Breast Cancer Screening and Diagnosis Guidelines

MINISTER FOREWORD

It is with utmost pleasure I introduce to you this new version of Breast Cancer Screening and Diagnosis Guidelines, which are on a national level set up to help and provide clear guidance for the task in prevention and control ofbreast cancer in Jordan.
The Ministry of Health, as part of its commitment towards the health of the population and their wellbeing, established the Jordan Cancer Registry as the basic pillar fronting the cancer burden in Jordan.

Over the last twenty years, the numbers and statistics of the registry showed that breast cancer is the most common cancer which is currently afflicting more than a thousand women as new cases annually.

This led to initiate a national program based on the directives of the Minister of health, Jordan Breast Cancer Program, (JBCP) . The program mission is to reduce morbidity and mortality from breast cancer, and shift the late stages to its earliest stages at diagnosis, where the disease is curable , survival rates are higher and treatment cost are lowest.

These last 12 years were a prime time to develop our understanding of screening breast cancer in Jordan. Beginning in 2007 with the breast cancer screening using mammography, there has been an unprecedented growth in our understanding of how to encourage the use of screening test , and a transformation of peoples' conceptualization and acceptance of screening test. The belief was if we could just get women to have the right attitude and the physicians to do their job, screening and follow-up would be successful.

Currently mammography machines are distributed all over the country, at the public clinics of the MoH and hospitals. Moreover, other health sectors in cooperation with the Jordan Breast Cancer Program, as well as two mammography mobile units that provide the service in remote areas.

The impact of screening program is clear: downstage, mortality and survival rate have improved.
My gratitude and thanks, wishing you all the best.

Minister of Health

Dr. Saad Fayez Jaber

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ACRONYMS

AABCS	Asian American Breast Cancer Study
ACR	American College of Radiology
ACS	American Cancer Society
ADH	atypical ductal hyperplasia
ALH	atypical lobular hyperplasia
BI-RADS®	Breast Imaging-Reporting and Data System
BRCA 1	Breast Cancer I, early onset gene
BRCA 2	Breast Cancer II, early onset gene
BSE	Breast Self-Examination
CBE	Clinical Breast Examination
CI	Confidence Interval
CISNET	Cancer Intervention and Surveillance Modeling Network
DBT	Digital Breast Tomosynthesis
DCIS	Ductal Carcinoma In Situ
DMIST	Digital Mammographic Imaging Screening Trial
FDA	Food and Drug Administration
FNA	Fine Needle Aspiration
IBC	Inflammatory Breast Cancer
JBCP	Jordan Breast Cancer Program
JNCR	Jordan National Cancer Registry
KHCC	King Hussein Cancer Center
LCIS	Lobular Carcinoma In Situ
MoH	Ministry of Health
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSABP	National Surgical Adjuvant Breast and Bowel Project
RCTs	Randomized Control Trials
RR	Relative risk
RT	Radio Therapy
STAR	Study of Tamoxifen and Raloxifene
UNRWA	United Nations Relief and Works Agency
USAID	United States Agency for International Development
WHO	World Health Organization
y	Year(s)
2D	Two Dimensional
3D	Three Dimensional

BREAST CANCER SCREENING AND DIAGNOSIS

The NCCN Guidelines Steering Committee has devised the following set of Categories of Evidence and Consensus. These annotations contain two dimensions: the strength of the evidence behind the recommendation and the degree of consensus about its inclusion.

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 noted.

OVERVIEW

The average lifetime risk of breast cancer for a woman in the United States has been estimated at 12.3% (ie, 1 in 8 women).[1] For 2017, the American Cancer Society (ACS) estimates that 63,410 cases of female carcinoma in situ of the breast and 255,180 cases of invasive breast cancer (252,710 women and 2,470 men) will be diagnosed in the United States.[2] About 41,070 deaths are estimated for 2017.[2] The good news is that mortality rate from breast cancer has dropped 38% from 1989 through 2014. [2]This decrease has been partly attributed to mammographic screening.[3]

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.

Breast Screening Components

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

The components of a breast screening evaluation are dependent on age and other factors such as medical and family history, and can include breast awareness (ie, patient familiarity with her breasts); regular clinical encounters, which include breast cancer risk assessment and clinical breast exam (CBE); breast imaging with screening mammography; and, in selected cases, ultrasound and 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%.4 Randomized trials comparing CBE versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize 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.[4]

Breast Awareness: Women should be familiar with their breasts and any changes to them.[5,6] Data from a large randomized trial of breast self-examination (BSE) screening have shown that instruction in BSE has no effect on reducing breast cancer mortality. In this study, 266,064 Chinese women not undergoing routine mammographic screening were randomized to either receive instruction in BSE or not.[7] Compliance was encouraged through feedback and reinforcement sessions. After 10 to 11 years of follow-up, 135 breast cancer deaths in the instruction group and 131 in the control group were observed and the cumulative breast cancer mortality rates were not significantly different between the two arms (relative risk [RR], 1.04; 95% CI, 0.82–1.33; P = .72). The number of benign breast lesions detected in the BSE instruction group was higher than that detected in the control group. Nevertheless, women should be encouraged to be aware of their breasts since this may facilitate detection of interval cancers between routine screenings. The NCCN panel recommends breast awareness, specifically that all women should be familiar with their breasts and promptly report any changes to their health care provider.

Breast Cancer Risk Assessment

If the physical examination is negative in an asymptomatic woman, the next decision point is based on risk stratification. Women can be stratified into two basic categories for the purpose of screening recommendations: those at average risk and those at increased risk. Risk assessment is outlined in the NCCN Guidelines for Breast Cancer Risk Reduction. The increased risk category consists of six groups: 1) women with a prior history of breast cancer; 2) women ≥35 years of age with a 5-year risk of invasive breast cancer ≥1.7% (per Gail Model); 3) women who have a lifetime risk >20% based on history of lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (ADH)/atypical lobular hyperplasia (ALH); 4)

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.[8,9]

In a study of 49,528 women who underwent both film and digital mammography, no difference was seen in the overall accuracy of the two procedures.[10,11] However, digital mammography was significantly more accurate in younger women with dense breasts, and there was a nonsignificant trend toward improved accuracy of film mammography in women aged 65 years and older. In another trial of women aged 45 to 69 years randomly assigned to film or digital screening mammography, the latter procedure was shown to result in a higher rate of cancer detection.[12]

More recently, combined use of digital mammography (two-dimensional, 2D) in conjunction with digital breast tomosynthesis (DBT) appears to improve cancer detection and reduce false-positive call-back rates.[13-22] 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.[14,23,24]

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.[25-28] About half of all women of screening age have "dense" breast tissue referred to as "heterogeneously dense" or "extremely dense" by American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS®) nomenclature. The presence of dense tissue is not abnormal and can change over time. Many states have passed legislation mandating patient notification of breast density, but few have required insurance coverage for supplemental screening.[29] However, the NCCN panel cautions that there is currently insufficient evidence to support routine universal supplemental screening in women with dense breasts and no other risk factors. Different supplemental imaging modalities may be considered based on risk and patient values/preference.[30]

Screening Ultrasound

Due to limitations of mammographic screening, especially in women with dense breasts, other imaging modalities are being explored to supplement mammography, most commonly ultrasound and MR. 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 incremental to screening mammograms in women with dense breasts. For example, a large prospective study in women with dense breasts and elevated risk for breast cancer found that adding screening ultrasound to mammography identified an additional 4.3 cancers per 1000 women screened (95% CI, 1.1–7.2 cancers per 1000) but increased the number of false-positive results.[30] Subsequent follow-up studies showed similar results.[31,32] However, in women with dense breasts, the mammographic sensitivity was found to be 50% (95% CI, 33.8%–66.2%) and the sensitivity of mammography plus ultrasound was 77.5% (95% CI, 61.6%–89.2%).30 Application of screening ultrasound to women with dense breasts in clinical populations has produced similar results.33

Although there is increasing evidence that breast ultrasonography can be useful in the incremental detection of breast cancer as an adjunct to screening mammography in the evaluation of women with dense breasts,[30,31,34-36] the routine use of ultrasound as a universal supplemental screening test in women with average risk is not recommended by the NCCN panel at this time. Ultrasonography is commonly used for diagnostic follow-up of an abnormality seen on screening mammography and palpable clinical concerns.

Screening MRI

The sensitivity of contrast-enhanced breast MRI at detecting breast cancer is higher than the sensitivity of mammography, although the specificity of the former procedure is often lower, resulting in a higher rate of false-positive findings.[37] In addition, microcalcifications are not detectable with MRI.[38,39] Similar to screening ultrasound, whether MRI screening impacts survival has not been addressed in randomized clinical trials. Therefore, careful patient selection for additional screening with MRI is needed. Although current evidence does not support the use of breast MRI to screen women at average risk of breast cancer, the benefits of screening MRI for early detection of breast cancer in women with high risk,

such as those ages 10 through 30 years with a history of prior thoracic radiation, a known genetic predisposition for breast cancer, or a strong family history of the disease have been demonstrated in multiple studies.[40-48] The ACS has published guidelines recommending use of breast MRI as an adjunct to screening mammography in certain populations of women at high risk of breast cancer.[49] Nevertheless, a high false-positive rate for screening MRI was identified in several studies. For example, in one study of high-risk women, many of whom were young and had very dense breast tissue, screening MRI led to 3 times as many benign biopsies as mammography.[50]

A single retrospective study of asymptomatic women with atypical hyperplasia or LCIS enrolled in a high-risk screening program has evaluated use of MRI in this population.[51] Approximately half of the women underwent screening with mammography and MRI, whereas the other half was screened with mammography alone. For those undergoing both types of screening, MRI detected breast cancer in 4% of patients with LCIS who had negative mammogram results. MRI screening did not affect the rate of cancer detection in women with atypical hyperplasia. Women who underwent screening with MRI were more likely to be younger and premenopausal, and to have a stronger family history of breast cancer than those who were evaluated by mammography alone. However, only one woman with cancer detected by MRI following a negative mammography finding had reported a family history of breast cancer, and no difference was seen in the percentages of patients who ultimately developed cancer in the two groups.

The FDA has issued a safety alert stating that it is investigating the risks of brain deposits of gadolinium, the contrast agent used with breast MRI. Studies have reported that deposits of gadolinium remain in the brain of some patients who undergo four or more contrast MRI scans, long after the last administration.[52-54] In women with a history of thoracic radiation between ages 10 and 30 years, a known genetic predisposition to breast cancer, or a lifetime risk of >20% based on models such as Claus or Tyrer-Cuzick, based on current evidence, and considering the FDA warning (Gadolinium-based contrast agents), the NCCN panel continues to recommend an annual MRI as an adjunct to mammography. Women with LCIS/ALH/ADH should be considered for breast MRI based on emerging evidence of the benefits and their overall breast cancer risk.

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.[55]

Other Breast Imaging Modalities

There is emerging evidence that breast scintigraphy and contrast- enhanced mammography may improve detection of early breast cancers among women with mammographically dense breasts;[56-59] 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 ductal lavage should not be a replacement for mammograms.[60]

Screening Recommendations for Women at Average Risk

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

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

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

Although the screening CBE by itself does not rule out disease,

the high specificity of certain abnormal findings by highly qualified clinicians increases the probability of finding certain breast cancers (eg, lobular carcinoma). The NCCN panel believes that a clinical encounter provides an opportunity for providers to perform a CBE, conduct a breast cancer risk assessment, provide risk reduction recommendations, and counsel on healthy lifestyles.

Women with Average Risk 40 Years and Older:

The NCCN panel recommends annual clinical encounter, which includes ongoing breast cancer risk assessment, risk reduction counseling, as well as a CBE, and encourages women to be aware of their breasts and promptly report any changes and annual screening mammography (category 1 recommendation) with the consideration of tomosynthesis. Women electing to undergo screening mammography should be counseled regarding its potential benefits, risks, and limitations. The NCCN panel is in agreement with ACS and other organizations that annual screening mammograms in average-risk women age 40

years and older should be covered by the health care payers without additional cost-sharing or copayments.

Mammographic screening and subsequent treatment has been shown to decrease breast cancer mortality beginning at age 40.[61,62] 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.

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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.[61,62] 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 beginnin at age 40 (category 1 recommendation), as it results in the greatest mortality reduction, most lives saved, and most life years gained.

The NCCN panel has not established an upper age limit for screening.

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

Rationale for Mammographic Screening Starting at Age 40:

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

While breast cancer screening guidelines put forth by all the organizations acknowledge mortality reduction benefit from current studies of mammography screening in women 40 to 49 years of age, those recommending breast cancer screening to begin at age 50[62] 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.[61] While showing there is benefit of screening for ages 40 to 44, a "qualified" rather than a "strong" recommendation is given for the younger age group due to the lower absolute benefit. However, the "qualified" recommendation means "most" women would want the earlier screening and only a "small proportion" would not.[61]

Benefits of Mammographic Screening:

Systematic reviews of RCTs have generally shown a reduction in breast cancer mortality with mammography screening.[63]

The UK Age trial specifically studied the effect of film-screen mammographic screening starting at age 40 years.[64]

A mean of 10.7 years of follow-up showed a non-statistically significant breast cancer mortality reduction in women invited to screening (RR, 0.83; 95% CI,0.66–1.04).[64] 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.[65] 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).[65] Other trials included women who were up to age 49 years at the time of entry into the trial, who were therefore in their 50s during the screening intervention. The results of the UK Age trial support the importance of annual mammography screening in women ages 40 to 49 years of age to reduce breast cancer-related mortality.[65]

A Swedish study compared breast cancer mortality rates in women 40 to 49 years living in different counties. Counties included those which invited women for screening starting at age 40 and others that did not invite the women to be screened at age 40 and started screening at age 50.[66] 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).[66] 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 observational studies still substantial.[66]

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

Case-control observational studies have shown benefits of reduction in breast cancer mortality ranging from 40% to 45%.[67,68] A meta-analysis of observational case-control studies found a significant reduction in breast cancer mortality with mammographic screening for women aged 40 to over 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.[69]

Relevant to the North American population, data from a Canadian study showed a mortality reduction of 44% (CI, 33%–55%) among screened women ages 40 to 49 years, which was similar to the overall reduction in mortality of 40% (CI, 33%–48%) found among women ages 40 to 79 years.[68]

A retrospective analysis evaluating the benefits of mammographic screening of women aged 40 to 49 years found that mammography- detected breast cancer coincides with lower-stage disease at detection, resulting in reduced treatment morbidity and lower rates of recurrence.70 A population-based study of data from the Netherlands Cancer Registry estimated the impact of tumor size in women with breast cancer in two time intervals: 1999 to 2005 and 2006 to 2012. The year 2005 was used to divide the data two time intervals studies, because trastuzumab and other effective adjuvant therapy were introduced after this year in the Netherlands. The analysis found tumor size remained a critical component of survival even with the availability of new and effective systemic therapy options.[71] These findings reiterate that fact that diagnosing breast cancer at an early stage is important.

The Cancer Intervention and Surveillance Modeling Network (CISNET) models from 2009 demonstrate a 29% to 54% (mean 39%) mortality reduction for annual screening for women ages 40 to 84 years.[72] The CISNET models from 2015 based on digital screening mammography show greater mortality reduction benefit.[73] Benefits for screening younger women (in their 40s) are more favorable when considered from the perspective of years of life saved compared exclusively to mortality reduction.[74] Women in their 40s have the highest number of life years at risk to be lost due to longevity even though their breast cancer risk is smaller. Breast cancer is the leading cause of cancer deaths for women in their 40s.

Women should be informed of the evidence demonstrating the value of detecting breast cancer early, before symptoms develop. The benefits of early detection include mortality reduction, less aggressive treatment, and a wide range of treatment options.

Harms of Mammographic Screening:

The harms or risk profile for breast cancer screening is weighted differently by different organizations.[61,62] This is a very subjective rating as there are limited data regarding a woman's perspective of the harms of screening. The clinical practice guidelines that recommend delaying screening to age 50 and older[61] place a greater emphasis on the risks of screening mammography, specifically false-positive results and over diagnosis. The reduction in breast cancer mortality is valued highly by most women, whereas many women do not consider false positives and potential overdiagnosis to be a "harm."[75] In this study, 63% of women thought 500 or more false positives per life saved was acceptable.[75]

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 require more extensive therapy and may prove lethal. There is evidence showing that women diagnosed with breast cancer who did not undergo screening had substantially more need for chemotherapy and more extensive surgery than women who underwent routine screening.[76]

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

A mammogram result is often considered a false positive when it prompts additional imaging tests and/or biopsy in an abnormality that is not cancerous. False-positive results can occur at any age. It is important to distinguish between recalls from screening and false-positive recommendations for biopsy.

bioRecalls are defined by the FDA as "incomplete" and not positive. Recalls are resolved by obtaining incremental diagnostic mammographic imaging 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.[62] While recalls are commonly thought to be higher in younger women, this primarily reflects higher recall rates at the prevalent or initial screen when prior mammograms are not available for

comparison and not at the age at which screening commences. The initiation of screening mammography at age 50 would shift this "prevalent" false positive to that decade. Furthermore, the decade-long false-positive biopsy recommendation rate is actually somewhat lower when screening begins at age 40 compared to age 50.

Less than 1% of screened women per year will be recommended for a biopsy that proves benign, whether annual screening commences at age 40 or 50. The vast majority of false-positive biopsies are now performed as outpatient image-guided needle biopsies using local anesthesia.

Those considering false positives as one of the harms of screening note psychosocial consequence as one of the negative consequences of false positives.[77] However, a cross-sectional survey of women's attitudes toward false positives found that women consider false positives as an acceptable consequence.[75]

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 years or 50 years or the screening interval were 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 the level or amount of diagnosis by symptomatic usual care is optimal. The estimates of overdiagnosis vary widely between various studies (from almost none up to 54%[61,63,78-80]) due to methods and parameters used for estimation and whether ductal carcinoma in situ (DCIS) is included or excluded. Furthermore, overdiagnosis estimates vary by age and duration of follow-up.

The most reliable estimates of overdiagnosis would be from RCTs in which there was no formal screening offered to the control group for a long period at the end of the screening period. The Malmo randomized trial, in which the older-age invited cohort group was not routinely screened at the end of the trial,[81] showed after an average of 15 years follow-up an overdiagnosis rate of 10%, which included invasive cancer

and DCIS. The rate was 7% for invasive cancer.[81] The National Breast Screening Studies in Canada conducted two randomized trials that included a control group that did not receive routine screening at the end of the trial. The follow-up period was 13 years. In the first trial, in which women were aged 40 to 49 years at recruitment, the estimated overdiagnosis was 14%. In the second trial, in which women were aged 50 to 59 years at recruitment, the estimated overdiagnosis rate was 11%.[82,83] Using these 3 studies, the UK review estimated overdiagnosis (including DCIS) to be 10.7%.[84] However, analysis of the UK AGE trial, which included women aged 40 to 49 years, showed a very low rate of overdiagnosis of 1%,[85] a value similar to estimates from Sweden for women in their 40s.[66] A recently reported population-based screening study showed a rate of only 0.3% overdiagnosis after 12 years of follow-up in either invited or uninvited women (n = 988, 090) and a 46% reduction in breast cancer mortality among attenders.[86]

Prevention of cancer death is highly valued compared with false-positive results/overdiagnosis by most women.[75] Science cannot predict which breast cancer may be overdiagnosed or be potentially lethal in any one individual. Personalized treatment programs are recommended. The treatment of cancer may cause suffering and anxiety, but that suffering is likely worth the gain from the potential reduction in breast cancer mortality.

According to the NCCN panel, the risk of overdiagnosis and false positives are outweighed by the benefit of mortality reduction in determining the age to recommend starting screening.

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

Screening Interval and Rationale for Annual Mammogram Screening:

Another consideration is the time interval between screening exams. Performing screening mammography annually versus every other year remains controversial. Most studies and models suggest incremental benefit with annual screening, especially among younger women and premenopausal women.[61,62,72,87] 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.[72] Additionally, mammograms can often detect a lesion 2 years before the

lesion is discovered by CBE. Interval cancer rates are lower among annually screened women. To reduce mortality from breast cancer, yearly screening is thought to be more beneficial. The panel also acknowledges that incomplete compliance will alter the outcome of any recommendation.

An evaluation of the CISNET modeling of benefits of screening women between 40 to 49 years found that using annual digital mammography saves 30% more lives and 34% more life-years than biennial digital mammography.[88] Also, with annual digital screening mammography, the deaths averted (0.6/1000) are similar for ages 40 to 44 and 45 to 49 (0.7/1000).[87,89]

A decline in breast cancer specific-mortality was observed in a cohort of women for every additional annual mammogram performed 5 years prior to breast cancer diagnosis; this further emphasizes the importance of annual mammography.[90] 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.[91]

While the risk of false positives are greater with annual compared to biennial mammograms,[62] the panel believes that the lower mortality and morbidity of annual screening outweighs this harm.

Age to Stop Mammographic Screening:

There are limited RCT data regarding screening of elderly women, because most trials for breast screening have used a cutoff age of 65 or 70 years.[92-94] However, observational studies and computer models show mortality benefit to age 80 to 84.[61,72] Considering the high incidence of breast cancer in the elderly population, the screening guidelines used for women who are age 40 or older are recommended in the elderly as well. Clinicians should always use judgment when applying screening guidelines. The mortality benefit of screening mammography is often delayed for 5 to 7 years in RCTs that emphasize the importance of life expectancy and overall health when considering age to stop screening. Mammography screening should be individualized weighing its potential benefits/risks in the context of the patient's overall health and estimated longevity.[95] If a patient has severe comorbid conditions limiting her life expectancy and no intervention would occur based on the screening findings, then the patient should not undergo screening, regardless of her age.[95,96]

Screening Recommendations for Women at Increased Risk

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

Women Aged 35 Years or Older with a 5-Year Risk of Invasive Breast Carcinoma Greater Than or Equal to 1.7% by the Modified Gail Model: For women aged 35 years and older, a risk assessment tool is available to identify those who are at increased risk. The National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Biostatistics Center has developed a computerized interactive risk-assessment tool based on the modified Gail model[97-101] that can be accessed at:

http://www.cancer.gov/bcrisktool/Default.aspx,

which provides risk projections on the basis of several risk factors for breast cancer. The modified Gail model assesses the risk of invasive breast cancer as a function of age, menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race. The model calculates 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify women who are at increased risk. The Gail model should not be used for women with a predisposing gene mutation, a strong family history of breast or ovarian cancer suggestive of a genetic predisposition, women with a prior history of thoracic radiation, or for those with LCIS.

The Gail model was updated using combined data from the Women's Contraceptive and Reproductive Experiences (CARE) study and the SEER database, as well as causes of death from the National Center for Health Statistics, to provide a more accurate determination of risk for African-American women.[102] It has also been updated using the data from the Asian American Breast Cancer Study (AABCS) and the SEER database to provide a more accurate risk assessment for Asian and Pacific Islander women in the United States.[103]

Increased risk of developing breast cancer is defined by the modified Gail model for women ≥35 years of age as a 5-year risk of 1.7% or greater. This is the average risk of a 60-year-old woman, which is the median age of diagnosis of breast cancer in the United States. The 5-year predicted risk of breast cancer required to enter the NSABP Breast Cancer Prevention Trial of tamoxifen versus placebo, as well as the Study of Tamoxifen and Raloxifene (STAR) trial, was 1.7% or greater. As previously mentioned, the modified Gail model risk assessment tool also provides an estimate of a woman's lifetime risk of breast cancer.

However, this estimate is based on the Gail model risk criteria, which differ from criteria used in risk assessment models predominantly based on family history (see below). Lifetime breast cancer risk as determined by the Gail model is not used in these guidelines to determine whether a woman is eligible for screening breast MRI.

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

Women Who Have a Lifetime Risk >20% Based on History of LCIS or ADH/ALH:

A diagnosis of LCIS or ADH/ALH is associated with high risk of development of cancer in either breast.[104-106]

For women with a history of LCIS or ADH/ALH, the NCCN panel encourages breast awareness and recommends a clinical encounter every 6 to 12 months beginning at the age of diagnosis and annual digital mammography, with the consideration of tomosynthesis, beginning at the age of diagnosis of LCIS or ADH/ALH but not less than 30 years of age. In addition, according to the NCCN panel, annual MRI should be considered beginning at the age of diagnosis of LCIS or ADH/ALH but not less than age 25 (based on emerging evidence).[51] Women in these groups should also be considered for risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

Women with a Lifetime Risk of Breast Cancer >20% Based on Models Largely Dependent on Family History:

A lifetime risk of breast cancer of >20% as assessed by models based largely on family history is another risk threshold used in the guidelines to identify a woman as a potential candidate for risk reduction strategies, as well as to direct screening strategies. According to the ACS guidelines for breast screening, MRI may be performed as an adjunct to mammography[49] in a high-risk woman if her lifetime risk of breast cancer is approximately 20% or greater based on models that rely mainly on family history. A cancer genetic professional should be involved in determining the lifetime risk of the individual based on models dependent on family history. These include Claus,[107] Tyrer-Cuzick,[108] and other models.[109-111] BRCAPRO[112] and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)[113] are more commonly used to estimate the risk of BRCA mutations. Strong genetic association between breast and ovarian cancer has been demonstrated in some families by linkage analyses.

For a woman with a >20% lifetime risk of breast cancer based on models largely dependent on family history, the NCCN panel encourages breast awareness and clinical encounter every 6 to 12 months to begin at the age identified as being at increased risk. The NCCN panel recommends annual digital mammography, with the consideration of tomosynthesis starting from 10 years prior to the youngest family member but not less than age 30. In addition, in accordance with the ACS guidelines,[49] the NCCN panel recommends annual breast MRI to begin 10 years prior to the youngest family member diagnosed but not less than 25 years of age for women who have a lifetime risk of breast cancer >20% based on models that rely mainly on family history. According to the NCCN panel, women in this group should be asked to consider risk reduction strategies in accordance with the NCCN Guidelines for Breast Cancer Risk Reduction.

Women Who Have Received Prior Thoracic Irradiation Between the Ages of 10 to 30 Years:

Results from several studies have demonstrated that women who received thoracic irradiation in their second or third decade of life have a substantially increased risk of developing

developing breast cancer by age 40 years.[114-119] 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.[115,118] 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.[118] Results from a case-control study of women treated with thoracic radiation at a young age for Hodgkin lymphoma indicated that the estimated cumulative absolute risk of breast cancer at 55 years of age was 29.0% (95% CI, 20.2%–40.1%)

for a woman treated at 25 years of age with at least 40 Gy of radiation and no alkylating agents.[120] Although there is a concern that the cumulative radiation exposure from mammography in a young woman may itself pose a risk for cancer, it is felt that the additional radiation in this population is negligible compared to overall radiation exposure. Findings from a survey of breast screening practices in this population of patients suggest that a sizable segment of this group is not undergoing regular mammographic screening.[121]

For women aged 25 years and older who have received prior thoracic irradiation, the NCCN panel recommends encouraging breast awareness, and a clinical encounter every 6 to 12 months be initiated 8 to 10 years after radiation exposure.[122] Breast imaging assessments

with annual digital mammograms, with the consideration of tomosynthesis, and annual MRI as an adjunct to mammograms[40] are recommended to begin 8 to 10 years after radiation exposure in those aged 25 years or older.

For women younger than 25 years who have received prior thoracic irradiation, the NCCN panel recommends encouraging breast awareness, counseling on risk, and an annual clinical encounter starting 8 to 10 years after radiation therapy.

Women with a Pedigree Suggestive Of or With a Known Genetic Predisposition: Accurate family history information is needed to adequately assess a woman's breast cancer risk. Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than expected based on statistics, they generally do not exhibit inheritance patterns or onset age consistent with hereditary cancers. Familial breast cancers may be associated with chance clustering, genetic variations in lower-penetrance genes, a shared environment,
small family size, and/or other factors.
The NCCN Guidelines for Genetic/Familial High-Risk Assessment Breast and Ovarian include recommendations for referral to a cancer genetics professional for further evaluation for individuals who have either a personal history or a close family history meeting certain criteria and also list screening recommendations for common hereditary syndromes that confer increased risk for breast and ovarian cancer. (See NCCN Guidelines for Genetic/Familial High-Risk Assessment:
Breast and Ovarian).

Diagnostic Evaluation

Breast symptoms are common among women. A retrospective study of women aged 40 to 70 years showed that 16% (total visits of 23 per 100 women) of women will present with symptoms to their provider during a decade with higher frequency among women ages 40 to 59 years compared to older women.[123] 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 even though most symptoms will be determined to be benign in etiology. Women younger than age 40, who are not usually recommended for routine breast screening, also frequently present for breast symptoms.

Unlike imaging for screening, which is used to detect cancer in
asymptomatic women, diagnostic evaluation is used to characterize a clinical finding or possible abnormality found during screening. There isconfusion regarding the term "diagnostic" imaging, as it is applied to two very different not specific enough to be truly "diagnostic."
imaging, as it is applied to two very different situations: 1) imaging for clinical finding such as a palpable mass; and 2) incremental imaging after a possible abnormal screening mammogram in an asymptomatic woman (also referred to as
recall or call-back). To add further confusion, insurance carriers may consider a routine mammogram to be "diagnostic" in certain asymptomatic women (eg, in women with prior cancer). Diagnostic evaluation in this review will be restricted to the former two situations.

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

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

Diagnostic Imaging After Screening Mammography Recall Diagnostic Mammography

Screening mammography consists of two standard x-ray images of each breast, whereas a diagnostic mammogram includes additional views, such as spot compression views or magnifications views, to investigate the finding in question. Diagnostic mammography is associated with higher sensitivity but lower specificity as compared to screening mammography. DBT may replace traditional diagnostic mammographic imaging in certain situations.[124-126]
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 andultrasound 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 MQSA and are reported using the similar ACR BI-RADS® assessment categories, which classify likelihood of the breast findings into six final assessment catergories.[127] The BI-RADS® assessment categories help to standardize both the reporting of mammographic findings and the recommendations for further management. The definitionsof the mammogram assessment categories are outlined in Mammographic Assessment Category Definitions in the algorithm.

NCCN Recommendations for Mammogram BI-RADS® Assessment Categories 1, 2, 3, 4, 5, and 6

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

For BI-RADS® Categories 4 and 5, 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.[128,129] For example, a negative needle biopsy associated with a spiculated category 5 mass 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 remain discordant. Women with a benign result exhibiting pathology/image concordance should be followed with mammography every 6 to 12 months for 1 to 2 years before returning to routine screening.

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

Breast Ultrasonography

Imaging by ultrasound is an important adjunct for diagnosing breast cancer.[130] However, breast ultrasonography does not detect most microcalcifications.[30,41,131-133] 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.[134] MRI may be used for suspicious nipple discharge when mammography and ultrasound are not diagnostic.[135-137]

Breast Tissue Biopsy

Breast biopsy is recommended if diagnostic imaging findings or clinical findings are suspicious or highly suggestive of malignancy.

Fine-Needle Aspiration (FNA) Biopsy

An FNA biopsy involves use of a smaller-bore needle to obtain cytologic samples from a breast mass. Advantages of FNA biopsy include its minimally invasive methodology and low cost,[138,139] 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.[140,141]

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.[142,143] It can be performed under imaging guidance (eg, stereotactic [mammographic] ultrasound or MRI) or directed by palpation.

Advantages of breast core needle biopsy include increased accuracy over FNA when the procedure is performed in situations where no mass is palpable and an ability to obtain tissue samples of sufficient size so as to eliminate the need for a follow-up biopsy to confirm malignancy.[144] In some situations, the core needle biopsy is performed under vacuum need for multiple needle insertions.[145-147] 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.[148] 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%.[89] 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.[148] Newer localization methods using radionucleotide seeds or reflector 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. In most cases, excisional biopsy is recommended following diagnosis by core biopsy of an indeterminate lesion, atypical hyperplasia, LCIS, or a benign and image-discordant
lesion. Other histologies that may require additional tissue include mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scars, or other histologies of concern to the pathologist.[139,144,149,150] Support for this recommendation includes results of studies demonstrating an underestimation of cancer when atypical hyperplasia and LCIS are diagnosed by core needle biopsy.[151-156] However, there are situations (eg, select cases of LCIS, ALH, papillomas, fibroepithelial lesions, and radial scars) where close observation may be substituted
for excisional biopsy in select patients.[139,149,157-163]

Diagnostic Evaluation For Symptomatic Findings on Physical Examination

In general, the breast imaging evaluations after physical exam include mammography and ultrasound. The addition of ultrasound to diagnostic mammography significantly increases cancer detection and detection of specific benign findings such as cysts. Imaging for women younger than age 30 begins with ultrasound while older women generally have both studies, unless a cyst is likely.[164,165 ,166-169] Negative imaging results place a patient a very low risk of malignancy (generally less than 3%); however, clinical judgment is necessary as some women with negative imaging may warrant biopsy and will be found to have malignant mass.[164,170-172] The recommendations for subsequent management follow imaging assessments and clinical level of suspicion. Imaging should proceed biopsy in most situations due to potential alteration of imaging findings by the biopsy.

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

Women with Palpable Mass Aged 30 Years or Older:

The main difference in the guidelines for evaluating a palpable mass in women aged 30 years or older compared with younger women is the increased degree of suspicion of breast cancer. The initial evaluation begins with a diagnostic mammogram and ultrasound. Ultrasound should be geographically correlated with the palpable mass in question. Observation without further evaluation is not an option in these women.
There are some clinical circumstances, such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30 to 39 years of age due to the high sensitivity of ultrasound alone.[167,168] After the diagnostic imaging assessment, the abnormality is placed into one of the following categories: negative or benign; probably benign; or suspicious or highly suggestive of cancer with management following BIRADS final assessment recommendations.

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

For women with mammographic findings that are suspicious or highly suggestive of breast cancer, the NCCN panel recommends ultrasound to determine lesion size and to guide tissue biopsy. The NCCN panel notes that FNA and core needle biopsy are both valuable. However, FNA requires cytologic expertise. When a core needle biopsy is utilized, concordance between the pathology report, 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 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 to 12 months for 1 to 2 years to assess stability of the solid mass.

There may be variability on the follow-up interval based on the level of suspicion. Numerous clinical studies now support the ability of ultrasound to accurately characterize palpable solid masses as probably benign with risk of malignancy generally less than 2%. However, these same studies have shown that many such masses will eventually warrant biopsy and compliance with follow-up may be low.[165,167,173-177] Progression of size or suspicion on follow-up studies warrants biopsy.

Cystic Masses:

Breast cysts are either classified as simple or non-simple cysts, with the latter class being subdivided into complicated cysts and complex (cystic) mass (see Table 1 for definitions).

Simple Cyst:

A cyst meeting all criteria of a simple cyst is considered to be benign (ie, BI-RADS® 2)[30,178] if the clinical findings and ultrasonographic results are concordant. Therapeutic fluid aspiration can be considered if clinical symptoms such as pain persist. These patients then can be followed with routine screening. Cytologic examination is recommended if bloody fluid is obtained during aspiration.

Non-Simple Complicated Cyst:

A complicated non-simple cyst is associated with a low risk of malignancy (<2%) (BI-RADS® 3).[30,179-181] 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. The option of aspiration may be more strongly considered in a patient likely to be lost to follow-up. Complicated cysts that increase in size or suspicion should be biopsied.

If the mass resolves after aspiration, and cytology results are negative, the NCCN panel recommends that the patient should return to routine screening. If the mass first resolves after aspiration and then recurs, then repeat assessment with imaging or a surgical excision may be warranted. If the mass persists after aspiration, the NCCN panel recommends ultrasound with image-guided biopsy. Surgical excision is appropriate if unable to perform core needle biopsy.

Non-Simple 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).[30,150,180-182] The NCCN panel recommends a tissue biopsy for complex (cystic) masses (BI-RADS® 4).

No Imaging Abnormality:

If no ultrasonographic or mammographic abnormality is detected (BI-RADS® 1), tissue biopsy (core needle biopsy or excision) should be carried out for suspicious clinical findings or for low clinical suspicion and observation at 3- to 6-month intervals for 1 to 2 years should be considered to assess stability. The negative predictive value of negative imaging is high, >96%.1[64,168,171 Soo, 2001 #674,172] If the clinical lesion increases in size or suspicion, tissue sampling should be repeated, whereas routine breast screening is recommended if the lesion remains stable. If the option of tissue biopsy is elected, the biopsy result indicates benign mass, and this finding is concordant with the imaging results, the NCCN panel recommends a physical examination every 6 to 12 months, with or without ultrasound or mammogram, for 1 to 2 years 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, atypical hyperplasia, LCIS that is non-concordant with imaging, or a benign and image discordant lesion, 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 atypical hyperplasia, LCIS, fibroepithelial lesions, radial scars) may be suitable for monitoring in lieu of surgical excision. For patients with classic LCIS that is concordant with imaging, the NCCN panel recommends routine screening along with risk reduction therapy according to the NCCN Guidelines for Breast Cancer Risk Reduction or surgical excision may be performed. Multiple-foci LCIS involving greater than 4 terminal ductal units on core biopsy is associated with increased risk of being invasive cancer.[162] Patients with pleomorphic LCIS are treated with surgical excision and managed according to the NCCN Guidelines for Breast Cancer.

Malignant Finding:

Malignant findings with image-guided biopsy or surgical excision should be treated according to the NCCN Guidelines for Breast Cancer.

Women with Palpable Mass Younger Than 30 Years of Age:

The preferred option for initial evaluation of a palpable mass is to proceed directly to ultrasound.[167] Mammogram may be considered if ultrasound or CBE results are highly suspicious or suggestive of cancer or if the patient is identified as having a high risk for breast cancer based on personal and family history. From this point, the decision tree for women younger than 30 years of age is almost identical to the pathway for older women. The main difference is consideration of a diagnostic mammogram in only some situations for the younger women. Because the incidence of malignancy in women who are younger than age 30 is low, observation of the mass for one

or two menstrual cycles is also an option in cases with low clinical suspicion. If observation is elected and the mass resolves after one or two menstrual cycles, the patient may return to routine screening. 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 (BI-RADS® 1), a mammogram is recommended in cases where there is high clinical suspicion or for those at higher risk due to known genetic mutation or family history. Based on the mammogram results, from this point the management is identical to the pathway for older women. If the clinical suspicion is low, physical examination every 3 to 6 months for 1 to 2 years is recommended with or without ultrasound. If the mass increases in size during the observation period, diagnostic mammogram may be considered followed by tissue biopsy. If the mass remains stable, routine breast screening is recommended.

Nipple Discharge Without a Palpable Mass

Nipple discharge is common, and, in many cases, unrelated to breast pathology.[183-189] For example, non-spontaneous discharge from multiple breast ducts in a non-lactating woman can occur during pregnancy, following breast stimulation, in women with certain thyroid conditions, and in those taking certain medications, such as estrogen, oral contraceptives, opiates, and particular antihypertensive agents.[183]

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.[190]

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

Women with suspicious nipple 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.[191,192] In certain situations, MRI or ductography 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.[135-137,193,194]

According to the NCCN panel, when an overall imaging BI-RADS® assessment is category 1-3, either a ductogram or MRI are optional to guide the duct excision. The management options include duct excision[195] or follow-up with physical exam after 6 months and imaging with diagnostic mammogram with or without ultrasound for 1 to 2 years.

If clinical suspicion increases during follow-up, tissue biopsy is recommended. For BI-RADS® category 4 or 5, the NCCN panel recommends a tissue biopsy. If the biopsy findings are indeterminate, a ductogram is optional, but surgical duct excision would still be necessary. If findings are indicative of malignancy, the patient should be treated according to the NCCN 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.164 If the patient is younger than age 30 years and has no high risk factors, ultrasound evaluation is appropriate followed by consideration of diagnostic mammography. Diagnostic mammograms for this age group are fairly low in yield because of the density of the breast

and low risk of breast cancer. In a woman aged 30 years or older, a diagnostic mammogram and an ultrasound evaluation should be obtained.

If the overall imaging findings are classified as BI-RADS® category 1-3 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 the 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, 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.[196,197] 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.[198,199] Pure Paget's disease is frequently occult on mammography[200] 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 on the basis of the imaging findings. If the breast imaging results are normal, further workup is still needed.

Punch biopsy of the skin or nipple biopsy should be performed following imaging findings consistent with an overall BI-RADS® assessment category 1-3. 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 pathological correlation should be reassessed. In addition, a breast MRI, a repeat biopsy, and consultation with a breast specialist should be considered.

If the skin biopsy is malignant, the patient should be treated according to the NCCN Guidelines for Breast Cancer.

A tissue biopsy should be performed if imaging findings are consistent of an overall BI-RADS® assessment category 4-5. 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 biopsyshowing 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 NCCN panel has developed guidelines to evaluate breast pain for cancer and provide reassurance.

The risk of cancer in a woman presenting with breast pain as the only symptom is low, between 1.2% and 6.7%.[4,123,201,202]

Evaluation of 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.[203] If the breast pain is focal and persistent 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, the panel recommends a clinical encounter every 6 to 12 months for 1 to 2 years along with symptomatic management of the breast pain, if desired. For a simple cyst (BI-RADS® assessment category 2) geographically correlated with focal pain, drainage may be considered for symptom relief. Aspiration is recommended for painful, complicated cysts (BIRADS 3) to rule out infection or malignancy. A tissue biopsy should be performed if imaging findings are consistent of an overall BI-RADS® assessment category 4-5.

Summary

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

Table 1: Breast Cysts - Types and Definitions

Simple cyst	Anechoic (cystic), well-circumscribed, round or oval with well-defined imperceptible wall and posterior enhancement.
Non-simple cyst • **Complicated**	Has one or more characteristics not found in a simple cyst. Has most but not all elements of a simplecyst. Complicated cysts do not contain solid elements, intracystic masses, thick walls, or thick septa. This type of cyst may contain low-level echoes or intracystic debris, and can be described as a round, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria of a simple cyst.
• **Complex**	Has some discrete solid component, which may include thick walls, thick septa, and/or intracystic mass. Complex cysts have both anechoic (cystic) and echogenic (solid) components.
References	**139,150,178-182,204**

JORDAN BREAST CANCER PROGRAM

The Jordan Breast Cancer Program (JBCP) is a nation-wide initiative for the development and provision of comprehensive services for the early detection and screening of breast cancer for all females in Jordan within the age group 40-59 for the purpose of:

1. Reducing morbidity and mortality from breast cance by screening and early detection; and,

2. Shifting the current state of diagnosis of breast cancer from its late stages (III- IV) to diagnosing breast cancer at its earlier stages (0-II) where the disease is most curable, survival rates are highest, and treatment costs are lowest.

GOALS & OBJECTIVES

JBCP aims to ensure the provision of quality services for screening and increase public awareness and education on the risk factors, symptoms, signs and benefits of early detection and screening of breast cancer. JBCP has a multi-dimensional approach covering the provision of screening services, education of females, capacity building of health professionals and quality assurance. The overall objectives of JBCP are as follows:

- To improve availability and accessibility of screening services across Jordan, especially to those with low income and those residing in remote areas with little access to healthcare services;
- To increase public knowledge of the benefits of breast cancer prevention and promote attitude and behavioral change in the target population so that they seek early detection services;
- To establish national unified protocols and guidelines that cover all processes of a comprehensive early detection and screening program that include best practice and quality assurance guidelines on training, medical equipment, diagnosis, and referral systems;
- To improve healthcare personnel education and training;
- To evaluate the quality of the program by collecting data for surveillance and epidemiological analysis to record and measure success of early detection.

GOVERNANCE

JBCP has been established under the directive of His Excellency the Minister of Health, and is governed by a National Steering Committee comprising most stakeholders in health including the Ministry of Health, King Hussein Cancer Foundation and Center, USAID's Private Sector Project for Women's Health, World Health Organization (WHO), United Nations Relief and Works Agency (UNRWA), Royal Medical Services, King Abdullah Hospital, Syndicate of Private Hospitals, Jordan University, and Hashemite University.

The King Hussein Cancer Foundation and Center have been tasked with the leadership of JBCP. An executive board led by the King Hussein Cancer Center oversees the operations of JBCP, provides direction, and ensures the implementation of action plans.

INTRODUCTION

PURPOSE AND DEVELOPMENT OF THE GUIDELINES

The publication of Jordan's Breast Cancer Screening and Diagnosis Guidelines is a crucial move in the direction of ensuring the provision of high-quality breast cancer screening and diagnostic services to females in Jordan. A variety of guidelines are currently resorted to by practitioners in the medical sector. Thus, these national guidelines have been published to provide healthcare professionals with a unified, standardized and user-friendly document of international standards in application.

Commencing in January 2018, the Jordan Breast Cancer Program undertook the long overdue task of developing breast cancer screening and diagnosis guidelines for Jordan. JBCP convened an expert panel that reviewed several established international guidelines and selected from among them the National Comprehensive Cancer Network (NCCN) Breast Cancer Screening and Diagnosis Guidelines as a baseline that was tailored and modified to suit the Jordanian context and needs. After the technical taskforce delivered their recommendations, a larger group of national experts were invited to review the draft guidelines.

The Breast Cancer Screening and Diagnosis Guidelines are intended to be useful for healthcare professionals and have been designed to provide a practical, consistent framework for screening and evaluating a spectrum of

breast lesions. Clinical judgment should always be an important component of the optimal management of the patient. If the physical breast examination, radiologic imaging, and pathologic findings are not concordant, the clinician should carefully reconsider the assessment of the patient's problem. Incorporating the patient into the healthcare team's decision-making empowers the patient to determine the level of breast cancer risk that is personally acceptable in the screening or follow-up recommendations.

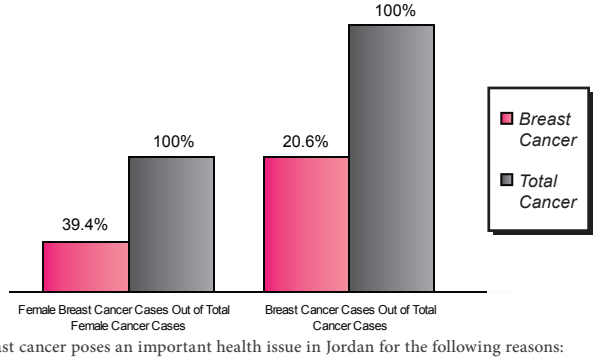
JBCP encourages the medical sector to adopt these Breast Cancer Screening and Diagnosis Guidelines as an important and indispensable resource. However, it is important to note that this document presents guidelines and does not claim to be an all-inclusive resource on breast cancer; clinicians seeking further information on the biology and epidemiology of breast cancer should consult the relevant texts.

These guidelines are a statement of consensus of the authors of the NCCN Breast Cancer Screening and Diagnosis Guidelines regarding their views of currently accepted approaches to screening, and have been modified by specialized reviewers in Jordan (listed in the Acknowledgements Section). They are based on the best evidence available at the time of publication, and will be updated periodically to include new findings and recommendations, in addition to being evaluated to determine their degree of use by practitioners.

BREAST CANCER IN JORDAN

Breast cancer is the most common cancer overall as well as the most common malignancy afflicting women in Jordan According to the latest statistics from the Jordan National Cancer Registry (JNCR), 1138 females and 7 males were diagnosed with breast cancer in 2015, accounting for 20.6% of the total new cancer cases. Breast cancer ranked first among cancers in females, accounting for 39.4 % of all female cancers.

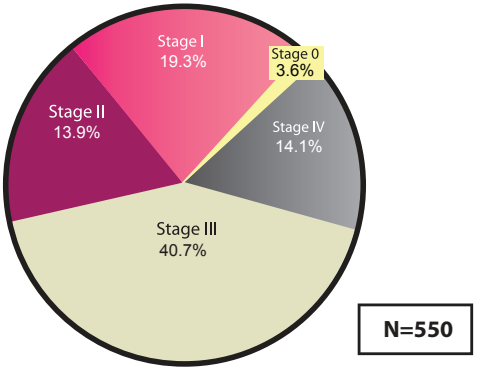
Comparison of Breast Cancer Cases to Total Cancer Cases in 2015



Breast cancer poses an important health issue in Jordan for the following reasons:

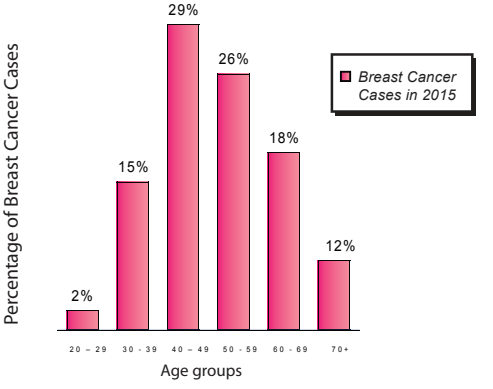
- 70 % of breast cancer cases in the country are presented at advanced stages (III-IV) during which survival rates are low and the disease is less curable. This is a reverse statistic in the West. Therefore, even though the incidence of breast cancer in Jordan is lower than incidence in Western countries, the mortality rate is very high due to late presentation of the disease;

Stages of Breast Cancer in Jordan Based on KHCC Experience in 2015/2016



- Jordanian women are afflicted with breast cancer at a much younger age (median age is 49) than women in Western countries (median age is 65), when they are still raising children, caring for their families, and contributing to the growth and development of society;

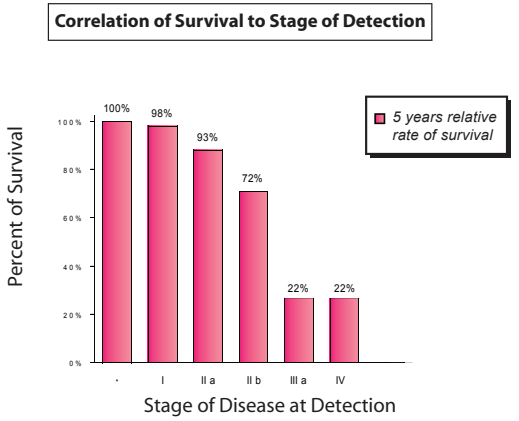
Distribution of Breast Cancer Cases Over Age, JNCR 2015



*Median age in developed countries = 65 years

- Survival rates and the early detection of breast cancer are directly connected; yet unfortunately, public awareness in Jordan regarding this fact is minimal and inadequate;

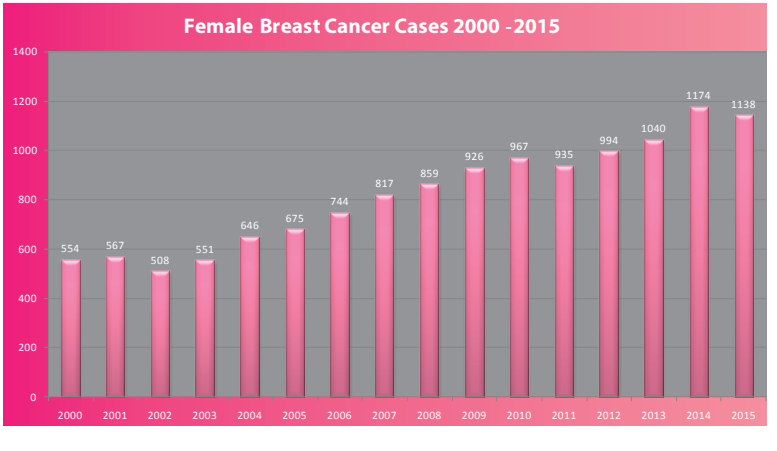
- Treatment of patients when breast cancer is at its earlier stages is generally less expensive and more successful than treatment during later stages of the disease;



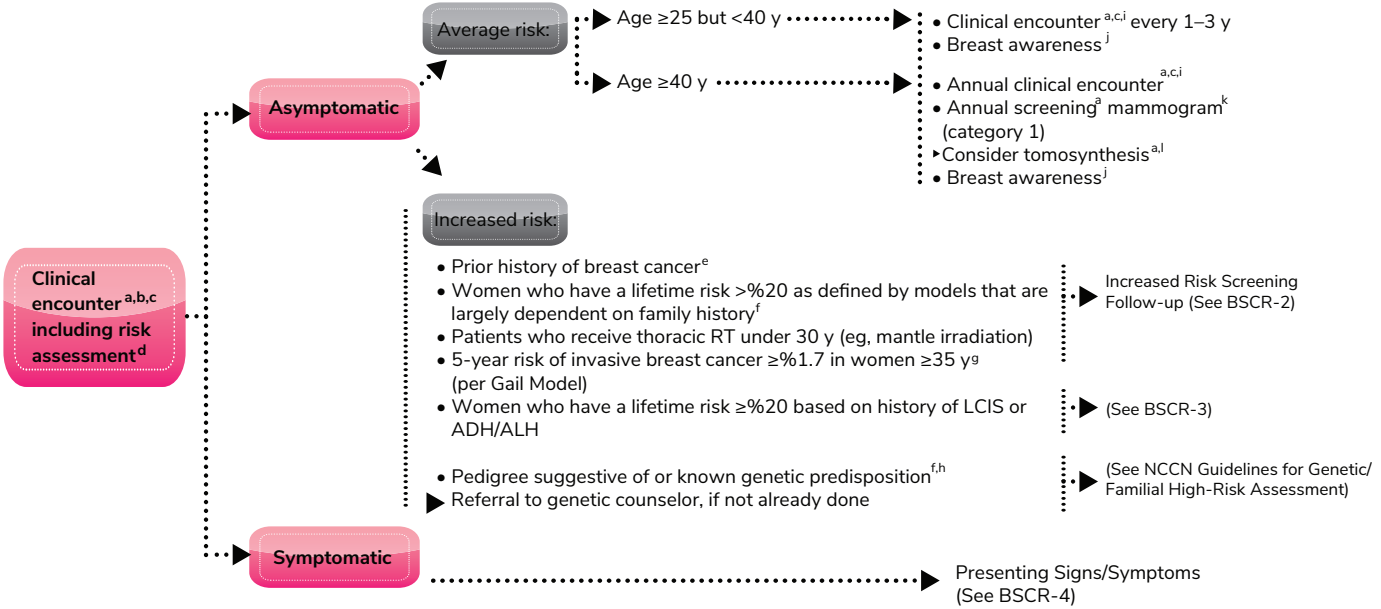
Survival rates and the early detection of breast cancer are directly connected; yet unfortunately, public awareness in Jordan regarding this fact is minimal and inadequate;

Treatment of patients when breast cancer is at its earlier stages is generally less expensive and more successful than treatment during later stages of the disease;

Year	Femal Breast Cancer Cases
2000	554
2001	567
2002	508
2003	551
2004	646
2005	675
2006	744
2007	817
2008	859
2009	926
2010	967
2011	935
2012	994
2013	1040
2014	1174
2015	1138
	13095



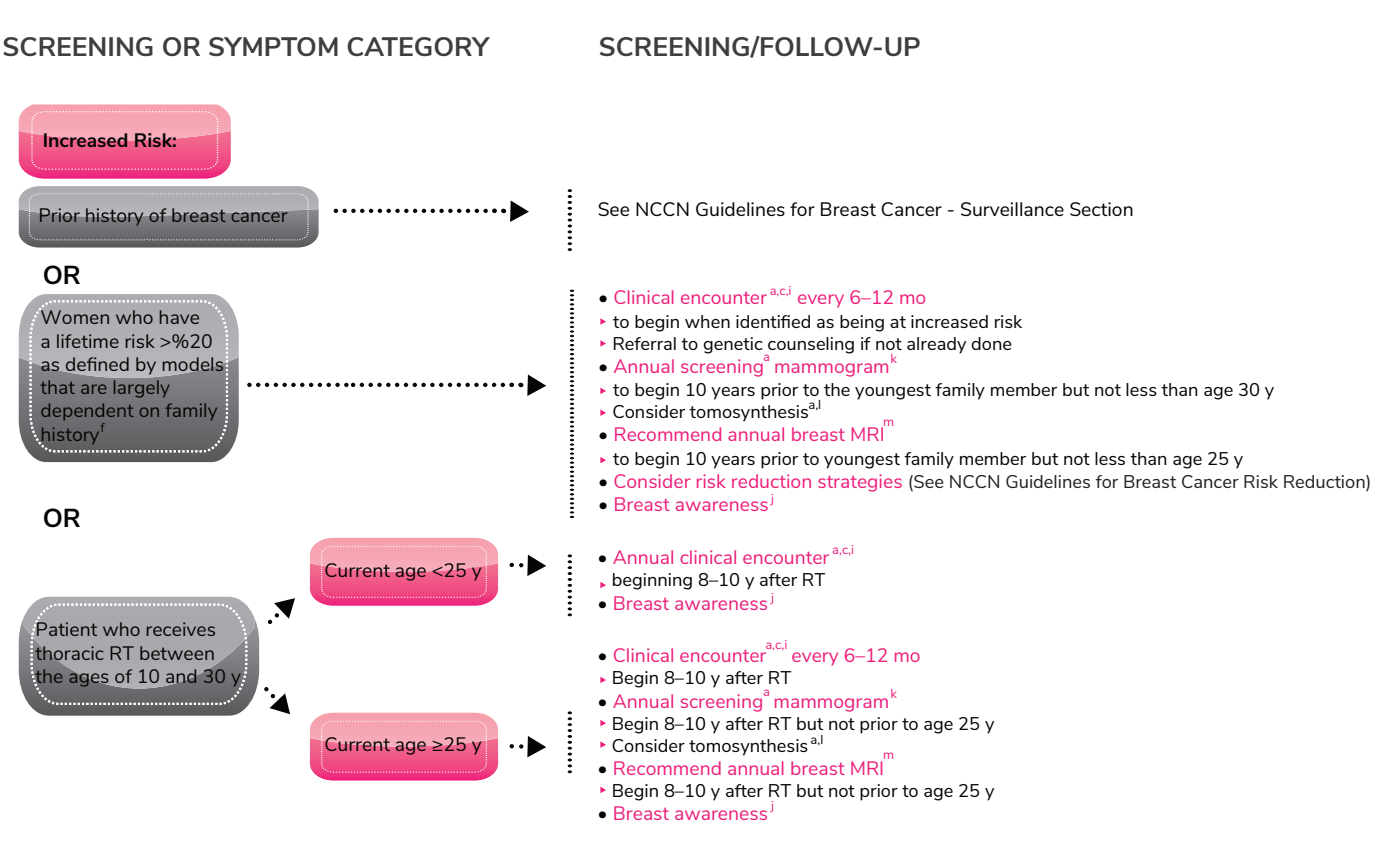
BREAST CANCER SCREENING AND DIAGNOSIS



[a]See Breast Screening Considerations (BSCR-A).
[b]Medicare and insurers allow the patient direct access to scheduling for mammography.
[c]At minimum medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, as well as a clinical breast exam.
[d]Refer to the NCCN Guidelines for Breast Cancer Risk Reduction for a detailed qualitative and quantitative assessment.
[e]See NCCN Guidelines for Breast Cancer - Surveillance Section.
[f]Risk models that are largely dependent on family history (eg, Claus, BRCAPRO, BOADICEA, Tyrer-Cuzick). See NCCN Guidelines for Breast Cancer Risk Reduction.
[g]See Risk Factor Used in the modified Gail Model, Age ≥35 years (BSCR-B)

[h]There is variation in recommendations for initiation of screening for different genetic syndromes. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
[i]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers.
[j]Women should be familiar with their breasts and promptly report changes to their health care provider.
[k]See Mammographic Evaluation (BSCR-19).
[l]Tomosynthesis improves cancer detection and reduces recall rates.

BREAST CANCER SCREENING AND DIAGNOSIS



[a] See Breast Screening Considerations (BSCR-A)

[c] At minimum medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, as well a a clinical breast exam.

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

[i] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliestdetection of breast cancers.

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

[k] See Mammographic Evaluation (BSCR-19).

[l] Tomosynthesis improves cancer detection and reduces recall rates.

[m] High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women. MRI should be integrated with other breast imaging modalities.

BREAST CANCER SCREENING AND DIAGNOSIS

SCREENING OR SYMPTOM CATEGORY

SCREENING/FOLLOW-UP

Increased Risk:

Women ≥35 y with 5 year Gail Model risk of invasive breast cancer ≥%1.7[g]

- Clinical encounter[a,c,i] every 6–12 mo
  - to begin when identified as being at increased risk by Gail Model
- Annual screening[a] mammogram[k]
  - to begin when identified as being at increased risk by Gail Model
  - Consider tomosynthesis[a,l]
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[j]

OR

Women who have a lifetime risk ≥%20 based on history of LCIS or ADH/ALH

- Clinical encounter[a,c,i] every 6–12 mo
  - to begin at diagnosis of LCIS or ADH/ALH
- Annual screening[a] mammogram[k]
  - to begin at diagnosis of LCIS or ADH/ALH but not less than age 30 y
  - Consider tomosynthesis[a,l]
- Consider annual MRI
  - to begin at diagnosis of LCIS or ADH/ALH but not less than age 25 y (based on emerging evidence)
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness

[a] See Breast Screening Considerations (BSCR-A)

[c] At minimum medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, as well as a clinical breast exam.

[g] See Risk Factors Used in the Modified Gail Model, Age ≥35 Years (BSCR-B).

[i] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers.

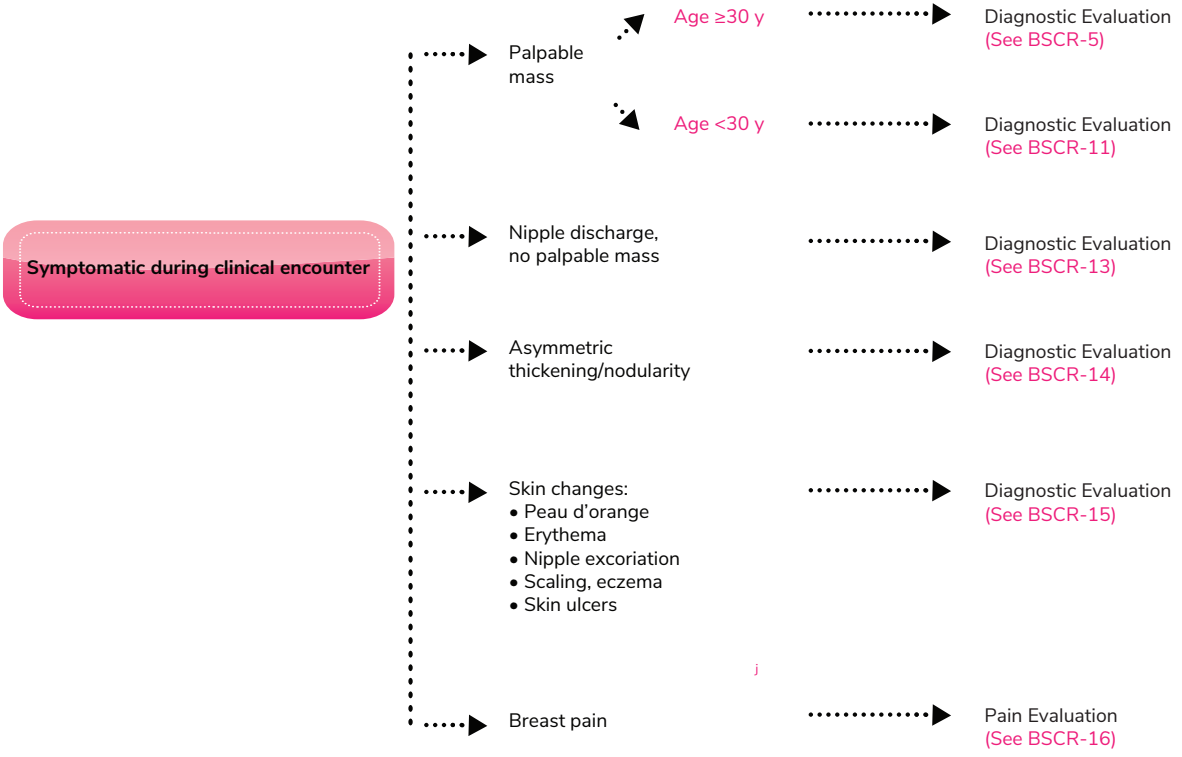
[j] Women should be familiar with their breasts and promptly report changes to their health care provider.

[k] See Mammographic Evaluation (BSCR-19).

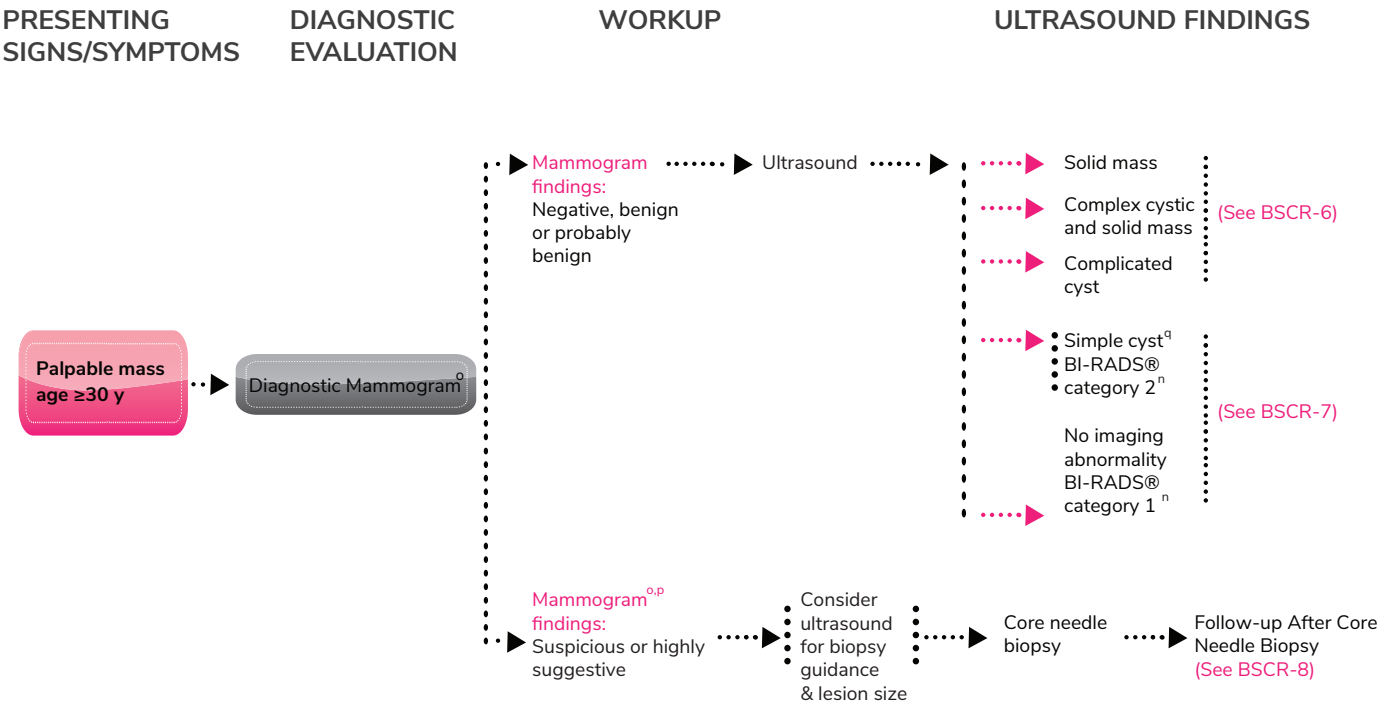
[l] Tomosynthesis improves cancer detection and reduces recall rates.

BREAST CANCER SCREENING AND DIAGNOSIS

PRESENTING SIGNS/SYMPTOMS



BREAST CANCER SCREENING AND DIAGNOSIS



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

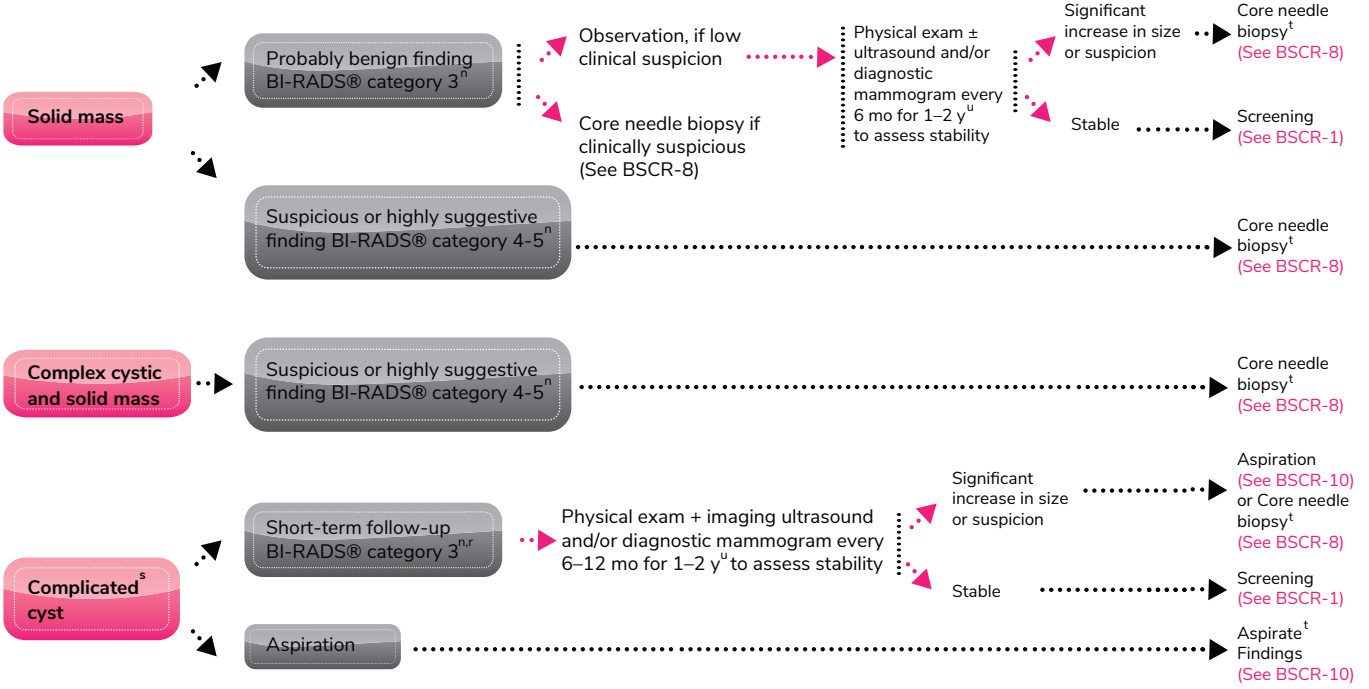
[o]There are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst in which ultrasound would be preferred and may suffice for women 30–39 years of age. See Discussion section.

[p]Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to mammogram findings: negative, benign or probably benign for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.

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

BREAST CANCER SCREENING AND DIAGNOSIS

ULTRASOUND FINDINGS/PALPABLE MASS



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

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

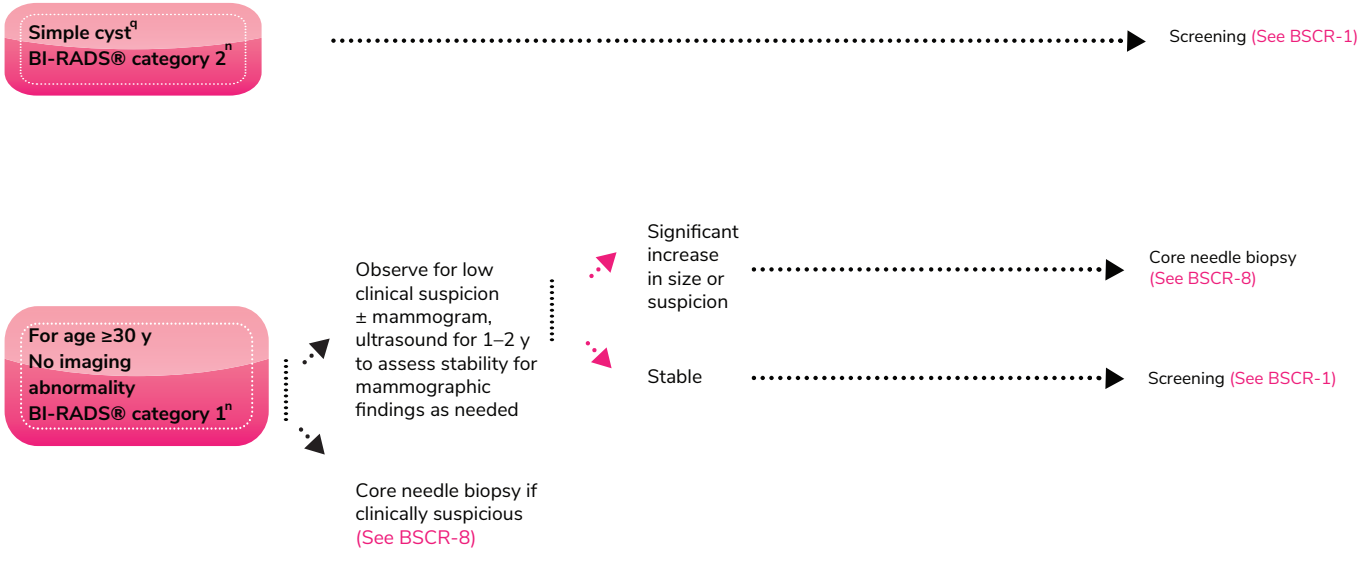
[s]Round or oval, circumscribed mass containing low-level echoes without vascular flow, fulfilling most but not all criteria for simple cyst.

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

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

BREAST CANCER SCREENING AND DIAGNOSIS

ULTRASOUND IMAGING FINDINGS/PALPABLE MASS



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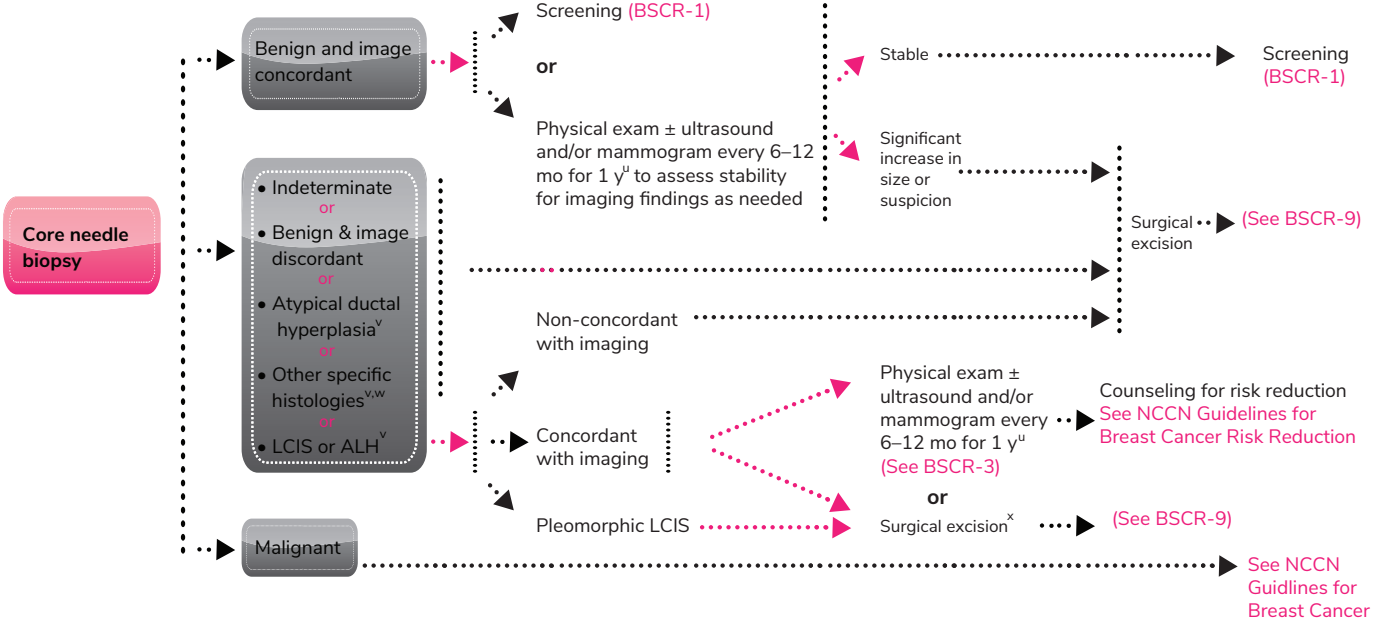
BREAST CANCER SCREENING AND DIAGNOSIS

ULTRASOUND FINDINGS/PALPABLE MASS



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

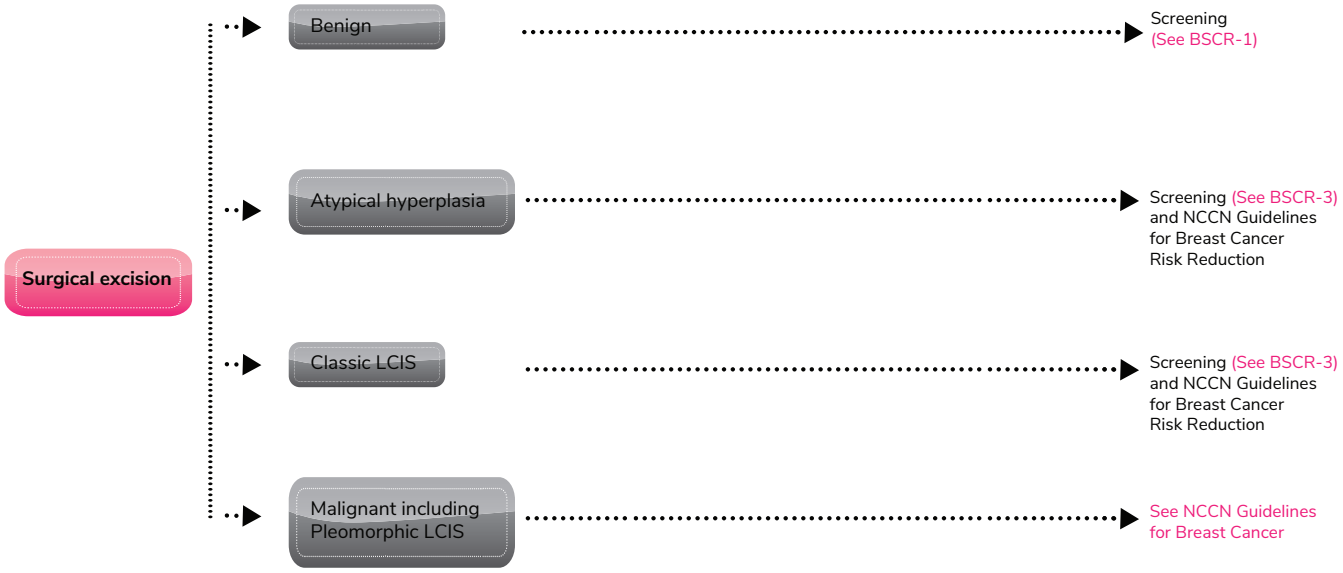
[v] Select patients may be suitable for monitoring in lieu of surgical excision (eg,FEA, papillomas, fibroepithelial lesions, radial scars).

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

[x] Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk for invasive cancer on surgical excision. (Rendi MH, Dintzis SM, Lehman CD, et al. Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. Ann Surg Oncol 2012;19:914-921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21861212).

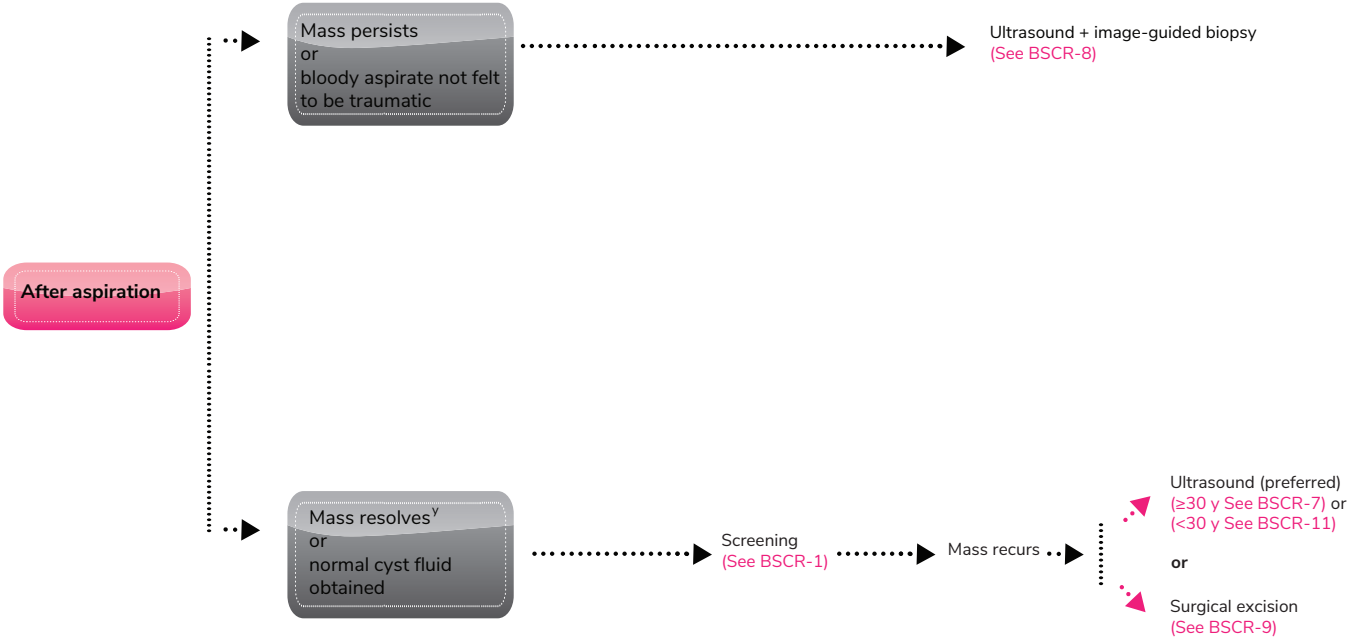
BREAST CANCER SCREENING AND DIAGNOSIS

FOLLOW-UP EVALUATION



BREAST CANCER SCREENING AND DIAGNOSIS

FOLLOW-UP EVALUATION

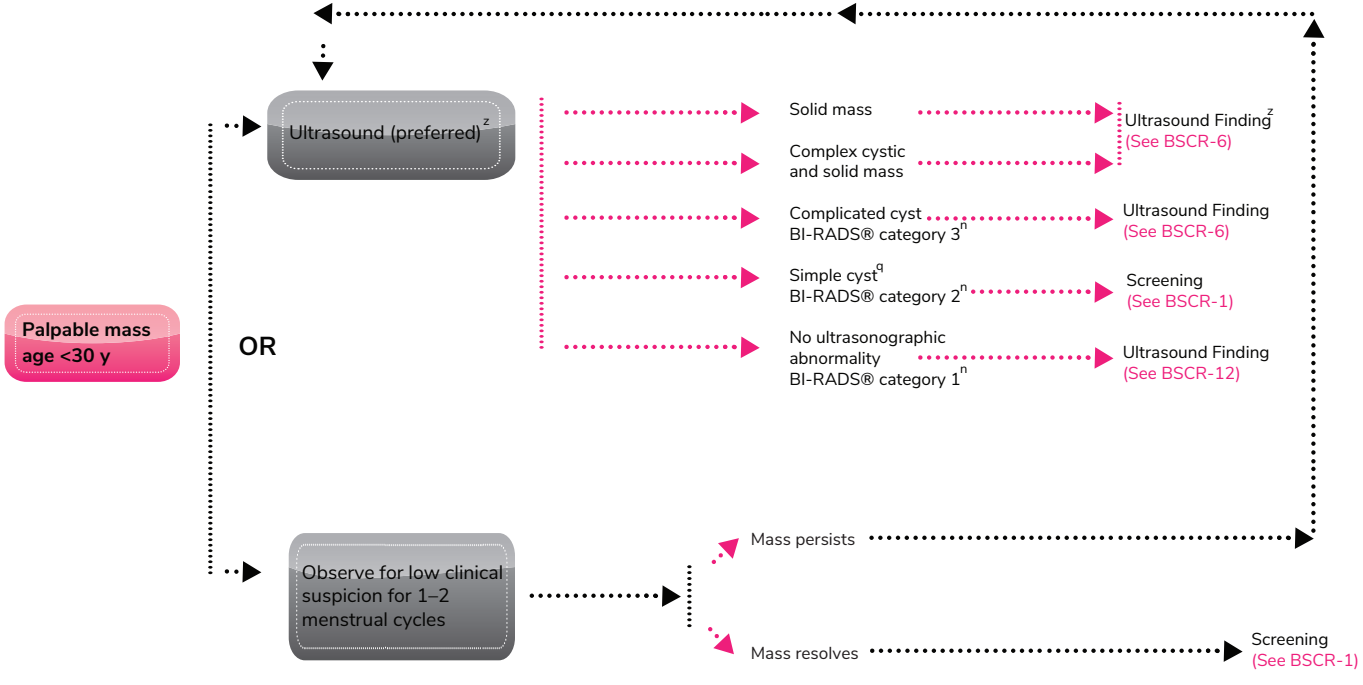


[y]Routine cytology is not recommended.

BREAST CANCER SCREENING AND DIAGNOSIS

PRESENTING SIGNS/SYMPTOMS

DIAGNOSTIC EVALUATION



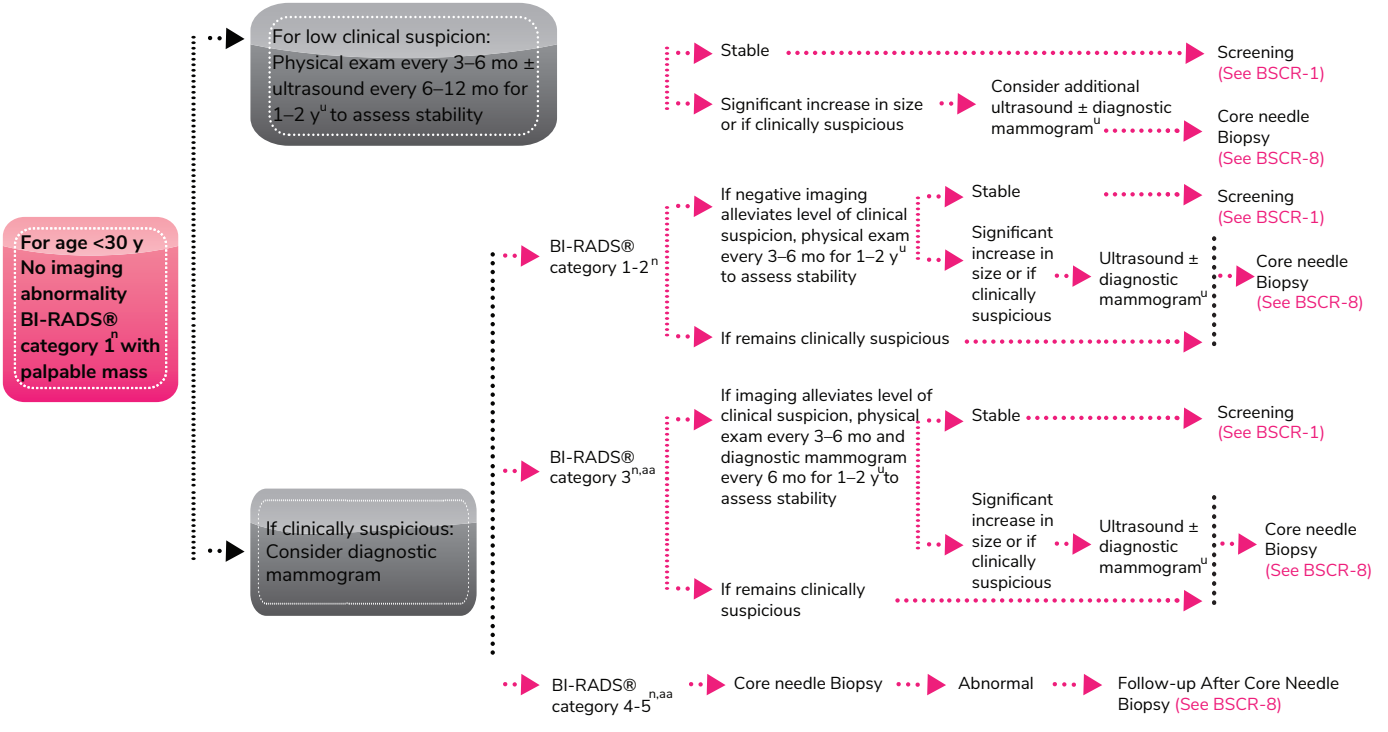
[n]See Assessment Category Definitions (BSCR-C).

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

[z]If suspicious or highly suggestive of malignancy obtain mammogram.

BREAST CANCER SCREENING AND DIAGNOSIS

ULTRASOUND IMAGING FINDINGS/PALPABLE MASS FOLLOW-UP EVALUATION



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

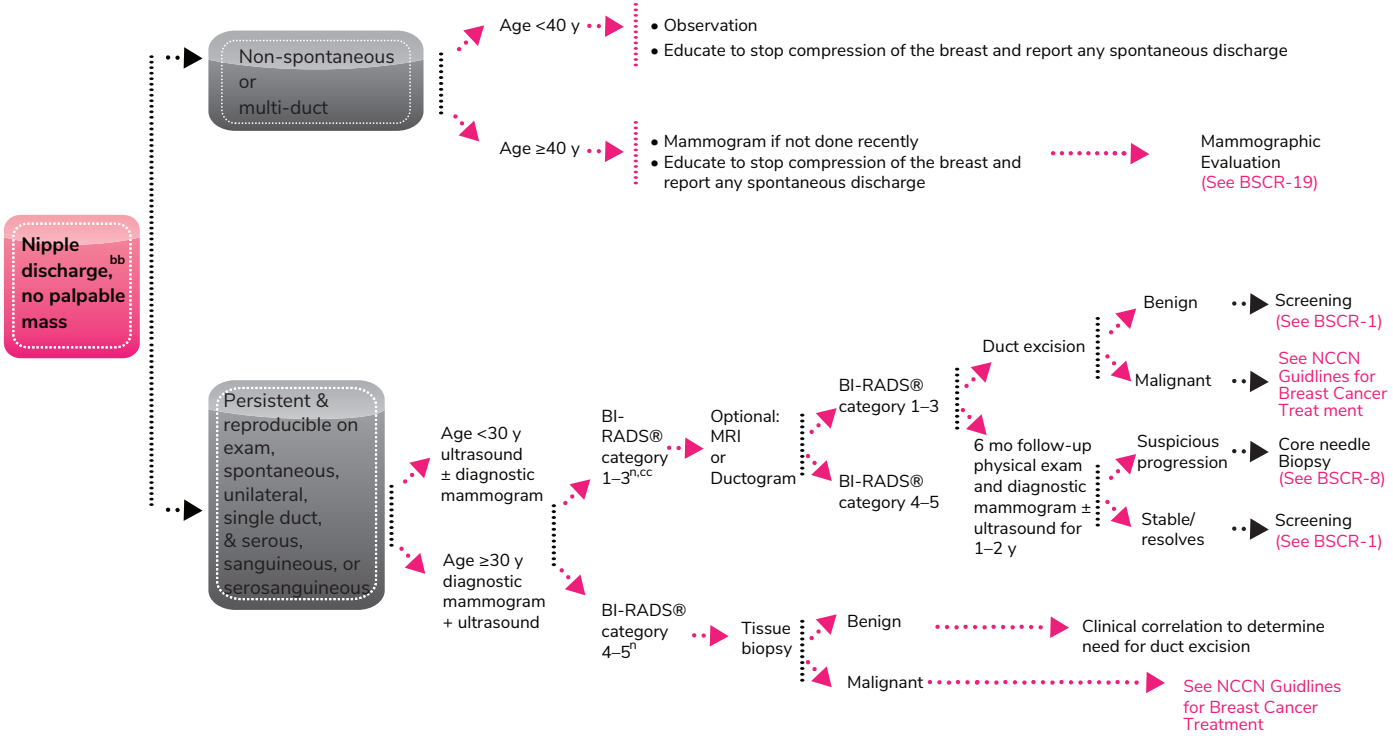
[aa] Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to BI-RADS category 1-2 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.

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

BREAST CANCER SCREENING AND DIAGNOSIS

PRESENTING SIGNS/ SYMPTOMS

DIAGNOSTIC FOLLOW-UP

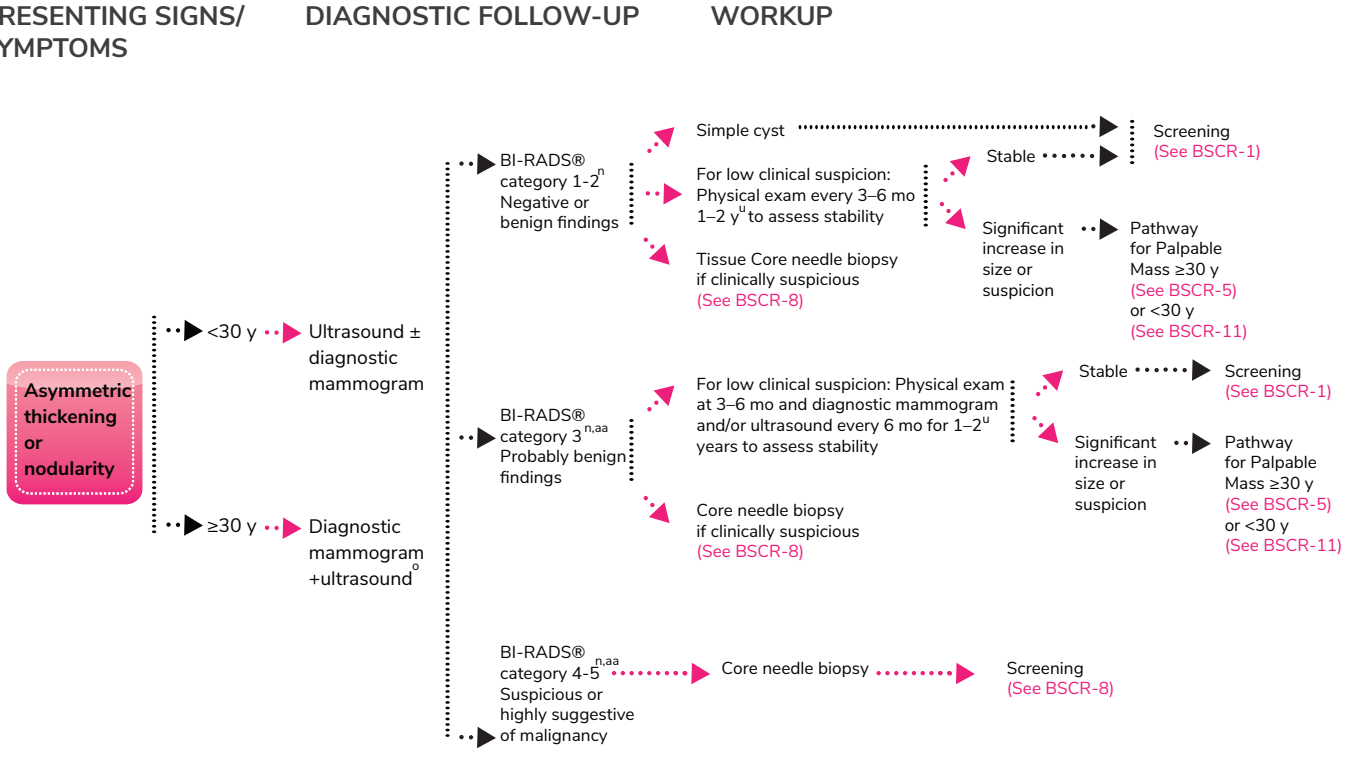


[n] See Assessment Category Definitions (BSCR-C).

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

[cc] If BI-RADS Category 3 finding is unrelated to nipple discharge, manage mammographic finding by BSCR-19.

BREAST CANCER SCREENING AND DIAGNOSIS



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

[o] There are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30–39 years of age. See Discussion section.

[aa] Assess geographic correlation between clinical and imaging findings. If there is a lack of correlation, return to BI-RADS category 1-2 for further workup of palpable lesion. If imaging findings correlate with the palpable finding, subsequent workup will answer the problem.

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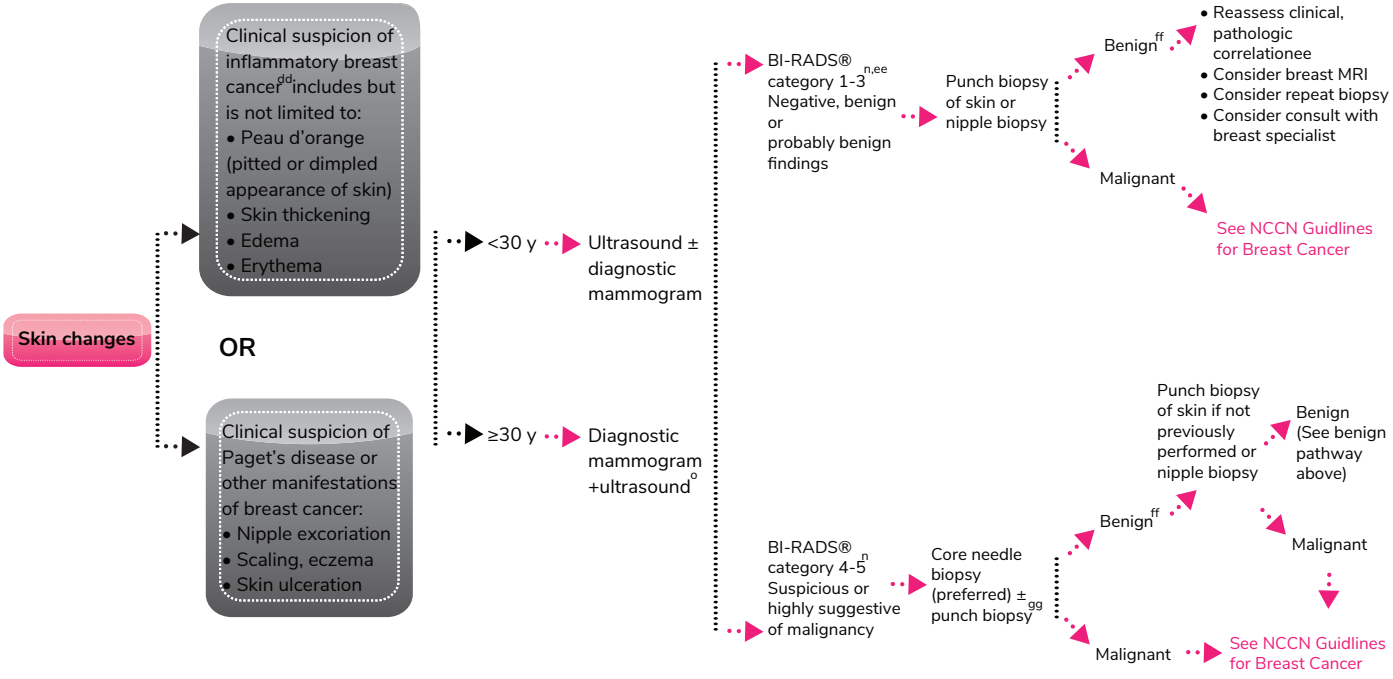
BREAST CANCER SCREENING AND DIAGNOSIS

PRESENTING SIGNS/ SYMPTOMS

DIAGNOSTIC FOLLOW-UP



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

[o] There are some clinical circumstances such as mass with low clinical suspicion or suspected simple cyst, in which ultrasound would be preferred and may suffice for women 30–39 years of age. See Discussion section.

[dd] This may represent serious disease of the breast and needs evaluation. (Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011;22(3):515-523. Available at https://www.ncbi.nlm.nih.gov/pubmed/20603440).

[ee] If clinically of low suspicion for breast cancer or high suspicion for infection, a short trial (7–10 days) of antibiotics for mastitis may be indicated.

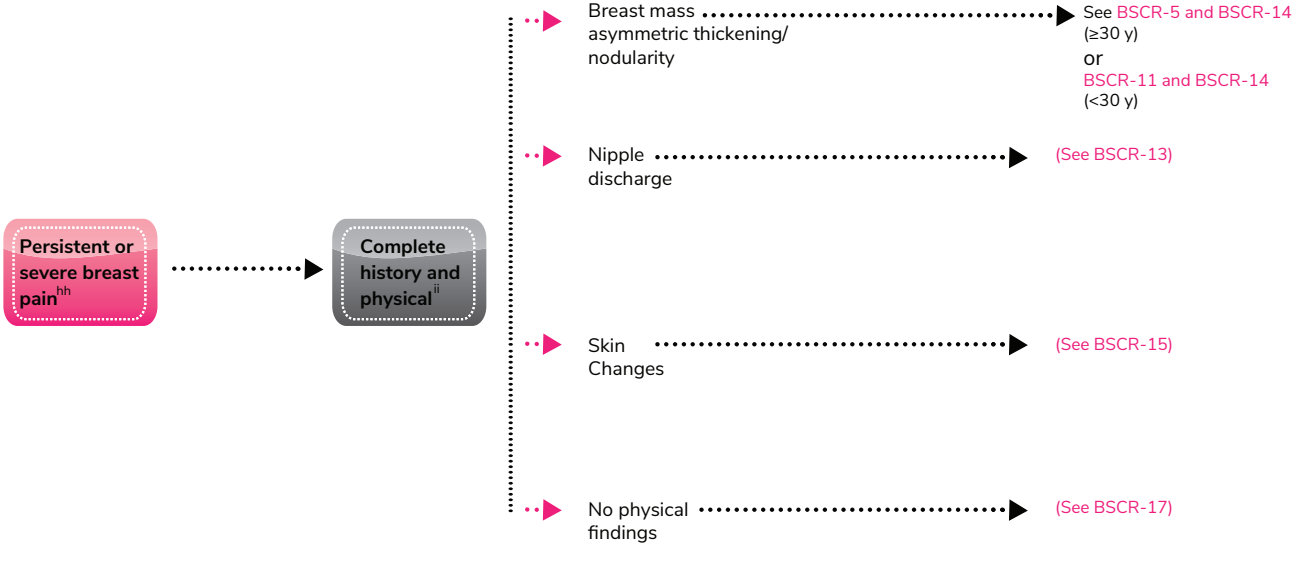
[ff] A benign skin punch biopsy in a patient with a clinical suspicion of inflammatory breast cancer does not rule out malignancy. Further evaluation is recommended.

[gg] Inflammatory breast cancer is a clinical diagnosis and is not dependent on a positive punch biopsy.

BREAST CANCER SCREENING AND DIAGNOSIS

PRESENTING SIGNS AND SYMPTOMS

FOLLOW-UP EVALUATION



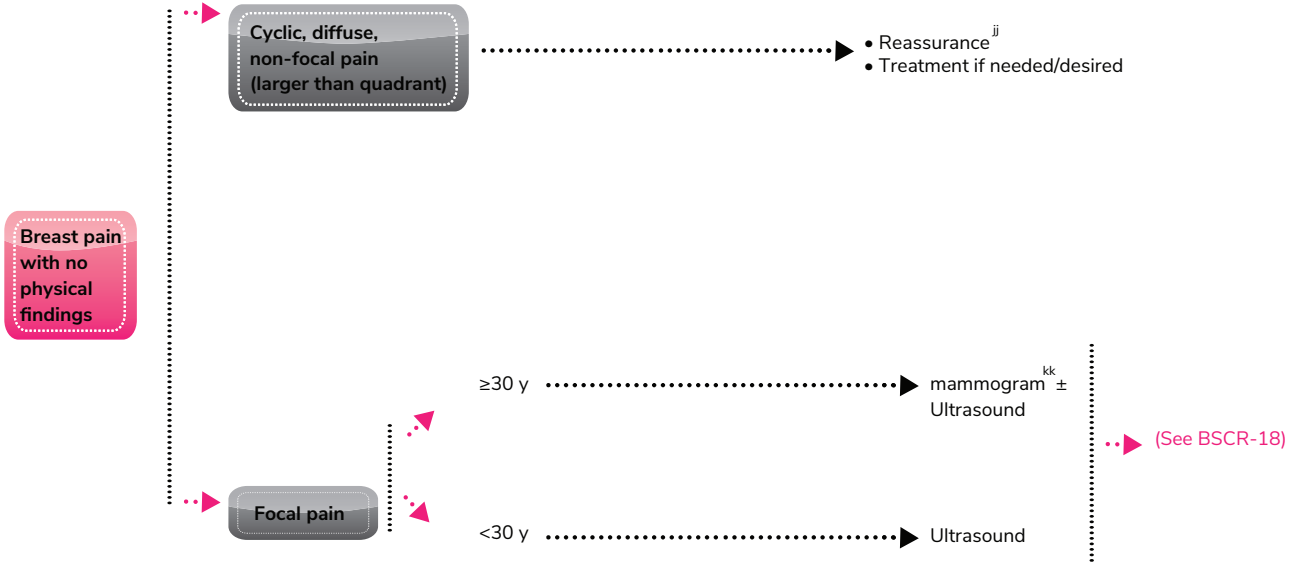
[hh]Defined as 4 to 6 weeks duration prior to that, symptomatic management.

[ii]Adequate clinical breast exams include the following: upright and supine position during inspection, and palpation of all components of the breast, axilla, and clavicular lymph node basins. Time spent on the palpable portion of the exam is associated with increased detection of palpable abnormalities. Location and distance from nipple facilitate geographic correlation with imaging findings. (See BSCR-1).

BREAST CANCER SCREENING AND DIAGNOSIS

PRESENTING SIGNS AND SYMPTOMS

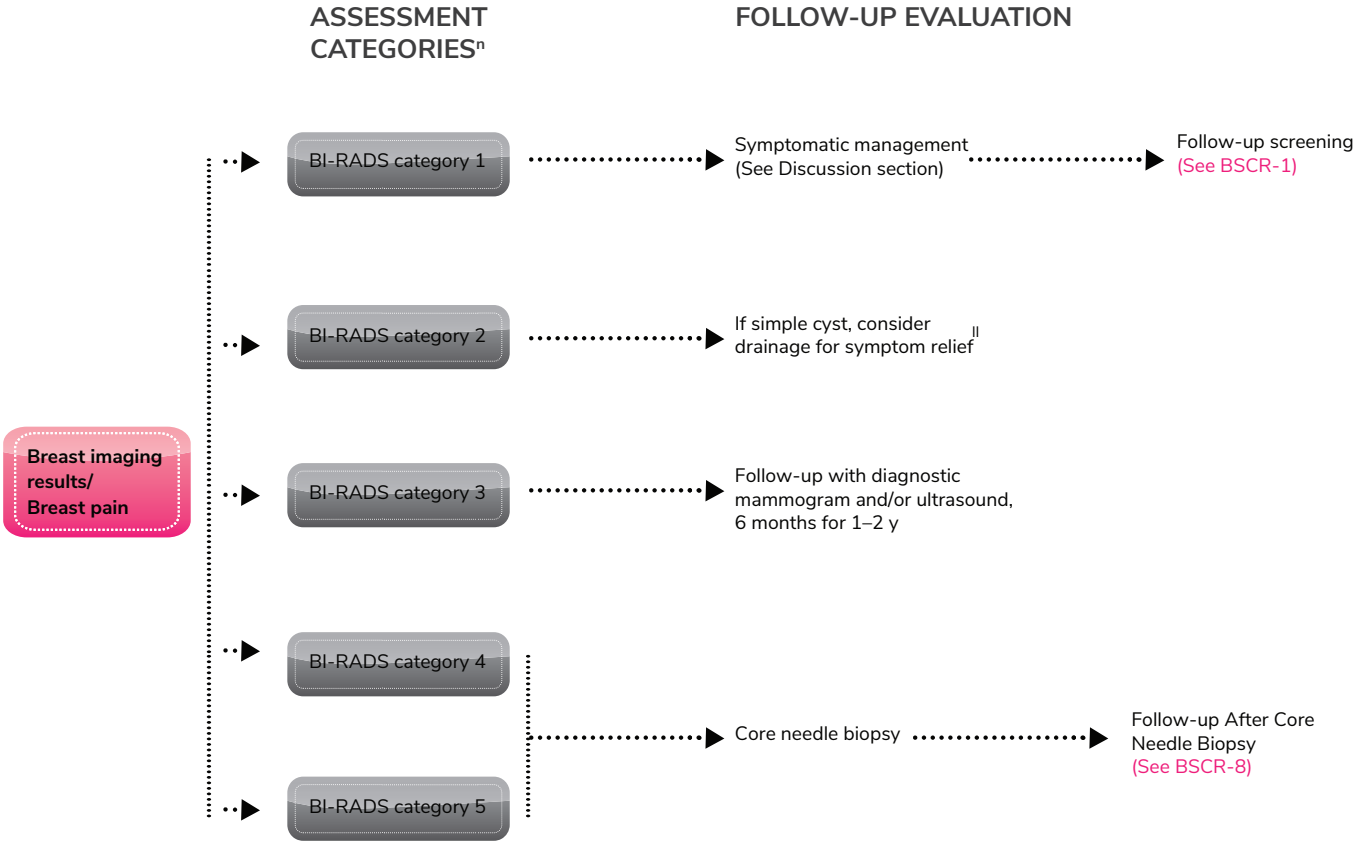
FOLLOW-UP EVALUATION



[jj]Assuming breast imaging screening is current.

[kk]There are some circumstances with low clinical suspicion; ultrasound would be preferred and may suffice for women 30–39 years of age.

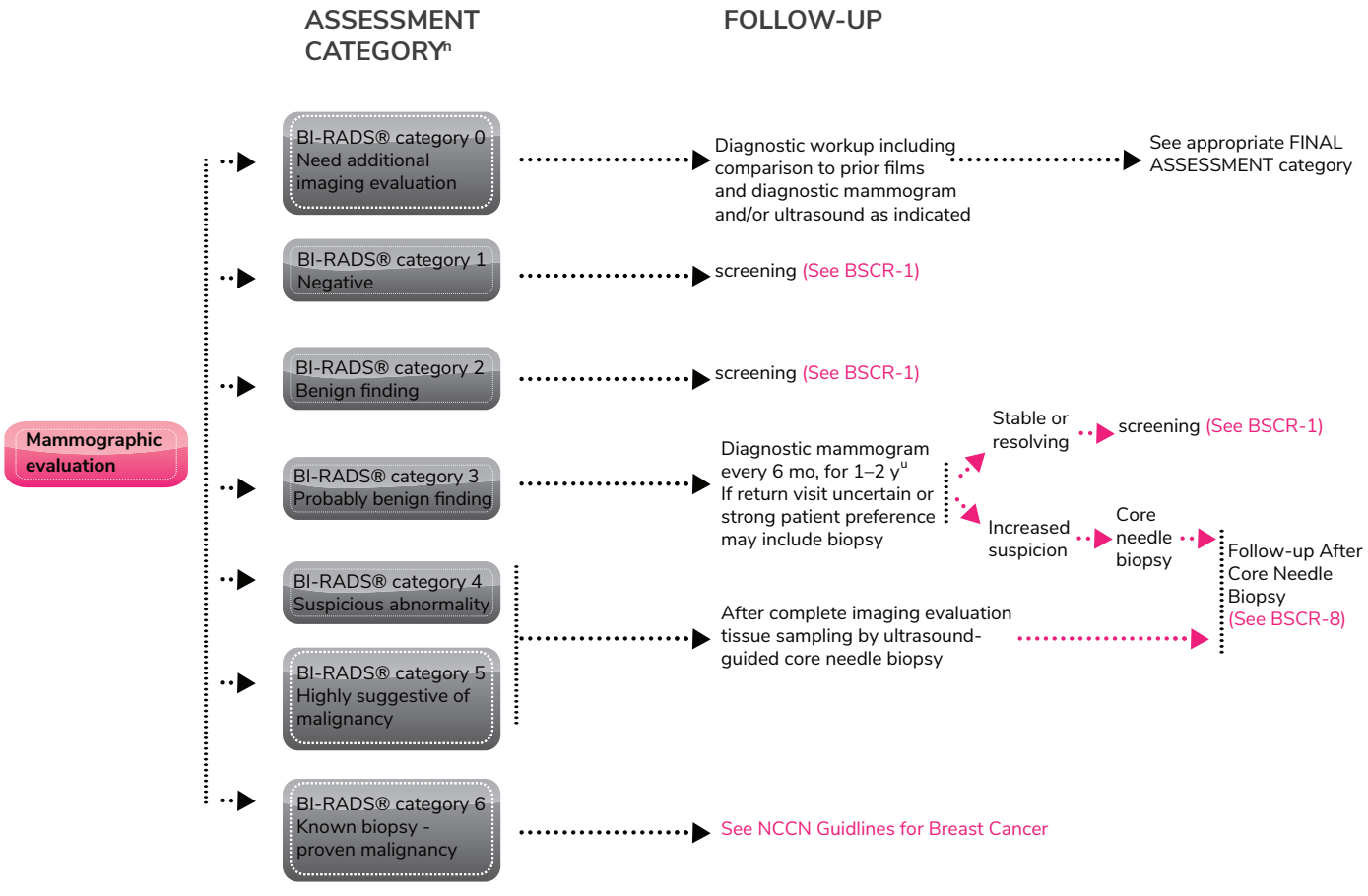
BREAST CANCER SCREENING AND DIAGNOSIS



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

[ll]If complicated cyst, consider aspiration.

BREAST CANCER SCREENING AND DIAGNOSIS



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

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

BREAST SCREENING CONSIDERATIONS

- Women should be counseled regarding potential benefits, risks, and limitations of breast screening. Shared decision making is encouraged based on a woman's values and preferences (See Discussion).
- Adequate clinical breast exams include the following: upright and supine position during inspection, and palpation of all components of the breast, axilla, and clavicular lymph node basins. Time spent on the palpable portion of the exam is associated with increased detection of palpable abnormalities.
  Location and distance from nipple facilitate geographic correlation with imaging findings.
- Consider severe comorbid conditions limiting life expectancy (eg, ≤10 years) and whether therapeutic interventions are planned.
- Upper age limit for screening is not yet established.
- For women with heterogeneous dense breasts and dense breast tissue, recommend counseling on the risks and benefits of supplemental screening.[1]
- Dense breasts limit the sensitivity of mammography. Dense breasts are associated with an increased risk for breast cancer.
- Full-field digital mammography appears to benefit young women and women with dense breasts.[2]
- Multiple studies show tomosynthesis appears to improve cancer detection and decrease call back rates. Of note, most studies used double the dose of radiation. The radiation dose can be minimized by using synthetic 2-D reconstruction.
- Current evidence does not support the routine use of breast scintigraphy (eg, sestamibi scan) as a screening procedure, but there is emerging evidence that breast scintigraphy may improve detection of early breast cancers among women with mammographically dense breasts.
- Current evidence does not support the routine use of thermography or ductal lavage as screening procedures.
- In high-risk settings based on current evidence and considering the FDA warning[3] (gadolinium-based contrast agents) we continue to recommend annual MRI in these select populations.

[1]Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs. mammography alone in women at elevated risk of breast cancer. JAMA 2008,299(18):2151-2163.

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

[3]FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm

BREAST SCREENING CONSIDERATIONS

RECOMMENDATIONS FOR BREAST MRI SCREENING AS AN ADJUNCT TO MAMMOGRAPHY [4,5] (FOR AGE TO BEGIN SCREENING EXCEPT WHERE NOTED BELOW: SEE BSCR-2)

Recommend Annual MRI Screening (Based on Evidence):

- BRCA mutation, commence at age 25-29 y
- First-degree relative of BRCA carrier, but untested: commence at age 25-29 y
- Lifetime risk 20% or greater, as defined by models that are largely dependent on family history
-

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

- Radiation to chest between age 10 and 30 years
- Li-Fraumeni syndrome and first-degree relatives
- Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
- >20% risk of breast cancer based on gene and/or risk level--ATM, CDH1, CHEK2, NF1, NBN, PALB2, PTEN, STK11, TP53

Consider MRI screening for LCIS and ALH/ADH based on emerging evidence if lifetime risk ≥20%

Insufficient Evidence to recommend for or Against MRI Screening:

- Lifetime risk 15%-20% as defined by models that are largely dependent on family history
- Heterogeneously or extremely dense breast on mammography
- Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)

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

- Women at <15% lifetime risk

[4]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.

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

RISK FACTORS USED IN THE MODIFIED GAIL MODEL, AGE ≥35 Years [1]

Current age

Age at menarche

Age at first live birth or nulliparity

Number of first-degree relatives with breast cancer

Number of previous benign breast biopsies[2]

Atypical hyperplasia in a previous breast biopsy

Race[3]

For calculations of risk, based on the modified Gail Model, see
http://www.cancer.gov/bcrisktool/Default.aspx

[1]For detailed information, see http://www.cancer.gov/bcrisktool/Default.aspx

[2]Needle biopsy counts for number of biopsies in the Gail Model.

[3]The current Gail Model may not accurately assess breast cancer risk in non-Caucasian, non-Asian, and non-African American women.

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. 2 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.

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 sugical 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 pther hand, the interpreter may choose not to describe such finding, 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 bengin 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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[2]Terminology in this table is reflective of the American College of Radiology (ACR). ACR-BI-RADS® --5th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas; BI-RADS. Reston VA. American College of Radiology, 2014. For more information, see www.acr.org
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MAMMOGRAPHIC ASSESSMENT CATEGORY DEFINITIONS [1,2]

BI-RADS® - MAMMOGRAPHY FINDINGS

Category 3: Probably Benign:

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

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

Three specific findings are validated as being probably benign (the noncalcified circumscribed solid mass, the focal asymmetry, and solitary group of punctate calcifications). All the previously cited studies emphasize the need to conduct a complete diagnostic imaging evaluation before making a probably benign (category 3) assessment; hence, it is recommended not to render such an assessment in interpreting a screening mammography examination. The practice of rendering category 3 assessments directly from screening examination also has been shown to result in adverse outcomes: 1) unnecessary follow-up of many lesions that could have been promptly assessed as benign; and 2) delayed diagnosis of a small number of cancers that otherwise may have been smaller in size and less likely to be advanced in stage. Also, all the previously cited studies exclude palpable lesions, so the use of a probably benign assessment for a palpable lesion is not supported by robust scientific data, although there are two single-institution studies that do report successful outcomes for palpable lesions. Finally, because evidence from previously cited studies indicates the need for biopsy rather than continued surveillance when a probably benign finding increases in size or extent, it is not prudent to render a category 3 assessment when a finding that otherwise meets "probably benign" imaging criteria is either new or has increased in size or extent.
While the vast majority of probably benign findings are managed with an initial short-interval follow-up (6-month) examination followed by additional examinations until long-term (2- or 3-year) stability is demonstrated, there may be occasions in which a biopsy is done instead (patient preference or overriding clinical concern).

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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 malignanacy and the floor for category 5 assessment is 95%, so category 4 assessments cover the wide range of likelihood of malignancy in between. Thus, almost all recommendations of breast interventional procedures will come from assessments made using this category. By subdividing category 4[3] into 4A, 4B, and 4C, as recommended in Guidance chapter and using the cut point indicated therein, it is hoped that patients and referring clinicians will more readily make informed decisions on the ultimate course of action.

Category 5: Highly Suggestive of Malignancy:

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

Category 6: Known Biopsy - Proven Malignancy:

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

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

[3]The new BI-RADS® cut points for the risk of malignancy are as follows: 4A (>2% – ≤10%), 4B (>10% – ≤50%), 4C (>50% – <95%).

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 4[3] into 4A, 4B, and 4C, it is hoped that patients and referring clinicians will more readily make informed decisions on the ultimate course of action. An example of separating the BI-RADS® assessment category from the management recommendation occurs when a simple cyst, correctly assessed as BI-RADS® 2, undergoes cyst aspiration for pain control.

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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%).

ULTRASOUND ASSESSMENT CATEGORY DEFINITIONS [1,2]

BI-RADS® - ULTRASOUND FINDINGS

Category 5: Highly Suggestive of Malignancy:

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

Category 6: Known Biopsy-Proven Malignancy:

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

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

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ACR Appropriateness Criteria®
Breast Imaging of Pregnant and Lactating Women

Variant 1: Breast cancer screening during lactation. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
Mammography screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant 2: Breast cancer screening during pregnancy. Age younger than 30 at high risk. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
Mammography screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant 3: Breast cancer screening during pregnancy. Age 30 to 39 years at elevated risk (intermediate or high risk). Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
Mammography screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant 4: Breast cancer screening during pregnancy. Age 40 years or older, any risk level. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
Mammography screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant 5: Pregnant women with a palpable breast mass. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	O
Digital breast tomosynthesis diagnostic	May Be Appropriate	☢☢
Mammography diagnostic	May Be Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢
Image-guided core biopsy breast	Usually Not Appropriate	Varies

Variant 6: Clinically suspicious nipple discharge during pregnancy. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
US breast	Usually Appropriate	O
Digital breast tomosynthesis diagnostic	Usually Appropriate	☢☢
Mammography diagnostic	Usually Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant 7: Breast cancer screening during pregnancy. Age 40 years or older, any risk level. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis diagnostic	Usually Appropriate	☢☢
Mammography diagnostic	Usually Appropriate	☢☢
US axilla	Usually Appropriate	O
US breast	Usually Not Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
Tc99-m sestamibi MBI	Usually Not Appropriate	☢☢☢

BREAST IMAGING OF PREGNANT AND LACTATING WOMEN

Expert Panel on Breast Imaging: Roberta M. diFlorio-Alexander, MD, MS[a] ; Priscilla J. Slanetz, MD, MPH[b] ; Linda Moy, MD[c] ; Paul Baron, MD[d] ; Aarati D. Didwania, MD[e] ; Samantha L. Heller, MD, PhD[f] ; Anna I. Holbrook, MD[g] ; Alana A. Lewin, MD[h] ; Ana P. Lourenco, MD[i] ; Tejas S. Mehta, MD, MPH[j] ; Bethany L. Niell, MD, PhD[k] ; Ashley R. Stuckey, MD[l] ; Daymen S. Tuscano, MDm; Nina S. Vincoff, MD[n] ; Susan P. Weinstein, MD[o] ; Mary S. Newell, MD.[p]

Summary of Literature Review

Introduction/Background

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy, throughout the first postpartum year, or during lactation [1-4]. With a reported incidence of 1 in 3,000 to 10,000 pregnancies, breast cancer is the most common invasive cancer diagnosed during pregnancy [5-10]. Representing up to 3% of all breast cancer diagnoses, PABC is increasing as more women delay child bearing into the fourth decade of life when the incidence of breast cancer is higher [7,10,11]. Breast imaging during pregnancy and lactation is challenging because of the unique physiologic and structural breast changes that increase the difficulty of clinical and radiological evaluation and the need to balance both maternal and fetal well-being.

Throughout pregnancy, there is an increase in the size and number of breast ducts and lobules, an increase in the fluid content of the breast, and involution of stromal adipose tissue [9,12]. After delivery, prolactin stimulates secretory changes and the lobular acini become distended with milk [9,13-15]. These physiologic changes lead to increased breast volume, firmness, and nodularity, thereby making the detection of palpable abnormalities on clinical examination more difficult. As a result, there is often a delay in the diagnosis of PABC, and women typically present with more advanced disease exhibiting larger tumors and a higher likelihood of axillary nodal disease compared to nonpregnant women of the same age [8,16].

There is ongoing controversy as to whether delayed diagnosis and young patient age account for the poor prognosis of PABC, or if there may be additional factors causing increased biologic aggressiveness of gestational breast cancer when matched for age and stage [17-19]. Significant vascular and stromal remodeling is necessary to support the expanded epithelium of pregnancy and lactation, and these changes in the breast microenvironment could potentially be leveraged by breast cancer cells, leading to an increase in biologic aggressiveness [2,18,20]. Despite the long-term decreased risk of breast cancer with pregnancy, there are some data to suggest that there may be a transient increased risk for breast cancer during pregnancy and lactation [6]. Some studies show that women with BRCA gene mutations are overrepresented in PABC, and pregnant and lactating women are more likely to have hormone-negative breast cancer than age-matched controls [7,18,21,22]. Although the underlying cause for these observations is not clear, they support the possibility that the tumor biology of PABC is more aggressive than non-PABC breast cancer in young women with equivalent stage and prognostic factors.

The most common presentation of PABC is a palpable mass. Therefore, imaging evaluation of a palpable lesion in a pregnant or lactating woman should not be delayed [7,20,23,24]. Less common presenting complaints include focal pain, diffuse breast enlargement, nipple discharge, and, rarely, unilateral milk rejection in which the infant rejects milk from the breast harboring cancer [7,24]. The imaging appearance of PABC is similar to breast cancer in nonpregnant patients. Because of the young age of these women and higher likelihood of triple negative breast cancer, PABC is more likely to demonstrate areas of necrosis [13,25]. In addition, PABC may have a falsely benign appearance presenting as a mass with relatively circumscribed margins, parallel orientation, and posterior acoustic enhancement [1,7].

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Although PABC most commonly presents as a palpable mass, greater than 80% of palpable masses that are biopsied in pregnant and breastfeeding women are benign [10,25]. Benign palpable masses may be due to enlargement of pre-existing benign masses, such as fibroadenomas and hamartomas, or they may represent masses unique to pregnancy and lactation, such as lactating adenomas and galactoceles [9,13]. When pre-existing lesions enlarge because of hormonal stimulation, they may appear atypical secondary to infarction or proliferative and lactational changes within the lesion [9,10,13]. These changes may lead to concerning imaging features and warrant further evaluation with biopsy. Some benign palpable masses are definitively benign on imaging evaluation (ie, cysts), whereas other masses may have benign imaging characteristics that allow for close followup.

Given the challenge of clinical examination in pregnant and lactating patients, diagnostic breast imaging, particularly breast ultrasound (US), plays a crucial role in characterizing the features of palpable lesions and in determining appropriate management. US has the highest sensitivity for the diagnosis of PABC [24-28]. Furthermore, because of the predominantly young patient age and the decreased sensitivity of mammography in the setting of dense breast tissue, breast US is the first-line imaging examination in pregnant and lactating patients. If breast US is negative, or if there are suspicious sonographic findings, additional imaging with
mammography or digital breast tomosynthesis (DBT) may be indicated.

Isolated bloody nipple discharge without associated palpable mass may occur in up to 20% of pregnant women and is most commonly due to benign causes. The proliferative epithelial changes and associated increased breast vascularity of pregnancy may result in unilateral or bilateral bloody nipple discharge that is considered physiologic and sometimes referred to as the "rusty pipe syndrome" [29,30]. This condition may occur during pregnancy or early lactation and is usually self-limited. However, persistent unilateral bloody nipple discharge may be secondary to infection, papilloma, or, less commonly, breast cancer. A review of limited available data from an older report suggests that in nonpregnant patients of similar age, up to 12% of cases of isolated bloody nipple discharge may be due to breast cancer [31,32]. Therefore, diagnostic imaging workup of persistent unilateral bloody nipple discharge is recommended in pregnant and lactating patients.

There is a limited role for advanced breast imaging techniques in pregnant women. The ACR does not recommend the intravenous (IV) administration of gadolinium during pregnancy [33]. The physiologic increased breast vascularity of pregnancy and lactation may limit the sensitivity of dynamic contrast-enhanced (DCE) breast MRI [12,33-35]. Biopsy should be recommended for any suspicious imaging findings, and patients should be informed regarding the possibility of milk fistula and increased risk of bleeding.

Breast cancer screening in lactating women has several important considerations, as outlined below. However, diagnostic breast imaging during lactation is the same as for nonlactating women. See the ACR Appropriateness Criteria® for "Palpable Breast Masses" [36], "Evaluation of Nipple Discharge" [32], and "Breast Cancer Screening" [37].

Discussion of Procedures by Variant

Variant 1: Breast cancer screening during lactation. Initial imaging.

There is limited evidence on breast cancer screening in lactating women. Because of the potential increased risk of breast cancer in this population, consider continued screening during lactation dependent upon the level of underlying risk and the expected duration of lactation

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Mammography and DBT

With the onset of lactation, mammographic density increases to variable degrees among patients because of the distention of lobules with milk. Sonographic evaluation of the distribution of glandular and adipose tissue during lactation has shown that up to half of the breast volume continues to consist of adipose tissue [14]. Nursing or pumping before mammography may decrease parenchymal density and thereby improve sensitivity of mammography in lactating patients [9,10,13,38]. There is no contraindication to performing mammography during lactation. There are limited data available concerning screen-detected PABC. In one recent study, 9 of 117 (7.7%) cancers in patients with PABC were subclinical, and 5 of these cases were detected only with screening mammography in high-risk women [7]. In another small study, 2 of 22 cases of PABC were detected on screening mammography [24]. Therefore, screening mammography may be of benefit in lactating women, in accordance with ACR Appropriateness Criteria® for "Breast Cancer Screening" [37], and breastfeeding or pumping should be encouraged prior to the examination to minimize breast density and optimize the sensitivity of screening mammography.

There are no studies specifically evaluating DBT in this patient population. The increased breast density seen in younger women and in the hormonally altered breasts of lactating women is more likely to mask small lesions. Therefore, this population may benefit from the ability of 3-D mammography to decrease the masking effect of dense breast tissue.

US Breast

There are no studies specifically evaluating hand-held or automated whole-breast US screening in women who are breastfeeding. Given the increased mammographic density during lactation, screening US could be considered as a supplemental screening option in lactating women at intermediate and high risk for breast cancer. It is, however, important to keep in mind that screening US may increase the false-positive rate and prompt additional biopsies with small additional risk of milk fistula in lactating women [39,40].

MRI Breast

The physiologic increased vascularity of lactation causes a marked increase in background parenchymal enhancement on breast DCE-MRI. Although this may limit the sensitivity for detecting small enhancing masses and nonmass enhancement, studies have shown that breast DCE-MRI can differentiate enhancing breast cancer from background parenchymal enhancement based on kinetics and morphology [19,34,35,38,41]. A study of 53 patients with known PABC demonstrated moderate or marked background parenchymal enhancement in 58% of patients. Despite increased background parenchymal enhancement, there was 98% sensitivity for detection of known PABC; however, it is unknown how many women were lactating at the time of the MRI [19].

There are scant data on MRI screening in lactating women. In one study, 4 breast cancers in 3 patients were detected on high-risk screening MRI [7]. It may be helpful to wait until 3 months after cessation of breastfeeding. However, if a woman plans to nurse for a long period, or is at very high risk for breast cancer, screening breast MRI during lactation may be considered [10]. The amount of gadolinium excreted in human breast milk over the first 24 hours after IV contrast administration is <1% of the permitted dose for neonates [42]. Up-to-date recommendations with regard to breastfeeding following IV administration of gadolinium are outlined in detail in the ACR Manual on Contrast Media [33]. Therefore, although not the initial imaging tool of choice, screening breast MRI is not contraindicated during lactation and may be considered in lactating women with a high lifetime risk of breast cancer. An informed decision should be made by the mother regarding continuation of breastfeeding after the examination [3,33,42].

Tc-99m Sestamibi MBI

There is no role for molecular breast imaging (MBI) in breast cancer screening during lactation. Variant 2: Breast cancer screening during pregnancy. Age younger than 30 at high risk. Initial imaging. Screening is not recommended for pregnant women at average or intermediate risk for breast cancer if younger than age 30. However, consider screening before age 30 for pregnant women at high risk for breast cancer. Criteria for high risk, and the age at which to begin screening in women at high risk, are discussed in the ACR Appropriateness Criteria® for "Breast Cancer Screening" [37].

Mammography and DBTV

Screening mammography can be performed in pregnant women at high risk. Mammography is not contraindicated during pregnancy, and the dose to the fetus is negligible. The fetal radiation dose from a 4-view mammogram is <0.03 mGy. No teratogenic effects have been demonstrated below 50 mGy [43]. The National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women [44]. Lead shielding should be utilized for pregnant patients undergoing mammographic screening. Screening mammography is not recommended for pregnant women who are at average or intermediate risk for breast cancer. However, in women who have a high risk of breast cancer, mammographic screening with lead shielding should be considered. There are no studies specifically evaluating DBT in this patient population. The increased breast density seen in younger women and in the hormonally altered breast of pregnant women is more likely to conceal small lesions. Therefore, this population may benefit from the ability of 3-D mammography to decrease the masking effect of dense breast tissue. Ductal and lobular hyperplasia, combined with increased water content and decreased stromal fat, may increase mammographic density throughout pregnancy. A small study has shown that the anticipated changes in breast density are less pronounced during pregnancy than during lactation, and that most pregnant patients had scattered ACR Appropriateness Criteria® 7 Breast Imaging of Pregnant and Lactating Women or heterogeneously dense fibroglandular tissue [45]. Many studies have shown that mammograms may be diagnostic in 74% to 100% of gravid pregnant women [7,24-28]. With current digital techniques and increased use of DBT, the ability to detect breast cancer with mammography in pregnant patients may improve. There are several studies that report screen-detected PABC in a small number of patients [7,24].

US Breast

Throughout pregnancy, there is progressive ductal and lobular hyperplasia as well as increased duct ectasia. These changes lead to prominent hypoechoic ducts and lobules with diffuse decreased breast echogenicity [9,10]. There are no studies available at this time evaluating the use of screening whole-breast US during pregnancy. Despite the physiologic changes that alter the sonographic appearance of the breasts during pregnancy, screening wholebreast US may be used as a supplemental screening modality in pregnant women younger than 30 at high risk for breast cancer. It is, however, important to keep in mind that screening US may increase the false-positive rate and prompt additional biopsies.

MRI Breast

It is well-established that IV gadolinium chelates cross the placenta and enter the fetal circulation. Although there are no reported adverse fetal effects due to IV gadolinium in the pregnant mother, there is the potential for the dissociation of free toxic gadolinium ion with limited data in this patient population. Guidelines regarding gadolinium administration during pregnancy are outlined in detail in the ACR Manual on Contrast Media [33]. Because of the concerns regarding gadolinium crossing the placenta and limited data regarding its safety in this setting, screening breast DCE-MRI is not recommended in pregnant women with any breast cancer risk profile.

Tc-99m Sestamibi MBI

There is no role for MBI in breast cancer screening during pregnancy. Variant 3: Breast cancer screening during pregnancy. Age 30 to 39 years at elevated risk (intermediate or high risk). Initial

imaging. Screening is not recommended for pregnant women who are at average risk for breast cancer if age 30 to 39 years. However, in pregnant women at high risk for breast cancer, breast cancer screening between the ages of 30 to 39 years may be appropriate. Pregnant women who are at intermediate risk for breast cancer may also benefit from screening before age 40. Criteria for intermediate and high risk, and the age at which to begin screening women at intermediate and high risk, are discussed in the ACR Appropriateness Criteria® for "Breast Cancer Screening" [37].

Mammography and DBT

Mammography is not contraindicated during pregnancy. The fetal radiation dose from a 4-view mammogram is <0.03 mGy. No teratogenic effects have been demonstrated below 50 mGy [43]. The National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women [44]. Lead shielding should be utilized for pregnant patients undergoing mammographic screening. There are no studies specifically evaluating DBT in this patient population. The increased breast density seen in younger women and in the hormonally altered breast of pregnant women is more likely to conceal small lesions. Therefore, this population may benefit from the ability of 3-D mammography to decrease the masking effect of dense breast tissue.

Ductal and lobular hyperplasia, combined with increased water content and decreased stromal fat, may increase mammographic density throughout pregnancy. A small study has shown that the anticipated changes in breast density are less pronounced during

pregnancy than during lactation, and that most pregnant patients had scattered or heterogeneously dense fibroglandular tissue [45]. Many studies have shown that mammograms may be diagnostic in 74% to 100% of pregnant women [7,24-28]. With current digital techniques and increased use of DBT, the ability to detect breast cancer with mammography in pregnant patients may improve. There are several studies that report screen-detected PABC in a small number of patients [7,24].

US Breast

Throughout pregnancy, there is progressive ductal and lobular hyperplasia as well as increased duct ectasia. These changes lead to prominent hypoechoic ducts and lobules with diffuse decreased breast echogenicity [9,10]. There are no studies available at this time evaluating the use of screening whole-breast US during pregnancy. Despite the physiologic changes that alter the sonographic appearance of the breasts during pregnancy, screening wholebreast US may be used as a supplemental screening modality in pregnant women between 30 and 39 years of age with a high risk of breast cancer. It is, however, important to keep in mind that screening US may increase the false-positive rate and prompt additional biopsies.

MRI Breast

It is well established that IV gadolinium chelates cross the placenta and enter the fetal circulation. Although there are no reported adverse fetal effects due to IV gadolinium in the pregnant mother, there is the potential for the dissociation of free toxic gadolinium ion with limited data in this patient population. Guidelines regarding gadolinium administration during pregnancy are outlined in detail in the ACR Manual on Contrast Media [33]. Because of the concerns regarding gadolinium crossing the placenta and limited data regarding its safety in this setting, screening breast DCE-MRI is not recommended in pregnant women with any breast cancer risk profile.

Tc-99m Sestamibi MBI

There is no role for MBI in breast cancer screening during pregnancy.Variant 4: Breast cancer screening during pregnancy. Age 40 years or older, any risk level. Initial imaging examination. Breast cancer screening during pregnancy is recommended for pregnant women age 40 or older who are at average risk of breast cancer as defined in the ACR Appropriateness Criteria® for "Breast Cancer Screening" [37].

Mammography and DBT

Mammography is not contraindicated during pregnancy. The fetal radiation dose from a 4-view mammogram is <0.03 mGy. No teratogenic effects have been demonstrated below 50 mGy [43]. The National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women [44]. Lead shielding should be utilized for pregnant patients undergoing mammographic screening. There are no studies specifically evaluating DBT in this patient population. The increased breast density seen in younger women and in the hormonally altered breast of pregnant women is more likely to conceal small lesions. Therefore, this population may benefit from the ability of 3-D mammography to decrease the masking effect of dense breast tissue.

Ductal and lobular hyperplasia, combined with increased water content and decreased stromal fat, may increase mammographic density throughout pregnancy. A small study has shown that the anticipated changes in breast density are less pronounced during pregnancy than during lactation, and that most pregnant patients had scattered or heterogeneously dense fibroglandular tissue [45]. Many studies have shown that mammograms may be diagnostic in 74% to 100% of pregnant women [7,24-28]. With current digital techniques and increased use of DBT, the ability to detect breast cancer with mammography in pregnant patients may improve. There are several studies that report screen-detected PABC in a small number of patients [7,24].

US Breast

Throughout pregnancy, there is progressive ductal and lobular hyperplasia as well as increased duct ectasia. These changes lead to prominent hypoechoic ducts and lobules with diffuse decreased breast echogenicity [9,10]. There are no studies available at this time evaluating the use of screening whole-breast US during pregnancy. Despite physiologic changes that alter the sonographic appearance of the breasts during pregnancy, screening wholebreast US may be used as a supplemental screening modality in pregnant women 40 and older, especially those at elevated risk. It is, however, important to keep in mind that screening US may increase the false-positive rate and prompt additional biopsies.

MRI Breast

It is well established that IV gadolinium chelates cross the placenta and enter the fetal circulation. Although there are no reported adverse fetal effects due to IV gadolinium in the pregnant mother, there is the potential for the dissociation of free toxic gadolinium ion with limited data in this patient population. Guidelines regarding gadolinium administration during pregnancy are outlined in detail in the ACR Manual on Contrast Media [33]. Because of the concerns regarding gadolinium crossing the placenta and limited data regarding its safety in this setting, screening breast DCE-MRI is not recommended in pregnant women with any breast cancer risk profile.

Tc-99m Sestamibi MBI

There is no role for MBI in breast cancer screening during pregnancy

Variant 5: Pregnant women with a palpable breast mass. Initial imaging.

The most common presentation of PABC is a palpable mass. Therefore imaging evaluation of a palpable lesion in a pregnant or lactating woman should not be delayed [7,20,23,24]. Given the challenge of clinical examination in pregnant and lactating patients, diagnostic breast imaging, particularly breast US, plays a crucial role in characterizing the features of palpable lesions and in determining appropriate management. US has the highest sensitivity for the diagnosis of PABC [24-28]. Furthermore, due to the predominantly young patient age and the decreased sensitivity of mammography in the setting of dense breast tissue, breast US is the first-line imaging examination in pregnant and lactating patients. If breast US is negative, or if there are suspicious sonographic findings, additional imaging with mammography or DBT may be indicated.

Mammography and DBT

Mammography has slightly decreased sensitivity compared to breast sonography in this clinical setting, ranging from 74% to 90% [7,24-27] in most studies. One recent study has reported 100% sensitivity of mammography that may in part be explained by use of full-field digital technique rather than film screen mammography [28]. The advanced stage of PABC may also contribute to the moderate sensitivity of diagnostic mammography given the physiologic increased breast density in these patients that may compromise mammography. Therefore, although diagnostic mammography is not recommended as the initial examination in patients with a palpable mass, there is a role for diagnostic mammography as an adjunct to US. If US does not show an etiology for the palpable mass, diagnostic mammography should be done to look for malignant calcifications or architectural distortion. If a suspicious finding is seen by US, mammography is also recommended to evaluate for additional suspicious findings, particularly microcalcifications that may be occult by US. Mammography is not contraindicated during pregnancy, and the dose to the fetus is negligible. The fetal radiation dose from a 4-view mammogram is <0.03 mGy, and no teratogenic effects have been demonstrated below 50 mGy [43]. The National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women [44]. There are no studies specifically evaluating DBT in this patient population. DBT may improve visualization of breast masses in pregnant women. The increased breast density seen in younger women and in the hormonally altered breast of pregnant women is more likely to conceal small lesions; therefore, this population may benefit from the ability of 3-D mammography to decrease the masking effect of dense breast tissue.

US Breast

PABC most commonly presents as a palpable mass, and breast US is recommended as the first-line imaging modality in pregnant and lactating women regardless of age [9,10,23,25,26,36,44]. Breast US can define benign etiologies for palpable masses that require no further evaluation, such as simple cysts or galactoceles. Breast US has the highest sensitivity for diagnosis of PABC in the setting of a palpable mass with 100% sensitivity reported in many studies [24-28,46,47]. Several authors have cautioned that PABC may have benign features, including parallel orientation, circumscribed margins, and posterior acoustic enhancement [7,24,26].

MRI Breast

It is well established that IV gadolinium chelates cross the placenta and enter the fetal circulation. Although there are no reported adverse fetal effects due to IV gadolinium in the pregnant mother, there is the potential for the dissociation of free toxic gadolinium ion with limited data in this patient population. Guidelines regarding gadolinium administration during pregnancy are outlined in detail in the ACR Manual on Contrast Media [33]. There is no role for MRI as the initial imaging evaluation in the diagnostic workup of palpable lumps in pregnant patients.

Tc-99m Sestamibi MBI

There is no role for MBI as the initial imaging evaluation in the diagnostic workup of palpable lumps in pregnant patients.

Image-Guided Core Biopsy

Image-guided core biopsy should not be the initial evaluation of a palpable mass as postbiopsy changes may obscure lesion visualization or negatively impact image interpretation. If initial diagnostic imaging evaluation demonstrates a suspicious mass, image-guided core biopsy should be obtained. Consent for low risk of milk fistula and increased risk of bleeding is recommended for pregnant and lactating women. If a palpable mass is ACR Appropriateness Criteria® 10 Breast Imaging of Pregnant and Lactating Women clinically suspicious and initial imaging does not demonstrate etiology for a clinically suspicious mass, non– image-guided biopsy should be performed via palpation.

Image-Guided Fine-Needle Aspiration

Fine-needle aspiration should not be the initial evaluation of a palpable mass as postaspiration changes may obscure lesion visualization or negatively impact image interpretation. If initial diagnostic imaging evaluation demonstrates a suspicious mass, image-guided core biopsy should be obtained. If initial imaging does not demonstrate etiology for a clinically suspicious mass, non–image-guided biopsy or fine-needle aspiration should be performed via palpation.

Variant 6: Clinically suspicious nipple discharge during pregnancy. Initial imaging.

Isolated bloody nipple discharge without associated palpable mass may occur in up to 20% of pregnant women and is most commonly due to benign causes. The proliferative epithelial changes and associated increased breast vascularity of pregnancy may result in unilateral or bilateral bloody nipple discharge that is considered physiologic and sometimes referred to as the "rusty pipe syndrome" [29,30]. This condition may occur during pregnancy or early lactation and is usually self-limited. However, persistent unilateral bloody nipple discharge may be secondary to infection, papilloma, or, less commonly, breast cancer. A review of limited available data from an older report suggests that in nongestational patients of similar age, up to 12% of cases of isolated bloody nipple discharge may be due to breast cancer [31,32]. The risk of malignancy in women younger than age 40 with isolated pathologic nipple discharge is approximately 3%. Therefore, although there are very little data on pathologic nipple discharge in pregnant women, diagnostic imaging workup of pathologic bloody nipple discharge is recommended in pregnant patients [31,32].

Mammography and DBT

There is wide variation in degree of mammographic density during pregnancy, and many studies have shown that mammograms have a sensitivity of 74% to 100% in the diagnostic setting [25,28]. This is particularly true for the detection of suspicious calcifications that may be detected despite mammographically dense breast tissue and that may be sonographically occult [7,24]. Mammography is not contraindicated during pregnancy, and the dose to the fetus is negligible. The fetal radiation dose from a 4-view mammogram is <0.03 mGy, and no teratogenic effects have been demonstrated below 50 mGy [43]. The National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women [44]. Therefore, diagnostic mammograms with retroareolar magnification views may be of benefit as the initial examination in pregnant women with persistent nipple discharge or as an adjunct to diagnostic breast US.

US Breast

Although there are no studies specifically evaluating diagnostic US for nipple discharge in pregnant women, retroareolar sonographic evaluation should be the first-line imaging examination to look for papilloma or other breast masses as the cause of pathologic nipple discharge regardless of patient age. The peripheral compression technique, 2-handed compression technique, and the rolled nipple technique described by Stavros may increase the ability of breast US to detect the cause for bloody nipple discharge [48].

MRI Breast

It is well established that IV gadolinium chelates cross the placenta and enter the fetal circulation. Although there are no reported adverse fetal effects due to IV gadolinium in the pregnant mother, there is the potential for the dissociation of free toxic gadolinium ion with limited data in this patient population. Guidelines regarding gadolinium administration during pregnancy are outlined in detail in the ACR Manual on Contrast Media [33]. There is no role for MRI as the initial imaging evaluation in nipple discharge during pregnancy.

Tc-99m Sestamibi MBI

There is no role for MBI as the initial imaging evaluation in nipple discharge during pregnancy. Variant 7: Locoregional staging of newly diagnosed breast cancer during pregnancy. Initial

imaging. Chemotherapy may be used to treat breast cancer after the first trimester of pregnancy [21,49]. Accurate staging is therefore important in order to determine optimal therapy while limiting harm to the fetus. The risk-to-benefit ratio will vary from patient to patient depending on many factors, including gestational age at the time of diagnosis and personal perspectives regarding pregnancy interruption. Locoregional staging is obtained to identify primary tumor size, regional node status, extent of disease, and additional foci of malignancy in the ipsilateral or contralateral breast. This information optimizes definitive local treatment and is used to determine the need for ACR Appropriateness Criteria® 11 Breast Imaging of Pregnant and Lactating Women systemic staging to evaluate for distant metastases. Locoregional staging in pregnant patients is discussed below. However, decisions regarding systemic breast cancer staging in pregnant women are best addressed via patientcentered multidisciplinary tumor boards in order to provide specialized care in this complex clinical scenario [11,50].

Mammography and DBT

Mammography is not contraindicated during pregnancy, and the dose to the fetus is negligible. The fetal radiation dose from a 4-view mammogram is <0.03 mGy, and no teratogenic effects have been demonstrated below 50 mGy [43]. The National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women [44]. Complete mammographic evaluation is recommended as a component of locoregional staging in pregnant women with newly diagnosed breast cancer. Microcalcifications due to ductal carcinoma in situ adjacent to the index cancer may not be seen by US. Therefore, mammography is recommended for evaluating extent of disease. Multifocal or multicentric disease presenting as microcalcifications due to sonographically occult ductal carcinoma in situ may similarly be identified with adjunctive mammographic breast cancer staging. These findings would affect surgical management and aid in obtaining clear margins and improved patient outcomes. There are no studies specifically evaluating DBT during pregnancy. DBT may improve visualization of breast masses in pregnant women. The increased breast density seen in younger women and in the hormonally altered breast of pregnant women is more likely to conceal small masses because of the masking effect of dense breast tissue.

US Breast

Whole-breast US, including US of the nodal basins, is a staging modality with no known adverse effects on the fetus. In a single study by Yang et al [51], preoperative breast US was performed in 23 pregnant patients for the purpose of evaluating response to neoadjuvant chemotherapy during pregnancy. In this small study, 15 of 18 axillary metastases were correctly diagnosed with sonographic staging of the axilla, and all breast masses were identified by breast US. Whole-breast US staging has been evaluated in nonpregnant patients with reported incremental cancer detection rates similar to those of staging breast MRI [52]. Several additional studies in nonpregnant women support the use of whole-breast US staging [25,53,54]. However, these studies were performed by breast radiologists with extensive experience in sonographic locoregional staging of breast cancer, and it is not clear to what degree these results would be reproducible in other centers. Therefore, although staging of the axilla via US is recommended, there is no evidence to support whole-breast US for locoregional staging in pregnant patients at this time. US Axilla Sonographic evaluation of the axilla is often performed to stage pregnant patients who are diagnosed with breast cancer. In a study of 23 pregnant patients undergoing neoadjuvant chemotherapy for newly diagnosed breast cancer, 15 of 18 axillary metastases were correctly diagnosed by sonographic evaluation of the axilla [51].

MRI Breast

It is well established that IV gadolinium chelates cross the placenta and enter the fetal circulation. Although there are no reported adverse fetal effects due to IV gadolinium in the pregnant mother, there is the potential for the dissociation of free toxic gadolinium ion with limited data in this patient population. Guidelines regarding gadolinium administration during pregnancy are outlined in detail in the ACR Manual on Contrast Media [33]. Because of the concerns regarding gadolinium crossing the placenta and limited data regarding its safety in this setting, breast DCE-MRI is therefore not recommended in pregnant women. However, immediately following delivery or pregnancy termination, breast MRI is recommended for locoregional staging. A small series evaluating PABC on breast MRI showed that 23% of patients had pathologically proven greater extent of disease than was identified with mammography and breast US. This study showed variable background parenchymal enhancement with 58% of patients demonstrating moderate or marked enhancement. Despite increased background parenchymal enhancement, this study showed 98% sensitivity for PABC [19].

Tc-99m Sestamibi MBI

There is no role for MBI as the initial imaging evaluation in locoregional breast cancer staging during pregnancy.

Discussion of Procedures by Variant

Summary of Recommendations

- **Variant 1**: For lactating women, DBT or mammography is indicated with minor modifications to address increased mammographic density, increased breast vascularity, and duration of lactation.
- **Variant 2**: Breast cancer screening is not contraindicated during pregnancy. For women younger than age 30 at high risk for breast cancer, DBT or mammography is appropriate.
- **Variant 3**: Breast cancer screening is not contraindicated during pregnancy. For women between 30 and 39 years of age atelevated risk for breast cancer (intermediate or high risk), DBT or mammography is appropriate.
- **Variant 4**: Breast cancer screening is not contraindicated during pregnancy. For women age 40 and older, screening DBT or mammography is appropriate.
- **Variant 5**: Pregnant women with a palpable mass should be evaluated initially by US. If US is suspicious for malignancy or does not show the etiology for the lump, diagnostic mammography is recommended.
- **Variant 6**: Pregnant women with pathologic nipple discharge should be initially evaluated by US. DBT or diagnostic mammography with retroareolar magnification views may be obtained as a complementary initial imaging examination to look for calcifications that may be sonographically occult or may be obtained if US does not show the etiology for nipple discharge.
- **Variant 7**: Pregnant women with newly diagnosed breast cancer should undergo locoregional staging via both diagnostic mammography and US of the axilla.

Summary of Evidence

Of the 59 references cited in the ACR Appropriateness Criteria® Breast Imaging of Pregnant and Lactating Women document, 1 is categorized as a therapeutic reference that may have design limitations. Additionally, 56 references are categorized as diagnostic references including 4 good-quality studies and 12 quality studies that may have design limitations. There are 40 references that may not be useful as primary evidence. There is 1 reference that is a meta-analysis study. The 59 references cited in the ACR Appropriateness Criteria® Breast Imaging of Pregnant and Lactating Women document were published from 1990-2017.

Although there are references that report on studies with design limitations, 4 good-quality studies provide good evidence.

Safety Considerations in Pregnant Patients Imaging of the pregnant patient

can be challenging, particularly with respect to minimizing radiation exposure and risk. For further information and guidance, see the following ACR documents:

- ACR–SPR Practice Parameter for the Safe and Optimal Performance of Fetal Magnetic Resonance Imaging (MRI) [55]
- ACR-SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation [56]
- ACR-ACOG-AIUM-SRU Practice Parameter for the Performance of Obstetrical Ultrasound [57]
- ACR Manual on Contrast Media [33]
- ACR Guidance Document for MR Safe Practices [58]

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	8 ,7, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	5 ,4, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benef it ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	2 ,1, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [59].

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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