

TriPath Imaging[®], Inc.
PrepStain[™] System Product Insert

INTENDED USE

The PrepStain[™] System (formerly the AutoCyte[®] PREP System) is a liquid-based thin layer cell preparation process. The PrepStain[™] System produces SurePath[®] slides that are intended as replacements for conventional gynecologic Pap smears. SurePath[®] slides (formerly 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.^{1,19}

SUMMARY AND EXPLANATION OF THE PROCEDURE

The PrepStain[™] System converts a liquid suspension of a cervical cell sample into a discretely stained, homogeneous thin-layer of cells while maintaining diagnostic cell clusters.²⁻⁹ The process includes cell preservation, randomization, enrichment of diagnostic material, pipetting, sedimentation, staining, and coverslipping to create a SurePath[®] slide for use in routine cytology screening and categorization as defined by The Bethesda System.¹ The SurePath[®] slide presents a well-preserved population of stained cells present within a 13mm 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 easier visualization of epithelial cells, diagnostically relevant cells and infectious organisms.

The SurePath process begins with qualified medical personnel using a broom-type sampling device (e.g., Cervex Brush[®] Rovers Medical Devices B.V., Oss - The Netherlands) or an endocervical brush/plastic spatula combination (e.g., Cytobrush[®] Plus GT and Pap Perfect[®] spatula, Medscand (USA) Inc., Trumbull, CT) with detachable head(s) to collect a gynecologic specimen. Rather than smearing cells collected by the sampling devices on a glass slide, the heads of the sampling devices detach from the handle and are placed into a vial of SurePath[™] Preservative Fluid. The vial is capped, labeled, and sent with appropriate paperwork to the laboratory for processing. The heads of the sampling devices are never removed from the preservative vial containing the collected sample.

In the laboratory, the preserved sample is mixed by vortexing and then transferred onto PrepStain[™] 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 pelleted cells are resuspended, mixed and transferred to a PrepStain[™] Settling Chamber mounted on a SurePath[™] PreCoat slide. The cells are sedimented by gravity, then stained using a modified Papanicolaou staining procedure. The slide is cleared with xylene or a xylene substitute and coverslipped. The cells, presented within a 13mm diameter circle, are examined under a microscope by trained cytotechnologists and pathologists with access to other relevant patient background information.

LIMITATIONS

- Gynecologic specimens for preparations using the PrepStain[™] System should be collected using a broom-type sampling device or an endocervical brush/plastic spatula combination with detachable head(s) according to the standard collection procedure provided by the manufacturer. Wooden spatulas should not be used with the PrepStain[™] System. Endocervical brush/plastic spatula combinations that are not detachable should not be used with the PrepStain[™] System.
- Training by authorized persons is a prerequisite for the production and evaluation of SurePath[®] slides. Cytotechnologists and pathologists will be trained in morphology assessment on the SurePath[®] slides. Training will include a proficiency examination. Laboratory customers will be provided with the use of instructional slide and test sets. TriPath Imaging[®], Inc. will also provide assistance in the preparation of training slides from each customer's own patient populations.
- Proper performance of the PrepStain[™] System requires the use of only those supplies supported by TriPath Imaging, or recommended by TriPath Imaging, for use with the PrepStain[™] System. 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.

Reagents



For In Vitro Diagnostic use. For laboratory use only.

Warnings



SurePath[®] Preservative Fluid contains an aqueous solution of denatured ethanol. The mixture contains small amounts of methanol and isopropanol. Do not ingest.



PrepStain[™] Density Reagent contains sodium azide. Do not ingest. 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.



PrepStain[™] EA/OG combination cytology stain contains alcohol. Toxic if ingested. Do not breath vapors. Use with adequate ventilation. Avoid contact with skin and eyes. Highly flammable.

PRECAUTIONS

- Good laboratory practices should be followed and all procedures for use of the PrepStain[™] 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 SurePath[®] Preservative Fluid without cytologic samples is up to 36 months from date of manufacture at room temperature (15° to 30° C). The storage limit for SurePath[®] Preservative Fluid with cytologic samples is 6 months at refrigerated temperature (2° to 10° C) or 4 weeks at room temperature (15° to 30° C).
- Avoid splashing or generating aerosols. Operators should use appropriate hand, eye and clothing protection.
- SurePath[®] Preservative Fluid was tested for antimicrobial effectiveness against: Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, Mycobacterium tuberculosis and Aspergillus niger and found to be effective. SurePath[®] Preservative samples inoculated with 10⁶ organism of each species yielded no growth after 1 day of 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 PrepStain[™] System Operator's Manual may compromise performance.

MATERIALS REQUIRED

Refer to the Operator's Manual of the PrepStain[™] System for complete information concerning reagents, components and accessories. Not all the materials listed below are required for preparing SurePath[®] slides manually (without using the PrepStain[™] instrument).

Materials Provided

- PrepStain[™] Instrument
- SurePath[®] Preservative Fluid Collection Vial (includes SurePath[®] Preservative Fluid)
- Cervical Sampling Device(s) with Detachable Head(s)
- PrepStain[™] Density Reagent
- PrepStain[™] Syringing Pipettes
- PrepStain[™] Settling Chambers
- Cytology Stain Kit
- SurePath[®] PreCoat 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
- Clearing Agent, Mounting Media and Glass Coverslips

Storage

The storage condition for SurePath[®] Preservative Fluid without cytologic samples is up to 36 months from date of manufacture at room temperature (15° to 30° C).

The storage limit for SurePath[®] Preservative Fluid with cytologic samples is 6 months at refrigerated temperatures (2° to 10° C) or 4 weeks at room temperature (15° to 30° C).

DIAGNOSTIC INTERPRETATION AND PREPARATION ADEQUACY

After TriPath Imaging-authorized user training on the PrepStain[™] System and SurePath[®] slides, the Bethesda System cytologic diagnostic criteria currently utilized in cytology laboratories for conventional Pap smears are applicable to SurePath[®] slides.¹ New guidelines recommended in the Bethesda 2001 Reporting System address liquid based preparations and define how to determine adequate cellularity specifically for these preparations.

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 5,000 squamous epithelial cells per preparation). The following are the recommended procedures for estimating the count of well-preserved squamous epithelial cells on SurePath[®] 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 mm² approximate cell deposition area of the SurePath[®] 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. The Bethesda 2001 guidelines indicating the approximate number of cells per field for a 13 mm preparation.
 - A minimum of ten fields should be counted horizontally or vertically along the center of the diameter of the preparation.

- 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 that precludes cytologic interpretation of the slide.

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.

PERFORMANCE CHARACTERISTICS: REPORT OF CLINICAL STUDIES

FIRST SPLIT-SAMPLE STUDY

TriPath Imaging conducted a prospective, masked, split-sample, matched-pair clinical investigation at multiple sites to compare the diagnostic results of SurePath® slides produced by the PrepStain™ System with conventionally prepared Pap smears. The objective of the study was to assess SurePath® 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 Devices¹⁰, each conventional Pap smear was prepared first, then the residual specimen remaining on the broom-type sampling device was deposited into a SurePath® Preservative Fluid Collection Vial.

After transport to the laboratory, each preserved cell suspension was processed according to the PrepStain™ System protocol. The resulting SurePath® 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 Shatzkin¹¹, 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.

STUDY RESULTS

The goal of the clinical trial was to compare the performance of SurePath® slides produced by the PrepStain™ System to conventionally prepared Pap smears. Slides for both preparation types were classified according to The Bethesda System criteria. The study protocol was biased in favor of the conventional Pap smear because a conventional Pap smear was always prepared first, thereby restricting the SurePath® 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 SurePath® test is a direct-to-vial application where all collected cells will be available to the PrepStain™ System.

To compare the sensitivities of the SurePath® 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 PrepStain™ System preparation of SurePath® slides versus conventional Pap smear preparation. The null hypothesis that the sensitivities of the two methods of slide preparation are equivalent was tested using the McNemar 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 SurePath® slides versus Conventional 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

Results by Site								
Site No.	Slide Type	WNL	ASCUS	AGUS	LSIL	HSIL	CA	Total
1	SP	873	56	2	42	5	0	978
	CN	881	46	2	29	20	0	978
2	SP	1,514	47	4	81	24	0	1,670
	CN	1,560	33	6	40	31	0	1,670
3	SP	668	15	1	13	7	0	704
	CN	673	11	0	13	6	1	704

4	SP	1,302	60	2	19	5	0	1,388
	CN	1,326	37	2	19	4	0	1,388
5	SP	465	25	1	5	1	0	497
	CN	444	45	1	4	3	0	497
6	SP	1,272	179	6	83	35	1	1,576
	CN	1,258	209	9	68	30	2	1,576
7	SP	438	66	17	13	14	23	571
	CN	417	93	19	4	22	16	571
8	SP	1,227	61	3	86	44	2	1,423
	CN	1,209	57	0	94	61	2	1,423
Total	SP	7,759	509	36	342	135	26	8,807
	CN	7,768	531	39	271	177	21	8,807

SP = SurePath®
CN = Conventional

Table 2 presents a direct comparison of all site results for the SurePath® preparation method vs. Conventional Pap smear preparation for all diagnostic treatment categories.

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

		Conventionally Prepared Pap Smear						
		WNL	ASCUS	AGUS	LSIL	HSIL	CA	Total
PrepStain™ Prepared SurePath® Slide	WNL	7,290	361	20	63	24	1	7,759
	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	7,768	531	39	271	177	21	8,807

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

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	113	205	318
	Error	180	229	409
		293	434	727

Success = ASCUS/AGUS
Error = WNL & Reactive/Reparative

Result of McNemar Test: $\chi^2_{mc} = 1.62, p = 0.2026$
Errors Conventional: 205
Errors SurePath®: 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 SurePath® 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

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	140	63	203
	Error	54	86	140
		194	149	343

Success = LSIL
Error = WNL, Reactive/Reparative & ASCUS/AGUS

Result of McNemar Test: $\chi^2_{mc} = 0.69, p = 0.4054$
Errors Conventional: 63
Errors SurePath®: 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)

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	160	28	188
	Error	36	38	74
		196	66	262

Success = HSIL+
Error = WNL, Reactive/Reparative & ASCUS/AGUS

Result of McNemar Test: $\chi^2_{mc} = 1.00, p = 0.3173$
Errors Conventional: 28
Errors SurePath®: 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)

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	19	2	21
	Error	5	1	6
		24	3	27

Success = Cancer
Error = WNL, Reactive/Reparative ASCUS/AGUS & LSIL

Result of McNemar Test: $\chi^2_{mc} = 1.645, p = 0.1980$
Errors Conventional: 2
Errors SurePath®: 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)

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	94	33	127
	Error	67	68	135
		161	101	262

Success = (HSIL+)
Error = WNL, Reactive/Reparative ASCUS/AGUS & LSIL

Result of McNemar Test: $\chi^2_{mc} = 11.56, p = 0.0007$
Errors Conventional: 33
Errors SurePath®: 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 protocol¹⁰, 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, SurePath® slides prepared by the PrepStain™ System would not be equivalent to the conventionally prepared 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. Study site results for the two preparations 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 (PrepStain™-prepared SurePath® slides and conventionally prepared slides) 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

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	153	26	179
	Error	24	6	30
		177	32	209

Success = HSIL+
Error = WNL, Reactive/Reparative ASCUS/AGUS & LSIL

Result of McNemar Test: $\chi^2_{mc} = 0.02, p = 0.8875$
Errors Conventional: 26
Errors SurePath®: 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)

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	32	3	35
	Error	3	0	3
		35	3	38

Success = Cancer
Error = WNL, Reactive/Reparative ASCUS/AGUS & LSIL

Result of McNemar Test: $\chi^2_{mc} = 0.00, p = 1.0000$
Errors Conventional: 3
Errors SurePath®: 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. One error resulted from a LSIL interpretation. All other errors involved interpretation of slides as ASCUS/AGUS or WNL. 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 Pathologist

	Conventionally Prepared Pap Smear							Total
	WNL	ASCUS	AGUS	LSIL	HSIL	CA		
WNL	1,561	128	0	47	30	0	1,766	
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	1,710	203	3	104	70	7	2,097	

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)

		Conventionally Prepared Slide		
		Success	Error	
PrepStain™ Prepared SurePath® Slide	Success	25	21	46
	Error	21	10	31
		46	31	77

Success = HSIL+
Error = WNL, Reactive/Reparative ASCUS/AGUS & LSIL

Result of McNemar Test: $\chi^2_{mc} = 0.00, p = 1.0000$
Errors Conventional: 21
Errors SurePath®: 21

Analysis of the discordant errors in Table 11 showed an equal number of HSIL+ misses for both preparation methods. 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 (No. of Patients: 8,807)	PrepStain™ Prepared SurePath® Slide		Conventionally Prepared Slide	
	N	%	N	%
Benign Cellular Changes				
*Infection:				
<i>Candida</i> species	440	5.0	445	5.1
<i>Trichomonas vaginalis</i>	118	1.3	202	2.3
Herpes	8	0.1	6	0.1
Gardnerella	85	1.0	44	0.5
<i>Actinomyces</i> 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 8,807 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 the 239 unsatisfactory cases, 151 were noted on conventional slides only; 70 on SurePath® only; and 18 were observed on both the conventional and SurePath® 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 (No. of Patients: 9,046)	PrepStain™ Prepared SurePath® Slide		Conventionally Prepared Slide	
	N	%	N	%
Satisfactory	7,607	84.1	6,468	71.5
Satisfactory But Limited By:	1,385	15.3	2,489	27.5
Endocervical Component Absent	1,283	14.2	1,118	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	1,018	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.

Additional unsatisfactory cases were determined by the reference pathologist, and the total numbers of unsatisfactory results are reflected in Table 15. In the table, SAT = Satisfactory, SBLB = Satisfactory But limited By (some specified condition), and UNSAT = Unsatisfactory.

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

		Conventionally Prepared Slide			
		SAT	SBLB	UNSAT	
PrepStain™ Prepared SurePath® Slide	SAT	5,868	1,693	46	7,607
	SBLB	579	772	34	1,385
	UNSAT	21	24	9	54
		6,468	2,489	89	9,046

UNSAT: Result of McNemar Test $\chi^2_{mc} = 9.33, p = 0.0023$
 SBLB: Result of McNemar Test $\chi^2_{mc} = 546.21, p = 0.0000$

Table 14 shows results from a comparison of preparation adequacy both preparation methods. There were significantly fewer Unsatisfactory and SBLB cases with SurePath® slides as compared to the conventional slides.

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

		Conventionally Prepared Slide		
		SAT	UNSAT	
PrepStain™ Prepared SurePath® Slide	SAT	8,807	151	8,958
	UNSAT	70	18	88
		8,877	169	9,046

Result of McNemar Test $\chi^2_{mc} = 29.69, p = 0.0000$

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

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

Site	Cases	SurePath® SBLB no ECCs N (%)	Conventional SBLB no ECCs N (%)
1	995	60 (6.0)	85 (8.5)
2	1,712	121 (7.1)	54 (3.2)
3	712	180 (25.3)	141 (19.8)
4	1,395	165 (11.8)	331 (23.7)
5	500	58 (11.6)	56 (11.2)
6	1,695	473 (28.2)	238 (14.2)
7	589	19 (3.3)	3 (0.5)
8	1,448	207 (14.3)	210 (14.5)
All Sites	9,046	1,283 (14.2)	1,118 (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 SurePath® methods, which is similar to previous studies involving split-sample methodology.^{16,17}

SurePath® slides produced by the PrepStain™ System provide similar results to conventional Pap smears in split-sample comparisons in a variety of patient populations and laboratory settings. In addition, there were significantly fewer Unsatisfactory and SBLB cases with SurePath® slides as compared to conventional Pap smears. The SurePath® slide may thus be used as a replacement for the conventional Pap smear for the detection of atypical cells, pre-cancerous lesions, cervical cancer, and all other cytologic categories defined by The Bethesda System.

EVALUATION OF SUREPATH® SLIDE PREPARATION USING THE PREPMATE® AND THE MANUAL METHODS

TriPath Imaging conducted a prospective, multi-center clinical trial to evaluate two modifications to the FDA-approved procedure of preparing SurePath® slides. The modifications to the approved process for preparing SurePath® slides were as follows:

- The addition of the PrepMate® accessory (PrepMate® method), which automates the initial manual steps of the PrepStain™ laboratory process. The PrepMate® automatically mixes and removes the specimen from the SurePath® Preservative Vials, and layers the specimen onto PrepStain™ Density Reagent in a test tube.
- The addition of the Manual method, in which, rather than using the PrepStain™ instrument for cell suspension and slide staining, the cell suspension is manually layered onto the slide and stained by a laboratory technician.

This study evaluated over 400 cases in a masked comparison of the two alternative methods to the currently approved procedure for preparing SurePath® slides. The comparison was based on morphological and quality criteria applied to the slides prepared by each method.

The primary objectives of the study were to:

- Evaluate the morphological and quality aspects of SurePath® slides prepared using the PrepMate® method as compared to slides prepared according to the approved method of using the PrepStain™ System (referred to as the PrepStain™ method).
- Evaluate the morphological and quality aspects of SurePath® slides prepared using the Manual method as compared to slides prepared according to the approved PrepStain™ method.

Additional objectives of the study were to:

- Determine if the amount of agreement between the approved PrepStain™ method and the PrepMate® method was greater than would be expected by chance alone.
- Determine if the amount of agreement between the approved PrepStain™ method and the Manual method was greater than would be expected by chance alone.
- Assess the specimen adequacy according to the PrepStain™ System standards for preparing SurePath® slides using the PrepMate® method.
- Assess the specimen adequacy according to the PrepStain™ System standards for preparing SurePath® slides using the Manual method.

PREPMATE® ACCESSORY

The PrepMate® is an accessory to the PrepStain™ System that automates two manual steps—sample mixing and layering—of the PrepStain™ laboratory process. The PrepMate® thoroughly mixes, accurately removes the specimen from the SurePath® Preservative Vials, and layers the specimen onto PrepStain™ Density Reagent in a test tube. A specimen rack preloaded with specimen vials, syringing pipettes, and test tubes (containing the Density fluid) is placed on the instrument's tray. The rack contains up to twelve vials, tubes, and syringing pipettes, which are arranged in three rows of four each. Vials, syringing pipettes, and tubes are disposable. They must be used only once to eliminate the possibility of specimen contamination.

MANUAL METHOD

The Manual method uses a manual procedure to layer the cell suspension onto the slides and stain the preparation. Gynecologic specimen collection and processing are identical for both the Manual and approved PrepStain™ methods up to the point of using the PrepStain™ instrument.

In the PrepStain™ method, centrifuged cell pellets are placed directly onto the PrepStain™ instrument for automated processing to produce stained SurePath® slides.

In the Manual method, deionized water is added to the centrifuged cell pellet followed by vortexing to resuspend and randomize the sample. The sample is transferred into a settling chamber mounted on a SurePath® PreCoat slide. After the sample is settled onto the slide, the sample is stained by a batch Papanicolaou staining procedure.

SLIDE ACCOUNTABILITY

Table 17 shows the slide accountability for the clinical study slides. It is important to note that the study set consisted of **three slides per case**.

Table 17 Slide Accountability

	Cases	Slides
Total number enrolled in study	471	1,413
Total number excluded from analysis	-68	-204
Incomplete Documentation	-39	-117
Slides Prepared Incorrectly	-24	-72
Other exclusion reasons *	-5	-15
Total number included in analysis	403	1,209

* Missing samples, duplicate patient numbers, etc.

POPULATION DEMOGRAPHICS

Table 18 lists the patient age demographics for all cases included in the study population.

Table 18 Patient Demographics

Age	Number of Cases
19 or younger	3
20 – 29	73
30 – 39	158
40 – 49	105
50 +	64
Total	403

Table 19 lists current clinical information and Table 20 lists clinical history for all cases included in the study population. Note that the selection of more than one item was allowed, so total case counts may not correlate to the total number of cases in the study population.

Table 19 Current Clinical Information

Clinical Information	Number of Cases
Cyclic	241
Irregular Cycle	69
Hysterectomy	16
Pregnant	9
Post Abortion	0
Post Natal	9
Post Menopausal	58
Peri-menopausal	1
Immune Depressed	0
Abnormal GYN Presentation	0
Vaginal Discharge	137
Estrogen Replacement Therapy	19
IUD	2
Oral Contraceptives/Implant	20
No Birth Control	181
Information not available	22

Table 20 Clinical History

History	Number of Cases
Previous abnormal cytology	13
History of abnormal bleeding	36
Biopsy	3
History of Cancer	1
Chemotherapy	0
Radiation	0
Colposcopy	9
HIV/AIDS	0
HPV (Wart Virus)	0
Herpes	1
History of BTL*	1
History of PID**	57
None Noted	363

* Bilateral tubal ligation

** Pelvic inflammatory disease

STUDY RESULTS

The purpose of this study was to establish that SurePath® slides prepared using the PrepMate® method and Manual method procedures compared favorably with those prepared using the approved PrepStain™ method. The clinical data show that the slides prepared by the PrepMate® and Manual methods are comparable in morphology and quality to those prepared by the approved PrepStain™ method.

The clinical data also show that the diagnostic performance is the same for the PrepMate® and Manual methods when compared to the approved PrepStain™ method. In addition, the adequacy of slides prepared by the PrepMate® and Manual methods does not differ from those prepared by the approved PrepStain™ method. These findings support the comparability of the PrepMate® and Manual methods to the approved PrepStain™ method.

SPECIMEN MORPHOLOGY AND QUALITY

Table 21 shows the results for the primary objectives. The acceptability of the slides prepared by each method was evaluated according to the morphology and quality criteria shown in the table. For each criterion, the proportion of acceptable slides was calculated along with the corresponding exact 95% confidence interval.

Table 21 Comparison of Rates and Confidence Intervals (CI) for Acceptability Criteria

	Slide Preparation Method						
	PrepStain™		PrepMate®		Manual Method		
	Rate (n/N)	Exact 95% CI	Rate (n/N)	Exact 95% CI	Rate (n/N)	Exact 95% CI	
Acceptability Criteria	Staining	0.9876 (398/403)	0.9713, 0.9960	0.9926 (400/403)	0.9784, 0.9985	0.9901 (399/403)	0.9748, 0.9973
	Clarity	0.9876 (398/403)	0.9713, 0.9960	0.9876 (398/403)	0.9713, 0.9960	0.9975 (402/403)	0.9863, 0.9999
	Nuclear	0.9901 (399/403)	0.9748, 0.9973	0.9901 (399/403)	0.9748, 0.9973	0.9975 (402/403)	0.9863, 0.9999
	Cytology	0.9950 (401/403)	0.9822, 0.9994	0.9901 (399/403)	0.9748, 0.9973	1.0000 (403/403)	0.9909, 1.0000
	Clustering	0.9926 (400/403)	0.9784, 0.9985	0.9975 (402/403)	0.9863, 0.9999	0.9603 (387/403)	0.9363, 0.9771
	Cellularity	0.9305 (375/403)	0.9011, 0.9533	0.9454 (381/403)	0.9185, 0.9655	0.9404 (379/403)	0.9127, 0.9615

The PrepMate® and Manual method acceptability rates are nearly always equal to or greater than those of the PrepStain™ method. In addition, the 95% exact confidence intervals for the PrepMate® and Manual methods substantially overlap those from the approved PrepStain™ method for each criterion. This implies that the slides prepared by the PrepMate® and Manual methods are of comparable morphology and quality as those prepared by the approved PrepStain™ method. Therefore, the preparation quality is the same for the approved method and the two test methods.

DIAGNOSTIC AGREEMENT

This analysis compares the diagnoses on slides prepared by each method. Because these data are derived from split samples, the diagnosis matrices presented in Table 22 and Table 23 are based on paired samples with each of the test slide preparation methods (PrepMate® and Manual method) being compared to the approved PrepStain™ method. Ideally, the diagnosis obtained from slides prepared by two methods will be the same. This is represented by the number of slides with identical diagnoses, which appear on the main diagonal of each table.

The first measure of agreement is the proportion of slides on the main diagonal and the corresponding exact 95% confidence intervals. The second measure of agreement is obtained from the kappa statistic, which was computed for each comparison and tested. The test determines if the amount of agreement between the two methods is greater than would be expected by chance alone. Because the observations are ordered, it is more important to have observations that lie on or near the main diagonal. The weighted kappa statistic gives more weight to observations that lie on or near the main diagonal in the tables.

COMPARISON OF APPROVED PREPSTAIN™ AND PREPMATE® METHODS

In Table 22, the number of slides on the main diagonal is 367 (2+334+8+6+5+11+1) and the proportion of slides on the main diagonal is 0.9107 (367/403) with exact 95% confidence limits of 0.8785 to 0.9366.

If unsatisfactory slides are excluded from the table by deleting the first row and first column, 397 slides remain. The proportion of slides on the main diagonal is 0.9194 (365/397) with 95% confidence limits of 0.8881 to 0.9442.

The results shown in Table 22 indicate that the approved PrepStain™ method and the PrepMate® method have a high proportion of slides with diagnostic agreement, as indicated by the proportion of slides on the main diagonal in the table. Further, the weighted kappa analysis indicates that the agreement was much greater than could be attributed to chance alone.

Table 22 Crosstabulation of Diagnoses by PrepStain™ and PrepMate® Methods

		PrepStain™ Method Diagnosis									
		Unsat	WNL	BCC-RR	Atypia	LSIL	HSIL	DYSPL	AIS	CA	Total
PrepMate® Method Diagnosis	Unsat	2	1	0	0	0	0	0	0	0	3
	WNL	2	334	2	7	2	0	0	0	0	347
	BCC-RR	0	6	8	0	1	0	0	0	0	15
	Atypia	1	3	2	6	0	0	0	0	0	12
	LSIL	0	3	0	3	5	0	0	0	0	11
	HSIL	0	1	0	1	0	11	0	0	0	13
	DYSPL	0	0	0	0	1	0	0	0	0	1
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	1	1
	Total	5	348	12	17	9	11	0	0	1	403

COMPARISON OF APPROVED PREPSTAIN™ AND MANUAL METHODS

In Table 23, the number of slides on the main diagonal is 353 (3+315+6+10+7+11+1). The proportion of slides on the main diagonal is 0.8759 (353/403). The exact binomial 95% confidence limits for this proportion are 0.8397 to 0.9065.

If unsatisfactory slides are excluded from the table by deleting the first row and first column, 398 slides remain. The proportion of slides on the main diagonal is 0.8794 (350/398) with 95% confidence limits of 0.8433 to 0.9097. The results shown in Table 23 indicate that the approved PrepStain™ method and the Manual method have a high proportion of slides with diagnostic agreement, as indicated by the proportion of slides on the main diagonal in the table. Further, the weighted kappa analysis indicates that the agreement was much greater than could be attributed to chance alone. Therefore, the diagnostic performance is the same for the approved method and the two test methods.

Table 23 Crosstabulation of Diagnoses by PrepStain™ and Manual Methods

		PrepStain™ Method Diagnosis									
		Unsat	WNL	BCC-RR	Atypia	LSIL	HSIL	DYSPL	AIS	CA	Total
Manual Method Diagnosis	Unsat	3	0	0	0	0	0	0	0	0	3
	WNL	1	315	1	3	1	0	0	0	0	321
	BCC-RR	0	19	6	0	0	0	0	0	0	25
	Atypia	0	12	4	10	0	0	0	0	0	26
	LSIL	0	1	1	3	7	0	0	0	0	12
	HSIL	1	1	0	1	1	11	0	0	0	15
	DYSPL	0	0	0	0	0	0	0	0	0	0
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	1	1
	Total	5	348	12	17	9	11	0	0	1	403

SLIDE ADEQUACY

Slide adequacy was assessed for each of the preparation methods. The data were analyzed using a two-sided McNemar test.¹⁸

Table 24 shows the adequacy results when comparing the approved PrepStain™ method to the PrepMate® method.

Table 24 Adequacy Results for PrepMate® and PrepStain™ Method Slides

		PrepStain™ Method Result		
		SAT or SBLB	UNSAT	
PrepMate® Method Result	SAT or SBLB	398	3	401
	UNSAT	0	2	2
		398	5	403

Table 25 shows the adequacy results when comparing the approved PrepStain™ method to the Manual method.

Table 25 Adequacy Results for Manual and PrepStain™ Method Slides

		PrepStain™ Method Result		
		SAT or SBLB	UNSAT	
Manual Method Result	SAT or SBLB	398	2	400
	UNSAT	0	3	3
		398	5	403

These two comparisons demonstrate that the PrepMate® and Manual methods do not differ from the approved PrepStain™ method with respect to slide adequacy.

DIRECT-TO-VIAL STUDY

Following the initial FDA approval of the PrepStain™ System, TriPath Imaging conducted a large, multi-center study of the PrepStain™ System when used as intended with direct-to-vial specimens. The previous clinical studies used a split-sample method in which the sample was first used to create a conventional Pap smear slide, and the remaining sample was placed in the SurePath® collection fluid and processed by the PrepStain™ System to create a SurePath® slide. It is well established that split-sample designs underestimate the true performance of the test that is prepared from the residual cellular material¹².

This study compared the performance of SurePath® slides produced from direct-to-vial samples to conventional Pap smears. Results obtained with SurePath were compared to results obtained from an historical cohort of conventional Pap smears. Specifically, this study evaluated whether SurePath® slides improved the detection of high-grade squamous intraepithelial lesions (HSIL), adenocarcinoma in-situ, and cancer (HSIL+). All available biopsy data was collected for both slide populations.

The SurePath® population consisted of 58,580 slides collected prospectively from 57 clinics that had converted almost 100% from conventional Pap smear collection to the SurePath® specimen collection. The specimens collected at these clinics were sent to three clinical sites for processing.

The conventional population consisted of 58,988 slides from the same clinics as the SurePath® slides. This historical population was collected beginning with most recent slides before the clinics converted to SurePath®, and then going back in time until the conventional and SurePath® slide populations at each clinical site were approximately equal in number.

The results from this study showed a detection rate of 405/58,580 for the SurePath® slides compared to 248/58,988 for the conventional slides, resulting in detection rates of 0.691% and 0.420%, respectively (see Table 26). For these clinical sites and these study populations, this indicates a 64.4% (p<0.00001) increase in detection of HSIL+ lesions for the SurePath® slides.

Table 26 Comparison of Detection Rates by Site

Site	Conventional			SurePath®		
	Total	HSIL+	Percent(%)	Total	HSIL+	Percent(%)
1	41,274	216	0.523	40,735	300	0.736
2	10,421	19	0.182	10,676	78	0.731
3	7,293	13	0.178	7,169	27	0.377
Total	58,988	248	0.420	58,580	405	0.691

Site	Conventional			SurePath®		
	Total	LSIL+	Percent(%)	Total	LSIL+	Percent(%)
1	41,274	765	1.853	40,735	1501	3.685
2	10,421	96	0.921	10,676	347	3.250
3	7,293	99	1.357	7,169	127	1.772
Total	58,988	960	1.627	58,580	1975	3.371

Site	Conventional			SurePath®		
	Total	ASCUS+	Percent(%)	Total	ASCUS+	Percent(%)
1	41,274	1,439	3.486	40,735	2,612	6.412
2	10,421	347	3.330	10,676	689	6.454
3	7,293	276	3.784	7,169	285	3.975
Total	58,988	2,062	3.496	58,580	3,586	6.122

Site	Conventional			SurePath®		
	Total	UNSAT	Percent(%)	Total	UNSAT	Percent(%)
1	41,274	132	0.320	40,735	37	0.091
2	10,421	163	1.564	10,676	89	0.834
3	7,293	20	0.274	7,169	4	0.056
Total	58,988	315	0.534	58,580	130	0.222

Note: Site to site variations in performance are expected. Each laboratory must carefully monitor the quality of its work

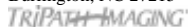
PROCEDURE

Complete procedures for preparing SurePath® slides are provided in the Operator's Manual for the PrepStain™ System.

BIBLIOGRAPHY

- Kurman RJ, Solomon D (editors): The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses: Definitions, Criteria and Explanatory Notes for Terminology and Specimen Adequacy. New York, Springer Verlag, 1994
- Bishop JW: Comparison of the CytoRich® System with conventional cervical cytology: Preliminary data on 2,032 cases from a clinical trial site. Acta Cytol 1997; 41:15-23
- Bishop JW, Bigner SH, Colgan TJ, Husain M, Howell LP, McIntosh KM, Taylor DA, Sadeghi M: Multicenter masked evaluation of AutoCyte PREP thin layers with matched conventional smears: Including initial biopsy results. Acta Cytol 1998; 42:189-197
- Geyer JW, Hancock F, Carrico C, Kirkpatrick M: Preliminary Evaluation of CytoRich®: An improved automated cytology preparation. Diagn Cytopathol 1993; 9:417-422
- Grohs HK, Zahner DJ, Geyer JW: Standardization of specimen preparation through mono/thin-layer technology in Automated Cervical Cancer Screening. Edited by HK Grohs, OAN Husain. New York, Igaku-Shoin, 1994, pp. 176-185
- Howell LP, Davis RL, Belk TL, Agdigos R, Lowe J: The AutoCyte preparation system for gynecologic cytology. Acta Cytol 1998; 42:171-177
- McGoogan E, Reith A: Would monolayers provide more representative samples and improved preparations for cervical screening? Overview and evaluation of systems available. Acta Cytol 1996; 40:107-119
- Vassilakos P, Cossali D, Albe X, Alonso L, Hohener R, Puget E: Efficacy of monolayer preparations for cervical cytology: Emphasis on suboptimal specimens. Acta Cytol 1996; 40:496-500
- Wilbur DC, Facik MS, Rutkowski MA, Mulford OK, Atkinson KM: Clinical trials of the CytoRich® specimen-preparation device for cervical cytology: Preliminary results. Acta Cytol 1997; 41:24-29
- Center For Devices and Radiological Health, Food and Drug Administration. Points to consider: Cervical cytology devices. July 25, 1994. This document is available from the Division of Small Manufacturers (DSMA), 1-800-638-2041
- Shatzkin A, Conner RJ, Taylor PR, Bunnag B: Comparing new and old screening tests when a reference procedure cannot be performed on all screeners. Am J Epidemiol 1987; 125: 672-678
- Austin RM, Ramzy I: Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations. A review of accumulated data. Acta Cytol 1998; 42: 178-184
- McNemar Q: Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947; 12:153-7
- Mayeaux EJ, Harper MB, Fleurette A, Pope JB, Phillips GS: A comparison of the reliability of repeat cervical smears and colposcopy in patients with abnormal cervical cytology. J Fam Pract 1995; 40: 57-62
- College of American Pathologists. Interlaboratory comparison program in cervicovaginal cytology (PAP). 1995
- Bur M, Knowles K, Pekow P, Corral O, and Donovan J: Comparison of ThinPrep preparations with conventional cervicovaginal smears: Practical considerations. Acta Cytol 1995; 39: 631-642
- Evans SK, Wilbur DC: Identification of endocervical cells and microorganisms on cervical thin layer cytology specimens: Comparison to paired conventional smears. Acta Cytol 1993; 37: 776
- Fleiss, Joseph L. Statistical Methods for Rates and Proportions. 2nd Ed. New York: John Wiley & Sons, 1981.
- Solomon D, Nayar R (editors): The Bethesda System for Reporting Cervical Cytology. New York, Springer Verlag, 2004

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