National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Breast Cancer Screening and Diagnosis

Version 1.2021 — May 6, 2021

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# NCCN Guidelines Version 1.2021
# Breast Cancer Screening and Diagnosis

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***Therese B. Bevers, MD/Chair Þ**
The University of Texas
MD Anderson Cancer Center

***Mark Helvie, MD/Vice-Chair ф Þ**
University of Michigan
Rogel Cancer Center

**Ermelinda Bonaccio, MD ф**
Roswell Park Comprehensive Cancer Center

**Melissa Camp, MD ¶**
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

**Sona Chikarmane, MD ф**
Dana-Farber/Brigham and
Women's Cancer Center

**Emily F. Conant, MD ф**
Abramson Cancer Center
at the University of Pennsylvania

**Maggie DiNome, MD ¶**
UCLA Jonsson Comprehensive Cancer Center

**Mohammad Eghtedari, MD, PhD ф**
UC San Diego Moores Cancer Center

**William B. Farrar, MD ¶**
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

**Meghan R. Flanagan, MD, MPH ¶**
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

**NCCN**
**Mary Anne Bergman**
**Giby V. George, MD**

**Randall E. Harris, MD, PhD Þ ≠**
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

**Linda Hodgkiss, MD ф**
St. Jude Children's Research Hospital/
The University of Tennessee Health
Science Center

**Tamarya L. Hoyt, MD ф**
Vanderbilt-Ingram Cancer Center

**Maxine S. Jochelson, MD ф**
Memorial Sloan Kettering Cancer Center

**Seema Khan, MD ¶**
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

**Constance D. Lehman, MD, PhD ф**
Massachusetts General Hospital Cancer Center

**Rachael B. Lancaster, MD ¶**
O'Neal Comprehensive Cancer Center at UAB

**Caitlin Mauer, MA, MS, CGC †**
UT Southwestern Simmons
Comprehensive Cancer Center

**Jessica Maxwell, MD, MS ¶**
Fred & Pamela Buffett Cancer Center

**Bethany L. Niell, MD, PhD ф**
Moffitt Cancer Center

**Bhavika K. Patel, MD ф**
Mayo Clinic Cancer Center

**Mark Pearlman, MD Ω ¶**
University of Michigan Rogel Cancer Center

**Liane Philpotts, MD ф**
Yale Cancer Center/Smilow Cancer Hospital

**Donna Plecha, MD ф**
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer
Center and Cleveland Clinic Taussig
Cancer Institute

**Jennifer K. Plichta, MD, MS ¶**
Duke Cancer Institute

**Mary Lou Smith, JD, MBA ¥**
Research Advocacy Network

**Roberta M. Strigel, MD, MS ф**
University of Wisconsin
Carbone Cancer Center

**Catherine Tuite, MD ф**
Fox Chase Cancer Center

**Lusine Tumyan, MD ф**
City of Hope National Medical Center

**Nicole S. Winkler, MD ф**
Huntsman Cancer Institute
at the University of Utah

**NCCN Guidelines Panel Disclosures**

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ф Diagnostic/Interventional radiology
Ω Gynecologic oncology/ Gynecology
Þ Internist/Internal medicine, including family practice, preventive management
† Medical oncology
≠ Pathology
¥ Patient advocacy
¶ Surgery/Surgical oncology
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National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2021
# Breast Cancer Screening and Diagnosis





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

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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# NCCN Guidelines Version 1.2021
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**Updates in Version 1.2021 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 1.2020 include:**

**General:**

- **"Women" changed to "Individuals" *and* "Men" *(sex assigned at birth)***

**BSCR-1**

**Average Risk:**

- **Deleted: <15% lifetime risk.**

**Increased Risk:**

- **~~Women who have a~~ Lifetime risk ≥20% as defined by models that are largely dependent on family history (Also for BSCR-2).**
- **~~Patients who receive~~ Thoracic RT *between the ages of 10 and 30 y* ~~< 30 y (eg, mantle irradiation)~~**
- **~~Women with a history of~~ Lobular neoplasia (LCIS/ALH) or ADH and ≥20% lifetime risk**
- **Modified the sub-bullet under "Pedigree suggestive of/or known genetic predisposition**
  - **Referr~~al~~ to *a* genetic counselor or *other health professional with expertise and experience in cancer genetics* ~~similarly trained provider, if not already done~~**

**Footnotes:**

- ***"For pregnant and lactating individuals*," is a new footnote directing the reader to the new pregnancy and lactation section of GLs.**
- ***"For* individuals *with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section*," is a new footnote corresponding to the header, "Screening or Symptom Category" (Also for BSCR-2).**
- **"d" modified: At minimum, medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, *and preferably a clinical breast exam even in asymptomatic individuals when feasible.* ~~as well as a clinical breast exam by a licensed provider.~~ (Also for BSCR-2)**
- **"g": *Individuals* ~~Women~~ *with a lifetime risk of 15%–20% may be considered for supplemental screening on an individual basis, depending on risk factors*, formerly corresponding to "<15% lifetime risk" now corresponds to the bullet 1 under Increased risk.**
- **"h": deleted "BOADICEA"**

**BSCR-2**

- **Clinical encounter:**
  - **Sub-bullet 2 modified: Consider referral to *a* genetic counselo~~ring,~~ or *other health professional with expertise and experience in cancer genetics* ~~similarly trained provider,~~ if not already done**
  - **Sub-bullet 3 new: *Consider referral to a breast specialist as appropriate***
- **Annual screening mammogram:**
  - **Added former sub-bullet, "consider tomosynthesis" to annual screening mammogram (Also for bottom pathway and BSCR-3)**
- **Recommend annual breast MRI:**
  - ***Consider contrast-enhanced mammography or whole breast ultrasound for those who qualify for but cannot undergo MRI* (Also for lower pathway and BSCR-3).**
- **Increased risk, bottom pathway:**
  - **1st column modified: ~~Patient who receives~~ Thoracic RT between the ages of 10 and 30 y**

**BSCR-3**

**Increased Risk:**

- **Bottom pathway, modified: ~~Women with a history of~~ Lobular neoplasia (LCIS/ALH) or ADH and ≥20% lifetime risk with the following footnote corresponding to ADH, *"Risk depends on age at diagnosis." (Also for BSCR-A (2 of 2).***
- **Consider annual breast MRI: Deleted following footnote: Except in rare circumstances of a family history of very early-onset breast cancers before the age of 30 y.**
  - **Sub-bullet 1 modified: to begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH but not prior to age 25 y ~~(based on emerging evidence)~~**

**BSCR-4**

- **Column 1 modified: For ~~additional~~ symptoms presenting in men.**

**BSCR-5**

- **Ultrasound findings, top pathway:**
  - **2nd bullet modified: ~~simple cyst~~ *Benign* BI-RADS category 2 (Also for BSCR-6).**
  - **3rd bullet: *Probably benign finding BI-RADS® category 3,* is new.**
- ***Imaging* ~~Mammogram~~ findings:**
  - ***Category 4* added to Suspicious BI-RADS® and *Category 5* added to highly suggestive BI-RADS®.**

**BSCR-6**

- ***Probably benign finding BI-RADS® category 3* is a new pathway for imaging findings with palpable mass.**

**Footnotes:**

- ***Palpation-guided tissue sampling (by FNA, core needle, or excision) when no imaging abnormality noted* is new to the page corresponding to "Core needle biopsy."**

**BSCR-7**

- **Column 1 modified: Complex ~~(~~cystic and solid~~)~~ mass**

**Footnotes:**

- **Modified: Imaging modality would depend on original imaging. Probably benign findings are *typically* monitored every 6, 12, and 24 months. ~~Some prefer to follow up at 18 months as well~~. (Also for BSCR-9, BSCR-11, BSCR-14, and BSCR-20)**

Continued

**UPDATES**

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**Updates in Version 1.2021 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 1.2020 include:**

**BSCR-8**

**Footnotes:**

- **"ff" modified: If *high* suspicion ~~us or highly suggestive of~~ *for* malignancy obtain mammogram.**

**BSCR-9**

- **2nd column: *Consider* physical exam ~~every~~ *in* 3-6 mo ~~± ultrasound every 6-12 mo for 1-2 y~~ to assess for changes. (Also for BI-RADS category 1-2).**

**BSCR-10**

- **Upper pathway, Age ≥40 y, bullet 1 modified to include: *Screening***

**BSCR-12**

**Footnotes:**

- **"rr" *Ultrasound may be sufficient, unless highly suspicious. For malignancy obtain mammogram,* is new to the page corresponding to "Diagnostic mammogram + ultrasound"**

**BSCR-15**

- **Column 7 modified: If *benign* ~~no malignancy~~**

**BSCR-16**

- **Column 1, middle pathway: *Or breast thickening* has been added.**
  - ***Bottom pathway: Palpable* breast mass *not explained by gynecomastia* ~~thickening~~**

**Footnotes:**

- **Deleted, footnote: Mammogram not indicated if patient is <25 y old.**

**BSCR-17**

- **Column 3, upper pathway, modified: Physical exam *and/or* imaging ~~for~~ *at* 6 or 12 mo for 1 y to assess for changes**
- **Column 4, lower pathway, modified: Physical exam ± ultrasound and/or mammogram at 6 *mo* ~~(preferred) or 12 mo~~ for 1 y *to assess for changes*, with the following corresponding footnote: *Initiation of high-risk MRI screening may obviate the need for 6-month mammogram/ultrasound.***

**Footnotes:**

- **"iii," modified: (eg, *ADH, LCIS, ALH*,flat epithelial atypia [FEA])**
- **"kkk," moved to Pleomorphic LCIS in 1st column.**

**BSCR-20**

- **Column 1 modified: Mammographic *and/or ultrasound* evaluation**

**BSCR-A 1 of 2**

- **Bullet 1 modified: *Individuals* ~~Women~~ should undergo breast cancer risk assessment *by age 25* and be counseled regarding potential benefits, risks, and limitations of breast screening in the context of their risk stratification. Shared decision-making is encouraged based on a ~~woman's~~ *patient's* values and preferences.**
- **Bullet 4 modified: Upper age limit for *mammographic* screening is not yet established.**
- **Bullet 9 new: *Contrast-enhanced mammography is also an emerging efficacious option for higher risk breast cancer screening.***
- **Bullet 12 modified to include the following: *Breast cancer screening MRI may also increase recall and increase benign breast biopsies.***
- **Bullet 13 deleted: For diagnostic management of pregnant patients, ultrasound and age-appropriate mammogram is recommended for palpable abnormalities. MRI with gadolinium is not recommended as the potential risk of the contrast agent to fetus is unknown.**
- **Bullet 14 new: *Abbreviated MRI used to replace traditional MRI is undergoing active investigation.***

**BSCR-A 2 of 2**

- **This page has been significantly modified.**

**BSCR-C**

- ***Recommendations for Breast Cancer Screening and Evaluation During Pregnancy and Lactation* is a new section.**

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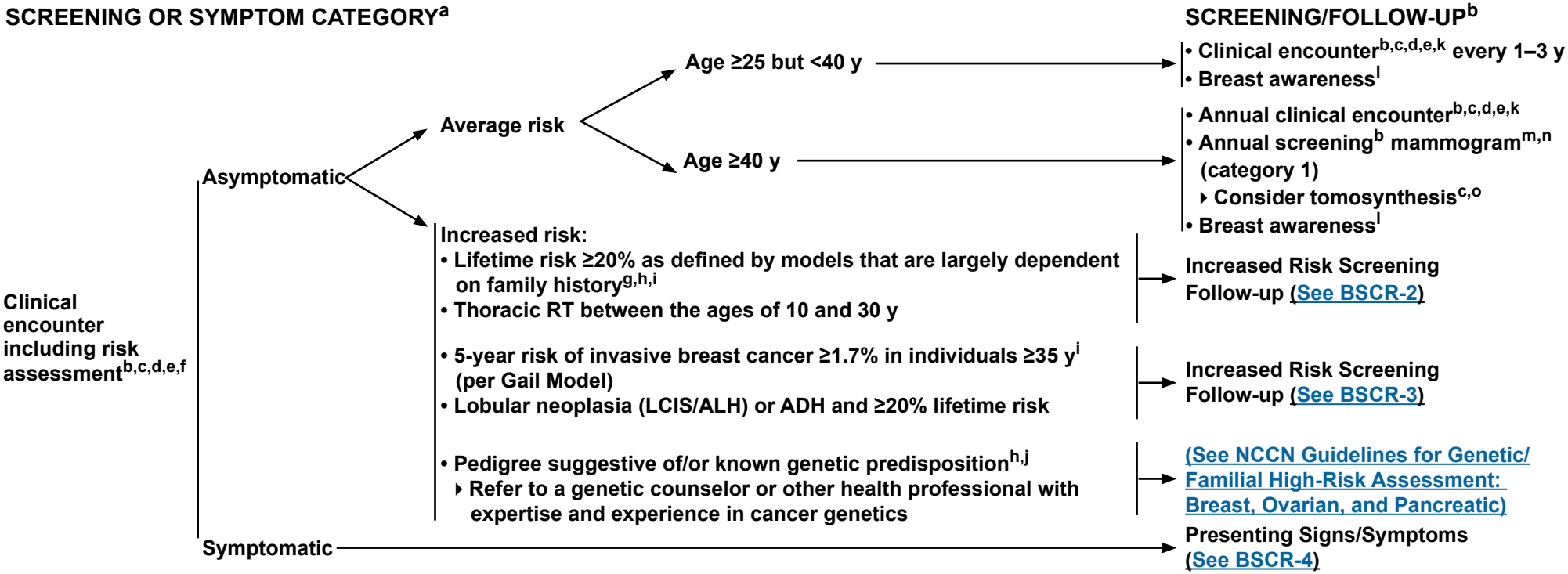


[a]For individuals with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section.

[b]See Breast Screening Considerations (BSCR-A).

[c]Medicare and insurers allow the individual direct access to scheduling for screening mammography.

[d]At minimum, medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a clinical breast exam even in asymptomatic individuals when feasible.

[e]Refer to the NCCN Guidelines for Breast Cancer Risk Reduction for a detailed qualitative and quantitative risk assessment.

[f]For pregnant and lactating individuals, see BSCR-C.

[g]Individuals with a lifetime risk of 15%–20% may be considered for supplemental screening on an individual basis, depending on risk factors.

[h]Risk models that are largely dependent on family history (eg, Claus, BRCAPRO, Tyrer-Cuzick). See NCCN Guidelines for Breast Cancer Risk Reduction.

[i]See Comparison of predictive models for risk assessment (NCCN Guidelines for Breast Cancer Risk Reduction).

[j]There is variation in recommendations for initiation of screening for different genetic syndromes. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[k]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment.

[l]Individuals should be familiar with their breasts and promptly report changes to their health care provider.

[m]See Mammographic Evaluation (BSCR-20).

[n]Shared decision-making is encouraged based on individuals' values and preferences.

[o]Tomosynthesis can decrease call back rates and improve cancer detection but has not been sufficiently studied to determine if it improves disease-specific mortality.

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**SCREENING OR SYMPTOM CATEGORY[a]** **SCREENING/FOLLOW-UP**

**Increased Risk:**

**Lifetime risk ≥20% as defined by models that are largely dependent on family history[g,h,i]** →

- Clinical encounter[b,c,d,e,k] every 6–12 mo
  - To begin when identified as being at increased risk, but not prior to age 21 y
  - Consider referral to a genetic counselor or other health professional with expertise and experience in cancer genetics, if not already done
  - Consider referral to a breast specialist as appropriate
- Annual screening[b] mammogram,[m] consider tomosynthesis[o]
  - To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 30 y or age 40 y (whichever comes first)
- Recommend annual breast MRI[p]
  - To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 25 y[q] or age 40 y (whichever comes first)
  - Consider contrast-enhanced mammography[b] or whole breast ultrasound[b] for those who qualify for but cannot undergo MRI
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[l]

**OR**

**Thoracic RT between the ages of 10 and 30 y**

**Current age <25 y** →

- Annual clinical encounter[b,c,d,e,k]
  - Beginning 8 y after RT
- Breast awareness[l]

**Current age ≥25 y** →

- Clinical encounter[b,c,d,e,k] every 6–12 mo
  - Begin 8 y after RT
- Annual screening[b] mammogram,[m] consider tomosynthesis[o]
  - Begin 8 y after RT but not prior to age 30 y
- Recommend annual breast MRI[p]
  - Begin 8 y after RT but not prior to age 25 y
  - Consider contrast-enhanced mammography[b] or whole breast ultrasound[b] for those who qualify for but cannot undergo MRI
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[l]

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## FOOTNOTES

[a]For individuals with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section.
[b]See Breast Screening Considerations (BSCR-A).
[c]Medicare and insurers allow the individual direct access to scheduling for screening mammography.
[d]At minimum, medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a clinical breast exam even in asymptomatic individuals when feasible.
[e]Refer to the NCCN Guidelines for Breast Cancer Risk Reduction for a detailed qualitative and quantitative risk assessment.
[g]Individuals with a lifetime risk of 15%–20% may be considered for supplemental screening on an individual basis, depending on risk factors.
[h]Risk models that are largely dependent on family history (eg, Claus, BRCAPRO, Tyrer-Cuzick). See NCCN Guidelines for Breast Cancer Risk Reduction.
[i]See Comparison of predictive models for risk assessment (NCCN Guidelines for Breast Cancer Risk Reduction).
[k]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment.
[l]Individuals should be familiar with their breasts and promptly report changes to their health care provider.
[m]See Mammographic Evaluation (BSCR-20).
[o]Tomosynthesis can decrease call back rates and improve cancer detection but has not been sufficiently studied to determine if it improves disease-specific mortality.
[p]High-quality breast MRI requires a dedicated breast coil, the access to biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. MRI should be correlated with other breast imaging modalities.
[q]Except in rare circumstances of a family history of very early-onset breast cancers before the age of 30 y.

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| SCREENING OR SYMPTOM CATEGORY[a] | SCREENING/FOLLOW-UP |
|---|---|
| **Increased Risk:** | |
| **5-year risk of invasive breast cancer ≥1.7% in individuals ≥35 y (per Gail Model)[i]** → | • Clinical encounter[b,c,d,e,k] every 6–12 mo<br>▸ to begin when identified as being at increased risk by Gail Model<br>• Annual screening[b] mammogram,[m] consider tomosynthesis[o]<br>▸ to begin when identified as being at increased risk by Gail Model<br>• Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)<br>• Breast awareness[l] |
| **OR** | |
| **Lobular neoplasia (LCIS/ALH) or ADH[r] and ≥20% lifetime risk** → | • Clinical encounter[b,c,d,e,k] every 6–12 mo<br>▸ To begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH<br>• Annual screening[b] mammogram,[m] consider tomosynthesis[o]<br>▸ To begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH but not prior to age 30 y<br>• Consider annual breast MRI[b,p]<br>▸ To begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH but not prior to age 25 y<br>▸ Consider contrast-enhanced mammography[b] or whole breast ultrasound[b] for those who qualify for but cannot undergo MRI<br>• Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)<br>• Breast awareness[l] |

[a] For individuals with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section.
[b] See Breast Screening Considerations (BSCR-A).
[c] Medicare and insurers allow the individual direct access to scheduling for screening mammography.
[d] At minimum medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a clinical breast exam even in asymptomatic individuals when feasible.
[e] Refer to the NCCN Guidelines for Breast Cancer Risk Reduction for a detailed qualitative and quantitative risk assessment.
[i] See Comparison of predictive models for risk assessment (NCCN Guidelines for Breast Cancer Risk Reduction).
[k] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment.
[l] Individuals should be familiar with their breasts and promptly report changes to their health care provider.
[m] See Mammographic Evaluation (BSCR-20).
[o] Tomosynthesis can decrease call back rates and improve cancer detection but has not been sufficiently studied to determine if it improves disease-specific mortality.
[p] High-quality breast MRI requires a dedicated breast coil, the access to biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. MRI should be correlated with other breast imaging modalities.
[r] Risk depends on age at diagnosis.

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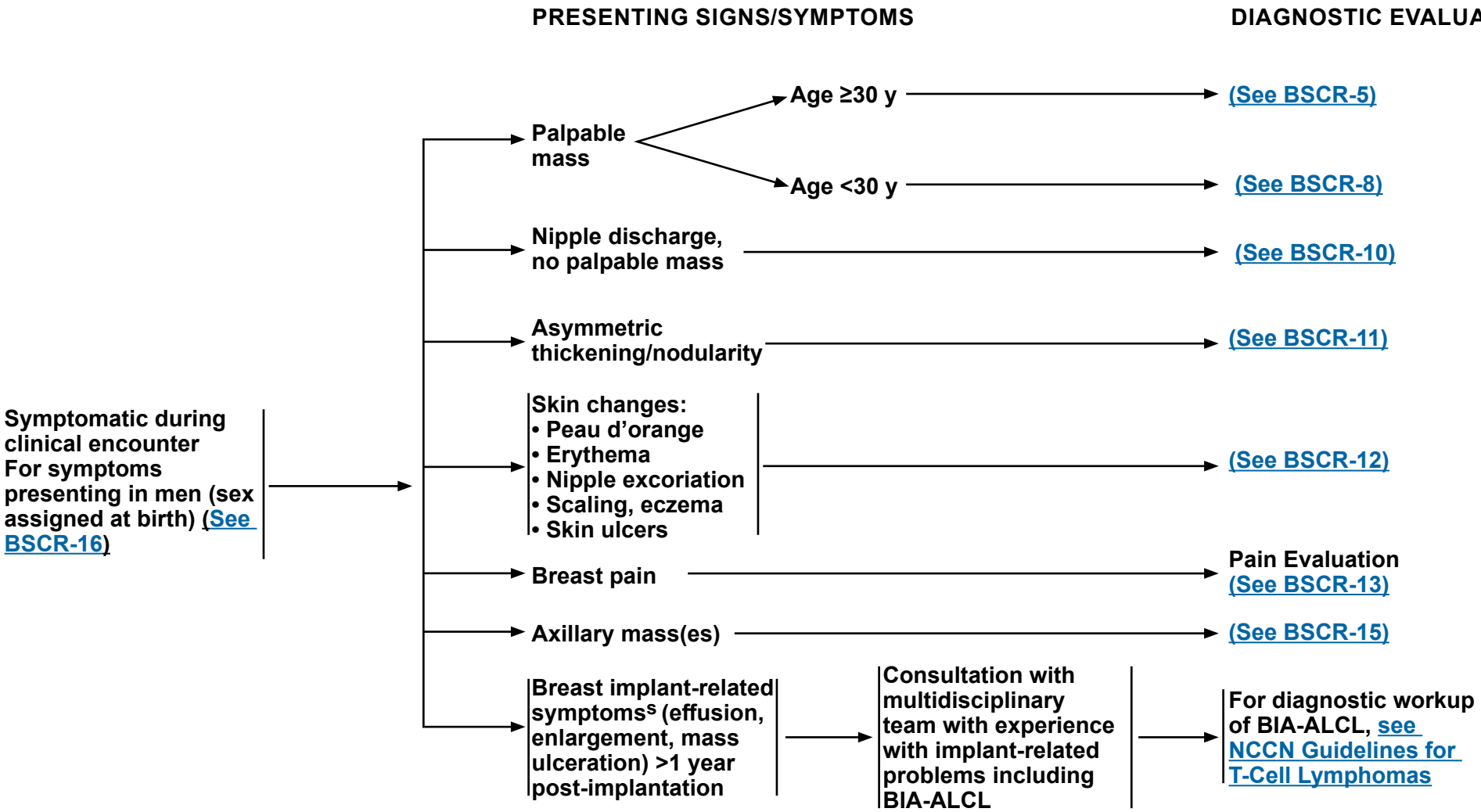


[s]Individuals with breast implants have a risk of developing breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) (average 7–9 years after implantation). Majority of cases have been seen in textured implants. Only symptomatic individuals need to be evaluated.

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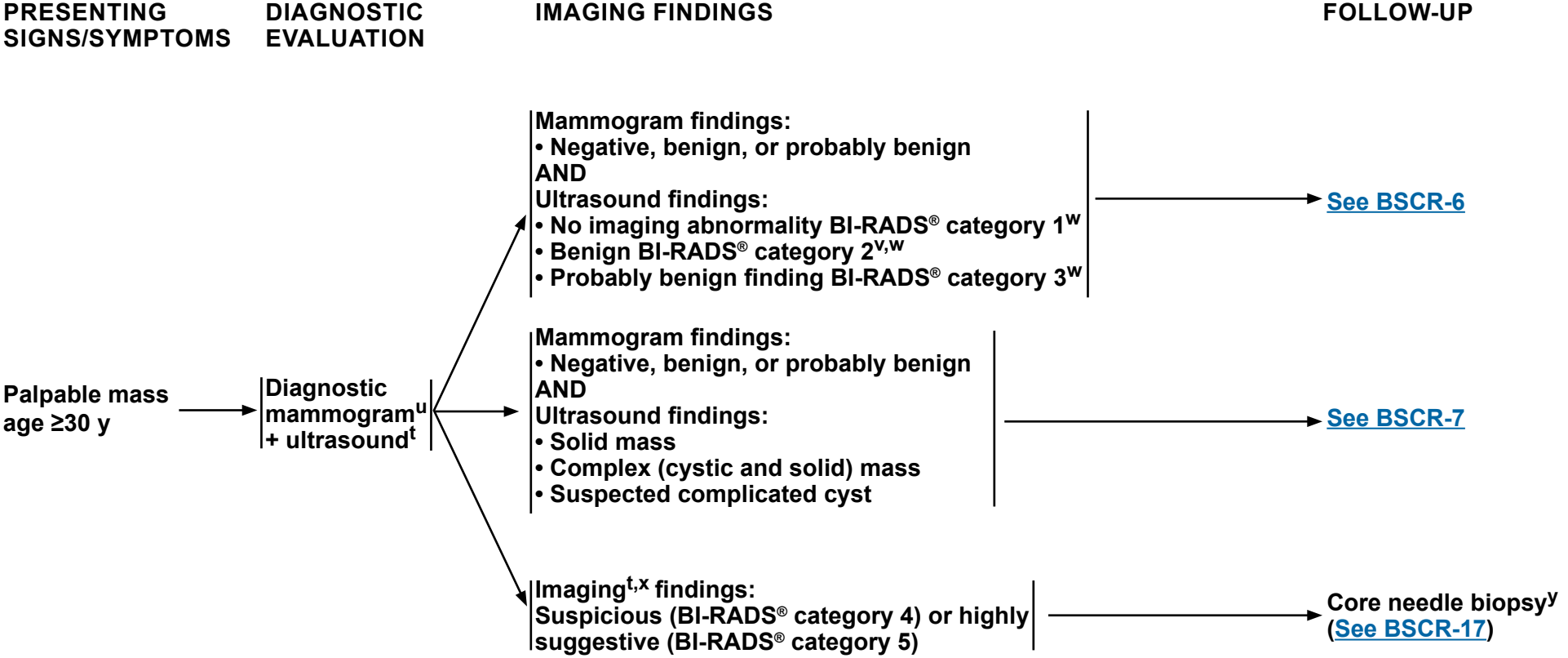


[t]There are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst in which ultrasound would be preferred as the first imaging modality and may suffice for individuals 30–39 years of age. See Discussion.
[u]Ultrasound is not necessary for a palpable finding with a definitively benign finding (eg, calcified fat necrosis) on mammogram.
[v]Concordance is needed between clinical exam and imaging results. Consider therapeutic aspiration for persistent clinical symptoms.
[w]See Assessment Category Definitions (BSCR-B).
[x]Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to mammogram findings: negative, benign, or probably benign for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.
[y]Core needle biopsy preferred; in some circumstances needle aspiration may be sufficient.

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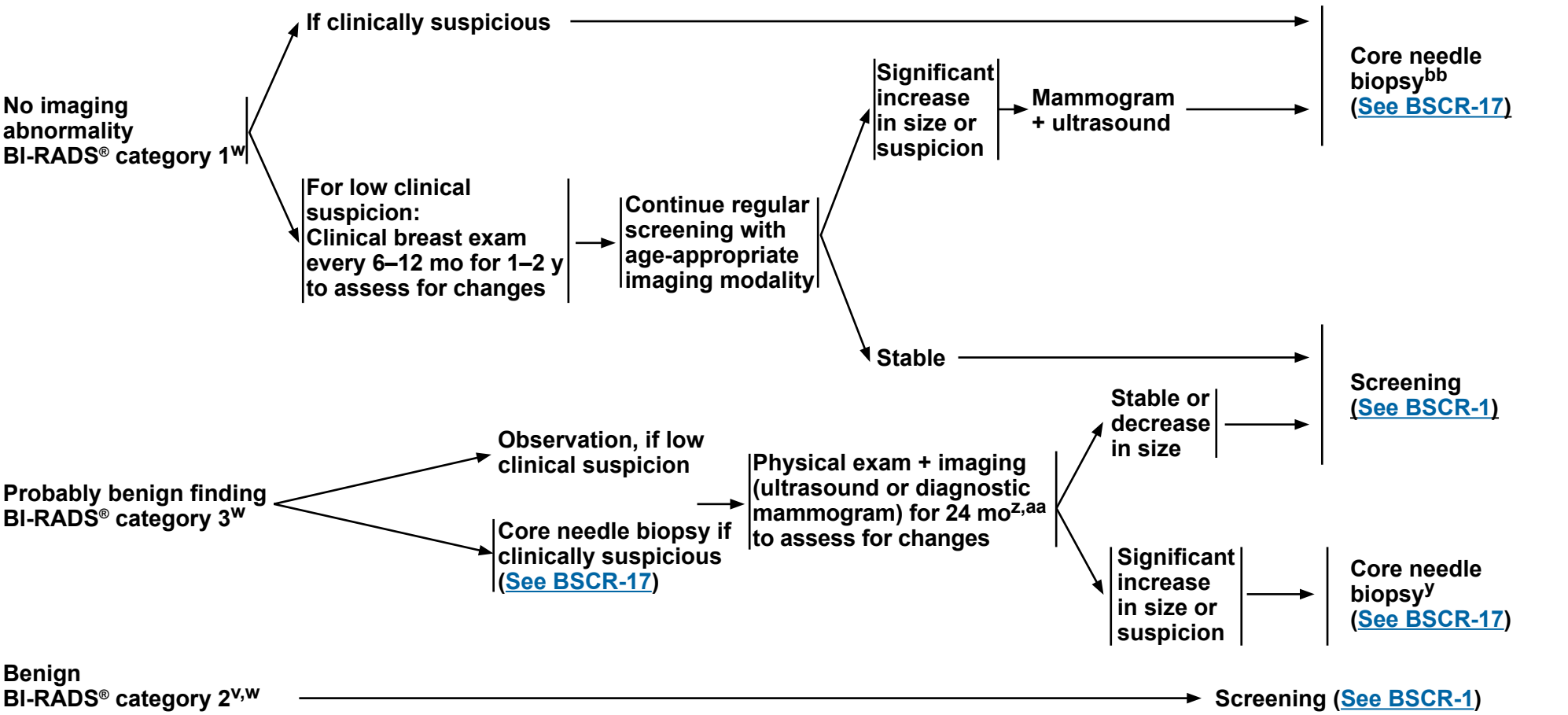


[v]Concordance is needed between clinical exam and imaging results. Consider therapeutic aspiration for persistent clinical symptoms.
[w]See Assessment Category Definitions (BSCR-B).
[x]See Assessment Category Definitions (BSCR-B).
[y]Core needle biopsy preferred; in some circumstances needle aspiration may be sufficient.
[z]Imaging modality would depend on original imaging. Probably benign findings are typically monitored every 6, 12, and 24 months.
[aa]There may be variability on the follow-up interval of physical exam based on the level of suspicion.
[bb]Palpation-guided tissue sampling (by FNA, core needle, or excision) when no imaging abnormality noted.

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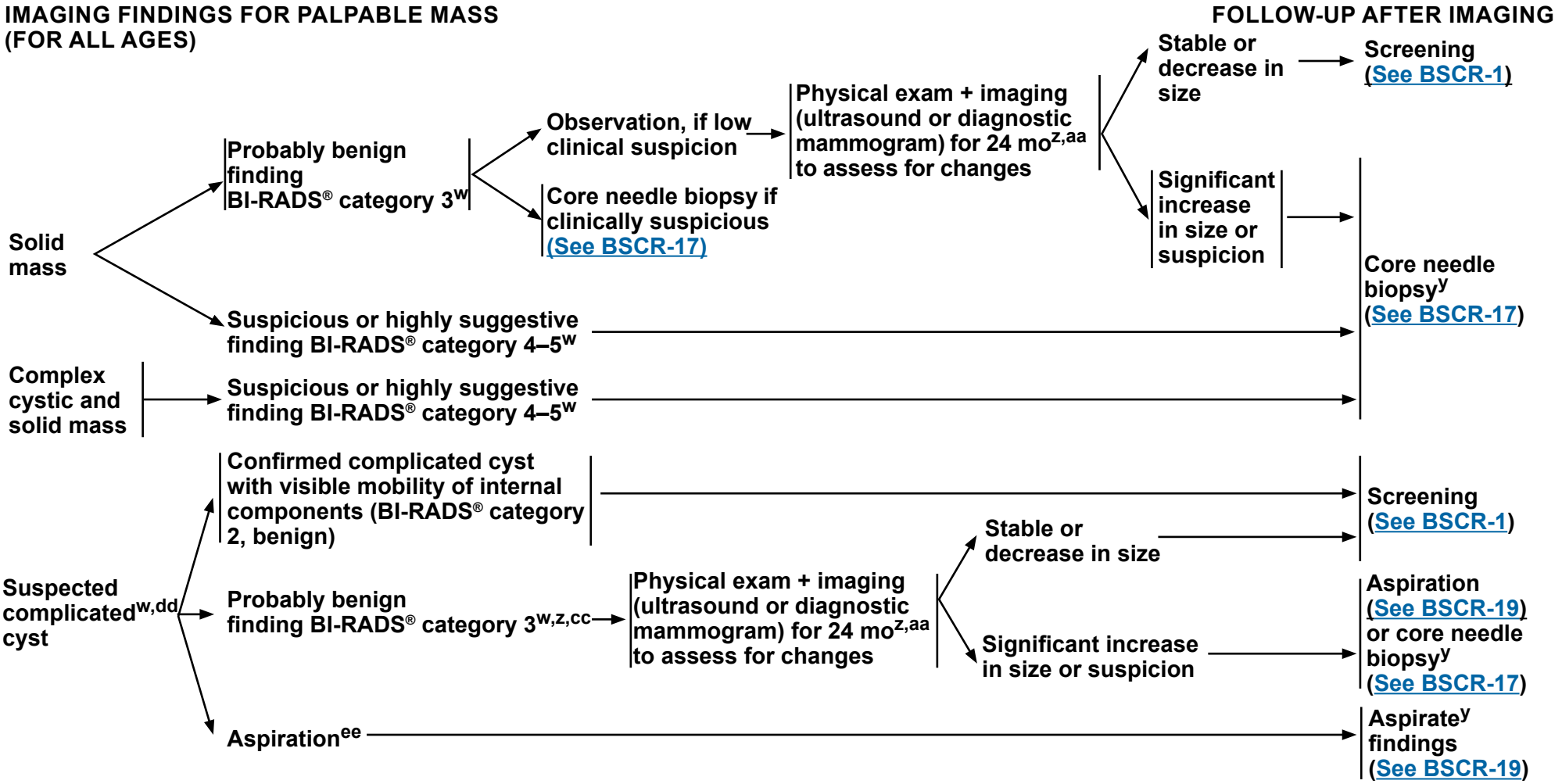


[w] See Assessment Category Definitions (BSCR-B).

[y] Core needle biopsy preferred; in some circumstances needle aspiration may be sufficient.

[z] Imaging modality would depend on original imaging. Probably benign findings are typically monitored every 6, 12, and 24 months.

[aa] There may be variability on the follow-up interval of physical exam based on the level of suspicion.

[cc] In the context of numerous simple cysts, a complicated cyst may be considered a benign finding.

[dd] Round or oval circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria for simple cyst.

[ee] May be considered to confirm the lesion is cystic or for symptomatic relief or possible abscess.

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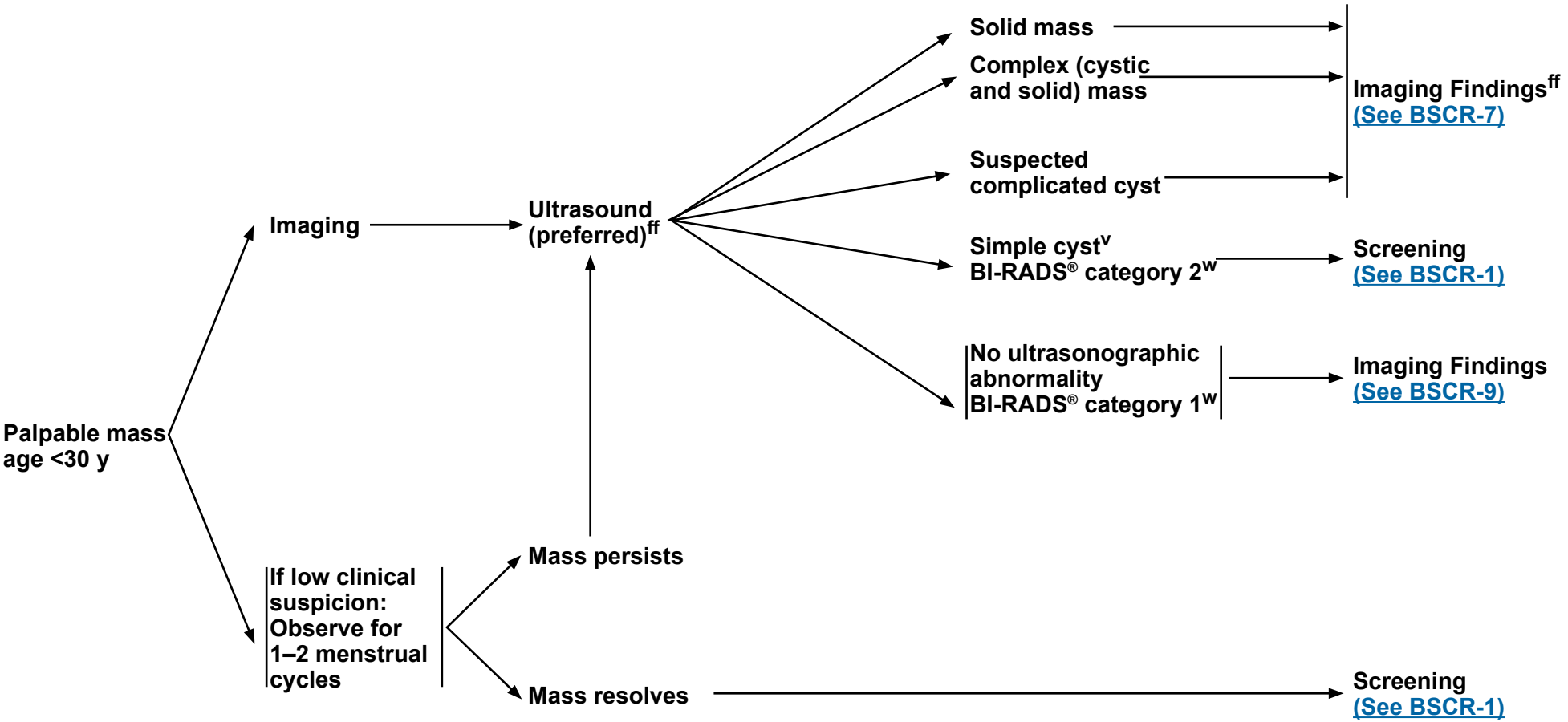
**PRESENTING SIGNS/SYMPTOMS** **DIAGNOSTIC EVALUATION**




[v]Concordance is needed between clinical exam and imaging results. Consider therapeutic aspiration for persistent clinical symptoms.
[w]See Assessment Category Definitions (BSCR-B).
[ff]If high suspicion for malignancy, obtain mammogram.

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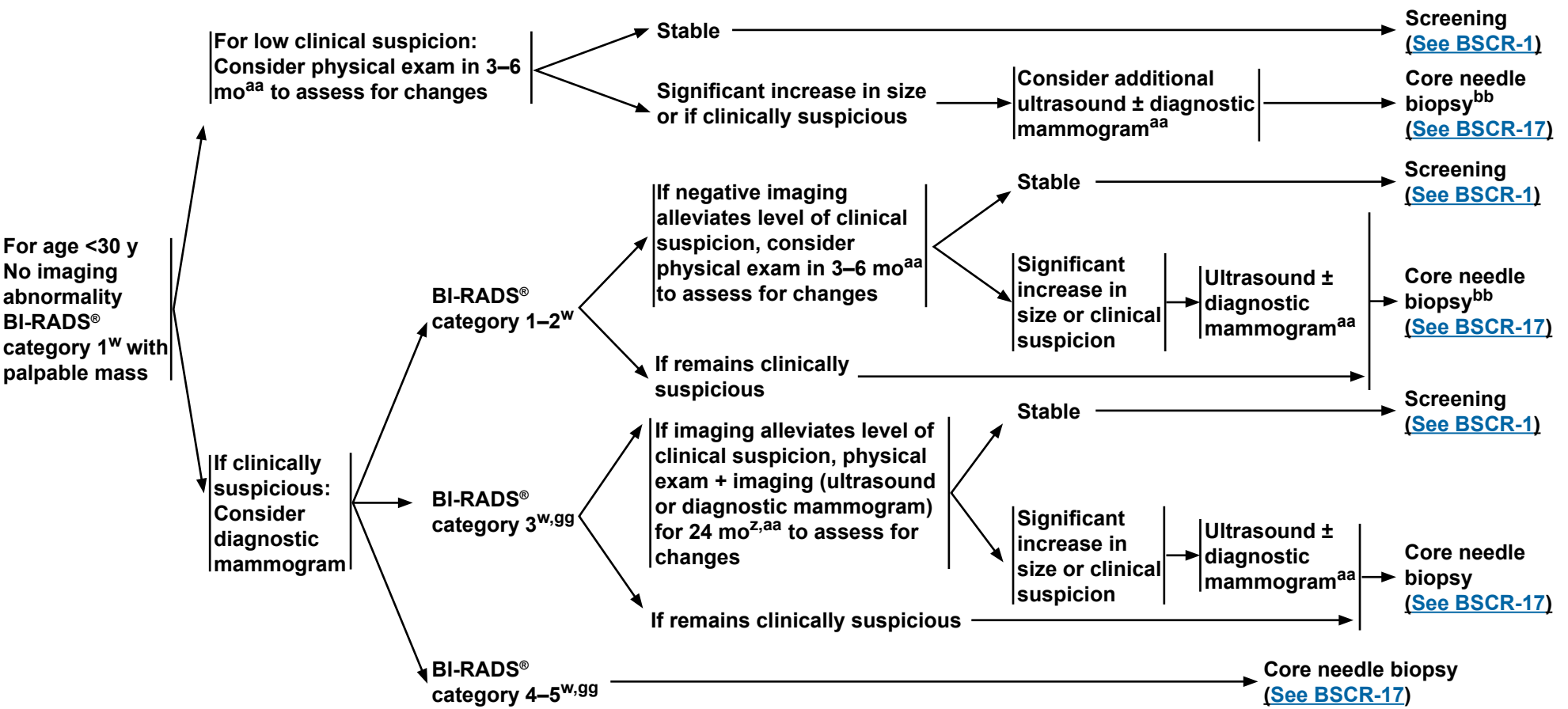
## IMAGING FINDINGS FOR PALPABLE MASS (FOR AGE <30 YEARS)




[w] See Assessment Category Definitions (BSCR-B).
[z] Imaging modality would depend on original imaging. Probably benign findings are typically monitored every 6, 12, and 24 months.
[aa] There may be variability on the follow-up interval of physical exam based on the level of suspicion.
[bb] Palpation-guided tissue sampling (by FNA, core needle, or excision) when no imaging abnormality noted.
[gg] Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to BI-RADS® category 1–2 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.

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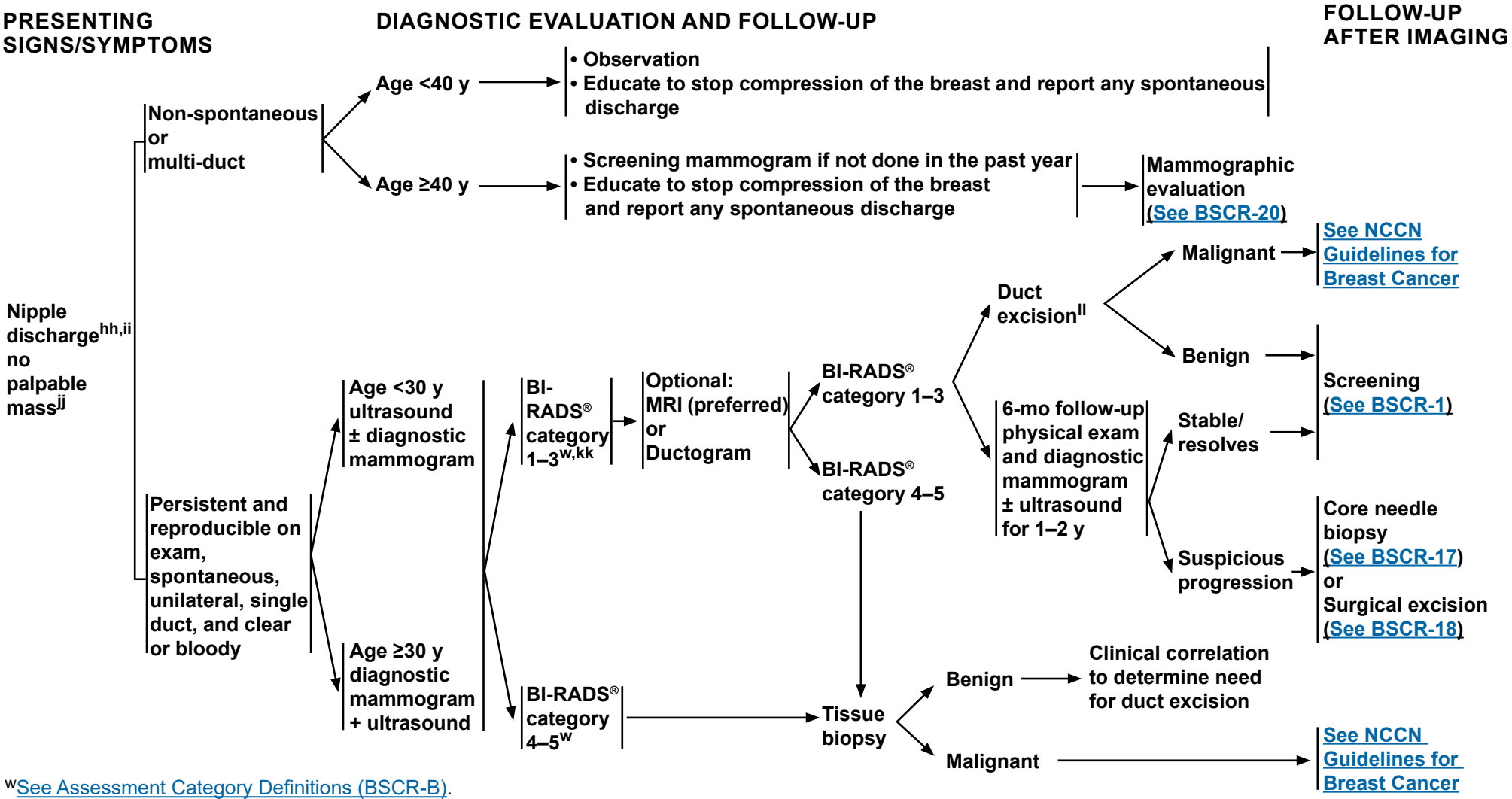


[w] See Assessment Category Definitions (BSCR-B).
[hh] A list of drugs that can cause nipple discharge (not all-inclusive): psychoactive drugs, antihypertensive medications, opiates, oral contraceptives, and estrogen.
[ii] For bilateral milky discharge consider endocrine workup.
[jj] If palpable mass, see BSCR-5 or BSCR-6.
[kk] If BI-RADS® category 3 finding is unrelated to nipple discharge, manage mammographic finding by BSCR-20.
[ll] Based on clinical suspicion and patient preference.

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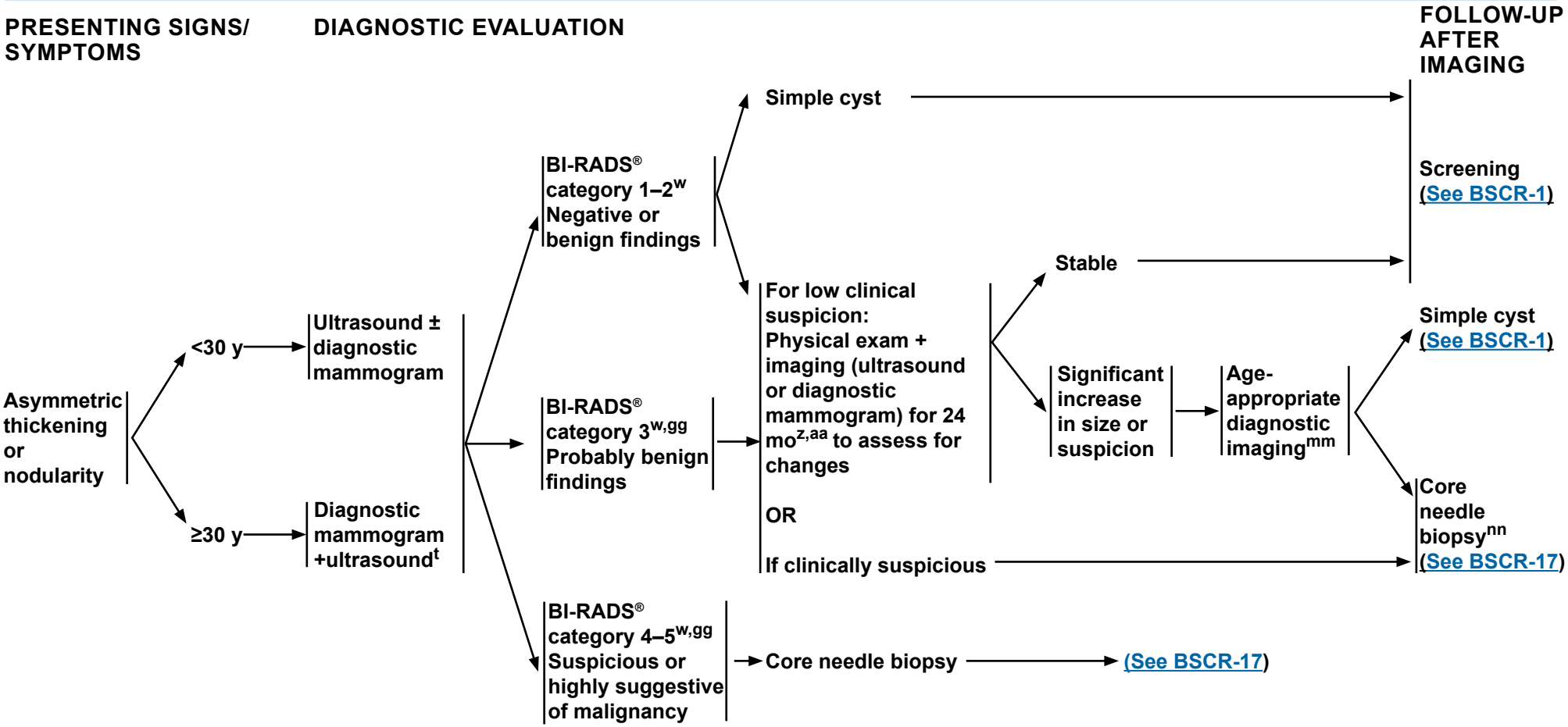


[t]There are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for individuals 30–39 years of age. See Discussion.
[w]See Assessment Category Definitions (BSCR-B).
[z]Imaging modality would depend on original imaging. Probably benign findings are typically monitored every 6, 12, and 24 months.
[aa]There may be variability on the follow-up interval of physical exam based on the level of suspicion.
[gg]Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to BI-RADS® category 1–2 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.
[mm]May consider MRI, if suspicious.
[nn]When there is no imaging finding, palpation-guided FNA or surgical biopsy can be performed.

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

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2021
# Breast Cancer Screening and Diagnosis

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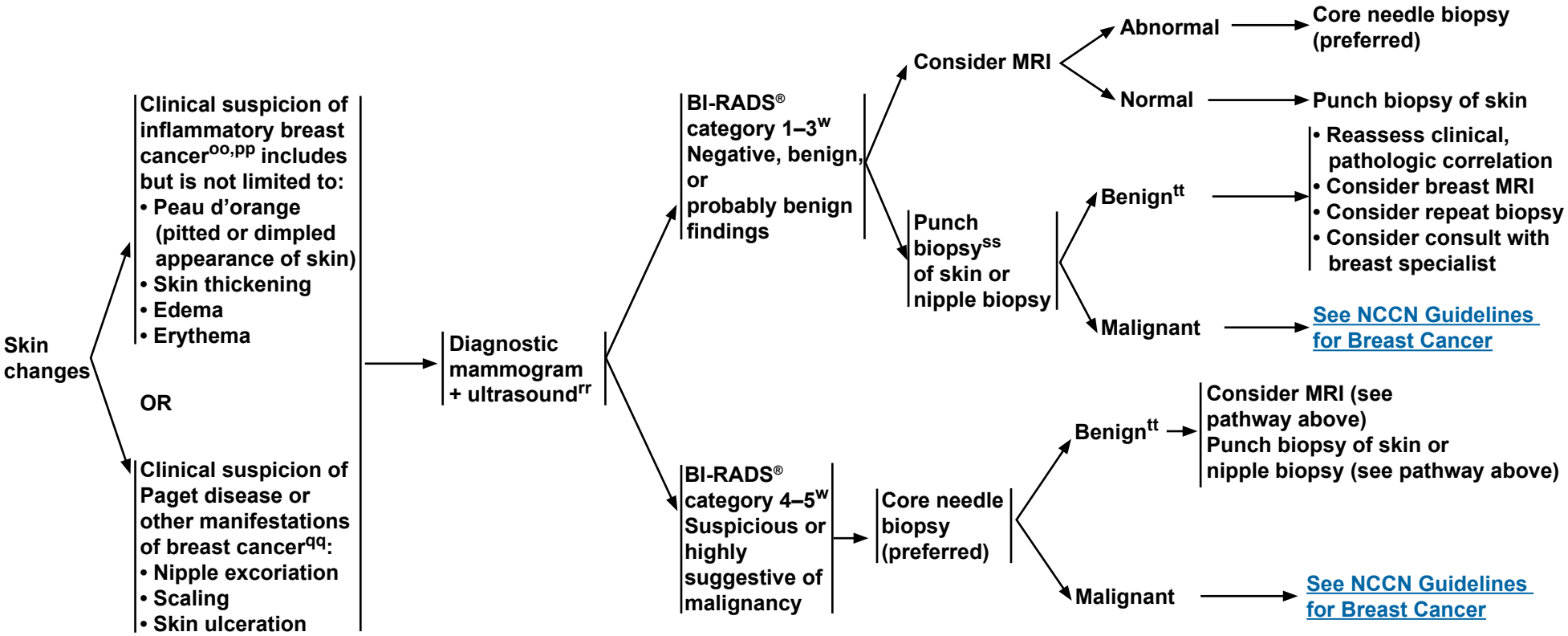
Discussion

## PRESENTING SIGNS/SYMPTOMS

## DIAGNOSTIC EVALUATION AND FOLLOW-UP




[w] See Assessment Category Definitions (BSCR-B).
[oo] This may represent serious disease of the breast and needs evaluation.
[pp] If clinically of low suspicion for breast cancer or high suspicion for infection, a short trial (eg, 7–10 days) of antibiotics for mastitis may be indicated.
[qq] If clinically of low suspicion for Paget's disease or high suspicion for eczema, a short trial of topical steroids may be indicated.
[rr] Ultrasound may be sufficient, unless highly suspicious. For malignancy obtain mammogram.
[ss] Inflammatory breast cancer is a clinical diagnosis and is not dependent on a positive punch biopsy.
[tt] 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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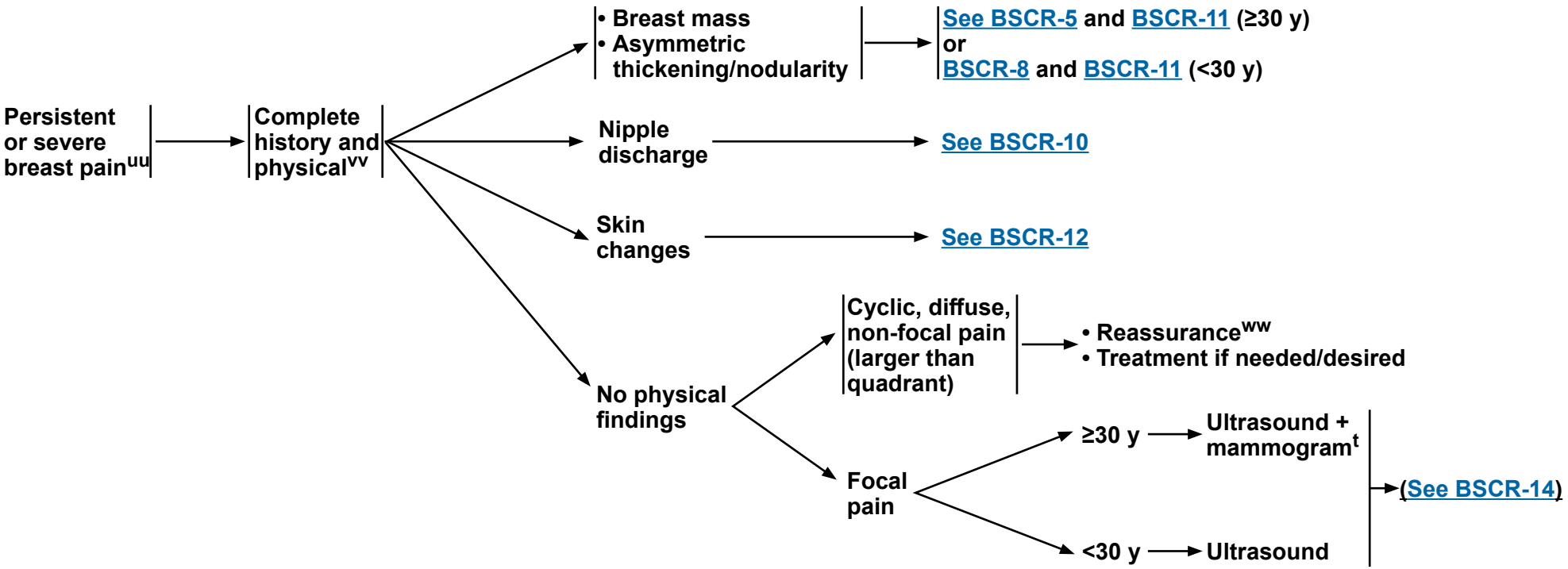
**PRESENTING SIGNS AND SYMPTOMS** **FOLLOW-UP EVALUATION**




[t]There are some clinical circumstances such as a suspected painful simple cyst in which ultrasound would be preferred as the first imaging modality and may suffice for individuals 30–39 years of age. Mammogram is not necessary if performed and results were negative within the past 6 months. See Discussion.
[uu]Defined as 4 to 6 weeks duration; prior to that, symptomatic management.
[vv]Adequate clinical breast exams include the following: upright and supine position during inspection, and palpation of all components of the breast, axilla, and clavicular lymph node basins. Time spent on the palpable portion of the exam is associated with increased detection of palpable abnormalities. Location and distance from nipple facilitate geographic correlation with imaging findings. (See BSCR-1).
[ww]Assuming breast imaging screening is current.

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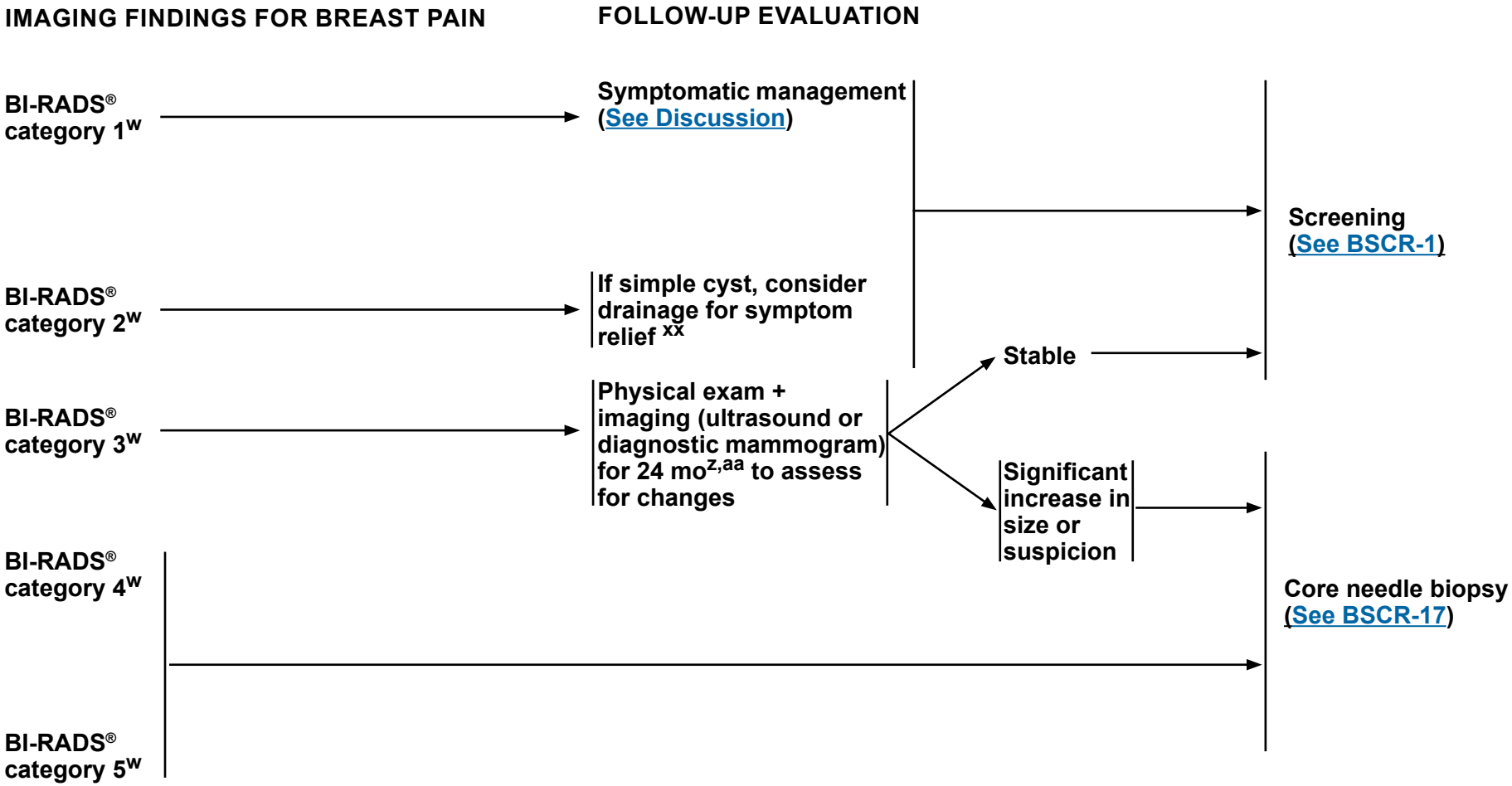


[w]See Assessment Category Definitions (BSCR-B).
[z]Imaging modality would depend on original imaging. Probably benign findings are typically monitored every 6, 12, and 24 months.
[aa]There may be variability on the follow-up interval of physical exam based on the level of suspicion.
[xx]If complicated cyst, consider aspiration.

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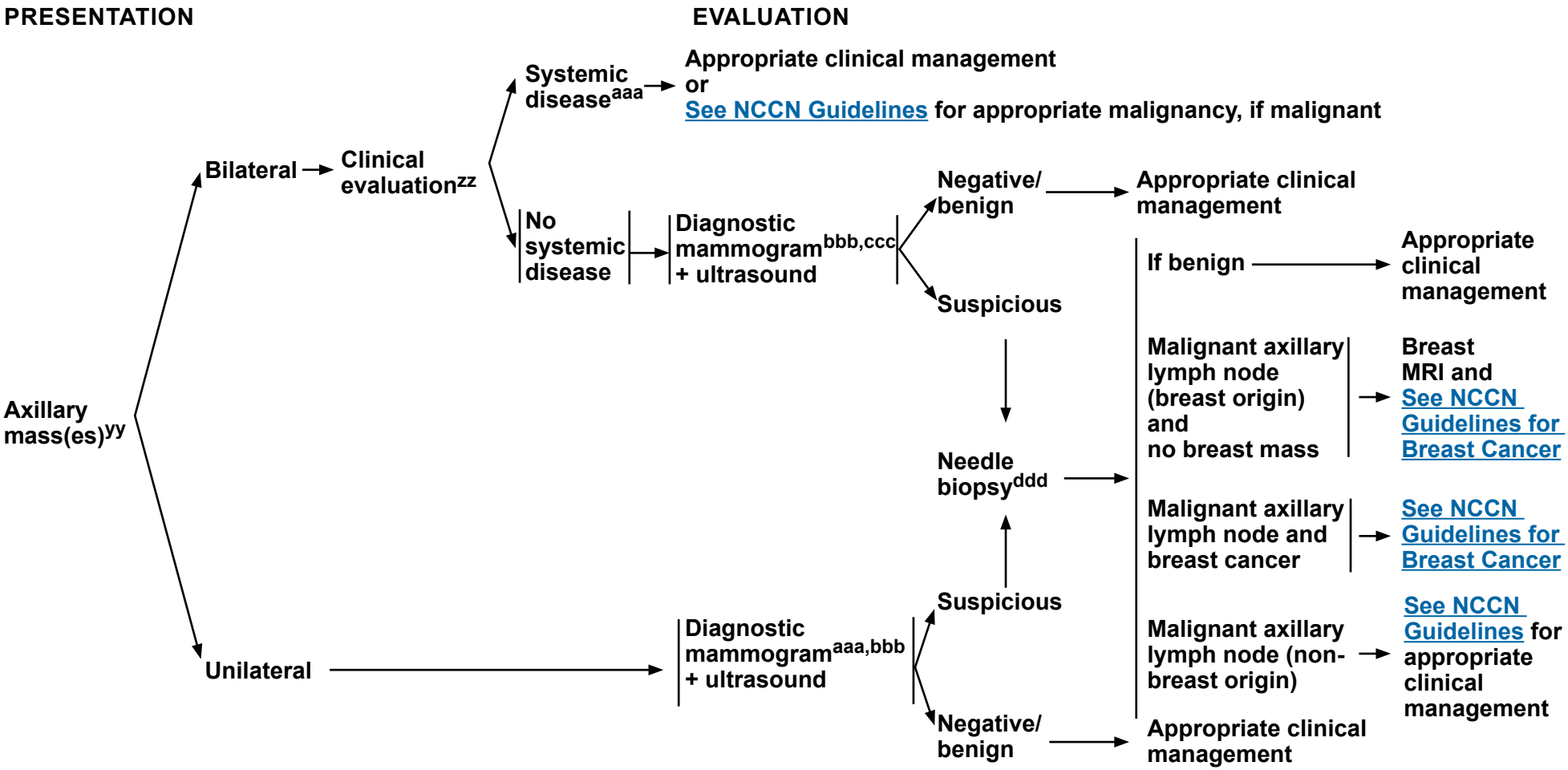
## RECOMMENDATIONS FOR WORKUP/DIAGNOSTIC EVALUATION OF AXILLARY MASS




yyLocalized to the axilla and no suspicion of lymphoma.
zzComplete clinical evaluation to assess for other sites of adenopathy and potential non-breast etiologies of adenopathy.
aaaEvidence of clinical conditions known to be associated with systemic adenopathy such as lupus, rheumatoid arthritis, HIV infection, and others.bbbIf <30 years of age, mammogram is optional unless ultrasound results are suspicious.
cccMammogram is strongly recommended in those ≥30 y if not done in the past 6 months or optional in those who had normal mammogram in past 6 months.
dddIf lymphoma suspected, may require special pathologic processing and/or surgical excision.

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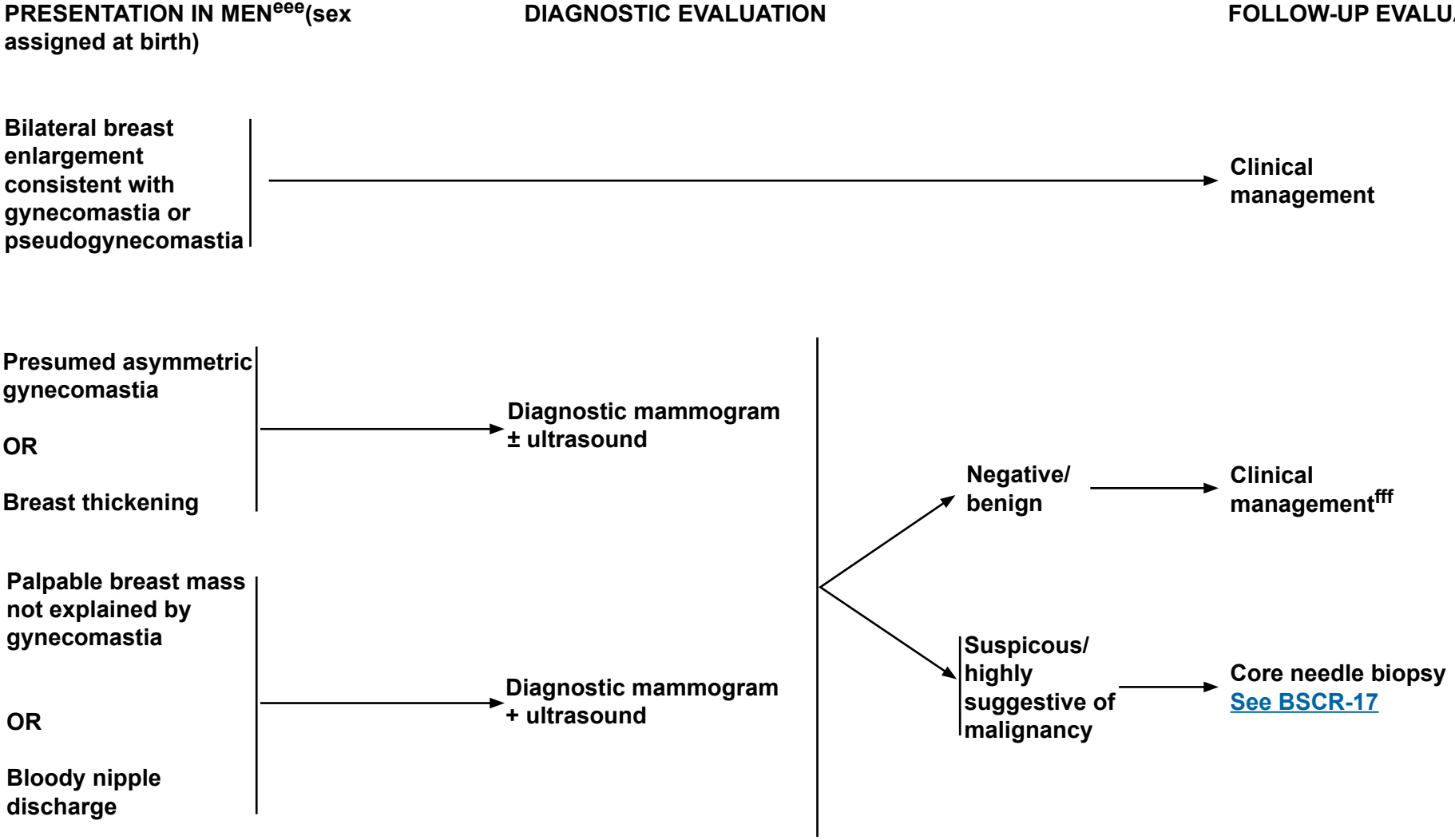


[eee] See NCCN Guidelines for Breast Cancer for management and special considerations for breast cancer in men (sex assigned at birth).
[fff] Consider surgical referral for suspicious clinical findings.

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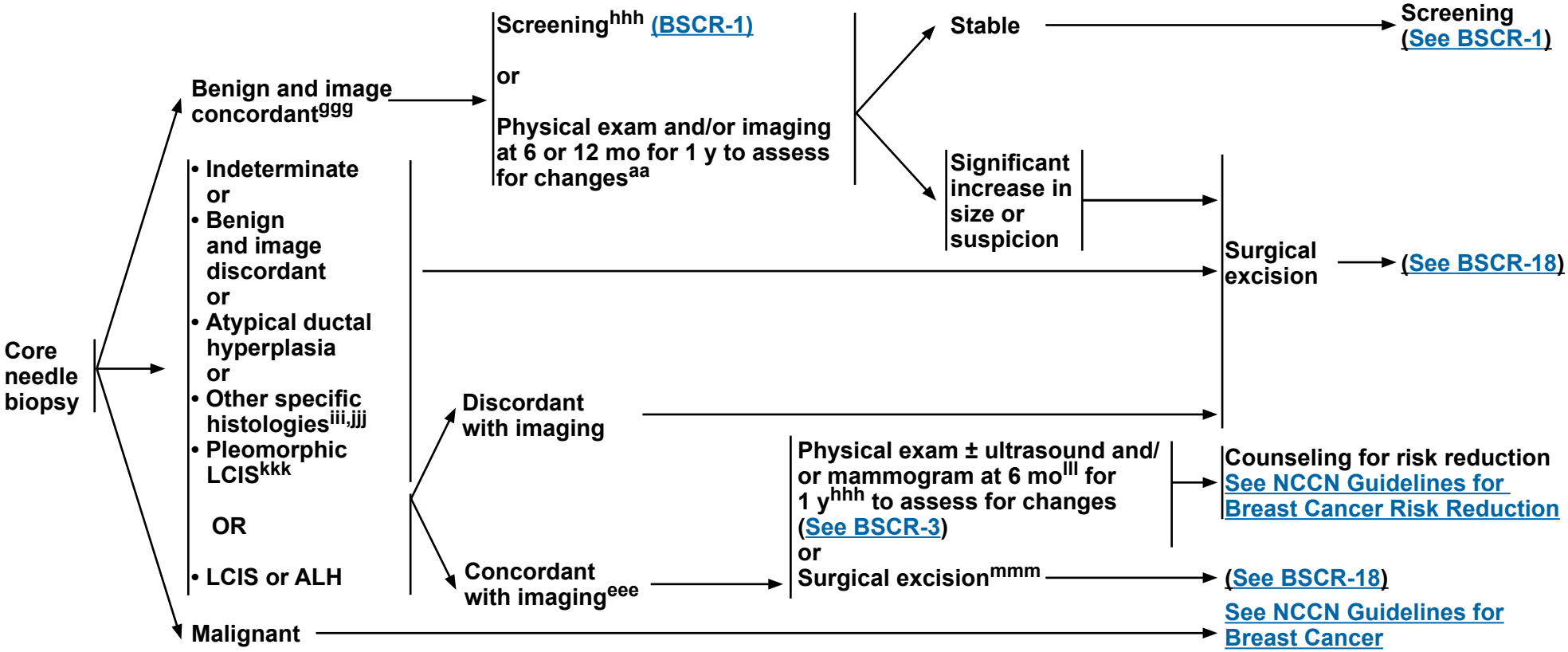
## FOLLOW-UP EVALUATION AFTER CORE NEEDLE BIOPSY




[aa]There may be variability on the follow-up interval of physical exam based on the level of suspicion.

[ggg]Pathology matches imaging findings.

[hhh]While most would return to annual screening, there is the option of physical exam with or without further imaging for individuals under 40 y of age.

[iii]Select patients may be suitable for monitoring in lieu of surgical excision (eg, ADH, LCIS, ALH, flat epithelial atypia [FEA], papillomas without atypia, fibroepithelial lesions favoring fibroadenoma, radial scars adequately sampled or incidental).

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

[kkk]Clinicians may consider complete excision with negative margins for pleomorphic LCIS. However, outcomes data regarding treatment of individuals with pleomorphic LCIS are lacking, due in part to a paucity of histologic categorization of variants of LCIS.

[lll]Initiation of high-risk MRI screening may obviate the need for 6-month mammogram/ultrasound.

[mmm]Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk for invasive cancer on surgical excision. (Rendi MH, et al. Ann Surg Oncol 2012;19:914-921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21861212).

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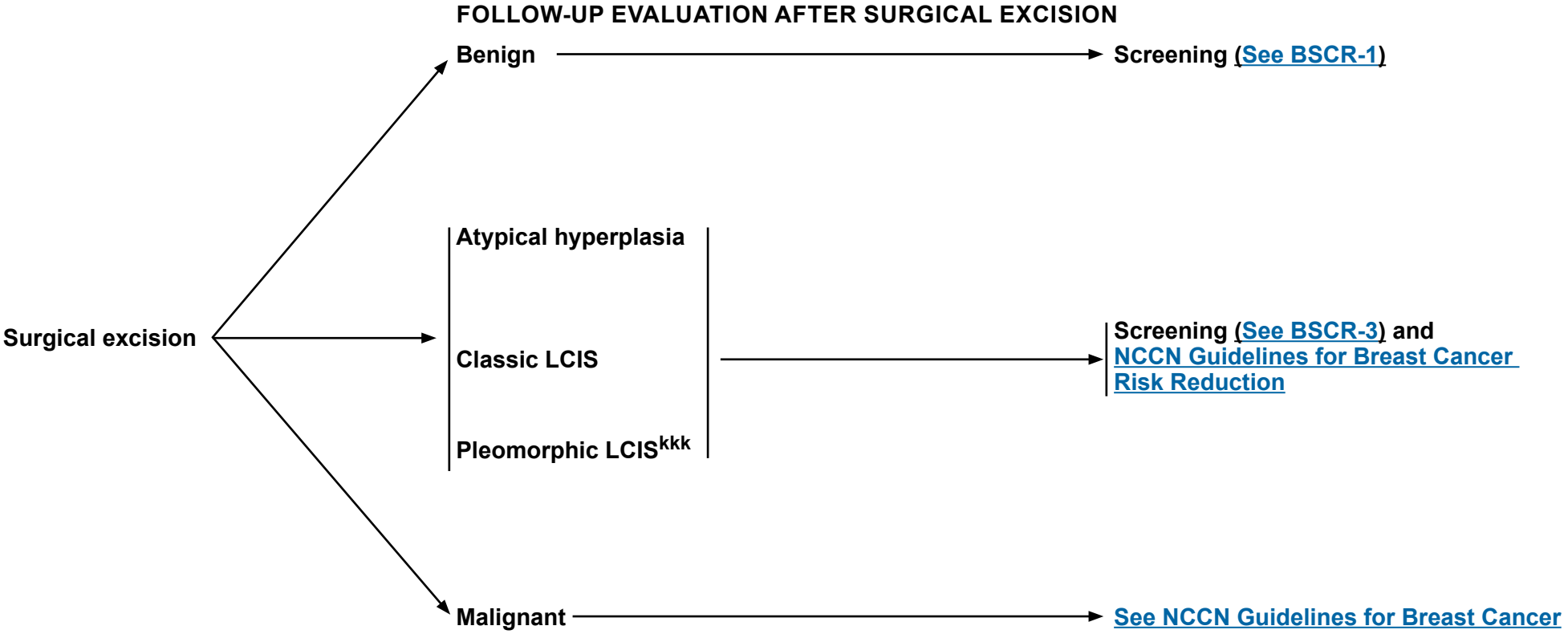


[kkk]Clinicians may consider complete excision with negative margins for pleomorphic LCIS. However, outcomes data regarding treatment of individuals with pleomorphic LCIS are lacking, due in part to a paucity of histologic categorization of variants of LCIS.

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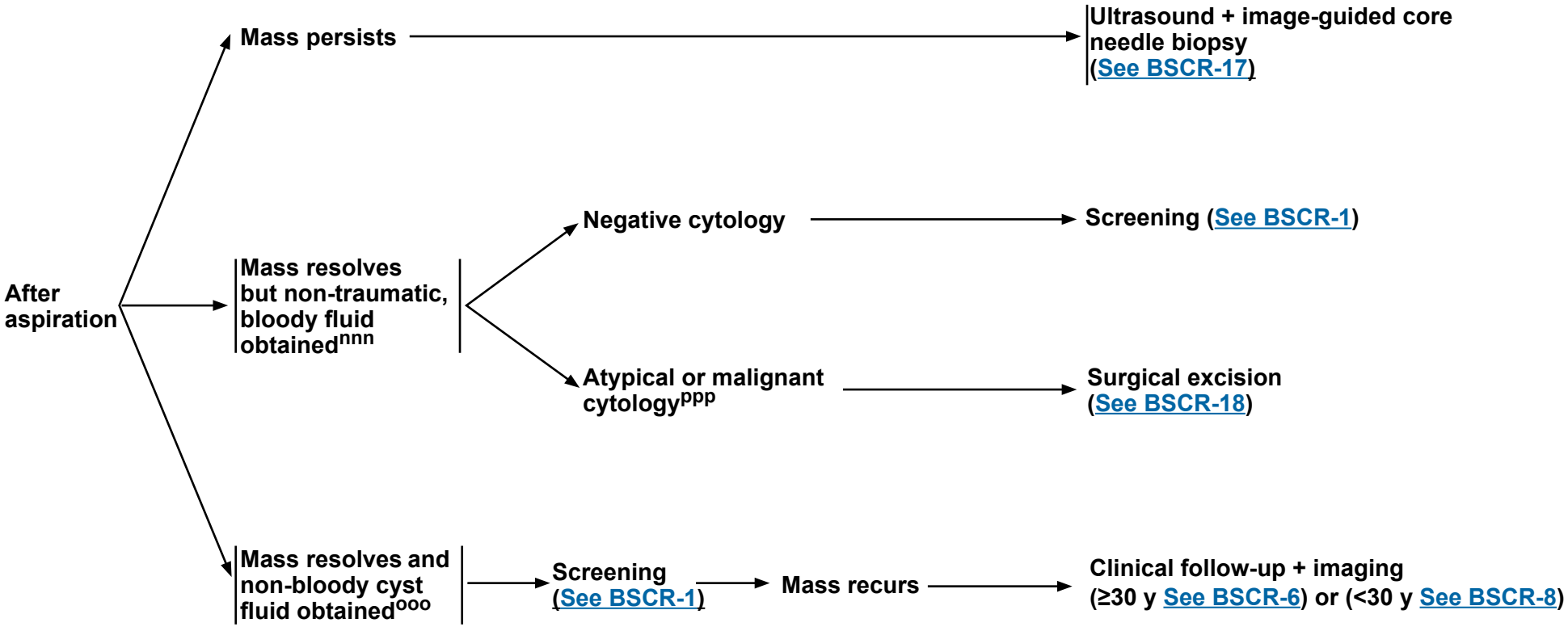
## FOLLOW-UP EVALUATION AFTER ASPIRATION




[nnn]Place marker clip and send to cytology.
[ooo]Routine cytology is not recommended.
[ppp]There are some circumstances in which cytology may be sufficient. If cytology is concordant core needle biopsy may not be needed.

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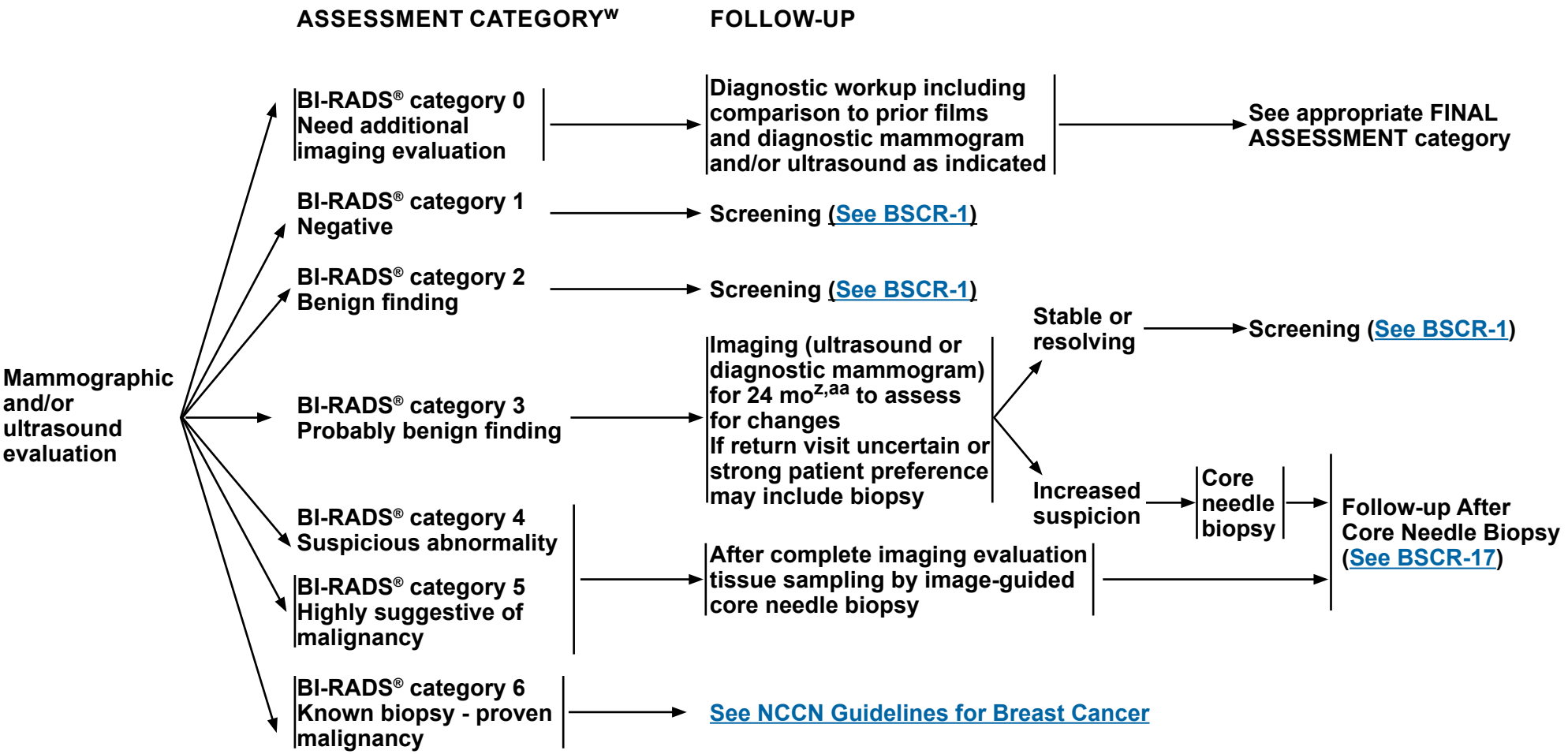


[w] See Assessment Category Definitions (BSCR-B).
[z] Imaging modality would depend on original imaging. Probably benign findings are typically monitored every 6, 12, and 24 months.
[aa] There may be variability on the follow-up interval of physical exam based on the level of suspicion.

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## BREAST SCREENING CONSIDERATIONS

- **Individuals should undergo breast cancer risk assessment by age 25 and be counseled regarding potential benefits, risks, and limitations of breast screening in the context of their risk stratification. Shared decision-making is encouraged based on a patient's values and preferences (See Discussion).**
- **Adequate clinical breast exams include the following: upright and supine position during inspection, and palpation of all components of the breast (lateral-medial: from mid-axillary line to sternum; cephalad-caudad: from clavicle to inframammary ridge), axilla, and clavicular lymph node basins. Time spent on the palpable portion of the exam is associated with increased detection of palpable abnormalities. Clock/quadrant location and distance from nipple facilitate geographic correlation with imaging findings.**
- **Consider severe comorbid conditions limiting life expectancy (eg, ≤10 years) and whether therapeutic interventions are planned.**
- **Upper age limit for mammographic screening is not yet established.**
- **For individuals with mammographically dense breast tissue (heterogeneously or extremely dense breast tissue), recommend counseling on the risks and benefits of supplemental screening.**
- **Dense breasts limit the sensitivity of mammography. Mammographically dense breast tissue is associated with an increased risk for breast cancer.**
- **Handheld or automated ultrasound can increase cancer detection rates in individuals with dense breast tissue, but may increase recall and increase benign breast biopsies.**
- **Multiple studies show that tomosynthesis can decrease call back rates and improve cancer detection. Of note, most studies used double the dose of radiation. This is still within the federal guidelines for radiation dosage for mammography. The radiation dose can be minimized by using synthesized 2-D reconstruction.**
- **Contrast-enhanced mammography is also an emerging efficacious option for higher risk breast cancer screening.**
- **While there is emerging evidence that molecular imaging (breast-specific gamma imaging, sestamibi scan, or positron emission mammography) as screening procedures may improve detection, whole-body effective radiation dose with these tests is substantially higher than that of mammography.**
- **Current evidence does not support the routine use of thermography or ductal lavage as screening procedures.**
- **In high-risk settings, based on current evidence and considering the FDA safety announcement[1] (gadolinium-based contrast agents) we continue to recommend annual MRI in select populations after shared decision-making. Breast cancer screening MRI may also increase recall and increase benign breast biopsies.**
- **Abbreviated MRI used to replace traditional MRI is undergoing active investigation.**

[1]FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue: https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm.

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## BREAST SCREENING CONSIDERATIONS

### RECOMMENDATIONS FOR BREAST MRI SCREENING AS AN ADJUNCT TO MAMMOGRAPHY[a,2,3]
### (FOR AGE TO BEGIN SCREENING EXCEPT WHERE NOTED BELOW: SEE BSCR-2)

**Recommend Annual MRI Screening:**
- **For individuals with a genetic mutation, or a first-degree relative of gene mutation carrier, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.**
- **For individuals who received thoracic RT between the ages of 10 and 30 y**
- **For individuals with a lifetime risk ≥20% as defined by models that are largely dependent on family history[b]**
- **Consider annual MRI screening for individuals with lobular neoplasia (LCIS/ALH) or ADH and ≥20% lifetime risk[c]**

**Insufficient Evidence to Recommend for or Against Routine Population-Based MRI Screening:**
- **Lifetime risk 15%–20%, as defined by models that are largely dependent on family history**
- **Heterogeneously or extremely dense breast on mammography**

**Recommend Against MRI Screening (Based on Expert Consensus Opinion):**
- **Individuals at <15% lifetime risk**

[a]For age over 75 years, screening recommendations are considered on an individual basis.

[b]Based on the extent of family history, consider referral for genetic testing. Refer to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic to see whether the patient meets the criteria. If testing is not performed or if negative genetic testing and if lifetime risk remains greater than (or risk still exceeds) 20%, recommend MRI.

[c]Risk depends on age at diagnosis.

[2]Adapted with permission from John Wiley and Sons. Copyright ©2007 American Cancer Society. Saslow D, Boetes C, Burke W, et al. American Cancer Society Guidelines for Breast Cancer Screening with MRI as an Adjunct to Mammography. CA: Cancer J Clin 2007;57:75-89.

[3]Individuals with a history of breast cancer with these risk factors should consider supplemental screening.

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## MAMMOGRAPHIC ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - MAMMOGRAPHY FINDINGS

**A. Assessment Is Incomplete:**

**Category 0: Incomplete - Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison:**
**There is a finding for which additional evaluation is needed. This is almost always used in a screening situation. Under certain circumstances this assessment category may be used in a diagnostic mammography report, such as when ultrasound equipment or personnel are not immediately available, or when the patient is unable or unwilling to wait for completion of a full diagnostic examination. A recommendation for additional imaging evaluation includes the use of spot compression (with or without magnification), special mammographic views, and ultrasound. Category 0 should not be used for diagnostic breast imaging findings that warrant further evaluation with MRI. Rather, the interpreting physician should issue a final assessment in a report that is made before the MRI examination is performed. In most circumstances and when feasible, if a mammography examination is not assessed as negative or benign, the current examination should be compared with prior examination(s). The interpreting physician should use judgment on how vigorously to attempt obtaining prior examinations, given the likelihood of success of such an endeavor and the likelihood that comparison will affect the final assessment. In this context, it is important to note that comparison with previous examination(s) may be irrelevant when a finding is inherently suspicious for malignancy.**

**Category 0 should be used for prior image comparison only when such comparison is required to make a final assessment. When category 0 is used in the context of awaiting prior examinations for comparison, there should be in place a tracking procedure guaranteeing with 100% reliability that a final assessment will be made within 30 days (preferably sooner) even if prior examinations do not become available. Some mammography practices may reasonably choose never to use category 0 in the context of awaiting prior examinations simply because they do not have a 100% reliable tracking procedure. If a mammography examination is assessed as category 0 in the context of awaiting prior examinations and then the prior examinations do become available, an addendum to the initial mammography report should be issued, including a revised assessment. For auditing purposes, the revised assessment should replace the initial assessment.**

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

[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
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## MAMMOGRAPHIC ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - MAMMOGRAPHY FINDINGS

**B. Assessment Is Complete - Final Assessment Categories:**

**Category 1: Negative:**
**There is nothing to comment on. This is a normal examination.**

**Category 2: Benign:**
**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, skin calcifications, metallic foreign bodies (such as core biopsy and surgical clips), and fat-containing lesions (such as oil cysts, lipomas, galactoceles, and mixed-density hamartomas) all have characteristically benign appearances and may be described 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. On the other hand, the interpreter may choose not to describe such findings, in which case the examination should be assessed as negative (category 1).**

**Note that both category 1 and category 2 assessments indicate that there is no mammographic evidence of malignancy. Both should be followed by the management recommendation for routine mammography screening. 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 (even if such findings are present).**

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

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## MAMMOGRAPHIC ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - MAMMOGRAPHY FINDINGS

**Category 3: Probably Benign:**

**A finding assessed using this category should have a ≤2% likelihood of malignancy, but greater than the essentially 0% likelihood of malignancy of a characteristically benign finding. A probably benign finding is not expected to change over the suggested period of imaging surveillance, but the interpreting physician prefers to establish stability of the finding before recommending management limited to routine mammography screening.**

**There are several prospective clinical studies demonstrating the safety and efficacy of periodic mammographic surveillance instead of biopsy for specific mammographic findings.**

**Three specific findings are validated as being probably benign (the noncalcified circumscribed solid mass, the focal asymmetry, and solitary group of punctate calcifications). All the previously cited studies emphasize the need to conduct a complete diagnostic imaging evaluation before making a probably benign (category 3) assessment; hence, it is recommended not to render such an assessment in interpreting a screening mammography examination. The practice of rendering category 3 assessments directly from screening examination also has been shown to result in adverse outcomes: 1) unnecessary follow-up of many lesions that could have been promptly assessed as benign; and 2) delayed diagnosis of a small number of cancers that otherwise may have been smaller in size and less likely to be advanced in stage. Also, all the previously cited studies exclude palpable lesions, so the use of a probably benign assessment for a palpable lesion is not supported by robust scientific data, although there are two single-institution studies that do report successful outcomes for palpable lesions. Finally, because evidence from previously cited studies indicates the need for biopsy rather than continued surveillance when a probably benign finding increases in size or extent, it is not prudent to render a category 3 assessment when a finding that otherwise meets "probably benign" imaging criteria is either new or has increased in size or extent.**

**While the vast majority of probably benign findings are managed with an initial short-interval follow-up (6-month) examination followed by additional examinations until long-term (2- or 3-year) stability is demonstrated, there may be occasions in which a biopsy is done instead (patient preference or overriding clinical concern).**

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[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
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## MAMMOGRAPHIC ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - MAMMOGRAPHY FINDINGS

**Category 4: Suspicious:**
**This category is reserved for findings that do not have the classic appearance of malignancy but are sufficiently suspicious to justify a recommendation for biopsy. The ceiling for category 3 assessment is a 2% likelihood of malignancy and the floor for category 5 assessment is 95%, so category 4 assessments cover the wide range of likelihood of malignancy in between. Thus, almost all recommendations of breast interventional procedures will come from assessments made using this category. By subdividing category 4[3] into 4A, 4B, and 4C, as recommended in Guidance chapter and using the cut point indicated therein, it is hoped that patients and referring clinicians will more readily make informed decisions on the ultimate course of action.**

**Category 5: Highly Suggestive of Malignancy:**
**These assessments carry a very high probability (≥95%) of malignancy. This category initially was established to involve lesions for which 1-stage surgical treatment was considered without preliminary biopsy, in an era when preoperative wire localization was the primary breast interventional procedure. Nowadays, given the widespread acceptance of imaging-guided percutaneous biopsy, 1-stage surgery is rarely, if ever, performed. Rather, current oncologic management almost always involves tissue diagnosis of malignancy via percutaneous tissue sampling to facilitate treatment options, such as when sentinel node biopsy is included in surgical management or when neoadjuvant chemotherapy is administered prior to surgery. Therefore, the current rationale for using a category 5 assessment is to identify lesions for which any non-malignant percutaneous tissue diagnosis is automatically considered discordant, resulting in the recommendation for repeat (usually surgical) biopsy.**

**Category 6: Known Biopsy - Proven Malignancy:**
**This category is reserved for examinations performed after biopsy proof of malignancy (imaging performed after percutaneous biopsy but prior to complete surgical excision) in which there are no mammographic abnormalities other than the known cancer that might need additional evaluation.**

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[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
[3]The new BI-RADS® cut points for the risk of malignancy are as follows: 4A (>2% – ≤10%), 4B (>10% – ≤50%), 4C (>50% – <95%).


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## ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - ULTRASOUND FINDINGS

**A. Assessment is Incomplete:**

**Category 0: Incomplete - Need Additional Imaging Evaluation:**

**There is a finding for which additional imaging evaluation is needed. This is almost always used in a screening situation. In this context, additional imaging evaluation includes the recording of (nonstandard) ultrasound images to supplement the standard images recorded for a screening examination. Note that this does not include repeat real-time scanning by the interpreting physician and/or colleague as long as additional images are not recorded. This respects the unique real-time nature of ultrasound and does not penalize its use.**

**Under certain circumstances, assessment category 0 may be used in a diagnostic ultrasound report, such as when equipment or personnel are not immediately available to perform a needed concurrent diagnostic mammography examination, or when the patient is unable or unwilling to wait for completion of a full diagnostic examination. Category 0 should not be used for diagnostic breast imaging findings that warrant further evaluation with MRI. Rather, the interpreting physician should issue a final assessment in a report that is made before the MRI examination is performed.**

**In most circumstances and when feasible, if a screening ultrasound examination is not assessed as negative or benign, the current examination should be compared to prior examination(s), if any exist. The interpreting physician should use judgment on how vigorously to attempt obtaining prior examinations, given the likelihood of success of such an endeavor and the likelihood that comparison will affect the final assessment. In this context, it is important to note that comparison to previous examination(s) may be irrelevant when a finding is inherently suspicious for malignancy.**

**Category 0 should be used for prior image comparison only when such comparison is required to make a final assessment. When category 0 is used in the context of awaiting prior examinations for comparison, there should be in place a tracking system guaranteeing with 100% reliability that a final assessment will be made within 30 days (preferably sooner), even if prior examinations do not become available. Some breast imaging practices may reasonably choose never to use category 0 in the context of awaiting prior examinations simply because they do not have a 100% reliable tracking system. If an ultrasound examination is assessed as category 0 in the context of awaiting prior examinations and then the prior examinations do become available, an addendum to the initial ultrasound report should be issued, including a revised assessment. For auditing purposes, the revised assessment should replace the initial assessment.**

**A need for previous studies to determine appropriate management might also temporarily defer a final assessment.**

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

[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
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## ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - ULTRASOUND FINDINGS

**B. Assessment is Complete — Final Categories:**

**Category 1: Negative:**
**There is nothing to comment on. This is a normal examination.**

**Category 2: Benign:**
**As with category 1, this is a "normal" assessment, but here the interpreter chooses to describe a benign finding in the ultrasound report. For example, the interpreter may choose to describe one or more simple cysts, intramammary lymph nodes, postsurgical fluid collections, breast implants, or complicated cysts/probable fibroadenomas that are unchanged for at least 2 or 3 years, while still concluding that there is no sonographic evidence of malignancy. On the other hand, the interpreter may choose not to describe such findings, in which case the examination should be assessed as negative (category 1).**

**Note that both category 1 and category 2 assessments indicate that there is no sonographic evidence of malignancy. Both should be followed by the management recommendation for routine age-appropriate screening. The difference is that category 2 should be used when describing one or more specific benign sonographic findings in the report, whereas category 1 should be used when no such findings are described (even if such findings are present).**

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

[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
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## ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - ULTRASOUND FINDINGS

**Category 3: Probably Benign:**
**Assessment category 3, probably benign, is not an indeterminate category for use simply when the radiologist is unsure whether to render a benign (BI-RADS® category 2) or suspicious (BI-RADS® category 4) assessment, but is one that is reserved for specific imaging findings known to have >0% but ≤2% likelihood of malignancy. For ultrasound, there is robust evidence that a solid mass with a circumscribed margin, oval shape, and parallel orientation (most commonly fibroadenoma) and an isolated complicated cyst have a likelihood of malignancy in the defined (≤2%), probably benign range, for which short-interval (6-month) follow-up sonography and then periodic sonographic surveillance may represent appropriate management. Similar data have been reported for clustered microcysts, but these data are less strong because they involve much fewer cases. The use of assessment category 3 for sonographic findings other than these three should be considered only if the radiologist has personal experience to justify a watchful-waiting approach, preferably involving observation of a sufficient number of cases of an additional sonographic finding to suggest a likelihood of malignancy within the defined (≤2%), probably benign range.**

**This edition of the BI-RADS® Atlas also emphasizes the recommendation that a category 3 assessment should not be made at screening; rather, this should be done only after completion of full diagnostic breast imaging examination. This recommendation is appropriate for screening mammography, for which batch interpretation usually is utilized, because in this setting there is no opportunity to complete the diagnostic workup before interpreting the screening examination. However, screening ultrasound almost always is interpreted online, so a full diagnostic examination also is completed while the patient remains in the breast imaging facility, and a single breast imaging report may be issued that combines the findings of both screening and diagnostic components of the examination. Hence, there is no purpose in recommending against category 3 assessment at screening ultrasound, because the diagnostic workup would be completed simultaneously. Note that for auditing purposes, the screening component of a category 3-assessed screening ultrasound examination will be audit-positive, not only because additional nonstandard (diagnostic) images will be recorded but also because a category 3 assessment at screening is defined as being audit-positive.**

[1]Mammography results are mandated to be reported using Final Assessment categories (Quality Mammography Standards: Final Rule. Federal Register. 1997;62:55988).
[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.


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## ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - ULTRASOUND FINDINGS

**For category 3 assessments, the initial short-term follow-up interval is usually 6 months and involves the breast(s) containing the probably benign finding(s). Assuming stability at this 6-month examination, a category 3 assessment again is rendered with a management recommendation for a second short-interval follow-up examination in 6 months. Again assuming stability at this second short-interval follow-up, the examination is once more assessed as category 3, but now the recommended follow-up interval usually is lengthened to 1 year due the already-observed 12-month stability. Note that although the 1-year follow-up coincides with the routine screening interval in the United States, a category 3 assessment is rendered to indicate that the period of imaging surveillance is still underway. As with surveillance using mammography, after 2 to 3 years of stability, the final assessment category should be changed to benign (BI-RADS® category 2). A benign evaluation may also be rendered before completion of category 3 analysis if, in the opinion of the interpreter, the finding has no chance of malignancy and is thus a category 2.**

**Category 4: Suspicious:**
**This category is reserved for findings that do not have the classic appearance of malignancy but are sufficiently suspicious to justify a recommendation for biopsy. The ceiling for category 3 assessment is a 2% likelihood of malignancy, and the floor for category 5 assessment is 95%, so category 4 assessments cover the wide range of likelihood of malignancy in between. Thus, almost all recommendations for breast interventional procedures will come from assessments made using this category. By subdividing category 4[3] into 4A, 4B, and 4C, it is hoped that patients and referring clinicians will more readily make informed decisions on the ultimate course of action. An example of separating the BI-RADS® assessment category from the management recommendation occurs when a simple cyst, correctly assessed as BI-RADS® 2, undergoes cyst aspiration for pain control.**

[1]Mammography results are mandated to be reported using Final Assessment categories (Quality Mammography Standards: Final Rule. Federal Register. 1997;62:55988).
[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
[3]The new BI-RADS® cut points for the risk of malignancy are as follows: 4A (>2% – ≤10%), 4B (>10% – ≤50%), 4C (>50% – <95%).


Continued

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## ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS[1,2]

### BI-RADS® - ULTRASOUND FINDINGS

**Category 5: Highly Suggestive of Malignancy:**
**These assessments carry a very high probability (≥95%) of malignancy. This category initially was established to involve lesions for which 1-stage surgical treatment could be considered without preliminary biopsy in an era when preoperative wire localization was the primary breast interventional procedure. Nowadays, given the widespread acceptance of imaging-guided percutaneous biopsy, 1-stage surgery rarely, if ever, is performed. Rather, current oncologic management almost always involves tissue diagnosis of malignancy via percutaneous tissue sampling to facilitate treatment options, such as when sentinel node imaging is included in surgical management or when neoadjuvant chemotherapy is administered prior to surgery. Therefore, the current rationale for using a category 5 assessment is to identify lesions for which any nonmalignant percutaneous tissue diagnosis is considered discordant, resulting in the recommendation for repeat (usually vacuum-assisted or surgical) biopsy. Also note that whereas the fourth edition simply indicated that "appropriate action should be taken" as management for category 5 assessments, the fifth edition provides the more directed management recommendation that "biopsy should be performed in the absence of clinical contraindication." This new text unequivocally specifies tissue diagnosis as the interpreting physician's management recommendation for category 5 assessments, appropriately and effectively transferring the burden of establishing a contraindication to this recommendation to the referring clinician.**

**Category 6: Known Biopsy-Proven Malignancy:**
**This category is reserved for examinations performed after biopsy proof of malignancy (imaging performed after percutaneous biopsy but prior to surgical excision), in which there are no abnormalities other than the known cancer that might need additional evaluation.**

[1]Mammography results are mandated to be reported using Final Assessment categories (Quality Mammography Standards: Final Rule. Federal Register. 1997;62:55988).
[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS®--5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS®. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org.
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## BACKGROUND INFORMATION ON BREAST IMAGING DURING PREGNANCY AND LACTATION

**1. Pregnancy-Associated Breast Cancer**

- Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring during pregnancy, while breastfeeding, or within one year of delivery. PABC complicates approximately 1 in 3000 to 1 in 10,000 pregnancies.[1] This is the most common invasive cancer diagnosed during pregnancy.[2]

**2. Anatomic/Physiologic Changes of Pregnancy and Lactation**

- Pregnancy and lactation are associated with profound changes in the structure of the breast. Breast changes at this time are due to hyperplasia and hypertrophy of the breast ducts and breast lobules with a substantial increase in the overall fluid content of the breast as well as a significant reduction of stromal adipose tissue. With lactation, under the influence of prolactin, there is production of milk with distention of the ducts as well as further propagation and enlargement of the lobular alveoli. As a result of these changes, there are visible alterations in the appearance of breast tissue in all modes of breast imaging as well as palpable changes on clinical breast exam.[3] These changes in the breast can lead to both reduction in the sensitivity of detecting small breast cancers, and also reduce the specificity of breast imaging (ie, more false-positive results).[4] Similarly, the breast changes resulting from pregnancy and lactation may result in a reduced ability to detect small breast cancers on clinical breast exam or may result in suspicious breast changes due to normal, physiologic changes.

**3. Possible Delayed Diagnosis of Breast Cancer during Pregnancy and Lactation**

- Delayed diagnosis of breast cancer during pregnancy or lactation does occur, which may result in individuals presenting with more advanced disease, larger tumors, and a greater likelihood of axillary nodal disease positivity.[5,6] More advanced breast cancers during pregnancy and lactation may occur as a result of changing physical characteristics of the breast as well as a reluctance to pursue breast imaging when suspicious clinical findings are detected. It remains uncertain whether the more advanced breast cancers diagnosed during pregnancy and lactation compared to age matched individuals is due to delayed diagnosis or due to increased biologic aggressiveness of PABC during pregnancy and lactation. More biologically aggressive tumors associated with PABC are theorized based on these tumors arising in the altered biology (more triple negative tumors compared to age-matched controls), hormonal and immunologic milieu of pregnancy, and lactation.

**4. Ionizing Radiation during Pregnancy**

- Avoiding ionizing radiation during pregnancy is frequently on the minds of both individuals and their providers. It should be reassuring to them that mammography results in extremely low fetal ionizing radiation doses, substantially below worrisome thresholds for harm. The generally accepted minimum threshold for inducing fetal teratogenic effect is 50 mGy.[7,8] The measured fetal radiation dose from a 4-view mammogram is <0.03 mGy, a magnitude of difference approximating 1600-fold.[9] While there are no specific studies evaluating the sensitivity and specificity of digital breast tomosynthesis (DBT) compared to digital mammography (DM) in pregnancy, the improved specificity of DBT in dense breast tissue in non-pregnant individuals may make this modality particularly useful in this setting of increased breast density in pregnant and lactating individuals. While there may be a small increase in ionizing radiation delivery with DBT compared to DM, this small increase should not have any expected effect on fetal safety.

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## BACKGROUND INFORMATION ON BREAST IMAGING DURING PREGNANCY AND LACTATION (Continued)

**5. Imaging in Lactating Individuals**

- In lactating individuals, nursing or breast pumping prior to mammography may improve sensitivity by decreasing the density of the breast parenchyma.[9] Mammography is always appropriate in individuals who are lactating who have an indication (ie, there are no contraindications to mammography in individuals who are lactating).

**6. Breast MRI in Pregnancy and Lactation**

- The use of contrast-enhanced breast MRI during pregnancy is generally considered to be contraindicated because gadolinium in all forms crosses the placenta and enters the fetal circulation.[8,10,11] There are concerns that the gadolinium ion may then dissociate in the fetal circulation and cause toxicity for the fetus. The exact frequency of this occurring and the associated impact of dissociated gadolinium on fetal toxicity is uncertain as there are no reliable data on fetal safety of gadolinium exposure during pregnancy. Therefore, gadolinium administered with breast MRI is best avoided during pregnancy, and other modes of breast imaging should be utilized.
- Fortunately, there is minimal excretion of gadolinium into human breast milk, with less than 1% of permitted neonatal dose of contrast over the first 24 hours after maternal administration.[12] Breast MRI appears to be highly sensitive for the detection of known PABC, though there appears to be lower specificity of breast MRI (higher false-positive rate) in individuals who undergo breast MRI while still lactating.[13] If individuals undergo breast MRI, due to the minimal contrast excretion into breast milk, individuals are not required to “pump and discard” breast milk after administration.[8] It is recommended that individuals pump prior to imaging.

**7. Molecular Breast Imaging**

- The American College of Radiology states that there is no role for molecular breast imaging (Tc-99m Sestamibi MBI) in breast cancer screening or evaluation of breast complaints during pregnancy or lactation.[10]

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## BACKGROUND INFORMATION ON BREAST IMAGING DURING PREGNANCY AND LACTATION
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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Average-Risk Screening in Individuals ≥40 Years | R | R | NR | NR | • While ionizing radiation exposure with mammography is many-fold below the threshold of fetal teratogenesis (see comments below), due to the infrequency of PABC and the decreased sensitivity and specificity of mammography during pregnancy, providers and patients may choose to delay routine breast imaging in average-risk individuals until after pregnancy.<br>• There are no data evaluating the use of ultrasound as an alternative screening method in average-risk individuals during pregnancy; therefore, this is not recommended as an alternative to screening mammography. |
| High-Risk Screening | R | R | O | NR | • In high-risk individuals, it is appropriate to recommend screening mammography at routine intervals (see BSCR-2 and BSCR-3).<br>• The use of screening ultrasound has not been evaluated as a method to reduce breast cancer mortality in high-risk individuals who are pregnant.<br>• Due to the trans-placental passage of gadolinium, and potential concerns of exposure of gadolinium to the fetus, contrast-enhanced breast MRI is not recommended during pregnancy. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Management of Palpable Breast Mass | R | O | R | NR | • Age-appropriate evaluation of a palpable mass during pregnancy should proceed similar to that outlined in BSCR-5 and BSCR-11.<br>• Begin evaluation of palpable breast masses during pregnancy with breast ultrasound. However, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information.<br>• While there is a small theoretical concern of milk fistula with biopsy, image-guided core needle biopsy should proceed in the usual prompt timeframe following a BI-RADS 4 or BI-RADS 5 imaging result during pregnancy.<br>• Breast MRI is not appropriate for the management of palpable masses during pregnancy. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Management of Abnormal Nipple Discharge* | R | O | R | NR | • Because of the frequency of normal nipple discharge during pregnancy, abnormal nipple discharge is defined as: Persistent, uni-ductal, unilateral bloody nipple discharge.<br>• Due to normal physiologic changes of pregnancy, bloody nipple discharge is common, but usually short-lived (eg, 1 or 2 episodes). Persistence beyond 1 or 2 episodes should undergo evaluation.<br>• Begin evaluation of abnormal nipple discharge during pregnancy with breast ultrasound. However, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information.<br>• While there is a small theoretical concern of milk fistula with biopsy, image-guided core needle biopsy should proceed in the usual prompt timeframe following a BI-RADS 4 or BI-RADS 5 imaging result during pregnancy.<br>• If there is persistent bloody nipple discharge without abnormal breast imaging, a breast surgical expert should be consulted to discuss possible further diagnostic testing (eg, duct excision).<br>• Breast MRI is not appropriate for the management of abnormal nipple discharge during pregnancy. |

*Abnormal nipple discharge includes bloody or clear, uniductal, unilateral discharge. Milky discharge is generally normal in pregnancy.

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Breast Erythema or Worrisome Skin Changes (eg, thickening or edema) | R | O | R | NR | • Breast erythema or suspicious skin changes should undergo age-appropriate breast imaging evaluation similar to individuals who are not pregnant (see BSCR-15).<br>• Begin evaluation of erythema during pregnancy with breast ultrasound. However, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information.<br>• Breast MRI is not appropriate for the management of worrisome skin changes during pregnancy. |
| Persistent, Focal Breast Pain | R | O | R | NR | • While breast pain is common due to the physiologic changes of pregnancy and is considered normal, focal persistent breast pain (defined as 4 to 6 weeks duration) should undergo evaluation similar to individuals who are not pregnant (see BSCR-16).<br>• Begin evaluation of persistent, focal breast pain during pregnancy with breast ultrasound. However, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information.<br>• While there is a small theoretical concern of milk fistula with core needle biopsy, image-guided biopsy should proceed in the usual prompt timeframe following a BI-RADS 4 or BI-RADS 5 imaging result during pregnancy.<br>• Breast MRI is not appropriate for the management of persistent, focal breast pain during pregnancy. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| BI-RADS Category 3 Imaging Follow-up (see BSCR-20) | R‡‡ | R‡ | R‡ | NR | • Pregnancy should not change the management of follow-up of a BI-RADS 3 finding and appropriate follow-up imaging and/or examination should proceed as outlined in BSCR-20.<br>• In the case of a BI-RADS 3 finding on MRI without associated ultrasound or mammography findings, a breast expert should be consulted to assist with counseling regarding follow-up and management recommendations (eg, defer to after pregnancy). |

R = Recommended
NR = Not recommended
O = Optional, depending on individual circumstances
‡Recommended if this is the imaging modality that initially resulted in the BI-RADS 3 finding.
‡‡If an abnormal CBE finding was associated with the BI-RADS 3 imaging result, it may be appropriate to repeat CBE.

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Average-Risk Screening in Individuals ≥40 Years | R | R | NR | NR | • While there is both decreased sensitivity and specificity of screening mammography during lactation, there is no contraindication to screening mammography during lactation.<br>• Lactating individuals and their providers may choose to defer screening until after lactating, particularly if they are not planning prolonged breastfeeding.<br>• It is recommended that the lactating woman either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |
| High-Risk Screening in Individuals w/Gene Mutation | R | R | NR | R | • In high-risk individuals, it is appropriate to recommend screening mammography at routine intervals (see BSCR-2 and BSCR-3).<br>• The use of screening ultrasound has not been evaluated as a method to reduce breast cancer mortality in high-risk individuals who are lactating.<br>• In high-risk individuals, it is appropriate to recommend screening breast MRI at routine intervals (see BSCR-2 and BSCR-3).<br>▸ There is minimal excretion of gadolinium into human breast milk, with less than 1% of permitted neonatal dose of contrast over the first 24 hours after maternal administration. Breast MRI appears to be highly sensitive for the detection of known PABC and may proceed if due during lactation in high-risk individuals.<br>• It is recommended that the lactating individuals either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Management of Palpable Breast Mass | R | R | R | NR | • Age-appropriate evaluation of a palpable mass during lactation should proceed similar to that outlined in BSCR-5 and BSCR-11.<br>• It is recommended that the lactating woman either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam.<br>• While there is a small theoretical concern of milk fistula with core needle biopsy, image-guided biopsy should proceed in the usual prompt timeframe following a BI-RADS 4 or BI-RADS 5 imaging result during lactation. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Management of Abnormal Nipple Discharge* | R | R | R | O | • Nipple discharge is normal during lactation. Abnormal nipple discharge is defined as: persistent (see next bullet), uniductal, unilateral bloody nipple discharge.<br>• Due to normal physiologic changes of pregnancy, bloody nipple discharge is common during lactation, but usually short-lived (eg, 1 or 2 episodes). Persistence of bloody nipple discharge beyond 1 or 2 episodes should undergo evaluation.<br>• Age-appropriate evaluation of abnormal nipple discharge during lactation should proceed similar to that outlined in BSCR-10.<br>• While there is a small theoretical concern of milk fistula with core needle biopsy, biopsy should proceed in the usual prompt timeframe following a BI-RADS 4 or BI-RADS 5 imaging result during pregnancy.<br>• If there is persistent bloody nipple discharge without abnormal breast imaging, a breast surgical expert should be consulted to discuss possible further diagnostic testing (eg, duct excision).<br>• Breast MRI is not contraindicated for the management of abnormal nipple discharge during lactation if clinically indicated.<br>• It is recommended that the lactating woman either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |

*Abnormal nipple discharge includes bloody or clear, uniductal, unilateral discharge. Milky discharge is generally normal in pregnancy.

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Breast Erythema or Worrisome Skin Changes (eg, thickening or edema) | R | O | R | O | • Breast erythema or worrisome skin changes may be due to puerperal mastitis and all patients should undergo evaluation and, if clinically consistent with mastitis, appropriate treatment should proceed, including the use of antimicrobials.<br>• In some circumstances, breast erythema or worrisome skin changes without other evidence of mastitis (absence of pain or fever) may prompt immediate evaluation for inflammatory breast cancer.<br>• Failure to resolve mastitis with usual treatment should result in an in-person evaluation for alternative etiologies (eg, breast abscess, inflammatory breast cancer).<br>▸ Breast imaging is nearly always indicated to assist in the diagnosis of persistent breast erythema or skin changes that have failed usual treatment for mastitis. In this circumstance, age-appropriate evaluation should proceed similar to individuals who are not pregnant (see BSCR-15).<br>▸ Breast ultrasound is particularly useful in diagnosing breast abscess and may be the appropriate first imaging modality and if found, drainage is usually indicated and provides a definitive diagnosis.<br>▸ However, if a breast abscess is not definitively identified, individuals should promptly undergo evaluation for inflammatory breast cancer (BSCR-15).<br>• It is recommended that the lactating individuals either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| Persistent, Focal Breast Pain | R | R | R | NR | • While breast pain is common due to the physiologic changes of lactation and is considered normal, focal persistent (defined as 4 to 6 weeks duration) breast pain should undergo evaluation similar to individuals who are not lactating (see BSCR-16).<br>• Begin evaluation of persistent, focal breast pain during lactation with breast ultrasound. However, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information.<br>• While there is a small theoretical concern of milk fistula with core needle biopsy, image-guided biopsy should proceed in the usual prompt timeframe following a BI-RADS 4 or BI-RADS 5 imaging result during pregnancy.<br>• While breast MRI is not contraindication for the management of persistent, focal breast pain during lactation, it is usually not indicated.<br>• It is recommended that the lactating individuals either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |

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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | Clinical Breast Exam | Mammography | Ultrasound | MRI | |
| BI-RADS Category 3 Imaging Follow-up (see BSCR-20) | R‡‡ | R‡ | R‡ | NR | • Lactation should not change the management of follow-up of a BI-RADS 3 finding and appropriate follow-up imaging and/or examination should proceed as outlined in BSCR-20.<br>• It is recommended that the lactating woman either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |
| Management of Axillary Mass during Lactation | R | R | R | O | • The development of an axillary mass during lactation is not uncommon and may be due to normal lactational changes in accessory axillary breast tissue that are present in ~15% of individuals. It is also not uncommon for this to be asymmetric. The development of an axillary mass within the first week or two following delivery is clinically consistent with lactational changes due to the presence of axillary breast tissue.<br>• If after clinical examination there remains concern that the physical findings are not due to normal axillary breast tissue, providers should proceed with evaluation as outlined in BSCR-18.<br>• It is recommended that the lactating individuals either pump or breastfeed just prior to imaging to improve sensitivity and comfort of the exam. |

R = Recommended
NR = Not recommended
O = Optional, depending on individual circumstances
‡Recommended if this is the imaging modality that initially resulted in the BI-RADS 3 finding.
‡‡If an abnormal CBE finding was associated with the BI-RADS 3 imaging result, it may be appropriate to repeat CBE.

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

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. |
| **Category 3** | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

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# Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/04/18

**Table of Contents**

## Overview

The average lifetime risk of breast cancer for a woman in the United States has been estimated at 12.3% (ie, 1 in 8 women).[1] For 2018, the American Cancer Society (ACS) estimates that 63,960 cases of female carcinoma in situ of the breast and 268,670 cases of invasive breast cancer (266,120 women and 2,550 men) will be diagnosed in the United States.[2] About 41,400 deaths are estimated for 2018.[3] The good news is that death rates have been falling an average of 1.8% each year over the course of 2006 through 2015.[4] This decrease has been attributed to mammographic screening and treatment advances.[5]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis are for facilitating 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 taken into account along with imaging results and histologic assessment.

## Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Breast Cancer Screening and Diagnosis, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: breast cancer screening; screening mammography; breast cancer diagnosis. The search results were narrowed by selecting studies in humans published in English. An updated search was carried out before the publication of this document. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

Search results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and/or discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

## Breast Screening Components

Breast screening is performed in women without any signs or symptoms of breast cancer so that disease can be detected as early as possible, which allows early treatment to reduce the mortality and morbidity associated with the disease. A diagnostic breast evaluation differs from breast screening in that it is used to evaluate an existing problem (eg, palpable mass, discharge from the nipple).

The components of a breast screening evaluation are dependent on age and other factors such as medical and family history, and can include breast awareness (ie, patient familiarity with her breasts); regular clinical encounters, which include breast cancer risk assessment and clinical breast exam (CBE); breast imaging with screening mammography; and, in selected cases, breast MRI.

## Clinical Encounter

The starting point of these guidelines for screening and evaluating breast abnormalities is a clinical encounter, which includes a complete medical history followed by breast cancer risk assessment and a CBE. The frequency of the clinical encounter depends on the age and risk assessment of the patient.

In a review of controlled trials and case-control studies that included CBE as part of the screening modality, sensitivity of CBE was found to be 54% and specificity 94%.[6] Randomized trials comparing CBE versus no screening have not been performed. Rationale for recommending the clinical encounter is to maximize the earliest detection of breast cancers. Overdiagnosis and overtreatment is not a significant issue with CBE, as the majority of palpable cancers found on a CBE are invasive cancers. CBE is an important component of a clinical encounter and is important in order to detect early-stage palpable cancers, especially those that are mammographically occult (eg, lobular carcinomas). According to the NCCN Panel, inspection of the breasts should be performed with the patient in both upright and supine positions. Positioning may be done so as to elicit any subtle shape or contour changes in the breast.[6]

*Breast Awareness:* Women should be familiar with their breasts and any changes to them.[7,8] Data from a large randomized trial of breast self-examination (BSE) screening have shown that instruction in BSE has no effect on reducing breast cancer mortality. In this study, 266,064 Chinese women who were not undergoing routine mammographic screening were randomized to either receive instruction in BSE or not.[9] Compliance was encouraged through feedback and reinforcement sessions. After 10 to 11 years of follow-up, 135 breast cancer deaths in the group that received instruction and 131 in the control group were observed. The cumulative breast cancer mortality rates were not significantly different between the two arms (relative risk [RR], 1.04; 95% CI, 0.82–1.33; $P$ = .72). 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. The NCCN Panel recommends breast awareness, specifically that all women should be familiar with their breasts and promptly report any changes to their health care provider.

## Breast Cancer Risk Assessment

If the physical examination is negative in an asymptomatic woman, the next decision point is based on risk stratification. Women are stratified into two basic categories of risk for the purpose of screening recommendations: average risk and increased risk. Risk assessment is outlined in the NCCN Guidelines for Breast Cancer Risk Reduction. The increased risk category consists of six groups: 1) women with a prior history of breast cancer; 2) women ≥35 years of age with a 5-year risk of invasive breast cancer ≥1.7% (per Gail Model); 3) women who have a lifetime risk >20% based on history of lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (ADH)/atypical lobular hyperplasia (ALH); 4) women who have a lifetime risk >20% as defined by models that are largely dependent on family history; 5) women between the ages 10 and 30 years with prior thoracic RT (eg, mantle irradiation); and 6) women with a pedigree suggestive of or known genetic predisposition.

## Breast Imaging Modalities

### *Screening Mammography*

Of the various imaging modalities, mammography remains the most important as it is the only one to demonstrate a mortality reduction. A screening mammogram typically involves two x-ray images of each breast (ie, one taken from the top [craniocaudal] of the breast and the other from the side [mediolateral oblique]). Technical aspects of mammography can affect the quality of screening results. Digital mammography, which has

replaced film-screen mammography in the United States, generates an electronic image of the breast and allows for computer storage and processing of the image, thereby increasing the ability to detect subtle abnormalities.[10,11]

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.[12,13] 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.[14]

More recently, combined use of digital mammography (two-dimensional, 2D) in conjunction with digital breast tomosynthesis (DBT) improves cancer detection and reduces false-positive call-back rates.[15-25] Tomosynthesis allows acquisition of three-dimensional (3D) data using a moving x-ray and digital detector. These data are reconstructed using computer algorithms to generate thin sections of images. The combined use of 2D and DBT results in double the radiation exposure compared with mammography alone. However, this increase in radiation dose falls below dose limits of radiation set by the U.S. Food and Drug Administration (FDA) for standard mammography. The radiation dose can be minimized by newer tomosynthesis techniques that create a synthetic 2D image, which may obviate the need for a conventional digital image.[16,26,27]

The presence of dense breast tissue decreases the sensitivity of mammography to detect small lesions and may obscure visualization of an underlying cancer. In addition, dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.[28-31] About half of all women of screening age have “dense” breast tissue referred to as “heterogeneously dense” or “extremely dense” by American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS®) nomenclature. The presence of dense tissue is not abnormal and can change over time. Many states have passed legislation mandating patient notification of breast density, but few have required insurance coverage for supplemental screening.[32] The NCCN Panel recommends counseling on the risks and benefits of supplemental screening for women with heterogeneously dense and extremely dense breast tissue.[33] Different supplemental imaging modalities may be considered based on risk and patient values/preference.[34]

***Screening Ultrasound***

Due to limitations of mammographic screening, especially in women with dense breasts, other imaging modalities are being explored to supplement mammography, most commonly ultrasound and MRI. Unlike mammographic screening, both technologies lack evidence from randomized controlled trials (RCTs) of screening efficacy, although ultrasound is widely used in the diagnostic setting. Most clinical ultrasound screening studies have found increased cancer detection to be incremental to screening mammograms in women with dense breasts; however, they may increase recall and benign breast biopsies. For example, a large prospective study in women with dense breasts and elevated risk for breast cancer found that adding screening ultrasound to mammography identified an additional 4.3 cancers per 1000 women screened (95% CI, 1.1–7.2 cancers per 1000) but increased the number of false-positive results.[34] Subsequent follow-up studies showed similar results.[35,36] However, in women with dense breasts, the mammographic sensitivity was found to be 50% (95% CI, 33.8%–66.2%) and the sensitivity of mammography plus ultrasound was 77.5% (95% CI, 61.6%–89.2%).[34] Application of screening ultrasound to women with dense breasts in clinical populations has produced similar results.[37]

Although there is increasing evidence that breast ultrasonography can be useful in the incremental detection of breast cancer as an adjunct to screening mammography in the evaluation of women with dense breasts,[34,35,38-40] the routine use of ultrasound as a universal supplemental *screening* test in women with average risk is *not* recommended by the NCCN Panel at this time. Ultrasonography is commonly used for *diagnostic* follow-up of an abnormality seen on screening mammography and palpable clinical concerns.

***Screening MRI***

The sensitivity of contrast-enhanced breast MRI at detecting breast cancer is higher than the sensitivity of mammography, although the specificity of the former procedure is often lower, resulting in a higher rate of false-positive findings.[41] In addition, microcalcifications are not detectable with MRI.[42,43] Similar to screening ultrasound, whether 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, the benefits of screening MRI for early detection of breast cancer in women with high risk, such as those ages 10 through 30 years with a history of prior thoracic radiation, a known genetic predisposition for breast cancer, or a strong family history of the disease have been demonstrated in multiple studies.[44-52] 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.[53] Nevertheless, a high false-positive rate for screening MRI was identified in several 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.[54]

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.[55] 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% of patients with LCIS who had negative mammogram results. MRI screening did not affect 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 two groups.

Studies have reported that deposits of gadolinium, a component of MRI contrast agents, remain in the brain of some patients who undergo 4 or more contrast MRI scans, long after the last administration.[56-59] Retention of gadolinium has also been seen in the bone.[60,61] The clinical significance and practice implications of these observations are unclear and are being investigated. In 2015, the FDA issued a safety warning alerting that investigations were ongoing for the risk associated with gadolinium deposits in the brain following its repeated use with MRI. In 2017, the FDA issued an update stating that its review of available data had not identified adverse health effects from gadolinium retained in the brain.[62] Patients will be asked to read a medication guide prior to receiving gadolinium.

In women with a history of thoracic radiation between ages 10 and 30 years, a known genetic predisposition to breast cancer, or a lifetime risk of >20% based on models such as Claus or Tyrer-Cuzick, based on current evidence, the NCCN Panel continues to recommend an annual MRI as an

adjunct to mammography. Women with LCIS or ALH/ADH with a lifetime risk of ≥20% should be considered for breast MRI based on emerging evidence of the benefits.

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. The ACR has published guidelines for the performance of contrast-enhanced MRI of the breast.[63]

***Other Breast Imaging Modalities***

There is emerging evidence that breast scintigraphy and contrast-enhanced mammography may improve detection of early breast cancers among women with mammographically dense breasts;[64-67] current evidence does *not* support their routine use as alternative screening procedures. Thermography and ductal lavage are *not* recommended by the NCCN Panel for breast cancer screening or diagnosis. The FDA has issued a safety alert stating that ductal lavage should not be a replacement for mammograms.[68]

## Screening Recommendations for Women at Average Risk

The NCCN Panel recognizes that the primary purpose of screening women with average risk for developing breast cancer is to detect breast cancer early, which allows treatment to decrease mortality and morbidity associated with breast cancer.

*Women with Average Risk Between the Ages of 25 and 39:*

The NCCN Panel recommends a clinical encounter, which includes ongoing breast cancer risk assessment, risk reduction counseling, as well as a CBE every 1 to 3 years, and encouraging women to be aware of their breasts and promptly report any changes to their health care provider.

Although the screening CBE by itself does not rule out disease, the high specificity of certain abnormal findings by highly qualified clinicians increases the probability of finding certain breast cancers (eg, lobular carcinoma). The NCCN Panel believes that a clinical encounter provides an opportunity for providers to perform a CBE, conduct a breast cancer risk assessment, provide risk reduction recommendations, and counsel on healthy lifestyles.

*Women with Average Risk 40 Years and Older:*

The NCCN Panel recommends annual clinical encounter, which includes ongoing breast cancer risk assessment, risk reduction counseling, as well as a CBE, and encourages women to be aware of their breasts and promptly report any changes and annual screening mammography (category 1 recommendation) with the *consideration* of tomosynthesis. Women electing to undergo screening mammography should be counseled regarding its potential benefits, risks, and limitations. The NCCN Panel is in agreement with ACS and other organizations that annual screening mammograms in average-risk women aged 40 years and older should be covered by health care payers without additional cost-sharing or copayments.

Mammographic screening and subsequent treatment have been shown to decrease breast cancer mortality beginning at age 40 years.[69,70] Meta-analysis of invitational RCTs, observational studies, and computer modeling of mammographic screening consistently show benefit, although the magnitude of benefit has varied in part due to the diversity of study designs and screening frequency. However, the RCTs are now old and may not reflect current mammography technology, interpretation, and oncologic care. Therefore, effectiveness may be better estimated in more modern observational studies.

The mammography screening guidelines put forth by various organizations vary with respect to age to initiate screening, the frequency of screening, and when to stop screening.[69,70] The assessment of the benefits of mammography versus the risks based on age are weighed on different scales by different organizations.

The NCCN Panel continues to support its long-standing recommendation of *annual* screening mammography beginning at age 40 years (category 1 recommendation), as it results in the greatest mortality reduction, most lives saved, and most life years gained.

The NCCN Panel has not established an upper age limit for screening. According to the panel, if a patient has severe comorbid conditions limiting her life expectancy and no further intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of her age.

*Rationale for Mammographic Screening Starting at Age 40*:
Reduction in breast cancer-related mortality is the major benefit of mammographic screening for breast cancer. This benefit is evident across studies, including RCTs, case-controlled observational studies, and computer modelling studies.

While breast cancer screening guidelines put forth by all the organizations acknowledge mortality reduction benefit from current studies of mammography screening in women 40 to 49 years of age, those recommending breast cancer screening to begin at age 50[70] view the benefits of screening as being balanced by the harms of screening during this decade. Other organizations, who have recommended screening commencement at age 45 as a “strong” recommendation, have shown the absolute benefit of ages 45 to 49 to be very similar to ages 50 to 54.[69] While showing there is benefit of screening for ages 40 to 44, a “qualified” rather than a “strong” recommendation is given for the younger age group due to the lower absolute benefit. However, the “qualified” recommendation means “most” women would want the earlier screening and only a “small proportion” would not.[69]

*Benefits of Mammographic Screening*:
Systematic reviews of RCTs have generally shown a reduction in breast cancer mortality with mammography screening.[71]

The UK Age trial specifically studied the effect of film-screen mammographic screening starting at age 40 years.[72] A mean of 10.7 years of follow-up showed a non-statistically significant breast cancer mortality reduction in women invited to screening (RR, 0.83; 95% CI, 0.66–1.04).[72] A follow-up of the UK AGE trial was carried out to study breast cancer mortality and incidence at a median of 17.7 years of follow-up, an increase of 7 years from the previous analysis.[73] There continued to be a non-significant overall reduction in risk of breast cancer mortality (RR, 0.88; 95% CI, 0.74–1.04) during a median of 17 years of follow-up. However, the reduction in breast cancer mortality noted in the first 10 years after diagnosis was now significant in the group that underwent screening compared with the control group (RR, 0.75, 0.58–0.97).[73] Other trials included women who were up to age 49 years at the time of entry into the trial, who were therefore in their 50s during the screening intervention. The results of the UK Age trial support the importance of annual mammography screening in women ages 40 to 49 years of age to reduce breast cancer-related mortality.[73]

A Swedish study compared breast cancer mortality rates in women 40 to 49 years of age living in different counties. Counties included those that invited women for screening starting at age 40 and others that did not invite women to be screened at age 40 and started screening at age 50.[74] After an average 16 years of follow-up, the investigators observed an overall 29% mortality reduction (RR, 0.71; 95% CI, 0.62–0.80). For age

groups 40 to 44 and 45 to 59 years, the RR estimates were 0.82 (95% CI, 0.67–1.00) and 0.63 (95% CI, 0.54–0.75).[74] Although the estimated reduction in breast cancer mortality was smaller for ages 40 to 44 compared with ages 45 to 49, the reduction in mortality seen for ages 40 to 44 was still substantial.[74]

It is important to note that the RCTs studying the benefits of screening mammography used screen film mammography, sometimes using only a single view. Therefore, they may not reflect results obtained with modern advances in imaging. Digital mammography has been shown to detect more breast cancers in women with dense breasts, which is common in younger women. The more recent observational studies better quantify the effectiveness of screening in the context of improved imaging techniques.

Case-control observational studies have shown benefits of reduction in breast cancer mortality ranging from 40% to 45%.[75,76] A meta-analysis of observational case-control studies found a significant reduction in breast cancer mortality with mammographic screening for women aged 40 to >79 years of age with a 48% mortality reduction (odds ratio [OR] 0.52; 95% CI, 0.42–0.65) after adjustment for self-selection.[77] Relevant to the North American population, data from a Canadian study showed a mortality reduction of 44% (CI, 33%–55%) among screened women ages 40 to 49 years, which was similar to the overall reduction in mortality of 40% (CI, 33%–48%) found among women ages 40 to 79 years.[76]

A retrospective analysis evaluating the benefits of mammographic screening of women aged 40 to 49 years found that mammography-detected breast cancer coincides with lower-stage disease at detection, resulting in reduced treatment morbidity and lower rates of recurrence.[78] A population-based study of data from the Netherlands Cancer Registry estimated the impact of tumor size in women with breast cancer in two time intervals: 1999 to 2005 and 2006 to 2012. The year 2005 was used to divide the data into two-time intervals studies, because trastuzumab and other effective adjuvant therapy were introduced after this year in the Netherlands. The analysis found that tumor size remained a critical component of survival even with the availability of new and effective systemic therapy options.[79] These findings reiterate the fact that diagnosing breast cancer at an early stage is important.

The Cancer Intervention and Surveillance Modeling Network (CISNET) models from 2009 demonstrate a 29% to 54% (mean 39%) mortality reduction for annual screening for women ages 40 to 84 years.[80] The CISNET models from 2015, based on digital screening mammography, show greater mortality reduction benefit.[81] Benefits of screening younger women (in their 40s) are more favorable when considered from the perspective of life years saved compared exclusively to mortality reduction.[82] Women in their 40s have the highest number of life years at risk to be lost due to longevity even though their breast cancer risk is smaller. Breast cancer is the second leading cause of deaths for women in their 40s, trailing only poisonings.

Women should be informed of the evidence demonstrating the value of detecting breast cancer early, before symptoms develop. The benefits of early detection include mortality reduction, less aggressive treatment, and a wide range of treatment options. Screening also identifies women with atypical hyperplasia or LCIS who may be candidates for risk reduction therapy to reduce their chance of developing breast cancer.

*Harms of Mammographic Screening:*
The harms or risk profile for breast cancer screening is weighted differently by different organizations.[69,70] This is a very subjective rating as there are limited data regarding a woman's perspective of the harms of screening. The clinical practice guidelines that recommend delaying screening to age 50 and older[69] place a greater emphasis on the risks of screening mammography, specifically false-positive results and

overdiagnosis. Most women highly value the reduction in breast cancer mortality, whereas many women do not consider false positives and potential overdiagnosis to be a "harm."[83] In this study, 63% of women thought 500 or more false positives per life saved was acceptable.[83]

The NCCN Panel believes that the harms analysis of mammographic screening is most informative if it includes the net harms of mammographic screening in individuals who underwent screening versus those who did not. According to the NCCN Panel, the major harm related to *not performing* any screening for breast cancer is diagnosis of later-stage breast cancer, which may prove to be lethal or require therapy that is more extensive. There is evidence showing that women diagnosed with breast cancer who did not undergo screening had substantially more need for chemotherapy and more extensive surgery than women who underwent routine screening.[84]

Furthermore, absence of mammographic screening for breast cancer does not mean absence of breast-related problems. Non-screened women develop signs and symptoms leading to diagnostic investigation, false-positive biopsies, or potential diagnosis of non-lethal conditions.

A mammogram result is often considered a false positive when it prompts additional imaging tests and/or biopsy in an abnormality that is not cancerous. False-positive results can occur at any age. It is important to distinguish between recalls from screening and biopsies that result in a false-positive outcome. Recalls are defined by the FDA as "incomplete" and not positive. Recalls are resolved by obtaining incremental diagnostic mammographic imaging and/or ultrasound with the vast majority of recalls proving negative and not requiring biopsy. The frequency of recalls from screening are the same per decade whether screening begins at age 40 or age 50.[70] While recalls are commonly thought to be higher in younger women, this primarily reflects higher recall rates at the prevalent or initial screen when prior mammograms are not available for comparison and not the age at which screening commences. Initiating screening mammography at age 50 would shift this "prevalent" false positive to that decade. Furthermore, the decade-long false-positive biopsy recommendation rate is somewhat lower when screening begins at age 40 compared to age 50. Less than 1% of screened women per year will be recommended for a biopsy that proves benign, whether annual screening commences at age 40 or 50. The vast majority of false-positive biopsies are now performed as outpatient image-guided needle biopsies using local anesthesia and are generally well-tolerated and acceptable to women.

Those considering false positives as one of the harms of screening note psychosocial consequence as one of the negative consequences of false positives.[85] However, a cross-sectional survey of women's attitudes toward false positives found that women consider false positives as an acceptable consequence.[83]

Overdiagnosis is the detection of a condition by screening that would not have become apparent by usual care absent screening. Overdiagnosis may lead to overtreatment, which is the more significant problem. It is important to understand that overdiagnosis would not influence the age to initiate screening or the screening interval. The mammographic abnormality that leads to a potential overdiagnosis does not go away without treatment. If the age to initiate screening is raised from 40 to 45 or 50 years, or the screening interval is lengthened to biennial, the potential overdiagnosis would occur at the next mammogram that showed the imaging abnormality.

Overdiagnosis is difficult to measure, because neither the clinician, pathologist, nor the patient can be sure whether the abnormality detected by screening would be harmless or life threatening to the patient. Furthermore, overdiagnosis assumes that the level or amount of diagnosis by symptomatic usual care is optimal. The estimates of overdiagnosis vary widely between various studies (from almost none to up to 54%[69,71,86-88])

due to methods and parameters used for estimation and whether ductal carcinoma in situ (DCIS) is included or excluded. Furthermore, overdiagnosis estimates vary by age and duration of follow-up.

The most reliable estimates of overdiagnosis would be from RCTs in which there was no formal screening offered to the control group for a long period at the end of the screening period. The Malmo randomized trial, in which the older-age invited cohort group was not routinely screened at the end of the trial,[89] showed an overdiagnosis rate of 10% after an average of 15 years follow-up, which included invasive cancer and DCIS. The rate was 7% for invasive cancer.[89] The National Breast Screening Studies in Canada conducted two randomized trials that included a control group that did not receive routine screening at the end of the trial. The follow-up period was 13 years. In the first trial, in which women were aged 40 to 49 years at recruitment, the estimated overdiagnosis was 14%. In the second trial, in which women were aged 50 to 59 years at recruitment, the estimated overdiagnosis rate was 11%.[90,91] Using these 3 studies, the UK review estimated overdiagnosis (including DCIS) to be 10.7%.[92] Yet, these studies are limited by their age and differing use of diagnostic mammography among non-screened women. However, analysis of the UK AGE trial, which included women aged 40 to 49 years, showed a very low rate of overdiagnosis of 1%,[93] a value similar to estimates from Sweden for women in their 40s.[74] A recently reported population-based screening study showed a rate of only 0.3% overdiagnosis after 12 years of follow-up in either invited or uninvited women (n = 988, 090) and a 46% reduction in breast cancer mortality among attenders.[94] Direct estimates of type 1 overdiagnosis for screened U.S. women show marked differences depending on age of diagnosis, with less than 1% among premenopausal women and 22% among women aged 80 years.[95]

Prevention of cancer death is highly valued compared with false-positive results/overdiagnosis by most women.[83] Current science cannot predict which breast cancer may be overdiagnosed or be potentially lethal in any one individual. Personalized treatment programs are recommended and advances in personalized treatment will diminish the risk of overtreatment and significance of overdiagnosis. The treatment of cancer may cause suffering and anxiety, but that suffering is likely worth the gain from the potential reduction in breast cancer mortality. According to the NCCN Panel, the risk of overdiagnosis and false positives are outweighed by the benefit of mortality reduction in determining the age to recommend starting screening.

The NCCN Panel emphasizes adopting strategies and research to reduce the harms of screening (false positives and overdiagnosis) rather than raising the age to initiate screening to potentially delay these issues. This includes newer imaging modalities that improve the detection of breast cancer with fewer recalls (eg, tomosynthesis). Research to better define the biology of breast cancer is needed so that lesions that are not destined to progress are either not treated or are treated less aggressively.

*Screening Interval and Rationale for Annual Mammogram Screening*: Another consideration is the time interval between screening exams. Performing screening mammography annually versus every other year remains controversial. Most studies and models suggest incremental benefit with annual screening, especially among younger women and premenopausal women.[69,70,80,96] The evaluation of benefits versus risk strongly supports the value of screening and the importance of adhering to a schedule of regular mammograms.

The NCCN Panel believes that the benefits of annual mammography outweigh the risks. Breast cancer mortality is estimated to be lower with annual compared to biennial screening mammograms.[80] Additionally, mammograms can often detect a lesion 2 years before the lesion is discovered by CBE. Interval cancer rates are lower among annually

screened women. To reduce mortality from breast cancer, yearly screening is thought to be more beneficial. The panel also acknowledges that incomplete compliance will alter the outcome of any recommendation.

An evaluation of the CISNET modeling of benefits of screening women between 40 to 49 years found that using *annual* digital mammography saves 30% more lives and 34% more life-years than *biennial* digital mammography.[97] Also, with annual digital screening mammography, the deaths averted (0.6/1000) are similar for ages 40 to 44 *and* 45 to 49 years (0.7/1000).[96,98]

A decline in breast cancer specific-mortality was observed in a cohort of women for every additional annual mammogram performed 5 years prior to breast cancer diagnosis; this further emphasizes the importance of annual mammography.[99] The results of a primary analysis to estimate the association between incidence of DCIS detected by screening and subsequent invasive interval cancer incidence showed a DCIS detection rate of 1.5 per 1000 screened and a reduction of one invasive interval cancer per 1.5 to 3 DCIS cases detected.[100]

While the risk of false positives is greater with annual compared to biennial mammograms,[70] the panel believes that the lower mortality and morbidity of annual screening outweighs this harm.

*Age to Stop Mammographic Screening:*
There are limited RCT data regarding screening of elderly women, because most trials for breast screening have used a cutoff age of 65 or 70 years.[101-103] However, observational studies and computer models show mortality benefit to age 80 to 84.[69,80] Considering the high incidence of breast cancer in the elderly population, the screening guidelines used for women who are age 40 or older are recommended in the elderly as well. Clinicians should always use judgment when applying screening guidelines. The mortality benefit of screening mammography is often delayed for 5 to 7 years in RCTs that emphasize the importance of life expectancy and overall health when considering age to stop screening. Mammography screening should be individualized, weighing its potential benefits/risks in the context of the patient's overall health and estimated longevity.[104] 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, regardless of her age.[104,105]

## Screening Recommendations for Women at Increased Risk

*Women with Prior History of Breast Cancer*: These women are treated according to the recommendations outlined in NCCN Guidelines for Breast Cancer.

*Women Aged 35 Years or Older with a 5-Year Risk of Invasive Breast Carcinoma Greater Than or Equal to 1.7% by the Modified Gail Model:* For women aged 35 years 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[106-110] that can be accessed at: http://www.cancer.gov/bcrisktool/Default.aspx, which provides risk projections on the basis of several 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 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 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify women who are at increased risk. The Gail model should not be used for women with a predisposing gene mutation, a strong family history of breast or

ovarian cancer suggestive of a genetic predisposition, women with a prior history of thoracic radiation, or for those with LCIS.

The Gail model was updated using combined data from the Women's Contraceptive and Reproductive Experiences (CARE) study and the SEER database, as well as causes of death from the National Center for Health Statistics, to provide a more accurate determination of risk for African-American women.[111] It has also been updated using the data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander women in the United States.[112]

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 for a 60-year-old woman, which is the median age of diagnosis of breast cancer in the United States. 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 eligible for screening breast MRI.

For a woman aged 35 years or older with a 5-year risk ≥1.7%, the NCCN Panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months and annual digital mammography, with the consideration of tomosynthesis, to begin at the age identified as being at increased risk by the Gail model. In addition, according to the NCCN Panel, women in this group should be counseled for consideration of risk-reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

*Women Who Have a Lifetime Risk >20% Based on History of LCIS or ADH/ALH:* A diagnosis of LCIS or ADH/ALH is associated with high risk of development of cancer in either breast.[113-118]

For women with a history of LCIS or ADH/ALH, the NCCN Panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months beginning at the age of diagnosis and annual digital mammography, with the consideration of tomosynthesis, beginning at the age of diagnosis of LCIS or ADH/ALH but not less than 30 years of age. In addition, according to the NCCN Panel, annual MRI should be considered beginning at the age of diagnosis of LCIS or ADH/ALH but not before age 25 (based on emerging evidence).[55] Women in these groups should also be considered for risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

*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. According to the ACS guidelines for breast screening, MRI may be performed as an adjunct to mammography[53] in a high-risk woman if her lifetime risk of breast cancer is approximately 20% or greater based on models that rely mainly on family history. A cancer genetic professional should be involved in determining the lifetime risk of the individual based on models dependent on family history. These include Claus,[119] Tyrer-Cuzick,[120] and other models.[121-123] BRCAPRO[124] and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)[125] are more commonly used to estimate the risk of *BRCA*

mutations. Strong genetic association between breast and ovarian cancer has been demonstrated in some families by linkage analyses.

For a woman with a >20% lifetime risk of breast cancer based on models largely dependent on family history, the NCCN Panel encourages breast awareness and clinical encounter every 6 to 12 months to begin at the age identified as being at increased risk. The NCCN Panel recommends annual digital mammography, with the consideration of tomosynthesis starting from 10 years prior to the youngest family member but not less than age 30. In addition, in accordance with the ACS guidelines,[53] the NCCN Panel recommends annual breast MRI to begin 10 years prior to the youngest family member diagnosed but not less than 25 years of age for women who have a lifetime risk of breast cancer >20% based on models that rely mainly on family history. According to the NCCN Panel, women in this group should be asked to consider risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

*Women Who Have Received Prior Thoracic Irradiation Between the Ages of 10 to 30 Years:* Results from several 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.[126-131] 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.[127,130] The RR of 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 >29 years.[130] 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.[132] 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 additional radiation in this population is negligible compared to overall radiation exposure. Findings from a survey of breast screening practices in this population of patients suggest that a sizable segment of this group is not undergoing regular mammographic screening.[133]

For women aged 25 years and older who have received prior thoracic irradiation, the NCCN Panel recommends encouraging breast awareness, and recommends a clinical encounter be initiated every 6 to 12 months 10 years after radiation exposure.[134] Breast imaging assessments with annual digital mammograms, with the consideration of tomosynthesis, are recommended 10 years after RT but not prior to age 30, and annual MRI[44] is recommended to begin 10 years after radiation exposure but not prior to age 25.

For women younger than 25 years who have received prior thoracic irradiation, the NCCN Panel recommends encouraging breast awareness, counseling on risk, and an annual clinical encounter starting 10 years after radiation therapy.

*Women with a Pedigree Suggestive Of or With a Known 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 based on 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.

The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian include recommendations for referral to a cancer genetics professional for further evaluation for individuals who have either a personal history or a close family history meeting certain criteria and also list screening recommendations for common hereditary syndromes that confer increased risk for breast and ovarian cancer. (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian).

## Diagnostic Evaluation

Breast symptoms are common among women. A retrospective study of women aged 40 to 70 years showed that 16% (total visits of 23 per 100 women) of women will present with symptoms to their provider during a decade with higher frequency among women ages 40 to 59 years compared to older women.[135] Pain is found to be the most common symptom followed by palpable mass. In addition, palpable areas of concern are identified during a breast physical exam. Breast clinical findings are not specific and there is variability in interpretation. Each symptom is associated with a risk of malignancy and warrants diagnostic evaluation; however, most symptoms will be determined to be benign in etiology. Women younger than age 40, who are not usually recommended for routine breast screening, also frequently present with breast symptoms.

Unlike imaging for screening, which is used to detect cancer in asymptomatic women, diagnostic evaluation is used to characterize a clinical finding or possible abnormality found during screening. There is confusion regarding the term “diagnostic” imaging, as it is applied to two very different situations: 1) imaging for clinical finding such as a palpable mass; and 2) incremental imaging after a possible abnormal screening mammogram in an asymptomatic woman (also referred to as recall or callback). To add further confusion, insurance carriers may consider a routine mammogram to be “diagnostic” in certain asymptomatic women (eg, in women with prior cancer). Diagnostic evaluation in this review will be restricted to the former two situations.

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

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

### Diagnostic Imaging After Screening Mammography Recall

#### *Diagnostic Mammography*

Screening mammography consists of two standard x-ray images of each breast, whereas a diagnostic mammogram includes additional views, such as spot compression views or magnifications views, to investigate the finding in question. Diagnostic mammography is associated with higher sensitivity but lower specificity as compared to screening mammography. DBT may replace traditional diagnostic mammographic imaging in certain situations.[136-138]

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

from screening, which is the most suspicious imaging outcome assessment.

The mammographic final assessments are mandated by the Mammography Quality Standards Act and Program (MQSA) and are reported using wording similar to the ACR BI-RADS® assessment categories, which classify likelihood of the breast findings into 6 final assessment catergories.[139] The BI-RADS® assessment categories (which include words and numbers) help to standardize both the reporting of mammographic findings and the recommendations for further management. The assessment wording and numbers are often used interchangeably. The definitions of the mammogram assessment categories are outlined in *Mammographic Assessment Category Definitions* in the algorithm. Importantly, the same imaging terms are used for screened (asymptomatic) recalled women and symptomatic women, which can create confusion regarding recommendations.

NCCN Recommendations for Screening Mammogram BI-RADS® Assessment Categories 1, 2, 3, 4, 5, and 6 are listed below. The NCCN recommendations following evaluation of symptomatic diagnostic women can be found in the next section. Importantly, Negative or Benign BIRADS® imaging assessments, in the setting of symptoms, rely upon correlation of clinical finding, which may indicate need for biopsy even with negative imaging. Conversely, suspicious imaging findings for women with clinical findings of very low suspicion still warrant biopsy.

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

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

For BI-RADS® categories 4 and 5 (suspicious or highly suggestive of malignancy), tissue diagnosis using core needle biopsy (preferred) or needle localization excisional biopsy with specimen radiograph is necessary. When a needle biopsy (aspiration or core needle biopsy) is performed, concordance between the pathology report and the imaging finding must be obtained.[140,141] For example, a negative needle biopsy associated with a spiculated category 5 mass (highly suggestive of malignancy) is discordant and clearly would not be an acceptable diagnosis. When the pathology and the imaging are discordant, the breast imaging should be repeated and/or additional tissue sampled or excised; surgical excision is recommended when pathology/image remains discordant. Women with a benign result exhibiting pathology/image concordance should be followed with mammography every 6 to 12 months for 1 to 2 years before returning to routine screening.

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

***Breast Ultrasonography***

Imaging by ultrasound is an important adjunct for diagnosing breast cancer.[142] However, breast ultrasonography does not detect most microcalcifications.[34,45,143-145] The definitions of the ultrasound assessment categories are outlined in *Ultrasonographic Assessment Category Definitions* in the algorithm.

***Diagnostic Breast MRI***

MRI can also play a role in the diagnostic setting. For patients with skin changes consistent with serious breast disease, consideration of breast MRI is included in the guidelines for those with benign biopsy of skin or nipple following BI-RADS® category 1-3 assessment. Since a benign skin punch biopsy in a patient with a clinical suspicion of inflammatory breast cancer (IBC) does not rule out malignancy, further evaluation is recommended. There is evidence that certain MRI features may facilitate diagnosis of IBC.[146] MRI may be used for suspicious nipple discharge when mammography and ultrasound are not diagnostic.[147-149]

## Breast Tissue Biopsy

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

***Fine-Needle Aspiration (FNA) Biopsy***

An FNA biopsy involves use of a smaller-bore needle to obtain cytologic samples from a breast mass. Advantages of FNA biopsy include its minimally invasive methodology and low cost,[150,151] 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.[152,153]

***Core Needle Biopsy***

A core needle biopsy, also called percutaneous core breast biopsy, is a procedure that typically involves obtaining multiple cores of solid tissue using standard techniques.[154,155] It can be performed under imaging guidance (eg, stereotactic [mammographic] ultrasound or MRI) or directed by palpation. Advantages of breast core needle biopsy include: 1) increased accuracy over FNA when the procedure is performed in situations where no mass is palpable; and 2) an ability to obtain tissue samples of sufficient size so as to eliminate the need for a follow-up biopsy to confirm malignancy.[156] 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.[157-159] Marker clip placement is done at the time of core needle biopsy so that the radiologist can identify the location of the lesion in the event that it is entirely removed or disappears during neoadjuvant treatment of a breast cancer.[160] With a few exceptions, core needle biopsy is preferred in the NCCN Guidelines over surgical excision when tissue biopsy is required. Sensitivity for core needle biopsy directed by ultrasound or stereotaxis is 97% to 99%.[98] According to the NCCN Panel, surgical excision is appropriate if unable to perform core needle biopsy.

***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.[160] Newer localization methods using radionucleotide seeds, reflector devices, or magnetic devices are being explored.

Excisional biopsy is included in the NCCN Guidelines as an option when tissue biopsy is required. Although excisional biopsy is 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. Excisional biopsy is recommended if the diagnosis by core needle biopsy is an indeterminate lesion, a benign lesion that is not concordant with imaging, ADH or other specific histologies that require additional tissue including mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist.[151,156,161,162] Support for this recommendation includes results of studies demonstrating an underestimation of cancer when atypical hyperplasia and LCIS are diagnosed by core needle biopsy.[163-168] However, there are situations (eg, select cases of LCIS or ALH such as those concordant with imaging, papillomas, fibroepithelial lesions, and radial scars) where close observation may be substituted for excisional biopsy in select patients.[151,161,169-176]

### Diagnostic Evaluation for Symptomatic Findings on Physical Examination

In general, the breast imaging evaluations after physical exam include mammography and ultrasound. The addition of ultrasound to diagnostic mammography significantly increases cancer detection and detection of specific benign findings such as cysts. Imaging for women younger than age 30 begins with ultrasound, while older women generally have both studies unless a cyst is likely.[177,178 ,179-182] Combined negative imaging results place a patient in a very low risk of malignancy (generally less than 3%) category; however, clinical judgment is necessary as some women with negative imaging may warrant biopsy that may identify a malignant mass.[177,183-185] The recommendations for subsequent management follow imaging assessments and clinical level of suspicion. Imaging should precede biopsy in most situations due to potential alteration of imaging findings by the biopsy. BIRADS imaging assessments, even if negative, must be correlated with the clinical findings prior to final clinical recommendations and do not stand alone as in the screening situation. There are clinical situations where biopsy is warranted even with negative imaging results.

Symptomatic or positive findings on physical examination include palpable mass in the breast, nipple discharge without a palpable mass, asymmetric thickening or nodularity, skin changes, axillary mass, and breast pain.

### Palpable Mass in the Breast

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

***Women with Palpable Mass Aged 30 Years or Older:***

The main difference in the guidelines for evaluating a palpable mass in women aged 30 years or older compared with younger women is the increased degree of suspicion of breast cancer. The initial evaluation begins with a diagnostic mammogram and ultrasound. Ultrasound should be geographically correlated with the palpable mass in question. Observation without further evaluation is not an option in these women. There are some clinical circumstances, such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30 to 39 years of age due to the high sensitivity of ultrasound alone.[180,181,186] After the diagnostic imaging assessment, the abnormality is placed into one of the following categories: negative or benign; probably benign; or suspicious or highly suggestive of cancer with management following BIRADS final assessment recommendations.

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

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

*Ultrasound Findings:*

***Solid Mass***:

If the solid mass found on the ultrasound is suspected to be probably benign (ie, BI-RADS® category 3), the options are: 1) observation, if clinical suspicion for breast cancer is low; or 2) tissue (core needle) biopsy, if the mass is clinically suspicious. Observation may be elected for those with low clinical suspicion; a physical examination follow-up with or without ultrasound or diagnostic mammogram is recommended every 6 months for 1 to 2 years to assess stability of the solid mass. There may be variability on the follow-up interval based on the level of suspicion. Numerous clinical studies now support the ability of ultrasound to accurately characterize palpable solid masses as probably benign with risk of malignancy generally less than 2%. However, these same studies have shown that many such masses will eventually warrant biopsy and compliance with follow-up may be low.[178,180,187-191] Progression of size or suspicion on follow-up studies warrants tissue biopsy. The NCCN Panel recommends a tissue (core needle) biopsy for solid masses with a BI-RADS® 4-5.

***Cystic Masses:***

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

*Simple Cyst*

A cyst meeting all criteria of a simple cyst is considered to be benign (ie, BI-RADS® 2)[34,192] if the clinical findings and ultrasonographic results are concordant. In a retrospective analysis of women (n = 14,602) with benign breast biopsies developing subsequent breast cancer, it was noted that simple cysts were not associated with subsequent breast cancer development.[193] Therefore, these patients then can be followed with routine screening.

*Complicated Cyst*

A complicated cyst is associated with a low risk of malignancy (<2%) (BI-RADS® 3).[34,194-196] Options for managing complicated cysts are either aspiration or short-term follow-up with physical examination and ultrasonography with or without mammography every 6 to 12 months for 1 to 2 years to assess stability. There may be variability on the follow-up interval based on the level of suspicion. Complicated cysts that increase in size or suspicion should be biopsied. Those that are stable or confirmed to be a complicated cyst with visible mobility of internal components can be followed with routine screening.

*Complex (Cystic and Solid) Mass:*

A complex cystic and solid mass has both cystic and solid components. Complex cysts have a relatively high risk of malignancy (eg, 14% and 23% in 2 studies).[34,162,195-197] The NCCN Panel recommends a tissue (core needle) biopsy for complex (cystic and solid) masses (BI-RADS® 4-5).

*No Imaging Abnormality:*

If no ultrasonographic or mammographic abnormality is detected (BI-RADS®) 1), tissue biopsy (core needle biopsy) should be carried out for suspicious clinical findings; and 2) those with low clinical suspicion observation with or without mammogram and ultrasound should be considered for 1 to 2 years to assess stability. The negative predictive

value of negative imaging is high, >96%.[177,181,184 Soo, 2001 #674,185] If the clinical lesion increases in size or suspicion, tissue biopsy should be performed, whereas routine breast screening is recommended if the lesion remains stable.

*Follow-up after Core Needle Biopsy*

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

If the diagnosis by tissue biopsy is an indeterminate lesion, a benign lesion that is not concordant with the imaging findings, or ADH, the NCCN Panel recommends surgical excision. Mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist may also require excisional biopsy. Select patients (ie, some patients with flat epithelial atypia, papillomas, fibroepithelial lesions, radial scars) may be suitable for monitoring in lieu of surgical excision. For patients with classic LCIS or ALH that is concordant with imaging, the NCCN Panel recommends physical exam with or without imaging for 6 to 12 months along with risk reduction therapy according to the NCCN Guidelines for Breast Cancer Risk Reduction or surgical excision. Multiple-foci LCIS involving greater than 4 terminal ductal units on core biopsy is associated with increased risk of being invasive cancer.[174] Patients with pleomorphic LCIS or LCIS/ALH that is non-concordant with imaging are treated with surgical excision.

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

***Women with Palpable Mass Younger Than 30 Years of Age:***

The preferred option for initial evaluation of a palpable mass is to proceed directly to ultrasound.[180] Mammogram may be considered if ultrasound or CBE results are highly suspicious or suggestive of cancer or if the patient is identified as having a high risk for breast cancer based on personal and family history. From this point, the decision tree for women younger than 30 years of age is almost identical to the pathway for older women. The main difference is consideration of a diagnostic mammogram in only some situations for the younger women. Because the incidence of malignancy in women who are younger than age 30 is low, observation of the mass for one or two menstrual cycles is also an option in cases with low clinical suspicion. If observation is elected and the mass resolves or is stable after one or two menstrual cycles, the patient may return to routine care. If there is significant increase in size or increase in clinical suspicion, ultrasound should be performed. Needle sampling prior to imaging is not recommended.

If no ultrasonographic abnormality is found (negative, BI-RADS® 1), a mammogram is recommended in cases where there is clinical suspicion. Based on the mammogram results, from this point the management is identical to the pathway for older women. If the clinical suspicion is low, physical examination every 3 to 6 months for 1 to 2 years is recommended with or without ultrasound. If the mass increases in size during the observation period, diagnostic mammogram may be considered followed by tissue (core needle) biopsy. If the mass remains stable, routine breast care is recommended.

### Nipple Discharge Without a Palpable Mass

Nipple discharge is common, and, in many cases, unrelated to breast pathology.[198-204] 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.[198]

Suspicion of underlying pathology (eg, ductal carcinoma, papilloma) is raised when nipple discharge is persistent and reproducible on examination, spontaneous, unilateral, from a single duct, serous, sanguineous, or serosanguineous.[205]

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

Women presenting with no palpable mass but with persistent, spontaneous, unilateral, single-duct, and clear or bloody discharge are imaged with age-appropriate diagnostic mammography and ultrasound. Several clinical studies have established a very low risk of malignancy when these tests are negative.[206,207] In certain situations, MRI or ductogram may play an adjunctive role, aiding in identifying a possible abnormality and its location. Several studies have shown that breast MRI aids in the diagnosis of suspected ductal disease.[147-149,208,209]

According to the NCCN Panel, when an overall imaging BI-RADS® assessment is category 1-3 (negative, benign, or probably benign), either a ductogram or MRI are optional to guide the duct excision. The management options include duct excision[210] or follow-up with physical exam after 6 months and imaging with diagnostic mammogram with or without ultrasound for 1 to 2 years. If clinical suspicion increases during follow-up, tissue biopsy is recommended.

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

### Asymmetric Thickening or Nodularity

Thickening, nodularity, or asymmetry is distinct from a palpable mass in that the finding is ill-defined and often vague on physical breast examination. Factors to consider include whether the thickening is a new or previous finding, and whether or not it appears to be representative of normal asymmetry. Imaging evaluation follows that of a palpable mass.[177] If the patient is younger than age 30 years and has no high risk factors, ultrasound evaluation is appropriate followed by consideration of diagnostic mammography. Diagnostic mammograms for this age group are low in yield because of the density of the breast and low risk of breast cancer. In a woman aged 30 years or older, a diagnostic mammogram and an ultrasound evaluation should be obtained.

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

findings indicate progression, it should be investigated as previously described for palpable mass.

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

### Skin Changes

Any type of unusual skin changes around the breast may represent serious disease and needs evaluation. IBC should be considered when dermal edema (peau d'orange) and breast erythema are present, and nipple excoriation, scaling, and eczema should increase clinical suspicion of Paget's disease. IBC is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States. IBC is a clinical diagnosis that requires erythema and dermal edema of a third or more of the skin of the breast with a palpable border to the erythema.[211,212] Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the nipple or areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions.[213,214] Pure Paget's disease is frequently occult on mammography[215] and a negative mammogram does not exclude Paget's disease, which requires skin biopsy.

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

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

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

### Breast Pain

Breast pain is the most common symptom in the breast. Individuals presenting with breast pain fear that this is a symptom of breast cancer, therefore causing significant anxiety. The risk of cancer in a woman presenting with breast pain as the only symptom is low, between 1.2% and 6.7%.[6,135,216,217]

Evaluation of persistent and severe breast pain includes comprehensive history, type of pain, relationship to menses, duration, location, impact on activities of daily living, factors that aggravate/alleviate pain, any other medical problems and comorbidities, and a thorough CBE. If CBE fails to identify any physical abnormality such as palpable mass, asymmetric thickening, nipple discharge, or skin changes; the pain is cyclic; or diffuse and non-focal and screening mammograms are current and negative, the

NCCN Panel recommends providing reassurance to the patient and treating the pain with symptomatic management (eg, over-the-counter pain medications, if needed; use of a good support bra; ice packs or heating pads). Cyclical breast pain may often spontaneously resolve. Reassurance alone has shown to help resolve the symptom in 86% of women with mild pain and in 52% of women with severe pain.[218] If the breast pain is focal in nature, the NCCN Panel recommends age-appropriate diagnostic imaging (diagnostic mammogram with or without ultrasound for those ≥30 years of age; and ultrasound for those <30 years of age).

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

### Axillary Mass

Localized axillary masses are more often related to benign disorders than malignancy.[219] Masses may relate to axillary lymph nodes, accessory breast tissue in the axilla, or other soft tissue abnormality. Infections, inflammation, and malignancy can cause lymphadenopathy. Breast implants can also cause benign axillary lymphadenopathy.[220] However, when cancer is identified in the axillary lymph nodes, breast cancer is the most common cause of axillary lymphadenopathy. In a study evaluating 31 patients with isolated axillary masses, 9 of the 17 cases with cancer had occult breast cancer (5 in the contralateral breast) [221]

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

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



## Summary

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

| Table 1: Breast Cysts - Types and Definitions | |
|---|---|
| Simple | Anechoic (cystic), well-circumscribed, round, or oval with well-defined imperceptible wall and posterior enhancement. |
| Complicated | Has most but not all elements of a simple cyst. Complicated cysts do not contain solid elements, intracystic masses, thick walls, or thick septa. This type of cyst may contain low-level echoes or intracystic debris, and can be described as a round, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria of a simple cyst. |
| Complex | Has some discrete solid component, which may include thick walls, thick septa, and/or intracystic mass. Complex cysts have both anechoic (cystic) and echogenic (solid) components. |
| References | 151,162,192,194-197,222 |

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