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- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

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Evaluation by Primary Care of Patient with Symptoms of Potential Breast Disease

1. Patient is seen by primary care physician because of a breast disease concern

2. Perform history and physical exam for breast-related symptoms and assess risk factors

3. Does patient have a palpable mass?
   - yes → 4. See Algorithm I, "Evaluation of Breast Mass"
   - no → 5. Does patient have spontaneous nipple discharge?
     - yes → 6. See Algorithm II, "Evaluation of the Breast for Spontaneous Nipple Discharge"
     - no → 7. Does patient have breast pain?
       - yes → 8. See Algorithm III, "Evaluation of Breast Pain"
       - no → 9. Is screening mammogram due?
         - yes → 10. Screening mammogram
         - no → 11. Abnormal mammogram?
           - yes → 12. Complete all radiologic recommendations
           - no → 13. Reassure patient and inform of next screening date
I. Evaluation of Breast Mass

14 Patient presents with palpable breast mass

15 Is there a dominant mass?
   A no
   B yes

   18 Perform diagnostic mammogram and/or ultrasound if patient > 30; ultrasound if patient < 30
   A

16 Breast imaging abnormal?
   A no
   B yes

   17 Negative imaging
   18 Uncomplicated (simple) cyst
   19 Solid lesion or complex cyst
   20 Refer to surgeon
   21 Consider aspiration if symptomatic or refer to the appropriate consultant

23 Residual mass or bloody aspirate?
   A yes
   B no

   22 See Algorithm V, "Image-Directed Core Needle Biopsy"

24 Follow-up clinical breast exam in 4-6 weeks at discretion of clinician

25 Refer to Algorithm IV, "Radiologic Evaluation of the Breast"

26 Follow-up clinical breast exam in 6-12 weeks at discretion of clinician

27 Residual mass?
   A yes
   B no

28 Inform patient of next screening date

29 Refer to radiology or surgery

A = Annotation
II. Evaluation of the Breast for Spontaneous Nipple Discharge

Patient presents with spontaneous nipple discharge

Assess discharge appearance

Clear or bloody discharge

Perform mammogram/ultrasound/ductography/MRI ductography

Refer to surgeon (+/- ductography/MRI ductography)

Follow-up visit scheduled at the discretion of the treating clinician

Milky, yellow, brown, green, gray discharge

Milky

Hormonal evaluation

Observe/reassure patient

Colored

A = Annotation

A = Annotation
III. Evaluation of Breast Pain

43 Patient presents with breast pain

44 Mammogram and/or ultrasound at the discretion of the clinician

45 Abnormal imaging?
   yes → 46 Refer to Algorithm IV, "Radiologic Evaluation of the Breast"
   no → 47 Quantitative pain assessment

47 Quantitative pain assessment

48 Pain requires intervention?
   yes → 49 Initiate non-pharmacologic and/or pharmacologic intervention(s)
   no → 50 Inform patient of next screening date
IV. Radiologic Evaluation of the Breast

- Abnormal screening or diagnostic mammogram
- Presence of: Solid mass? Abnormal microcalcifications? Architectural distortion?
  - yes: Additional mammographic studies and/or ultrasound if needed
  - no: Repeat mammogram and/or ultrasound at 6-month intervals for 1-2 years

- Abnormality present but appears to be probably benign?
  - yes: Repeat mammogram and/or ultrasound at 6-month intervals for 1-2 years
  - no: Progression?
    - yes: Report to ordering provider
    - no: Increased risk?
      - yes: Consider MRI
      - no: Mass
        - yes: Calcification suspicious for cancer
          - yes: See Algorithm V, "Image-Directed Core Needle Biopsy" and/or Algorithm VI, "Surgical Evaluation of the Breast"
          - no: Ultrasound (if not already performed)

- Non-palpable solid mass?
  - yes: Fits benign criteria?
    - yes: Aspirate and perform single-view mammogram
    - no: Residual mass?
      - yes: Aspirate and perform single-view mammogram
      - no: Findings abnormal?
        - yes: Return to screening mammography
        - no: Report to ordering provider

- Indications for aspiration?
  - yes: Aspirate and perform single-view mammogram
  - no: Findings abnormal?
    - yes: Return to screening mammography
    - no: Report to ordering provider
V. Image-Directed Core Needle Biopsy

1. Patient referred for image-directed biopsy
   - Yes: Definitive therapy
   - No: Surgical consult

2. Cancer?
   - Yes: Definitive therapy
   - No: Rebiopsy by core or open biopsy

3. Lobular neoplasia (atypical lobular hyperplasia, lobular carcinoma in situ) atypical ductal hyperplasia, phylloides tumor, papillary lesions?
   - Yes: Surgical consult
   - No: Rebiopsy by core or open biopsy

4. Pathology and radiology conclusions concordant?
   - Yes: Mammogram and/or ultrasound in 6-12 months
   - No: Open biopsy or repeat image-guided core needle biopsy

5. Is mass benign fibroadenoma?
   - Yes: Inform patient of next screening date
   - No: Open biopsy or repeat image-guided core needle biopsy

6. Mammogram and/or ultrasound in 6-12 months for 1-2 years

7. Stable?
   - Yes: Inform patient of next screening date
   - No: Open biopsy or repeat image-guided core needle biopsy
VI. Surgical Evaluation of the Breast

Patient referred to surgeon for evaluation

- Palpable mass
- Spontaneous nipple discharge
- Breast pain
- Abnormal mammogram, ultrasound or MRI

Consider imaging prior to aspiration

- Aspirate mass if symptomatic

Suspicious solid mass? Abnormal microcalcifications? Progressive changes? Architectural distortion?

- yes
  - Image-directed biopsy
  - Definitive therapy
    - Lobular neoplasia (atypical lobular hyperplasia, lobular carcinoma in situ) papillary lesions
  - Cancer

- no
  - Re-examine in 4-6 weeks

- Residual mass or bloody aspirate?
  - yes
    - Return in 6 months for breast examination and imaging
  - no
    - Image-directed or open biopsy
      - Does mass recur?
        - yes
          - Open biopsy
          - Consider open biopsy
          - Definitive therapy
          - Progression
          - Stable, benign or regression
        - no
          - Inform patient of next screening date
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Work Group Leader
Michael Nelson, MD
Radiology, University of MN Physicians

Work Group Members
Family Practice
Tara Cole, DO
Fairview Health Services
Ann Francesca Valerio, MD
Marshfield Clinic

Internal Medicine
Deepi Pandita, MD
Park Nicollet Health Services

Radiology
Mary Lechner, MD
Center for Diagnostic Imaging
Joseph Tashjian, MD
St. Paul Radiology

Surgery
Judy Boughey, MD
Mayo Clinic
Audrey Park-Skinner, MD
St. Mary's/Duluth Clinic Health System
Todd Morris, MD
HealthPartners Medical Group and Regions Hospital
Omer Sanan, MD
Aspen Medical Group

Nursing
Barbara Maclin, RN, OC
HealthPartners Medical Group and Regions Hospital
Lisa Starr, CNP
St. Mary's/Duluth Clinic Health System

Facilitators
Sylvia Robinson, BSN, MBA
ICSI
Linda Setterlund, MA, CPHQ
ICSI

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Foreword

Scope and Target Population

This guideline applies to all patients who have a breast concern or abnormality.

Clinical Highlights and Recommendations

- It is imperative that communications between the radiologic and surgical consultants and the primary care provider are thorough and consistent. (*Algorithm I, Annotation #13*)
- A bloody tap or a persistent mass following aspiration of a palpable dominant mass should be referred to a surgeon or radiologist for additional workup regardless of negative imaging. (*Algorithm I, Annotation #23; Aim #2*)
- Patients with a spontaneous bloody or watery discharge should be referred to a radiologist for imaging studies and a surgeon if appropriate. (*Annotations #35, 36; Aim #3*)
- The risk of cancer with a negative evaluation for breast pain is less than 1%. (*Algorithm III, Annotation #49*)
- Any questionable abnormal pathologic findings from image-directed biopsy requires a surgical consultation and possible open biopsy. (*Algorithm V, Annotation #80; Aim #4*)

Priority Aims

1. Reduce the length of time between first knowledge of a breast abnormality and diagnostic resolution.
2. Ensure that a bloody tap or a persistent mass following aspiration of a palpable dominant mass is referred to a surgeon regardless of negative imaging.
3. Ensure that patients with spontaneous bloody or watery discharge have a mammogram (with or without an ultrasound) and are referred to a surgeon or radiologist.
4. Ensure that needle biopsies demonstrating abnormal (any questionable or pathologic findings that do not correlate with imaging pathologic findings) are followed by performance of an open biopsy.
5. Ensure that all women with a breast concern that is indeterminate will have a follow-up clinical assessment within two to three months.
Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Primary Care, Radiology and Surgery:
   Establish a communication plan to include all providers involved in the patient's treatment plan:
   • Patients undergoing biopsy should have results reported to the radiologist and/or surgeon performing the procedure, as well as the primary care provider.

2. Primary Care:
   Establish a system for education of all female patients regarding self breast examination and age-appropriate mammographic screening intervals.
   Develop a system for timely assessment of palpable breast masses including necessary imaging studies, follow-up, and referral to radiology or surgery for biopsy.

3. Radiology:
   Establish a process that ensures that abnormalities of the breast are accurately identified and sorted, and that all appropriate radiologic imaging studies necessary to the evaluation process are efficiently completed.

4. Surgery:
   Establish a process for timely completion of evaluation of breast lesions and provide additional surgical breast consultation as needed.

5. Documentation:
   Develop a system to document time frame from receipt of pathology to patient information.
   • Telephone call documentation

Related ICSI Scientific Documents

Guidelines

• Preventive Services for Adults
• Assessment and Management of Chronic Pain
Disclosure of Potential Conflict of Interest

ICSI has adopted a policy of transparency, disclosing potential conflict and competing interests of all individuals who participate in the development, revision and approval of ICSI documents (guidelines, order sets and protocols). This applies to all work groups (guidelines, order sets and protocols) and committees (Committee on Evidence-Based Practice, Cardiovascular Steering Committee, Women's Health Steering Committee, Preventive & Health Maintenance Steering Committee and Respiratory Steering Committee).

Participants must disclose any potential conflict and competing interests they or their dependents (spouse, dependent children, or others claimed as dependents) may have with any organization with commercial, proprietary, or political interests relevant to the topics covered by ICSI documents. Such disclosures will be shared with all individuals who prepare, review and approve ICSI documents.

Mary Lechner, MD, had received speaker's fees from Dilon Technologies in 2009.

No other work group members have potential conflicts of interest to disclose.

Introduction to ICSI Document Development

This document was developed and/or revised by a multidisciplinary work group utilizing a defined process for literature search and review, document development and revision, as well as obtaining input from and responding to ICSI members.


Evidence Grading System

A. Primary Reports of New Data Collection:
   - Class A: Randomized, controlled trial
   - Class B: Cohort study
   - Class C: Non-randomized trial with concurrent or historical controls
     - Case-control study
     - Study of sensitivity and specificity of a diagnostic test
     - Population-based descriptive study
   - Class D: Cross-sectional study
     - Case series
     - Case report

B. Reports that Synthesize or Reflect Upon Collections of Primary Reports:
   - Class M: Meta-analysis
     - Systematic review
     - Decision analysis
     - Cost-effectiveness analysis
   - Class R: Consensus statement
     - Consensus report
     - Narrative review
   - Class X: Medical opinion

Citations are listed in the guideline utilizing the format of (Author, YYYY [report class]). A full explanation of ICSI’s Evidence Grading System can be found at http://www.icsi.org.
Algorithm Annotations

Evaluation by Primary Care of Patient with Symptoms of Potential Breast Disease

2. Perform History and Physical Exam for Breast-Related Symptoms and Assess Risk Factors

See also Annotations #32, "Patient Presents with Spontaneous Nipple Discharge," and #43, "Patient Presents with Breast Pain," for specific symptom-related history and physical.

Guidelines for primary care evaluation are initiated with a history aimed at uncovering and characterizing any breast-related symptoms. Likewise, a risk assessment should also be undertaken for identified risk factors: personal history of any breast cancer, personal history of ductal hyperplasia with atypia on previous breast biopsies, or family history of breast cancer in first-degree relatives. A high-risk patient would be one with a mother, sister or daughter who had breast or ovarian cancer before age 50, or a history of prior radiation before age 30, or is a carrier of mutated breast cancer genes (Smith, 2003 [R]). She should be referred for genetic counseling and consider testing.

A physical examination should include inspection of the breast for any evidence of ulceration or contour changes. This includes examining the nipple for Paget's disease, and the presence of breast nodule(s), nipple disease, evidence of infection and/or spontaneous discharge. Palpation should be performed both in the upright and supine position to determine the presence of a palpable mass (Barton, 1999 [C]). Abnormalities detected during a clinical breast examination – such as masses or nodules, nipple discharge or inflammatory changes – require thorough evaluation and prompt treatment.

9. Is Screening Mammogram Due?

Following completion of a physical examination in which no palpable mass is identified, a routine screening mammogram should be obtained if one has not been done within the recommended interval.

Refer to the ICSI Preventive Services for Adults guideline for mammography screening intervals.

10. Screening Mammogram

Regular mammographic screening has been shown to reduce mortality in breast cancer. The results of the mammogram are provided to the primary care physician for reporting to the patient (Fletcher, 2003 [R]; Jonsson, 2000 [C]; Tabar, 2001 [A]).

12. Complete All Radiologic Recommendations

Should any abnormality be uncovered, it will be the responsibility of the radiologist to complete any additional imaging studies required for the complete radiographic characterization of the lesion. The radiologist should make certain that all recommendations including additional views, follow-up films, ultrasounds, etc., have been completed prior to referral to surgery. However, it is important that the provider ordering the mammogram review the results of these studies to fully understand the impression of the radiologist, and to assure that all recommendations by the radiologist have been completed within the department of radiology. Should the recommendation be made by radiology that a surgical consultation is warranted, it will be the responsibility of the primary care provider to establish this referral.

See Algorithm IV, "Radiologic Evaluation of the Breast."
13. Reassure Patient and Inform of Next Screening Date

Refer to the ICSI Preventive Services for Adults guideline for recommended mammography screening intervals.

I. Evaluation of Breast Mass Algorithm Annotations

15. Is there a Dominant Mass?

A dominant mass is a palpable finding that is discrete, solid and clearly different than the surrounding parenchyma. Should a palpable mass be identified, it should be characterized as to whether it represents a dominant (i.e., discrete) mass that requires immediate evaluation. Should physical examination demonstrate a palpable mass that is not clearly discrete and dominant (indeterminant), its size, location and character should be documented in anticipation of follow-up examination (Pruthi, 2001 [R]).

16. Perform Diagnostic Mammogram and/or Ultrasound If Patient > 30; Ultrasound If Patient < 30)

Prior to the referral, a mammogram should be obtained. Patients under the age of 30 should receive an ultrasound. For women under age 50, digital mammography is preferable for dense breast tissue (Pisano, 2005 [C]). Also see Annotation #51, "Abnormal Screening or Diagnostic Mammogram."

21. Consider Aspiration If Symptomatic or Refer to the Appropriate Consultant

Key Point:

- The importance of communication between the radiologic and surgical consultants and the primary care provider cannot be overstated. Patients undergoing biopsy should have results reported to both the radiologist or surgeon performing the biopsy and to the primary care provider. More importantly, patients who do not require biopsy following radiologic or surgical consultation should be returned to the routine screening process. This process is under the supervision of the primary care provider. Therefore, it is absolutely necessary for the primary care provider to know when the patient reenters the routine screening population. In the event that new symptoms arise or occur during the screening interval, the patient should be evaluated by the primary care provider using the primary care evaluation process of this guideline.

Aspiration of an uncomplicated (simple) cyst (i.e., absence of internal echoes, posterior enhancement, smooth border, imperceptible wall, thin margin shadows, and width greater than height) is only necessary if the cyst is symptomatic and may be performed by the primary care provider or by the appropriate consultant (radiologist, surgeon). A successful aspirate would yield a non-bloody fluid with complete resolution of the dominant mass. The breast skin is prepped with alcohol. Then, with the lesion immobilized by the non-operating hand, an 18-25 gauge needle mounted on a 10 cc syringe is directed to the central portion of the mass for a single attempt at aspiration. If the lesion is a simple cyst, the mass should completely resolve.

Cyst fluid should be examined cytologically if it is bloody or unusually tenacious. Typical watery green fluid may be discarded.
For recommendations regarding appropriate further workup and possible biopsy, refer to the following algorithms in this guideline:

- Algorithm IV. Radiologic Evaluation of the Breast
- Algorithm V. Image-Directed Core Needle Biopsy
- Algorithm VI. Surgical Evaluation of the Breast

**23. Residual Mass or Bloody Aspirate?**

Should the mass remain following the attempt at aspiration or should a bloody aspirate be obtained during the process, the presence of a malignancy cannot be ruled out. Patients with a residual mass or a bloody aspirate should proceed to image-directed core biopsy or surgical consult.

Bloody aspirate should be considered for cytology.

*(Schnitt, 1996 [R]; Silverstein, 2009 [R]*)

**24. Follow-up Clinical Breast Exam in 4-6 Weeks at Discretion of Clinician**

If no residual mass or blood aspirate remains, a repeat examination should be performed in 4-6 weeks at the discretion of clinician. The optimum time for this exam is after one menstrual cycle.

**28. Residual Mass?**

Persisting palpable masses not resolving in one month and all recurring cystic masses should be referred to radiology for further evaluation. If subsequent ultrasound is unable to confirm the presence of a benign cystic lesion, or if the lesion is worrisome to the patient, surgical consultation is indicated.

**29. Inform Patient of Next Screening Date**

If no mass is apparent at the time of this examination, the patient should be informed of the appropriate date of her next routine screening evaluation.

Refer to the ICSI Preventive Services for Adults guideline for mammography screening intervals.

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**II. Evaluation of the Breast for Spontaneous Nipple Discharge**

**Algorithm Annotations**

**32. Patient Presents with Spontaneous Nipple Discharge**

Guidelines for primary care evaluation of patient presenting with complaint of spontaneous nipple discharge are initiated with a history aimed at uncovering and characterizing any breast-related symptoms, including whether discharge has been spontaneous, persistent, unilateral vs bilateral, single or multiple ducts, its relation to menses, pregnancy, exercise, trauma, medications and/or thyroid disorders.

The site around the nipple should be examined for discharge upon pressure and for a mass. Hemocult test for blood may also be administered.

33. Assess Discharge Appearance

*Pathologic* discharges are spontaneous, may be associated with a mass, and are usually bloody, blood-containing or sometimes watery (clear). They are usually unilateral, involve a single duct, and are more worrisome in patients greater than 50 years old.

*Physiologic* discharges usually are bilateral, involve multiple ducts, are multicolored or milky, sticky and those that are stimulated rather than spontaneous.

(Harris, 2009 [R])

34. Clear or Bloody Discharge

Bloody or, less commonly, clear watery discharge raises the possibility of cancer, although the most common causes of hemoccult-positive discharges are benign. The most common causes of bloody nipple discharge are intraductal papilloma (45%), duct ectasia (36%), carcinoma (8%-15%), and infection and other causes (5%-10%).

Bloody discharge needs further evaluation to determine the etiology.

(Bauer, 1998 [D]; Schnitt, 1996 [R]; Winchester, 1996 [R])

35. Perform Mammogram/Ultrasound/Ductography/MRI Ductography

A mammogram and ultrasound should be obtained. An ultrasound may be helpful to locate an intraductal nodule or duct ectasia. Ductography and/or MRI ductography may be useful as an adjunct to the ultrasound to further evaluate for a nodule, cystic disease or duct ectasia. A patient with an abnormal mammogram or ultrasound should be further evaluated within the department of radiology to best characterize the lesion, and then be referred to surgery if appropriate. Make certain that all recommendations for additional views, ultrasound examinations, and follow-up studies have been obtained prior to referral to surgery. A ductogram may be completed as part of the radiologic workup.

(Winchester, 1996 [R])

36. Refer to Surgeon (+/- Ductography/MRI Ductography)

Most pathologic nipple discharges should be treated with duct excision. The use of ductography and/or MRI ductography is dependent on the decision of the surgeon and radiologist.

(Dennis, 2000 [D]; Kenney, 2003 [R]; Klein, 2002 [R])

37. Milky, Yellow, Brown, Green, Gray Discharge

The appearance of the fluid generally correlates with the cause. Yellow, brown, green or gray fluid is associated with fibrocystic change in most patients. Purulent discharge can result from duct ectasia or partial duct obstruction.

39. Hormonal Evaluation

Prolactin and TSH levels are obtained to determine an endocrinologic basis for the nipple discharge. A prolactinoma typically causes a milky or clear discharge bilaterally (Schnitt, 1996 [R]; Winchester, 1996 [R]).

Assay should be performed for prolactin and TSH as both of these pituitary hormones may induce galactorrhea, may have a reversible cause, and may likewise reflect further underlying pathology (e.g., pituitary adenoma, hypothyroidism, etc.) (Schnitt, 1996 [R]; Winchester, 1996 [R]).
42. Follow-Up Visit Scheduled at the Discretion of the Treating Clinician

If the mammogram and the endocrinologic screening studies are normal, the patient should schedule a follow-up visit at the discretion of the responsible clinician.

If the evaluation at the time of that follow-up visit fails to reveal any palpable or visible abnormalities, the patient should be returned to the routine screening process.

III. Evaluation of Breast Pain Algorithm Annotations

43. Patient Presents with Breast Pain

Key Points:

- The information gathered should include location and severity of pain, relationship to menstrual cycle or physical activities and hormonal influences.
- As appropriate, an exam directed at the cervical and thoracic spine, chest wall and upper extremities may be helpful in assessing other causes of pain.

Breast pain is one of the most common symptoms evaluated in primary care, surgery or specialty breast clinics. Approximately 41% to 69% of women report having experienced breast pain (Ader, 1997 [D]). Breast pain may interfere with daily activities, relationships and quality of life.

History and Physical Exam

The symptom of breast pain prompts many patients to make an appointment for a medical examination out of concern for the possible presence of breast cancer. A patient history is directed toward identifying and characterizing breast-related symptoms. The information gathered should include location and severity of pain, relationship to physical activities or the menstrual cycle, and interference with routine activities. Hormonal influences, such as pregnancy, use of contraceptives and hormone therapy should also be reviewed. Obtaining a history may also provide information identifying non-breast sources of pain. The patient should also be asked about any new medications or those that can be associated with breast pain should be noted. Risk assessment for breast cancer should include the appropriate reproductive, medical and family history.

A clinical examination of the breast should be performed with careful inspection and palpation of each breast, nipple-areolar complex and regional lymph nodes. Localized, generalized or bilateral breast tenderness should be noted. In addition to palpating the breasts while the patient is supine, examining the breasts while the patient is sitting or lying on her side may allow breast and chest wall tenderness to be distinguished.

Laboratory studies are generally not useful. A pregnancy test, however, should be considered in women of reproductive age if the history or examination suggests pregnancy. Other hormone levels (e.g., estrogen, progesterone and prolactin) are typically normal in patients with breast pain.

Breast pain may occur as a result of pregnancy, mastitis, trauma, thrombophlebitis, macrocysts, benign tumors or cancer; however, only a minority of breast pain is explained by these conditions. Most breast pain is of unknown cause. A variety of conditions can result in pain perceived in the breast. A variety of conditions can be revealed as a result of a directed history and physical. As appropriate, an exam directed at the cervical and thoracic spine, chest wall, shoulders and upper extremities, sternum, heart, lungs and abdomen may be helpful in assessing other potential causes of the pain.

(Ader, 1997 [D]; Ader, 2001 [D]; Dixon, 1999 [R])
Breast pain is commonly categorized into three classifications (Smith, 2004 [R]):

- **Cyclic mastalgia** occurs in premenopausal women and is clearly related to the menstrual cycle. The pain is typically bilateral and diffuse, often located in the upper outer quadrants of the breasts with frequent radiation to the axilla and the ipsilateral arm. Occasionally, breast pain may be unilateral or more intense in one breast.

- **Non-cyclic mastalgia** may involve continuous or intermittent pain that does not concur with the menstrual cycle. The pain is more often unilateral and localized with the pain in the lower inner portions of the breast. Non-cyclic breast pain generally occurs in older women, with symptoms often occurring in postmenopausal women.

- **Non-mammary pain** may present with the symptom of breast pain. Following the history and physical exam, differentiating breast pain and pain radiating from the chest wall or another site is usually straightforward. Occasionally the origin of pain is not evident, or there are multiple origins of pain, making evaluation more challenging.

### 44. Mammogram and/or Ultrasound at the Discretion of the Clinician

Imaging studies are frequently utilized in the evaluation of the breast. A mammogram should be considered especially in women with a family history of early breast cancer. Ultrasound may be useful for focal breast pain in both younger and older women. Subclinical breast cancer has been reported to occur in 2%-7% of women who have pain as the only symptom. It is unclear whether the pain is related to the cancer or whether this symptom initiates a breast evaluation in which an asymptomatic cancer is identified. Breast pain secondary to malignancy is typically unilateral and persistent. In these cases, imaging with directed ultrasound may be a more valuable assessment tool (Duijm, 1998 [B]; Smith, 2004 [R]).

### 47. Quantitative Pain Assessment

Breast pain may be difficult to assess as the symptoms may appear and subside without provocation, with certain activities or with the menstrual cycle. An attempt must be made to measure the amount and severity of the patient's breast pain over time, which is difficult as there is no standard unit of pain. Prospective assessment of breast pain may be a valuable tool when considering an intervention. Possible tools to document an individual's pain include pain rating instruments, a daily breast pain chart or a diary to document the occurrence and severity of pain, use of medications and interferences with lifestyle. These tools are particularly important in making an initial diagnosis of cyclic mastalgia and response to therapy (Adler, 2001 [D]; Dixon, 1999 [R]; Smith, 2004 [R]). For more information on pain assessment, see ICSI Assessment and Management of Chronic Pain guideline.

### 49. Initiate Non-Pharmacologic and/or Pharmacologic Intervention(s)

- The first line of treatment for breast pain is to reassure the patient that she does not have breast cancer. The risk of malignancy following a negative examination has been estimated to be only 0.5%, so reassurance following a negative evaluation is appropriate (Smith, 2004 [R]). Approximately 15% of women choose a treatment intervention to reduce the symptom of pain. During encounters for breast pain, the patient's description of the pain, quantitative assessment of the pain and decisions regarding reassurance, follow-up or therapeutic intervention should be documented.

- Few women will require treatment with more than reassurance and well-tolerated medications such as evening primrose oil. For those with severe, refractory breast pain, the significant side effects of some of these medications must be balanced against the potential benefit in ameliorating breast discomfort and pain.
• Non-pharmacologic interventions for breast pain are appropriate for women with breast pain. Although there has been little scientific investigation into the effectiveness of these non-pharmacologic approaches, they are frequently found to improve breast pain symptoms in clinical practice and are of low risk and expense to the patient.

Potential non-pharmacologic therapies include:

Mechanical support

A professionally fitted support bra, irrespective of age, cup size or underlying breast disease has been shown to relieve breast pain even in patients who have not responded to hormonal treatments. Support bras are recommended for exercise. A soft supportive bra during sleep may also improve symptoms.

Lifestyle changes

Lifestyle changes such as smoking cessation, stress reduction and improving coping skills may be possible low-risk interventions. Hot packs, cold packs and massage may also relieve symptoms.

The effectiveness of dietary measures is unclear. Studies have demonstrated improvement in breast pain symptoms following dietary reduction of saturated fat. Caffeine reduction or elimination has been found to be helpful by some patients, particularly those who consume large quantities of caffeine. Clinical studies have not shown this to be a consistent outcome.

Pharmacologic interventions

The decision whether to treat breast pain along with the selection of a particular agent to utilize requires balancing the need for symptom relief against the likelihood of medication side effects. If considering a pharmacologic therapy, consult with a specialist should be considered.

Pharmacologic interventions may include the adjustment of medications that may be contributing to breast pain, such as oral contraceptives, hormone therapy, spironolactone and others. Eliminating or decreasing the dose of estrogen in an oral contraceptive or hormone regimen is often effective.

Possible pharmacologic therapies include:

Evening primrose oil

Evening primrose oil is often used as an initial treatment for breast pain because of its low incidence of side effects and positive response rates for cyclic and non-cyclic pain. It is rich in gamma-linolenic acid and is believed to alter the saturated/polyunsaturated fat balance and decrease sensitivity to hormonal influences. The average dose is 2 x 500 mg soft-gel capsules three times a day for a minimum of three to four months.

Analgesics

Analgesics, such as ibuprofen, 400 mg every four to six hours may reduce breast pain.

Danazol

Danazol is the only medication that is labeled by the United States Food and Drug Administration for treatment of breast pain. Danazol is an antigonadotropin with some androgenic activity. It is the only medication that is labeled by the United States Food and Drug Administration for treatment of breast pain.

Danazol relieves breast pain in 75%-92% of women. A typical initial dose of 200 mg per day is recommended, with gradual tapering to an alternate day or luteal phase dosing; doses from 100-400 mg per day have also been described. Reported side effects are common and include hair loss, acne, decrease in voice pitch, weight gain, irregular menses and depression. There may also be a possible increase in venous thromboembolic events. Barrier contraception must be utilized. Danazol administered in the luteal phase only
has been found to relieve premenstrual breast pain in women with premenstrual syndrome with minimal side effect. It was not effective for other premenstrual syndrome symptoms (O’Brien, 1999 [A]).

**Bromocriptine**

One of the few hormonal abnormalities detected in breast pain has been an increase in thyrotropin induced prolactin secretion. Bromocriptine has been shown to decrease serum prolactin levels in normal and hyperprolactinemic women and may decrease dynamic secretion of prolactin in cyclic mastalgia patients. In several European studies, bromocriptine has shown significant decreases in breast pain (approximately 54%), as well as heaviness and tenderness in the breasts. Prolactin levels decline during therapy while estrogen, progesterone, testosterone and gonadotropin releasing hormones do not significantly change. Side effects are common and dose related, including nausea, vomiting, headache, dizziness and fatigue. An incremental dosing regimen is used beginning with 1.25 mg at bedtime, gradually increasing until a dose of 2.5 mg twice daily is reached. The beneficial effects lasted three to six months after bromocriptine was discontinued (Mansel, 1990 [A]).

**Tamoxifen**

Tamoxifen is a selective estrogen receptor modulator (SERM) utilized for the prevention and treatment of breast cancer. Response rates have demonstrated tamoxifen to be effective in reducing pain in 75%-90% women with cyclic and 56% of women with non-cyclic mastalgia in controlled trials. Tamoxifen has significant side effects with the principle concerns being from thromboembolic disease and endometrial cancer. Additional side effects include hot flashes, nausea, menstrual irregularity and vaginal dryness or discharge. The 10 mg daily dose of tamoxifen appeared to be as effective as the 20 mg daily dose with fewer side effects. Tamoxifen, like other hormonal interventions, should be reserved for women with severe mastalgia. Contraception must be utilized (Fentimen, 1988 [A]).

Other medications that have been found to be effective for the treatment of breast pain include goserelin, gestrinone, buserelin, leuprolide, quinagolide, cabergoline, thyroxine and topical nonsteroidal anti-inflammatory agents. Medroxyprogesterone has shown variable results in the treatment of breast pain. In general, antibiotics, diuretics and most vitamins have not been effective in the treatment of breast pain (Ader, 2001 [D]; BeLieu, 1994 [R]).

50. Inform Patient of Next Screening Date

Refer to the ICSI Preventive Services for Adults guideline for recommended mammography screening intervals.

IV. Radiologic Evaluation of the Breast Algorithm Annotations

51. Abnormal Screening or Diagnostic Mammogram

**Key Points:**

- It is recommended that an abnormal finding on routine mammography be evaluated under the direction of a radiologist.

Patients referred to the department of radiology most commonly enter for screening mammography. However, patients will occasionally be referred for diagnostic mammography, based on the presence of symptoms or findings on examination. In the event of an abnormal finding on mammography, it is recommended that a complete evaluation be undertaken within the department of radiology under the direction of a radiologist in order that a full characterization of the lesion will be provided back to the primary care physician ordering the original study. It will be the responsibility of the radiologist to complete the radiologic assessment of
the patient within the department of radiology so that the best possible characterization of the abnormality may be provided to the primary care physician in an expeditious fashion. Any recommendations for referral to the department of surgery for possible biopsy should be made directly to the primary care physician. However, the ultimate responsibility to make the referral will rest with the primary care provider.

**Nuclear medicine breast imaging**

Because the PPV (Positive Predictive Value) of x-ray mammography is only 10%-30%, nuclear medicine may use a radionucleotide and high-resolution gamma camera to increase positive predictive values. Nuclear medicine imaging is a way of obtaining functional or metabolic information that could potentially decrease the number of unnecessary breast biopsies performed. This imaging technique may also work for patients with radiodense breasts.

New digital gamma cameras are now developed and available clinically to find smaller (2-3 mm) breast cancers.

**Sentinel lymph node**

Lymph scintimammography using Tc-99m colloids is used for preoperative and intraoperative localization of non-palpable breast tumors (Brem, 2007 [D]). Many breast centers are studying lymphoscintigraphy for the detection of a "sentinel node" in the evaluation of axillary lymph nodes for metastatic involvement (Bongers, 1999 [D]; Gill, 2009 [A]; Khalkhali, 1997 [D]).

**Conclusion**

Continued research in breast imaging will include collaboration among the fields of functional imaging, molecular biology and pathology. This research will create clinical studies for:

- detecting earlier breast cancer,
- more accurately quantifying the extent of disease,
- non-invasive evaluation of lymph node involvement,
- identifying residual microscopic disease, and
- image biomarker or tumor-specific delivery of chemotherapy or radiosensitizing agents to breast tumors.


For patients referred with an abnormal mammogram, the surgeon or radiologist should determine whether the above suspicious changes are present. If not, the patient should report to ordering provider for follow-up and clinical exam. Recommend repeat mammogram in six to twelve months (Kerlikowske, 2003 [M]; Michell, 2003 [R]; Picca, 2003 [R]).

**54. Increased Risk?**

Patients considered at increased risk may have one or more of the following* (Saslow, 2007 [R]; Smith, 2003 [R]):

- Previous breast biopsy demonstrating ductal hyperplasia with atypia and LCIS
- Family history of breast or ovarian cancer in the patient's mother, sister or daughter under age 50, or breast cancer in male family member
• Past, personal history of breast cancer
• A breast cancer gene mutation (BRCA1, BRCA2, or other)
• Previous radiation to the chest (i.e., Hodgkin's Disease)

* This is not an all-inclusive list

Consider genetic counseling for possible genetic testing and lifetime risk analyses. The following Web address provides access to the Gail clinical risk assessment: http://www.cancer.gov/bcrisktool/.

55. Consider MRI

The use of MRI in the evaluation of breast disease has progressed rapidly over the last several years. MRI has previously been proven extremely useful in the evaluation, staging and monitoring of breast cancer and other breast problems. Recently, however, several studies have also demonstrated its ability to detect early breast cancer in high-risk women (screening). This has prompted the American Cancer Society to issue formal guidelines for Breast MRI screening of high-risk women IN ADDITION to the recommended yearly mammogram. Below is a synopsis of the new guidelines along with a reference to the recent review (Saslow, 2007 [R]).

The following women SHOULD undergo yearly breast MRI screening* beginning at or around 30 years of age and consider continuing as long as the woman is in good health (however, there is no data about screening with MRI beyond 69 years of age).

• Known carriers of BRCA 1 or BRCA 2 mutations
• Patients with therapeutic radiation to the chest between ages 10 and 30
• First-degree relatives with known BRCA 1 or BRCA 2 mutations
• Clinical lifetime risk estimated at greater than 20% using clinical risk estimator (the Gail, Claus or BRCAPRO models are among the tools suggested). The following Web address provides access to the Gail clinical risk assessment: http://www.cancer.gov/bcrisktool/.
• Known Cowden's, Li-Fraumeni or Bannayan-Riley-Ruvalcaba syndrome or first-degree affected relative

* Recommended at six-month offset interval from yearly mammogram, as recommended by a radiologist (Saslow, 2007 [R])

In women with increased lifetime risk due to strong family history or genetics, MRI has high sensitivity (up to 100%) for the detection of breast cancer when used as an adjunct to mammography. There is also evidence to support the use of MRI screening in women who were exposed to chest radiation as children or young adults. Because of the high rate of false positives, MRI screening should only be recommended to women at high risk of breast cancer. There is insufficient evidence to make recommendations for other groups of women. [Conclusion Grade II:  See Conclusion Grading Worksheet A – Annotation #55 (Magnetic Resonance Imaging)] (Kriege, 2004 [C]; Lehman, 2005 [C]; MARIBS, 2005 [C]; Saslow, 2007 [R]; Stoutjesdijk, 2001 [C]; Warner, 2004 [C])

Evidence is inconclusive regarding the following situations and DOES NOT YET SUPPORT routine breast MRI screening:

• Clinical lifetime risk estimated at 15%-20% using clinical risk estimator
• Previous LCIS, ALH, ADH biopsy results
• Previous history of breast cancer including DCIS
• Extremely dense mammogram (density 4)

(Saslow, 2007 [R])

**Gadolinium warning**

In patients who receive gadolinium contrast media used in MRI, there is the potential for renal toxicity and the rare complication (3%-5% risk in patients with moderate to end-stage renal disease) of life-threatening nephrogenic systemic fibrosis.

It is recommended that gadolinium use be avoided when possible in patients with advanced renal disease.

### 56. Additional Mammographic Studies and/or Ultrasound If Needed

Upon obtaining an abnormal finding on a mammogram, the radiologist will determine whether further mammographic images or ultrasound are required for completion of the evaluation process. Alternatively, spot compression, magnification and/or ultrasound may be necessary to obtain further characterization of indeterminate lesions of the breast. These additional studies should be done with the radiologist present, to reduce the risk of patient recall for further studies necessary to evaluate the same lesion (Kolb, 2000 [R]; Kolb, 2002 [C]).

### 57. Abnormality Present but Appears to be Probably Benign?

The term Probably Benign is an assessment category from the Breast Imaging and Reporting Data System (BI-RADS).

### 58. Repeat Mammogram and/or Ultrasound at 6-Month Intervals for 1-2 Years

If further mammographic studies or sonography demonstrate findings that are felt to be Probably Benign, a repeat image of the breast at six months is warranted to document stability of low-risk, probably benign lesions. Perform mammograph and/or ultrasound again at six month intervals for 1-2 years.

### 60. Sort Abnormalities

Upon completion of these views, each and every abnormality uncovered for each independent lesion of the breast studied should be sorted according to the nature of the abnormality. The radiologist should classify the lesion as representing either suspicious microcalcifications, architectural distortion or a soft tissue mass.

### 61. Mass

In the event that a soft tissue mass is identified in the mammogram, further studies are required to determine its relative risk for malignancy.

### 66. Ultrasound (if Not Already Performed)

Should the mass not be immediately suspicious for cancer, an ultrasound should be performed (if not already done) to determine whether or not the lesion is solid. (See Annotation #56, "Additional Mammographic Studies and/or Ultrasound If Needed.")
68. Fits Benign Criteria?
A solid mass should be further characterized for its risk of malignancy according to three criteria. Lesions may be observed and followed with studies repeated in six months if they fit all three of the following criteria:

- Size less than 15 mm
- Three or fewer lobulations
- More than 50% of the lesion margin appears well circumscribed in any view

Any lesion not fitting all three of the above criteria should be considered indeterminate and the patient should be referred for surgical evaluation regarding open biopsy or large core image-guided core biopsy.

(Dennis, 2001 [D]; Madabhushi, 2003 [C]; Stavros, 1995 [C])

72. Indications for Aspiration?
If the ultrasound of the soft tissue mass demonstrates that this is a cystic lesion, the cyst should be further categorized according to the following criteria:

- Internal echoes
- Palpability within the region of the ultrasound-proven cyst
- Complex septated appearance

All cysts do not have to be aspirated if they meet benign criteria with an ultrasound exam. If one or more of the preceding criteria is present, ultrasound-directed aspiration of the cyst may be indicated. Likewise, aspiration should be offered if the patient so requests.

73. Aspirate and Perform Single-View Mammogram
Following cyst aspiration, a single-view mammogram may be performed to demonstrate complete resolution of the mammographic lesion. However, if the cyst completely disappears with ultrasound, a mammogram may not be necessary. If sufficiently complex, a pneumocystogram with post-mammogram view may be completed by radiology.

75. Return to Screening Mammography/Report to Ordering Provider
If the lesion represents a simple cyst not fitting any of the criteria mentioned in Annotation #72, "Indications for Aspiration?" the patient should be referred back to the screening process and completion of this evaluation should be reported to the ordering provider. Refer to the ICSI Preventive Services for Adults guideline for mammography screening intervals.

V. Image-Directed Core Needle Biopsy Algorithm Annotations

76. Patient Referred for Image-Directed Biopsy
Patients referred for biopsy based on the presence of a mammographic and/or sonographic MRI or breast specific gamma imaging (BSGI) finding that is suspicious for or highly suggestive of malignancy will undergo either conventional open excisional biopsy (see Algorithm VI, "Surgical Evaluation of the Breast") or large core needle biopsy (Parker, 1996 [R]; Silverstein, 2009 [R]).
Large core imaging-guided breast biopsy is now the technique of choice in most institutions in the United States for biopsy of non-palpable breast masses and abnormal calcifications. Either stereotactic or ultrasound-guided breast biopsy may be used for reliable diagnosis of breast cancer. Stereotactic guidance is preferable for biopsy of calcifications. Most solid breast masses are amenable to large core needle biopsy with either stereotactic or ultrasound guidance. The location of the lesion, its visibility at ultrasound, equipment availability and the radiologist's expertise will determine the approach selected.

In some institutions, large core image-guided needle breast biopsy is performed for tissue diagnosis in cases of obvious cancer, as it saves the patient an additional surgical procedure, as well as expediting the diagnostic process.

**Current changes in breast disease diagnosis**

Over the past 20 years, advances in mammographic and sonographic technology have established a new subspecialty in radiology. Image-guided vacuum assisted breast biopsy, and core needle biopsy under image guidance have changed diagnostic breast biopsy from a surgical open biopsy to image-guided needle biopsy (Silverstein, 2009 [R]).

The following percutaneous techniques have been developed over the past 15 years:

- **Fine-needle aspiration (FNA):**
  A 22- to 24-gauge needle is used for cytology. This is best used with a cytopathology department. It is also used in abnormal cyst aspiration (where fluid is obviously benign). FNA has limited use in most community hospitals because of inadequate specimens (in 30%-40% of FNA biopsies). Therefore, large core image-directed breast biopsy has replaced most FNA biopsies (Liao, 2004 [M]; Minkick, 1996 [D]; Norton, 1988 [C]; Pisano, 1998 [A]; National Cancer Institute Sponsored Conference, 1997 [R]).

- **Core needle biopsy (CNB):**
  Spring loaded devices are used for image-guided biopsies more than any other percutaneous needle. They may be used with solid lesions of any size; used with ultrasound guidance (Israel, 1995 [D]; Liberman, 1998b [M]; Nguyen, 1996 [D]; Philpotts, 2003 [B]; Silverstein, 2009 [R]; Smith, 2001[D]).

- **Vacuum-assisted large core image-guided biopsy under stereotactic guidance:**
  Vacuum-assisted needles, 8, 9-, 11- or 12-gauge are used for microcalcifications, small masses or architectural distortion. Larger, vacuum-assisted electro-cautery devices may be used. These larger needles may help with avoiding undersampling and atypia diagnostic problems (Burbank, 1997 [C]; Dennis, 2000 [D]; Liberman, 1998a [D]; Meyer, 1997 [D]).

**78. Definitive Therapy**

If cancer is diagnosed, definitive therapy may be performed on the basis of stereotactic or image-guided needle biopsy alone.

**80. Surgical Consult**

Any questionable pathologic findings or pathologic findings that do not correlate with the imaging are indications for repeat biopsy by excision to rule out the presence of occult malignancy in the region of the mammographic abnormality (Jackman, 1997 [C]).
82. **Rebiopsy by Core or Open Biopsy**

The original specimen (pathology block) can be reexamined and recut for pathology exam if calcifications were noted. If calcifications cannot be demonstrated mammographically in the specimen, repeat biopsy, open or stereotactic, is necessary to assure that the abnormal mammographic lesion has been sampled. Biopsy must be repeated until the calcifications can be confirmed in the specimen.

84. **Mammogram and/or Ultrasound in 6-12 Months**

If the mass is a fibroadenoma, then follow up with mammogram or ultrasound in 6 to 12 months. However, if the patient is experiencing extreme pain and/or extreme tenderness, the fibroadenoma may be surgically removed or undergo cryotherapy *(Kaufman, 2005 [D]; Littrup, 2005 [D])*.

85. **Mammogram and/or Ultrasound in 6-12 Months, for 1-2 Years**

For all patients who have benign results from stereotactic or image-guided biopsy, a repeat mammogram and/or ultrasound of the involved breast in 6 to 12 months, for 1 to 2 years, is necessary to document stability of the lesion. The radiologist should correlate the pathology results with the mammographic abnormalities for all patients. If they do not correlate, rebiopsy with image-directed core needle or open biopsy is necessary. *(National Comprehensive Cancer Network, 2009 [R])*

87. **Open Biopsy or Repeat Image-Guided Core Needle Biopsy**

Any lesion that has grown or has become more dense on mammography, despite a previous benign core biopsy, must be rebiopsied or excised to rule out cancer.

88. **Inform Patient of Next Screening Date**

Refer to the ICSI Preventive Services for Adults guideline for mammography screening intervals.

VI. **Surgical Evaluation of the Breast Algorithm Annotations**

89. **Patient Referred to Surgeon for Evaluation**

Patients referred to the department of surgery for evaluation of breast disease will have undergone previous mammography that has demonstrated an abnormality warranting biopsy, or the patient may be referred on the basis of a physical finding uncovered in the primary care provider's office. It is the role of the surgeon to evaluate each and every abnormality uncovered in each patient. It is important for the surgeon to recognize that mammographically depicted lesions and palpable abnormalities may co-exist as separate entities within the breast. It is therefore important that each lesion be evaluated for its own merit, using this algorithm.

The importance of communication between the surgical consultant and the primary care provider cannot be overstated. Patients undergoing biopsy should have results reported both to the surgeon and the primary care provider. More importantly, patients who do not require biopsy following surgical consultation should be returned to the routine screening process. This process is under the supervision of the primary care provider. Therefore, it is absolutely necessary for the primary care provider to know when the patient reenters the routine screening population. In the event that new symptoms arise or occur during the screening interval, the patient should be evaluated by the primary care physician using the primary care evaluation process stated in Algorithm I, "Evaluation of Breast Mass," in this guideline.
90. Palpable Mass
Patients with palpable masses referred to surgery should first be evaluated to determine the presence of a dominant and discrete mass.

91. Consider Imaging Prior to Aspiration
Consider an ultrasound and determine if the mass is solid or cystic.

92. Aspirate Mass If Symptomatic
If a palpable and discrete mass is present and symptomatic, an attempt should be made by the surgeon to aspirate the mass to rule out the presence of a simple cyst. An 18-25 gauge needle mounted on a syringe is inserted into an alcohol-prepped dominant breast mass for attempted aspiration.

(Bassett, 1997 [R])

93. Residual Mass or Bloody Aspirate?
A simple cyst is one that resolves with aspiration of non-bloody fluid. If fluid is clear and non-spontaneous (i.e., as in compression mammogram), a workup is not always necessary, as this is benign. Surgical excision should be performed for those cysts with bright red bloody aspirates and those that do not completely resolve with aspiration. A cyst that recurs may be re-aspirated, but the number of times this procedure can be repeated without surgical excision will depend upon the surgeon and patient's level of confidence that the lesion is benign.

Non-bloody fluids should be discarded, based on a study where no cancers were detected among 6,747 non-bloody specimens (Ciatto, 1987 [C]).

Among 401 patients with cystic masses, only 4 had cancer and all had either bloody fluid or a residual mass. This would be demonstrated by palpation or imaging (Hamed, 1989 [D]).

97. Spontaneous Nipple Discharge
Patients who present with nipple discharge or morphologic abnormality should be evaluated to determine the presence of bloody or unilateral discharge or palpable abnormality. Paget's disease of the nipple must be excluded. Open biopsy is recommended if any of these symptoms are present.

See Algorithm II, "Evaluation of the Breast for Spontaneous Nipple Discharge."

99. Breast Pain
Patients with breast pain referred to the surgical department should be evaluated for any focal findings identified on physical examination or on mammography. Any abnormalities uncovered warrant biopsy before consideration of symptomatic treatment of the process.

See Algorithm III, "Evaluation of Breast Pain."

For patients referred with an abnormal mammogram, the surgeon should determine whether the above suspicious changes are present. If not, the patient should undergo a repeat mammogram in six months, at a minimum, to document stability of the lesion.
104. Image-Directed Biopsy

Patients referred for biopsy based on the presence of a mammographic and/or sonographic finding highly suspicious for cancer will undergo either conventional open excisional biopsy or image-directed needle core biopsy. (See Algorithm V, "Image-Directed Core Needle Biopsy.") Indications for biopsy are establishing a definitive diagnosis, finding multicentric lesions or associated intraductal pathology that may influence the choice to perform either mastectomy or breast conserving surgery for definitive treatment of the malignancy.

Image-directed core biopsy is the method of choice if sentinel lymph node study will be completed.

See the following algorithms in this guideline for other indications for open excisional breast biopsy:

- Evaluation of the Breast for Spontaneous Nipple Discharge
- Radiologic Evaluation of the Breast
- Image-Directed Core Needle Biopsy

108. Consider Open Biopsy

Any questionable pathologic findings should have a repeat biopsy by excision to rule out the presence of occult malignancy in the region of the mammographic abnormality (Silverstein, 2009 [R]).

110. Definitive Therapy

If cancer is diagnosed, definitive therapy may be performed on the basis of stereotactic core biopsy alone.

111. Benign

Benign fibroadenomas should be followed at routine screening intervals. However, if the patient is experiencing extreme pain and/or extreme tenderness, the fibroadenoma may be surgically removed or undergo cryotherapy (Kaufman, 2005 [D]; Littrup, 2005 [D]).

112. Return in 6 Months for Breast Examination and Imaging

If no focal findings are uncovered, a repeat examination within six months is warranted to rule out the presence of occult neoplastic process.

114. Progression

If the lesion is progressing in size and density or is otherwise worrisome, open biopsy is recommended.

115. Inform Patient of Next Screening Date

Refer to the ICSI Preventive Services for Adults guideline for mammography screening intervals.
Supporting Evidence:
Diagnosis of Breast Disease

Original Work Group Members

Jeanne M. Anderson, MD  
Family Practice  
MinnHealth, P.A.  
John Bordwell, MD  
Family Practice  
Coon Rapids Medical Center  
Candey Corey, MD  
Oncology  
Group Health, Inc.  
John Gisvold, MD  
Radiology  
Mayo Clinic  
Jay Gutenkauf, MD  
Family Practice  
Group Health, Inc.  
Ruth Johnson, MD  
Internal Medicine  
Mayo Clinic  
Dee Kemnitz  
Business Health Care Action Group  
Carlson Companies  
Charles McCoy, MD  
Family Practice  
Park Nicollet Medical Center  
Michael Nelson, MD  
Radiology  
Park Nicollet Medical Center  
Jackie Rikhus, RN  
Facilitator  
Park Nicollet Medical Center  
Cheri Rolnick, MD  
Measurement Advisor  
Group Health Foundation  
Thamrong Suwam, MD  
Surgeon  
Group Health, Inc.

The next scheduled revision will occur within 24 months.
Brief Description of Evidence Grading

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

A full explanation of these designators is found in the Foreword of the guideline.

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in the Foreword and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols +, –, ø, and N/A found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.
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**Work Group's Conclusion:** In women with increased lifetime risk due to strong family history or genetics, MRI has high sensitivity (up to 100%) for the detection of breast cancer when used as an adjunct to mammography. There is also evidence to support the use of MRI screening in women who were exposed to chest radiation as children or young adults. Because of the high rate of false positives, MRI screening should only be recommended to women at high risk of breast cancer. There is insufficient evidence to make recommendations for other groups of women.

**Conclusion Grade:** II

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<th>Author/Year</th>
<th>Design Type</th>
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<th>Population Studied/Sample Size</th>
<th>Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)</th>
<th>Authors' Conclusions / Work Group's Comments (italicized)</th>
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| Stoutjesdijk et al., 2001 | Sensitivity and specificity of a diagnostic test | C     | ø        | 179 women from a single institution in the Netherlands. All pts had a > 15% lifetime risk of breast cancer based on family history of breast and/or ovarian cancer or germline mutation in the BRCA1 or BRCA2 genes. Patients with a history of breast cancer or who did not have adequate follow-up data to confirm radiologic findings were excluded. -- Age range was 21-71 years. -- 40 pts received mammograms only, 49 had received MRI only, and 90 had received both mammography and MRI. -- Exams were prospectively interpreted; radiologists interpreting the results from one test were blinded to results from the other modality. -- Breast Imaging Reporting and Data System (BI-RADS™) was used, with the following values: 0: additional imaging required 1: negative 2: benign 3: probably benign 4: suspicious abnormality 5: highly suggestive of malignancy -- Biopsy used as final diagnosis | No difference in age or in risk category between patients given mammography and those given MRI. 13 malignant tumors were detected (one of the cancers was a low-grade non-Hodgkin's lymphoma). Of the remaining 12, MRI detected all of them with mammography missing 7 tumors (using a BI-RADS threshold of 3). The sensitivity (sens), specificity (spec), positive predictive value (PPV) and negative predictive value (NPV) are specified below. BI-RADS™ score of 3 or higher as operating point
Mammography
Sens 42% Spec 99% PPV 63% NPV 97%
MRI 100% 93% 43% 100%
BI-RADS™ score of 4 or higher as operating point
Mammography
Sens 42% Spec 99% PPV 63% 97%
MRI 92% 98% 71% 96%
Area under the receiver-operator characteristic (ROC) curve (AUC) for mammography using entire BI-RADS™ range was 0.74 and for MRI was 0.99. Difference in AUCs between the groups was statistically significant (p<0.001). | The authors conclude that this retrospective study shows that annual screening with breast MRI is more accurate than mammography in the early detection of breast cancers in women with a significant hereditary risk of such tumors. This result needs to be confirmed by larger prospective studies. Several factors that the authors identified as possibly leading to bias include selection biases due to the retrospective nature of the study, the use of only one radiologist for the identification of false negative results and the low number of breast cancers. |
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<th>Quality</th>
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<th>Primary Outcome Measure(s) / Results (e.g., (p)-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)</th>
<th>Authors’ Conclusions / Work Group’s Comments (italicized)</th>
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<tbody>
<tr>
<td>Kriege et al., 2004</td>
<td>Sensitivity and specificity of a diagnostic test</td>
<td>C</td>
<td>+</td>
<td>1909 women with a cumulative lifetime risk of breast cancer of 15% or more and an age of 25 to 70 years (mean age = 40) were included in multicenter study in the Netherlands. Women with a history of breast cancer were excluded. – Women were screened every six months with a clinical breast examination (CBE) and once per year by both mammography and MRI, with independent readings. – Cancers detected in the screening group were compared with those detected in two age-sex matched control groups (one of which consisted of women in a database of breast cancers, and the other control group consisting of a population with characteristics similar to the investigational population but without undergoing the screening protocol). – Median follow-up of 2.9 years – 358 women were carriers of germ-line mutations. – Biopsy used as final diagnosis</td>
<td>51 tumors were detected (44 invasive cancers, 6 ductal carcinomas in situ, and 1 lymphoma) during the follow-up period. – The following summarizes the relative efficacy of the various modalities in detecting invasive cancer.</td>
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<td></td>
<td>Sensitivity Specificity</td>
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<td></td>
<td>CBE</td>
<td>17.9%               98.1%</td>
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<td>Mammography</td>
<td>33.3%               95.0%</td>
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<td></td>
<td>MRI</td>
<td>79.5%               89.8%</td>
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<td>When a BI-RADS™ score of 3 or higher was used as a discriminator, sensitivity of CBE, mammography, and MRI scanning were 17.8%, 40.0% and 71.1%; PPV was 9.6%, 8.0% and 71.1%, respectively.</td>
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<td>45 cancers were evaluated for comparing the methods including 4 interval cancers detected between two screening exams (5 breast cancers were excluded for various reasons as was the lymphoma).</td>
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<td>– 32 breast cancers were detected on MRI (22 of these were not visible on mammography). Mammography detected 18 tumors and missed 27 tumors.</td>
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<td>– MRI missed 13 breast cancers (8 of the 13 were visible on mammography, including 2 DCIS). 4 of the undetected tumors were interval cancers, and 1 was detectable only on CBE.</td>
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<td>– The AUC for mammography was 0.686 and the AUC for MRI was 0.827 (difference between groups was significant at (p &lt; 0.05)).</td>
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<td>– None of the 50 patients with breast Ca died prior to the end of the study period (median f/u = 1.5 yrs).</td>
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<td>Authors conclude that the sensitivity of MRI was higher than that for mammography although the specificity and PPV were lower.</td>
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<td>– Differences in sensitivity between MRI and mammography was larger when only invasive cancers were included.</td>
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<td>– Tumors in the study group were significantly smaller and less likely to have lymph node involvement than those in the two control groups.</td>
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<td>– Authors concluded that MRI screening overall contributed to the early detection of hereditary breast cancer, although it has a lower specificity than mammography leading to the generation of more “uncertain” findings requiring short-term follow-up or additional testing/investigations.</td>
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<tr>
<td>Author / Year</td>
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<td>Warner et al., 2004</td>
<td>Sens/spec of diagnostic test</td>
<td>C</td>
<td>+</td>
<td>Surveillance study of 236 Canadian women aged 25 to 65 years (mean age 46.6) and who have a BRCA 1 or BRCA 2 mutation. Exclusions included pts with history of bilateral breast Ca, pts who are currently receiving chemotherapy, or who were known to have metastatic disease. Pts underwent 1 to 3 screening examinations with MRI, mammography and ultrasound. CBE was performed at 6-month intervals. BI-RADS™ scales were used to score results from mammography and MRI. All participants were followed up for one year after last screening test and all new cancers and prophylactic mastectomies were noted. Biopsy used as final diagnostic result (all lesions with a score of 4 or 5 were biopsied)</td>
<td>100% of women completed at least 1 screening episode, 58% completed at least 2 episodes, and 36% completed 3 episodes. 120 women were still undergoing screening at the time of this writing. 31 women left prior to finishing all 3 rounds. 2 cancers were found (16 invasive, 6 DCIS) in 21 women. 9.1% were detected by CBE, 36% were detectable by mammography, 33% by ultrasound and 77% by MRI. MRI was significantly more sensitive than either of the other imaging modalities (p=0.002 vs. mammography; p = 0.006 vs. ultrasound). Specificities were 95.4% for MRI, 99.8% for mammography, 96% for ultrasound and 99.3% for CBE. Only one interval cancer found (between screens). All four screening modalities had a combined sensitivity of 95%; mammography and MRI combined had a sensitivity of 45% when combined; CBE, mammography and MRI combined had a sensitivity of 86%; the sensitivity of all imaging modalities other than MRI was 64%. 32% of cancers were detected on MRI but missed by other imaging methods; 2 cancers were found by mammography alone, with 2 more cancers detected by ultrasound alone; MRI detected 75% of cancers missed by mammography and CBE (i.e., conventional surveillance). All 22 pts with Ca are currently disease-free. AUC: 0.89 for MRI, 0.77 for mammography, 0.65 for ultrasound, 0.48 for CBE, 0.93 for all 4 modalities, 0.94 for CBE, mammography and MRI, and 0.77 for mammography and CBE.</td>
<td>Addition of annual MRI and ultrasound to mammography and CBE significantly improves the sensitivity of surveillance for early detection of breast cancers, although adding ultrasound may increase false-positive rate. High breast density in younger women makes mammography alone less useful. Needs further investigation to show that such surveillance in this population lowers breast cancer mortality.</td>
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<tr>
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<tr>
<td>MARIBS Study Group,</td>
<td>Sens/spec of diagnostic test</td>
<td>C</td>
<td>ø</td>
<td>-- Part of the Magnetic Resonance Imaging Breast Screening (MARIBS) study -- Multicenter study in 649 women aged 35-49 years (mean age of 40) with a strong family history of breast cancer and/or with a high probability of BRCA 1, BRCA 2 or TP53 mutation. -- All participants were offered annual screening with mammography and contrast-enhanced MRI for 2 to 7 years. -- Exclusions included pts with previous history of breast Ca or who have any other cancer for which the prognosis (life-expectancy) was less than 5 years. -- To measure sensitivity and specificity, BI-RADS scores of 0, 3, 4, 5 were considered to be positive outcomes. -- Biopsy used as final diagnostic result.</td>
<td>-- 30 women withdrew from study since became ineligible for further work up (accounting for most of dropout rate). -- 6 cancers were detected by mammography only, 19 by MRI only, and 8 only by both modalities, with 2 interval cases (total of 35 cancers). -- Sensitivities were 77%, 40% and 94% for MRI, mammography and both modalities, respectively. Sensitivity was significantly higher for MRI than for mammography (p = 0.01); sensitivities for mammography and MRI had the largest difference for BRCA 1 mutation carriers (p = 0.004). -- Specificities were 81%, 93% and 77% for MRI, mammography and both modalities, respectively. -- PPVs were 7.3% and 10% for MRI and mammography, respectively, whereas the NPV was 99% for mammography and 99% for MRI. -- AUC: 0.85 for MRI, 0.70 for mammography (p = 0.035 for difference) -- Cancer detection rates were 26.9 per 1000 woman-years on initial examination (prevalence) and 12.8 per 1000 woman years on subsequent testing (incidence). -- Using only the prevalence tests (20 cancers), sensitivities were 75% and 40% for MRI and mammography, respectively (p = 0.12 for difference), along with specificities of 82% and 93% for MRI and mammography, respectively (p &lt; 0.0001).</td>
<td>-- In women at high risk for breast cancer based on family history, screening with MRI is more sensitive but less specific than mammography. Through combining both modalities, sensitivity increases although there is a further decline in specificity. -- Need assessment of effect of screening exams on mortality. -- Attrition rate low.</td>
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<tr>
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| Lehman et al., 2005 | Sens/spec of a diagnostic test | C     | ø       | Multicenter study analyzing results from 367 asymptomatic women with a lifetime risk of breast cancer of greater than 25% based on family history or genetic testing. Subjects also needed to be 25 years of age or over. | - 38 biopsies were recommended based on imaging results; 27 biopsies were performed leading to a diagnosis of 4 cancers (1.1% cancer yield).  
- Biopsy recommendation rate for MRI was 8.2% and the rate for mammography was 2.2%.  
- 11 lesions recommended for biopsy did not undergo biopsy for various reasons (e.g., cystic lesions, patient preference).  
- All 4 cancers were found on MRI; mammography detected only 1 cancer, although additional cancer yield for MRI was not significantly different from mammography (likely due to the small number of cancers).  
- MRI resulted in 20 false positives; mammography resulted in 3 false-positive findings.  
- All women were node-negative without metastatic disease. | - There is a higher false-positive rate for MRI than for mammography.  
- Authors state that limitations to the study include no long-term follow-up to identify false-negative results, the fact that only a single round of screening was provided, lack of detailed information on prior screening histories.  
- MRI is not recommended as a replacement for mammography but as a complement. A negative MRI should not overrule the use of biopsy based on a suspicious mammogram.  
- Risk of having a benign biopsy was about 5% overall in high-risk women. |
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<tr>
<td>Saslow et al., 2007</td>
<td>Consensus statement, reviewed mostly observational studies.</td>
<td>R</td>
<td>+</td>
<td>An expert panel convened to review the literature from 2002 to 2006.</td>
<td>The primary objective of this paper was to update the guideline for use of MRI in breast cancer screening. MRI efficacy is greater than mammography. They compared sensitivity and specificity of ultrasound, mammography and MRI for breast cancer screening in women with strong family history of the disease. The sensitivity results ranged from 16%-40%, 16%-40% and 77%-100%; and specificity results 91%-96%, 93%-99% and 81%-99% respectively. The authors put forth the following recommendations for MRI screening as adjunct to mammography:  • Based on evidence, annual MRI screening is recommended for women with BRCA mutation, first-degree relative of BRCA carrier, or other models that identify strong family history indicating &gt;20% increased risk.  • Based on expert opinion, annual MRI screening should be recommended for women who underwent radiation to the chest (such as Hodgkin's survivors) between ages 10 and 30, and those with family history of predisposing genetics syndromes. In addition, the authors state that there is insufficient evidence to make conclusion for or against for other groups.</td>
<td>The recommendations outlined were based on consideration of a woman’s risk level and the extent to which subgroup specific evidence is available. The authors conclude that MRI screening is highly sensitive but has relatively low specificity, which can result in false-positives. Because of the high false-positive rate associated with MRI screening, this method should be recommended only to women who have a high probability of breast cancer. In addition, women who are at higher risk will benefit more from MRI screening. [NOTE: the conclusions in this report are based on review of three of the same studies in the previous version of the CGW, plus additional studies with congruent findings.]</td>
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This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
  - Measurement Specifications
- Key Implementation Recommendations
- Knowledge Resources
- Resources Available
Priority Aims and Suggested Measures

1. Reduce the length of time between first knowledge of a breast abnormality and diagnostic resolution.
   Possible measures for accomplishing this aim:
   a. Average number of days between patient phone call about breast abnormality and RN or MD visit.
   b. Average number of days between a breast abnormality noted by RN or MD and a diagnostic workup to be maximum of 7-10.
   c. Percentage of BI-RADS category 4 or BI-RADS category 5 mammograms that are followed by a biopsy within 7-10 days.
   d. Average number of days between pathology report and documentation that patient was informed of results.
   The ultimate goal is to decrease the time from identification of a breast abnormality to notification of the patient of biopsy results.

2. Ensure that a bloody tap or a persistent mass following aspiration of a palpable dominant mass is referred to a surgeon or radiologist regardless of negative imaging.
   Possible measures for accomplishing this aim:
   a. Percentage of patients with bloody tap following aspiration of a palpable dominant mass who are referred to a surgeon or radiologist regardless of a negative mammogram or ultrasound.
   b. Percentage of patients with residual mass following aspiration of a palpable dominant mass who are referred to a surgeon or radiologist regardless of a negative mammogram or ultrasound.

3. Ensure that patients with spontaneous bloody or watery discharge have a mammogram (with or without an ultrasound) and are referred to a surgeon or radiologist.
   Possible measure for accomplishing this aim:
   a. Percentage of patients with spontaneous bloody or watery discharge who have a mammogram (with or without an ultrasound) and are referred to a surgeon or radiologist.

4. Ensure that needle biopsies demonstrating abnormal (any questionable or pathologic findings that do not correlate with imaging pathologic findings) are followed by performance of an open biopsy.
   Possible measure for accomplishing this aim:
   a. Percentage of patients with a diagnosis of abnormal pathologic findings (lobular neoplasia, ductal hyperplasia with atypia, phylloides tumor lobular carcinoma insitu [LCIS] or papillary lesions) on needle biopsy who subsequently have an open biopsy performed.

5. Ensure that all women with breast concern that is indeterminate will have a follow-up clinical assessment in two or three months.
   Possible measure for accomplishing this aim:
   a. Percentage of women with an indeterminate breast concern who have a follow-up clinical exam within three months.
Measurement Specifications

Possible Success Measure #1c

Percentage of BI-RADS category 4 or BI-RADS category 5 mammograms that are followed by a biopsy within 7-10 days.

Population Definition

Women through age 74 with biopsy for possible diagnosis of breast cancer.

Data of Interest

Percentage of BI-RADS category 4 or BI-RADS category 5 abnormal mammograms that are followed by a biopsy within 7-10 days.

Numerator/Denominator Definitions

Numerator: Total # of patients with less than 10 days between the first documentation of a mammogram abnormality and a completed biopsy for all records reviewed.

Denominator: Total # of patients with an abnormal mammogram undergoing biopsy.

Method/Source of Data Collection

A list of all patients with breast biopsies for mammogram abnormalities during the previous target period. The medical records can be reviewed to determine the number of days between first documentation of an abnormal mammogram and completion of a biopsy.

Time Frame Pertaining to Data Collection

Data may be collected semiannually.

Notes

The intent of this measure is to determine the time interval involved and provide a sense of the extent of "sleepless nights" for the patient.
Key Implementation Recommendations

1. Primary Care, Radiology and Surgery:
   Establish a communication plan to include all providers involved in the patient's treatment plan:
   - Patients undergoing biopsy should have results reported to the radiologist and/or surgeon performing
     the procedure, as well as the primary care provider.

2. Primary Care:
   Establish a system for education of all female patients regarding self breast examination and age-appropriate mammographic screening intervals.
   Develop a system for timely assessment of palpable breast masses including necessary imaging studies, follow-up, and referral to radiology or surgery for biopsy.

3. Radiology:
   Establish a process that ensures that abnormalities of the breast are accurately identified and sorted, and that all appropriate radiologic imaging studies necessary to the evaluation process are efficiently completed.

4. Surgery:
   Establish a process for timely completion of evaluation of breast lesions and provide additional surgical breast consultation as needed.

5. Documentation:
   Develop a system to document time frame from receipt of pathology to patient information.
   - Telephone call documentation
Knowledge Resources

Criteria for Selecting Resources

The following resources were selected by the Diagnosis of Breast Disease guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are only available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Available table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.
## Resources Available

<table>
<thead>
<tr>
<th>*</th>
<th>Author/Organization</th>
<th>Title/Description</th>
<th>Audience</th>
<th>Web Sites/Order Information</th>
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</table>
|   | American Cancer Society                          | Web site is rich in information about breast cancer risk factors, screening and treatment. Diagrams assist with understanding of breast anatomy and surgery. By calling organization, this educational information can be ordered:  
- *For Women Facing Breast Cancer* (booklet, #4652.00)  
- *For Women Facing a Breast Biopsy* (English or Spanish)  
- *ABCs of Breast Health-A Personal Plan of Action* (#3416.01)  
- *The Older You Get, the More You Need a Mammogram* (#5020.00)  
- *Guidelines for the Early Detection of Cancer* (#2070.00)  
- *Breast Health* (#2048.00, available in multiple languages)  
- *Cancer Facts for Women* (#2007.00, Spanish available)  
- *After Diagnosis: A Guide for Patients and Families* (#9440.00) | Public   | http://www.cancer.org/ Phone#: 800-ACS-2345 |
|   | American College OB/GYN                          | Detecting and Treating Breast Lumps Early                                         | Women    | http://www.acog.org                           |
|   | HealthEast Care System                            | Information from health library index includes topics related to breast disease, cancer and breast self-exam. | Women    | http://www.healtheast.org                     |
|   | Krames Experts in Patient Education              | This educational literature can be ordered from Web site:  
- *Breast Biopsy*  
- *Stereotactic Breast Biopsy* | Women    | http://www.krames.com                         |
|   | Living Beyond Breast Cancer                      | Information/support includes online chats specifically for women under age 45, women with metastatic breast cancer, and those with general questions. Transcripts of educational teleconferences about the latest information in breast cancer. Links to reputable sites. | Public   | http://www.lbbc.org                           |

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<tr>
<td>Mayo Clinic</td>
<td>The Condition Center on Breast Cancer Web site provides information on frequently asked questions. A search on breast disease yields multiple topics. Women may e-mail questions to Mayo physicians.</td>
<td>Public</td>
<td><a href="http://www.mayoclinic.com">http://www.mayoclinic.com</a></td>
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<td>National Alliance of Breast Cancer Organizations (NABCO)</td>
<td>Calender of conferences, as well as data from clinical trials. Information on choosing support groups. E-mail reminders of breast exam available.</td>
<td>Public; Health Care Professionals</td>
<td><a href="http://www.nabco.org">http://www.nabco.org</a></td>
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<tr>
<td>National Cancer Institute</td>
<td>The latest information on cancer treatment at both the professional and lay public level, the latest cancer research news, and clinical trial information. Cancer information hotline and ability to search cancer scientific literature. All NCI publications are available online. Additionally, calling NCI can obtain: • <em>What You Need to Know About Breast Cancer</em> (booklet) • <em>Mammograms: Not Just Once but for a Lifetime</em> (booklet)</td>
<td>Public</td>
<td><a href="http://www.cancer.gov">http://www.cancer.gov</a> 1-800-4-CANCER</td>
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<tr>
<td>Park Nicollet Health Services</td>
<td>Mammography and Breast Cancer Screening (brochure)</td>
<td>Women</td>
<td><a href="http://www.icsi.org">http://www.icsi.org</a> Search: mammography</td>
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