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Original Research Report

Comparison of computer-assisted and manual screening of cervical cytology

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Abstract

Objective. The Pap smear, introduced over 50 years ago, has significantly contributed to the reduction of mortality due to cervical cancer. The shortage of skilled cytotechnologists to screen and diagnose Pap slides has always been a concern, thus driving the goal to develop an automated system. This study evaluated the diagnostic performance of an automated computer imaging system for routine cervical cancer screening in a high-volume independent laboratory.

Methods. Validation and training were conducted upon installation of the computer imaging system. Following validation, data were evaluated comparing cytologic detection rates of a six-month cohort of slides screened with computer imaging assistance versus a historic control of manually screened slides.

Results. For each cytologic abnormal category, the Imager-assisted detection rates were significantly greater than the manually screened historic cohort. The Imager increased the detection of HSIL+ by 38% and LSIL by 46% compared to manual screening. There was an increase in the rate of ASC in the Imager cohort (6.5%) compared to manual screening (4.1%), however, the ASC rate decreased during the time of the study period suggesting learning affect.

Conclusions. The results indicate that computer-imaging-assisted screening significantly increased the cytologic detection of cervical abnormalities compared to manual screening. The initial increase in ASC rates is partially due to a new stain protocol that may be corrected with additional experience. The implementation of the Imager, however, did not adversely affect the ASC:SIL ratio.

Keywords: Computer-assisted screening; Manual screening; Cervical cytology; Cytyc imager

Introduction

It is well-known that the cervicovaginal Papanicolaou (Pap) smear is credited with having had a significant contribution to the reduction of morbidity and mortality due to cervical cancer since its introduction more than 50 years ago. What is less well-known is that efforts to automate cervical cytology screening began shortly after widespread introduction of the Pap smear in the 1950s. The impetus at that time was the shortage of skilled cytotechnologists to screen and diagnose the sudden increased workload of smears [1], not unlike a similar challenge laboratories are facing today [2].

The original goal was to fully automate the process and eliminate or significantly reduce the need for human intervention. This goal proved to be more difficult than anticipated primarily due to the complexity of interpreting the Pap smear and the unique human skills demanded by this task. Two computer screening systems were approved by the U.S. Food and Drug Administration (FDA) in the 1990s. The PAPNET system (Neuromedical Systems Inc., Suffern, NY) and AutoPap 300 QC (NeoPath, Redmond, WA) were approved to screen previously (manually) screened conventional Pap smears to identify screening false-negative results [3]. The AutoPap system was later approved for primary screening and is currently marketed as FocalPoint™ (Tripath Imaging, Inc., Burlington, NC). The FocalPoint slide profiler reviews and ranks slide by potential abnormality. The system as approved allows a percentage of slides to be immediately archived with no further review, and the remainder are screened manually by the laboratory personnel. The PAPNET system is no longer marketed in the U.S. A number of possible factors may have led to the lack of commercial success of PAPNET. A serious barrier was lack of additional reimbursement since PAPNET

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review was deemed a quality control procedure that was already paid. For pathologists, the system required viewing digitized slides on a television monitor, which was a difficult adjustment for many. Finally, a study published in JAMA in 1998 by O'Leary et al. [4] raised questions regarding the cost-efficacy of the system. Because the PAPNET system was based on review of the conventional Pap smear, it was not able to demonstrate a significant increase in disease detection that required addressing the sampling error through liquid-based sample collection.

One of the major challenges for developers of computerized Pap screening systems was the lack of homogeneity and clarity of the conventional smear and the limitations of computer technology. The latter two challenges were addressed in the 1990s. Computer technology made tremendous advances in the late 1990s, and in 1996 the FDA approved the first fluid-based, thin-layer slide preparation system (ThinPrep® Pap Test, Cytyc Corporation, Marlborough, MA), which provided a more consistent cervical cytology slide that was easier to read [5]. There remained the challenge of developing a computerized slide imaging system that could match the skills of a trained cytotechnologist.

In June 2003, the FDA approved the first fully integrated, interactive computer imaging system that assists cytotechnologists in the primary screening of ThinPrep (TP) slides. The ThinPrep® Imaging System [TIS] (Cytyc Corporation, Marlborough, MA) combines advanced imaging technology with human interpretive expertise to improve cervical cancer screening efficiency and performance.

The TIS consists of an Image Processor and automated Review Scopes (RS). The Image Processor rapidly scans and locates 22 areas of clinical interest or fields of view (FOV) for every slide and then stores the coordinates of the FOVs along with the slide identification information. Cytotechnologists review each slide at the RS. The cytotechnologist places a slide onto the RS where a numeric identifier is read, which prompts the system to retrieve the coordinates of the 22 FOVs to be reviewed. The RS automatically takes the cytotechnologist to each FOV in geographic order. The cytotechnologist evaluates each FOV, selecting and electronically dotting those areas which require further pathologist review, or the cytotechnologist can determine that the slide is negative and simply sign out the case. If the cytotechnologist identifies and selects any abnormalities, the system automatically directs the cytotechnologist to complete a full review of all fields of this slide.

In the pre-market approval study for the FDA, the TIS cohort showed a statistically significant improvement in sensitivity for ASC-US+ lesions and a statistically significant improvement in specificity for high-grade lesions [6]. Sensitivity and specificity were determined based on a panel review by independent pathologists. This study was limited to a relatively small test cohort and was performed in a clinical trial setting. The objective of our present study is to evaluate the diagnostic performance of the TIS in a high-volume independent laboratory in routine use.

Material and methods

Pathology and Cytology Labs is a medium- to high-volume laboratory in central Kentucky. We process approximately 120,000 Pap tests annually, and 96% of those are liquid-based ThinPrep slides. Our patient population represents primarily a normal screening population, and our rates of cytologic abnormalities are similar to the median laboratory rates reported in the College of American Pathologist Q-probes analysis [7].

Pathology and Cytology Labs introduced the ThinPrep Imaging System in May 2004. Prior to routine implementation, we conducted the manufacturer's recommended validation protocols. The Imaging System employs a proprietary stoichiometric stain, and all cytotechnologists and pathologists were trained and passed proficiency tests before using the system. After stain validation, our laboratory also conducted training and a validation study to assure familiarization with the Review Scopes. In May 2004, following completion of training, validation and proficiency evaluation, we implemented the Imaging System and converted all of our OB-GYN accounts to the Imaging System (72% of all cases). Health department accounts comprise of 28% of all cases and were not converted to the Imaging System (they were conventional Pap smears and were converted to manual ThinPrep in 2004 and thus did not participate in either arm of the study).

The patient population was similar in both arms of this study. The manual ThinPrep population was completely converted to TIS. Within the study groups, in 2003, the mean patient age for manually screened TP was 40.0 (range 10–99), in 2004, the mean patient age for TIS was 40.7 (range 12–99). In 2003, 91.4% of the manually screened TP were screening Pap tests, in 2004, 91.8% of the TIS were screening Pap tests.

For this retrospective study, we evaluated rates of cytologic abnormalities and specimen adequacy for slides processed using the Imaging System for the six-month period from May 2004 through October 2004 (Imager cohort). We compared these results with our ThinPrep rates for similar cytologic categories for the full year 2003, when all samples were processed manually (manual cohort). The Bethesda 2001 criteria were employed [8].

The pool of cytotechnologists and pathologists did not change during the period of study. All cytotechnologists were either ThinPrep trained and certified in 1997 or in cytotechnology school prior to employment. In 2003, there were 10 cytotechnologists with an average of 10.3 years experience (range 5–14 years) and 5 pathologists with an average of 10.2 years experience (range 1–19 years). In 2004, the same cytotechnologists averaged 11.3 years experience while the same pathologists averaged 11.2 years experience. All cytotechnologists were trained on the ThinPrep imager system (TIS), and all participated in this study. While cytotechnologists were clearly more experienced with manual screening, it should be emphasized that, other than a slight change in stain, the cytotechnologists are still reviewing and evaluating ThinPrep slides, albeit selected fields of view.

We also evaluated biopsy follow-up results for high-grade and more severe squamous intraepithelial lesions (HSIL+) to determine the positive predictive value. In addition, ASC results were tested for high-risk HPV types using the Hybrid Capture 2 (Digene, Gaithersberg, MD) as recommend by ASCCP guidelines [9].

Statistical analysis was performed by independent biostatistician (StatNet, Plaistow, NH) using a chi-square analysis.

Results

The Imager cohort consisted of 39,717 cases reported from May through October 2004. A total of 87,267 previously screened and reported cases were included in the manual cohort.

Table 1 shows detection rates of general cytologic abnormalities for the Imager cohort and the manual cohort. For each cytologic abnormal category, the Imager-assisted detection rates were significantly greater than the manually screened historic cohort. The Imager increased the detection of high-grade squamous intraepithelial or more severe lesions (HSIL+) by 38% compared to the manual cohort (318/39, 717 [0.80%] vs. 509/87, 267 [0.56%], $p<.0001$). There was also a 46% increase in the detection of low-grade squamous intraepithelial lesions (LSIL) with the Imager compared to manual screening (911/39, 717 [2.29%] vs. 1372/87, 267

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Table 1
General cytology laboratory statistics

	Manual screening 2003	Imager screening 2004	% Increase (decrease)	p value
ASC	3569 (4.09%)	2588 (6.52%)	59.41%	$p<.0001$
AGC	105 (0.1%)	64 (0.1%)	None	N/S
LSIL	1372 (1.57%)	911 (2.29%)	45.85%	$p<.0001$
HSIL	509 (0.58%)	318 (0.80%)	37.93%	$p<.0001$
Unsatisfactory	484 (0.55%)	216 (0.54%)	(1.81%)	N/S
ASC:SIL ratio	1.9:1	2.1:1		
Total	87,267	39,717		

[1.57%], $p<.0001$). We also noted a 59% increase in the rate of ASC in the Imager cohort (2588/39, 717 [6.52%] vs. 3569/87, 267 [4.09%], $p<.0001$). However, the ASC to SIL ratio was similar with the Imager (2.1:1 vs. 1.9:1). Rates of Unsatisfactory specimens in the Imager cohort were essentially unchanged from the manual cohort (216/39, 717 [0.54%] vs. 484/87, 267 [0.55%], N/S).

Of the 509 HSIL manual screened diagnoses, 329 (64.7%) were biopsied, compared to 200 of the 318 (62.9%) TIS screened HSIL diagnoses. The biopsy interval in both study groups was less than or equal to 6 months (range 0–6 months) according our standard laboratory procedure, although the specific time interval of the biopsy was not recorded for this study.

All biopsies are reviewed with the understanding that there is a previous abnormal Pap test. All biopsy diagnoses are correlated to the previous Pap test results, and as such, the previous Pap test results are known to the pathologist at the time of sign out. Biopsy follow-up statistics for LSIL are collected; however, since this is done retrospectively (at the time of biopsy sign out), it is not known whether the preceding Pap test was ThinPrep or TIS. Most ASC diagnoses are followed up with HR-HPV testing not biopsy.

Table 2 presents biopsy correlation data for HSIL cytology for each cohort. CIN 2+ was confirmed by histology for 83% of HSIL diagnoses in the Imager cohort and 84% in the manually screened cohort. CIN 1 or more severe was confirmed for 98% of HSIL cytology in the Imager cohort and 96% of HSIL in the manual cohort. In each case, the positive predictive value (PPV) was statistically equivalent, thus suggesting that the increased detection of HSIL was not the result of overcall in the Imager cohort.

Table 3 presents ASC, ASC:SIL and high-risk HPV monthly results for ASC diagnoses during each month of the evaluation period. Slides categorized as ASC in the Imager cohort decreased and the ASC:SIL ratio and HR-HPV positive rate improved demonstrating a learning curve for this category (Fig. 1).

We did not observe any change in the detection of infectious organisms during the study period with the introduction of the Imager.

Table 2
Biopsy confirmation following an HSIL diagnosis

High grade cytology	Predictive value=biopsy correlation		Biopsy follow-up
	CIN 2–3 biopsy	CIN 1+ biopsy	
2003 (Manual)	84% (276)	96% (316)	64.7% (329)
2004 May–Oct (Imager)	83% (166)	98% (196)	62.9% (200)

Table 3
ASC:SIL ratio and ASC rates following implementation of TPI

	ASC rate %	ASC:SIL ratio	HR-HPV positive rate %
2003	(3569) 4.1	1.9 to 1	(1433 of 3005) 48
May 2004	(208) 10	2.1 to 1	(135 of 206) 66
June 2004	(562) 7.7	2.4 to 1	(95 of 375) 25
July 2004	(461) 6.5	2.1 to 1	(159 of 503) 32
August 2004	(509) 6.5	2.1 to 1	(160 of 510) 31
September 2004	(588) 6.3	1.8 to 1	(156 of 467) 33
October 2004	(406) 5.4	1.7 to 1	(121 of 294) 41

Discussion/conclusions

The results of the present study indicate that computer-assisted screening with the ThinPrep Imaging System significantly increased the cytologic detection of cervical abnormalities compared to manual screening. Increases in the detection of LSIL and HSIL lesions are not only statistically significant but are also clinically significant. Biopsy confirmation statistics show that the positive predictive value for a computer-assisted HSIL diagnosis remains high. This is particularly significant considering the level of increased disease detection seen with the TIS. The continued high correlation with biopsy results reflects the accuracy of this new methodology.

We believe the increased detection of HSIL is largely due to the TIS algorithms for identifying small single cells and hyperchromatic groups, particularly when they are rare events. We know surveillance fatigue is a factor as well as attention, distractions and the inability to view every cell on a given slide. The Imager forces cytotechnologists to consider and concentrate on these crucial atypical cells. The increased detection of LSIL might also be attributable to the ability of the Imager to assist in identifying rare events. We also believe that it is possible that the proprietary stoichiometric stain, which presents darker and perhaps slightly more vivid nuclei, may have been a contributing variable in the Imager cohort. However, given the fact that regular Pap stains vary significantly in intensity, this is not likely the only source of increased performance.

We were somewhat concerned with the concomitant increase in ASC in the Imager cohort. The data reflected in this study include all computer-assisted slides for only the initial 6 months after implementation. We did observe a consistent decline in the ASC rate during and after that time. ASC rates initially increased to 10% during the first month before settling back to 5.4% by October. We believe the initial increase in ASC rates is partially due to the new stain protocol and partially due to the TIS focus on small cells. Additional experience is necessary, for both the cytotechnologist and pathologist, for accurate classification of these smaller cells.

We also believe that a more important measurement of laboratory performance of new technology is the ASC to SIL

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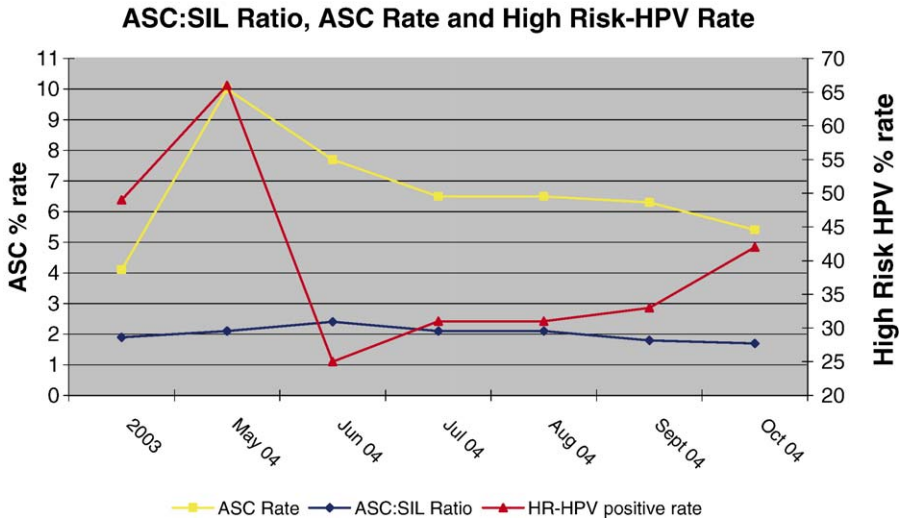

Fig. 1. ASC:SIL ratio, ASC rate and high risk-HPV rate.

ratio. This ratio reflects disease prevalence and is the laboratory statistic that is tracked and reported to regulatory agencies. The implementation of the TIS did not adversely affect the ASC:SIL ratio and showed a slight improvement at the conclusion of data collection. Currently, we have maintained an ACS rate of 5.3%.

There was no difference in the detection of glandular lesions. This may be a result of the relatively small sample size and the inherently low prevalence of glandular lesions.

A previously published study based on the clinical trial data submitted to the FDA for pre-market approval [6] showed a statistically significant improvement in sensitivity for ASC-US+ lesions and a statistically significant improvement in specificity for high-grade lesions. This study showed a slight but not statistically significant increase in sensitivity for HSIL but was based on a smaller sample size than the current study. Preliminary data presented at the 2004 Annual Meeting of the American Society of Cytopathology showed a range of improvements in sensitivity, specificity, false negative fraction and biopsy correlation [10,11]. Our laboratory statistics confirm the early analysis and literature findings.

Under TBS 2001, both infections as well as endometrial cells in women over 40 are categorized as Negative for intraepithelial lesions or malignancy. In our laboratory, separate statistics are not maintained for these entities. No noticeable change was observed in these diagnostic categories during the study period. This is consistent with adequacy and infection detection reported by Biscotti et al. [6].

As with the introduction of any new technology, there are invariably challenges to overcome and learning curves. In the case of the ThinPrep Imaging System, both the cytotechnologist and pathologist must become accustomed to a new Pap stain, this is a significant challenge when we consider that cytology is as much an interpretive art as a science based on a visual representation. In addition, to stain, extra care must applied to the cover slipping process. Air bubbles are the most frequent contributor for the Imager to not read a slide, requiring full manual review. Our TIS rejection rate is approximately similar to, or less than the 7.1% reported in the TIS package insert. Although specific data are not available, our laboratory policy is to investigate any stain batch in which the rejection rate exceeds 5% and this was, and still is, an infrequent event.

Though not a focus of this study, we noted there was no appreciable change in cytotechnologist screening rates or productivity. In 2003, an average of 77 slides were screened per tech per day (range 56–99). During the study period in 2004, an average of 78 slides were screened per tech per day (range 61–111).

Our results suggest that the ThinPrep Imaging System has successfully combined modern computer technology and image analysis with the unique human interpretive skills of the cytotechnologist and pathologist. Overall, we believe this technology will make a significant contribution to cervical cancer screening and patient management.

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