

Can Technology Expedite the Cervical Cancer Screening Process?

A Hong Kong Experience Using the AutoPap Primary Screening System With Location-Guided Screening Capability

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Key Words: Pap smears; Conventional screening; Automated screening; Comparison; Location-guided screening

Abstract

We studied the usefulness of an automated screening instrument for processing Papanicolaou (Pap) smears to determine whether it could speed human examination by recording the time to screen 1,007 cervical Pap smears with an AutoPap primary screening instrument with location-guided screening (LGS) software and by conventional microscopic examination. We also assessed the accuracy of the methods to determine preparation adequacy, and we compared the diagnosis by each method. The AutoPap with LGS satisfactorily determined the adequacy of Pap smears and identified the marked abnormal cells for human examination. An accurate diagnosis was possible when only the marked cells were examined, and this method reduced the screening time to less than half that required for conventional screening. With low-grade squamous intraepithelial and more severe lesions as a threshold, there were 37 cases in the conventional group and 29 cases in the LGS group. With atypical squamous cells of undetermined significance as the threshold, there were 111 cases in the LGS group and 93 cases in the conventional group. The AutoPap with LGS can significantly speed the examination of Pap smears without lowering the detection rate of clinically important lesions, thus helping alleviate the cytotechnologist shortage.

The Papanicolaou (Pap) test is one of the most effective methods for cancer prevention. A group of experts concluded that “with the exception of stopping the population from smoking, cervical cytological screening offers the only major proved public health measure for significantly reducing the burden of cancer today.”¹ Yet in Hong Kong, which is a world financial center, with the most up-to-date medical treatment available, 60% to 70% of women have never had a Pap test.²⁻⁴ Consequently, cervical cancer is the fourth-ranking malignant neoplasm diagnosed in Hong Kong women, exceeded only by breast, lung, and colorectal malignant neoplasms.⁵ Recruiting more women to have Pap tests will, however, overburden existing laboratories. This was graphically demonstrated when a free Pap smear clinic (supported by the Hong Kong Cancer Fund) was set up at the Chinese University of Hong Kong’s teaching facility, The Prince of Wales Hospital. Owing to a shortage of experienced cytotechnologists, the additional smears could not be accommodated easily, and results took more than an additional month to be reported.

Using one of the new automated cervical screening technologies as a productivity enhancement in the cytology laboratory is a potential solution to the overburdened manual screening process. The AutoPap Primary Screening System (TriPath Imaging, Burlington, NC) is now available for examining Pap smears. Clinical trial and preliminary in-use results have been reported; these studies have shown that use of the device may increase the overall accuracy of the cervical screening process, and they have shown the potential for significant improvements in laboratory productivity.⁶⁻⁹ Any primary screening system used must have high sensitivity so that cancers and precursor lesions are detected. In addition, high specificity is important if laboratory and clinical productivity is

to be optimized. Other important requirements to maximize the usefulness of any system are the ability to identify inadequate samples, the ability to specifically identify the location of abnormal cells for subsequent human examination, and increased throughput of cases (compared with manual screening) at a reasonable cost. To test a system for the aforementioned parameters in the laboratory examination of Pap tests, a grant was obtained from the Hong Kong Cancer Fund to purchase the AutoPap Primary Screening System with location-guided screening (LGS) for the cytology laboratory.⁸

The AutoPap uses a high-resolution scanner and a high-speed video microscope to obtain cell images from conventional Pap smears. The images are digitized and the data processed with image interpretation software. Specially designed algorithms are used to recognize, analyze, and identify cases that have the highest probability of containing abnormal cells. Slides having the lowest probability of being abnormal can be safely reported as “within normal limits (WNL)” without further manual review by a cytologist. Slides having a higher probability of abnormality require manual cytologist screening, with an additional quality control rescreening on the highest probability slides deemed WNL on initial manual screening. Currently, the AutoPap is the only instrument approved by the US Food and Drug Administration (FDA) for primary screening. The FDA approval allows for the safe and effective archiving of up to 25% of non-high-risk slides screened by the device. Internationally, up to 50% of slides are being archived with performance reported to be at least equivalent to that achieved by manual screening.¹⁰ In addition to overall slide classification, the LGS system produces a printed map of the slide (PAPMAP) that contains up to 15 circles, less than 10% of the total slide area. Each circle is 2.5 mm in diameter, equivalent to one 10× objective visual field, and independent of microscope type. One such circle is referred to as a field of view (FOV). In abnormal cases, the FOVs are highly likely to contain individual abnormal cells, but the LGS software also will allocate FOVs for review even in Pap smears that are normal. In the latter cases, such FOVs might contain reactive cells or variants of normal cells that may contain some features that also may be found in abnormal cells or groups of cells.⁸ Accompanying each slide map is information on specimen adequacy, the presence of endocervical cells, the degree of obscuration by inflammatory cells, and the overall ranking of the case. Data supporting the use of LGS have been previously reported and confirm the efficacy of its use.¹¹ At present, the AutoPap Primary Screening System with LGS has been released by the manufacturer for international use but has not been approved by the FDA for use in the United States.

An experienced cytotechnologist will take approximately 5 minutes to screen a Pap smear.¹² The screening

time potentially could be shortened substantially if an accurate cytologic interpretation was obtainable by looking only at the FOVs that the LGS process identified as containing potentially abnormal cells, without the need to screen the entire slide.

The main objective of the present study was to determine whether the interpretation reached by the process of conventional screening of Pap tests differs from interpretations obtained by examining only FOVs identified by LGS. In addition, other parameters examined were the ability of the 2 methods to determine specimen adequacy, the concordance in cytologic interpretation, and the time required to examine the Pap smear by each method.

Materials and Methods

Routine and unselected conventional Pap smears from the Shatin Community Clinic for the Prevention of Cervical Cancer and the Prince of Wales Hospital's (Hong Kong, People's Republic of China) gynecologic and antenatal services were used in the study. Before processing, each slide was stained by the method of Papanicolaou, a coverglass was applied, a bar-code label was attached, and each slide was cleaned and loaded into special trays and scanned by the AutoPap. The instrument was set at a 50% sort rate, meaning that up to 50% of cases could be reported immediately as WNL, with the remaining slides triaged for an LGS manual review. A PAPMAP of each slide to be manually reviewed was generated. The FOVs were transferred to each slide by overlaying the slide on the printed map and tracing the circle with a marker pen **Image 1** and **Image 2**. The time to undertake these manual steps, before the actual slide review, was recorded. The FOVs on each slide were reviewed by cytotechnologists, all certified by the International Academy of Cytology, who had 5 or more years of screening experience. All screening was performed as part of each cytotechnologist's normal daily workload. Areas of the slide outside the FOVs were not examined. A cytologic interpretation was given at this point—constituting the LGS interpretation (LGSi)—and the time taken to examine the cells within the FOVs and reach each interpretation was recorded in the laboratory's PathFinder system (NeoPath, Redmond, WA). This system is a computerized microscopy station, which allows tracking and timing of the microscopist's actions in the slide review process. A further reason for using the PathFinder unit was to ensure optimal evaluation, as the areas examined on each slide were recorded and could be retrieved for analysis. A pathologist and a senior cytotechnologist reviewed all smears that had abnormal cells. The Bethesda System nomenclature was used for reporting all cases.¹³ As a

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Image 11 Individual Papanicolaou smears arranged over their corresponding location-guided screening PAPMAP (a map produced by the AutoPap system, TriPath Imaging, Burlington, NC) printout with the fields of view drawn on the coverglasses with a marker pen.

quality control measure, 15% of Pap tests that were designated as WNL and all smears from patients with a history of cervical abnormality were rescreened manually.

In the second part of the study, the circles on the slides were erased. The slides were shuffled to avoid recognition and interspersed with the normal workload of the laboratory and distributed to the screeners as part of their daily routine work. All the Pap smears were examined manually, and the following information was recorded: time taken to screen the slide, the screening coverage of each slide, and the interpretation. This information was recorded using the laboratory PathFinder system. The manual screening interpretation was designated the conventional screening interpretation (CSI).

In addition to the initial screening, a senior cytotechnologist and a pathologist reviewed all smears having 1 or more of the following features: (1) insufficient cells, (2) marked drying artifact, (3) obscuring blood or inflammation, and (4) abnormal cells. Resolution of discrepancies between the CSI and LGSI diagnoses to determine the final truth for each case was done by one of us (A.R.C.), who was masked to the original interpretations of each study arm, thereby preventing bias in favor of one method or the other. Both study arms were performed in temporal proximity (generally within 24 hours). There were no differences in laboratory personnel or general procedures in the laboratory between the 2 arms.

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Image 2 The individual Papanicolaou smears with drawn fields of view displayed alongside their corresponding location-guided screening printout.

Results

In the 4-week study period, 2,921 slides (264 were reruns) were processed. Eventually, there were 2,145 qualified cases. Of these, 1,055 (49.2%) were in the “no further review” category, while 1,090 cases (50.8%) were classified as “review.” From the latter group, 1,007 cases were entered into the study, and 83 cases were excluded because they could not be examined fully during the study period owing to time constraints. In total, there were 776 cases (512 + 264 rerun cases) that did not qualify and were screened totally in the normal manner. The average time taken to draw the FOVs on each slide was 0.41 minutes, and the average time for evaluating the cells in

the FOVs was 2.30 minutes. Consequently, the average time taken to reach the LGSI was 2.71 minutes per slide. In contrast, the average time to reach the CSI was 5.74 minutes. Therefore, the average screening time taken to reach the LGSI was just under half (47%) of the time needed to reach the CSI.

One key cytologic criterion for an adequate smear is the presence of endocervical cells. The LGSI identified endocervical cells in 591 cases, while the CSI identified endocervical cells in 624 cases. This difference was statistically insignificant ($P = .138$; chi-square). Overall, the LGSI identified 17 cases as inadequate, while the CSI process detected 29 inadequate cases. This difference was not statistically different ($P = .073$).

Table 1
Contingency Table of LGSI Diagnosis vs CSI Diagnosis

LGSI Diagnosis	CSI Diagnosis								Total
	WNL	Unsatisfactory*	QI	ASCUS	AGUS	LSIL	HSIL	Cancer	
WNL	862	8	9	0	0	0	0	0	879
Unsatisfactory*	5	7	1	1	0	0	0	0	14
QI	0	1	2	0	0	0	0	0	3
ASCUS	16	1	0	50	0	10	0	0	77
AGUS	2	0	0	0	3	0	0	0	5
LSIL	0	0	0	2	0	17	0	0	19
HSIL	0	0	0	0	0	0	10	0	10
Cancer	0	0	0	0	0	0	0	0	0
Total	885	17	12	53	3	27	10	0	1,007

AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical squamous cells of undetermined significance; CSI, conventional screening interpretation; HSIL, high-grade squamous intraepithelial lesion; LGSI, location-guided screening interpretation; LSIL, low-grade squamous intraepithelial lesion; QI, insufficient cells; WNL, within normal limits.

* Marked drying, excess blood.

The final LGSI and CSI diagnoses are detailed in **Table 1**. In both LGSI and CSI diagnoses there were 10 high-grade squamous intraepithelial lesions (HSILs). When smears with low-grade squamous intraepithelial lesions (LSILs) and HSILs were considered together, there were 37 cases in the CSI group and 29 cases in the LGSI group. This difference was not statistically significant ($P = .986$). When all Pap smears with abnormalities were considered, including atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance along with the LSIL and HSIL groups, there were 111 cases in the LGSI group and 93 cases in the CSI group. The binomial P value of less than .0001 confirmed that the LGS process, in the context of this study using ASCUS as a threshold, detected significantly more abnormal cases than did human manual screening alone.

Discussion

This study demonstrates that the AutoPap Primary Screening System with the LGS feature can accurately determine the adequacy of Pap smears and identify and locate abnormal cells efficiently for human screening. Overall, LGS detects more abnormal cases than do experienced human screeners using the conventional manual method. The most significant finding of this study is that the FOVs that are identified by LGS contained sufficient cells for cytotechnologists to make a sensitive cytologic interpretation. Furthermore, LGS uses one half of the screening time compared with the manual conventional method. These results were achieved despite the fact that abnormal cells found in the FOVs did not generate a reflex complete review of the slide for final interpretation, a process the manufacturer of the

AutoPap recommends and a previous study¹¹ included. Therefore, this study shows that detection of abnormality on cervical cytologic specimens may be accurate and reliable based on FOV review alone. The latter is a potential significant productivity enhancement over FOV triage of cases to WNL or to full manual review. Presumably the 10 cases of ASCUS identified by LGS that were found to be LSIL by full manual screening would have had a high probability of being interpreted as such on a full reflex slide review on FOV detection of "atypical cells." Full slide review triage is a process that is expected to further improve the specificity of the overall procedure. With a relatively small number of cases being triaged for full manual review, the overall productivity drop compared with the present study would be expected to be minor.

Computer screening instruments^{9,14} are capable of efficient and accurate processing of Pap smears, but the technology comes with a high price tag, as manufacturers need to recover the cost of research and development and also to reward shareholders. In addition, further expenditures are inevitable, including regular instrument servicing and spare parts. Moreover, laboratories using such instruments must have sufficient expertise to ensure that Pap smears are well prepared, such as staining and applying coverglasses, or they will not be processed successfully. The process review rate was very high (18%) in the study period and was traced to a coverglass and mountant problem. Following completion of the study, another mountant was substituted, along with a wider coverglass (50 × 24 mm in place of the previous 50 × 22 mm), and following these changes, the process review rate subsequently dropped to between 10% and 12%.

Therefore, while theoretically desirable, the placement of automated device screening programs in developing countries where there is a high incidence of cervical cancer may

not be entirely realistic because of cost, lack of experienced cytotechnologists, and inadequate preparatory standards. However, advances in automated devices, such as adding LGS to the currently available AutoPap System, may serve to further increase productivity while maintaining high levels of accuracy. Such an advance brings the possibility of cervical screening in populations with a high cervical cancer incidence closer to reality as unit prices and the need for a large trained workforce necessary for implementation decline.

In addition, combination of this technology with new methods of liquid-based cervical cytology preparations may ultimately prove to further increase cytology laboratory productivity and accuracy. Data generated from numerous studies using liquid-based technologies with manual screening have shown substantial improvements in detection sensitivity and specimen adequacy.^{15,16} Preliminary data linking the AutoPap LGS System with liquid-based cervical cytology have shown that accuracy equivalent to manual screening of the entire slide can be achieved with examining only 5 FOVs on liquid-based specimens.¹⁷ At present, liquid-based preparation methods are expensive, adding between \$5 and \$10 (US dollars) per case. In the future, decline in liquid-based prices achieved with increased volume of use or with the addition of new competitors¹⁸ may ease this burden, again making the introduction of this method of cervical cancer screening in developing countries with high cancer incidence more feasible.

The vexing question of the overall cost-effectiveness of automated screening was not addressed in the present study. The study was designed to show that technology is currently available for eliminating a significant portion of the time expended in Pap smear examination, without sacrificing the accuracy of the overall interpretation. Given the shortage of experienced cytotechnologists in Hong Kong, if this territory were to initiate a comprehensive Pap screening program, the AutoPap with LGS may have an important role. The recently commissioned Hong Kong Government–Harvard Health Report has recommended radical health reforms, including greater emphasis on disease prevention.¹⁹ Ultimately the major question for cervical cancer screening, like many other health programs, will be about trying to obtain maximum benefits at a reasonable cost. The development of cost-effective automated methods will be paramount for the success of such programs.

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