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Digital cytology part 1: digital cytology implementation for practice: a concept paper with review and recommendations from the American Society of Cytopathology Digital Cytology Task Force

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Digital cytology and artificial intelligence (AI) are gaining greater adoption in the cytopathology laboratory. However, peer-reviewed real-world data and literature are lacking regarding the current clinical landscape. The American Society of Cytopathology in conjunction with the International Academy of Cytology and the Digital Pathology Association established a special task force comprising 20 members with expertise and/or interest in digital cytology. The aim of the group was to investigate the feasibility of incorporating digital cytology, specifically cytology whole slide scanning and AI applications, into the workflow of the laboratory. In turn, the impact on cytopathologists, cytologists (cytotechnologists), and cytology departments were also assessed. The task force reviewed existing literature on digital cytology, conducted a worldwide survey, and held a virtual roundtable discussion on digital cytology and AI with multiple industry corporate representatives. This white paper, presented in 2 parts, summarizes the current state of digital cytology and AI practice in global cytology practice. Part 1 of the white paper presented herein is a review and offers best practice recommendations for incorporating digital cytology into practice. Part 2 of the white paper provides a comprehensive review of AI in cytology practice along with best practice recommendations and legal considerations. Additionally, the results of a global survey regarding digital cytology are highlighted.

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Introduction

Digitization of data entails the conversion of analog to digital data. The Digital Pathology Association (DPA) defines digital pathology (DP) as "a dynamic, image-based environment that enables the acquisition, management, and interpretation of pathology information generated from a digitized glass slide."[1] DP is now a mature technology that has existed for more than 2 decades. Its adoption has been accelerated during the Coronavirus Disease 2019 (COVID-19) pandemic. Many institutions are interested in exploring the applications of DP in pathology including primary diagnosis, telepathology, image analysis, education, and research.

DP is based on the capability of whole slide scanners to generate a digital slide or whole slide image (WSI) of an entire corresponding glass slide. The field has witnessed several technologic advancements in WSI including high-throughput scanners capable of rapidly acquiring high-resolution digital slides with excellent image quality. Interest in employing WSI for clinical diagnostic work in cytopathology is rapidly growing, particularly after the Food and Drug Administration (FDA) in the United States has approved at least 3 DP systems for primary diagnosis in surgical pathology.[2,3]

With growing adoption of DP, the American Society of Cytopathology (ASC) in conjunction with the International Academy of Cytology (IAC) and Digital Pathology Association (DPA) present this digital cytology whitepaper. The aim of the whitepaper is to provide practical considerations and guidance for cytology laboratories in adopting DP for cytology practice. Topics discussed include applications, validation, clinical implementation, maintenance, quality assurance, and regulations. The aim of this paper is to serve as a useful reference regarding the implementation of WSI and digital cytology.

Defining digital cytology

Most DP applications in surgical pathology can be applied to cytology. However, cytology has its own unique characteristics. Cytology samples include material processed with stains including modified Giemsa/Diff Quik, Papanicolaou (Pap), and Hematoxylin and Eosin (H&E), whereas surgical pathology generally uses only H&E. Additionally, cytology slides, both smears and to a lesser degree liquid-based cytology (LBC) preparations, are characterized by an uneven cellular distribution and thickness. These differences, relative to surgical pathology tissue sections which have a uniform thickness and simple topography, pose a greater challenge for WSI with respect to focusing on 3D cell groups for both image acquisition and end-user navigation. Unlike surgical pathology, where tissue might occupy a smaller portion of the slide, smeared cytology material may cover the entire length of a slide, often extending beyond the coverslip. Moreover, cytology material may contain obscuring background material such as blood, inflammatory exudate, matrix or exogenous material (eg, lubricant, ultrasound gel) overlying diagnostic cells. In addition, it is often harder to carefully screen cytology cells in order to examine every cell on a slide at high magnification. These challenges accordingly require cytology-tailored WSI solutions, including cytology-specific cell detection algorithms, higher magnification scanning, Z-stacking or volumetric (extended focus) applications, as well as easy-to-use navigation and annotation tools. WSI scanners may require scanning of cytology glass slides using multiple image layers (Z-stacking) to visualize the uneven thickness and 3D cell groups of cytology material. However, Z-stacking that employs multiple focal planes significantly increases the time of slide scanning, file size, and bandwidth for data transmission.[4] Enhanced or automated smearing techniques to produce slides with evenly distributed materials in a monolayer would potentially reduce the necessity for Z stack scanning. Additionally, certain preparations, like ThinPrep, are more conducive to digitizing process due to less 3D materials on slides. Digital slides also require user-friendly navigation and annotation tools, especially if these cytology slides are to be screened digitally by cytologists (formerly termed cytotechnologists) prior to sign-out by cytopathologists, ideally in an environment integrated with laboratory information systems. Nonetheless, despite these challenges, the main benefits of digital cytology include the fact that this technology obviates the need for glass slides handling once the slides have been digitized. This, in turn, permits portability, facilitates easy image sharing and archiving, enables virtual education, and ushers in the ability to analyze image pixels using artificial intelligence (AI)-based algorithms. The adoption of digital cytology has the potential to streamline, automate, and shorten workflows from the time of image acquisition to case distribution, to electronic and paperless signout, as well as slide storage and retrieval.[5]

Digital cytology applications

For the current consideration of usage of digital cytology, a detailed discussion of AI is reserved for part 2 of this white paper that is presented as a separate manuscript.

Virtual education

Digital cytology offers a broad range of educational benefits such as allowing multiple users on the network to review digital slides simultaneously from any location and at any time.[6,7] Moreover, annotations can be easily added, hidden, and/or revealed. Virtual teaching sets can also include rare cases and are easier to maintain. Unlike glass teaching sets, digital slides do not break, get misplaced, and their stains do not fade.[8,9] This allows learners to easily review digital slides, even prior to them developing glass slide microscopic skills. Digital review reduces the need for traditional microscopes, which can be expensive. Finally, utilization of WSI allows standardization of the evaluation process as instructors can equally distribute teaching cases among all students. Sharing of WSI databases for cytology education programs is currently being investigated by the ASC C.E.L.L (Cytology Education Learning Lab). Additionally, IAC is establishing an international board examination using WSIs.

Quality program

For compliance purposes, regulations such as the Clinical Laboratory Improvement Amendment (CLIA) require cytology laboratories to adhere to specific guidelines. Digitization of glass slides can allow greater automation and make compliance much more efficient. For example, CLIA regulations require 10% prospective re-screening of Pap tests before releasing final results, a 5-year retrospective screen of any new diagnosis that is of high grade squamous intraepithelial lesion (HSIL) or carcinoma and performing cytology-histopathology correlations. These quality control and assurance (QC/QA) activities require slide retrieval, which can be a time-consuming and labor-intensive process. A dedicated individual is often required to manage this mandated slide retrieval and filing process, and digital cytology could allow a significant time savings both from the perspective of staff hours needed for slide logistics as well as case turnaround time.

Archiving digital slides

Glass slides for clinical use in pathology need to be stored for a defined period, as per College of American Pathologists (CAP) regulations. However, archived slides may deteriorate over time. Stain colors may fade, and coverslips may warp or retract resulting in air bubbles. In addition, there may be physical slide damage, slides may be missing from the file due to misfiling, incorporation into teaching sets, research projects, or the need for outside review. In cytology, most slides are irreplaceable as there is no analogous specimen reserve as for surgical formalin-fixed paraffin-embedded (FFPE) slides can be replaced by recuts from the paraffin block. WSI can help overcome these issues as digitized slides maintain their quality over time and are less likely to be lost, especially if there is backup storage. Cytology slides such as smears that have been archived by digital cytology can also be used for ancillary studies that result in permanent destruction of the original material (eg, DNA/RNA extraction), allowing greater clinical utility of the specimen.

Image-based research

Digital cytology presents clear benefits in its potential for research, including the potential for downstream image analysis. WSIs can minimize or eliminate the risk of losing diagnostic material during slide transport and review for research studies. WSI datasets can be easily deidentified, annotated, linked to pertinent metadata (eg, patient demographics, genomic results), as well as shared for review and consensus interpretation among multiple research sites while ensuring patient anonymization is strictly upheld. WSIs can be reused for multiple studies. Moreover, curated datasets have recently become valuable assets for training deep learning algorithms. Image analysis has also greatly advanced research by ushering in new mechanisms to study disease, new biomarkers and treatment outcomes (eg, evaluate heterogeneity and spatial biology of tumors).

Routine digital workflow

Transitioning to a digital workflow still requires glass slides to be prepared. However, these slides may need to be optimized prior to scanning. For example, glass slides with fiduciary marks may be needed so that the scanner is aware of the region on the slide to be scanned and can correctly focus on the cellular material underneath the coverslip. Barcoded slides are a prerequisite to automate high volume slide scanning, and to link digital slides to the correct patient case if the digital system is integrated with the laboratory information system (LIS). Digitization of slides will require additional steps in the workflow process such as someone to load and unload slides on the scanner, perform quality checks of scanned slides, manage images within the digital cytology system, and troubleshoot technical problems. A key difference between routine digital pathology workflow in surgical pathology and cytology practice is the need for cytology slides to be screened by cytologists. Thus, it is vital that both cytologists and pathologists participate in the selection and implementation of a digital cytology platform for diagnostic use. Several computer-assisted Pap test screening systems have integrated the cytologist into their proposed workflow. In academic medical centers, cytology and pathology trainees will also have a need to review slides and even perform independent annotations before the cytopathologist receives slides.[8]

Primary diagnosis

Primary diagnosis refers to the final interpretation rendered on a digital slide(s), without having to ever review the corresponding glass slide. Digital pathology for primary diagnosis has the ability to streamline workflows from scanning to signout and case retrieval. For example, digital slides can be scanned centrally to support laboratory consolidation, more easily and quickly distributed, and shifted around on a network to address workload needs as well as support subspecialization by getting the right slides to the right pathologist at the right time. However, very few cytology laboratories to date have utilized digital cytology for the purpose of performing primary diagnosis. This is attributed to technical challenges (eg, focus difficulty with image acquisition and slide navigation for screening), and lack of regulatory approved commercial solutions for this purpose. Moreover, clinical validation of WSI for cytology primary diagnosis is currently excluded from the applicable CAP guideline due to lack of sufficient published evidence.[9] More well-conducted studies in this area are clearly needed, in addition to clinical guidelines that safely promote the adoption of WSI for primary diagnosis in routine cytology practice.

Digital cytology survey: current state and attitudes towards digital cytology

Various benefits of WSI in cytology for clinical and nonclinical use have been published.[8,10-15] To better understand this emerging digital cytology landscape and its impact on the cytology community, the ASC Digital Cytology Task Force conducted a global survey. These survey results were utilized to guide future recommendations pertaining to digital cytology and AI.

The survey encompassed 43 questions concerning current practice and experience of WSI and AI in both surgical pathology and cytology. This survey was distributed to members of the ASC, IAC, and Papanicolaou Society of Cytopathology (PSC). The questions were developed to focus on ascertaining how WSI and the application of AI is used (cytology versus surgical pathology), as well as the perceived challenges, benefits, and needs of the greater cytology community for utilizing digital imaging technology. Demographic information such as participant practice setting, their years of experience, and position/role were also collected to interpret the survey results.

Cytology WSI landscape

In total, there were 327 participants representing different regions/countries, practice settings, positions/roles, and experience with digital pathology. The majority of participants were from the United States (64%), Asia (23%), and Europe (6%). Most participants were from an academic practice setting (69%) compared to other settings such as nonacademic practices (18%) or commercial entities (9%). The survey respondents were mainly pathologists with more than 10 years of pathology experience (70%). However, experience specifically with DP was lower, with most stating only 2-4 years of experience (42%) and less than 1 year of experience (33%).

The survey results corroborated similar findings reported by previous studies related to WSI and AI applied to cytology.[16-18] Most participants in this survey reported that their affiliated laboratory routinely scanned surgical pathology slides (61%), with fewer scanning cytology slides (46%). This is consistent with what was reported in prior studies that highlight the clinical use of WSI predominantly for surgical pathology.[16-18] However, most survey respondents who did not scan cytology slides reported plans to do so in the near future (35.8%), highlighting the need for guidance on how to safely implement, validate and maintain digital technology suited for cytology practice.

For participants that do scan cytology slides, all cytology preparations [cell block H&E, cell block immunohistochemistry (IHC), smears, GYN/non-GYN LBC preparations] were scanned at equal rates except for cytospins which were infrequently scanned. Most participants scanned their cytology slides at 40x magnification (48.1%), with slightly fewer scanning at 20x magnification (41.5%). For surgical pathology slides, most survey respondents reported scanning slides at 20x (58%) rather than 40x. According to the literature, the majority of cytology WSI studies were conducted with 40x scanned cytology slides regardless of sample preparation.[8,12,19-21] A study by Wright et al. evaluated the diagnostic accuracy of cervical vaginal cytology WSI at 20x, 40x, and 40x with Z-stacked magnifications.[14] This particular study concluded that 40x WSI with and without Z-stacking yielded higher diagnostic accuracy compared to 20x WSI. As the interpretation of cytology material often requires the evaluation of subtle cytologic features, routinely scanning slides at a 40x magnification is advocated. It should be noted, however, that scanning slides at higher magnification increases scan times and may generate larger WSI file sizes which requires greater digital storage space.

One commonly mentioned concern regarding cytology WSI was poor image quality. Scanning at high magnification as well as employing Z-stacking, a feature offered by some whole slide scanners, may improve image quality of cytology WSIs. Z-stacking can be accomplished by multifocal Z (vertical) plane scanning, which can be coupled with extended focusing (volumetric scanning) to minimize the final WSI file size. WSI with Z-stacking enables end users to focus on different planes and thereby permits clearer images of cellular structures, especially when dealing with 3-dimensional (3D) intact cells or structures in cytology specimens. Most participants reported scanning cytology slides without Z-stacking (66.7%). There have been a few studies examining the optimal Z-stack setting or if any Z-stacking is even necessary for certain cytology preparations.[8,12,14,19,22] No ideal Z-stacking setting has been established. Therefore, further studies evaluating the need for Z-stacked images are needed to help guide best practice. Close collaboration between cytology personnel, computer scientists and engineers is encouraged to facilitate the development of both hardware and software to improve image quality.

The survey inquired about the various clinical applications for cytology WSI. Participants primarily used cytology WSI for nondiagnostic purposes. The most common uses for cytology WSI were accordingly for education (49%), archiving (43%), and research (37%). With respect to the usage for surgical pathology WSI, most respondents leveraged this technology for education (64%), tumor board presentations (58%), and archiving (51%). However, more individuals reported using surgical WSI for primary diagnosis (44.7%) compared to cytology WSI (15%) or screening with WSI (29%). This is consistent with the current literature.[23-25] These published studies regarding the use of WSI for diagnostic purposes report excellent concordance rates when compared to conventional light microscopy for surgical pathology. Various studies have also been published demonstrating good diagnostic concordance rates for various cytology specimens and preparations. Some of the cytology specimens that have been studied include GYN/cervical, urine, thyroid, and thoracic cytology.[8,14,19,20,26-32] All show concordance rates similar to surgical pathology WSI. However, several of these published studies underscore that scan time, screening time, image quality, and data storage were less optimal for cytology WSI compared to surgical pathology WSI.

Beyond primary diagnosis, WSI has proven to be useful for other aspects of clinical care such as archiving, teleconsultation, virtual tumor boards, QC/QA, and image analysis. Not surprisingly, survey participants reported utilizing cytology WSI for many of these applications. The major perceived benefits of WSI for these practices were similar for both surgical pathology and cytology. Among the highest benefits of WSI reported by participants were the ability to develop AI algorithms (cytology: 56.8%, surgical pathology: 54%), ability to remotely review slides (cytology: 51.4%, surgical pathology: 58%), and perform remote consultations (cytology: 47.7%, surgical pathology: 49%). Interestingly, the potential for AI applications ranked extremely high.

Cytology WSI challenges

Major challenges and areas for improvement for WSI reported by participants differed for cytology and surgical pathology. For cytology WSI, the major issue reported was poor image quality (69.5%) and difficulty interpreting cytomorphologic features (62.7%) indicating the need to acquire higher quality images for cytology specimens. Other challenges noted in this survey were cost (54.1%), difficulty in manipulating cytology WSIs (48.1%), and disruption of workflow (30.9%). This differed from the challenges reported for surgical pathology WSI where cost was the major issue (61.7%). Other challenges for surgical pathology slides included difficulty in navigating/manipulating WSI (51.9%), poor image quality (49.7%), difficulty interpreting morphologic features (48.6%), and workflow disruption (33.3%). All the major challenges for cytology WSI were also reported to be challenges for surgical WSI, but to a lesser degree. Lack of regulations and clinical guidance on the use of this technology was an area participants would like to see improvement for both cytology (42.2%) and surgical pathology (29.7%).

Digital cytology implementation and workflow

Whilst the implementation of DP for cytology can be extrapolated from surgical pathology experience, there are nuances specific to cytology workflow. Furthermore, unlike in surgical pathology practice, no digital slide scanning platform has yet been approved by US regulatory agencies for digital cytology diagnostic use.

Phases of digital cytology implementation

Implementation of a digital cytology platform involves multiple phases. Key considerations for each phase are outlined below.

System selection

This exploratory phase involves investigating a variety of digital cytology platforms and obtaining input from a variety of stakeholders (eg, cytologists, pathologists, informaticians, information technology staff, and administrators). This may require a formal request for proposal (RFP), request for information (RFI), and/or request for quote (RFQ). Product demonstrations can be very helpful, including bringing a system on premises for the laboratory to digitize their own slides for a brief period.

Planning and purchasing

Prior to deploying a desired DP system, it is important for the laboratory to undertake detailed planning (eg, budget, facility renovation, data storage plan, and roll-out design). If transitioning from an existing platform, it is best to have a period of overlap to allow ample time for validation to be completed and to avoid any interruption to clinical workflow. A budget should factor in the need to pay for hardware (eg, scanner, monitors), software, storage, maintenance, and personnel (eg, scan technologists, DP manager).

Deployment

When a digital cytology system arrives on site, the vendor may provide assistance with setup, either on site or remotely. Laboratories must ensure appropriate validation if the system is being acquired for clinical purposes. This is also an important time to begin laboratory staff training and ensure that all components are in good working order.

Clinical validation

Validation is recommended before utilizing digital cytology system for clinical use. Validation is the "confirmation, by examination and provision of objective evidence, that the particular requirements for a specific intended use can be consistently fulfilled," as defined by the International Organization for Standardization (ISO) and similarly by the FDA.[33] This contrasts with verification which is defined as "confirmation, through the provision of objective evidence, that specified requirements have been fulfilled". In short, validation is the process of confirmation that a method or equipment works as expected in its intended use. Practically, in the case within the United States, validation is needed for a non-FDA approved method/equipment or if it is FDA approved but used outside its intended use. Verification requires less steps and is performed for FDA approved methods/equipment used for its approved purpose as it has undergone testing to achieve FDA approval. Such definitions and requirements may hold for laboratories globally and each laboratory should check with their respective regulatory bodies for specific requirements for validation.

Clinical validation is recommended irrespective of whether a digital cytology platform is FDA-approved within the United States for clinical use. Currently, the CAP recommends a validation set of 60 cases (not just slides) with 95% concordance between WSI and manual glass slide interpretation for surgical pathology WSI primary diagnosis.[9] According to this CAP recommendation, cytology was considered out of scope due to insufficient literature to draw upon.[9] Nevertheless, the ASC Digital Cytology Task Force members believe adopting some of the same recommendations for validation of digital cytology is sensible. A summary of recommendations for digital cytology validation along with notes are presented in Table 1. The validation recommendations have been formed from current publications and experiences regarding digital cytology with consensus from the ASC Digital Cytology Task Force members. The recommendations may change as more cytology WSI validation data and experiences become available in the future.

For digital cytology validation, it is recommended that a set of at least 60 cytology cases, not slides, with 95% concordance between WSI and manual glass slide interpretation be evaluated. The use case(s) should be defined by the individual cytology laboratory, and it can be the entire or a part of the cytology practice. Cytology cases used in the validation set should be representative of the expected variation in clinical caseload, including different stains, preparation types, and distribution of diagnoses. Ideally, the cytology cases selected should include a range of benign and neoplastic diagnosis and incorporate a few nondiagnostic specimens which are often harder to screen than adequate samples. After initial validation, expanding into new preparations (eg, smears, liquid-based slides, and cell block sections) should include additional slides for repeat validation. For surgical pathology, the CAP recommends 20 additional cases for expanding the validation set.[9] An addition of 20 cases is also recommended for digital cytology validation with the addition of IHC and/or special stains. However, if significantly different sample preparation types will be added, such as smears, LBC, or cytospins, it is recommended that laboratories consider a full revalidation with 60 cases. The number of cases to be validated is a minimum recommendation and additional cases can be included if a laboratory determines that more cases should be validated for either a sample type, preparation, or stain. Additionally, this number may need to be reviewed if further evidence emerges.

The CAP recommendations for validating WSI for primary diagnosis in surgical pathology suggest that intra-observer reproducibility be employed, which should establish at least 95% concordance between digital and glass slide diagnoses after a 2-week washout period.[9] A similar recommendation with a 2-week washout period is applicable to cytology for primary interpretation. Inter-observer reads are best avoided, since diagnostic discrepancies between cytologists and cytopathologists would introduce undue noise in the evaluation.

The CAP also recommends that validation encompass the entire DP system, and that individual components do not need to be validated separately.[9] This should similarly apply to a digital cytology workflow. However, if any major component is changed after initial validation, such as but not limited to a new slide scanner, new slide viewer, or new scanning objective type or magnification, then repeat validation with the new components is recommended. If cytology WSI will also be used for screening purpose, screening should be included as part of the validation with a screening concordance study of at least 95% concordance. During the validation process and for any new users after,

Table 1 Summary of recommendations for validating digital cytology system.

Recommendations
1. The validation study should include a sample set of at least 60 cytology cases per use case. The validation study cases should closely emulate the clinical practice of the cytology lab, including sample type (GYN, Non-GYN, FNA), preparation (smear, LBC, cell block, and cytospin), stain (Pap, Diff-Quick, H&E), and usage for screening (see examples and further explanations in the notes below).
2. Diagnostic concordance between digital slides and glass slides in the validation study should be established. A concordance of less than 95% should be investigated.
3. A washout period of at least 2 weeks should occur between viewing digital slides and glass slides to establish concordance.
4. Formal personnel training is necessary for familiarization before using digital cytology for primary diagnosis or primary screening.
5. Establishment of a digital cytology QC/QA program is recommended after validation to detect any errors or issues that may arise in order to provide high quality digital cytology services.
6. If any major aspect of an already validated digital cytology workflow is changed/updated (eg, change in scanner, scanning objectives, updated slide viewer, etc.) then repeat validation is recommended.
7. If additional sample types/preparations are to be clinically evaluated via the digital cytology system after the initial validation, the system should be revalidated using a set of cases with the new sample types/preparations mimicking the intended practice.
Notes
I. The digital cytology use case should be defined by the individual laboratory, and it can be entire or part of cytology practice. As an example, in a cytology laboratory with GYN, non-GYN and FNA samples, the laboratory can implement digital cytology for GYN samples only or the entire cytology practice.
II. As recommended, the samples for validation should reflect the variety of samples seen in routine clinical practice as well as its intended use. In the above-mentioned cytology laboratory, if digital cytology will be used for the entire cytology practice, the 60 cases in the validation study should closely emulate the entire cytology practice, including GYN, non-GYN, and FNA samples. However, if the digital cytology slides will be used only for GYN cytology samples, including only GYN cytology samples for the validation would be appropriate.
III. The preparation and stain type in the validation should emulate the samples in the individual cytology laboratory practice. As an example, if the laboratory uses LBC only for thyroid FNAs, including only LBC slides for validation is sufficient for thyroid FNA cases. However, if the laboratory uses Diff-Quik, Pap-stained smears, and LBC for thyroid FNAs, the thyroid FNA cases in this laboratory's validation study should include Diff-Quik stained smears, Pap-stained smears, and LBC slides. If a preparation/stain will be evaluated clinically by the digital cytology system, that preparation/stain should be included in the validation study before clinical use.
IV. The number of slides that should be included per validation study case is at the individual laboratory's discretion. However, at least one slide per preparation/stain combination for the validation study case is needed to emulate the lab's practice.

formal personnel training is necessary for familiarization of reviewing cytology WSI for primary diagnosis and primary screening. This is to ensure all necessary staff are familiar with navigating and interacting with the WSI for clinical purposes.

Lastly, a robust QC/QA program should be developed to detect any errors and troubleshoot any issues that may arise in digital cytology operations. Scanning performance metrics such as the number of slides scanned, types of cytology slides scanned, scanning failure rates, and rates of poor-quality cytology WSI requiring rescanning should be recorded and monitored.

Maintenance

Routine maintenance for digital cytology systems should apply to all components: hardware (slide scanners, monitors, other information technology), software (updates), data storage (servers), and laboratory information system or other integration. Maintenance of competency for all staff associated with the digital cytology workflow (eg, information technology personnel, slide scanning team, cytology lab team) is also recommended by either proficiency testing as is done for cytologists and cytopathologists or as part of a QC/QA program.

The CAP recommendation noted that insufficient evidence was available to make specific recommendations regarding competency evaluation in DP.[9] The CAP guideline also noted that validation should not be used for training. A sensible approach to screening or diagnostic competency would be to develop a set of at least 20 cases including a range of diagnoses and establishing an appropriate "passing" score.

Comparison to surgical pathology

Recommendations for DP in surgical pathology practice[9,34,35] are more mature than for cytology.[36] Regardless, we can draw on this greater experience from the surgical pathology literature. A summary of existing surgical pathology recommendations relative to cytology-specific considerations is included in Table 2.

Image retention

If digital slides are used for primary diagnosis, depending on storage availability and cost we recommend retaining these images for at least as long as glass slides are required to be retained. The cytology laboratory policy for the retention of digital slides may be dictated by institution, state,

Table 2 Comparison of surgical pathology and cytology recommendations for clinical digital pathology practice.

Categories	Surgical pathology recommendation	Cytology consideration
Digital pathology attribute		
Color preservation	Image and display should have color calibration (33)	Same recommendations apply
Image compression	Image compression should not affect image quality, color integrity or introduce artifacts (33)	Same recommendations apply
Z-stacking	Not typically employed	Employed to overcome 3D multiplane focus needs
Interoperability	DICOM is recommended (33)	Same recommendations apply
Workflow and regulatory aspects		
Validation set case count	60 cases per use case (additional 20 for new use case/additional applications such as IHC)[9]	60 cases per use case representing the expected spectrum of cytologic specimens and preparations. (Full revalidation if additional preparations are to be included, see text)
Validation study design	Validation should closely emulate the real-world clinical environment for which the technology will be used. Intraobserver variability should be established with a 2-week washout period[9]	Similar recommendations apply (see text)
Validation composition	Cases should be representative of the expected variation in clinical cases (stains, preparation types, distribution of diagnoses) (10)	Additional preparation and stain types beyond typical histopathology approaches
Validation of components	Validation Should encompasses the entire workflow. Components need not be validated individually[9]	Similar recommendations apply (see text)
Competency testing	Insufficient evidence available[9]	Consider competency needs for cytologists and pathologists (see text)
Retention QA requirements	Documentation should be maintained recording the method, measurements, and final approval of validation for the WSI system to be used in the anatomic pathology laboratory.	Same recommendations apply. Similar metrics should be recorded on an ongoing basis for QA purposes. Ensure minimum retention requirements met for WSI used for diagnostic purposes.

DICOM = Digital Imaging and Communications in Medicine.

government and/or accrediting agency regulations. According to current CAP requirements, Pap test glass slides should be stored for 5 years, while nongynecologic glass slides (including FNA slides) should be stored for 10 years. If a glass slide that was digitized is to be subsequently destroyed (eg, cytology material on the slide is scraped off for molecular testing), then it may be imperative to retain the corresponding digital slide. Digital slides may also be retained for other reasons, such as medicolegal purposes.

Return on investment

Examples of considerations for specific practice settings and applications for digital cytology implementation and workflows are listed in Table 3. For each use case of digital cytology, financial considerations are likely to be an important driver for decision making. In general, investing in digital pathology has resulted in cost savings through improved productivity and portability, more accurate diagnoses with a resultant decrease in unnecessary treatment,[37] reduced turnaround time, and decreased ancillary test orders.[38] Whilst similar or even more potential cost savings are expected with digital cytology, further cost-benefit analysis is needed.

Conclusion

The incorporation of DP into clinical practice has been growing rapidly with advances in technology and practical applications. However, widespread adoption of DP in cytology practice has been slower than in surgical pathology, mainly due to differences in specimen preparation, workflow, technology challenges and regulations. In addition, specific recommendations to guide safe validation of digital cytology in clinical practice have been lacking. Not surprisingly, a global survey conducted by the ASC digital cytology task group revealed the need for such practical recommendations by the cytology community. This white paper aims to fill this

Table 3 Practical considerations for implementation of a digital cytology workflow.

Categories	WSI benefits	Challenges and considerations
Academic practice	Education, research, consultation	Administration buy-in
Community practice	Consultation and telepathology, remote staffing	Use-cases with financial benefits
Commercial laboratory	Consultation, telepathology, remote staffing	Use-cases with financial benefits
High volume setting	Slide logistics, physical storage	Throughput and turnaround time
Low volume setting	Consultation, telepathology, remote staffing	Use cases with financial benefits
Specimen/preparation/stain type variation	Downstream analysis and workflows may allow multiparameter analysis	Performance/quality may be less with cytologic stains and preparations beyond H&E/histopathology
Routine evaluation	Slide logistics	Throughput and turnaround time
Rapid On-Site Evaluation/Adequacy Assessment	Remote review	Need for rapid scanning or live viewing prior to scan completion
Other subspecialty applications (surgical pathology, hematopathology, etc.)	Integration of WSI across subspecialties facilitates correlation of concurrent samples	Finding an all-purpose system to meet diverse subspecialty needs Benefits/disadvantages of implementing multiple systems
Education	Allows sharing across institutions/ geography, easy replication of teaching slides digitally (33)	Screening and evaluating WSI is recognized as a distinct skill that should be developed.
Research	Digital images are important for many multiparametric and spatial biomarker studies[34]	Requires additional infrastructure. Regulation for sharing digital slides for research purposes not fully established.
Tumor board and interdisciplinary clinical care conferences	Benefits over glass slide and static image presentations, require some advance planning; no need for special equipment for pathology presentation	Requires additional infrastructure.

need by offering cytology laboratories best practice recommendations for incorporating digital pathology into their cytology practice. To offer updated evidence-based guidelines for digital cytology, it is vitally important for cytology groups to publish their experience with implementation, validation, and competency assessment.

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