



**BREAST
CANCER
INITIATIVE^{2.5}**
Making breast health a global priority

DIAGNOSIS

Biopsy, Pathology and Subtypes

Knowledge Summary



INTRODUCTION

The success of an effective breast health care program is directly related to the availability and quality of breast pathology. Accurate tissue diagnosis is the cornerstone of cancer therapy. All women with a suspected breast mass require an accurate pathologic diagnosis before initiating treatment, even when the clinical findings are strongly suggestive of cancer. Data from high-income countries show that as few as 20% of biopsied breast masses will be malignant. Establishing the presence and type of malignant changes and the presence or absence of tumor biomarkers that affect treatment (such as hormone receptors and HER2) is critical to determining prognosis and appropriate treatment.

There is a significant deficit in pathology services in low- and middle-income countries (LMICs). This can be attributed to shortages in the workforce, high demand, limited training opportunities and underfunded and under-resourced laboratories. Improper handling of tissue during the pre-analytic phase, as well as delays in processing tissue, negatively affects the quality and validity of the diagnosis and subsequent treatment. Many women do not have adequate access to proximate pathology services. As a result, women with breast masses, many of which may not be cancerous, are often subjected to unnecessary surgical procedures.

Following a thorough health history and clinical exam, the decision must be made as to what resource-appropriate diagnostic imaging will be performed on a patient with a breast abnormality, and how to obtain tissue to confirm the diagnosis. The options for biopsy include fine needle aspiration cytology (FNAC), core needle (CNB), which may be image-guided with ultrasound or mammogram or vacuum assisted. Surgical biopsy may be excisional (removing the entire palpable tumor), or incisional (removing a portion of the tumor to obtain a diagnosis). Each technique carries specific advantages and disadvantages, costs and resource requirements. Minimally invasive techniques offer advantages over surgical biopsy but require additional resources. Improvements are needed in advancing minimally invasive biopsy techniques and processing pathological samples.

KEY SUMMARY

Essential components of breast cancer diagnosis

- Adequate pathology services are essential to breast cancer control programs.
- Adequate histopathologic diagnosis is necessary for all patients with findings suspicious for breast cancer before initiating treatment.
- Easy access to diagnostic procedures, including biopsies, is essential for patients with breast abnormalities.
- Out-of-pocket costs and geographic distribution of services affect access to diagnosis and care.
- Coordination of services between local providers and diagnostic pathology services are necessary to ensure timely diagnosis and treatment.
- Benign findings are more common than malignant findings; therefore, removal of the breast should never be used as a diagnostic method.
- Minimally invasive biopsy techniques (such as core needle biopsy or fine needle aspiration cytology) may reduce the morbidity to the patient and improve the efficiency of the health system.

Health systems and coordination of care

- Ensure health professionals are trained to perform a breast health history and clinical breast examination (CBE), to know the types of biopsies available, when to refer patients for diagnostic biopsy and the pathologic diagnoses that require additional follow up and/or treatment.
- Establish standardized protocols and procedures for referring patients who need diagnostic biopsies.
- Train appropriate personnel to perform incisional, excisional and minimally invasive biopsy techniques and in the proper labeling, handling, and transportation of diagnostic biopsy samples
- Pathologic services, including the number of trained histopathologists, are required to meet existing and future needs.
- Pathologic services should include the identification of benign breast lesions, malignant cancers and histologic types, as well as testing for tumor biomarkers that may guide treatment.
- Develop adequate social support services and patient navigation to ensure patients obtain the necessary diagnostic biopsies and understand the results of biopsy testing, and are referred for adequate treatment.
- Coordination of services between local providers and diagnostic pathology services are necessary to ensure timely diagnosis and treatment.

Resource-stratified pathways across the continuum of care

- Follow a resource-stratified pathway for the development of breast cancer diagnosis and pathology programs to allow for coordinated, incremental program improvement across the continuum of care.
- A 'pathway' is a progression of resource investment, program development, quality improvements and interval health gains.
- Program design and improvements should be based on outcome goals, identified barriers and needs and available resources.



POINTS FOR POLICYMAKERS:

OVERVIEW

Preplanning

- Identify data sources to estimate the disease incidence and stage and subtype distribution.
- Identify data on the time from presentation of a suspicious breast concern to definitive diagnosis, and the time from referral for imaging and pathology studies to report generation.
- Identify who will lead the process as well as other stakeholders and key decision makers.

Planning Step 1: Where are we now?

Investigate and assess

- Assess workforce capacity, quality of services and resources.
- Evaluate existing pathology practices and training programs.
- Review and assess referral processes to optimize the system for timely diagnosis and coordination of care.
- Evaluate patient access and barriers to accessing diagnostic services [structural, sociocultural, personal, financial].

Planning Step 2: Where do we want to be?

Set objectives and priorities

- Identify gaps and introduce policies, training and services to reduce barriers to providing a timely and accurate histopathologic diagnosis.
- Set objectives that advance the breast cancer diagnosis process.
- Optimize the system for timely breast cancer diagnosis. Breast cancer diagnosis requires coordination of care that includes clinical assessment, imaging studies, biopsy capabilities and pathology services with timely report generation.
- Assess feasibility and sustainability of interventions.

Planning Step 3: How do we get there?

Implement and evaluate

- Partner with and engage appropriate stakeholders and resources.
- Follow a resource-stratified approach for breast cancer diagnosis that considers available resources and equitable access to services for all women.
- Implement quality assurance measures and monitor process metrics.

WHAT WE KNOW

Biopsy techniques

All biopsy techniques require training and expertise to ensure adequate tissue sampling. Benign breast conditions are four times more prevalent than breast cancer. Therefore, obtaining a diagnostic biopsy rather than performing open surgery for diagnosis of breast lumps will reduce cost and morbidity. Minimally invasive biopsy techniques may decrease the number of hospital visits and allow for more efficient use of surgical suite services by decreasing the number of surgical excisions.

Surgical biopsy: Surgical excisional or incisional biopsy of a palpable breast mass is a basic-level intervention. Surgical biopsy requires basic-level training and resources to obtain a histologic [tissue] sample. An advantage of this technique is that a definitive diagnosis can be made and biomarkers can be obtained on the biopsy specimen. This type of biopsy can often be performed with local anesthesia. A disadvantage of the surgical biopsy is that most often an additional patient visit is required for the surgical biopsy procedure itself. Once the biopsy is performed and cancer is diagnosed, another surgical visit is required for the treatment of the breast tumor and axillary staging. Health systems need to ensure that patients referred for biopsy actually follow up and obtain the procedure. An additional visit for the surgical diagnostic procedure increases the potential for a patient to be lost to the system.

Fine needle aspiration biopsy: Fine needle aspiration cytology [FNAC] is a biopsy technique in which a small, hollow needle and syringe are used to obtain cells from a palpable breast lump for examination under a microscope by a cytopathologist. A quick stain may be performed at the patient's bedside to assess adequacy of the sampled material. The advantage of diagnostic FNAC is that it is a rapid, safe and usually less-painful procedure than either a surgical biopsy or a core needle biopsy in women with a palpable breast lesion. In some settings, a preliminary interpretation of whether or not the patient has cancer can often be done at the time of FNAC, which may facilitate patient flow, expedite early discussion about the diagnosis and assist in treatment planning. A disadvantage of FNAC is that the incidence of false negative results has been estimated to be 4–27%. Thus, the absence of cancer cells upon FNAC does not rule out invasive cancer, and a tissue based biopsy [large core needle or surgical] may be needed if the FNAC results are nondiagnostic or negative. The accuracy of FNAC can be improved by having a trained cytopathologist present during the procedure. At the present time, FNAC is not suitable for the evaluation of asymptomatic women without a palpable lump.

Core needle biopsy: A core needle biopsy [CNB] consists of the removal of a tissue specimen with a hollow cutting needle [usually 14 gauge]. False negative results can occur with core needle biopsies, especially if insufficient tissue is obtained. Obtaining 4 specimens with a 14 gauge needle usually provides enough tissue for diagnosis. A small metallic marker or clip should be placed at the biopsy site so the area can be seen on radiographic imaging studies and the surgeon can localize the area of the tumor.

The advantages of CNB over FNAC include lower sampling error and larger volume of tissue retrieved, allowing the pathologist to document invasive versus in situ disease, grade the tumor accurately and often perform tumor biomarker tests. In addition, since the large bore needle obtains a tissue sample [rather than cells], CNB does not require a trained cytopathologist. CNB is less costly than a surgical biopsy and can demonstrate benign findings that may spare women unnecessary surgical biopsies.

Vacuum-assisted biopsy: Vacuum-assisted biopsy [VAB] devices use a large bore hollow needle and permit removal of greater tissue volumes [up to 10 fold, often using an 11-gauge instrument]. VAB is considered the preferred approach for the sampling of nonpalpable lesions or suspicious calcifications seen on mammography because the volume of tissue obtained is greater and there is a lower incidence of false negative findings due to insufficient material. Similar to CNB, clips are placed at the biopsy site in VAB. This is important for imaging correlation of the biopsied lesion and facilitates subsequent surgical identification and resection.

Image-guided biopsy: Image-guided tissue sampling is required when the CBE is normal and an abnormality is seen only with screening imaging. It can be done under mammographic [i.e., stereotactic] or ultrasound guidance. Generally, ultrasound guided CNB is faster and better tolerated than stereotactic techniques, but there may be sampling limitations. Stereotactic biopsy is effective and can be performed at the same or lower cost than needle-localized surgical biopsy with less morbidity.

Benign lesions

Benign epithelial breast lesions can be classified histologically into three categories: nonproliferative [e.g., simple breast cyst, papillary apocrine change, mild hyperplasia of usual type], proliferative without atypia [e.g., usual ductal hyperplasia, fibroadenoma, intraductal papilloma, sclerosing adenosis, radial scar], and atypical hyperplasia [e.g., atypical ductal hyperplasia [ADH], atypical lobular hyperplasia [ALH] and lobular carcinoma in situ [LCIS]]. Surgical excision may be indicated for some benign epithelial breast lesions because of the possibility of associated malignancy that was not captured on initial biopsy. This upgrade to invasive breast cancer can occur in 10–40% of patients. Diagnoses for which surgical excision and risk-reducing interventions are warranted include ADH, ALH, and LCIS [see *Breast Cancer Risk Factors and Risk Reduction*].

Breast cancer subtypes

Ductal carcinoma in situ [DCIS]: Pure DCIS is a noninvasive lesion that rarely presents as a palpable mass. The diagnosis of DCIS increased dramatically with the introduction of screening asymptomatic women with mammography. Because DCIS is noninvasive, it is not considered life threatening. However, since DCIS may be a precursor to invasive breast cancer, patients diagnosed with DCIS are treated with local therapy [i.e., surgery with or without radiation] to prevent the development of an invasive cancer. If the DCIS is hormone receptor positive, patients may be offered hormonal therapy to prevent the occurrence of invasive cancer in either breast.



Histologic subtypes of invasive cancer: The diagnosis of breast cancer is generally made on the presence of malignant epithelial cells showing evidence of stromal invasion (on histology). There are various histologic types of invasive breast cancer. The most common histologic types of epithelial breast carcinoma are infiltrating ductal carcinoma (IDC) [70–80% of invasive lesions], infiltrating lobular carcinoma (ILC) [8% of invasive breast cancers] and mixed ductal/lobular invasive carcinoma [7% of invasive breast cancers]. Other histologic subtypes include metaplastic, mucinous, tubular, medullary and papillary carcinoma (<5% of invasive cancers). Additional classification can be done according to molecular subtypes (based on gene expression). Histologic types of breast cancer differ greatly in their pathophysiologic etiology, tumor biology, clinical presentations, hormone receptor profiles and ultimately clinical outcome.

Inflammatory breast cancer (IBC) is an aggressive subtype of invasive cancer [1–5%] that is usually ductal in histology. IBC is a clinical diagnosis. Patients with IBC have diffuse erythema [redness] and ridged or pitted skin (peau d'orange) caused by edema [swelling] that covers one third or more of the breast. Patients with IBC may have dermal lymphatic invasion by tumor cells on skin biopsy; however, this finding is not necessary to make a diagnosis of IBC.

Hormone receptors: The presence or absence of hormone receptors—specifically estrogen receptor (ER) and progesterone receptor (PR)—will affect the treatment plan and prognosis. Many breast cancers are dependent upon estrogen and/or progesterone for growth, mediated through the ER and PR. Testing for hormone receptors (ER and PR), usually using immunohistochemistry, should be performed routinely in all invasive breast cancers beginning at the limited level of resources. The probability of a tumor being hormone receptor positive depends on patient age, demographic factors, and tumor biology. Poor sample preparation and fixation can result in false negative ER/PR findings.

HER2: HER2 (also called HER2/neu) is a biomarker that is overexpressed or amplified in approximately 20% of breast cancers. Since patients with HER2-positive tumors have been shown to have increased survival with HER2 targeted therapies, this biomarker should be tested at the enhanced level and at the limited level if targeted therapy (e.g., trastuzumab) is available. Measurement of HER2 overexpression or gene amplification is commonly done by either IHC or fluorescence in situ hybridization (FISH), respectively.

Clinical Categories

Survival impact: Assessing hormone receptor status and HER2 expression level also informs tumor biology and survival. Currently, IHC testing of biomarkers can differentiate three major clinical categories of breast cancer.

Hormone receptor negative and HER2-negative: This subtype of cancer is often referred to as “triple negative” because the tumor is ER negative, PR negative, and negative for the overexpression of HER2. Patients with triple-negative breast cancer are candidates for chemotherapy and tend to have a worse prognosis than those with hormone receptor-positive breast cancer.

Hormone receptor-(ER and/or PR) positive and HER2-negative: Patients with hormone receptor-positive and HER2-negative breast cancer tend to have a better prognosis than either triple-negative or HER2-positive breast cancer, but tumor recurrences can occur very late, even decades after original diagnosis in early stage disease. Patients with this subtype breast cancer should receive hormonal therapy and may also receive chemotherapy depending on the stage at diagnosis and other factors.

HER2-positive: About 20% of breast cancers are HER2 positive, with approximately half of these tumors also being ER and /or PR-positive and approximately half being hormone receptor negative. Patients with HER2-positive tumors who are also hormone receptor-positive should receive hormonal therapy in addition to HER2 directed therapy. WHO has recently added trastuzumab, which targets HER2, to the list of essential medicines [see *Systemic Therapy: Hormonal Therapy and Targeted Agents*].

Cost of testing and availability of resources

Cost: Increasing pathology capacity is a high priority in many settings. Hormone receptor testing can be performed at affordable prices in many low-resource settings; however, insufficient numbers of trained pathologists and adequate laboratories in these settings can cause a delay in providing the results needed to initiate appropriate treatment. The price of HER2 testing varies by setting but can be more costly than hormone receptor testing due to reagent costs. The cost of one year of HER2 directed therapy [trastuzumab] is substantial but can be lifesaving and therefore accurate biomarker assessment is required [see *Systemic Therapy: Hormonal Therapy and Targeted Agents*].

Reporting outcome and quality assurance: IHC is easier, safer and less costly than hormone binding assays and can detect levels as low as 1% positive-staining carcinoma cells. Tumors with any level of ER expression should be considered ER-positive because patients with tumors that have low levels of ER may benefit from hormonal therapy. IHC analysis of overexpression of the HER2 oncogene should be conducted in settings where the testing will affect therapeutic selection. HER2 can also be tested using FISH, but this technique tends to require more resources. Newer techniques, such as the RNA reverse transcription and DNA polymerase chain reaction [RT-PCR] method as part of a multigene assay for measuring biomarkers such as ER or HER2, are being developed and employed to identify high-risk tumor biology and predict responses to therapy.

Quality assurance: Quality assurance measures must be in place to ensure optimal testing and confirm accuracy. Up to 20% of current IHC determinations worldwide may be inaccurate. Many factors can contribute to this, including pre-analytic variables, such as specimen processing and storage, and analytic variables, such as reagents, testing parameters and others. Concordance rates between high-volume laboratories and initial sites of patient evaluation are approximately 90% in settings where rigorous quality-assurance measures have been implemented. Core elements used to reduce assay variability include defining appropriate specimen handling [e.g., minimize time to fixation, preferably less than 1 hour], fixation technique [e.g., use 10% neutral buffered formalin—no less than 6 hours, no more than 72 hours] and analytical testing methods [thresholds for interpretation and quality assurance methods].



WHAT WORKS

Coordination of care: Implementation of a breast pathology program requires an integrated, comprehensive system that addresses all facets of care for a woman with a breast mass. There must be mechanisms for appropriate referral; for specimen labelling, handling, processing and analyzing; for the documentation of pathology results, as well as timely communication of the biopsy results to the health care providers and the patient.

All women presenting with a breast mass must undergo biopsy—minimally invasive or excisional—even when clinical findings are strongly suspicious of cancer. Mastectomy should never be used as a method of tissue diagnosis. Additionally, testing for hormone receptor positivity should be done before initiating treatment with hormonal agents. Some have suggested that hormonal therapy should still be initiated in settings that lack the ability to test for hormone receptors because a majority of women may benefit from this relatively low-cost intervention. However, this approach may cause harm and increase financial costs in the approximately 30% of women with hormone receptor-negative tumors and is therefore **not** recommended.



Minimally invasive breast biopsy program: Developing a minimally invasive breast biopsy program may augment diagnostic resources in the community while reducing the costs and morbidity associated with surgical excisional biopsy. Practitioners who perform FNAC or CNB should be adequately trained to ensure the success of a minimally invasive breast biopsy program. If IHC testing is done centrally, infrastructure needs to be in place to transport the specimens safely and return the results to the health care provider in a timely fashion.

Data: The minimum data reported by pathologists should include the histologic type, tumor grade, hormone receptor status and HER2 status [if HER2 targeted therapies are available] for all tissue samples; for surgical samples, whether or not there is tumor at the margins of the surgical sample and nodal involvement should be assessed and reported. A standardized reporting of pathology results can provide a checklist of important findings. It can also facilitate the discussion of pathology as part of a larger multidisciplinary breast care working group consisting of oncologists, pathologists, radiologists and surgeons to ensure an accurate understanding of a woman's diagnosis and staging and form a consensus treatment plan tailored to a woman's needs.

Quality assurance and process indicators: All diagnostic and pathology testing must ensure that the information provided is useful and reliable to determine prognosis and direct treatment. Formal quality assurance procedures should be implemented to monitor the accuracy of diagnostic findings over time. The Breast Health Global Initiative (BHGI) has encouraged standardization of pathology reporting with seven process indicators: percentage of pathology reports with sufficient information for proper clinical management; percentage of reports meeting reasonable/locally established turnaround time; percentage of nondiagnostic pathology reports for FNAC; percentage of inadequate specimen for biopsies; percentage of suboptimal samples compromising diagnosis; percentage of change of diagnosis on second review and percentage of treatment planning conferences or working group meetings attended by pathologists. Measures to assess the effectiveness of process improvement are: percentage of pathology reports that include margin status; percentage of differences between intraoperative and final pathologic diagnoses and percentage of breast cancer cases tested for ER, PR and HER2.

PLANNING STEP 1: WHERE ARE WE NOW?

Investigate and assess

Assess the burden of breast cancer and diagnostic needs

- Determine percentage of breast biopsies done surgically, by FNAC, by CNB, and with image guidance.
- Assessing existing programs for pathology review in the region can inform decision-making as to how to expand coverage.

Assess existing biopsy and pathology capacity

- Assess the availability and quality of pathology services.
- Assess provider knowledge of biopsy techniques and diagnosis procedures.
- Assess pathology resources for tissue diagnosis and staging of cancer.

Assess patient access and barriers to diagnosis

- Identify structural barriers to diagnosis [e.g., lack of trained expertise, location of services, lack of adequate referral network, equipment shortages, etc.]
- Identify sociocultural, personal and financial factors that may impact a woman's willingness and ability to present for clinical evaluation and adhere to the multiple steps required for diagnosis [e.g., lack of awareness, fear, stigma, cost, etc.]. Women may fear having surgical excision of a breast mass with its resultant cosmetic effects and stigma. These fears need to be addressed and women encouraged to seek care earlier.

Assess health system capacity

- Assess qualification and training of personnel involved in performing, processing, handing and interpreting pathology specimens.
- Evaluate existing pathology training programs and continuing education for diagnosis and staging of breast cancer.
- Review the efficacy and efficiency of the existing referral process.
- Assess integration of pathologists as members of breast care working groups and multidisciplinary care teams.

Assess monitoring and evaluation capacity

- Assess existing quality assurance programs, such as governing bodies to ensure adequate standards are being followed.
- Assess the collection of accurate data regarding breast cancer diagnosis and staging.
- Assess the process of reporting cancer diagnoses to local or national cancer registries.
- Health systems should monitor time from presentation to diagnosis and treatment as a quality metric.

PLANNING STEP 2: WHERE DO WE WANT TO BE?

Set objectives and priorities

Identify community and health system partnerships

- Identify where women are most likely to present for initial breast evaluation to help focus health professional training programs on clinical assessment strategies.
- Identify partners (institutions or organizations) that may provide patient education or navigation.
- Consider the need for additional awareness and educational programs for health care providers, community health workers and the lay population.

Identify gaps in current health system

- Use data on time from presentation of a suspicious breast concern to definitive diagnosis and time from referral for imaging and pathology studies to report generation to identify health system and patient barriers to care.
- Identify local and regional needs in diagnostic services, such as the performance of CBEs, imaging capability, diagnostic biopsy procedures and pathology services.

Set achievable objectives

- Objectives should promote one common goal: equitable access to efficient and accurate diagnosis and staging for all women with a suspicious finding.
- Include quality standards, monitoring and evaluation in new diagnostic services programs.
- Develop national breast cancer diagnosis guidelines.
- All women presenting with breast masses or screening abnormalities should undergo diagnostic breast biopsy. Minimally invasive procedures are less costly than a surgical biopsy performed in an operating suite but depend heavily on available skills and expertise.
- Obtained tissue at all levels should undergo pathology review for histologic type, nuclear grade and biomarker testing, which will affect treatment decisions, measured extent of the lesion and whether lymph nodes contain tumor.
- Balance local needs (including patient access to care) and expertise with the advantages of centralized services for resource-intensive or speciality services and/or equipment.
- Address gaps in referral networks to ensure diagnostic follow up for all breast health complaints.
- Report and document clinical findings, including the sharing of data with a cancer registry.
- Set goals for improving diagnostic services. [e.g., short-term goal: reduce by 50% the number of surgical biopsies; medium-term goal: increase the percentage of reports that meet locally established turnaround time; and long-term goal: increase the number of trained pathologists in a region, to improve access to technological advancements in diagnosis].

Set priorities and determine feasibility of interventions

- Assess the feasibility of new programs by using demonstration or pilot projects with measurable outcomes.
- The feasibility of each incremental improvement in services should be directed by the available expertise, cost, competing health priorities and resources in each community.
- Follow a resource-stratified pathway for program development that identifies available resources across the continuum of care.
 - At the basic level of resources, pathologic analysis should focus on histology with processes to establish hormone receptor status. Each target population (influenced by age, tumor type, geographic location) may have a different percentage of hormone-positive tumors, which directly affects the use of hormone therapy as a preventative or therapeutic modality.
 - At the limited and enhanced level of resources HER2 overexpression or gene amplification should be assessed if routine access to trastuzumab is available.



PLANNING STEP 3: HOW DO WE GET THERE?

Implement and evaluate

Establish financial support and partnerships

- Develop partnerships that involve community stakeholders.
- Consider regional and international partnerships to build capacity and skills.
- Consider financial feasibility of scaling up diagnostic capacity and pathology services.

Implement and disseminate

- Introduce educational programs for health professionals that outline appropriate diagnostic procedures and staging studies.
- Strengthen the referral network. Coordination of a multi-step diagnostic process for breast cancer requires a strong referral network and timely communication between service providers.
- Health systems analysis requires coordination of pathology services at the different access points of a health system (e.g., where should a biopsy be performed, who should review it, and what health care providers will want to access the results before initiating treatment). These interventions can be facilitated at a centralized location of cancer care but must be balanced against current preference of women seeking care locally.
- Telepathology, short-term expert missions and transport of tissue for international review may not be sustainable long-term programs but may be considered to fill essential gaps in expertise at the current time.

Monitor and evaluate:

- Develop process metrics to evaluate quality of care delivery, using a resource-stratified approach (see Table 1).
- Process metrics may include: percentage of patients referred for diagnostic biopsy that undergo this procedure; percentage of patients diagnosed with a benign versus malignant tumor; percentage of nondiagnostic biopsies; percentage of reports that include histology, grade, and extent of tumor, as well as ER, PR and HER2 status and the number of lymph nodes identified and the number of lymph nodes with tumor involvement.

CONCLUSION

Accurate histopathologic diagnosis is the cornerstone of cancer care and is needed to direct therapy. The histologic subtype and receptor status must be tested on each tumor to inform prognosis and select treatment. Many programs have been explored to bridge the existing deficits in expert pathology resources, most notably the centralization of services. Implementation of the minimally invasive breast biopsy produces significant benefit for a woman with a breast mass and may reduce overall costs to the hospital and system by reducing the number of surgical biopsies. In low-resource settings, where many women present for care locally, significant effort must be made to ensure these women are accessing and receiving appropriate diagnosis and treatment.

Table 1: Diagnosis resource allocation and process metrics

Level of resources	Basic	Limited	Enhanced	Maximal
Clinical	History Physical examination Clinical Breast Exam (CBE) Tissue sampling for cancer diagnosis [cytologic or histologic] prior to initiation of treatment	Ultrasound-guided FNAB of sonographically suspicious axillary nodes Sentinel lymph node (SLN) biopsy with blue dye	Image guided breast sampling Preoperative needle localization under mammography and/or ultrasound guidance SLN biopsy using radiotracer	
Imaging and lab tests	*	Diagnostic breast ultrasound Plain chest and skeletal radiography Liver ultrasound Blood chemistry profile* Complete blood count (CBC)*	Diagnostic mammography Specimen radiography Bone scan, CT scan Cardiac function monitoring	PET scan, MIBI scan, breast MRI, BRCA1/2 testing Mammographic double reading
Pathology	Pathology diagnosis obtained for every breast lesion by an available sampling procedure Pathology report containing appropriate diagnostic and prognostic/predictive information to include tumor size, lymph node status, histologic type and tumor grade Process to establish hormone receptor status possibly including empiric assessment of response to therapy Determination and reporting of TNM stage	Determination of ER status by IHC Determination of margin status, DCIS content, presence of LVI Frozen section or touch prep SLN analysis	Measurement of HER2 overexpression or gene amplification Determination of PR status by IHC	IHC staining of sentinel nodes for cytokeratin to detect micrometastases Pathology double reading Gene profiling
Process metrics	No. of patients with tissue diagnosis/no. of patients with suspicious mass	% Patients with biopsy-proven cancer diagnosis who have documented TNM stage	% Patients with biopsy-proven cancer diagnosis who have documented HER2 status	Process metrics determined based upon standards of care in high-income countries

Source: Eniu A, Carlson RW, El Saghir NS, et al. Breast Health Global Initiative Treatment Panel. Guideline implementation for breast healthcare in low- and middle-income countries: treatment resource allocation. *Cancer*. 2008 Oct 15;113(8 Suppl):2269-81.

*Systemic chemotherapy requires blood chemistry profile and CBC testing for safety. When chemotherapy is available at the basic level, these tests also should be provided. ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, IHC testing of ER status also should be provided.

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