AutoCyte PREP™ SYSTEM (formerly CytoRich® PREPARATION PROCESS)

For In Vitro Diagnostic Use

INTENDED USE

The AutoCyte PREP™ System is a liquid-based thin-layer cell preparation process. The AutoCyte PREP System produces slides that are intended as replacements for conventional gynecologic Pap smears. AutoCyte PREP slides are intended for use in the screening and detection of cervical cancer, pre-cancerous lesions, atypical cells and all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses.[1]

SUMMARY AND EXPLANATION OF THE PROCEDURE

The AutoCyte PREP System converts a liquid suspension of a cervical cell sample into discretely stained, homogeneous thin-layer of cells while maintaining diagnostic cell clusters.[2-9] The process includes cell preservation, randomization, enrichment of diagnostic material, automated pipetting, sedimentation and staining to create an AutoCyte PREP slide. The AutoCyte PREP instrument is a robotic pipetter that automatically performs the mixing, transfer, sedimentation, and discrete staining portions of the process. The result is an AutoCyte PREP slide for use in routine cytology screening and categorization as defined by The Bethesda System.[1] The AutoCyte PREP presents a well preserved population of stained cells present within a 13 mm diameter circle. Air-drying artifact, obscuring, overlapping cellular material and debris are largely eliminated. The numbers of white blood cells are significantly reduced, allowing for the easier visualization of epithelial cells, diagnostically relevant cells and infectious organisms.

The AutoCyte PREP process begins with qualified medical personnel using a broom-type sampling device (e.g. Cervex-Brush®, Rovers Diagnostic Devices, Oss, The Netherlands) to collect a gynecologic specimen. Rather than smearing cells collected by the sampling device on a glass slide, the entire head of the broom is removed from the handle and placed into a vial of CytoRich® Preservative Fluid. The vial is capped, labeled and sent with appropriate paperwork to the laboratory for processing.

In the laboratory, the preserved sample is mixed by vortexing and dispersed using the AutoCyte PREP CyRinge and transferred onto CytoRich® Density Reagent. An enrichment step, consisting of centrifugal sedimentation through Density Reagent, partially removes non-diagnostic debris and excess inflammatory cells from the sample. After centrifugation, the tube containing the enriched cellular component is placed on the AutoCyte PREP instrument. The pelleted cells are robotically resuspended, mixed and transferred to an AutoCyte PREP Settling Chamber mounted on a microscope slide

coated with CytoRich® Slide Coat to enhance cell adhesion. The cells are sedimented by gravity, then discretely stained by the AutoCyte PREP instrument using a modified Papanicolaou staining procedure. The slide is cleared with xylene or a xylene substitute and coverslipped. The cells, presented within a 13 mm diameter circle, are microscopically examined by trained cytotechnologists and pathologists with access to other relevant patient background information.

LIMITATIONS

- Gynecologic specimens for preparations using the AutoCyte PREP System should be collected using a broom-type sampling device according to the standard collection procedure provided by the manufacturer.
- Training by authorized persons is a prerequisite for the production and evaluation of AutoCyte PREP slides. Cytotechnologists and pathologists will be trained in morphology assessment on the AutoCyte PREP slides. Training will include a proficiency examination. Laboratory customers will be provided with the use of instructional slide and test sets. AutoCyte will also provide assistance in the preparation of training slides from each customer's own patient populations.
- AutoCyte PREP System supplies include the following: CytoRich Preservative Fluid Collection Vials, CytoRich Density Reagent, CytoRich Slide Coat, AutoCyte PREP CyRinges, AutoCyte PREP Settling Chambers and AutoCyte PREP Microscope Slides. Proper performance of the AutoCyte PREP System requires the use of only those supplies listed above; substitution with other supplies not listed above will compromise the performance of the product and cannot be supported by AutoCyte, Inc. Used supplies should be disposed of properly in accordance with institutional and governmental regulations.
- All supplies are intended for single use only and cannot be reused.

WARNINGS

- CytoRich® Preservative Fluid contains a dilute solution of denatured ethanol and is not intended for human consumption. The mixture contains small amounts of methanol and isopropanol which can be harmful and may cause blindness if ingested.
- CytoRich® Density Reagent contains sodium azide. Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. On disposal, flush with a large volume of water to prevent buildup of azide. For further information, refer to publication DHHS (NIOSH) No. 78-127 Current 13 issued by the Centers for Disease Control. See website:www.cdc.gov/niosh/78127_13.html.

PRECAUTIONS

- Good laboratory practices should be followed and all procedures for use of the AutoCyte PREP System should be strictly observed.
- Reagents should be stored at room temperature (15° to 30° C) and used prior to their expiration dates to assure proper performance. The storage condition for CytoRich Preservative Fluid *without* cytologic samples is up to 30 months from date of manufacture at 15° to 30° C. The storage limit for CytoRich Preservative Fluid *with* cytologic samples is 6 months at 2° to 10° C.
- Avoid splashing or generating aerosols. Operators should use appropriate hand, eye and clothing protection.
- CytoRich® Preservative Fluid was tested for antimicrobial effectiveness against: *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans* and *Aspergillus niger* and found to be bactericidal. CytoRich Preservative samples inoculated with 10^6 organism of each species yielded no growth after 7 days incubation under standard conditions. However, universal precautions for safe handling of biological fluids should be practiced at all times.
- Failure to follow recommended procedures as outlined in the AutoCyte PREP System Operator's Manual may compromise performance.

MATERIALS REQUIRED

Refer to the Operators Manual of the AutoCyte PREP System for complete information concerning reagents, components and accessories.

Materials Provided

- The AutoCyte PREP System
- CytoRich® Preservative Fluid Collection Vial
- Cervex-Brush® (Rovers Diagnostic Devices, Oss, The Netherlands)
- CytoRich® Preservative Fluid
- CytoRich® Density Reagent
- CytoRich® Slide Coat
- AutoCyte PREP CyRinges
- AutoCyte PREP Settling Chambers
- Cytology Stain Kit

- AutoCyte PREP Glass Slides
- Centrifuge Tubes
- Slide and Tube Racks
- Disposable Transfer and Aspirator Tips

Materials Required But Not Provided

- Vortex Mixer
- Deionized Water (pH 7.5 to 8.5)
- Isopropanol and Reagent Grade Alcohol
- Plastic Coplin Jars or Slide Tank
- Clearing Agent, Mounting Media and Glass Coverslips

Storage

The storage condition for CytoRich Preservative Fluid *without* cytologic samples is up to 30 months from date of manufacture at 15° to 30° C.

The storage limit for CytoRich Preservative Fluid *with* cytologic samples is 6 months at 2° to 10° C.

PROCEDURE

- Complete procedures for preparing AutoCyte PREP slides are provided in the Operation Manual for the AutoCyte PREP System.

DIAGNOSTIC INTERPRETATION AND PREPARATION ADEQUACY

- After AutoCyte authorized user training, the Bethesda System cytologic diagnostic criteria currently utilized in cytology laboratories for conventional Pap smears are applicable to AutoCyte PREP slides[1]. The exceptions are the criteria for adequacy of numbers of epithelial cells (see below).
- Any abnormal or questionable screening observations should be referred to a pathologist for review and diagnosis. The pathologist should note any diagnostically significant cellular morphologic changes.
- In the absence of abnormal cells, a preparation is considered unsatisfactory if one or more of the following conditions are present:
    1. Inadequate numbers of diagnostic cells (fewer than approximately 5,000 epithelial cells per preparation). The following are the recommended procedures for estimating the count of well-preserved

squamous epithelial cells on AutoCyte PREP slides:

- For each microscope model used in screening, examine the manufacturer's microscope manual or contact the microscope manufacturer to determine the area of the field of view using the preferred ocular and the 40x objective. Alternatively, calculate the Field Area using a hemocytometer or similar microscopic slide measurement scale (Field area = πr^2 where r is the radius of the field).
- The minimum average number of cells per 40x objective field should be determined by dividing the 130 mm^2 approximate cell deposition area of the AutoCyte PREP slide by the field area for the specific microscope. The resulting number is then divided into the 5000 cell minimum. The resulting number is the recommended minimum average adequacy number for epithelial cells in a 40x objective field of view. Record this number and keep it for routine reference use by the cytotechnologist.
- AutoCyte recommends that this minimum average adequacy number be checked for cases of scant cellularity in 5 to 10 randomly selected AutoCyte PREP fields of view.
- AutoCyte suggests avoiding fields that contain large clusters of cells, as this can distort the accuracy of the total cell count.
- As a practical means of assessing cellularity, macroscopic evaluation of the visual density of the stained preparation can be used to check the adequacy of preparation production runs. There is, however, no substitute for the primary microscopic evaluation by the cytotechnologist during the screening process.

2. 75% or more of the cellular components are obscured by inflammation, blood, bacteria, mucus or artifact which precludes cytologic interpretation of the slide.

PERFORMANCE CHARACTERISTICS: REPORT OF CLINICAL STUDIES

AutoCyte, Inc. conducted a prospective, masked, split-sample, matched-pair clinical investigation at multiple sites to compare the diagnostic results from the AutoCyte PREP with the conventional Pap smear. The objective of the study was to assess AutoCyte PREP performance as compared to the conventional Pap smear for the detection of cervical cancer, pre-cancerous lesions and atypical cells in various patient populations and laboratory settings. Adequacy was also assessed for both preparations.

Following the recommendations of the FDA "Points to Consider" document for Cervical Cytology Devices[10], each conventional Pap smear was prepared first, then the residual specimen remaining on the broom-type sampling device was deposited into a CytoRich® Preservative Fluid Collection Vial.

After transport to the laboratory, each preserved cell suspension was processed according to the AutoCyte PREP System protocol. The resulting AutoCyte PREP slide and the matching conventional Pap smear slide were screened manually and diagnosed independently using diagnostic categories consistent with The Bethesda System. At each site, a pathologist evaluated all abnormal slides.

Consistent with the method described by Shatzkin[11], this study used an independent reference pathologist at a designated referral site who reviewed all abnormal and discrepant cases, repair cases and 5% of the normal cases from all sites in a masked fashion to provide diagnostic "truth" for each case.

Patient Characteristics

The ages of women in the study ranged from 16 to 87 years, with 772 being post-menopausal. Of the 8,807 patients represented in the study, 1,059 presented a history of prior abnormal Pap smears. The entire patient population studied consisted of the following racial groups: Caucasian (44%), Black (30%), Asian (12%), Hispanic (10%), Native American (3%) and Other (1%).

Exclusions were made for incorrect paperwork, patients under age 16, patients with hysterectomies, and cytologically unsatisfactory and inadequate specimens. An effort was made to include as many cases of cervical cancer and pre-cancerous disease as possible by accessing high risk, infrequently screened and referral patients.

Of 10,335 total cases, 9,046 were accepted and evaluated across eight different study sites. Of those 9,046 cases, 8,807 met The Bethesda System requirements for preparation adequacy and were available for complete diagnosis of both preparations.

Clinical Study Results

- **First Split-Sample Study**

The goal of the clinical trial was to compare the performance of the conventional Pap smear and the AutoCyte PREP using diagnostic classification according to The Bethesda System. The study protocol was biased in favor of the conventional Pap smear because a conventional Pap smear was always prepared first, thereby restricting the AutoCyte PREP slide to residual material remaining on the broom-type device (the portion of the sample that normally would have been discarded)[12]. The intended use of the AutoCyte PREP is a direct-to-vial application where all collected cells will be available to the AutoCyte PREP.

To compare the sensitivities of the AutoCyte PREP and conventional Pap smear slides when read manually, the level of abnormality for the cases was determined by the

reference pathologist and compared to diagnoses made by the study sites. The reference diagnosis was based upon the most abnormal diagnosis of either slide preparation by the independent reference pathologist. This result was used as the "truth" diagnosis or reference value for the comparison of the site results using AutoCyte PREP System verses the conventional Pap smear. The null hypothesis that the sensitivities of the two methods of slide preparation are equivalent was tested using McNemar's chi-square test for paired data.[13] In this statistical test, discrepant results for the two preparation methods were compared.

Table 1 presents a direct comparison of all site results for AutoCyte PREP slides versus Conventional Pap smear slides for the diagnostic treatment categories Within Normal Limits (WNL), Atypical Squamous Cells of Undetermined Significance / Atypical Glandular Cells of Undetermined Significance (ASCUS / AGUS) Low-grade Squamous Intraepithelial Lesion (LSIL), High-grade Squamous Intraepithelial Lesion (HSIL) and Cancer (CA).

Table 1 **First Split-Sample Study: 8,807 Matched Samples – Site Results Comparison – No Reference Pathologist**

SITE NO.	RESULTS BY SITE							
	SLIDE TYPE	WNL	ASCUS	AGUS	LSIL	HSIL	CA	Total
1	PREP	873	56	2	42	5	0	978
	CONV	881	46	2	29	20	0	978
2	PREP	1514	47	4	81	24	0	1670
	CONV	1560	33	6	40	31	0	1670
3	PREP	668	15	1	13	7	0	704
	CONV	673	11	0	13	6	1	704
4	PREP	1302	60	2	19	5	0	1388
	CONV	1326	37	2	19	4	0	1388
5	PREP	465	25	1	5	1	0	497
	CONV	444	45	1	4	3	0	497
6	PREP	1272	179	6	83	35	1	1576
	CONV	1258	209	9	68	30	2	1576
7	PREP	438	66	17	13	14	23	571
	CONV	417	93	19	4	22	16	571
8	PREP	1227	61	3	86	44	2	1423
	CONV	1209	57	0	94	61	2	1423
Total	PREP	7759	509	36	342	135	26	8807
	CONV	7768	531	39	271	177	21	8807

Table 2 presents a direct comparison of all site results for AutoCyte PREP slides vs Conventional Pap smear slides for all diagnostic treatment categories.

Table 2 **First Split-Sample Study: 8,807 Matched Samples –All Site Results Comparison – No Reference Pathologist**

AUTOCYTE PREP	CONVENTIONAL						
	WNL	ASCUS	AGUS	LSIL	HSIL	CA	Total
WNL	7290	361	20	63	24	1	7759
ASCUS	343	101	4	44	15	2	509
AGUS	26	6	4	0	0	0	36
LSIL	87	52	2	147	53	1	342
HSIL	20	10	7	17	79	2	135
CA	2	1	2	0	6	15	26
Total	7768	531	39	271	177	21	8807

No independent reference pathologist results are reflected in **Table 1 or Table 2.**

Table 3 **First Split-Sample Study: Comparison of All Site Results for Cases Designated by the Reference Method as ASCUS/AGUS – Discordant Error Analysis**

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR		
	SUCCESS (ASCUS/AGUS)	ERROR (WNL & Reactive/Reparative)	Total
SUCCESS (ASCUS/AGUS)	113	205	318
ERROR (WNL & Reactive/Reparative)	180	229	409
Total	293	434	727

Result of McNemar test: $X^2mc = 1.62$, $p = 0.2026$
Errors Conventional: 205
Errors PREP: 180

Table 3 shows the results for cases identified by the reference pathologist to be ASCUS or AGUS. This evaluation allows analysis of the discordant errors to assess the sensitivity of the methods in the split-sample study design. Errors include WNL and Reactive / Reparative. Since the p-value determined by the McNemar test exceeded 0.05, the AutoCyte PREP and conventional Pap smear results were equivalent.

Table 4 First Split-Sample Study: Comparison of All Site Results for Cases Designated by the Reference Method as LSIL – Discordant Error Analysis

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR		
	SUCCESS (LSIL)	ERROR (WNL, Reactive/ Reparative & ASCUS/AGUS)	Total
SUCCESS (LSIL)	140	63	203
ERROR (WNL, Reactive/ Reparative & ASCUS/AGUS)	54	86	140
Total	194	149	343

Result of McNemar test: $X^2mc = 0.69$, $p = 0.4054$
Errors Conventional: 63
Errors PREP: 54

Table 4 shows the results for cases identified by the reference pathologist to be LSIL. Errors include WNL, Reactive / Reparative and ASCUS / AGUS. As with ASCUS/AGUS, the sensitivity of the two methods in the split-sample study was statistically equivalent with a p-value in excess of 0.05.

Table 5 First Split-Sample Study: Comparison of All Site Results for Cases Designated by the Reference Method as HSIL+ Discordant Error Analysis (LSIL is not an error)

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR		
	SUCCESS (HSIL+)	ERROR (WNL, Reactive/ Reparative & ASCUS/ AGUS)	Total
SUCCESS (HSIL+)	160	28	188
ERROR (WNL, Reactive/ Reparative & ASCUS/ AGUS)	36	38	74
Total	196	66	262

Result of McNemar test: $X^2mc = 1.00$, $p = 0.3173$
Errors Conventional: 28
Errors PREP: 36

Table 5 shows results for cases identified by the reference pathologist to be HSIL+. In

this comparison, LSIL was not considered an error but rather a discrepancy.[10,14,15] Error includes WNL, Reactive / Reparative and ASCUS/AGUS. The sensitivity analysis of the discordant errors showed statistical equivalence of the methods in the split-sample study.

Table 6 **First Split-Sample Study: Discordant Error Analysis for Cancer Cases (HSIL is not an error; LSIL is considered an error)**

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR			
		SUCCESS (CA)	ERROR (WNL, Reactive/ Reparative, ASCUS/AGUS & LSIL)	Total
	SUCCESS (CA)	19	2	21
	ERROR (WNL, Reactive/ Reparative, ASCUS/AGUS & LSIL)	5	1	6
	Total	24	3	27

Result of McNemar's Test: $X^2mc = 1.645$, $p = 0.1980$
Errors Conventional: 2
Errors PREP: 5

Table 6 shows results (all sites) for cases judged to be cancer by the reference method. Errors include WNL, Reactive / Reparative, ASCUS/AGUS and LSIL. The sensitivity analysis of the discordant errors showed statistical equivalence of the methods. (These 27 cancer cases were included in the re-evaluation study. This data can be found in Table 9).

Table 7 First Split-Sample Study: Comparison of All Site Results for Cases Designated by the Reference Method as HSIL+ Discordant Error Analysis (LSIL was considered an error in this analysis)

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR			
		SUCCESS (HSIL+)	ERROR (WNL, Reactive/ Reparative, ASCUS/ AGUS & LSIL)	Total
	SUCCESS (HSIL+)	94	33	127
	ERROR (WNL, Reactive/ Reparative, ASCUS/ AGUS & LSIL)	67	68	135
	Total	161	101	262

Result of McNemar test: $X^2mc = 11.56$, $p = 0.0007$
Errors Conventional: 33
Errors PREP: 67

Table 7 shows results for cases identified by the reference pathologist to be HSIL+. Error includes WNL, Reactive / Reparative, ASCUS/AGUS and LSIL. Though not consistent with the original study protocol[10], a statistical comparison of methods was performed where LSIL was considered a diagnostic error against a case determined to be HSIL+ by the single independent reference pathologist. In this statistical comparison of diagnostic sensitivities, when LSIL is considered an error, as opposed to a minor discrepancy, AutoCyte PREP would not be equivalent to the conventional Pap smear for detection of HSIL abnormality in the split-sample study.

- **Masked Re-evaluation of HSIL+ Cases**

A new evaluation was conducted to determine if the results were affected by preparation quality or interpretational subjectivity. In order to assess the 262 cases which were diagnosed as HSIL+ in the original study (**Table 7**), an additional evaluation was conducted after implementing a new training program for cytology professionals designed to emphasize consistent interpretation between the diagnostic groups of The Bethesda System. These HSIL+ cases were re-masked as part of a re-evaluation consisting of a total of 2,438 specimens prepared using the same split sample protocol. Conventional and AutoCyte PREP study site results were then compared to a new reference value which required agreement of at least two of three independent reference pathologists as to the most abnormal cytology diagnosis.

In the reference process for the re-evaluation, both slide preparations from the discordant cases (AutoCyte PREP and the conventional Pap smears) were rescreened by a second

cytotechnologist, and newly identified abnormalities were added to those from the initial screening. Three reference cytopathologists then evaluated all discordant cases using a masked protocol. This more stringent reference method reduced the number of HSIL+ reference cases from 262 in the original study to 209 in the re-evaluation. The 53 case difference may be explained as follows: 48 cases were diagnosed by the more stringent reference method as LSIL or less severe; the adequacy of 3 cases was judged unsatisfactory upon re-evaluation; and the remaining 2 cases were not available for assessment in the masked re-evaluation study.

Table 8 **Re-Evaluation Study: Discordant Error Analysis for 209 Original HSIL+ Cases Re-Evaluated by the More Stringent Reference Criteria Involving Three Independent Reference Pathologists**

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR			
		SUCCESS (HSIL+)	**ERROR (WNL, Reactive/ Reparative, ASCUS/ AGUS & LSIL)**	**Total**
	SUCCESS (HSIL+)	153	26	179
	ERROR (WNL, Reactive/ Reparative, ASCUS/ AGUS & LSIL)	24	6	30
	Total	177	32	209

Result of McNemar Test: $X^2mc = 0.02$, $p = 0.8875$

Errors Conventional: 26

Errors PREP: 24

Table 8 shows results for cases identified by the reference pathologist to be HSIL+. Error includes WNL, Reactive / Reparative, ASCUS/AGUS and LSIL. In this comparison, LSIL was considered a diagnostic error against a case determined to be HSIL+ by the independent reference pathologist. Comparison of diagnostic sensitivities showed statistical equivalence between the two methods.

Table 9 **Re-Evaluation Study: Discordant Error Analysis for Cancer Cases (HSIL is not an error; LSIL is considered an error)**

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR		
	SUCCESS (CA)	ERROR (WNL, Reactive/ Reparative, ASCUS/AGUS & LSIL)	Total
SUCCESS (CA)	32	3	35
ERROR (WNL, Reactive/ Reparative, ASCUS/AGUS & LSIL)	3	0	3
Total	35	3	38

Result of McNemar's Test: $X^2mc = 0.00$, $p = 1.0000$
Errors Conventional: 3
Errors PREP: 3

Table 9 shows results for cases judged to be cancer by the new reference method (all sites). Errors include WNL, Reactive / Reparative, ASCUS/AGUS and LSIL. The sensitivity analysis of the discordant errors showed statistical equivalence of the methods.

The masked re-evaluation contained 2097 new cases that were used to re-mask the original HSIL+ samples. The analysis and comparison of the preparations from these new cases follows in **Table 10**.

Table 10 Re-Evaluation Study: 2097 Direct Site Results Comparison – No Reference Pathologists

AUTOCYTE PREP	CONVENTIONAL						
	WNL	ASCUS	AGUS	LSIL	HSIL	CA	Total
WNL	1561	128	0	47	30	0	1766
ASCUS	80	37	1	6	8	1	133
AGUS	9	7	0	0	1	0	17
LSIL	33	11	1	33	11	1	90
HSIL	26	18	1	18	19	3	85
CA	1	2	0	0	1	2	6
Total	1710	203	3	104	70	7	2097

Of the 2097 new cases described above, 77 were diagnosed HSIL+ by the reference pathologists. **Table 11**presents the sensitivity analysis for those 77 HSIL+ cases.

Table 11 Re-Evaluation Study: Comparison of All Site Results for Cases Designated by the Reference Method as HSIL+ Discordant Error Analysis (LSIL was considered an error in this analysis)

AUTOCYTE PREP	CONVENTIONAL PAP SMEAR		
	SUCCESS (HSIL+)	ERROR (WNL, Reactive/ Reparative, ASCUS/ AGUS & LSIL)	Total
SUCCESS (HSIL+)	25	21	46
ERROR (WNL, Reactive/ Reparative, ASCUS/ AGUS & LSIL)	21	10	31
Total	46	31	77

Result of McNemar test: $X^2mc = 0.00$, $p = 1.0000$
Errors Conventional: 21
Errors PREP: 21

Analysis of the discordant errors in **Table 11** showed an equal number of HSIL+ misses for both the AutoCyte PREP and conventional Pap smear. Error includes WNL, Reactive / Reparative, ASCUS/AGUS and LSIL. The statistical test demonstrated equivalence between the two methods in the split-sample design even when LSIL is considered an error against a reference value of HSIL+.

Table 12 summarizes the descriptive diagnoses of benign findings for all sites.

Table 12 First Split-Sample Study: Summary of Benign Cellular Changes

Descriptive Diagnosis Number of Patients: 8,807	AutoCyte PREP		Conventional	
	N	%	N	%
Benign Cellular Changes				
*Infection:				
Candida species	440	5.0	445	5.1
Trichomonas vaginalis	118	1.3	202	2.3
Herpes	8	0.1	6	0.1
Gardnerella	85	1.0	44	0.5
Actinomyces species	6	0.1	2	<0.1
Bacteria (other)	52	0.6	191	2.2
**Reactive Reparative Changes	424	4.8	319	3.6

*For Infection category above, observations of infectious agents are reported. More than one class of organism may be represented per case.

**Reactive reparative changes included reactive changes associated with inflammation, atrophic vaginitis, radiation and IUD use, as well as typical repair involving squamous, squamous metaplastic or columnar epithelial cells.

A total of 8807 cases contained no "unsatisfactory" assessment by either the trial sites or the reference site. An additional 239 samples were scored "unsatisfactory" by either or both the trial sites or reference site on either or both preparations. Of those 239 unsatisfactory cases, 151 were noted on conventional slides only; 70 on PREP slides only; and 18 were observed on both the conventional and PREP slides. All unsatisfactory cases were excluded from diagnostic comparison by The Bethesda System categories, but were added back for comparison of preparation adequacy.

Tables 13 through 16 show preparation adequacy results for all sites.

Table 13 First Split-Sample Study: Preparation Adequacy Results

Preparation Adequacy Number of Patients: 9,046	AutoCyte PREP		Conventional	
	N	%	N	%
Satisfactory	7607	84.1	6468	71.5
Satisfactory for Evaluation But Limited By:	1385	15.3	2489	27.5
Endocervical Component Absent	1283	14.2	1118	12.4
Air-Drying Artifact	0	0	17	0.2
Thick Smear	1	<0.1	0	0
Obscuring Blood	53	0.6	121	1.3
Obscuring Inflammation	102	1.1	310	3.4
Scant Squamous Epithelial Cells	4	<0.1	7	0.1
Cytolysis	10	0.1	11	0.1
No Clinical History	0	0	0	0
Not Specified	60	0.7	1018	11.3
Unsatisfactory for Evaluation:	54	0.6	89	1.0
Endocervical Component Absent	42	0.5	42	0.5
Air-Drying Artifact	0	0	0	0
Thick Smear	0	0	2	<0.1
Obscuring Blood	7	0.1	6	0.1
Obscuring Inflammation	6	0.1	6	0.1
Scant Squamous Epithelial Cells	6	0.1	0	0
Cytolysis	0	0	1	<0.1
No Clinical History	0	0	0	0
Not Specified	37	0.4	32	0.5

Note: Some patients had more than one subcategory.

The additional unsatisfactory cases determined by the reference pathologist, and the total number of unsatisfactory results are reflected in **Table 15**.

Table 14 First Split-Sample Study: Summary of Preparation Adequacy Results – All Clinical Trial Sites

AutoCyte PREP	CONVENTIONAL			
	SAT	SBLB	UNSAT	Total
SAT	5868	1693	46	7607
SBLB	579	772	34	1385
UNSAT	21	24	9	54
Total	6468	2489	89	9046

SAT = Satisfactory, SBLB = Satisfactory But limited By(some specified condition), UNSAT = Unsatisfactory

UNSAT: Result of McNemar Test X^2 mc = 8.57, p = 0.0034
SBLB: Result of McNemar Test X^2 mc = 546.21, p = 0.0000

Table 14 shows results from a comparison of preparation adequacy for the conventional Pap smear and AutoCyte PREP slides. There were significantly fewer Unsatisfactory and SBLB cases with AutoCyte PREP as compared to the conventional Pap smear

Table 15 First Split-Sample Study: Comparison of Unsatisfactory Results From The Clinical Trial Sites and The Reference Site

AutoCyte PREP	CONVENTIONAL		
	SAT	UNSAT	Total
SAT	8807	151	8958
UNSAT	70	18	88
Total	8877	169	9046

Result of McNemar Test X^2 mc = 29.69, p = 0.0000

Table 15 shows comparison of satisfactory and unsatisfactory preparations from the evaluations at both the trial sites and the reference site. AutoCyte PREP slides show a statistically significant reduction of unsatisfactory cases compared to the conventional Pap smear.

Table 16 Preparation Adequacy Results by Site - SBLB Rates for No Endocervical Component (ECC)

Site	Cases	AutoCyte PREP SBLB no ECCs N (%)	Conventional SBLB no ECCs N (%)
1	995	60 (6.0)	85 (8.5)
2	1712	121 (7.1)	54 (3.2)
3	712	180 (25.3)	141 (19.8)
4	1395	165 (11.8)	331 (23.7)
5	500	58 (11.6)	56 (11.2)
6	1695	473 (28.2)	238 (14.2)
7	589	19 (3.3)	3 (0.5)
8	1448	207 (14.3)	210 (14.5)
All Sites	9046	1283 (14.2)	1118 (12.4)

Detection of endocervical cells **(Table 16)** varied at different trial sites. Overall, there was a 1.8% difference in endocervical cell detection between the conventional Pap smear and AutoCyte PREP methods, which is similar to previous studies involving split-sample methodology.[16,17]

The AutoCyte PREP System provides similar results to the conventional Pap smear in split-sample comparisons in a variety of patient populations and laboratory settings. In addition, there were significantly fewer Unsatisfactory and SBLB cases with AutoCyte PREP as compared to the conventional Pap smear. The AutoCyte PREP System may thus be used as a replacement for the conventional Pap smear method for the detection of atypical cells, precancerous lesions, cervical cancer, and all other cytologic categories defined by The Bethesda System.

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