National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Breast Cancer Screening and Diagnosis

Version 3.2023 — October 31, 2023

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# Breast Cancer Screening and Diagnosis

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Ω Gynecologic oncology/ Gynecology
Þ Internist/Internal medicine, including family practice, preventive management
₪ Medical genetics/ genomics
† Medical oncology
≠ Pathology
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**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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**Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.**

**Updates in Version 3.2023 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 2.2023 include:**

**MS-1**

• The Discussion was updated to reflect the changes in the algorithm.

**Updates in Version 2.2023 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 1.2023 include:**

**BSCR-7**

• An edit was made to the top pathway to clarify that BI-RADS Category 1 (negative) findings, if clinically suspicious or if low clinical suspicion but with subsequent significant increase in size or clinical suspicion, should be *clinically managed as appropriate* with a new footnote; *This may include a referral to a breast specialist, supplemental imaging, and/or tissue sampling*.

**Updates in Version 1.2023 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 1.2022 include:**

**Global Updates**

• All instances of screening or diagnostic mammography within the algorithm (excluding footnotes) have been modified to include *with tomosynthesis*
• All instances of MRI within the algorithm (excluding footnotes) have been modified to include *with and without contrast*

**BSCR-1**

Average Risk Age ≥40 y:

• Deleted: Tomosynthesis is recommended, if available. (Also for BSCR-2, BSCR-3, BSCR-4).
• Bullet 4, New: Consider supplemental screening for those with heterogeneous or extremely dense breasts (BSCR-A). (Also for BSCR-4).

Footnotes

• h, modified: Risk models that are largely dependent on family history (eg, ~~Claus~~, BRCAPRO, Tyrer-Cuzick, BOADICEA/CanRisk). See NCCN Guidelines for Breast Cancer Risk Reduction. *There are significant limitations in interpretation of polygenic risk scores (PRS). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations.* See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. (Also for BSCR-2).
• k, modified: Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment, *particularly in regions where mammographic screening may not be accessible.* Randomized trials comparing *incremental* CBE versus ~~no~~ *mammographic* screening have not been performed. (Also for BSCR-2, BSCR-3, BSCR-4).

**BSCR-2**

Screening/Follow-Up:

• Consider contrast-enhanced mammography *(CEM)* or *molecular breast imaging (MBI)* ~~whole breast ultrasound~~ for those who qualify for but cannot undergo MRI. *Whole breast ultrasound may be done if contrast-enhanced imaging or functional imaging is not available/accessible. (*Also for BSCR-3, BSCR-4).

Footnotes

• p, new: Consider mammogram beginning at age 25 y on a case by case basis depending on family history.
• r, new*:* Many experts recommend alternating the mammogram and breast MRI with and without contrast every 6 months. While there is limited data to support this approach, the presumption is that this may lead to earlier identification of cancer. (Also for BSCR-3, BSCR-4).

**BSCR-5**

• Column 2, row 2, new: Acquired/new onset nipple inversion/retraction, with or without palpable mass.
  ▸ Bottom pathway, modified:
    ◊ Bullet 1: *Breast implant associated anaplastic large cell lymphoma (BIA-ALCL)* (effusion, enlargement, mass)
    ◊ Bullet 2: *Breast implant associated squamous cell carcinoma (BIA-SCC)* (ulceration)

Diagnostic evaluation

• Row 6, modified: ~~Pain evaluation~~, (*See BSCR-11*)
• Bottom pathway, modified:
  ▸ Bullet 1: Consultation with multidisciplinary team with experience *in managing BIA-ALCL and BIA-SCC* ~~with implant-related problems including BIA-ALCL~~
  ▸ *Bullet 2: For* ~~diagnostic workup of~~ *BIA-ALCL, also* See NCCN Guidelines for T-Cell Lymphomas

Footnotes

• v, modified: Including mass, *new onset* asymmetric thickening/nodularity, asymmetric breast enlargement, or change in shape/contour.
• w, modified: Individuals with breast implants have a *very small* risk of developing BIA-ALCL (average 7–9 years after implantation) *and BIA-SCC.* The majority of cases of BIA-ALCL have been seen in textured implants*, while BIA-SCC is associated with either smooth or textured implants.* ~~Only symptomatic individuals need to be evaluated.~~

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**Updates in Version 1.2023 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 1.2022 include:**

**BSCR-6**
- Column 3, bottom pathway, modified: If low clinical suspicion: *Consider* observ*ing* for 1-2 menstrual cycles
- Column 4, top pathway, modified: Diagnostic mammogram *with tomosynthesis or CEM if available* + ultrasound
- Column 5, bullet 2, modified to include, *of malignancy*

Footnotes
- x, new: CEM may be considered if available when clinically suspicious. (Also for BSCR-10, BSCR-13).
- y, modified: ...CBE to be documented, as *clock/quadrant* location and distance...

**BSCR-7**
- This page has been significantly updated.

**BSCR-8**
- New page: *Management of Nipple Inversion/Retraction*

**BSCR-9**
- Column 6, *MRI* added to BI-RADS 1-3 and BI-RADS 4-5
- Column 7, modified: 6-mo follow-up physical examination ± *imaging* ~~diagnostic mammogram ± ultrasound~~ for 1-2 y

Footnotes
- ff, new: Patients should have clinical follow up and/or be instructed to monitor for and report any changes.
- nn, new: Nipple smear cytology is rarely helpful and NOT recommended.

**BSCR-10**
- Column 2, bottom pathway, modified: ...Paget disease or other manifestations of breast cancer *includes but is not limited to*:
- Column 5, deleted: Reassess clinical suspicion
- Column 6, modified:
  - Abnormal clinical *and/or* MRI imaging findings
  - Normal clinical *and* ~~or~~ MRI imaging findings
- Deleted following pathway: Biopsy of skin or nipple, Benign/Malignant, Approprite clinical management, See NCCN Guidelines for Breast Cancer.

Footnotes
- Deleted: This may include a referral to a breast specialist, supplemental imaging, and tissue sampling.

**BSCR-13**

Footnotes
- eee, modified: ...Assess recent ~~COVID-19~~ vaccination status and manage accordingly.
- iii, modified: If lymphoma is suspected, ~~it~~ *tissue/specimen* may require special pathologic processing and/or surgical excision.

**BSCR-14**

Footnotes
- kkk, new: Mammogram generally not performed prior to age 25 y for individuals AMAB.
- lll, new: Clinical management depends on the presumed cause (drug-induced, hypogonadism, hyperthyroidism, idiopathic), age of patient, duration, and presence of symptoms.

**BSCR-15**
- This page has been significantly updated.

**BSCR-16**
- Modified: ~~Pleomorphic~~ *Non-Classic* LCIS.

Footnotes
- ppp, modified: Clinicians should consider complete excision with negative margins for ~~pleomorphic~~ *non-classic* LCIS*, florid LCIS, and multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy*.

**BSCR-A, 1 of 2**
- This page has been significantly updated.

**BSCR-A, 2 of 2**
- Bullet 1, modified: For individuals with a genetic mutation, or ~~a~~ *an untested* first-degree relative of gene mutation carrier, see...

Footnotes
- a, modified: For age >75 years, *supplemental* screening recommendations are considered on an individual basis.
- Deleted: Risk depends on age at diagnosis.

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UPDATES

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**Updates in Version 1.2023 of the NCCN Guidelines for Breast Cancer Screening and Diagnosis from Version 1.2022 include:**

**BSCR-B, 1 of 11**

**Increased Risk Screening**

- Column 1, bullet 1, modified: Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier *who remains untested.* (Also for BSCR-B, 6*)*

**Rational for Recommendation/Other Considerations**

- Bullet 3, modified to include: *Non-contrast MRI is not recommended due to lack of sensitivity*.

Footnotes

- a, new: There are significant limitations in interpretation of PRS. PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations. (Also for BSCR-B, 6)
- c, new: Consider supplemental screening for those with heterogeneous or extremely dense breasts. (Also for BSCR-B, 6)

**BSCR-B, 2 of 11**

**Rational for Recommendation/Other Considerations**

- Column 6, bullet 4, modified: ~~Breast MRI is not appropriate for the management of palpable symptom during pregnancy.~~ *Contrast-enhanced breast MRI is not recommended during pregnancy due to the trans-placental passage of gadolinium, and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. (*Also for BSCR-B 3, *and* BSCR-B 4)

**BSCR-B, 3 of 11**

**Rational for Recommendation/Other Considerations**

- Column 6, bullet 1 modified: Because of the frequency of normal nipple discharge during pregnancy, abnormal nipple discharge is defined as: Persistent, *spontaneous* uniductal, unilateral bloody *or clear* nipple discharge. (Also for BSCR-B 8)

Footnotes

- Deleted: Abnormal nipple discharge includes bloody or clear, uniductal, unilateral discharge. Milky discharge is generally normal in pregnancy. (Also for BSCR-B 8)

**BSCR-B, 4 of 11**

- Column 1, top pathway, modified: Breast Erythema or *Suspicious* ~~Worrisome~~ Skin Changes...

**BSCR-B, 5 of 11**

- Bottom pathway, new: Management of Axillary Mass

**BSCR-B, 8 of 11:**

**Rational for Recommendation/Other Considerations**

- Column 6, bullet 4, modified: 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 *lactation*. ~~pregnancy~~

**BSCR-B, 9 of 11**

- Column 1, modified: Breast Erythema or *Suspicious* ~~Worrisome~~ Skin Changes (eg, thickening or edema)

**Rational for Recommendation/Other Considerations**

- Column 6, bullet 1, modified: Breast erythema or *suspicious* ~~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.
  - Bullet 2, modified: In some circumstances, breast erythema or *suspicious* ~~worrisome~~ skin changes without other evidence of mastitis (absence of pain or fever) may prompt immediate evaluation for inflammatory breast cancer.
  - Bullet 3, sub-bullet 1, modified: 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 *lactating* ~~pregnant~~ (BSCR-10).

**BSCR-B, 11 of 11**

- Column 5, Under MRI, Not recommended, new: Recommended if MRI was the imaging modality that initially resulted in the BI-RADS 3 finding and there are no ultrasound or mammographic correlates.

**BSCR-B 12 through BSCR-B 14**

- These pages have been deleted.

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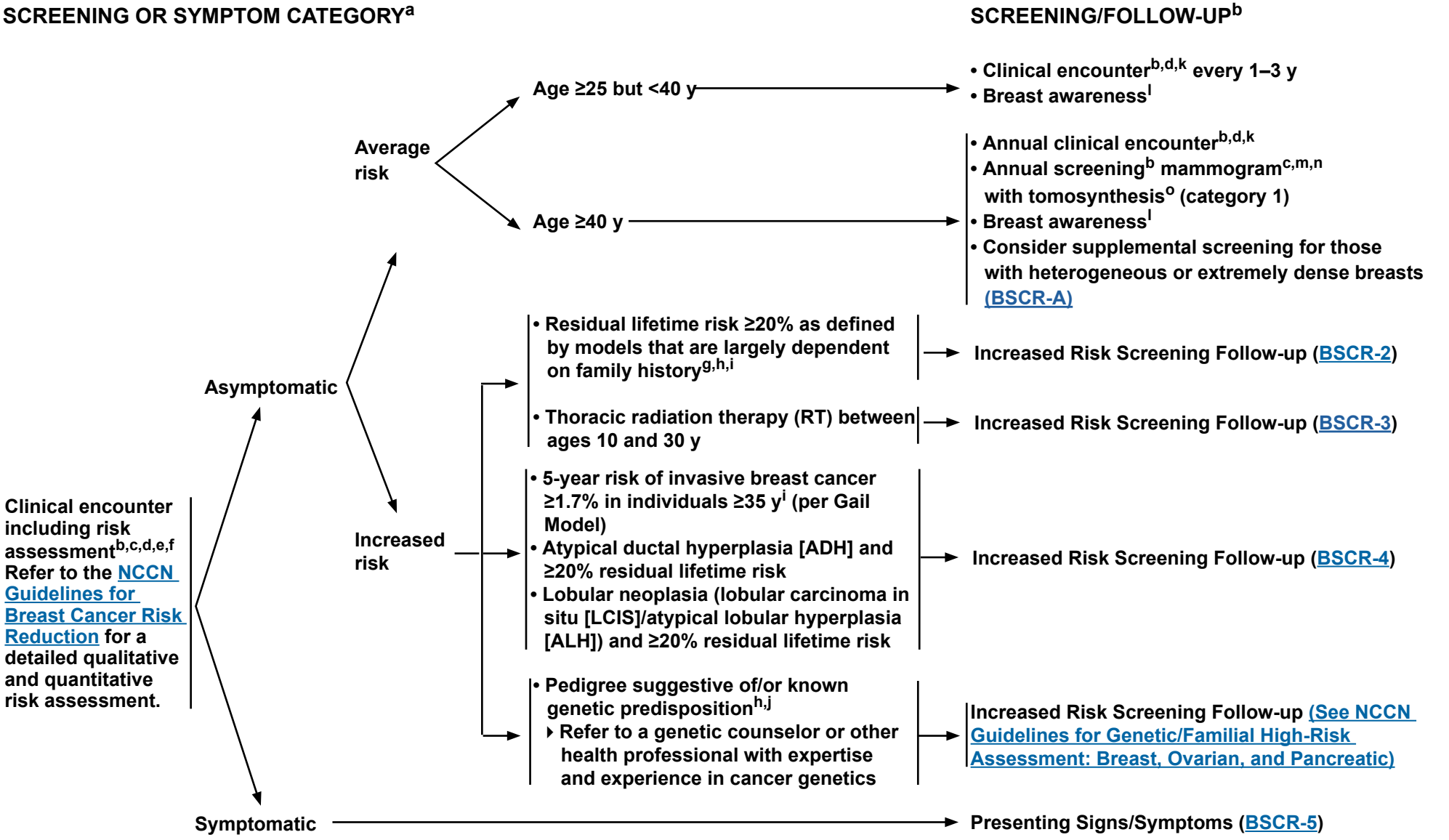


**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES

[a] For individuals with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section.
[b] 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 reviewed and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a clinical breast examination (CBE) even in individuals who are asymptomatic when feasible.
[e] There is limited data on screening in individuals with increased risk for breast cancer assigned male at birth (AMAB).
[f] For pregnant and lactating individuals, see BSCR-B.
[g] Individuals with a residual 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, BRCAPRO, Tyrer-Cuzick, BOADICEA/CanRisk). See NCCN Guidelines for Breast Cancer Risk Reduction. There are significant limitations in interpretation of polygenic risk scores (PRS). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[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] Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment, particularly in regions where mammographic screening may not be accessible. Randomized trials comparing incremental CBE versus mammographic screening have not been performed.
[l] Individuals should be familiar with their breasts and promptly report changes to their health care provider. See Symptomatic During Clinical Encounter, Presenting Signs and Symptoms (BSCR-5).
[m] Mammographic Evaluation (BSCR-18).
[n] Shared decision-making is encouraged based on individuals' values and preferences.
[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

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| SCREENING OR SYMPTOM CATEGORY[a] | SCREENING/FOLLOW-UP |
|---|---|
| **Increased Risk:** | |
| **Residual lifetime risk ≥20% as defined by models that are largely dependent on family history[g,h,i]** → | • **Clinical encounter[b,d,k] every 6–12 mo**<br>  ▸ **To begin when identified as being at increased risk, but not prior to age 21 y**<br>  ▸ **Consider referral to a genetic counselor or other health professional with expertise and experience in cancer genetics, if not already done**<br>  ▸ **Consider referral to a breast specialist as appropriate**<br>• **Annual screening[b] mammogram[c,m] with tomosynthesis[o]**<br>  ▸ **To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 30 y[p] or begin at age 40 y (whichever comes first)**<br>• **Annual breast MRI[q,r] with and without contrast**<br>  ▸ **Consider contrast-enhanced mammography (CEM)[b] or molecular breast imaging (MBI)[b] for those who qualify for but cannot undergo MRI. Whole breast ultrasound[b] may be done if contrast-enhanced imaging or functional imaging is not available/accessible**<br>  ▸ **To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 25 y[s] or begin at age 40 y (whichever comes first)**<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] 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 reviewed and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a CBE even in individuals who are asymptomatic when feasible.
[g] Individuals with a residual 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, BRCAPRO, Tyrer-Cuzick, BOADICEA/CanRisk). See NCCN Guidelines for Breast Cancer Risk Reduction. There are significant limitations in interpretation of PRS. PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[i] See Comparison of Predictive Models for Risk Assessment (NCCN Guidelines for Breast Cancer Risk Reduction).
[k] Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment, particularly in regions where mammographic screening may not be accessible. Randomized trials comparing incremental CBE versus mammographic screening have not been performed.
[l] Individuals should be familiar with their breasts and promptly report changes to their health care provider. See Symptomatic During Clinical Encounter, Presenting Signs and Symptoms (BSCR-5).
[m] Mammographic Evaluation (BSCR-18).
[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[p] Consider mammogram beginning at age 25 y on a case by case basis depending on family history.
[q] High-quality breast MRI requires a dedicated breast coil, access to biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. MRI should be correlated with other breast imaging modalities.
[r] Many experts recommend alternating the mammogram and breast MRI with and without contrast every 6 months. While there is limited data to support this approach, the presumption is that this may lead to earlier identification of cancer.
[s] Except in rare circumstances of a family history of very early-onset breast cancers before age 30 years.

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

**Increased Risk:**

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

**Current age <25 y →**

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

**Current age ≥25 y →**

- **Clinical encounter[b,d,k] every 6–12 mo**
  - **Begin 8 y after RT**
- **Annual screening[b] mammogram[c,m] with tomosynthesis[o]**
  - **Begin 8 y after RT but not prior to age 25 y**
- **Annual breast MRI[q,r] with and without contrast**
  - **Consider CEM[b] or MBI[b] for those who qualify for but cannot undergo MRI. Whole breast ultrasound[b] may be done if contrast-enhanced imaging or functional imaging is not available/accessible**
  - **Begin 8 y after RT but not prior to age 25 y**
- **Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)**
- **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] 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 reviewed and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a CBE even in individuals who are asymptomatic when feasible.
[k] Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment, particularly in regions where mammographic screening may not be accessible. Randomized trials comparing incremental CBE versus mammographic screening have not been performed.
[l] Individuals should be familiar with their breasts and promptly report changes to their health care provider. See Symptomatic During Clinical Encounter, Presenting Signs and Symptoms (BSCR-5).
[m] Mammographic Evaluation (BSCR-18).
[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[q] High-quality breast MRI requires a dedicated breast coil, access to biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. MRI should be correlated with other breast imaging modalities.
[r] Many experts recommend alternating the mammogram and breast MRI with and without contrast every 6 months. While there is limited data to support this approach, the presumption is that this may lead to earlier identification of cancer.

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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,d,k] every 6–12 mo**<br>▸ **To begin when identified as being at increased risk by Gail Model**<br>• **Annual screening[b] mammogram[c,m] with 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]**<br>• **Consider supplemental screening for those with heterogeneous or extremely dense breasts (BSCR-A)** |
| **ADH[t] or Lobular neoplasia (LCIS/ALH) and ≥20% residual lifetime risk** | • **Clinical encounter[b,d,k] every 6–12 mo**<br>▸ **To begin at diagnosis of ADH or lobular neoplasia (LCIS/ALH)**<br>• **Annual screening[b] mammogram[c,m] with tomosynthesis[o]**<br>▸ **To begin at diagnosis of ADH or lobular neoplasia (LCIS/ALH) but not prior to age 30 y**<br>• **Consider annual breast MRI[b,q,r] with and without contrast**<br>▸ **Consider CEM[b] or MBI[b] for those who qualify for but cannot undergo MRI. Whole breast ultrasound[b] may be done if contrast-enhanced imaging or functional imaging is not available**<br>▸ **To begin at diagnosis of ADH or lobular neoplasia (LCIS/ALH) but not prior to age 25 y**<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] 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 reviewed and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a CBE even in individuals who are asymptomatic when feasible.
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[l] Individuals should be familiar with their breasts and promptly report changes to their health care provider. See Symptomatic During Clinical Encounter, Presenting Signs and Symptoms (BSCR-5).
[m] Mammographic Evaluation (BSCR-18).
[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[q] 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] Many experts recommend alternating the mammogram and breast MRI with and without contrast every 6 months. While there is limited data to support this approach, the presumption is that this may lead to earlier identification of cancer.
[t] Risk depends on age at diagnosis.

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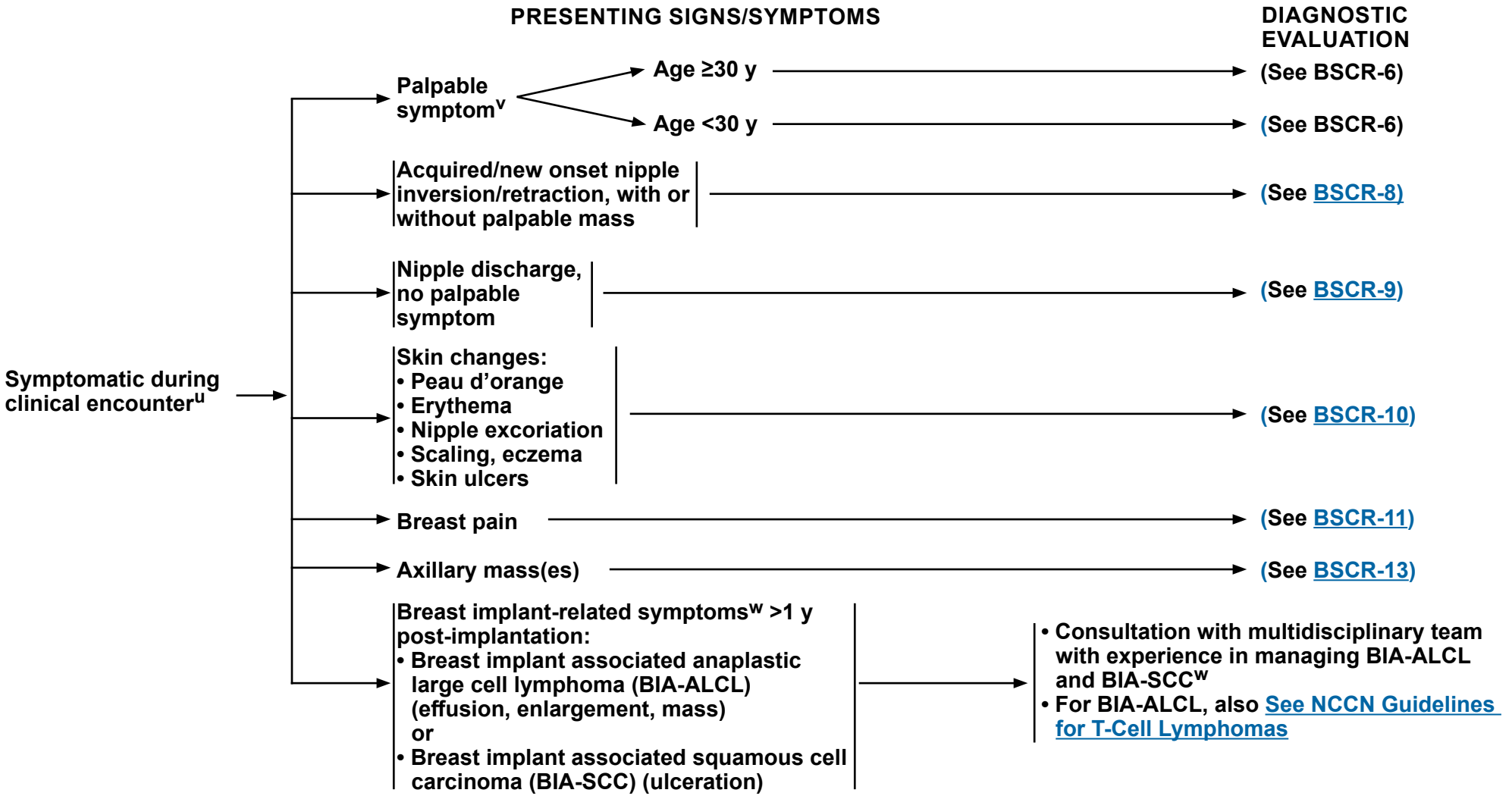


[u] For symptoms in individuals AMAB, see BSCR-14.
[v] Including mass, new onset asymmetric thickening/nodularity, asymmetric breast enlargement, or change in shape/contour.
[w] Individuals with breast implants have a very small risk of developing BIA-ALCL (average 7–9 years after implantation) and BIA-SCC. The majority of cases of BIA-ALCL have been seen in textured implants, while BIA-SCC is associated with either smooth or textured implants.

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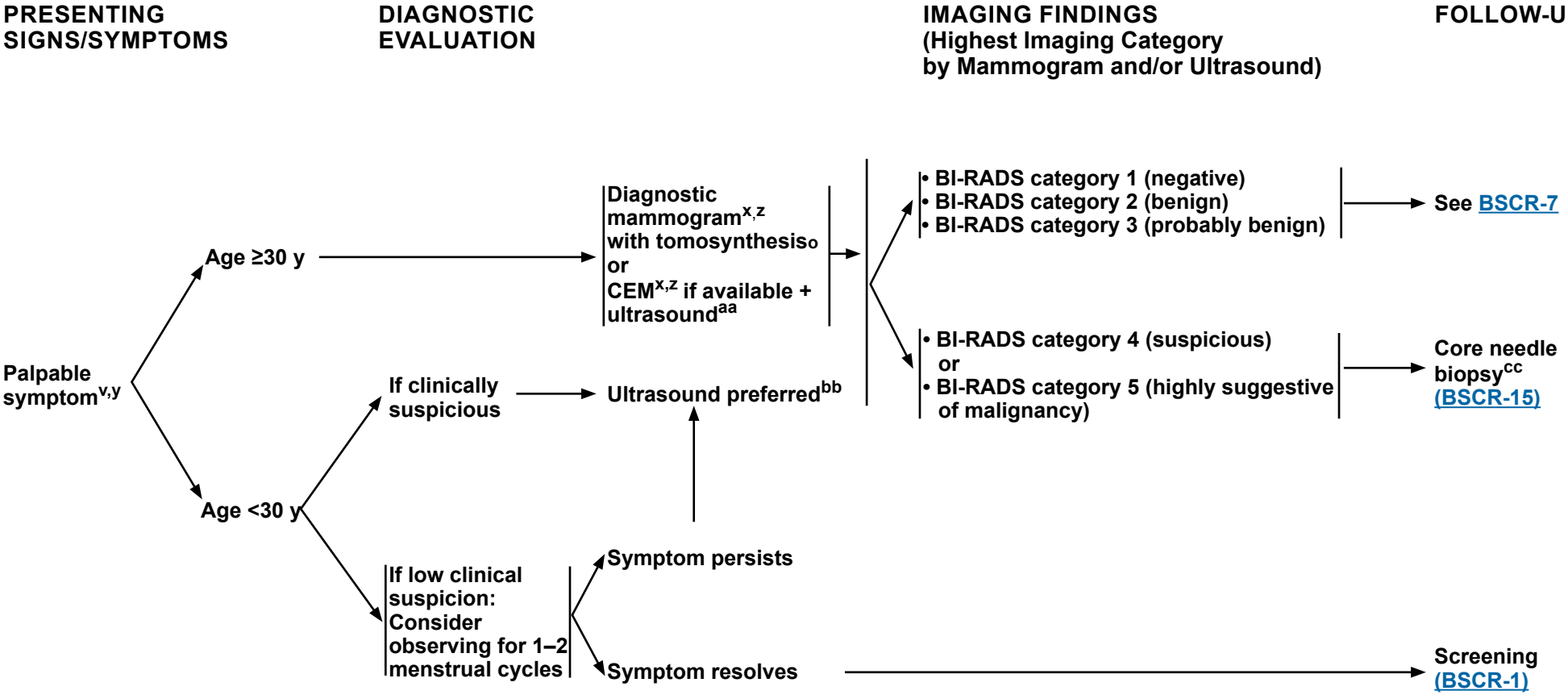


[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[v] Including mass, new onset of asymmetric thickening/nodularity, asymmetric breast enlargement or change in shape/contour.
[x] CEM may be considered if available when clinically suspicious.
[y] It is critical for the location of physical findings from CBE to be documented, as clock/quadrant location and distance from nipple to facilitate geographic correlation with imaging findings.
[z] 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 aged 30–39 years. Mammogram may not be necessary if performed and results were negative within the past 6 months. See Discussion.
[aa] Ultrasound may not be necessary for a palpable finding with a definitively benign finding (eg, calcified fat necrosis) on mammogram.
[bb] If high suspicion for malignancy, obtain mammogram.
[cc] Confirm geographic correlation between clinical and imaging findings.

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# NCCN Guidelines Version 3.2023
# Breast Cancer Screening and Diagnosis

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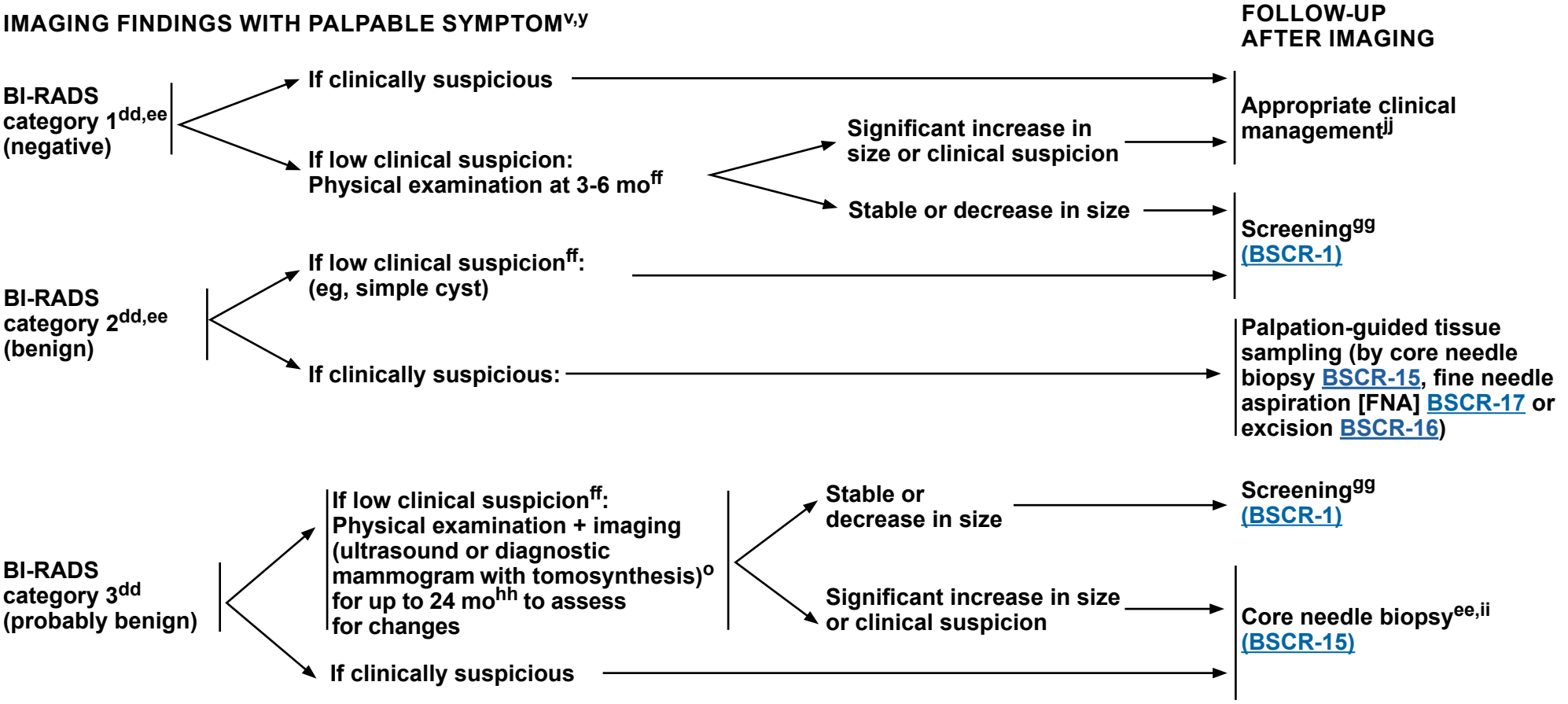


[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[v] Including mass, new onset of asymmetric thickening/nodularity, asymmetric breast enlargement or change in shape/contour.
[y] It is critical for the location of physical findings from CBEs to be documented, as clock/quadrant location and distance from nipple to facilitate geographic correlation with imaging findings.
[dd] Assessment Category Definitions (BSCR-C).
[ee] Aspiration may be considered for symptomatic relief or possible abscess. (BSCR-17).
[ff] Patients should have clinical follow up and/or be instructed to monitor for and report any changes.
[gg] Continue regular screening with age-appropriate imaging modality.
[hh] Imaging modality would depend on original imaging. Probably benign findings are typically monitored at 6, 12, and 24 months.
[ii] Core needle biopsy preferred; in some circumstances needle aspiration may be sufficient.
[jj] This may include a referral to a breast specialist, supplemental imaging, and/or tissue sampling.

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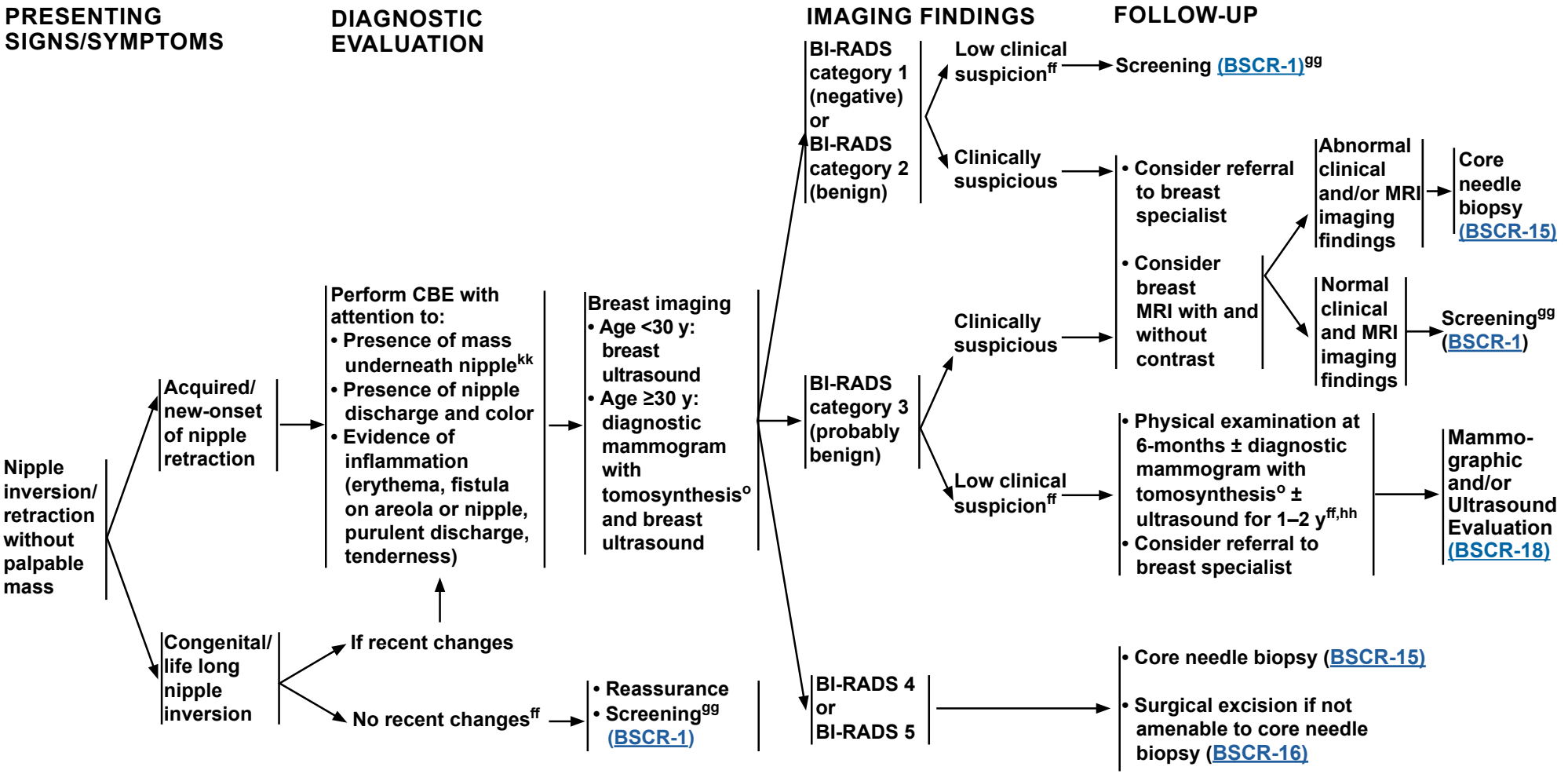
## MANAGEMENT OF NIPPLE INVERSION/RETRACTION




[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[ff] Patients should have clinical follow up and/or be instructed to monitor for and report any changes.
[gg] Continue regular screening with age-appropriate imaging modality.
[hh] Imaging modality would depend on original imaging. Probably benign findings are typically monitored at 6, 12, and 24 months.
[kk] For palpable mass see BSCR-6.

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# NCCN Guidelines Version 3.2023
# Breast Cancer Screening and Diagnosis

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**PRESENTING SIGNS/SYMPTOMS** | **DIAGNOSTIC EVALUATION AND FOLLOW-UP** | **FOLLOW-UP AFTER IMAGING**

**Nipple discharge[ll,mm] no palpable symptom[nn,oo]**

- **Non-spontaneous or multi-duct**
  - **Age <40 y** → • Observation • Educate to stop compression of the breast and report any spontaneous discharge
  - **Age ≥40 y** → • Screening mammogram with tomosynthesis[o] if not done in the past year • Educate to stop compression of the breast and report any spontaneous discharge → **Mammographic evaluation (BSCR-18)**
- **Persistent and reproducible on examination, spontaneous, unilateral, single duct, and clear or bloody**
  - **Age <30 y ultrasound ± diagnostic mammogram with tomosynthesis[o]** → **BI-RADS category 1–3[dd,pp]** → • MRI with and without contrast • Refer to breast specialist → **MRI BI-RADS category 1–3** → **6-mo follow-up physical examination ± imaging for 1–2 y[ff,hh]**
    - **Suspicious progression** → **Core needle biopsy if imaging abnormality (BSCR-15) or Surgical excision (BSCR-16)**
    - **Stable/ resolves** → **Screening[gg] (BSCR-1)**
  - **MRI BI-RADS category 4–5** → **Surgical consultation for duct excision[qq]**
    - **Benign** → **Screening[gg] (BSCR-1)**
    - **Malignant** → **See NCCN Guidelines for Breast Cancer**
  - **Age ≥30 y diagnostic mammogram with tomosynthesis[o] + ultrasound** → **BI-RADS category 4–5[dd]** → **Core needle biopsy (BSCR-17); surgical excision (BSCR-16) if not amenable to core needle biopsy**
    - **Malignant** → **See NCCN Guidelines for Breast Cancer**
    - **Benign** → **Consider surgical consultation for duct excision[qq]**

[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[dd] Assessment Category Definitions (BSCR-C).
[ff] Patients should have clinical follow up and/or be instructed to monitor for and report any changes.
[hh] Imaging modality would depend on original imaging. Probably benign findings are typically monitored at 6, 12, and 24 months.
[ll] A list of drugs that can cause nipple discharge (not all-inclusive): psychoactive drugs, antihypertensive medications, opiates, oral contraceptives, and estrogen.
[mm] For bilateral milky discharge consider endocrine workup.
[nn] If palpable symptom, see BSCR-6.
[oo] Nipple smear cytology is rarely helpful and NOT recommended.
[pp] If BI-RADS category 3 finding is unrelated to nipple discharge, manage mammographic finding by BSCR-18.
[qq] Based on clinical suspicion and patient preference.

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# NCCN Guidelines Version 3.2023
# Breast Cancer Screening and Diagnosis

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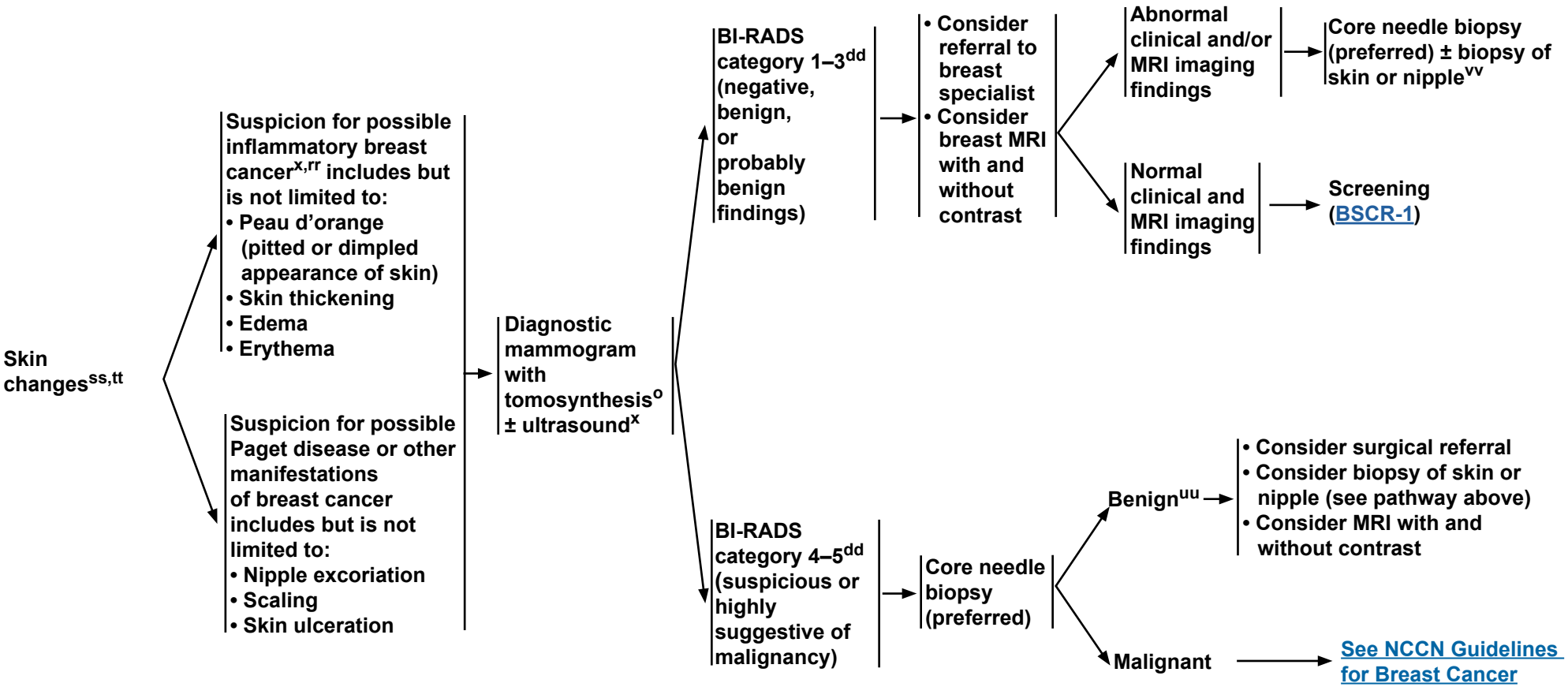
## PRESENTING SIGNS/SYMPTOMS

## DIAGNOSTIC EVALUATION AND FOLLOW-UP




[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[x] CEM may be considered if available when clinically suspicious.
[dd] Assessment Category Definitions (BSCR-C).
[rr] This may represent serious disease of the breast and needs evaluation.
[ss] If clinically low suspicion for breast cancer or high suspicion for infection, a short trial (eg, 7–10 days) of antibiotics for mastitis may be indicated.
[tt] If clinically low suspicion for Paget's disease or high suspicion for eczema, a short trial of topical steroids may be indicated.
[uu] 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.
[vv] Inflammatory breast cancer is a clinical diagnosis and is not dependent on a positive punch biopsy.

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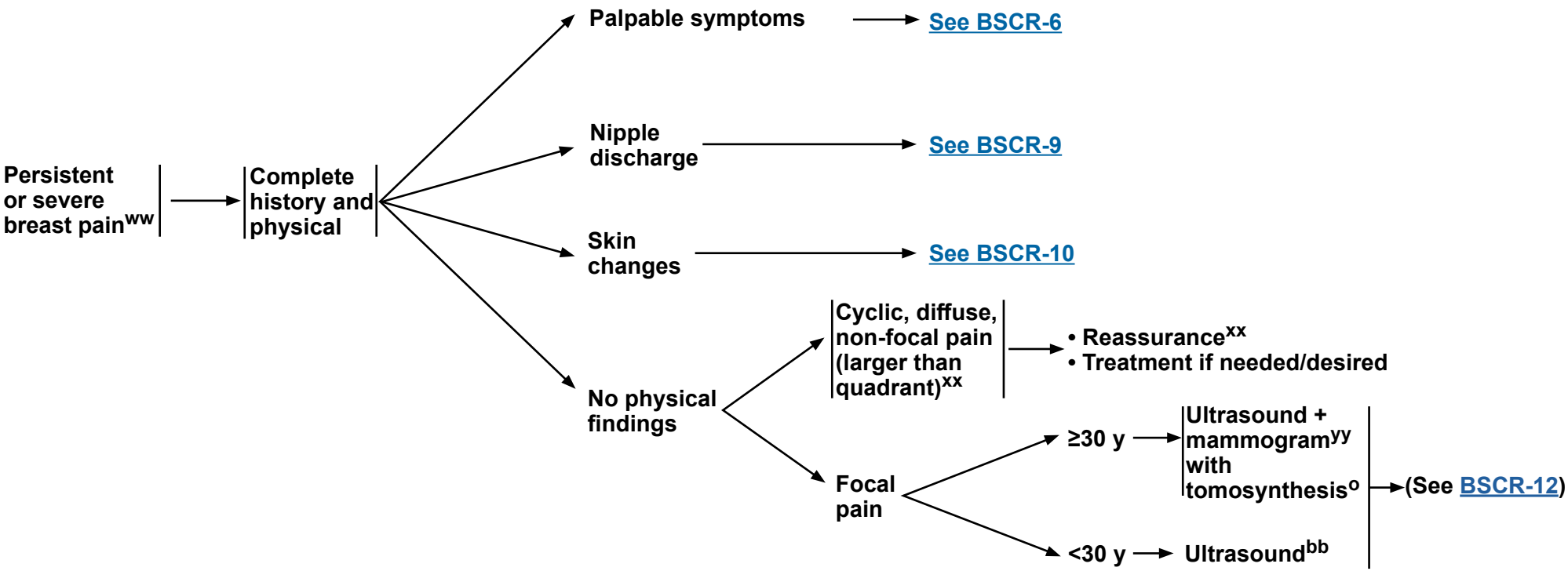
**PRESENTING SIGNS AND SYMPTOMS** **FOLLOW-UP EVALUATION**




[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[bb] If high suspicion for malignancy, obtain mammogram.
[ww] Defined as a minimum of 4 to 6 weeks duration; prior to that, symptomatic management unless patient reports other symptoms also present such as associated redness or mass. If other symptoms present, physical examination should be done at that time.
[xx] Ensure that mammographic screening is up-to-date.
[yy] 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 aged 30–39 years. Mammogram may not be necessary if performed and results were negative within the past 6 months. See Discussion.

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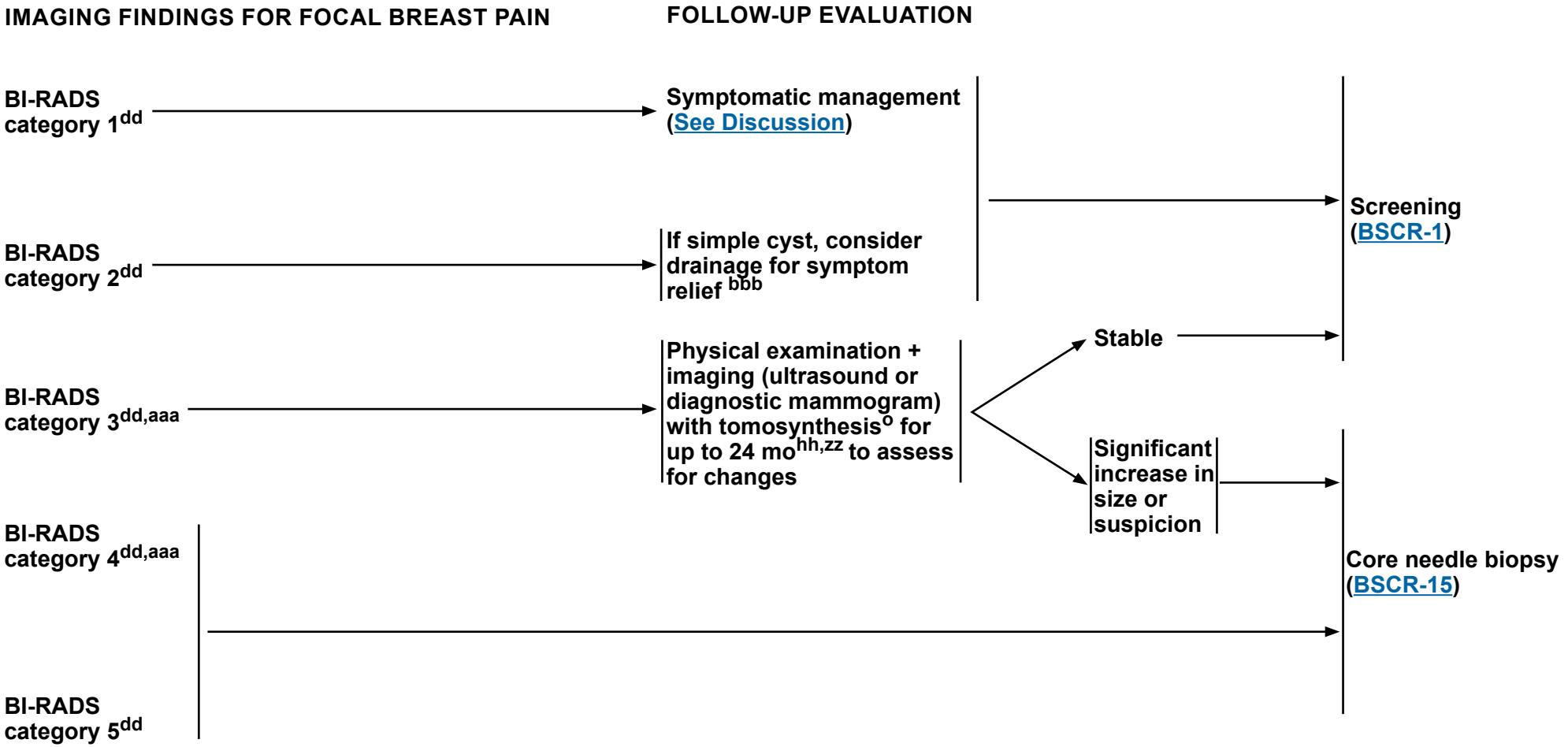


o Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
dd Assessment Category Definitions (BSCR-C).
hh Imaging modality would depend on original imaging. Probably benign findings are typically monitored at 6, 12, and 24 months.
zz There may be variability on the follow-up interval of physical examination based on the level of suspicion.
aaa When imaging indicates possible abscess as cause of focal pain, consider aspiration or surgical consultation.
bbb If complicated cyst, consider aspiration.

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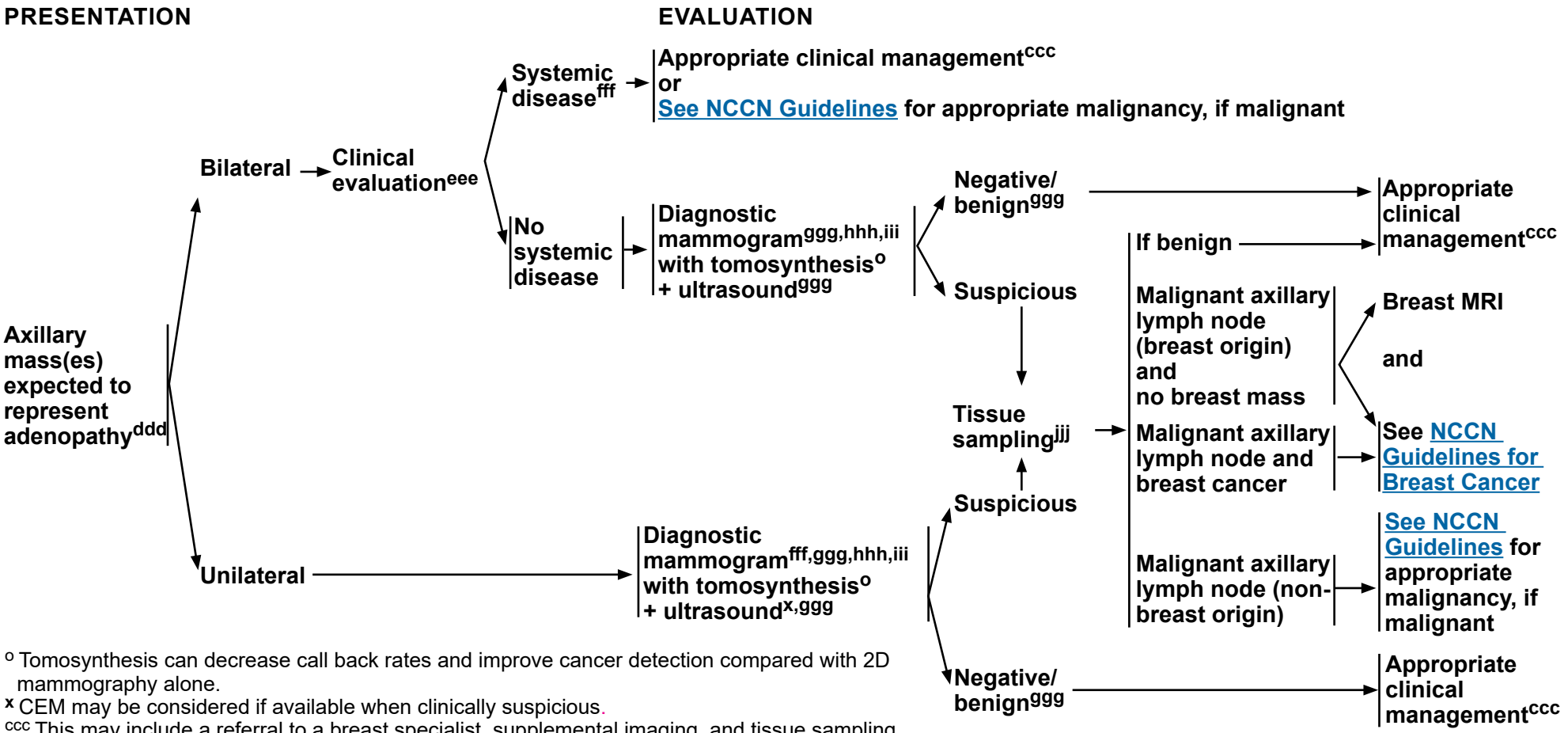
## RECOMMENDATIONS FOR WORKUP/DIAGNOSTIC EVALUATION OF AXILLARY MASS




[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

[x] CEM may be considered if available when clinically suspicious.

[ccc] This may include a referral to a breast specialist, supplemental imaging, and tissue sampling.

[ddd] If not expected to represent adenopathy, see BSCR-5.

[eee] Complete clinical evaluation to assess for other sites of adenopathy and potential non-breast etiologies of adenopathy.

[fff] Evidence of clinical conditions known to be associated with systemic adenopathy such as lupus, rheumatoid arthritis, human immunodeficiency virus (HIV) infection, and others. Assess recent vaccination status and manage accordingly.

[ggg] For additional guidance based upon BI-RADS category 3 (probably benign) assessment, see BSCR-18.

[hhh] If aged <30 years, mammogram is optional unless ultrasound results are suspicious.

[iii] Mammogram is recommended in those ≥30 years.

[jjj] If lymphoma is suspected, tissue/specimen may require special pathologic processing and/or surgical excision.

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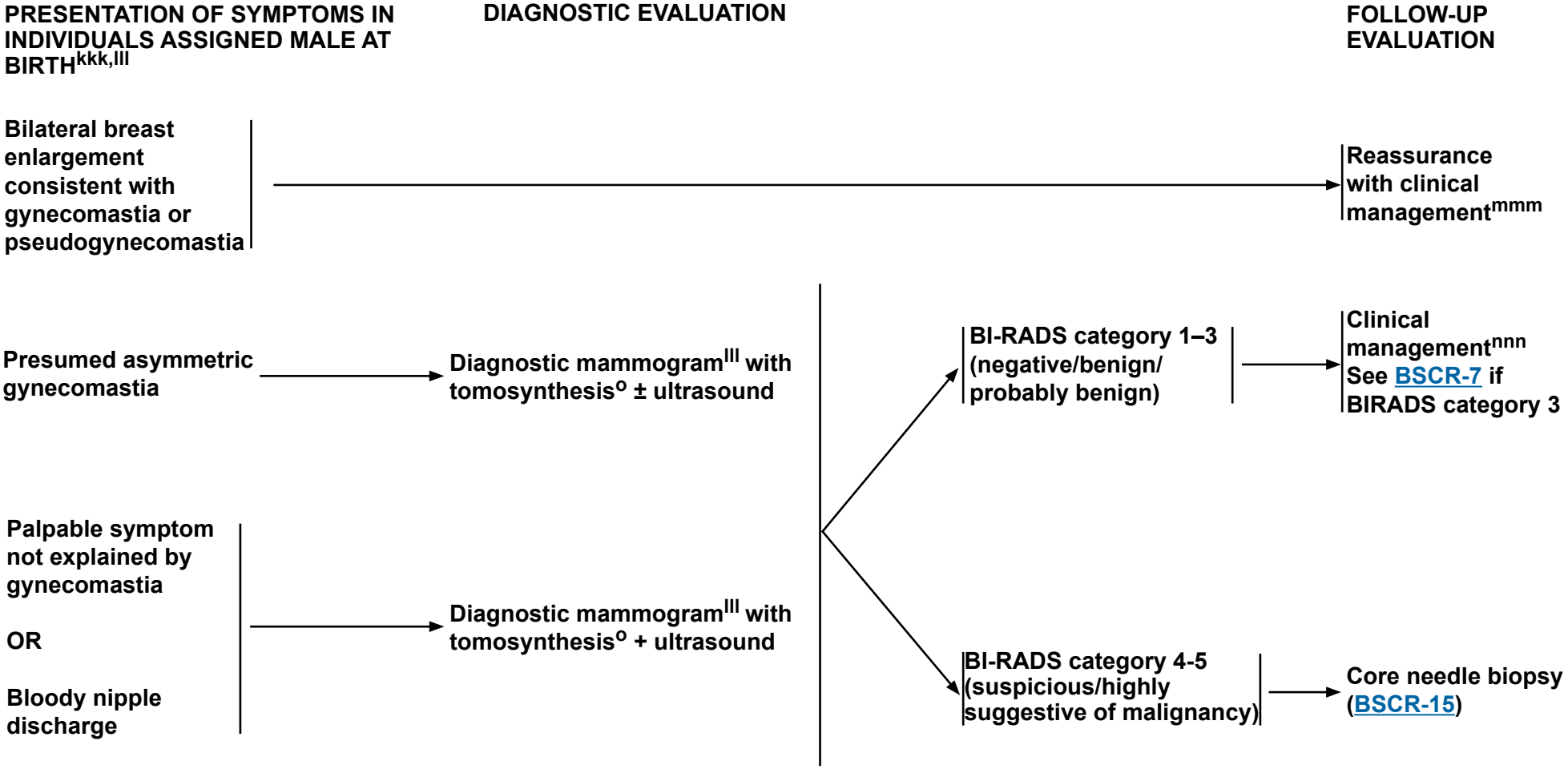


[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[kkk] See NCCN Guidelines for Breast Cancer for management and special considerations for breast cancer in individuals AMAB.
[lll] Mammogram generally not performed prior to age 25 y for individuals AMAB.
[mmm] Clinical management depends on the presumed cause (drug-induced, hypogonadism, hyperthyroidism, idiopathic), age of patient, duration, and presence of symptoms.
[nnn] Consider surgical referral for suspicious clinical findings.

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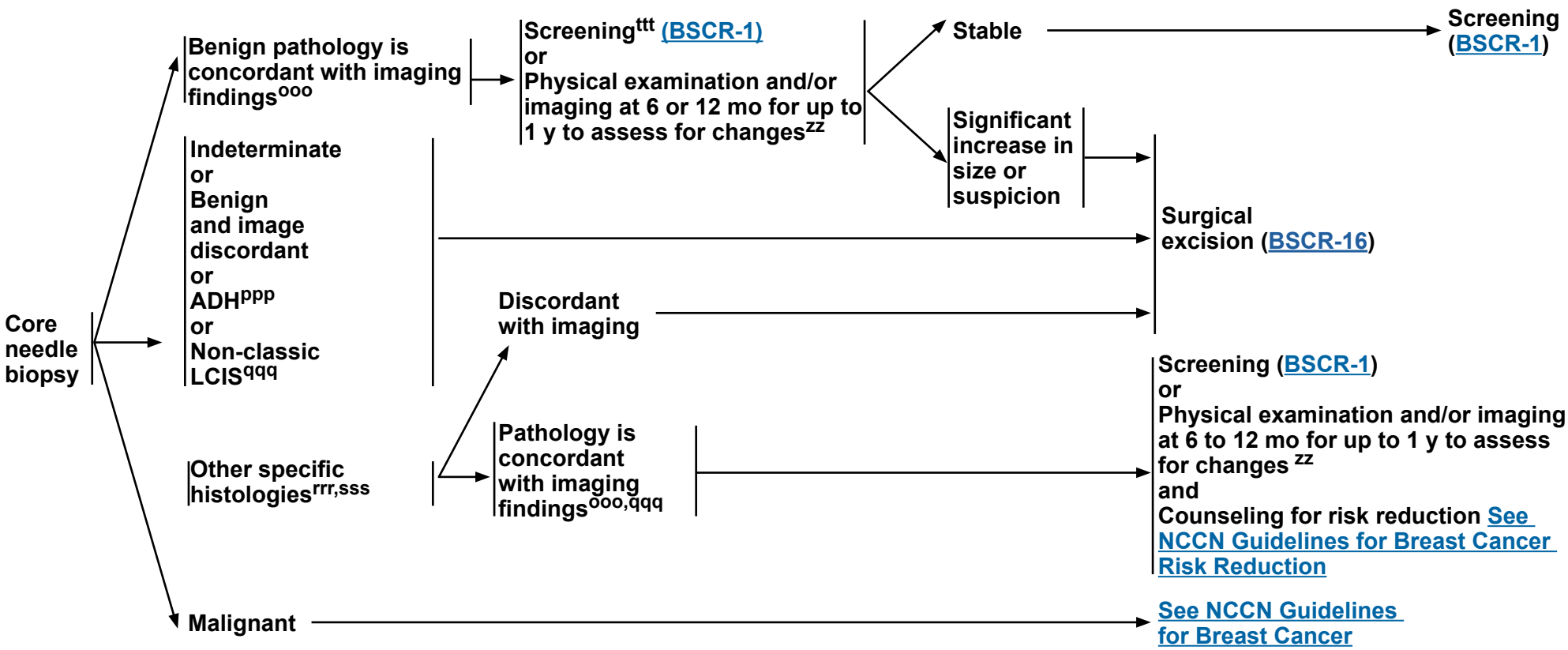
## FOLLOW-UP EVALUATION AFTER CORE NEEDLE BIOPSY




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

[ooo] Concordance established by radiologist/breast specialist after review of core needle biopsy pathology report and imaging findings. This may require discussion/review with pathologist.

[ppp] Select patients may be suitable for monitoring in lieu of surgical excision.

[qqq] Clinicians should consider complete excision with negative margins for non-classic LCIS, florid LCIS, and multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy. However, outcomes data regarding treatment of individuals with non-classic LCIS are limited, due in part to a paucity of histologic categorization of variants of LCIS.

[rrr] For select patients with other specific histologies (eg, classic LCIS, ALH, flat epithelial atypia [FEA], papillomas without atypia, fibroepithelial lesions favoring fibroadenoma, radial scars adequately sampled or incidental, ADH) excision may be considered depending on level of suspicion.

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

[ttt] While most would return to annual screening, there is the option of physical examination with or without further imaging for individuals <40 years.

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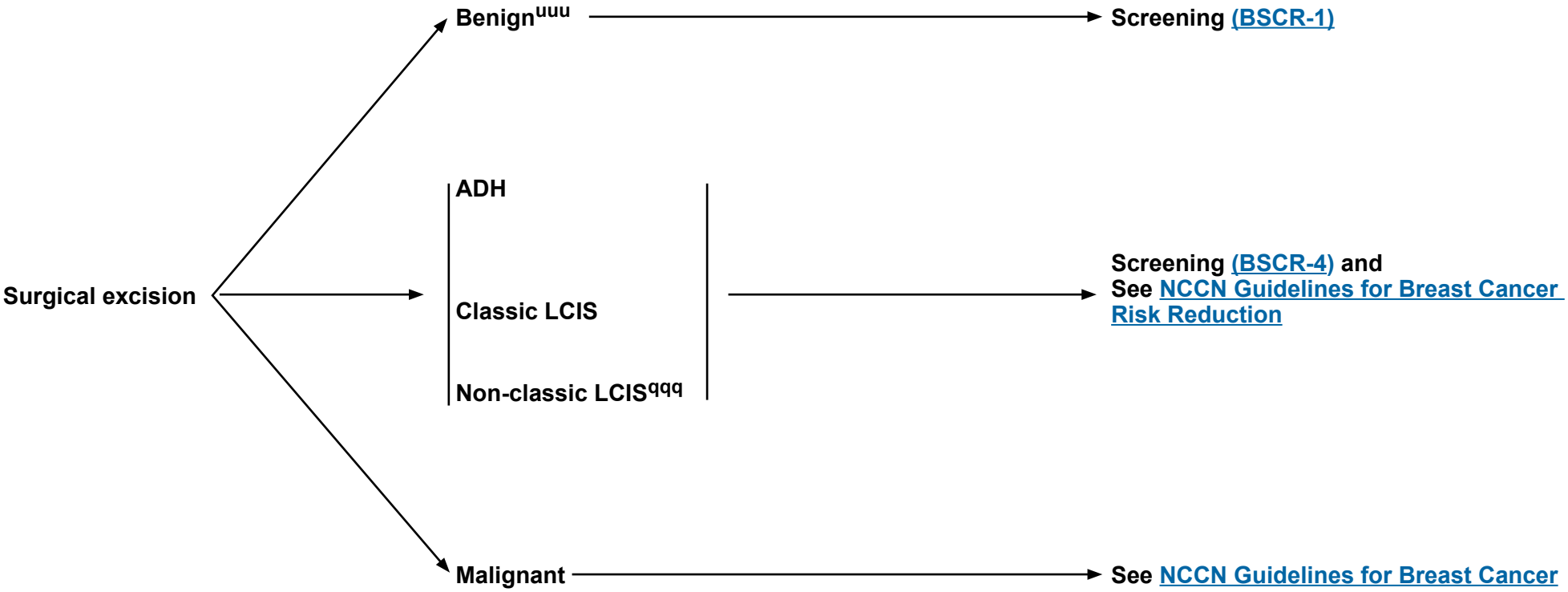
## FOLLOW-UP EVALUATION AFTER SURGICAL EXCISION




[qqq] Clinicians should consider complete excision with negative margins for non-classic LCIS, florid LCIS, and multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy. However, outcomes data regarding treatment of individuals with non-classic LCIS are limited, due in part to a paucity of histologic categorization of variants of LCIS.

[uuu] Includes lesions such as radial scar, papillomas, and FEA.

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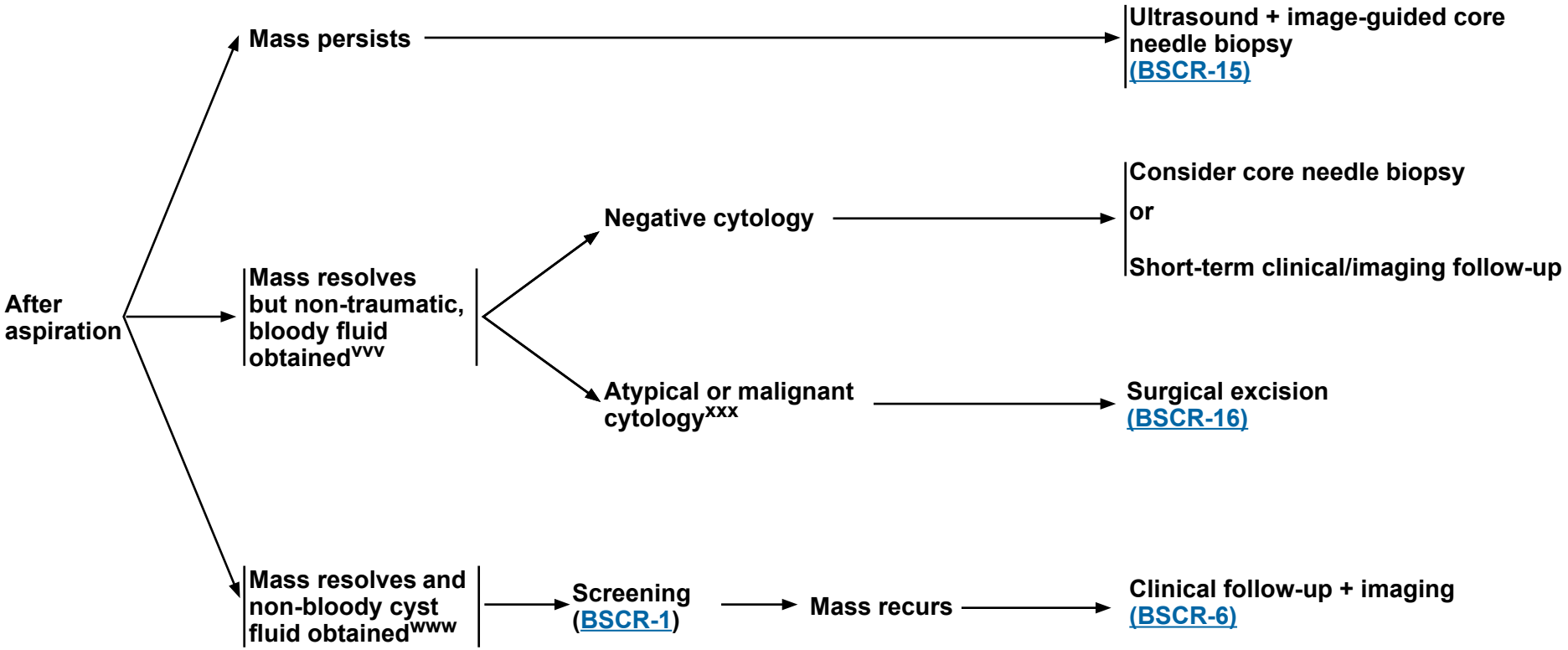
## FOLLOW-UP EVALUATION AFTER ASPIRATION




[vvv] Place marker clip and send to cytology.
[www] Routine cytology is not recommended.
[xxx] 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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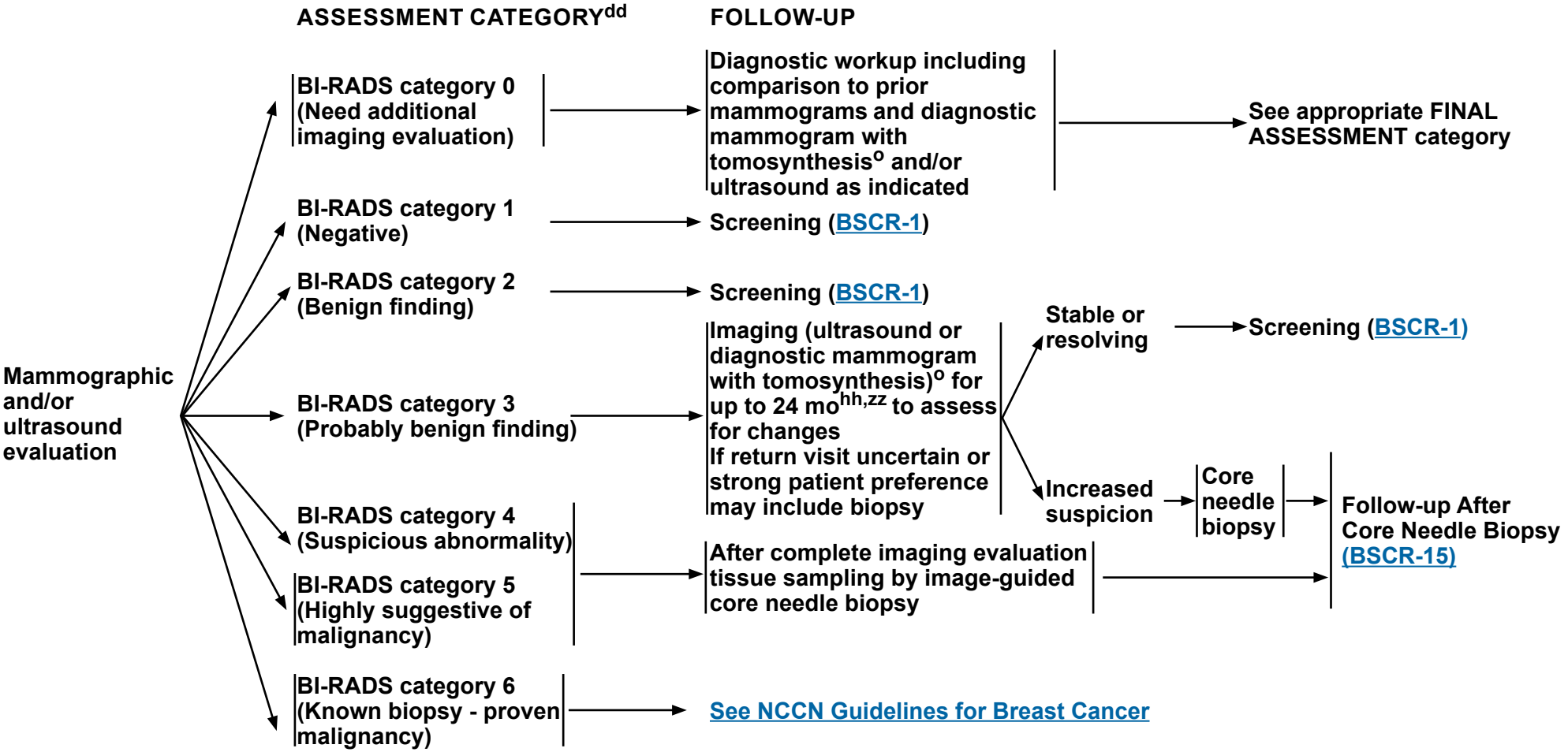


[o] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[dd] Assessment Category Definitions (BSCR-C).
[hh] Imaging modality would depend on original imaging. Probably benign findings are typically monitored at 6, 12, and 24 months.
[zz] There may be variability on the follow-up interval of physical examination based on the level of suspicion.

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## BREAST SCREENING CONSIDERATIONS

### General Considerations

- Individuals should undergo breast cancer risk assessment by age 25 years 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).
- Multiple studies show that tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone. Radiation exposure may be increased, but remain within FDA guidelines and can be reduced with FDA-approved synthesized 2D reconstruction.
- Current evidence does not support the routine use of thermography as screening procedures.
- Due to lack of clinical evidence, these guidelines do not provide screening guidance for transgender individuals. Certain organizations have developed consensus-based guidelines for transgender individuals, such as the ACR Appropriateness Criteria. NCCN endorses these criteria. Transgender individuals should consult with their primary care physician to determine when/whether screening would be appropriate.

### Upper Age Limit for Screening

- Upper age limit for mammographic screening is not yet established.
- Consider severe comorbid conditions limiting life expectancy (eg, ≤10 years) and whether therapeutic interventions are planned.

### Dense Breasts

- Dense breasts limit the sensitivity of mammography. Mammographically dense breast tissue is associated with an increased risk for breast cancer.
- For individuals with mammographically dense breast tissue (heterogeneously or extremely dense breast tissue), recommend counseling on the risks and benefits of supplemental screening.
- Handheld or automated ultrasound can increase cancer detection rates in individuals with dense breast tissue, but may increase recall and benign breast biopsies.

### High Risk Individuals

- 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 has a higher cancer detection rate than mammography with tomosynthesis and likely has similar sensitivity compared to full diagnostic protocol breast MRI.
- CEM and MBI are also options for higher risk breast cancer screening. CEM has the risk of iodinated contrast reactions. CEM and MBI also have a higher breast radiation exposure per exam than standard mammography. MBI has a whole-body effective radiation dose substantially higher than that of mammography.

[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.

Continued

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## BREAST SCREENING CONSIDERATIONS

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

**Recommend Annual MRI Screening:[3]**
- **For individuals with a genetic mutation, or an untested 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 years**
- **For individuals with a residual lifetime risk ≥20% as defined by models that are largely dependent on family history[b]**
- **Consider annual MRI screening for individuals with ADH or lobular neoplasia (LCIS/ALH) and ≥20% residual lifetime risk**

**Insufficient Evidence to Recommend for or Against Routine Population-Based MRI Screening:**
- **Residual 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% residual lifetime risk**

[a] For age >75 years, supplemental 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 residual lifetime risk remains greater than (or risk still exceeds) 20%, recommend MRI.
[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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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| Average Risk Screening in Individuals ≥40 Years | R | R | NR[c] | NR | • There is no contraindication to screening mammography during pregnancy.<br>• While ionizing radiation exposure with mammography is many-fold below the threshold of fetal teratogenesis (see comments below), due to the infrequency of pregnancy-associated breast cancers (PABC) and the decreased sensitivity and specificity of mammography during pregnancy, providers and patients may implement a short delay in routine breast imaging based on prior imaging and date of delivery in individuals who are at average risk until after pregnancy.<br>• There are no data evaluating the use of ultrasound alone as an alternative screening method in individuals who are at average risk during pregnancy; therefore, this is not recommended as an alternative to screening mammography. |
| Increased Risk Screening<br>• Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier who remains untested<br>• Individuals who received thoracic RT between ages 10 and 30 years<br>• Individuals with a residual lifetime risk ≥20% as defined by models that are largely dependent on family history[a]<br>• Individuals with ADH or lobular neoplasia (LCIS/ ALH) and ≥20% residual lifetime risk. | R | R | O | NR | • In individuals who are at increased risk for breast cancer, it is appropriate to recommend screening mammography at routine intervals (see BSCR-2 and BSCR-3).<br>• The use of screening ultrasound alone has not been evaluated as a method to reduce breast cancer mortality in individuals who are at increased risk for breast cancer and pregnant.<br>• Contrast-enhanced breast MRI is not recommended during pregnancy due to the trans-placental passage of gadolinium, and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. |

R = Recommended, NR = Not recommended, O = Optional, depending on individual circumstances.

[a] There are significant limitations in interpretation of PRS. PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

[c] Consider supplemental screening for those with heterogeneous or extremely dense breasts.

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| Management of Palpable Breast Symptom | R | O | R | NR | • Age-appropriate evaluation of a palpable symptom during pregnancy should proceed similar to that outlined in BSCR-6.<br>• Begin evaluation of palpable breast symptom 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>• Contrast-enhanced breast MRI is not recommended during pregnancy due to the trans-placental passage of gadolinium, and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. |

R = Recommended, NR = Not recommended, O = Optional, depending on individual circumstances.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | 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, spontaneous uniductal, unilateral bloody or clear 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>• Contrast-enhanced breast MRI is not recommended during pregnancy due to the trans-placental passage of gadolinium, and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. |

R = Recommended, NR = Not recommended, O = Optional, depending on individual circumstances.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| Breast Erythema or Suspicious 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 that outlined on (BSCR-10).<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>• Contrast-enhanced breast MRI is not recommended during pregnancy due to the transplacental passage of gadolinium,and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. |
| 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 that outlined on (BSCR-10).<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>• Contrast-enhanced breast MRI is not recommended during pregnancy due to the transplacental passage of gadolinium and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. |

R = Recommended, NR = Not recommended, O = Optional, depending on individual circumstances.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

**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.**

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| BI-RADS Category 3 Imaging Follow-up (BSCR-18) | 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-18.<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). |
| Management of Axillary Mass | R | R | R | NR | • The development of an axillary mass during pregnancy may be due to normal breast enlargement that occurs during pregnancy in accessory axillary breast tissue that are present in ~15% of individuals. It is not uncommon for this to be asymmetric.<br>• If after clinical examination there remains concern that the physical findings are not due to normal axillary breast tissue that has enlarged due to pregnancy, providers should proceed with evaluation as outlined in BSCR-13.<br>• Contrast-enhanced breast MRI is not recommended during pregnancy due to the transplacental passage of gadolinium and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity. |

R = Recommended.
NR = Not recommended.
‡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.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

**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.**

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| Average Risk Screening in Individuals ≥40 Years | R | R | NR[c] | NR | • While there is both decreased sensitivity and specificity of screening mammography during lactation, there is no contraindication to screening mammography during lactation.<br>• A short delay in routine breast imaging may be implemented until after lactation, in those with average risk of getting breast cancer based on prior imaging results particularly if they are not planning prolonged breastfeeding<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination |
| Increased Risk<br>• Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier who remains untested<br>• Individuals who received thoracic RT between ages 10 and 30 years Individuals with a residual lifetime risk ≥20% as defined by models that are largely dependent on family history.[a]<br>• Individuals with ADH or lobular neoplasia (LCIS/ ALH) and ≥20% residual lifetime risk. | R | R | NR | R | • In individuals who are at increased risk for breast cancer, it is appropriate to recommend screening mammography at routine intervals (see BSCR-2 and BSCR-3).<br>• The use of screening ultrasound alone has not been evaluated as a method to reduce breast cancer mortality in individuals who are at increased risk for breast cancer and lactating.<br>• In individuals who are at increased risk for breast cancer, 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 individuals who are at increased risk for breast cancer.<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination. |

R = Recommended, NR = Not recommended.

[a] There are significant limitations in interpretation of PRS. PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations.
[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.
[c] Consider supplemental screening for those with heterogeneous or extremely dense breasts.

**Note: All recommendations are category 2A unless otherwise indicated.**
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## MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION (Continued)

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| Management of Palpable Breast Symptom | R | R | R | NR | • Age-appropriate evaluation of a palpable symptom during lactation should proceed similar to that outlined in BSCR-6 and BSCR-7.<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination<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. |

R = Recommended, NR = Not recommended.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

**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.**

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | 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), spontaneous, uniductal, unilateral bloody or clear 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-9.<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 lactation.<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 to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination. |

R = Recommended, NR = Not recommended, O = Optional, depending on individual circumstances.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

**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.**

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| Breast Erythema or Suspicious Skin Changes (eg, thickening or edema) | R | O | R | O | • Breast erythema or suspicious 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 suspicious 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 that outlined on (BSCR-10).<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-10).<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination |

R = Recommended, O = Optional, depending on individual circumstances.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | 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 that outlined on (BSCR-11).<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 contraindicated for the management of persistent, focal breast pain during lactation, it is usually not indicated.<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination |

R = Recommended, NR = Not recommended.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

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

| Condition | Recommendation | | | | Rationale for Recommendation/Other Considerations |
|---|---|---|---|---|---|
| | CBE | Mammogram with Tomosynthesis[b] | Ultrasound | MRI | |
| BI-RADS Category 3 Imaging Follow-up (BSCR-18) | 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-18.<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination. |
| 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 2 weeks 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-13.<br>• It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination. |

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.
‡‡‡ Recommended if MRI was the imaging modality that initially resulted in the BI-RADS 3 finding and there are no ultrasound or mammographic correlates.

[b] Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

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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).

[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 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).**

[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

**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.**

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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.


Continued

**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.**

## 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.**

[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

**Note: All recommendations are category 2A unless otherwise indicated.**
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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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## ABBREVIATIONS

| | |
|---|---|
| **ADH** | **atypical ductal hyperplasia** |
| **AMAB** | **assigned male at birth** |
| **ALH** | **atypical lobular hyperplasia** |
| **CBE** | **clinical breast exam** |
| **CEM** | **contrast-enhanced mammography** |
| **FEA** | **flat epithelial atypia** |
| **LCIS** | **lobular carcinoma in situ** |
| **MBI** | **molecular breast imaging** |
| **PABC** | **pregnancy-associated breast cancers** |
| **PRS** | **polygenic risk scores** |
| **RT** | **radiation therapy** |

| 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.

**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 Guidelines Version 3.2023
# Breast Cancer Screening and Diagnosis

## Discussion

This discussion corresponds to the NCCN Guidelines for Breast Cancer Screening and Diagnosis. Last updated: October 31, 2023.

**Table of Contents**

# NCCN Guidelines Version 3.2023
# Breast Cancer Screening and Diagnosis

## Overview

The average lifetime risk of breast cancer for a female in the United States has been estimated at 12.3% (or 1 in 8 females).[1] For 2023, the American Cancer Society (ACS) estimates that 300,590 cases of invasive breast cancer (299,540 in females and 2800 in males) and 55,720 cases of carcinoma in situ of the breast in females will be diagnosed in the United States.[2] About 43,700 breast cancer related deaths are estimated for 2023.[2] While breast cancer incidence rates increased by 0.5% each year from 2010 through 2019, mortality rates declined, falling an average of 1.3% each year from 2011 to 2020.[3] This decrease has been attributed to a combination of screening and treatment advances.[4]

The National Comprehensive Cancer Network 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 (HCPs) need to be aware that mammography with tomosynthesis or any other imaging modality is not a stand-alone procedure. Neither the current technology of mammography with tomosynthesis 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.

## Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

## Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Breast Cancer Screening and Diagnosis, an electronic search of the PubMed database was performed to obtain key literature in Breast Cancer Screening and Diagnosis published since the previous Guidelines updates, using the following search terms: breast cancer screening; screening mammography; breast cancer diagnosis; or breast MRI. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[5] Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in

future studies and organizations to use more inclusive and accurate language in their future analyses.

## Breast Screening Components

Breast screening is performed in individuals without any signs or symptoms of breast cancer so that disease can be detected as early as possible. Earlier disease detection may decrease the overall treatment needed and reduces morbidity and mortality rates. Diagnostic breast evaluation and imaging differ from breast screening in that they are used to evaluate an existing problem (eg, palpable mass, discharge from the nipple, mammographic finding). NCCN screening recommendations are largely intended for cisgender females due to the preponderance of data in this population. For breast cancer screening of transgender individuals, the NCCN Panel endorses the consensus-based guidelines developed by the American College of Radiology (ACR) Appropriateness Criteria.[6] Transgender individuals should consult with their primary care provider to determine when and/or whether screening would be appropriate.

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, familiarity with one's own breasts); regular clinical encounters, which include breast cancer risk assessment and clinical breast exam (CBE); breast imaging with screening mammography with tomosynthesis; and, in selected cases, breast MRI with and without contrast or breast ultrasound.

### Clinical Encounter

The starting point of these guidelines for screening and evaluating breast abnormalities is a clinical encounter, which includes at a minimum, a complete medical history and family history followed by breast cancer risk assessment, risk reduction counseling, and preferably a CBE even in asymptomatic individuals when feasible. The frequency of the clinical encounter depends on the age and risk assessment of the patient (see *Clinical Encounter Including Risk Assessment* in the algorithm).

The rationale for recommending the clinical encounter is to maximize the earliest detection of breast cancers and to assure ongoing risk assessment, particularly in regions where mammographic screening may not be easily accessible. 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%.[7] While randomized trials comparing incremental CBE versus mammographic screening have not been performed, a study based in Mumbai, India comparing CBE and cancer awareness information to no screening revealed that the addition of CBE and cancer awareness information led to an earlier age at breast cancer diagnosis, a significant reduction in breast cancers diagnosed at stages III or IV, a non-significant reduction in mortality of 15% in the overall study population (ages 35–64 years), as well as a significant relative reduction in mortality of nearly 30% in individuals >50 years of age.[8]

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). Inspection of the breasts should be performed with the patient in both upright and supine positions and should include 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. Positioning may be done so as to elicit any subtle shape or contour changes in the breast.[7] Time spent on the palpable portion of the exam is associated with increased detection of palpable abnormalities. It is critical for the location of any physical findings from a CBE to be documented, as

clock/quadrant location and distance from nipple to facilitate geographic correlation with imaging findings.

### Breast Awareness

Individuals should be familiar with their breasts and any changes to them.[9,10] 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 females of Chinese descent who were not undergoing routine mammographic screening were randomized to either receive instruction in BSE or not.[11] Adherence 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, individuals 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 individuals 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 individual, the next decision point is based on risk stratification. Individuals should undergo breast cancer risk assessment by 25 years of age 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.

Individuals are stratified into two basic categories of risk for the purpose of screening recommendations: average risk and increased risk of developing breast cancer. Risk assessment is outlined in the NCCN Guidelines for Breast Cancer Risk Reduction. The increased risk category consists of six groups: 1) those who have a lifetime risk ≥20% as defined by models that are largely dependent on family history (eg, BRCAPRO,[12] Tyrer-Cuzick,[13] Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA]/CanRisk[14]); 2) those that received prior thoracic radiation therapy (RT) between the ages of 10 and 30 years (eg, mantle irradiation); 3) those ≥35 years of age with a 5-year risk of invasive breast cancer ≥1.7% (per Gail Model); 4) those who have a lifetime risk ≥20% based on history of atypical ductal hyperplasia (ADH); 5) those who have a lifetime risk ≥20% based on history of lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH); and 6) those with a known genetic predisposition or a pedigree suggestive of a 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.[15,16]

In a study of 49,528 females who underwent both film and digital mammography, no difference was seen in the overall accuracy of the two

procedures.[17,18] However, digital mammography was significantly more accurate in females <50 years of age with dense breasts, and there was a nonsignificant trend toward improved accuracy of film mammography in females ≥65 years of age. In another trial of females 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.[19]

More recently, combined use of digital mammography (two-dimensional, 2D) in conjunction with tomosynthesis improves cancer detection and reduces false-positive call-back rates,[20-32] including for those with dense breasts.[33,34] Tomosynthesis allows acquisition of multiple low-dose x-ray images across a limited arc and a digital detector. These data are reconstructed using computer algorithms to generate thin sections displayed in a quasi-3D format. The combined use of 2D and tomosynthesis results in double the radiation exposure compared with mammography alone. However, this increase in radiation dose falls below the 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 from the tomosynthesis acquisition, which may obviate the need for a conventional digital image.[21,35,36] A meta-analysis comparing the use of synthetic 2D mammography rather than standard 2D digital mammography with tomosynthesis revealed comparable diagnostic accuracy, with 85% versus 84% sensitivity and 93% versus 91% specificity, respectively.[37]

The presence of increased dense breast tissue decreases the sensitivity of mammography due to the obscuration or “masking” of cancers by overlying dense breast tissue. In addition, dense breast tissue as measured by mammography is increasingly recognized as an important risk factor for breast cancer.[38-41] About half of all females of screening age have “dense” breast tissue referred to as “heterogeneously dense” or “extremely dense” by ACR Breast Imaging Reporting and Data System (BI-RADS) nomenclature. Of note, the presence of dense tissue is not abnormal and can change over time. While many individual states have passed legislation mandating patient notification of breast density,[42] not all states require insurance coverage for supplemental screening. Recently, the FDA issued a final rule, effective nationally September 10, 2024, to update the Mammography Quality Standards Act by requiring a breast density assessment be reported to patients and HCPs, with additional language notifying patients that in the setting of dense breast tissue, supplemental imaging studies beyond mammography may help detect cancer and that individual’s should discuss their risk of breast cancer and review their personal preferences with their HCPs.[43] The NCCN Panel recommends consideration of supplemental screening for individuals ≥40 years of age with heterogeneously dense and extremely dense breast tissue who are otherwise considered at average risk of developing breast cancer. The risks and benefits of such screening should be discussed with individual patients.[44] Different supplemental imaging modalities may be considered based on risk and patient values/preference.[45] The ACR has published guidelines for supplemental screening based on breast density.[46]

***Screening Ultrasound***

Due to limitations of mammographic screening, especially in those with dense breasts, other imaging modalities are being explored to supplement mammography, including ultrasound, MRI, contrast-enhanced mammography (CEM), and molecular breast imaging (MBI). Unlike mammographic screening, these 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 females with dense breasts; however, they may increase recall and benign breast biopsies. For

example, a large prospective study in females with dense breasts and elevated risk for breast cancer found that adding screening ultrasound to mammography identified an additional 4.3 cancers per 1000 females screened (95% CI, 1.1–7.2 cancers per 1000) but increased the number of false-positive results.[45] Subsequent follow-up studies showed similar results.[47,48] However, in females 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%).[45] Application of screening ultrasound to females with dense breasts in clinical populations has produced similar results.[49]

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 females with dense breasts,[45,47,50-52] the routine use of ultrasound as a universal supplemental *screening* test in individuals at average risk of breast cancer 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.[53] In addition, microcalcifications are not detectable with MRI.[54,55] 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 females at average risk of breast cancer, the benefits of screening MRI for early detection of breast cancer in females at high risk of breast cancer, 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.[56-64] The ACS has published guidelines recommending use of breast MRI as an adjunct to screening mammography in certain populations of females at high risk of breast cancer.[65] Nevertheless, a high false-positive rate for screening MRI was identified in several studies. For example, in one study of females at high risk of breast cancer, many of whom were young (age range of entire cohort, 35–49 years) and had very dense breast tissue, screening MRI led to 3 times as many benign biopsies as mammography.[66]

A single retrospective study of asymptomatic females with atypical hyperplasia or LCIS enrolled in a high-risk screening program has evaluated use of MRI in this population.[67] Approximately half of the females 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 females with atypical hyperplasia. Females 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 female 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 four or more contrast MRI scans, long after the last administration.[68-71] Retention of gadolinium has also been seen in the bone.[72,73] 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.[74] Patients will be asked to read a medication guide prior to receiving gadolinium.

Abbreviated MRI has a higher cancer detection rate than mammogram with tomosynthesis[75] and meta-analyses comparing abbreviated versus full diagnostic protocol MRI revealed similar sensitivity and specificity between the two modalities.[76,77]

In individuals with a genetic mutation, or an untested first-degree relative of a gene mutation carrier, or those with a history of thoracic radiation between ages 10 and 30 years, or a lifetime risk of ≥20% based on models such as BRCAPRO, Tyrer-Cuzick, or BOADICEA/CanRisk, based on current evidence, the NCCN Panel continues to recommend an annual MRI with and without contrast as an adjunct to mammography with tomosynthesis. Individuals with LCIS or ALH/ADH with a lifetime risk of ≥20% should be considered for breast MRI with and without contrast 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, the ability to perform MRI-guided needle sampling and/or wire localization of MRI-detected findings, and regional availability. MRI findings should be correlated with findings from other breast imaging modalities. The ACR has published guidelines for the performance of contrast-enhanced MRI of the breast.[78]

***Other Breast Imaging Modalities***

CEM and MBI are also options for high-risk breast cancer screening. There is emerging evidence that CEM and MBI may improve detection of early breast cancers among females with mammographically dense breasts.[79-83] CEM carries a risk of iodinated contrast reactions, though a systematic review revealed a pooled rate of adverse events of only 0.82%.[84] CEM also has a higher breast radiation exposure per exam than standard mammography, though the radiation dose remains below the dose limits set by the FDA for standard mammography.[84,85] Additionally, MBI has a whole-body effective radiation dose that is substantially higher than that of mammography.[79]

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.[86]

## Screening Recommendations for Individuals at Average Risk of Breast Cancer

The NCCN Panel recognizes that the primary purpose of screening individuals 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.

### Those 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 individuals to be aware of their breasts and promptly report any changes to their HCP. 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.

### Those with Average Risk ≥40 Years of Age

The NCCN Panel recommends annual clinical encounter, which includes ongoing breast cancer risk assessment, risk reduction counseling, as well as a CBE, encourages individuals to be aware of their breasts and promptly report any changes, and recommends annual screening mammography with tomosynthesis (category 1 recommendation). Those electing to undergo screening mammography with tomosynthesis 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 individuals ≥40 years of age at average-risk for breast cancer should be covered by health care payers without additional cost-sharing or copayments. For individuals ≥40 years of age with heterogenous or extremely dense breasts, consideration should be made for supplemental screening.

Mammographic screening and subsequent treatment have been shown to decrease breast cancer mortality beginning at age 40 years.[87,88] 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.[87-89] 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. Mammography with tomosynthesis is now recommended as previously discussed, as multiple studies show that tomosynthesis can decrease call back rates and improve cancer detected compared with 2D mammography alone.[20-34] Radiation exposure may be increased, but remain within FDA guidelines and can be reduced with FDA-approved synthesized 2D reconstruction.[21,35,36]

The NCCN Panel has not established an upper age limit for screening. According to the panel, if a patient has severe comorbid conditions limiting life expectancy and no further intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of age. Similarly, ACS guidelines have not established an upper age limit for screening, and recommend that individuals in overall good health should continue screening if their life expectancy is ≥10 years.[87] Current U.S. Preventive Services Task Force (USPSTF) and draft recommendations are for screening for individuals aged 50 to 74 years and state that there is insufficient evidence to weight the benefits and harms of screening in individuals ≥75 years of age.[88,89]

### 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 females 40 to 49 years of age, those

recommending breast cancer screening to begin at age 50[88] view the benefits of screening as being balanced by the harms of screening during this decade. While current USPSTF recommendations are for screening to begin at age 50,[88] in their recent draft the recommendation has been updated for screening to begin at age 40.[89] 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.[87] 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" females would want the earlier screening and only a "small proportion" would not.[87]

***Benefits of Mammographic Screening***

Systematic reviews of RCTs have generally shown a reduction in breast cancer mortality with mammography screening.[90]

The UK Age trial specifically studied the effect of film-screen mammographic screening starting at age 40 years.[91] A mean of 10.7 years of follow-up showed a non-statistically significant breast cancer mortality reduction in females invited to screening (RR, 0.83; 95% CI, 0.66–1.04).[91] 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.[92] 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; 95% CI, 0.58–0.97).[92] Other trials included females 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 females 40 to 49 years of age to reduce breast cancer-related mortality.[92]

A Swedish study compared breast cancer mortality rates in females 40 to 49 years of age living in different counties. Counties included those that invited females for screening starting at age 40 and others that did not invite females to be screened at age 40 and started screening at age 50.[93] 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).[93] 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.[93]

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 females with dense breasts, which is common in younger females. 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%.[94,95] A meta-analysis of observational case-control studies found a significant reduction in breast cancer mortality with mammographic screening for females 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.[96] Relevant to the North American population, data from a Canadian study showed a mortality reduction of 44% (95% CI, 33%–55%) among females screened between the ages of 40 to 49 years, which was similar to the overall

reduction in mortality of 40% (95% CI, 33%–48%) found among females ages 40 to 79 years.[95]

A retrospective analysis evaluating the benefits of mammographic screening of females 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.[97] A population-based study of data from the Netherlands Cancer Registry estimated the impact of tumor size in females 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.[98] 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 females ages 40 to 84 years.[99] The CISNET models from 2015, based on digital screening mammography, show greater mortality reduction benefit.[100] Benefits of screening females in their 40s are more favorable when considered from the perspective of life years saved compared exclusively to mortality reduction.[101] Females 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 females in their 40s, trailing only poisonings.

Individuals 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 those 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 risk profile for harms of breast cancer screening, such as false-positive results and overdiagnosis, are weighted differently by different organizations.[87,88] This is a very subjective rating as there are limited data regarding a female's perspective of the harms of screening. The clinical practice guidelines that recommend delaying screening to age ≥50 years[87] place a greater emphasis on the risks of screening mammography, specifically false-positive results and overdiagnosis. Most females highly value the reduction in breast cancer mortality, whereas many females do not consider false positives and potential overdiagnosis to be a "harm."[102] In this study, 63% of females thought 500 or more false positives per life saved was acceptable.[102]

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 females diagnosed with breast cancer who did not undergo screening had substantially more need for chemotherapy and more extensive surgery than females who underwent routine screening.[103]

Furthermore, absence of mammographic screening for breast cancer does not mean absence of breast-related problems. Females who are not screened 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.[88] While recalls are commonly thought to be higher in younger females, 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 females screened 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 females.

Those considering false positives as one of the harms of screening note psychological consequence as one of the negative consequences of false positives.[104] However, a cross-sectional survey of female’s attitudes toward false positives found that females consider false positives as an acceptable consequence.[102]

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 be influenced by 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 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%[87,90,105-107]) 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 invited cohort group aged 55 to 69 years was not routinely screened at the end of the trial,[108] 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.[108] 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 females were aged 40 to 49 years at recruitment, the estimated overdiagnosis was 14%. In the second trial, in which females were aged 50 to 59 years at recruitment, the estimated overdiagnosis rate was 11%.[109,110] Using these three studies, the UK review estimated overdiagnosis (including DCIS) to be 10.7%.[111] Yet, these studies are

limited by their age and differing use of diagnostic mammography among females who were not screened. However, analysis of the UK AGE trial, which included females aged 40 to 49 years, showed a very low rate of overdiagnosis of 1%,[112] a value similar to estimates from Sweden for females in their 40s.[93] A reported population-based screening study showed a rate of only 0.3% overdiagnosis after 12 years of follow-up in females either invited or uninvited (n = 988, 090) and a 46% reduction in breast cancer mortality among attenders.[113] Direct estimates of type 1 overdiagnosis for females screened in the United States show marked differences depending on age of diagnosis, with less than 1% among females who are premenopausal and 22% among females aged 80 years.[114]

Prevention of cancer death is highly valued compared with false-positive results/overdiagnosis by most females.[102] 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 females and females who are premenopausal.[87,88,99,115] 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.[99] Additionally, mammograms can often detect a lesion 2 years before the lesion is discovered by CBE. Interval cancer rates are lower among annually screened females. 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 females between 40 to 49 years found that using *annual* digital mammography saves 30% more lives and 34% more life-years than *biennial* digital mammography.[116] 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).[115,117]

A decline in breast cancer specific-mortality was observed in a cohort of females for every additional annual mammogram performed 5 years prior to breast cancer diagnosis; this further emphasizes the importance of annual mammography.[118] 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.[119]

While the risk of false positives is greater with annual compared to biennial mammograms,[88] the panel believes that the lower mortality and morbidity of annual screening outweighs this harm.

***Age to Stop Mammographic Screening***

Most trials for breast screening have used a cutoff age of 65 or 70 years.[120-122] However, observational studies and computer models show mortality benefit to age 80 to 84.[87,99] Considering the high incidence of breast cancer in individuals who are older, the screening guidelines used for those ≥40 years of age are recommended for all individuals age 40 and above with no age cutoff to stop screening. 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, thus emphasizing 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.[123] If a patient has severe comorbid conditions limiting life expectancy and no intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of age.[123,124]

## Screening Recommendations for Individuals at Increased Risk of Breast Cancer

### Those 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 a risk threshold used in the guidelines to identify an individual 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[65] in a female at high risk if the 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 Tyrer-Cuzick,[13] BRCAPRO,[12] BOADICEA/CanRisk,[14] and other models.[65,125,126] BRCAPRO[12] and BOADICEA[127] are also 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 those 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, but not prior to age 21 years. The NCCN Panel recommends annual screening mammography with tomosynthesis starting from 10 years prior to when the youngest family member was diagnosed with breast cancer, but not prior to age 30. Beginning annual screening mammography with tomosynthesis at age 25 can be considered on a case-by-case basis depending on the extent of family history and age(s) of diagnosis. In addition, in accordance with the ACS guidelines,[65] the NCCN Panel recommends annual breast MRI with and without contrast to begin 10 years prior to when the youngest family member was diagnosed but prior to age 25 years or beginning at age 40 (whichever comes first). Many experts recommend alternating the mammogram and MRI every 6 months. While there is limited data to support this approach, the presumption is that this may lead to earlier identification of interval cancers.[128] For those who qualify for but cannot undergo MRI, CEM or MBI can be considered. Whole breast ultrasound may be done if contrasted imaging or functional imaging is not available or accessible. According to the NCCN Panel, individuals in this group should

be asked to consider risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

### Those Who Have Received Prior Thoracic Irradiation Between the Ages of 10 to 30 Years

Results from several studies have demonstrated that females 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.[129-134] 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.[130,133] The RR of breast cancer in females 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.[133] Results from a case-control study of females 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 female treated at 25 years of age with at least 40 Gy of radiation and no alkylating agents.[135] Although there is a concern that the cumulative radiation exposure from mammography in a young female may itself pose a risk for cancer, it is felt that the additional radiation in this population is negligible compared to overall radiation exposure. Unfortunately, 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.[136]

For those ≥25 years of age 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 beginning 8 years after radiation exposure.[137] Breast imaging assessments with annual mammograms with tomosynthesis and annual MRI with and without contrast are recommended 8 years after RT but not prior to age 25.[137] As noted previously, the NCCN Panel recommends alternating the mammogram and breast MRI every 6 months.

For those <25 years of age who have received prior thoracic irradiation, the NCCN Panel recommends encouraging breast awareness, counseling on risk, and an annual clinical encounter starting 8 years after radiation therapy.

### Individuals Aged ≥35 Years with a 5-Year Risk of Invasive Breast Carcinoma ≥1.7% by the Modified Gail Model

For individuals aged ≥35 years, 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[138-142] that can be accessed at: https://bcrisktool.cancer.gov/, 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 those who are at increased risk. The Gail model should not be used for those with a predisposing gene mutation, a strong family history of breast or ovarian cancer suggestive of a genetic predisposition, those 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 females.[143] 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 females in the United States.[144]

Increased risk of developing breast cancer is defined by the modified Gail model for females ≥35 years of age as a 5-year risk of ≥1.7%. This is the average risk for a 60-year-old female, 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%. As previously mentioned, the modified Gail model risk assessment tool also provides an estimate of a female'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 an individual is eligible for screening breast MRI.

For an individual aged ≥35 years 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 tomosynthesis, to begin at the age identified as being at increased risk by the Gail model. In addition, according to the NCCN Panel, those in this group should be counseled for consideration of risk-reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction. The NCCN Panel also recommends consideration of supplemental screening for individuals with heterogenous or extremely dense breasts.

### Those Who Have a Lifetime Risk ≥20% Based on History of ADH or Lobular Neoplasia (LCIS/ALH)

A diagnosis of ADH or LCIS/ALH is associated with high risk of development of cancer in either breast.[145-150]

For those with a history of ADH or LCIS/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 mammography with tomosynthesis, beginning at the age of diagnosis of ADH or LCIS/ALH but not prior to age 30. In addition, according to the NCCN Panel, annual MRI with and without contrast should be considered beginning at the age of diagnosis of ADH or LCISALH but not prior to age 25.[67] Many experts recommend alternating the mammogram and MRI every 6 months. While there is limited data to support this approach, the presumption is that this may lead to earlier identification of interval cancers.[128] For those who qualify for but cannot undergo MRI, CEM or MBI can be considered. Whole breast ultrasound may be done if contrasted imaging or functional imaging is not available or accessible. Individuals in these groups should also be considered for risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

### Those with a Known Genetic Predisposition or Pedigree Suggestive of a Genetic Predisposition

Accurate family history information is needed to adequately assess 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, Ovarian, and Pancreatic 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, Ovarian, and Pancreatic).

## Diagnostic Evaluation

Breast symptoms are common. A retrospective study of females aged 40 to 70 years showed that 16% (total visits of 23 per 100 females) of females will present with symptoms to their provider during a decade with higher frequency among those ages 40 to 59 years compared to those ages 60 to 79 years.[151] 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. Those <40 years of age, 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 individuals, 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 individual (also referred to as recall or callback). To add further confusion, insurance carriers may consider a routine mammogram to be “diagnostic” in certain asymptomatic individuals (eg, in those with prior cancer). Diagnostic evaluation in this review will be restricted to the former two situations.

Diagnostic evaluation includes physical examination and diagnostic imaging for symptomatic individuals and diagnostic imaging for those recalled from screening. Diagnostic imaging may include diagnostic mammography with tomosynthesis, ultrasound, and at times diagnostic breast MRI with and without contrast. 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. The NCCN Panel recommends that tomosynthesis replace traditional diagnostic mammographic imaging.[152-156]

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 the ACR BI-RADS assessment categories, which classify likelihood of the breast findings into six final assessment categories.[157] 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 both asymptomatic and symptomatic individuals that are screened, which can create confusion regarding recommendations.

NCCN Recommendations for Screening Mammogram BI-RADS Assessment Categories 0, 1, 2, 3, 4, 5, and 6 are listed below. The NCCN recommendations following evaluation of symptomatic diagnostic individuals 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 those with clinical findings of very low suspicion still warrant biopsy.

For BI-RADS category 0 (incomplete), the NCCN Panel recommends diagnostic workup, including comparison to prior mammograms, and additional imaging evaluation with diagnostic mammogram with tomosynthesis and/or ultrasound as indicated.

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

For BI-RADS category 3 (probably benign), the NCCN Panel recommends diagnostic mammograms with tomosynthesis at 6 months, then every 6 to 12 months for up to 24 months as appropriate. If the lesion remains stable or resolves mammographically, the patient resumes routine screening intervals for mammography with tomosynthesis. If, in any of the interval mammograms, the lesion increases in size or changes its benign characteristics, a core needle 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 image-guided core needle biopsy is necessary. When a core needle biopsy is performed, concordance between the pathology report and the imaging finding must be obtained.[158,159] For example, a negative core 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, surgical excision is recommended. Those with a benign result exhibiting pathology/image concordance may either resume routine screening or be followed with physical examination and/or imaging every 6 to 12 months for up to 1 year to assess for changes. If the exam or imaging findings remain stable, routine screening can resume. If the lesion increases in size or changes its benign characteristics, surgical excision is recommended.

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

***Breast Ultrasonography***

Imaging by ultrasound is an important adjunct for diagnosing breast cancer.[160] However, breast ultrasonography does not detect most microcalcifications.[45,57,161-163] The definitions of the ultrasound assessment

categories are outlined in *Ultrasound 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 with and without contrast is included in the guidelines for those with BI-RADS category 1–3 assessment or for those with benign biopsy of skin or nipple following BI-RADS category 4–5 assessment (See *Symptomatic During Clinical Encounter, Presenting Signs/Symptoms: Skin Changes* in the algorithm). 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.[164] MRI with and without contrast may also be used for suspicious nipple inversion/retraction, nipple discharge, and axillary mass(es) expected to represent adenopathy when mammography and ultrasound are not diagnostic.[165-167]

## 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 Biopsy***

A fine-needle aspiration (FNA) biopsy involves use of a smaller-bore needle to obtain cytologic samples from a breast mass. Advantages of FNA biopsy include its minimally invasive methodology and low cost,[168,169] 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.[170,171] The NCCN Panel only recommends use of FNA for symptomatic relief of a cyst or possible abscess.

***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.[172,173] It can be performed under imaging guidance (eg, stereotactic [mammographic] ultrasound, 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.[174] 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.[175-177] 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.[178] 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%.[117] 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.[178] 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, non-classic LCIS, 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.[169,174,179,180] For select patients with other specific histologies (eg, classic LCIS, ALH, flat epithelial atypia [FEA], papillomas without atypia, fibroepithelial lesions favoring fibroadenoma, ADH), excision may be considered depending on the level of suspicion. Support for this recommendation includes results of studies demonstrating an underestimation of cancer when atypical hyperplasia and LCIS are diagnosed by core needle biopsy.[181-186]

### Diagnostic Evaluation for Symptomatic Findings on Physical Examination

In general, the breast imaging evaluations after physical exam include mammography with tomosynthesis and ultrasound. The addition of ultrasound to diagnostic mammography with tomosynthesis significantly increases cancer detection and detection of specific benign findings such as cysts. Imaging for individuals <30 years of age begins with ultrasound, while those ≥30 years of age generally have both studies unless a cyst is likely.[187,188 ,189-192] 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 individuals with negative imaging may warrant biopsy that may identify a malignant mass.[187,193-195] 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 symptom in the breast, acquired/new onset nipple inversion/retraction without palpable mass, nipple discharge without a palpable symptom, skin changes, breast pain, axillary mass(es), and breast implant-related symptoms (>1-year post-implantation).

#### *Palpable Symptom in the Breast*

A palpable mass is a discrete lesion that can be readily identified during a physical exam. There are other palpable symptoms in the breast that warrant diagnostic evaluation, including new onset asymmetric thickening/nodularity, asymmetric breast enlargement, or change in shape/contour of the breast. The NCCN Guidelines separate the evaluation of individuals with palpable symptoms into two age groups: those ≥30 years of age and those <30 years of age.

*Those ≥30 Years of Age with Palpable Symptom*

The main difference in the guidelines for evaluating a palpable symptom in those ≥30 years of age compared with those <30 years of age is the increased degree of suspicion of breast cancer. The initial evaluation begins with a diagnostic mammogram with tomosynthesis and ultrasound. CEM may be considered, if available, in lieu of mammogram with tomosynthesis when clinical suspicious is high. Ultrasound should be geographically correlated with the palpable symptom in question.

Observation without further evaluation is not an option in these individuals. 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 those 30 to 39 years of age due to the high sensitivity of ultrasound alone.[190,191,196] 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 those with mammographic or ultrasound findings that are suspicious or highly suggestive of breast cancer, the NCCN Panel recommends core needle biopsy. When core needle biopsy is utilized, concordance between pathology, imaging, and clinical findings must be obtained.

**Mammographic and/or Ultrasound Findings:**

***BI-RADS category 1; low clinical suspicion***

No imaging abnormality detected on mammogram and/or ultrasound is a BI-RADS category 1 finding. The negative predictive value of negative imaging is high, >96%.[187,191,193-195] For palpable masses with negative mammography and/or ultrasound, and clinical suspicion for breast cancer is low, the NCCN Panel recommends physical examination at 3 to 6 months. Patients should also be instructed to monitor for and report any changes to their breasts. If the palpable symptom remains stable or decreases in size, routine screening can resume. If there is a significant increase in size of the palpable symptom or clinical suspicion has increased, additional age-appropriate diagnostic evaluation is warranted.

***BI-RADS category 1; clinically suspicious***

For palpable masses that are clinically suspicious but with negative mammography and/or ultrasound, the NCCN Panel recommends appropriate clinical management, which may include referral to a breast specialist, supplemental imaging, and tissue sampling.

***BI-RADS category 2; low clinical suspicion***

For palpable masses found to be benign and concordant on mammography and/or ultrasound, and clinical suspicion for breast cancer is low, routine screening can resume. Aspiration may be considered for symptomatic relief of cysts.

Simple cystic masses fall into this category. Breast cysts are classified as simple, complicated, or complex based on the characteristics identified by ultrasound evaluation (see Table 1 for definitions). A cyst meeting all criteria of a simple cyst is considered to be benign (ie, BI-RADS 2)[45,197] if the clinical findings and ultrasonographic results are concordant. In a retrospective analysis of females (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.[198]

***BI-RADS category 2; clinically suspicious***

For palpable masses that are found to be benign on mammography and/or ultrasound, but are clinically suspicious, the NCCN Panel recommends palpation guided tissue sampling by core needle biopsy, FNA, or excision.

***BI-RADS category 3; low clinical suspicion***

For palpable masses suspected to be probably benign on mammography and/or ultrasound, and clinical suspicion for breast cancer is low, the NCCN Panel recommends physical examination and imaging, with ultrasound or diagnostic mammogram with tomosynthesis, every 6 to 12 months for up to 24 months to assess for changes. Patients should also be encouraged to monitor and report any changes to their breasts. If the

palpable symptom remains stable or decreases in size, routine screening can resume. If there is a significant increase in size of the palpable symptom or clinical suspicion has increased, tissue sampling is recommended. Core needle biopsy is preferred; however, in some circumstances FNA may be sufficient.

Complicated cysts fall into this category and are associated with a low risk of malignancy.[45,199-201]

***BI-RADS category 3; clinically suspicious***

For palpable masses suspected to be probably benign on mammography and/or ultrasound, but are clinically suspicious, the NCCN Panel recommends tissue sampling. While core needle biopsy is preferred, FNA be sufficient in certain circumstances.

***BI-RADS category 4–5***

For palpable masses considered to be suspicious (ie, BI-RADS category 4) or highly suggestive of malignancy (ie, BI-RADS category 5) on mammography and/or ultrasound, the NCCN Panel recommends core needle biopsy. It is important to confirm geographic correlation between clinical and imaging findings.

Complex cysts, which have both cystic and solid components, fall into this category. Complex cysts have a relatively high risk of malignancy (eg, 14% and 23% in 2 studies).[45,180,200-202]

*Those ≤30 Years of Age with Palpable Symptom*

The preferred option for initial evaluation of a palpable symptom that is clinically suspicious is to proceed directly to ultrasound.[190] Mammogram with tomosynthesis should be performed if ultrasound results are highly suspicious or suggestive of cancer. Tissue sampling prior to imaging is not recommended. From this point, the decision tree for those <30 years of age with clinically suspicious symptoms is identical to the pathway for those ≥30 years of age.

Because the incidence of malignancy in those who are <30 years of age is low, observation of the symptom for one or two menstrual cycles can be considered in cases with low clinical suspicion. If observation is elected and the symptom resolves after one or two menstrual cycles, the patient may return to routine screening. If the symptom persists, ultrasound should be performed.

*Follow-up after Core Needle Biopsy*

If the biopsy result indicates benign pathology, and this finding is concordant with the imaging results, the NCCN Panel recommends either resumption of routine screening or a physical examination at 6 or 12 months, with or without ultrasound or mammogram with tomosynthesis, for up to 1 year to assess for changes. Physical examination with or without further imaging is an option for those <40 years of age. Concordance is established by the radiologist or breast specialist after review of the core needle biopsy pathology report and imaging findings. This may require discussion or review with the pathologist as well. Resumption of routine screening is recommended if the lesion remains stable. If the lesion significantly increases in size or if clinical suspicion is high, 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, ADH, or non-classic LCIS, the NCCN Panel recommends surgical excision. However, outcomes data regarding treatment of individuals with non-classic LCIS are limited, due in part to a paucity of histologic categorization of variants of LCIS. Select patients with ADH may be suitable for monitoring in lieu of surgical excision.

For select patients with other specific histologies (eg, classic LCIS, ALH, FEA, papillomas without atypia, fibroepithelial lesions favoring fibroadenoma, radial scars adequately sampled or incidental) excision may be considered depending on the level of suspicion, and excision is recommended if pathology is discordant with imaging. Complete excision with negative margins should be considered for florid LCIS, and multifocal/extensive LCIS involving >4 terminal ductal lobular lesions on a core biopsy, the latter being associated with an increased risk of being invasive cancer.[203]

Other histologies that may require additional tissue include mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist.

For patients with other specific histologies that are concordant with imaging, the NCCN Panel recommends resumption of routine screening or physical examination and/or imaging at 6 to 12 months for up to 1 year to assess for changes. There may be variability on the follow-up interval based on the level of suspicion. Counseling for risk reduction as outlined in the NCCN Guidelines for Breast Cancer Risk Reduction is also recommended.

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

***Nipple Inversion/Retraction Without Palpable Mass***

In patients with acquired or new-onset of nipple retraction, the NCCN Panel recommends CBE with attention to the presence of a mass underneath the nipple, the color of the nipple, the presence and color of nipple discharge, and evidence of inflammation, such as erythema, the presence of a fistula on the areola or nipple, purulent discharge, or tenderness. Breast imaging should also be obtained, with breast ultrasound recommended for those <30 years of age and diagnostic mammogram with tomosynthesis and breast ultrasound recommended for those ≥30 years of age.

If mammographic and/or ultrasound findings are suspected to be negative (ie, BI-RADS category 1) or benign (ie, BI-RADS category 2) and the clinical suspicion for breast cancer is low, routine screening can be resumed. Patients should also be instructed to monitor for and report any changes to their symptoms. If there is clinical suspicion, consideration should be made for obtaining a breast MRI with and without contrast and/or referring the patient to a breast specialist. If clinical and/or MRI findings are abnormal, core needle biopsy is recommended. If clinical and MRI findings are normal, routine screening can resume.

If mammographic and/or ultrasound findings are suspected to be probably benign (ie, BI-RADS category 3) and the clinical suspicion for breast cancer is low, the NCCN Panel recommends physical exam with or without diagnostic mammogram with tomosynthesis for 1 to 2 years. Patients should also be instructed to monitor for and report any changes to their symptoms. If there is clinical suspicion, follow up mirrors that for clinically suspicious BI-RADS category 1 or category 2 findings.

If mammographic and/or ultrasound findings are considered to be suspicious (ie, BI-RADS category 4) or highly suggestive of malignancy (ie, BI-RADS category 5), the NCCN Panel recommends core needle biopsy. If the abnormality is not amenable to core biopsy, surgical excision is recommended.

For patients with congenital or lifelong nipple inversion without recent changes, reassurance can be provided, and routine screening can resume. Patients should also be instructed to monitor for and report any changes to their symptoms. In the setting of recent changes to a congenital or lifelong nipple inversion, the clinical pathway mirrors the pathway for acquired or new-onset of nipple retraction.

***Nipple Discharge Without a Palpable Symptom***

Nipple discharge is common, and, in many cases, unrelated to breast pathology.[204-210] For example, non-spontaneous discharge from multiple breast ducts in an individual that is not lactating can occur during pregnancy, following breast stimulation, in the setting of certain thyroid conditions, and in those taking certain medications, such as estrogen, oral contraceptives, opiates, and particular psychoactive drugs or antihypertensive agents.[204,211]

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, and clear or bloody.[212] An endocrine work up should be considered in the setting of bilateral milky discharge.

In patients with a nipple discharge but no palpable symptom, an evaluation of the characteristics of the nipple discharge is the first step. Nipple smear cytology is rarely helpful and not recommended. The appropriate follow-up of non-spontaneous or multiple-duct discharge in those <40 years of age is observation, coupled with education to stop compression of the breast and to report the development of any spontaneous discharge. In those ≥40 years of age, screening mammography with tomosynthesis should be performed if not done within the past year, with further workup based on the BI-RADS category, along with education similar to that for those <40 years of age is recommended. Evaluation of this type of nipple discharge is based on the overall BI-RADS category of the diagnostic mammogram with tomosynthesis, if not done previously.

Patients presenting with no palpable symptom but with discharge that is persistent and reproducible on examination, spontaneous, unilateral, single-duct, and clear or bloody are imaged with age-appropriate imaging. For those <30 years of age, ultrasound with or without diagnostic mammogram with tomosynthesis is recommended. For those ≥30 years of age, both diagnostic mammography with tomosynthesis and ultrasound are recommended. Several clinical studies have established a very low risk of malignancy when mammogram and ultrasound are negative.[213,214] In certain situations, MRI 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.[165-167,215-217]

According to the NCCN Panel, when an overall imaging BI-RADS assessment is category 1–3 (negative, benign, or probably benign),[218] an MRI with and without contrast should be performed and the patient should be referred to a breast specialist. If subsequent MRI assessment is BI-RADS category 1–3, management options include surgical consultation for duct excision[218] or follow-up with physical exam every 6 months, with or without imaging, for 1 to 2 years, with imaging modality dependant on the original imaging. Patients should also be instructed to monitor for and report any changes in symptoms. For those referred for duct excision with subsequent benign pathology, routine screening can be resumed. Malignant findings should be managed according to the NCCN Guidelines for Breast Cancer. For those who are followed with physical exam with or without imaging and symptoms remain stable or resolve, routine screening can be resumed. If there is suspicious progression in symptoms, core needle biopsy if an imaging abnormality is present, or surgical excision is recommended.

When mammographic and/or ultrasound or follow up MRI assessment is BI-RADS category 4 or 5 (suspicious or highly suggestive of malignancy), the NCCN Panel recommends core needle biopsy. Surgical excision is recommended if core needle biopsy is not possible. If the pathology findings are benign, referral for surgical duct excision is recommended. If findings are indicative of malignancy, the patient should be treated according to the NCCN Guidelines for Breast Cancer.

***Skin Changes***

Any type of unusual skin changes around the breast may represent serious disease and needs evaluation. IBC should be considered when dermal pitting or dimpling (peau d'orange), skin thickening, and breast erythema and edema are present, and nipple excoriation, scaling, and skin ulceration 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.[219,220] 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.[221] Pure Paget's disease is frequently occult on mammography[222] 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 diagnostic mammogram with tomosynthesis, 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. If clinical suspicion is low for IBC or highly suspicious for infection, a short trial (eg, 7–10 days) of antibiotics may be considered. Similarly, if clinical suspicion is low for Paget's disease or highly suspicious for eczema, a short trial of topical steroids may be considered.

Referral to a breast specialist and breast MRI with and without contrast should be considered following imaging findings consistent with an overall BI-RADS assessment category 1–3 (negative, benign, or probably benign). If clinical and/or MRI findings are abnormal, tissue sampling is recommended. Core needle biopsy is preferred, with or without biopsy of the skin or nipple. Of note, IBC is a clinical diagnosis and is not dependent on a positive skin biopsy. If both clinical and MRI findings are normal, routine screening can be resumed.

A tissue biopsy should be performed if imaging findings are consistent with 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. A benign skin biopsy does not rule out malignancy when clinical suspicion of IBC is high, and further evaluation is recommended. If biopsy results are benign, surgical referral, biopsy of the skin or nipple, or MRI with and without contrast should be considered. A biopsy showing a malignant finding should be managed according to the NCCN Guidelines for Breast Cancer.

***Persistent or Severe 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 female presenting with breast pain as the only symptom is low, between 1.2% and 6.7%.[7,151,223,224]

Breast pain is considered persistent if present for a minimum of 4 to 6 weeks. During the first 4 to 6 weeks of breast pain, symptomatic management is appropriate if the patient is without other symptoms such as associated redness or mass. If other symptoms are present, physical examination should be done at that time.

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 symptoms, nipple discharge, or skin changes; the pain is cyclic; or diffuse and non-focal (larger than a quadrant) 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 females with mild pain and in 52% of females with severe pain.[225] If the breast pain is focal in nature, the NCCN Panel recommends age-appropriate diagnostic imaging (ultrasound with diagnostic mammogram with tomosynthesis for those ≥30 years of age; and ultrasound for those <30 years of age). 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 aged 30 to 39 years. Mammogram may not be necessary if performed and results were negative within the past 6 months. Conversely, for those <30 years of age, there are some clinical circumstances, such as when clinical suspicion for malignancy is high, that mammogram with tomosynthesis would be preferred over ultrasound.

For those with BI-RADS assessment category 1 (negative findings), the NCCN Panel recommends appropriate symptomatic 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, aspiration may be considered. For those with BI-RADS assessment category 3 (probably benign) findings, the Panel recommends physical examination and imaging, with ultrasound or diagnostic mammogram with tomosynthesis, every 6 to 12 months for up to 24 months to assess for changes. If imaging indicates possible abscess of focal pain, aspiration or surgical consultation should be considered. If imaging or exam findings remain stable or resolve, routine screening can resume. If imaging or exam findings significantly increase in size or if level of suspicion increases, core needle biopsy is recommended. Core needle biopsy should also be performed if imaging findings are consistent of an overall BI-RADS assessment category 4–5 (suspicious or highly suggestive of malignancy).

***Axillary Mass(es) Expected to Represent Adenopathy***

Localized axillary masses are more often related to benign disorders than malignancy.[226] 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.[227] 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 patients with cancer had occult breast cancer (5 in the contralateral breast) [228]

For an individual presenting with a unilateral axillary mass expected to represent adenopathy, the NCCN Panel recommends imaging with diagnostic mammogram with tomosynthesis and ultrasound. Diagnostic mammogram with tomosynthesis is optional in those <30 years of age unless ultrasound results are suspicious. CEM may be considered if available when clinically suspicious. If imaging findings are suspicious for malignancy, tissue sampling is recommended. If lymphoma is suspected, the tissue or specimen may require special pathologic processing and/or surgical excision. If tissue sampling results indicate malignancy of breast origin, management per the NCCN Guidelines for Breast Cancer is recommended. If no breast mass is evident, the panel also recommends a breast MRI with and without contrast. If tissue sampling results indicate malignant axillary lymph node of non-breast origin, the panel recommends referring to the appropriate NCCN Guidelines for management. A unilateral axillary mass with negative or benign imaging or tissue sampling

findings should be clinically managed, as appropriate depending on the level of clinical suspicion, which may include a referral to a breast specialist, supplemental imaging, and tissue sampling if not done previously.

For an individual presenting with bilateral axillary masses expected to represent adenopathy, the NCCN Panel recommends complete clinical evaluation to assess for other sites of adenopathy and potential non-breast etiologies of adenopathy, including but not limited to lupus, rheumatoid arthritis, or HIV infection.[229] Recent vaccination status should also be assessed, as lymphadenopathy is common following vaccines that elicit a strong immune response, reported in up to 16% of individuals following COVID-19 vaccination.[230] In a study examining the effect of influenza vaccination on fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT imaging in patients with cancer, FDG uptake in the axillary lymph nodes was increased in 50% of individuals who received the vaccine within 1 week before the FDG-PET/CT.[231] If no systemic disease is found, evaluation recommendations mirror those for unilateral adenopathy. If systemic disease is discovered, appropriate clinical management is recommended, which may include a referral to a breast specialist, supplemental imaging, and/or tissue sampling. If malignancy is discovered, the NCCN Panel recommends referring to the appropriate NCCN Guidelines for management.

***Breast Implant-Related Symptoms***

Individuals with breast implants have a very small risk of developing breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) and breast-implant associated squamous cell carcinoma (BIA-SCC). BIA-ALCL is a rare type of peripheral T-cell lymphoma that occurs on average 7.5 to 11 years following implantation.[232] BIA-SCC is also exceedingly rare, with only 19 cases reported in current literature.[233] The majority of cases of BIA-ALCL have been associated with textured implants, while BIA-SCC is associated with either smooth or textured implants.[234]

For those with breast implant-related symptoms concerning for BIA-ALCL (effusion, enlargement, mass), or BIA-SCC (ulceration) occurring >1 year post-implantation, the NCCN Panel recommends consultation with a multidisciplinary team with experience in managing BIA-ALCL and BIA-SCC.

**Presentation of Symptoms in Individuals AMAB**

For individuals assigned male at birth (AMAB) with bilateral breast enlargement consistent with gynecomastia or pseudogynecomastia, reassurance should be provided. Appropriate clinical management of gynecomastia or pseudogynecomastia depends on the age of the patient, presence of symptoms, and the presumed cause, whether drug-induced or related to hypogonadism or hyperthyroidism.

For individuals AMAB with presumed asymmetric gynecomastia, a palpable symptom not explained by gynecomastia, or with bloody nipple discharge, the NCCN Panel recommends diagnostic mammogram with tomosynthesis, with or without ultrasound. Mammograms are not generally performed prior to age 25 years for individuals AMAB.

For BI-RADS assessment category 1–3 (negative, benign, or probably benign) findings, the NCCN Panel recommends appropriate clinical management, which may include surgical referral for suspicious clinical findings.

For BI-RADS assessment category 4–5 (suspicious or highly suggestive of malignancy) findings, the NCCN Panel recommends core needle biopsy.

## Breast Imaging During Pregnancy and Lactation

Pregnancy associated breast cancer (PABC) is defined as breast cancer occurring during pregnancy, while breastfeeding, or within 1 year of delivery. PABC complicates approximately 1 in 3000 to 1 in 10,000 pregnancies[235] and is the most common invasive cancer diagnosed during pregnancy.[236]

Pregnancy and lactation are associated with profound changes in the structure of the breast. Breast changes during 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 CBE.[237] 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).[238] Similarly, the breast changes resulting from pregnancy and lactation may result in a reduced ability to detect small breast cancers on CBE or may result in suspicious breast changes due to normal, physiologic changes.

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.[239,240] 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.

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 suspicious worrisome thresholds for harm. The generally accepted minimum threshold for inducing fetal teratogenic effect is 50 mGy.[241,242] The measured fetal radiation dose from a 4-view mammogram is <0.03 mGy, a magnitude of difference approximating 1600-fold.[243] While there are no specific studies evaluating the sensitivity and specificity of mammogram with tomosynthesis compared to digital mammography in pregnancy, the improved specificity of mammogram with tomosynthesis in dense breast tissue in individuals who are not pregnant may make this modality particularly useful in this setting of increased breast density in individuals who are pregnant and lactating. While there may be a small increase in ionizing radiation delivery with mammogram with tomosynthesis compared to digital mammography, this small increase should not have any expected effect on fetal safety and appropriate diagnostic mammography should not be withheld.

In individuals who are lactating, nursing or breast pumping prior to mammography may improve sensitivity by decreasing the density of the breast parenchyma.[243] 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). There is no contraindication to routine screening mammography with tomosynthesis in individuals when lactating, and if an individual is due for

their routine screening mammogram with tomosynthesis, this should not be delayed due to ongoing lactation.

The use of contrast-enhanced breast MRI during pregnancy is contraindicated because gadolinium in all forms crosses the placenta and enters the fetal circulation.[242,244,245] 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 used. Non-contrast MRI is not recommended due to lack of sensitivity.

It is recommended that individuals who are lactating either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination. 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.[246] Breast MRI appears to be highly sensitive for the detection of known PABC, although there appears to be lower specificity of breast MRI (higher false-positive rate) in individuals who undergo breast MRI while still lactating.[247] 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.[242] 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.[244]

## Breast Cancer Screening During Pregnancy and Lactation

***Screening in Individuals ≥40 years at Average Risk of Breast Cancer***

Recommendations for breast cancer screening in individuals ≥40 years who are pregnant or lactating and who are at average risk for developing breast cancer include a CBE and mammogram with tomosynthesis. While ionizing radiation exposure with mammography is manyfold below the threshold of fetal teratogenesis,[243] due to the infrequency of PABC[235] and the decreased sensitivity and specificity of mammography during pregnancy and lactation,[238] providers and patients may implement a short delay in routine breast imaging based on date of delivery and/or prior imaging in individuals who are at average risk of breast cancer until after pregnancy and lactation. There are no data evaluating the use of ultrasound alone as an alternative screening method in individuals at average risk of breast cancer during pregnancy or lactation; therefore, it is not recommended as an alternative to screening mammography. Supplemental screening should be considered for individuals who are pregnant and lactating that have heterogenous or extremely dense breasts and are at average risk of breast cancer.

***Screening in Individuals at Increased Risk of Breast Cancer***

Recommendations for breast cancer screening in individuals at increased risk of developing breast cancer who are pregnant or lactating, including those with a genetic mutation, a first-degree relative of a gene mutation carrier who remains untested, those who received thoracic RT between the ages of 10 to 30 years, those with a residual lifetime risk of ≥20% as defined by models largely dependent on family history, and those with ADH or lobular neoplasia (LCIS/ALH) and ≥20% residual life time risk, include CBE and mammogram with tomosynthesis. The use of screening ultrasound alone has not been evaluated as a method to reduce breast cancer mortality in individuals who are pregnant or lactating and are at increased risk for breast cancer. While contrast-enhanced MRI is not recommended during pregnancy due to the trans-placental passage of

gadolinium,[242,244,245] it is appropriate to recommend screening breast MRI at routine intervals for individuals at increased risk of developing breast cancer who are lactating given the minimal excretion of gadolinium into human breast milk.[246]

### Management of Breast Symptoms During Pregnancy and Lactation

#### *Palpable Breast Symptom*

Age-appropriate evaluation of a palpable symptom during pregnancy or lactation should proceed similar to that for individuals who are not pregnant or lactating (See *Palpable Symptom* in the algorithm). Breast ultrasound is recommended as the initial imaging method to evaluate a palpable breast symptom during pregnancy; however, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information.

#### *Abnormal Nipple Discharge*

Because of the frequency of normal nipple discharge during pregnancy and lactation, the NCCN Panel defines abnormal nipple discharge as persistent, spontaneous uni-ductal, unilateral bloody, or clear nipple discharge. Due to normal physiologic changes of pregnancy and lactation, bloody nipple discharge is common, but usually short-lived.[248,249] Persistence beyond one or two episodes should undergo evaluation. Evaluation of abnormal nipple discharge during pregnancy should begin with breast ultrasound; however, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information. Age-appropriate evaluation of abnormal nipple discharge during lactation should proceed similar to that for individuals who are not pregnant or lactating (See *Nipple Discharge, No Palpable Symptom* in the algorithm). Breast MRI is not contraindicated for the management of abnormal nipple discharge during lactation if clinically indicated. 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).

#### *Breast Erythema or Suspicious Skin Changes*

Individuals who are pregnant with breast erythema or suspicious skin changes such as thickening or edema should undergo age- appropriate breast imaging evaluation similar to that for individuals who are not pregnant or lactating (See *Skin Changes* in the algorithm). Evaluation should begin with breast ultrasound; however, mammography may be appropriate if the provider or radiologist believes that it will add important clinical information.

Breast erythema or suspicious skin changes in individuals who are lactating may be due to puerperal mastitis. If symptoms are clinically consistent with mastitis, appropriate treatment should proceed, including the use of antimicrobials. In some circumstances, breast erythema or suspicious skin changes without other evidence of mastitis (absence of pain or fever) may prompt immediate evaluation for inflammatory breast cancer. Failure to resolve mastitis with usual treatment should result in an in-person evaluation for alternative etiologies (eg, breast abscess, inflammatory breast cancer). 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 that for individuals who are not lactating (See *Skin Changes* in the algorithm).

Breast ultrasound is particularly useful in diagnosing breast abscess and may be the appropriate first imaging modality. If breast abscess is found, drainage is usually indicated and provides a definitive diagnosis.

#### *Persistent, Focal Breast Pain*

While breast pain is common due to the physiologic changes of pregnancy and lactation and is considered normal, focal persistent breast pain

(defined as lasting 4–6 weeks in duration), should undergo evaluation as outlined for individuals who are not pregnant or lactating (See *Persistent or Severe Breast Pain* in the algorithm). Evaluation of persistent, focal breast pain during pregnancy and lactation should begin with breast ultrasound; however, mammography is an appropriate breast imaging modality if the provider or radiologist believes that it will add important clinical information. While breast MRI is not contraindicated for the management of persistent, focal breast pain during lactation, it is usually not indicated.

***Axillary Mass***

The development of an axillary mass during pregnancy may be due to normal breast enlargement that occurs during pregnancy or lactation in accessory axillary breast tissue that are present in ~15% of individuals. It is not uncommon for this to be asymmetric. If after clinical examination there remains concern that the physical findings are not due to normal axillary breast tissue that has enlarged due to pregnancy, providers should proceed with evaluation as outlined for individuals who are not pregnant or lactating (See *Axillary Mass* in the algorithm).

***BI-RADS Category Imaging Follow-up***

Pregnancy or lactation should not change the management of follow-up of a BI-RADS 3 imaging finding, and appropriate follow-up imaging and/or examination should proceed as outlined for individuals who are not pregnant or lactating (See *Mammographic or Ultrasound Evaluation and Follow-up* in the algorithm). In the case of a BI-RADS 3 finding on MRI without associated ultrasound or mammography findings in an individual who is pregnant, a breast expert should be consulted to assist with counseling regarding follow-up and management recommendations (eg, defer to after pregnancy).

While there is a small theoretical concern of milk fistula with biopsy,[250] 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 or lactation.

## Summary

The intent of the NCCN Guidelines for Breast Cancer Screening and Diagnosis is to give clinicians a practical, consistent framework for screening and evaluating a spectrum of clinical breast presentations. 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 | 169,180,197,199-202,251 |

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