



Why Current Breast Pathology Practices Must Be Evaluated

Susan G. Komen for the Cure White Paper: June 2006

EXECUTIVE SUMMARY

The eradication of breast cancer as a life-threatening disease has long been the mission of Susan G. Komen for the Cure. To this end, Komen for the Cure has a strong interest and proven track record in ensuring public investment in quality breast health and breast cancer care. Recently, Komen identified major issues in the practice of pathology that we believe are having a negative impact on the lives of thousands of breast cancer patients in the United States. These issues were identified through a comprehensive literature review and interviews with experts in oncology, breast pathology, surgery, and radiology who practice in community, academic, and cooperative group settings (Appendix I).

The issues set forth herein must be further explored to ensure that patients are receiving appropriate care based on accurate diagnoses and accurate identification of predictive and prognostic markers. A pathologic diagnosis is the foundation upon which all other treatment decisions are made and with breast cancer, the pathology dictates the use of potentially curable therapy. An incorrect pathologic diagnosis may lead to negative outcomes as serious as failure to treat a missed case of breast cancer or provision of unnecessary surgery, chemotherapy, and radiation. While it is exceedingly difficult to determine the incidence of incorrect breast cancer diagnoses in the United States, our consultants estimate that the error rate could be as high as 2% to 4%. If accurate, as many as 5,000 to 10,000 patients diagnosed with invasive or in-situ breast cancer each year may have been misdiagnosed and inappropriately treated (Appendix II). More than 90,000 people currently living with breast cancer may, in fact, be living (or dying) with an incorrect diagnosis (Appendix II).

Concerns over the quality and practice of breast pathology are not limited to diagnostic accuracy, although many of the issues are inter-related. Other concerns relate to the training and proficiency of pathologists who are evaluating breast specimens; the lack of integration of pathologists into the clinical care team, particularly in smaller hospitals and non-hospital based pathology practices; the disconnect between reimbursement and the work required to analyze the nuances and complexities inherent in breast pathology; the impediment of patient and information flow to appropriate team members by a cumbersome healthcare infrastructure; the potential decrement in translational research as a result of privacy regulations; and a lack of mandatory uniform practice standards, which allows practice variation to occur without quantification or remedy.

Susan G. Komen for the Cure believes the following questions must be addressed:

1. How can the accuracy of breast pathology diagnostics be improved?

While the rate of errors in breast pathology is exceedingly difficult to estimate for a variety of reasons, we do know that certain diagnoses are more difficult to make and that testing for certain prognostic and predictive factors is subject to an unacceptably high degree of error. Increasing and standardizing pathology training and specialization in breast pathology have the potential to improve diagnostic accuracy at the population level. Encouraging or mandating second opinions for appropriate patients could improve diagnostic accuracy for specific patients. Professional organizations have developed practice guidelines and quality control (QC) programs, yet compliance with both is generally voluntary. The need to mandate compliance should be assessed. Finally, pathologists need better integration into the patient care team to facilitate consensus diagnosis. The optimal management of breast cancer requires an interdisciplinary team that determines the diagnosis and treatment plan by consensus. Roadblocks to such an approach need to be understood and addressed.

2. What effects do the current health insurance and reimbursement environment have on patients who are being evaluated for a possible breast cancer diagnosis?

We heard repeatedly from experts that reimbursement rates are generally not commensurate with the workload when it comes to breast pathology. If reimbursement for this important work is not adequate, there is a risk that the extent of the pathologic review may be suboptimal in some cases. Moreover, inadequate reimbursement may encourage the use of unproven or unvalidated techniques and methods, a particular concern for the testing of markers such as the estrogen receptor (ER) or human epidermal growth factor receptor 2 (HER2). Reimbursement must reflect the complexity of each individual case. Reimbursement could be tied to compliance with appropriate practice guidelines, but the adequacy of existing guidelines for this purpose must be assessed. Finally, insurance may limit a patient's ability to get a necessary second opinion and hinder consensus diagnosis by dictating where pathology services are performed. To achieve a certain economy of scale, some insurance companies may be contracting with pathology programs that lack sufficient experience or expertise with breast pathology.

3. Why has participation in tissue banking decreased substantially, particularly during a time of rapid advances in biologically correlated clinical science?

Tissue banking facilitates translational research, which turns scientific discoveries into treatments or tools that are used in patient care. Indeed, each day we are moving closer to personalized medicine, where a tumor's molecular profile and a patient's genetic makeup will guide treatment decisions. For this progress to continue, researchers need access to tumor tissue taken from patients whom they can monitor for long-term outcome many years after surgery. Alarming, several experts reported that their institutions are storing less tumor tissue now than in the past. Also, some clinical sites are not sharing samples with cooperative groups, which can affect their ability to conduct appropriate correlative tests during the course of a clinical trial. Clinical trial enrollment may even be affected since tissue banking is often a condition of participation. Some roadblocks to tissue banking appear to be unique to the United States and may be related to the Health Insurance Portability and Accountability Act (HIPAA). These issues must be examined.

4. What roles should Susan G. Komen for the Cure, pathology professional societies, and the Federal government play in ensuring that breast pathology practices meet the highest possible standards in the United States?

Our challenge is to determine how to ensure that breast pathology practices are meeting or exceeding acceptable standards throughout the United States without placing undue burden on practitioners. Several professional societies are already addressing some of these issues. For example, practice guidelines, policy statements, and QC programs have been developed in an effort to standardize and improve breast pathology practice. Nonetheless, concerns remain regarding the adequacy of specimen handling, pathology reporting, laboratory testing, personnel training, and quality control. The sufficiency of current practice guidelines must be examined to determine whether additional guidelines are needed and whether the use of such guidelines should be mandated. Komen for the Cure stands ready to work with the appropriate parties to address the important issues raised herein.

The following provides additional background about the genesis of the questions set forth herein. This paper does not attempt to directly answer these questions. Rather, it provides insight into the importance of these issues and a framework for further study.

Question 1: How can the accuracy of breast pathology diagnostics be improved?

- Should all women have their pathology reviewed by a breast pathology specialist? If so, how would these specialists be trained and certified?
- Should all women have a second pathology opinion? If not, are there specific diagnoses that should always be referred for a second opinion? Should second opinions be mandated for certain patients?
- How can we ensure that the surgical and radiologic data reach the pathologist? That is, how can multidisciplinary collaboration and consensus diagnosis be facilitated?

Accuracy

Breast cancer is not one disease but many, and the approach to the diagnosis and treatment of breast cancer must reflect this reality. Breast pathology is a dynamic discipline; many consider it to be the most complicated and nuanced subset of surgical pathology. During interviews with breast cancer specialists, it became apparent that many have concerns that the quality of breast pathology done by general pathologists in community and commercial laboratories is suboptimal. A lack of accuracy can be gauged and defined in three ways: 1) an incorrect diagnosis refers to a major error, such as failure to distinguish benign and malignant disease or invasive and non-invasive disease, or failure to accurately identify ER or HER2 status, 2) an incomplete diagnosis refers to the omission of information crucial to the treatment plan, such as tumor size or HER2 status, and 3) an inconsistent diagnosis refers to the use of arbitrary, inconsistent, or obsolete terminology that could be misunderstood by a treating physician.

It is exceedingly difficult to estimate the rate of major breast cancer pathology errors that occurs in the United States each year. There is no uniform process in place to capture errors, and fear of disclosure may limit reporting. [Raab 2005] For all cancer specimens, the frequency of anatomic pathology errors has been reported to range from 1% to 43%. [Raab 2005] Specific to breast cancer pathology, our interviewees who routinely provide second opinions estimate that 2% to 4% of breast cancer diagnoses in the United States may be incorrect. [personal communication, Drs. Kivitz, Page, Allred] Some diagnoses are more difficult to distinguish, and some are so rare that a general pathologist may never see a case in his or her lifetime. The misclassification rate for atypia, microinvasion, or in-situ disease is estimated to be 20%. [personal communication, Dr. Lagios] Predictive and prognostic factors are also at risk for error; ER status may be misclassified in as many as 20% of cases [Allred 2002; CAP 2004] and HER2 in 26% of cases. [CAP 2004] Published data support these findings. [Wells 1998; Collins 2004] Concordance among pathologists is generally high, but there are clinically significant variations, particularly for non-invasive diagnoses and lobular pathology. Indeed, great inter-observer variation in diagnosing atypical breast lesions is well-known in this field. [Fitzgibbons 2000] Possible solutions to increasing diagnostic accuracy include training more pathologists to specialize in breast pathology and requiring (and reimbursing for) second pathology opinions and determination of concordance between pathology and radiology. These issues are further described below.

Specialization

Training in breast pathology is just one small component of a surgical pathology residency, and there are no national standards dictating how much time is spent on breast pathology in a residency program. There are also no professional society or regulatory guidelines that describe qualifications for pathologists who interpret breast biopsies, as there are for radiologists who read mammograms.[Silverstein 2005]. The American Board of Pathology (ABP) offers several subspecialty certifications, such as neuropathology, dermatopathology, and hematology, but breast pathology is not currently a recognized subspecialty. Several institutions offer fellowships in breast pathology; these programs are designed and administered by the individual institutions, generally using their own funds. Consequently, there is no uniform national curriculum or certification program. One specialist estimates that there are currently about 40 pathologists in the United States with the skills commensurate to be considered breast pathology specialists. However, more than 200 would be needed to ensure that every women diagnosed with invasive breast cancer had access to review by a specialist.[personal communication, Dr. Bleiweiss] This estimate does not include women diagnosed with benign lesions or in situ disease; significantly more specialists would be needed to review all breast specimens.

There are market forces working against the idea that all women undergoing a work-up for possible breast cancer have their pathology reviewed by a specialist. These pressures can come from general pathologists who do not want to lose part of their practice and from small, rural hospitals that do not have the volume or funds to support hiring such a specialist. In addition, there may not be a sufficient job market for breast pathology specialists outside academic centers or centers of breast cancer excellence. Although the creation of breast pathology centers of excellence appears to resolve the volume issue for smaller hospitals, such a system may not work well within the current healthcare infrastructure. The issues surrounding breast pathology specialization are complex but must be explored. Existing subspecialties, such as neuropathology, overcame considerable obstacles owing to great need. Breast pathology has become markedly more complex in the last decade as a result of scientific advancements, and the need for specialization is increasingly apparent.

Second Opinions

Another option to improve diagnostic accuracy is to encourage or mandate that appropriate patients receive a second opinion on their pathology and to ensure that reimbursement is available for such services. Which patients require a second opinion remains to be determined. Certain diagnoses may be more difficult to make and therefore may require a mandated expert review. For example, an international expert panel recently recommended that patients with high-risk histologic findings, including atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ, receive second opinions from breast pathology experts before a treatment course is determined.[Silverstein 2005]

A paper published by Staradub and colleagues confirms the value of a second opinion.[Staradub 2002] Complete agreement was found in only 20% of the 340 cases in their study. Major changes (failure to confirm a diagnosis of malignancy, a change from invasive to in situ disease and vice versa, or a change in diagnosis that altered the recommended surgical procedure) were identified in 7.8% of cases reviewed. Half, or thirteen, of these cases involved differing opinions on the presence of an invasive carcinoma, but in only five of those cases did the initial pathologist express diagnostic uncertainty. These data support a role for second opinions, and also further support the urgent need for improvements in breast pathology.

Integrating Pathology into Clinical Care Teams

The optimal management of breast cancer requires an interdisciplinary team composed of oncologists, radiologists, surgeons, and pathologists who determine a diagnosis and treatment plan by consensus.[Masood 2003] Correlation between the radiologist's films and the pathologist's review is crucial for an accurate diagnosis as well as for continuous quality improvement for each practitioner, particularly for the evaluation of non-palpable lesions and microcalcifications.[Parikh 2005, Guinebretiere 2005; Silverstein 2005] Several pathologists have told Komen for the Cure that this correlation is not routinely done outside academic centers, and the results of a published interinstitutional study concur, demonstrating correlation in only 62% of cases involving mammographically directed breast biopsies.[Nakhleh 1997] Moreover, pathologists are not generally integrated into most patients' clinical care teams, hindering communication and consensus diagnosis.

There are many possible reasons that pathology does not play a more active role in clinical care:

- Some pathologists may be reluctant to expand the scope of their practice beyond the confines of the laboratory
- Many surgeons and oncologists do not work closely with pathologists and have not sought a more collaborative working relationship
- Insurance can dictate where slides are prepared and reviewed (eg, commercial laboratory, which may not have access to the patient's images and generally has no communication with clinicians or radiologists)
- Insurance can dictate where images are taken, which may prevent a patient from having all images taken at the same institution, making it more difficult for the team to obtain a complete set
- HIPAA regulations are perceived to hinder the sharing of patient information across institutions
- Professional organizations that promote education and interdisciplinary interactions have complex membership guidelines that may exclude membership to certain professions, such as pathology specialists
- Hospitals and multispecialty group practices may not currently extend staff privileges to pathologists

These issues are further discussed in Questions 2 and 4.

Question 2: What effects do the current health insurance and reimbursement environment have on patients who are evaluated for a possible breast cancer diagnosis?

- Are current reimbursement rates discouraging optimal breast tissue pathology review?
- How are reimbursement rates affecting the adoption of new pathology techniques?
- How can we ensure that important standard-of-care testing (eg, ER, PR, HER2) is provided at reasonable reimbursement rates?
- Does a patient's specific insurance coverage affect the timeliness or accuracy of any breast related diagnosis?

Reimbursement Rates

Pathologists, radiologists, and surgeons generally agree that pathologists are not adequately compensated for performing breast pathology. A pathologist who is thorough is likely to lose money, yet a thorough review is needed for diagnostic accuracy. The average stereotactic vacuum-assisted biopsy specimen requires review of slides from approximately 2 to 3 paraffin blocks, whereas a wire-localized surgical breast specimen averages 15 to 20 blocks; however, reimbursement is generally not based on the type of specimen reviewed or the complexity of the case.[personal communication, Dr. Ibarra] For example, a breast core biopsy, which requires multiple levels (often 3 to 6) and needs correlation with imaging, is reimbursed at the same rate as seborrheic keratosis, a non-cancerous skin growth that can be diagnosed with the review of only one slide. This clearly demonstrates the lack of connection between workload and reimbursement and should be particularly concerning given that one condition is potentially fatal while the other is relatively benign. Low rates of reimbursement may also lead to suboptimal review of ductal carcinoma in situ (DCIS) resections. A DCIS resection may require up to 40 paraffin blocks, and a pathologist needs to examine 100% of the specimen to determine the size and margin status and confirm the absence of occult invasive disease, information crucial to the subsequent treatment decision. This thorough review is time-consuming, and current reimbursement is not commensurate with the work or materials used. Since the incidence of DCIS is rising, the low reimbursement rate is a major issue.

One potential solution is to tie reimbursement to the number of slides that are reviewed or the complexity of each individual case. In addition, the feasibility of developing concrete national standards should be assessed. Current guidelines simply recommend that an "adequate" number of slides be prepared from a single paraffin block. Because reimbursement rates are relatively low and vary by geography, some pathologists may err by reviewing relatively few slides when in fact a more complete review of the tissue is needed to assure accuracy. Suboptimal review can lead to misclassification. The difficulty in creating national standards is related to the variability among tissue specimens. For example, the number of slides deemed necessary is based in part on the thickness of the tissue section and the nature of the tissue (eg, fatty vs. fibrous) as well as on communication with the physician who obtained the sample and correlation with the imaging characteristics of the lesion. Despite the inherent difficulty, there may be a way to create standards that minimize the risk of misclassification due to insufficient sampling, provide a benchmark from which to determine appropriate reimbursement, and ensure that oversampling does not occur solely to obtain more favorable reimbursement.

In addition to penalizing thorough pathologists, reimbursement rates can impede the appropriation and use of new technologies. For example, the adoption of one promising new technique, the large section or large block technique used routinely in Sweden since the early 1980s, has been slow in the United States due to financial concerns.[personal communication, Dr. Ibarra] This technique has particular advantages over small block sectioning for the review of DCIS, including improved accuracy of the evaluation of the resection margins and better determination of the microscopic size of the tumor. The technique takes longer to complete, and start-up costs are greater due to the need for additional equipment and personnel training. However, the superiority of this technique over small block sectioning is supported in the literature.[Jackson 1994; Mechine-Neuville 2000; Tot 2005; Tot 2000]

Reimbursement rates also appear to have impacted prognostic and predictive marker testing techniques, leading to the use of unvalidated technology in some situations. For example, reimbursement for ER and PR testing varies by method. The fee for manual assessment of receptor assays by immunohistochemistry, a clinically validated method, is less than that for the use of an automated scanner, a method that has not been validated but is increasingly used.[personal communication, Dr. Osborne] With HER2 testing, reimbursement may affect the choice of method (immunohistochemistry versus fluorescence *in situ* hybridization [FISH]), the choice of antibody and reagents, and the decision of when to triage immunohistochemistry results to FISH testing.[Ross 2004] Regardless of which test is used, strict QC control measures are recommended.[Yazili 2004; Bilous 2003] However, the specialists we interviewed raised concerns that compliance with voluntary QC programs for HER2 testing is low, possibly due to reimbursement rates.

Insurance Coverage

Insurance can dictate which imaging facility a patient must use as well as where diagnostic tissue samples are processed and where pathology slides are prepared and read. This is particularly problematic when insurance companies require that outpatient samples be sent to a distant reference laboratory without access to the patient's radiologic and surgical information. When a patient's insurance changes or when the insurers' contracts with pathology providers change, a patient can end up with images and pathology material at multiple centers. The current infrastructure makes it difficult for any one physician to view all of the images and pathology material and have a complete medical record. Pathology contracts to large commercial laboratories may achieve an economy of scale, but there is some concern about the level of care or expertise that is available at these centers. Moreover, many insurers refuse to pay for second pathology opinions. The failure to pay for a second opinion may result in unnecessary procedures and ultimately cost the insurance company more money. Hospitals may require re-review prior to surgery, and if this review is not covered by insurance, the hospital sustains a financial loss in the fee-for-service healthcare system. Many experts believe that the current system is untenable and provides inferior, decentralized care.

Question 3: Why has participation in tissue banking decreased substantially, particularly during a time of rapid advances in biologically correlated clinical science?

- Is the Health Insurance Portability and Accountability Act (HIPAA) impeding the storage of tumor samples and slowing progress in translational research?
- What can be done to improve the number of tumor specimens available in tissue banks?

Tissue Banking

The banking of human tumor tissue and its links to patient-specific clinical outcome data are critical to translational research. Historically, institutions have archived excess tumor tissue in order to later correlate outcomes with as-yet-undefined tumor markers. This process led to the identification of both ER and HER2, for example, which in turn led to the development of the targeted therapies tamoxifen and trastuzumab. More recently, tissue banking facilitated the validation of the Oncotype DX assay. This assay is used to quantify the risk of disease recurrence in women with early-stage, node-negative, ER-positive disease who will be treated with tamoxifen and has the potential to help determine the need for chemotherapy for individual patients.

It is clear that major treatment advances have come directly from tumor tissue banking; however, these and other potential advances are currently being hampered by a lack of available tissue. For example:

- Baylor College of Medicine had 150,000 samples in its archival bank that were collected in the decades prior to HIPAA; these samples were lost in the 2001 Houston flood. Efforts to rebuild the tissue bank have been severely compromised due to the HIPAA regulations, and few samples have been added in recent years.[personal communication, Dr. Osborne]
- The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial enrolled more than 9,000 women but only 15% of the tumor samples have been banked, which reduces the statistical power needed to accurately identify markers associated with treatment response.[personal communication, Dr. Allred] Moreover, the majority of these banked samples came from Europe; centers outside the United States banked samples from approximately 33% of their patients, while in the United States, the rate was approximately 7%, which suggests that there are impediments unique to the United States.
- National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-14 enrolled more than 4,000 women but banked tissue from only 1,000, despite repeated requests for submission of blocks; these blocks were used for the Oncotype DX validation study, but a larger sample size would have been preferable [personal communication, Dr. Paik]
- Cooperative group clinical trial enrollment may be hindered since some studies require tissue banking as a condition of participation. It is unknown whether centers refuse to collect and store the tissue or whether they store the tissue but refuse to share their samples with the cooperative groups.

Institutional logistics, a lack of national tissue banking guidelines, concern over institutional review board compliance, interpretation of the College of American Pathologists (CAP) regulations regarding block storage, and interpretation of HIPAA requirements may all be reasons for the current impediments to tissue banking. Some institutions have determined that their procedures did not comply with the HIPAA regulations, but making the necessary changes is time-consuming and onerous. For example, prior to HIPAA, consent for tissue banking was included in the surgical consent form. With HIPAA, a separate consent is required, which increases personnel needs and costs. There is a state-by-state patchwork of laws regarding how long to save tissue, and some institutional lawyers now suggest destroying tissue as soon as allowed by law. There is a need to clarify the HIPAA and NCI banking regulations as well as to consider uniform national guidelines or legislation to facilitate tissue banking.

There is interest in the creation of a national or standardized tissue bank, which would offer several advantages over the current system, including clarification of storage and confidentiality issues and increased statistical power for analyses. Such a system could be arranged as a virtual tissue bank, where tissue is stored locally and only sent to a central location or individual research upon request. However, virtual banks are already nominally in existence, and they have not worked well at the local level.[personal communication, Dr. Paik] In general, virtual banks lack solid follow-up data and provide incomplete treatment data. Plans for a National Biospecimen Network were conceived in 2002, with the goal of providing an accessible national bio-informatics data bank for all scientists. Other tools, such as the voluntary caBIG (cancer Biomedical Informatics Grid) program and caTissue central data repository, are being developed by the NCI Center for Bioinformatics. None will be successful without the cooperation of the individuals who handle tumor specimens at the local level.

Question 4: What roles should Komen for the Cure, pathology professional societies, and the Federal government play in ensuring that breast pathology practices meet the highest possible standards in the United States?

- Is there a need for the Federal government to develop a breast cancer pathology quality standards act, similar to the Mammography Quality Standards Act that guides mammography practice?
- What initiatives are underway in professional societies?
- Are current practice guidelines sufficient? How can the usage of such guidelines be encouraged or increased? Should usage be legally mandated?

Historically, medical professions determine their own best practices and strive to meet or exceed the standards of care. Currently there are significant practice variations in breast pathology that likely affect diagnostic accuracy and compromise patient outcomes. Our challenge is to determine how to ensure that breast pathology practices meet or exceed acceptable standards throughout the United States without placing undue burden on practitioners. Areas of particular interest include but are not limited to:

- Specimen handling and pathology reporting
- Pathology training and personnel
- Frequency of correlating pathology with radiology
- Quality control programs, particularly for ER and HER2 testing and other markers as the science evolves

Specimen Handling and Pathology Reporting

Appropriate specimen handling and processing are crucial but experts voiced concern that these processes are not uniform throughout the United States. For example, specimen orientation by the surgeon is critical in order for the pathologist to adequately assess the margin status: appropriate orientation allows for targeted re-excision of close or involved margins, which results in clearer margins and a better cosmetic effect for the patient. As a result of concerns about inappropriate or missing orientation for excised breast specimens, the American Society for Breast Disease released a policy statement on this topic in 2005.[ABSD website] This is an important step in standardizing practice, but it is not known how widely these recommendations are followed. Another issue that requires further investigation was addressed with Question 2, concerning whether national guidelines can quantify “adequate” numbers for tissue blocks and slides for different types of breast excisions. Finally, regarding testing on cancer tissues, some laboratories may not be using optimal methodologies or reagents, which can affect the outcome of certain tests (eg, reagents and tissue processing procedures used for HER2 testing; antibody choice and ER testing; fixation and processing for Ki-67). All of these specimen handling issues have the potential to compromise outcomes.

The quality of pathology reports is also highly variable. Retrospective studies show that most reports lack at least some of the clinically relevant information.[Imperato 2003; Wilkinson 2003] Moreover, some elements of the pathology report can be misinterpreted. For example, multiple terms can be used for the same lesion (eg, columnar cell lesion and blunt duct adenosis), and some terms are inherently unclear (eg, papillomatosis could refer to multiple papillomas or to ductal hyperplasia).[personal communication, Dr. Parikh] Any missing or unclear information in the pathology report has the potential to delay treatment or even lead to inappropriate treatment. Studies show that quality improvement programs can increase compliance with reporting guidelines, although such programs require personnel and financial support.[Imperato 2003; Torres 2003]

As of January 1, 2004, the American College of Surgeons (ACS) Commission on Cancer (CoC) requires for accreditation that ACS-approved cancer programs in the United States adhere to the CAP pathology reporting guidelines. Although this requirement may help alleviate the problem of incomplete reporting, the 1,400 CoC-approved programs in the United States cover approximately 80% of newly diagnosed cancer patients, leaving 20% of patients to be diagnosed at non-accredited institutions.[ACS 2004] In addition, it is unclear if the CAP guidelines are sufficiently universal; some pathologists believe that these guidelines comprise minimum standards and that pathologists who currently specialize in breast pathology are providing important information above and beyond what is recommended by the CAP guidelines. Moreover, the guidelines apply only to cases of invasive breast cancer, not to all breast tissue pathology (eg, DCIS).

Pathology Training and Personnel

Issues involving specialization were included in Question 1. With respect to standardizing pathology training, one consideration would be a national standard dictating the amount of time spent on breast pathology during a pathology residency or the completion of a specific number of specimen reviews of different types during the program. Continuing medical education (CME) programs also hold promise to improve performance in breast pathology. The provision of CME credits provides an incentive for participation. CME material can now be provided on intranets, local hard disks, CD-ROM, or secure internet sites, and these approaches have been used with success in pathology.[Velan 2002; Demartines 2000]

Competence- and performance-based assessments are important components of personnel management and quality improvement (QI) efforts. The Q-Probes program, initiated by CAP in 1989, is a voluntary QI program that has identified benchmarks for quality practice in pathology and laboratory medicine.[CAP 2004b] Of the numerous

publications resulting from the use of the program, one relevant to breast pathology reveals that there are indeed discrepancies between what the pathologist reports and what the clinician wants reported, as well as incomplete correlation between pathology and radiology findings.[Nakhleh 1997] The Q-Probes program may be a good foundation on which to build a more universal QI program specific to breast pathology.

Correlation between Pathology and Radiology

As introduced in Question 1, radiology and pathology are critically linked when evaluating breast biopsy specimens. Discordant results (eg, a lesion that appears radiologically benign but is proven malignant on biopsy or a lesion suspicious for malignancy on imaging but deemed benign by pathology) require prompt attention. Discordant results also provide a potentially valuable educational opportunity for all members of the team.[Parikh 2005] Several of the interviewed experts explicitly stated a need to have QC and QI programs that direct radiology departments to routinely determine their own concordance with pathology reports, as well as similar programs directing pathology departments to assess concordance with and provide feedback to radiology regarding the quality of their image-assisted samples. In addition, reimbursement from Medicare could be tied to successful participation in a QC and QI program or other demonstrations of multidisciplinary collaboration and consensus diagnosis. Finally, the potential negative impact that the HIPAA regulations may have on this process needs to be assessed.

Quality Control Programs

Quality control programs are common in other laboratory disciplines (eg, cytopathology), but anatomic pathology is far behind on this issue. The US government's Clinical Laboratory Improvement Amendments program was designed to ensure quality laboratory testing, but the standards apply to pathology in general, not specifically to anatomic pathology or breast cancer pathology.

There is a need for a national QC program for common procedures, such as HER2 and ER testing. The false-positive rate for HER2 testing has been found to be unacceptably high in laboratories that do a small volume of HER2 testing or that do not use automated staining.[CAP 2004] Discordance was 18% between community laboratories and the central lab in the NSABP B-31 trial [Paik 2002] and 26% in the Intergroup N9831 trial.[Roche 2002] False-positive results can result in the inappropriate use of trastuzumab, which exposes patients to unnecessary costs and toxicities, whereas false-negative results may deny effective therapy to others. The authors of the NSABP and Intergroup trials concluded that QC programs and additional studies of inter-laboratory concordance are needed to ensure optimal HER2 testing throughout the United States. Indeed, data from the NSABP demonstrate that the false-positive rate can be decreased dramatically after QC measures are implemented (from 20% false-positives to 6% in the B-31 trial).[personal communication, Dr. Paik] The College of American Pathologists offers proficiency testing, but it is estimated that only 30% of the labs performing HER2 testing in the United States participate in this process.[CAP 2004] It is possible that the lack of participation in these programs is related to the current reimbursement environment.

Estrogen receptor testing is also problematic. Data from the QC program in the United Kingdom demonstrate a false-negative rate ranging from 30% to 60% when evaluating low-positive tumor samples; these patients could benefit from antiestrogen therapy, but antiestrogens are not prescribed if the tumor is called ER-negative.[Rhodes 2000] Data from NSABP B-24 suggest that the error rate for ER testing in the United States is also unacceptably high. This randomized, placebo-controlled trial was designed to assess the efficacy of tamoxifen in patients with DCIS, regardless of hormone receptor status. Tamoxifen use was associated with a 57% reduction in the relative risk of recurrence in the group called ER-negative by outside laboratories, but it had no impact on the ER-negative group classified by results of the central lab analysis. These results are explained by the fact that external laboratories

classified 30% of the patients in the trial as ER-negative, whereas the central laboratory determined that only 20% were ER-negative. These data clearly show that false-negative results are occurring in the community. Moreover, when therapy is prescribed according to ER test results, some women will be denied effective medications due to a false-negative ER test.

In the 1980s when ER status was determined by ligand-binding assay, there was a national QC program for ER testing coordinated by the NCI. Participation in the program was required for participation in federally funded clinical trials. Over time, immunohistochemical methods came to replace ligand-binding assays in many laboratories and the national QC program was discontinued. Potential problems with immunohistochemistry testing that may lead to interlaboratory discordance include use of a diverse set of reagents (antibodies), different detection systems, different methods of scoring, and different definitions of positivity (>1% positive cells versus >10% positive cells).[CAP 2004] The UK National External Quality Assessment Scheme for Immunocytochemistry (NEQAS-ICC), which evaluates the quality of ER and HER2 testing on a quarterly basis, could serve as a model for the United States.[Rhodes] Recognizing the need to ensure that women with low ER positivity are not mistakenly diagnosed as ER-negative, the UK NEQAS-ICC program has effectively identified laboratories with poor performance, identified reasons for poor results, and improved laboratory performance as part of the country's multifaceted approach to laboratory quality assurance. Another possible solution to increase compliance with the voluntary proficiency testing programs already in place in the United States (eg, CAP Q-Probes) would be to link proficiency testing to Medicare reimbursement. Other insurers would likely follow the example, resulting in improved performance at labs throughout the country.

Role of the Federal Government and Pathology Professional Societies

The specific examples delineated in Question 4 appear to be reasonable practices to subject to quality control programs. Other issues, such as determining the need for routine second opinions and the establishment of breast pathology as a subspecialty, are more difficult to address. What these issues have in common, however, is a need for action, coordinated by pathology professional societies, Komen for the Cure, or the Federal government. As discussed above, professional societies such as CAP and the American Society for Breast Disease have programs in place to standardize and improve certain aspects of breast pathology practice. The International Society of Breast Pathology was established in 1998 to foster excellence in breast pathology and is now considered a companion society of CAP.[personal communication, Dr. Masood] The Society had already identified many of the issues discussed in this White Paper as areas in need of improvement, and as part of its mission, it works with the Congress, the National Cancer Institute, the National Institutes of Health, and the Centers for Disease Control and Prevention to address these issues. Komen for the Cure has a proven track record in ensuring public investment in quality breast health and breast cancer care. Working together, Komen for the Cure and pathology professional societies could begin the difficult work of finding solutions to these problems. It is unclear at the current time whether new Federal legislation is appropriate, particularly for the issues that deal with pathologic interpretation. For example, the Mammography Quality Standards Act has improved the quality of mammography in this country, but its provisions focus largely on the technical quality of imaging more than on the accuracy or reproducibility of reader interpretation. What is needed at the current time is a more complete evaluation of the issues raised here so that a plan of action can be created.

CONCLUSIONS

In addition to funding ground-breaking research, Susan G. Komen for the Cure is committed to ensuring that all people facing a possible diagnosis of breast cancer have access to the best care currently available. Pathology is the navigator of the ship and the foundation upon which important decisions are made. To receive the best possible care, women must first receive an accurate and high quality pathologic work-up.

Komen for the Cure has serious concerns about the lack of uniform standards currently available to guide the practice of breast pathology in this country. Whether the issue is pathology reporting, personnel training, specimen handling and storage, or quality improvement programs, the common thread connecting these issues is an apparent lack of uniformity throughout the country. A thorough review of current breast pathology practices is warranted. The ultimate goal is the identification of ways to improve diagnostic accuracy and facilitate progress in biologically correlated clinical science without placing undue burden on physicians. Cooperation across the spectrum of medical professions will be a key component in achieving this outcome. Solutions are likely to involve patients themselves, all members of the clinical care team, and the relevant professional societies. The need for new federal legislation remains to be determined.

References

- Allred D, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP protocol B-24. Proceedings of the San Antonio Breast Cancer Symposium 2002. Abstract 30.
- American Cancer Society website. Breast cancer facts & figures 2005-2006. Available at: <http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf>. Accessed May 11, 2006.
- American College of Surgeons website. Commission on Cancer: cancer program standards 2004 (revised edition). Available at: <http://www.facs.org/cancer/coc/cocprogramstandards.pdf>. Accessed May 11, 2006.
- American Society for Breast Disease website. Policy statement on routine orientation of excised breast specimens. Available at: <http://www.asbd.org/pages/newsarchives.html#Anchor-FOR-40558>. Accessed June 1, 2006.
- Bilous M, Dowsett M, Hanna W, et al. Current perspectives on HER2 testing: a review of national testing guidelines. *Mod Pathol*. 2003; 16:173-182.
- College of American Pathologists website. Predictive cancer factors 2004: what's next and what matters? Available at: http://www.cap.org/apps/docs/annual_meeting/presentations/2004/wednesday/AP120_Predictive_Cancer_Factors.pdf. Accessed July 14, 2005.
- College of American Pathologists website. About Q-Probes. Available at: http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl_t&cntvwrPtl_t%7BactionForm.contentReference%7D=q_probes%2Fqprobes_desc.html&_state=maximized&_pageLabel=cntvwr. Accessed June 13, 2006.
- Collins LC, Connelly JL, Page DL, et al. Diagnostic agreement in the evaluation of image-guided breast core needle biopsies: results from a randomized clinical trial. *Am J Surg Pathol*. 2004;28:126-131.
- Demartines N, Mutter D, Vix M, et al. Assessment of telemedicine in surgical education and patient care. *Ann Surg*. 2000;231:282-291.
- Fitzgibbons PL. Atypical lobular hyperplasia of the breast – a study of pathologists' responses in the College of American Pathologists Performance Improvement Program in surgical pathology. *Arch Pathol Lab Med*. 2000;124:463-464.
- Guinebretiere JM, Becette V, Hagay C, Belichard C, Tardivon A, Vanel D. Use of radiology for the pathologist in the management of breast lesions. *Eur J Radiol*. 2005;54:15-25.
- Imperato PJ, Waisman J, Wallen MD, Llewellyn CC, Pryor V. Improvements in breast cancer pathology practices among Medicare patients undergoing unilateral extended simple mastectomy. *Am J Med Qual*. 2003;18:164-170.
- Jackson PA, Merchant W, McCormick CJ, Cook MG. A comparison of large block macrosectioning and conventional techniques in breast pathology. *Virchows Arch*. 1994;425:243-248.
- Masood S, for the Worldwide Excellence in Breast Pathology Program. The expanding role of pathologists in the diagnosis and management of breast cancer: Worldwide Excellence in Breast Pathology Program. *Breast J*. 2003;9(Suppl 2):S94-S97.
- Mechine-Neuville A, Chenard MP, Gairard B, Mathelin C, Bellocq JP. Large sections in routine breast pathology. A technique adapted to conservative surgery. *Ann Pathol*. 2000;20:275-279.
- Nakhleh RE, Jones B, Zarbo RJ. Mammographically directed breast biopsies: a College of American Pathologists Q-Probes study of clinical physician expectations and of specimen handling and reporting characteristics in 434 institutions. *Arch Pathol Lab Med*. 1997;121:11-18.
- Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing—National Surgical Adjuvant Breast and Bowel Project experience. *J Natl Cancer Inst*. 2002;94:852-854.

- Parikh J, Tickman R. Image-guided tissue sampling: where radiology meets pathology. *Breast J*. 2005;11:403-409.
- Raab SS, Grzybicki DM, Janosky JE, et al. Clinical impact and frequency of anatomic pathology errors in cancer diagnoses. *Cancer*. 2005;104:2205-2213.
- Rhodes A, Jasani B, Barnes DM, Bobrow LG, Miller KD. Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. *J Clin Pathol*. 2000;53:125-130.
- Rhodes A. Quality assurance of immunohistochemistry for hormonal receptors and HER-2/neu. Available at: <http://www.pathsoc.org.uk/pathCda/UploadedFileDisplay?Type=general&Source=general&Id=1384>. Accessed July 19, 2005.
- Roche PC, Suman VJ, Jenkins RB, et al. Concordance between local and central laboratory HER2 testing in The Breast Intergroup Trial N9831. *J Natl Cancer Inst*. 2002;94:855-857.
- Ross JS, Fletcher JA, Bloom KJ, et al. Targeted therapy in breast cancer: the HER-2/neu gene and protein. *Mol Cell Proteomics*. 2004;3:379-398.
- Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg*. 2005;201:586-597.
- Staradub VL, Messenger KA, Hao N, Wiley EL, Morrow M. Changes in breast cancer therapy because of pathology second opinions. *Ann Surg Oncol*. 2002;9:982-987.
- Torres MI, Webster FB, Bilous AM, et al. Supporting the implementation of breast pathology recommendations: feasibility of a feedback mechanism to pathologists. *Pathology*. 2003;35:402-408.
- Tot T, Tabar L, Dean PB. The pressing need for better histologic-mammographic correlation of the many variations in normal breast anatomy. *Virchows Arch*. 2000;437:338-344.
- Tot T. Correlating the ground truth of mammographic histology with the success or failure of imaging. *Technol Cancer Res Treat*. 2005;4:23-28.
- Wells WA, Carney PA, Eliassen MS, Tosteson AN, Greenberg ER. Statewide study of diagnostic agreement in breast pathology. *J Natl Cancer Inst*. 1998;90:142-145.
- Wilkinson NW, Shahryarnejad A, Winston JS, Watroba N, Edge SB. Concordance with breast cancer pathology reporting practice guidelines. *J Am Coll Surg*. 2003;196:38-43.
- Velan GM, Kumar RK, Dziegielewski M, Wakefield D. Web-based self-assessments in pathology with Questionmark Perception. *Pathology*. 2002;34:282-284.
- Yaziji H, Goldstein LC, Barry TS, et al. HER-2 testing in breast cancer using parallel tissue-based methods. *JAMA* 2004;291:1972-1977.

Appendix I.

Susan G. Komen for the Cure would like to thank the following individuals for their assistance with the development and review of this paper:

D. Craig Allred, MD

Professor of Pathology
Head of Breast Pathology
Baylor College of Medicine
Houston, Texas

J. Valerie Ravan Andrews, MD, FACS

Clinical Assistant Professor
Division of Surgical Oncology
UT Southwestern Medical Center at Dallas
Dallas, Texas

Ira J. Bleiweiss, MD

Director of Surgical Pathology
Director, Division of Breast Pathology
Mt. Sinai Medical Center
New York, New York

Melissa Bondy, PhD

Professor of Epidemiology
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas

David M. Euhus, MD, FACS

Marilyn R. Corrigan Distinguished Chair in
Breast Cancer Surgery
UT Southwestern Medical Center
Dallas, Texas

Phil Evans, MD, FACR

Director, Southwestern Center for Breast Care
Professor of Radiology
University of Texas
Dallas, Texas

Julio Ibarra, MD

Medical Director, Breast Pathology and Cytopathology
Orange Coast Memorial Medical Center
Fountain Valley, California

Philip B. Kivitz, MD

Clinical Professor of Radiology
Stanford University Medical Center
Stanford, California

Gerald R. Kolb

President and CEO
Breast Health Management, Inc.
Bend, Oregon

Michael D. Lagios, MD

Medical Director, Breast Cancer Consultation Service
St. Mary's Medical Center
San Francisco, California

Shahla Masood, MD, FASCP

Professor and Associate Chair, University of Florida
Department of Pathology
Founder, International Society of Breast Pathology
Jacksonville, Florida

Joyce A. O'Shaughnessy, MD

Co-Director, Breast Cancer Research
Baylor Charles A. Sammons Cancer Center
Dallas, Texas

C. Kent Osborne, MD

Director, The Cancer Center
Director, Breast Center
Professor of Medicine and Molecular and Cellular Biology
Baylor College of Medicine
Houston, Texas

David Page, MD

Professor of Pathology and Epidemiology
Vanderbilt University Medical Center
Nashville, Tennessee

Soonmyung Paik, MD

Director, Division of Pathology
NSABP Foundation
Pittsburgh, Pennsylvania

Jay Parikh, MD, FRCP(c), CPE, FSBI

Medical Director,
Women's Diagnostic Imaging Center
Swedish Cancer Institute
Seattle, Washington

Jane Reese-Colbourne, MS, MBA

Past Executive Director of the United States National Breast
Cancer Coalition
Arlington, Virginia

Lorraine Tafra, MD, FACS

Director, Anne Arundel Medical Center Breast Center
Annapolis, Maryland

Ann Denise Thor, MD

EB Todd and JC Todd Chair of Pathology University of
Colorado Health Sciences Center
Denver, Colorado

Appendix II.

Breast cancer incidence

269,730 new cases were estimated to occur in 2005, including
211,240 cases of invasive disease and 58,490 cases of in situ
disease (American Cancer Society, 2006)

$$269,730 \times 0.02 = 5,395$$

$$269,730 \times 0.04 = 10,790$$

Breast cancer prevalence (as of January 2002):

2,300,000 women have a history of breast cancer (includes
women who are disease-free plus those undergoing treatment)
(American Cancer Society, 2006)

$$2,300,000 \times 0.02 = 46,000$$

$$2,300,000 \times 0.04 = 92,000$$



5005 LBJ Freeway, Suite 250
Dallas, Texas 75244
1-877 GO KOMEN (1-877-465-6636)
www.komen.org

©2007 Susan G. Komen for the Cure