic contrast-enhanced breast MRI is contraindicated in the first trimester due to the reported increased risk of a broad set of rheumatological, inflammatory, or dermal conditions, as well as stillbirth or neonatal death, associated with gadolinium-based contrast agents (GBCAs) used during the MRI, albeit all of these remain very rare [34]. A recent literature review on MRI contrast agent safety during pregnancy concluded that there are still many uncertainties, and healthcare providers should meticulously evaluate the potential risks and benefits of GBCA use during pregnancy on an individual basis [35]. Alternatively, unenhanced MRI with diffusion-weighted images could be considered in pregnant women. DCE-MRI (with gadolinium contrast) is not contra-indicated for lactating women and is preferable to evaluate the extent of breast cancer [34]. There is even less data on the role of CEM in

this context. Iodinated contrast may be administered in selected cases, where the expected benefit outweighs risks. The European Society of Urogenital Radiology recommended that neonatal thyroid function should be checked during the 1st week after birth if iodinated contrast media was given during pregnancy [36].

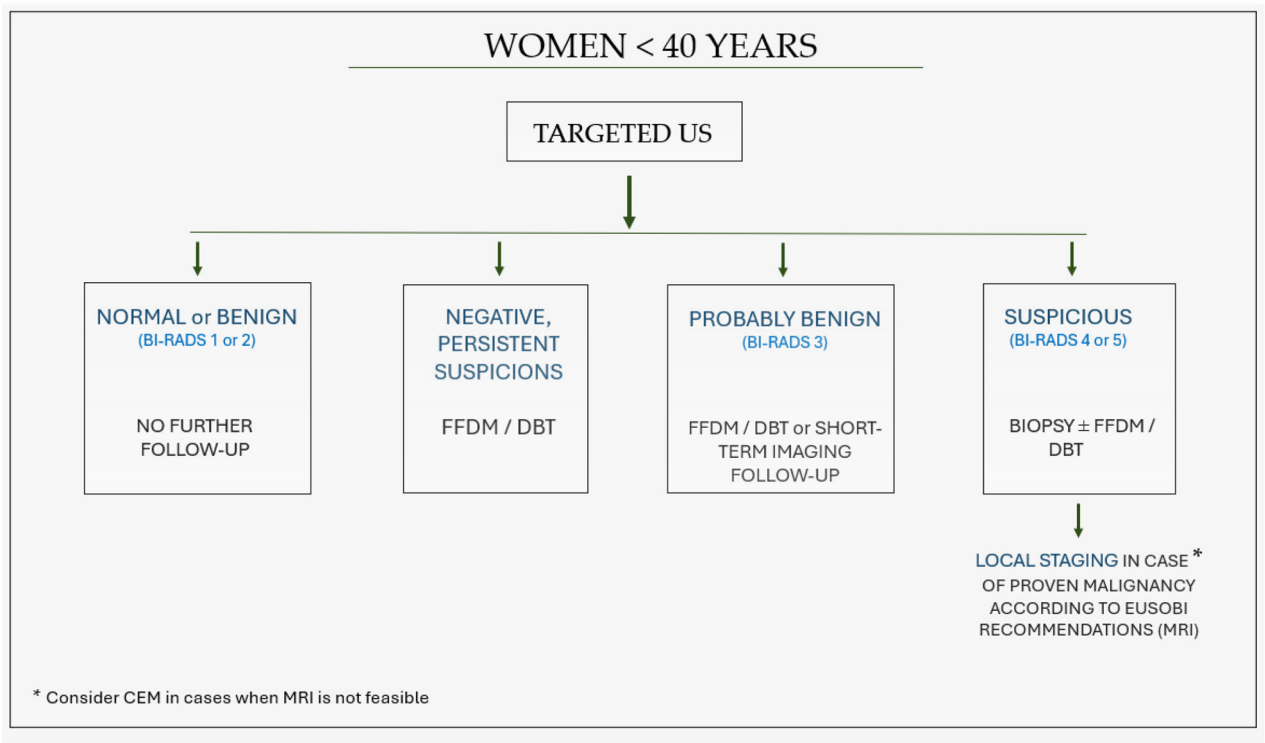
A summary of recommended steps can be summarized in the flowcharts A and B.

Pathologic nipple discharge

Nipple discharge is the third most common symptom after breast pain and palpable lumps. It is reported that up to 50% of women might encounter an episode of nipple discharge during their life [37]. Nipple discharge is characterized as physiologic when it is provoked under breast compression, it is usually bilateral, involving multiple ducts, and has a white, yellow, or green color. In physiologic nipple discharge, no imaging is necessary. Nipple discharge is deemed pathologic when it is spontaneous, unilateral, bloody, serous or clear, or associated with an underlying mass. Although the most common causes of pathologic nipple discharge are benign entities such as duct ectasia (17–36%) or intraductal papillomas (35–48%), breast cancer cannot be excluded, hence the need for further diagnostic workup. Indeed, ductal carcinoma in situ (DCIS) is found in up to 12% of cases [37]. Large retrospective analyses have reported rates of malignancy or high-risk histopathologic lesions (papillomas with or without atypia) in 11–16% of patients presenting with pathologic nipple discharge [10].

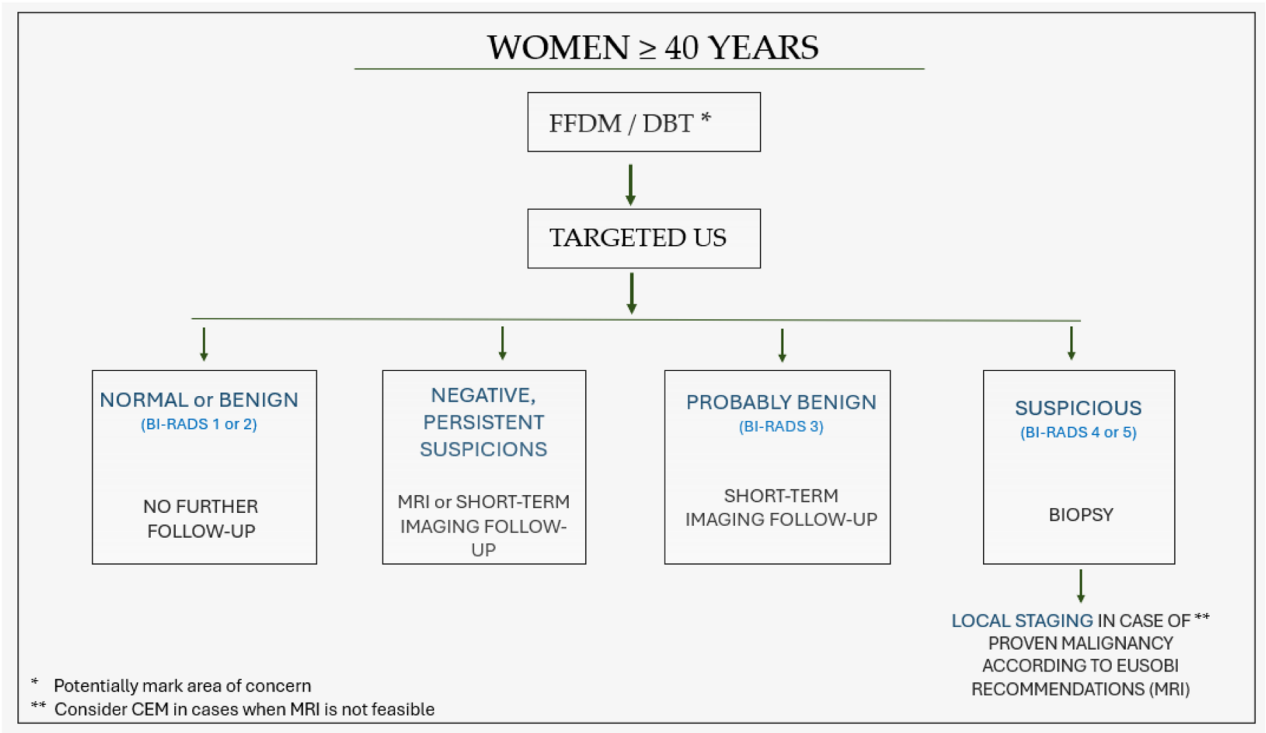
Whereas initially, cytology and ductography were routinely performed, the advent of modern breast imaging with advanced US systems and high-frequency US probes has changed this approach. Cytological analysis is not routinely recommended as the absence of malignant cells does not exclude cancer, though it remains possible to perform this test if nipple discharge can be provoked during the examination [38]. Ductography is an invasive procedure that requires experienced operators and discharge must be present on the day of the exam in order to correctly identify and catheterize the correct orifice. About 10–15% of procedures are technically inadequate or inconclusive. The procedure is contra-indicated in lactating women, in patients with iodine-contrast allergies, and in cases of active infection. A recent retrospective analysis concluded that in patients with breast cancer, ductography and noninvasive breast imaging had similar sensitivities, whereas for women with benign pathology and/or normal imaging, noninvasive imaging showed a significantly higher specificity than ductography [37].

A.



A. Flowchart of diagnostic work-up in women < 40 years

B.



B. Flowchart of diagnostic work-up in women ≥ 40 years

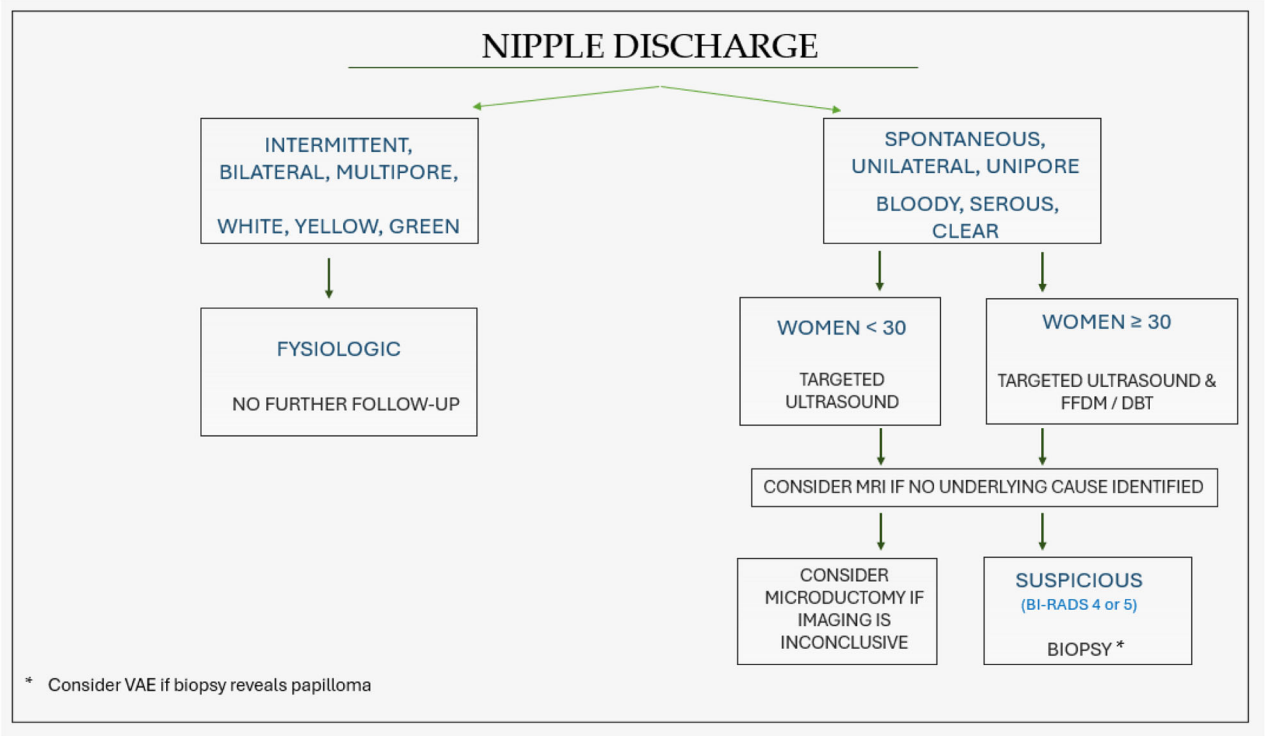
The diagnostic workup is again stratified by age [39]. For women < 30-years-old, US is the modality of choice. US alone has a reported sensitivity (56–80%), specificity (61–75%), PPV (29–39%), and NPV (90–91%) for the detection of single underlying malignancy in patients with pathologic nipple discharge [10, 37]. For women between 30 and 39-years-old and for those > 40-years-old, FFDM or DBT along with targeted US is the recommended approach. FFDM or DBT can safely diagnose suspicious microcalcifications in this context, which are the only type of lesions that the US cannot readily depict (and considering the common diagnosis of DCIS in women presenting with nipple discharge, this is important). However, high-risk lesions and malignant lesions are only in a minority of cases identified by mammography, with a reported sensitivity of 10–26%, specificity of 94–95%, PPV of 18%, and NPV of 88% [10].

Breast MRI may be considered in cases in which mammography and US cannot identify the underlying cause of pathologic nipple discharge. Reported sensitivities of breast MRI in this clinical setting are 86–100% for invasive cancer and 40–100% for noninvasive disease [10]. Several studies including metanalyses have shown that MRI has higher sensitivity and specificity than US and ductography for lesion detection in women with nipple discharge and MRI has, therefore, effectively replaced ductography [40, 41].

Microductectomy is still the surgical approach when imaging is inconclusive. When imaging depicts suspicious lesions with positive histology on subsequent biopsy, then local staging with MRI can be an option. There is scarce data on the role of CEM in this context. When image-guided biopsy is in favor of papillomas without concomitant atypia, recent recommendations favor the use of vacuum-assisted excision (VAE) to remove the lesion [42, 43]. Papillomas are considered as lesions of unknown malignant potential (B3 lesions), due to the possible pathology underestimation on core biopsy and subsequent upgrade to malignancy on surgical excision. Although papillomas with atypia can present an upgrade to malignancy rates up to 27–36%, papillomas without atypia are upgraded to malignancy in less than 10% of cases [43]. The choice between VAE and open excision should be evaluated by a multidisciplinary team where shared decisions with the patient are also considered. The best conditions for VAE are a small breast lesion (< 3 cm), safe distance between the lesion and overlying skin and/or nipple (> 1 cm), and, obviously, good visibility of the lesion on targeted US. If the target lesion is completely removed, radiological follow-up is sufficient [42, 43],

The above-proposed steps are summarized in flowchart C.

C.



C. Flowchart of diagnostic work-up of nipple discharge

Skin changes

Skin changes such as retraction, redness, tenderness, or "peau d' orange" (dimpling similar to an orange rind) are also symptoms that require further imaging. In the absence of additional symptoms, like a palpable lump, further imaging is still necessary according to the age-stratified choice of modalities as stated in the previous paragraphs. MRI can be particularly useful in cases of peau d'orange and may be conducted after a skin punch biopsy. This finding may be caused by inflammatory breast cancer (IBC), which is a rare form of breast cancer that accounts for only 2–4% of all breast cancer cases, but contributes to 7–10% of breast cancer-related mortality [44]. MRI is the most accurate imaging technique for detecting primary breast cancer in this context and should be considered whenever suspicion of IBC exists. US can be useful in diagnosing regional nodal disease. Positron emission computed tomography (PET-CT) provides additional information on distant metastasis and should be considered in the initial staging of IBC [45, 46].

Axillary abnormalities (with negative clinical breast exam)

For women < 40-years-old, US is the first imaging modality. For women > 40 years, US and FFDM or DBT (in case of suspicious lymph nodes in the US) are recommended. If there is suspicious axillary lymphadenopathy without another explanation (for example rheumatoid arthritis, chronic lymphocytic leukemia, or recent vaccination) and whole breast US + FFDM is negative, a US-guided core biopsy of the suspicious lymph nodes should be performed. If histology is in favor of breast metastasis, MRI is indicated. Computed tomography (CT) or PET-CT is indicated to look for primary malignancy elsewhere if a non-breast primary cancer is suspected [10]. Automated breast ultrasound (ABUS) is being increasingly used in the screening setting. In the diagnostic setting of axillary abnormalities, ABUS might have inherent difficulty in correctly assessing all three axillary levels [47, 48]. Handheld US should be preferred over ABUS in this context.

Male patients

Gynecomastia is the most common cause of pain, breast enlargement, or a palpable mass in men. It is physiological in neonates and adolescents; in adults, it can be a side effect of many drugs, so a thorough clinical history is imperative. US is the modality of choice in this setting. If FFDM/DBT has been performed as the first modality and depicts clear findings of gynecomastia, the US can be deferred.

Men presenting with a mass and nipple discharge have a rate of breast cancer as high as 75%. A palpable mass

alone or nipple discharge alone presents positive rates up to 57% [10, 49].

Palpable masses, nipple discharge, or any other symptom occurring in men > 25-years-old (especially when unilateral) should be imaged with mammography or DBT and US. Core biopsy should be performed in case of suspicious findings.

Summary statement

Breast symptoms are commonly encountered in clinical practice; updated guidelines and flowcharts are provided in this paper to optimize diagnostic approaches and ensure optimal patient care.

Patient summary

Focal breast symptoms such as palpable breast or axillary lump, nipple discharge, skin changes, or pain should be thoroughly examined by medical specialists. In most cases, a patient-tailored diagnostic imaging approach is recommended in order to determine if the underlying cause is benign or malignant. For most women < 40 years, US is the modality of choice, with FFDM or DBT added when indicated; for the > 40-year age group, mammography or tomosynthesis are standardly used. In case of indeterminate or suspicious findings, a core biopsy should be performed. In case of negative imaging and strong clinical concern, a biopsy or additional imaging techniques such as MRI or CEM are recommended. Persistence of symptoms after a negative initial diagnostic workup should prompt a new consultation.

Abbreviations

ABUS	Automated breast ultrasound
CEM	Contrast enhanced mammography
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
FFDM	Full field digital mammography
GBCA	Gadolinium-based contrast agent
IBC	Inflammatory breast cancer
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PABC	Pregnancy-associated breast cancer
PET-CT	Positron emission-computed tomography
US	Ultrasonography or ultrasound
VAE	Vacuum-assisted excision

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Compliance with ethical standards

Guarantor

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Conflict of interest

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Informed consent

Written informed consent was not required.

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Study subjects or cohorts overlap

Not applicable.

Methodology

- Practice recommendations

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