Guideline Implementation for Breast Healthcare in Low- and Middle-Income Countries

Diagnosis Resource Allocation

A key determinant of breast cancer outcome in any population is the degree to which newly detected cancers can be diagnosed correctly so that therapy can be selected properly and provided in a timely fashion. A multidisciplinary panel of experts reviewed diagnosis guideline tables and discussed core implementation issues and process indicators based on the resource stratification guidelines. Issues were then summarized in the context of 1) clinical assessment, 2) diagnostic breast imaging, 3) tissue sampling, 4) surgical pathology, 5) laboratory tests and metastatic imaging, and 6) the healthcare system. Patient history provides important information for the clinical assessment of breast and comorbid disease that may influence therapy choices. Focused clinical breast examination and complete physical examination provide guidance on the extent of disease, the presence of metastatic disease, and the ability to tolerate aggressive therapeutic regimens. Breast imaging improves preoperative diagnostic assessment and also permits image-guided needle sampling. Diagnostic mammography was not considered mandatory in low- and middle-income countries when resources are lacking. Needle biopsy is preferred to surgical excision for the initial diagnosis of suspicious breast lesions, unless resources are unavailable. Mastectomy should never be used as a method of tissue diagnosis. The availability of predictive tumor markers, especially estrogen receptor testing, is critical when endocrine therapies are available; quality assessment of immunohistochemistry testing is important to avoid false-negative results. Incremental allocation of resources can help address economic disparities and help ensure equity in access to timely diagnosis.

In October 2002, a panel of breast cancer experts and advocates from around the world met at the first Breast Health Global Initiative (BHGI) Consensus Conference in Seattle, Washington to develop consensus guidelines for the early detection, diagnosis, and treatment of breast cancer in the setting of limited healthcare resources. The results of this first BHGI Global Summit were published in 2003 and describe healthcare disparities as they relate to breast cancer early detection, diagnosis, and treatment in low- and middle-income countries (LMCs).1-4 In addition to providing fundamental principles for resource utilization in breast healthcare, the 2003 reports emphasized additional program elements that were viewed as necessary for the successful operation of breast cancer programs, including a supportive environment for women to seek care at the first indication of symptoms and access to appropriate, affordable diagnostic tests and treatment.

The BHGI guidelines were expanded at the second BHGI Global Summit in Bethesda, Maryland held in January 2005 and published as a set of consensus statements in 2006.5-9 In this second set of reports, resources for early detection, diagnosis, treatment, and healthcare systems were stratified according to a 4-tiered system, depending on the availability of resources: basic, limited, enhanced, and maximal.5 The purpose of this stratification was to provide a framework for systematic and comprehensive improvement in care.

Each of the prior Global Summits included a Diagnosis Panel, the purpose of which was to address methods of cancer diagnosis in LMCs.3,7 The 2 previous BHGI Diagnosis Panels emphasized the need for a ‘pathologic diagnosis’ (based on microscopic examination of tissue or cellular specimens) before initiating breast cancer treatment. The 2005 Diagnosis Panel described options for tissue sampling (fine-needle aspiration biopsy [FNAB], core needle biopsy, and surgical biopsy) and indicated that the choice between these methods should be based on available tools and expertise. Correlation of clinical, imaging, and pathology findings to improve diagnostic effectiveness and accuracy was emphasized. Organized training of pathologists and the creation of centralized and international pathology facilities also were discussed.

The purpose of this third BHGI Global Summit was to address guideline implementation as it relates to resource allocation in LMCs and to consider process indicators that may provide benchmarks for implementation success and possibly for programmatic expansion to the next higher resource allocation level. The 2007 BHGI Diagnosis Panel expanded on prior guideline iterations to examine how key diagnostic elements of breast cancer clinical evaluation, laboratory tests, imaging, tissue sampling, and surgical pathology can be integrated programatically to form a functional diagnostic clinic module within breast care programs in LMCs, given differing levels of available resources. The previously formulated BHGI guidelines are broadened to include process indicators that can be used by medical professionals and healthcare authorities to assess the functionality of their breast health programs.

MATERIALS AND METHODS
The BHGI Consensus Conference methodology for the 2007 Global Summit (held in Budapest, Hungary, October 1 through 4, 2007) was used for the 2 prior Global Summits and has been described previously.5 Diagnostic resources were stratified according to the same 4-tiered system based on the availability of resources relevant to diagnosis:

- **Basic level**—Core resources or fundamental services are those that are absolutely necessary for any breast healthcare system to function. Basic-level services typically are applied in a single clinical interaction.
- **Limited level**—Second-tier resources or services are those that are intended to produce major improvements in outcome, such as increased survival, and are attainable with limited financial means and modest infrastructure. Limited-level services may involve single or multiple clinical interactions.
- **Enhanced level**—Third-tier resources or services are those that are optional but important. Enhanced-level resources should produce further improvements in outcome and increase the number and quality of therapeutic options and patient choice.
- **Maximal level**—High-level resources or services are those that may be used in some high-resource
countries and/or may be recommended by breast care guidelines that do not adapt to resource constraints but that nonetheless should be considered a lower priority than those resources or services listed in the basic, limited, or enhanced categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment. To be useful, maximal-level resources typically depend on the existence and functionality of all lower level resources.

The evaluation by the Diagnosis Panel was divided into 6 parts: 1) clinical assessment, 2) diagnostic breast imaging, 3) tissue sampling, 4) surgical pathology, 5) laboratory tests and metastatic imaging, and 6) healthcare system issues related to diagnosis. The panel reviewed the previous stratification tables, discussed the core implementation issues related to these programs, and made relevant changes based on consensus opinion. Then, process indicators were developed based on the priorities established in the guideline stratification.

RESULTS
Resource Stratification for Diagnosis Program
Implementation (Figure 1, Columns 1-3)
There was fairly uniform agreement regarding the diagnostic tools appropriate for countries of limited resources, but there was more variability within and between BHGI panels regarding the stratification levels of each diagnostic tool as a function of available resources. The panel noted that basic, limited, enhanced, and maximal resources may coexist in different areas within a country and that decisions regarding which tools to allocate to the different resource levels must be made in part on an individual basis that considers available personnel, equipment, and facilities as well as the unique needs of a specific population and competing national healthcare priorities.

Basic-level resources
At the basic level, diagnosis is made on the basis of clinical history; clinical breast examination (CBE); and, in the absence of imaging services, tissue sampling using pathology services adequate to distinguish benign from cancer diagnoses. Minimum requirements for diagnosis at the basic level include the ability to take a history, perform CBE, make a pathologic diagnosis of breast cancer (cytologic or pathologic), determine clinical and pathologic TNM stage, and record this information in the medical record. A pathology diagnosis must be obtained for every breast lesion by any available sampling procedure, and the pathology report must contain appropriate diagnostic and prognostic/predictive information.

The panel uniformly agreed that the assessment of an invasive cancer’s hormone receptor status is critical to therapeutic decision-making, but there was debate regarding whether hormone receptor analysis using immunohistochemistry (IHC) should be provided at a basic or limited resource level. For example, in the absence of IHC testing, it may be possible to assess hormone receptor status on clinical grounds at the basic level in the absence of IHC testing by observing clinical response to neoadjuvant endocrine therapy. Such an approach is considered nonstandard and arguably is not the most effective use of resources. When IHC testing is used, whether at the basic or limited level, quality-assurance measures must be in place to confirm testing accuracy. The panel emphasized that, even at the basic level, the availability of accurate information regarding breast cancer size and stage at presentation, breast cancer diagnosis, treatment, competing health problems, and outcome is invaluable to determine the next steps required to decrease breast cancer mortality.

Limited-level resources
Diagnostic imaging, especially breast ultrasound (US), needs to be available to support limited-level treatment. The availability of breast US, in addition to providing diagnostic information regarding primary tumors in the breast, also allows for the use of US-guided FNAB for sonographically suspicious lymph nodes, which is a simple, cost-effective method for staging lymph node-positive cancers and can avoid an additional surgical procedure (sentinel lymph node [SLN] biopsy). It is noteworthy that a negative lymph node FNAB does not rule out lymph node-positive cancer because of the potential for sampling error in the lymph nodes with needle sampling.

A process should be in place to perform SLN biopsy using blue dye at the limited level. Plain chest and skeletal radiography and liver US studies are recommended to assess for distant spread of disease in patients with locally advanced and lymph node-positive cancer. Because chemotherapy is available at the limited level, a blood chemistry profile and a complete blood count should be provided. These laboratory tests are useful both for the safe application of systemic therapy and as a method (albeit insensitive) for detecting metastatic disease, the presence and/or absence of ductal carcinoma in situ, and the presence of lymphovascular invasion. Pathology tumor marker assays, starting with estrogen receptor (ER) testing by IHC, should be available to support limited-level treatment, because the test results
determine key questions regarding therapy choices for endocrine therapy. Pathology reports at the limited level of resources should include margin status.

**Enhanced-level resources**

With enhanced-level resources, image-guided tissue sampling should be available to facilitate the diagnosis of nonpalpable disease. These procedures include preoperative needle localization under mammographic or US guidance, image-guided needle biopsy, and SLN biopsy using radionuclide. US guidance for needle biopsy has the advantages of lower cost and multipurpose equipment use. Stereotactic guidance for biopsy or preoperative localization typically requires higher (maximal) level resources of support because of the cost of dedicated stereotactic imaging equipment and disposable sampling needles.

A process should be in place to determine the status of HER-2/neu oncogene overexpression at the enhanced level, because this test result drives important systemic therapy choices both for the use of trastuzumab (when it is available) and for determining chemosensitivity to some drug regimens. Measures should be in place to determine the status of HER-2/neu overexpression and/or gene amplification as indicated by the table.

### Table: Diagnosis Resource Allocation and Process Metrics

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Clinical</th>
<th>Imaging and Lab Tests</th>
<th>Pathology</th>
<th>Process Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>History</td>
<td></td>
<td>Pathology diagnosis obtained for every breast lesion by any available sampling procedure</td>
<td># Pts with tissue dx / # Pts with suspicious mass</td>
</tr>
<tr>
<td></td>
<td>Physical examination</td>
<td></td>
<td>Pathology report containing appropriate diagnostic and prognostic predictive information to include tumor size, lymph node status, histologic type and tumor grade</td>
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</tr>
<tr>
<td></td>
<td>CBE</td>
<td></td>
<td>Process to establish hormone receptor status possibly including empirical assessment of response to therapy*</td>
<td>Determination and reporting of TNM stage</td>
</tr>
<tr>
<td>Limited</td>
<td>US-guided FNAB of sonographically suspicious axillary nodes</td>
<td>Diagnostic breast ultrasound (US)</td>
<td>Determination of ER status by IHC*</td>
<td>% Pts with biopsy-proven cancer diagnosis who have documented TNM stage</td>
</tr>
</tbody>
</table>
|                    | Sentinel lymph node (SLN) biopsy with blue dye | Plain chest and skeletal radiography | Determination of margin status, DCIS content, presence of LVI | frozen section or touch prep SLN analysis
|                    |          | Liver US | | § |
|                    |          | Blood chemistry profile* | | | |
|                    |          | Complete blood count (CBC)* | | | |
| Enhanced           | Image-guided breast sampling | Diagnostic mammography | Measurement of HER-2/neu overexpression or gene amplification§ | % Pts with biopsy-proven cancer diagnosis who have documented HER-2/neu status |
|                    | Preoperative needle localization under mammography and/or US guidance | Specimen radiography | Determination of PR status by IHC | % Pts with biopsy-proven cancer diagnosis who have documented HER-2/neu status |
|                    | SLN biopsy using radionuclide | Bone scan, CT scan | | |
|                    |          | Cardiac function monitoring | | |
| Maximal            | PET scan, MIBI scan, breast MRI, BRCA1/2 testing | IHC staining of sentinel nodes for cytokeratin to detect micrometastases | Pathology double reading | Maximal category process metrics determined based upon standards of care in high-income countries |
|                    | Mammothographic double reading | | Gene profiling tests | | |

*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. ‡ The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. §If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.
progesterone receptor (PR) by IHC and to measure HER-2/neu overexpression or gene amplification. More sophisticated studies (such as diagnostic mammography, specimen radiology, bone scan, computerized tomography, and cardiac function monitoring) should be provided at the enhanced level.

Maximal-level resources

The 2007 Global Summit emphasized the implementation of guidelines for breast cancer diagnosis in countries with less than maximal resources. However, the panel recognized that maximal resources enable the availability of other methods for detection, diagnosis, and treatment, including (but not limited to) stereotactic biopsy, positron emission tomography (PET) scanning, methoxy-isobutyl-isonitrile (MIBI) scanning, breast magnetic resonance imaging (MRI), and breast cancer gene (BRCA1/BRCA2) testing. The use of breast MRI to determine the extent of disease of a known cancer in the breast may be useful (at significant cost) in resource-replete, high-income settings with well established, population-based screening mammography. However, it has not been demonstrated that breast MRI contributes significantly to improvements in local control in breast-conservation therapy compared with standard breast imaging (mammography, US) and surgical excision with negative margins. Regarding pathology, the assessment of the presence or absence of micrometastasis in an SLN can be performed with IHC. This resource is placed at the maximal level, because the value of this information in the context of LMCs is unclear and debatable.

Quality-assurance and Process Metrics

Diagnostic capacity is critical to the success of any comprehensive breast healthcare program in LMCs. Because treatment decisions and estimates of prognosis will be based on the results of diagnostic and pathology tests, these tests must be done at a level that ensures that the information they provide is reliable and useful. Therefore, all programs must consider the implementation of formal quality-assurance procedures for imaging and pathology in which diagnostic findings are recorded and the accuracy of these findings is monitored over time. Such procedures identify areas for programmatic improvement. Standardization of pathology procedures and reports is important for characterizing breast lesions better and for improving communication among healthcare providers. A pathology service should provide not only diagnostic information but also prognostic and predictive information whenever possible.

Process metrics

Quality improvement is an important daily routine for healthcare professionals and is a statutory obligation in many countries. Quality can be improved without measuring it, but measurement plays an important part in improvement. Quality indicators are explicitly defined and measurable items that refer to the structures, processes, or outcomes of care. They are retrospectively measured elements of performance for which there is evidence or consensus that they can be used to assess quality. The development of indicators requires supporting information or evidence derived by systematic or nonsystematic research methods.

Process metrics are related but distinct indicators of care delivery. These metrics allow programmatic assessment of resource use. The panel identified the following process metrics by which quality of care could be measured specific to the level of resources.

- Basic—the ratio of the number of patients with a (benign or malignant) tissue diagnosis to the number of patients with a suspicious mass (a finding on CBE that warranted further evaluation);
- Limited—the percentage of patients who had a biopsy-proven breast cancer diagnosis with documented TNM staging; or
- Enhanced—the percentage of patients who had biopsy-proven breast cancer with documented HER-2/neu status (see Fig. 1, Column 4).

Other potential process metrics were evaluated by the panel but were placed in appropriate positions in the Health Care Systems Panel metrics grid. For example, the median pathologically determined size of an invasive primary cancer would be determined at the time of diagnosis. However, this indicator is cross-functional and is considered representative of multiple factors associated with breast cancer detection in a program or center that provides breast care. Thus, it was identified as a quality indicator for the Health Care Systems Panel at the basic level of resources.

DISCUSSION

General Principles of Diagnosis Resource Allocation

The 2007 Diagnosis Panel reaffirmed 4 main themes of the 2003 and 2005 Summits:

1) The improvement of breast cancer awareness and education facilitates diagnosis of breast cancer at an early stage;
2) Early diagnosis of breast cancer is advantageous, because it is life-saving, cost-effective, and
requires less aggressive, less resource-intensive therapy;
3) The simplicity of diagnostic processes is critical in a limited-resource setting, because patients may face numerous barriers that prevent repeated visits; diagnostic tests should be used in combinations that enable establishing the diagnosis in a single visit as best as possible; and
4) The collection of accurate national statistics regarding breast cancer (type, size, stage, treatment, and outcome), available resources (personnel, equipment, facilities), and competing priorities (health or other issues) will help to tailor the recommendations for breast cancer diagnosis to the needs of an individual country.

Clinical Assessment (Figure 1, Column 1)
Clinical versus pathologic diagnosis
An accurate diagnosis is essential to confirm the presence of breast cancer, to assess prognosis, and to guide treatment. The tools for clinical diagnosis include a patient history and CBE and are guided further by diagnostic imaging studies, especially diagnostic mammography and breast US. The 2007 panel agreed with the prior consensus panels regarding the critical distinction between a 'clinical diagnosis' of breast cancer (based on signs, symptoms, and imaging findings) and a 'pathologic diagnosis' of breast cancer (based on microscopic evaluation of tissue or cellular specimens). A correct pathologic diagnosis of breast cancer must be established before initiating definitive treatment.

Clinical history and review of systems
Self-detection of a breast mass is the most common breast complaint for which women seek medical advice. The clinical history provides guidance in evaluating any breast complaint and is considered an essential component of clinical evaluation. Healthcare providers should obtain baseline information regarding breast symptoms and their nature and duration, and note should be taken concerning the degree to which the findings have changed over time as appreciated by the patient. Related historic findings associated with breast cancer risk, such as reproductive history, menopausal status, personal cancer history, and family history of breast cancer, also should be ascertained; and these findings should be documented in the patient's record for future reference. In addition to obtaining the history relevant to breast health, an overall medical history and review of systems are helpful to appropriately document the presence or absence of comorbid disease that may affect treatment decisions, especially in relation to the degree to which the patient can tolerate therapy.

CBE and complete physical examination
CBE is important for comparing the 2 breasts, confirming the presence of a dominant mass, documenting tumor size, and determining the local extent of disease. In patients who have findings suggestive of early breast cancer, a complete physical examination is unlikely to provide diagnostic information beyond that provided by CBE regarding the known cancer; however, used in conjunction with a good clinical history and review of systems, a complete physical examination may confirm physical evidence of comorbid illness that are suggested by findings on history or review of systems. In patients who have findings suggestive of advanced breast cancer, a complete physical examination may provide information regarding the presence of metastases in the lymph nodes and/or at distant sites.

Diagnostic Breast Imaging (Figure 1, Column 2)
Definitions
The distinction between screening and diagnostic imaging is important to recognize in the context of resource allocation. Diagnostic mammography is performed in women who have symptoms on self-examination or physical findings on CBE to clarify and classify the nature of the target lesion. By contrast, screening mammography is performed in target groups of asymptomatic women to identify clinically occult breast cancer and to facilitate early breast cancer detection. Screening mammography is resource-intensive, because it must be performed on large groups of women to be effective at finding significant numbers of cancers. By contrast, diagnostic mammography can be offered in settings with far fewer resources even when screening mammography cannot be sustained, because it offers significant diagnostic information and is applied in a much smaller group of women, and those who have clinical findings will warrant a workup.

Similarly, a distinction can be made between screening and diagnostic US, although this appears to be less relevant in clinical practice. Diagnostic breast US refers to the use of US to assess targeted, localized findings on physical examination, mammography, or both. Although screening breast US (US performed in asymptomatic women to look for nonpalpable breast cancer) is being evaluated, it has not been identified as an effective screening tool, because it is highly user-dependent in its efficacy, and it has a high false-positive rate and can require a large number of benign biopsies.

Diagnostic mammography
Diagnostic mammography requires trained personnel, equipment, facilities, reporting, and follow-up
systems. For women with clinical signs or symptoms suspicious for breast cancer, diagnostic mammography can help define the extent of disease in the breast and the axilla. If mastectomy is the only available surgical treatment for breast cancer, then diagnostic mammography is not essential. The 2005 Diagnosis Panel concluded that diagnostic mammography was essential for a center to offer breast-conservation therapy. It was pointed out that diagnostic mammography is not essential. The 2005 Diagnosis Panel concluded that diagnostic mammography was essential for a center to offer breast-conservation therapy. It was pointed out that diagnostic mammography is not essential. The 2005 Diagnosis Panel concluded that diagnostic mammography was essential for a center to offer breast-conservation therapy. It was pointed out that diagnostic mammography is not essential. The 2005 Diagnosis Panel concluded that diagnostic mammography was essential for a center to offer breast-conservation therapy. 

Specifically, Nadkarni et al reviewed their institutional experience in Mumbai, India to assess how often diagnostic mammography added to clinical assessment in the selection of patients for breast-conserving surgery. During 2004, 307 patients underwent modified radical mastectomy, and 428 patients underwent breast-conservation surgery at Tata Memorial Hospital. The investigators observed that, if mammography had not been performed in the 735 patients undergoing surgery, then breast conservation could have been performed erroneously in only 38 patients (5%), including 13 patients with impalpable, multicentric disease and 25 patients with extensive microcalcifications. The remaining patients were assessed correctly as warranting breast-conservation therapy or mastectomy on the basis of clinical assessment performed by an experienced surgeon. Furthermore, had breast conservation been attempted in the 38 patients who had clinically occult disease, most (if not all) would have been recognized and rectified postoperatively on the basis of positive surgical margins. Thus, whereas diagnostic mammography has been considered indispensable for breast conservation on historic grounds, that belief was not validated in a limited-resource setting in this current analysis from India.

The 2007 BHGI Diagnosis Panel reviewed the study by Nadkarni et al, as presented by Dr. Badwe, and concluded that a modification of the 2005 Diagnosis Panel's conclusion was warranted. It is noteworthy that Nadkarni et al were not arguing that diagnostic mammography is without value, nor were they suggesting that it should be eliminated as a tool in their country. Rather, their study demonstrated that women in LMCs who are treated at facilities that offer surgery, radiotherapy, and adequate pathology services should not unnecessarily be denied breast-conservation therapy simply because they lack diagnostic mammography services.

**Diagnostic breast ultrasound**

Diagnostic breast US is among the most useful diagnostic imaging applications in the evaluation of palpable lesions, distinguishing cystic from solid masses, characterizing the morphology and borders of solid masses, evaluating the axilla, and guiding percutaneous interventional procedures. Advantages of US as a diagnostic breast imaging technique include its ability to assess findings in real time, its accessibility to all parts of the breasts and axillae, the multipurpose use of the equipment, the absence of ionizing radiation, and the generally lower cost of US compared with mammography. Disadvantages of diagnostic breast US include the dependence of the method on the skill and training of the observer and the potential low quality of US imaging equipment.

**Tissue Sampling (Figure 1, Column 1)**

Accurate tissue diagnosis is the cornerstone of cancer therapy. All women with suspected breast cancer should receive an accurate cytologic or histopathologic diagnosis that confirms the presence of cancer before they are given definitive treatment. A formal pathologic diagnosis should not be bypassed, even when clinical findings are strongly suggestive of cancer or when healthcare resources are limited. The 2007 Panel reaffirmed the strong recommendation from the 2002 and 2005 Consensus Panels that mastectomy is a form of treatment and never should be used to diagnose breast cancer.

Two approaches for tissue sampling have comparable accuracy if they are used properly: minimally invasive biopsy, also called percutaneous or needle biopsy (ie, FNAB, core needle biopsy, and, in high-resource settings, vacuum-assisted biopsy) versus surgical biopsy (ie, incisional biopsy or excisional biopsy). The choice among these methods in the limited-resource setting will be influenced by factors such as the availability of necessary equipment and expertise. Whereas surgical biopsy traditionally has been the gold standard for pathologic diagnosis, it has been demonstrated that needle sampling is more cost-effective than surgical excision as an initial diagnostic intervention for suspicious breast lesions. Efforts should be made to make simple, minimally invasive techniques available in the breast clinic.
and/or breast imaging facility. Surgical excision for diagnosis should be reserved for those situations in which needle sampling is unavailable, cannot be performed for technical reasons, or benign histologic results of the needle sampling are discordant with the highly suspicious findings on breast imaging.\(^{21}\)

**Needle biopsy**

Compared with surgical biopsy, needle biopsy is less invasive, less expensive, does not cause scarring or deformity, and can be performed in an outpatient clinic. For women with locally advanced or metastatic breast cancer, needle biopsy can provide a tissue diagnosis, enabling the initiation of treatment.\(^{19}\)

For women with early-stage breast cancer, needle biopsy can convert what otherwise would have been 2 operations (surgical biopsy for diagnosis followed by definitive surgery for treatment) into 1 operation (a single, definitive surgery after needle biopsy). Needle biopsy techniques differ with respect to 2 parameters: the needle (eg, fine needle vs core needle) and the method used to guide needle placement (palpation or imaging). For most palpable lumps, the needle can be placed with the guidance of palpation. The use of image-guided needle biopsy is discussed below. The approaches for needle sampling of the breast include FNAB (discussed above for the evaluation of clinically suspicious lymph nodes), core needle (14-gauge) biopsy, and vacuum-assisted (11-gauge or 8-gauge) biopsy.

FNAB is the simplest and least costly to perform. A 22-gauge or smaller, beveled, straight needle is used to obtain a cytologic sample from a mass. The cells are smeared on a slide and put immediately in fixative or allowed to air dry. The slides can be stained and read immediately with a standard light microscope. Advantages of FNAB include the ability to provide a diagnosis within minutes and that it is the least invasive and least expensive breast biopsy method. Disadvantages include the need for personnel trained in obtaining and interpreting breast cytology specimens, and a moderately high frequency of insufficient samples.\(^{22}\)

Although FNAB is the most cost-effective method of obtaining tissue specimens, the accurate interpretation of an FNAB sample demands the availability of a well-trained breast cytopathologist.\(^{23}\) However, the ultimate choice of the sampling technique is not critical as long as the tissue diagnosis is accurate and provides important prognostic and predictive information. Key quality assurance questions for core needle and open biopsy are primarily concerned with pretesting management of tissue, most importantly the issues of immediate tumor fixation, the use of buffered formalin, and the optimal duration of fixation.

When a patient appears to have locally advanced disease, a core needle biopsy is preferred to FNAB for the definitive diagnosis of invasive cancer. This is a common issue in LMCs, because patients are more likely to present with clinically obvious, locally advanced disease. These late-stage patients should be considered for neoadjuvant chemotherapy before surgery. FNAB is a suboptimal biopsy procedure in this setting, because it cannot differentiate invasive cancer from noninvasive cancer. However, if metastatic disease in lymph nodes is confirmed with FNAB or if there is obvious clinical evidence of invasive disease (such as skin involvement, fixation to the chest wall, etc), then FNA is sufficient for diagnosis. Furthermore, to use FNAB in this clinical setting, there is a need to establish the availability of routine hormone receptor status in FNA samples, such as cell-block material.

In core needle biopsy, tissue specimens are removed with a cutting needle and automated gun. A variety of equipment is available, including disposable gun-needle combinations and disposable needles with a reusable gun. Obtaining multiple specimens (eg, 3-5 specimens) maximizes the opportunity to make a definitive diagnosis. Core needle biopsy is a safe, accurate, and cost-saving alternative to surgical biopsy for breast diagnosis.\(^{24}\) Compared with FNAB, core needle biopsy is slightly more invasive and has a lower rate of insufficient samples but with higher cost. The choice of FNAB versus core needle biopsy should depend on available resources and expertise.

Vacuum-assisted biopsy obtains the largest tissue specimens for needle sampling. Its advantage is that larger bore (8-gauge or 11-gauge) samples are obtained because of the technical assistance of vacuum suction and large-bore, automatic cutting needles. The disadvantage is extreme cost. Vacuum-assisted biopsy is the most expensive method of tissue sampling because the disposable devices used to sample tissue are complex, expensive, and should be used only once. It is not clear that vacuum-assisted sampling actually improves diagnostic outcome over 14-gauge core needle biopsy sampling, especially in an LMC, in which patients present most commonly with palpable rather than image-detected cancer.

**Surgical biopsy**

For palpable lesions, surgical biopsy can be excisional (removing the entire tumor) or incisional (removing a sample of the tumor for diagnosis). Surgical biopsy is a highly accurate procedure. Disadvantages of surgical biopsy include its invasive nature, expense, and potential scarring and deformity. When cancer is suspected, needle sampling is the preferred initial diagnostic approach. If the needle sample does
not show cancer but the lesion still is clinically suspicious, then surgical excision should be performed, because sampling errors can occur.\textsuperscript{23, 26}

When a benign lesion is suspected on the basis of CBE and diagnostic breast US, a cosmetic surgical excision can be performed under local anesthesia for a small, well circumscribed, benign-appearing mass (presumed fibroadenoma). The advantage of surgical excision of these most likely benign masses is that it makes a definitive tissue diagnosis, and it eliminates the need for follow-up beyond a postoperative visit.

**Image-guided breast procedures**

Diagnostic breast imaging enables the identification of abnormalities that are not detected on CBE. To make a pathologic diagnosis for nonpalpable abnormalities that are suspicious for cancer, special tissue sampling methods are needed. Image-guided procedures include image-guided needle breast biopsy and preoperative wire localization for surgical excision.\textsuperscript{24} These methods typically require enhanced (rather than basic or limited) resources.

Breast biopsy with FNAB or core needle biopsy can be performed under image guidance, which can be provided by US or by stereotactic biopsy (specialized mammography equipment that enables calculation of the 3-dimensional location of abnormalities identified on mammograms). Because of its multipurpose utility and lower cost, US is preferable to stereotactic biopsy as the initial modality to guide breast needle biopsy in LMCs.\textsuperscript{12}

Although lumps that are readily palpable may undergo needle biopsy under the guidance of palpation, there are specific scenarios in which image guidance is useful. US guidance may be particularly valuable for palpable lumps that are small (eg, \( \leq 2 \) cm), deep, mobile, vaguely palpable, or multiple. Imaging guidance is essential for needle biopsy of nonpalpable lesions that are identified on imaging studies; these lesions will be identified more often with the increasing use of diagnostic mammography and US and with the addition of mammographic screening.

**Surgical Pathology (Figure 1, Column 3).**

The central role of diagnosis highlights the importance of training healthcare providers in pathology and its subspecialties. The availability of pathologists with expertise in breast pathology differs around the globe. Approaches for improving breast pathology include training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services. Panelists expressed divergent viewpoints regarding the advisability of training nonpathologist healthcare providers (such as nurses) to perform preliminary steps in diagnostic procedures, such as obtaining aspirates for FNAB.

The most basic function of pathology in breast care is the formulation of timely and accurate diagnosis. This can be achieved by the use of appropriate biopsy (tissue sampling) techniques, optimal tissue processing, and competent interpretation of gross and microscopic pathology findings. A successful pathology service requires timely, accurate, comprehensive reporting as well as archiving of slides, tissue blocks, and reports with accurate patient and specimen identification. The Surgical Pathology Focus Group developed specific recommendations for resource management, which are published in a separate article in this supplement.\textsuperscript{27}

**Pathology reporting**

Breast pathology is the foundation for appropriate clinical care, and a pathologic diagnosis must be available as the basis for any kind of intervention. The first priority in the examination of every breast biopsy specimen is to arrive at an accurate diagnosis. The panel strongly emphasized the need to have pretreatment tissue sampling and diagnosis with a standardized report that includes appropriate diagnostic and predictive/prognostic information, ER status, and TNM stage. Although generation of the pathology report is the responsibility of the pathologist, the determination of an accurate diagnosis requires the close collaboration of pathologists with surgeons and radiologists. Accurate pathologic diagnosis starts with the clinician who provides relevant historic and physical examination information. Correlation of the clinical, imaging, and pathologic outcome of a biopsy is crucial to minimize errors in diagnosis, particularly when minimally invasive biopsy (core needle or FNAB) is used.

**Microscopic margins of resection**

One of the most important pieces of information obtained from pathologic examination of breast excision specimens in patients who undergo breast-conservation surgery is the status of the microscopic margins. Patients with invasive cancer who undergo breast conservation have a documented higher recurrence rate in the face of involved margins. Nevertheless, the definition of a negative or positive margin varies in the literature.\textsuperscript{28} Conceptually, the assessment of resection margins involves an estimate of the volume of residual disease; thus, it is a measure of the risk of recurrence.\textsuperscript{29} Patients with significantly involved margins have a 3-fold to 4-fold heightened risk of recurrence over patients with focally positive margins.\textsuperscript{30} Therefore, it is important to communicate
not only that a margin is involved but to provide information regarding the extent of involvement (focal or diffuse) and to specify the distance to and site of the margin or margins involved, which will guide further therapy and, in particular, surgical reexcision in patients who undergo breast-conservation surgery. The panel agreed that determination of margin status should be provided at the limited level of resources.

**Evaluation of prognostic and predictive markers**

Because breast cancer varies in its natural history due to variation in the propensity for growth and spread, assays for prognostic markers can be useful for assessing cancer prognosis. Prognostic markers are clinical, pathologic, and biologic characteristics of cancers that forecast clinical outcome. Accurate prognostic information can have an impact on a patient’s expectations and decision-making. The most general measurement of prognosis is TNM staging, which reports on the degree of cancer progression at the time of diagnosis, directly corresponds to the likelihood of cancer recurrence after treatment, and is considered to be a fundamental aspect of pathology reporting.

Predictive factors, in contrast, are clinical, pathologic, and biologic characteristics that are used to estimate the likelihood of response to a particular type of systemic therapy. Predictive factors are used to select specific therapies that target hormone or signal-transduction receptors. It has been demonstrated that ER status and HER-2/neu overexpression correspond to responsiveness to different therapeutic interventions. The determination of endocrine responsiveness is so fundamental to the management of breast cancer that its evaluation by some methodology is recommended even at the basic level if endocrine management of some type is available.

ER status should be measured by IHC if hormone therapy, such as tamoxifen, aromatase inhibitors, or ovarian ablation, is possible. However, a substantial proportion of ER-positive patients fail to respond to hormone therapy. Because of this observation, additional markers are needed to improve the ability to predict response and better select patients for therapy. The presence of PR should serve as an indicator of a functionally intact estrogen response pathway and may indicate increased likelihood of response to endocrine therapy.

Among patients who receive endocrine therapy, the presence of both ER and PR is a stronger marker for the benefit of adjuvant endocrine therapy than the presence of ER alone. Thus, assessment of PR status by IHC should be implemented at an enhanced level.

The measurement of HER-2/neu is more problematic because the cost and technical complexity of HER-2/neu receptor analysis and trastuzumab treatment is prohibitive in most LMCs. However, if the therapeutic agent is available in the country or in the region, then both ER and HER-2/neu status are critically important to make the most accurate therapeutic decisions and patient selection. Testing for HER-2/neu overexpression and providing available drugs for HER-2/neu-positive patients is definitely more cost-effective than giving trastuzumab to all patients or not giving it to anyone. Therefore, the panel recommended assessing HER-2/neu overexpression or gene amplification at the enhanced level.

**Laboratory and Metastatic Imaging**

**Tests (Figure 1, Column 2)**

A judicious approach to the use of laboratory and imaging studies to assess for the presence of metastatic disease is recommended universally, regardless of the level of available resources. Extensive, routine laboratory and imaging studies are not justifiable in patients with early breast cancer in the absence of symptoms or physical findings, because the likelihood of false-positive test results exceeds the likelihood of finding occult metastatic disease by several orders of magnitude.

In contrast, patients with locally advanced or lymph node-positive breast cancers are more likely to benefit from bone scan, chest radiography, and liver US, which have a higher yield in the setting of advanced disease. These metastatic screening studies are indicated when resources permit, because the finding of distant metastases markedly changes prognosis and treatment. When patients present with advanced disease, chest radiography and liver US are recommended (limited level), and bone scans are included when resources permit (enhanced level). Complete blood count (CBC) and blood chemistry profiles are required to safely administer systemic chemotherapy and should be implemented at a level of resources for which such treatment is available (basic or limited levels).

**Healthcare System Issues Related to Diagnosis**

**Interdisciplinary communication**

A coordinated, multidisciplinary approach is fundamental to the provision of optimal breast cancer treatment at all stages.

No single specialist is able to treat patients with breast cancer from every aspect, so the success of the treatment relies on the effective communication between the surgeon, pathologist, medical oncologist, radiation oncologist, and other
professionals, such as nurses, social workers, and others.\textsuperscript{33} Similarly, interdisciplinary collaboration and coordination is vital for breast diagnosis.\textsuperscript{7} Especially critical is the communication between the clinician, imager, and pathologist; because an erroneous pathology report can lead to over treatment or under treatment of patients, which can be devastating and can have a negative impact on quality of life and/or survival. The clinical presentation, imaging findings, and description of the procedure by which the tissue was obtained frames the proper pathologic interpretation and, thus, must be provided to the pathologist before preparation of the report.

Importance of training
One of the important obstacles for breast healthcare in LMCs is lack of proper education and training of personnel involved in the diagnostic process other than the clinicians themselves. Technicians, nurses, and those involved in the handling and transport of specimens are critical in this process and often lack adequate training, which can lead to devastating mistakes in diagnosis. Even at the basic level of resources, an effective breast program should be organized in a manner that ensures the proper transportation and processing of tissue and the effective communication of a pathology report to the clinician. In general, anyone who touches the patient or a specimen should receive proper training.\textsuperscript{34}

Telemedicine
In LMCs, breast care often is hampered by insufficient numbers of pathologists and radiologists who are overwhelmed by the large volume of cases for review. Telepathology, as a method of reviewing tissue specimens over great distances, can be a useful tool in such circumstances; however, this modality faces technical and logistic challenges. A benefit of telepathology is its educational value in centers that have basic facilities but lack expertise in breast pathology. Telepathology can improve communication between pathologists in geographically disparate centers and ultimately may improve the quality of the pathology services.

However, a key feature for a successful telepathology program is the development of good onsite pathology services, because what the expert gets at the receiving site depends entirely on the expertise of the pathologist at the local site and the way the sample is processed. The telecommunication system of the country also must be suitable for transfer of the clinical data as well as the pathology slide images. Thus, telemedicine may be a useful tool but cannot be recommended for implementation as long as these types of healthcare system problems remain unsolved. Experts emphasized the need for a pilot project that could demonstrate how low-cost, effective telemedicine could be used to augment healthcare delivery in pathology.

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