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Evaluation of CellSolutions BestPrep® Automated Thin-Layer Liquid-Based Cytology Papanicolaou Slide Preparation and BestCyte® Cell Sorter Imaging System

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Key Words
BestCyte® · BestPrep® · Cancer screening · Cervix · Cytology · Human papillomavirus · Imaging systems

Abstract
Objective: A double-blind study was conducted to compare the performance of the new BestPrep® (CellSolutions) liquid-based thin-layer Papanicolaou (Pap) test with ThinPrep® (Hologic). ***Study Design:*** Samples from the study patients (n = 105) were collected twice in the same encounter with the ThinPrep sample always taken first and the BestPrep sample collected second. Slides were prepared according to both manufacturers' protocols and evaluated using manual microscopic review and the BestCyte® cell sorter imaging system (CellSolutions). Diagnostic truth for each case was determined by independent manual review of both slides by multiple pathologists and histology when available. The presence of atypical squamous cells of undetermined significance was the threshold for positive for sensitivity and specificity calculations. ***Results:*** BestPrep and ThinPrep, by manual review, had sensitivities for high-grade squamous intraepithelial lesion (HSIL) cases of 100 and 95.6%, respectively. Using the BestCyte cell sorter, both had 100% sensitivity. For the same HSIL cases, the *digene* HC2 high-risk human papillomavirus DNA test had sensitivities of 100% (BestPrep) and 95.6% (ThinPrep). Specificities were 71.4% (BestPrep) and 54.8% (ThinPrep). ***Conclusions:*** BestPrep was equivalent to ThinPrep for manual review even though BestPrep was always the second sample collected. The BestCyte cell sorter provides a practical alternative to manual review for both BestPrep and ThinPrep slides.

Introduction

Liquid-based thin-layer Papanicolaou (Pap) smears have become the standard primary preparation for cervical cytology in most of the developed world replacing conventional Pap smears. The two major competitors in the liquid-based cervical cytology market, ThinPrep® (Hologic, Bedford, Md., USA) and SurePath (Becton Dickinson, Burlington, N.C., USA), offer both automated slide preparation and image analysis (automated screening). Automated screening, as a primary screen or prescreen for normal cases, is now accepted in many cytology laboratories, with manual follow-up of cases determined to be abnormal. CellSolutions LLC (Greensboro, N.C., USA) is a new entrant into this competition to im-

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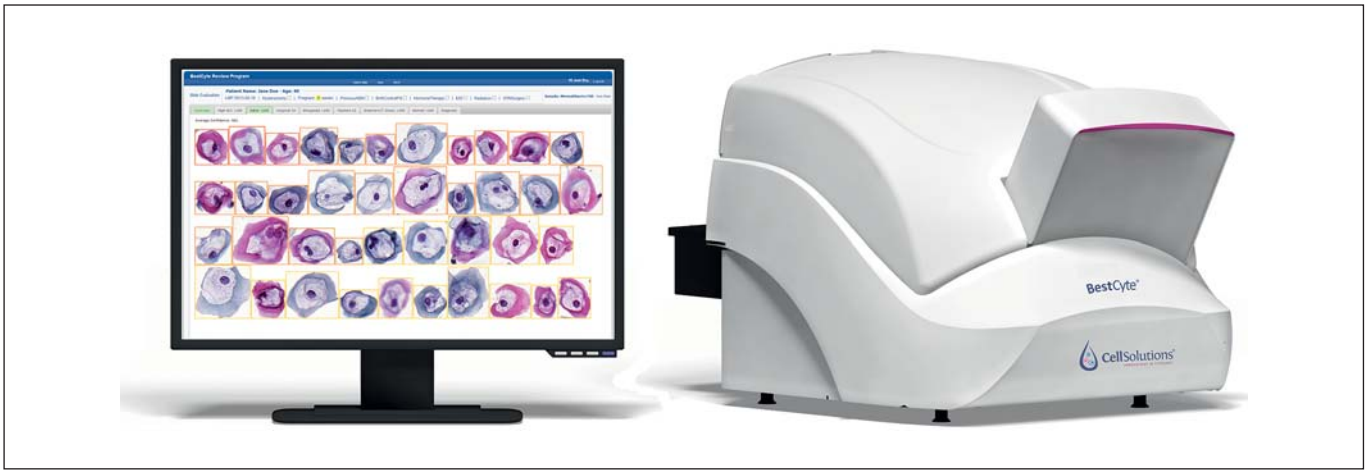

Fig. 1. Slide scanner and BestCyte® cell sorter.

prove cytology and is offering an automated liquid-based Pap test preparation (BestPrep®) and an automated interactive digital slide imaging system (BestCyte® cell sorter) as a primary screening device.

The BestPrep process starts with the collection of the cervical cytology sample using a Rovers brush (Rovers Medical Devices B.V., Oss, The Netherlands). The head of the collection device is then placed into the BestPrep collection vial containing 10 ml of the BestPrep ethanol-based liquid preservative. The collected specimen is transferred to centrifuge tubes, and the cells are concentrated by precentrifugation. The cell pellet is resuspended based on cellularity determined by the automated measurement of the cell pellet size, and the BestPrep Pap slide is then prepared automatically using the BestPrep preparation device (CS-30 or CS-120). The BestPrep includes positive sample identification and barcoding. Staining and coverslipping are done independently based on the method chosen by the laboratory.

The BestCyte cell sorter is a very high-speed automated digital cytology scanner and imaging software that sorts and displays digital images on a high-resolution monitor (2,560 × 1,440 pixels; fig. 1). The system scans and saves the digital image of the entire cell deposition area and then selects, sorts and presents selected cells and cell clusters in galleries based on predefined cytological classifications (fig. 2–4). In addition to the review of the galleries, the user also has the capability to do a full slide review of the virtual digital slide image. The two other cytology imaging systems, BD FocalPoint GS Imaging System and ThinPrep Imaging System, relocate 10–22 entire fields of view on a microscope (hundreds to thousands of cells) without marking or presenting specific potentially abnormal cells or groups of cells [1, 2]. With the BestCyte cell sorter, the entire digital slide and selected potentially abnormal cells and cell groups are displayed in high resolution for the reviewer. Consequently, the cytologist is given a strong indication of the number of abnormal cell types and therefore evidence as to the degree of abnormality. Since saved images of the entire cell deposition area are available for review with the BestCyte cell sorter, the actual glass slide is not required in most cases, thus allowing for remote screening from any location using a web browser. As with the glass slide, the reviewer is able to pan and scan the digital image for determination of adequacy and the presence of organisms.

This study was designed to evaluate the new automated liquid-based thin-layer Pap slide preparation BestPrep against the ThinPrep Pap test as the predicate method. The ThinPrep sample was always collected first in this study. The relative sensitivities and specificities of the two liquid-based thin-layer cytology methods, ThinPrep and BestPrep, were compared using both manual screening and BestCyte cell sorter imaging review. Using the same patient cohort, this study also compared sensitivities and specificities for the *digene* HC2 high-risk human papillomavirus (HPV) test (Qiagen, Gaithersburg, Md., USA) between the two liquid-preserved samples (ThinPrep and BestPrep).

Materials and Methods

A double-blind, institutional review board-approved study was conducted to compare the performance of the new BestPrep (CellSolutions) liquid-based thin-layer Pap test with ThinPrep (Holog-

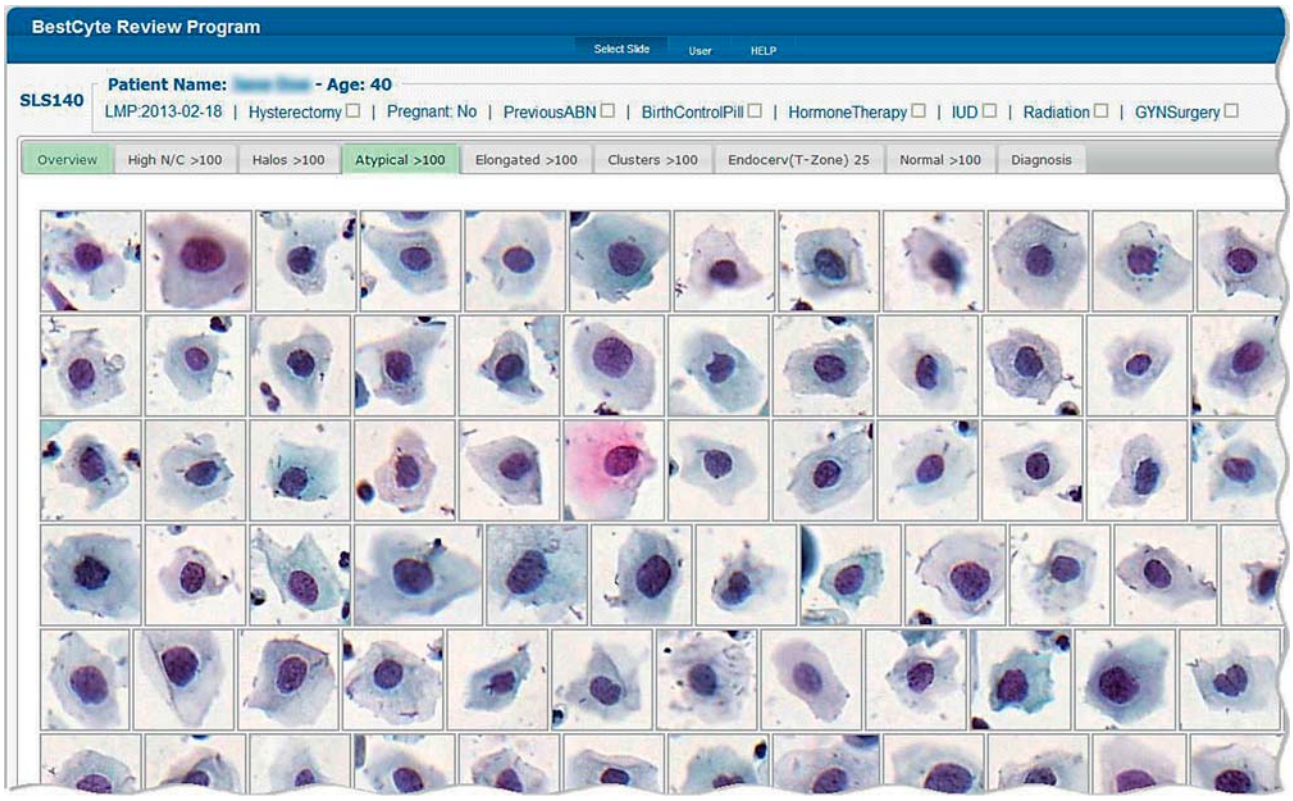

Fig. 2. Example of an atypical gallery on the BestCyte cell sorter.

ic). The patient cohort in this study included 105 women aged 21–84 years (mean age: 41 years). Many of the women had been referred to colposcopy due to a prior abnormal Pap test or were considered to be at high risk for abnormality. Pap tests were performed at two hospitals, the University Hospital of Liège (site N.-D. des Bruyères) and the Citadelle Regional Hospital, by gynecologists or their professional staff who were trained in the collection of cervical cytology samples using a Rovers Cervex-Brush®. Although the data presented are based on only 105 paired samples, the study cohort provided enriched sampling of abnormal cells due to the number of patients with prior clinical diagnoses of abnormality, thus allowing for a smaller sample size in this preliminary evaluation.

In the collection of the samples, two separate Rovers Cervex-Brushes were used, one for the ThinPrep sample and one for the BestPrep sample. In every case, the BestPrep sample was always taken second, which usually implies the disadvantage of acquiring only residual exfoliated cells and possibly additional blood [3, 4]. This recognized disadvantage in sampling was tolerated to allow collection of the ThinPrep sample per current methodology and for reporting of patient results per accepted institutional practice. In both cases, the manufacturers' recommendations were followed for slide preparation.

The six cytotechnologists and two cytopathologists who were involved in the study were blinded as to patient identity, and slides were randomized for review. Study participants did not have access to the identification key for the slides. As with routine laboratory practice, both slide types (ThinPrep and BestPrep) were initially screened manually by the cytotechnologists, and all slides determined to be abnormal were reevaluated and diagnosed by the cytopathologists.

Following manual evaluation, both slide types (ThinPrep and BestPrep) were cleaned of all markings and subsequently microscopically scanned and imaged with the BestCyte cell sorter imager. This imaging device, developed by CellSolutions LLC, automatically scans the entire cell deposition area of the slide (≈300 mm^2 or 15 × 20 mm for BestPrep and ≈314 mm^2 or 20 mm in diameter for ThinPrep), using a ×20 objective and a high-resolution CCD digital camera. The digital images are saved and simultaneously analyzed by the BestCyte classifier software, which has been developed to recognize normal and abnormal cells and clusters. The software then selects and sorts cells and cell clusters based on cell appearance characteristics for display in image galleries. Images are then reviewed by cytology professionals using the interactive user interface.

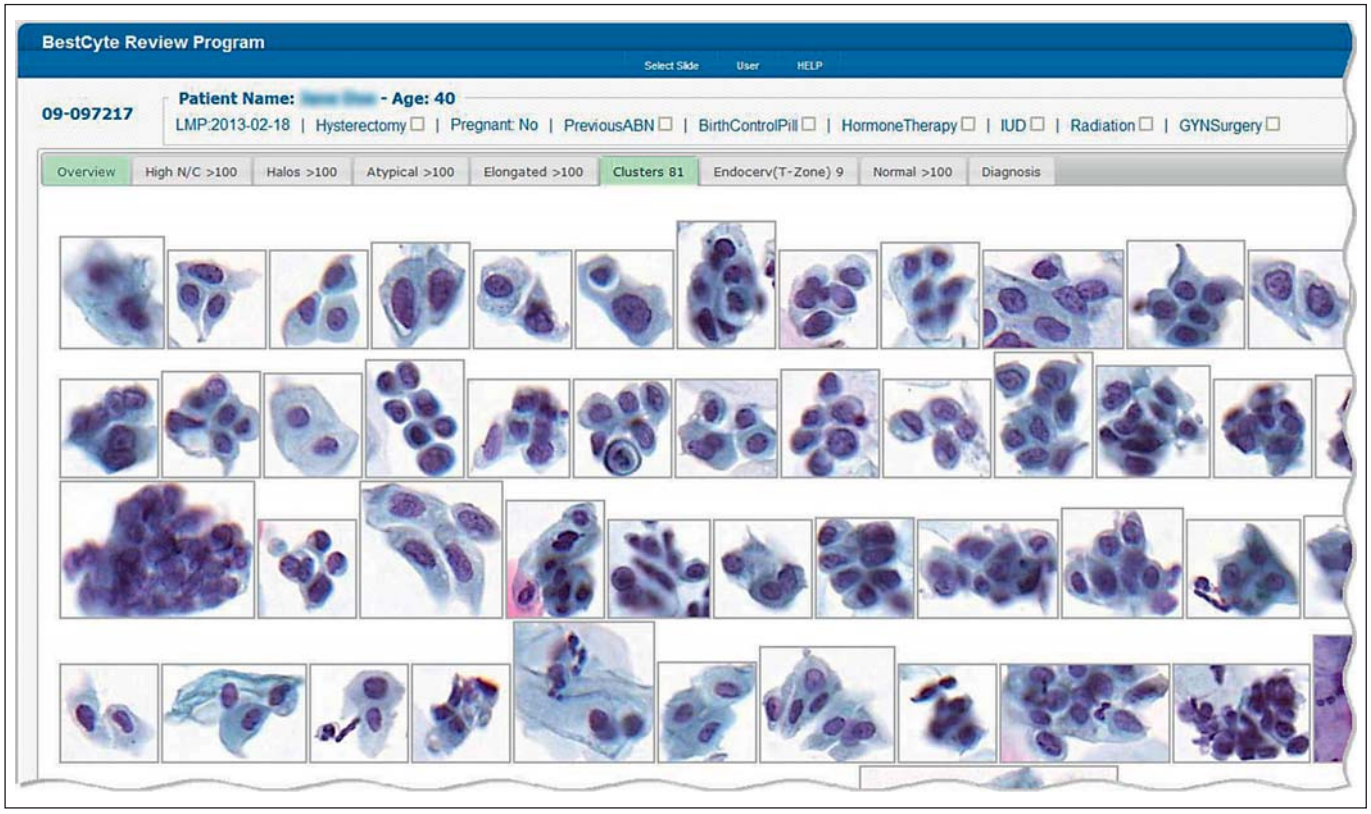

Fig. 3. Example of cell clusters in gallery on the BestCyte cell sorter.

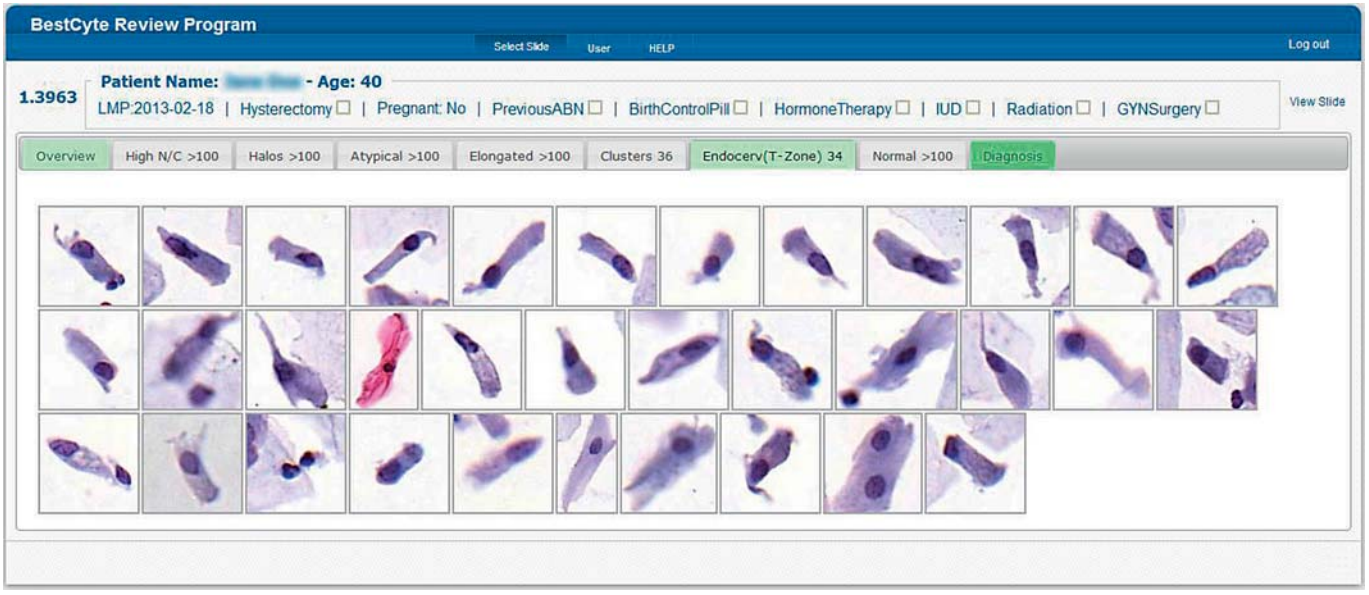

Fig. 4. Example of an endocervical gallery on the BestCyte cell sorter.

Unlike the ThinPrep imaging system, which provides 22 selected field-of-view locations for review with the actual glass slide, image review with the BestCyte cell sorter is conducted using the digital image alone for most cases, without the requirement for the actual glass slide to be present during review. Additionally, the BestCyte cell sorter imager was designed to facilitate current laboratory practice for manual review by providing the entire slide image as well as selected cells in the image galleries.

The BestCyte does not automatically annotate cells and cell clusters, but it essentially annotates cells and cell clusters by placement in specific galleries based on cell characteristics. In addition, there is an annotation tool that allows users to electronically mark and specifically annotate cells of interest similar to the practice of dotting an actual glass slide. Once annotated, these specific annotations are then available to all follow-on reviewers, including the pathologist. However, annotations may be modified at the discretion of a more senior reviewer. For determination of adequacy and presence of organisms, selected fields of view are displayed. These or the whole slide image allow the reviewer to scan and pan all or part of the entire cell deposition area similar to a manual review. For case diagnosis, the BestCyte cell sorter provides selections from a diagnostic result window that includes all of the Bethesda cytology classifications for diagnosis by the primary, quality control and pathologist reviewers. Image review using the ThinPrep Imaging System was not part of this study.

The dual collection from the same patient into two different types of cytological preservatives, gynecological not general (GYN) cytology preservative (CellSolutions) and PreservCyt (Hologic), afforded the opportunity to do a comparison of HPV sensitivity and specificity between the two preservative media using residual cell material following slide preparation. For HPV testing, the *digene* HC2 high-risk HPV DNA test was used according to the approved protocol for ThinPrep and a slightly modified protocol provided for BestPrep.

Diagnostic truth for each case (paired ThinPrep and BestPrep slides from the same patient) in the study was based upon agreement of diagnostic category (using established Bethesda classifications) between two cytopathologists. For most of the abnormal cases, current histology results were available to support diagnostic truth for the cases. Any new abnormal determination from the image review was adjudicated based on the manual review results by multiple cytologists reviewing both slides and images as necessary.

For statistical analysis, the cases were grouped according to the determined Bethesda diagnostic truth for each case. Sensitivity was then calculated for each preparation method (ThinPrep vs. BestPrep), and low- (LSIL) and high-grade squamous intraepithelial lesion (HSIL) cases. In like fashion, manual and imaging results were compared for the same slides. Likewise, specificity was calculated for the two preparation methods and screening methods based on the number of true-negative cases and the number of false-positive cases for all negative 'truth' cases. Sensitivity and specificity for HPV results (positive vs. negative results) for specimens collected in the two types of preservative fluid (ThinPrep PreservCyt vs. GYN cytology preservative) were also calculated.

Confidence intervals (CI) for estimates of sensitivity and specificity were calculated using the binominal distribution (i.e. they were exact CI). All CI provide an estimated interval within which we can be 95% confident that the actual sensitivity or specificity occurred.

Table 1. ThinPrep manual versus BestPrep manual (HSIL is truth for the cases – ASC-US is the threshold for positive)

	BestPrep manual							
	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	UNSAT	total
ThinPrep manual								
NILM						1		1
ASC-US		1						1
AGC								
LSIL								
ASC-H						2		2
HSIL				1	2	16		19
UNSAT								
Total		1		1	2	19		23

AGC = Atypical glandular cells of undetermined significance; ASC-H = atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesions; NILM = negative for intraepithelial lesions or malignancy; UNSAT = unsatisfactory. ThinPrep manual sensitivity: 95.6% (95% CI = 78.1–99.9%). BestPrep manual sensitivity: 100% (95% CI = 85.2–100%).

Table 2. ThinPrep manual versus BestPrep manual (LSIL is truth for the cases – ASC-US is the threshold for positive)

	BestPrep manual							
	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	UNSAT	total
ThinPrep manual								
NILM	3	1	1	1		1		7
ASC-US		1		1				2
AGC								
LSIL	1	2		12	2	3		20
ASC-H								
HSIL					1			1
UNSAT	1	2			2			5
Total	5	6	1	14	5	4		35

See table 1 for abbreviations. ThinPrep manual sensitivity: 80.0% (95% CI = 63.1–91.6%). BestPrep manual sensitivity: 85.7% (95% CI = 69.7–95.2%).

Results

The overall preparation quality and cell presentation were comparable between the ThinPrep and BestPrep slides. Specimen adequacy and the recovery of endocervical cells and infectious agents were similar between the two preparation methods. There were 7 unsatisfactory ThinPrep slides and 2 unsatisfactory BestPrep slides in the manual review arm of the study (statisti-

Table 3. BestPrep manual versus BestPrep BestCyte (HSIL is truth for the cases – ASC-US is the threshold for positive)

	BestPrep BestCyte							
	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	UNSAT	total
BestPrep manual								
NILM								
ASC-US		1						1
AGC								
LSIL						1		1
ASC-H					1	1		2
HSIL		3		1	1	14		19
UNSAT								
Total		4		1	2	16		23

See table 1 for abbreviations. BestPrep manual sensitivity: 100% (95% CI = 85.2–100%). BestPrep BestCyte sensitivity: 100% (95% CI = 85.2–100%).

Table 4. BestPrep manual versus BestPrep BestCyte (LSIL is truth for the cases – ASC-US is the threshold for positive)

	BestPrep BestCyte							
	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	UNSAT	total
BestPrep manual								
NILM	2	3						5
ASC-US		2		2	1	1		6
AGC	1							1
LSIL	1	2		8		3		14
ASC-H		1			3	1		5
HSIL	1			3				4
UNSAT								
Total	5	8		13	4	5		35

See table 1 for abbreviations. BestPrep manual sensitivity: 85.7% (95% CI = 69.7–95.2%). BestPrep BestCyte sensitivity: 85.7% (95% CI = 69.7–95.2%).

Table 5. ThinPrep manual versus ThinPrep BestCyte (HSIL is truth for the cases – ASC-US is the threshold for positive)

	ThinPrep BestCyte							
	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	UNSAT	total
ThinPrep manual								
NILM							1	1
ASC-US		1						1
AGC								
LSIL								
ASC-H				1			1	2
HSIL		4		1	1	12	1	19
UNSAT								
Total		5		2	1	12	3	23

See table 1 for abbreviations. ThinPrep manual sensitivity: 95.6% (95% CI = 78.1–99.9%). ThinPrep BestCyte sensitivity: 100% (95% CI = 85.2–100%).

Table 6. ThinPrep manual versus ThinPrep BestCyte (LSIL is truth for the cases – ASC-US is the threshold for positive)

	ThinPrep BestCyte							
	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	UNSAT	total
ThinPrep Manual								
NILM	5						2	7
ASC-US		2						2
AGC								
LSIL	2	2		14		2		20
ASC-H								
HSIL						1		1
UNSAT					1		4	5
Total	7	4		14	1	3	6	35

See table 1 for abbreviations. ThinPrep manual sensitivity: 80.0% (95% CI = 63.1–91.6%). ThinPrep BestCyte sensitivity: 80.0% (95% CI = 63.1–91.6%).

cally significant, p = 0.05). In the imaging arm of the study, unsatisfactory slide determinations were always referred to manual microscopic evaluation along with any imaged slide that was selected for manual review by either a cytotechnologist or cytopathologist. Selection for manual review is done when the result from the image review yields an uncertain diagnostic outcome. In this study, there were 9 ThinPrep cases and 7 BestPrep cases marked for manual review by one or more of the cytologists performing image review. In these cases, the manual result was also used for the image-based determination.

Sensitivity and specificity calculations for the two preparation and screening methods are reported and compared in tables 1–7 grouped according to diagnostic truth using the Bethesda classifications listed. Sensitivity and specificity calculations for the HPV test results from cytological collections made from ThinPrep versus BestPrep preservative fluid are shown in tables 8 and 9.

Table 7. Specificity for four methods evaluated (negative is truth for these cases – ASC-US is the threshold for positive)

	ASC-US	AGC	LSIL	ASC-H	HSIL	Specificity (95% CI)
ThinPrep manual	4		1			88.1% (74.4–96.0%)
ThinPrep BestCyte	2					95.2% (83.8–99.4%)
BestPrep manual	4		1			88.1% (74.4–96.0%)
BestPrep BestCyte	2			1		92.8% (80.5–98.5%)

AGC = Atypical glandular cells of undetermined significance; ASC-H = atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesions. In 42 cases, truth was negative.

Table 8. HPV sensitivity for both PreservCyt and CellSolutions GYN cytology preservative for cases that are ASC-US+ (truth for the cases are shown)

Truth	Hologic PreservCyt			CellSolutions preservative		
	pos.	neg.	sensitivity (95% CI)	pos.	neg.	sensitivity (95% CI)
HSIL+	22	1	95.6% (70–99.9%)	23	0	100% (85.2–100%)
LSIL	30	5	86% (69.7–95.2%)	31	4	88.6% (74.8–96.4%)
ASC-US	2	2	50.0% (6.8–93.2%)	2	2	50.0% (6.8–93.2%)

Table 9. HPV specificity for both PreservCyt and CellSolutions GYN cytology preservative (42 cases had HPV tests with truth for the cases being negative)

	Neg. truth cases	Neg. HPV test	Pos. HPV test	Specificity (95% CI)
PreservCyt	42	23	19	54.8% (47.1–62.4%)
CellSolutions	42	30	12	71.4% (64.5–78.4%)

Discussion

In this study, the predicate method, ThinPrep, always had the advantage of being the first sample collected, with BestPrep always relegated to the second collection. It is widely accepted that the first sample, in situations where abnormal cells are scarce, is more likely to contain the abnormal material. The second sample has a greater likelihood to contain blood, which can obscure cells on the preparation. In spite of this disadvantage, the data suggest that this had no effect on BestPrep.

As can be seen in the tables 1–7, there is an excellent agreement of sensitivities and specificities for both preparations and both methods of analysis when the presence of atypical squamous cells of undetermined significance (ASC-US) is used as the threshold for positive. Diagnostic accuracy as to the specific Bethesda classification is similar for both study arms with some variation as to specific diagnostic interpretation as is typical of cytology diagnoses among different preparations and different reviewers. Variation in the specific Bethesda diagnosis from the 'truth diagnosis' was greater using the BestCyte. This may be expected to improve with better training and more experience in diagnostic image review (tables 3–6).

The BestCyte cell sorter timed operator involvement with image review for each slide. For the majority of cases, review time was between 0.5 and 3 min per slide. Cytotechnologists typically screen between 40 and 100 slides per day – with an average manual review time per slide ranging from 5 to 10 min [5]. When one considers that study cytotechnologists had limited experience using BestCyte cell sorter, this suggests that much less time may be spent using BestCyte image review than with traditional microscopic screening. Image-based evaluation

may have a varied learning curve impacting users in different ways. Individual performance, such as speed and perceived user friendliness, may well depend on personal experience with computers, digital pathology and the number of years of experience with conventional cytology screening.

HPV results from cytological collections made from ThinPrep versus BestPrep preservative fluid are shown in tables 8 and 9. The HPV test results from GYN cytology preservative fluid were slightly more specific and in better agreement with cytological evaluation than HPV testing from ThinPrep PreservCyt.

The review of performance of the BestCyte cell sorter suggests that the BestCyte offers an efficient way to screen slides in that it reduces screening time to less than half of the time typically spent screening slides manually. Sensitivities, using ASC-US+ as the diagnostic threshold of positive, shows similar sensitivity and specificity to manual microscopic evaluation. This study suggests that the BestCyte cell sorter may play a role in improving efficiency and productivity in the evaluation of both ThinPrep and BestPrep liquid-based thin-layer slides.

When ASC-US+ is used as the cutoff for positivity, cytological evaluation by either method (BestPrep or ThinPrep) is similar to *digene* HC2 high-risk HPV DNA testing as to sensitivity and better than HPV testing relative to specificity. This is not a new finding. If one reviews the literature, as Nanda et al. [6] reported in a previous publication, cytology often performs well in sensitivity and specificity in quality laboratories using typical ASC-US standards of interpretation with ASC-US as the positive cutoff. As an example of achievable cytology sensitivity and specificity, Bolick and Hellman [7] reported sensitivity for ThinPrep LSIL+ for cervical intraepithelial neoplasia (CIN) 2–3 cases or higher of 94.2% and specificity of 57.7% [8]. Zhao et al. [9] reported that verification bias-adjusted Pap screening sensitivity was 93% in the cytology laboratory of Magee-Womens Hospital. In a recent publication, Pan et al. [10] reported sensitivities and specificities using liquid-based cytology in a very large trial. Sensitivity and specificity for cytology was 81 and 95.4% for CIN 2+ and 88.5 and 94.3% for CIN 3+. Often when cytology is perceived as having lower sensitivity, laboratory quality and interpretation strategies should be scrutinized (e.g. ASC-US calls may be discouraged, a less-sensitive image-based prescreener may be in use or a higher cutoff than ASC-US was used).

Data generated in this study suggest that both cytology and HPV testing can be equivalent as to sensitivity, and both therefore may be suitable for prescreening or 'first-test' methods, but it demonstrates that HPV testing alone is less specific. Certainly, positive HPV tests should be followed by cytology because of the characteristic low specificity of HPV. Both tests are complementary, sometimes adding valuable, clarifying data points that may be important to consider before referring to colposcopy and biopsy. This study suggests reconsideration of screening with both methods when the greatest diagnostic sensitivity and specificity are mandated, and when costs are not an issue. Screening sensitivities of HPV testing are not always high, as evidenced in the FDA Summary of Safety and Effectiveness Data (SSED) for the recent Roche cobas HPV test (ATHENA Evaluation; Roche Molecular Systems, Inc., Pleasanton, Calif., USA) where HPV screening sensitivity for all CIN 3+ cases was only 58.26% (95% CI: 44.02–74.37%) for women ≥25 years (table 39 from SSED) and 53.56% (95% CI: 36.79–76.01%) for women aged ≥30 (table 40 from SSED) [11]. Regarding costs, the respective costs of either method, cytology or HPV testing, should be a major determinant in cost-restrained screening programs. Both prescreening costs, and the number and costs of 'follow-on' second tests need to be carefully determined. New methods that impact costs and performance should also be taken into consideration before making final decisions. Cytology supply pricing is adjusting downward as new products offer competitive options. HPV test reagents are usually expensive compared to cytology. When HPV alone is performed as the primary test, the additional costs of cytology follow-up on high numbers of samples and the possibility of an additional collection is mandated by the poor specificity of HPV. If cytology is performed in a quality laboratory with similar sensitivities to those of HPV, the cost of a secondary test is less frequently required.

Cytology has, without question, improved women's health and reduced morbidity [12]. It is the most successful cancer screening test for decades and the standard of achievement among all efforts to eradicate high-incidence types of cancer. At this point, cytology, as opposed to HPV, has the distinct advantage of suggesting the degree of potential abnormality based upon the level of cellular dysplasia that is visible microscopically. Cytology results often directly correlate to histopathology diagnoses as both are based on observed morphologic changes in cells. Microscopy can also supply other important diagnostic information, such as evidence of active infections involving HPV, trichomonas, candida, herpes, bacteria and other infectious agents. These microscopic observations of active infection are available at no additional cost with cytology. Cytology has continued to

improve academically and commercially over time through new technology innovation, including advances in preservatives, preparation quality, imaging and molecular diagnostics. These improved new technologies are in various stages of implementation and can be expected to improve further as to sensitivities, specificities and predictive outcomes. Care should be taken to weigh all new technology carefully and thoughtfully as to actual quality contributions and real cost benefits before altering the long-established, proven diagnostic paradigm and the resulting benefits that are correctly attributed to cytology and Pap screening.

This study demonstrated the excellent sensitivity and specificity of cytology achievable with both traditional microscopic screening and a new approach, involving review of high-resolution digital images selected and sorted according to cell characteristics. In this study, cytology-based sensitivities were as good as those achieved using molecular testing for HPV-DNA. Cytology specificity, as in most comparisons, was better than that of the HPV-DNA testing.

The performance of the new CellSolutions BestPrep was equivalent to that of the Hologic ThinPrep for manual screening even though BestPrep was always relegated to the second sample collection. The BestCyte cell sorter appears to be a practical alternative to manual microscopic evaluation of both BestPrep and ThinPrep slide preparations.

Disclosure Statement

CellSolutions and Klinipath supplied reagents, materials and financially supported some of the labor involved in the study. Qiagen supplied the *digene* HC2 high-risk HPV DNA test kits.

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