J Pathol Inform

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View Point

21st century workflow: A proposal

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Received: 12 July 2014 Accepted: 14 October 2014 Published: 28 November 2014

This article may be cited as:
Fine JL. 21 st century workflow: A proposal. J Pathol Inform 2014;5:44.

Available FREE in open access from: http://www.jpathinformatics.org/text.asp?2014/5/1/44/145733

Abstract

Digital pathology is rapidly developing, but early systems have been slow to gain traction outside of niche applications such as: Second-opinion telepathology, immunostain interpretation, and intraoperative telepathology. Pathologists have not yet developed a well-articulated plan for effectively utilizing digital imaging technology in their work. This paper outlines a proposal that is intended to begin meaningful progress toward achieving helpful computer-assisted pathology sign-out systems, such as pathologists' computer-assisted diagnosis (pCAD). pCAD is presented as a hypothetical intelligent computer system that would integrate advanced image analysis and better utilization of existing digital pathology data from lab information systems. A detailed example of automated digital pathology is presented, as an automated breast cancer lymph node sign-out. This proposal provides stakeholders with a conceptual framework that can be used to facilitate development work, communication, and identification of new automation strategies.

Key words: Automated microscopy, digital pathology, image analysis, pathologists computer assisted diagnosis, pathology informatics, virtual microscopy, whole slide imaging, workflow

Access this article online

Website: www.jpathinformatics.org

DOI: 10.4103/2153-3539.145733

Quick Response Code:

INTRODUCTION

"Digital Pathology" has become a widely used buzzword. Aside from early successes in telepathology and gross digital photography,[1-4] surgical pathologists have yet to realize more advanced value from digital imaging. Clinical image analysis has thus far been limited to computer-assisted immunostain interpretation,[5,6] and whole slide image (WSI) systems have been slow to gain traction outside of a few niche environments (e.g. immunostains, education, telepathology consults).[7,8] With nearly universal adoption of Anatomic Pathology Laboratory Information Systems (APLIS's), pathology is highly computerized but still dependent on paperwork despite enthusiastic efforts to change this state of affairs.

Routine WSI diagnostic work remains elusive, partly due to a series of challenges related to regulation, validation, implementation logistics, resistance to change, and cost.[9-11] However, just as with other digital efforts, early WSI development has occurred as a nearly-isolated upgrade without complete reassessment of the entire workflow. This is important because modest efficiency gains may not suffice; without disruptive innovation early routine WSI implementations may fail despite determined effort and support.[11]

States the problem: The central issue is that current WSI systems seek to faithfully replicate much of the existing glass microscopy workflow, utilizing increasingly sophisticated virtual microscopy (VM) software and

better integration with APLIS data. Regardless of whether one uses VM or a microscope, the basic workflow does not change significantly. Pathologists access the APLIS or use its paperwork to manually read specimen information, including the gross description. They then review the slides in a linear fashion, from slide A to slide Z (or from slide 1 to slide n). As they work, pathologists manually construct a pathology report, via transcription, typing, or speech recognition. Although some of the report construction labor is delegated or facilitated with preformatted (i.e. canned) text, the pathologist will still manually review the formatting and text content prior to finalizing the report. Synoptic reporting exists, but often requires manual data entry and may also be redundantly included alongside free text diagnoses. Finally, the pathologist may also rely upon existing APLIS-generated paperwork for tasks related to note-taking, report construction, and trainee interaction. Even the most carefully designed VM environments essentially propose to do the same thing as before, only with WSI instead of glass slides. Unless something fundamentally changes the existing value proposition, WSI may not compare favorably with traditional glass workflow, given the resources and time needed to accommodate this technology.[10]

By carefully emulating traditional tools, current digital systems are trying to be something they are not. Such an approach may have been useful in early stages of WSI development, but use of the term "WSI" (versus "virtual slide") grew out of a desire to remind pathologists that these images are not glass microscope slides.[12-15] Rather, images are persistent data sets that can be manipulated in ways that would break glass slides. Pathologists usually review glass slides one at a time; within a slide individual histologic sections (i.e. tissue cuts) and tissue fragments are also reviewed one at a time. This is a highly optimized workflow for glass microscopy, but current WSI systems doggedly follow these conventions even though they need not apply to a digital workflow. Instead of slowly dragging oneself around WSIs, a computer could help a pathologist jump around in order to review the most important areas first. Clinically relevant areas could theoretically be triaged and presented for review independently from the underlying glass slide medium. A partial analogy might be onscreen viewing of radiology computed tomography slices in a stack versus viewing them side-by-side (i.e. as if printed onto film). Further, image data can be organized and summarized, just as with nonimage data; this means that clinically important images can be preferentially retained and accessed for subsequent patient care. Current WSI systems do not make automated distinctions between the key tumor image and included images of benign uninvolved tissue. Complete sets of WSI data are dumped into the pathologist's lap for manual interpretation. WSI systems and scanners may be automated, but not in ways that optimally support diagnostic work in an intelligent fashion.

What to do about problem: Pathologists currently drive microscopes, but perhaps it would be better to be chauffeured by a hypothetical computer system. Such a system could use all available data to intelligently organize and triage WSIs into a series of clinically relevant regions of interest (ROIs). The sign-out work would feature interactive review of these ROIs, in the context of diagnostic tasks (e.g. margin assessment, tumor characterization, etc.). The result of such interactive sessions would then be used to automatically construct pathology report data. Using image analysis, histopathology-based rules, APLIS data and clinical information, such a system might be able to significantly automate the pathology sign-out process. The chief advantage of such an approach would be a high level of assistance that focused pathologists' expertise on clinical decisions that only they can perform. We term such a system, pathologists' computer-assisted diagnosis (pCAD). This pCAD should increase pathologist productivity as less time is spent on nondiagnostic work such as note-taking, report construction and proofreading, slide dotting/annotation, and manual assimilation of APLIS data (e.g. gross description).

Although every specimen is unique, it is the author's experience that most specimens can be generalized or pigeonholed as archetypal specimen types or tests. That is, almost all breast cancer sentinel lymph node biopsy (SLNB) specimens essentially require the same diagnostic tasks. Even if rare cases required manual intervention, such automation should be hugely beneficial if it could work with most specimens. An example of pCAD may be useful for explaining this concept; tumor staging lymph node examination is a relatively common specimen that should be relatable to a wide range of pathologists.

Example: Axillary SLNB in breast cancer patients.

Axillary SLNB is an excisional biopsy test used to stage breast cancer patients.[16] The pathologist must decide whether the lymph node contains metastatic breast carcinoma. If tumor is present then it is measured and described. The following scenario is hypothetical but illustrates the thrust of this paper:

The future pathologist starts an axillary SLNB review by viewing ROIs of the primary tumor from a previous biopsy specimen; the prior report is also present on-screen. As the pathologist moves on to review the SNLB specimen, known tumor ROIs remain on the screen for easy reference. Rather than manually navigating the WSI, the pathologist instead clicks through a series of triaged lymph node ROIs, one at a time, in rapid succession, looking

for tumor in the lymph node. Almost immediately, the pathologist sees a small fragment of probable tumor and takes control of the virtual microscope to zoom in and look more closely. The pathologist confirms the tumor finding and also verifies the computer's preliminary measurement of the metastasis [Figure 1]. Since tumor has been identified, the remainder of the review can be abbreviated; the pathologist could view the entire lymph node at lower magnification, or could review another 20% of the lymph node area microscopically. After the review, the pathologist reads the computer-generated report and then verifies it without having to make any manual corrections [Figure 2].

As presented, such a system requires sophisticated computer assistance that relies on image analysis and integrated APLIS data. To facilitate automation of this work it is useful to understand exactly what the work tasks entail for SLNB: (1) Review pathology reports and slides to understand the tumor's expected morphology; (2) find any metastatic tumor in the lymph nodes; (3) characterize and correlate tumor if it is present; (4) count lymph nodes; (5) note other findings not related to metastatic breast carcinoma (e.g. benign inclusions, subcapsular nevus cells, lymphoma); and (6) construct and sign-out a report. These are high-level tasks that can be further broken down to make them more accessible targets for automation.

Review of the primary tumor facilitates a pathologist's work because it trains the eye to recognize tumor metastases. Computer systems should also review the tumor because this could help the system choose the best tumor-finding algorithm or create a personalized algorithm (e.g. invasive lobular breast cancer algorithms or biopsy-trained personal tumor algorithms). This review activity can be complex and includes assimilating APLIS data such as specimen types, gross descriptions, and previous pathology reports. Slide review could include material from previous cases and/or from the current case. Computer systems should theoretically be able to perform some or most of these tasks, but where they fall short (i.e. natural language reading) APLIS data could be modified to facilitate automation using templates, synoptic gross descriptions, better-detailed histology data, etc., Finally, if the prior specimen had been signed out with pCAD, then it should already be computer-annotated as a result of that previous review. This could greatly facilitate review of the previous pathology.

Next is the actual task of finding tumor. SLNB slides typically contain one or more histologic sections of lymph node and fat fragments, and the hypothetical computer system would be able to identify these [Figure 3]. Further, individual lymph node fragments can generally be divided into three compartments: Subcapsular sinus, lymph node interior, and peri-nodal fat [Figure 4]. These compartments can be further subdivided into ROIs that are small enough for rapid pathologist review. The computer would preview the ROIs; optimally it would dependably identify and prioritize tumor-positive ROIs.

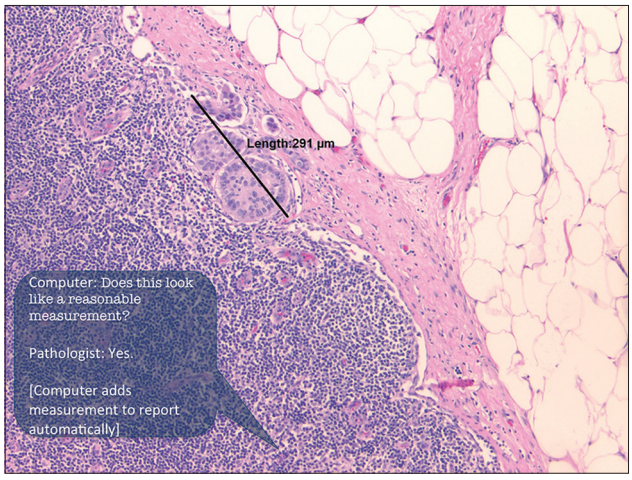

Figure 1: Example of interactive workflow in axillary sentinel lymph node biopsy for breast cancer staging: This region of interest (ROI) contains a breast cancer micrometastasis within the subcapsular sinus of an axillary lymph node. The finding of tumor has already been confirmed by the pathologist, and a speech bubble demonstrates the interactive nature of the ROI review activity. In this example the computer shows a measurement line (291 µm) and it asks the pathologist for confirmation. The pathologist concurs with the proposed measurement and the computer will then add this data to the pathology report automatically

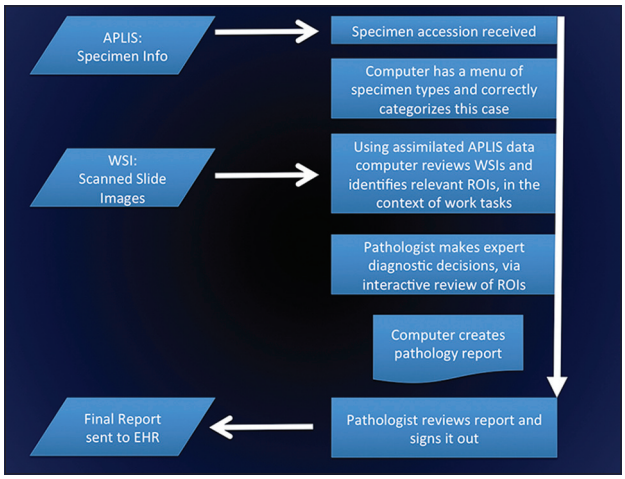

Figure 2: High level flow diagram of pathologists' computer assisted diagnosis (pCAD). After a specimen is accessioned, the pCAD system reviews the specimen information from the Anatomic Pathology Laboratory Information System (APLIS) in order to classify the specimen into one or more predetermined templates (e.g., sentinel lymph node biopsy, benign supracervical hysterectomy, etc.). Once a template workflow has been selected, the pCAD assimilates both APLIS data and whole slide images. In the context of predefined work tasks, clinically relevant regions of interests (ROIs) are identified and triaged. Together, a pathologist and pCAD review the ROIs interactively; as they work through the case, a pathology report is automatically constructed by pCAD. When the case work is completed, the pathologist reviews the pathology report then releases it

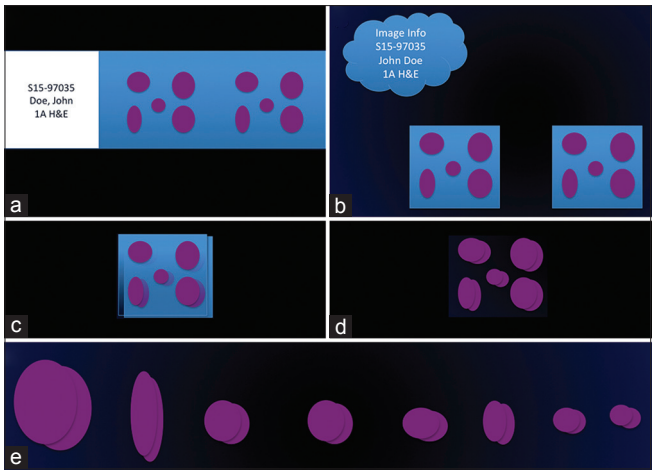

Figure 3: Breakdown of a complete whole slide image (WSI) into its elemental fragments, using an example of lymph node tissue in a cancer staging case. (a) A complete clinical WSI ideally includes all tissue and the slide label; this is generally as far as current WSI system delve into the WSI. (b) However, if the label is machine-labeled, then the WSI can associate the label data with more extensive anatomic pathology lab information system data, depicted as a cloud. Further, the tissue could be divided into histologic levels or cuts (two cuts are pictured but cuts could be included from multiple slides). The levels are depicted side-by-side, as separate image objects. (c) Although there are many possible approaches, the author would prefer to view multiple tissue levels either as a stack (pictured) or simultaneously (pictured, top level is partially transparent). (d) Subdivision into individual tissue fragments is also possible. Here, the individual lymph node fragments are depicted as separate objects, each one with two levels (stacked). (e) If individual tissue fragments are separate objects, then they can be reviewed independently. The pathologist can focus on the review without having to track the fragments' locations on the original slides, because the computer manages this information

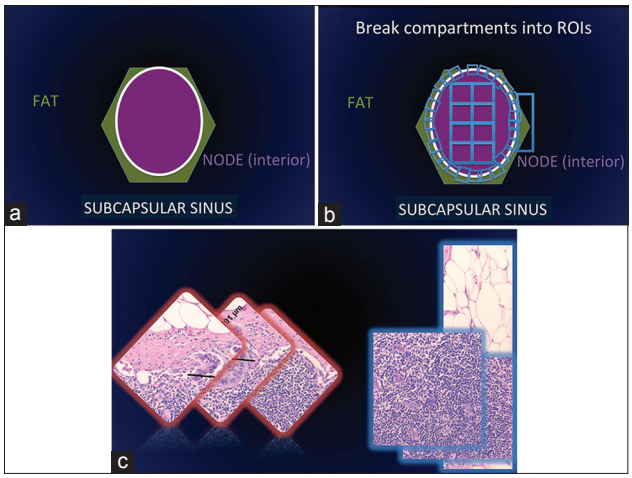

Figure 4: Breakdown of a tissue fragment image into individual regions of interests (ROIs), using example of lymph node for cancer staging. (a) Axillary lymph nodes can generally be divided into three compartments: Subcapsular sinus, lymph node interior and peri-nodal fat. (b) Rectangular ROI outlines are superimposed on the lymph node fragment. As subcapsular sinus is more likely to harbor small metastases, the ROIs there are smaller (i.e., higher magnification ROIs). Tumor is rarely only in the fat, so those ROIs are larger. This correlates with glass microscopy wherein such areas might be viewed at lower magnification, yielding larger fields of view. (c) Triaged ROIs are shown, arranged from most suspicious (orange outlined ROIs, left) to least suspicious (blue outlined ROIs, right). Although tumor is visible in the left-most ROI, other criteria could be also used for triage including anatomic compartment (i.e. lymph node vs fat), specimen title (i.e. lymph node #1 may be riskier than #3), etc. If no positive ROIs were present in a specimen, then these alternate rules would be used for triage

If no ROIs were positive, then the ROIs should be ranked or triaged based on risk and/or atypia assessment. Multiple factors could be used, but the goal is to deliver the most relevant ROIs to the pathologist as early as possible [Figure 5]. Clearly benign fat or lymphoid tissue should be reviewed later, if at all. The computer would show ROIs to the pathologist interactively, and the pathologist would confirm any tumor findings.

In the event that metastatic tumor is identified, there are additional tumor-related tasks. First, does the tumor resemble the primary tumor? Although this may someday be automated, the computer could still facilitate manual comparison by displaying both primary and metastasis tumor ROIs side by side. The computer can also display a provisional measurement for the pathologist's approval [Figure 1]. If the measurement is not acceptable, it could be manually adjusted but once approved by the pathologist then the final measurement would be automatically added to the report data (i.e. no note taking, no transcription, etc.).

A preliminary total lymph node count can be generated based on APLIS data; the gross description can specify how many lymph nodes are present and in what blocks. Alternatively, histology block data could furnish this information. A low-magnification algorithm could verify this preliminary count by determining whether the expected lymph nodes were present in the WSIs. In ambiguous cases, the system could ask the pathologist for a targeted, focused decision about the lymph node count. As the tumor finding work progressed, the computer would track the positive lymph node count data for later inclusion in the report.

Although the vast majority of SLNB are either positive or negative for tumor, there are several uncommon findings that may need to be addressed. Benign duct inclusions, papilloma emboli, or capsular nevus cells are three examples. Primary lymph node pathology or malignant lymphoma can also present in SNLB. These uncommon findings should be detected, or at least flagged as abnormal by the computer. A more sophisticated system might be able to recognize these features and suggest or initiate appropriate consultation or work-up. If appropriate, the computer might even flag the case for priority review in order to facilitate timely sign-out, thus accommodating the extra attention that the case might require (i.e. consultation, stains, clinical communication, etc.).

The final task is reporting the tissue findings. If the system has successfully captured the interactive ROI

review data, then this should be straightforward. A preexisting template structure can be used, with the data points filled in automatically. Free text would be limited but should still be available for unusual cases. In general, the goal would be to accommodate the majority of axillary SLNB reports with a computer-generated report that does not require manual text editing before sign-out. In the author's experience most such specimens do follow a similar report structure. Finally, computer-generated reports would almost certainly consist of structured data, which would facilitate additional utilization (e.g. specialized oncologists' dashboard systems, educational packages for patients, de-identified research, clinical trials, etc.).

DISCUSSION

This outline of a computer-assisted pathology sign-out (i.e. pCAD) may seem quite futuristic, but complete automation does not need to occur in a single step. This proposal is a framework that can be used to facilitate or guide early efforts of automation. It can help pathologists to begin the process of creating specimen classes, and within each class they can understand and describe the required work tasks. If mystical pathology sign-out work can be partially or mostly described in terms of concrete work tasks, then it will be much easier for software engineers and imagine analysis scientists to help create pCAD style automation.

There are a limited number of different surgical pathology specimen types. For example, almost all breast resection specimens could be described as: Mastectomy, lumpectomy, SLNB, axillary lymph node dissection, or breast reduction (or a combination thereof [Table 1]). There are a small number of other specimens, but this list would encompass greater than 90% of the author's breast resection work. Some specimens are bundled; resections can include a SLNB, mastectomies could be bilateral, or multiple excisional biopsies can occur in one specimen. Specimen classifications would evolve with time, such as when new procedures are performed by surgeons (e.g. nipple-sparing total mastectomy).

Similar specimen classification is already performed with specimen grossing and is a cornerstone to the current widespread practice of delegating grossing work to pathologists' assistants. Grossing manuals, nearly universally available in grossing labs, classify specimens into distinct archetypes and include detailed instructions on what is to be described, measured, and sampled for histological evaluation. They facilitate the delegation

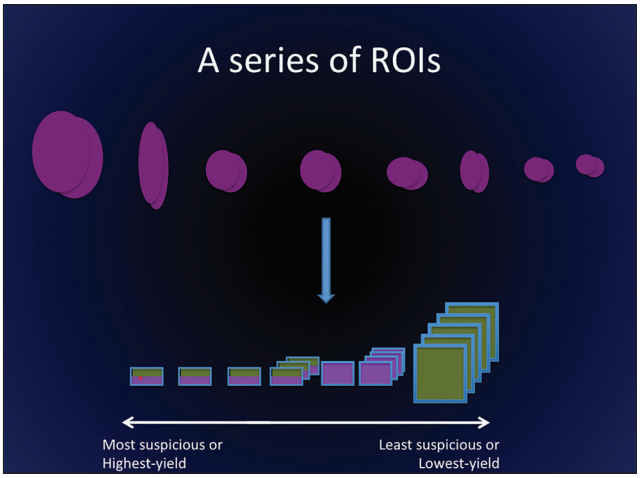

Figure 5: A pathologists' computer assisted diagnosis (pCAD) system organizes images of lymph node fragments into a series of well triaged regions of interests (ROIs) that are ready for rapid pathologist review. At top are the lymph node fragments, displayed in order from largest to smallest, without regard to the source WSIs (i.e., neighboring fragments may not be from the same WSI or slide). Through a series of image analysis and anatomic rules, the pCAD system subdivides the imaged fragments into clinically relevant ROIs (not shown in detail but depicted by the vertical blue arrow). For the specific work task of finding tumor metastases, the ROIs are triaged or sorted for pathologist review, from most-suspicious (left) to least (right). The riskiest, left-most ROI is a subcapsular sinus image that contains a small tumor metastasis that is highlighted by a red dot. Remaining ROIs are benign appearing, but are still sorted by other factors, including lymph node compartment, surgical designation, etc. Note that the least suspicious peri-nodal fat ROIs are off to the right; such ROIs could be reviewed last, rapidly (i.e., low magnification), or perhaps not at all if the pCAD system were clinically trustworthy

Table 1: List of common breast pathology specimens (in no particular order)

Breast core biopsy (subclassified by radiology imaging modality)
Stereotactic
Ultrasound-guided
Magnetic resonance imaging-guided
Lumpectomy (organized by reason for surgery)
Invasive cancer diagnosis
Ductal carcinoma *in situ* diagnosis
Other malignant diagnosis (e.g., phyllodes tumor)
Other risky diagnosis (e.g., lobular carcinoma *in situ*, papilloma, etc.)
Re-excision
Total mastectomy
Malignant diagnosis
Re-excision
Prophylactic (e.g. for BRCA or other known risk)
Lymph node sampling
Axillary sentinel lymph node biopsy
Axillary dissection
Combinations of the above
Modified radical mastectomy (total mastectomy with axillary dissection)
Bilateral prophylactic mastectomy
Miscellaneous
Breast skin or nipple biopsy
Reduction mammoplasty
Mastectomy scar revision or other post-reconstruction sampling

BRCA: Breast cancer gene

of grossing so that most specimens do not demand a pathologist's personal intervention. However, key to this system's success is the capability for delegates to recognize grossing situations that require the attention of the pathologist. Automated sign-out systems should similarly possess this capability to alert pathologists to special situations.

Once a specimen archetype has been defined, pathologists should explicitly define the required work tasks. This was presented in the preceding example of a breast cancer lymph node specimen. The rationale is to facilitate the automation by translating pathologists' expert knowledge into actionable concrete information that could be useful to collaborating scientists and vendors. A basic example is lymph node counting; pathologists take this for granted, but it requires integration of the gross description, low-magnification microscopic tissue findings and histology data (e.g. summary of cassettes). From an automation standpoint, there are several small targets that can facilitate automation of counting. In a current-generation APLIS system, the grosser might annotate the tissue block with histology data that could be used to derive the number of lymph nodes in that cassette. A sophisticated computer might read the gross description, but natural language processing is technically difficult, and this may not be reliable in the near future. Finally, a future APLIS may shift to synoptic grossing in order to facilitate counting, especially if it enhanced automation and workflow for the prosector. The point is that pathologists need to translate vague requests (e.g. "count the lymph nodes") into actionable steps (e.g. "compare the summary of cassettes with the low-magnification appearance of the lymph node slides").

Although this paper presents an advanced, idealized version of computer-assisted workflow, such advances will not occur at once. Early efforts could focus on better utilizing existing EHR/APLIS data, as well as on describing or distilling diagnostic work to facilitate automation efforts. This approach creates a modular, guiding framework that presents developers with concrete automation targets and permits automation to occur gradually where resources and technology permit. Starting modestly, automation benefits should sharply increase with refinements, evolving validation/trust, and acceptance by pathologists, clinical colleagues and patients. Automation-resistant or difficult steps would continue to require manual (expert) attention, which would mean that pathologists could focus on the decisions and work that only they can perform. Even imperfect, this should be an improvement over current workflow, where pathologists engage in a large number of non-critical, error-prone tasks such as manual report construction.

There are additional potential benefits that an intelligent computer system can provide. Pathologists could be reassured that the computer system would alert them to problem cases early (e.g. cases needing immunostains or regrossing). The computer could proactively alert a pathologist to critical findings that require urgent communication with the clinician (e.g. positive "bug" stains or small bowel tissue in an endometrial biopsy). Automated report generation would likely mean that report data could be standardized and also transmitted to external systems as structured data rather than as free text; this could greatly facilitate clinicians' ability to access and rapidly understand pathology reports. Finally, such a system could greatly improve both the value and the cost of the digital archive because the case would be automatically annotated during the interactive review. This means that important ROIs such as tumor images are easily available to future pathologists, and if WSI are eventually purged to save space these ROIs could be selectively retained at a fraction of the cost of retaining the entire case.

There may be issues with automation. Clearly, the biggest risk is system failure. Automation efforts will need to proceed slowly at first as pathologists may not be comfortable entrusting computer assistants. Careful validation is only the first step; ongoing supervision of the system will be a requirement as well. In the author's opinion, such supervision should be part of existing quality assurance efforts – imaged cases might be re-reviewed at a higher rate initially, just as new pathologists' cases are often reviewed at a higher rate than those of established pathologists within a practice. Events or issues could also trigger retrospective reviews. A well-executed QA infrastructure would be a prerequisite to this process, just as with imaged Pap test systems.

A trickier issue is the perception that the automation could make pathologists unnecessary. If the pathologist's only value to the health care system is manual sign-out labor, then this could be true. However, meaningful use and related movements for value added medicine make this dystopian scenario unlikely. While more efficient pathologists might simply do more work, this would be a wasted opportunity. Increased pathologist efficiency potentially creates opportunities to provide better value to patient care. This includes integration and reporting of ancillary specimen tests, more responsive consultation, and closer clinical cooperation with other physicians (e.g. multidisciplinary breast cancer team).

CONCLUSION

Diagnostic automation in surgical pathology is desperately needed, if it is not already too late. Cost control efforts, increasing clinical expectations, growing workloads and shifting measurement of pathologist productivity are real-world pressures that jeopardize traditional pathology practice.[17-19] Numerous digital pathology

systems are available, but in the author's experience clinical image analysis has thus far failed to provide meaningful automation of daily work.[20] This is perhaps reflected in the relevant literature, which conveys a sense of frustration over the sluggishness of clinical WSI adoption.[21] There should be a sense of urgency however, as such trends may adversely affect the practice of pathology because at some point there may be a shortage of pathologists.[22] That is, unless pathologist productivity can be substantially increased by real automation.

The hypothetical pCAD presented in this paper may seem far-fetched but there are many examples of existing technology that would have appeared fictional a decade ago. Google's self-driving car project has now accrued nearly 700,000 accident-free miles.[23] Inexpensive digital cameras, including those in cell phones, can perform real-time image analysis to focus on subjects' faces. Wireless communication is globally available, with 6.8 billion subscriptions globally.[24] Pathologists seem to be waiting for digital pathology to deliver fully formed automation and productivity increases for surgical pathology. Instead, they should plan to adopt automation where it can be developed without awaiting perfection as was done in cervical cancer screening and intraoperative telepathology.[1,2,25] To facilitate this, there must be a high level vision for such automation efforts, without which digital pathology may continue to stagnate.

This paper outlined one possible way forward, in the framework of an interactive computer-assisted slide review with automated reporting. Explicitly stating required work goals is an exercise that permits nonpathologist collaborators to understand the where, how and what of automation work. Not an instant solution, it outlines a path that can lead from contemporary manual practice via a route of increasing automation. Appropriate human supervision, in the form of quality assurance activities, can guide the automation to ensure that validated automation strategies proceed safely. It is hoped that this 21st century workflow proposal will spur fruitful rethinking of the current approach to so-called "digital pathology."

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