



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer Screening and Diagnosis

Version 2.2023 — October 4, 2023

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NCCN Guidelines Version 2.2023

Breast Cancer Screening and Diagnosis

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φ Diagnostic/Interventional radiology	▯ Medical genetics/genomics
Ω Gynecologic oncology/Gynecology	† Medical oncology
P Internist/Internal medicine, including family practice, preventive management	‡ Pathology
	¥ Patient advocacy
	¶ Surgery/Surgical oncology
	* Discussion Section Writing Committee

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[NCCN Breast Cancer Screening and Diagnosis Panel Members](#) [Summary of the Guidelines Updates](#)

[Clinical Encounter Including Risk Assessment \(BSCR-1\)](#)

[Average Risk, Screening/Follow-Up \(BSCR-1\)](#)

[Increased Risk, Screening/Follow-Up \(BSCR-2\)](#)

[Symptomatic During Clinical Encounter, Presenting Signs/Symptoms \(BSCR-5\)](#)

- [Breast Implant-Related Symptoms \(BSCR-5\)](#)
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[Breast Screening Considerations \(BSCR-A\)](#)

[Recommendations for Breast Cancer Screening and Evaluation During Pregnancy and Lactation \(BSCR-B\)](#)

[Breast Imaging Assessment Category Definitions \(BSCR-C\)](#)

[Abbreviations \(ABBR-1\)](#)

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

[See NCCN Categories of Evidence and Consensus.](#)

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NCCN Guidelines Version 2.2023

Breast Cancer Screening and Diagnosis

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

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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Breast Cancer Screening and Diagnosis

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 observing* 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, Appropriate 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-Classical* 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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Breast Cancer Screening and Diagnosis

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](#)

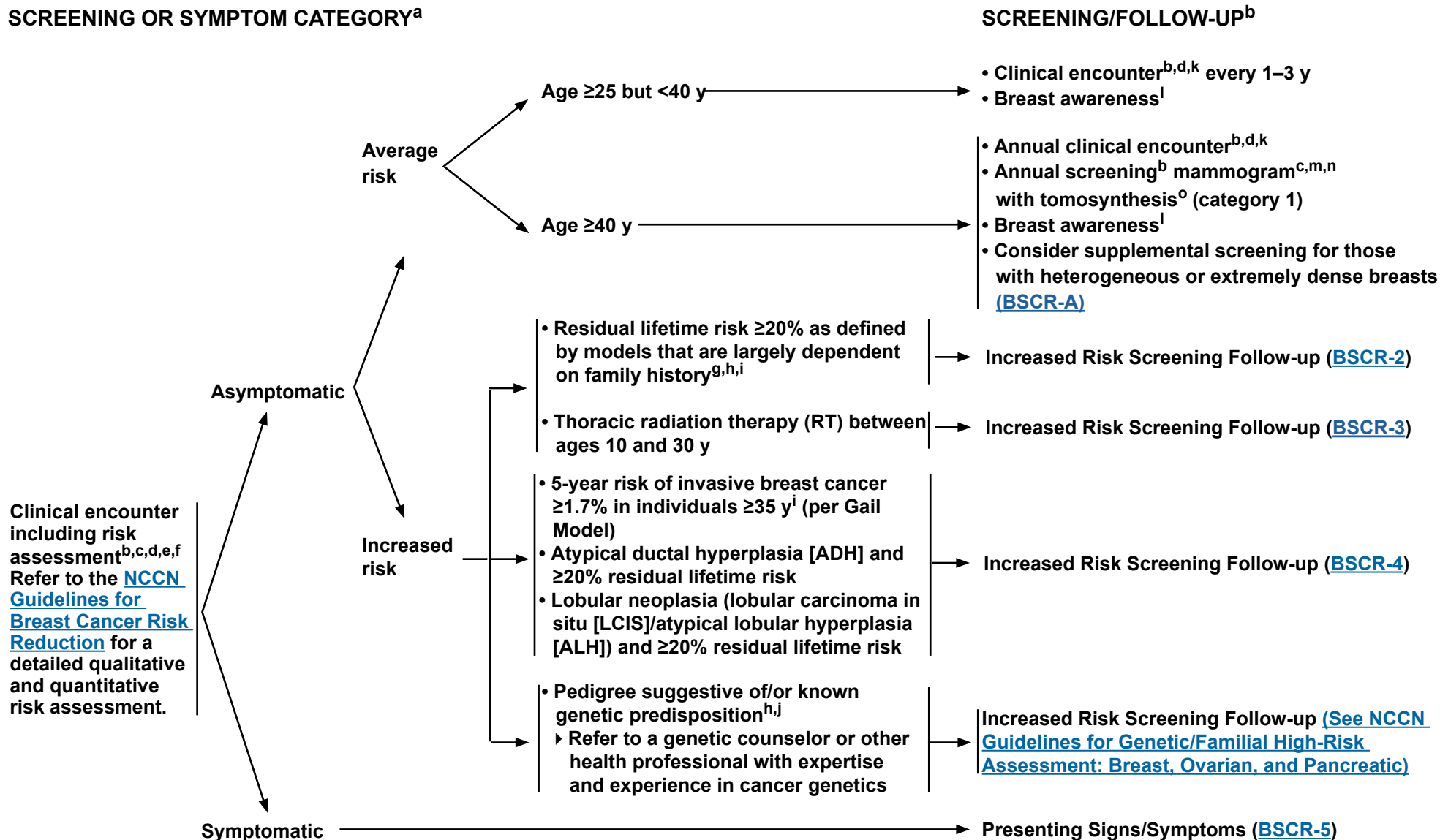
- Column 5, Under MRI, Not recommended, new: Recommended if MRI was the imaging modality that initially resulted in the BI-RADS 3 finding and there are no ultrasound or mammographic correlates.

[BSCR-B 12 through BSCR-B 14](#)

- These pages have been deleted.



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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 $\geq 20\%$ as defined by models that are largely dependent on family history^{g,h,i}

- Clinical encounter^{b,d,k} every 6–12 mo
 - ▶ To begin when identified as being at increased risk, but not prior to age 21 y
 - ▶ Consider referral to a genetic counselor or other health professional with expertise and experience in cancer genetics, if not already done
 - ▶ Consider referral to a breast specialist as appropriate
- Annual screening^b mammogram^{c,m} with tomosynthesis^o
 - ▶ 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)
- Annual breast MRI^{q,r} with and without contrast
 - ▶ 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
 - ▶ 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)
- 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.

^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](#).

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^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.

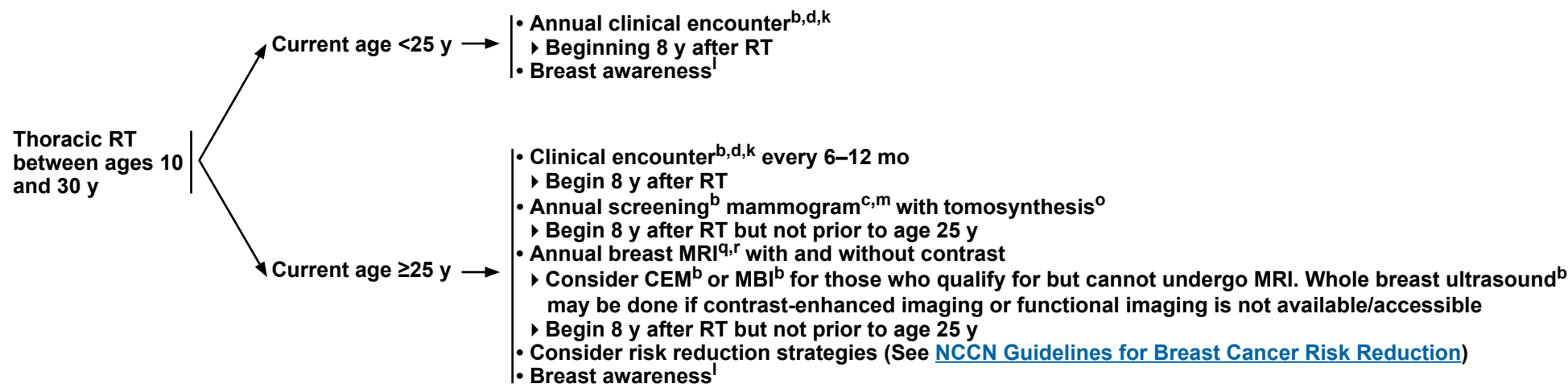
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SCREENING OR SYMPTOM CATEGORY^a SCREENING/FOLLOW-UP

Increased Risk:



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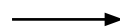
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Breast Cancer Screening and Diagnosis

SCREENING OR SYMPTOM CATEGORY^a

Increased Risk:

5-year risk of invasive breast cancer
≥1.7% in individuals ≥35 y (per Gail
Model)ⁱ



SCREENING/FOLLOW-UP

- Clinical encounter^{b,d,k} every 6–12 mo
 - ▶ To begin when identified as being at increased risk by Gail Model
- Annual screening^b mammogram^{c,m} with tomosynthesis^o
 - ▶ To begin when identified as being at increased risk by Gail Model
- Consider risk reduction strategies (See [NCCN Guidelines for Breast Cancer Risk Reduction](#))
- Breast awareness^l
- 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
 - ▶ To begin at diagnosis of ADH or lobular neoplasia (LCIS/ALH)
- Annual screening^b mammogram^{c,m} with tomosynthesis^o
 - ▶ To begin at diagnosis of ADH or lobular neoplasia (LCIS/ALH) but not prior to age 30 y
- Consider annual breast MRI^{b,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
 - ▶ To begin at diagnosis of ADH or lobular neoplasia (LCIS/ALH) 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.

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ⁱ See Comparison of Predictive Models for Risk Assessment ([NCCN Guidelines for Breast Cancer Risk Reduction](#)).

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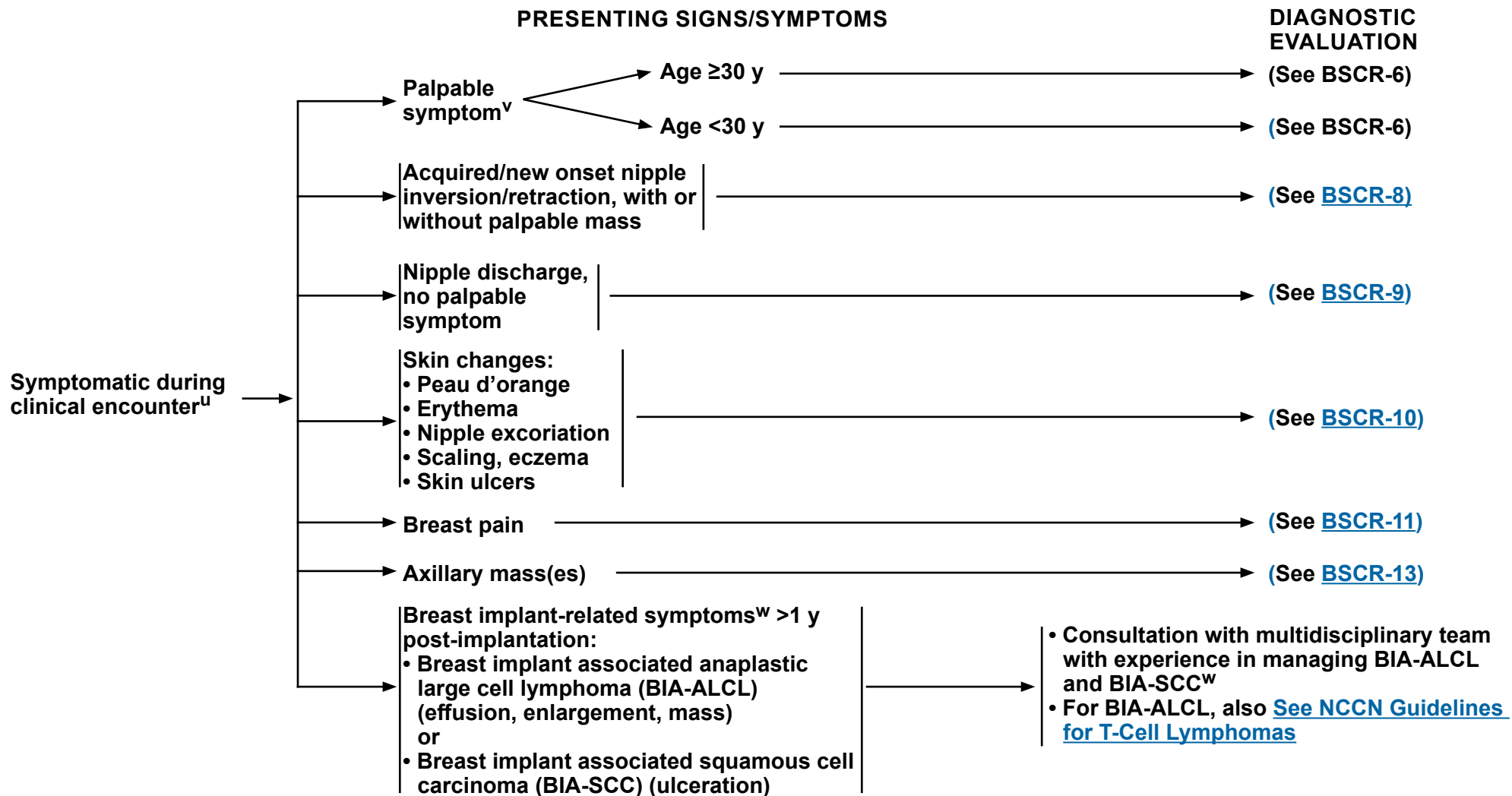
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^u For symptoms in individuals AMAB, see [BSCR-14](#).

^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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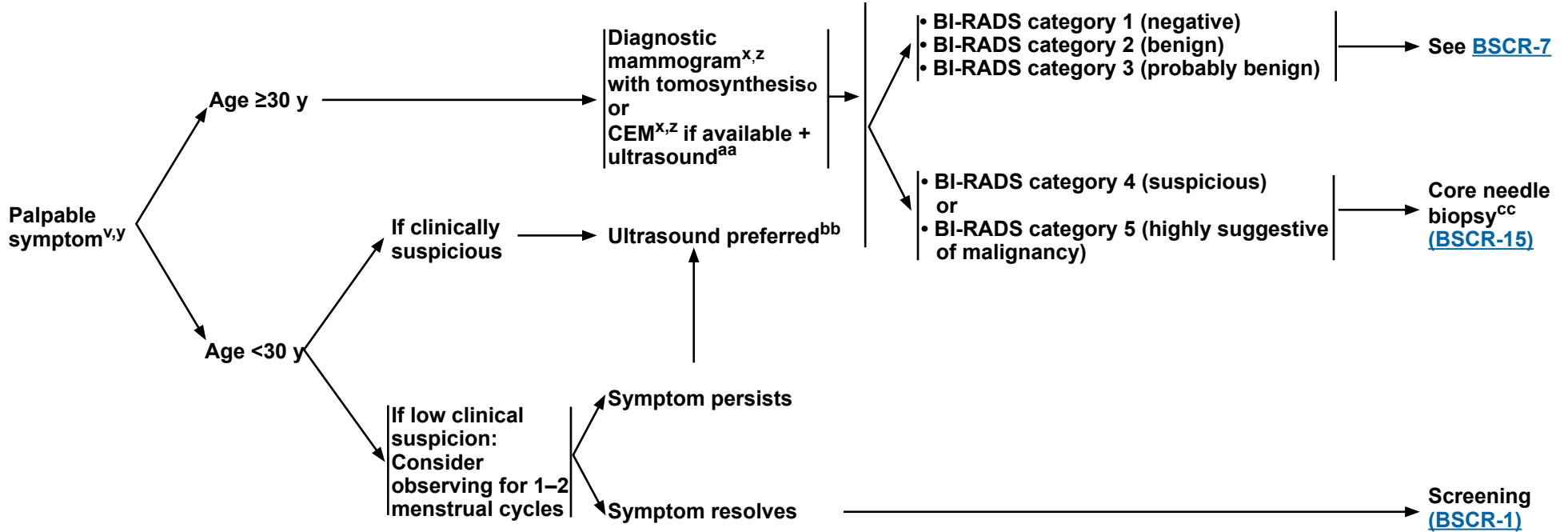
Breast Cancer Screening and Diagnosis

**PRESENTING
SIGNS/SYMPTOMS**

**DIAGNOSTIC
EVALUATION**

**IMAGING FINDINGS
(Highest Imaging Category
by Mammogram and/or Ultrasound)**

FOLLOW-UP



^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.

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.

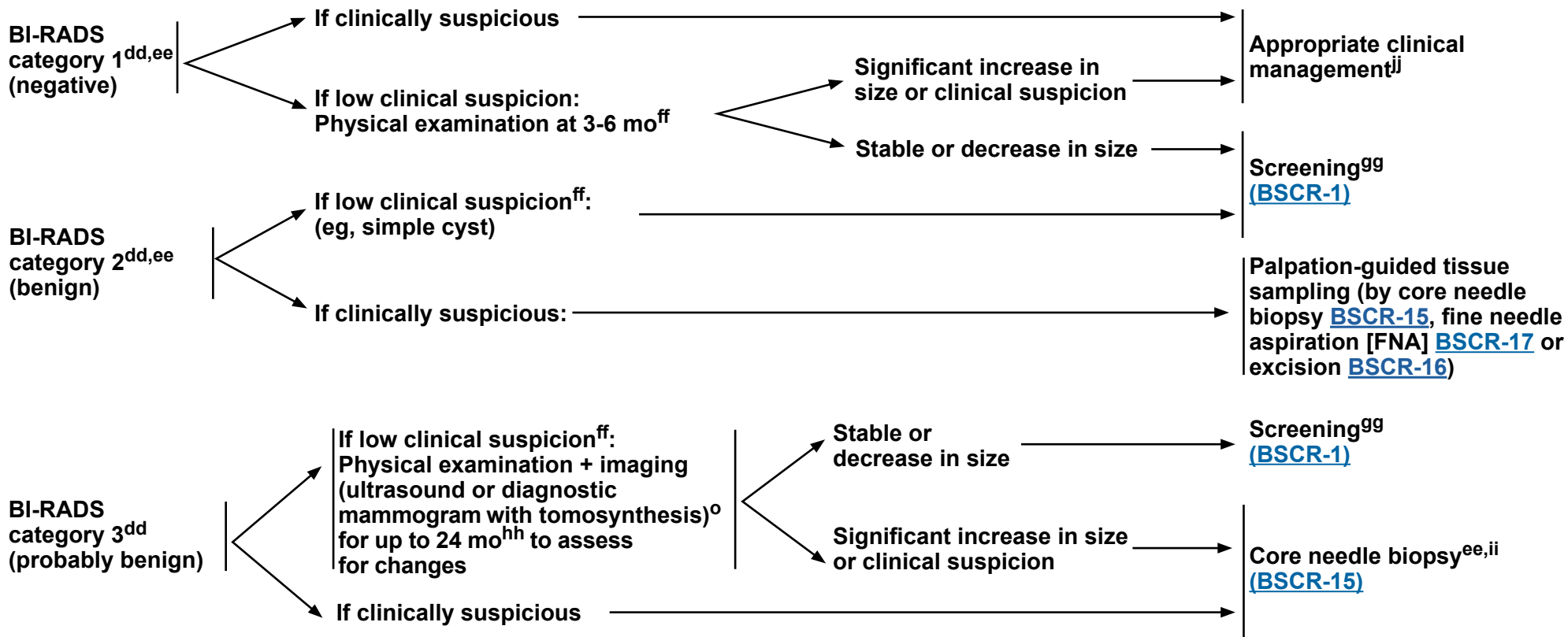


NCCN Guidelines Version 2.2023

Breast Cancer Screening and Diagnosis

IMAGING FINDINGS WITH PALPABLE SYMPTOM^{v,y}

FOLLOW-UP AFTER IMAGING



^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.

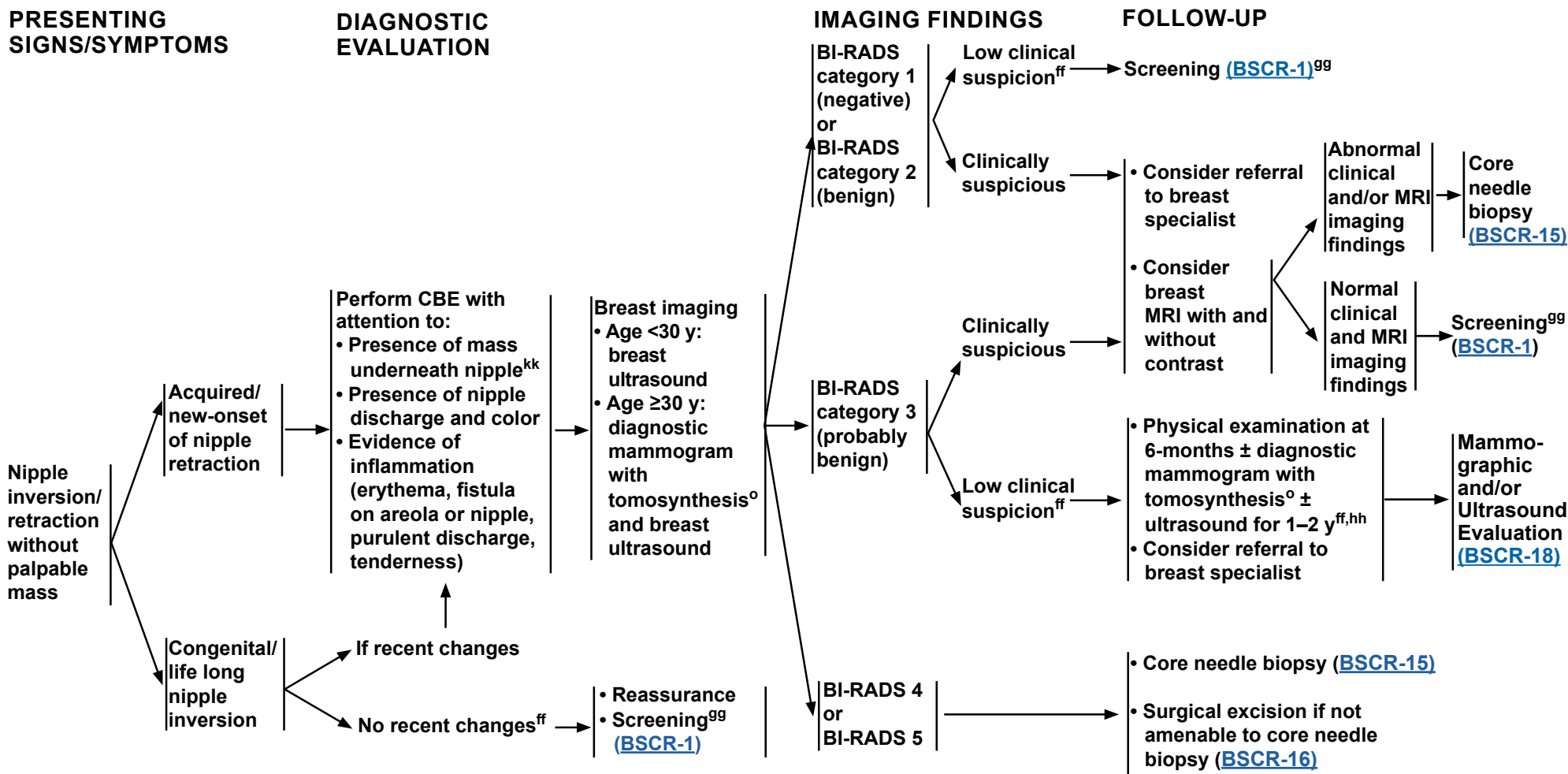
ⁱⁱ Core needle biopsy preferred; in some circumstances needle aspiration may be sufficient.

^{jj} This may include a referral to a breast specialist, supplemental imaging, and/or tissue sampling.

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 NIPPLE INVERSION/RETRACTION



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.

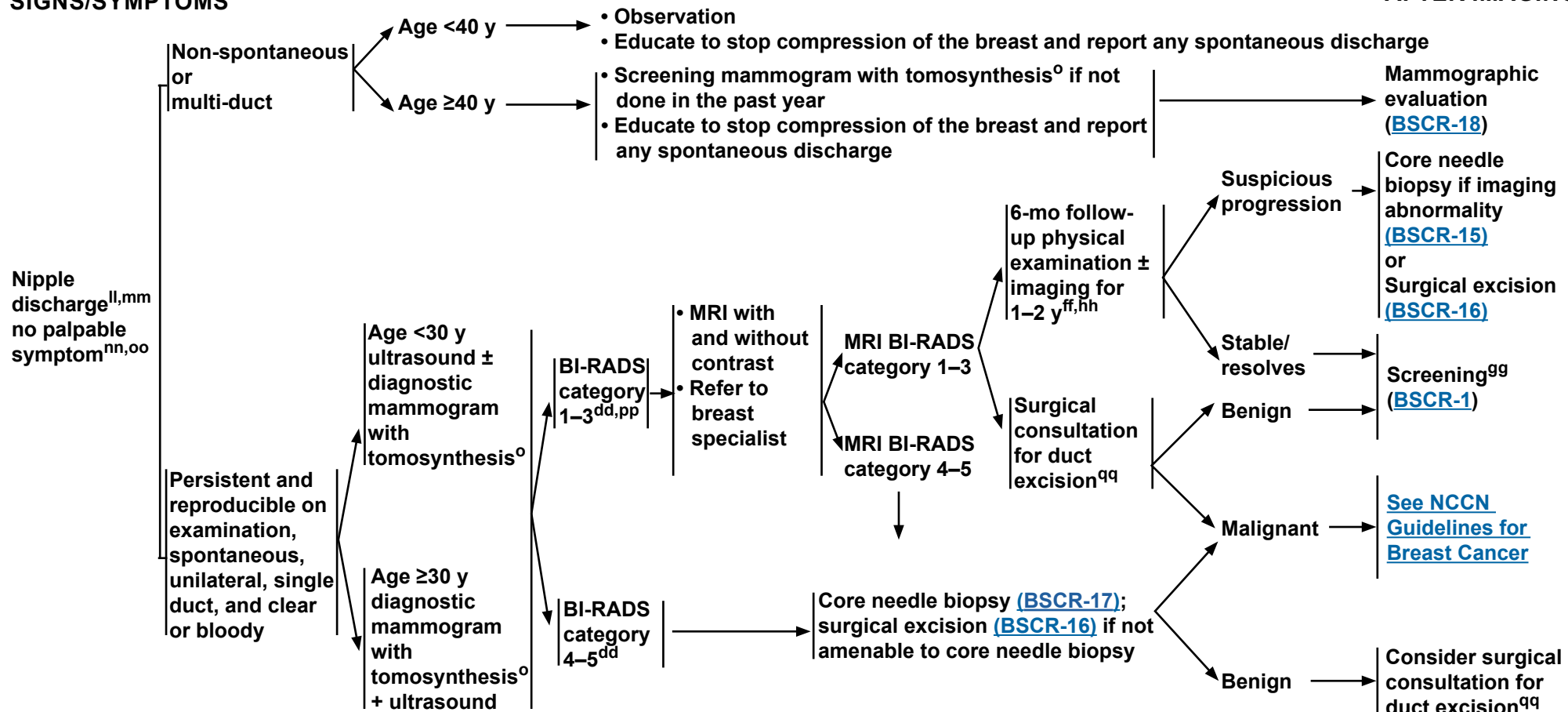


NCCN Guidelines Version 2.2023 Breast Cancer Screening and Diagnosis

PRESENTING SIGNS/SYMBOLS

DIAGNOSTIC EVALUATION AND FOLLOW-UP

FOLLOW-UP AFTER IMAGING



^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.

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

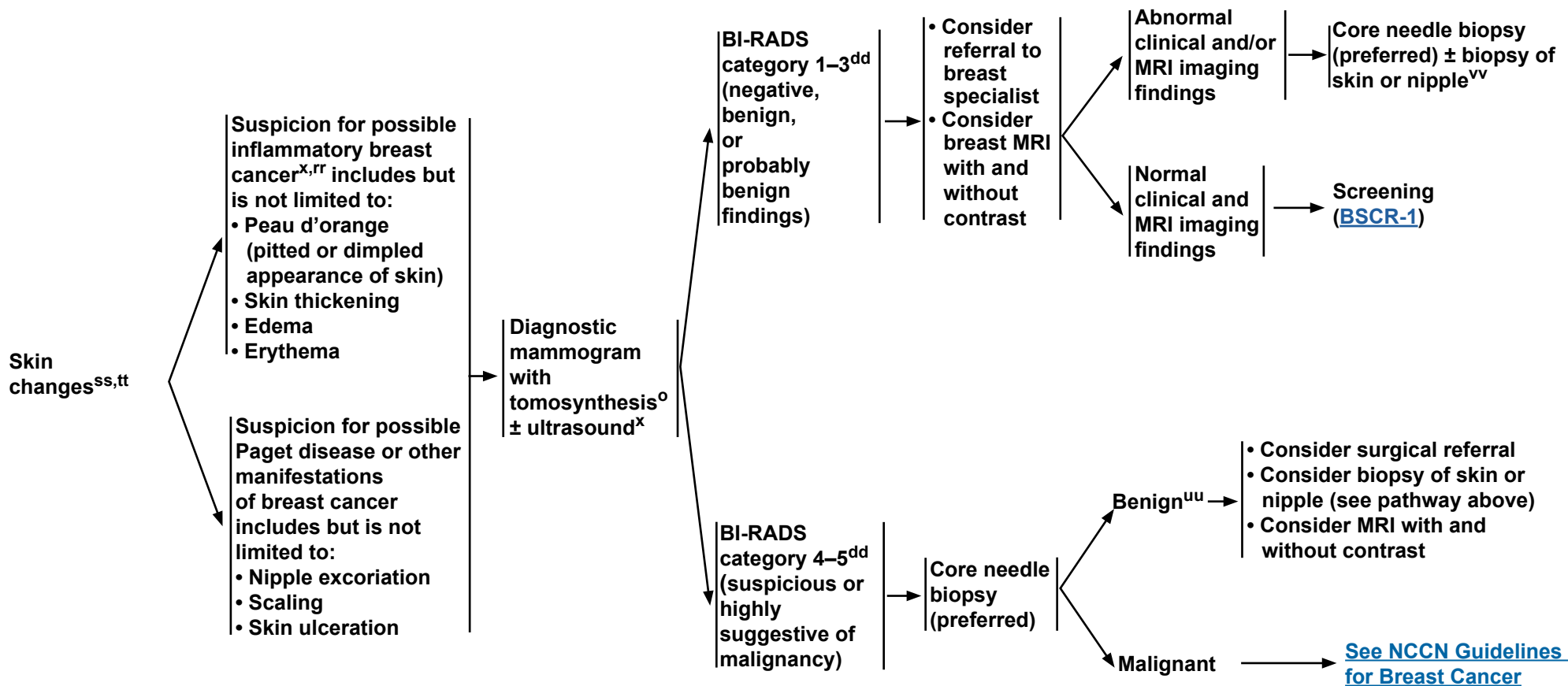
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2023 Breast Cancer Screening and Diagnosis

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.

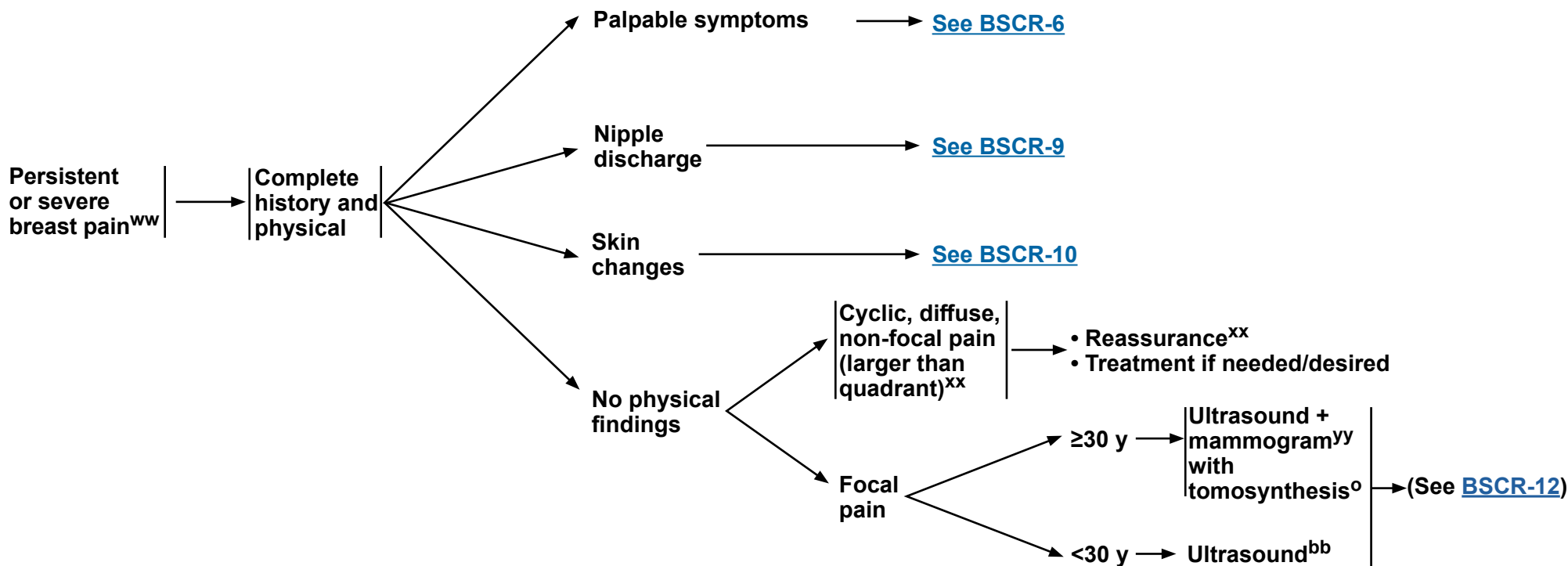
^{vv} Inflammatory breast cancer is a clinical diagnosis and is not dependent on a positive punch biopsy.

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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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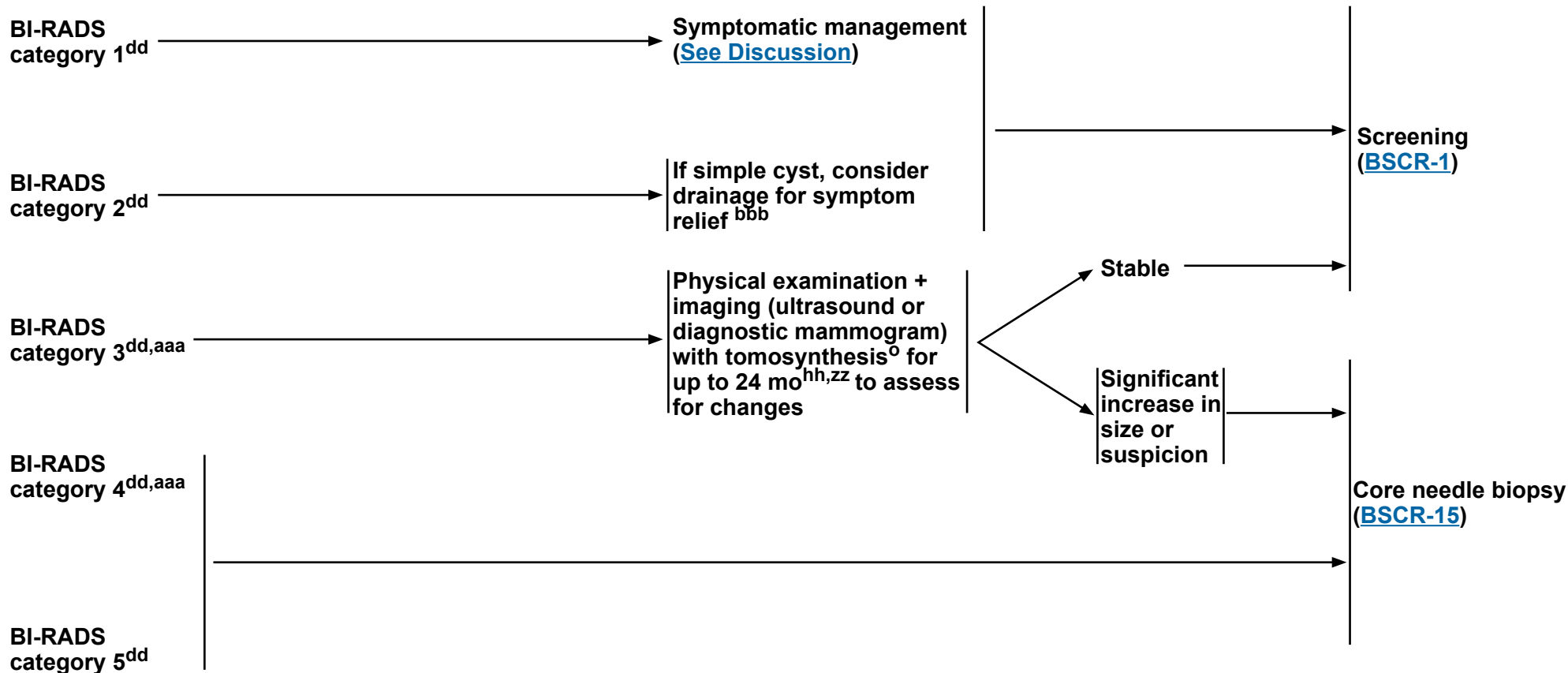


NCCN Guidelines Version 2.2023

Breast Cancer Screening and Diagnosis

IMAGING FINDINGS FOR FOCAL BREAST PAIN

FOLLOW-UP EVALUATION



^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.

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

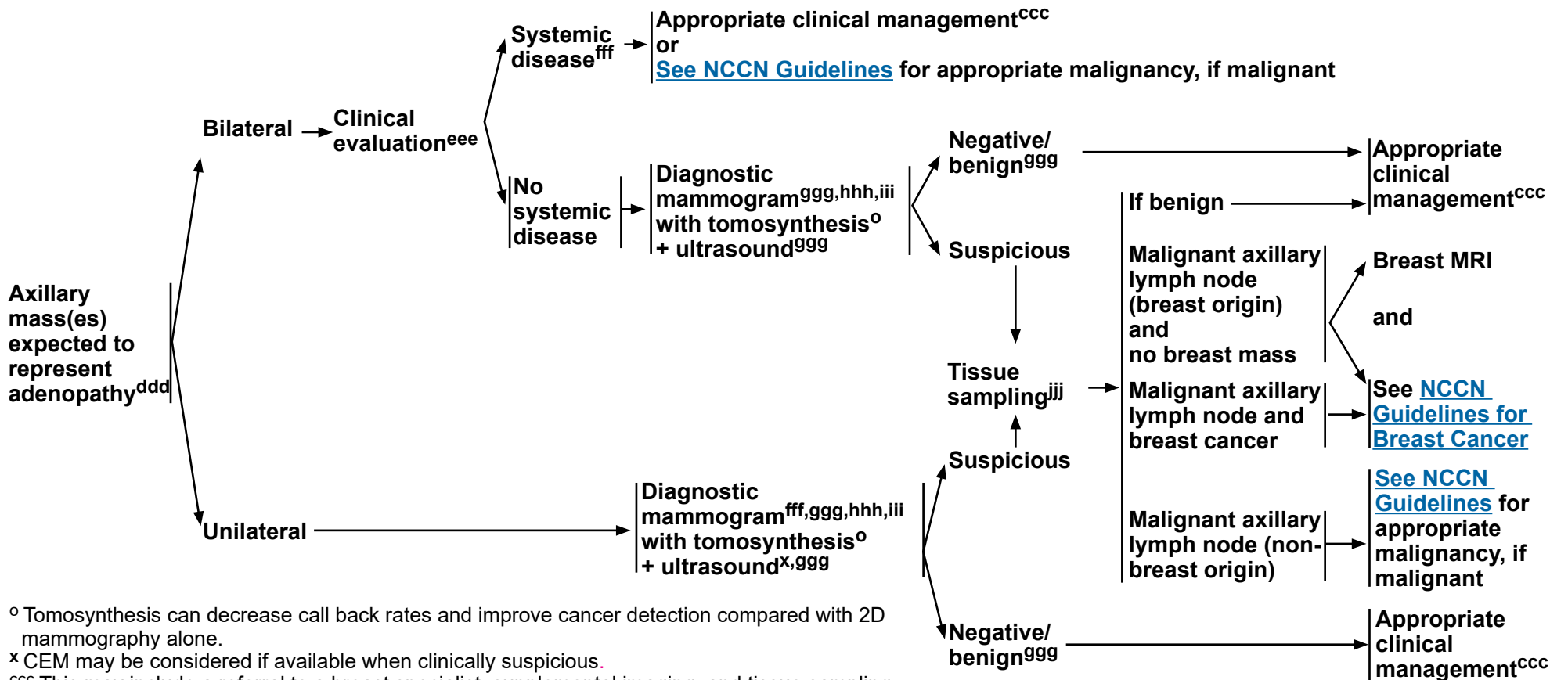
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



RECOMMENDATIONS FOR WORKUP/DIAGNOSTIC EVALUATION OF AXILLARY MASS

PRESENTATION

EVALUATION



^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.
^{jij} If lymphoma is suspected, tissue/specimen may require special pathologic processing and/or surgical excision.

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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.

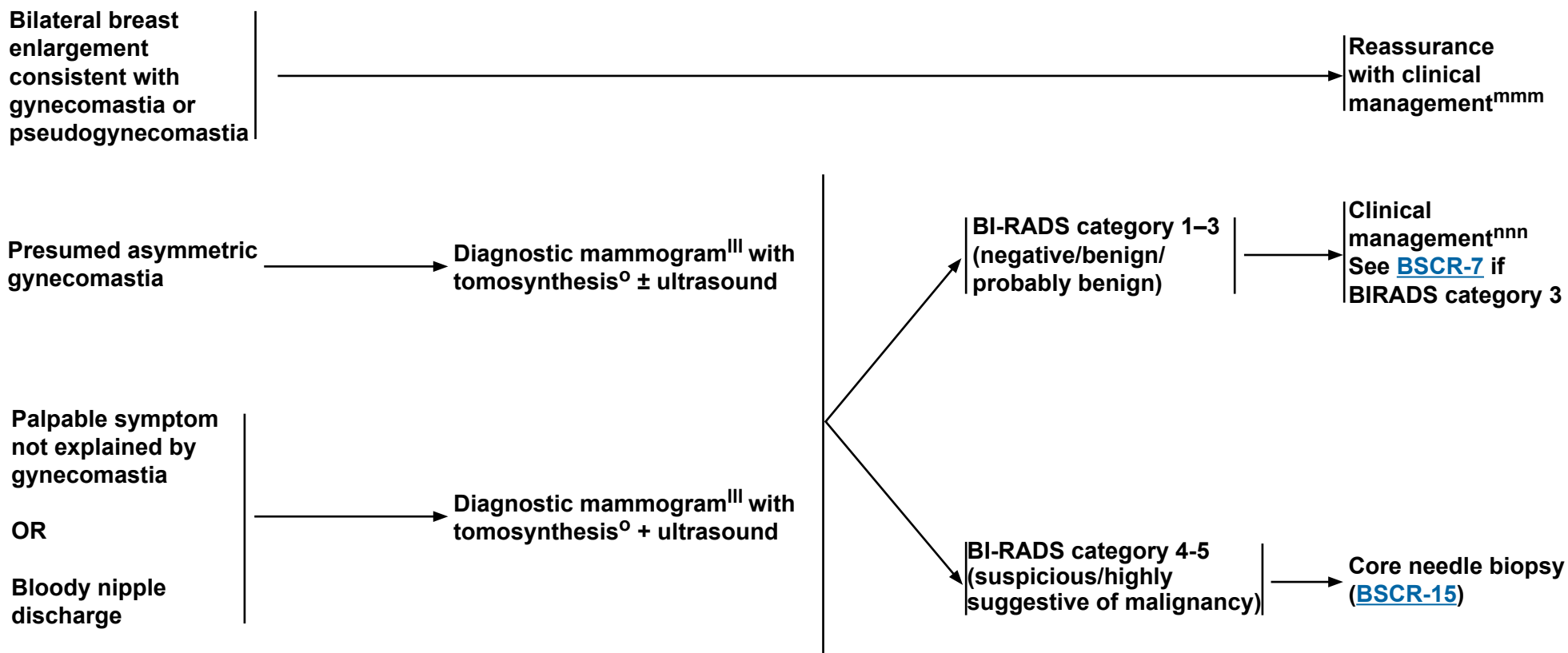


NCCN Guidelines Version 2.2023 Breast Cancer Screening and Diagnosis

PRESENTATION OF SYMPTOMS IN INDIVIDUALS ASSIGNED MALE AT BIRTH^{kkk,III}

DIAGNOSTIC EVALUATION

FOLLOW-UP EVALUATION



^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.

^{III} 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.

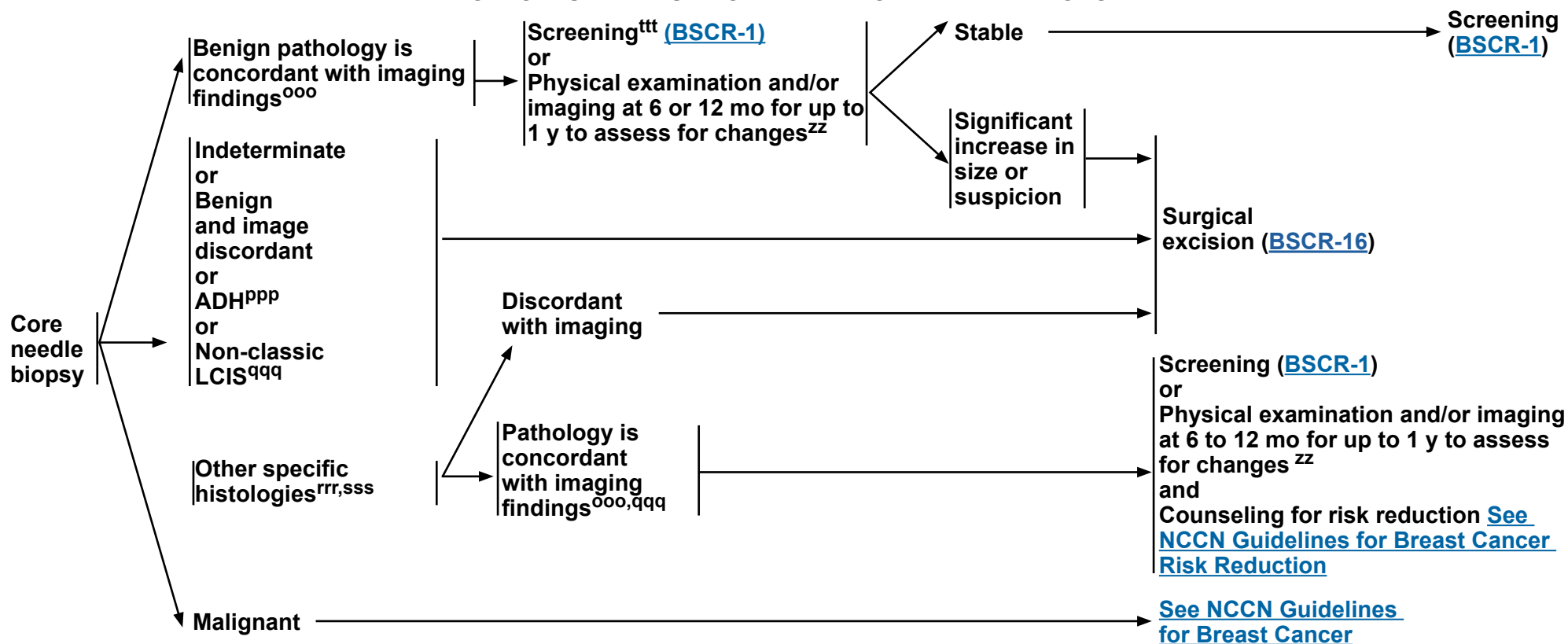
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NCCN Guidelines Version 2.2023

Breast Cancer Screening and Diagnosis

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.

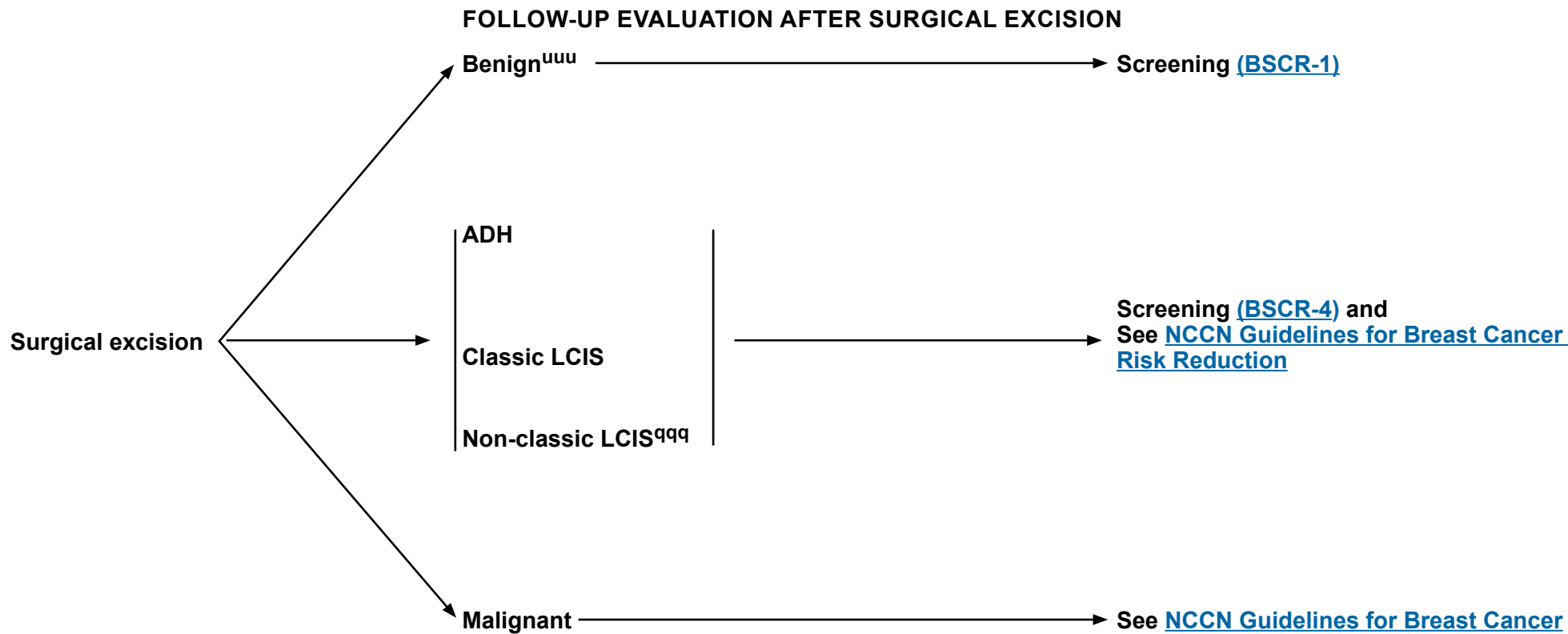
^{qqq} Clinicians should consider complete excision with negative margins for non-classic LCIS, florid LCIS, and multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy. However, outcomes data regarding treatment of individuals with non-classic LCIS are limited, due in part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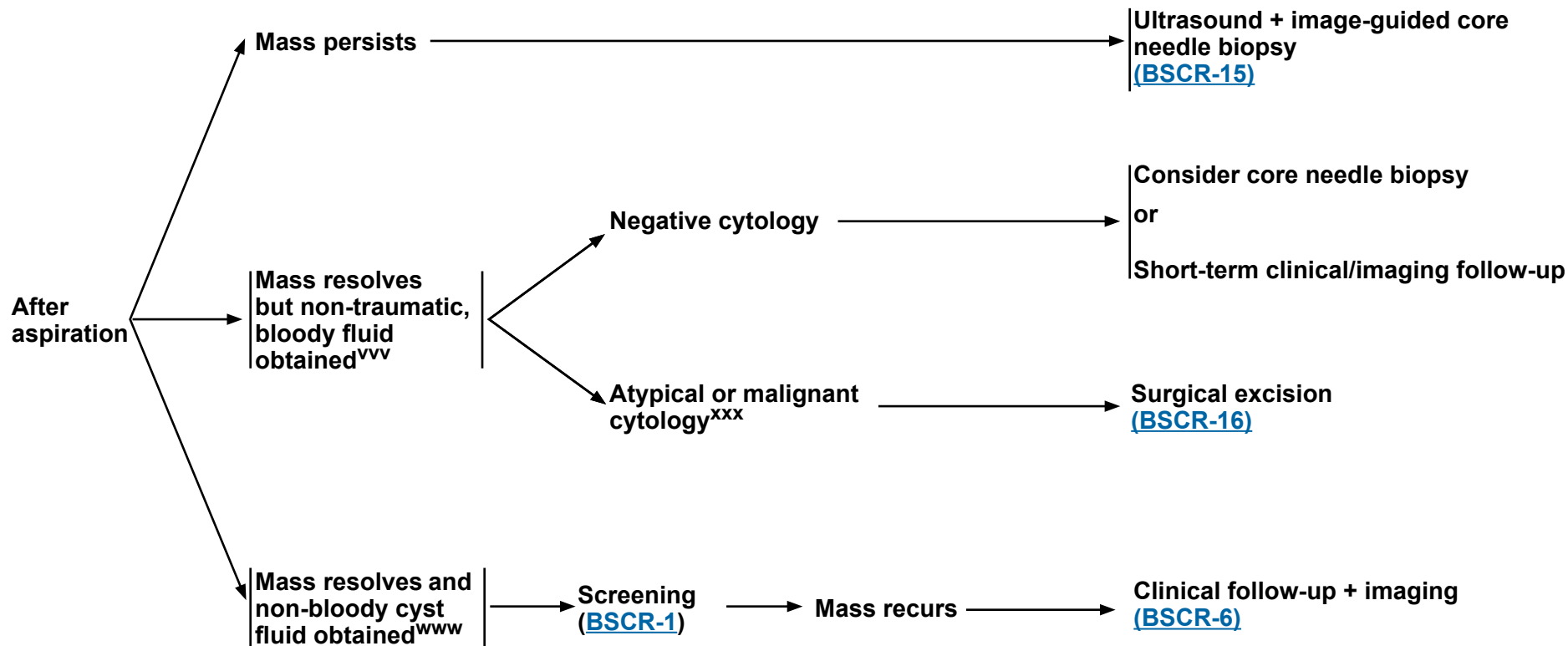
^{qqq} Clinicians should consider complete excision with negative margins for non-classic LCIS, florid LCIS, and multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy. However, outcomes data regarding treatment of individuals with non-classic LCIS are limited, due in part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

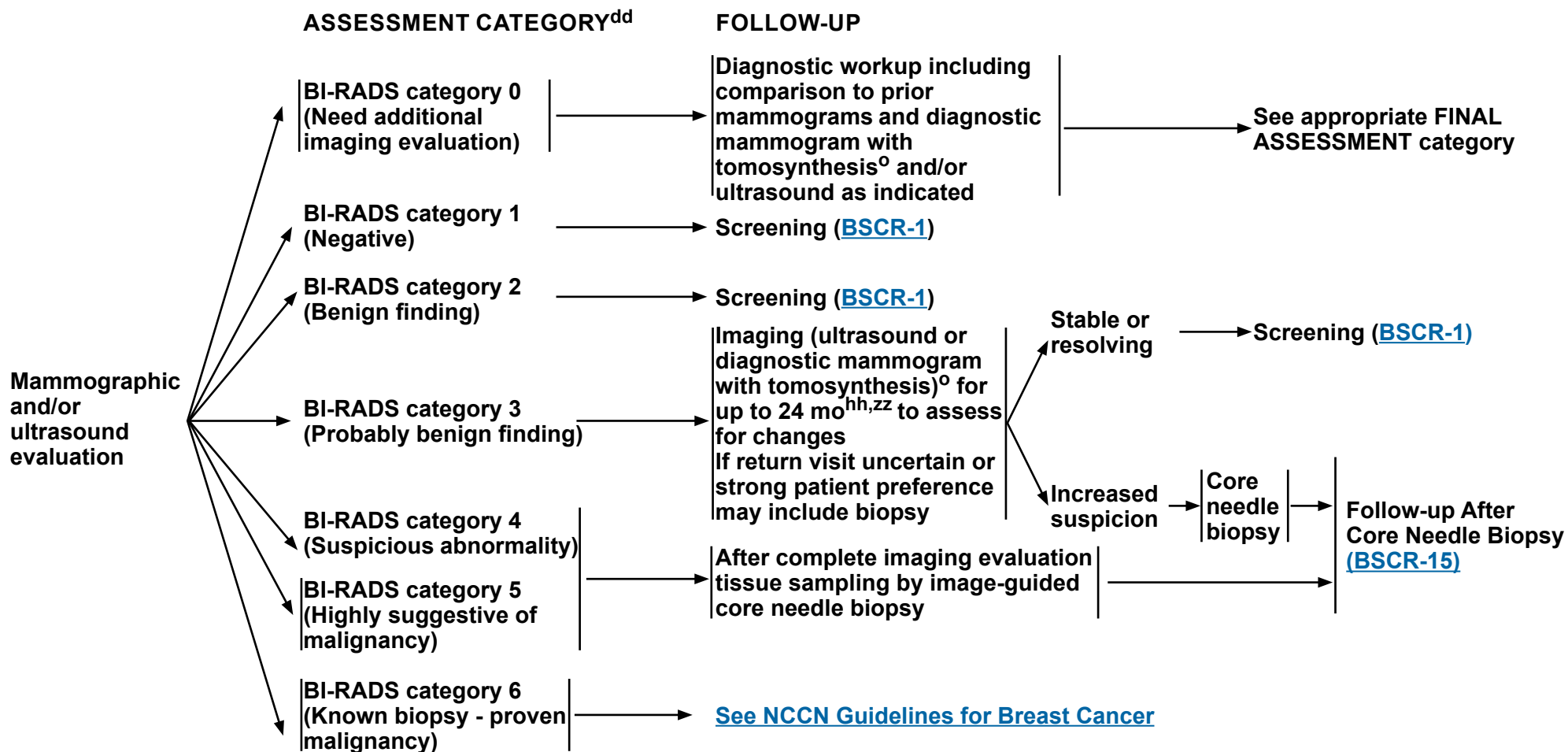
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Breast Cancer Screening and Diagnosis



^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 announcement¹ (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>.

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[Continued](#)**BSCR-A**
1 OF 2



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 $\geq 20\%$ 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 $\geq 20\%$ 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	<ul style="list-style-type: none"> • There is no contraindication to screening mammography during pregnancy. • 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. • 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 <ul style="list-style-type: none"> • Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier who remains untested • 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 • Individuals with ADH or lobular neoplasia (LCIS/ALH) and ≥20% residual lifetime risk. 	R	R	O	NR	<ul style="list-style-type: none"> • 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). • 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. • 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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Breast Cancer Screening and Diagnosis

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	<ul style="list-style-type: none"> • Age-appropriate evaluation of a palpable symptom during pregnancy should proceed similar to that outlined in BSCR-6. • 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. • 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. • 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.

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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	<ul style="list-style-type: none"> 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. 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. 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. 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. 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). 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.

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Breast Cancer Screening and Diagnosis

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	<ul style="list-style-type: none"> Breast erythema or suspicious skin changes should undergo age-appropriate breast imaging evaluation similar to that outlined on (BSCR-10). 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. 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	<ul style="list-style-type: none"> 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). 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. 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. 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.

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Breast Cancer Screening and Diagnosis

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	<ul style="list-style-type: none"> 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. 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	<ul style="list-style-type: none"> 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. 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. 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	<ul style="list-style-type: none"> While there is both decreased sensitivity and specificity of screening mammography during lactation, there is no contraindication to screening mammography during lactation. 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 It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination
Increased Risk <ul style="list-style-type: none"> Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier who remains untested 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 Individuals with ADH or lobular neoplasia (LCIS/ ALH) and ≥20% residual lifetime risk. 	R	R	NR	R	<ul style="list-style-type: none"> 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). 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. 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). <ul style="list-style-type: none"> 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. 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.****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 2.2023

Breast Cancer Screening and Diagnosis

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	<ul style="list-style-type: none"> • Age-appropriate evaluation of a palpable symptom during lactation should proceed similar to that outlined in BSCR-6 and BSCR-7. • It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination • 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	<ul style="list-style-type: none"> Nipple discharge is normal during lactation. Abnormal nipple discharge is defined as: persistent (see next bullet), spontaneous, uniductal, unilateral bloody or clear nipple discharge. 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. Age-appropriate evaluation of abnormal nipple discharge during lactation should proceed similar to that outlined in BSCR-9. 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. 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 MRI is not contraindicated for the management of abnormal nipple discharge during lactation if clinically indicated. 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.
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Breast Cancer Screening and Diagnosis

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	<ul style="list-style-type: none"> 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. 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). <ul style="list-style-type: none"> 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). 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. However, if a breast abscess is not definitively identified, individuals should promptly undergo evaluation for inflammatory breast cancer (BSCR-10). 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	<ul style="list-style-type: none"> • 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). • 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. • 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. • While breast MRI is not contraindicated for the management of persistent, focal breast pain during lactation, it is usually not indicated. • 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 ^{‡‡‡}	<ul style="list-style-type: none"> 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. 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	<ul style="list-style-type: none"> 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. 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. 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. Reprinted with permission from the American College of Radiology. No other representation of this document is authorized without express, written permission from the American College of Radiology.

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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).

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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 $\leq 2\%$ likelihood of malignancy, but greater than the essentially 0% likelihood of malignancy of a characteristically benign finding. A probably benign finding is not expected to change over the suggested period of imaging surveillance, but the interpreting physician prefers to establish stability of the finding before recommending management limited to routine mammography screening.

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

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

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

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**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 4³ 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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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).

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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.

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**ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS^{1,2}****BI-RADS® - ULTRASOUND FINDINGS**

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

Category 4: Suspicious:

This category is reserved for findings that do not have the classic appearance of malignancy but are sufficiently suspicious to justify a recommendation for biopsy. The ceiling for category 3 assessment is a 2% likelihood of malignancy, and the floor for category 5 assessment is 95%, so category 4 assessments cover the wide range of likelihood of malignancy in between. Thus, almost all recommendations for breast interventional procedures will come from assessments made using this category. By subdividing category 4³ 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.

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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****Category 5: Highly Suggestive of Malignancy:**

These assessments carry a very high probability ($\geq 95\%$) 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. Reprinted with permission from the American College of Radiology. No other representation of this document is authorized without express, written permission from the American College of Radiology.

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.



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



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NCCN Categories of Evidence and Consensus

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

All recommendations are category 2A unless otherwise 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.



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Discussion

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

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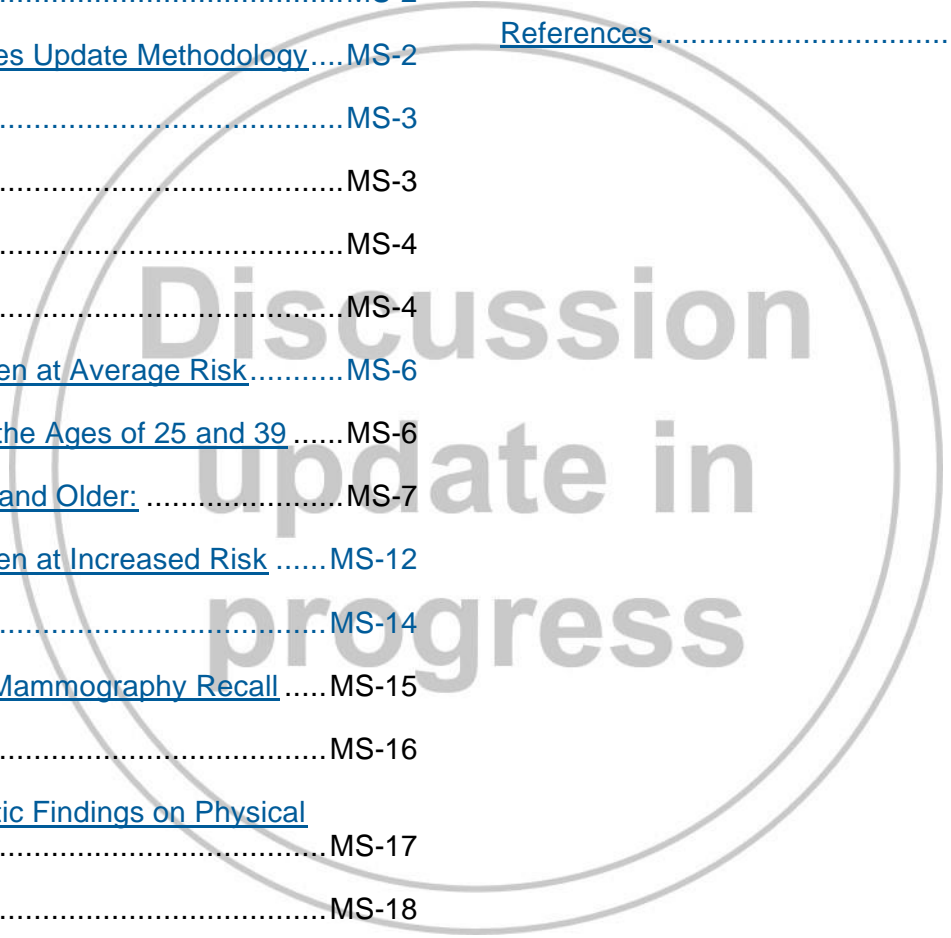
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Overview

The average lifetime risk of breast cancer for a female in the United States has been estimated at 12.3% (ie, 1 in 8 females).¹ For 2018, the American Cancer Society (ACS) estimates that 63,960 cases of female carcinoma in situ of the breast and 268,670 cases of invasive breast cancer (266,120 in females and 2,550 in males) will be diagnosed in the United States.² About 41,400 deaths are estimated for 2018.³ The good news is that death rates have been falling an average of 1.8% each year over the course of 2006 through 2015.⁴ This decrease has been attributed to mammographic screening and treatment advances.⁵

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis are for facilitating clinical decision-making. The general public and health care providers need to be aware that mammography or any other imaging modality is not a stand-alone procedure. Neither the current technology of mammography or other imaging tests nor the subsequent interpretation of such tests is foolproof. Clinical judgment is needed to ensure appropriate management. The patient's concerns and physical findings must be taken into account along with imaging results and histologic assessment.

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Breast Cancer Screening and Diagnosis, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: breast cancer screening; screening mammography; breast cancer diagnosis. The search results were narrowed by selecting studies in humans published in English. An updated search was carried out before the publication of this document. The PubMed database was

chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

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

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

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

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.



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

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

Clinical Encounter

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

In a review of controlled trials and case-control studies that included CBE as part of the screening modality, sensitivity of CBE was found to be 54% and specificity 94%.⁶ Randomized trials comparing CBE versus no

screening have not been performed. Rationale for recommending the clinical encounter is to maximize the earliest detection of breast cancers. Overdiagnosis and overtreatment is not a significant issue with CBE, as the majority of palpable cancers found on a CBE are invasive cancers. CBE is an important component of a clinical encounter and is important in order to detect early-stage palpable cancers, especially those that are mammographically occult (eg, lobular carcinomas). According to the NCCN Panel, inspection of the breasts should be performed with the patient in both upright and supine positions. Positioning may be done so as to elicit any subtle shape or contour changes in the breast.⁶

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



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Breast Cancer Risk Assessment

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

Breast Imaging Modalities

Screening Mammography

Of the various imaging modalities, mammography remains the most important as it is the only one to demonstrate a mortality reduction. A screening mammogram typically involves two x-ray images of each breast (ie, one taken from the top [craniocaudal] of the breast and the other from the side [mediolateral oblique]). Technical aspects of mammography can affect the quality of screening results. Digital mammography, which has replaced film-screen mammography in the United States, generates an electronic image of the breast and allows for computer storage and processing of the image, thereby increasing the ability to detect subtle abnormalities.^{10,11}

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

procedures.^{12,13} However, digital mammography was significantly more accurate in females <50 years of age with dense breasts, and there was a nonsignificant trend toward improved accuracy of film mammography in those ≥ 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.¹⁴

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

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



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screening for individuals AFAB with heterogeneously dense and extremely dense breast tissue.³³ Different supplemental imaging modalities may be considered based on risk and patient values/preference.³⁴

Screening Ultrasound

Due to limitations of mammographic screening, especially in those with dense breasts, other imaging modalities are being explored to supplement mammography, most commonly ultrasound and MRI. Unlike mammographic screening, both technologies lack evidence from randomized controlled trials (RCTs) of screening efficacy, although ultrasound is widely used in the diagnostic setting. Most clinical ultrasound screening studies have found increased cancer detection to be incremental to screening mammograms in 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.³⁴ Subsequent follow-up studies showed similar results.^{35,36} 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%).³⁴ Application of screening ultrasound to females with dense breasts in clinical populations has produced similar results.³⁷

Although there is increasing evidence that breast ultrasonography can be useful in the incremental detection of breast cancer as an adjunct to screening mammography in the evaluation of females with dense breasts,^{34,35,38–40} the routine use of ultrasound as a universal supplemental *screening* test in individuals AFAB 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.⁴¹ In addition, microcalcifications are not detectable with MRI.^{42,43} Similar to screening ultrasound, whether MRI screening impacts survival has not been addressed in randomized clinical trials. Therefore, careful patient selection for additional screening with MRI is needed. Although current evidence does not support the use of breast MRI to screen 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.^{44–52} 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.⁵³ Nevertheless, a high false-positive rate for screening MRI was identified in several studies. For example, in one study of females at high risk, 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.⁵⁴

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.⁵⁵ 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



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

In individuals AFAB with a history of thoracic radiation between ages 10 and 30 years, a known genetic predisposition to breast cancer, or a lifetime risk of >20% based on models such as Claus or Tyrer-Cuzick, based on current evidence, the NCCN Panel continues to recommend an annual MRI as an adjunct to mammography. Individuals AFAB with LCIS or ALH/ADH with a lifetime risk of $\geq 20\%$ should be considered for breast MRI based on emerging evidence of the benefits.

Criteria for the performance/interpretation of high-quality breast MRI include a dedicated breast coil, radiologists experienced in breast MRI, and the ability to perform MRI-guided needle sampling and/or wire

localization of MRI-detected findings. The ACR has published guidelines for the performance of contrast-enhanced MRI of the breast.⁶³

Other Breast Imaging Modalities

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

Screening Recommendations for Individuals AFAB at Average Risk of Breast Cancer

The NCCN Panel recognizes that the primary purpose of screening individuals AFAB at 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 of Breast Cancer 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 health care provider.

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



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risk assessment, provide risk reduction recommendations, and counsel on healthy lifestyles.

Those with Average Risk of Breast Cancer ≥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, and encourages individuals to be aware of their breasts and promptly report any changes and annual screening mammography (category 1 recommendation) with the *consideration* of tomosynthesis. Those electing to undergo screening mammography should be counseled regarding its potential benefits, risks, and limitations. The NCCN Panel is in agreement with ACS and other organizations that annual screening mammograms in individuals AFAB ≥40 years of age at average-risk of breast cancer should be covered by health care payers without additional cost-sharing or copayments.

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

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

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

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

Rationale for Mammographic Screening Starting at Age 40:

Reduction in breast cancer-related mortality is the major benefit of mammographic screening for breast cancer. This benefit is evident across studies, including RCTs, case-controlled observational studies, and computer modelling studies.

While breast cancer screening guidelines put forth by all the organizations acknowledge mortality reduction benefit from current studies of mammography screening in females 40 to 49 years of age, those recommending breast cancer screening to begin at age 50⁷⁰ view the benefits of screening as being balanced by the harms of screening during this decade. Other organizations, who have recommended screening commencement at age 45 as a “strong” recommendation, have shown the absolute benefit of ages 45 to 49 to be very similar to ages 50 to 54.⁶⁹ While showing there is benefit of screening for ages 40 to 44, a “qualified” rather than a “strong” recommendation is given for the younger age group due to the lower absolute benefit. However, the “qualified” recommendation means “most” females would want the earlier screening and only a “small proportion” would not.⁶⁹

Benefits of Mammographic Screening:

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Systematic reviews of RCTs have generally shown a reduction in breast cancer mortality with mammography screening.⁷¹

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

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 50.⁷⁴ After an average 16 years of follow-up, the investigators observed an overall 29% mortality reduction (RR, 0.71; 95% CI, 0.62–0.80). For age groups 40 to 44 and 45 to 59 years, the RR estimates were 0.82 (95% CI, 0.67–1.00) and 0.63 (95% CI, 0.54–0.75).⁷⁴ Although the estimated reduction in breast cancer mortality was smaller for ages 40 to 44 compared with ages 45 to 49, the reduction in mortality seen for ages 40 to 44 was still substantial.⁷⁴

It is important to note that the RCTs studying the benefits of screening mammography used screen film mammography, sometimes using only a single view. Therefore, they may not reflect results obtained with modern advances in imaging. Digital mammography has been shown to detect more breast cancers in 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%.^{75,76} 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.⁷⁷ Relevant to the North American population, data from a Canadian study showed a mortality reduction of 44% (CI, 33%–55%) among screened females ages 40 to 49 years, which was similar to the overall reduction in mortality of 40% (CI, 33%–48%) found among females ages 40 to 79 years.⁷⁶

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.⁷⁸ 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



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systemic therapy options.⁷⁹ These findings reiterate the fact that diagnosing breast cancer at an early stage is important.

The Cancer Intervention and Surveillance Modeling Network (CISNET) models from 2009 demonstrate a 29% to 54% (mean 39%) mortality reduction for annual screening for females ages 40 to 84 years.⁸⁰ The CISNET models from 2015, based on digital screening mammography, show greater mortality reduction benefit.⁸¹ Benefits of screening females in their 40s are more favorable when considered from the perspective of life years saved compared exclusively to mortality reduction.⁸² 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 AFAB 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 harms or risk profile for breast cancer screening is weighted differently by different organizations.^{69,70} This is a very subjective rating as there are limited data regarding a female's perspective of the harms of screening. The clinical practice guidelines that recommend delaying screening to age 50 and older⁶⁹ 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."⁸³ In this study, 63% of females thought 500 or more false positives per life saved was acceptable.⁸³

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

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

A mammogram result is often considered a false positive when it prompts additional imaging tests and/or biopsy in an abnormality that is not cancerous. False-positive results can occur at any age. It is important to distinguish between recalls from screening and biopsies that result in a false-positive outcome. Recalls are defined by the FDA as "incomplete" and not positive. Recalls are resolved by obtaining incremental diagnostic mammographic imaging and/or ultrasound with the vast majority of recalls proving negative and not requiring biopsy. The frequency of recalls from screening are the same per decade whether screening begins at age 40 or age 50.⁷⁰ While recalls are commonly thought to be higher in younger 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



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decade. Furthermore, the decade-long false-positive biopsy recommendation rate is somewhat lower when screening begins at age 40 compared to age 50. Less than 1% of screened females 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 psychosocial consequence as one of the negative consequences of false positives.⁸⁵ However, a cross-sectional survey of female's attitudes toward false positives found that females consider false positives as an acceptable consequence.⁸³

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

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

carcinoma in situ (DCIS) is included or excluded. Furthermore, overdiagnosis estimates vary by age and duration of follow-up.

The most reliable estimates of overdiagnosis would be from RCTs in which there was no formal screening offered to the control group for a long period at the end of the screening period. The Malmö randomized trial, in which the invited cohort group aged 55-69 years was not routinely screened at the end of the trial,⁸⁹ showed an overdiagnosis rate of 10% after an average of 15 years follow-up, which included invasive cancer and DCIS. The rate was 7% for invasive cancer.⁸⁹ The National Breast Screening Studies in Canada conducted two randomized trials that included a control group that did not receive routine screening at the end of the trial. The follow-up period was 13 years. In the first trial, in which 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%.^{90,91} Using these 3 studies, the UK review estimated overdiagnosis (including DCIS) to be 10.7%.⁹² Yet, these studies are limited by their age and differing use of diagnostic mammography among non-screened females. However, analysis of the UK AGE trial, which included females aged 40 to 49 years, showed a very low rate of overdiagnosis of 1%,⁹³ a value similar to estimates from Sweden for females in their 40s.⁷⁴ A recently reported population-based screening study showed a rate of only 0.3% overdiagnosis after 12 years of follow-up in either invited or uninvited females (n = 988, 090) and a 46% reduction in breast cancer mortality among attendees.⁹⁴ Direct estimates of type 1 overdiagnosis for screened U.S. females show marked differences depending on age of diagnosis, with less than 1% among premenopausal females and 22% among females aged 80 years.⁹⁵

Prevention of cancer death is highly valued compared with false-positive results/overdiagnosis by most females.⁸³ Current science cannot predict



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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 premenopausal females.^{69,70,80,96} The evaluation of benefits versus risk strongly supports the value of screening and the importance of adhering to a schedule of regular mammograms.

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

screened 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.⁹⁷ Also, with annual digital screening mammography, the deaths averted (0.6/1000) are similar for ages 40 to 44 and 45 to 49 years (0.7/1000).^{96,98}

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

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

Age to Stop Mammographic Screening:

Most trials for breast screening have used a cutoff age of 65 or 70 years.¹⁰¹⁻¹⁰³ However, observational studies and computer models show mortality benefit to age 80 to 84.^{69,80} Considering the high incidence of breast cancer in older individuals, 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 that



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emphasize the importance of life expectancy and overall health when considering age to stop screening. Mammography screening should be individualized, weighing its potential benefits/risks in the context of the patient's overall health and estimated longevity.¹⁰⁴ If a patient has severe comorbid conditions limiting her expectancy and no intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of age.^{104,105}

Screening Recommendations for Individuals AFAB at Increased Risk of Breast Cancer

Those with Prior History of Breast Cancer: These individuals are treated according to the recommendations outlined in [NCCN Guidelines for Breast Cancer](#).

Those ≥35 Years of Age with a 5-Year Risk of Invasive Breast

Carcinoma ≥ 1.7% by the Modified Gail Model: For those ≥35 years of age, 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 model¹⁰⁶⁻¹¹⁰ that can be accessed at:

<http://www.cancer.gov/bcrisktool/Default.aspx>, which provides risk projections on the basis of several risk factors for breast cancer. The modified Gail model assesses the risk of invasive breast cancer as a function of age, menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race. The model calculates 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify 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.¹¹¹ It has also been updated using the data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander females in the United States.¹¹²

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 AFAB ≥35 years of age with a 5-year risk ≥1.7%, the NCCN Panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months and annual digital mammography, with the consideration of tomosynthesis, to begin at the age identified as being at increased risk by the Gail model. In addition, according to the NCCN Panel, those in this group should be counseled for consideration of risk-



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reduction strategies in accordance with the [NCCN Guidelines for Breast Cancer Risk Reduction](#).

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

For those with a history of LCIS or ADH/ALH, the NCCN Panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months beginning at the age of diagnosis and annual digital mammography, with the consideration of tomosynthesis, beginning at the age of diagnosis of LCIS or ADH/ALH but not prior to age 30. In addition, according to the NCCN Panel, annual MRI should be considered beginning at the age of diagnosis of LCIS or ADH/ALH but not before age 25 (based on emerging evidence).⁵⁵ 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 Lifetime Risk of Breast Cancer >20% Based on Models Largely Dependent on Family History: A lifetime risk of breast cancer of >20% as assessed by models based largely on family history is another risk threshold used in the guidelines to identify 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 mammography⁵³ 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 Claus,¹¹⁹ Tyrer-Cuzick,¹²⁰ and other models.¹²¹⁻¹²³ BRCAPRO¹²⁴ and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)¹²⁵ are more commonly used to estimate the risk of *BRCA*

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

For 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. The NCCN Panel recommends annual digital mammography, with the consideration of tomosynthesis starting from 10 years prior to the youngest family member but not prior to age 30. In addition, in accordance with the ACS guidelines,⁵³ the NCCN Panel recommends annual breast MRI to begin 10 years prior to the youngest family member diagnosed but not prior to age 25 for those who have a lifetime risk of breast cancer >20% based on models that rely mainly on family history. 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.¹²⁶⁻¹³¹ For example, in the Late Effects Study Group trial, the overall risk of breast cancer associated with prior thoracic irradiation at a young age was found to be 56.7-fold (55.5-fold for female patients) greater than the risk of breast cancer in the general population.^{127,130} The RR of female breast cancer according to follow-up interval was 0 at 5 to 9 years; 71.3 at 10 to 14 years; 90.8 at 15 to 19 years; 50.9 at 20 to 24 years; 41.2 at 25 to 29 years; and 24.5 at >29 years.¹³⁰ Results from a case-control study of 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



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agents.¹³² 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. Findings from a survey of breast screening practices in this population of patients suggest that a sizable segment of this group is not undergoing regular mammographic screening.¹³³

For 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 10 years after radiation exposure.¹³⁴ Breast imaging assessments with annual digital mammograms, with the consideration of tomosynthesis, are recommended 10 years after RT but not prior to age 30, and annual MRI¹⁴⁴ is recommended to begin 10 years after radiation exposure but not prior to age 25.

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 10 years after radiation therapy.

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

Diagnostic Evaluation

Breast symptoms are common among individuals AFAB. 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 who are older.¹³⁵ Pain is found to be the most common symptom followed by palpable mass. In addition, palpable areas of concern are identified during a breast physical exam. Breast clinical findings are not specific and there is variability in interpretation. Each symptom is associated with a risk of malignancy and warrants diagnostic evaluation; however, most symptoms will be determined to be benign in etiology. 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



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(eg, in those with prior cancer). Diagnostic evaluation in this review will be restricted to the former two situations.

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

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

Diagnostic Imaging After Screening Mammography Recall

Diagnostic Mammography

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

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

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

NCCN Recommendations for Screening Mammogram BI-RADS[®] Assessment Categories 1, 2, 3, 4, 5, and 6 are listed below. The NCCN recommendations following evaluation of symptomatic diagnostic individuals AFAB 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 1 (negative finding) or category 2 (benign), the panel recommends resuming routine screening.

For BI-RADS[®] category 3 (probably benign), the panel recommends diagnostic mammograms at 6 months, then every 6 to 12 months for 1 to 2 years as appropriate. If the lesion remains stable or resolves mammographically, the patient resumes routine screening intervals for mammography. If, in any of the interval mammograms, the lesion increases in size or changes its benign characteristics, a biopsy is then



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performed. The exception to this approach of short-term follow-up is when a return visit is uncertain or the patient strongly desires or has a strong family history of breast cancer. In those cases, initial biopsy with histologic sampling may be a reasonable option.

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

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

Breast Ultrasonography

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

Diagnostic Breast MRI

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

Breast Tissue Biopsy

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

Fine-Needle Aspiration (FNA) Biopsy

An FNA biopsy involves use of a smaller-bore needle to obtain cytologic samples from a breast mass. Advantages of FNA biopsy include its minimally invasive methodology and low cost,^{150,151} whereas the need for pathologists with specific expertise in the interpretation of test results and the necessity of performing a follow-up tissue biopsy when atypia or malignancy is identified are disadvantages of the procedure. FNA of nonpalpable lesions can be performed under imaging guidance (eg, ultrasound), although there is evidence to indicate that both core needle biopsy and excisional biopsy are more accurate than FNA in the evaluation of nonpalpable breast lesions.^{152,153}

Core Needle Biopsy

A core needle biopsy, also called percutaneous core breast biopsy, is a procedure that typically involves obtaining multiple cores of solid tissue using standard techniques.^{154,155} It can be performed under imaging



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guidance (eg, stereotactic [mammographic] ultrasound or MRI) or directed by palpation. Advantages of breast core needle biopsy include: 1) increased accuracy over FNA when the procedure is performed in situations where no mass is palpable; and 2) an ability to obtain tissue samples of sufficient size so as to eliminate the need for a follow-up biopsy to confirm malignancy.¹⁵⁶ In some situations, the core needle biopsy is performed under vacuum assistance, which can facilitate collection of adequate tissue from a breast lesion without the need for multiple needle insertions.¹⁵⁷⁻¹⁵⁹ Marker clip placement is done at the time of core needle biopsy so that the radiologist can identify the location of the lesion in the event that it is entirely removed or disappears during neoadjuvant treatment of a breast cancer.¹⁶⁰ With a few exceptions, core needle biopsy is preferred in the NCCN Guidelines over surgical excision when tissue biopsy is required. Sensitivity for core needle biopsy directed by ultrasound or stereotaxis is 97% to 99%.⁹⁸ According to the NCCN Panel, surgical excision is appropriate if unable to perform core needle biopsy.

Excisional Biopsy

An excisional biopsy involves removal of the entire breast mass or suspicious area of the breast by a surgeon in an operating room setting. Needle or wire localization is done by the radiologist immediately prior to an excisional biopsy of a nonpalpable mammographic or sonographic finding to direct surgical excision. The wire localization may bracket a lesion that had a clip placed in it at the time of the core needle biopsy.¹⁶⁰ Newer localization methods using radionuclide seeds, reflector devices, or magnetic devices are being explored.

Excisional biopsy is included in the NCCN Guidelines as an option when tissue biopsy is required. Although excisional biopsy is a more invasive method than core needle biopsy and requires needle localization when lesions are not palpable, there are situations where larger tissue samples

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

Diagnostic Evaluation for Symptomatic Findings on Physical Examination

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



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

Palpable Mass in the Breast

A palpable mass is a discrete lesion that can be readily identified during a physical exam. The NCCN Guidelines separate the evaluation of individuals AFAB with the palpable mass into two age groups: those ≥ 30 years of age and those < 30 years of age.

Those with Palpable Mass ≥ 30 Years of Age:

The main difference in the guidelines for evaluating a palpable mass 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 and ultrasound. Ultrasound should be geographically correlated with the palpable mass in question. Observation without further evaluation is not an option for 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.^{180,181,186} After the diagnostic imaging assessment, the abnormality is placed into one of the following categories: negative or benign; probably benign; or suspicious or highly suggestive of cancer with management following BIRADS final assessment recommendations.

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

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

Ultrasound Findings:

Solid Mass:

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

Cystic Masses:

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



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Simple Cyst

A cyst meeting all criteria of a simple cyst is considered to be benign (ie, BI-RADS® 2)^{34,192} if the clinical findings and ultrasonographic results are concordant. In a retrospective analysis of 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.¹⁹³ Therefore, these patients then can be followed with routine screening.

Complicated Cyst

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

Complex (Cystic and Solid) Mass:

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

No Imaging Abnormality:

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

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

Follow-up after Core Needle Biopsy

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

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

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



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Those with Palpable Mass <30 Years of Age:

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

If no ultrasonographic abnormality is found (negative, BI-RADS® 1), a mammogram is recommended in cases where there is clinical suspicion. Based on the mammogram results, from this point the management is identical to the pathway for those ≥30 years of age. If the clinical suspicion is low, physical examination every 3 to 6 months for 1 to 2 years is recommended with or without ultrasound. If the mass increases in size during the observation period, diagnostic mammogram may be considered followed by tissue (core needle) biopsy. If the mass remains stable, routine breast care is recommended.

Nipple Discharge Without a Palpable Mass

Nipple discharge is common, and, in many cases, unrelated to breast pathology.¹⁹⁸⁻²⁰⁴ For example, non-spontaneous discharge from multiple breast ducts in an individual that is not lactating can occur during

pregnancy, following breast stimulation, in females with certain thyroid conditions, and in those taking certain medications, such as estrogen, oral contraceptives, opiates, and particular antihypertensive agents.¹⁹⁸

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

In patients with a nipple discharge but no palpable mass, an evaluation of the characteristics of the nipple discharge is the first step. The appropriate follow-up of a non-spontaneous, multiple-duct discharge in individuals AFAB <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, mammography and a 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, if not done previously.

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

According to the NCCN Panel, when an overall imaging BI-RADS® assessment is category 1-3 (negative, benign, or probably benign), either a ductogram or MRI are optional to guide the duct excision. The management options include duct excision²¹⁰ or follow-up with physical



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exam after 6 months and imaging with diagnostic mammogram with or without ultrasound for 1 to 2 years. If clinical suspicion increases during follow-up, tissue biopsy is recommended.

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

Asymmetric Thickening or Nodularity

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

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

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

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

Skin Changes

Any type of unusual skin changes around the breast may represent serious disease and needs evaluation. IBC should be considered when dermal edema (peau d'orange) and breast erythema are present, and nipple excoriation, scaling, and eczema should increase clinical suspicion of Paget's disease. IBC is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States. IBC is a clinical diagnosis that requires erythema and dermal edema of a third or more of the skin of the breast with a palpable border to the erythema.^{211,212} Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the nipple or areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions.^{213,214} Pure Paget's disease is frequently occult on mammography²¹⁵ and a negative mammogram does not exclude Paget's disease, which requires skin biopsy.

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

Punch biopsy of the skin or nipple biopsy should be performed following imaging findings consistent with an overall BI-RADS® assessment



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category 1-3 (negative, benign, or probably benign). Antibiotics may or may not be given, depending on the clinical suspicion for breast infection, but should not delay diagnostic evaluation. If biopsy results are benign, clinical and pathologic correlation should be reassessed. In addition, a breast MRI, a repeat biopsy, and consultation with a breast specialist should be considered. If the skin biopsy is malignant, the patient should be treated according to the [NCCN Guidelines for Breast Cancer](#).

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

Breast Pain

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

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

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

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

Axillary Mass

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



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

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

Summary

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

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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.
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