Integrated Pathology Informatics Enables High-Quality Personalized and Precision Medicine

Digital Pathology and Beyond

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Context.—The critical role of pathology in diagnosis, prognosis, and prediction demands high-quality subspecialty diagnostics that integrates information from multiple laboratories.

Objective.—To identify key requirements and to establish a systematic approach to providing high-quality pathology in a health care system that is responsible for services across a large geographic area.

Design.—This report focuses on the development of a multisite pathology informatics platform to support high-quality surgical pathology and hematopathology using a sophisticated laboratory information system and whole slide imaging for histology and immunohistochemistry, integrated with ancillary tools, including electron microscopy, flow cytometry, cytogenetics, and molecular diagnostics.

Results.—These tools enable patients in numerous geographic locations access to a model of subspecialty pathology that allows reporting of every specimen by the right pathologist at the right time. The use of whole slide imaging for multidisciplinary case conferences enables better communication among members of patient care teams. The system encourages data collection using a discrete data synoptic reporting module, has implemented documentation of quality assurance activities, and allows workload measurement, providing examples of additional benefits that can be gained by this electronic approach to pathology.

Conclusion.—This approach builds the foundation for accurate big data collection and high-quality personalized and precision medicine.


The scope of modern pathology encompasses many classical disciplines and technologies, including clinical biochemistry, laboratory hematology, medical microbiology, anatomic pathology, and laboratory molecular genetics. Progress in all of these areas has resulted in structural variability of pathology departments throughout the world. The resulting complexities of reporting responsibilities and financial drivers have confounded a world where electronic data are a major driver.

The importance of pathology as the basis of diagnostic medicine has been recognized for more than a century and remains embodied in the statement of Sir William Osler, who recognized that, “As is our pathology, so is our practice; what the pathologist thinks today, the physician does tomorrow.” However, for many reasons, pathology has had challenges in maintaining its profile and recruiting sufficient interest to support the number of pathologists required to adequately serve the need in many countries. The challenge facing underserviced areas with shortages of expertise has served as a driver of innovation to provide high-quality diagnostics in a fiscally responsible fashion.

The 21st century has seen the implementation of transformative technologies that have impacted laboratory medicine. The move to electronic medical records, interfaced with automated laboratory testing, and increasingly complex molecular diagnostics to support precision medicine are significant advances that have spawned an entire new field within the discipline: “pathology informatics.” The digitization of traditional microscopy using whole slide imaging (WSI) provides an opportunity to revitalize the most complex area of pathology, the bastion of interpretive medicine-anatomic pathology.

The aim of this project was to identify key requirements and establish a systematic approach to providing high-quality pathology in a publicly funded health care system that is responsible for services across a large geographic area that includes a heavily populated urban metropolis, large suburban communities, and remote towns that serve as

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hubs for large rural areas with scattered populations. This report will focus mainly on the development of a system to support high-quality subspecialized anatomic pathology and hematopathology that require interpretation of data that involve images. The system also includes biochemistry, automated hematology including coagulation, transfusion medicine, and microbiology, but these aspects will not be reported here.

MATERIALS AND METHODS

Institutions

This article reviews the pathology informatics implemented to support interpretive pathology between 2001 and 2015 at the University Health Network and its Laboratory Medicine partners in Ontario, Canada. The system was initiated in a consolidation of 3 major academic hospitals that serve as tertiary care centers as well as local service providers in the center of a large metropolis (Figure 1). During the course of development, partnerships were initially developed with 2 hospitals in remote areas (Figure 2); 1 of these was the hub of a group of 10 hospitals, with the 9 others providing services in smaller communities along a major highway. A second major partnership was developed with a large community hospital that had become the core of a partnership of 4 hospitals servicing a large and growing suburban population (Figure 2). Additional partners included a smaller independent community hospital south of Toronto, a remote hospital in northern Ontario that joined the 10-hospital group, a large academic psychiatric hospital as well as an academic rehabilitation hospital in the large metropolis, and a smaller academic health science center that required a niche application for occasional subspecialty coverage (Figure 2).

Human Resources

The medical and scientific staff involved in clinical care included subspecialty-trained pathologists practicing in specific areas of anatomic pathology and hematopathology (Table 1), and scientists with expertise in molecular genetics and cytogenetics. The biochemists, microbiologists, and hematologists with expertise in coagulation and transfusion medicine and immunogenetics (histocompatibility) are not included in this report.

Experts were recruited to support the development of electronic initiatives of this project. A member of the information technology team who was recruited to oversee the development of the laboratory information system (LIS) is a registered technologist with the College of Medical Laboratory Technologists of Ontario and has a bachelor’s degree; 10 years of experience working in the organization as a technologist enabled this person to optimize the LIS to suit the specific needs and workflow of the system. An engineer with training in pathology and laboratory workflow worked initially for the vendor of the WSI hardware and software and was subsequently recruited to the academic center to oversee workflow improvements after the implementation of WSI and to facilitate the introduction of image analysis and computer-aided diagnostics. An individual was recruited to oversee the implementation of electronic pathology initiatives at the largest hub outside the central core; this individual had experience as a pathologists’ assistant as well as managerial experience in histology.

Information Technology Hardware and Software

CoPathPlus, purchased from Cerner (Cerner Corp, Kansas City, Missouri), is an anatomic pathology LIS with add-on features that include an image capture and storage module (PICSPlus), a customizable synoptic reporting module that features database storage, and an advanced bar code and tracking (AB&T) module for unique specimen, block, and slide identification. It is a flexible, customizable system that can be scaled to the size of the lab, working just as well for small laboratories as multisite large organizations.

Kaluza analysis software (Beckman Coulter, Corporate Office, Brea, California) was implemented for analysis of data generated by flow cytometry. Kaluza was interfaced with CoPathPlus, allowing
users to upload the text files generated by Kaluza with the data imported into a CoPathPlus synoptic template.

The Vantage system (Roche, Ventana, Tucson, Arizona) uses a bidirectional interface that allows the communication of CoPathPlus immunohistochemistry (IHC) stain orders with Ventana automated stainers. This interface was implemented to facilitate automated tracking and importation of IHC slides into CoPathPlus for WSI.

Remote imaging was initiated in 2004. In the initial phase of providing remote frozen section coverage, we used a dynamic server-client remote-controlled robotic Leica TPS2 microscope purchased from Leica Microsystems (Richmond Hill, Ontario, Canada). The server component comprised a microscope equipped with 6 objectives (×2.2 to ×63) and a mounted Sony 3CCD camera (Sony, Tokyo, Japan) as well as a macroscopy station allowing pathologists to remotely review gross specimens submitted for intraoperative consultation. These components were coupled to a Dell Pentium computer (Round Rock, Texas), which was connected to the hospital network. Remote access to the server component was set up at 2 client stations located at 2 sites. Although the robotic microscope was used successfully for a period of approximately 2 years, there were limitations in the speed with which frozen section slides could be reviewed. Accordingly, remote imaging was altered to implement WSI technology for remote frozen section coverage. Scanners for the generation of images of microscopic slides were purchased from Aperio (2006–2012) and Leica Biosystems (2012–2016; Vista, California); these included Aperio ScanScope CS scanners with a 5-slide stage, as well as a higher-throughput Aperio ScanScope XT Turbo scanner with 120 slides, and most recently, the Aperio ScanScope AT2 scanner for up to 400 slides per run. The initial image management system was Spectrum version 10 with the ImageScope viewer; the system was subsequently upgraded to Eslide Manager version 12.1 in conjunction with the WebViewer uScope (all from Aperio/Leica).

### Laboratory Configuration

Laboratories were evaluated to determine the volume and scope of expertise of each aspect of pathology. Analyses were carried out with the aim of maintaining services as close to the patient origin as possible without compromising quality. Changes were made to optimize specimen flow and turnaround time. In some instances, laboratories were closed and work was realigned in different sites that could better support the service.

### LIS Configuration

The hospitals in this project all initially used anatomic pathology modules that were part of the individual hospital electronic medical record systems. These included QuadraMed QCPR (Reston, Virginia) and several versions of Meditech (Magic and Meditech C/S, Meditech, Canton, Massachusetts). The implementation of the dedicated CoPathPlus LIS allowed configuration by the laboratory system and provided an opportunity for customization. This was determined by a team of information technology specialists working with technical and medical laboratory directors. Changes
were implemented as upgrades became available from the vendor and with customization by the LIS team. The CoPathPlus LIS was interfaced with each hospital's electronic medical record system to allow specimen orders to be accessioned into CoPathPlus and to allow completed reports to cross back into the medical records.

**Whole Slide Imaging**

Due diligence before implementing this technology included internal validation studies specific to each intended use of the technology, local education, and administrative approvals, as well as regulatory approval, which was sought from Health Canada in 2006. Local education involved extensive discussions with surgeons to ensure their understanding of the changed processes; pathologist interactions with treating care teams were enhanced by ensuring easy access by email or telephone as well as regular face-to-face interactions at sites where local pathologists were not available on a day-to-day basis.

Pathologists, histotechnologists, and selected office administrative staff at each site with a WSI scanner were trained on the use of the integrated WSI system. Training with respect to the use of the Aperio scanners and viewing software was initially provided by the vendor, with refresher training being provided by expert user pathologists and histotechnologists as required. Training on how to access digital slides, both within the LIS module and directly from a central server, was provided by LIS specialists with assistance from the institutional information technology division using staff dedicated to this project. The training of all staff was documented according to guidelines from the College of American Pathologists (CAP) and in accordance with CAP laboratory accreditation program requirements.

**Integration of WSI Into the LIS**

CoPathPlus leverages several of its add-on components to enable integration of WSI into the LIS. The Digital Slides HL7 interface works in conjunction with the AB&T module and its PICSLink desktop integration module to make this happen. The PICSLink technology is an XML-based communication protocol that allows information exchange between CoPathPlus and imaging devices.

**Integration of Flow Cytometry, Electron Microscopy, Molecular Diagnostics, and Cytogenetics**

Reporting of procedures, including flow cytometry, electron microscopy, molecular diagnostics, and cytogenetics, is often performed separately because of the time delays and special requirements involved. In this model, the goal was to ensure consolidation of all information obtained on a specimen. These components were all established as procedures in the LIS and could be ordered for any type of specimen (autopsy, blood and bone marrow, cytology, and surgical pathology).

The ability to capture digital images in PICSPlus provided a tool for documentation of data, including scanned documents received with cases, especially consultations from external institutions, electron micrographs, and molecular/cytogenetics data. The use of synoptic data capture was applied to all areas, including synoptic capture of flow cytometry data obtained from Kaluza and reporting of molecular and cytogenetic results.

**RESULTS**

**Laboratory Configuration**

Pathology laboratories, including cytology, histology, IHC, electron microscopy, flow cytometry, molecular and cytogenetics, and autopsy were evaluated to determine volumes, manpower, and skill sets; the configuration of biochemistry, automated hematology, microbiology, and transfusion medicine testing is not the subject of this report. The goal was to ensure fiscally responsible, high-quality services in a sustainable manner. The anatomic pathology laboratories at the 3 large metropolitan academic institutions were reconfigured to centralize the core anatomic pathology, flow cytometry, molecular, and cytogenetics laboratories at 1 location. The labs were rebuilt and situated physically adjacent to office space for the medical staff; medical staff offices were configured to optimize interactions among subspecialty groups. Surgical pathology laboratories were built at each large hospital where specimens were accessioned from the operating rooms and clinics; they are staffed by medical laboratory assistants who accession the cases, and pathologists’ assistants who are trained to perform gross examination and sectioning of specimens. Gross photographs are uploaded through the PICSPlus module as part of the record for individual cases. Blocks are then sent to the core lab for processing. Excess diagnostic tissue is collected when available at accessioning for storage in an institutional research biobank with research ethics approval and in accordance with legal and accreditation guidelines; this includes fresh tissue that can be collected under sterile conditions, fresh frozen tissue stored in liquid nitrogen, and formalin-fixed, paraffin-embedded tissue.

This model was then repeated in the partner sites as they joined. Accessioning, gross examination, and histology were centralized at the hub hospital of the 10-hospital cluster, and at the other independent remote hospital. In contrast, autopsy, cytology, and IHC were not adequately resourced or supervised and were repatriated to the central core laboratories. Accessioning, gross examination, histology, IHC, and cytogenetics were consolidated at the core of the 4-partner community hospital group. Cost and expertise analyses determined that autopsy, cytology, flow cytometry, electron microscopy, and molecular diagnostics should remain at only the large academic core. Biobanking was implemented in limited fashion based on the institutional needs of the individual hospitals.

This report will describe the configuration up until 2015, when it included 6 surgical pathology accessioning areas staffed by pathologists’ assistants, 4 core histology laboratories, 2 IHC laboratories, 2 cytogenetics laboratories, and 1 laboratory each for cytology, flow cytometry, electron microscopy, and molecular diagnostics.

**Pathologist Distribution**

The initial consolidation of 3 large academic hospitals in 2001 resulted in a medical and scientific staff cohort of 29 anatomic pathologists, 7 hematopathologists, 2 molecular scientists, and 1 cytogenetic scientist. The anatomic pathologists had already agreed to redistribution of workload into a subspecialty model as shown in Table 1. With the addition of new partners, additional medical staff resources were added based on existing allocations. The large community hospital had an allocation of 11 pathologists. The remote partners had financial allocations for 4 pathologists each, but 1 of those sites had only 1.5 individuals performing the work for the central hub hospital and its 9 partner hospitals at the time it joined the partnership.

The 2015 distribution included 49 anatomic pathologists (subspecialties as identified in Table 1) and 10 hematopathologists; 41 anatomic pathologists and all hematopathologists were on site at the large academic center, whereas 5 subspecialty anatomic pathologists remained at the large community site and 3 general anatomic pathologists stayed at 1 of the remote hospitals. Pathologists visit the various sites regularly to ensure clinical integration and medical oversight of the laboratories. Molecular and cytogenetic
scientific staffing increased to 4 individuals and remained at the central core.

**Case Numbers, Types, and Distribution**

The central 3 academic hospitals generate approximately 38,000 surgical pathology cases, 21,000 cytology cases, and 16,000 bone marrow biopsies/aspirates and blood samples for molecular testing per annum. This work includes specimens derived from complex cancer surgeries; hematologic malignancies; renal, cardiac, lung, and small bowel transplantation; and neurosurgical procedures. The large community hospitals affiliated in 1 cluster generate approximately 25,000 surgical pathology specimens, 5000 cytology specimens, and 1100 blood and bone marrow specimens, reflecting the cluster’s position as a cancer center and general community hospital. The smaller partners generate 20,000 surgical pathology specimens, 2500 cytology specimens, and 350 blood and marrow specimens; these tend to be less complex.

It should be noted that gynecologic screening cytology is minimal in this configuration because this is usually sent to community laboratories that are dedicated to this high-throughput process.

**LIS Configuration**

The LIS was established with 4 number wheels to identify 4 classes of specimens: autopsy (A), blood and bone marrow (B), cytology (C), and surgical pathology (S). Geographically distinct laboratories were established as specimen classes of each number wheel, as were external consultations. Customized HL7 orders and results interfaces were implemented between the respective hospital’s electronic medical record system and the LIS. Orders from 1 organization must be associated with that organization’s specimen class, and if not, then an error is generated to the user. Access to information from individual sites and permissions to view and, later, data within the LIS, were determined based on the need, responsibility, and qualifications of the individual.

Routine reporting included inputs describing specimen type and characteristics and the results of analysis to include any procedure performed. Gross examination and histology, including IHC, were not classified as procedures for surgical pathology or bone marrow specimens; orders for all slides, including deeper sections, special stains, and IHC, were ordered through the LIS for AB&T identification. Procedures were ordered through the LIS when required for electron microscopy, flow cytometry, molecular diagnostics, and cytogenetics.

The CoPathPlus AB&T module offers the ability to track the processing of individual cassettes and slides through the lab. Specimens are tracked from accession through sign-out and beyond. Key features include matching of cassettes with containers at grossing, and matching slides with blocks at microtomy. This is achieved by labeling all cassettes and slides with 2-dimensional bar codes that uniquely identify the block or stain. This component was not only implemented for specimen identification and tracking from a quality perspective, but also was a necessary prerequisite for integration of WSI into the workflow. The Vantage interface allowed IHC stains performed on the Ventana platform to be tracked and status updates sent back to CoPathPlus, and allowed integration of WSI of those slides into the case.

Reports were structured to include synoptic data whenever possible. The implementation of the CAP cancer protocols and electronic cancer checklists (formerly called synoptic checklists) in 2004 introduced discrete data entry for cancer diagnostic data. Discrete capture of tumor type, size, stage, and grade meant not only consistency in reporting, but also timely reporting of these data to the provincial cancer registry. Medical and scientific staff members were encouraged to develop synoptic formats for specimens of all types and for all procedures to allow for rapid diagnostic reporting in a format that maximizes data capture for future analysis, and for workload measurement.\(^9\) Synoptic data capture for flow cytometry was implemented using the Kaluza interface. Synoptic data capture was interfaced with the institutional research database, where it annotated clinical data as well as the biobank samples.

Additional supports embedded in the LIS included the PICSPlus module that allows capture of photographs as well as documents in PDF format; specimen photographs and electron micrographs are integrated using this module, and scanned documents include clinical and radiologic information that may not be in the patient chart, as well as all information sent with consultations from external institutions. A quality assurance (QA) module was expanded for documentation of all quality assurance activities (Table 2). Creation of a workload module has been previously published.\(^18\)

The life cycle of a pathology report is not static, and in many cases initial reports are provided to allow clinical action before all procedures are complete. The benefit of the consolidated report was diminished by the traditional location of additional information at the bottom of the existing report. To overcome this and to allow a comprehensive pathology consultation, the concept of the Consolidated Theranostic Report (A. V. Parwani, MD, PhD, MBA, oral communication, October 2012) was applied. This field was built to rise to the top of the consultation report and to provide the pathologist with the opportunity to consolidate and summarize all of the relevant diagnostic, prognostic, and predictive information obtained on a specimen (Figures 3 and 4).

**WSI Deployment**

Telepathology using a robotic microscope was used initially to support frozen sections at a location 1.5 miles away from the consolidated department; that site generates a small number of intraoperative consultations, most of which are in the area of neuropathology. Initially there was a neuropathologist on site, and the few consultations for other types of intraoperative consultations required a pathologist from another site to physically go to that first site. Consolidation of the department resulted in neuropathology not being available at all times on site, and the rare other requests were not considered to be an efficient use of pathologist time. The results of this program have been previously reported.\(^13\) The move to WSI from the robotic microscope was associated with a 4-fold reduction in the time taken to review a frozen section slide (9.65 minutes per slide with the robotic microscope versus 2.25 minutes by WSI).\(^12\)

Armed with the experience of using WSI at a site a mile away from the core facility, the application of WSI was then expanded to support intraoperative consultations at remote sites and pathologist-to-pathologist consultation so that pathologists at remote sites could access the opinions of their colleagues. The availability of WSI facilitated rapid pathologist-to-pathologist consultation within subspecial-
ties, which was particularly useful for intraoperative consultations and off-hours call, which remain common responsibilities of the group. When all members of a subspecialty group wished to participate in major meetings outside the institution, WSI provided the ability to be available for urgent case consultation for intraoperative consultation or rush biopsies, irrespective of where the team had traveled, either locally or across the world. Ultimately, another academic medical center with a single neuropathologist participated in the program for coverage of intraoperative neuropathology consultations during vacations and other absences.

Primary diagnosis for surgical pathology was initiated in 2011 at the large community hospital that had full histology and IHC laboratories on site. The program was rolled out by subspecialty; with sufficient volume to support gastrointestinal, skin, and breast pathologists on site, these subspecialties were not initially part of the program. In contrast, genitourinary, endocrine, liver, and head and neck pathologists, as well as a pathologist with expertise in the reporting of placentas, were initially included in the program. Because cytology, hemopathology, and medical renal pathology required additional tissue processing for procedures at the core site, they were not included initially.

**Table 2. Quality Assurance Activities**

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<tr>
<th>During sign-out</th>
<th>Intraoperative versus final</th>
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<td>Cytotechnologist/pathologist correlations</td>
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<td>Prospective—prior to sign-out</td>
<td>Clinical chart review</td>
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<td>Direct communication with treating physician/team</td>
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<td>Slide review of previous/related cases</td>
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<td>Technical quality assessment</td>
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<td>Retrospective—after sign-out</td>
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<td>Correlation with subsequent procedure/test results</td>
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<td>Technical quality assessment</td>
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**Figure 3.** The consolidated theranostic report: blood and bone marrow. An example, de-identified to ensure privacy, illustrates the value of consolidating information from multiple laboratory processes that may have taken place at different geographic sites, including flow cytometry and cytogenetics, to provide a consultative opinion that includes the diagnosis with associated predictive and prognostic information and interpretation for the treating health care team.
Whole slide imaging was implemented to allow the capture of glass slides as electronic images at all sites where they were generated. These included the 6 sites where pathologists’ assistants were stationed; these individuals were trained to support intraoperative consultations that required either touch preparations or frozen sections. Scanners were available for histology and IHC laboratories.

For digital imaging to be successful in diagnostic pathology, the WSI of all slides of individual cases was required to mimic the workflow of microscope-based diagnosis. To accomplish this, an interface was built between the CoPathPlus LIS and the ImageScope viewer. Pathologist workflow using a “pathologist console” provides a list of cases assigned to each individual pathologist. With the integration of WSI, the pathologist list was structured to include a column dedicated to WSI that provides the number of scanned slides available for each case (Figure 5). The pathologist can then choose to open a case based on the complexity reflected initially by the number of slides. The integration allows the pathologist to launch 1 slide or the entire case, based on personal preference. In the whole-case model, the pathologist can see thumbnails of the slides, analogous to viewing a slide tray with glass slides (Figure 6, A).

In order to provide a good viewing experience for cases larger than 25 slides/images, the pathologists’ workstations were upgraded from 32-bit to 64-bit computers with 8 GB of RAM. Additionally, Aperio ImageScope was upgraded to Aperio WebViewer (uScope), which allowed a snappy display of all images of the case, as this viewer was found to be more stable compared with ImageScope. When a case is launched from the LIS to the WebViewer, it takes about 20 seconds to display the eSlideTray with all images (Figure 6, B); after that, each image can be viewed in the dedicated viewport immediately upon selection of an image. Slides that have been viewed flip to document this status, mimicking what many pathologists do with glass slides, and annotations of slides are stored for future documentation, similar to marks that pathologists place on glass slides.

Although we have not performed formal time-motion studies comparing WSI to glass slide review, some of the pathologists who use WSI frequently say that the time to review a case is not longer using WSI. This was not the case for all pathologists initially, but time to review cases improved with time and experience. Informal studies by some of the authors suggest that it may be faster, but the
comparisons have been confounded by potential differences in the complexity of cases obtained at the different sites in the network.

To ensure the ability of pathologists to read digital slides, a number of challenges have been addressed by performing quality reviews. Slides that fail the scan or are suboptimal represent less than 5% of total WSI; the reasons include failure to recognize the bar code—and therefore the slide is missing from the case—failure to capture the entire tissue, and blurred scans. These errors are usually identified by the technologist performing the scans at the time of reconciliation of slides using eSlide Manager, but they occasionally are detected by the pathologist. When an error is detected, the slide is rescanned; if this does not solve the problem, the glass slide is provided to the pathologist.

Deferral to glass slides is rare. The reasons for deferral are provided in a recent review.19

**Integrated Reporting**

The LIS configuration allows a single report to be generated for each specimen. In most cases, the initial consultation report includes all relevant information, with synoptic discrete data capture of histologic and IHC data, as well as flow cytometry when performed. In complex cases that require delayed procedures, a diagnostic report is issued initially and subsequently supplemented with one or more procedures; procedures drop to the bottom of the report. In cases where procedures provide important ancillary information, the data are summarized in the consolidated theranostic report at the top of the document, providing clear consultative opinions of the diagnosis, prognosis, and predictive test results.

**QA Activities**

The QA module has been adapted to provide documentation of multiple activities (Table 2). These include the usual
correlations between intraoperative consultation diagnosis and final diagnosis, cytology-histology correlations, and the results of external reviews of cases. For external consultations, original slides are scanned and the report provided as a PDF file, all assembled on a DVD or a USB drive that is mailed to the consultant required or provided to the patients who request a second opinion.

In addition, emphasis has been placed on activities performed prior to case completion to ensure that the initial report is the right report. Pathologists document their review of clinical data either in the e-chart or through discussion with treating physicians and surgeons, radiology review, review of previous slides that are relevant to their case, review of gross specimens with pathologists’ assistants or trainees, or review of paraffin blocks as required for discrepancies. They also document prospective review of cases for colleagues prior to completion. Prospective internal reviews should be encouraged because they will significantly reduce the number of amended reports resulting from retrospective review and will result in optimal patient care. These internal consultations may entail review of only one or a few slides for specific questions or they may involve review of an entire case, and the effort required is reflected in the annotations to be used for workload assessment. Postcompletion QA activities include reviews of cases for multidisciplinary case conferences, research, and teaching activities, as well as reviews of cases when subsequent pathology is obtained for a patient. Workload statistics are captured for each of these activities as well as documentation for annual review of quality metrics.

Figure 6. The pathologist cockpit: integrated whole slide imaging viewer and laboratory information system workflow. A, A workstation showing ImageScope integrated with CoPathPlus. B, A workstation showing Leica WebViewer (uScope) integrated with CoPathPlus.
Outcome measures that are monitored on a regular basis include the usual turnaround times as well as results of these pathologist QA entries into the LIS, in particular any major or minor discrepancies, incident reports, reporting times, and satisfaction surveys that are carried out regularly at all institutions. With the implementation of WSI, turnaround time was reduced by 1 to 2 days on average, because of the time saved by not shipping glass slides. Efficiencies were gained by not having to package slides for shipping, by not having to unpackage and barcode track slides at each site, and by allowing pathologists to see recuts, special stains, and immunostains immediately on completion.

Detailed cost analysis has not yet been performed for this model. It should be noted that savings were obtained to the health care system by expanding a single LIS that had been implemented for a large academic center rather than establishing an individual LIS for each partner site. This is particularly critical in Ontario, where every hospital is required to perform synoptic data transfer to the Cancer Care Ontario registry. The cost of WSI has largely been a hardware cost of purchasing multiple low-throughput 5-slide and high-throughput scanners. The manpower for support of the LIS and WSI is essentially 2 full-time LIS support individuals. As work transitioned from sorting slides to scanning, individuals within the system were retrained. Most importantly, the system saved time and money by accessing the diagnostic expertise of a subspecialist pathologist, who provided the correct answer and obviated the need for secondary consultations within all hospitals of the system, as well as by encouraging more cost-effective care for the patients awaiting the results of their tests.

**DISCUSSION**

**Multisite Primary Diagnosis by Subspecialty**

Although the impact of subspecialization in pathology has only recently garnered interest, the quality improvement resulting from subspecialization has been documented in other fields, such as cardiology, emergency medicine, gynecologic oncology, pediatrics, radiology, surgery, and administration. Early data indicate that in pathology the subspecialist approach reduces error, increases quality, and decreases cost. A model of workflow showing the increased efficiency that should translate into reduced cost and time by the subspecialty model is shown in Figure 7, A, contrasting with Figure 7, B. Although some may argue that the benefit only accrues to complex, difficult, and unusual cases, experience from other specialties indicates that even routine cases are more efficiently managed by experts and that unusual features are detected earlier and more efficiently by those with extensive experience.

The ability to provide primary diagnosis for patients by subspecialist pathologists requires sufficient case volumes by subspecialty to warrant a critical mass of medical expertise to ensure sustainability, cost effectiveness, and redundancy. In our model, we have developed the critical mass to ensure that specimens are handled by pathologists who have expertise in the area and a depth of knowledge to allow full integration into clinical teams and a clear understanding of the impact of their diagnosis on the patient. There is sufficient redundancy to ensure coverage during absences in a sustainable manner.

Although multiple sites are required to generate case volumes that justify the subspecialty model, the challenges of providing subspecialty care to multiple sites include the many demands of interacting with multiple care teams. The oversight of highly trained pathologists’ assistants and gross examinations of specimens require dedicated effort, and the availability of gross photographs in the LIS aids in ensuring appropriate handling of specimens. Daily interaction with individual physicians and surgeons requires ongoing efforts, and participation in rounds, including multidisciplinary case conferences, provides opportunities for active conversation that are known to improve patient care. The system supports virtual communications, including provincial rounds, that can be accessed from all sites through the Ontario Telemedicine Network (https://otn.ca; accessed November 1, 2016).

The traditional approach to obtaining subspecialty opinions involves primary diagnosis by a generalist with referral to a subspecialist who is usually an academic in a tertiary care center. One of the fundamental mindset changes that had to occur was that not every subspecialist had to be an academic. The outcome of this initiative can be measured by the satisfaction of nonacademic staff in the model as well as the medical outcomes and patient satisfaction. Insight into this last component can be obtained from multiple Web sites (Table 3).

Pathologist satisfaction involves more than just workplace conditions. In our system there were pathologists who, for personal reasons, preferred to live in smaller communities rather than the expensive and congested metropolis. One novel aspect of this system is that an individual pathologist could be located anywhere in the system and still maintain expertise in a subspecialty, with cases in that area channeled to that individual. Despite this opportunity, there are still a few generalists who wish to remain such; they handle more than one area of diagnostics but have access to all the subspecialists who can review the case, offer advice, or take over management before the case is completed. This provides 2 benefits: timely and correct initial diagnosis, and a single report that is paid for once, rather than the multiple bills that derive from primary reports and secondary consultations.

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*a* Lakeridge Health is a group of 4 hospitals within the Durham Region of Ontario, Canada.

*b* Accessed November 1, 2016.
Figure 7. Conventional versus primary subspecialist workflow. A, In a conventional model, cases that are more than routine often require a complex workflow that is illustrated in this schematic drawing. Unfortunately, sometimes the efforts made by the generalist are counterproductive, involving excess and inappropriate tests that can exhaust small biopsies in addition to adding to cost and delay. B, In the subspecialist model, the workflow is simplified, resulting in faster, cheaper completion of work.
Our model has limitations that remain to be resolved. Some pathologists remain concerned that subspecialization limits their future employment potential in centers that do not espouse this model.

An important challenge of moving to digital pathology is the culture shift associated with working from an electronic worklist in a hybrid glass slide–WSI environment. Although many pathologists have learned to work this way, others have not, or they refuse to adopt it. This has the potential to delay case handling if pathologists only respond to the delivery of glass slides to their offices. A related issue concerns notification of when additional slides, including deeper sections, special stains, and immunostains, are ready for review; our system currently contains no automated notifiers of these events, and pathologists need to manually check electronic worklists, which is problematic.

The lack of cytology participation in WSI initiatives was the natural result of a need for z-stacking in WSI. The advances in this field are now making it possible to consider implementation of this new technology. This will provide new opportunities for cytopathologists to perform evaluations of biopsies with technologist support when biopsies are performed at remote locations or even in various parts of a single institution, such as radiology suites, where rapid on-site evaluation takes place.38

Although hematology was not initially involved in WSI, the application of this technology to IHC has provided an initial introduction to this addition. As the technology improves, the need for z-stacking will allow full participation for this group as well. The advent of scanners that can capture fluorescence images and can be integrated into the LIS workflow will further expand the applications to include cases that require this ancillary tool.

Staffing requirements for this model are not trivial, and the development of a workload model was required to provide accurate information. In the initial phases of the process, this information was not available, and new pathologist positions were added based on projected increasing workloads from multiple sources. Site groups that were impacted to the greatest degree received an additional pathologist allocation, whereas those that were impacted to a lesser degree were required to accommodate the increased work without additional person power. With the development of the Automatable Activity-Based Approach to Complexity Unit Scoring workload system,18 the justifications for staffing became more objective, including calculations of protected time for pathologists who generated salary support for research activities; however, there remain pathologists who are not convinced of the legitimacy of this model.

Despite these challenges, our model proves that the application of sophisticated electronic initiatives enables the implementation of primary subspecialty pathology diagnosis in a multisite, single-tier approach.

Integrated Pathology Reporting

The importance of the integration of multiple testing modalities in pathology cannot be overemphasized. The early growth of pathology established the role of laboratories in biochemistry, hematology, and microbiology; the flourishing of surgical pathology led to the separation of anatomic pathology that extended beyond the autopsy. That discipline itself grew to apply electron microscopy, IHC, and flow cytometry to study specimens, and in the last 2 decades, molecular and cytogenetic tools have been increasingly applied. The evolution of new technologies has traditionally been led by an expert who initially provided the expertise, but eventually pathologists became trained in understanding the new tools and applied them. In the 1970s, many institutions had separate trained individuals reporting electron microscopy or IHC, but today, pathologists should not issue reports that do not include the results of these morphologic parameters as part of a complete anatomic pathology report. The numerous and different requirements for each area of pathology pose a challenge for a single LIS to be successful at tailoring a high-quality, user-friendly, and easily implemented integrated system. Some organizations use 1 LIS that reports all results but usually is unable to integrate with all aspects of automation or perform many of the specialized functions. Other institutions have instead taken the approach of using a different LIS for each component. The result is a multitude of reports, each with part of the information, but no single report that consolidates the pathologist consultation.

Allowing multiple reports to flow from various laboratories directly to treating physicians can result in errors of interpretation. For example, sampling can explain discrepancies when a malignancy is detected in one test but not another. Handling and processing errors can result in erroneous results in one test but not another. Differences in specificities and sensitivities of various tests can confuse results. Pathologists who oversee the various labs are best placed to identify, interpret, and explain these occurrences.

We provide here a novel approach to design the LIS and workflow to address these needs and consolidate lab results in a single report. The CoPathPlus LIS has been tailored to integrate information from multiple labs on a single specimen. A tissue obtained as cytology or surgical pathology, or a blood or bone marrow sample can receive a single accession number. Portions are used for procedures, including histology and IHC, electron microscopy, flow cytometry, molecular diagnostics, cytogenetics, and in situ hybridization. After the initial diagnosis, additional components are reported as addenda as they are completed. Once the various components are all available, the pathologist creates a “consolidated theranostic report,” which, unlike addenda, does not fall to the bottom of the report, where critical information could be missed by treating physicians if they do not scroll all the way through the report. The consolidated theranostic report was structured to go to the top of the report and provides the pathologist with the opportunity to integrate the results of the various procedures.

Quality Measures in Pathology

Our model has made the assumption that subspecialty pathology provides higher quality at lower cost, and there are published data to support this assumption.21,22 Within the subspecialist groups, validation and confirmation of diagnostic impressions by multiple experts add to the quality, and in situations where more than one type of expertise is required, subspecialists rely on the contributions and assistance of their colleagues in other areas. A study of timing of review showed that review of cases before sign-out prevents potential serious errors without delaying reporting time38; this method was applied in our model with success.

The outcome measures for pathology are traditionally largely restricted to laboratories themselves; however, quality metrics, costs, and efficiencies are not the place
where pathology quality metrics provide real value. Indeed, the real value of high-quality pathology is outside the laboratories, where the costs of patient management must be evaluated when expensive therapies are wrongly administered, unnecessary procedures are performed, or patients are kept in the hospital waiting for external consultations when the required expertise is not available. Analyses of these aspects of health care finance are sorely lacking, and the societal impact is even more difficult to estimate. In our model, primary diagnosis by subspecialists provided the right diagnosis as the initial diagnosis, without the delay usually required for second opinion by a subspecialist. In many cases, there may be input from more than one subspecialist to ensure the highest quality diagnosis; this is most often done prior to initial sign-out of the case. The ability to act on this information is likely to save the health care system significant amounts in avoiding inappropriate therapies, unnecessary procedures, and extended hospitalizations.

Indirect measures of pathology quality can be captured by academic productivity, national and international education, research, and development. Annual reports providing metrics of these activities showed continuous improvements with increased activity in all aspects during the 15-year period under review.

Ongoing initiatives include the addition of digital image analysis that is facilitated by the availability of the digital slides examined during case review. There are numerous publications supporting the notion that these automated assessments yield more accurate and reproducible data than visual assessments, and they are more efficient than formal manual counts.

Future Directions

The digitization of pathology in WSI will provide a huge source of data that will ultimately lead to computer-assisted diagnostics. The model described has formed the basis for a large database that includes patient demographics, morphologic images, immunoprofiles, and molecular genetics of huge numbers of cases that have been accurately classified by subspecialist pathologists who work in multidisciplinary health care teams. The value of this big data will be considerable and, unlike many other databases, is more likely to be properly annotated. Application of this has already been proven by the participation of the institution in multiple efforts of The Cancer Genome Atlas to molecularly characterize specific tumor types.

The integration of all the various data obtained in laboratories is the future of pathology. The importance of the pathologist as a consultant physician can only be recognized if pathologists do not simply report results. If data are generated by labs and pathologists in a fragmented process, the many results end up with the treating physician, who then must interpret them and make decisions despite his or her lack of familiarity with the limitations of each technology. In this scenario, the pathologist functions as no more than a technician.

The pathologist is a trained physician who has expertise in making the correct diagnosis, determining the likely prognosis, and, with the additional information derived from multiple tests, providing a consultative opinion about treatment approaches. As laboratory testing plays an increasing role in the era of personalized medicine, the role of the pathologist increases, and the need for consolidated interpretive reporting becomes critical. Just as electron microscopy and IHC have become standards of routine practice that are included in the pathology report, so too must new ancillary techniques, including flow cytometry, molecular genetics, and cytogenetics, become consolidated into the final interpretation and reporting of a given sample. The depth of knowledge required to integrate these various ancillary technologies demands the insight of subspecialty pathology and promotes a critical role for pathologists in the implementation of precision medicine.

It would be hard to imagine a situation where a patient does not know his or her oncologist or surgeon. However, despite the fact that pathologists play a critical role in the diagnosis, prognosis, and prediction of every patient’s disease, few patients know their pathologist. Fragmentation of pathology reporting results in loss of the consultation, and pathologists relinquish their responsibilities to treating physicians and surgeons. This initiative was intended to promote the concept of integrated subspecialty diagnostics to ensure that pathologists continue to remain indispensable consultants to their colleagues and patients.

References


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**Submissions Now Accepted for the CAP18 Abstract Program**

Abstract and case study submissions to the College of American Pathologists (CAP) 2018 Abstract Program are now being accepted. Pathologists, laboratory professionals, and researchers in related fields are encouraged to submit original studies for possible poster presentation at the CAP18 meeting.

Submissions will be accepted until 5 p.m. Central Friday, March 9, 2018. Accepted submissions will appear on the *Archives of Pathology & Laboratory Medicine* Web site as a Web-only supplement to the September 2018 issue. The CAP18 meeting will be held from October 20 to 24 in Chicago, Ill.

Visit the CAP18 Web site (www.thepathologistsmeeting.org) and the *Archives* Web site (www.archivesofpathology.org) for additional abstract program information as it becomes available.