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Digital cytology part 2: artificial intelligence in cytology: 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 cytology laboratory. However, peer-reviewed real-world data and literature are lacking in regard to 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 is presented as a separate paper which details a review and best practice recommendations for incorporating digital cytology into practice. Part 2 of the white paper presented here provides a comprehensive review of AI in cytology practice along with best practice recommendations and legal considerations. Additionally, the cytology global survey results highlighting current AI practices by various laboratories, as well as current attitudes, are reported.

Contents

Introduction

A major application of digital cytology that has received interest in recent years has been the use of artificial intelligence (AI) algorithms in clinical practice. AI refers to a broad term that encompasses any machine or deep learning algorithm that emulates human intelligence and decision-making. Multiple different AI algorithms have been developed in medicine that assist in a wide variety of narrow tasks from workflow optimization to diagnostics and prognostication. Cytology is no stranger to AI integration for clinical practice, as some of the first AI algorithms were developed to assist with cervical cytology screening in the late 1990s. The Hologic ThinPrep Imager and FocalPoint GS Imaging System, which have been in use since the late 1990s and early 2000s, are widely used by many cytology departments for cervical screening. Both systems represent some of the first examples of AI application in pathology. There has been even greater interest recently due to the emergence of deep learning algorithms that can extract morphologic features from whole slide images (WSI). As a result, there have been many studies detailing AI algorithms applied to cytology demonstrating successful cytomorphological analysis for diagnostic use and research discovery. To date, most cytology AI papers have focused on Pap tests (GYN cytology). However, there are also AI-related studies investigating the application of this technology for urine, thyroid, pancreatobiliary, lung, breast, and pleural effusion specimens. In this part, we aimed to comprehensively review AI applications and current AI practice in cytology, provide recommendations for evaluating cytology AI applications, reporting AI aided cytology results and legal considerations.

Artificial intelligence applications in GYN cytology

Artificial intelligence systems using glass slides

AI has been applied in GYN cytology practice for a relatively long time. PAPNET was the first commercially available AI-based screening system which was approved by the United States Food and Drug Administration (FDA) in 1995. PAPNET was designed to identify abnormal cells in Pap tests that were already screened and interpreted as negative by a cytologist. The intent was to reduce the false-negative rate as an added quality control measure. PAPNET selected 128 potentially abnormal cells or clusters for review by a cytologist using a monitor. If any of these findings were concerning to the cytologist, a full manual review was subsequently necessary. Several studies have demonstrated that PAPNET outperformed rapid manual rescreening, a method of secondary manual review in which a cytologist quickly reviewed the slide at low power, as well as full rescreening.[1-3] However, additional studies revealed that PAPNET significantly increased the cost of cervical screening, while only yielding relatively small gains in sensitivity.

AutoPap 300QC (Neopath/Tripath) was approved by the FDA in 1998. This system was acquired by BD Diagnostics in 2006 and renamed the BD FocalPoint Slide Profiler. The system can be used to identify conventional or SurePath smears as normal without further review; the remaining Pap tests are divided into 5 categories with abnormal risks. The BD FocalPoint GS Imaging System was developed from the original AutoPap/FocalPoint system by adding a robotic microscope, which enabled slides to be dotted in advance of manual screening, thereby allowing cytologists to more quickly and reliably see the cells identified as the most concerning by the automated system.[4-6] The BD FocalPoint GS Imaging System was approved by the FDA in November of 2008. The BD FocalPoint Slide Profiler is a classification screening system with no manual review required for negative slides; however, it is no longer commercially available. Cytyc developed an interactive system with computer pre-screening to select abnormal cells on ThinPrep Pap test slides for further examination by cytologists. In 2003, this imaging system was approved by the Food and Drug Administration (FDA), was acquired by Hologic in 2007 and became known as the ThinPrep Imaging System. Both the BD FocalPoint GS and ThinPrep Imaging System are interactive screening systems that rely on a location guided process combined with required manual review. The ThinPrep Imaging System and BD FocalPoint GS Imaging System are compared in Table 1.

A clinical trial comparing the ThinPrep Imaging System to manual screening alone showed a statistically significant improvement in sensitivity for ASC-US + slides, equivalent sensitivity for LSIL+ and HSIL + slides, and statistically significant improvement in specificity for HSIL+.[7] The adjudicated results for ASC-US + showed a 39% reduction

Table 1 Comparison between the FocalPoint GS and ThinPrep imaging system.

System	FocalPoint GS	ThinPrep imaging system
Method	N/C ratio with reference to example images	Imaging algorithm considers cellular features and nuclear darkness
Stain	Pap stain	ThinPrep stain
Samples	SurePath	ThinPrep
FOV	10 FOVs	22 FOVs
Image storage	10 days	Permanent
Slides/hour	170 slides/8 hours	200 slides/8 hours
FDA clearance	2008 approved for screening	2003 approved for screening

Abbreviations: FDA, Food and Drug Administration; FOV, field of view; N/C, nuclear/cytoplasmic.

in false-negative slides using the ThinPrep Imaging System. The workload limit for the ThinPrep Imaging System has been established at 200 slides in no less than an 8-hour workday utilizing only a 22 field of view (FOV) triage as the slide with FOV only review counts as 0.5 slide. However, the slide with full manual review (FMR) using the Autoscan feature counts as 1 slide, and slide with both FOV and FMR counts as 1.5 slides. Any combination of FOV-only and FMR must be integrated to not exceed workload limits. Since most daily routine cases do not need FMR, cytologist screening rates are usually faster using ThinPrep Imaging System than using the manual review method.

FDA approval of the BD FocalPoint GS System was based on data generated in a clinical trial comprised of 12,732 SurePath slides across 4 different sites in the United States, with adjudication performed at a fifth site.[8] In the trial, the results of manual screening were directly compared to screening using the BD FocalPoint GS System. Data from the clinical trial showed an increase of 19.6% in sensitivity for the precise diagnosis of HSIL+ (with a decline in specificity of 2.6%), an increase of 9.8% in sensitivity for the precise diagnosis of LSIL+ (with a decline in specificity of 1.9%), and a decrease of 1.5% for the precise diagnosis of ASC-US+ (with an increase in specificity of 1.8%). Several follow-up studies have reported that this same system performs at least as well as manual screening in routine clinical use.[9-11]

The MAVARIC trial from England was conducted to compare both automated systems (ThinPrep Imaging System and BD FocalPoint GS Imaging System) with manual screening. The trial confirmed that automated systems could indeed increase productivity, but was not conclusive about increased sensitivity.[12,13] Trials from Australia and Scotland also confirmed increased productivity without increased sensitivity.[14,15] The results from these trials support the premise that implementation of an automated cervical screening system could increase productivity, but probably did not improve overall screening quality or cost-effectiveness. In summary, these computer-assisted Pap test screening systems still use glass slides and a light microscope, although FOV selections and guided localization are provided by machine learning software coupled with a motorized microscope.

Artificial intelligence systems using digital whole slide images

Digital imaging in pathology has progressed from static and live video imaging to WSI. WSI success in surgical pathology is exemplified by the FDA approval of this technology for primary diagnosis, as well as the development of guidelines for standardizing clinical validation.[16] Although WSI in cytopathology has not been as pervasive as in surgical pathology,[17-19] WSI-based GYN cytology screening AI algorithms have been developed to primarily analyze liquid-based cytology (LBC) samples.[20-39] The reported accuracy of these AI algorithms is variable. One study has demonstrated that a model using a convolutional neural network (CNN) was able to classify Pap test images into benign or malignant with an accuracy of 98.3% and a specificity of 98.3%.[40] However, when using a CNN model to distinguish the 5 different categories in The Bethesda System for reporting cervical cytology on Pap WSIs, an overall average accuracy of only 60% was reported.[41]

Of note, a cloud-based WSI platform with a deep-learning classifier for p16/Ki-67 dual-stained (DS) cytology slides was recently developed. This AI-based tool had equal sensitivity and substantially higher specificity compared with both Pap ($P < 0.001$) and manual DS ($P < 0.001$), respectively. Compared with just the Pap test, AI-based DS reduced referral to colposcopy by one-third (41.9% versus 60.1%, $P < 0.001$).[42]

Several WSI-based AI platforms for screening Pap tests are commercially available and summarized in Table 2 and representative images are shown in Fig. 1.

CytoProcessor. CytoProcessor™ (DATEXIM, Caen, France) was designed to incorporate multiple AI algorithms optimized for cervical cytology WSIs scanned using 3DHISTECH Panoramic scanners from any type of LBC preparation and staining protocol.[20,21] However, the slides are not scanned with z-stacking or volumetric scanning. CytoProcessor platform displays abnormal cervical cells in gallery format for review. One study has demonstrated that the sensitivity of detection of ASCUS and LSIL+ was significantly higher using CytoProcessor™ (1.5% false negative rate) than using the ThinPrep Imaging System (4% false negative rate).[21] The CytoProcessor™ workflow

Table 2 Commercially available WSI-based Pap test screening AI platforms.

Product	CytoProcessor	BestCyte	Hologic Genius	Landing Med	CytoSIA	Techcyte	KFBIO AI-assisted system
Vendor	DATEXIM	CellSolutions	Hologic	Landing Med	OptraSCAN	Techcyte	KFBIO
Slide preparation	ThinPrep, SurePath	BestPrep, other LBC	ThinPrep[c]	LBC	ThinPrep, SurePath	ThinPrep, SurePath	LBC
Scanner	3DHISTECH	3DHISTECH	Hologic Genius	LD Patho 320A/340A, LD Cyto2200	OptraSCAN-ULTRA/OS-LITE	Nanozoomer, Grundium, Motic, 3DHISTECH	KFBIO
Magnification	40x	20x[a]	Up to 40x	20x, 40x	40x, 20x	40x	20x
Z-stacking	No	Yes	Volumetric scan	Yes[f]	No	Yes	Yes
Image Gallery view	Yes	Yes[b]	Yes[d]	Yes	Yes	Yes	Yes
Certified/approved	CE Marked	CE Marked	CE IVDR Marked	CE-IVD NMPA	None	ISO 13485, SOC2, CE IVDD	NMPA
Indication	Screening	Screening, Reporting, QC	Screening[e]	Screening	Screening	Screening, QC	Screening

Abbreviations: CE, Conformité Européene; LBC, liquid based cytology; ISO, the International Organization for Standardization; IVD/IVDR, In vitro diagnostics/in vitro diagnostic regulation; NMPA, National Medical Products Administration (China); QC, Quality control.

[a]The BestCyte platform uses the 3DHISTECH scanner to scan slides using 20x. The images displayed in galleries are simulated 40x. The platform offers 4 optional magnifications for WSI viewing: 5x, 10x, 20x, & 40x.

[b]The BestCyte platform displays images in galleries with variable image sizes, not as equidistant images in lattices.

[c]Includes ThinPrep Pap test slides, ThinPrep nongynecological slides, and ThinPrep UroCyte slides.

[d]Genius Cervical AI provides a gallery image view.

[e]When used with Genius Cervical AI, the intent is to assist in cervical cancer screening. The Genius Digital Diagnostics System can also be used with ThinPrep® non-gynecological microscope slides and ThinPrep® UroCyte® microscope slides to provide a digital image of the whole cell spot for screening.

[f]Z-stack functionality for the listed Landing Med scanners will be available by the end of 2023.

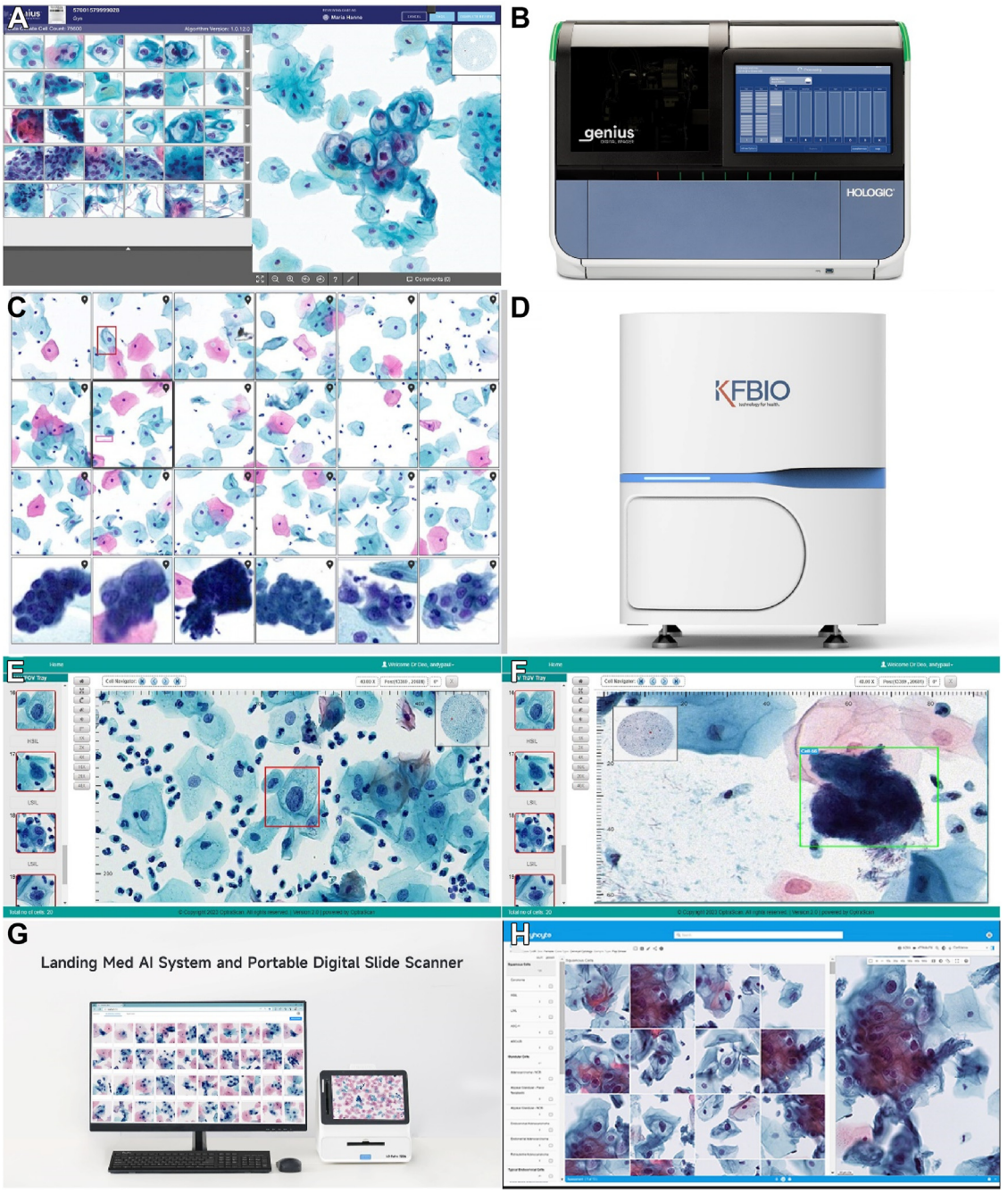

Figure 1 Representative images from several whole slide image (WSI) based artificial intelligence (AI) platforms for screening Pap tests. (A, B) Hologic Genius AI platform and WSI scanner; (C, D) KFBIO AI-assisted system and WSI scanner; (E, F) OptraSCAN CytoSIA platform with abnormal cells (E) and microorganism (F); (G) Landing Med AI platform and its WSI scanner; (H) Techcyte AI platform.

appears to be 1.6 times faster in terms of worker time compared to manually using a microscope.[20]

BestCyte. The BestCyte® cell sorter imaging system from CellSolutions (Greensboro, NC) is a WSI-based cytology screening system. The BestCyte® cell sorter imaging system displays abnormal cervical cells in gallery format on a monitor screen to facilitate cytologist interpretation. One study has demonstrated that the BestPrep liquid-based thin-layer Pap test and BestCyte cell sorter imaging system is equivalent to ThinPrep for manual review.[43] Additional studies also demonstrated that the BestCyte enables shorter ThinPrep review times with optimal intraobserver concordance, facilitates improved specificity and reduced labor.[44,45]

Hologic Genius. The Genius Digital Diagnostics System (Hologic, Marlborough, MA) is a digital cytology platform

that combines an advanced AI algorithm with volumetric imaging technology of ThinPrep Pap test slides to identify abnormal (squamous and glandular) and normal (endocervical component) cells, as well as certain infections (*Candida*, *Trichomonas vaginalis*, herpes).[46] Volumetric imaging is a novel scanning method in which a single scan simultaneously acquires up to 14 focal planes, eliminating the need to scan each layer individually. After the volumetric scan, image processing merges in-focus pixels from multiple planes into a single layer, which thereby reduces slide scan time. The Genius system analyzes all the cells in a ThinPrep Pap test digital image but presents only (up to 30) static images in a gallery display of the most diagnostically relevant images, known as objects of interest (OOIs). The gallery is comprised of 6 image tiles of OOIs shown in 5 categories (low-grade cells, high-grade cells, clusters, glandular cells, potential microorganisms). The entire system includes the Digital Imager (scanner), AI algorithm, Image Management Server, and Review Stations. Cytologists only need to examine the AI-selected representative image tiles (snapshots) of cells in the gallery, instead of screening through thousands of cells. If necessary, the cytologist will still be given the option to review the WSI of the cell spot on the right portion of the display.

One recent study examined the Genius Digital Diagnostics System's performance in 555 Pap test cases with a digital scan (volumetric scan) at 14 levels relative to the ThinPrep Imaging System.[46] In 86.56% of cases, a complete match between both systems was observed using the same 5 cytology categories. When also considering the cervical histology results, the match was 90.37%. In addition, when a cytology follow-up and/or a retrospective review was applied, the match reached 97.34%. Significantly, more cases of higher severity, atypical squamous cells cannot exclude high grade (ASC-H) and HSIL, were identified with the Genius Digital Diagnostics System, and its negative predictive value was higher. The screening time was significantly shorter with the Genius Digital Diagnostics System. With the Genius system for digital cytology, the sensitivity for ASC-H/HSIL+ and the specificity for LSIL and HSIL were superior to liquid-based cytology and computer assistance.

Landing Med. The Landing Med™ (Wuhan, Hubei, China) AI platform is a supervised deep learning algorithm trained on 188,542 digital LBC cytological images. AI-assisted reading detected 92.6% of CIN 2% and 96.1% of CIN 3+, significantly higher than or similar to manual reading of Pap test slides. AI-assisted reading had an equivalent sensitivity (relative sensitivity 1.01, 95% CI, 0.97-1.05) and higher specificity (relative specificity 1.26, 1.20-1.32) compared to skilled cytologists; whereas it demonstrated higher sensitivity (1.12, 1.05-1.20) and specificity (1.36, 1.25-1.48) compared to cytopathologists.[22] An additional cohort study demonstrated an overall agreement rate between AI and manual Pap test reading of 94.7% (95% confidential interval [CI], 94.5%-94.8%), and a kappa that was 0.92 (0.91-0.92). The detection rates of CIN2+ increased with the severity of cytology abnormality performed by both AI and manual reading ($P_{trend} < 0.001$). General estimated equations, used to apply repeated measures to different groups, showed that the detection of CIN2+ among women with ASC-H or HSIL by AI were significantly higher than corresponding groups classified by cytologists (for ASC-H: odds ratio [OR] = 1.22, 95% CI 1.11-1.34, $P < 0.001$; for HSIL: OR = 1.41, 1.28-1.55, $P < 0.001$). AI-assisted cytology was 5.8% (3.0%-8.6%) more sensitive for the detection of CIN2+ than manual reading with a slight reduction in specificity.[34]

KFBIO. KFBIO (Konfoong Biotech International Co., Ltd., Zhejiang, China) is a digital pathology platform primarily providing AI solutions for both GYN and non-GYN samples. The platform is a complete system that includes slide preparation, scanning, laboratory information system integration, AI algorithm, and viewer. Metrics for KFBIO based on information from the company include a sensitivity $\geq$98.2% and specificity $\geq$63.5% for detecting GYN lesions (both squamous and glandular lesions) with high accuracy which makes it ideal for screening. The algorithm was trained with 43,000 positive Pap test samples that were annotated by trained pathologists. After scanning, the AI algorithm detects and presents selected images of concern that can be reviewed in a gallery view. While there currently are no peer-reviewed publications for the KFBIO platform detailing its performance, per the manufacturer's provided materials, it has the potential to increase efficiency and decrease the number of samples requiring pathologist review.[47]

CytoSiA. OptraSCAN's CytoSiA (OptraSCAN, Pune, Maharashtra, India) is a digital cytology platform employed to screen LBC Pap test slides to differentiate between normal and abnormal cervical cells. In addition, the platform can identify reactive squamous cells, endometrial cells, and various infections including *Actinomyces*, *Candida*, clue cells, *Trichomonas vaginalis*, and herpes. CytoSiA uses a volumetric scan to provide a dual mode for scanning and viewing cytology smears and utilizes Z-stacking and an extended depth focusing algorithm. For Z-stacking scanned multiplane images, the viewing software enables the user to navigate, as well as zoom up and down to different planes to detect three-dimensional (3D) regions in focus. OptraSCAN's extended depth of field algorithm generates a single, entirely focused composite image with a relatively smaller file size than multiplane images for faster acquisition and image retrieval.[48] Currently, there are no peer-reviewed publications using the CytoSiA platform to evaluate its performance.

Techcyte. The Techcyte (Orem, UT, USA) Cervical Cytology System is a digital cytology screening tool that

helps cytologists and pathologists read Hologic ThinPrep or BD SurePath slides. The end user is presented with the most diagnostically relevant cells and/or microorganisms using an AI-based system. The Techcyte platform accepts any good quality 40x image from a compatible scanner. Their AI algorithm uses a CNN to identify differentiating features and determine which combinations indicate diagnostically significant objects. The AI system then places these objects into the most likely classification and displays them in order of atypia for review. The whole process takes several minutes. A cytologist or pathologist can log into Techcyte on any web-enabled device and review available scans, determining specimen adequacy and evaluating the AI-based results for diagnostic relevancy. They can also add notes and request a secondary consult.[49] Currently, there are no peer-reviewed publications using Techcyte to evaluate its performance with Pap test screening.

AI in non-GYN cytology

With the promising results achieved to date in GYN cytology, AI applications have been gradually expanded to non-GYN cytology including urine, effusion cytology, and fine needle aspiration (FNA) cytology. However, at this time, almost all non-GYN AI algorithms are still at a research stage and their integration into routine clinical workflow has not been fully evaluated.

AI for urine cytology

AI algorithms have been developed to evaluate urine cytology cases with promising preliminary results.[50-54] Some of these AI algorithms were trained to classify urine cytology cases into benign, low-grade, and high-grade urothelial carcinomas while others were developed to classify individual cell types such as benign, atypical, and malignant urothelial cells, squamous cells, etc. The performance of these AI algorithms has been high (AUCs up to 0.989, F1 scores up to 0.900). However, most of the datasets utilized in these studies were limited, without quantitative data analyses performed at the whole-slide level.[50-54] One recent study developed a deep learning−based instance segmentation computational model primarily by using the N:C ratio (approximately 0.5-0.7 for low-risk cells and >0.7 for high-risk cells) in accordance with The Paris System (TPS) 2.0.[55] This particular AI algorithm demonstrated performance results that were comparable to human expert panel consensus (sensitivity 79.5% and 82.1% versus 92.3%, respectively; specificity 100% and 98.9% versus 100%, respectively). Furthermore, the performance of AI-assisted analyses of WSIs compared with the microscopic diagnosis by a cytopathologist demonstrated superior sensitivity (92.3% versus 87.2%) and negative predictive value (96.8% versus 94.8%).[55]

The VISIOCYT1 trial comprised an initial phase to develop and evaluate VisioCyt® test (VitaDX International, Rennes, France), a deep learning-based automated image processing tool to analyze urothelial cell morphology,[56] and a second to validate the clinical performance of the VisioCyt® diagnostic test. The first phase included a total of 598 patients (219 high-grade, 230 low-grade urothelial carcinomas and 149 negative controls) and the results demonstrated that the overall sensitivity was highly improved by the VisioCyt test compared to cytology (84.9% versus 43%) with 92.6% versus 61.1% for high-grade and 77% versus 26.3% for low-grade cases.[56] The second phase included 391 participants and the results demonstrated VisioCyt®'s sensitivity was 80.9% (95% CI 73.9%-86.4%) and specificity was 61.8% (95% CI 53.4%-69.5%). In high-grade tumors, the sensitivity was 93.7% (95% CI 86.0%-97.3%) and in low-grade tumors, the sensitivity was 66.7% (95% CI 55.2%-76.5%).[57]

AI for effusion cytology

In one study, an artificial neural network (ANN) model was developed using 114 image patches of pleural fluids to classify benign and metastatic carcinoma cases. The results demonstrated excellent performance (AUC: 1.00) without misclassifying any single case.[58] In another study, a deep convolutional neural network model (DCNN) (Inception-ResNet-V2) was trained and validated using 569 effusion slides to classify malignant pleural effusion of metastatic breast cancer and the results showed the DCNN model outperformed the pathologists by demonstrating higher accuracy, sensitivity, and specificity compared to the pathologists (81.1% versus 68.7%, 95.0% versus 72.5%, and 98.6% versus 88.9%, respectively).[59] A weakly supervised deep learning method was also reported to classify lung carcinoma cells in 404 effusion cytology cases and demonstrated an accuracy, sensitivity, and specificity respectively of 91.67%, 87.50% and 94.44% and an AUC of 0.9526.[60] A deep learning model was also built to differentiate mesothelioma from normal mesothelial cells in effusion cytology specimens and this model achieved a sensitivity and specificity of 100%, respectively.[61] Recently, the Deepcell platform (Deepcell, Inc.) that combines microfluidic sorting, brightfield imaging, and real-time deep learning interpretations based on multidimensional morphology to enrich carcinoma cells from malignant effusions without cell staining or labels.[62]

AI for fine needle aspiration (FNA) cytology

AI technology has been explored in classifying FNA cytology specimens from thyroid, lung, breast, pancreas, and other anatomic sites.

For thyroid FNAs, most studies focused on identifying/differentiating papillary thyroid carcinoma,[63-66] while a few studies tried to differentiate follicular adenoma from follicular carcinoma.[67] Cytology samples were prepared using either LBC or smears. The performance of AI algorithms was variable in these studies with the best accuracy reaching up to 100%.[67] However, the datasets used in these studies

were limited. In a recent study with a large dataset (a training set of 964 and a test set of 601 FNAs), a deep-learning algorithm was developed to definitively classify 45.1% (130/288) of the WSIs as either benign or malignant with risk of malignancy rates of 2.7% and 94.7%, respectively. It also reduced the number of indeterminate cases by reclassifying 21.3% as benign.[68] A deep learning-based ensemble model termed FNA-Net was developed to screen unstained thyroid FNA smears for adequacy and the results showed FNA-Net achieved a 0.81 F1 score and 0.84 AUC in the precision-recall curve for detecting the nondiagnostic slides.[69]

For lung cytology, AI models have been developed to identify and/or classify lung carcinomas into different morphologic types (adenocarcinoma, squamous cell carcinoma, etc.) based on image patches.[70-72] In another study, a deep learning algorithm was trained on WSIs (including direct smears and H&E stained cell block sections) from 20 cases to differentiate small cell carcinoma from large cell neuroendocrine carcinoma.[73] These results demonstrated that the algorithm showed high precision in distinguishing between these 2 categories on H&E sectioned material and direct smears.[73]

To date, AI algorithms were also shown in a few studies to classify breast or pancreatic FNA cytology specimens.[74-76] In the pancreatic cytology study, a multilayer perceptron neural network (MNN) was trained on images from ThinPrep slides prepared from pancreatic FNA cases and then tested for its ability to distinguish benign from malignant cases. The MNN was 100% accurate for classifying benign and malignant cases, but was only 77% accurate for atypical cases.[76]

AI for rapid on-site evaluation (ROSE)

Another area of cytology in which assistance from AI algorithms can improve patient care and efficiency is for rapid on-site evaluation (ROSE). For many cytology services, performing ROSE entails a great deal of logistics and effort. Specifically, staffing needs to perform these adequacy assessments is time consuming and something AI algorithms may assist with to increase efficiency. Additionally, AI-assisted ROSE can greatly help in resource limited settings by potentially providing adequacy evaluations instead of relying solely on cytologists.

A few pilot studies have been reported in the literature that describe AI algorithms for ROSE developed and tested at a single institution. All these studies were developed using a CNN trained on a specific organ of interest. The study by researchers Ai et al. developed a CNN based AI algorithm for ROSE during bronchoscopy.[77] Trained on 627 ROSE slides, the algorithm achieved an AUC of 0.98 with an accuracy of 84.57%. This study also compared the accuracy of determining adequacy on-site to a senior pathologist who was 96.90% accurate, and 2 junior cytopathologists with an accuracy of 83.30%. A separate study by Lin et al reported an AI algorithm designed to support ROSE for GI endoscopic ultrasound-FNAs.[78] Their algorithm was also CNN-based and was trained on 467 Diff-Quik stained smear samples. The accuracy was 83.4% similar to the bronchoscopy ROSE AI algorithm, with a sensitivity of 79.1%. Neither study described turnaround times for AI assisted ROSE, which is a crucial consideration, especially in clinical settings where ROSE is already established. Additionally, both studies were conducted at a single institution and therefore this raises concerns for overfitting and questions the generalizability of this work in other settings. However, as pilot studies they show promise in the development of AI algorithms for ROSE with a need for future research in this area.

Survey of current practice in cytology AI

The ASC Digital Cytology Task Force survey, detailed in part 1 of the white paper, sought to evaluate the current practices and perspectives of AI algorithms in cytology. The vast majority of survey participants indicated that they do not use AI algorithms in their clinical practice for either surgical pathology (84%) or cytology (77%). This is not surprising, as to date very few commercial AI algorithms have been adequately validated and adopted in cytology practice, except for the ThinPrep Imager and FocalPoint GS Imaging Systems. While studies of AI models for various cytology specimens describe good results, most are pilot studies with few if any employed in a prospective clinical setting. Other barriers to integration of new generation AI tools in cytology that remain to be overcome are the lack of AI algorithms approved by regulatory agencies such as the FDA, as well as the appropriate infrastructure needed to deploy such algorithms. When asked about the comfort level of using AI algorithms for clinical cytology purposes, almost half of participants (49%) responded that they would be completely or very comfortable using an AI algorithm that has been approved by the FDA or other regulatory agency. In contrast, there were 8% of participants who stated that they would feel completely or very comfortable using an AI algorithm without approval by the FDA or other regulatory agency.

For those users that do use AI in clinical practice, utilization differs between cytology and surgical pathology practice. The vast majority of participants that use AI for cytology utilize AI for screening Pap tests, which could include screening systems such as the Hologic ThinPrep Imaging System or the BD FocalPoint GS. Participants that utilized AI for surgical pathology practice mainly used AI algorithms for biomarker quantification (65%). When it comes to future AI algorithms, participants would like to see tools developed to help screen cytology specimens (73%), assist with biomarker quantification (62%), and leverage algorithms that would help with QA/QC (38%). Most of the recent algorithms developed with deep learning models reported in the published pathology literature focused on

diagnostics rather than screening, as well as the detection of histologic lesions rather than cytology. The survey results also highlight the need to develop AI models for improving workflow rather than merely replacing diagnostic human expertise.

Evaluating and validating AI for cytology

A variety of factors are likely to affect the implementation and successful outcome of adopting AI technology in a clinical cytology setting. Among the factors to consider are (1) intended use case (eg screening, diagnostics, etc.): and reasons for adopting AI technology (eg automation, standardization, etc.); (2) resources required, including hardware, software and personnel cost; (3) evaluation of AI performance and clinical validation; (4) integration into cytology workflow, including digitization of cytology slides and storage of digital images, integration image manage system and AI into laboratory information system, and cytologists and pathologists' workstation setup; (5) adherence to federal, state, and individual laboratory policies, regulations and/or guidelines; and (6) return of investment and/or reimbursement.

Published AI cytology studies have utilized a variety of different AI models such as neural networks, support vector machines, k-nearest neighbors, or a combination (ensemble) of models.[32,34,55,61,79] Currently, not one model has been shown to be superior in pathology evaluation. Different models may be better suited based on specimen type and clinical need. While most studies of cytology AI models demonstrate good sensitivity (>80%) and specificity (>80%) on average, these AI models are not always published with sufficient independent validation. Moreover, performance of these AI systems may differ based upon variations within the clinical setting and needs of the cytology team. There is also a question of what performance characteristics are best used to evaluate or compare an AI model. To address this question, the ASC Digital Cytology Task Force survey asked participants what data points would be helpful in evaluating AI algorithms developed for cytology practice. Beyond the standard set of performance metrics such as sensitivity and specificity, other useful metrics for AI model evaluation include area under the curve (AUC) analysis, F1 Score, and mean squared error, amongst others. However, most survey participants preferred relying on familiar statistics measures of evaluation such as sensitivity, specificity, and AUC. Other metrics participants considered helpful were providing end users with a gallery of predicted images to review or a prediction heat map overlaid on the slide of interest.

The guidelines for validating AI for clinical pathology practice are still lacking. Indeed, most participants felt that best practice guidelines and recommendations for clinical AI usage would be either very useful (38%) or useful (36%). While standard clinical validation steps can be applied to AI algorithms as with other clinical tests, there may be AI specific issues that need to be evaluated. As more AI algorithms arise for application in cytology practice, there is a need to help guide pathologists in the evaluation of AI algorithms and how best to integrate them into practice. As with any laboratory test, pathologists must be aware of the benefits and limitations of using an AI tool in a clinical setting.

Due to insufficient data and wide variability of AI algorithms in cytology, the ASC Digital Cytology Task Force feels it is premature to recommend a specific number of cases needed for validating AI algorithms in general at this moment. The ASC Digital Cytology Task Force also notes that AI algorithms can vary drastically in their intended use (e.g. QA, billing, diagnostics) and that the below considerations may not apply depending on their usage. However, the following can be considered during the validation/verification study of AI algorithms in the cytology laboratory (Table 3).

Reporting recommendation and legal considerations

Reimbursement for using computational pathology tools in clinical practice is necessary to further support adoption. In the United States, reimbursement of computer-assisted screening of Pap tests has existed for many years: current procedural terminology (CPT) code 88174 is reported for cervical or vaginal cytology specimen collected in preservative fluid by automated thin layer preparation and screened by automated system under physician supervision and CPT code 88175 is reported when automated screening is followed by manual rescreening or review under physician supervision. The American Medical Association (AMA) has recently published Appendix S to the CPT coding scheme which outlines the approach to categorizing AI applications. Computer-aided detection (CAD) algorithms used by radiologists currently have CPT codes and are classified in the "Assistive" category, the lowest level of AI in the taxonomy. These CAD algorithms are similar to pathology AI algorithms currently in development in that they detect areas of interest for human interpretation. CPT coding protocols for more advanced "Augmentative" and "Autonomous" categories are in their infancy and other specialties will likely pave the way before pathology.

Since the FDA has not yet approved any digital platform for primary diagnosis of cytology specimens in the United States, any application of WSI such as AI for cytology would need to be validated as a laboratory developed test (LDT). As such, the presence of a disclaimer in a cytology report that relied on using AI technology is advisable.

The legal implications of applying deep learning AI algorithms to analyze cytology specimens other than Pap tests is uncertain.[81] Machine learning algorithms have been used for many years to assist with screening Pap tests, even allowing slides to be signed out as negative without full slide review by a human. This has not precipitated a fundamental

Table 3 Summary of considerations for validating artificial intelligence (AI) algorithms in cytology.

Considerations

1. The validation study should closely emulate the clinical workflow practice intended for the AI algorithm and comprises of samples intended for the AI algorithm.
2. Several performance metrics including precision, accuracy, sensitivity, and specificity of the AI algorithm should be evaluated during the validation study.
3. While there is no specific number of cases that should be included for AI validation, a sufficient number of cases reflecting the diversity and complexity of the samples encountered at the laboratory should be included to adequately evaluate the AI algorithms performance metrics (see note).
4. Formal personnel training is necessary for familiarization before using AI algorithms for clinical practice.
5. Establishment of a quality assurance program is recommended after AI implementation to detect any errors or issues that may arise.
6. If the intended use of the AI algorithm changes from the initial validation, a revalidation for the new use should be performed.

Notes

I. The CAP published guidelines for HER2 quantitative imaging analysis (QIA) to recommend that 20 positive and 20 negative cases are needed to validate FDA approved QIA or double the numbers for QIA without FDA approval.[80] If the AI algorithms to be validated for cytology practice are similar to HER2 QIA, the validation study may include a sample set of at least 20 cases per AI classification category for AI algorithm approved/certified by regulatory agency or 40 cases for others. The number may be modified based on the performance of AI algorithm.

II. In the ASC Digital Cytology Task Force survey, regarding the number of cases needed to validate AI algorithm in cytology, the majority of respondents answered a number in the range of 100-200 (60% of 231 respondents), thus, a number within this range can be considered.

change in the legal landscape. The "black box" nature of advanced deep learning algorithms as well as their ability to continuously adapt in response to new data raises profound questions about the ultimate responsibility in the event of errors and mistakes. Physicians, health care systems, and algorithm developers could all potentially bear responsibility, but formulation of a coherent and binding legal framework in this context is necessary.[82] It is anticipated that cytopathologists will likely accept that liability remains with them in scenarios where AI provides assistance, especially when the cytology report is ultimately signed out by a human.[83] For this reason, it is important to consider whether the analysis of images shown to the cytopathologist is retained and archived in case of the need for medicolegal review, in addition to glass slide and WSI retention requirements. Matters may become more problematic in scenarios where AI algorithms may be used to make a diagnosis in the absence of human oversight. Until these issues are resolved, liability issues are likely to strongly inhibit deployment of these more advanced systems.[84]

Conclusion and future direction

In recent years, the largest area of global growth in any industry has been AI. This holds true for the application of AI to medicine, including cytology. Cytology has a long history with AI, given that computers have been leveraged for decades now for computer-assisted screening of Pap tests. As more complex AI models are developed and applied to non-GYN use cases in cytology, guidance and recommendations are needed in order to best assess and incorporate these tools in clinical practice. The second part of this white paper accordingly addresses AI as it pertains to cytology to offer such recommendations for AI us in clinical cytology practice. A collective effort is needed from the cytology community to share their experience when using AI in order to establish more evidence-based guidelines.

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