Breast Pathology Guideline Implementation in Low- and Middle-Income Countries

The quality of breast healthcare delivery and the ultimate clinical outcome for patients with breast cancer are directly related to the quality of breast pathology practices within the healthcare system. The Breast Health Global Initiative (BHGI) held its third Global Summit in Budapest, Hungary from October 1 to 4, 2007, bringing together internationally recognized experts to address the implementation of breast healthcare guidelines for the early detection, diagnosis, and treatment in low-income and middle-income countries (LMCs). From this group, a subgroup of experts met to address the specific needs and concerns related to breast pathology program implementation in LMCs. Specific recommendations were made by the group and process indicators identified in the areas of personnel and training, cytology and histopathology interpretation, accuracy of pathology interpretation, pathology reporting, tumor staging, causes of diagnostic errors, use of immunohistochemical markers, and special requirements to facilitate breast conservation therapy. The group agreed that the financial burden of establishing and maintaining breast pathology services is counterbalanced by the cost savings from decreased adverse effects and excessive use of treatment resources that result from incorrect or incomplete pathologic diagnosis. Proper training in breast pathology for pathologists and laboratory technicians is critical and provides the underpinnings of programmatic success for any country at any level of economic wealth. Cancer 2008;113(8 suppl):2297–304. © 2008 American Cancer Society.

KEYWORDS: breast cancer diagnosis, breast pathology, breast health global initiative, countries of limited resources, quality of care, breast pathology education, implementation of pathology practice, improved breast pathology reporting, standardization of test results, prognostic and predictive factors.

The quality of breast healthcare and the ultimate clinical outcome of patients with breast cancer are directly related to the quality of breast pathology practice. Pathology is the study of human...
illness. Thus, pathologists are central to the diagnosis of cancer-related disease processes. If this task is not done properly, the clinicians are misled, the patients suffer from the wrong treatment or no treatment at all, and resources are incorrectly expended. The recognition of breast pathology as the foundation of breast healthcare is essential for the design of any program aimed to improve the quality of breast healthcare and influence change within healthcare systems. The barriers to providing optimal pathology service in different regions of the world are discussed in previous Breast Health Global Initiative (BHGI) publications.1,2

In 2005, the BHGI developed resource-stratified guidelines, which emphasized the necessity for reliable surgical pathologic diagnoses of breast cancer in low-income and middle-income countries (LMCs).3-6 Pathology methods and applications were stratified into 4 levels by the 2005 Diagnosis and Pathology Panel (basic, limited, enhanced, and maximal) by considering the relative necessity, therapeutic benefit, and cost.6 The 2005 panel noted that fine-needle aspiration biopsy (FNAB) was the most economic method for diagnosis but required the capacity for cytologic interpretation.

Immunohistochemical (IHC) marker assessment was considered necessary to determine estrogen receptor (ER) status, but the resources needed were nontrivial. The 2005 guidelines included assessment of HER-2/neu oncogene status and IHC detection of metastases in axillary lymph nodes including sentinel lymph nodes at a high level of resource. The importance of the development of optimal breast pathology services was recognized as a fundamental requirement for the delivery of quality breast healthcare with an emphasis on patient outcome.7

The focus of the 2007 BHGI Global Summit was to identify effective ways to implement the 2005 guidelines and to measure the success of that implementation, identify barriers to implementation, and establish key process measures to assess the effectiveness of the process.

MATERIALS AND METHODS
A panel of interested pathologists, breast cancer clinician specialists, and patient advocates were invited by Dr. Benjamin O. Anderson, Chair and Director of the BHGI, to form the Breast Pathology Focus Group (BPFG). The charge was to assess how to adapt the previous resource-stratified guideline tables into real-world implementation in LMCs, to develop process indicators for each of the 4 levels of resources, and to identify systems changes necessary for implementation. The BPFG met during the 2007 October meeting of the BHGI in Budapest, Hungary, exchanged ideas, and provided the core information summarized into manuscript form, revised and edited into this final form by the group, following the publication protocol described in prior iterations of the BHGI guidelines.7

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<td><strong>Pathology Personnel, Processes, and Interdisciplinary Teamwork</strong></td>
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Implementation of Breast Pathology Guidelines

**Personnel and training**

The BPFG recognized the necessity to have well-trained personnel available to obtain and process diagnostic FNAB and/or tissue for histopathology (Table 1). In many regions of the world, there are few or no onsite pathologists and attempts should be made to find another pathology laboratory to assist with processing specimens and interpretation of the pathology samples, as well as identify opportunities to increase the number of available pathologists in a region.

The experience of a joint Ghana and Norway project provides an example of a successful pathology project. In this project, the Pathology Department in Tromso, Norway, established a mutual relationship with the physicians in Kumasi, Ghana, to provide pathology diagnosis for patients in Ghana. Ghana paid for the transportation of specimens and Norway provided professional interpretation costs. The problems observed in the Ghana laboratory, such as poor specimen quality and inadequate macroscopic descriptions, led to the development of new onsite guidelines for fixation procedures, macroscopic examination, and block selection in Ghana. The project was designed to transition to an independent sustainable program by including a training
component. Technicians from Ghana were trained in tissue processing and slide production, and a program to educate Ghanaian physicians to become pathologists will be completed in 2009. These new well-trained specialists will then train more technicians and pathologists locally in Ghana.8

The process metrics to ensure quality breast cancer pathology programs include qualifications and appropriate training of personnel involved in the handling, processing, and interpretation of pathology samples. This included the need for physicians/surgeons involved in breast cancer surgery to be educated about appropriate submission of the specimen and timely placement of the specimen in an appropriate fixative. Adopting process measures can allow for nonphysician healthcare personnel who are appropriately trained to perform FNAB procedures.

**Diagnostic errors in relation to poor specimen preparation**

False-negative and false-positive diagnoses result in over- and undertreatment. Specimen quality plays an important role in false-negative and positive diagnostic errors. False-negative diagnoses of cancer are most often attributed to a nonrepresentative specimen or to severe artifactual changes in the tissue material (Table 1), whereas false-positive diagnoses of cancer are commonly attributable to interpretation errors. Overinterpretation of specimens is more likely to occur in a poor-quality specimen because of either limited material on which to base the diagnosis or because of significant artifactual changes from poor fixation or slide preparation, making interpretation more difficult. Process measures that ensure adequate specimen quality are needed as well as measures to ensure pathologists acquire and maintain high-level diagnostic skills in breast pathology. The variability in the diagnosis of breast cancer has been shown to be reduced after education and adoption of time-challenged pathologic methods, criteria for diagnosis, and optimization of testing procedures.9-11

**Choice of diagnostic technique for establishing a pathology diagnosis**

The 2007 BPFG reaffirmed the necessity of obtaining a pathology diagnosis for every breast lesion by any available sampling procedures, and that FNAB is highly preferable to surgical excision for reasons fully delineated in prior BHGI publications.2-4 Under no circumstances should mastectomy be considered an acceptable method for tissue ‘sampling.’2 FNAB is recognized as the most cost-effective procedure with a short turnaround time.12,13 However, the choice of sampling procedures (FNAB, core needle biopsy, or excisional biopsy) should be based on the availability and access to cytopathologists/pathologists in each medical community, and the training and experience of the available pathology specialists.14-16

**Accuracy of pathology interpretation and reporting**

The BPFG emphasized the importance of providing comprehensive pathology reports for each breast lesion (Table 2). Pathology reports should follow established guidelines and include appropriate diagnostic and prognostic/predictive information based on the submitted specimen type.9 The accuracy of breast pathology reports is fundamental to treatment decisions and good outcomes. Process measures for pathology reporting should be implemented at all levels of care.

The BPFG emphasized the importance of accurate interpretation of pathology samples and test results. Even a small, 2% to 4% incidence of misdiagnosis at the global level will result in thousands of patients living with an inaccurate diagnosis of cancer. Inaccurate cancer diagnoses also impact the results of breast cancer research and outcome-based studies.17-20

Telepathology has the potential to enhance training in some settings and can be used for consultation on challenging cases on an ongoing basis using expertise at a distance.21 The availability of a broadband connection capable of handling the large amount of information that needs to be transferred, as well as the availability of adequately trained

**TABLE 2**

<table>
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<tr>
<th>Procedure</th>
<th>Process</th>
<th>Quality Indicator</th>
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<tr>
<td>FNAB</td>
<td>Facility and equipment to process diagnostic FNA and/or tissue for histopathology</td>
<td>% of reports that meet reasonable locally established turnaround time</td>
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<tr>
<td>FNAB</td>
<td>Measures to assure appropriate diagnostic and prognostic/predictive information</td>
<td>% nondiagnostic pathology reports for every pathology specimen</td>
</tr>
<tr>
<td>FNAB</td>
<td>Measures to establish standardized pathology reporting</td>
<td>% of pathology reports with information that allows proper clinical staging</td>
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FNA indicates fine-needle aspiration.
personnel at both ends, remain issues to be dealt with in many low-income and medium-resource settings.\(^1\)

It was also suggested that a pathologist should participate as an active member of a breast care working group, if possible. Effective communication among pathologists and other physicians involved in breast healthcare provides an opportunity to better understand the impact of the pathology report on the management of patients and may minimize the level of misunderstanding about the nature and extent of the disease.\(^1,17,20\)

**Tumor staging**

Proper breast cancer therapy requires a clear understanding of the extent of a disease (TNM cancer staging). Pathologists are expected to provide complete information regarding the specimen including tumor type and description, orientation, and analysis of surgical margins as well as full reporting of histologic features and biomarkers. The College of American Pathologists developed and published guidelines for reporting cancer specimens in 1997,\(^22\) as have other organizations. However, there is still extensive diversity in pathology reporting of factors that affect the treatment of breast cancer. Complete and accurate reporting of pathologic information is the primary responsibility of the pathologist.\(^23,24\)

**Use of immunohistochemical markers**

The BPFG recommended that the capacity for determination of hormone receptor status by IHC for each breast cancer diagnosis should be made available when endocrine therapies such as tamoxifen, aromatase inhibitors, or surgical or medical ovarian ablation are available (Table 3). However, the variability in the results of prognostic/predictive factors in breast cancer is a long-standing issue, which to our knowledge has not received any real resolution. The error rate in the reporting of ER and HER-2/neu oncogene have been reported to be as high as 18%.\(^25,26\) Others have previously reported similar variability in the results of prognostic/predictive factors. These findings cross over many areas, which include quality of patient care and increased medical expenses.\(^25-28\)

In regions that do not have onsite ancillary testing such as ER IHC available, alternatives must be developed such as outsourcing to a laboratory that has the capacity to perform the needed test or adding IHC to an existing onsite facility.\(^29\) It is critically important to realize that administration of tamoxifen to breast cancer patients without any knowledge of the status of ER is not acceptable. Aside from the expense of tamoxifen therapy for 5 years, there are significant side effects to consider. These side effects include the possibility of stroke, endometrial cancer, weight gain, and menopausal symptoms. Therefore, measures should be in place to find innovative ways to determine the ER status for every newly diagnosed breast cancer patient across the world.

In higher-level resource settings, the assessment of progesterone receptor (PR) by IHC is recommended. In addition, IHC analysis of the overexpression status of HER-2/neu oncogene should be in place in settings in which this determination will affect therapeutic selection. HER-2/neu assessment can be performed by IHC locally or referred to another laboratory because of the technical variability of results of this particular assay and the related requirement for extreme quality control. Recent guidelines have been proposed by the American Society of Clinical Oncology and the American College...
of Pathologist to ensure quality and reproducibility of HER-2 testing.30

Clinical and radiographic correlation of pathology findings
The interaction of the pathologist with the radiologist and the surgeon (interdisciplinary team approach) is critical because the clinical situation in which the specimen was obtained can markedly influence the significance of certain pathologic findings, and in the case of cancer, can be critical in determining accurate tumor staging.

Adaptation of pathology services to allow for breast conservation therapy
The possibility of offering breast conservation therapy in LMCs requires that adjustments be made to the pathology guidelines (Table 4). The pathology report should delineate the pathologic status of the surgical margins, the presence/absence as well as amount (percent of tumor area) of ductal carcinoma in situ, and the presence or absence of lymphovascular invasion. Although not directly part of breast conservation therapy, the ability to sample sentinel lymph nodes can generally be established in conjunction with breast conservation surgical techniques. The provision of intraoperative interpretation of sentinel lymph nodes can improve the efficiency of surgical care delivery by potentially decreasing the number of surgical procedures required for the clinically negative but histologically positive lymph node.31-34

Process indicators in breast pathology
Appropriate process measures should be integrated in all anatomic pathology laboratories. Nonpunitive reporting of errors in cancer diagnosis and in the interpretation of prognostic/predictive factors is a critical step in improving patient safety and overall processes. Focusing efforts at improving performance in problem areas assures efficient use of resources and the maximization of the positive impact.

The BPFG considered standardization of the pathology report and analysis and reporting of ER status to be important area and agreed on 7 process indicators:

- Percentage of pathology reports with sufficient information for proper clinical staging.
- Percentage of reports meeting reasonable/locally established turnaround time.
- Percentage of nondiagnostic pathology reports for FNAB.
- Percentage of inadequate specimen for biopsies.
- Percentage of suboptimal samples compromising diagnosis.
- Percentage of change of diagnosis on second review.
- Percentage of treatment planning conferences or working group meetings attended by pathologists.

The measures to assess the effectiveness of the process improvement were:

- Percentage of pathology reports, which include margin status.
- Percentage of differences between intraoperative and final pathologic diagnoses.
- Percentage of breast cancer cases tested for ER, PR, and the HER-2/neu oncogene.

The above indicators were considered essential for optimal breast pathology reporting. The BPFG, however, refrained from assigning a specific percentage as a requirement because of the paucity of evidenced-based data regarding the current acceptable range. It is more reasonable for every medical center to establish their own threshold and monitor their progress to achieve their own expected goals.

DISCUSSION
The importance of improving the quality of breast pathology practice has been the focus of significant

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### TABLE 4
Special Considerations for Breast Conservation and Sentinel Lymph Node Biopsy

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<tr>
<th>Guideline</th>
<th>Process</th>
<th>Quality Indicator</th>
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<tr>
<td>Pathology report should include the status of margins, the presence and extent of ductal carcinoma in situ, and the presence of lymphovascular invasion</td>
<td>Adopt standardized methods of orienting specimen, and inking and sampling the surgical margins</td>
<td>% of pathology reports that include margin status, ductal carcinoma in situ, and lymphovascular invasion</td>
</tr>
<tr>
<td>Measures in place to provide intraoperative evaluation of sentinel lymph nodes</td>
<td>Adopt standardized methods for processing and reporting of sentinel lymph nodes</td>
<td>% of diagnostic discordance between intraoperative and final pathologic diagnosis for sentinel lymph nodes</td>
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attention over recent years. International efforts such as the establishment of the International Society of Breast Pathology in 1997 and the integration of breast pathology as one of the main components of the BHGI guidelines has sent a strong message about the importance of developing international guidelines and standardizing the practice of breast pathology.\textsuperscript{35}

Currently, there is significant variation in the practice of breast pathology at the global level. There are important differences in tissue sampling and processing, interpretation of pathology findings, and analysis of breast samples for biomarkers. Contributing factors for these differences include financial constraints and variation in the level and extent of training of pathology personnel in breast pathology.

Adequate tissue sampling and processing, and appropriate use of ancillary studies such as biomarker studies for prognostic/predictive factors, require sufficient healthcare and financial resources. The financial burden of these resources to the broader healthcare system is counterbalanced by the benefits of having an intact surgical pathology program. The cost of providing optimal pathology services is offset by the savings in adverse effects and excessive treatment resource utilization when the pathologic diagnosis is incorrect or incomplete. For instance, the accurate determination of ER status allows the avoidance of endocrine therapy and its expense in women with ER-negative breast cancer.

The BPFG acknowledges the challenges associated with the current practice pattern in breast pathology. Ideally, studies should be designed to appropriately analyze the problems in pathology practice and to quantify their impact on therapy, patient outcome, and health economy. Key components of change include sufficient training in breast pathology during general pathology training and accessible continuing medical education programs in breast pathology to assist the practicing pathologists to become more familiar with the new and evolving concepts in this discipline.\textsuperscript{36}

During the last several years, there have been significant changes in the fundamental understanding of breast cancer, early diagnosis, and prevention, as well as therapy and the follow-up management. These changes have brought new challenges to the practicing pathologists. Pathologists are no longer required to only differentiate between a malignant versus a benign process, but they are also expected to recognize the spectrum of borderline breast disease and to diagnose earlier-stage small carcinomas. They are also expected to serve as partners in the process of breast healthcare and are required to provide appropriate prognostic/predictive factors. These expectations require knowledgeable and interested pathologists who have access to optimal pathology laboratory infrastructure.

In countries of limited resources, these challenges are more difficult to overcome. Limited financial resources, inadequate number of appropriately trained pathologists and technologists, and differences in stage of breast cancer presentation are serious limiting factors. In reality, the majority of established guidelines from high-resource countries are difficult to implement in low-resource regions of the world. The implementation of guidelines require a real understanding of the current issues at a regional level and development of partnerships between the high-resource and low-resource healthcare providers to establish a different level of breast pathology service in limited resource settings. The success of this approach is exemplified by the story of the collaboration between the physicians from Ghana and Norway.

Another strategy that may be effective is to encourage international collaboration among interested pathologists to form the building blocks for a voluntary breast pathology educational program. This initiative may be realized by the establishment of an “International Institute of Breast Pathology.”\textsuperscript{37} This institute may serve as a bridge to connect diverse groups of pathologists and healthcare providers who share the same vision of providing a better quality of breast pathology to women of the world. This institute may be the first step to introducing innovative approaches in enhancing the knowledge regarding the optimal practice of breast pathology, including the utilization of telepathology as a global technology that allows for expert information sharing across the globe.

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REFERENCES


