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Evolution of Papanicolaou Staining in Cervical Cytology: From Conventional Smears to Liquid-Based and Digital Cytopathology - A Narrative Review

Tenggrik R Marak[1], Gonya Gadi[1], Sushma Devi Gurung[1], R. Lalbiakdika[1], Hage Kanya[1]

[1]MMLS Student, Department of Medical Laboratory Science, Regional Institute of Paramedical and Nursing Sciences, Aizawl, Mizoram – 796017

Abstract

Background: Papanicolaou staining remains central to cervical cytology, but its laboratory context has expanded from conventional smears to liquid-based preparation, automated screening, digital cytopathology, molecular testing, and artificial intelligence.

Objective of the review: To critically synthesize the evolution of Papanicolaou staining and cervical cytology, with emphasis on staining principles, conventional and liquid-based methods, quality assurance, automation, digital imaging, HPV-based triage, artificial intelligence, workflow, and implementation challenges.

Key findings: Conventional smears are inexpensive and information-rich but remain vulnerable to sampling, fixation, transfer, and screening variability. Liquid-based cytology improves preparation standardization and facilitates residual-sample molecular testing, although diagnostic advantage is setting- and platform-dependent. Automation can improve reproducibility and throughput, whereas digital cytopathology enables remote review and computational analysis but introduces scanning, storage, validation, and governance requirements. Artificial intelligence may support prioritization, quality control, and classification, but dataset shift, external validation, and human oversight remain critical.

Conclusion: The evolution of Pap cytology is cumulative rather than substitutive. Effective cervical screening depends on validated workflows, specimen quality, laboratory quality systems, appropriate infrastructure, equitable access, and integration of cytology with HPV testing and human-supervised digital decision support.

Keywords; Papanicolaou Test; Uterine Cervical Neoplasms; Cytodiagnosis; Artificial Intelligence; Digital Pathology

INTRODUCTION

Compared to other cancers, cervical cancer is more socially and economically diversified [1,2,76]. It is still geographically widespread, and measures suggest that it is largely preventable [76,77]. The International Federation of Gynecology and Obstetrics (FIGO) have suggested that the recent worldwide decline in cervical cancer is largely attributable to the introduction of public health interventions which, among other things, include vaccination against human papillomavirus (HPV) [78,98]. Nonetheless, most public health experts agree that the major responsibility for the control and eventual elimination of cervical cancer will rest on the effectiveness of prevention and control strategies [1,2].

Cervical cancer is one of the few cancers for which preventive measures are available [3,4,5]. As such, several national public health programs have been launched to eliminate cervical cancer [5,6]. Pap tests form the mainstay of cervical cancer prevention and control programs [62,63]. A Pap test is easy to perform and inexpensive [64,65]. Compared to other cancer screening tests, compliance with

Pap tests is acceptable [67,71]. Digital systems used to process and analyze cervical cytopathology are rapidly advancing [76,77]. Such systems are user friendly and have the potential to standardize and improve the quality of Pap tests and cervical cancer prevention and control programs [3,4].

This review discusses the recent versions of the Pap stain [8,15,29]. More recent publications are cited, and older publications are included to give background [29,61]. It is shown that cervical cancer screening plays larger roles compared to replacement of outdated methods of cervical cancer screening [71,75]. Various roles are discussed including the introduction of automated systems in laboratories [85,89].

The focus of this review is to examine what roles different methods play in facilitating implementation of secure and equitable cancer screening and preventive services in different health care systems [96,98]. The role of new and emerging methods in cancer screening and prevention, integration of digital and molecular technologies in laboratory medicine, and automation of laboratory processes are discussed [8,15].

LITERATURE SEARCH STRATEGY

The basic literary search strategy was to find studies that discussed new and emerging technologies in cervical cancer screening and prevention [16,24,29]. These include liquid based cytology, whole slide digital images, automation and Artificial Intelligence in cervical cancer screening and prevention [29,31]. Older and more seminal studies were included to explain the rationale and background of more recent studies [41,61].

RECENT HISTORY OF PAPANICOLAOU STAINING:

Recognition that changes in the cervix associated with cancer and precancer are reflected in the exfoliated cervix cells led to the establishment of a screening program for cervical cancer [7,8]. During the 1940s, several studies showed that vaginal smears have the potential to detect cancer of the female genital organs [68,96]. In order to increase the accuracy of screening for cervical cancer, a number of factors including the fixedness of the smear, the type of fixative, and the kind of stain used must be standardized [7,8]. It has been shown that some stains, by virtue of their various colors and the order of their addition, influence the final result [68,96].

Standardizing population-based cytology helped standardize terminologies for specimen adequacy, diagnoses, and case management [14,15,68]. The Bethesda System introduced a system to standardize terminologies for case management and a structure to incorporate the views of clinicians and pathologists [68,72]. The System acknowledged the presence of uncertainty and subjectivity in the field of pathology [73,74]. Pathologists cope with inter-sample variability in numerous ways including variability in the quality and quantity of the sample, presence of substances that obstruct the sample, and other factors beyond their control [75,14].

In the fast-paced and ever-evolving field of cytopathology, Pap test and related procedures play a dominant role for a considerable period [29,61,85]. More recently, automation and integration of artificial intelligence revolutionized cytopathology [85,89]. Cytopathology and related procedures have benefitted from a host of recently adopted Standard Operating Procedures [91,92]. As a result, cytological examinations have been reintegrated into the primary prevention strategies and related procedures for cervical cancer [95,29].

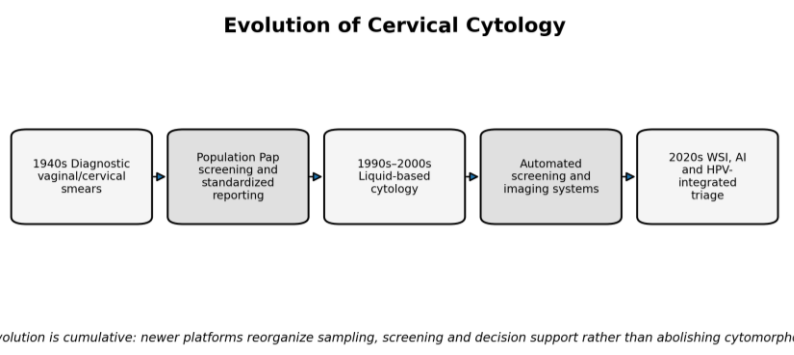

Figure 1. Historical evolution of cervical cytology and Papanicolaou-based screening. [7,8,14,29,96]

Table 1. Major milestones in the evolution of Papanicolaou staining and cervical cytology [7,8,14,16,29,68]

Period	Milestone	Critical significance
1940s	Diagnostic value of vaginal/cervical smears established	Created the morphologic basis for exfoliative cervical cancer detection [7].
Mid–late 20th century	Population Pap screening and protocol standardization	Converted a laboratory observation into organized prevention; reproducibility and terminology became central.
Bethesda era	Standardized reporting categories	Linked specimen adequacy and cytologic categories to clinical management [68,14].
1990s–2000s	LBC adoption	Shifted pre-analytic variability toward laboratory-controlled processing and enabled residual-sample testing.
2000s–2010s	Automated imaging and rapid/modified stain protocols	Improved throughput and process control while preserving Pap-based morphology.
2020s	WSI, cloud workflows and AI	Made cervical cytology shareable and computable; introduced new validation, storage and governance requirements [29].

SCIENTIFIC PRINCIPLES AND CHEMISTRY OF PAPANICOLAOU STAINING:

Papanicolaou (Pap) staining has two parts: nuclear staining, and cytoplasmic staining [8,9,10]. Fixation, the first step in the procedure, stops further chemical and biological activity in a sample by denaturing cellular proteins [10,11]. For the cytoplasmic staining, the samples are air dried [12,13]. Afterward, the nuclei are stained using hematoxylin (an acidic stain) which gives them a purplish-blue color [96,8]. This staining procedure (like others) can be done in a semiautomated way, using various stains (i.e. Orleans's reagents) and solvents [9,10]. The goal of the staining process is to have just enough staining so that the nuclei and cytoplasm retain their structures [11,12]. Staining that is done too heavily loses its clinical value [13,96].

The assessment of epithelial changes in various parts of the body, e.g. the lower lip, can be made using the staining methods described above [8,9,10]. Orange G stains the keratinized epithelium of the lower lip and provides useful information in the assessment of various epithelial changes of the lip [10,11]. Eosin-A (EA) stains the cytoplasm of epithelial cells and provides useful information in interpretation of epithelial changes of the skin, e.g. dysplasia [12,13].

A variety of methods have been developed for obtaining cervical smears [8,9,10]. Some methods require elaborate procedures while others are simpler [10,11]. Good cytologic details can be obtained with simpler methods of cervical smear preparation if the procedures are properly performed [12,13]. These methods of preparation of cervical smears for cytopathologic studies are fast and simple [96,97]. However, these methods have their own limitations [8,9]. For example, age and pH of the staining solution and alcohol and the bluing agent used in the solution affect the final result of the stained smears [10,11].

While it can be concluded that the staining procedure has been performed, it cannot be assumed that staining has contributed to the final outcome of the smear [8,14]. Detection of atypical nuclear changes and cytoplasmic changes in cervical smear is of diagnostic importance [96,8].

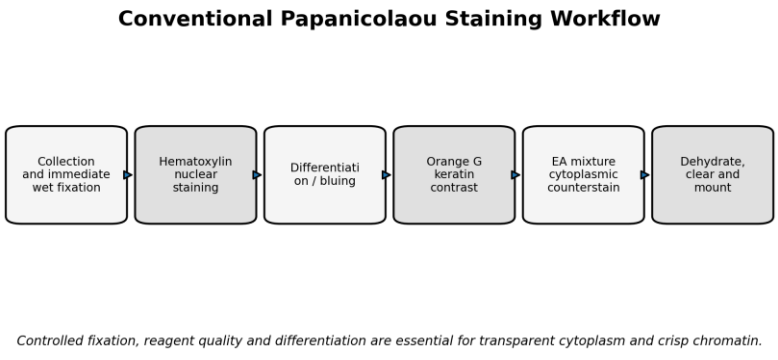

Figure 2. Core workflow of conventional Papanicolaou staining. [8-13]

Table 2. Principal reagents used in Papanicolaou staining and their functions [8-13]

Component	Primary role	Diagnostic consequence of poor control
Alcohol fixation	Preserves wet-cell morphology and nuclear structure	Air drying can enlarge/distort nuclei and obscure chromatin interpretation.
Hematoxylin	Nuclear chromatin stain	Under/over differentiation alters perceived hyperchromasia and membrane detail.
Orange G	Highlights keratinized cytoplasm	Imbalance can reduce recognition of keratinization or overwhelm counterstain.
Eosin Y in EA	Provides pink cytoplasmic tones	Affects maturation contrast and color balance.
Light green SF yellowish in EA	Blue-green staining of metabolically active/nonkeratinized cytoplasm	Poor selectivity reduces cytoplasmic transparency and differentiation.
Phosphotungstic acid	Modulates dye competition/selectivity in EA formulations	Changes counterstain balance and reproducibility.
Dehydration, clearing, mounting	Produces optical clarity and preserves slide	Residual water, poor clearing or mounting artifacts can impair screening.

CONVENTIONAL PAPANICOLAOU SMEAR CYTOLOGY:

Papanicolaou (Pap) tests, developed in the 1920s, are now over 80 years old [7,8,14]. Although original versions of the test have been replaced with automated, improved processes, testing still relies on sampling the transformation zone [14,16]. One reason for this is cost [17,18]. Many laboratories in developing nations do not have the means to process slides or do PCR testing; therefore, these countries have not adopted more complex and expensive methods to replace the Pap test [19,20]. A fixed slide is evidence of the specimen as it was when collected [21,22]. Changes seen on the slide may include tumor cells, inflammation, blood and other abnormalities [23,59]. Interpretation of these abnormalities is described by the Bethesda System [60,96].

Pap testing has several limitations [16,17,18]. Because the same person performs all the steps in the process (collection, transport, and fixation of the specimen), the collector must be highly skilled and trained [18,19]. The fixation of the specimen on the slide does not guarantee that all the cells on the slide will be distributed evenly [20,21]. Inflammation and/or blood may be present on the slide and mask diagnostic cells [22,23]. Variability among pathologists increases with low quality specimens [59,60]. If the specimens are borderline, it may not be possible to make a diagnosis [69,100].

Limitations of conventional cytology in India is a case study in challenges not directly linked to the program [5,62,63]. The availability of Pap tests can be useful if the health worker is able to perform the test correctly and is able to follow up on the results [63,64]. Coverage and inequity reduce the impact of the program [65,67]. In these circumstances, it is irrelevant to the program to discuss the adequacy of the Pap test [76,77]. The only thing that really matters is the program's performance [5,62]. The program fails if the health workers are unable to reach the women on whom the test and program is intended to benefit [63,64]. The program fails if there is inadequate follow up and remedial action for an abnormal test result [65,67]. The program ultimately fails due to the absence of peer review [76,77].

IMPROVEMENT IN PAPANICOLAOU STAINING:

The major drawback of the Papanicolaou method is that it lacks objectivity [9,10,11]. The main way to obtain objective standardization of the procedure has been to use a known standard and adjust the staining time accordingly [11,12]. All types of staining endpoints (i.e. color changes) are susceptible to variations in the background and the fixation and processing of the specimens [13,96]. In order to improve the efficiency of the staining process and to maintain good objective control over the process, a number of rapid and ultrafast staining procedures have been described [9,10].

Automation alters staining to more of an engineering challenge [24,29,89]. Variability in staining can still occur, and is often due to inconsistent control over the duration of exposure to reagents, the speed and uniformity of agitation, and the time that samples are allowed to dwell in reagents

[89,93]. Automation will not control pre-analytical variations [96,97]. Malfunctions in automation can result in artifacts [24,29]. Consequently, to ensure the validity and appropriateness of the interpretive data of automation systems, laboratories establish and communicate to instrument systems acceptability limits (MAL) for different types of staining [89,93]. Instrument controls and reagents are calibrated to these MAL [96,97]. Drifts in control and process slides indicate process non-conformance, and require an investigation [24,29]. As the methods of staining and of Pap testing continue to evolve, greater emphasis is placed on the role of quality systems [89,93].

Rapid staining methods improve the turn-around time for test results [9,10]. As the specific features of concern on the Pap test become better defined, rapid staining methods may not be as valuable for use in staining samples for other forms of the test [11,12].

The difference in sample transport is the main difference between the two types of cytology [16,17,18]. In conventional cytology, a sample is transferred to a slide by a lab tech [18,19]. In liquid-based cytology (LBC), the sample is transported in a liquid [20,21]. An LBC sample is then processed to remove substances that can obstruct a sample [22,23]. LBC, similar to other procedures in science and technology, employs filtration and other techniques to achieve a clean sample [59,60]. Residual reagents from the process are retained for further analysis [69,97].

STANDARDIZATION AND SUBOPTIMALITY:

Standardizing liquid-based techniques for the preparation of cytologic samples does not ensure that cervical smears are adequate [16,17,18]. Biological completeness of a sample is paramount for adequacy [18,19].

Cellular components of the sample can be transformed and deformed and the background can be altered due to different staining techniques [20,22]. LBC preparations can be interpreted in numerous ways and so the personnel interpreting these preparations must be trained in the various techniques and philosophies of LBC [23,69].

Though a number of studies have recently been conducted, LBC has been prevalent for many years [16,17,18]. How LBC compares to other cytologic techniques is largely dependent on the facility and commitment of the user lab [18,19]. One of the strengths of LBC is the potential to consolidate numerous diagnostic tests from cellular specimens [20,21].

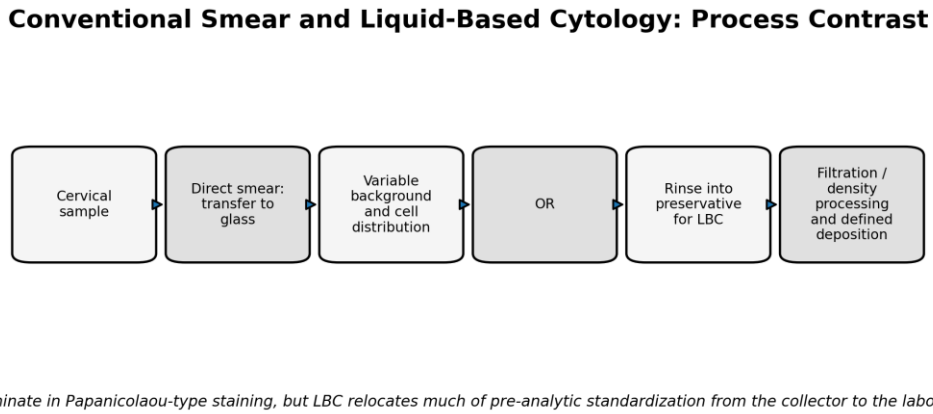

Figure 3. Process contrast between conventional smear preparation and liquid-based cytology. [16-23,59,60]

CONVENTIONAL CYTOLOGY VERSUS LIQUID-BASED CYTOLOGY:

Typically, discussions regarding liquid-based cytology (LBC) compare methods on the basis of sensitivity [16,17,18]. However, both conventional and LBC methods have particular errors [18,19]. Air drying of samples is a drawback of conventional methods, along with incomplete transfer of sample, and/or presence of foreign matter that obstructs the sample [20,21]. Variations related to the automated platform are associated with LBC [22,23]. Because the thresholds for various diseases and the populations being sampled differ from study to study, as do

the types of reviewers and methods of verification, it is not appropriate to make generalized statements regarding the measures of sensitivity and specificity for a given study [59,60].

Liquid-based cytology is becoming the standard methodology for screening because of its potential for automation, reflexivity, and integration with molecular methods [16,17,18]. When coupled with automation and reflexive molecular methods, LBC aids in the categorization of HPV, and facilitates the completion of HPV testing [18,19]. LBC produces cytological specimens that are more uniform with less background compared to conventional methods [20,21]. Conventional cytology often results in unsatisfactory specimens [22,23]. It is unclear if LBC has an overall greater impact in reducing the rate of unsatisfactory specimens compared to conventional cytology [70,99]. LBC is more appropriate for high throughput and automation [16,17]. Studies support LBC is more sensitive and specific compared to conventional methods of cytology [16,17,18].

Table 3. Conventional cytology versus liquid-based cytology [16-23,59,60,69]

Domain	Conventional smear	Liquid-based cytology	Interpretive point
Cell transfer	Direct onto slide; transfer loss possible	Collected into preservative then processed	LBC standardizes preparation but cannot correct inadequate cervical sampling.
Distribution	Often uneven with thick/thin areas	More defined deposition area	Can shorten screening path and facilitate automation.
Background	Blood/inflammation may obscure cells	Often cleaner after processing	Cleaner is not synonymous with universally higher disease detection.
Morphology	Familiar contextual background	Platform-specific dispersion and grouping	Training must address altered cellular presentation.
Unsatisfactory rate	Sensitive to smear/fixation quality	Often reduced, but varies by platform	Meta-analysis shows platform-specific differences [69].
HPV/ancillary testing	Usually requires separate or planned specimen	Residual vial supports reflex testing	A major systems advantage in HPV-based programs.
Cost	Low capital; labor-intensive screening	Higher consumable/processor cost	Economic value depends on throughput and integrated testing [70].

AUTOMATION OF PAPANICOLAOU STAINING:

Automation is impacting both phases of the Pap test [29,39,40]. The automation of staining introduces costs and variability, but can help improve the consistency of the process [40,61]. Automation of the screening process can help direct and prioritize the fields to be reviewed by a cytotechnologist [79,89]. Further, automation and artificial intelligence can help screen and analyze cytopathology slides [91,92].

The ThinPrep Imaging System automates several aspects of the cytopreservation process and helps prioritize fields to be reviewed by a cytotechnologist [29,61]. Use of automation in cytology helps standardize and enhance the consistency of the test and helps in the overall control and management of the laboratory [92,94]. Other innovations in automation are forthcoming and will help streamline high volume areas of cytopathology [29,61,89].

QUALITY ASSURANCE AND STANDARDIZATION

In cytology, quality assurance consists of performing checks to ensure reagents are working, adequate staining times are achieved, and adequate nuclear detail is present [24,25,26]. Both pre-analytic and analytic controls are defined and built into the cervical cytology process [26,27]. Errors in the cervical cytology process can be reduced through post analytic means [28,29]. Unlike surgical pathology, continuous quality improvement and proficiency through education and testing is lacking in cytology [30,58]. Incorporation of a cytology and histology correlations would be of value [89,90]. Recent emphasis in quality assurance in cytology has been directed at the correlation of clinical and cytology data as well as the restructuring of quality programs to improve the processes related to the originally defined and designed programs [93,24]. Cytology laboratories need to be proactive to facilitate process improvements and quality assurance rather than relying on out-of-date and/or inadequate systems [24,25,28]. Unexpected changes in the public health emphasis on cervical cancer may facilitate process improvement [28,29].

The "human factors" that affect the quality of a cytology screening system include the experience of the personnel, the criteria and standards used to interpret a specimen, and the cytology reference standard [58,89].

TRANSFORMING CYTOPATHOLOGY

As with other pathology specialties, cytopathology can be pursued in a digital context [24,25,26]. Of these, digitization of cytopathology may prove challenging [26,27]. Similar to other digitized pathology specialties, incorporation of digital cytopathology with various artificial intelligence (AI) algorithms is conceivable [28,29]. Given the nature of the specimen, most of the cytopathology specimens are relatively difficult to interpret [30,89]. Three dimensional cellular structures and architectural components, if present, are difficult to interpret in a two dimensional digitized cytopathology specimen [90,93]. When interpreted in the context of digitized histopathology, interpretation of cellular and architectural components may require digitization using z-stack [94,24]. However, digitization of cyto- and histopathology specimens using z-stack is challenging due to the large file sizes and time consumption [25,26].

In studies dealing with validation of digitized cytopathology specimens, the concordance rates with traditional stained specimens have been reasonably good [24,25,26]. However, in a significant number of cases, cytopathology specimens were rescanned prior to final report [26,28]. The major reasons for rescanning of cytopathology specimens are insufficient (paucity of) cellularity, suboptimal smear (smeared cellular) morphology, and/or technical problems with coverslips [29,30]. Digitization of cytopathology specimens has the potential to augment cytopathology interpretation; however, many issues become apparent only during digitization and do not resolve with digitization [58,89]. The available literature focuses on the local validation of the hardware and software used, as well as the case mix [90,93].

There are real-world issues to consider [29,61,85]. The particular challenges to installing whole-slide imaging (WSI) in a laboratory will depend on the existing infrastructure [85,86]. WSI is a technology that has the potential to augment laboratories, but this will depend on investments in the existing infrastructure (storage, IT, and cyber security) [87,88]. The same survey noted that while laboratories are willing to adopt digital cytology, this field is at a more immature stage when compared to digital pathology [89,90]. For this reason, the same study suggested that the first digitized cytology programs should provide additional benefits, for example, better training and access to remote specialists [93,29].

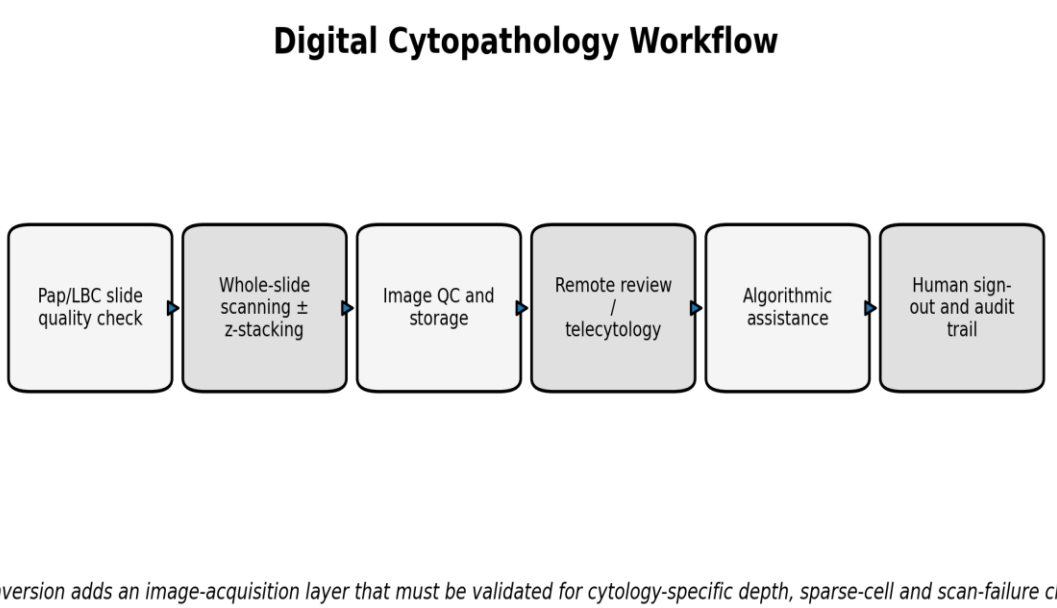

Figure 4. Digital cytopathology workflow from slide quality control to human sign-out. [24-30,89,90]

Table 4. Digital cytopathology technologies and applications [24-30,61,89,90]

Technology	Application	Major benefit	Principal limitation
Whole-slide imaging	Primary/secondary digital review	Remote access and complete-slide navigation	Sparse cells, thickness, focal depth and file size [28].
Z-stacking / multiplane scanning	Three-dimensional groups	Improves access to different focal planes	Longer scan time and larger files.
Telecytology	Remote consultation and education	Extends expertise across sites	Network, image-quality and governance dependence.
Digital archives	QA, teaching and retrospective review	Reproducible case retrieval and annotation	Storage and retention costs.
AI overlay / prioritization	Screening assistance and QC	Can focus attention on high-risk fields	Requires external validation and lifecycle monitoring.

ARTIFICIAL INTELLIGENCE IN CERVICAL CYTOLOGY:

Cervical cytology is a prime candidate for automation using AI [31,32,33]. Classification and segmentation of cell and nuclear structures on cervical smears have been successfully achieved using various deep learning architectures [33,34]. A number of studies have been directed toward automated identification of abnormalities in cervical smears, with subsequent comparison to the Bethesda Classification [35,36]. Further, the classification of cervical smears using various stains and methods of preparation has been studied using deep learning [37,38].

More recently, it has been more common to create new AI applications in this field, rather than optimize existing applications [31,32,33]. Several computer-based applications for pathologists, as part of their regular work, have been developed [33,34]. AI applications for centralized review of cytology specimens have also been developed [35,36]. Applications for automation of routine cervical screening, as well as for the triage of cervical specimens, have been developed and tested [37,38]. A number of applications for interpretation and classification of cervical cytology specimens have been developed and hosted on the cloud [39,40].

Although there is some overlap, there are important differences between performance metrics [31,32,33]. For instance, class imbalance can increase model accuracy [33,34]. Just because a model correctly classifies cells, doesn't mean it correctly classifies tissue or makes the correct diagnosis for the patient [35,36]. Additionally, 'validating' a model can mean running the model multiple times [37,38]. Some of the major bottlenecks for advancing Pathology-related Artificial Intelligence (PATH) have been the small size and poor quality of training data, standardization, and insufficient benchmarking [61,66]. Other aspects of the field, like joint modeling and Artificial Intelligence (e.g. Modality Unitation, Knowledge distillation, and Privacy Preserving Deep Learning, have expanded the field [79,85]. When incorporating artificial intelligence and pathology, the goal should be to synergize the two [39,40,61]. In the context of pathology, several studies have shown the potential of Artificial Intelligence (AI) to complement Pathologists in quality control and assurance as well as education [61,79]. It is prudent for the field to move in this direction [85,86].

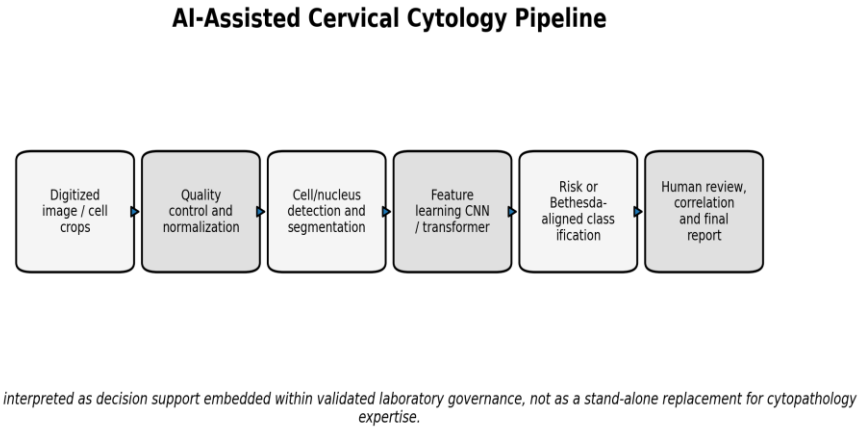

Figure 5. Conceptual AI-assisted cervical cytology pipeline. [31-40,61,79,95]

INTEGRATION OF HPV TESTING AND CYTOLOGY:

The use of cytology for primary screening of cervical cancer will decrease with the implementation of primary HPV testing [3,4,5]. Pap tests identify changes on the cervix [5,6]. Some changes may be pre-cancerous and potentially caused by high risk HPV [41,42]. But, it is expected that the large majority of women will be infected with high risk HPV at some point in their life and therefore, a positive HPV test would not lead to further evaluation [43,44]. Consequently, cytology programs will change from primary to selective or risk-based [45,46]. It is recommended that clinical risk, cytology (with dual staining or other methods) and HPV testing be integrated in a single evaluation, rather than a universal triage be performed [47,54].

With primary HPV testing, the field of cervical cancer screening moves beyond cytology and into other realms of diagnostics [43-47,50-57,84,99]. Some of the existing evidence supports the use of other molecular methods in cytology-based triage [43-47,50-57,84,99]. Additionally, self-collected HPV testing adds another layer of complexity [48,49,80-83].

Ultimately, with the integration of other molecular diagnostics and biomarkers, cervical cancer screening will move beyond cytology and incorporate other platforms [2,3,4]. However, the largest burden of cervical cancer occurs in low-to-middle income countries, where resources are constrained and cervical cancer screening programs are often nonexistent [4,5]. Cytology has an established and proven role in diagnosis and prevention of cervical cancer, and it will not be completely replaced [62,63].

As in other areas, AI and digital innovations are used to validate and standardize cytology technologies in various areas, from traditional to advanced screening and diagnosis [29,31,39].

Different technologies can be assessed for performance in many ways, and often patient-level outcomes are used for traditional and LBC cytology studies [16,17,18]. Endpoint studies for digital cytology can be evaluation of agreement with traditional diagnoses [18,19]. For AI studies performance is assessed at the cellular or pixel level [20,21].

Current evidence suggests that LBC outperforms conventional technologies for some types of cervical cancer screening, and in some cases improves operational characteristics of the assay [16,17,18]. However, it should be noted that LBC can fail to detect other types of cervical cancers [18,19]. Performance of various cervical cancer screening methods and technologies, including newer LBC and ThinPrep cytologies, varies with geography and setting [20,21]. For digital cervical cancer screening, diagnostic agreement is influenced by several factors, including the dataset, the focal plane and the AI/ML technologies [22,23].

The authors resist the trend to create a numeric rank ordering of generations to describe their clinical value [24,29,39]. More clinically relevant changes may occur at a system level, for example, improvements in the service (e.g. increased availability of the service for remote expert consultations and/or transport of samples for triage), the cytopathology laboratory operation (e.g. improved throughput of the service, reduced turnaround time for negative samples), and/or changes in the workflow and/or equipment (e.g. automation of sampling and transport) [39,61].

EVALUATION OF WORKFLOW AND ECONOMICS:

The assessment of workflow economics includes the expense of supplies and equipment, personnel and time, laboratory tests and procedures, and out-of-lab activities including storage and referral [62,63,64]. Of all the cancer screening tests, the conventional cytology-based tests are among the least expensive [64,65]. The largest variable cost, personnel, is determined by the volume of specimens to be screened [70,76]. Automation and other innovations can reduce the expense of personnel time [77,85]. The priority of a specimen for review can be determined by the results of specialized laboratory tests or by the use of special stains [89,90]. Staff can be directed by artificial intelligence to review specimens of highest risk [62,63]. The use of digital technologies can reduce the expense of personnel time and increase access to subspecialty services [64,65]. The costs of digital pathology can be assessed to determine what costs have been shifted or eliminated [70,76].

Cytology is innovating their methods of screening and testing [3,6,29]. As a result, the frequency of Pap tests a person may need to undergo may decrease, or in some cases, be eliminated [29,61]. Consequently, it is anticipated the Pap test specimen volume may decrease [70,71]. Additionally, as advances in the field of cytology occur, the cytology laboratory may be required to spend more time and effort to analyze each slide [76,77]. Laboratory workforce planning should account for the impact of automation and other innovative technologies [85,3].

WORKFORCE CHALLENGES IN LOW- AND MIDDLE-INCOME COUNTRIES:

In low and middle income countries, a growing burden of cervical cancer is accelerated by inadequate functional cervical cancer screening programs, and weak laboratory systems [2,4,5]. It is of no benefit to introduce improved methods for the diagnosis of precancerous changes of the cervix when other components of the cancer control continuum are missing (e.g. reliability of specimen transport, maintenance of equipment and consumables, a trained colposcopist, and systems to ensure follow-up) [5,62]. It is crucial to provide equitable and improved (traditional and modern) methods of service delivery to improve public health outcomes [63,64].

A number of advanced and emerging technologies exist to modify cytology [29,31,39]. These include digital and artificial intelligence (AI) based systems and liquid based cytology [39,40]. All the mentioned technologies have the potential to transform cytology if implemented appropriately [61,62]. However, for meaningful advancement of cytology, a comprehensive strategy is warranted [63,64]. This strategy must address improvement of cytology specimens, strengthening laboratories, innovation and technologies that are in alignment with the country's health strategic plans [65,66].

RESEARCH GAPS

Most of the studies presenting the use of artificial intelligence (AI) in pathology are usually short communications [31,32,33]. There are very few comparative studies and larger multicenter studies [33,34]. In addition, AI has not been adopted widely in the diagnostic arena [35,36]. Authors should give a detailed explanation of the reasons for failure of AI in specific cases including the nature of the data and reasons for omission of specific data sets [37,38].

The second limitation is in the field of digital cytology [24,25,26]. Best practices to digitize cytology specimens have not been formally described [26,27]. However, the need to define standards to identify an adequate and an acceptable digital image in digital cytology has been acknowledged [28,29]. Trade economy studies should be performed to define the opportunity cost and benefits associated with the implementation of AI-Pathology [30,58]. Such studies should define the economic impact of digital pathology on a pathology laboratory [61,85]. As such, studies should define the cost to implement digital pathology, including labor and operational costs [89,90]. Privacy and security studies should also be performed to define the cost to implement and use AI in the pathology laboratory [93,95].

Table 5. Current limitations, research gaps and future priorities [24-40,61,66,89,95,97]

Problem	Why it matters	Priority action
Dataset shift	Stain, scanner and population differences can degrade AI performance	Prospective multicenter external validation and domain monitoring.
Cytology-specific WSI limitations	Focal depth and sparse cells can cause scan misses	Define z-stack, rescan and completeness standards.
Inter-platform LBC differences	Adequacy and morphology are not interchangeable	Platform-specific competency and local QA benchmarks.
Economic uncertainty	Capital price alone misses downstream workflow effects	Full pathway cost-effectiveness and budget-impact studies.
Data fragmentation	HPV, cytology, histology and outcome data may be disconnected	Interoperable structured data and registries.
Algorithm governance	Model updates can silently change behavior	Version control, change management, audit trails and revalidation.
Resource inequity	Technology may widen access gaps	Tiered deployment, telecytology networks and locally validated solutions.

FUTURE DIRECTIONS

There are several barriers for full automation in a cytology lab in the short term [29,31,32]. In the near future, the best approach will be to include automated systems to augment currently manual systems and processes in a cytology lab [32,33]. Automated systems have the potential to analyze cytology specimens to identify high risk patients [39,40]. Additionally, the technologies have the potential to integrate and interpret the risk assessment derived from alternative diagnostic tests [61,66]. Currently, pap tests are evaluated in a wet lab, therefore, the processes are not automated [79,85]. Alternatively, pap tests can be performed using digital or other systems and artificial intelligence [86,88]. Other ongoing research studies evaluate the integration of digital and computational systems to traditional cytology and HPV testing [89,91].

The use of digitized images of cytology slides and related systems, allows for remote expert consultation, training, and quality assurance [24,25,28]. As with other subspecialties of pathology, it is expected that artificial intelligence and other computational systems will enhance the performance of laboratories and professionals, and enable the pathologists to perform quality assurance and control functions [28,29]. Computers can perform certain routine functions to support pathologists, thus freeing pathologists time to perform additional, more complex functions [39,40].

We should focus on innovations in workflows rather than components [29,31,33]. Diversification in workflows is less restrictive and reliant on supply [33,39]. Many systems can account for uncertainty [40,61]. If there is insufficient confidence in a case, the system should prompt a case review [66,79]. The system should be designed to adjust to shifts in case review [85,89]. The system must facilitate case review should an improvement to the case review framework occur [91,95].

Advances in cervical screening have been stifled by the same systems and implementation challenges [2,4,5]. For example, the lack of efficient use of available resources has been well documented [5,62]. These challenges include the prioritization and allocation of personnel and other resources [63,64]. Similar challenges occur at all levels of the screening process, e.g. inadequate follow-up, case review and management [65,67]. These challenges are particularly pronounced in low and middle income countries [76,77].

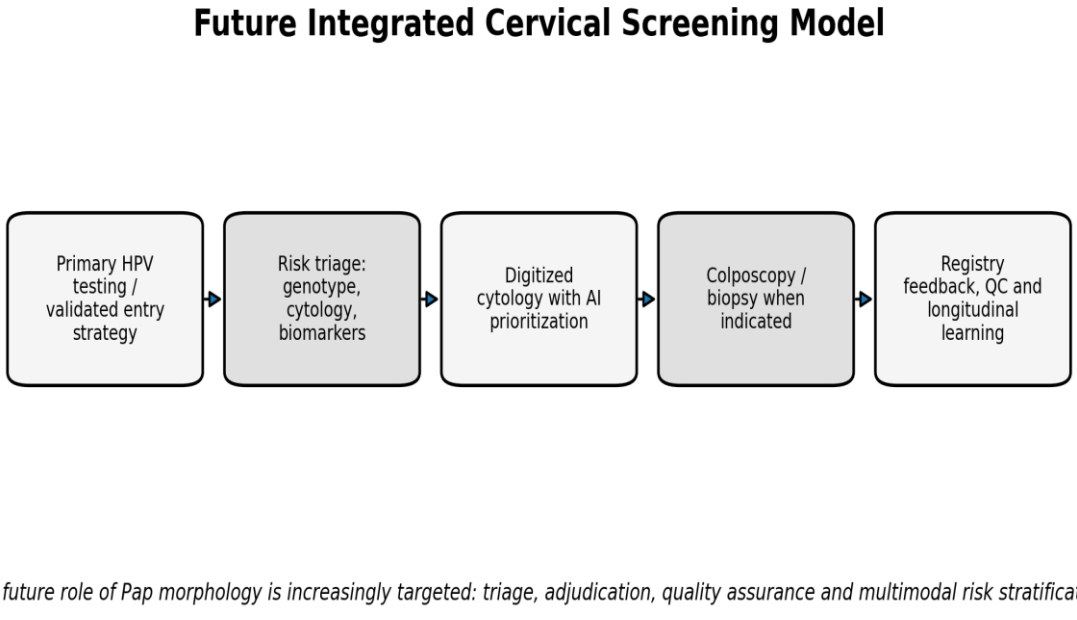

Figure 6. Future integrated cervical screening model combining HPV testing, cytology, digital imaging and AI. [3,29,61,71,79,84,95,98]

CONCLUSION:

Papanicolaou (Pap) staining has reduced variability in diagnostic testing [8,16,21]. Many types of cervical smears allow for the identification of cervical cancer, and, in addition to the experience and skill of the health care worker, depend on the condition of the specimen at the time of collection and the effectiveness of the cytopathologic laboratory [21,23]. With the modification of staining techniques and automation of staining processes, the elements of the staining process and the Pap staining procedure, in general, can be changed to support digital imaging [29,31]. Other recent advances in cytopathology have been in the areas of automation, digitalization and the integration of molecular techniques [33,39]. These recent developments improved the quality and type of control in cytopathology [40,61]. Artificial Intelligence (AI) further enhanced and accelerated the processes undertaken in these recent developments [71,79]. It is expected that digital and automated systems will integrate other new and upcoming omics and related technologies to improve specimen and staining processes in cytopathology [84,89].

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