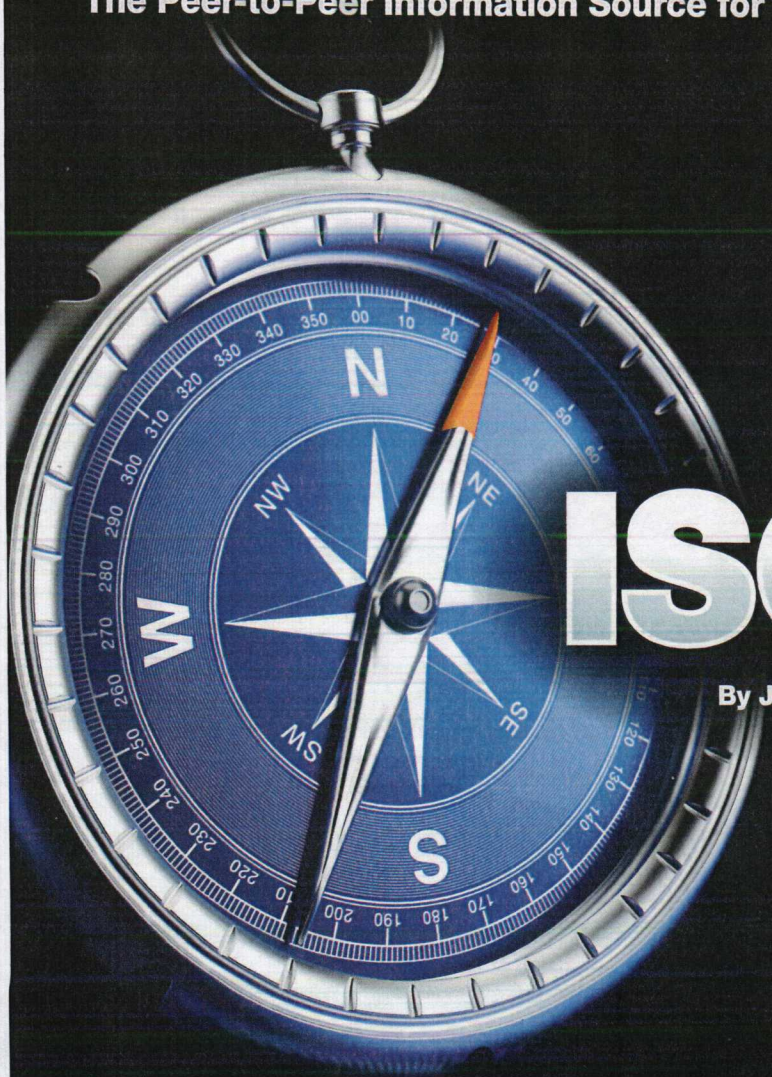
July/August 2015 • Volume 4, Number 4



# Medical Lab MANAGEMENT

The Peer-to-Peer Information Source for Clinical Laboratory Management



## NAVIGATING ISO 15189

By Jennifer Dawson, MHA, DLM(ASCP)CMSLS, QIHC

PAGE 6



w.MedLabMag.com

30 Garber Square, Suite A, Ridgewood, NJ 07450 Electronic Service Requ

By David Smith, MD

# Expanding Utilization of Whole Slide Digital Imaging

Since the beginning of surgical pathology as a medical discipline, pathologists have handled pieces of glass mounted with stained portions of human tissue, sliding them across microscope stages in order to render disease diagnoses. Accompanied by numerous mechanical and technical developments through the years, the examination of patient samples using a microscope has proven a tried and true method for disease identification. However, over the past decade, technological advances have combined modern microscope optics with the incredible power of computerized digital image capture. By enabling the production of digital images of an entire specimen slide (ie, whole slide digital imaging), pathologists are presented with dynamic new uses for microscopy and digital image analysis, as well as the enticement of virtual microscopy.

Nevertheless, this new technology also elicits concern regarding its scope and capabilities, and presents new operational challenges. Issues that laboratories must address prior to the widespread adoption of digital pathology and imaging technologies include:

- Determining the infrastructure necessary to manipulate and house large amounts of digital data (see **SIDEBAR**)
- Working with information technology resources to gain sufficient network bandwidth to allow for rapid file transfer, without hindering workflow
- Balancing the time and effort required to learn about, acquire, and implement digital imaging technology alongside the regulatory approvals necessary for routine use

The laboratory team at Riverside Regional Medical Center (RRMC)—a 450-bed hospital located in Newport News, Virginia—is now working with its third generation of digital imaging technology. The first two systems were spot image capture systems (not whole-slide imagers), which required a pathologist to sit at the system's microscope and capture images of specific cell groups. The results—used exclusively for digital image analysis, not diagnosis—were beneficial, but the limiting factors of requiring the physical presence of a pathologist (ie, no virtual aspect) and lack of whole slide digital imaging rendered the technology insufficient for consultation or primary diagnosis.

## Finding the Best Use for Digital Imaging

Breast cancer biomarker (largely, estrogen receptor [ER], progesterone receptor [PR], HER2/neu, and perhaps Ki-67) testing and

## Digital Imaging and Software-Based Image Analysis

By applying a computerized algorithm that analyzes each cell nucleus on an entire specimen slide, the software can determine whether the intensity of the immunohistochemical stain is at, or above, a predetermined threshold.

analysis have come under greater regulatory scrutiny in the last few years. As a result, many laboratories have devoted considerable time and resources to complying with College of American Pathologists (CAP) guidelines for controlling the pre-analytic variables of breast cancer biomarker stains. This is where entirely manual methods of sample analysis can fall victim to variability. Under traditional practices, pathologists are asked to count a percentage of cells positive or negative for a specific biomarker, but there are no widely accepted methodologies or rules governing this practice. Thus, a single case reviewed by multiple pathologists often produces a broad range of analytical results. While there are several reasons for this variability, chief among them may be pathologists' unwillingness to spend long periods of time meticulously counting cells one by one. The rigors of other duties render most pathologists ill suited for such tedious work. Therefore, it is common practice for pathologists to estimate the percentage of positive staining cells in a sample.

Beyond the obvious fallibilities of this practice, one inherent problem is that the joint CAP/ASCO (American Society of Clinical Oncology) guideline for hormone receptor analysis in breast can-

cers states that any tumor with greater than 1% staining is positive for the hormone receptor. Under existing methods of manual cell counting, breast cancers with low ER and PR expression are unlikely to gain agreement among pathologists regarding positive versus negative results.

This is where imaging technology can flex its capabilities—high-resolution digital imaging combined with software-based image analysis largely solves the problem. By applying a computerized algorithm that analyzes each cell nucleus on an entire specimen slide, the software can determine whether the intensity of the immunohistochemical stain is at, or above, a predetermined threshold. If the intensity exceeds the threshold, then the software counts the cell as positive. Pathologists or analysts simply digitally circle the tumor cells on the slide (for a specific field of view) and allow the system to rapidly count and analyze thousands of cellular nuclei. If the staining intensity of a given nucleus is above the set threshold as mentioned, the cell is counted a positive for the assay. This process essentially eliminates the guesswork involved in cell counting and qualifying.

**Under traditional practices, pathologists are asked to count a percentage of cells positive or negative for a specific biomarker, but there are no widely accepted methodologies or rules governing this practice.**

## Looking Ahead to Virtual Microscopy

The ubiquity of the internet combined with robust and secure data networking has invoked several medical disciplines to explore telemedicine practices that have the potential to extend quality health care to underserved areas, as well as create an environment for large scale collaboration. This idea gave rise to the concept of digital pathology, and its potential is considerable. By extension, virtual microscopy conceives, for example, that routine hematoxylin and eosin (H&E) stained slides can be digitally imaged at a central laboratory, and a remote pathologist can simply acquire the images over the internet and use them to virtually review and diagnose a case.

It is quite common for pathologists to provide pathology services at multiple facilities. On any given day, pathologists may travel to sister sites separate from the core laboratory to provide on-site services. I travel approximately 80 miles once or twice a month to a critical access hospital on Virginia's Eastern Shore. On these trips, the slides have to be physically carried from the main hospital where the histology laboratory is located. However, it is not uncommon for some of the slides or special stains to not yet be available when it is time to leave for the outside facility. At the remote location, I always have a computer with internet access. If I were able to produce high-resolution images of the slides at our main histology lab, I could then access the slides and diagnose the case remotely; hence, virtual microscopy.

Currently, RRMC has a system that produces high-quality images, but the size of the files renders the transfer rate too slow to support remote slide review with the speed of traditional, physical microscopy. However, many pathologists, myself included, would consider working a bit slower in exchange for increased access. Regardless, this point remains moot until the FDA approves virtual microscopy for primary diagnosis of disease.

## Regulatory Status

Despite having both the technology to perform virtual microscopy and practitioners willing to utilize it, the FDA has ruled that whole slide digital imagers are medical devices subject to regulation. Therefore, manufacturers must submit their devices as complete systems for review and approval. Each component of the system must be described and evaluated, including the microscope components, light intensity, image-capture system, digital file type, storage requirements, software analytics, etc. Above all this, central questions remain: Is the pathologist being given the same information and can he or she make the same diagnosis using a high-resolution digital imaging system as with routine, physical microscopy? Does digital analysis offer the same level of patient safety? Based upon my experience, I believe that the answer to these questions is yes.

While these questions remain in debate, there are logistical issues that also must be addressed. For example, a single high-resolution digital file—a single view of a tissue sample—of the quality necessary for diagnostic use, may require a relatively large amount of digital storage capacity. When compounded by the total number of slides per patient and the total number of patients, digital storage has the potential to become a serious challenge. Historically, laboratories are required to save all glass slides and paraffin blocks used for diagnostic purposes for a minimum of 10 years. In the case of whole slide digital imaging, perhaps just the portion of the digital image that contains evidence of malignancy should be retained. This is just one example of how digital pathology technologies can complicate existing laboratory practices.

For now, laboratories may use digital imaging systems while analyzing parts of a pathology case as long as the pathologist uses the traditional glass-slide-and-microscope method for the primary diagnosis. For example, digital image analysis of immunohistochemical stains is allowed as long as the primary H&E diagnosis is made using traditional methodology. Likewise, virtual pathologist consultations also are allowed as long as the primary pathologist of record is making the official diagnosis using the traditional glass and scope method.

**SIDEBAR**

## Value of Human Resources

**Prior to implementing a digital imaging solution,** it is critical to first fully review and acquire the appropriate infrastructure, and educate staff on how the system will be used. Failing to do so can introduce unexpected strain on staff resources.

When RRMC began adopting digital imaging technology, the laboratory first purchased a bar coding solution with interfaces between the pathology LIS and the histology testing and imaging systems. This key step added one or more bar codes to every slide in the histology laboratory. Each slide could then be read by any of the system components throughout the laboratory. Without this step, an employee would have to sit at the digital scanning computer and manually enter data, including patient demographics, test types, etc. A solution that will interface with other systems and transmit demographics and test orders mitigates stress on existing staff while improving patient safety by driving out data entry errors. Many pathology and histology laboratories do not currently employ specimen bar coding and tracking, but such a system is highly recommended before considering a digital imaging solution.

## The Clock Is Ticking

The FDA's timetable for approving digital imaging solutior for routine primary diagnosis remains unclear. Howeve some consolation is provided by the fact that the FDA ha set a precedent by allowing digital imaging in radiology- a medical specialty with multiple similarities to patholog (eg, diagnostics-centered, often hospital-based). Clearl widespread adoption of digital imaging systems will requi federal approval first, and the initial limiting factors a likely to relate to information systems infrastructure, avai able network bandwidth, and file storage capacity. Yet, th unleashed power of digital imaging technologies on labora tory and pathology practices seems boundless. Until suc time as systems are approved for primary read and diag nosis, laboratories with significant breast cancer program can still benefit from biomarker digital image analysis. ■

David Smith, MD, is the medical director for labo ratories at Riverside Regional Medical Center Newport News, Virginia. He also is the managin partner of his medical group, Peninsula Patholog Associates.