

Final 3-3-06

SAVANT LABORATORY SYSTEM™

MONoprep®

LIQUID-BASED PREPARATION
PROCESSOR

MonoPrep Pap Test (MPPT)

Laboratory Information and Instructions

Doc. 13501 Rev. 1.0



MonoGen, Inc.
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Distributed exclusively in the USA
By **Cardinal Health**
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INTENDED USE

The MonoPrep Pap Test (MPPT or MonoPrep) is intended for use in collecting and preparing cervical-vaginal cytology specimens for Pap stain-based screening for cervical cancer, its precursor lesions and other cytologic categories and conditions defined by *The 2001 Bethesda System: terminology for reporting results of cervical cytology*.¹ The MonoPrep Pap Test produces slides that are intended to replace conventionally prepared Pap smear slides.

SUMMARY AND EXPLANATION OF THE MPPT

MonoPrep is a liquid-based Pap test. Liquid-based Pap tests are a well-established alternative to Pap smears. The MonoPrep process begins with the clinician collecting ectocervical and endocervical specimens in accordance with current accepted practice (see *MonoPrep Pap Test Collection Site Package Insert*) using the provided MonoPrep vials and collection devices. The clinician transfers the specimen to the MonoPrep vial by rinsing the collection devices in the MPPT collection vial. The vial is closed and sent to the laboratory for processing. The preprinted vial barcode facilitates accurate accessioning at the laboratory. The laboratory prepares Pap test slides from the MPPT vials using the MPPT filters and MonoPrep Processor. MonoPrep slides have unique laser etched barcodes that ensure accurate specimen identity and chain of custody. The laboratory stains and evaluates MPPT slides in accordance with its customary practice.

The MonoPrep process deposits a representative sample of the specimen within a 20mm circle on the barcoded MonoPrep slides. MonoPrep slides display the uniformity and the reduction of artifacts and obscuration associated with liquid-based Pap tests, while retaining many of the morphological features associated with Pap smears. Individual cells display minimal shrinkage with well-preserved morphology. MonoPrep is designed to minimize obscuring cell overlap, debris, and other material as well as air-drying and other artifacts, permitting visualization of diagnostically relevant cells and infectious organisms.

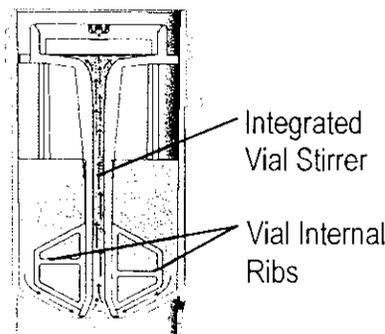
PRINCIPLE OF THE PROCEDURE

Procedure Summary: In the MonoPrep process, the clinician transfers patient specimen to a liquid medium that prevents air-drying artifacts during transport to the laboratory. At the laboratory, the specimen is agitated to disperse obscuring mucus, as well as loose clumps and aggregates. Mixing also enables transfer of cells representative of the entire specimen to the slides. During processing, cells are collected on a disposable MPPT filter and, subsequently, transferred to slides for staining and evaluation.

MPPT Procedure: The alcohol-based MPPT-Specimen Transport Solution (MPPT-STS) preserves the specimen's cellular morphology and prevents microbial growth. The MPPT-STS has been demonstrated to preserve specimen for 12 months from collection when stored under typical laboratory and shipping conditions (see *Storage and Stability, p4*).

The MonoPrep vial design employs proprietary features unique to the MonoPrep Pap Test. The integrated vial stirrer and the vial internal ribs work together to mix the specimen efficiently, and to disperse mucus, clumps and aggregates without requiring mucolytic agents.

A well-dispersed specimen is then aspirated or "drawn up" the stirrer and the MonoPrep dual-flow technology captures the representative sample on the frit-backed filter. The



The vial employs proprietary features unique to the MonoPrep processing method.

MonoPrep filter is then gently pressed against the slide to transfer the cells. The compliant frit assures uniform pressure and cell distribution on the resultant slide.

Slides are individually fixed using a pre-measured amount of fixative dispensed directly onto the slide. The MPPT-STS also helps maintain the stability of the cells on the MonoPrep slides in a dry state for at least seven days following cell transfer.

MonoPrep processing is designed to prevent specimen carry-over or cross contamination. In a non-clinical study, specimens with high concentrations of cellular material were interleaved with MPPT-STS blanks. In that study, no cellular carry-over was detected using microscopic examination of the resulting slides.

Based on a laboratory study, MPPT specimens are not affected by interfering substances that might be encountered with cervical specimens: (e.g., blood, mucus, vaginal lubricants, contraceptives, cleansing feminine hygiene products, or yeast infection treatments). Excessive amounts of blood or debris, however, can reduce cellularity, cause obscuration, or interfere with testing. In most cases, proper collection prevents this problem.

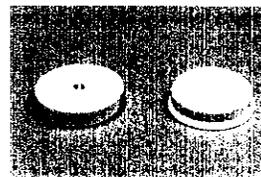
MATERIALS SUPPLIED



MonoPrep Pap Test
Collection Vial



MonoPrep Pap Test
Collection Kits



MonoPrep Pap Test Filters

MATERIALS REQUIRED BUT NOT SUPPLIED

- MonoPrep Processor and consumables
- Disposable forceps and pipette
- Gloves and other standard Universal Precaution supplies

NOTE: See MonoPrep Processor Operator's Manual for operating instructions.

WARNINGS



DANGER: MonoPrep Pap Test Specimen Transport Solution contains Methanol. Do not take internally. Vapor is harmful. May be fatal or cause blindness if swallowed. Cannot be made nonpoisonous. MonoPrep Pap Test Specimen Transport Solution and specimen should be stored and disposed of in accordance with local, state, and federal regulations.



POISON



FLAMMABLE



WARNING: Potential Biohazard. MonoPrep Specimen Transport Solution was tested per USP 26 [51]-Antimicrobial Effectiveness. MPPT Specimen Transport Solution met the requirements for that test, demonstrating antimicrobial effect on the following organisms: *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans* and *A. niger*. However, Universal Precautions per OSHA regulations [29 CFR 1910. 1030] should be observed with all specimen containing or exposed vials, reagents, waste and equipment.

PRECAUTIONS

In Vitro diagnostic use only. The MonoPrep Pap Test is intended for professional use only.



Caution: Do not write on the collection vial or label other than in the blank lined area indicated. Use only permanent markers.

SPECIMEN HANDLING**Storage and Stability:****MPPT Specimen Transport Solution (MPPT-STS) in MPPT Collection Vials and 1L bottles****Store and Ship MPPT Collection Vials at 15-30°C**

Do not use beyond expiration date printed on container
(12 months from manufacture date)

MPPT-STS is unaffected by brief exposures to temperatures outside of intended storage and shipping condition:

<u>As low as</u>	<u>As high as</u>	<u>Period</u>
2°C	37°C	3 weeks
-20°C	55°C	6 hours

Specimens in MPPT Collection Vials**Store and Ship MPPT Specimens at 15-30°C**

Specimens are preserved for 12 months from collection date.

Specimens are unaffected by brief exposures to temperatures outside of intended storage and shipping condition:

<u>As low as</u>	<u>As high as</u>	<u>Period</u>
2°C	37°C	3 weeks
-20°C	55°C	6 hours

Handling: Inspect vials prior to collection and accessioning. Do not use vials with damaged (e.g., torn or defaced) or detached vial labels (tamper evident label should be intact prior to specimen collection and broken at accessioning), or if the MPPT-STS is not a clear teal blue color prior to specimen addition.

Specimen Collection: Collect specimens using the MonoPrep Pap Test Specimen Collection Kit. For collection instructions, see attached *Doc. 12369 Package Insert: MonoPrep® Pap Test Specimen Collection Kit*

Shipping: Specimens should be transported in accordance with applicable DOT/IATA/ISTA guidelines. For hazard notification information, see attached *Doc. 12372 Material Safety Data Sheet: MonoPrep® Pap Test Specimen Transport Solution*.

Processing: Accession vials and process using the MonoPrep Processor and consumables. For specimen accessioning, see attached *Doc. 13504 Procedure: MonoPrep® Pap Test Specimen Accessioning Instructions*. MPPT processing on other systems has not been validated. Load vials and process per operating instructions. Unload, and store vials per laboratory procedure and processor operating instructions. Stain and coverslip slides per

laboratory protocol. Processed slides may be stored in dry condition (e.g., without staining and coverslipping for up to seven days at 15-37°C prior to staining.

Filters: Load MonoPrep Pap Test Filters per operating instructions. Discard any dropped or damaged filters. Do not reuse filters or filter tubes.

Vial Transfer and Specimen Reprocessing: Most MPPT specimens can be reprocessed in the case of UNSAT, lost or damaged slides, damaged vials, or to make additional slides. Vial reprocessing involves transferring of the remaining specimen to a new vial and loading on the MonoPrep Processor to prepare a new slide. UNSAT specimens due to excessive blood, mucus or other causes are rare (1.17% (126/10,739) in the clinical study). In the event a slide is UNSAT due to breakage, an unreadable bar code, or instrument issues, a satisfactory slide often can be prepared following reprocessing (91.1% [41/45] of the time in the clinical study). In the event a slide is UNSAT due to scant cellularity, obscuring inflammation or other obscuring matter, a satisfactory slide was prepared in 32% (18/56) cases in the clinical study. This excludes the 45 cases for which acetic acid treatment was used. (i) Doc. 13502 Procedure: MonoPrep® Specimen Reprocessing and (ii) Doc. 13503 Procedure: MonoPrep® Specimen Transfer.

QUALITY CONTROL

Slides should be considered successful using Bethesda 2001 criteria if they are deemed "Satisfactory" (i.e., >5,000 well visualized squamous epithelial cells). Most slides should have consistent, uniform deposition, staining and morphological appearance. In a random sample of slides from the pivotal clinical study, the number of squamous epithelial cells on a slide ranged from 27,000 to 143,000, in 90% of the slides. The average number of squamous epithelial cells was 60,000 with 95%CI: 42,000~78,000. In the event of UNSAT slides, the specimen should be reprocessed. Unexplained increased in the frequency of slides with deviations in slide quality, absent endocervical material, or significant obscuring matter, should be investigated for procedural conformance with MPPT specimen collection and processing instructions, and for laboratory staining and handling procedures.

LIMITATIONS OF THE PROCEDURE

Preparation of samples with MPPT has only been validated using the MonoPrep Processor. Use with other instruments or manual procedures has not been validated.

Use only MonoPrep consumables with the MonoPrep Pap Test. Use of other consumables (such as slides) has not been validated.

Use only endocervical cytobrush and plastic cytospatula for collection. Do not use "breakaway" tipped collection devices.

Treating UNSAT bloody specimens with acetic acid has not been validated for the MonoPrep Pap Test.

Only individuals who have completed MonoGen, Inc. authorized training should evaluate slides (see attached *Doc. 13505 Summary: The MonoPrep® Pap Test Morphology Training Program*).

CONTRAINDICATIONS

There are no contraindications for use of the MonoPrep Pap Test.

PERFORMANCE CHARACTERISTICS

Clinical Study Design

A prospective, multi-center, masked, split-sample study was conducted in which the objective was to assess MonoPrep Pap Test (MPPT) performance as compared to the conventional Pap smear (PS) for the detection of cervical cancer, pre-cancerous lesions and atypical cells, in subjects representing a spectrum of high, intermediate, and low-risk populations. In addition, an assessment of specimen adequacy, endocervical cells and other analyses was performed. This study used a split-sample design, in which the Pap smear was collected and prepared using FDA-cleared spatula and endocervical cytobrush. The smear residuum remaining on the collection device was then rinsed in the MPPT collection vial which was used to prepare the MPPT slide by the study laboratory. Hence, each case consisted of two slides, one prepared by MPPT and one by PS. MPPT and conventional Pap smear slides were subjected to independent, masked review by the laboratory.

Both MPPT and conventional Pap smear slides of the subjects for whom either the MPPT or Pap smear slides were diagnosed as Reactive/Reparative or more severe by the study laboratory, and at least 5% of all cases where both slides were diagnosed as NILM-WNL or UNSAT were submitted to one of the five experts, board-certified cytopathologists for masked independent reference review. The review process was used to establish an independent reference diagnosis for each patient for comparing the clinical performance of MPPT to Pap smears.

Laboratory and Patient Characteristics: The study was conducted at four regional laboratory laboratories. Each laboratory was fully accredited, and all study personnel were required to have documented competence with screening Pap smears and liquid-based Pap tests. Each laboratory typically performs at least 100,000 Pap tests per year. Each laboratory was also required to have at least two certified cytotechnologists and at least one board certified cytopathologist to participate in the study.

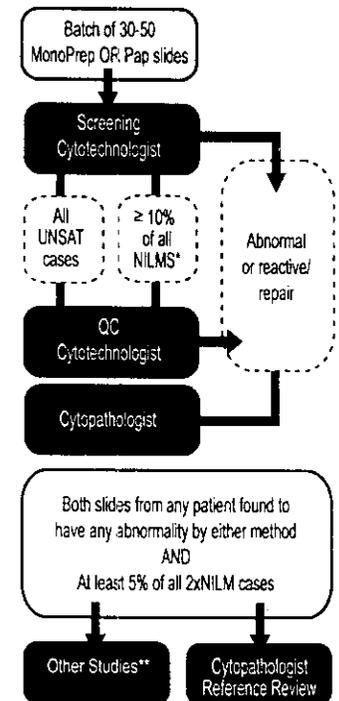
A total of 11,244 subjects were enrolled in the study. Of these 11,244, the specimens from 339 (3.0%) were received after study cutoff date and not processed or evaluated. Of 10,905 subjects whose specimens were accepted for processing and evaluation, 121 (1.1%) were excluded from the statistical analysis due to at least one major protocol violation. Among these subjects, there were 45 cases in which acetic acid was used for the preparation of the MPPT slides; these cases were also excluded from the statistical analysis of effectiveness. The total number of subjects included in the statistical analysis of effectiveness was **10,739**.

Table 1 provides the annual Pap smear and liquid-based Pap test volume and number of subjects evaluated at each of the four study labs. In nearly all cases, the matching Pap smear and MPPT specimen were sent to the same laboratory.

Table 1. Laboratory Description and Number of Subjects Evaluated

Site	Pap Volume		Subjects Evaluated
	Smear	Liquid	
1	21,000	191,700	3,045
2	24,400	80,700	2,147
3	126,200	54,200	2,119
4	310,100	78,300	3,428

Specimen Processing and Examination Flow Chart



* Chosen first from all high-risk NILMs + balance composed of randomly selected non-high risk NILMs.

** Other: additional specimen studies no part of this study.

Specimens were collected from gynecology medical practices, health clinics, and medical referral centers providing gynecology services to patients representing a spectrum of high to low prevalence populations and diverse ethnic and racial heritage, age and geographical location. These included 75 US and 13 international (11 South African and 2 Venezuelan) collection sites. The following tables present the laboratory and subject information. IRB approved informed consent was obtained from all evaluable subjects. The demographic characteristics of the study population are provided in Table 2.

Table 2. Subject Demographics

Parameter	All Subjects (n=10,739)	
	n	(%)
US subjects	7,689	(72%)
International subjects	3,050	(28%)
Age		
Range	18 to 90	
Mean±SD	35.4±12.2	
Cervical Risk		
High-risk subjects	3,513	(33%)
Abnormal Pap in previous five years	1610	(15.0%)
Race/Ethnic		
White	5,213	(49%)
Hispanic	2,690	(25%)
Black	1,400	(13%)
Other (or not provided)	1,141	(11%)
Asian	227	(2.1%)
Indian	37	(0.3%)
Pacific	31	(0.3%)

Laboratory Cytology Review: Each laboratory had the participation of at least two screening cytotechnologists, at least one quality-control (QC) cytotechnologist, and at least one board-certified cytopathologist. Pap smear and MonoPrep slides were prepared, screened, and interpreted by the participating laboratories' study cytotechnologists and cytopathologists in the same manner as their routine practice, except in the case of certain protocol procedures intended to maintain consistency across the laboratory sites (e.g., common definition of "high-risk" to be used for selection of cases requiring QC review). All slides were interpreted for the study in accordance with CLIA requirements using TBS2001 nomenclature, including the criteria for a satisfactory slide. All reading of MonoPrep slides was performed independently of Pap smear reviews. Tables 3 and 4 present the comparison of the TBS2001 diagnostic categories for MPPT slides vs. conventional Pap smear slides obtained by laboratory cytology review (Lab MPPT vs Lab PS) for all four sites combined (Table 3) and each site separately (Table 4).

Table 3. Laboratory MPPT Diagnosis vs Laboratory PS Diagnosis (Combined Sites)

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT	43	58	6	12			5	2				126
NILM-WNL	209	7,744	198	459	16	35	55	15			1	8,732
NILM-RR	11	214	59	40	1	1	6	2		1		335
ASC-US	23	538	41	201	4	7	73	7				894
ASC-H	1	9		10			2	2		1		25
AGC	4	21	1	4	1	1	1		1			34
LSIL	6	135	1	112	1		176	27		1		459
HSIL	2	4		10	7	1	22	50		6		102
AIS	1								2			3
SCC	2			1	4			5		13		25
AC								1		2	1	4
Total	302	8,723	306	849	34	45	340	111	3	24	2	10,739

Table 4. Summary Laboratory Diagnosis vs Site

Site	Method	Lab Dx											Total
		UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	
	MPPT	61	2,367	64	245	14	12	195	58	3	22	4	3,045
	PS	120	2,283	45	298	21	13	163	77	3	21	1	3,045
2	MPPT	21	1,684	195	172	4	8	51	11		1		2,147
	PS	74	1,646	201	159	9	13	36	6		2	1	2,147
3	MPPT	33	1,828	76	102	7	2	63	7		1		2,119
	PS	80	1,853	58	75	4	1	41	7				2,119
4	MPPT	11	2,853		375		12	150	26		1		3,428
	PS	28	294	2	317		18	100	21		1		3,428
Combined	MPPT	126	8,732	335	894	25	34	459	102	3	25	4	10,739
	PS	302	8,723	306	849	34	45	340	111	3	24	2	10,739
Grouped Diagnoses	MPPT	UNSAT/NILM (WNL/RR)		9,193	ASCUS+	1,546	LSIL+	593	HSIL+	134	Cancer	32	
	PS			9,331		1,408		480		140		29	

Reference Diagnosis by Independent Pathologist:

The independent pathology (IP) review panel was composed of five (5) board-certified cytopathologists. The cases which had either PS or MPPT laboratory diagnoses of NILM-RR and above were designated for IP review. There were 2,690 cases in the study with laboratory diagnoses of NILM-RR and above on PS and/or MPPT slides; 2,684 cases (99.8%) were referred to the panel. In addition, 508 cases (6.3%) randomly selected from the 8,094 cases that were diagnosed at the laboratories as NILM-WNL or UNSAT on both PS and MPPT were referred for IP review.

Each of the slides in the referred cases was separately randomized to one of the five cytopathologists for review. Randomization was independently performed for MPPT and PS, and for slides from each site to ensure a balanced random allocation of slides among five reference cytopathologists. The two slides were reviewed by the reference cytopathologists for 3,192 referred cases. Each slide was masked as to the laboratory

Diagnostic Abbreviation:

UNSAT = Unsatisfactory;
NILM-WNL = Negative for Intraepithelial Lesions or Malignancy, Within Normal Limits;

NILM-RR = Negative for Intraepithelial Lesions or Malignancy, Reparative/Reactive;

ASC-US = Atypical Squamous Cells of Undetermined Significance;

ASC-H = Atypical Squamous Cells, cannot exclude HSIL;

AGC = Atypical Glandular Cells;

LSIL = Low-grade Squamous Intraepithelial Lesion;

HSIL = High-grade Squamous Intraepithelial Lesion;

AIS = Adenocarcinoma in situ;

SCC = Squamous Cell Carcinoma;

AC = Adenocarcinoma.

diagnosis for either slide in the case. Seven (7) cases, for which acetic acid was used to reprocess the MPPT slides, were excluded from the statistical analysis.

For each case (3,185 in all), the reference diagnosis was recorded as the most abnormal diagnosis from the two IP-reviewed slides. This result was used as the cytological "truth" diagnosis for the case or Reference Diagnosis by Independent Pathologist ("Reference Diagnosis", or RDIP). To assess the performance of the MPPT relative to conventional Pap smear for each IP-reviewed case, the laboratory diagnoses made by the study site using the two methods were compared to the RDIP.

Table 5. Independent Pathologist MPPT Diagnosis vs Independent Pathologist PS Diagnosis (Combined Sites)

IP MPPT Dx	IP PS Dx											
	UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	Total
UNSAT	26	24	8	11	4	1	5	3			1	83
NILM-WNL	100	568	174	162	17	3	36	14				1,074
NILM-RR	62	217	104	93	14	4	23	11				528
ASC-US	67	248	89	131	22	2	56	17			1	633
ASC-H	11	27	18	12	6	1	8	6				89
AGC	1	13	3	3	2		1	1		1		25
LSIL	35	136	34	116	6		153	13		1		494
HSIL	8	38	18	50	8	1	28	66	1	5		223
AIS	1	1							1			3
SCC	7		1	1	2			9		10	1	31
AC					1						1	2
Total	318	1,272	449	579	82	12	310	140	2	17	4	3,185

The Reference Diagnosis for a case was the more severe diagnosis from either MPPT or PS slides as determined by the Independent Pathologist. In the clinical study, there were 46 cases with Reference Diagnosis of Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS), 328 cases with Reference Diagnosis of HSIL+, 937 cases with Reference Diagnosis of LSIL+, 1,101 cases with Reference Diagnosis of ASC-H+, and 1,902 cases with Reference Diagnosis of ASC-US+.

Outcome Measures: MonoPrep Pap Test screening performance was compared to Pap smear by assessing the relative detection of cervical abnormalities and other conditions, as defined in *The Bethesda System 2001* (TBS2001). Clinical sensitivity and specificity (e.g., with reference to a histological diagnosis) cannot be measured in this study, which relied on cytological examination alone. Instead, laboratory positive and false positive diagnoses by both methods, MPPT and PS, for the cases with a Reference Diagnosis by the Independent Pathologists (RDIP) of ASC-US+, ASC-H/AGC+, LSIL+, HSIL+ and cancer were compared. The prospectively designed primary objective was to demonstrate that MPPT provides a statistically significant improvement over screening with Pap smears for the detection of cases with RDIP-confirmed ASC-US+ and LSIL+ cases.

About 6% of the cases with both PS and MPPT results of NILM-WNL were referred for RDIP. A result is that the data set of the 3,185 cases with RDIP necessarily have a statistical verification bias because only random sample of cases with both PS and MPPT results of NILM-WNL are submitted for RDIP. Despite this verification bias, the ratio of true positive rates by the two methods and the ratio of false positive rates by the two methods are unbiased.^(7,8) For the various comparisons made below, true positive results are those for which a positive laboratory diagnosis is matched by a positive RDIP. Results

without such a match were false positive. The ratios of true positive rates (TPR_{MPPT}/TPR_{PS}) and ratios of false positives rates (FPR_{MPPT}/FPR_{PS}) and their 95% confidence intervals were calculated for the cases with Reference Diagnosis of ASC-US+, ASC-H/AGC+, LSIL+, HSIL+, and cancer. The statistical significance of ratios differing from 1.0 was demonstrated when the 95% confidence interval did not include 1.0.

CLINICAL STUDY DATA RESULTS AND ANALYSIS

Tables 6 through 10 present the comparison of laboratory true positive and false positive rates for ASC-US+ (Table 6); ASC-H+/AGC+ (Table 7); LSIL+ (Table 8); HSIL+ (Table 9) and Cancer (Table 10). Tables present the number of RDIP positive and negative cases for each cutoff, the number of positive and negative laboratory results, and their ratio. These data are presented for each site, and include the 95%CI of the ratio for the pooled result of all sites for each cutoff. Data for each site are presented to illustrate the degree of consistency of the results across all sites.

Table 6. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of ASC-US+

In this table, "Positive" means "ASC-US+" (combined ASC-US, ASC-H, AGC, LSIL, HSIL, and Cancer) and "Non-Positive" means "Non-ASC-US+" (combined NILM-RR, NILM-WNL, and UNSAT).

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio TPR_{MPPT}/TPR_{PS}	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio FPR_{MPPT}/FPR_{PS}
Site 1	702	489	479	1.02	361	64	117	0.55
Site 2	303	163	135	1.21	535	83	91	0.91
Site 3	272	171	115	1.49	105	11	13	0.85
Site 4	625	451	382	1.18	282	113	75	1.51
Combined (95% CI)	1,902	1,274	1,111	1.15 (1.09; 1.20)	1,283	271	296	0.92 (0.77; 1.06)

The results presented in Table 6 show that for the cases with a Reference Diagnosis of ASC-US+, the MPPT method detected 1.15 (1,274/1,111) times more true positive cases than the PS method detected, for all sites combined. This increase was statistically significant, with the lower limit of the 95% confidence interval at 1.09. The observed ratios of the true positive rates varied among the sites from 1.02 to 1.49.

The ratio of the false positive rates was 0.92 (271/296), for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with 95% confidence interval of 0.77 to 1.06.

Table 7. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of ASC-H/AGC+

In this table, "Positive" means "ASC-H/AGC+" (combined ASC-H, AGC, LSIL, HSIL, and Cancer) and "Non-Positive" means "Non-ASC-H/AGC+" (combined ASC-US, NILM-RR, NILM-WNL, and UNSAT).

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	444	274	247	1.11	619	34	52	0.65
Site 2	131	49	43	1.14	707	26	24	1.08
Site 3	159	75	45	1.67	218	5	8	0.63
Site 4	367	139	103	1.35	540	50	37	1.35
Combined (95% CI)	1,101	537	438	1.23 (1.13; 1.32)	2,084	115	121	0.95 (0.72; 1.18)

The results presented in Table 7 show that for the cases with a Reference Diagnosis of ASC-H/AGC+, the MPPT method detected 1.23 (537/438) times more true positive cases than the PS method detected, for all sites combined. This increase was statistically significant with the lower limit of the 95% confidence interval at 1.13. The observed ratios of the positive rates varied among the sites from 1.11 to 1.67.

The ratio of the false positive rates was 0.95 (115/121) for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with 95% confidence interval of 0.72 to 1.18.

Table 8. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of LSIL+

In this table, "Positive" means "LSIL+" (combined LSIL, HSIL, and Cancer) and "Non-Positive" means "Non-LSIL+" (combined AGC, ASC-H, ASC-US, NILM-RR, NILM-WNL, and UNSAT).

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	388	250	220	1.14	675	32	45	0.71
Site 2	97	43	32	1.34	741	20	13	1.54
Site 3	141	66	43	1.53	236	5	5	1.00
Site 4	311	127	90	1.41	596	50	32	1.56
Combined (95% CI)	937	486	385	1.26 (1.16; 1.36)	2,248	107	95	1.13 (0.84; 1.41)

The results presented in Table 8 show that for the cases with a Reference Diagnosis of LSIL+, the MPPT method detected 1.26 (486/385) times more true positive cases than the PS method detected, for all sites combined. This increase was statistically significant with the lower limit of the 95% confidence interval at 1.16. The observed ratios of the positive rates varied among the sites from 1.14 to 1.53.

The ratio of the false positive rates was 1.13 (107/95) for all sites combined. The observed increase in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with 95% confidence interval of 0.84 to 1.41.

Table 9. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of HSIL+

In this table, "Positive" means "HSIL+" (combined HSIL, and Cancer) and "Non-Positive" means "Non-HSIL+" (combined LSIL, AGC, ASC-H, ASC-US, NILM-RR, NILM-WNL, and UNSAT).

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	156	79	82	0.96	908	8	20	0.40
Site 2	32	8	6	1.33	806	4	3	1.33
Site 3	31	7	6	1.17	346	1	1	1.00
Site 4	109	19	15	1.27	798	8	7	1.14
Combined (95% CI)	328	113	109	1.04 (0.88; 1.19)	2,857	21	31	0.68 (0.33; 1.02)

The results presented in Table 9 show that for the cases with a Reference Diagnosis of HSIL+, the MPPT method detected 1.04 (113/109) times more true positive cases than the PS method detected, for all sites combined. This increase was not statistically significant with the 95% confidence interval of 0.88 to 1.19. The observed ratios of the positive rates varied among the sites from 0.96 to 1.33.

The ratio of the false positive rates was 0.68 (21/31) for all sites combined. The observed increase in the false positive MPPT rate relative to the false positive PS rate was not statistically significant with a 95% confidence interval of 0.33 to 1.02.

Table 10. Laboratory MPPT Results Versus Laboratory PS Results for the Cases with Reference Diagnosis by Independent Pathologist of Cancer

In this table, "Positive" means "Cancer" (combined AIS, Squamous Cell Carcinoma, and Adenocarcinoma) and "Non-Positive" means "Non-Cancer" (combined HSIL, LSIL, AGC, ASC-H, ASC-US, NILM-RR, NILM-WNL, and UNSAT).

Site	Cases Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{TPR_{MPPT}}{TPR_{PS}}$	Cases Non-Pos. by IP	MPPT Pos.	PS Pos.	Ratio $\frac{FPR_{MPPT}}{FPR_{PS}}$
Site 1	40	26	21	1.24	1,023	3	4	0.75
Site 2	1	0	1	0.0	837	1	2	0.5
Site 3	1	1	0	n/a	376	0	0	n/a
Site 4	4	1	1	1.0	903	0	0	n/a
Combined (95% CI)	46	28	23	1.22 (0.87; 1.75)	3,139	4	6	0.66

The results presented in Table 10 show that for the cases with a Reference Diagnosis of Cancer, the MPPT method detected 1.22 (28/23) times more true positive cases than the PS method detected, for all sites combined. This increase was not statistically significant with the 95% confidence interval of 0.87 to 1.75. The ratio of the false positive rates was 0.66 (4/6) for all sites combined. The observed decrease in the false positive MPPT rate relative to the false positive PS rate was not statistically significant.

LABORATORY MPPT VERSUS PAP SMEAR RESULTS FOR INDIVIDUAL RDIP-ESTABLISHED TBS2001 CATEGORIES

Tables 11-19 show the comparison of the laboratory MPPT diagnosis and laboratory PS diagnosis for the cases with the following Reference Diagnoses: Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS), HSIL, LSIL, AGC, ASC-H, ASC-US, NILM-RR, and NILM-WNL separately. This comparison illustrates the diversity of laboratory results with MPPT and Pap smear method for each Reference Diagnosis. An IP diagnosis was made for each slide, and may or may not be the same within a case. The RDIP was the most severe of the two IP diagnoses.

Table 11. Cases with Reference Diagnosis of NILM-WNL

Lab MPPT Dx	Lab PS Dx											
	UNSAT	NILM-WNL	NILM-RR	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	SCC	AC	Total
UNSAT		1	1	3								5
NILM-WNL	5	310	69	93	3	7	6					493
NILM-RR	4	58	18	8			1					89
ASC-US	1	82	3	10		1						97
ASC-H		2										2
AGC		2										2
LSIL		4										4
HSIL												
AIS												
SCC												
AC												
Total	10	459	91	114	3	8	7					692

Among the 692 cases with a Reference Diagnosis of NILM-WNL, 493 (71.2%) cases had a laboratory MPPT diagnosis of NILM-WNL and 459 cases (66.3%) had a laboratory PS diagnosis of NILM-WNL; 4 cases (0.6%) had laboratory MPPT diagnosis of LSIL+ and 7 (1.0%) cases had laboratory PS diagnosis of LSIL+.

Table 12. Cases with Reference Diagnosis of NILM-RR

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT			3				2					5
NILM-WNL	3	95	75	102	4	10	8	1				298
NILM-RR	5	72	20	10								107
ASC-US	5	105	10	9	1	1	3					134
ASC-H				1								1
AGC		5	1	1								7
LSIL	1	10		1								12
HSIL					1							1
AIS												
SCC												
AC												
Total	14	287	109	124	6	11	13	1				565

Among the 565 cases with a Reference Diagnosis of NILM-RR, 107 (18.9%) cases had a laboratory MPPT diagnosis of NILM-RR and 109 cases (19.3%) had a laboratory PS diagnosis of NILM-RR; 13 cases (2.3%) had laboratory MPPT diagnosis of LSIL+ and 14 (2.5%) cases had laboratory PS diagnosis of LSIL+.

Table 13. Cases with Reference Diagnosis of ASC-US

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT	1			2			2	1				6
NILM-WNL		58	45	163	7	6	20					299
NILM-RR	2	53	11	12			2					80
ASC-US	7	211	15	79	1	2	15	1				331
ASC-H		1		3								4
AGC	1	5										6
LSIL		34	1	25			9	3				72
HSIL		1		1	1							3
AIS												
SCC												
AC												
Total	11	363	72	285	9	8	48	5				801

Among the 801 cases with a Reference Diagnosis of ASC-US, 416 (51.9%) cases had a laboratory MPPT diagnosis of ASC-US+ and 355 cases (44.3%) had a laboratory PS diagnosis of ASC-US+; 379 cases (47.3%) had laboratory MPPT diagnosis of NILM and 435 (54.3%) cases had laboratory PS diagnosis of NILM.

Table 14. Cases with Reference Diagnosis of ASC-H

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT			2	2								4
NILM-WNL	1	13	8	21	2	2	3	5				55
NILM-RR		8	5	1	1		1					16
ASC-US		21	2	10		1	4	1				39
ASC-H		1						1				2
AGC				1								1
LSIL		6		4				2				12
HSIL								1				1
AIS									1			1
SCC												
AC												
Total	1	49	17	39	3	3	8	10	1			131

Among the 131 cases with a Reference Diagnosis of ASC-H, 17 (13.0%) cases had a laboratory MPPT diagnosis of ASC-H+ and 25 cases (19.1%) had a laboratory PS diagnosis of ASC-H+; 71 cases (54.2%) had laboratory MPPT diagnosis of NILM and 66 (50.4%) cases had laboratory PS diagnosis of NILM.

Table 15. Cases with Reference Diagnosis of AGC

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT												
NILM-WNL		8		4		3	1					16
NILM-RR		3	2									5
ASC-US		5			1							6
ASC-H												
AGC		2		1	1				1			5
LSIL				1								1
HSIL												
AIS												
SCC												
AC												
Total		18	2	6	2	3	1		1			33

Among the 33 cases with a Reference Diagnosis of AGC, 6 (18.2%) cases had a laboratory MPPT diagnosis of ASC-H+ and 7 cases (21.2%) had a laboratory PS diagnosis of ASC-H+; 21 cases (63.6%) had laboratory MPPT diagnosis of NILM and 20 (60.6%) cases had laboratory PS diagnosis of NILM.

Table 16. Cases with Reference Diagnosis of LSIL

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT				1			1	1				3
NILM-WNL		3		49			16	2				70
NILM-RR		7		6			1					14
ASC-US	4	89	8	72	1	1	44	1				220
ASC-H		1		2			1					4
AGC	1	1										2
LSIL	3	69		61	1		140	7				281
HSIL				3	1		9	2				15
AIS												
SCC												
AC												
Total	8	170	8	194	3	1	212	13				609

Among the 609 cases with a Reference Diagnosis of LSIL, 296 (48.6%) cases had a laboratory MPPT diagnosis of LSIL+ and 225 cases (36.9%) had a laboratory PS diagnosis of LSIL+; 84 cases (13.8%) had laboratory MPPT diagnosis of NILM and 178 (29.2%) cases had laboratory PS diagnosis of NILM.

Table 17. Cases with Reference Diagnosis of HSIL

Lab MPPT Dx	Lab PS Dx											Total
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	
UNSAT				1								1
NILM-WNL		2	1	22		5	1	7				38
NILM-RR		10	2	2			1	2				17
ASC-US	2	19	2	21		1	7	4				56
ASC-H		4		4			1	1				10
AGC	1	5		1			1					8
LSIL	2	12		20			27	15				76
HSIL	2	3		6	4		13	42		3		73
AIS												
SCC								2		1		3
AC												
Total	7	55	5	77	4	6	51	73		4		282

Among the 282 cases with a reference diagnosis of HSIL, 76 (27.0%) cases had a laboratory MPPT diagnosis of HSIL+ and 77 cases (27.3%) had a laboratory PS diagnosis of HSIL+; 55 cases (19.5%) had laboratory MPPT diagnosis of NILM and 60 (21.3%) cases had laboratory PS diagnosis of NILM.

Table 18. Cases with Reference Diagnosis of Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS)

Lab MPPT Dx	Lab PS Dx											
	UNSAT	NILM- WNL	NILM- RR	ASC- US	ASC- H	AGC	LSIL	HSIL	AIS	SCC	AC	Total
UNSAT				1		0						1
NILM-WNL						1					1	2
NILM-RR										1		1
ASC-US												
ASC-H	1									1		2
AGC		1				1						2
LSIL										1		1
HSIL						1		5		3		9
AIS	1								1			2
SCC	2			1	4			3		12		22
AC								1		2	1	4
Total	4	1		2	4	3		9	1	20	2	46

Among the 46 cases with a Reference Diagnosis of Cancer (Adenocarcinoma, Squamous Cell Carcinoma, or AIS), 37 (80.4%) cases had a laboratory MPPT diagnosis of HSIL+ and 32 (69.6%) cases had a laboratory PS diagnosis of HSIL+; 3 (6.5%) cases had a laboratory MPPT diagnosis of NILM, and 1 (2.2%) case had a laboratory PS diagnosis of NILM.

Twenty-eight (60.9%) of the 46 cases had a laboratory MPPT diagnosis of Cancer and 23 (50.0%) had a laboratory PS diagnosis of Cancer. None of the 46 (0.0%) cases had a MPPT IP diagnosis of NILM (WNL or RR); 2 (4.3%) had a PS IP diagnosis of NILM (WNL or RR). For the three cases with a MPPT Laboratory diagnosis of NILM, none were NILM by IP diagnosis of that slide.

In one case, the IP diagnosis for cancer was made only on the MPPT slide, with the Pap smear IP diagnosis being UNSAT. In post-study review by two additional cytopathologists, the MPPT slide was considered extremely difficult to diagnose because of cytolysis with poor preservation and pre-collection necrosis. There were cells suggestive of atypical repair. The PS slide was thick, air dried and poorly preserved "except for sprinkling of well preserved atypical keratinizing cells s/o squamous carcinoma."

The second case was cancer by IP diagnosis for the Pap smear, though AGC by the laboratory diagnosis of that slide. The MonoPrep laboratory diagnosis was NILM, with only primary screening cytotechnologist review, without QC review. The MPPT IP diagnosis was ASC-US. In post-study review by two additional cytopathologists, the abnormal cells in the Pap smear were considered diagnostically difficult, consistent with either endometrial adenocarcinoma or endometrial AGC. For the MPPT slide, the secondary reviewing cytopathologists concurred that "rare small atypical groups" were present.

The third case's IP diagnoses were cancer for the Pap smear and UNSAT for the MPPT slide. The MonoPrep laboratory diagnosis was NILM, with only primary screening cytotechnologist review, without QC review. In post-study review by two additional cytopathologists, both slides were considered very difficult recognition cases, with the Pap smear being UNSAT except for the identification of a "few isolated individual clearly malignant cells buried in the blood." On extensive review "some isolated but poorly preserved similar cells" were identified on the MPPT slide.

For the case with a Laboratory PS diagnosis of NILM (WNL or RR), the PS IP diagnosis was NILM (WNL or RR), while MPPT IP diagnosis was Cancer and Laboratory MPPT diagnosis was AGC. At the laboratory, the PS slide was reviewed and diagnosed as NILM-WNL by both primary and Senior QC CTs. This case was not part of the post-study slides review.

SPECIMEN ADEQUACY

Table 19 shows results from a comparison of preparation adequacy for the conventional PS and MPPT methods laboratory cytotechnologists for all sites combined and each site separately:

Table 19. Specimen Adequacy Findings

		Lab PS		
		UNSAT	SAT	Total
Lab MPPT	UNSAT	43	83	126
	SAT	259	10,354	10,613
	Total	302	10,437	10,739
		Lab		
Site	Method	UNSAT	Total Number of Slides	%UNSAT
1	MPPT	61	3,045	2.0%
	PS	120	3,045	3.9%
2	MPPT	21	2,147	1.0%
	PS	74	2,147	3.4%
3	MPPT	33	2,119	1.6%
	PS	80	2,119	3.8%
4	MPPT	11	3,428	0.3%
	PS	28	3,428	0.8%
Combined	MPPT	126	10,739	1.2%
	PS	302	10,739	2.8%

The estimated unsatisfactory slide rates observed in the laboratories (i.e., without confirmation by independent pathologist (IP)) for the MPPT method were lower than for the PS method (1.2% vs 2.8%). However, these estimates take no account of MPPT slides that might not have been recognized at the laboratories as unsatisfactory. Few (15) slide pairs with laboratory diagnoses confined to UNSAT or NILM-WNL were sent for IP review, including 13 pairs called UNSAT by PS and NILM-WNL by MPPT. Four MPPT slides from these 13 pairs were categorized as UNSAT by the IP. The number of these slide pairs, and the even smaller number of IP-reviewed pairs called UNSAT by MPPT and NILM-WNL by PS, make evaluation of this finding inconclusive.

ABUNDANCE OF ENDOCERVICAL / TRANSFORMATION ZONE COMPONENT

Laboratories assessed slides for the presence of endocervical and transformation zone component. In the split-sample study, MPPT slides demonstrated no statistically significant difference in abundance of Endocervical/Transformation zone component to matching Pap smear slides as shown in Table 20. ECC/Tz were absent in fewer MPPT (1.0%) PS slides, but the difference was not statistically significant (-3.3% (95%CI: -4.0% to 11.0%).

Table 20. Cross-Tabulation of Endocervical and Transformation Zone Component

		Pap Smear		
		Diagnosis	Absent	Detectable
MonoPrep	Absent	640	606	1,246
	Detectable	649	8,604	9,253
	Total	1,289	9,210	10,499

ABUNDANCE OF ABNORMAL CELLS

Laboratories also were asked to assess the relative abundance of abnormal/reactive cells in cases identified as abnormal/reactive. The categories were Abundant (>25) Typical (11-25), and Detectable (1-10). Table 21 presents the comparison for cases where both slides were abnormal/reactive. As shown by the results, there were no statistically significant differences in the abundance of such cells. This demonstrates that MonoPrep presents, on average, at least as many abnormal/reactive cells as a Pap smear, even when made from a split specimen.

Table 21. Cross-Tabulation of Abnormal Cell Abundance

		Pap Smear				
		Abundance	Abundant (>25)	Typical (11-25)	Detectable (1-10)	Total
MonoPrep	Abundant (>25)	121	74	29	224	31%
	Typical (11-25)	83	116	82	281	39%
	Detectable (1-10)	25	73	113	211	29%
	Total	229	263	224	716	100%
	Col. % of Cases	32%	32%	31%	100%	

DETECTION OF INFECTIOUS ORGANISMS, REACTIVE/REPARATIVE AND OTHER BENIGN CONDITIONS

Screening with MPPT and Pap smear slides presented no statistically significant difference in detection of benign, reactive/reparative conditions and infectious agents. Table 22 shows the detection rates for these conditions and agents.

Table 22. Summary Table Summary of Benign Conditions: MonoPrep versus Pap Smear

Condition	MonoPrep (n=10,739)	Pap Smear (n=10,739)

	n	%	n	%
Reactive / Reparative	335	3.1%	306	2.8%
Inflammation	249	2.3%	231	2.2%
IUD	0	0.0%	4	0.0%
Atrophic Vaginitis	0	0.0%	1	0.0%
Radiation	3	0.0%	1	0.0%
Other*	67	0.6%	77	0.7%
Infectious Agent	1,507	14.0%	1,496	13.9%
Candida / Fungus	523	4.8%	426	4.0%
Trichomonas Vaginalis	105	1.0%	158	1.5%
Actinomyces	0	0.0%	0	0.0%
Bacterial Vaginosis / Coccobaccilli	980	9.1%	1,035	9.6%
Herpes Simplex	3	0.0%	9	0.1%
Other**	0	0.0%	2	0.0%

* includes unusual observations, such as those resulting from chemical irritation, drug reactions, or cervical trauma.
**includes appearance of microbial infection or sequela of unidentified or unusual taxonomy

CLINICAL INVESTIGATION CONCLUSIONS

For all sites combined, slides prepared by MPPT, compared to PS slides, yielded statistically significant increases in true positive cytological results for the following diagnostic classes: ASC-US+ (1.15, CI: 1.09 to 1.20); ASC-H/AGC+ (1.23, CI: 1.13 to 1.32); and LSIL+ (1.26, CI: 1.16 to 1.36). Hence the increases in true positive yield were at least 9% for ASCUS+, 13% for ASC-H/AGC+, and 16% for LSIL+.

Comparisons of false positive rates did not show a statistically significant difference between MPPT and PS for ASC-US+, ASC-H/AGC+ or LSIL+.

For all sites combined, slides prepared by MPPT, compared to PS slides, did not yield statistically significant differences in true positive or false positive cytological results for the following diagnostic classes: HSIL+ (1.04, CI: 0.88 to 1.19); and Cancer (1.22, CI: 0.87 to 1.75).

Presentation of endocervical cell and transformation zone component, abnormal cells and benign conditions showed no statistically significant difference between MPPT and PS slides.

The data from the clinical trial and clinical support studies demonstrate that the MPPT system is safe and effective for preparing gynecologic cytology slides to screen for cervical abnormalities.

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ATTACHMENTS

- Procedure: MonoPrep® Specimen Transfer
(Doc. 13502)
- Procedure: MonoPrep® Specimen Reprocessing
(Doc. 13503)
- Procedure: MonoPrep® Pap Test
Specimen Accessioning Instructions
(Doc. 13504)
- Summary: The MonoPrep® Pap Test
Morphology Training Program
(Doc. 13505)
- Package Insert: MonoPrep® Pap Test
Specimen Collection Kit
(Doc. 12369)
- Material Safety Data Sheet: MonoPrep® Pap Test Specimen
Transport Solution (MPPT-STs)
(Doc. 12372)

REVISION DATE

March, 2006

Procedure: MonoPrep® Specimen Transfer

This procedure is for the transfer of MonoPrep specimens (e.g., during reprocessing or for storage when the original vial is damaged). Specimen transfer can be performed by pouring or by pipetting.

Preparation

Set up a clean workspace. Each transfer will require clean new consumables (vial, forceps, dowel, and pipette). Always grasp vial in the labeled area. Pipetting can be performed with manual or automated pipetting/fluid transfer instruments. Single use transfer pipettes or aerosol-barrier pipette tips are recommended.

- Use **Procedure A** if the specimen will be transferred by pouring.
- Use **Procedure B** if the specimen will be transferred by pipetting.



Warning: Potential Biohazard. The MonoPrep Specimen Transport Solution inactivates microbial organisms per USP 26 Preservative Effectiveness Test (see MonoPrep Operator's Manual or Product Insert). However, Universal Precautions per OSHA regulations [29 CFR 1910.1030] should be observed with all specimen containing or specimen exposed vials, reagents, waste and equipment.



Laboratory personnel should review and understand the entire procedure before conducting any specimen transfers. Practice with expired specimens is recommended.

A Procedure A: Transfer by pouring	B Procedure B: Transfer by pipetting
① RESUSPEND vial contents by swirling.	① RESUSPEND vial contents by swirling. <i>Clean</i> the top surface of film seal (if present) with alcohol wipe.
② OPEN/UNSEAL ORIGINAL VIAL: <i>Capped vial:</i> Remove cap. Place vial upright on bench. NOTE ON STIRRER: If stirrer is dislodged, remove from vial with disposable forceps and discard. Tap the tip of the stirrer gently against the vial's internal ribs to drain. <i>Film-sealed vial:</i> Hold vial on bench upright. <i>Cut</i> the film seal against the rim, along $\frac{1}{3}$ to $\frac{1}{2}$ of the vial circumference ("smile" or "half-moon" pattern) with clean, disposable forceps, wooden dowel or other suitable tool. <i>Bend</i> the cut area of film upward, exposing the stirrer top.	② OPEN/UNSEAL ORIGINAL VIAL: <i>Capped vial:</i> Remove cap; place vial upright on bench. NOTE ON STIRRER: If the original vial is to be retained and the stirrer has been dislodged from the cap, remove it from vial and discard (replace with new cap/stirrer). <i>Film-sealed vial:</i> Hold vial upright on bench. <i>Puncture</i> the seal at its center (directly over the stirrer shaft) with a pipette or other clean, disposable tool. Do not enlarge the hole.
③ TRANSFER: <i>Pour</i> the entire specimen contents into the new vial or optionally; <i>Pour</i> half of the specimen into the new vial, swirl the original vial gently 5 times , and <i>pour</i> the remaining specimen into the new vial. <i>Tap</i> the rim of the old vial onto the rim of the new vial, to transfer the specimen. <i>Ensure</i> that fluid level in new vial is <i>between</i> the two marked fill lines. Add MonoPrep Pap Test Specimen Transport Solution (MPPT-STs) as necessary to achieve correct fluid level.	③ TRANSFER: <i>Hold</i> vial on counter firmly. Holding pipette straight, <i>seat</i> tip into the stirrer's center hole (through hole in film for film-sealed vials). If there is no stirrer, then pipette specimen directly. <i>Aspirate</i> the specimen and dispense into new vial. <i>Ensure</i> that fluid level in new vial is <i>between</i> the two marked fill lines. Add MonoPrep Pap Test Specimen Transport Solution (MPPT-STs) as necessary to achieve correct fluid level.
④ CAP: <i>Cap</i> the new vial using a new cap assembly (with attached stirrer).	④ CAP/RESEAL: <i>Capped vial:</i> <i>Discard</i> or <i>Recap</i> the original vial with the original or new cap. Cap new vial with new vial cap/stirrer assembly. <i>Film-sealed vial:</i> Reseal a punctured film seal using a resealing tab.



DOCUMENT: Record vial transfer per laboratory procedure. If using the Savant DMS, accession the new vial into the DMS using the "Vial Reprocessing" screen. **NOTE:** See MonoPrep Reprocessing Procedure for instructions regarding bloody specimens.

DISPOSE: Dispose of used consumables per standard laboratory procedures.

Procedure: MonoPrep® Specimen Reprocessing

This procedure is for the reprocessing of MonoPrep specimens that are UNSAT due to obscuration (e.g., blood or inflammation) or inadequate cellularity. MonoPrep reprocessing procedures are effective in resolving slides that are UNSAT due to obscuring blood and other matter without affecting morphology. Most MonoPrep specimens can be reprocessed in the case of UNSAT, lost or damaged slides, damaged vials, or to make additional slides. Vial reprocessing involves transferring of the remaining specimen to a new vial and loading on the MonoPrep Processor to prepare a new slide.

Preparation

Set up a clean workspace. Assemble all reagents and supplies before conducting any reprocessing. Each reprocessing will require clean new consumables (vial, disposable supplies). Always grasp vial in the labeled area. Pipetting can be performed with manual or automated pipetting/fluid transfer instruments. Single use transfer pipettes or aerosol-barrier pipette tips are recommended.

- Use **Procedure A** for UNSAT Bloody/Inflammatory Specimens, including cases that are scant in the presence of blood, inflammatory, mucus, debris or other obscuring matter.
- Use **Procedure B** for all other specimens that are UNSAT or require reprocessing (eg, unprocessed vial, new slide).



Warning: Potential Biohazard. The MonoPrep Specimen Transport Solution inactivates microbial organism per USP 26 Preservative Effectiveness Test (see MonoPrep Operator's Manual or Product Insert). However, Universal Precautions per OSHA regulations [29 CFR 1910.1030] should be observed with all specimen containing or exposed vials, reagents, waste and equipment.



Laboratory personnel should review and understand the entire procedure before conducting any specimen transfers. Practice with expired specimens or MPPT-STs is recommended.

A Procedure A: UNSAT Bloody/Inflammatory Specimens	B Procedure B: All Other UNSAT And Reprocessed Specimens
<p>SPECIMEN TRANSFER: Transfer specimen into a new, clean vial per the MonoPrep Specimen Transfer Procedure.</p>	<p>1 SPECIMEN TRANSFER: Transfer specimen into a new, clean vial per the MonoPrep Specimen Transfer Procedure.</p>
<p>2 Reprocess <i>Accession the vial using Vial Reprocessing.</i> <i>Select specimen specific alternate processing method (e.g., "GYN-Alternate").</i></p>	<p>2 Reprocess <i>Accession the vial using Vial Reprocessing.</i> <i>Select specimen specific normal processing method (e.g., "Gyn-Normal").</i></p>
<p>A or B DOCUMENT: Record vial transfer per laboratory procedure.</p> <p>END DISPOSE: Dispose of used consumables per standard laboratory procedures.</p>	

Procedure: MonoPrep® Specimen Accessioning

Processing specimens on the MonoPrep Processor requires that the vials be accessioned into the Savant Data Management System, directly or through the laboratory LIS. General specimen accessioning instructions for accessioning to the Savant DMS are provided in the MonoPrep Processor Operator's Manual. The following procedure provides additional instructions specific to accessioning MonoPrep Pap Test specimens into the Savant DMS. It also provides instructions for accessioning bloody specimens at initial processing, or when reprocessing specimens that produced unsatisfactory slides.

PROCEDURE: Accessioning Steps



Caution: Accessioning should only be performed by qualified persons who have been trained on the MonoPrep Processor accessioning process. Follow all accessioning procedures described in the MonoPrep Processor Operator's Manual and in the instructions below



Laboratory personnel should review and understand the entire procedure before conducting any specimen accessioning.

A

Procedure A: Normal Specimens

B

Procedure B: Bloody Specimens

A or B



Begin Accessioning:

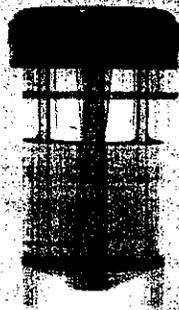
At Vial Accessioning or Vial Reprocessing screens, ensure the appropriate process is selected. The photos below provide examples of the typical, bloody, and very bloody specimens and can be used as a guide in selecting specimen process. In the illustration below, vial labels have been removed for clarity. Using the Vial Reprocessing screen ensures that the reprocessing vial and resulting slide are linked to the original collection vial bar code number in the Savant DMS.

①

Select Processing Method: Gyn Pap — Normal

This process should be used for processing all normal MPPT specimens except as indicated at right. Note: most vials will have visible particles of specimen and often mucus.

The Savant DMS will automatically default to the GYN-Normal process unless the user selects the GYN-Alternate process.



Normal Specimen

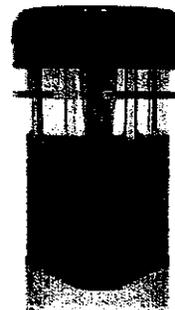
(Teal blue, clear, specimen particles and mucus may be visible)

①

Select Processing Method: Gyn Pap — Alternate

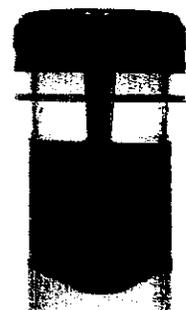
This process should be selected for specimens that are Bloody to Very Bloody (see color photos below), or if reprocessing specimens that yielded slides with bloody/inflammatory obscuration.

GYN—Alternate should be selected when reprocessing specimens that yielded slides with scant cellularity in the presence of blood, inflammation, or visible specimen in the collection vial. These specimen types may yield slides that are UNSAT due to scant cellularity (UNSAT/scant) with the GYN—Normal process. Selecting the GYN—Alternate process reduces the frequency of UNSAT/scant slides from such specimens.



Bloody Specimen

(Greenish, hazy)



Very Bloody Specimen

(Dark green / brown opaque)

A or B



SELECT NUMBER OF SLIDES:

If desired, increase the number of slides from the default of "1" for the MPPT. One to three slides can be selected; however, the actual number of adequate slides produced will depend on the quantity of cellular material in the specimen.

ENTER VIAL BAR CODE NUMBER:

Enter or scan the vial bar code number.

Summary: MonoPrep® Pap Test Morphology Training Program

For to screening MPPT slides, cytoprofessionals should complete and pass the MonoPrep Pap Test Morphology Training Program from MonoGen or its authorized providers. The MPPT Morphology Training Program provides a rigorous combination of lectures and presentations, well-characterized cases and photomicrographs representing a broad range of conditions and diagnostic presentations. It was designed by cytotechnology education experts to provide training for the cytotechnologists and pathologists who will screen and diagnose MPPT slides in their routine practice. The program teaches the morphologic and presentation features of MPPT slides relevant to screening and differential diagnosis. It is based on the program used to instruct participants in the MonoPrep Pap Test pivotal trial.

Instructional materials include a broad range of diagnostic entities from benign through malignant as classified by The 2001 Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses. In most cases, specimens were prepared from split sample cases (MPPT produced from residual Pap smear), with reviews by multiple, expert cytotechnologists and board certified cytopathologists, and where applicable histological verification of abnormality. The program has three segments, providing at least 8.5hr of program training time. The program is designed to accommodate laboratory and participant schedules, and typically provided over 1.5 working days. All training is directly provided by MonoGen authorized board-certified cytotechnologists or pathologists, who are qualified to teach MonoPrep morphology and are experienced in providing morphology training.

Segment 1. In the first segment, participants receive instruction on the morphology and cellular display encountered with MPPT slides. The first part of the tutorial explains the MonoPrep slide process and clinical data, especially as they relate to the difference in MonoPrep presentation and morphology from other preparation methods. The balance of the tutorial uses photomicrographs covering a wide variety of benign through malignant conditions described in TBS2001 and diagnostic criteria lists for each entity. This part emphasizes details of MonoPrep-specific morphology for each diagnostic entity, and how they compare to the appearance of similar entities on other presentations. Participants will complete a brief examination at the end of this portion to assess their understanding of the material presented. Any errors, misconceptions or questions are addressed before proceeding to the next segment.

Segment 2. This segment is focused on extensive review of individual cases. During the first part of this segment, participants review numerous cases presenting various presentations of the broad spectrum of benign conditions and cell types that can be encountered in daily practice. Cases from patients ranging in age from 18 through 70 are presented. A wide variety of benign conditions, including: reactive, reparative, infectious organisms, post-partum changes, endometrial cells, various differential exemplars of UNSAT and adequate cases. This part includes review of numerous textbook quality examples as well as many challenging presentations of a full range pre-malignant and malignant conditions, both squamous and glandular. Participants review known and unknown cases that allow them to practice the skills learned in the first segment. After completing the review, each participant's diagnoses for unknown cases are reviewed against the established diagnoses. Participants receive feedback on their screening and differential diagnoses and, where needed, additional instruction.

Segment 3. In this segment, participants take a qualifying examination of 20 validated cases that are considered classic examples each of a specific diagnostic entity. Participants are only given relevant patient demographics (e.g., age and LMP). Test sets use validated cases (i.e., those with exact diagnostic agreement by three board certified cytopathologists and other applicable criteria such as histological verification of abnormality). Cases for the examination will cover the spectrum of benign through malignant processes including both squamous and glandular conditions, and will include UNSAT, NILM, LSIL, HSIL, AIS, squamous and glandular carcinomas. MPPT qualification is established for all cytoprofessionals that score at 90% or better on the exam. Passing cytoprofessionals receive certification of their qualification to screen and/or diagnose MPPT slides. Further instruction and re-testing will be available to those needing additional remediation to qualify with the MonoPrep diagnostic morphology.

Participants are provided training materials to prepare for the program and additional post-program reference materials that can be reviewed as needed during their screening and/or diagnostic practice.

MONOPREP® Pap Test

Specimen Collection Kit

Intended Use

The MonoPrep Pap Test (MPPPT or MonoPrep) is intended for use in collecting and preparing cervical-vaginal cytology specimens for Pap stain-based screening for cervical cancer, its precursor lesions and other cytologic categories and conditions defined by *The 2001 Bethesda System: terminology for reporting results of cervical cytology*.¹ The MonoPrep Pap Test produces slides that are intended to replace conventionally prepared Pap smear slides.

Summary and Explanation of the MPPPT

The MPPPT is a liquid-based Pap test. Liquid-based Pap tests are a well-established alternative to Pap smears. The MonoPrep process begins with the clinician collecting ectocervical and endocervical specimens in accordance with current accepted practice using the provided MPPPT specimen vials and collection devices. The clinician transfers the specimen to the vial by rinsing the collection devices in the vial. The vial is closed and sent to the laboratory for processing. The preprinted vial barcodes on the vial (one permanent and one peel-off) facilitate accurate accessioning at the laboratory and automated specimen chain of custody management. The laboratory prepares Pap test slides from the specimen vial using the MPPPT Filters and MonoPrep Processor. The processor mixes the specimen, collects cells with filter and transfers them to the MonoPrep Slides. The slides have unique laser etched barcodes that ensure accurate specimen identity and chain of custody. The laboratory stains and evaluates the slides in accordance with its customary practice.

Principle of the Procedure

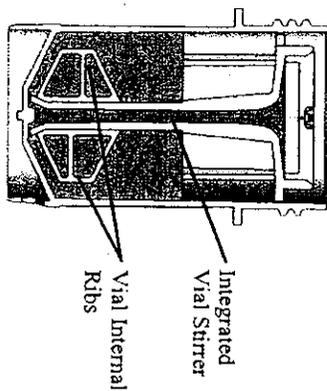
Procedure Summary: In the MonoPrep process, the clinician transfers patient specimen to a liquid media that prevents air-drying artifacts during transport to the laboratory. At the laboratory, the specimen is agitated to disperse obscuring mucus, as well as loose clumps and aggregates. Mixing also enables transfer of cells representative of the entire specimen to the slides. During processing, cells are collected on a disposable MPPPT Filter and, subsequently, transferred to slides for staining and evaluation.

MPPPT Procedure: The alcohol-based MPPPT-Specimen Transport Solution (MPPPT-STS) preserves the specimen's cellular morphology and prevents microbial growth. The MPPPT-STS has been demonstrated to preserve specimen for 12 months from collection when stored under typical laboratory and shipping conditions (*see Storage and Stability*)

The MonoPrep Vial design employs proprietary features unique to the MonoPrep Pap Test. The integrated vial stirrer and the vial internal ribs work together to mix the specimen efficiently, and to disperse mucus, clumps and aggregates without requiring mucolytic agents. The well-

dispersed specimen is then aspirated or "drawn up" the stirrer and the MonoPrep dual-flow technology captures the representative sample on the frit-backed filter. The MonoPrep Filter is then gently pressed against the slide to transfer the cells. The compliant frit assures uniform pressure and cell distribution on the resultant slide.

Slide-based samples are individually fixed using a pre-measured amount of fixative dispensed directly onto the slide. The MPPPT-STS also helps maintain the stability of the cells on the MonoPrep Slides in a dry state for at least seven days following cell transfer.

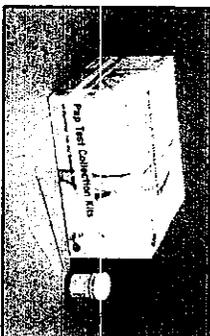


The MPPPT Vial employs proprietary features unique to the MonoPrep processing method.

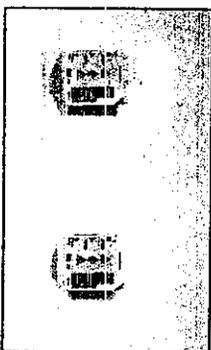
Based on a laboratory study, MPPPT specimens are not affected by interfering substances that might be encountered with cervical specimens: (e.g., blood, mucus, vaginal lubricants, contraceptives, cleansing feminine hygiene products, or yeast infection treatments). Excessive amounts of blood or debris, however, can reduce cellularity, cause obscuration, or interfere with testing. In most cases, proper collection prevents this problem.

MonoPrep processing is designed to prevent specimen carry-over or cross-contamination. In a non-clinical study, specimens with high concentrations of cellular material were interleaved with MPPPT STS blanks. In that study, no cellular carry-over was detected using microscopic examination of the resulting slides.

Materials Supplied



50 MonoPrep Pap Test Vials & Collection Device Sets



MonoPrep Pap Test Collection Vials

3-3-66
Fernal

Trials Required But Not Supplied

Gloves and other standard Universal Precaution supplies
 Speculum

Warnings

DANGER: MPTT Specimen Transport Solution contains methanol. Do not take internally. Vapor is harmful. May be fatal or cause blindness if swallowed. Cannot be made nonpoisonous. MonoPrep Pap Test Specimen Transport Solution and specimen should be stored and disposed of in accordance with local, state, and federal regulations.

POISON

FLAMMABLE

WARNING: Vials with specimen are a Potential Biohazard. MonoPrep Specimen Transport Solution was tested per USP 26 [51]-Antimicrobial Effectiveness. MPTT Specimen Transport Solution met the requirements for that test, demonstrating anti-microbial effect on the following organisms: *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans* and *A. niger*. However, Universal Precautions per OSHA regulations [29 CFR 1910.1030] should be observed with all specimen containing or exposed vials, reagents, waste and equipment.

Instructions

In vitro diagnostic use only. The MonoPrep Pap Test is intended for professional use only.

Caution: Do not write on the collection vial or label other than in the blank lined area indicated.

Collection Procedure

Follow accepted procedures for collection of cervical-vaginal specimens.² Wipe excessive blood and mucus from the endocervical and ectocervical areas. Avoid collection during menses.

	<ol style="list-style-type: none"> 1. Inspect the MPTT Vial for proper fluid levels and an intact tamper-evident seal. Confirm the expiration date. 2. Open the MPTT Vial and place it on the tabletop or in a vial holder so that the stirrer does not contact any surface. The stirrer should remain connected to the cap at all times. <p>Caution: Discard and use a different vial if any of the following conditions are observed before use: (i) the stirrer is dislodged from the vial, (ii) tamper-evident seal is broken; (iii) signs of deterioration or adulteration (e.g., particulate matter or debris), (iv) the vial is expired, or (v) the vial fluid level is not within the fill lines or not a clear, teal blue solution.</p>
	<ol style="list-style-type: none"> 3. Collect patient specimen using the provided collection devices in accordance with medical guidelines.² Collect the patient's ectocervical sample with the spatula, then the endocervical sample with the cytobrush. 4. Caution: Immediately place each collection device in the MPTT Vial, specimen end down, and leave in place to avoid air drying. <p>Keeping the specimen-containing regions of both devices submerged in the MPTT Specimen Transport Solution, completely scrape devices against one another. This process will dislodge the cells from the collection devices. Take care to avoid splashing the MPTT Specimen Transport Solution and specimen.</p> <p>First Scrape cells off the brush with spatula. Firmly hold brush against vial bottom and spatula bottom edge against brush. Scrape bristles with up and down spatula movement while twisting brush to scrape all brush sides.</p> <p>Second Gently wipe specimen off the spatula with the brush tip. Swish brush in fluid to remove any remaining adhering material.</p>
	<ol style="list-style-type: none"> 5. Remove and discard collection devices in accordance with standard laboratory procedure. Ample cellular material should be readily visible in the vial, indicating sufficient specimen is collected. 6. Replace vial cap and tighten until it will not turn any further. Invert vial to check for leaks and adequate specimen. Note: Visible specimen in the vial usually assures material is sufficient for testing.
	<ol style="list-style-type: none"> 7. Gently peel off removable barcode and place on laboratory requisition or patient chart per office/laboratory practice. Avoid tearing or damaging vial label when removing barcode. Write only on indicated space. 8. Place vial and requisition in a specimen bag for transport to the laboratory. Ship specimens in accordance with product and laboratory instructions.

Specimen Handling Storage and Stability

MPPPT Specimen Transport Solution (MPPPT-STS)

in MPPPT Collection Vials

15°C $\sqrt{30^{\circ}\text{C}}$

Store & Ship MPPPT Collection Vials at $15\text{-}30^{\circ}\text{C}$

Do not use beyond expiration date printed on container.
(12 months from manufacture date) MPPPT-STS is unaffected by

brief exposures to temperatures outside of intended storage and shipping conditions:

As low as	As high as	Period
2°C	37°C	3 weeks
-20°C	55°C	6 hours

Specimens in MPPPT Collection Vials

Store and Ship MPPPT Specimens at $15\text{-}30^{\circ}\text{C}$

Specimens are preserved for 12 months from collection date. Specimens are unaffected by brief exposures to temperatures outside of intended storage and shipping conditions:

As low as	As high as	Period
2°C	37°C	3 weeks
-20°C	55°C	6 hours

Handling: Inspect vials prior to collection and accessioning. Do not use vials with damaged (e.g., torn or detached or detached) labels, or if the MPPPT-STS is not a clear, teal blue solution prior to specimen addition.

Shipping: Specimens should be transported in accordance with applicable DOT/IATA/ISTA guidelines. For hazard notification information, see Doc. 12372

Material Safety Data Sheet: MonoPrep[®] Pap Test Specimen Transport Solution.

Limitations of the Procedure

Preparation of samples with MPPPT has only been validated using the MonoPrep Processor. Use with other instruments or manual procedures has not been validated.

Use only MonoPrep consumables with the MonoPrep Pap Test. Collect with endocervical cytobrush and plastic cytopanula, do not use "breakaway" tipped collection devices.

Only individuals who have completed MonoGen, Inc. authorized training should evaluate slides

Contraindications

There are no contraindications for use of the MonoPrep Pap Test.

Summary Performance Characteristics

The MPPPT effectiveness was demonstrated in a multi-center, split-sample, masked study, including 10,739 evaluable subjects with expert adjudication of cases abnormal (reactive/repairative or higher) by either method, and 6% of all cases that are NILM-WNL or UNSAT by both methods. This study demonstrated the following benefits of MonoPrep Pap Test in comparison to Pap smear slides:

1. For all sites combined, slides prepared by MPPPT, compared to PS slides, yielded statistically significant increases in the following diagnostic classes: ASC-US+ (1.15, 95%CI: 1.09 to 1.20); ASC-H/AGC+ (1.23, 95%CI: 1.13 to 1.32); and LSIL+ (1.26, 95%CI: 1.16 to 1.36), and non-statistically significant increases for HSIL+ (1.04, 95%CI 0.88 to 1.19) and Cancer (1.22, 95%, CI 0.87 to 1.75).
2. Comparisons of false positive rates did not show statistically significant differences between MPPPT and PS for ASC-US+, ASC-H/AGC+, LSIL+, HSIL+ or Cancer.
3. Presentation of abundance of endocervical cell and transformation zone component, abnormal cells and the detection of benign conditions showed no statistically significant differences between MPPPT and PS slides

The data from the clinical trial and clinical support studies demonstrate that the MPPPT system is safe and effective for preparing gynecologic cytology slides to screen for cervical abnormalities. Complete information on the MPPPT performance characteristics are provided in the MPPPT Laboratory Instructions and Information which can be obtained from MonoGen.

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References

1. Solomon D., Davey D., Kuman R., et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(16):2114-9.
2. NCCLS, GP15-A2. (2001). Papanicolaou technique. Approved Guideline-Second Edition. 21(17), 1-30.

Patents & Copyright Notices

MonoPrep[®] Pap Test Collection Vial - patents pending
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