

NCCN

Breast Cancer Screening and Diagnosis, Version 3.2018

Clinical Practice Guidelines in Oncology

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Overview

The average lifetime risk of breast cancer for a woman in the United States has been estimated at 12.3% (ie, 1 in 8 women).¹ For 2018, the American Cancer Society (ACS) estimates that 63,960 cases of female carcinoma in situ of the breast and 268,670 cases of invasive breast cancer (266,120 women and 2,550 men) will be diagnosed in the United States.² About 41,400 deaths are estimated for 2018.³ The good news is that death rates have been falling on average

Abstract

The NCCN Guidelines for Breast Cancer Screening and Diagnosis have been developed to facilitate clinical decision making. This manuscript discusses the diagnostic evaluation of individuals with suspected breast cancer due to either abnormal imaging and/or physical findings. For breast cancer screening recommendations, please see the full guidelines on NCCN.org.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

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Disclosures for the NCCN Breast Cancer Screening and Diagnosis Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Breast Cancer Screening and Diagnosis Panel members can be found on page 1389. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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1.8% each year between 2006 and 2015.⁴ This decrease has been attributed to mammographic screening and treatment advances.⁵

Diagnostic Evaluation

Breast symptoms are common among women. A retrospective study of women aged 40 to 70 years showed that 16% (total visits of 23 per 100 women) of women will present with symptoms to their provider during a decade, with higher frequency among women aged 40 to 59 years compared with older women.⁶ Breast pain is the most common symptom followed by palpable mass. In addition, palpable areas of concern are identified during a breast physical exam. Breast clinical findings are not specific, and there is variability in interpreta-

tion. Each symptom is associated with a risk of malignancy and warrants diagnostic evaluation; however, most symptoms will be determined to be benign in etiology. Women younger than age 40, who are not usually recommended for routine breast screening, also frequently present with breast symptoms.

Unlike imaging for screening, which is used to detect cancer in asymptomatic women, diagnostic evaluation is used to characterize a clinical finding or possible abnormality found during screening. There is confusion regarding the term “diagnostic imaging,” as it is applied to 2 very different situations: (1) imaging for a clinical finding such as a palpable mass; and (2) incremental imaging after a possible abnormal screening mammogram in an asymptomatic woman (also referred

Text cont. on page 1380.

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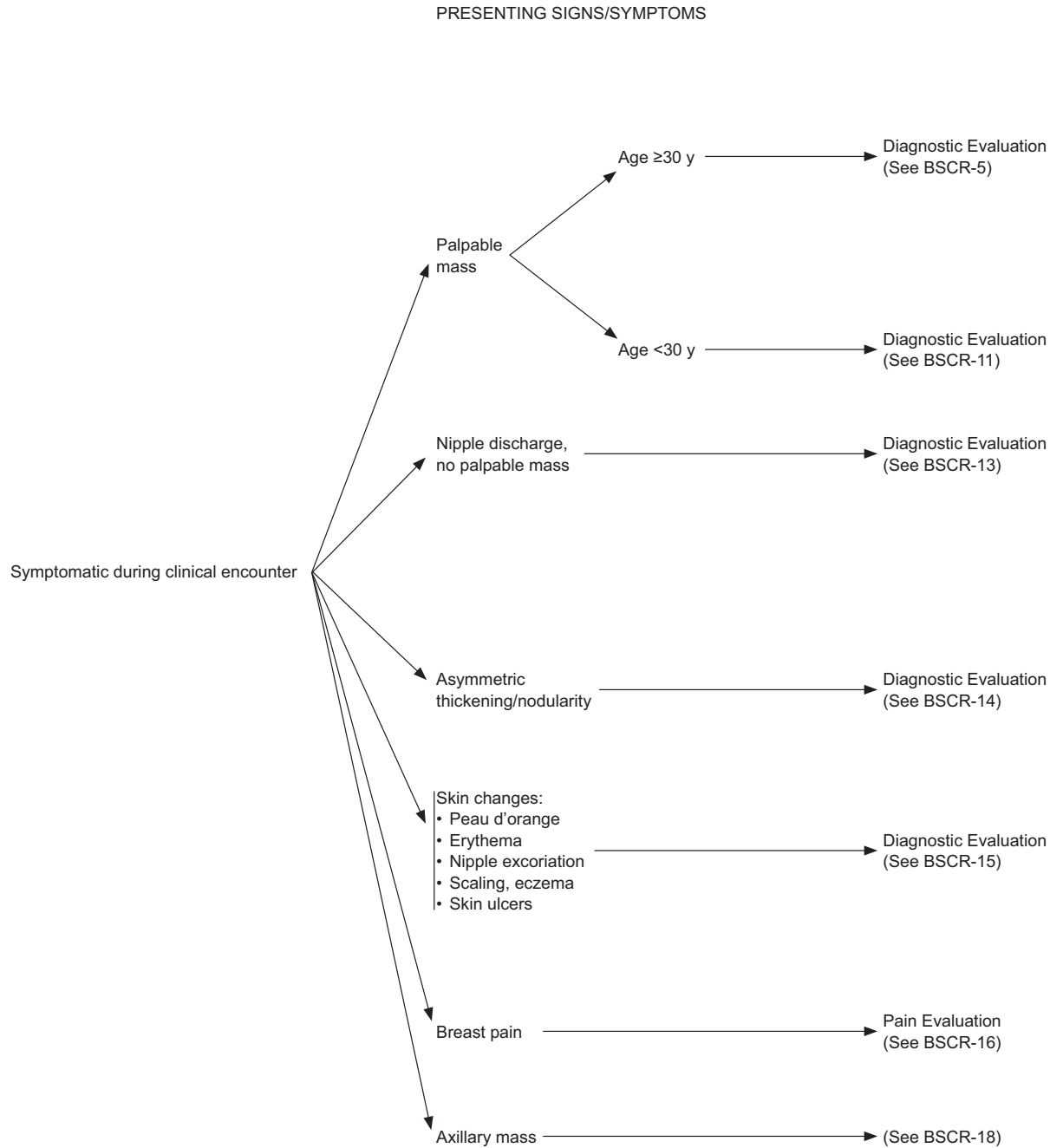
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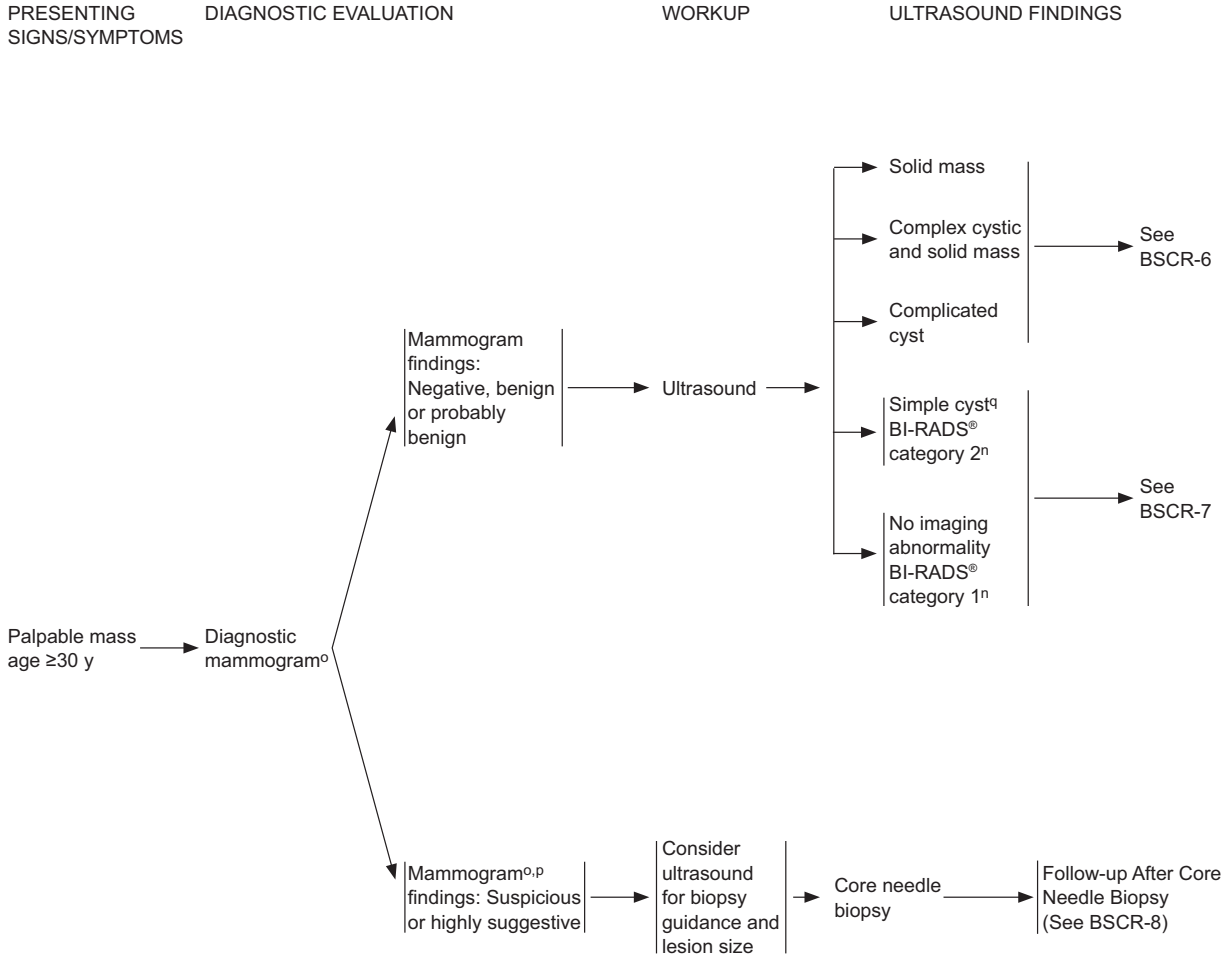
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BSCR-4

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

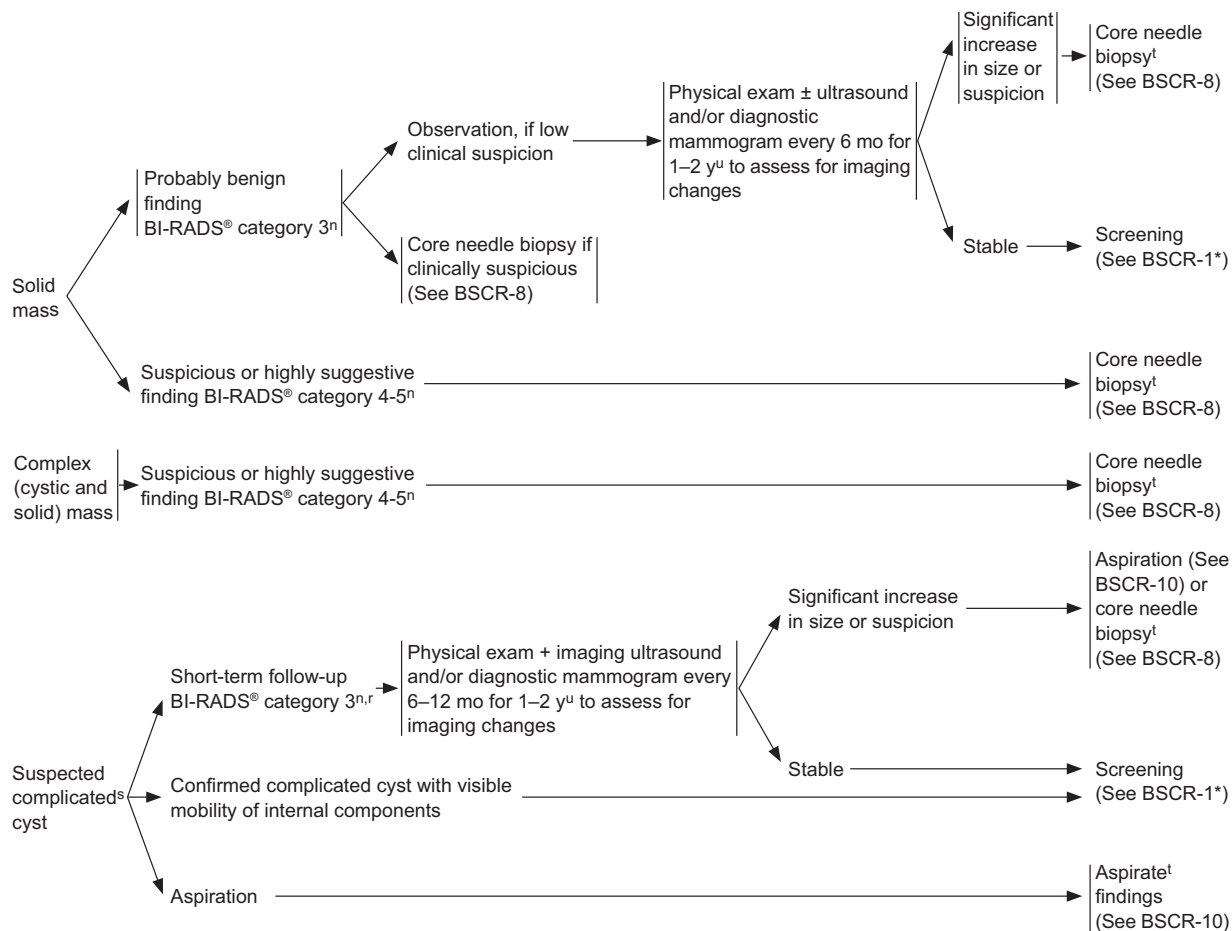
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^oSee Assessment Category Definitions (BSCR-C, available online, in these guidelines, at NCCN.org).
^oThere are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst in which ultrasound would be preferred and may suffice for women 30–39 years of age. See Discussion.
^pAssess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to mammogram findings: negative, benign, or probably benign for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.
^qConcordance is needed between clinical exam and imaging results. Consider therapeutic aspiration for persistent clinical symptoms.

BSCR-5

ULTRASOUND FINDINGS/PALPABLE MASS



*Available in online, in these guidelines, at NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).

^rIn the context of numerous simple cysts, a complicated cyst may be considered a benign finding.

^sRound or oval, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria for simple cyst.

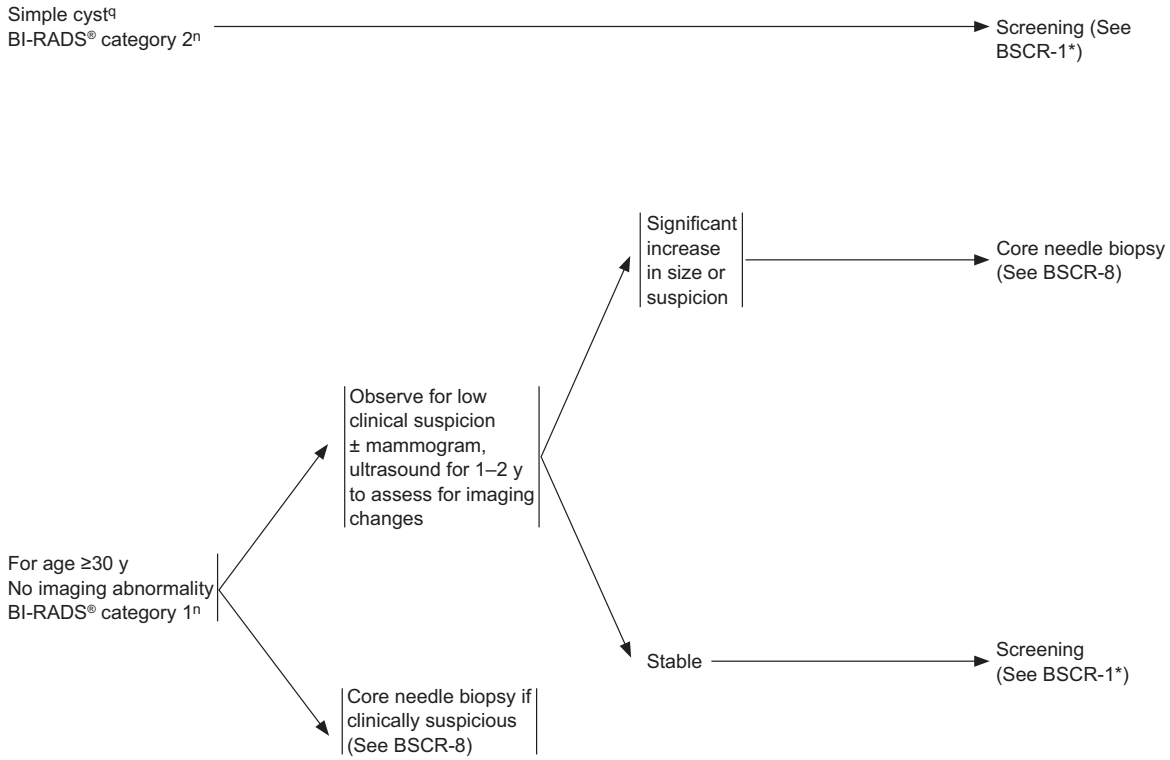
^tCore needle biopsy preferred; in some circumstances needle aspiration may be sufficient.

^uThere may be variability on the follow-up interval based on the level of suspicion.

BSCR-6

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ULTRASOUND IMAGING FINDINGS/PALPABLE MASS



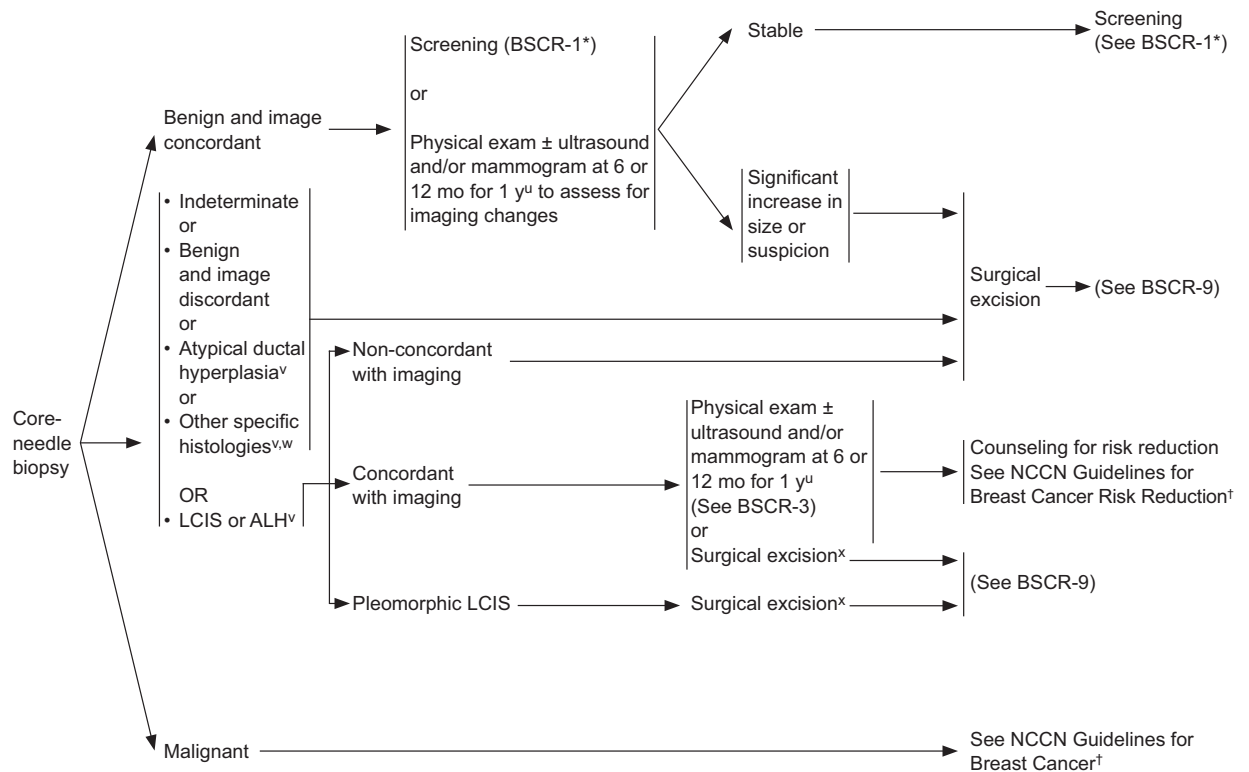
*Available in online, in these guidelines, at NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).

^qConcordance is needed between clinical exam and imaging results. Consider therapeutic aspiration for persistent clinical symptoms.

BSCR-7

FOLLOW-UP EVALUATION AFTER CORE NEEDLE BIOPSY



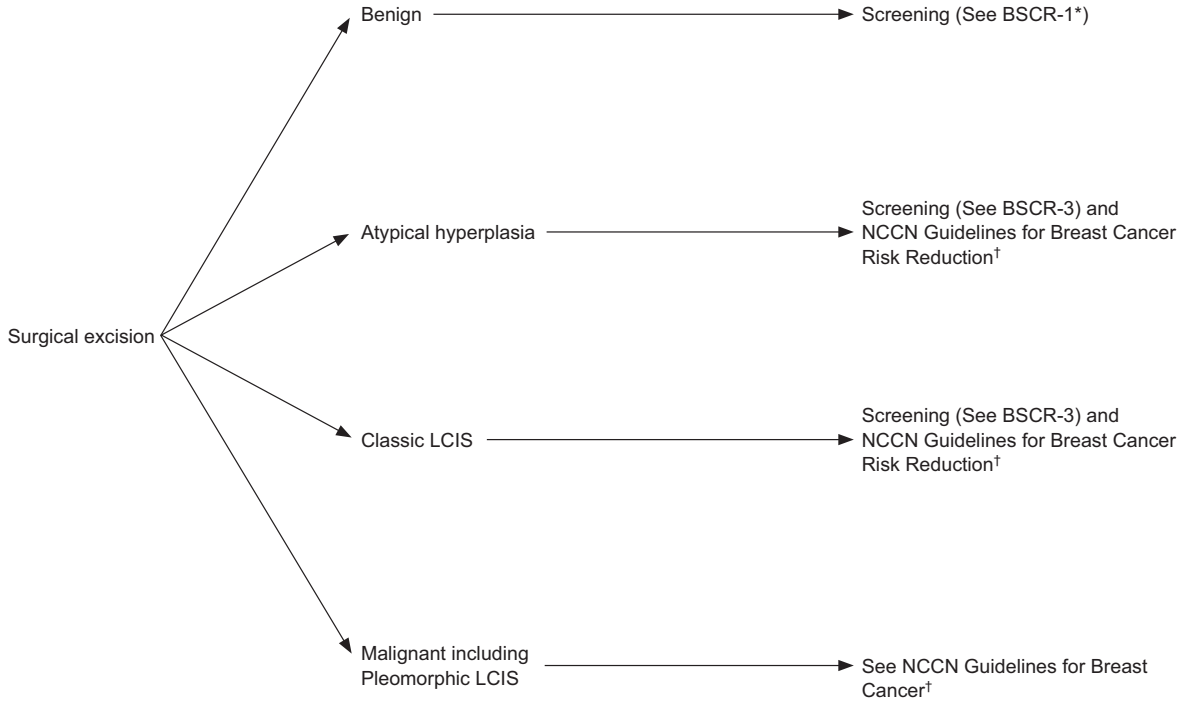
*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

^uThere may be variability on the follow-up interval based on the level of suspicion.
^vSelect patients may be suitable for monitoring in lieu of surgical excision (eg, flat epithelial atypia [FEA], papillomas, fibroepithelial lesions, radial scars).
^wOther histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or histologies of concern to pathologist.
^xMultifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk for invasive cancer on surgical excision. (Rendi MH, Dintzis SM, Lehman CD, et al. Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. Ann Surg Oncol 2012;19:914-921. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21861212>).

BSCR-8

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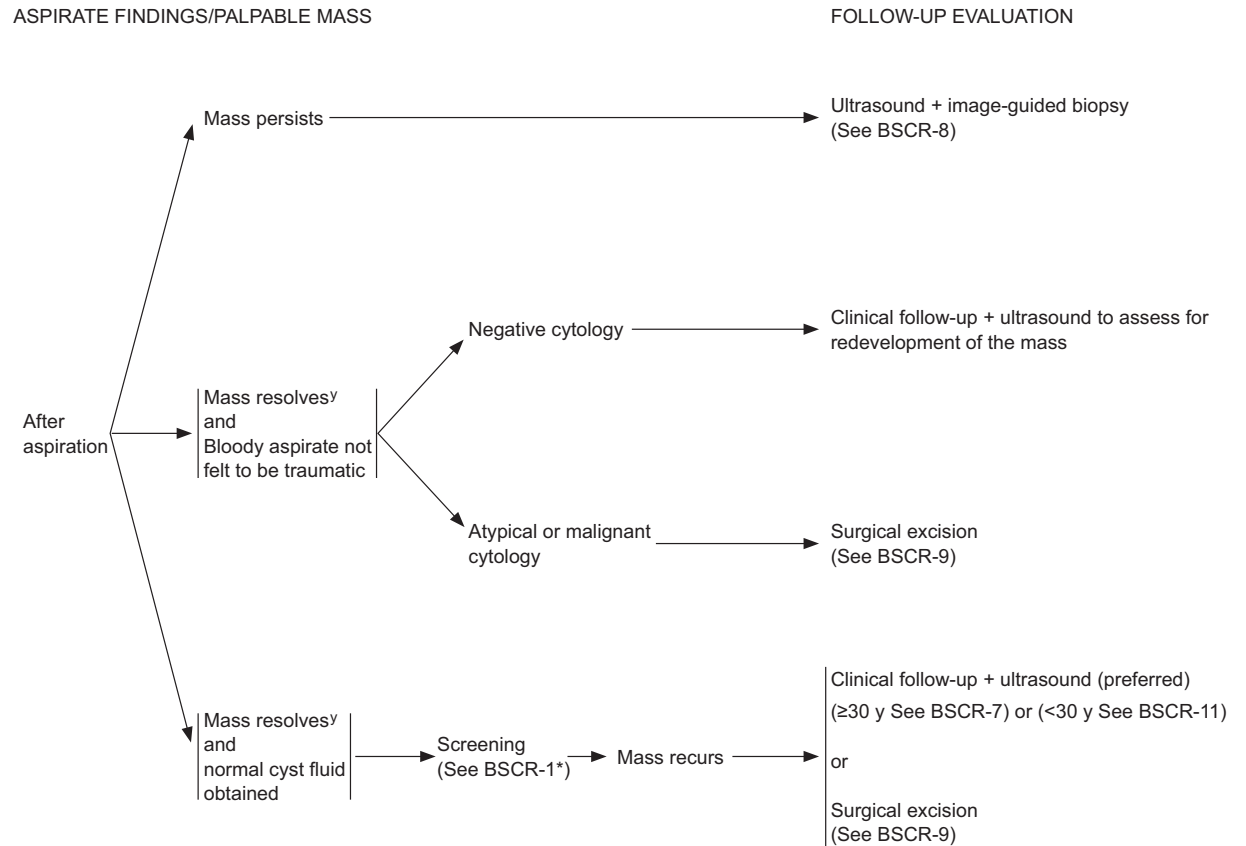
FOLLOW-UP EVALUATION



*Available online, in these guidelines, at NCCN.org.
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BSCR-9

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*Available online, in these guidelines, at NCCN.org.

^yRoutine cytology is not recommended.

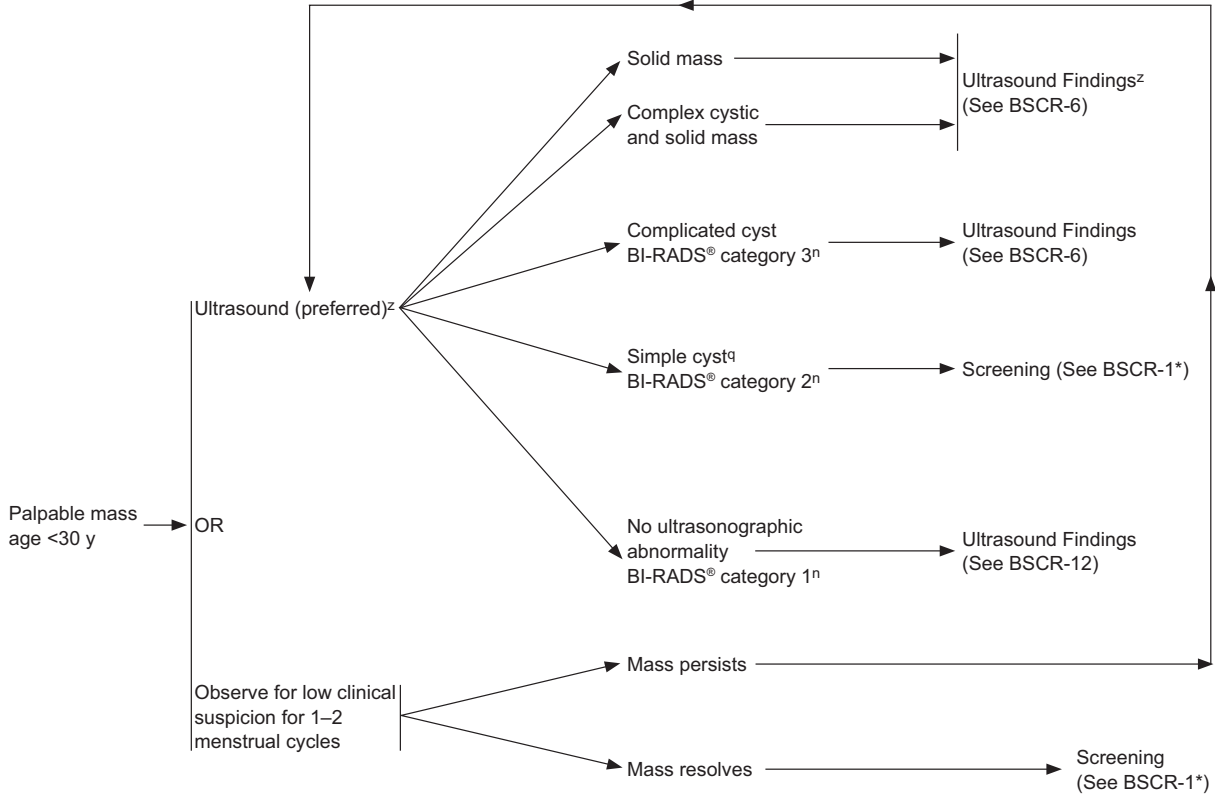
BSCR-10

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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PRESENTING SIGNS/SYMPTOMS

DIAGNOSTIC EVALUATION



*Available online, in these guidelines, at NCCN.org.

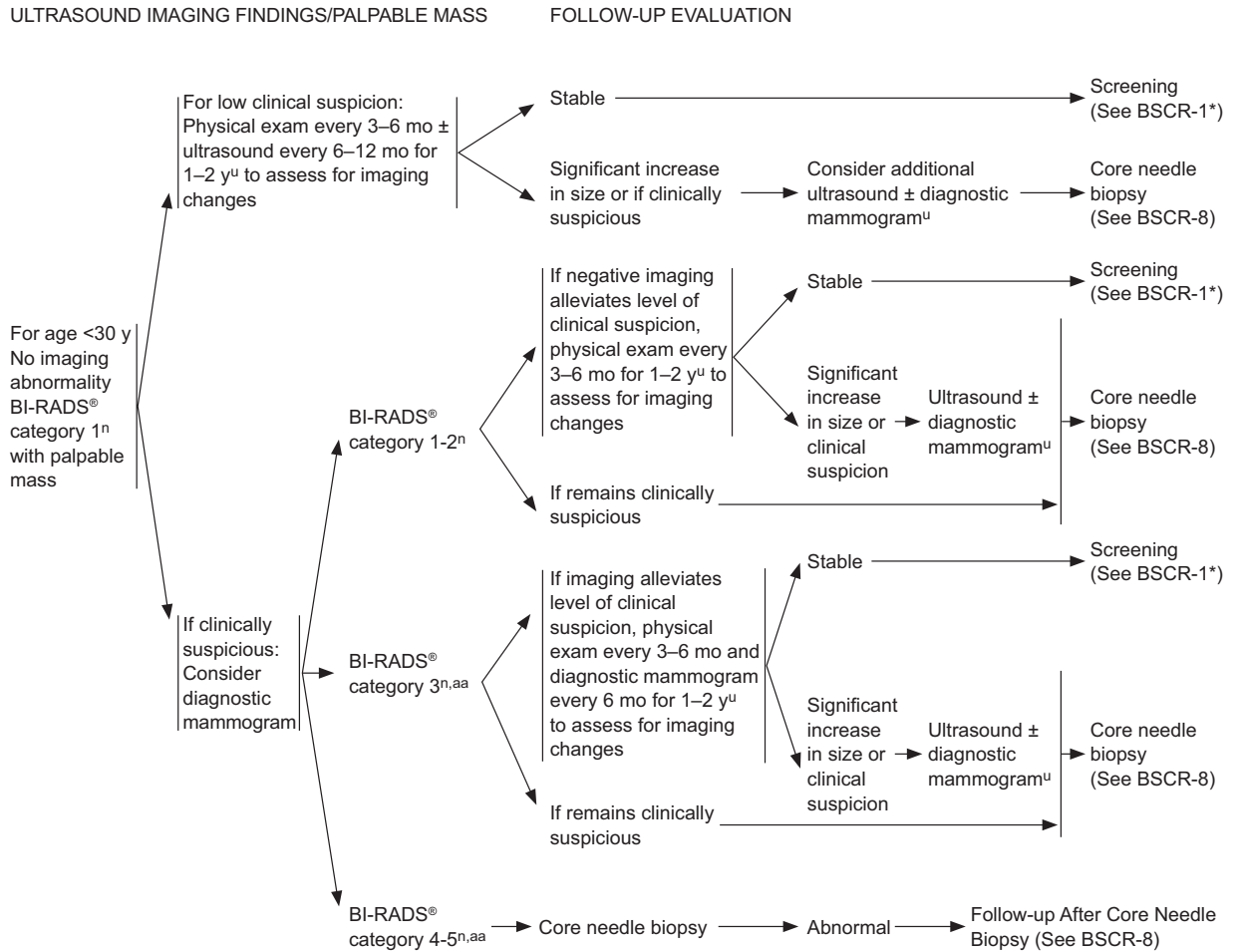
ⁿSee Assessment Category Definitions (BSCR-C*).

^qConcordance is needed between clinical exam and imaging results. Consider therapeutic aspiration for persistent clinical symptoms.

^zIf suspicious or highly suggestive of malignancy obtain mammogram.

BSCR-11

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*Available online, in these guidelines, at NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).

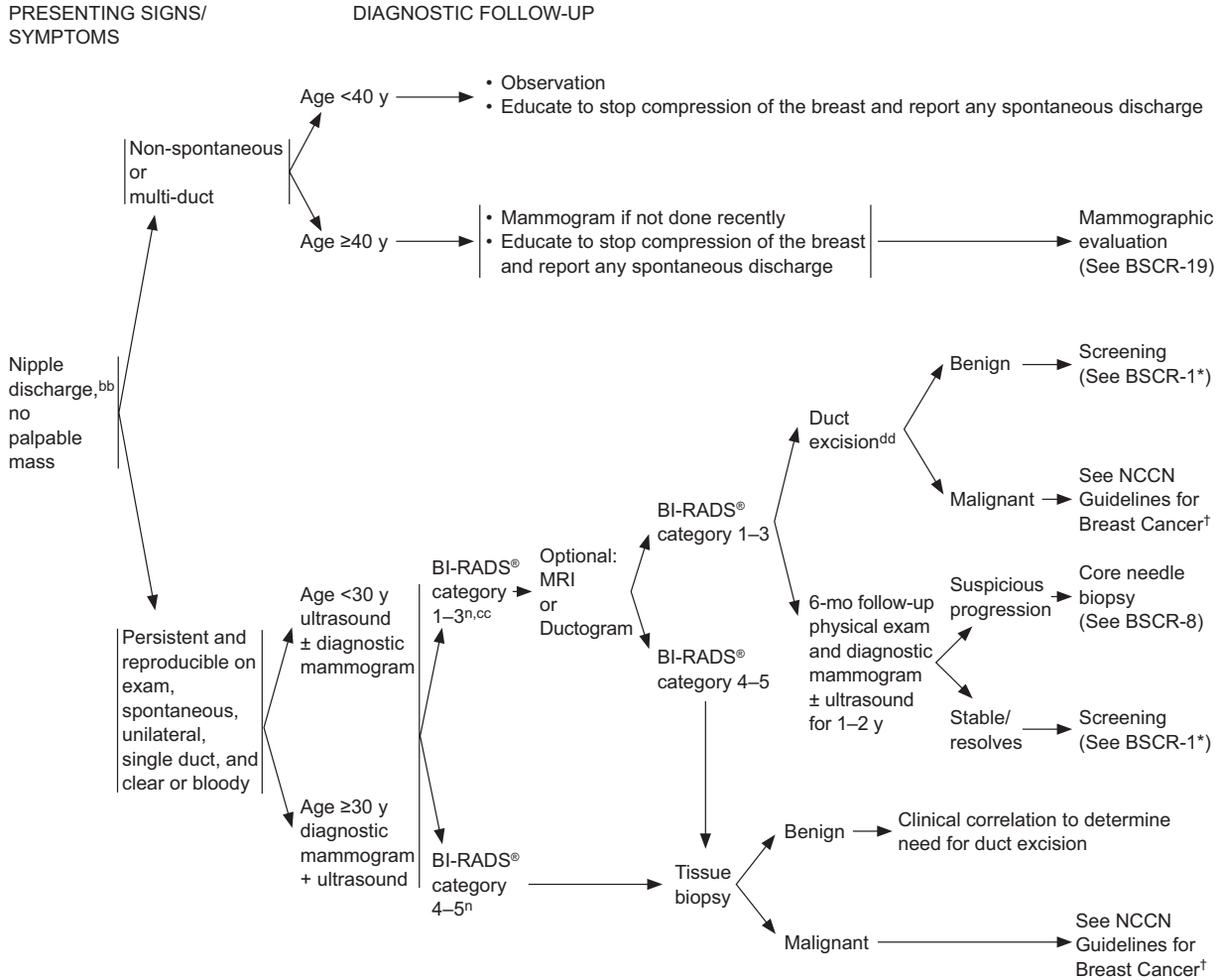
^uThere may be variability on the follow-up interval based on the level of suspicion.

^{aa}Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to BI-RADS category 1-2 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.

BSCR-12

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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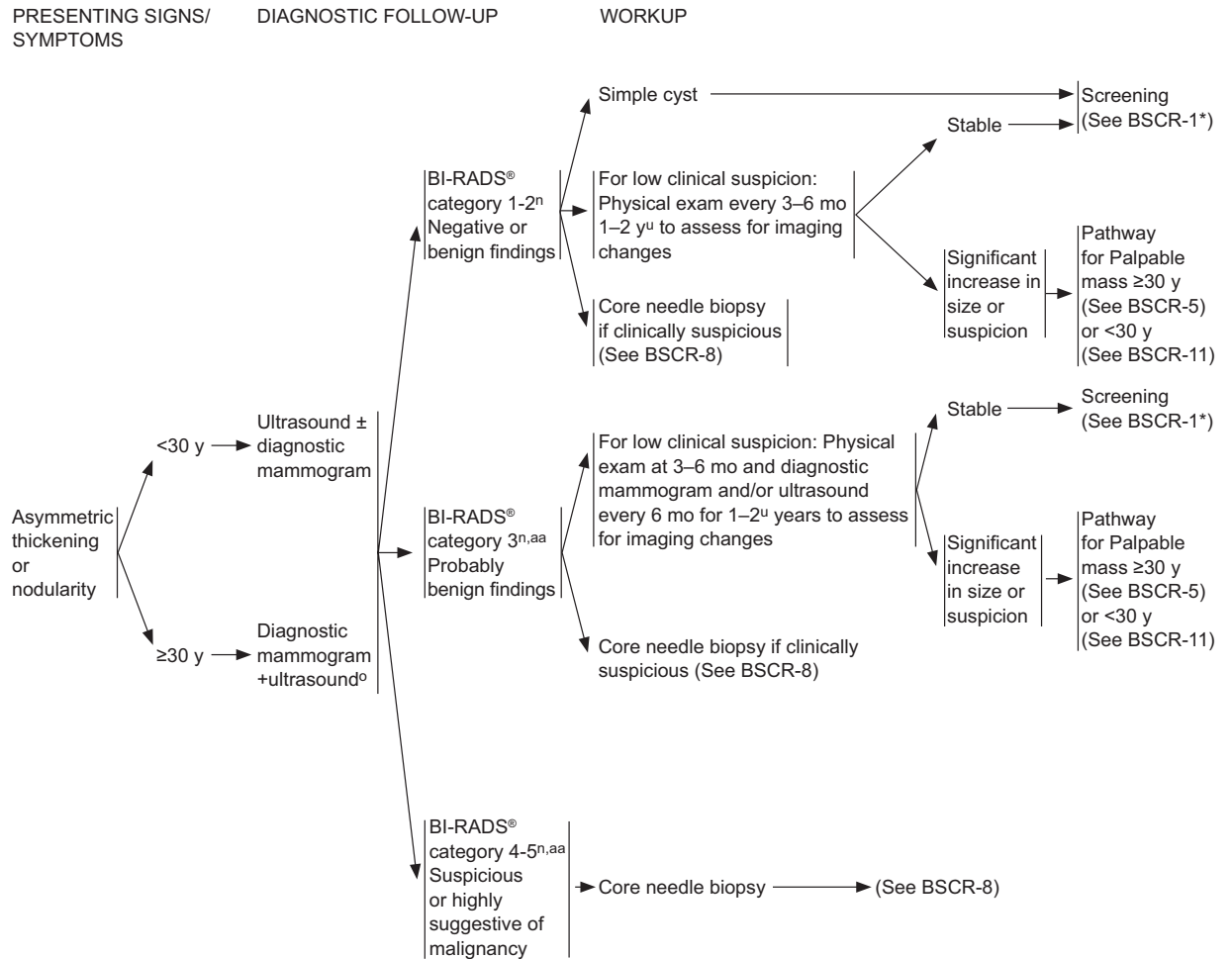


*Available online, in these guidelines, at NCCN.org.
 †To view the most recent version of these guidelines, visit NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).
^{bb}A list of drugs that can cause nipple discharge (not all-inclusive): psychoactive drugs, antihypertensive medications, opiates, oral contraceptives, and estrogen.
^{cc}If BI-RADS category 3 finding is unrelated to nipple discharge, manage mammographic finding by BSCR-19.
^{dd}Based on clinical suspicion and patient preference.

BSCR-13

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*Available online, in these guidelines, at NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).

^oThere are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30–39 years of age. See Discussion.

^uThere may be variability on the follow-up interval based on the level of suspicion.

^{aa}Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to BI-RADS category 1-2 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.

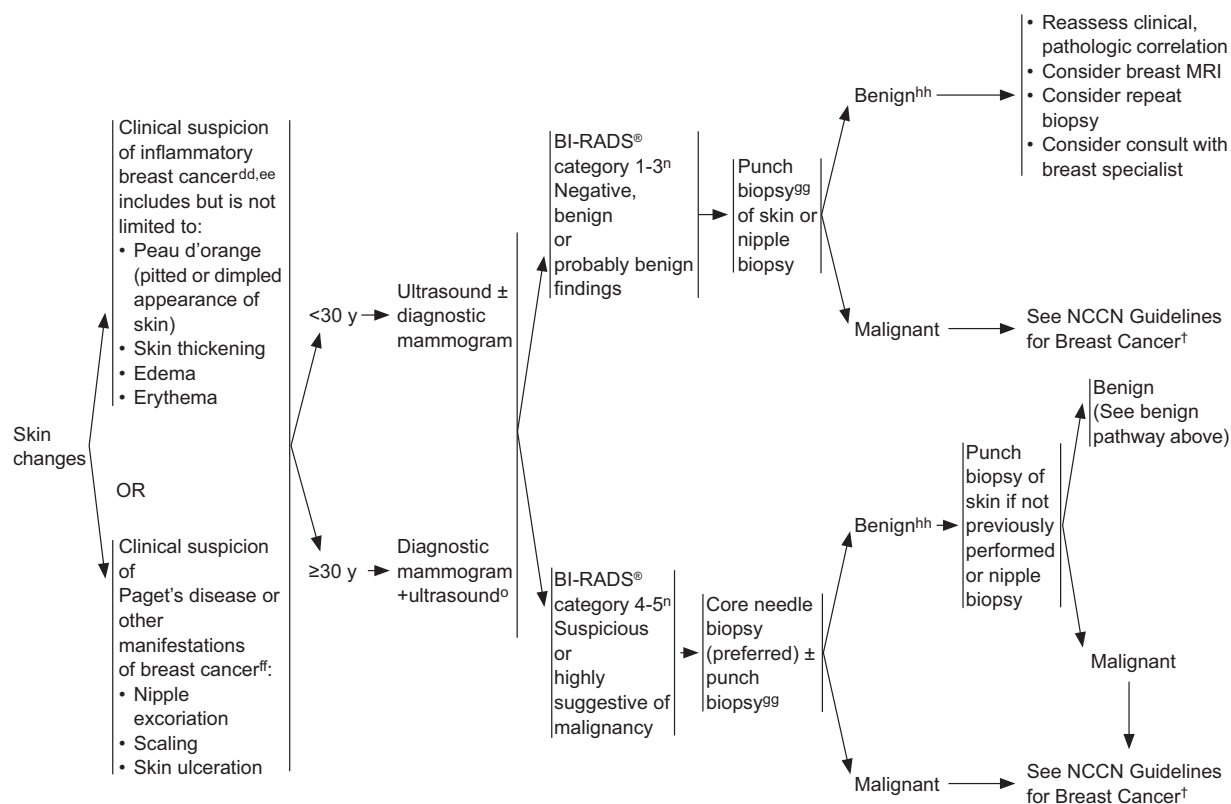
BSCR-14

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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PRESENTING SIGNS/
SYMPTOMS

DIAGNOSTIC FOLLOW-UP



*Available online, in these guidelines, at NCCN.org.

†To view the most recent version of these guidelines, visit NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).

^oThere are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30–39 years of age. See Discussion.

^{dd}This may represent serious disease of the breast and needs evaluation. (Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol* 2011;22(3):515-523. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20603440>).

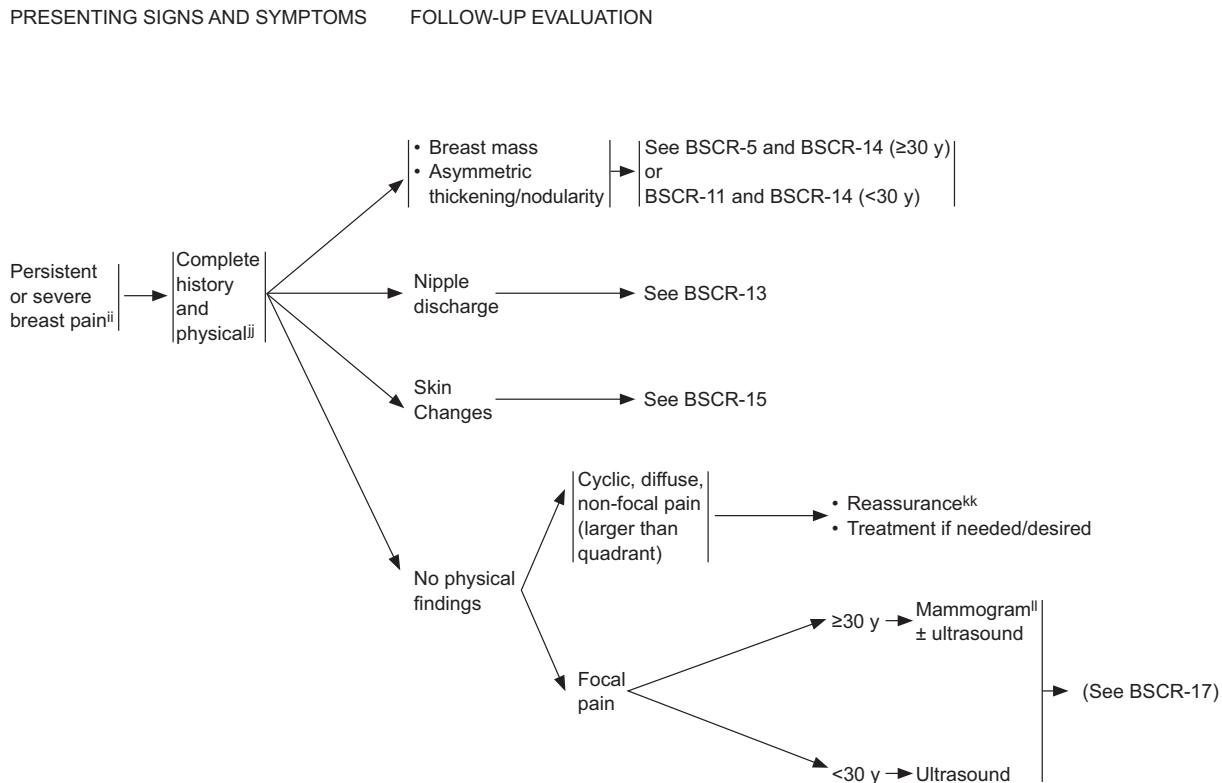
^{ee}If clinically of low suspicion for breast cancer or high suspicion for infection, a short trial (7–10 days) of antibiotics for mastitis may be indicated.

^{ff}If clinically of low suspicion for Paget's disease or high suspicion for eczema, a short trial of topical steroids may be indicated.

^{gg}Inflammatory breast cancer is a clinical diagnosis and is not dependent on a positive punch biopsy.

^{hh}A benign skin punch biopsy in a patient with a clinical suspicion of inflammatory breast cancer does not rule out malignancy. Further evaluation is recommended.

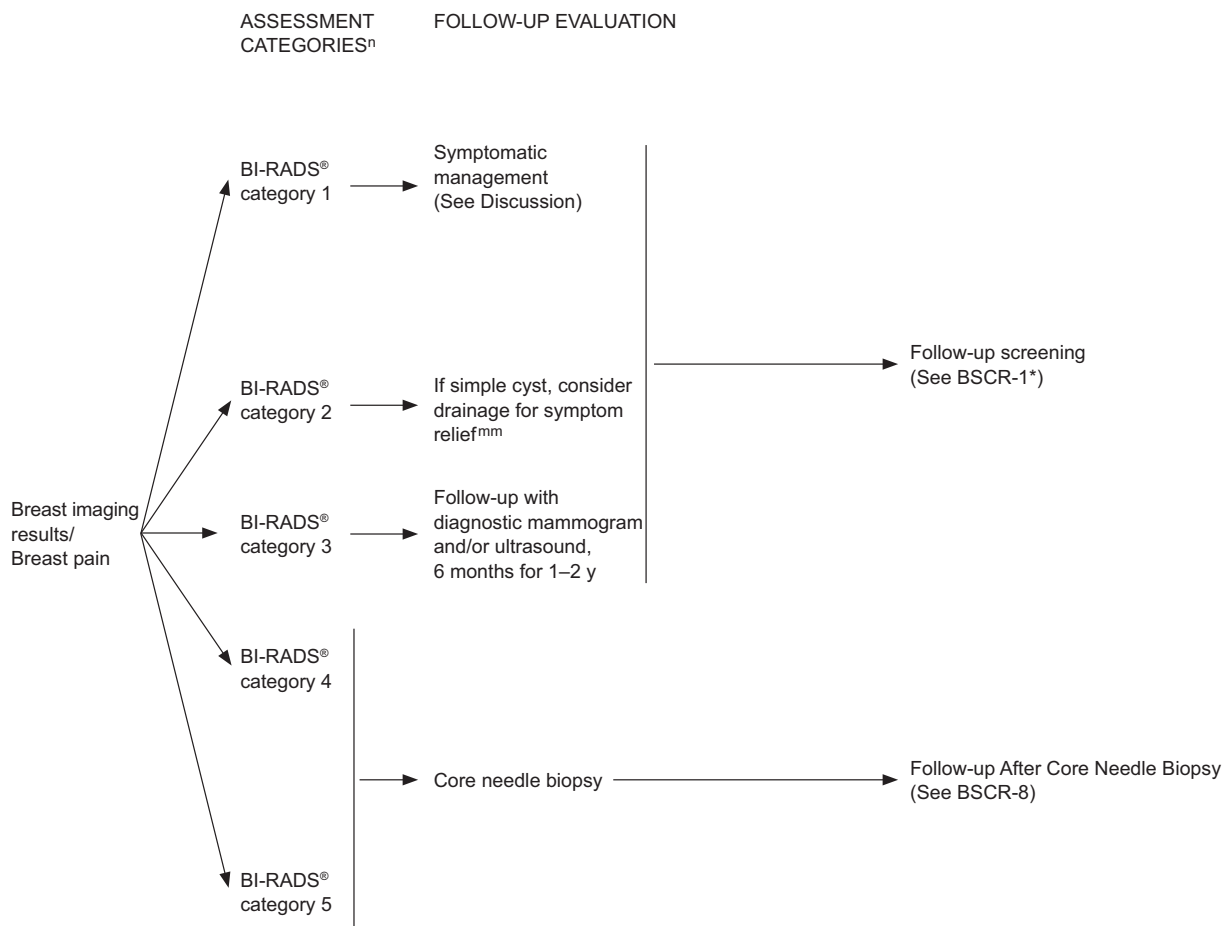
BSCR-15



ⁱⁱDefined as 4 to 6 weeks duration prior to that, symptomatic management.
^{jj}Adequate clinical breast exams include the following: upright and supine position during inspection, and palpation of all components of the breast, axilla, and clavicular lymph node basins. Time spent on the palpable portion of the exam is associated with increased detection of palpable abnormalities. Location and distance from nipple facilitate geographic correlation with imaging findings. (See BSCR-1, available online, in these guidelines, at NCCN.org).
^{kk}Assuming breast imaging screening is current.
^{ll}There are some circumstances with low clinical suspicion; ultrasound would be preferred and may suffice for women 30–39 years of age.

BSCR-16

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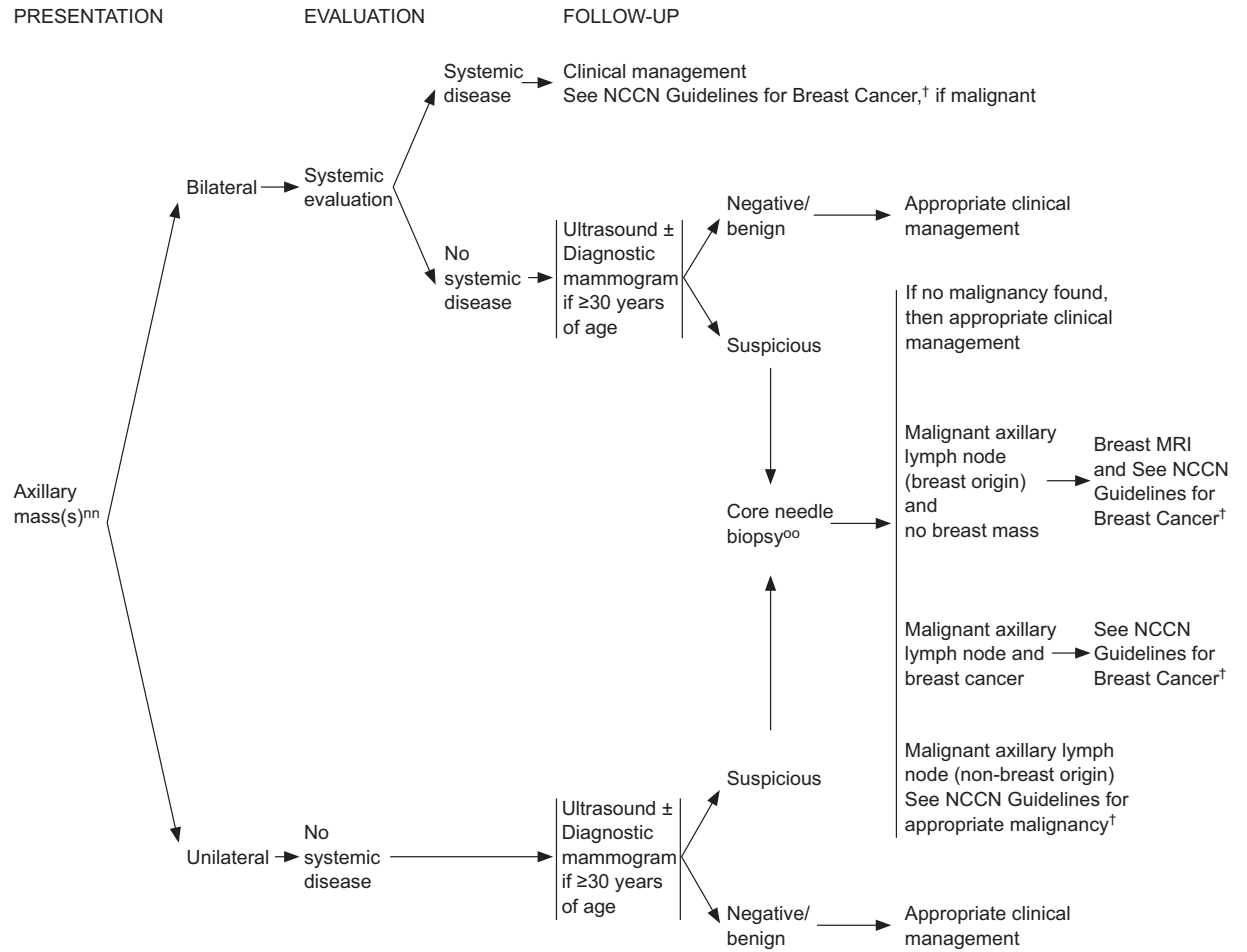


*Available online, in these guidelines, at NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C*).
^{mm}If complicated cyst, consider aspiration.

BSCR-17

RECOMMENDATIONS FOR FOLLOW-UP OF AXILLARY MASS

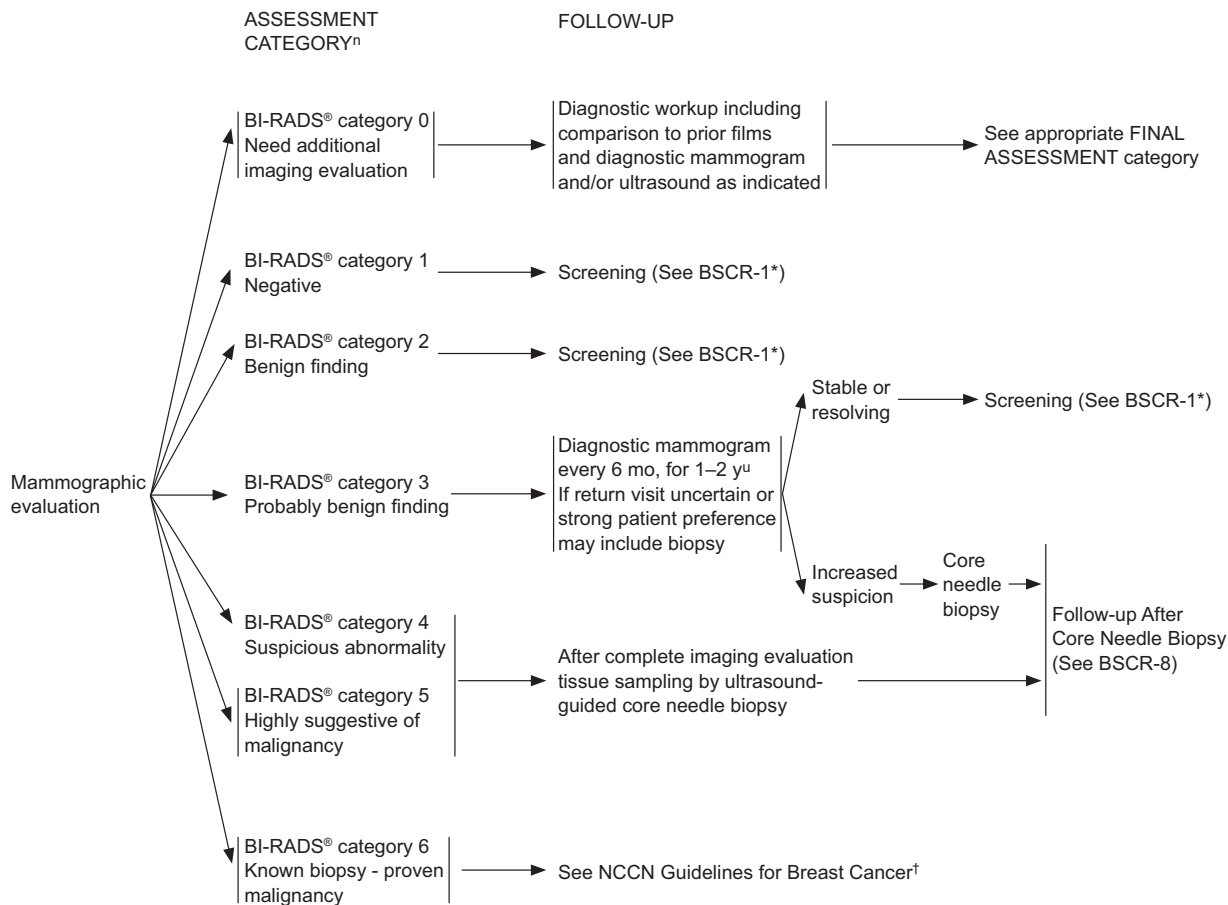


[†]To view the most recent version of these guidelines, visit NCCN.org.

ⁿⁿLocalized to the axilla and no signs of lymphoma.
^{oo}If lymphoma suspected, may require special pathologic processing and/or surgical excision.

BSCR-18

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†To view the most recent version of these guidelines, visit NCCN.org.

ⁿSee Assessment Category Definitions (BSCR-C).

^uThere may be variability on the follow-up interval based on the level of suspicion.

BSCR-19

to as *recall* or *callback*). To add further confusion, insurance carriers may consider a routine mammogram to be “diagnostic” in certain asymptomatic women (eg, in women with prior cancer). Diagnostic evaluation in this review will be restricted to the former 2 situations.

Diagnostic evaluation may include physical examination and diagnostic imaging for symptomatic women and diagnostic imaging for women recalled from screening. Diagnostic imaging may include diagnostic mammography, ultrasonography, and at times diagnostic breast MRI. The eventual decision regarding need for tissue sampling is based on level of suspicion on imaging and/or clinical examination. Biopsy is needed in situations in which imaging is negative but clinical findings are suspicious, because imaging is not completely sensitive for cancer detection.

Although the term *diagnostic* implies diagnosis, imaging results are often not specific enough to be truly “diagnostic.”

Diagnostic Imaging After Screening Mammography Recall

Diagnostic Mammography: Screening mammography consists of 2 standard x-ray images of each breast, whereas a diagnostic mammogram includes additional views, such as spot compression views or magnification views, to investigate the finding in question. Diagnostic mammography is associated with higher sensitivity but lower specificity as compared with screening mammography. Digital breast tomosynthesis may replace traditional diagnostic mammographic imaging in certain situations.⁷⁻⁹

Frequently, especially for masses or asymmetries, diagnostic ultrasound is also performed. Each imaging modality may be positive or negative, which allows 4 outcomes: both imaging modality results are negative; both are positive; mammogram is positive and ultrasound is negative; and mammogram is negative and ultrasound is positive. In general, a “final” combined imaging assessment category is rendered after a “recall” from screening, which is the most suspicious imaging outcome assessment.

The mammographic final assessments are mandated by the Mammography Quality Standards Act and Program (MQSA) and are reported using wording similar to the ACR BI-RADS assessment categories, which classify likelihood of the breast findings

into 6 final assessment categories.¹⁰ The BI-RADS assessment categories (which include words and numbers) help to standardize both the reporting of mammographic findings and the recommendations for further management. The assessment wording and numbers are often used interchangeably. The definitions of the mammogram assessment categories are outlined in “Mammographic Assessment Category Definitions” in the algorithm (available online, in these guidelines, at NCCN.org). Importantly, the same imaging terms are used for screened (asymptomatic) recalled women and symptomatic women, which can create confusion regarding recommendations.

NCCN Recommendations for Screening Mammogram BI-RADS Assessment Categories 1–6 are listed subsequently. The NCCN recommendations following evaluation of symptomatic diagnostic women can be found in the next section. Importantly, negative or benign BIRADS imaging assessments, in the setting of symptoms, rely on correlation of clinical findings, which may indicate need for biopsy even with negative imaging. Conversely, suspicious imaging findings for women with clinical findings of very low suspicion still warrant biopsy.

For BI-RADS category 1 (negative finding) or category 2 (benign), the panel recommends resuming routine screening.

For BI-RADS category 3 (probably benign), the panel recommends diagnostic mammograms at 6 months, then every 6 to 12 months for 1 to 2 years as appropriate. If the lesion remains stable or resolves mammographically, the patient resumes routine screening intervals for mammography. If in any of the interval mammograms the lesion increases in size or changes its benign characteristics, a biopsy is then performed. The exception to this approach of short-term follow-up is when a return visit is uncertain or the patient strongly desires biopsy or has a strong family history of breast cancer. In those cases, initial biopsy with histologic sampling may be a reasonable option.

For BI-RADS categories 4 and 5 (suspicious or highly suggestive of malignancy), tissue diagnosis using core needle biopsy (preferred) or needle localization excisional biopsy with specimen radiograph is necessary. When a needle biopsy (aspiration or core needle biopsy) is performed, concordance between the pathology report and the imaging finding must be obtained.^{11,12} For example, a negative needle bi-

opsy associated with a spiculated category 5 mass (highly suggestive of malignancy) is discordant and clearly would not be an acceptable diagnosis. When the pathology and the imaging are discordant, the breast imaging should be repeated and/or additional tissue sampled or excised; surgical excision is recommended when pathology and image remain discordant. Women with a benign result exhibiting pathology/image concordance should be followed up with mammography every 6 to 12 months for 1 to 2 years before returning to routine screening.

For BI-RADS category 6 (proven malignancy), the patient should be managed according to the NCCN Guidelines for Breast Cancer (available at NCCN.org).

Breast Ultrasonography: Imaging by ultrasound is an important adjunct for diagnosing breast cancer.¹³ However, breast ultrasonography does not detect most microcalcifications.^{14–18} The definitions of the ultrasound assessment categories are outlined in “Ultrasonographic Assessment Category Definitions” in the algorithm (available online, in these guidelines, at NCCN.org).

Diagnostic Breast MRI: MRI can also play a role in the diagnostic setting. For patients with skin changes consistent with serious breast disease, consideration of breast MRI is included in the guidelines for those with benign biopsy of skin or nipple following BI-RADS category 1–3 assessment. Since a benign skin punch biopsy in a patient with a clinical suspicion of inflammatory breast cancer (IBC) does not rule out malignancy, further evaluation is recommended. There is evidence that certain MRI features may facilitate diagnosis of IBC.¹⁹ MRI may be used for suspicious nipple discharge when mammography and ultrasound are not diagnostic.^{20–22}

Breast Tissue Biopsy

Breast biopsy is recommended if diagnostic imaging findings or clinical findings are suspicious (BI-RADS 4) or highly suggestive of malignancy (BI-RADS 5).

Fine-Needle Aspiration (FNA) Biopsy:

An FNA biopsy involves use of a smaller bore needle to obtain cytologic samples from a breast mass. Advantages of FNA biopsy include its minimally invasive methodology and low cost,^{23,24} whereas the need for pathologists with specific expertise in the interpretation of test results and the necessity of performing

a follow-up tissue biopsy when atypia or malignancy is identified are disadvantages of the procedure. FNA of nonpalpable lesions can be performed under imaging guidance (eg, ultrasound), although there is evidence to indicate that both core needle biopsy and excisional biopsy are more accurate than FNA in the evaluation of nonpalpable breast lesions.^{25,26}

Core Needle Biopsy: A core needle biopsy, also called percutaneous core breast biopsy, is a procedure that typically involves obtaining multiple cores of solid tissue using standard techniques.^{27,28} It can be performed under imaging guidance (eg, stereotactic [mammographic] ultrasound or MRI) or directed by palpation. Advantages of breast core needle biopsy include (1) increased accuracy over FNA when the procedure is performed in situations where no mass is palpable; and (2) an ability to obtain tissue samples of sufficient size so as to eliminate the need for a follow-up biopsy to confirm malignancy.²⁹ In some situations, the core needle biopsy is performed under vacuum assistance, which can facilitate collection of adequate tissue from a breast lesion without the need for multiple needle insertions.^{30–32} Marker clip placement is done at the time of core needle biopsy so that the radiologist can identify the location of the lesion in the event that it is entirely removed or disappears during neoadjuvant treatment.³³ With a few exceptions, core needle biopsy is preferred in the NCCN Guidelines over surgical excision when tissue biopsy is required. Sensitivity for core needle biopsy directed by ultrasound or stereotaxis is 97% to 99%.³⁴ According to the NCCN panel, surgical excision is appropriate if core needle biopsy cannot be performed.

Excisional Biopsy: An excisional biopsy involves removal of the entire breast mass or suspicious area of the breast by a surgeon in an operating room setting. Needle or wire localization is done by the radiologist immediately before an excisional biopsy of a nonpalpable mammographic or sonographic finding to direct surgical excision. The wire localization may bracket a lesion that had a clip placed in it at the time of the core needle biopsy.³³ Newer localization methods using radionuclide seeds, reflector devices, or magnetic devices are being explored.

Excisional biopsy is included in the NCCN Guidelines as an option when tissue biopsy is required. Although excisional biopsy is more inva-

sive than core needle biopsy and requires needle localization when lesions are not palpable, there are situations in which larger tissue samples may be needed. Excisional biopsy is recommended if the diagnosis by core needle biopsy is an indeterminate lesion, a benign lesion that is not concordant with imaging, atypical ductal hyperplasia (ADH) or other specific histologies that require additional tissue, including mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist.^{24,29,35,36} Support for this recommendation includes results of studies showing an underestimation of cancer when atypical hyperplasia and lobular carcinoma in situ (LCIS) are diagnosed by core needle biopsy.³⁷⁻⁴² However, there are situations (eg, select cases of LCIS or atypical lobular hyperplasia [ALH] such as those concordant with imaging, papillomas, fibroepithelial lesions, and radial scars) where close observation may be substituted for excisional biopsy in select patients.^{24,35,43-50}

Diagnostic Evaluation for Symptomatic Findings on Physical Examination

In general, the breast imaging evaluations after physical exam include mammography and ultrasound. The addition of ultrasound to diagnostic mammography significantly increases cancer detection and detection of specific benign findings such as cysts. Imaging for women younger than age 30 begins with ultrasound, whereas older women generally have both studies unless a cyst is likely.⁵¹⁻⁵⁶ Combined negative imaging results place a patient in a very low risk of malignancy (generally less than 3%) category; however, clinical judgment is necessary because some women with negative imaging may warrant biopsy that may identify a malignant mass.^{51,57-59} The recommendations for subsequent management follow imaging assessments and clinical level of suspicion. Imaging should precede biopsy in most situations due to potential alteration of imaging findings by the biopsy. BI-RADS imaging assessments, even if negative, must be correlated with the clinical findings before final clinical recommendations and do not stand alone as in the screening situation. There are clinical situations in which biopsy is warranted even with negative imaging results.

Symptomatic or positive findings on physical examination include palpable mass in the breast, nip-

ple discharge without a palpable mass, asymmetric thickening or nodularity, skin changes, axillary mass, and breast pain.

Palpable Mass in the Breast

A palpable mass is a discrete lesion that can be readily identified during a physical exam. The NCCN Guidelines separate the evaluation of women with a palpable mass into 2 age groups: women aged 30 years or older and women younger than 30 years of age.

Women with Palpable Mass Aged 30 Years or Older: The main difference in the guidelines for evaluating a palpable mass in women aged 30 years or older compared with younger women is the increased degree of suspicion of breast cancer. The initial evaluation begins with a diagnostic mammogram and ultrasound. Ultrasound should be geographically correlated with the palpable mass in question. Observation without further evaluation is not an option in these women. However, in some clinical circumstances, such as a mass with low clinical suspicion or suspected simple cyst, ultrasound would be preferred and may suffice for women 30 to 39 years of age due to the high sensitivity of ultrasound alone.^{54,55,60} After the diagnostic imaging assessment, the abnormality is placed into one of the following categories: negative or benign; probably benign; or suspicious or highly suggestive of cancer with management following BIRADS final assessment recommendations.

If geographic correlation between clinical and imaging findings is lacking, further evaluation is recommended. Sensitivity of combined mammography and ultrasound for evaluation of palpable masses is high for cancer detection, although specificity may be relatively low.

For women with mammographic findings that are suspicious or highly suggestive of breast cancer, the NCCN Panel recommends ultrasound to determine lesion size and to guide tissue biopsy. The NCCN Panel notes that FNA and core needle biopsy are both valuable. However, FNA requires cytologic expertise. When a needle biopsy is used, concordance between pathology, imaging, and clinical findings must be obtained.

Ultrasound Findings:

Solid Mass: If the solid mass found on ultrasound is suspected to be probably benign (ie, BI-RADS cat-

egory 3), the options are (1) observation, if clinical suspicion for breast cancer is low; or (2) tissue (core needle) biopsy, if the mass is clinically suspicious. Observation may be elected for those with low clinical suspicion; a physical examination follow-up with or without ultrasound or diagnostic mammogram is recommended every 6 months for 1 to 2 years to assess stability of the solid mass. The follow-up interval may be variable based on the level of suspicion. Numerous clinical studies now support the ability of ultrasound to accurately characterize palpable solid masses as probably benign with risk of malignancy generally less than 2%. However, these same studies have shown that many such masses will eventually warrant biopsy and compliance with follow-up may be low.^{52,54,61-65} Progression of size or suspicion on follow-up studies warrants tissue biopsy. The NCCN Panel recommends a tissue (core needle) biopsy for solid masses with a BI-RADS 4 to 5.

Cystic Masses: Breast cysts are classified as simple, complicated, or complex based on the characteristics identified by ultrasound evaluation (see Table 1 for definitions).

Simple Cyst: A cyst meeting all criteria of a simple cyst is considered to be benign (ie, BI-RADS 2)^{14,66} if the clinical findings and ultrasonographic results are concordant. A retrospective analysis of women (n=14,602) with benign breast biopsies developing subsequent breast cancer noted that simple cysts were not associated with subsequent breast cancer development.⁶⁷ Therefore, these patients then can be followed with routine screening.

Complicated Cyst: A complicated cyst is associated with a low risk of malignancy (<2%) (BI-RADS 3).^{14,68-70} Options for managing complicated cysts are either aspiration or short-term follow-up with physical examination and ultrasonography with or without mammography every 6 to 12 months for 1 to 2 years to assess stability. There may be variability on the follow-up interval based on the level of suspicion. Complicated cysts that increase in size or suspicion should be biopsied. Those that are stable or confirmed to be a complicated cyst with visible mobility of internal components can be followed up with routine screening.

Complex (Cystic and Solid) Mass: A complex cystic and solid mass has both cystic and solid components. Complex cysts have a relatively high risk of malignancy (eg, 14% and 23% in 2 studies).^{14,36,69-71} The NCCN Panel recommends a tissue (core needle) biopsy for complex (cystic and solid) masses (BI-RADS 4-5).

No Imaging Abnormality: If no ultrasonographic or mammographic abnormality is detected (BI-RADS 1) tissue biopsy (core needle biopsy) should be performed for suspicious clinical findings, and (2) for those with low clinical suspicion, observation with or without mammogram and ultrasound should be considered for 1 to 2 years to assess stability. The negative predictive value of negative imaging is high, >96%.^{51,55,57-59} If the clinical lesion increases in size or suspicion, tissue biopsy should be performed, whereas routine breast screening is recommended if the lesion remains stable.

Follow-up after Core Needle Biopsy: If the biopsy result indicates benign mass, and this finding is concordant with the imaging results, the NCCN Panel recommends either routine screening or a physical examination at 6 or 12 months, with or without ultrasound or mammogram, for 1 year to ensure that the lesion is stable. Routine breast screening is recommended if the lesion is stable. If the lesion increases in size, the NCCN Panel recommends surgical excision.

If the diagnosis by tissue biopsy is an indeterminate lesion, a benign lesion that is not concordant with the imaging findings, or ADH, the NCCN Panel recommends surgical excision. Mucin-producing lesions, potential phyllodes tumor, papillary lesions, ra-

Table 1: Breast Cysts: Types and Definitions^{24,36,66,68-71,97}

Simple	Anechoic (cystic), well-circumscribed, round or oval with well-defined imperceptible wall and posterior enhancement.
Complicated	Has most but not all elements of a simple cyst. Complicated cysts do not contain solid elements, intracystic masses, thick walls, or thick septa. This type of cyst may contain low-level echoes or intracystic debris, and can be described as a round, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria of a simple cyst.
Complex	Has some discrete solid component, which may include thick walls, thick septa, and/or intracystic mass. Complex cysts have both anechoic (cystic) and echogenic (solid) components.

dial scars, or other histologies of concern to the pathologist may also require excisional biopsy. Select patients (ie, some patients with flat epithelial atypia, papillomas, fibroepithelial lesions, radial scars) may be suitable for monitoring in lieu of surgical excision. For patients with classic LCIS or ALH that is concordant with imaging, the NCCN Panel recommends physical exam with or without imaging for 6 to 12 months along with risk reduction therapy according to the NCCN Guidelines for Breast Cancer Risk Reduction (available at NCCN.org) or surgical excision. Multiple-foci LCIS involving more than 4 terminal ductal units on core biopsy is associated with increased risk of being invasive cancer.⁴⁸ Patients with pleomorphic LCIS or LCIS/ALH that is nonconcordant with imaging are treated with surgical excision.

Any malignant findings with biopsy or surgical excision should be treated according to the NCCN Guidelines for Breast Cancer (available at NCCN.org).

Women with Palpable Mass Younger Than 30 Years of Age: The preferred option for initial evaluation of a palpable mass is to proceed directly to ultrasound.⁵⁴ Mammogram may be considered if ultrasound or CBE results are highly suspicious or suggestive of cancer or if the patient is identified as having a high risk for breast cancer based on personal and family history. From this point, the decision tree for women younger than 30 years of age is almost identical to the pathway for older women. The main difference is consideration of a diagnostic mammogram in only some situations for the younger women. Because the incidence of malignancy in women who are younger than age 30 is low, observation of the mass for 1 or 2 menstrual cycles is also an option in cases with low clinical suspicion. If observation is elected and the mass resolves or is stable after 1 or 2 menstrual cycles, the patient may return to routine care. If there is significant increase in size or increase in clinical suspicion, ultrasound should be performed. Needle sampling before imaging is not recommended.

If no ultrasonographic abnormality is found (negative, BI-RADS 1), a mammogram is recommended in cases where there is clinical suspicion. Based on the mammogram results, from this point the management is identical to the pathway for older women. If the clinical suspicion is low, physical examination every 3 to 6 months for 1 to 2 years is recommended with or without ultrasound. If the mass increases in size during the observation period,

diagnostic mammogram may be considered followed by tissue (core needle) biopsy. If the mass remains stable, routine breast care is recommended.

Nipple Discharge Without a Palpable Mass

Nipple discharge is common, and, in many cases, unrelated to breast pathology.^{72–78} For example, non-spontaneous discharge from multiple breast ducts in a non-lactating woman can occur during pregnancy, following breast stimulation, in women with certain thyroid conditions, and in those taking certain medications, such as estrogen, oral contraceptives, opiates, and particular antihypertensive agents.⁷²

Suspicion of underlying pathology (eg, ductal carcinoma, papilloma) is raised when nipple discharge is persistent and reproducible on examination, spontaneous, unilateral, from a single duct, serous, sanguineous, or serosanguineous.⁷⁹

In patients with a nipple discharge but no palpable mass, an evaluation of the characteristics of the nipple discharge is the first step. The appropriate follow-up of a nonspontaneous, multiple-duct discharge in women younger than age 40 is observation, coupled with education of the patient to stop compression of the breast and to report the development of any spontaneous discharge. In women aged 40 years or older, mammography and a further work-up based on the BI-RADS category along with education similar to that for younger women is recommended. Evaluation of this type of nipple discharge is based on the overall BI-RADS category of the diagnostic mammogram, if not done previously.

Women presenting with no palpable mass but with persistent, spontaneous, unilateral, single-duct, and clear or bloody discharge are imaged with age-appropriate diagnostic mammography and ultrasound. Several clinical studies have established a very low risk of malignancy when these tests are negative.^{80,81} In certain situations, MRI or ductogram may play an adjunctive role, aiding in identifying a possible abnormality and its location. Several studies have shown that breast MRI aids in the diagnosis of suspected ductal disease.^{20–22,82,83}

According to the NCCN Panel, when an overall imaging BI-RADS assessment is category 1–3 (negative, benign, or probably benign), either a ductogram or MRI are optional to guide the duct excision. The management options include duct excision⁸⁴ or follow-up with physical exam after 6 months and imag-

ing with diagnostic mammogram with or without ultrasound for 1 to 2 years. If clinical suspicion increases during follow-up, tissue biopsy is recommended.

For BI-RADS category 4 or 5 (suspicious or highly suggestive of malignancy), the NCCN Panel recommends a tissue biopsy. If the biopsy findings are benign, a ductogram is optional, but surgical duct excision would still be necessary. If findings are indicative of malignancy, the patient should be treated according to the NCCN Guidelines for Breast Cancer (available at NCCN.org).

Asymmetric Thickening or Nodularity

Thickening, nodularity, or asymmetry is distinct from a palpable mass in that the finding is ill defined and often vague on physical breast examination. Factors to consider include whether the thickening is a new or previous finding and whether or not it appears to be representative of normal asymmetry. Imaging evaluation follows that of a palpable mass.⁵¹ If the patient is younger than age 30 years and has no high risk factors, ultrasound evaluation is appropriate followed by consideration of diagnostic mammography. Diagnostic mammograms for this age group are low in yield because of the density of the breast and low risk of breast cancer. In a woman aged 30 years or older, a diagnostic mammogram and an ultrasound evaluation should be obtained.

If the overall imaging findings are classified as BI-RADS category 1–3 (negative, benign, or probably benign) *and* the clinical assessment is benign, the patient should be clinically reexamined with imaging as needed in 3 to 6 months to assess stability. Age-appropriate diagnostic mammogram and/or ultrasound may be performed every 6 to 12 months for 1 to 2 years to assess stability. If the findings on physical exam and/or imaging are stable, routine screening can be resumed. If either or both findings indicate progression, it should be investigated as previously described for palpable mass.

If a clinically suspicious change is noted or the overall imaging findings are classified as BI-RADS assessment category 4 or 5 (suspicious or highly suggestive of malignancy), a tissue biopsy is recommended.

Skin Changes

Any type of unusual skin changes around the breast may represent serious disease and needs evaluation. IBC should be considered when dermal edema (peau

d'orange) and breast erythema are present, and nipple excoriation, scaling, and eczema should increase clinical suspicion of Paget's disease. IBC is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States. IBC is a clinical diagnosis that requires erythema and dermal edema of a third or more of the skin of the breast with a palpable border to the erythema.^{85,86} Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the nipple or areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions.^{87,88} Pure Paget's disease is frequently occult on mammography,⁸⁹ and a negative mammogram does not exclude Paget's disease, which requires skin biopsy.

The initial evaluation of a patient with breast skin changes begins with a bilateral diagnostic mammogram with or without ultrasound imaging. If the imaging results are abnormal, the evaluation proceeds based on the imaging findings. If the breast imaging results are normal, further workup is still needed.

Punch biopsy of the skin or nipple biopsy should be performed after imaging findings consistent with overall BI-RADS assessment category 1–3 (negative, benign, or probably benign). Antibiotics may or may not be given, depending on the clinical suspicion for breast infection, but should not delay diagnostic evaluation. If biopsy results are benign, clinical and pathologic correlation should be reassessed. In addition, a breast MRI, a repeat biopsy, and consultation with a breast specialist should be considered. If the skin biopsy is malignant, the patient should be treated according to the NCCN Guidelines for Breast Cancer (available at NCCN.org).

A tissue biopsy should be performed if imaging findings are consistent with an overall BI-RADS assessment category 4 or 5 (suspicious or highly suggestive of malignancy). According to the NCCN Panel, core needle biopsy is the preferred option with or without punch biopsy, although surgical excision is also an option. A benign biopsy result should be followed by a punch biopsy of the skin, if not previously performed, or nipple biopsy, with reassessment as described previously for BI-RADS category 1–3. A biopsy showing

a malignant finding should be managed according to the NCCN Guidelines for Breast Cancer.

Breast Pain

Pain is the most common symptom in the breast. Individuals presenting with breast pain fear that this is a symptom of breast cancer, therefore causing significant anxiety. The risk of cancer in a woman presenting with breast pain as the only symptom is low, between 1.2% and 6.7%.^{6,90–92}

Evaluation of persistent and severe breast pain includes comprehensive history, type of pain, relationship to menses, duration, location, impact on activities of daily living, factors that aggravate/alleviate pain, any other medical problems and comorbidities, and a thorough clinical breast exam (CBE). If CBE fails to identify any physical abnormality such as palpable mass, asymmetric thickening, nipple discharge, or skin changes; the pain is cyclic or diffuse and nonfocal; and screening mammograms are current and negative, the NCCN Panel recommends providing reassurance to the patient and treating the pain with symptomatic management (eg, over-the-counter pain medications, if needed; use of a good support bra; ice packs or heating pads). Cyclic breast pain may often spontaneously resolve. Reassurance alone has shown to help resolve the symptom in 86% of women with mild pain and in 52% of women with severe pain.⁹³ If the breast pain is focal in nature, the NCCN Panel recommends age-appropriate diagnostic imaging (diagnostic mammogram with or without ultrasound for those ≥ 30 years of age; and ultrasound for those < 30 years of age).

For those with BI-RADS assessment category 1 (negative findings), the panel recommends appropriate symptom management of breast pain. For a simple cyst (benign or BI-RADS assessment category 2) geographically correlated with focal pain, drainage may be considered for symptom relief. For complicated cysts (probably benign or BI-RADS 3), the panel recommends appropriate imaging every 6 months for 1 to 2 years along with symptomatic management of the breast pain, if desired. A tissue (core needle) biopsy should be performed if imaging findings are consistent with an overall BI-RADS assessment category 4 or 5 (suspicious or highly suggestive of malignancy).

Axillary Mass

Localized axillary masses are more often related to benign disorders than malignancy.⁹⁴ Masses may re-

late to axillary lymph nodes, accessory breast tissue in the axilla, or other soft tissue abnormality. Infections, inflammation, and malignancy can cause lymphadenopathy. Breast implants can also cause benign axillary lymphadenopathy.⁹⁵ However, when cancer is identified in the axillary lymph nodes, breast cancer is the most common cause of axillary lymphadenopathy. In a study evaluating 31 patients with isolated axillary masses, 9 of the 17 cases with cancer had occult breast cancer (5 in the contralateral breast).⁹⁶

For an individual presenting with unilateral or bilateral localized axillary mass and no signs of lymphoma, the NCCN Panel recommends complete clinical evaluation to assess for other sites of adenopathy and potential non-breast etiologies of adenopathy. If no systemic disease is found, the NCCN Panel recommends age-appropriate diagnostic imaging (ultrasound with mammogram for those ≥ 30 years of age; and ultrasound for those < 30 years of age). Palpable axillary mass with negative/benign imaging results should be clinically managed as appropriate, depending on level of clinical suspicion. A core needle biopsy is recommended for palpable axillary mass that is suspicious or highly suggestive on imaging. However, suspicion of lymphoma in axillary lymph nodes may require special pathologic evaluation and/or surgical excision of the axillary mass.

If the core needle biopsy results indicate malignancy of breast origin in the axillary lymph node but no breast abnormality is evident with ultrasound or mammogram, the panel recommends performing MRI and then following the NCCN Guidelines for Breast Cancer (available at NCCN.org) as needed for management of the axillary mass. For malignant axillary node with confirmed malignant breast mass or for other types of malignant axillary lymph nodes, the panel recommends referring to the appropriate NCCN Guidelines for management.

Summary

The intent of the NCCN Guidelines for Breast Cancer Screening and Diagnosis is to give health care providers a practical, consistent framework for screening and evaluating a spectrum of clinical breast lesions. Clinical judgment should always be an important component of the optimal management of the patient.

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Individual Disclosures for Breast Cancer Screening and Diagnosis Panel				
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Therese B. Bevers, MD	Menssana Research, Inc., and Toray Industries, Inc.	Biden Cancer Initiative	None	5/9/18
Ermelinda Bonaccio, MD	None	None	None	10/14/18
Kristine E. Calhoun, MD	None	None	None	9/26/17
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William B. Farrar, MD	None	None	None	7/30/18
Judy E. Garber, MD, MPH ^a	None	Helix Biopharma Corp., and Novartis Pharmaceuticals Corporation	None	2/5/18
Richard Gray, MD	None	None	None	10/11/18
Caprice C. Greenberg, MD, MPH	None	None	None	5/28/18
Rachel Greenup, MD, MPH	None	None	None	10/9/17
Nora M. Hansen, MD	None	None	Genentech, Inc.	7/13/17
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Linda Hodgkiss, MD	None	None	None	10/10/18
Tamarya L. Hoyt, MD	None	None	None	10/16/18
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Constance Dobbins Lehman, MD, PhD	General Electric	General Electric	None	10/2/17
Barbara Monsees, MD	None	None	None	11/1/17
Bethany L. Niell, MD, PhD	None	None	None	10/11/18
Catherine C. Parker, MD	None	None	None	7/19/18
Mark Pearlman, MD	None	Expert witness med mal suit -alleged delayed breast cancer dx	None	10/10/18
Liane Philpotts, MD	None	Hologic, Inc.	Hologic, Inc	10/12/17
Laura B. Shepardson, MD	None	None	None	9/26/17
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The NCCN Guidelines Staff have no conflicts to disclose.

^aThe following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:

Judy E. Garber, MD, MPH: Gtx Pharmaceuticals, and Oric Pharmaceuticals