National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Breast Cancer Screening and Diagnosis

Version 1.2011

NCCN.org

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NCCN Guidelines™ Version 1.2011 Panel Members
Breast Cancer Screening and Diagnosis

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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.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 1.2011 Updates Breast Cancer Screening and Diagnosis

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Updates in Version 1.2011 of the NCCN Guidelines from Version 1.2010 include:

BSCR-1
- Added "per Gail Model" under Increased risk, 2nd bullet.
- Changed 4th bullet to read, "Pedigree suggestive of genetic predisposition."
- Changed footnote "d" to read, "Per models other than Gail."

BSCR-2
- Under Screening Follow-up, 4th bullet changed the word Consider to "Recommend."
- Under Increased Risk, 2nd branch, added "or LCIS."

BSCR-3
- Deleted 3rd branch of algorithm.

BSCR-4
- Changed Dominant mass to "Palpable Mass" (Also for BSCR-4 thru BSRC-9).

BSCR-5
- Under Follow-up Evaluation, added "BI-RADS category 3 and 4" to Short term follow-up and Aspiration respectively.
- Changed "surgical excision" to "Image-guided biopsy" and added new footnote, "Surgical excision if image-guided/core needle biopsy not possible."

BSCR-6
- Under Ultrasound Findings, deleted first and second branch and under Follow-up Evaluation.

BSCR-7
- Deleted Tissue diagnosis under Ultrasound findings.

BSCR-8
- Fluid cyst, mass resolves and bloody fluid: added (if possible) after Place tissue marker.

BSCR-10
- Under Follow-up Evaluation flipped "Tissue biopsy" and "Observe every 3-6 mo."

BSCR-13
- Added BI-RADS® Category 3.

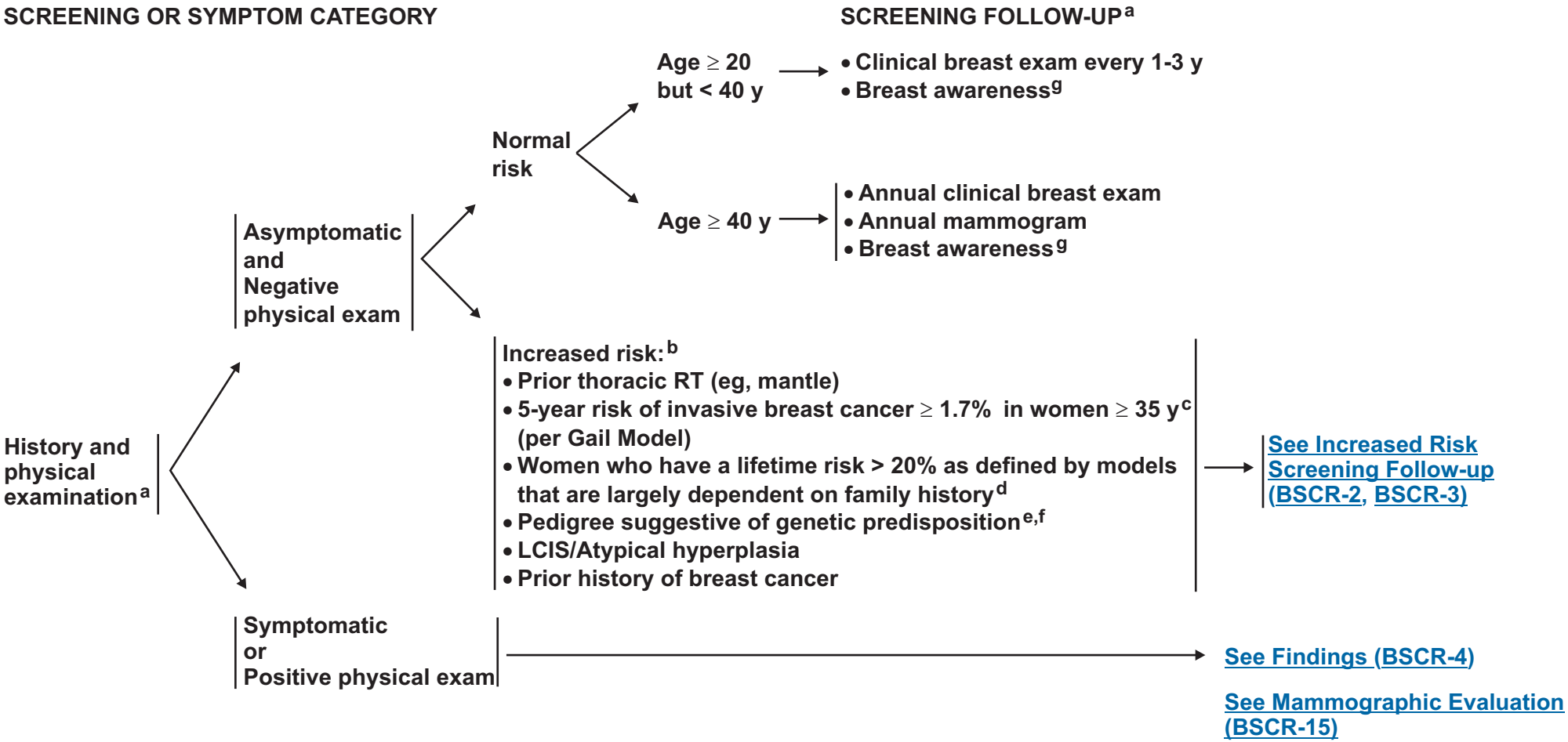
BSCR-16
- Under Diagnostic Mammogram Follow-up deleted "Needle localization excisional biopsy + specimen radiograph" and corresponding branches.

BSCR-A
- Added a new table; ACS recommendations on using MRI in screening and footnote which specifically describes the type of breast imaging required.

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[a] See Breast Screening Considerations (BSCR-A).
[b] Refer to the NCCN Breast Cancer Risk Reduction Guidelines for a detailed qualitative and quantitative assessment.
[c] See Risk Factors Used in the Modified Gail Model (BSCR-B).
[d] Per models other than Gail.
[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 Guidelines.
[g] Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

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SCREENING OR SYMPTOM CATEGORY	SCREENING FOLLOW-UP
Increased Risk:	
Prior thoracic RT: Age < 25 y	• Annual clinical breast exam • Breast awareness[g]
Prior thoracic RT: Age ≥ 25 y	• Annual mammogram + clinical breast exam every 6-12 mo ➤ Begin 8-10 y after RT or age 25, whichever occurs last • Recommend annual breast MRI as an adjunct to mammogram and clinical breast exam • Breast awareness[g]
Women ≥ 35 y with 5-year risk of invasive breast cancer ≥ 1.7%[c] OR LCIS	• Annual mammogram + clinical breast exam every 6-12 mo • Breast awareness[g] • Consider risk reduction strategies (See NCCN Breast Cancer Risk Reduction Guidelines)
Women who have a lifetime risk > 20% as defined by models that are largely dependent on family history[d]	• Annual mammogram + clinical breast exam every 6-12 mo • Breast awareness[g] • Consider risk reduction strategies (See NCCN Breast Cancer Risk Reduction Guidelines) • Consider annual breast MRI

See Physical Exam (BSCR-1)
See Mammographic Evaluation (BSCR-15)

[c] See Risk Factors Used in the Modified Gail Model (BSCR-B).
[d] Per models other than Gail.
[g] Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

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SCREENING OR SYMPTOM CATEGORY	SCREENING FOLLOW-UP
Increased Risk:	
Strong family history[d] or genetic predisposition[e,f] — **Age < 25 y[h]**	• Annual clinical breast exam • Breast awareness[g] • Consider referral to genetic counselor
Strong family history[d] or genetic predisposition[e,f] — **Age ≥ 25 y[h]**	• Annual mammogram + clinical breast exam every 6-12 mo ➤ Starting at age 25 y for Hereditary Breast and Ovarian Cancer (HBOC)[f] patients ➤ 5-10 y prior to youngest breast cancer case for strong family history or other genetic predispositions • Breast awareness[g] • Annual breast MRI as an adjunct to mammogram and clinical breast exam • Consider risk reduction strategies (See NCCN Breast Cancer Risk Reduction Guidelines) • Consider referral to genetic counselor
Prior history of breast cancer	See NCCN Breast Cancer Guidelines - Surveillance Section

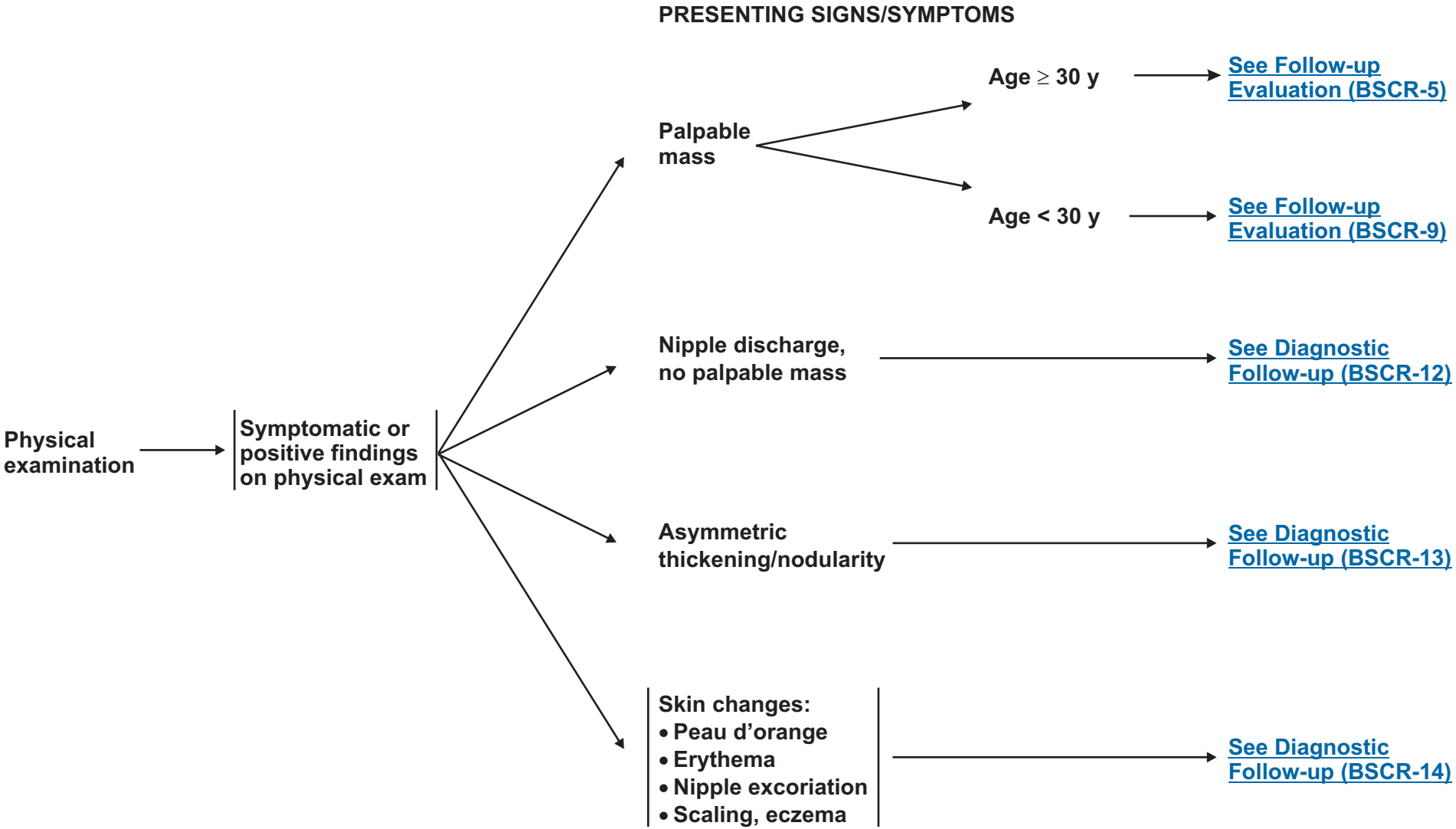
See Physical Exam (BSCR-1)
See Mammographic Evaluation (BSCR-15)

[d] Per models other than Gail.
[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 Guidelines.
[g] Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent 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.

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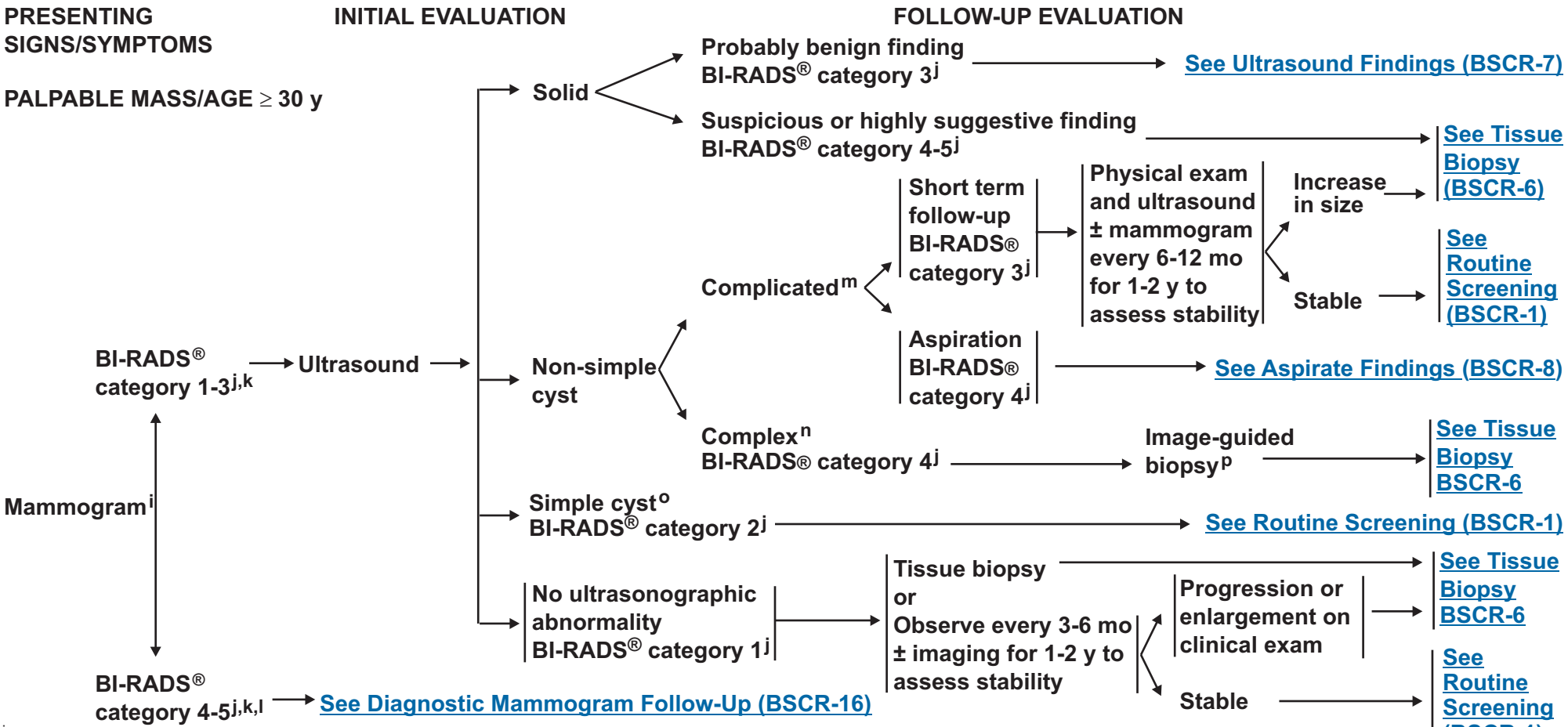
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Breast Cancer Screening and Diagnosis

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[i] There are a few clinical circumstances in which ultrasound would be preferred (eg, suspected simple cyst).

[j] See Assessment Category Definitions (BSCR-C).

[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988,1997).

[l] Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation return to Category 1-3 for further work-up 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.

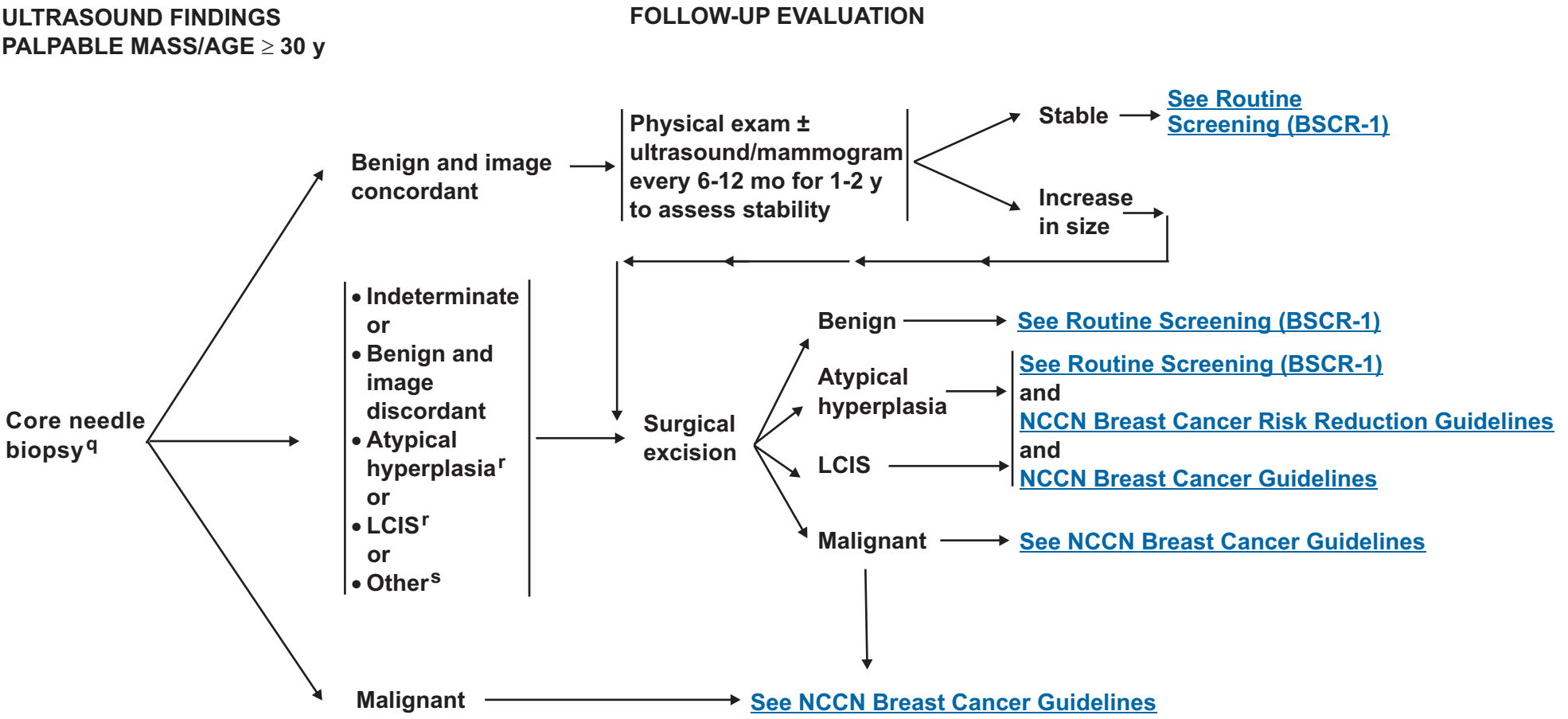
[o] Concordance is needed between clinical exam and ultrasound results. Consider therapeutic aspiration for persistent clinical symptoms.

[p] Surgical excision if image-guided/core needle biopsy not possible.

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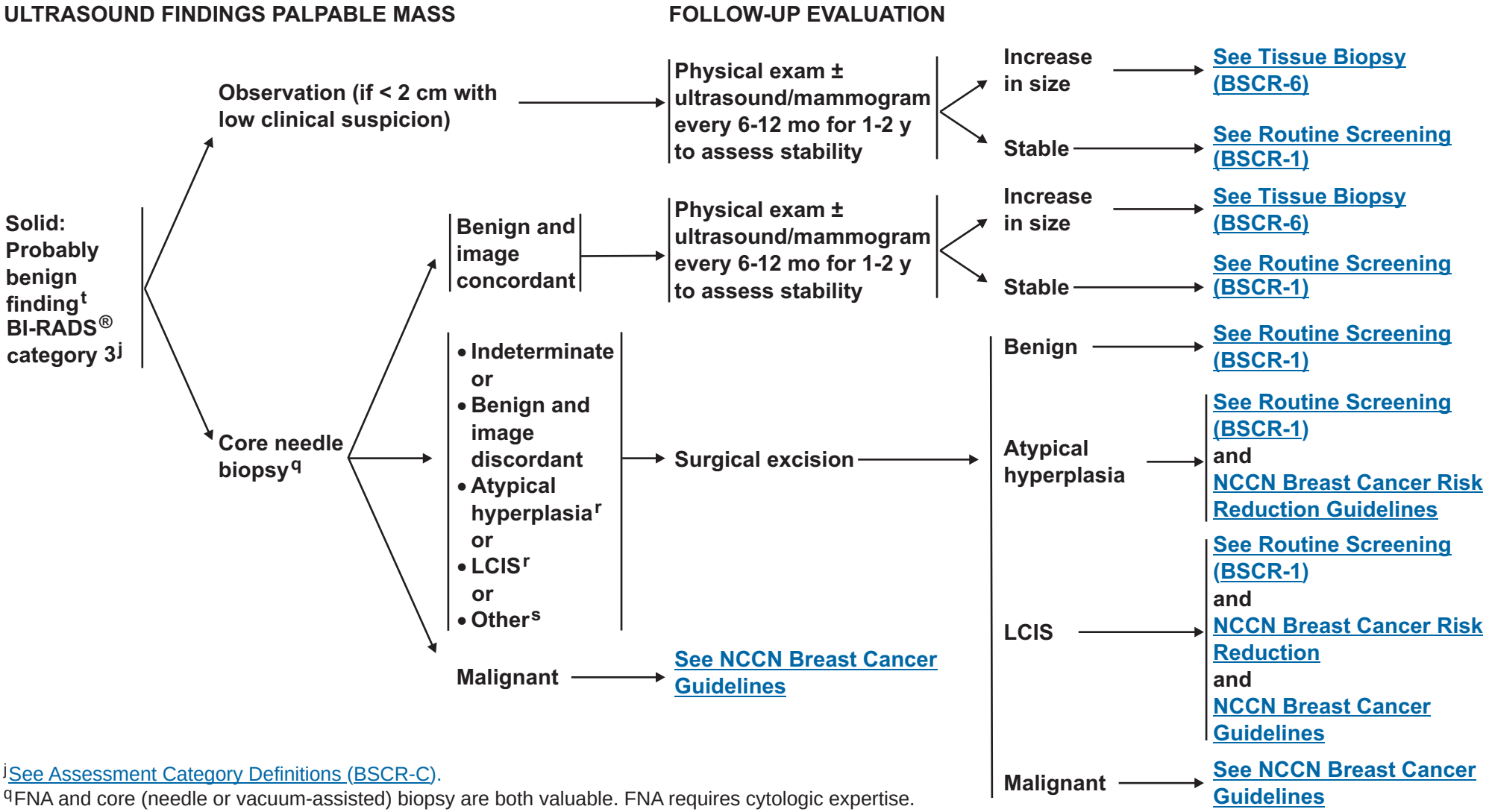


[q]FNA and core (needle or vacuum-assisted) biopsy are both valuable. FNA requires cytologic expertise.
[r]Select patients may be suitable for monitoring in lieu of surgical excision (eg., ALH, LCIS, papillomas, fibroepithelial lesions, radial scars, etc).
[s]Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar or histologies of concern to pathologist.

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[r] Select patients may be suitable for monitoring in lieu of surgical excision (eg., ALH, LCIS, papillomas, fibroepithelial lesions, radial scars, etc).

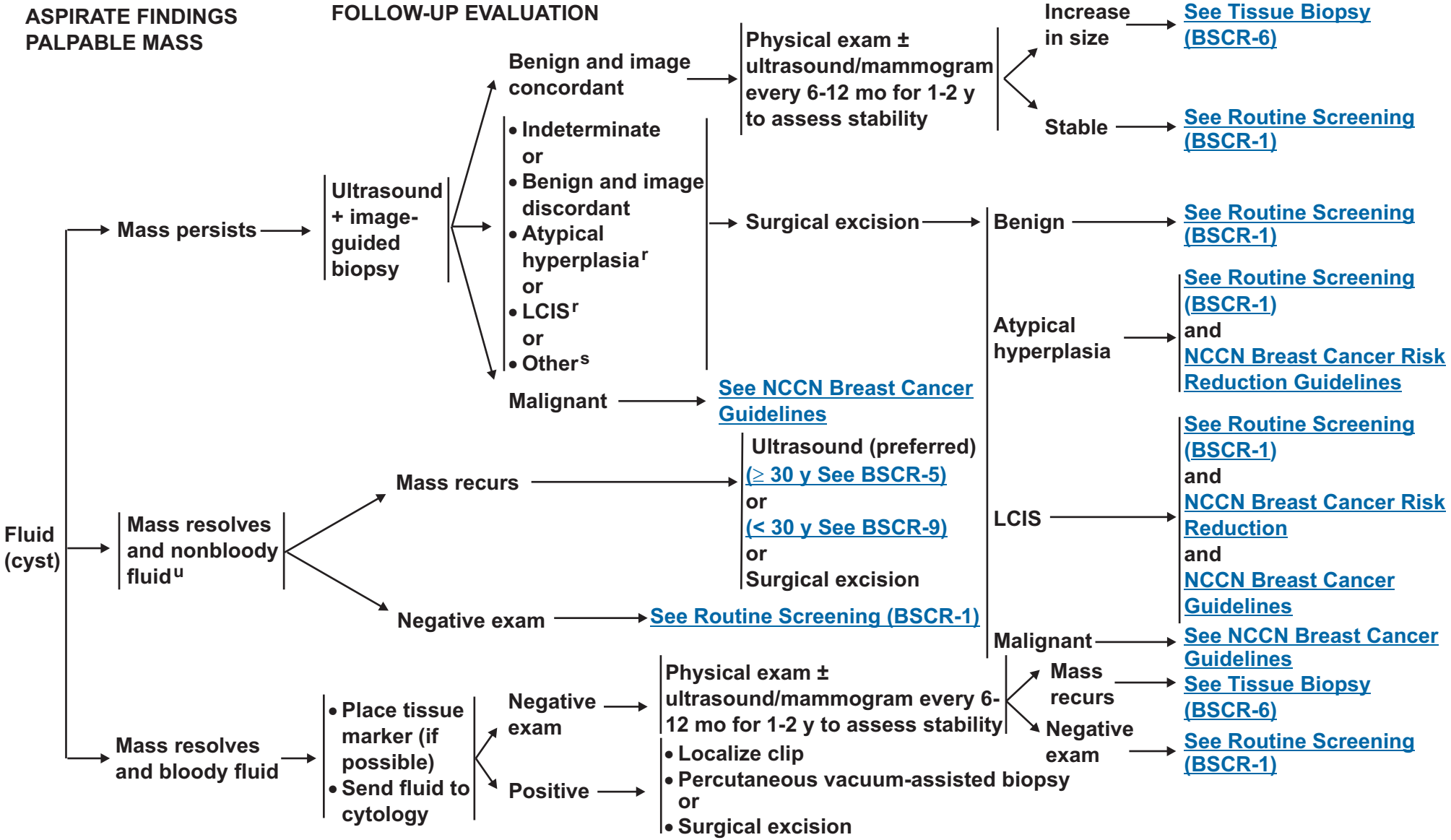
[s] Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar or histologies of concern to pathologist.

[t] 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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[r]Select patients may be suitable for monitoring in lieu of surgical excision (eg., ALH, LCIS, papillomas, fibroepithelial lesions, radial scars, etc.
[s]Other histologies that may requires additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesion, radial scar or histologies of concern to pathologist.
[u]Routine cytology not recommended.

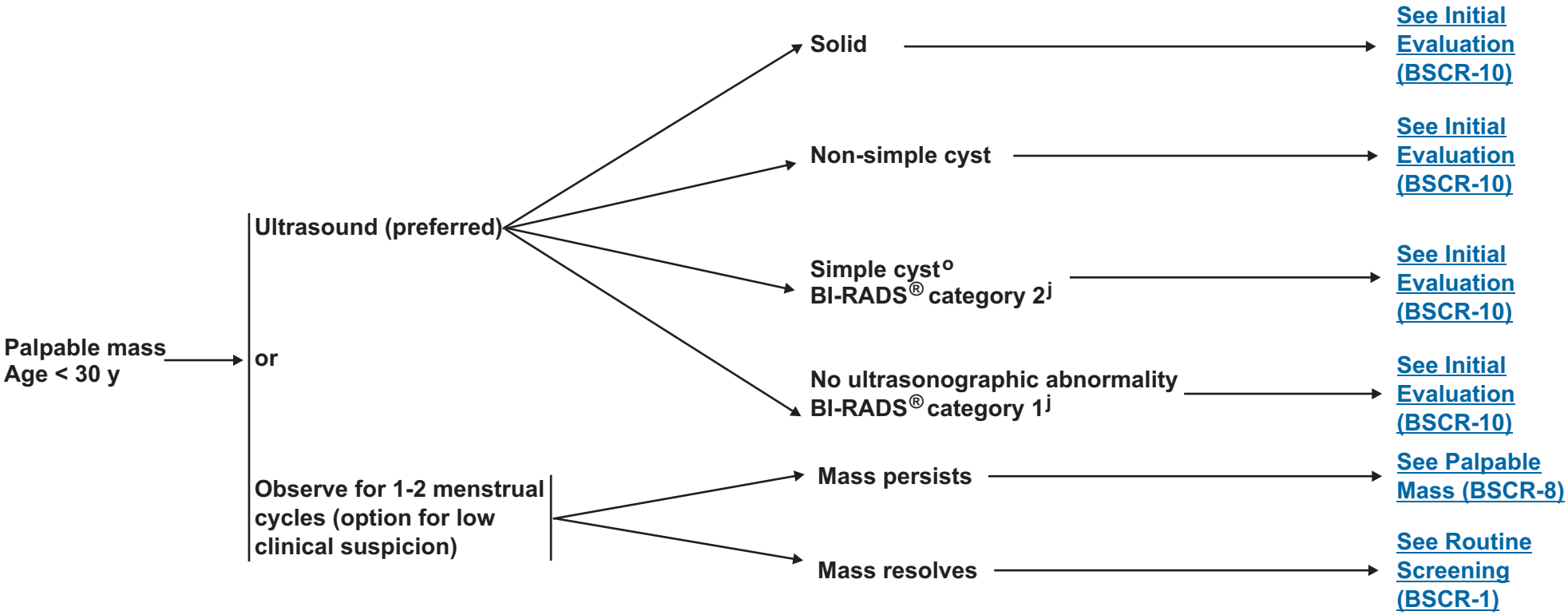
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PRESENTING SIGNS/SYMPTOMS
PALPABLE MASS/AGE < 30 y

INITIAL EVALUATION



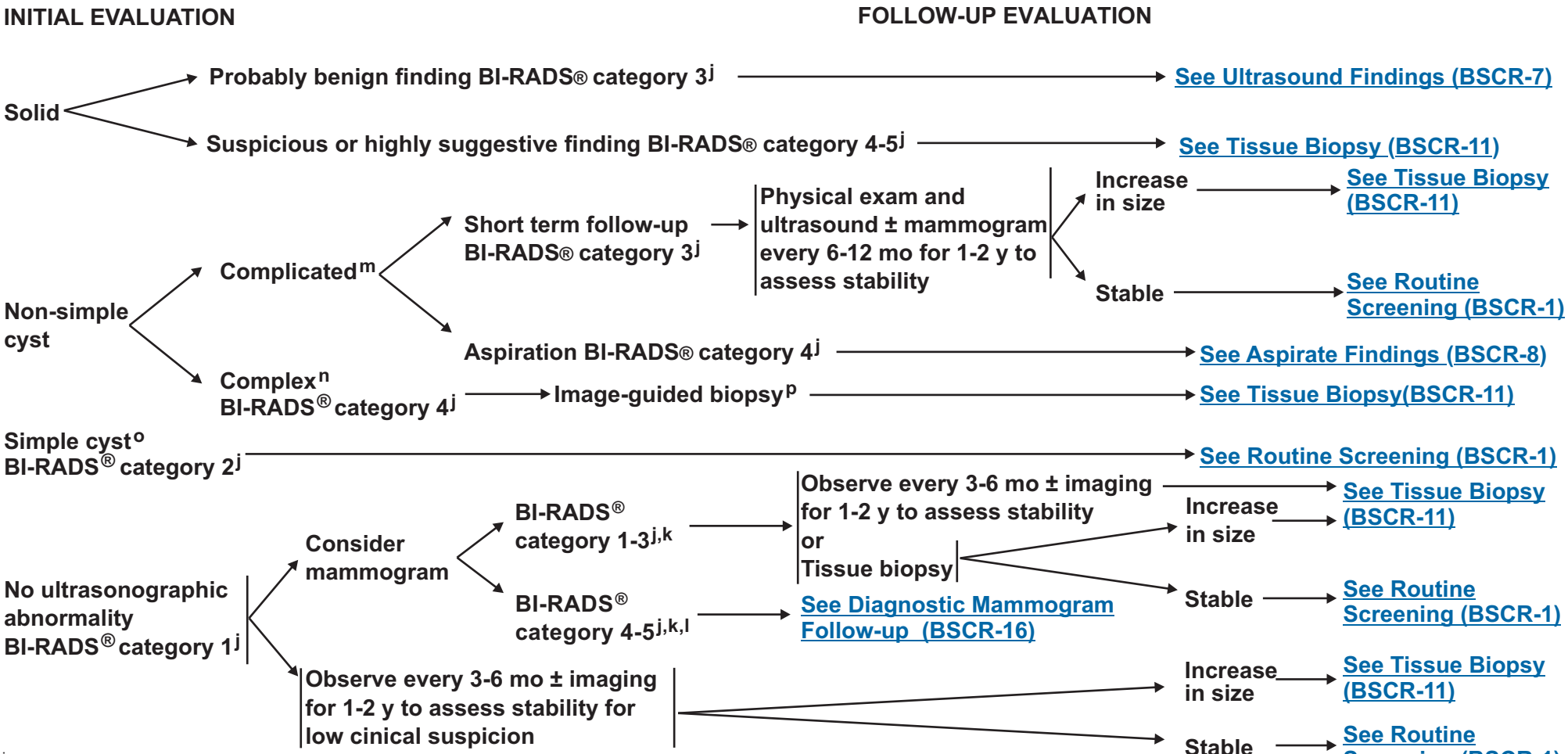
[j] See Assessment Category Definitions (BSCR-C).

[o] Concordance is needed between clinical exam and ultrasound results. Consider therapeutic aspiration for persistent clinical symptoms.

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[j] See Assessment Category Definitions (BSCR-C).

[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988,1997).

[l] Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation return to Category 1-3 for further work-up 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.

[p] Surgical excision if image-guided/core needle biopsy not possible.

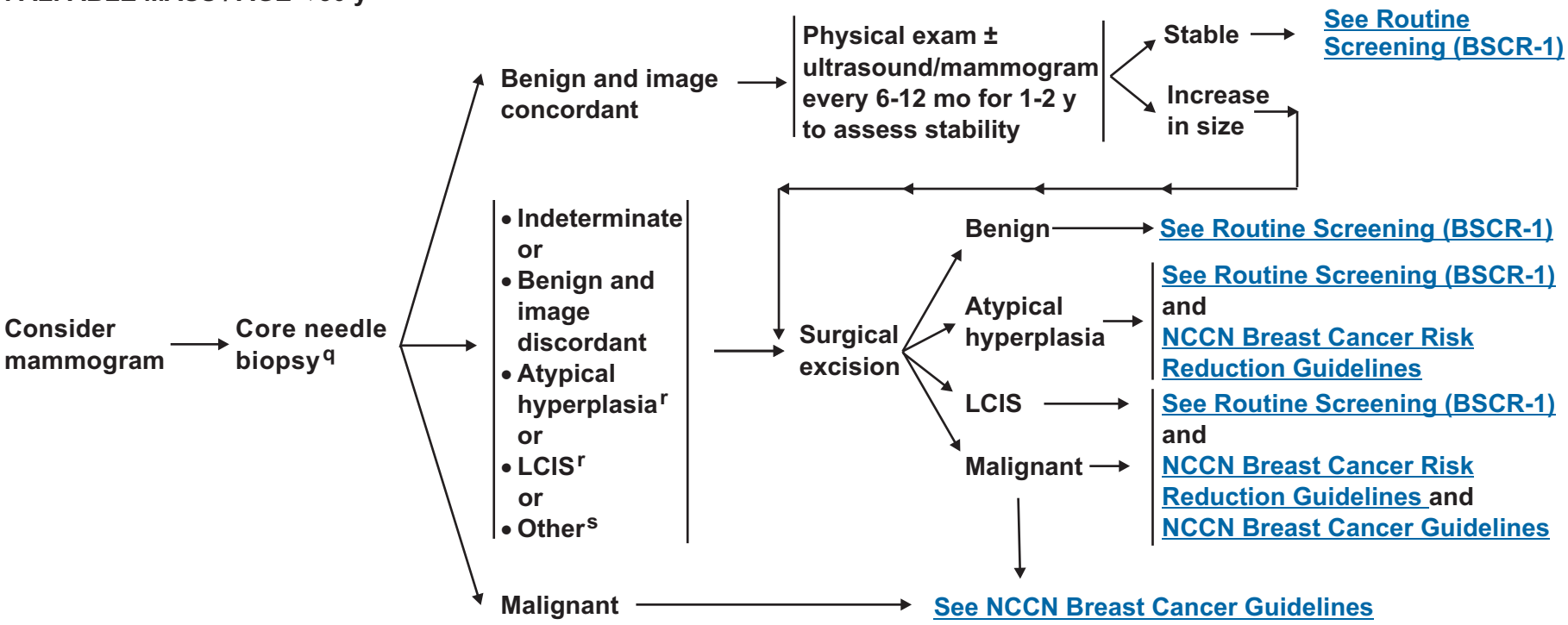
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ULTRASOUND FINDINGS
PALPABLE MASS / AGE < 30 y

FOLLOW-UP EVALUATION

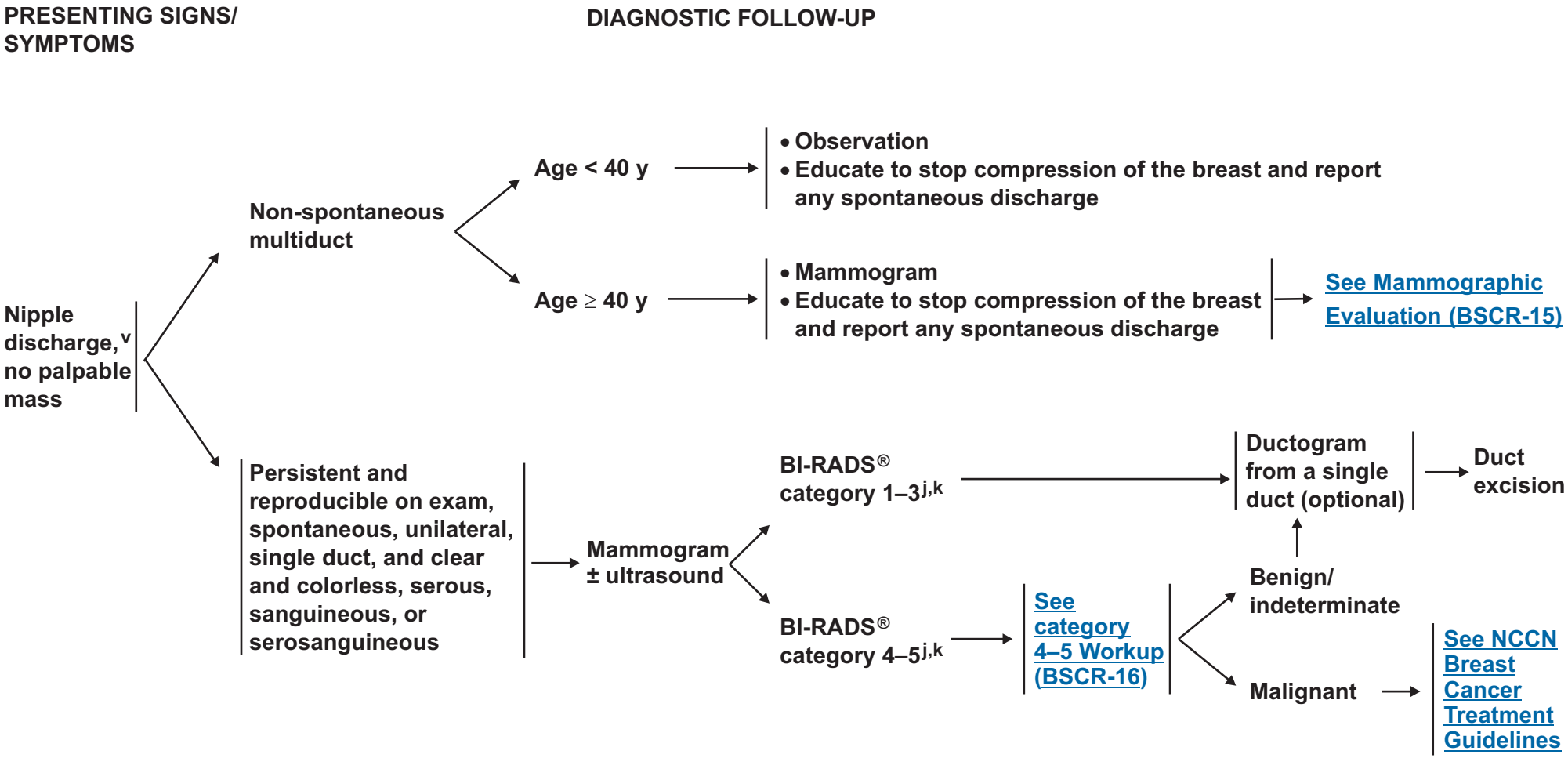


[j] See Assessment Category Definitions (BSCR-C).
[q] FNA and core (needle or vacuum-assisted) biopsy are both valuable. FNA requires cytologic expertise.
[r] Select patients may be suitable for monitoring in lieu of surgical excision (eg., ALH, LCIS, papillomas, fibroepithelial lesions, radial scars,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

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[j] See Assessment Category Definitions (BSCR-C).

[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).

[v] A list of drugs that can cause nipple discharge (not all inclusive): Psychoactive drugs, antihypertensive medications, opiates, oral contraceptives, and estrogen.

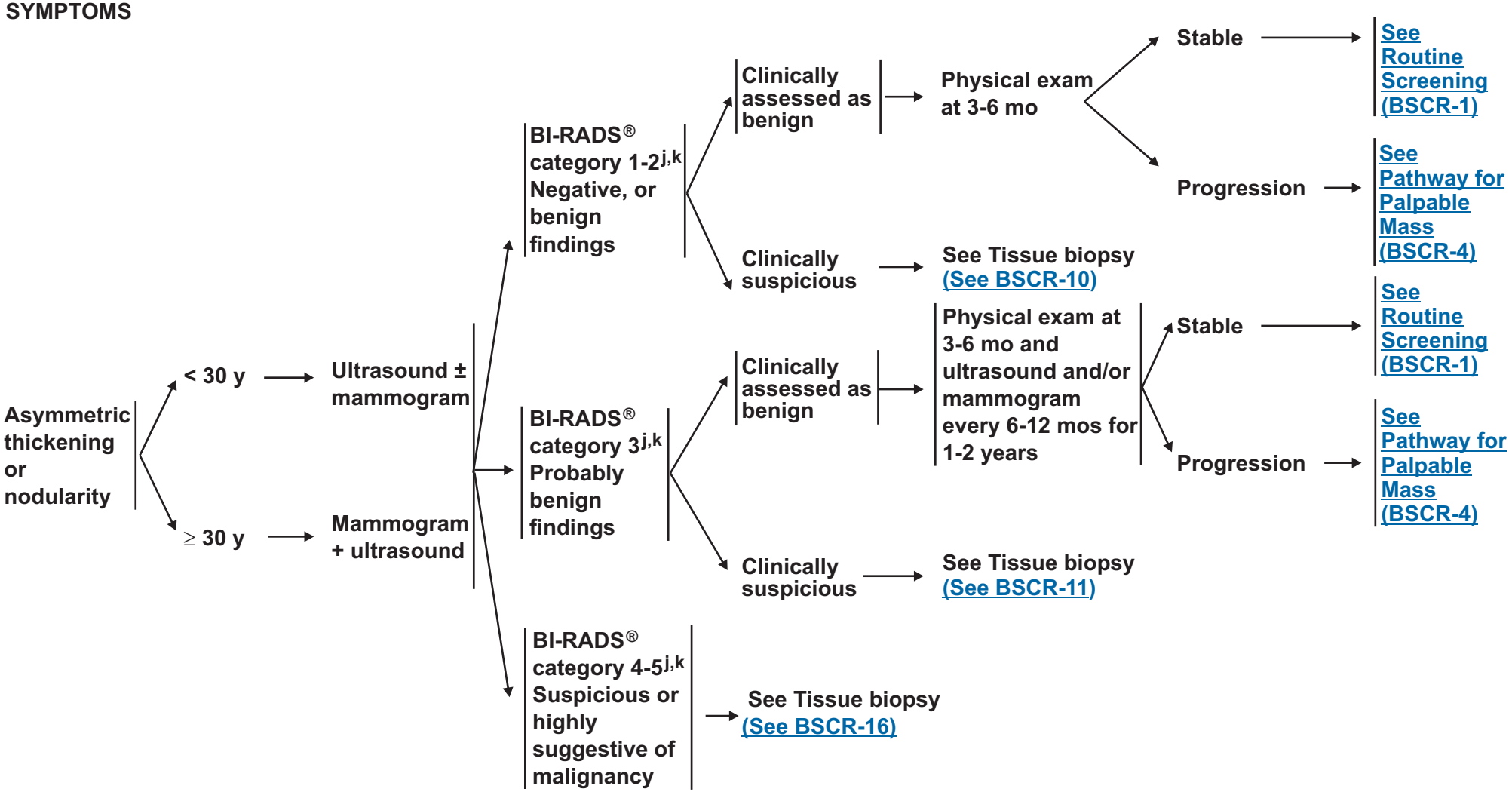
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PRESENTING SIGNS/ SYMPTOMS

DIAGNOSTIC FOLLOW-UP



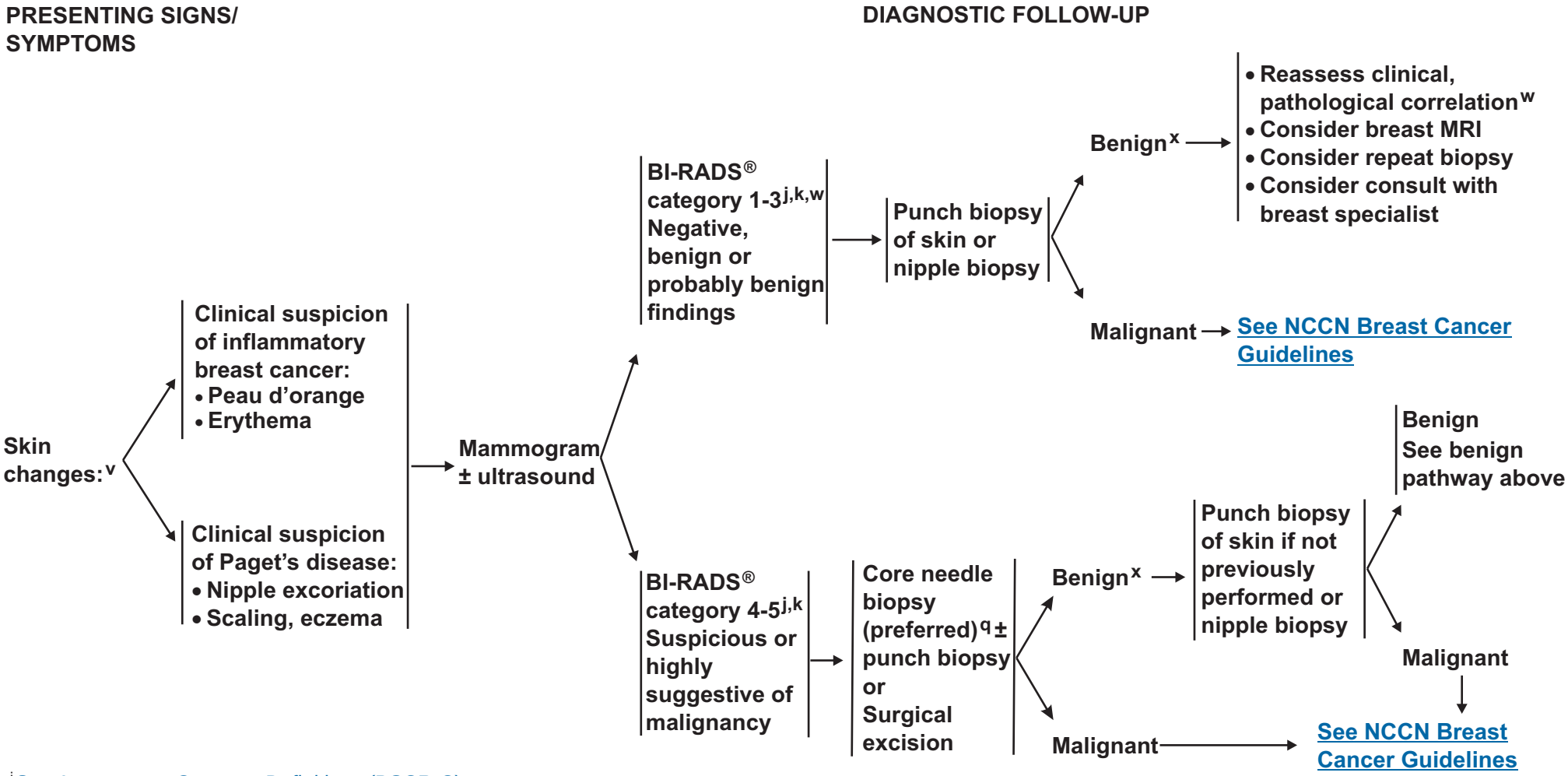
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[j] See Assessment Category Definitions (BSCR-C).

[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).

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

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

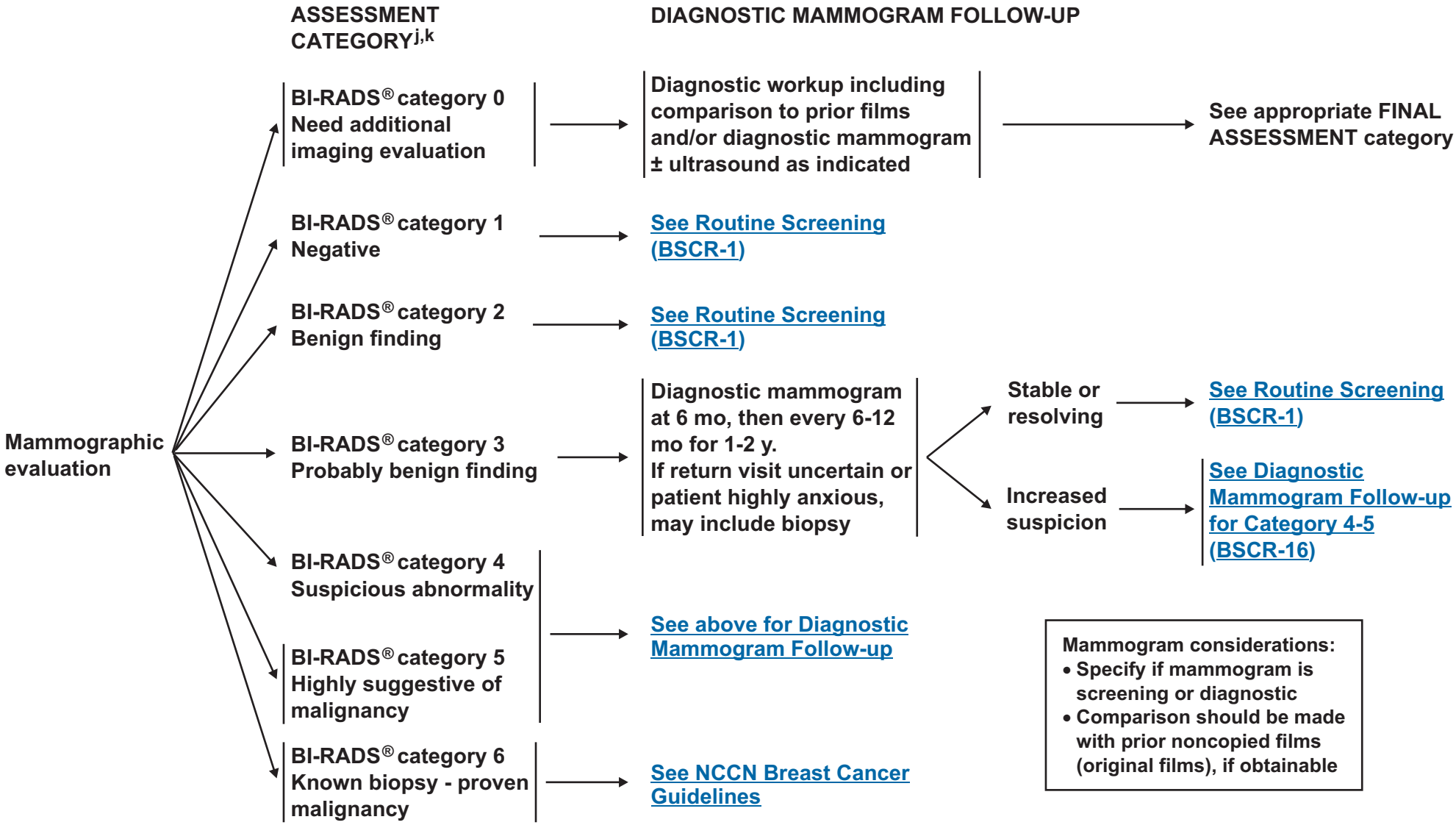
[w] If clinically of low suspicion, a short trial (7-10 days) of antibiotics for mastitis may be indicated.

[x] 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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[j] See Mammographic Assessment Category Definitions (BSCR-C).

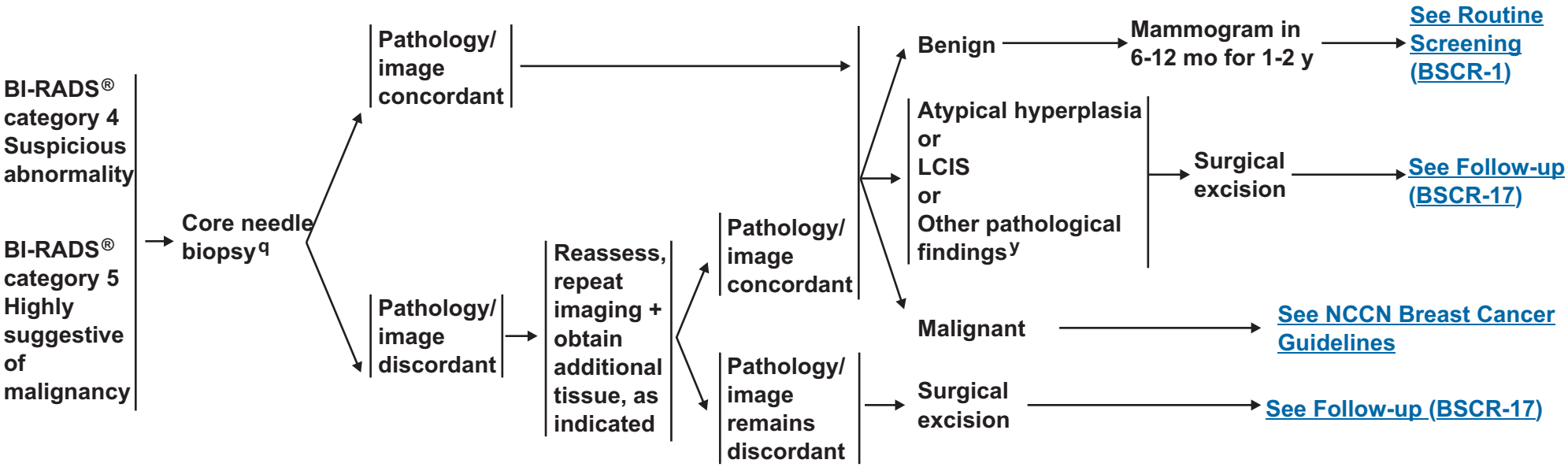
[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).

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ASSESSMENT CATEGORY[j,k] **DIAGNOSTIC MAMMOGRAM FOLLOW-UP**



[j] See Mammographic Assessment Category Definitions (BSCR-C).

[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).

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

[y] Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar or other histologies of concern to pathologist.

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FOLLOW-UP EVALUATION

Surgical excision

- **Benign** → See Routine Screening (BSCR-1)
- **Atypical hyperplasia** → See Routine Screening (BSCR-1) and NCCN Breast Cancer Risk Reduction Guidelines
- **LCIS** → See Routine Screening (BSCR-1) and NCCN Breast Cancer Risk Reduction and NCCN Breast Cancer Guidelines
- **Malignant** → See NCCN Breast Cancer Guidelines

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BREAST SCREENING CONSIDERATIONS

- Women should be counseled regarding potential benefits, risks, and limitations of breast screening.
- 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 (eg, sestamibi scan), or ductal lavage as screening procedures.
- There are several studies supporting the use of ultrasound for breast cancer screening as an adjunct to mammography for high risk women or women with dense breast tissue.[1]
- Digital mammography appears to benefit young women and women with dense breasts.[2]

RECOMMENDATIONS FOR BREAST MRI SCREENING AS AN ADJUNCT TO MAMMOGRAPHY[3,4]

Recommend Annual MRI Screening (Based on Evidence):[5]

- BRCA mutation
- First-degree relative of BRCA carrier, but untested
- Lifetime risk ~ 20–25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history

Recommend Annual MRI Screening (Based on Expert Consensus Opinion):[6]

- Radiation to chest between age 10 and 30 years
- Li-Fraumeni syndrome and first-degree relatives
- Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives

Insufficient Evidence to Recommend for or Against MRI Screening:[7]

- Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history
- Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
- Atypical ductal hyperplasia (ADH)
- Heterogeneously or extremely dense breast on mammography
- Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)

Recommend Against MRI Screening (Based on Expert Consensus Opinion):

- Women at < 15% lifetime risk

[1] 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(18):2151-63

[2] Pisano ED, Gatsonis C, Hendrick E et al for the Digital Mammographic Imaging Screening Trial (DMIST) Investigators. Diagnostic performance of digital versus film mammography for breast cancer screening. N Engl J Med 2005;353:1773-1783.

[3] 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.

[4] Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation The imaging center should have the ability to preform MRI guided needle sampling and/or wire localization of MRI Detected findings.

[5] Evidence from nonrandomized screening trials and observational studies.

[6] Based on evidence of lifetime risk for breast cancer.

[7] Payment should not be a barrier. Screening decisions should be made on a case-by-case basis, as there may be particular factors to support MRI. More data on these groups is expected to be published soon.

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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.

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ASSESSMENT CATEGORY DEFINITIONS[1,2] (continued)

BI-RADS® - MAMMOGRAPHY FINDINGS

A. Assessment Is Incomplete:

Category 0- Need Additional Imaging Evaluation and/or Prior Mammograms For Comparison:

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 to 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 such comparison is 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 here, the interpreter chooses to describe a benign finding in the mammography report. Involuting, calcified fibroadenomas, multiple secretory calcifications, 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 there is no mammographic evidence of malignancy.

Note that both Category 1 and Category 2 assessments indicate that there is no mammographic evidence of malignancy. 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.

[1] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).

[2] Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS® -- 4th Edition. *ACR Breast Imaging Reporting and Data System*, Breast Imaging Atlas; BI-RADS. Reston VA. American College of Radiology, 2003. For more information, see www.acr.org.

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BI-RADS® - MAMMOGRAPHY FINDINGS

Category 3: Probably Benign Finding - Short Interval Follow-Up Suggested:

A finding placed in this category should have less than a 2% risk of malignancy. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability.

There are several prospective clinical studies demonstrating 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, the focal asymmetry and the 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; hence it is inadvisable to render such an 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.

While 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 or longer) stability is demonstrated, there may be occasions where biopsy is done (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 probability 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 her physician can make an informed decision on the ultimate course of action.

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.

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[2] Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS® -- 4th Edition. *ACR Breast Imaging Reporting and Data System*, Breast Imaging Atlas; BI-RADS. Reston VA. American College of Radiology, 2003. For more information, see www.acr.org.

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ASSESSMENT CATEGORY DEFINITIONS[1,2] (continued)

BI-RADS® - ULTRASOUND FINDINGS

A. Assessment is Incomplete:

Category 0 - Need Additional Imaging Evaluation:

In many instances, the US examination completes the evaluation of the patient. If US is the initial study, other examinations may be indicated. An example would be the need for mammography if US were the initial study for a patient in her late 20's evaluated with US for a palpable mass that had suspicious sonographic features. Another example might be where mammography and US 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 US 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 percent risk of malignancy. Although additional multicenter data may confirm safety of follow-up rather than biopsy based on US 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.

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[2] Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS® -- 4th Edition. *ACR Breast Imaging Reporting and Data System*, Breast Imaging Atlas; BI-RADS. Reston VA. American College of Radiology, 2003. For more information, see www.acr.org.

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ASSESSMENT CATEGORY DEFINITIONS[1,2] (continued)

BI-RADS® - ULTRASOUND FINDINGS

Category 4: Suspicious Abnormality—Biopsy Should be Considered:
Lesions in this category would have an intermediate probability of cancer, ranging from 3 percent to 94 percent. 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 percent or higher risk of 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 BeTaken:
This category is reserved for lesions with biopsy proof of malignancy prior to institution of therapy, including neoadjuvant chemotherapy, surgical excision or mastectomy.

[1] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).

[2] Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS® -- 4th Edition. *ACR Breast Imaging Reporting and Data System*, Breast Imaging Atlas; BI-RADS. Reston VA. American College of Radiology, 2003. For more information, see www.acr.org.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 11/03/09

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.

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] In 2009, an estimated 194,280 cases of invasive breast cancer (192,370 women and 1,919 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] The good news is that mortality from breast cancer has dropped slightly. This decrease had been attributed, in part, to mammographic screening.[3]

These practice guidelines developed by the National Comprehensive Cancer Network (NCCN) Breast Cancer Screening and Diagnosis Panel are designed to facilitate clinical decision-making. The general public and health care providers need to be aware that mammography or any other imaging modality is not a stand-alone procedure. Neither the current technology of mammography or other imaging tests nor the subsequent interpretation of such tests is foolproof. Clinical judgment is needed to ensure appropriate management. The patient's concerns and physical findings must be considered along with imaging results 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 are dependent on patient age and other factors such as medical and family history, and can include breast awareness (ie, patient familiarity with her breasts), physical examination, risk assessment, screening mammography, and, in selected cases, screening magnetic resonance imaging (MRI).

A diagnostic breast evaluation differs from breast screening in that it is used to evaluate an existing problem (eg, dominant mass, discharge from the nipple). Although there is preliminary evidence that breast ultrasonography can be a useful screening adjunct to mammography in the evaluation of high-risk women with dense breasts,[4] its use as a screening test is not recommended at this time. These guidelines include ultrasonography only in the diagnostic work-up of selected women on the basis of specific positive findings. Current evidence does not support the routine use of breast scintigraphy (eg, sestamibi scan) or ductal lavage as screening procedures.

Discussion update in progress

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History and physical examination

The starting point of these guidelines for screening and evaluating breast abnormalities is a complete medical history followed by the clinical breast examination (CBE). Inspection of the breasts should be performed with the patient in upright and supine positions. Positioning may be done so as to elicit any subtle shape or contour changes in the breast. The CBE should involve palpation of the entire breast with the patient in the upright and supine position, and include the axillary region as well as all nodal basins that involve the breasts (ie, axillary, supraclavicular, and internal mammary nodes).[5] Symptoms or positive findings on physical exam 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] This does not need to be done in any specific formalized education program. Data from a large randomized trial of breast self examination (BSE) screening has 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 were observed and the cumulative breast cancer mortality rates were not significantly different between the two 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 since this may facilitate detection of interval cancers between routine screenings.

Risk Assessment

If the physical examination is negative in an asymptomatic woman, the next decision point is based on risk stratification. Women can be stratified into two basic categories for the purpose of screening recommendations: those at normal risk and those at increased risk. The increased risk category consists of six groups: (1) women who have previously received therapeutic thoracic irradiation or mantle irradiation; (2) women 35 years or older with a 5-year risk of invasive breast carcinoma ≥1.7% (3) women with a lifetime risk of breast cancer > 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 ages 20 and 39 years, a clinical breast examination every 1 to 3 years is recommended, with breast awareness encouraged. For women aged 40 years and older, annual clinical breast examination and screening mammography are recommended, with breast awareness 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. The recommendation that women begin annual mammographic screening at age 40 years is based on a consensus statement from the American Cancer Society (ACS) and National Cancer Institute in 1997 and is supported by the ACS guidelines for breast cancer screening published in 2003,[11] as well as 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

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annually or every other year remains controversial. The NCCN Breast Cancer Screening and Diagnosis Guidelines Panel elected to follow the ACS guidelines of yearly mammography since mammograms can often detect a lesion 2 years before the lesion is discovered by clinical breast examination. To reduce mortality from breast cancer, yearly screening may be more beneficial.

There are limited data regarding screening of elderly women because most clinical trials for breast screening have used a cutoff age of 65 or 70 years.[16-18] With the high incidence of breast cancer in the elderly population, the same screening guidelines used for women who are age 40 or older are recommended. Clinicians should always use judgment when applying screening guidelines. If a patient has severe comorbid conditions limiting her life expectancy and no intervention would occur based on the screening findings, then the patient should not undergo screening.[11]

Women at Increased Risk

Women Who Have Received Prior Thoracic Irradiation: Results from a number of studies have demonstrated that women who received thoracic irradiation in their second or third decade of life have a substantially increased risk of developing breast cancer by age 40 years.[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 of breast cancer in the general population.[19, 20] In that study, the relative risk of female breast cancer according to follow-up interval was: 0 at 5-9 years; 71.3 at 10-14 years; 90.8 at 15-19 years; 50.9 at 20-24 years; 41.2 at 25-29 years; and 24.5 at > 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 of 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 there is a concern that the cumulative radiation exposure from mammography in a young woman may itself pose a risk for cancer, it is felt that the benefit of early detection of breast cancer in this high-risk group would outweigh the 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 received prior thoracic irradiation, annual mammograms and a clinical breast examination 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 age 25 years, whichever occurs last.[27] The consensus of the panel is that an annual breast MRI should be considered as part of the screening evaluation of women in this group although data are lacking regarding the benefits and risks of adding breast MRI to the screening program of these women. For women younger than 25 years, an annual clinical breast examination 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 age 35 and older, a risk assessment tool is available to identify those who are at increased risk. The National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Biostatistics Center has developed a computerized interactive risk-assessment tool based on the modified Gail model[28-32] which provides risk projections on the basis of a number of risk factors for breast cancer. The modified Gail model assesses the risk of invasive breast cancer as a function of age, menarche, age at first live birth or

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nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race. The model calculates and prints 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify women who are 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 for 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.

Increased risk of developing breast cancer is defined by the modified Gail model for women ≥35 years of age 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 U.S. The 5-year predicted risk of breast cancer required to enter the NSABP Breast Cancer Prevention Trial of tamoxifen versus placebo, as well as the Study of Tamoxifen and Raloxifene (STAR) trial, was 1.7% or greater. As previously mentioned, the modified Gail model risk assessment tool also provides an estimate of a woman's lifetime risk of breast cancer. However, this estimate is based on the Gail model risk criteria which differ from criteria used in risk assessment models predominantly based on family history (see below); lifetime breast cancer risk as determined by the Gail model is not used in these guidelines to determine whether a woman is at increased risk of breast cancer.

For a woman aged 35 years or older with a 5-year risk ≥1.7%, clinical breast examinations 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.

Women with a Lifetime Risk of Breast Cancer >20% based on models largely dependent on family history:

A lifetime risk of breast cancer of >20% as assessed by 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, as well as to direct screening strategies. In a recent update to the ACS guidelines on breast screening which incorporates MRI,[34] a woman was identified as being at high risk of breast cancer if her lifetime risk of breast cancer was approximately 20%-25% or greater based on models that rely mainly on family history. These models include BRCAPRO,[35] BOADICEA,[36] and others.

For a woman with a >20% lifetime risk of breast cancer based on models largely dependent on family history, clinical breast examinations every 6 to 12 months and annual mammography are recommended, and breast awareness is encouraged. In addition, women in this group should be asked to consider risk reduction strategies. Annual MRI should be considered for women who have a lifetime risk of breast cancer >20% based on models that rely mainly on family history.[34]

Women with a Strong Family History or Genetic Predisposition:
Accurate family history information is needed to adequately assess a woman's breast cancer risk. Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than expected on the basis of statistics, they generally 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.

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The NCCN Genetic/Familial High-Risk Assessment Guidelines include a recommendation for referral to a cancer genetics professional for further evaluation for an individual who has either a personal history or a close family history meeting any of the following criteria:

- Early-age onset breast cancer (ie, ≤ 50 years)
- Two breast cancer primaries in a single individual or 2 or more breast cancer primaries diagnosed from the same side of the family (maternal or paternal)
- Breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual or from the same side of the family
- 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 Syndrome or leukemia/lymphoma
- Member of a family with a known mutation in a breast cancer susceptibility gene or a member of a population at risk (eg, Ashkenazi Jewish)
- Male breast cancer
- Ovarian/fallopian tube/primary peritoneal cancer

In the statement on Genetic Testing for Cancer Susceptibility from the American Society of Clinical Oncology (ASCO) updated in 2003, genetic counseling/testing is recommended when there is: (i) a personal or family history suggesting genetic cancer susceptibility (ii) the test can be adequately interpreted and (iii) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.[37] Additional genetic testing criteria are included in the NCCN Genetic/Familial High-Risk Assessment Guidelines. Genetic testing should be done only in the setting of pre-and post-test genetic counseling.

Women 25 years or older with a genetic predisposition for breast and ovarian cancer syndrome should have clinical breast exams every 6-12 months and annual mammograms; those with a strong family history or other genetic predisposition to breast cancer should start annual clinical breast examination and mammography 5-10 years prior to the youngest breast cancer case in the family. Breast awareness is encouraged. Annual breast MRI is also recommended as an adjunct to mammogram and clinical breast exam in women ≥25 years of age. This recommendation is consistent with the recent recommendations from the ACS on breast screening with MRI.[34] Women younger than age 25 years with strong family history or genetic predisposition should have an annual clinical breast exam 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 following multidisciplinary consultation in accordance with the NCCN Breast Cancer Risk Reduction Guidelines.

The risk from radiation exposure due to mammography in young women with an inherited cancer predisposition is unknown, and there is some concern 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 in breast cancer when the overall group was considered; however, a small increase in risk was seen when only those women with BRCA1 mutations were evaluated.[38] Because the lifetime risk of breast cancer in BRCA1 or BRCA2 mutation carriers is estimated to be 3-6 fold greater (40% to 80% range)[39] than in the general population, the benefit of screening may justify the radiation exposure.

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Women with Lobular Carcinoma in Situ (LCIS) or Atypical Hyperplasia*:* Women with benign proliferative disease (eg, atypical hyperplasia) are at increased risk of breast cancer.[40,41] In addition, a diagnosis of LCIS is associated with estimated risks of 10%-20% for the subsequent development of cancer in either breast over the next 15 years, although it is not in itself considered to be a site of origin for cancer.[42,43] For women with LCIS or atypical hyperplasia, an annual mammogram and clinical breast examination every 6 to 12 months are recommended. In addition, the panel also recommends consideration of MRI annually for women with LCIS. 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.

Women with Prior History of Breast Cancer: These women should be treated according to the surveillance and follow-up section of the NCCN Breast Cancer Guidelines.

Mammographic Evaluation

A screening mammogram typically involves 2 x-ray images of each breast (ie, one taken from the top [craniocaudal] of the breast and the other from the side [mediolateral oblique]). Randomized clinical trials have demonstrated that screening mammography lowers the rate of death from breast cancer,[3,44] with a reported overall sensitivity of about 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 to have dense breasts.[47] Other reasons for the low sensitivity of mammography in women with BRCA mutation carriers include an increased likelihood of developing tumors with more benign mammographic characteristics (eg, 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 two 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 two procedures.[53,54] However, digital mammography was significantly more accurate in younger women with dense breasts, and there was a nonsignificant trend 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 two procedures include possible differences in recall rates, and cost and availability issues.

Mammographic results are mandated to be reported using Final Assessment Categories (Breast Imaging Reporting and Data System (BI-RADS®) categories developed by the American College of Radiology.[Mammography Quality Standards Act, 1997[55]] The purpose of the Final Assessment Category definitions is to create a uniform system of reporting mammography results with a recommendation associated with each category. The fourth edition of BI-RADS® is adopted in these guidelines. In this edition, substantive changes have been incorporated and category 6 has been added.[56] BI-RADS® assessment categories apply to an individual imaging method if only one type of imaging is done (eg, mammography), but if multiple imaging

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modalities are used (e.g. additional ultrasonography and MRI), the BI-RADS® categories represent the cumulative findings of the examinations that were performed. Therefore, the overall BI-RADS® assessment category can change depending on subsequent imaging findings (ie, the BI-RADS® assessment category given following a mammographic study may increase, decrease, or remain the same upon diagnostic ultrasonography or MRI). 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 there are no masses, architectural distortion or suspicious calcification.
- ***Category 2 - Benign Finding(s)****:* This is also a negative mammogram, but there may be an actual finding 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 there is no mammographic evidence of malignancy.
- ***Category 3 - Probably Benign Finding(s) - 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 of malignancy is estimated to be less than 2%.
- ***Category 4 - Suspicious Abnormality –Biopsy Should Be Considered:*** These lesions fall into the category of having a wide range of probability of being malignant but are not obviously malignant mammographically. The risk of 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, etc.
- ***Category 6 - Known Biopsy - Proven Malignancy-Appropriate Action Should Be Taken****:* This category has been added in this edition for breast lesions identified on the imaging study with biopsy proof of malignancy but prior to definitive therapies.

There is also another BI-RADS® category - ***Category 0 –*** which represents an incomplete assessment. Category 0 is defined as ***Needs Additional Imaging Evaluation and/or Prior Mammograms For Comparison****.* It has identified a finding requiring additional evaluation. This category is almost always used in the context of a screening situation. A recommendation for additional imaging evaluation may include, but is not limited to 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.

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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. When screening mammography reveals 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, after a comparison of films, there is still a questionable area that is not clearly benign, then a diagnostic mammogram, with or without ultrasonography should be performed.

For follow-up of patients with mammograms categorized as BI-RADS® 0 and 3 or higher.

Magnetic Resonance Imaging (MRI) Evaluation

The sensitivity of breast MRI at detecting breast cancer is higher than the sensitivity of mammography, although the specificity of the former procedure 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 of breast cancer, benefits of screening MRI for women with a genetic predisposition for breast cancer have been demonstrated in a number of studies,[47,60-66] and the ACS has published guidelines recommending use of breast MRI as an adjunct to screening mammography in certain populations of women at high risk of breast cancer.[34] Nevertheless, a high false-positive rate for screening MRI was identified in a number of these studies. 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 of asymptomatic women with atypical hyperplasia or LCIS enrolled in a high-risk screening program has evaluated use of MRI in this population.[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, breast cancer was detected by MRI in 4% of patients 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 than those who were evaluated by mammography alone. However, only one woman with cancer detected by MRI following a negative mammography finding had 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 clinical breast examination for women with a genetic predisposition/strong family history for breast cancer who are aged 25 years or older. Consideration of an annual MRI is recommended in women who have a >20% lifetime risk of breast cancer as defined by models largely based on family history as described in the ACS Guidelines.[34] Consideration of an annual MRI as an adjunct to screening mammogram and clinical breast examination is also recommended for women diagnosed with LCIS, and those ≥25 years of age with a history of exposure to thoracic irradiation beginning at age 40 years or 8-10 years after radiation exposure.

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Criteria for the performance/interpretation of 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 American College of Radiology has also published guidelines for the performance of contrast-enhanced MRI of the breast.

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 X-ray 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 views or magnifications 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 aged < 30 years presenting with a dominant mass or asymmetric thickening/nodularity and sections on (Dominant Mass in Breast and Asymmetric Thickening or Nodularity).

Breast ultrasonography is recommended for women ≥ 30 years of age with a dominant mass and a diagnostic mammogram assessed as BI-RADS® 1-3, and as an adjunct to diagnostic mammography for women in this age group with a finding of asymmetric thickening/nodularity. In addition, breast ultrasonography should be considered as an adjunct to mammography for those of all ages with skin changes consistent with serious breast disease or with spontaneous nipple discharge in the absence of a palpable mass, and as a possible option for women with a BI-RADS® category 0 screening mammographic assessment. 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 also more detailed recommendations, below.) Ultrasound-guided biopsy is included in the guidelines for women with a complex cyst or a persistent mass following cyst aspiration.

Recommendations for interpretation of ultrasonography

After the ultrasonographic evaluation is completed, the results are classified according to one of the following BI-RADS® categories.[73]

- ***Category 1 - Negative****:* This is a negative ultrasound. No abnormalities are detected.
- ***Category 2 - Benign Finding(s)****:* This is also a negative ultrasound, but there may be an actual finding that is benign. Included in this category are simple cysts and breast implants.
- ***Category 3 - Probably Benign Finding(s) - Short-Interval Follow-up Suggested:*** This is a ultrasound that is usually benign. Close monitoring of the finding is recommended to ensure its stability. The risk of malignancy is estimated to be less than 2%. Fibroadenomas and nonpalpable complicated cysts and

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clustered microcysts might be placed in this category for short-interval follow-up.

- ***Category 4 - Suspicious Abnormality –Biopsy Should Be Considered:*** These lesions fall into the category of having a wide range of probability of being malignant but are not obviously malignant ultrasonographically. The risk of 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 has been added in this edition for breast lesions identified on the imaging study with biopsy proof of malignancy but prior to definitive therapies.

There is also another BI-RADS® category - ***Category 0 –*** which represents an incomplete assessment. Category 0 is defined as ***Needs Additional Imaging Evaluation****.* It has identified a finding requiring additional evaluation. If ultrasound is the initial study, mammography might be indicated, or if mammography and ultrasound findings are nonspecific, MRI might be appropriate.

Breast cysts

Breast cysts are either classified as simple or non-simple cysts, with the latter class being subdivided into complicated cysts and complex cysts. A cyst meeting all criteria of a simple cyst is considered to be 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 with routine screening.

Cytologic examination is recommended if bloody fluid is obtained. The risk of 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 6-12 months for 1-2 years to assess stability. The option of aspiration may be more strongly considered in a patient likely to be lost to follow-up. Complicated cysts which increase in size 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. 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 6-12 months for 1-2 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. Complex cysts have a relatively high risk of malignancy (eg, 14% and 23% in 2 studies).[74,76,79,80] Hence, these cysts should be evaluated by tissue biopsy.

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

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recommended. There is evidence that certain MR imaging 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 (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,[82,83] 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.[84,85]

Core needle biopsy

A core needle biopsy (CNB), also called percutaneous core breast biopsy, is an automated procedure that typically involves use of a large-bore cutting needle to remove three to five solid cores of tissue.[82,83] It can be performed under imaging guidance (eg, stereotactic [mammographic] or ultrasound). Advantages of breast CNB include increased accuracy over FNA when the procedure is performed in situations where no mass is palpable and an ability to obtain tissue samples of sufficient size so as to eliminate the need for a follow-up biopsy to confirm malignancy.[86] 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.[87,88] 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 of a breast cancer.[89] With a few exceptions, CNB is preferred in the guidelines over surgical excision when tissue biopsy is required (see section on Excisional biopsy, below).

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 prior to 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.[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 core needle biopsy and requires needle localization when lesions are not palpable, there are situations where larger tissue samples may be needed. In most cases, excisional biopsy is recommended following diagnosis by core biopsy of an indeterminate lesion, atypical hyperplasia, LCIS, or a benign and image discordant lesion. Other histologies that may require additional tissue include mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars or other histologies of concern to the pathologist.[77,83,84,90] Support for this recommendation includes results of studies demonstrating an underestimation of cancer when atypical hyperplasia and LCIS are diagnosed by CNB.[91-96] However, there are situations (eg, select cases of LCIS, ALH, papillomas, fibroepithelial lesions, radial scars) where close observation may be substituted for excisional biopsy in select patients.[83,90,97-99]

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Duct excision with or without prior ductography

Nipple discharge is common, and, in many cases, unrelated to breast pathology.[100,101] 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.[100] Suspicion of underlying pathology (eg, papilloma, ductal ectasia) is raised when nipple discharge is persistent and reproducible on examination, spontaneous, unilateral, 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. A tissue biopsy should be performed for women with an overall BI-RADS® assessment category 4-5. In the event a malignancy is present, the woman should be managed according to the NCCN Breast Cancer Guidelines. Those women with an overall BI-RADS® assessment category 1-3 or a benign or indeterminate result following tissue biopsy should undergo duct excision. Ductography is an option prior to duct excision. Conventional ductography is an invasive procedure that involves retrograde filling of the milk duct with contrast material followed by mammographic evaluation to help characterize lesion(s) responsible for symptoms prior to duct excision.[102] More recently, MR ductography, a noninvasive alternative which does not use either radiation or contrast agents, has been described, although it has not yet been endorsed by the NCCN panel.[103,104]

Recommendations for work-up of patient with mammogram BI-RADS® assessment categories 0, 3, 4, 5 and 6.

For BI-RADS® category 0 (need additional imaging evaluation), the diagnostic work-up includes comparison to prior films and/or diagnostic mammogram with or without ultrasound scan.

For BI-RADS® category 3 (probably benign), diagnostic mammograms at 6 months, 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, either annually with bilateral mammograms or every 6 months for the breast in question, for a total of 1-2 years.

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 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 using core needle biopsy (preferred) or needle localization excisional biopsy with specimen radiograph is necessary. When a needle biopsy is used (aspiration or core needle biopsy), concordance between the pathology report and the imaging finding must be obtained.[56,105] For example, a negative fine-needle aspiration associated with a spiculated category 5 mass is discordant and clearly would not be an acceptable diagnosis.

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When the pathology and the imaging are discordant, the breast imaging should be repeated and additional tissue sampled or excised; surgical excision is recommended in pathology/image remain discordant. Women with a benign result exhibiting pathology/image concordance should be followed with mammography every 6-12 months for 1-2 years before returning to routine screening. Those with a finding of atypical hyperplasia, LCIS or other potentially pathological conditions should undergo surgical excision and be followed as described on.

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

Recommendations for work-up of patients with positive findings on physical exam

Dominant Mass in Breast

A mass is a discrete lesion that can be readily identified during a clinical breast examination. The guidelines separate the evaluation of the mass into two age groups: women aged 30 years or older and women under 30 years of age.

Women aged 30 years or older*:* The main difference in the guidelines for evaluating a dominant mass in women age 30 or older compared with younger women is the increased degree of suspicion of breast cancer. 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 six BI-RADS® categories.

For BI-RADS® categories 1, 2, and 3, the next step is to obtain an ultrasound and the findings are discussed below. For BI-RADS® categories 4 and 5, assessment of the geographic correlation between clinical and imaging findings is indicated. If there is a lack of correlation, further evaluation is 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 core needle biopsy (preferred), or needle localization excisional biopsy with specimen radiograph is necessary. When a core needle biopsy is utilized, concordance between the pathology report and imaging finding must be obtained as described in the Mammographic Evaluation section of this manuscript.

If ultrasound indicates a solid lesion that is suspicious or highly suggestive of malignancy, (ie, BI-RADS® categories 4-5), tissue biopsy should be obtained using core needle biopsy (preferred) or surgical excision. 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 time intervals if clinically indicated. If the solid lesion increases in size, it should be surgically excised. Routine breast screening is followed for stable lesions. If the findings are indeterminate, atypical hyperplasia, or benign and image discordant, or LCIS, or other (ie, 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 (ie, some patients with atypical hyperplasia, LCIS, fibroepithelial lesions, radial scars, etc.) may be suitable for monitoring in lieu of surgical excision. Routine breast screening is followed 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 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.

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If the solid lesion on ultrasound is probably benign (ie, BI-RADS® 3), several options are available: surgical excision, core needle biopsy (preferred), or observation. 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 1-2 years to assess stability. 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 and the patient should be counseled to maintain regular breast screening. Malignant lesions are treated according to the NCCN Breast Cancer Guidelines. If the option of core needle biopsy 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. If the lesion is indeterminate or atypical hyperplasia, LCIS, or benign and image discordant, or other (ie, 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 (ie, some patients with atypical hyperplasia, LCIS, fibroepithelial lesions, radial scars, etc.) may be suitable for monitoring in lieu of surgical excision.

If the ultrasound evaluation reveals the mass to be consistent with an asymptomatic simple cyst (ie, BI-RADS® 2), it is important that there is concordance between the clinical breast examination and the ultrasound results before routine screening is recommended. Therapeutic aspiration of such a simple cyst can be performed if persistent clinical symptoms are present. If the cyst is classified as a complicated (BI-RADS® 3) non-simple cyst, options include aspiration or short-term follow-up with physical examination and ultrasound with or without mammography every 6-12 months for 1-2 years to assess stability. A tissue biopsy should be performed for a complicated cyst which increases in size on follow-up. If blood-free fluid is obtained on aspiration and the mass resolves, the patient should be monitored for any change. If the physical examination remains negative, the patient should return to routine screening. If the mass recurs after aspiration, or the non-simple cyst is classified as complex on ultrasound (ie, BI-RADS® 4), then ultrasound with image-guided biopsy or surgical excision is warranted. If the ultrasound with image-guided biopsy findings are benign and image concordant, physical exam with or without ultrasound or mammogram every 6-12 months for 1-2 years is recommended. If the mass increases in size, tissue sampling should be repeated, with a routine breast screening recommended if the mass remains stable. If the ultrasound and image guided biopsy findings are interpreted as benign and image discordant or indeterminate or atypical hyperplasia or LCIS or other (ie, 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 (ie, some patients with atypical hyperplasia, LCIS, fibroepithelial lesions, radial scars, etc.) may be suitable for monitoring in lieu of surgical excision. If the mass has been surgically excised and proven to be benign, the patient undergoes routine screening. 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. Malignant findings either on ultrasound with image guided biopsy or surgical excision should be treated according to the NCCN Breast Cancer Guidelines.

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

***Women under 30 years of age**:* The preferred option for initial evaluation of a dominant mass is to proceed directly to ultrasound. From this point, the decision tree for women under 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 degree of suspicion in women who are under the age of 30 is low, observation of the mass for one or two menstrual cycles is also an option in cases with low clinical suspicion. If observation is elected and the mass resolves after one or two menstrual cycles, the patient may return to routine screening. If the mass persists, ultrasound should be performed. Needle sampling prior to imaging is not recommended.

Nipple Discharge without a Palpable Mass

In patients with a nipple discharge but no palpable mass, an evaluation of the characteristics of the nipple discharge is the first step. If the nipple discharge is bilateral and milky, then pregnancy or an endocrine etiology 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 non-spontaneous, multiple-duct discharge in women under age 40 is observation, coupled with education of 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 and a further workup based upon the BI-RADS® category along with 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 serosanguinous. A guaiac test and cytology of the nipple discharge is not recommended, as 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 category 1, 2, or 3, a ductogram is optional to guide the duct excision. Ductal excision is indicated for diagnosis of an abnormal nipple discharge, even if the ductogram is negative. However, the ductogram is useful to exclude multiple lesions and to localize the lesions prior to surgery. For an overall BI-RADS® assessment category 4 or 5, a tissue biopsy should be obtained. If the findings are benign or indeterminate, 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 Breast Cancer Guidelines.

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. 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. If the patient is under the age of 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 fairly low in yield because of the density of the breast and low risk of breast cancer. In a

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

Skin Changes

Any type of unusual skin changes around the breast may represent serious disease and needs evaluation. Inflammatory breast cancer (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%-6% of breast cancer cases in the U.S. 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.[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]

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 on the basis of the imaging findings. If the breast imaging results are normal, further workup is still needed.

Punch biopsy of skin or nipple biopsy should be performed following imaging findings consistent with an overall BI-RADS® assessment category 1-3. Antibiotics may or may not be given, depending on the clinical scenario but should not delay diagnostic evaluation. If biopsy results are benign, clinical and pathological 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 Breast Cancer Guidelines.

A tissue biopsy should be performed if imaging findings are consistent of an overall BI-RADS® assessment category 4-5. Core needle biopsy 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. 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 above.

Summary

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

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. Incorporating the patient into the

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health care team's decision-making empowers the patient to determine the level of breast cancer risk that is personally acceptable in the screening/follow-up settings.

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Table 1: Breast Cysts - Types and Definitions

Simple cyst	Anechoic (cystic), well circumscribed, round or oval with well-defined imperceptible wall and posterior enhancement.
Non-simple cyst	Has 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.

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