National Comprehensive Cancer Network®

The NCCN

Breast Cancer Screening and Diagnosis

Clinical Practice Guidelines in Oncology™

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Overview

Women in the United States have a 12.3% estimated lifetime risk for developing breast cancer (i.e., 1 in 8 women).[1] In 2009, an estimated 194,290 cases of invasive breast cancer (192,370 women and 1919 men) and 62,280 cases of female carcinoma in situ of the breast will be diagnosed in the United States, with 40,610 deaths from invasive breast cancer predicted.[2] However, mortality from breast cancer has decreased slightly, attributed partly to mammographic screening.[3]

The NCCN Breast Cancer Screening and Diagnosis Panel designed these practice guidelines to fa-

Breast Cancer Screening and Diagnosis Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, breast carcinoma, carcinoma in situ, screening, diagnosis, mammography, risk assessment, biopsy, hyperplasia (*JNCCN* 2009;7:1060–1096)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Breast Cancer Screening and Diagnosis Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Breast Cancer Screening and Diagnosis Guidelines Panel members can be found on page 1096. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at NCCN.org.)

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

cilitate clinical decision-making. The general public and health care providers must be aware that mammography or any other imaging modality is not a standalone procedure. Neither the current technology of mammography or other imaging tests nor the subsequent interpretation of these tests is foolproof. Clinical judgment is needed to ensure appropriate management. Patient concerns and physical findings must be considered along with the results of imaging and histologic assessment.

Breast Screening

Breast screening is performed in women without any signs or symptoms of breast cancer so that disease can be detected as early as possible. The components of a breast screening evaluation depend on patient age and other factors, such as medical and family history, and can include breast awareness (i.e., patient familiarity with her breasts), physical examination, risk assessment, screening mammography, and, in selected cases, screening MRI.

A diagnostic breast evaluation differs from breast screening in that it is used to evaluate an existing problem (e.g., dominant mass, discharge from the nipple). Although preliminary evidence suggests that breast ultrasonography can be a useful screening adjunct to mammography in evaluating high-risk women with dense breasts,[4] its use as a screening test is currently not recommended. These guidelines include ultrasonography only in the diagnostic work-up of select women based on specific positive

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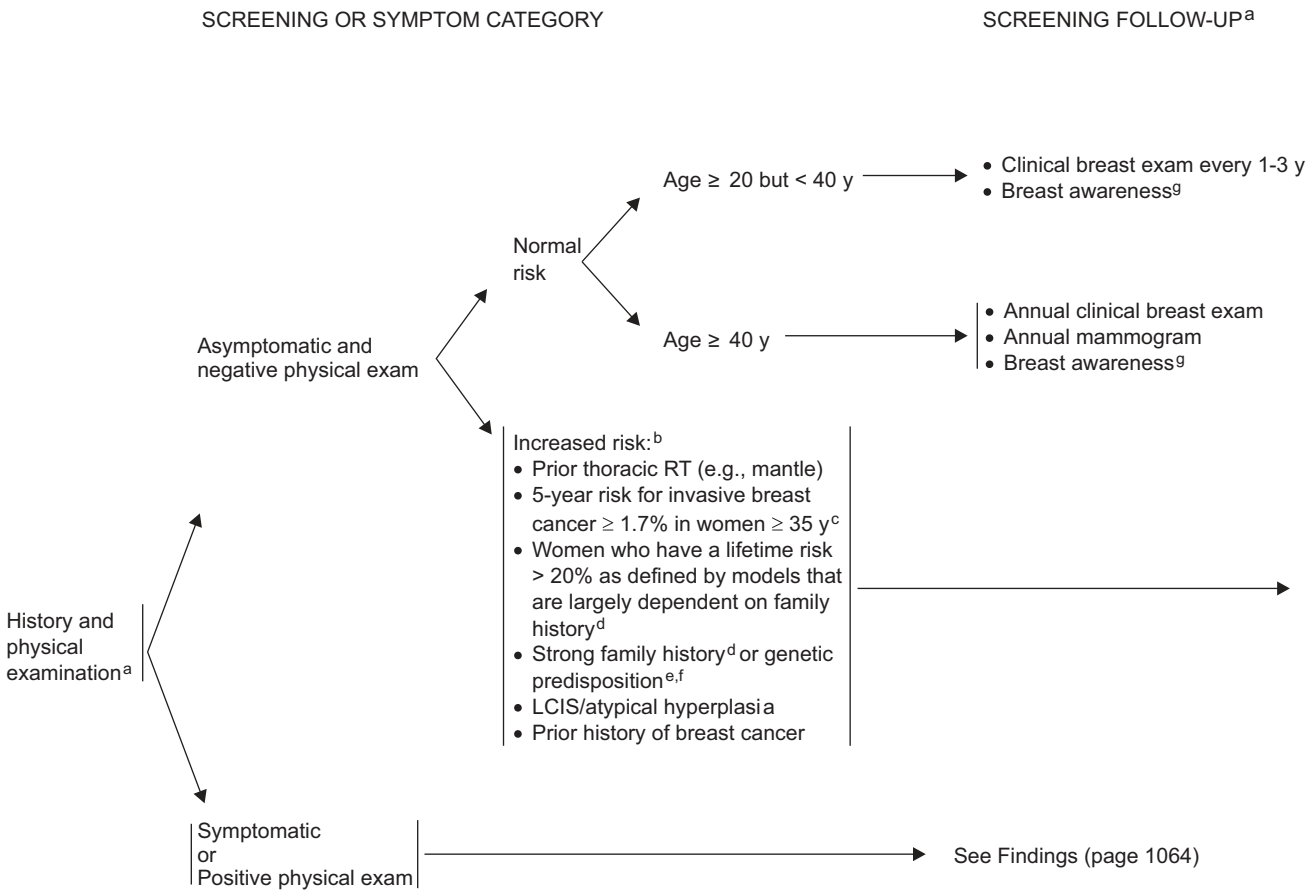

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See Mammographic Evaluation (page 1074)

[a] See Breast Screening Considerations (page 1077).
[b] Refer to the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction* for a detailed qualitative and quantitative assessment.
[c] See Risk Factors Used in the Modified Gail Model (page 1077).
[d] For a definition of strong family history, see NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High Risk Assessment: Breast and Ovarian.*
[e] As currently defined in the American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397-2406.
[f] See NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian Guidelines.*
[g] Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self-examination (BSE) may facilitate breast self-awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

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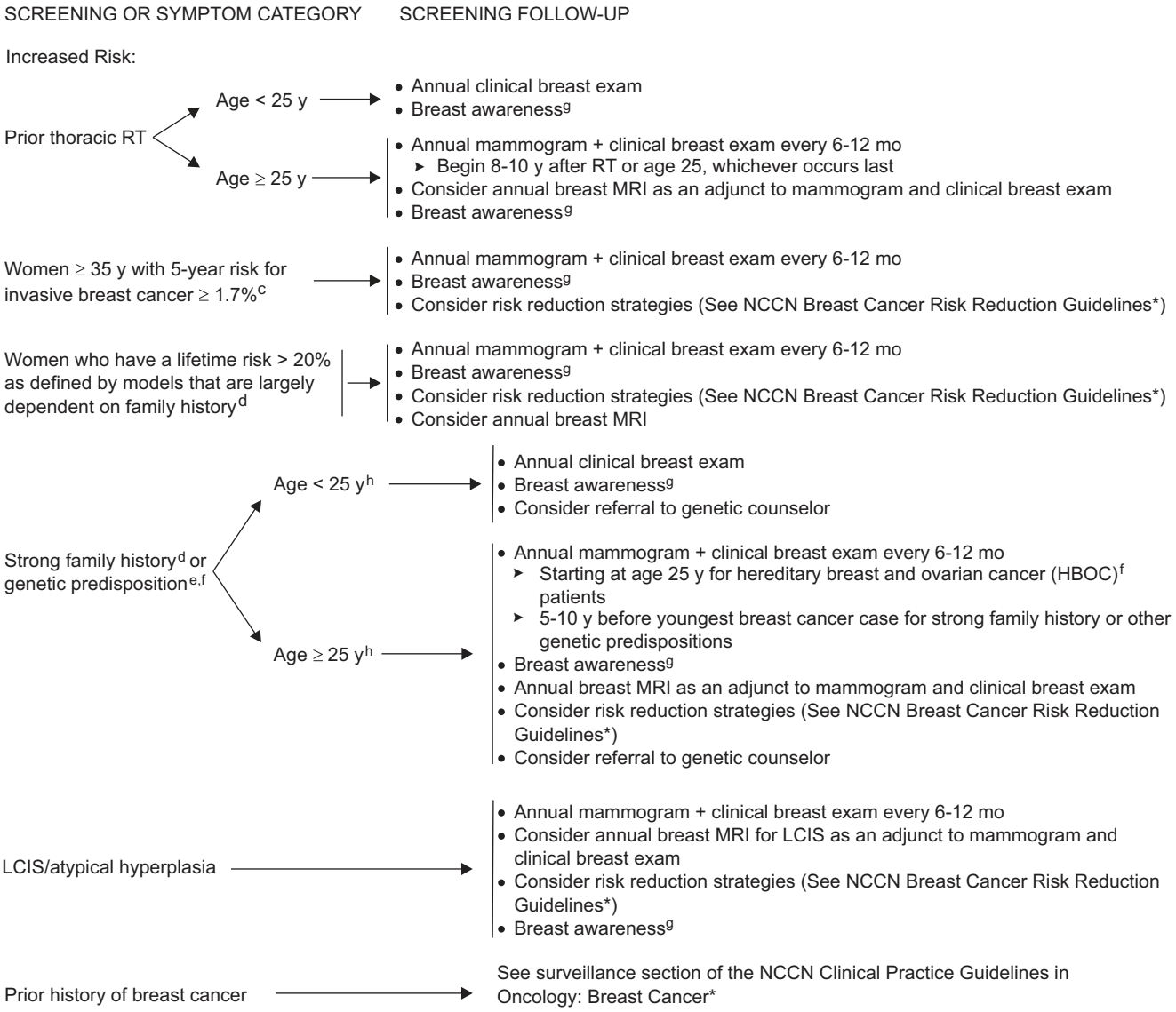

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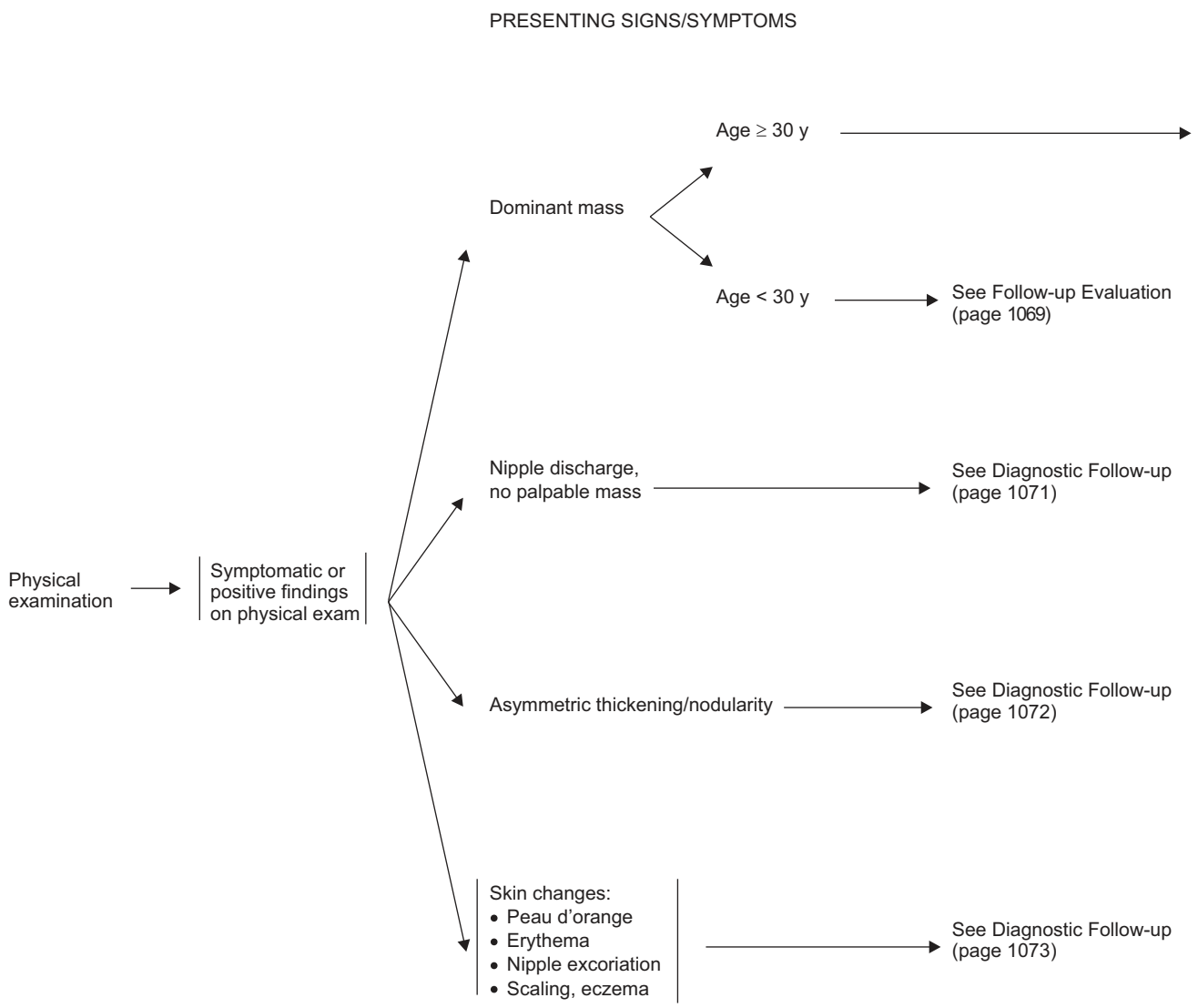
[g] Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self-examination (BSE) may facilitate breast self-awareness. Premenopausal women may find BSE most informative when performed at the end of menses.
[h] Earlier screening may be appropriate in some patients.


PRESENTING SIGNS/SYMPTOMS
Physical examination
Symptomatic or positive findings on physical exam
Dominant mass
Age ≥ 30 y
Age < 30 y
See Follow-up Evaluation (page 1069)
Nipple discharge, no palpable mass
See Diagnostic Follow-up (page 1071)
Asymmetric thickening/nodularity
See Diagnostic Follow-up (page 1072)
Skin changes:
• Peau d'orange
• Erythema
• Nipple excoriation
• Scaling, eczema
See Diagnostic Follow-up (page 1073)

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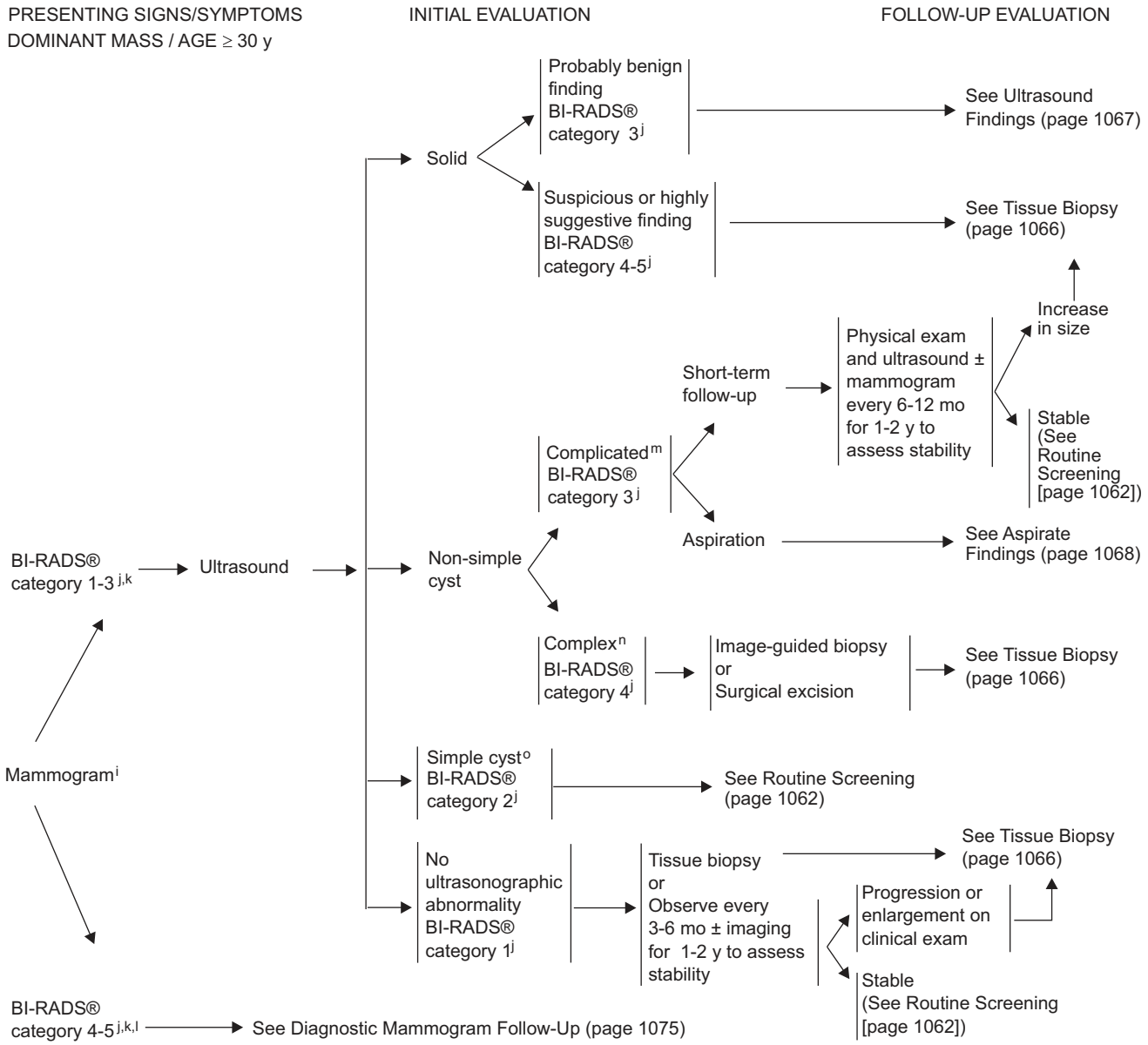
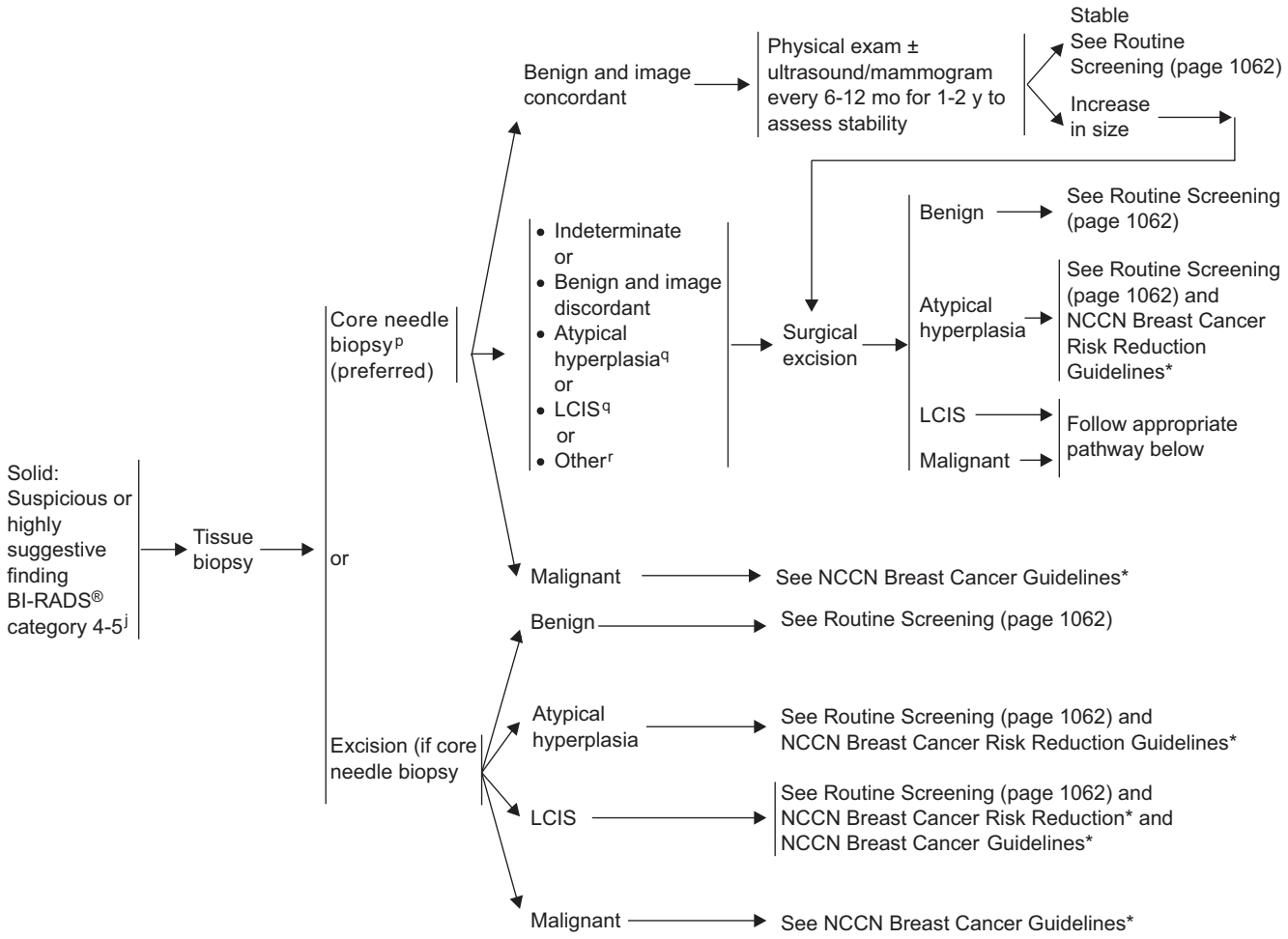


[i] There are a few clinical circumstances in which ultrasound would be preferred (e.g., suspected simple cyst).
[j] See Mammographic Assessment Category Definitions (pages 1078 and 1079).
[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 1997;62:55988).
[l] Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to category 1-3 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, workup of the imaging problem will answer the palpable problem.
[m] Round, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria for simple cyst.
[n] A complex cyst has both cystic and solid components.
[o] Concordance is needed between clinical exam and ultrasound results. Consider therapeutic aspiration for persistent clinical symptoms.

ULTRASOUND FINDINGS
DOMINANT MASS / AGE ≥ 30 y

FOLLOW-UP EVALUATION



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[j] See Assessment Category Definitions (pages 1078 and 1079).
[p] FNA and core (needle or vacuum-assisted) biopsy are both valuable. FNA requires cytologic expertise.
[q] Select patients may be suitable for monitoring in lieu of surgical excision (e.g., ALH, LCIS, papillomas, fibroepithelial lesions, radial scars).
[r] Other histologies that may require additional tissue include mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or histologies of concern to pathologist.

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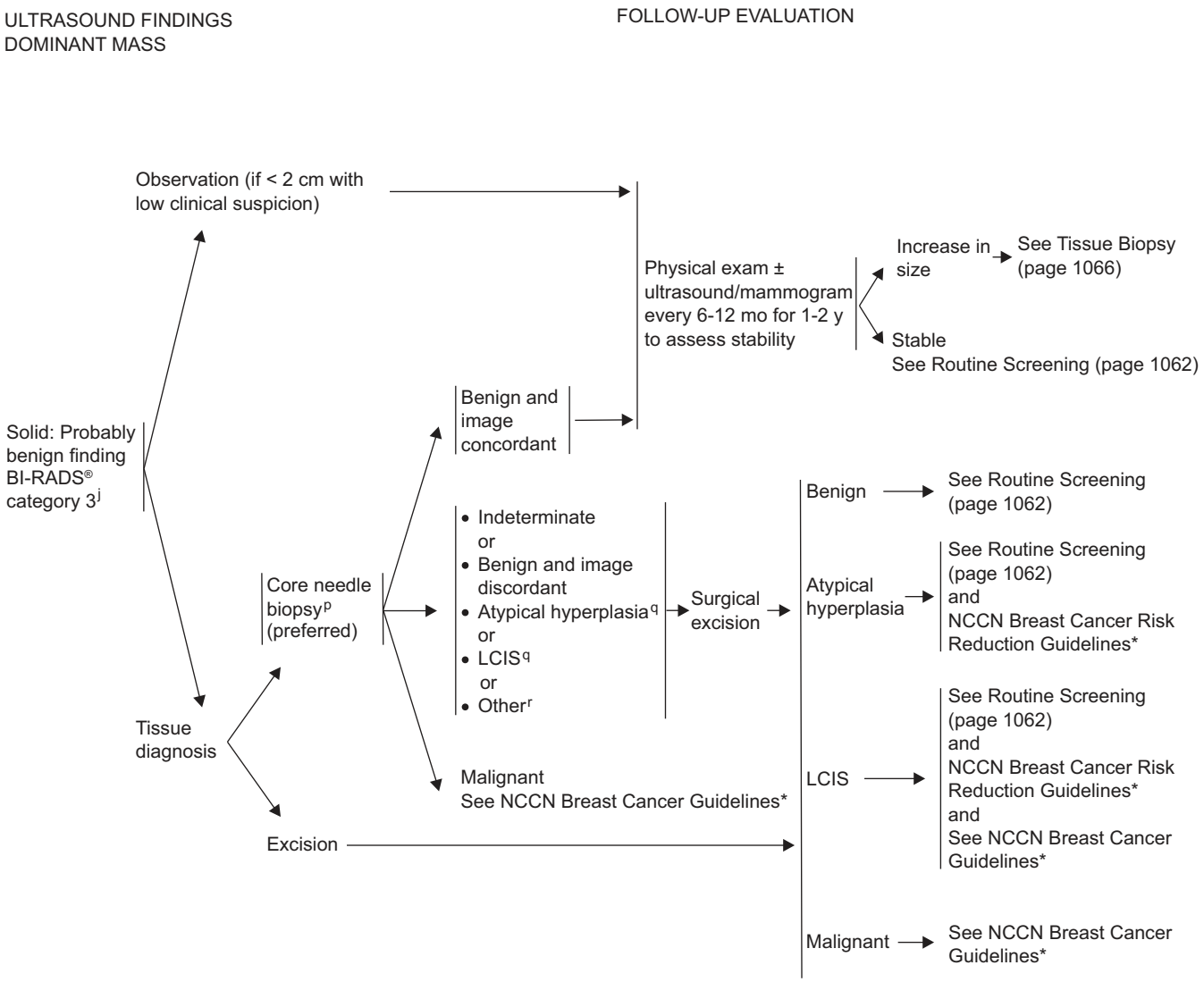

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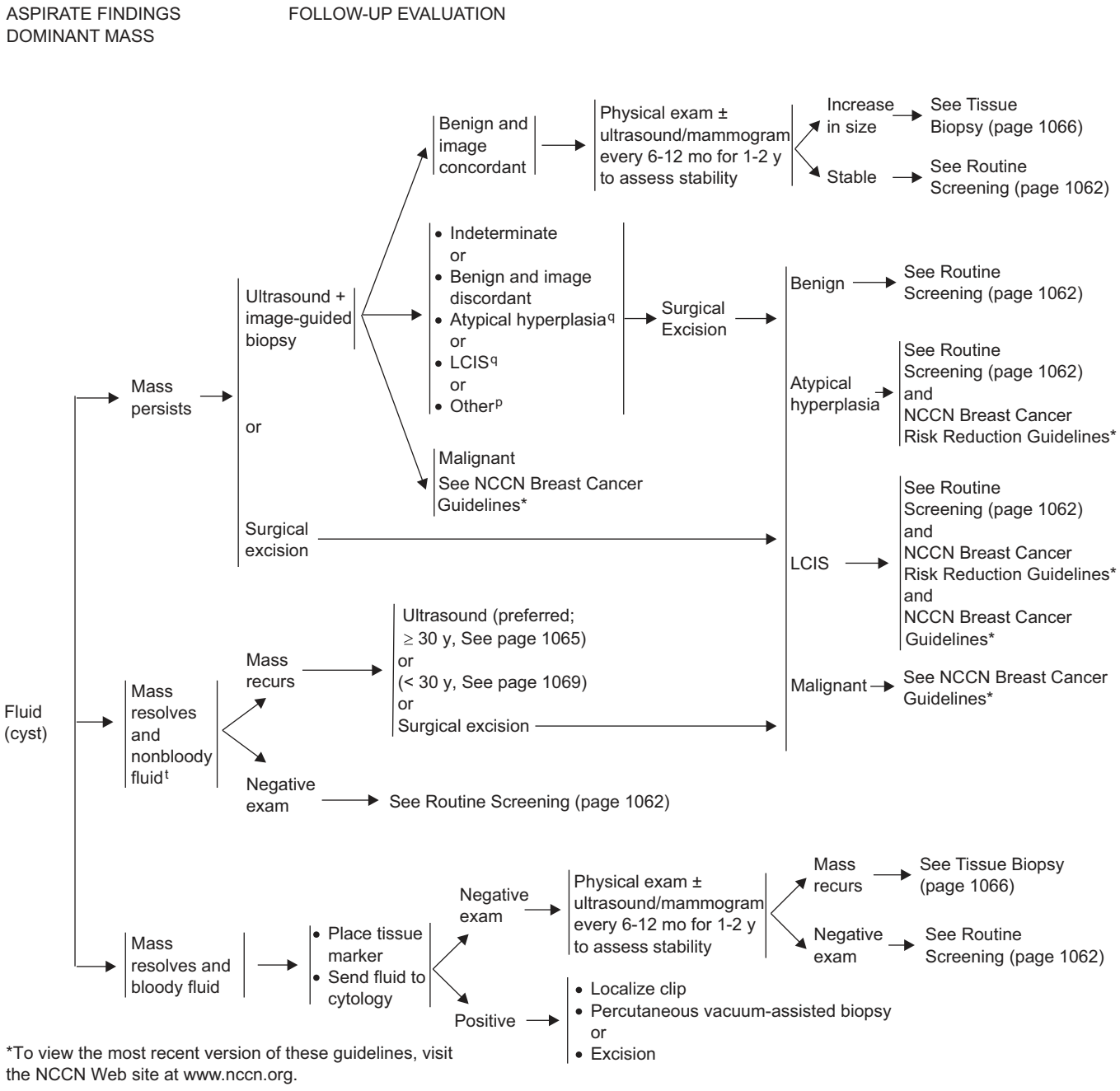
[s] Stavros A, Thickman D, Rapp C, et al. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology 1995;196:123-124.



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[q]Select patients may be suitable for monitoring in lieu of surgical excision (e.g., ALH, LCIS, papillomas, fibroepithelial lesions, radial scars).
[r]Other histologies that may require additional tissue include mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or histologies of concern to pathologist.
[t]Routine cytology not recommended.

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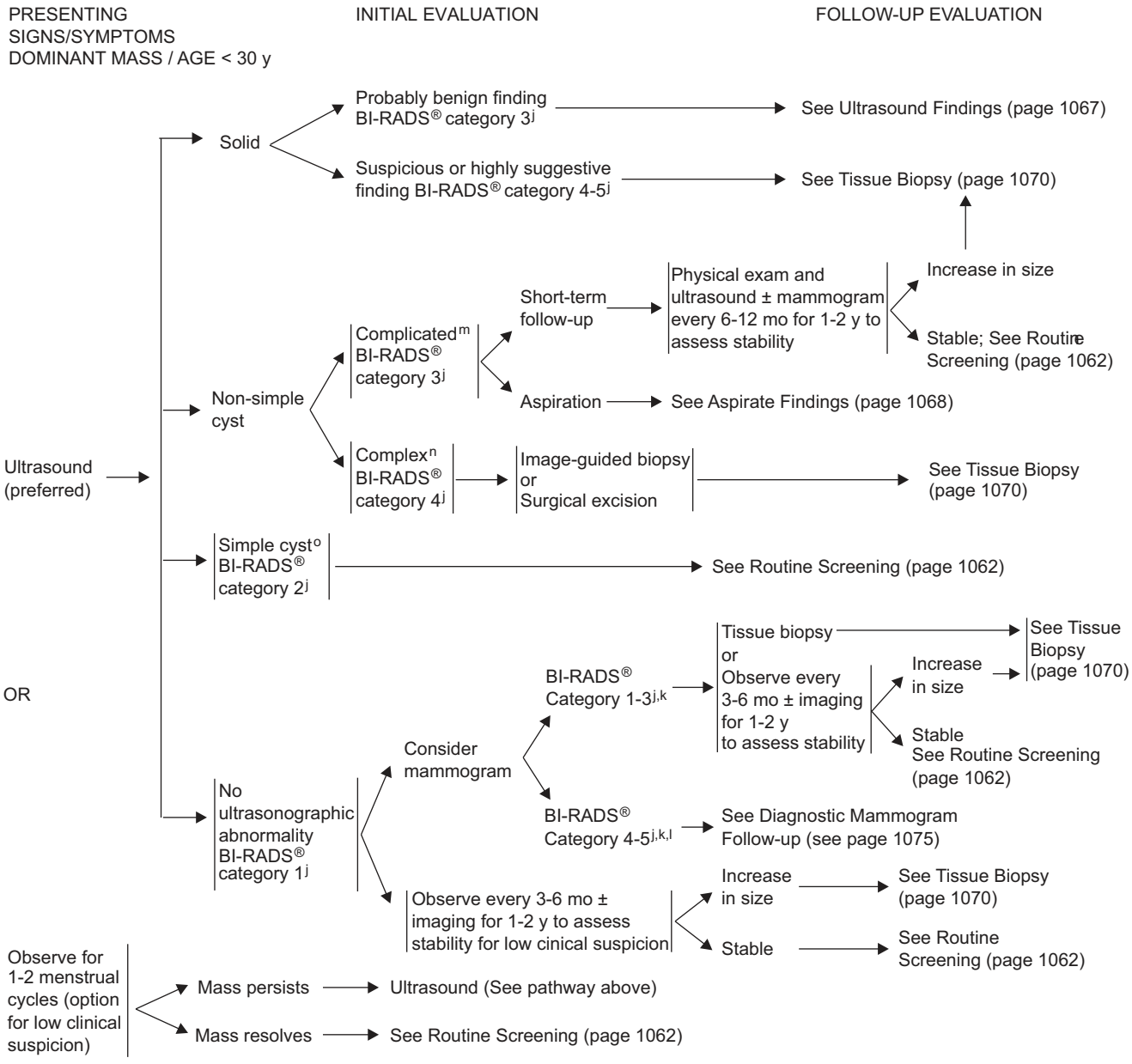

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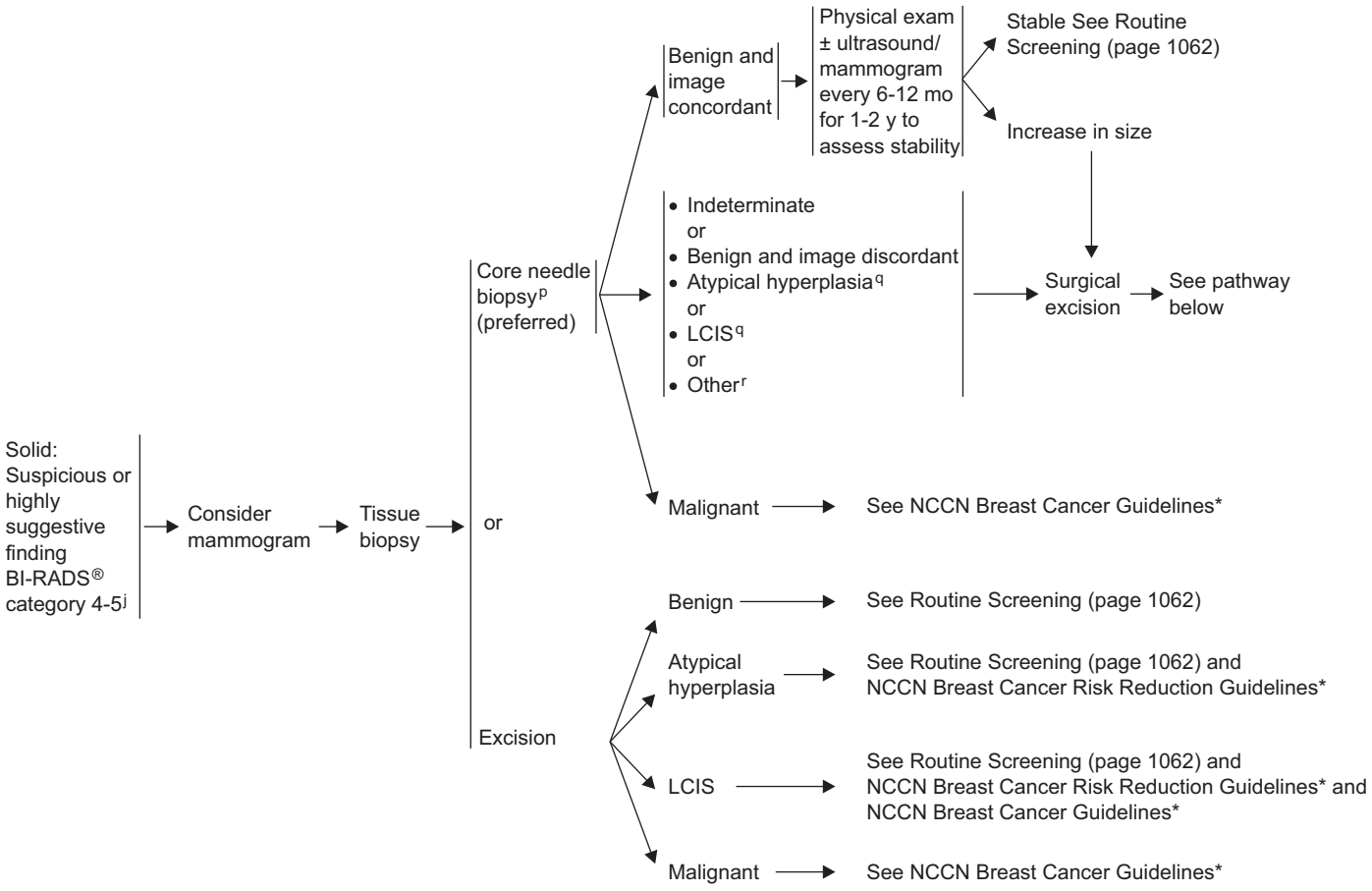
[m] Round, circumscribed mass containing low level echoes without vascular flow, fulfilling most but not all criteria for simple cyst.
[n] A complex cyst has both cystic and solid components.
[o] Concordance is needed between clinical exam and ultrasound results. Consider therapeutic aspiration for persistent clinical symptoms.

ULTRASOUND FINDINGS
DOMINANT MASS / AGE < 30 y

FOLLOW-UP EVALUATION



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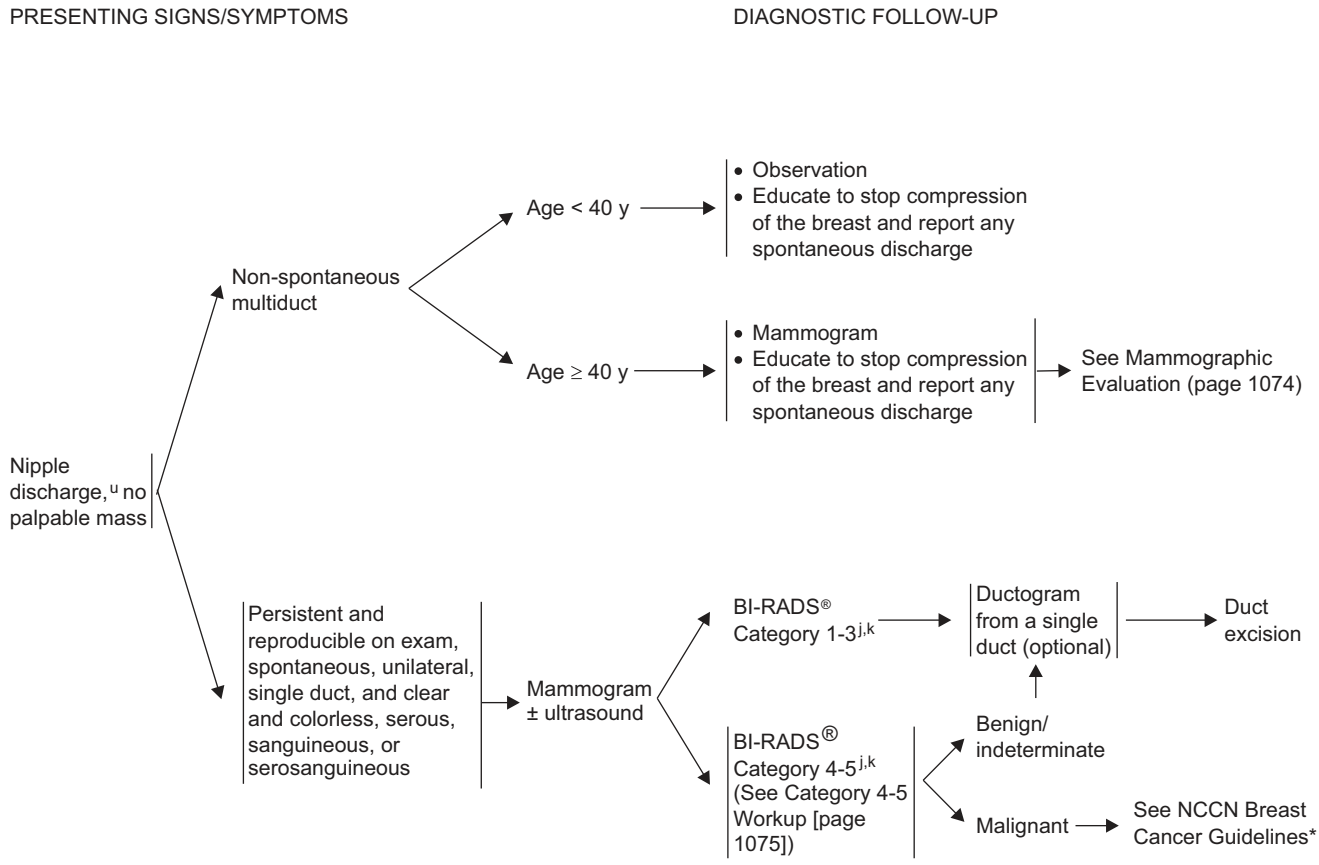

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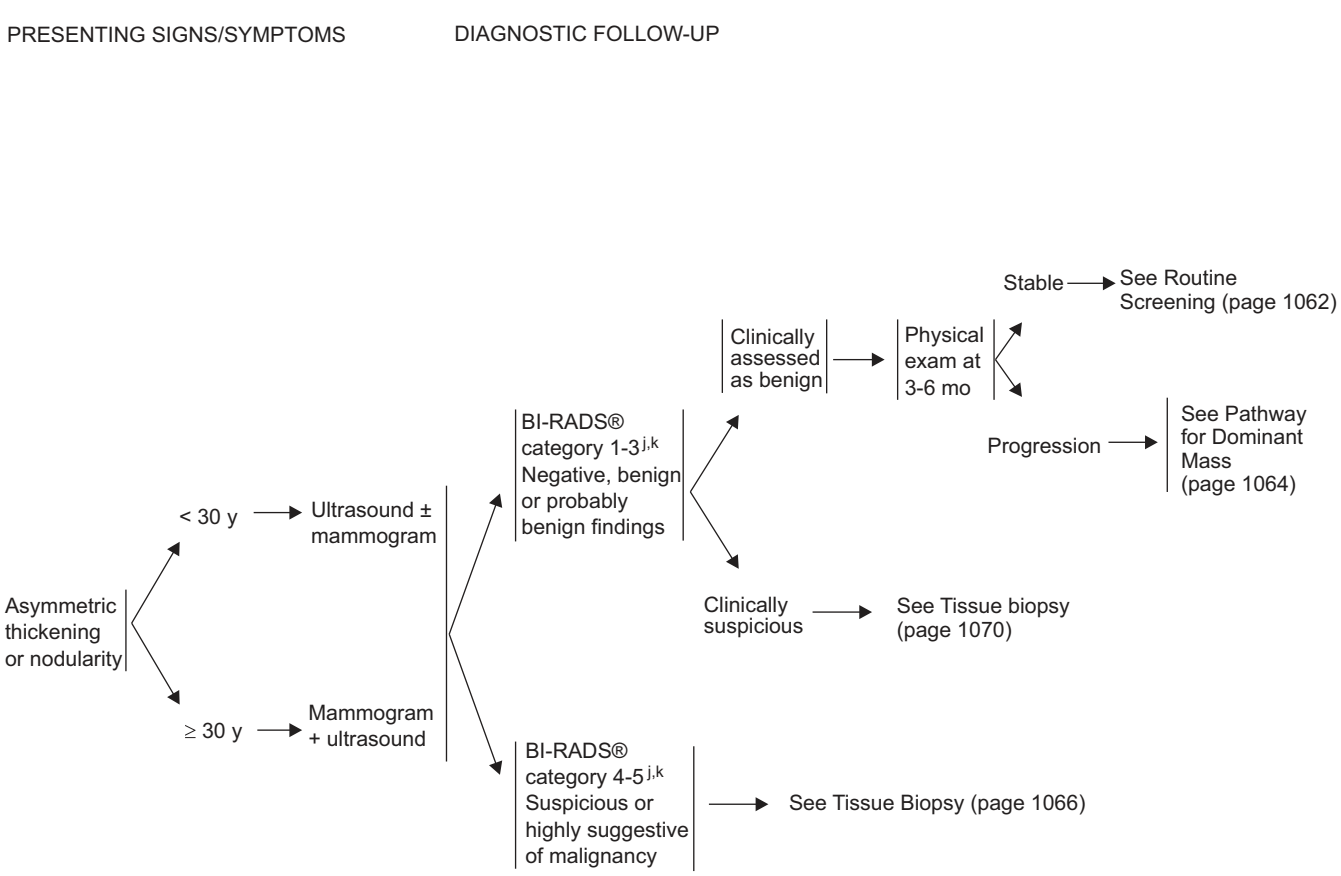
[j]See Mammographic Assessment Category Definitions (pages 1078 and 1079).
[k]Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register1997;62:55988.
[u]Drugs that can cause nipple discharge include psychoactive drugs, antihypertensive medications, opiates, oral contraceptives, and estrogen.



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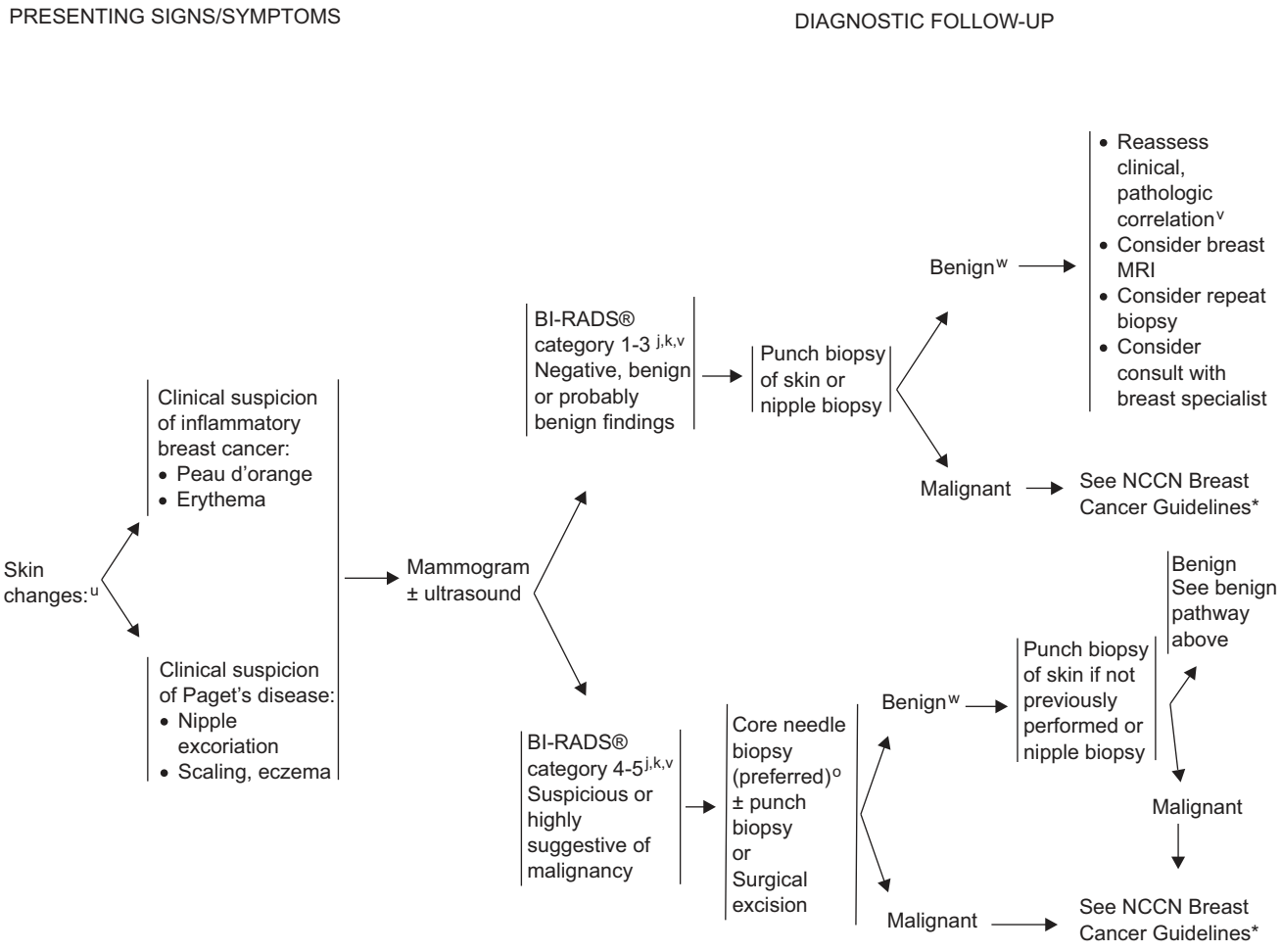

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j See Assessment Category Definitions (pages 1078 and 1079).

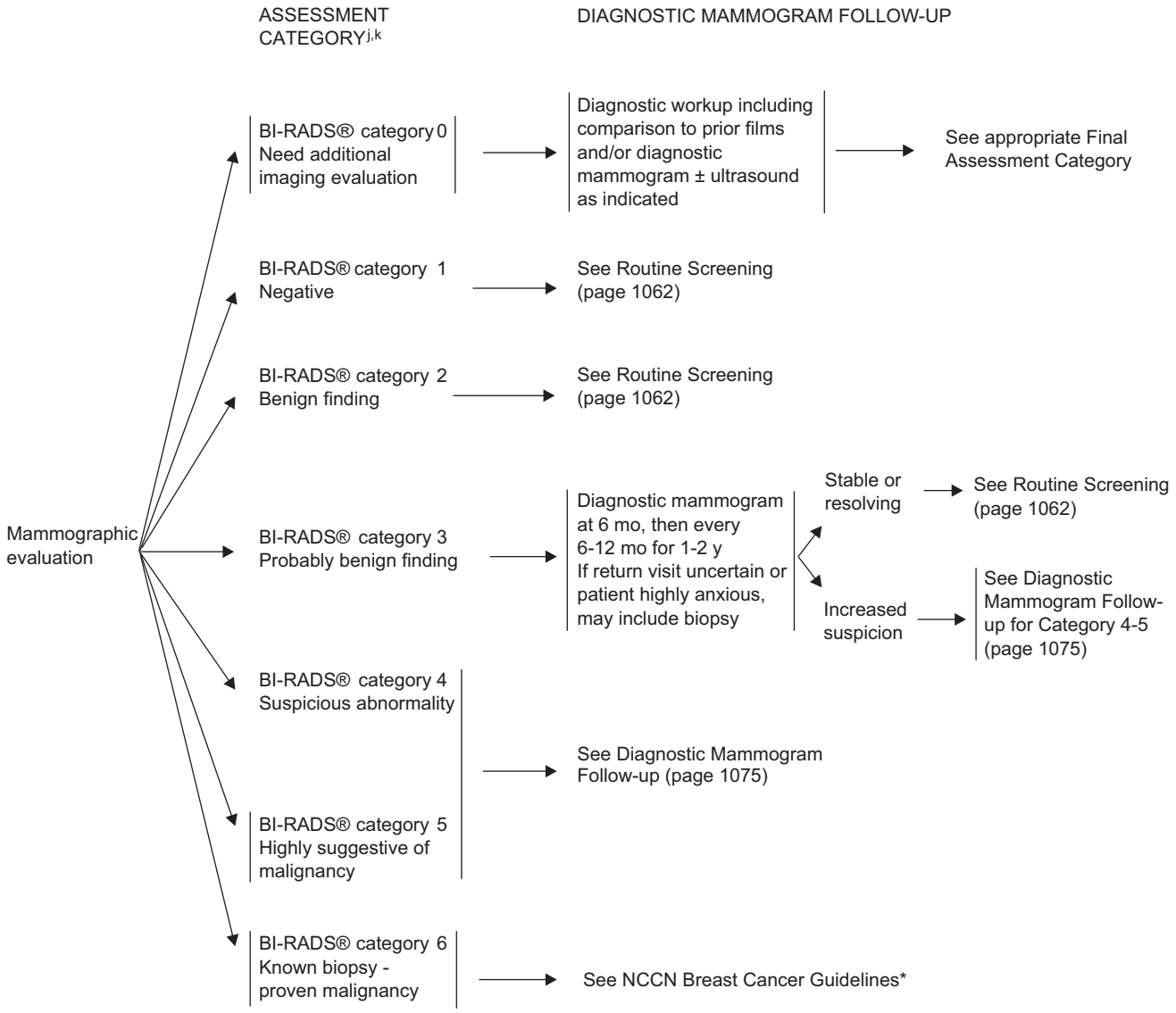
kMammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 1997;62:55988).

[o]FNA and core (needle or vacuum-assisted) biopsy are both valuable. FNA requires cytologic expertise.

[u]This may represent serious disease of the breast and needs evaluation.

[v]If clinically of low suspicion, a short trial (7-10 days) of antibiotics for mastitis may be indicated.

[w]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.



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Mammogram considerations:
- Specify if mammogram is screening or diagnostic
- Comparison should be made with prior noncopied films (original films), if obtainable

[j] See Mammographic Assessment Category Definitions (pages 1078 and 1079).
[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 1997;62:55988).

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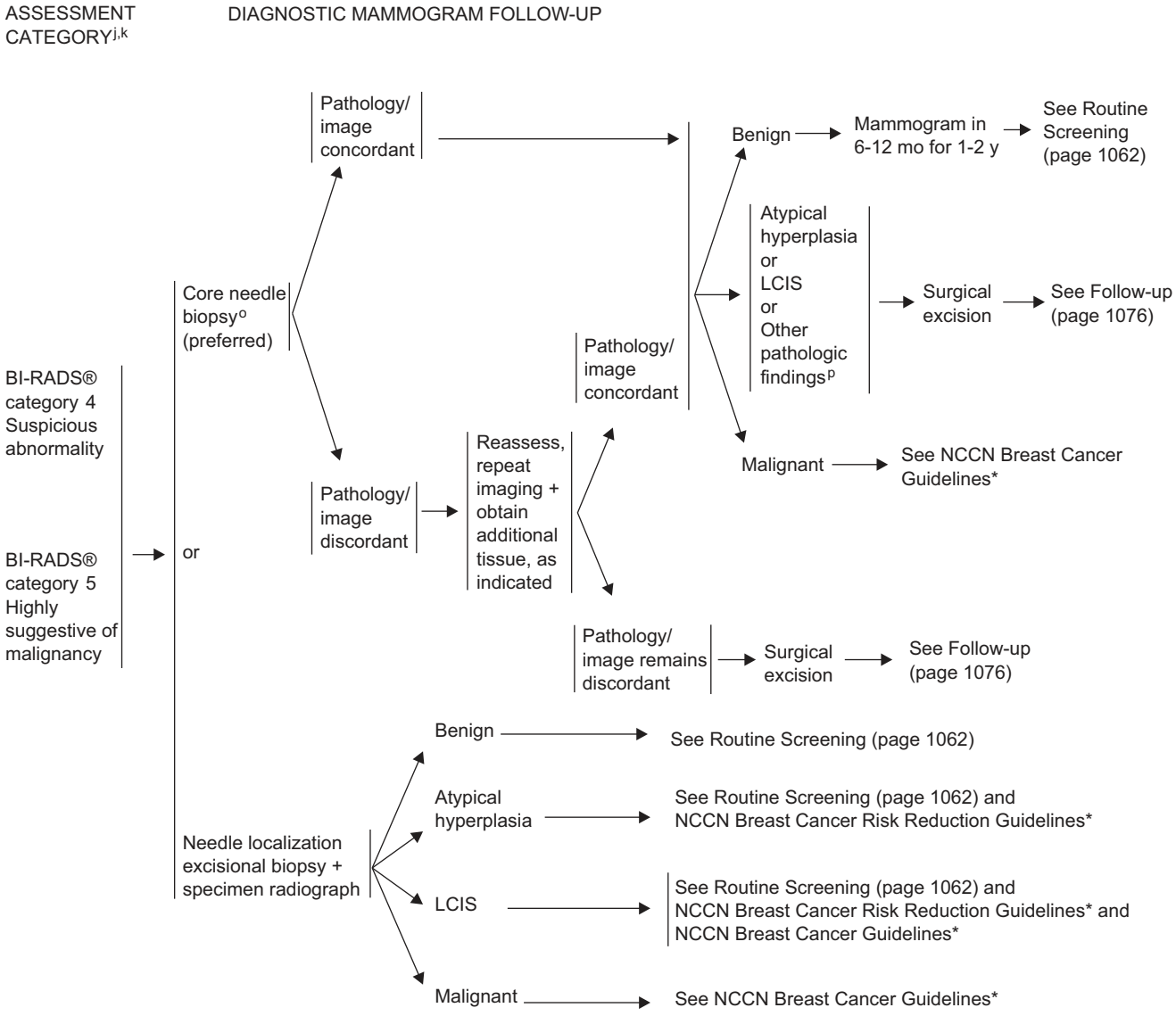

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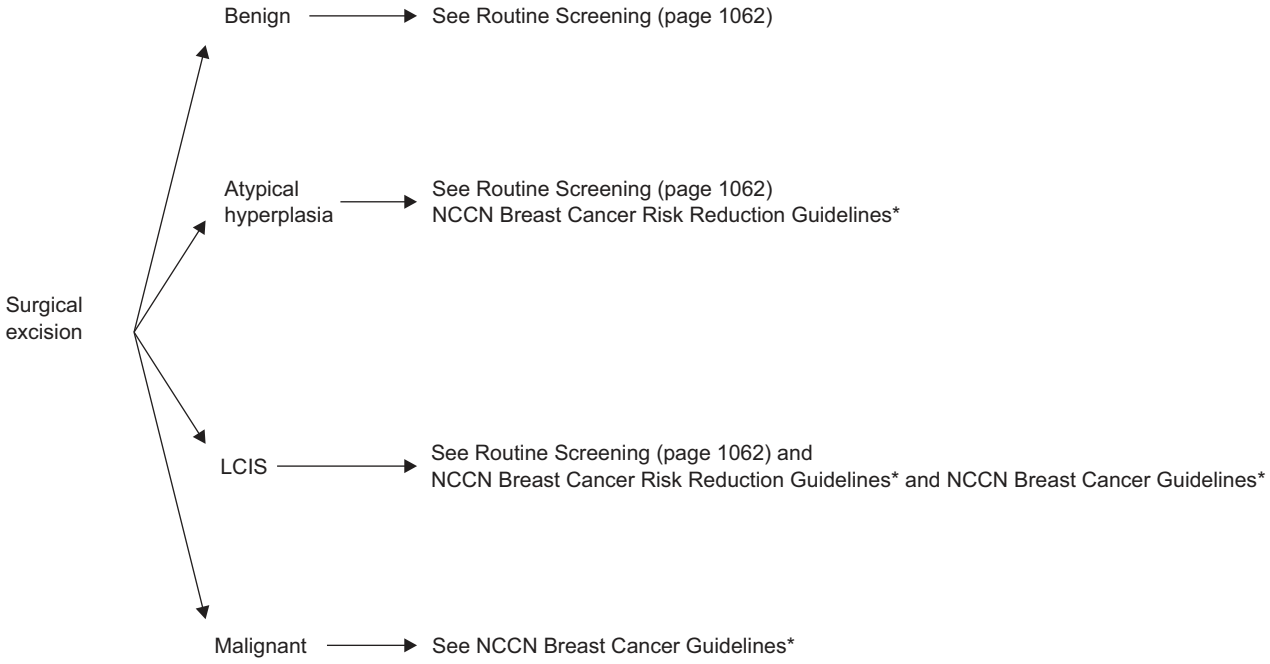
FOLLOW-UP EVALUATION



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BREAST SCREENING CONSIDERATIONS

- Thorough clinical breast exam involves inspection and palpation of all breast tissue, including lymph node basins.
- Consider severe comorbid conditions limiting life expectancy and whether therapeutic interventions are planned.
- Upper age limit for screening is not yet established.
- Current evidence does not support the routine use of breast scintigraphy (e.g., sestamibi scan) or ductal lavage as screening procedures.
- Current evidence does not support the routine use of breast MRI as a screening procedure in average-risk women.
- Criteria for the use of breast MRI screening as an adjunct to mammography for high-risk women include:[1]
  - Having a BRCA 1 or 2 mutation
  - Having a first-degree relative with a BRCA 1 or 2 mutation and are untested
  - Having a lifetime risk of breast cancer of 20%-25% or more as defined by models that are largely dependent on family history
  - Received radiation treatment to the chest between ages 10 and 30, such as for Hodgkin's disease
  - Carry or have a first-degree relative who carries a genetic mutation in the TP53 or PTEN genes (Li-Fraumeni, Cowden, and Bannayan-Riley-Ruvalcaba syndromes).

Several studies support the use of ultrasound for breast cancer screening as an adjunct to mammography for high-risk women or those with dense breast tissue.[2]

- A single study (DMIST) suggested benefit of digital mammography in young women and women with dense breasts.[3]

[1] Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75-89.
[2] Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008,299:2151-2163.
[3] Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast cancer screening. N Engl J Med 2005;353:1773-1783.

RISK FACTORS USED IN THE MODIFIED GAIL MODEL[1]

- Current age
- Age at menarche
- Age at first live birth or nulliparity
- Number of first-degree relatives with breast cancer
- Number of previous benign breast biopsies
- Atypical hyperplasia in a previous breast biopsy
- Race[2]

For calculation of risk based on the modified Gail model, see www.nci.nih.gov.

[1] For detailed information, see www.nci.nih.gov.
[2] The current Gail model may not accurately assess breast cancer risk in non-Caucasian women.

ASSESSMENT CATEGORY DEFINITIONS[1,2]

BI-RADS - MAMMOGRAPHY FINDINGS

A. Assessment Is Incomplete:

Category 0: Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison:
A finding for which additional evaluation is needed. This is almost always used in a screening situation. Under certain circumstances, this category may be used after a full mammographic workup. A recommendation for additional imaging evaluation may include, but is not limited to, spot compression, magnification, special mammographic views, and ultrasound. Whenever possible, if the study is not negative and does not contain a typically benign finding, the current examination should be compared with previous studies. The radiologist should use judgment on how vigorously to attempt obtaining previous studies. Category 0 should only be used for old film comparison when required to make a final assessment.

B. Assessment Is Complete - Final Assessment Categories:

Category 1: Negative:
There is nothing to comment on. The breasts are symmetric and no masses, architectural distortion, or suspicious calcifications are present.

Category 2: Benign Finding(s):
Like Category 1, this is a normal assessment, but the interpreter chooses to describe a benign finding in the mammography report. Involuting, calcified fibroadenomas, multiple secretory calcifications, and fat-containing lesions, such as oil cysts, lipomas, galactoceles, and mixed-density hamartomas, all have characteristically benign appearances and may be labeled with confidence. The interpreter may also choose to describe intramammary lymph nodes, vascular calcifications, implants, or architectural distortion clearly related to prior surgery while still concluding that no mammographic evidence of malignancy is present.
Note that both category 1 and 2 assessments indicate that no mammographic evidence of malignanc is present. The difference is that category 2 should be used when describing one or more specific benign mammographic findings in the report, whereas category 1 should be used when no such findings are described.

Category 3: Probably Benign Finding - Short-Interval Follow-Up Suggested:
A finding placed in this category should have a less than 2% risk for malignancy. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability.
Several prospective clinical studies are showing the safety and efficacy of initial short-term follow-up for specific mammographic findings. Three specific findings are described as being probably benign (the noncalcified mass, focal asymmetry, and cluster of round [punctate] calcifications; the latter is anecdotally considered by some radiologists to be an absolutely benign feature). All the published studies emphasize the need to conduct a complete diagnostic imaging evaluation before making a probably benign (category 3) assessment; therefore it is inadvisable to render this assessment when interpreting a screening examination. Also, all the published studies exclude palpable lesions, so the use of a probably benign assessment for a palpable lesion is not supported by scientific data. Finally, evidence from all published studies indicate the need for biopsy rather than continued follow-up when most probably benign findings increase in size or extent.
Although the vast majority of findings in this category will be managed with an initial short-term follow-up (6 mo) examination followed by additional examinations until longer-term (≥ 2 y) stability is demonstrated, occasions may occur when biopsy is performed (patient wishes or clinical concerns).

Category 4: Suspicious Abnormality - Biopsy Should Be Considered:
This category is reserved for findings that do not have the classic appearance of malignancy but have a wide range of probabili ty of malignancy that is greater than those in category 3. Thus, most recommendations of breast interventional procedures will be placed within this category. It is encouraged that the relevant probabilities be indicated so the patient and physician can make an informed decision on the ultimate course of action.

[1] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 1997;62:55988).
[2] Terminology in this table is reflective of the American College of Radiology (ACR) Breast Imaging Reporting and Data System Atlas (BI-RADS Atlas). Reston, VA: American College of Radiology; 2003. For more information, see www.acr.org.

ASSESSMENT CATEGORY DEFINITIONS (CONTINUED)

Category 5: Highly Suggestive of Malignancy - Appropriate Action Should Be Taken:
These lesions have a high probability (≥ 95%) of being cancer. This category contains lesions for which one-stage surgical treatment could be considered without preliminary biopsy. However, current oncologic management may require percutaneous tissue sampling as, for example, when sentinel node imaging is included in surgical treatment or when neoadjuvant chemotherapy is administered at the outset.

Category 6: Known Biopsy - Proven Malignancy - Appropriate Action Should Be Taken:
This category is reserved for lesions identified on the imaging study with biopsy proof of malignancy prior to definitive therapy.

BI-RADS - ULTRASOUND FINDINGS

A. Assessment is Incomplete:

Category 0: Need Additional Imaging Evaluation:
In many instances, the ultrasound examination completes the evaluation of the patient. If ultrasound is the initial study, other examinations may be indicated. An example would be the need for mammography if ultrasound were the initial study for a patient in her late 20s evaluated with ultrasound for a palpable mass that had suspicious sonographic features. Another example might be where mammography and ultrasound are nonspecific, such as differentiating between scarring and recurrence in a patient with breast cancer treated with lumpectomy and radiation therapy. Here, MRI might be the recommendation. A need for previous studies to determine appropriate management might also defer a final assessment.

B. Assessment is Complete — Final Categories:

Category 1: Negative:
This category is for sonograms with no abnormality, such as a mass, architectural distortion, thickening of the skin, or microcalcifications. For greater confidence in rendering a negative interpretation, an attempt should be made to correlate the ultrasound and mammographic patterns of breast tissue in the area of concern.

Category 2: Benign Finding(s):
Essentially a report that is negative for malignancy. Simple cysts would be placed in this category, along with intramammary lymph nodes (also possible to include in category 1), breast implants, stable postsurgical changes, and probable fibroadenomas noted to be unchanged on successive ultrasound studies.

Category 3: Probably Benign Finding - Short-Interval Follow-Up Suggested:
With accumulating clinical experience and by extension from mammography, a solid mass with circumscribed margins, oval shape, and horizontal orientation, most likely a fibroadenoma, should have a less than 2% risk for malignancy. Although additional multicenter data may confirm safety of follow-up rather than biopsy based on ultrasound findings, short-interval follow-up is currently increasing as a management strategy. Nonpalpable complicated cysts and clustered microcysts might also be placed in this category for short-interval follow-up.

Category 4: Suspicious Abnormality - Biopsy Should be Considered:
Lesions in this category would have an intermediate probability of cancer, ranging from 3% to 94%. An option would be to stratify these lesions, giving them a low, intermediate, or moderate likelihood of malignancy. In general, category 4 lesions require tissue sampling. Needle biopsy can provide a cytologic or histologic diagnosis. Included in this group are sonographic findings of a solid mass without all of the criteria for a fibroadenoma and other probably benign lesions.

Category 5: Highly Suggestive of Malignancy - Appropriate Action Should be Taken:
(Almost certainly malignant)
The abnormality identified sonographically and placed in this category should have a 95% or higher risk for malignancy so that definitive treatment might be considered at the outset. With the increasing use of sentinel node imaging as a way of assessing nodal metastases and also with the increasing use of neoadjuvant chemotherapy for large malignant masses or those that are poorly differentiated, percutaneous sampling, most often with imaging-guided core needle biopsy, can provide the histopathologic diagnosis.

Category 6: Known Biopsy-Proven Malignancy - Appropriate Action Should Be Taken:
This category is reserved for lesions with biopsy proof of malignancy before institution of therapy, including neoadjuvant chemotherapy, surgical excision, or mastectomy.

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findings (see Breast Ultrasonography, page 1085). Current evidence does not support the routine use of breast scintigraphy (e.g., sestamibi scan) or ductal lavage as screening procedures.

History and Physical Examination

In these guidelines, the starting point for breast screening and evaluating abnormalities is a complete medical history followed by a clinical breast examination (CBE). Breasts should be inspected with patients in the upright and supine position. Patients may also be positioned to elicit any subtle shape or contour changes in the breast. The CBE should involve palpation of the entire breast with patients in the upright and supine position, and include the axillary region and all nodal basins that involve the breasts (i.e., axillary, supraclavicular, and internal mammary nodes).[5] Symptoms or positive findings on physical examination can include a palpable lump or mass, asymmetric thickening/nodularity, nipple discharge in the absence of a palpable mass, and skin changes such as peau d'orange, erythema, nipple excoriation, and scaling/eczema.

Women should be familiar with their breasts and promptly report any change to their health care provider.[6] Breast self-examination (BSE) instruction does not need to be performed in any specific formalized education program. Data from a large randomized trial of BSE screening have shown that instruction in BSE has no effect on reducing breast cancer mortality. In this study, 266,064 women were randomly assigned to either receive instruction in BSE or not.[7] Compliance was encouraged through feedback and reinforcement sessions. After 10 to 11 years of follow-up, 135 breast cancer deaths in the instruction group and 131 in the control group occurred and the cumulative breast cancer mortality rates were not significantly different between the arms. The number of benign breast lesions detected in the BSE instruction group was higher than that detected in the control group. Nevertheless, women should be encouraged to be aware of their breasts because this may facilitate detection of interval cancers between routine screenings.

Risk Assessment

If an asymptomatic woman has negative findings on physical examination, the next decision point is based on risk stratification. Women can be stratified into 2 basic risk categories for the purpose of screening recommendations: normal and increased risk. The increased risk category consists of 6 groups: 1) women who have undergone previous therapeutic thoracic irradiation or mantle irradiation; 2) women aged 35 years or older with a 5-year risk for invasive breast carcinoma of 1.7% or greater; 3) women with a lifetime risk for breast cancer greater than 20% based on models largely dependent on family history; 4) women with a strong family history or genetic predisposition; 5) women with lobular carcinoma in situ (LCIS) or atypical hyperplasia; and 6) women with a prior history of breast cancer.

Women at Normal Risk: For women between 20 and 39 years of age, a CBE every 1 to 3 years is recommended, with breast awareness encouraged. For women aged 40 years and older, annual CBE and screening mammography are recommended, and breast awareness is encouraged. Although controversies persist regarding the benefits and risks of mammographic screening in certain age groups,[8–14] most medical experts reaffirmed current recommendations supporting screening mammography (see Mammographic Evaluation, page 1083). The recommendation that women begin annual mammographic screening at 40 years of age is based on a consensus statement from the American Cancer Society (ACS) and National Cancer Institute (NCI) in 1997, and is supported by the ACS guidelines for breast cancer screening published in 2003[11] and the results of meta-analyses of randomized clinical trials.[3,15]

A second consideration is the time interval of screening in women aged 40 to 49 years. Whether breast screening should be performed annually or every other year remains controversial. The panel elected to follow the ACS guidelines of yearly mammography because mammograms can often detect a lesion 2 years before it is discovered by CBE. To reduce mortality from breast cancer, yearly screening may be more beneficial.

Data on screening of elderly women are limited because most clinical trials for breast screening have used a cutoff age of 65 or 70 years.[16–18] Because of the high incidence of breast cancer in the elderly population, the same screening guidelines are recommended as for women aged 40 years or older. Clinicians should always use judgment when applying screening guidelines (see page 1077). Patients who have severe comorbid conditions limiting life expectancy and who would have no intervention based on

screening findings should not undergo screening.[11]

Women at Increased Risk: *Women Who Have Undergone Prior Thoracic Irradiation:* Results from several studies have shown that women who underwent thoracic irradiation in their second or third decade of life have a substantially increased risk for developing breast cancer by 40 years of age.[19–24] For example, in the Late Effects Study Group trial, the overall risk of breast cancer associated with prior thoracic irradiation at a young age was found to be 56.7-fold (55.5-fold for female patients) greater than the risk for breast cancer in the general population.[19,20] In that study, the relative risk for developing female breast cancer according to follow-up interval was 0 at 5 to 9 years; 71.3 at 10 to 14 years; 90.8 at 15 to 19 years; 50.9 at 20 to 24 years; 41.2 at 25 to 29 years; and 24.5 at greater than 29 years.[20]

Results from a case-control study of women treated with thoracic radiation at a young age for Hodgkin lymphoma indicated that the estimated cumulative absolute risk for developing breast cancer at 55 years of age was 29.0% (95% CI, 20.2%–40.1%) for a woman treated at 25 years of age with at least 40 Gy of radiation and no alkylating agents.[25] Although a concern exists that the cumulative radiation exposure from mammography in a young woman may itself pose a risk for cancer, experts believe that the benefit of early detection of breast cancer in this high-risk group would outweigh this potential side effect. Findings from a recent survey of breast screening practices in this population of patients suggest that a sizable segment of this group is not undergoing regular mammographic screening.[26]

For women aged 25 years and older who have undergone prior thoracic irradiation, annual mammograms and a CBE every 6 to 12 months are recommended. Breast awareness should be encouraged. For these patients, annual mammogram screening should be initiated 8 to 10 years after radiation exposure or at 25 years of age, whichever occurs last.[27] The panel agrees that an annual breast MRI should be considered as part of the screening evaluation of these women, although data are lacking regarding the benefits and risks of adding breast MRI to the screening program (see MRI Evaluation, page 1085). For women younger than 25 years, an annual CBE is recommended and breast awareness is encouraged.

Women Aged 35 Years or Older With a 5-Year Risk of Invasive Breast Carcinoma Greater Than or Equal to 1.7%: For women aged 35 and older, a risk assessment tool is available to identify those who are at increased risk. The NCI and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Biostatistics Center developed a computerized interactive risk-assessment tool based on the modified Gail model[28–32] (http://www.cancer.gov/bcrisktool/Default.aspx), which provides risk projections based on several risk factors for breast cancer. The modified Gail model assesses the risk for invasive breast cancer as a function of age, menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race (see page 1077). The model calculates and prints 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify at increased risk.

Recently, the Gail model was updated using data from the Women's Contraceptive and Reproductive Experiences (CARE) study to better estimate breast cancer risk in African American women.[33] The Gail model should not be used for women with a predisposing gene mutation or strong family history of breast or ovarian cancers, or for those with LCIS.

According to the modified Gail model for women aged 35 years or older, increased risk for developing breast cancer is defined as a 5-year risk of 1.7% or greater. This is the average risk of a 60-year-old woman, which is the median age of diagnosis of breast cancer in the United States. A 5-year predicted risk for breast cancer of 1.7% or greater was required to enter the NSABP Breast Cancer Prevention Trial of tamoxifen versus placebo and the Study of Tamoxifen and Raloxifene (STAR) trial.

The modified Gail model risk assessment tool also provides an estimate of a woman's lifetime risk for developing breast cancer. However, this estimate is based on the Gail model risk criteria (see page 1077), which differ from those used in risk assessment models predominantly based on family history (see following section), and is not used in these guidelines to determine whether a woman is at increased risk for developing breast cancer.

In women aged 35 years or older with a 5-year risk of 1.7% or greater, CBEs every 6 to 12 months and annual mammography are recommended and breast awareness is encouraged. In addition, women in these groups should be asked to consider risk

reduction strategies outlined in the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction (for the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

A Lifetime Risk of Breast Cancer Greater Than 20% Based on Models Largely Dependent on Family History: A lifetime risk of greater than 20% for developing breast cancer as assessed using models based largely on family history is another risk threshold used in the guidelines to identify a woman as a potential candidate for risk reduction strategies, and to direct screening strategies. In a recent update to the ACS guidelines on breast screening which incorporates MRI,[34] a woman is identified as being at high risk for developing breast cancer if her lifetime risk is approximately 20% to 25% or greater based on models that rely mainly on family history. These models include BRCAPRO,[35] BOADICEA,[36] and others.

For women with a greater than 20% lifetime risk for developing breast cancer based on models largely dependent on family history, CBEs every 6 to 12 months and annual mammography are recommended and breast awareness is encouraged. Women in this group also should be asked to consider risk-reduction strategies in accordance with the NCCN Breast Cancer Risk Reduction Guidelines. Annual MRI also should be considered.[34]

A Strong Family History or Genetic Predisposition: Accurate family history information is needed to adequately assess breast cancer risk. Familial cancers share some features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than expected based on statistics, generally they do not exhibit inheritance patterns or onset age consistent with hereditary cancers. Familial breast cancers may be associated with chance clustering, genetic variations in lower-penetrance genes, a shared environment, small family size, and/or other factors.

The NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org) recommend women be referred to a cancer genetics professional for further evaluation if they have either a personal history or a close family history meeting any of the following criteria:

- Early-age onset of breast cancer (i.e., ≤ 50 years)
- Two breast cancer primaries in a single individual
- Breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations of Cowden disease, or leukemia/lymphoma
- Family member with a known mutation in a breast cancer susceptibility gene or a member of a population at risk (e.g., Ashkenazi Jewish)
- Male breast cancer
- Ovarian/fallopian/primary peritoneal cancer

In the statement on Genetic Testing for Cancer Susceptibility updated in 2003, ASCO recommended women undergo genetic counseling/testing when 1) a personal or family history suggests genetic cancer susceptibility, 2) the test can be adequately interpreted, and 3) the results will help diagnose or influence the medical or surgical management of the patient or family members at hereditary risk for developing cancer.[37] Additional genetic testing criteria are included in the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines (available at www.nccn.org). Genetic testing should be performed only in the setting of pre- and post-test genetic counseling.

Women aged 25 years or older with a genetic predisposition for breast and ovarian cancer syndrome should have CBEs every 6 to 12 months and annual mammograms; those with a strong family history or other genetic predisposition to breast cancer should start annual CBEs and mammography at an age that is 5 to 10 years earlier than that of the youngest breast cancer case in the family (see NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines; available at www.nccn.org). Breast awareness is encouraged.

Annual breast MRI is also recommended as an adjunct to mammogram and CBE in women aged 25 years or older. This recommendation is consistent with recent recommendations from ACS on breast screening with MRI (see MRI Evaluation, page 1085).[34] Women younger than 25 years with strong family history or genetic predisposition should have an annual CBE and be encouraged to develop breast awareness. Women in this group aged 25 years or older should be afforded the opportunity to consider risk reduction

strategies after multidisciplinary consultation in accordance with the NCCN Breast Cancer Risk Reduction Guidelines (available at www.nccn.org).

Risk due to radiation exposure from mammography in young women with an inherited cancer predisposition is unknown, and some concern exists about whether this genetic factor may increase sensitivity to irradiation. A recent study of *BRCA1/BRCA2* mutation carriers showed that lifetime mammogram exposure was not associated with an increased risk for breast cancer when the overall group was considered; however, a small increase in risk was seen when only women with *BRCA1* mutations were evaluated.[38] Because the lifetime risk for developing breast cancer in women carrying a *BRCA1* or *BRCA2* mutation is estimated to be 3- to 6-fold greater (range, 40%–80%)[39] than in the general population, the benefit of screening may justify radiation exposure.

LCIS or Atypical Hyperplasia: Women with benign proliferative disease (e.g., atypical hyperplasia) are at increased risk for developing breast cancer.[40,41] In addition, although it is not considered a site of origin for cancer, LCIS is associated with an estimated risk of 10% to 20% for the subsequent development of cancer in either breast over the next 15 years.[42,43] An annual mammogram and CBE every 6 to 12 months are recommended for women with LCIS or atypical hyperplasia. The panel also recommends annual MRI be considered for women with LCIS (see MRI Evaluation, page 1085), and breast awareness is encouraged. These women should also be asked to consider risk reduction strategies as described in the NCCN Breast Cancer Risk Reduction Guidelines (available at www.nccn.org).

Prior History of Breast Cancer: Women with a history of breast cancer should be treated according to the surveillance and follow-up section of the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

Mammographic Evaluation

A screening mammogram typically involves 2 radiographic images of each breast (i.e., one taken from the top [craniocaudal] of the breast and the other from the side [mediolateral oblique]). Randomized clinical trials have shown that screening mammography lowers the rate of death from breast cancer,[3,44] with a reported overall sensitivity of approximately 75%.[45] Nevertheless, the overall sensitivity of screening mammography was reported to be only 50% in a study of women with at least heterogeneous dense tissue,[46] and 33% in a study of women with suspected or known *BRCA* mutations who were more likely to be younger and have dense breasts.[47] One reason for the low sensitivity in women with *BRCA* mutations is their increased likelihood of developing tumors with more benign mammographic characteristics (e.g., less likely to appear as a spiculated mass).[48]

Technical aspects of mammography can affect the quality of screening results. Digital mammography differs from conventional film mammography in that the former generates an electronic image of the breast and allows for computer storage and manipulation. Four large-scale trials have compared these procedures, although the designs and findings of these trials differ.[49–54] In a study of 49,528 women who underwent both film and digital mammography, no difference was seen in the overall accuracy of the procedures.[53,54] However, digital mammography was significantly more accurate in younger women with dense breasts, and a nonsignificant trend was seen toward improved accuracy of film mammography in women aged 65 years and older. In another trial of women aged 45 to 69 years randomly assigned to film or digital screening mammography, the latter procedure was shown to result in a higher rate of cancer detection.[51] Other outstanding issues related to these procedures include possible differences in recall rates, and cost and availability issues.

Mammographic results are mandated to be reported using final assessment categories of the Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology (ACR; Mammography Quality Standards Act, 1997[55]). The purpose of the final assessment category definitions is to create a uniform system for reporting mammography results with a recommendation associated with each category. These guidelines adopted the fourth edition of BI-RADS, in which substantive changes have been made and category 6 was added (see pages 1078 and 1079).[56] It is available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/BIRADSAtlas/BIRADSAtlasexcerptedtext/BIRADSMammographyFourthEdition/AssessmentCategoriesDoc1.aspx.

BI-RADS assessment categories apply to an individual imaging method if only one type of imaging is performed (e.g., mammography), but if mammography and ultrasonography are performed, the BI-RADS categories represent the cumulative findings of both. Therefore, the overall BI-RADS assessment category can change depending on subsequent imaging findings (i.e., the BI-RADS assessment category given after a mammographic study may increase, decrease, or remain the same after diagnostic ultrasonography follow-up). In the event that multiple abnormalities are identified on imaging, the overall final BI-RADS assessment category is based on the most worrisome findings present.

After the mammographic evaluation is completed, the results are classified according to one of the following BI-RADS categories:

- **Category 1:** *Negative:* This is a negative mammogram. The breasts are symmetric and no masses, architectural distortion, or suspicious calcification are present.
- **Category 2:** *Benign Findings:* This is also a negative mammogram, but an actual finding may be present that is benign. The typical case scenarios include benign-appearing calcifications, such as a calcifying fibroadenoma; an oil cyst; or a lipoma. The interpreter may also choose to describe intramammary lymph nodes, vascular calcification, implants, or architectural distortion clearly related to prior surgery while still concluding that no mammographic evidence of malignancy is present.
- **Category 3:** *Probably Benign Findings; Short-Interval Follow-up Suggested:* This is a mammogram that is usually benign. Close monitoring of the finding is recommended to ensure its stability. The risk for of malignancy is estimated to be less than 2%.
- **Category 4:** *Suspicious Abnormality; Biopsy Should Be Considered:* These lesions have a wide range of probability of being malignant but are not obviously malignant mammographically. The risk for malignancy is widely variable and is greater than that for category 3 but less than that for category 5.
- **Category 5:** *Highly Suggestive of Malignancy; Appropriate Action Should Be Taken:* These lesions have a high probability (≥ 95%) of being a cancer. They include spiculated mass or malignant-appearing pleomorphic calcifications.
- **Category 6:** *Known Biopsy-Proven Malignancy; Appropriate Action Should Be Taken:* This category was added to the fourth edition for breast lesions identified on the imaging study that are confirmed to be malignant through biopsy but before definitive therapies.

Another BI-RADS category, category 0, represents an incomplete assessment. Category 0 is defined as "Needs Additional Imaging Evaluation and/or Prior Mammograms for Comparison." This category is assigned when a finding requires additional evaluation. This category is almost always used in the context of a screening situation. A recommendation for additional imaging evaluation may include spot compression, magnification, special mammographic views, and ultrasound. Under certain circumstances this category may be used after a full mammographic workup. Whenever possible, if the study is not negative and does not contain a typical benign finding, the current examination should be compared to previous studies. The radiologist should use judgment on how vigorously to attempt obtaining previous studies.

The practice guideline for the performance of screening and diagnostic mammography from the ACR can be accessed at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/breast/Screening_Diagnostic.aspx.

Recommendations for Mammogram Interpretation and Follow-up

For BI-RADS categories 1 and 2, in which the mammogram is completely normal or the finding is benign mammographically, the recommendation is routine screening mammography in 1 year (see page 1074). When screening mammography shows an abnormal finding, the radiologist should attempt to obtain any prior mammograms. This is most important for lesions that are of low suspicion mammographically. If a questionable area remains that is not clearly benign after the films are compared, then a diagnostic mammogram should be performed (see Diagnostic Mammography, facing page), with or without ultrasonography (see Breast Ultrasonography, facing page).

For follow-up of patients with mammograms categorized as BI-RADS 0 and 3 or higher, see Diagnostic Evaluation for Positive Findings, facing page.

MRI Evaluation

MRI has a higher sensitivity for detecting breast cancer than mammography, although the specificity of MRI is lower, resulting in a higher rate of false-positive findings.[57] In addition, microcalcifications are not detectable with MRI,[58,59] and the issue of whether breast MRI screening impacts survival has not been addressed in randomized clinical trials. Therefore, careful patient selection for additional screening with MRI is needed.

Although current evidence does not support the use of breast MRI to screen women at average risk for developing breast cancer, several studies have shown the benefits of screening MRI for women with a genetic predisposition for breast cancer,[47,60–66] and the ACS published guidelines recommending use of breast MRI as an adjunct to screening mammography in certain populations of women at high risk for developing breast cancer (see page 1077).[34] Nevertheless, several of these studies identified a high false-positive rate for screening MRI. For example, in one study of high-risk women, many of whom were young and had very dense breast tissue, screening MRI led to 3 times as many benign biopsies as mammography.[67]

A single retrospective study evaluated the use of MRI in asymptomatic women with atypical hyperplasia or LCIS enrolled in a high-risk screening program.[68] Approximately half of the women underwent screening with mammography and MRI, whereas the other half was screened with mammography alone. For those undergoing both types of screening, MRI detected breast cancer in 4% with LCIS who had negative mammogram results. MRI screening did not impact the rate of cancer detection in women with atypical hyperplasia. Women who underwent screening with MRI were more likely to be younger and premenopausal, and to have a stronger family history of breast cancer compared with those evaluated with mammography alone. However, only one woman with cancer detected by MRI after a negative mammography finding reported a family history of breast cancer, and no difference was seen in the percentages of patients who ultimately developed cancer in the 2 groups.

An annual MRI is recommended as an adjunct to screening mammogram and CBE for women aged 25 years or older with a genetic predisposition/strong family history for breast cancer (see page 1077). Consideration of an annual MRI is also recommended for women who have a greater than 20% lifetime risk for developing breast cancer as defined by models largely based on family history as described in the ACS guidelines.[34] The guidelines recommend an annual MRI be considered as an adjunct to screening mammogram and CBE for women diagnosed with LCIS and those aged 25 years or older with a history of exposure to thoracic irradiation beginning at age 40 years or 8 to 10 years after radiation exposure (see page 1063).

Criteria for performing/interpreting high-quality breast MRI include a dedicated breast coil, radiologists experienced in breast MRI, and the ability to perform MRI-guided needle sampling and/or wire localization of MRI-detected findings. Recently published breast MRI guidelines from the European Society of Breast Imaging include detailed descriptions of the technical aspects of the use of breast MRI.[57] The ACR has also published guidelines for the performance of contrast-enhanced MRI of the breast (see http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/breast/mri_breast.aspx).

Diagnostic Evaluation for Positive Findings

Additional evaluations in selected patients with positive findings can include diagnostic mammography, breast MRI, ultrasonography, and tissue sampling.

Diagnostic Mammography

Screening mammography, which consists of 2 standard radiographic images of each breast, differs from diagnostic mammography in that the latter is used to evaluate a patient with a positive clinical finding, such as a breast lump or an abnormal screening mammogram. A diagnostic mammogram includes additional views, such as spot compression or magnification views, to investigate the finding in question.

Breast Ultrasonography

Mammography and ultrasound are complementary imaging methods for diagnosing breast cancer. However, breast ultrasonography does not detect most microcalcifications.[46,69–72]

Initial diagnostic imaging with breast ultrasonography is recommended as the preferred option for women younger than 30 years presenting with a dominant mass or asymmetric thickening/nodularity

(see pages 1069 and 1072, Dominant Mass in Breast [page 1089], and Asymmetric Thickening or Nodularity [page 1091]). Breast ultrasonography is recommended for women aged 30 years or older with a dominant mass and diagnostic mammogram assessed as BI-RADS 1 through 3 (see page 1065), and as an adjunct to diagnostic mammography for women in this age group with a finding of asymmetric thickening/nodularity (see page 1072).

In addition, breast ultrasonography should be considered as an adjunct to mammography for women of all ages with skin changes consistent with serious breast disease (see page 1073) or with spontaneous nipple discharge in the absence of a palpable mass (see page 1071), and as a possible option for women with a BI-RADS category 0 screening mammographic assessment (see page 1074). Consideration of follow-up ultrasound testing is also recommended when initial ultrasound findings of a solid mass (< 2 cm with low clinical suspicion) are classified as a probably benign finding, or when biopsy results are found to be benign and image-concordant (see page 1067 and more detailed recommendations below). Ultrasound-guided biopsy is included in the guidelines for women with a complex cyst or persistent mass after cyst aspiration (see pages 1065, 1068, and 1069).

Recommendations for Interpretation of Ultrasonography: After the ultrasonographic evaluation is complete, the results are classified according to the BI-RADS categories (see list of BI-RADS categories on page 1084, and see pages 1078 and 1079);[73]

- **Category 1:** *Negative:* This is a negative ultrasound; no abnormalities are detected.
- **Category 2:** *Benign Findings:* This is also a negative ultrasound, but an actual finding may be present that is benign. Included in this category are simple cysts (see Breast Cysts, opposite column) and breast implants.
- **Category 3:** *Probably Benign Findings; Short-Interval Follow-up Suggested:* This is an ultrasound that is usually benign. Close monitoring of the finding is recommended to ensure its stability. The risk for malignancy is estimated to be less than 2%. Fibroadenomas and nonpalpable complicated cysts and clustered microcysts might be placed in this category for short-interval follow-up (see Breast Cysts, opposite column).
- **Category 4:** *Suspicious Abnormality; Biopsy Should Be Considered:* These lesions have a wide range of probability of being malignant but are not obviously malignant ultrasonographically. The risk for malignancy is widely variable and is greater than that for category 3 but less than that for category 5. A complex cyst would be included in this group (see Breast Cysts, below).
- **Category 5:** *Highly Suggestive of Malignancy; Appropriate Action Should Be Taken:* These lesions have a high probability (≥ 95%) of being a cancer.
- **Category 6:** *Known Biopsy-Proven Malignancy; Appropriate Action Should Be Taken:* This category was added in the fourth edition for breast lesions identified on the imaging study that are confirmed to be malignant through biopsy but before definitive therapies.

Another BI-RADS category, category 0, represents an incomplete assessment. Category 0 is defined as "Needs Additional Imaging Evaluation." This category is assigned when a finding requires additional evaluation. If ultrasound is the initial study, mammography might be indicated, or if mammography and ultrasound findings are nonspecific then MRI might be appropriate.

The practice guideline for the performance of a breast ultrasound examination can be accessed at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/breast/us_breast.aspx

Breast Cysts: Breast cysts are either classified as simple or non-simple cysts, with the latter being subdivided into complicated and complex cysts (Table 1). A cyst meeting all criteria of a simple cyst is considered benign[74–76] if the clinical findings and ultrasonographic results are concordant. Therapeutic fluid aspiration can be considered if clinical symptoms persist, and these patients can be followed up with routine screening (see pages 1065 and 1069). Cytologic examination is recommended if bloody fluid is obtained (page 1068). The risk for malignancy associated with a complicated non-simple cyst is very low (< 2%).[74,76–78]

Options for managing complicated cysts are either aspiration or short-term follow-up with physical examination and ultrasonography with or with mammography every 6 to 12 months for 1 to 2 years to assess stability (see pages 1065 and 1069). The option of aspiration may be more strongly considered in a patient likely to be lost to follow-up. Complicated cysts that increase in size

Table 1 Breast Cysts: Types and Definitions

Simple cyst	Anechoic (cystic); well circumscribed; round or oval with well-defined imperceptible wall and posterior enhancement.
Nonsimple cyst	One or more characteristics not found in a simple cyst.
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.

Data from Refs. 73–80.

should be biopsied. As with simple cysts, cytologic analysis of fluid aspirated from a complicated cyst is required only if bloody fluid is obtained. In the event of a persistent mass, a biopsy is needed (see page 1068). For cysts which resolve following aspiration but are characterized by bloody fluid, the panel recommends placement of a tissue marker followed by cytologic evaluation of fluid. Follow-up of a positive finding includes percutaneous vacuum-assisted biopsy or excision. If findings are negative, physical examination with or without ultrasound/mammogram every 6 to 12 months for 1 to 2 years is recommended to assess stability. Tissue biopsy is recommended for a recurrent mass whereas routine screening is the recommended strategy when follow-up examinations are negative (see page 1068). Complex cysts have a relatively high risk of malignancy (e.g., 14% and 23% in 2 studies).[74,76,79,80] Hence, these cysts should be evaluated by tissue biopsy (see pages 1065 and 1069).

Diagnostic Breast MRI

MRI can also play a role in the diagnostic setting. For patients with skin changes consistent with serious breast disease, the guidelines recommend breast MRI be considered when biopsy of skin or nipple is found to be benign and the lesion is classified as BI-RADS category 1 to 3. Because 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 (see page 1073). Evidence suggests that certain MRI features may facilitate diagnosis of IBC.[81]

Breast Biopsy

Breast biopsy is recommended if diagnostic mammogram and/or ultrasound findings are suspicious or highly suggestive of malignancy.

Fine Needle Aspiration Biopsy: A fine needle aspiration (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,[82,83] whereas disadvantages include the need for pathologists with specific expertise in interpreting test results and the need to perform a follow-up tissue biopsy when atypia or malignancy is identified. FNA of nonpalpable lesions can be performed under imaging guidance (e.g., ultrasound), although evidence indicates that both core needle biopsy (CNB) and excisional biopsy are more accurate than FNA for evaluating nonpalpable breast lesions.[84,85]

Core Needle Biopsy: A CNB, also called *percutaneous core breast biopsy*, is an automated procedure that typically involves use of a large-bore cutting needle to remove 3 to 5 solid cores of tissue.[82,83] It can be performed under imaging guidance (e.g., stereotactic [mammographic] or ultrasound). Advantages of breast CNB include increased accuracy compared with FNA when the procedure is performed when no mass is palpable and the ability to obtain tissue samples of sufficient size to eliminate the need for a follow-up biopsy to confirm malignancy.[86]

In some situations, the CNB is performed under vacuum assistance, which can facilitate collection of adequate tissue from a breast lesion without the need for multiple needle insertions.[87,88] Clips are placed at CNB so that the radiologist can identify the location of the lesion if it is entirely removed or disappears during neoadjuvant breast cancer treatment.[89] With a few exceptions, the guidelines prefer CNB over surgical excision when tissue biopsy is required (see Excisional Biopsy, below).

Excisional Biopsy: An excisional biopsy involves removal of the entire breast mass or suspicious area of

the breast by a surgeon. Needle or wire localization is performed 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 at CNB.[89]

Excisional biopsy is included in the guidelines as an option when tissue biopsy is required. Although excisional biopsy is a more invasive method than CNB and requires needle localization when lesions are not palpable, sometimes larger tissue samples are needed. In most cases, excisional biopsy is recommended after CNB diagnoses an indeterminate lesion, atypical hyperplasia, LCIS, or a benign and image discordant lesion.

Other histologies that may require additional tissue samples include mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist.[77,83,84,90] This recommendation is supported by results of studies showing an underestimation of cancer when atypical hyperplasia and LCIS are diagnosed by CNB.[91–96] However, situations occur (e.g., select cases of LCIS, atypical lobular hyperplasia, papillomas, fibroepithelial lesions, radial scars) in which close observation may be substituted for excisional biopsy in select patients.[83,90,97–99]

Duct Excision With or Without Prior Ductography

Nipple discharge is common and often unrelated to breast pathology.[100,101] For example, nonspontaneous discharge from multiple breast ducts in a nonlactating woman can occur during pregnancy, after breast stimulation, in women with certain thyroid conditions, and in those taking certain medications, such as estrogen, oral contraceptives, opiates, and particular antihypertensive agents.[100] Suspicion of underlying pathology (e.g., papilloma, ductal ectasia) is raised when nipple discharge is persistent and reproducible on examination, spontaneous, unilateral, and from a single duct with fluid characterized as clear and colorless, serous, sanguineous, or serosanguineous.[101]

A woman exhibiting these symptoms should first undergo mammography with or without ultrasound (see page 1071), and those with an overall BI-RADS assessment of category 4 or 5 should have a tissue biopsy (see pages 1075 and 1076). If a malignancy is present, the woman should be managed according to the NCCN Breast Cancer Guidelines (for the most recent version of these guidelines, visit www.nccn.org). Women with an overall BI-RADS assessment of category 1 through 3 or a benign or indeterminate result after tissue biopsy should undergo duct excision. Ductography is an option before duct excision. Conventional ductography is an invasive procedure performed before duct excision that involves retrograde filling of the milk duct with contrast material followed by mammographic evaluation to help characterize lesions responsible for symptoms.[102] More recently, MR ductography, a noninvasive alternative that does not use either radiation or contrast agents, has been described, although it is not yet endorsed by the NCCN panel.[103,104]

Recommendations for Workup of Patients With Mammogram BI-RADS Assessment Categories 0, 3, 4, 5, and 6

For BI-RADS category 0 (i.e., additional imaging evaluation required), the diagnostic workup includes comparison with prior films and/or diagnostic mammogram with or without ultrasound scan.

For BI-RADS category 3 (probably benign), diagnostic mammograms at 6 months, and then every 6 to 12 months for 1 to 2 years, are appropriate. At the first 6-month follow-up, a unilateral mammogram of the index breast is performed. The 12-month study would be bilateral in women aged 40 years and older so that the contralateral breast is imaged at the appropriate yearly interval. Depending on the level of concern, the patient is then followed up either annually with bilateral mammograms or every 6 months for the breast in question, for a total of 1 to 2 years.

If the lesion remains stable or resolves mammographically, the patient resumes routine screening intervals for mammography. If any of the interval mammograms show that the lesion has increased in size or that its benign characteristics have changed, a biopsy is performed. The exception to this approach of short-term follow-up is when a return visit is uncertain or the patient is highly anxious 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, tissue diagnosis is necessary using CNB (preferred) or needle localization excisional biopsy with specimen radiograph. When needle biopsy is performed (aspiration or CNB), concordance between the pathology report

and imaging finding must be obtained.[56,105] For example, a negative FNA associated with a spiculated category 5 mass is discordant and clearly would not be an acceptable diagnosis. When the pathology and imaging are discordant, breast imaging should be repeated and additional tissue sampled or excised; surgical excision is recommended if pathology/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 (see page 1075). Those with a finding of atypical hyperplasia, LCIS, or other potentially pathologic conditions should undergo surgical excision and be followed up as described on page 1076.

For BI-RADS category 6 (proven malignancy), the patient should be managed according to the NCCN Breast Cancer Guidelines (for the most recent version of these guidelines, visit www.nccn.org).

Recommendations for Workup of Patients With Positive Findings on Physical Examination

Dominant Mass in Breast

A mass is a discrete lesion that can be readily identified during a CBE. The guidelines separate the evaluation of the mass into 2 age groups: women aged 30 years or older and those younger than 30 years.

Women Aged 30 Years or Older: The main difference in the guidelines for evaluating a dominant mass in women aged 30 years or older compared with younger women is the increased degree of suspicion of breast cancer (see page 1065). The initial evaluation begins with a bilateral diagnostic mammogram. Observation without further evaluation is not an option. After the mammographic assessment, the abnormality is placed in one of the 6 BI-RADS categories.

For BI-RADS categories 1, 2, and 3, the next step is to obtain an ultrasound. For BI-RADS categories 4 and 5, assessment of the geographic correlation between clinical and imaging findings is indicated. If no correlation can be found, further evaluation is the same as for BI-RADS categories 1, 2, or 3. If the imaging findings correlate with the palpable findings, workup of the imaging problem answers the palpable problem; tissue diagnosis through CNB (preferred) or needle localization excisional biopsy with specimen radiograph is necessary (see page 1075). When a CNB is used, concordance between the pathology report and imaging finding must be obtained, as described in Mammographic Evaluation (page 1083).

If ultrasound indicates a solid lesion that is suspicious or highly suggestive of malignancy (i.e., BI-RADS categories 4–5), tissue biopsy should be obtained using CNB (preferred) or surgical excision (see page 1066). If the pathology is benign and image-concordant with the ultrasound, physical examination with or without ultrasound or mammogram is recommended every 6 to 12 months for 1 to 2 years to assess stability. Follow-up may be considered at earlier intervals if clinically indicated. If the solid lesion increases in size, it should be surgically excised. Routine breast screening is recommended for stable lesions. If the findings are indeterminate, are benign and image-discordant, or indicate atypical hyperplasia, LCIS, or another pathology (e.g., mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or other histologies of concern to the pathologist), surgical excision should be performed, although select patients (e.g., some with atypical hyperplasia, LCIS, fibroepithelial lesions, or radial scars) may be suitable for monitoring in lieu of surgical excision (see Excisional Biopsy, page 1087). Routine breast screening is indicated for the confirmed benign lesion. If the lesion is classified as atypical hyperplasia or LCIS, the physician should consider risk-reduction therapy according to the NCCN Breast Cancer Risk Reduction Guidelines (for the most recent version of these guidelines, visit www.nccn.org) and the patient should be counseled to maintain regular breast screening. If the lesion is malignant, the patient is treated according to the NCCN Breast Cancer Guidelines (available at www.nccn.org).

If the results of the ultrasound show that the solid lesion is probably benign (i.e., BI-RADS 3), several options are available, including surgical excision, CNB (preferred), or observation (see page 1067). Observation may be elected only if the lesion is less than 2 cm and there is low clinical suspicion, in which case a physical examination with or without ultrasound or mammogram is recommended every 6 months for 1 to 2 years to assess stability (see page 1067). If the lesion has been surgically excised and proven to be benign, the patient undergoes routine screening. If the lesion is classified as atypical hyperplasia or LCIS, the physician should consider risk-

reduction therapy according to the NCCN Breast Cancer Risk Reduction Guidelines (available at www.nccn.org) and the patient should be counseled to maintain regular breast screening. Malignant lesions are treated according to the NCCN Breast Cancer Guidelines (available at www.nccn.org).

If a CNB is elected and the result is benign and image-concordant, a physical examination with or without ultrasound or mammogram is recommended every 6 to 12 months for 1 to 2 years to ensure that the lesion is stable. If the solid lesion increases in size, the tissue biopsy should be repeated. Routine breast screening is recommended if the lesion is stable (see page 1062). If the lesion is indeterminate or benign and image-discordant, or indicates atypical hyperplasia, LCIS, or another pathology (e.g., mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or other histologies of concern to the pathologist), surgical excision is recommended, although select patients (e.g., some with atypical hyperplasia, LCIS, fibroepithelial lesions, or radial scars) may be suitable for monitoring in lieu of surgical excision (see Excisional Biopsy, page 1087).

If the ultrasound evaluation shows the mass to be consistent with an asymptomatic simple cyst (i.e., BI-RADS category 2), the CBE and ultrasound results must be concordant before routine screening is recommended (see page 1065). Therapeutic aspiration of this type of simple cyst can be performed if persistent clinical symptoms are present.

If the cyst is classified as a complicated (BI-RADS category 3) nonsimple cyst, options include aspiration or short-term follow-up with physical examination and ultrasound with or without mammography every 6 to 12 months for 1 to 2 years to assess stability.

A tissue biopsy should be performed for a complicated cyst that increases in size on follow-up (see pages 1065 and 1069). If blood-free fluid is obtained on aspiration and the mass resolves, the patient should be monitored for any change (see page 1068). If the physical examination remains negative, the patient should return to routine screening. If the mass recurs after aspiration, or the nonsimple cyst is classified as complex on ultrasound (i.e., BI-RADS category 4), then ultrasound with image-guided biopsy or surgical excision is warranted (see pages 1065 and 1068).

If the ultrasound with image-guided biopsy findings are benign and image-concordant, physical examination with or without ultrasound or mammogram every 6 to 12 months for 1 to 2 years is recommended. If the mass increases in size, tissue sampling should be repeated (see page 1066), and if the mass remains stable, routine breast screening is recommended (see page 1062). If the ultrasound and image-guided biopsy findings are benign and image-discordant or indeterminate, or indicate atypical hyperplasia, LCIS, or another pathology (e.g., mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or other histologies of concern to the pathologist), surgical excision is recommended, although select patients (e.g., those with atypical hyperplasia, LCIS, fibroepithelial lesions, radial scars) may be suitable for monitoring in lieu of surgical excision (see Excisional Biopsy, page 1087). If the mass has been surgically excised and proven to be benign, the patient should undergo routine screening (see page 1062). If the mass is classified as atypical hyperplasia or LCIS, routine breast screening along with risk-reduction therapy according to the NCCN Breast Cancer Risk Reduction Guidelines is recommended (for the most recent version of these guidelines, visit www.nccn.org). Malignant findings on either ultrasound with image-guided biopsy or surgical excision should be treated according to the NCCN Breast Cancer Guidelines (available at www.nccn.org).

If no ultrasonographic abnormality is detected (BI-RADS category 1), tissue biopsy (CNB or excision) or observation at 3- to 6-month intervals with or without imaging for 1 to 2 years should be considered to assess stability (see page 1065). If the lesion increases in size, tissue sampling should be repeated, whereas routine breast screening is recommended if the lesion remains stable.

Women Younger than 30 Years: The preferred option for initial evaluation of a dominant mass is to proceed directly to ultrasound. From this point, the decision tree for women younger than 30 years (see pages 1069 and 1070) is almost identical to that for older women. The main difference is consideration of a diagnostic mammogram in only some situations for younger women. Because the degree of suspicion is low in women younger than 30 years, observing the mass for 1 or 2 menstrual cycles is an option. If observation is elected and the mass resolves after 1 or 2 menstrual cycles, the patient may return to routine screening. If the mass persists, then ultrasound should be performed (see page 1069). Needle sampling before imaging is not recommended.

Nipple Discharge Without a Palpable Mass

In patients with nipple discharge but no palpable mass, evaluation of the discharge characteristics is the first step (see page 1071). If the nipple discharge is bilateral and milky, then pregnancy or an endocrine origin must be considered. Medications that may be associated with nipple discharge include psychoactive drugs, antihypertensive medications, opiates, oral contraceptives, and estrogen. The appropriate follow-up of a nonspontaneous, multiple-duct discharge in women younger than 40 years is observation, coupled with educating the patient to stop compression of the breast and to report any spontaneous discharge, if appropriate. In women aged 40 years or older, screening mammography, further workup based on the BI-RADS category, and education similar to that for younger women is recommended.

The most worrisome nipple discharge is one that is persistent, spontaneous, unilateral, from a single duct, and characterized as clear and colorless, serous, sanguinous, or serosanguineous. A guaiac test and cytology of the nipple discharge is not recommended, because a negative result should not stop further evaluation. Evaluation of this type of nipple discharge is based on the overall BI-RADS category of the diagnostic mammogram with or without adjunctive ultrasound. For an overall BI-RADS assessment of category 1, 2, or 3, a ductogram is optional to guide the duct excision. Ductal excision is indicated for diagnosing abnormal nipple discharge, even if the ductogram is negative. However, the ductogram is useful to exclude multiple lesions and localize the lesions before surgery. For an overall BI-RADS assessment of category 4 or 5, a tissue biopsy should be obtained (see page 1075). If the findings are benign or indeterminate, a ductogram is optional, but surgical duct excision would still be necessary. If findings indicate malignancy, the patient should be treated according to the NCCN Breast Cancer Guidelines (for the most recent version of these guidelines, visit www.nccn.org).

Asymmetric Thickening or Nodularity

Thickening, nodularity, or asymmetry is distinct from a dominant mass in that the finding is ill-defined and often vague on physical breast examination (see page 1072). Factors to consider include whether the thickening is a new or previous finding, and whether it appears to be representative of normal asymmetry.

If the patient is younger than 30 years and has no high-risk factors, ultrasound evaluation is appropriate, followed by consideration of diagnostic mammography. Diagnostic mammograms for this age group have fairly low yield because of the density of the breast and low risk for breast cancer. In a woman aged 30 years or older, a bilateral diagnostic mammogram and an ultrasound evaluation should be obtained.

If the overall imaging findings are classified as BI-RADS category 1 through 3 and the clinical assessment is benign, the patient should be re-examined in 3 to 6 months. If the finding is stable, annual screening can be resumed (see page 1062), whereas clinical progression of the finding should be investigated as previously described for a dominant mass (see pages 1065 and 1069). If a clinically suspicious change is noted or the overall imaging findings are classified as BI-RADS category 4 or 5, a tissue biopsy is recommended (see pages 1065 and 1069).

Skin Changes

Any unusual skin changes around the breast may represent serious disease and require evaluation. IBC should be considered when peau d'orange and breast erythema are present, and nipple excoriation, scaling, and eczema should increase clinical suspicion of Paget's disease (see the NCCN Breast Cancer Guidelines, available at www.nccn.org).

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 characterized by erythema and dermal edema (peau d'orange) of a third or more of the skin of the breast with a palpable border to the erythema.[106,107] 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 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.[108]

Initial evaluation of a patient with breast skin changes begins with a bilateral diagnostic mammogram with or without ultrasound imaging (see page

1073). If the imaging results are abnormal, evaluation proceeds based on these findings. If the breast imaging results are normal, further workup is still needed.

Punch biopsy of skin or nipple biopsy should be performed when imaging findings are consistent with an overall BI-RADS assessment of category 1 through 3. Antibiotics may be given, depending on the clinical scenario, but should not delay diagnostic evaluation. If biopsy results are benign, clinical and pathologic correlation should be reassessed. In addition, a breast MRI, 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 Breast Cancer Guidelines (to view the most recent version of these guidelines, visit www.nccn.org).

A tissue biopsy should be performed if imaging findings are consistent with an overall BI-RADS category 4 or 5. CNB with or without punch biopsy is the preferred option, although surgical excision is also an option. A biopsy showing a malignant finding should be managed according to the NCCN Breast Cancer Guidelines (for the most recent version of these guidelines, visit www.nccn.org). A benign biopsy result should be followed by a punch biopsy of skin, if not previously performed, or nipple biopsy, with follow-up as described earlier.

Summary

The goal of these guidelines is to give health care providers a practical and consistent framework for screening and evaluating a spectrum of breast lesions. Clinical judgment should always be an important component of optimal patient management.

If the physical breast examination, radiologic imaging, and pathologic findings are not concordant, the clinician should carefully reconsider the assessment of the patient's problem. Involving patients in treatment decisions empowers them to determine an acceptable level of breast cancer risk in the screening and/or follow-up procedures.

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