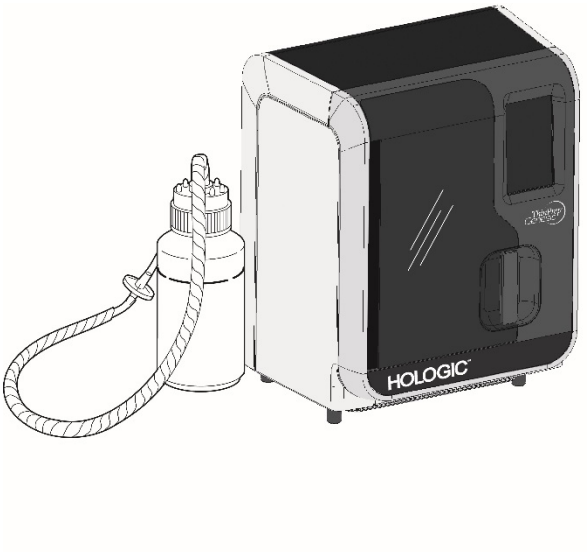
ThinPrep® Genesis™ Processor



Instructions for Use

IVD

INTENDED USE

The ThinPrep Genesis processor is used to prepare ThinPrep® Pap test slides from ThinPrep® PreservCyt® sample vials to screen for the presence of atypical cells, cervical cancer including adenocarcinoma or its precursor lesions (Low-grade Squamous Intraepithelial Lesions, High-grade Squamous Intraepithelial Lesions), as well as all other cytologic categories, as defined by *The Bethesda System for Reporting Cervical Cytology*[1].

The ThinPrep Genesis processor can be used for automated removal of a 1-ml aliquot from the sample vial to a specimen transfer tube.

SUMMARY AND EXPLANATION OF THE SYSTEM

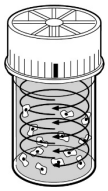
The ThinPrep process begins with the patient's gynecologic sample being collected by the clinician using a cervical sampling device which, rather than being smeared on a microscope slide, is immersed and rinsed in a vial filled with 20 ml of PreservCyt® Solution (PreservCyt). The ThinPrep sample vial is then capped, labeled, and sent to a laboratory equipped with a ThinPrep Genesis processor.

At the laboratory, the PreservCyt sample vial is placed into a ThinPrep Genesis processor. A laboratory can elect to set up the ThinPrep Genesis processor to track the chain of custody for the sample, and to set up printing IDs on each glass microscope slide. Specimens are processed from the PreservCyt sample vial by one of three processes: "Aliquot + Slide", "Aliquot", or "Slide." In the Slide process, a cytology slide is prepared from the PreservCyt sample vial. In the Aliquot process, the ThinPrep Genesis processor can remove a 1-ml aliquot from the sample vial and transfer the aliquot to a specimen transfer tube. In the Aliquot + Slide process, the ThinPrep Genesis processor first transfers a 1-ml aliquot to a specimen transfer tube and then prepares a cytology slide. If a manual aliquot is prepared, the Slide process should be used.

A gentle dispersion step mixes the cell sample by currents in the fluid that are strong enough to separate debris and disperse mucus, but gentle enough to have no adverse effect on cell appearance.

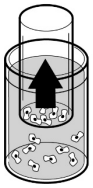
The cells are then captured on a gynecological ThinPrep Pap test filter that is specifically designed to collect cells. The ThinPrep Genesis processor constantly monitors the rate of flow through the ThinPrep Pap test filter during the collection process to prevent the cellular presentation from being too scant or too dense. A thin layer of cells is then transferred to a glass slide in a 20 mm-diameter circle, and the slide is automatically deposited into a fixative solution.

The ThinPrep Sample Preparation Process



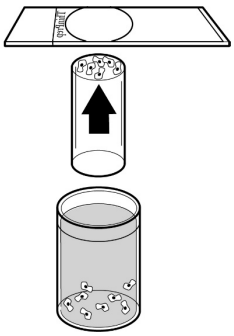
(1) Dispersion

The sample vial is rotated, creating currents in the fluid that are strong enough to separate debris and disperse mucus, but gentle enough to have no adverse effect on cell appearance.



(2) Cell Collection

A gentle vacuum is created within the ThinPrep Pap test filter, which collects cells on the exterior surface of the membrane. Cell collection is controlled by the ThinPrep Genesis processor's software that monitors the rate of flow through the ThinPrep Pap test filter.



(3) Cell Transfer

After the cells are collected on the membrane, the ThinPrep filter is inverted and gently pressed against the ThinPrep microscope slide. Natural attraction and slight positive air pressure cause the cells to adhere to the ThinPrep microscope slide resulting in an even distribution of cells in a defined circular area.

As with conventional Pap smears, slides prepared with the ThinPrep® Genesis processor are examined in the context of the patient's clinical history and information provided by other diagnostic procedures such as colposcopy, biopsy, and human papillomavirus (HPV) testing, to determine patient management.

The PreservCyt® Solution component of the ThinPrep Genesis processor is an alternative collection and transport medium for the testing of Human Papilloma Virus (HPV) and sexually transmitted infections (STIs) in gynecological specimens, including, but not limited to:

Chlamydia trachomatis and Neisseria gonorrhoeae (Aptima Combo 2® assay),
Chlamydia trachomatis (Aptima® CT assay),
Neisseria gonorrhoeae (Aptima® GC assay),
Mycoplasma genitalium (Aptima® Mycoplasma genitalium assay),
Trichomonas vaginalis (Aptima® Trichomonas vaginalis assay),
Human papillomavirus (Aptima® HPV assay), and
Human papillomavirus (Aptima® HPV 16 18/45 genotype assay)

Note: **Refer to the respective manufacturer's package inserts for instructions** for using PreservCyt Solution for collection, transport, storage, and preparation of specimens for use in those systems.

In addition to preparing a slide from a PreservCyt sample vial, the ThinPrep Genesis processor has the ability to remove a 1-ml aliquot from the sample vial and transfer the aliquot to a specimen transfer tube.

The ThinPrep Genesis processor is also used to prepare ThinPrep slides from non-gynecologic (non-gyn) samples.

LIMITATIONS

- Gynecologic samples collected for preparation using the ThinPrep Genesis processor should be collected using a broom-type or endocervical brush/plastic spatula combination collection devices. Refer to the instructions provided with the collection device for warnings, contraindications, and limitations associated with specimen collection.
- Preparation of microscope slides using the ThinPrep Genesis processor should be performed only by personnel who have been trained by Hologic or by organizations or individuals designated by Hologic.
- Evaluation of microscope slides produced with the ThinPrep Genesis processor should be performed only by cytotechnologists and pathologists who have been trained to evaluate ThinPrep prepared slides by Hologic or by organizations or individuals designated by Hologic.
- Supplies used by the ThinPrep Genesis processor are those designed and supplied by Hologic specifically for the ThinPrep Genesis processor. These include PreservCyt Solution vials, ThinPrep Pap test filters, ThinPrep microscope slides, and tubes for the aliquot. These supplies are required for proper performance of the system and cannot be substituted. Product performance will be compromised if other supplies are used. After use, supplies should be disposed of in accordance with local, state, and federal regulations.
- A ThinPrep Pap test filter must be used only once and cannot be reused.
- Aliquots taken by the ThinPrep Genesis processor have not been evaluated for specific assays. Please refer to the instructions provided with a specific assay.
- The performance of HPV and STI ancillary testing on sample vials reprocessed using glacial acetic acid has not been evaluated.

WARNINGS

- For In Vitro Diagnostic Use
- Danger. PreservCyt Solution contains methanol. Toxic if swallowed. Toxic if inhaled. Causes damage to organs. Flammable liquid and vapor. Keep away from heat, sparks, open flames and hot surfaces. Other solutions cannot be substituted for PreservCyt Solution. PreservCyt Solution should be stored and disposed of in accordance with all applicable regulations.

- Do not process a cerebral spinal fluid (CSF) specimen or other sample type that is suspected of possessing prion infectivity (PrPsc) derived from a person with a TSE, such as Creutzfeldt- Jakob disease, on the ThinPrep Genesis processor. A TSE-contaminated processor cannot be effectively decontaminated and therefore must be properly disposed of in order to avoid potential harm to users of the processor or service personnel.
- Strong oxidizers, such as bleach, are incompatible with PreservCyt Solution and therefore should not be used to clean the waste bottle.
- For professional use only.

PRECAUTIONS

- This equipment generates, uses and can radiate radio frequency energy, and if not installed and used in accordance with the operator's manual, may cause interference to radio communications. Operation of this equipment in a residential area is likely to cause harmful interference, in which case the user will be required to correct the interference at his/her own expense.
- PreservCyt Solution *with* cytologic sample intended for ThinPrep Pap testing must be stored between 15°C (59°F) and 30°C (86°F) and tested within 6 weeks of collection.
- Testing for certain sexually transmitted infections (STIs) and for Human Papilloma Virus (HPV) in conjunction with cytology may be performed. Refer to assay specific guidance for the collection, transport, and storage conditions of specimens for use in those systems.
- PreservCyt Solution was challenged with a variety of microbial and viral organisms. The following table presents the starting concentrations of viable organisms, and the log reduction of viable organisms found after 15 minutes in the PreservCyt Solution. As with all laboratory procedures, universal precautions should be followed.

Organism	Initial Concentration	Log Reduction After 15 Minutes
Candida albicans	5.5 x 10^5 CFU/ml	≥4.7
Candida auris	2.6 x 10^5 CFU/ml	≥5.4
Aspergillus niger	4.8 x 10^5 CFU/ml	2.7*
Escherichia coli	2.8 x 10^5 CFU/ml	≥4.4
Staphylococcus aureus	2.3 x 10^5 CFU/ml	≥4.4
Pseudomonas aeruginosa	2.5 x 10^5 CFU/ml	≥4.4
Mycobacterium tuberculosis†	9.4 x 10^5 CFU/ml	4.9**
Rabbitpox virus	6.0 x 10^6 PFU/ml	5.5***

Organism	Initial Concentration	Log Reduction After 15 Minutes
HIV-1	3.2×10^7 $TCID_{50}$/ml	≥7.0***
Hepatitis B virus†	2.2×10^6 $TCID_{50}$/ml	≥4.25
SARS-CoV-2 virus	1.8×10^6 $TCID_{50}$/ml	≥3.75

* After 1 hour 4.7 log reduction

** After 1 hour 5.7 log reduction

*** Data is for 5 minutes

† Organisms were tested with similar organisms from the same genus to assess antimicrobial effectiveness

Note: All log reduction values with a ≥ designation yielded undetectable microbial presence after exposure to PreservCyt Solution. The listed values represent the minimum allowable claim given the initial concentration and the detection limit of the quantitative method.

PERFORMANCE CHARACTERISTICS: REPORT OF CLINICAL STUDIES

The ThinPrep Genesis processor uses similar cell collection and slide preparation technology as the ThinPrep 2000 system. The performance characteristics of the ThinPrep Genesis processor are predicated on those of the ThinPrep 2000 system. Both clinical studies for the ThinPrep 2000 system and those comparing the ThinPrep Genesis processor to the ThinPrep 2000 system are described in the following sections.

ThinPrep 2000 System Compared to Conventional Pap Smear

A prospective multi-center clinical study was conducted to evaluate the performance of the ThinPrep 2000 system in direct comparison to the conventional Pap smear. The objective of the ThinPrep clinical study was to demonstrate that gynecologic specimens prepared using the ThinPrep 2000 system were at least as effective as conventional Pap smears for the detection of atypical cells and cervical cancer or its precursor lesions in a variety of patient populations. In addition, an assessment of specimen adequacy was performed.

The initial clinical study protocol was a blinded, split sample, matched pair study, for which a conventional Pap smear was prepared first, and the remainder of the sample (the portion that normally would have been discarded) was immersed and rinsed into a vial of PreservCyt Solution. At the laboratory, the PreservCyt sample vial was placed into a ThinPrep 2000 system and a slide was then prepared from the patient's sample. ThinPrep and conventional Pap smear slides were examined and diagnosed independently. Reporting forms containing patient history as well as a checklist of all possible categories of The Bethesda System were used to record the results of

the screening. A single independent pathologist reviewed all discrepant and positive slides from all sites in a blinded fashion to provide a further objective review of the results.

Since the time of the ThinPrep 2000 system study, terminology in The Bethesda System categories was revised. The data below retains the terminology from the original study.

LABORATORY AND PATIENT CHARACTERISTICS

Cytology laboratories at three screening centers (designated as S1, S2, and S3) and three hospital centers (designated as H1, H2, and H3) participated in the clinical study. The screening centers in the study serve patient populations (screening populations) with rates of abnormality (Low-grade Squamous Intraepithelial Lesion [LSIL] and more severe lesions) similar to the United States average of less than 5%.[2] The hospital centers in the study serve a high risk referral patient population (hospital populations) characterized by high rates (>10%) of cervical abnormality. Data on race demographics was obtained for 70% of the patients that participated in the study. The study population consisted of the following race groups: Caucasian (41.2%), Asian (2.3%), Hispanic (9.7%), African American (15.2%), Native American (1.0%) and other groups (0.6%).

Table 1 describes the laboratories and the patient populations.

Table 1: Site Characteristics (ThinPrep 2000 System Study)

	Laboratory Characteristics			Clinical Study Demographics			
Site	**Type of Patient Population**	**Laboratory Volume - Smears per Year**	**Cases**	**Patient Age Range**	**Post-Menopausal**	**Previous Abnormal Pap Smear**	**Convent. Prevalence LSIL+**
S1	Screening	300,000	1,386	18.0 - 84.0	10.6%	8.8%	2.3%
S2	Screening	100,000	1,668	18.0 - 60.6	0.3%	10.7%	2.9%
S3	Screening	96,000	1,093	18.0 - 48.8	0.0%	7.1%	3.8%
H1	Hospital	35,000	1,046	18.1 - 89.1	8.1%	40.4%	9.9%
H2	Hospital	40,000	1,049	18.1 - 84.4	2.1%	18.8%	12.9%
H3	Hospital	37,000	981	18.2 - 78.8	11.1%	38.2%	24.2%

CLINICAL STUDY RESULTS

The diagnostic categories of The Bethesda System were used as the basis of the comparison between conventional and ThinPrep® findings from the clinical study. The diagnostic classification data and statistical analyses for all clinical sites are presented in Tables 2 through 11. Cases with incorrect paperwork, patient's age less than 18 years, cytologically unsatisfactory slides, or patients with a hysterectomy were excluded from this analysis. Few cases of cervical cancer (0.02%[3]) were represented in the clinical study, as is typical in the United States patient population.

Table 2: Diagnostic Classification Table, All Categories (ThinPrep 2000 System Study)

		Conventional							
		NEG	**ASCUS**	**AGUS**	**LSIL**	**HSIL**	**SQ CA**	**GL CA**	**TOTAL**
ThinPrep	**NEG**	5224	295	3	60	11	0	0	5593
	ASCUS	318	125	2	45	7	0	0	497
	AGUS	**13**	**2**	**3**	**0**	**1**	**0**	**1**	**20**
	LSIL	**114**	**84**	**0**	**227**	**44**	**0**	**0**	**469**
	HSIL	**11**	**15**	**0**	**35**	**104**	**2**	**0**	**167**
	SQ CA	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**1**
	GL CA	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	TOTAL	**5680**	**521**	**8**	**367**	**167**	**3**	**1**	**6747**

*Abbreviations for Diagnoses: **NEG** = Normal or negative, **ASCUS** = Atypical Squamous Cells of Undetermined Significance, **AGUS** = Atypical Glandular Cells of Undetermined Significance, **LSIL** = Low-grade Squamous Intraepithelial Lesion, **HSIL** = High-grade Squamous Intraepithelial Lesion, **SQ CA** = Squamous Cell Carcinoma, **GL CA** = Glandular Cell Adenocarcinoma*

Table 3: Three Category Diagnostic Classification Table (ThinPrep 2000 System Study)

		Conventional			
		NEG	**ASCUS/AGUS+**	**LSIL+**	**TOTAL**
ThinPrep	**NEG**	5224	298	71	**5593**
	ASCUS/AGUS+	331	132	54	**517**
	LSIL+	125	99	413	**637**
	TOTAL	5680	529	538	**6747**

Table 4: Two Category Diagnostic Classification Table, LSIL and More Severe Diagnoses (ThinPrep 2000 System Study)

		Conventional		
		NEG/ASCUS/ AGUS+	**LSIL+**	**TOTAL**
ThinPrep	**NEG/ASCUS/ AGUS+**	5985	125	**6110**
	LSIL+	224	413	**637**
	TOTAL	6209	538	**6747**

Table 5: Two Category Diagnostic Classification Table, ASCUS/AGUS and More Severe Diagnoses (ThinPrep 2000 System Study)

		NEG	**ASCUS/AGUS+**	**TOTAL**
ThinPrep	**NEG**	5224	369	**5593**
	ASCUS/AGUS+	456	698	**1154**
	TOTAL	5680	1067	**6747**

The diagnostic data analysis from the sites is summarized in Table 6 and 7. When the p-value is significant ($p < 0.05$), the method favored is indicated in the tables.

Table 6: Results by Site, LSIL and More Severe Lesions (ThinPrep 2000 System Study)

Site	Cases	ThinPrep LSIL+	Convent. LSIL+	Increased Detection*	p-Value	Method Favored
S1	1,336	46	31	48%	0.027	ThinPrep
S2	1,563	78	45	73%	<0.001	ThinPrep
S3	1,058	67	40	68%	<0.001	ThinPrep
H1	971	125	96	30%	<0.001	ThinPrep
H2	1,010	111	130	(15%)	0.135	Neither
H3	809	210	196	7%	0.374	Neither

**Increased detection =* $\frac{\text{ThinPrep® LSIL+ - Conventional LSIL+}}{\text{Conventional LSIL+}} \times 100\%$

For LSIL and more severe lesions, the diagnostic comparison statistically favored the ThinPrep® method at four sites and was statistically equivalent at two sites.

Table 7: Results by Site, ASCUS/AGUS and More Severe Lesions (ThinPrep 2000 System Study)

Site	Cases	ThinPrep ASCUS+	Convent. ASCUS+	Increased Detection*	p-Value	Method Favored
S1	1,336	117	93	26%	0.067	Neither
S2	1,563	124	80	55%	<0.001	ThinPrep
S3	1,058	123	81	52%	<0.001	ThinPrep
H1	971	204	173	18%	0.007	ThinPrep
H2	1,010	259	282	(8%)	0.360	Neither
H3	809	327	358	(9%)	0.102	Neither

**Increased detection = ThinPrep® ASCUS+ - Conventional ASCUS+ x 100%*
Conventional ASCUS+

For ASCUS/AGUS and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at three sites and was statistically equivalent at three sites.

One pathologist served as an independent reviewer for the six clinical sites, receiving both slides from cases where the two methods were either abnormal or discrepant. Since a true reference cannot be determined in such studies and therefore true sensitivity cannot be calculated, the use of an expert cytologic review provides an alternative to histologic confirmation by biopsy or human papillomavirus (HPV) testing as a means for determining the reference diagnosis.

The reference diagnosis was the more severe diagnosis from either of the ThinPrep or conventional Pap slides as determined by the independent pathologist. The number of slides diagnosed as abnormal at each site, compared to the reference diagnosis of the independent pathologist, provides the proportion of LSIL or more severe lesions (Table 8) and the proportion of ASCUS/AGUS or more severe lesions (Table 9). The statistical analysis allows a comparison of the two methods and a determination of which method is favored when using the independent pathologist for expert cytologic review as the adjudicator of the final diagnosis.

Table 8: Independent Pathologist Results by Site, LSIL and More Severe Lesions (ThinPrep 2000 System Study)

Site	Cases Positive by Independent Pathologist	ThinPrep Positive	Conventional Positive	p-Value	Method Favored
S1	50	33	25	0.0614	Neither
S2	65	48	33	0.0119	ThinPrep
S3	77	54	33	<0.001	ThinPrep
H1	116	102	81	<0.001	ThinPrep
H2	115	86	90	0.607	Neither
H3	126	120	112	0.061	Neither

For LSIL and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at three sites and was statistically equivalent at three sites.

Table 9: Independent Pathologist Results by Site, ASCUS/AGUS and More Severe Lesions (ThinPrep 2000 System Study)

Site	Cases Positive by Independent Pathologist	ThinPrep® Positive	Conventional Positive	p-Value	Method Favored
S1	92	72	68	0.0511	Neither
S2	101	85	59	0.001	ThinPrep
S3	109	95	65	<0.001	ThinPrep
H1	170	155	143	0.090	Neither
H2	171	143	154	0.136	Neither
H3	204	190	191	1.000	Neither

For ASCUS/AGUS and more severe lesions, the diagnostic comparison statistically favored the ThinPrep method at two sites and was statistically equivalent at four sites.

Table 10 below shows the summary for all sites of the descriptive diagnosis for all Bethesda System categories.

Table 10: Summary of Descriptive Diagnosis (ThinPrep 2000 System Study)

Descriptive Diagnosis	ThinPrep		Conventional	
Number of Patients: 6747	N	%	N	%
Benign Cellular Changes:	**1592**	**23.6**	**1591**	**23.6**
Infection:				
Trichomonas Vaginalis	136	2.0	185	2.7
Candida spp.	406	6.0	259	3.8
Coccobacilli	690	10.2	608	9.0
Actinomyces spp.	2	0.0	3	0.0
Herpes	3	0.0	8	0.1
Other	155	2.3	285	4.2
Reactive Cellular Changes Associated with:				
Inflammation	353	5.2	385	5.7
Atrophic Vaginitis	32	0.5	48	0.7
Radiation	2	0.0	1	0.0
Other	25	0.4	37	0.5
Epithelial Cell Abnormalities:	**1159**	**17.2**	**1077**	**16.0**
Squamous Cell:				
ASCUS	501	7.4	521	7.7
favor reactive	128	1.9	131	1.9
favor neoplastic	161	2.4	140	2.1
undetermined	213	3.2	250	3.7
LSIL	469	7.0	367	5.4
HSIL	167	2.5	167	2.5
Carcinoma	1	0.0	3	0.0
Glandular Cell:				
Benign Endometrial cells in Postmenopausal Women	7	0.1	10	0.1
Atypical Glandular Cells (AGUS)	21	0.3	9	0.1
favor reactive	9	0.1	4	0.1
favor neoplastic	0	0.0	3	0.0
undetermined	12	0.2	2	0.0
Endocervical Adenocarcinoma	0	0.0	1	0.0

Note: Some patients had more than one diagnostic subcategory.

Table 11 shows the rates of detection for infection, reactive changes, and the total benign cellular changes for both the ThinPrep® and conventional methods at all sites.

Table 11: Benign Cellular Changes Results (ThinPrep 2000 System Study)

		ThinPrep		Conventional	
		N	%	N	%
Benign Cellular Changes	Infection	1392	20.6	1348	20.0
	Reactive Changes	412	6.1	471	7.0
	Total*	1592	23.6	1591	23.6

** Total includes some patients that may have had both an infection and reactive cellular change.*

Tables 12, 13, and 14 show the specimen adequacy results for the ThinPrep method and conventional smear method for all of the study sites. Of the 7,360 total patients enrolled, 7,223 are included in this analysis. Cases with patient's age less than 18 years or patients with a hysterectomy were excluded from this analysis.

Two additional clinical studies were conducted to evaluate specimen adequacy results when samples were deposited directly into the PreservCyt® vial, without first making a conventional Pap smear. This specimen collection technique is the intended use for the ThinPrep 2000 system. Tables 15 and 16 present the split sample and direct to vial results.

Table 12: Summary of Specimen Adequacy Results (ThinPrep 2000 System Study)

Specimen Adequacy Number of Patients: 7223	ThinPrep		Conventional	
	N	**%**	**N**	**%**
Satisfactory	5656	78.3	5101	70.6
Satisfactory for Evaluation but Limited by:	**1431**	**19.8**	**2008**	**27.8**
Air-Drying Artifact	1	0.0	136	1.9
Thick Smear	9	0.1	65	0.9
Endocervical Component Absent	1140	15.8	681	9.4
Scant Squamous Epithelial Component	150	2.1	47	0.7
Obscuring Blood	55	0.8	339	4.7
Obscuring Inflammation	141	2.0	1008	14.0
No Clinical History	12	0.2	6	0.1
Cytolysis	19	0.3	119	1.6
Other	10	0.1	26	0.4
Unsatisfactory for Evaluation:	**136**	**1.9**	**114**	**1.6**
Air-Drying Artifact	0	0.0	13	0.2
Thick Smear	0	0.0	7	0.1
Endocervical Component Absent	25	0.3	11	0.2
Scant Squamous Epithelial Component	106	1.5	47	0.7
Obscuring Blood	23	0.3	58	0.8
Obscuring Inflammation	5	0.1	41	0.6
No Clinical History	0	0.0	0	0.0
Cytolysis	0	0.0	4	0.1
Other	31	0.4	9	0.1

Note: Some patients had more than one subcategory.

Table 13: Specimen Adequacy Results (ThinPrep 2000 System Study)

		Conventional			
		SAT	**SBLB**	**UNSAT**	**TOTAL**
ThinPrep	**SAT**	4316	1302	38	5656
	SBLB	722	665	44	1431
	UNSAT	63	41	32	136
	TOTAL	5101	2008	114	7223

SAT=Satisfactory, SBLB=Satisfactory But Limited By, UNSAT=Unsatisfactory

Table 14: Specimen Adequacy Results by Site (ThinPrep 2000 System Study)

Site	Cases	ThinPrep SAT Cases	Convent. SAT Cases	ThinPrep SBLB Cases	Convent. SBLB Cases	ThinPrep UNSAT Cases	Convent. UNSAT Cases
S1	1,386	1092	1178	265	204	29	4
S2	1,668	1530	1477	130	178	8	13
S3	1,093	896	650	183	432	14	11
H1	1,046	760	660	266	375	20	11
H2	1,049	709	712	323	330	17	7
H3	981	669	424	264	489	48	68
All Sites	7,223	5656	5101	1431	2008	136	114

The Satisfactory But Limited By (SBLB) category can be broken down into many subcategories, one of which is the absence of Endocervical Component. Table 15 shows the Satisfactory But Limited By category "No ECC's" for ThinPrep® and conventional slides.

Table 15: Specimen Adequacy Results by Site, SBLB Rates for no Endocervical Component (ThinPrep 2000 System Study)

SBLB Due to No ECC's

Site	Cases	ThinPrep SBLB- no ECC's	ThinPrep SBLB- no ECC's (%)	Conventional SBLB- no ECC's	Conventional SBLB- no ECC's (%)
S1	1,386	237	17.1%	162	11.7%
S2	1,668	104	6.2%	73	4.4%
S3	1,093	145	13.3%	84	7.7%
H1	1,046	229	21.9%	115	11.0%
H2	1,049	305	29.1%	150	14.3%
H3	981	120	12.2%	97	9.9%
All Sites	7,223	1140	15.8%	681	9.4%

For the results of the clinical study involving a split-sample protocol, there was a 6.4 percent difference between conventional and ThinPrep methods in detecting endocervical component. This is similar to previous studies using a split sample methodology.

DIRECT-TO-VIAL ENDOCERVICAL COMPONENT (ECC) STUDIES

For the intended use of the ThinPrep® 2000 system, the cervical sampling device will be rinsed directly into a PreservCyt® vial, rather than splitting the cellular sample. It was expected that this would result in an increase in the pick-up of endocervical cells and metaplastic cells. To verify

this hypothesis, two studies were performed using the direct-to-vial method and are summarized in Table 16. Overall, no difference was found between ThinPrep and conventional methods in these two studies.

Table 16: Summary of Direct-to-Vial Endocervical Component (ECC) Studies (ThinPrep 2000 System Study)

Study	Number of Evaluable Patients	SBLB due to No Endocervical Component	Comparable Conventional Pap Smear Percentage
Direct-to-Vial Feasibility	**299**	**9.36%**	**9.43%[1]**
Direct-to-Vial Clinical Study	**484**	**4.96%**	**4.38%[2]**

1. Direct-to-Vial Feasibility study compared to overall clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.

2. Direct-to-Vial Clinical study compared to site S2 clinical investigation conventional Pap smear SBLB-No Endocervical Component rate.

DIRECT-TO-VIAL HSIL+ STUDY

Following initial FDA approval of the ThinPrep system, Hologic conducted a multi-site direct-to-vial clinical study to evaluate the ThinPrep 2000 system versus conventional Pap smear for the detection of High Grade Squamous Intraepithelial and more severe lesions (HSIL+). Two types of patient groups were enrolled in the trial from ten (10) leading academic hospitals in major metropolitan areas throughout the United States. From each site, one group consisted of patients that were representative of a routine Pap test screening population and the other group made up of patients representative of a referral population enrolled at the time of colposcopic examination. The ThinPrep specimens were collected prospectively and compared against a historical control cohort. The historical cohort consisted of data collected from the same clinics and clinicians (if available) used to collect the ThinPrep specimens. These data were collected sequentially from patients seen immediately prior to the initiation of the study.

The results from this study showed a detection rate of 511 / 20,917 for the conventional Pap smear versus 399 / 10,226 for the ThinPrep slides. For these clinical sites and these study populations, this indicates a 59.7% increase in detection of HSIL+ lesions for the ThinPrep specimens. These results are summarized in Table 17.

Table 17: Summary of Direct-to-Vial HSIL+ Study (ThinPrep 2000 System)

Site	Total CP (n)	HSIL+	Percent (%)	Total TP (n)	HSIL+	Percent (%)	Percent Change (%)
S1	2,439	51	2.1	1,218	26	2.1	+2.1
S2	2,075	44	2.1	1,001	57	5.7	+168.5
S3	2,034	7	0.3	1,016	16	1.6	+357.6
S4	2,043	14	0.7	1,000	19	1.9	+177.3
S5	2,040	166	8.1	1,004	98	9.8	+20.0
S6	2,011	37	1.8	1,004	39	3.9	+111.1
S7	2,221	58	2.6	1,000	45	4.5	+72.3
S8	2,039	61	3.0	983	44	4.5	+49.6
S9	2,000	4	0.2	1,000	5	0.5	+150.0
S10	2,015	69	3.4	1,000	50	5.0	+46.0
Total	20,917	511	2.4	10,226	399	3.9	59.7(p<0.001)

*Percent Change (%) = ((TP HSIL+/TP Total)/(CP HSIL+/CP Total)-1) *100*

GLANDULAR DISEASE DETECTION – PUBLISHED STUDIES

The detection of endocervical glandular lesions is an essential function of the Pap test. However, abnormal glandular cells in the Pap sample may also originate from the endometrium or from extrauterine sites. The Pap test is not intended to be a screening test for such lesions.

When suspected glandular abnormalities are identified, their accurate classification as true glandular versus squamous lesions is important for proper evaluation and subsequent treatment (*e.g.* choice of excisional biopsy method versus conservative follow-up). Multiple peer-reviewed publications[4-9] report on the improved ability of the ThinPrep 2000 system to detect glandular disease versus the conventional Pap smear. Although these studies do not consistently address sensitivity of different Pap testing methods in detecting specific types of glandular disease, the reported results are consistent with more frequent biopsy confirmation of abnormal glandular findings by the ThinPrep Pap Test compared to conventional cytology.

Thus, the finding of a glandular abnormality on a ThinPrep Pap Test slide merits increased attention for definitive evaluation of potential endocervical or endometrial pathology.

ThinPrep Genesis Processor Compared to ThinPrep 2000 System

A multi-center clinical study was conducted to evaluate the performance of the ThinPrep Genesis processor in direct comparison to the ThinPrep 2000 system. The objective of the ThinPrep clinical study was to estimate the Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) for gynecologic specimens prepared using the ThinPrep Genesis processor as compared with processing using the ThinPrep 2000 system.

CLINICAL STUDY DESIGN

This study was a multi–center, split-sample, blinded evaluation of pairs of ThinPrep slides generated from the ThinPrep 2000 system and ThinPrep Genesis processor from the same residual cytological specimen. The study was conducted at three (3) laboratories in the United States. All study specimens were processed on both a ThinPrep 2000 system (TP-2000) and a ThinPrep Genesis processor using “Slide Only” process. All slides were reviewed independently by three (3) cytotechnologists (CT) and three (3) pathologists at each site. Following manual review, all slides were adjudicated by an independent site, the fourth site. All cytological diagnoses were determined in accordance with the Bethesda System criteria for all slides.

1,260 patients’ ThinPrep Pap Test specimens were enrolled in this study. 1,260 samples were enrolled from February 2019 through June 2020. Each study site enrolled 420 specimens selected from their residual inventory (population of gynecological ThinPrep Pap Test specimens sent to the study sites’ cytology laboratory). The samples for the study included specimens in each of the diagnostic categories being evaluated. Each study site produced 2 slides per specimen, 1 slide prepared on the ThinPrep Genesis processor and 1 slide prepared on the TP-2000 processor, yielding 840 slides (420 pairs of slides) per site for diagnostic review. A total of 2,520 slides were analyzed for the study. The order in which the slides were processed was randomized. All slides were stained, coverslipped and read manually following standard laboratory procedures; all slides prepared at the site were reviewed independently by each of three (3) pairs of cytotechnologists/pathologists. All cytologic diagnoses were determined in accordance with Bethesda System 2001 criteria.

LABORATORY AND PATIENT CHARACTERISTICS

Of the 1260 specimens enrolled, 7 specimens were excluded (3 specimens were excluded because of expiration time and 4 specimens were excluded because there were no adjudication results). Total number of specimens for an evaluation of the ThinPrep Genesis processor was 1253. The study population included women with median age ≈36 years, ≈7% of women were postmenopausal and ≈2% of women had hysterectomy. Table 18 describes the patient populations at each of the study sites:

Table 18: Clinical Study Characteristics

Parameter	Statistic	Site 1 (N=417)	Site 2 (N=418)	Site 3 (N=418)	All Sites (N=1253)
Age (years)	n	417	418	418	1253
	Mean	38.7	39.9	38.7	39.1
	SD	12.89	12.71	13.97	13.20
	Median	36.0	38.0	35.0	36.0
	Min - Max	20 - 78	18 - 82	15 - 82	15 - 82
Postmenopausal					
Yes	n (%)	19 (4.6)	31 (7.7)	35 (8.4)	85 (6.9)
No	n (%)	398 (95.4)	386 (92.3)	383 (91.6)	1167 (93.1)
Hysterectomy					
Yes	n (%)	5 (1.2)	3 (0.7)	18 (4.3)	26 (2.1)
No	n (%)	412 (98.8)	415 (99.3)	400 (95.7)	1227 (97.9)

REFERENCE DIAGNOSIS BY ADJUDICATION REVIEW

After all study slides were reviewed, the ThinPrep Genesis slides and ThinPrep 2000 slides were subject to an adjudication review. Adjudication was done at a facility that was not one of the study sites conducting the study. Slides for adjudication were evenly divided between three adjudication panels each consisting of one (1) cytotechnologist and three (3) independent pathologists. Each adjudication panel reviewed one-third of the slides prepared from each study site for a total of 2512 slides). Each adjudication panel was blinded to the original review diagnosis for all slides and each independent pathologist within each panel was also blinded to other adjudicator's diagnoses for all slides. Adjudication consensus agreement was obtained for

each slide reviewed. Consensus agreement was achieved when at least two of the three pathologists from a panel rendered an identical diagnosis. In cases where the pathologist review process did not reach a consensus, the panel of pathologists was brought together at a multi-headed microscope to manually review those slides for consensus diagnosis. Each panel of pathologists participating in the multi-head review was blinded to all previous diagnoses obtained in the adjudication review.

Adjudicated results for both the ThinPrep 2000 system and the Genesis processor are presented in Table 19.

Table 19: Adjudicated ThinPrep Genesis Processor Diagnosis vs Adjudicated ThinPrep 2000 System Diagnosis (Combined Sites)

		Adjudicated Results (ThinPrep 2000 System)								
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Adjudicated Results (ThinPrep Genesis Processor)	**UNSAT**	2	2	0	0	0	0	1	0	5
	NILM	3	593	65	4	10	11	4	1	691
	ASCUS	1	69	48	2	25	2	2	1	150
	AGUS	0	2	0	0	0	1	1	1	5
	LSIL	0	10	27	0	143	2	18	0	200
	ASC-H	0	6	6	2	2	6	9	1	32
	HSIL	0	1	4	1	10	13	113	6	148
	Cancer	0	0	0	2	0	2	4	14	22
	Total	6	683	150	11	190	37	152	24	1253

Nine (9) sample vials had UNSAT either with ThinPrep Genesis processor, with ThinPrep 2000 system, or with both. Using the severity ordering of the diagnostic result (NILM, ASC-US, AGUS, LSIL, ASC-H, HSIL, Cancer), a single reference diagnosis was formed for each sample vial (specimen) by choosing the most severe of the diagnoses in each pair to create the adjudication reference (“truth”) result for each sample, or slide pair. In the study, there were 32 Cancer, 176 HSIL, 38 ASC-H, 215 LSIL, 8 AGUS, 182 ASC-US, and 593 NILM specimens. 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 negative diagnoses by both methods, ThinPrep Genesis processor and ThinPrep 2000 system, for the specimens with Reference Diagnosis of ASC-US+ (combined ASC-US, AGUS, LSIL, ASC-H, HSIL, and Cancer), LSIL+ (combined LSIL, ASC-H, HSIL, and Cancer), ASC-H+ (combined ASC-H, HSIL, and Cancer), HSIL+ (combined HSIL and Cancer) and Cancer were compared.

CLINICAL STUDY RESULTS

Tables 20 through 29 present the comparison of Laboratory true positive and true negative rates for ASC-US+, LSIL+, ASC-H+, HSIL+ and Cancer for the first pair of cytotechnologist/pathologist at each site and combined for the three sites for the first pair of cytotechnologist/pathologist data.

1. Reference Diagnosis ASC-US+

In the study, there were 651 specimens with Reference Diagnosis of ASC-US+ (combined ASC-US, AGUS, LSIL, ASC-H, HSIL and Cancer) and 593 specimens with Reference Diagnosis of NILM.

Table 20: Laboratory ThinPrep Genesis Results vs Laboratory ThinPrep 2000 Results for the Specimens with Reference Diagnosis of ASC-US+

		Laboratory ThinPrep 2000								
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Laboratory ThinPrep Genesis	**UNSAT**	0	1	0	0	1	0	1	0	3
	NILM	1	148	26	0	6	6	2	1	190
	ASCUS	0	30	50	0	22	8	2	0	112
	AGUS	0	2	0	1	0	1	1	0	5
	LSIL	0	9	12	0	106	2	7	0	136
	ASC-H	0	5	6	0	3	16	12	1	43
	HSIL	0	4	3	0	7	12	105	7	138
	Cancer	0	0	1	0	0	1	4	18	24
	Total	1	199	98	1	145	46	134	27	651

Table 21: Positive Percent Agreement and Negative Percent Agreement for Laboratory ThinPrep Genesis Diagnoses and Laboratory ThinPrep 2000 Diagnoses

In this table, Laboratory "Positive" means ASC-US+ or UNSAT, and Laboratory "Negative" means NILM.

	Positive Percent Agreement				Negative Percent Agreement			
Site	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**
Site #1	220	76.8% (169/220) (70.8%; 81.9%)	75.5% (166/220) (69.4%; 80.7%)	1.4% (-3.5%; 6.3%)	192	96.4% (185/192) (92.7%; 98.2%)	94.8% (182/195) (90.7%; 97.1%)	1.6% (-1.9%; 5.4%)
Site #2	205	71.2% (146/205) (64.7%; 77.0%)	72.7% (149/205) (66.2%; 78.3%)	-1.5% (-5.8%; 2.8%)	212	93.4% (198/212) (89.2%; 96.0%)	92.0% (195/212) (87.5%; 94.9%)	1.4% (-2.9%; 5.8%)
Site #3	226	64.6% (146/226) (58.2%; 70.5%)	60.6% (137/226) (54.1%; 66.8%)	4.0% (-1.9%; 9.8%)	189	97.9% (185/189) (94.7%; 99.2%)	96.3% (182/189) (92.6%; 98.2%)	1.6% (-1.7%; 5.2%)
Combined	651	70.8% (61/651) (67.2%; 74.2%)	69.4% (452/651) (65.8%; 72.8%)	1.4% (-1.5%; 4.3%)	593	95.8% (568/593) (93.9%; 97.1%)	94.3% (559/593) (92.1%; 95.9%)	1.5% (-0.5%; 3.6%)

2. Reference Diagnosis LSIL+

In the study, there were 461 specimens with Reference Diagnosis of LSIL+ (combined LSIL, ASC-H, HSIL, and Cancer) and 783 specimens with Reference Diagnosis of (combined NILM, ASC-US/AGUS).

Table 22: Laboratory ThinPrep Genesis Results vs Laboratory ThinPrep 2000 Results for the Specimens with Reference Diagnosis of LSIL+

		Laboratory ThinPrep 2000								
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Laboratory ThinPrep Genesis	**UNSAT**	0	0	0	0	1	0	1	0	2
	NILM	0	29	8	0	6	5	1	1	50
	ASCUS	0	15	38	0	18	7	2	0	80
	AGUS	0	1	0	1	0	0	1	0	3
	LSIL	0	7	10	0	105	2	7	0	131
	ASC-H	0	3	4	0	3	11	12	1	34
	HSIL	0	4	2	0	7	12	105	7	137
	Cancer	0	0	1	0	0	1	4	18	24
	Total	0	59	63	1	140	38	133	27	461

Table 23: Positive Percent Agreement and Negative Percent Agreement for Laboratory ThinPrep Genesis Diagnoses and Laboratory ThinPrep 2000 Diagnoses

In this table, Laboratory "Positive" means LSIL+ or UNSAT, and Laboratory "Negative" means NILM or ASC-US/AGUS.

	Positive Percent Agreement				Negative Percent Agreement			
Site	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**
Site #1	162	74.7% (121/162) (67.5%; 80.8%)	76.5% (124/162) (69.5%; 82.4%)	-1.9% (-7.3%; 3.6%)	250	96.4% (241/250) (93.3%; 98.1%)	96.0% (240/250) (92.8%; 97.8%)	0.4% (-2.4%; 3.3%)
Site #2	138	81.9% (113/138) (74.6%; 87.4%)	84.8% (117/138) (77.9%; 89.8%)	-2.9% (-9.0%; 3.1%)	279	96.4% (269/279) (93.5%; 98.0%)	94.3% (263/279) (90.9%; 96.4%)	2.2% (-1.2%; 5.7%)
Site #3	161	58.4% (94/161) (50.7%; 65.7%)	60.2% (97/161) (52.5%; 67.5%)	-1.9% (-9.3%; 5.6%)	254	97.6% (248/254) (94.9%; 98.9%)	98.4% (250/254) (96.0%; 99.4%)	-0.8% (-3.2%; 1.3%)
Combined	461	71.1% (328/461) (66.9%; 75.1%)	73.3% (338/461) (69.1%; 77.2%)	-2.2% (-5.8%; 1.5%)	783	96.8% (758/783) (95.3%; 97.8%)	96.2% (753/783) (94.6%; 97.3%)	0.6% (-0.9%; 2.2%)

3. Reference Diagnosis ASC-H+

In the study, there were 246 specimens with Reference Diagnosis of ASC-H+ (combined ASC-H, HSIL, and Cancer) and 998 specimens with Reference Diagnosis of (combined NILM, ASC-US, AGUS, and LSIL).

Table 24: Laboratory ThinPrep Genesis Results vs Laboratory ThinPrep 2000 Results for the Specimens with Reference Diagnosis of ASC-H+.

		Laboratory ThinPrep 2000								
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Laboratory ThinPrep Genesis	**UNSAT**	0	0	0	0	0	0	1	0	1
	NILM	0	12	2	0	0	5	1	1	21
	ASCUS	0	3	6	0	1	5	2	0	17
	AGUS	0	1	0	1	0	0	1	0	3
	LSIL	0	0	0	0	12	2	5	0	19
	ASC-H	0	3	4	0	1	9	12	1	30
	HSIL	0	3	2	0	5	11	103	7	131
	Cancer	0	0	1	0	0	1	4	18	24
	Total	0	22	15	1	19	33	129	27	246

Table 25: Positive Percent Agreement and Negative Percent Agreement for Laboratory ThinPrep Genesis Diagnoses and Laboratory ThinPrep 2000 Diagnoses
(In this table, Laboratory "Positive" means ASC-H+ or UNSAT, and Laboratory "Negative" means NILM or ASC-US/AGUS or LSIL)

	Positive Percent Agreement				Negative Percent Agreement			
Site	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**
Site #1	89	82.0% (73/89) (72.8%; 88.6%)	84.3% (75/89) (75.3%; 90.4%)	-2.2% (-10.0%; 5.3%)	323	96.3% (311/323) (93.6%; 97.9%)	96.6% (312/323) (94.0%; 98.1%)	-0.3% (-2.5%; 1.9%)
Site #2	75	81.3% (61/75) (71.1%; 88.5%)	80.0% (60/75) (69.6%; 87.5%)	1.3% (-8.6%; 11.3%)	342	96.5% (330/342) (94.0%; 98.0%)	95.6% (327/342) (92.9%; 97.3%)	0.9% (-1.8%; 3.7%)
Site #3	82	63.4% (52/82) (52.6%; 73.0%)	65.9% (54/82) (55.1%; 75.2%)	-2.4% (-12.7%; 7.9%)	333	98.2% (327/333) (96.1%; 99.2%)	98.2% (327/333) (96.1%; 99.2%)	0.0% (-1.7%; 1.7%)
Combined	246	75.6% (186/246) (69.9%; 80.6%)	76.8% (189/246) (71.2%; 81.7%)	-1.2% (-6.4%; 4.0%)	998	97.0% (968/998) (95.7%; 97.9%)	96.8% (966/998) (95.5%; 97.7%)	0.2% (-1.0%; 1.4%)

4. Reference Diagnosis HSIL+

In the study, there were 208 specimens with Reference Diagnosis of HSIL+ (combined HSIL and Cancer) and 1036 specimens with Reference Diagnosis of (combined NILM, ASC-US, AGUS, LSIL, and ASC-H).

Table 26: Laboratory ThinPrep Genesis Results vs Laboratory ThinPrep 2000 Results for the Specimens with Reference Diagnosis of HSIL+

		Laboratory ThinPrep 2000								
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Laboratory ThinPrep Genesis	**UNSAT**	0	0	0	0	0	0	1	0	1
	NILM	0	0	0	0	0	2	1	1	4
	ASCUS	0	1	3	0	1	3	1	0	9
	AGUS	0	1	0	1	0	0	1	0	3
	LSIL	0	0	0	0	12	1	5	0	18
	ASC-H	0	3	3	0	1	8	9	0	24
	HSIL	0	2	2	0	5	11	99	7	126
	Cancer	0	0	1	0	0	1	3	18	23
	Total	0	7	9	1	19	26	120	26	208

Table 27: Positive Percent Agreement and Negative Percent Agreement for Laboratory ThinPrep Genesis Diagnoses and Laboratory ThinPrep 2000 Diagnoses

(In this table, Laboratory "Positive" means HSIL+ or UNSAT, and "Negative" means NILM or ASC-US/AGUS or LSIL or ASC-H.)

	Positive Percent Agreement				Negative Percent Agreement			
Site	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**
Site #1	76	85.5% (65/76) (75.9%; 91.7%)	80.3% (61/76) (70.0%; 87.7%)	5.3% (-4.2%; 14.9%)	336	98.5% (331/336) (96.6%; 99.4%)	99.1% (333/336) (97.4%; 99.7%)	-0.6% (-2.4%; 1.0%)
Site #2	64	73.4% (47/64) (61.5%; 82.7%)	79.7% (51/64) (68.3%; 87.7%)	-6.3% (-18.0%; 5.6%)	353	97.5% (344/353) (95.2%; 98.7%)	96.0% (339/353) (93.5%; 97.6%)	1.4% (-0.9%; 3.9%)
Site #3	68	55.9% (38/68) (44.1%; 67.1%)	50.0% (34/68) (38.4%; 61.6%)	5.9% (-5.0%; 16.5%)	347	98.8% (343/347) (97.1%; 99.6%)	98.6% (342/347) (96.7%; 99.4%)	0.3% (-1.2%; 1.9%)
Combined	208	72.1% (150/208) (65.7%; 77.8%)	70.2% (146/208) (63.7%; 76.0%)	1.9% (-4.1%; 7.9%)	1036	98.3% (1018/1036) (97.3%; 98.9%)	97.9% (1014/1036) (96.8%; 98.6%)	0.4% (-0.6%; 1.4%)

5. Reference Diagnosis Cancer

In the study, there were 32 specimens with Reference Diagnosis of Cancer and 1212 specimens with Reference Diagnosis of (combined NILM, ASC-US, AGUS, LSIL, ASC-H, and HSIL).

Table 28: Laboratory ThinPrep Genesis Results vs Laboratory ThinPrep 2000 results for the Specimens with Reference Diagnosis of Cancer.

		Laboratory ThinPrep 2000								
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Laboratory ThinPrep Genesis	**UNSAT**	0	0	0	0	0	0	0	0	0
	NILM	0	0	0	0	0	0	0	1	1
	ASCUS	0	0	0	0	0	0	0	0	0
	AGUS	0	1	0	0	0	0	1	0	2
	LSIL	0	0	0	0	1	0	0	0	1
	ASC-H	0	0	0	0	0	1	0	0	1
	HSIL	0	0	0	0	0	1	3	4	8
	Cancer	0	0	1	0	0	0	1	17	19
	Total	0	1	1	0	1	2	5	22	32

Table 29: Positive Percent Agreement and Negative Percent Agreement for Laboratory ThinPrep Genesis Diagnoses and Laboratory ThinPrep 2000 Diagnoses

(In this table, Laboratory "Positive" means Cancer or UNSAT, and "Negative" means NILM or ASC-US/AGUS or LSIL or ASC-H or HSIL).

	Positive Percent Agreement				Negative Percent Agreement			
Site	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**	**N**	**ThinPrep Genesis (95%CI)**	**ThinPrep 2000 (95%CI)**	**Difference (95%CI)**
Site #1	14	78.6% (11/14) (52.4%; 92.4%)	78.6% (11/14) (52.4%; 92.4%)	0.0% (-24.8%; 24.8%)	398	99.5% (396/398) (98.2%;99.9%)	99.7% (397/398) (98.6%;100.0%)	-0.3% (-1.5%;0.8%)
Site #2	7	71.4% (5/7) (35.9%; 91.8%)	100.0% (7/7) (64.6%; 100%)	-28.6% (-64.1%; 12.3%)	410	98.5% (404/410) (96.8%; 99.3%)	98.5% (404/410) (96.8%; 99.3%)	0.0% (-1.9%; 1.9%)
Site #3	11	27.3% (3/11) (9.7%; 56.6%)	36.4% (4/11) (15.2%; 64.6%)	-9.1% (-39.6%; 24.0%)	404	99.3% (401/404) (97.8%; 99.7%)	99.3% (401/404) (97.8%; 99.7%)	0.0% (-1.2%; 1.2%)
Combined	32	59.4% (19/32) (42.3%; 74.5%)	68.8% (22/32) (51.4%; 82.0%)	-9.4% (-25.3%; 7.4%)	1212	99.1% (1201/1212) (98.4%; 99.5%)	99.2% (1202/1212) (98.5%; 99.6%)	-0.1% (-0.8%;0.6%)

Results of the clinical study for 32 specimens with Reference Diagnosis of Cancer were analyzed where "Positive" means HSIL+ (combined Cancer and HSIL).

Both the ThinPrep Genesis processor and the ThinPrep 2000 system have HSIL+ results for 27 out of 32 specimens (PPAs for both are 84.4% (27/32) and difference is 0.0% with 95%CI: (-14.9%; 14.9%)).

Both the ThinPrep Genesis processor and the ThinPrep 2000 system have ASC-US+ results for 31 out of 32 specimens (PPAs for both are 96.9% (31/32) and difference is 0.0% with 95%CI: (-14.2%; 14.2%)).

Table 30 provides additional details on one specimen with NILM adjudicated result on the ThinPrep Genesis slide and with Cancer adjudicated result on the ThinPrep 2000 slide.

Table 30: Laboratory and Adjudicated Diagnoses of Specimen with NILM Adjudicated Result on Slide Prepared on ThinPrep Genesis Processor and Cancer Result on Slide Prepared with the ThinPrep 2000 System

	Slide	Diagnoses from slide prepared on TP-2000 (second slide)	Diagnoses from slide prepared on ThinPrep Genesis (first slide)
Lab-oratory	**Manual 1**	CANCER	CANCER
	Manual 2	CANCER	CANCER
	Manual 3	CANCER	CANCER
Adjudication	**Adjudicated result 1**	CANCER	NILM
	Adjudicated result 2	CANCER	NILM
	Adjudicated result 3	AGUS	NILM
	Final Adjudicated result	CANCER	NILM

Results of the clinical study for 20 specimens with Reference Diagnosis of Adenocarcinoma are also presented in Table 31.

Table 31: Adjudicated Results for 32 Specimens with Reference Diagnosis of Cancer

		ThinPrep 2000 Adjudicated Results											
		NILM	**ASC-US**	**ASC-H**	**HSIL**	**SCC**	**AGC-NOS**	**AGC favor neo**	**AIS**	**Adeno-NOS**	**Adeno EC**	**Adeno EM**	**Total**
ThinPrep Genesis Adjudi-cated Results	**NILM**							1					1
	ASC-US							1					1
	ASC-H					1							1
	HSIL					3		1	1		1		6
	SCC			2	1	4							7
	AGC-NOS					1							1
	AGS favor neo						1						1
	AIS				2				1				3
	Adeno-NOS										1		1
	Adeno EC				1								1
	Adeno EM						1			1		7	9
Total				2	4	9	2	3	2	1	2	7	32

Among 32 specimens with Reference Diagnosis of Cancer, there were 20 specimens with Reference Diagnosis of Adenocarcinoma. Both the ThinPrep Genesis processor and the ThinPrep 2000 system have adjudicated results of Adenocarcinoma for 75% (15/20) specimens.

6. UNSAT Slides by Adjudication Panels

Tables 32 and 33 provide details on the various levels of agreement among the CT and pathologist pairs for the specimens determined to be unsatisfactory for evaluation by the adjudication panels. The tables also indicate if a specimen was first run on the ThinPrep Genesis processor, or if was first run on the ThinPrep 2000 System. In the study, there were 0.4% (5 out of 1253) UNSAT ThinPrep Genesis slides and 0.5% (6 out of 1253) UNSAT ThinPrep 2000 slides.

Table 32: UNSAT Specimen Details, ThinPrep Genesis Slides

UNSAT Genesis slides	Processing Order from Vial	Manual Diagnosis by CT/Path#1	Manual Diagnosis by CT/Path#2	Manual Diagnosis by CT/Path#3	Reason for adj. UNSAT result
Genesis sample 1	First	ASCUS	NILM	NILM	Hypocellular
Genesis sample 2	First	HSIL	HSIL	HSIL	Hypocellular
Genesis sample 3	Second	NILM	NILM	NILM	Hypocellular, Obscuring inflammation
Genesis sample 4	First	NILM	NILM	NILM	Obscuring inflammation (UNSAT on multihead)
Genesis sample 5	Second	UNSAT	NILM	NILM	Hypocellular, Bloody
Sensitivity (95%)		60.0% (3/5) (23.1%; 88.2%)	20.0% (1/5) (3.6%; 62.5%)	20.0% (1/5) (3.6% ; 62.5%)	

The positive percent agreement averaged over 3 pairs of CT/Pathologist for ThinPrep Genesis UNSAT slides was 33.3%.

Table 33: UNSAT Specimen Details, ThinPrep 2000 Slides

UNSAT TP-2000 slides	Processing Order from Vial	Manual Diagnosis by CT/Path#1	Manual Diagnosis by CT/Path#2	Manual Diagnosis by CT/Path#3	Reason for adj. UNSAT result
TP-2000 sample 1	First	UNSAT	NILM	NILM	Hypocellular
TP-2000 sample 2	Second	UNSAT	UNSAT	UNSAT	Hypocellular
TP-2000 sample 3	First	UNSAT	NILM	UNSAT	Hypocellular
TP-2000 sample 4	Second	NILM	NILM	NILM	Hypocellular, Obscuring inflammation
TP-2000 sample 5	Second	UNSAT	NILM	NILM	Hypocellular
TP-2000 sample 6	First	UNSAT	NILM	UNSAT	Hypocellular
Sensitivity (95% score CI)		83.3% (5/6) (43.7%; 97.0%)	16.7% (1/6) (3.0%; 56.4%)	50.0% (3/6) (18.8%; 81.2%)	

The positive percent agreement averaged over 3 pairs of CT/Pathologist for ThinPrep 2000 UNSAT slides was 50.0%.

Precision Studies

Within-instrument precision and between-instrument precision (reproducibility) of the ThinPrep Genesis processor was evaluated in laboratory studies using a split-sample technique.

WITHIN-INSTRUMENT PRECISION

A total of 160 specimens were enrolled in the study. Each specimen was split into three portions and processed on three separate runs on a single instrument using “Slide Only” process. The slides were stained, coverslipped, and then reviewed by cytotechnologists according to the Bethesda System for Reporting Cervical Cytology. Seven specimens were excluded from the analysis because at least one slide was unavailable for CT review. The resulting diagnoses are summarized in Table 36 with comparisons of the different runs in Tables 37, 38, and 39.

Table 36: Within-Instrument Precision

	Specimen Diagnostic Level			
Sample processing run on the ThinPrep Genesis processor	**NILM**	**ASCUS or AGUS**	**LSIL**	**ASC-H or HSIL or Cancer**
Run 1 (n = 153)	109	12	18	14
Run 2 (n = 153)	111	11	16	15
Run 3 (n = 153)	109	11	19	14
	Number of specimens with three matching replicates			
	107	9	16	14

Percent of specimens with 3 matching replicates was 95.4% (146/153), 95%CI: (90.9%; 97.8%)

Table 37: Run-to-Run Precision: Run 1 vs Run 2

Run 2	**Run 1**						
	UNSAT	**NILM**	**ASCUS/ AGUS**	**LSIL**	**ASC–H**	**HSIL**	**Cancer**
UNSAT	0	0	0	0	0	0	0
NILM	0	107	2	2	0	0	0
ASCUS/AGUS	0	1	10	0	0	0	0
LSIL	0	0	0	16	0	0	0
ASC–H	0	0	0	0	1	0	0
HSIL	0	1	0	0	0	13	0
Cancer	0	0	0	0	0	0	0

Table 38: Run-to-Run Precision: Run 1 vs Run 3

Run 3	Run 1						
	UNSAT	NILM	ASCUS/ AGUS	LSIL	ASC–H	HSIL	Cancer
UNSAT	0	0	0	0	0	0	0
NILM	0	107	2	0	0	0	0
ASCUS/AGUS	0	1	10	0	0	0	0
LSIL	0	0	0	18	0	1	0
ASC–H	0	0	0	0	1	0	0
HSIL	0	1	0	0	0	12	0
Cancer	0	0	0	0	0	0	0

Table 39: Run-to-Run Precision: Run 2 vs Run 3

Run 3	Run 2						
	UNSAT	NILM	ASCUS/ AGUS	LSIL	ASC–H	HSIL	Cancer
UNSAT	0	0	0	0	0	0	0
NILM	0	107	2	0	0	0	0
ASCUS/AGUS	0	2	9	0	0	0	0
LSIL	0	3	0	16	0	1	0
ASC–H	0	0	0	0	1	0	0
HSIL	0	0	0	0	0	13	0
Cancer	0	0	0	0	0	0	0

BETWEEN-INSTRUMENT REPRODUCIBILITY

A total of 160 specimens were enrolled in the study. Each specimen was split into three portions and processed on three different ThinPrep Genesis processors using “Slide Only” process. The slides were stained, coverslipped, and then reviewed by cytotechnologists using Imager-assisted review according to the Bethesda System for Reporting Cervical Cytology. Ten specimens were excluded because at least one slide was unavailable for CT review. The resulting diagnoses are presented in Table 40, with comparisons of the different runs in Tables 41, 42, and 43.

Table 40: Between-Instrument Reproducibility

	Specimen Diagnostic Level Number of specimens with three matching replicates			
ThinPrep Genesis Processor	**NILM**	**ASCUS or AGUS**	**LSIL**	**ASC-H or HSIL or Cancer**
ThinPrep Genesis Instrument 1 (n = 150)	112	2	22	14
ThinPrep Genesis Instrument 2 (n = 150)	109	3	23	15
ThinPrep Genesis Instrument 3 (n = 150)	111	2	21	16
	Number of specimens with three matching replicates			
	104	0	18	9

Percent of specimens with 3 matching replicates was 87.3% (131/150), 95%CI: (81.1%; 91.7%)

Table 41: Instrument-to-Instrument Reproducibility, ThinPrep Genesis Instrument 1 versus ThinPrep Genesis Instrument 2

	ThinPrep Genesis Instrument 1						
ThinPrep Genesis Instrument 2	**UNSAT**	**NILM**	**ASCUS/ AGUS**	**LSIL**	**ASC–H**	**HSIL**	**Cancer**
UNSAT	0	0	0	0	0	0	0
NILM	0	105	1	3	0	0	0
ASCUS/AGUS	0	2	1	0	0	0	0
LSIL	0	3	0	18	1	1	0
ASC–H	0	1	0	0	1	1	0
HSIL	0	1	0	1	1	8	0
Cancer	0	0	0	0	0	0	1

Table 42: Instrument-to-Instrument Reproducibility, ThinPrep Genesis Instrument 1 versus ThinPrep Genesis Instrument 3

ThinPrep Genesis Instrument 3	ThinPrep Genesis Instrument 1						
	UNSAT	NILM	ASCUS/ AGUS	LSIL	ASC–H	HSIL	Cancer
UNSAT	0	0	0	0	0	0	0
NILM	0	108	1	2	0	0	0
ASCUS/AGUS	0	1	0	1	0	0	0
LSIL	0	1	0	18	1	1	0
ASC–H	0	2	1	0	0	1	0
HSIL	0	0	0	1	2	8	0
Cancer	0	0	0	0	0	0	1

Table 43: Instrument-to-Instrument Reproducibility, ThinPrep Genesis Instrument 2 versus ThinPrep Genesis Instrument 3

ThinPrep Genesis Instrument 3	ThinPrep Genesis Instrument 2						
	UNSAT	NILM	ASCUS/ AGUS	LSIL	ASC–H	HSIL	Cancer
UNSAT	0	0	0	0	0	0	0
NILM	0	104	2	4	0	1	0
ASCUS/AGUS	0	2	0	0	0	0	0
LSIL	0	2	0	18	0	1	0
ASC–H	0	1	1	0	2	0	0
HSIL	0	0	0	1	1	9	0
Cancer	0	0	0	0	0	0	1

Cell Count Study

A study was conducted to evaluate the quantity of cellular material transferred onto slides, comparing the ThinPrep Genesis processor to the ThinPrep 2000 system.

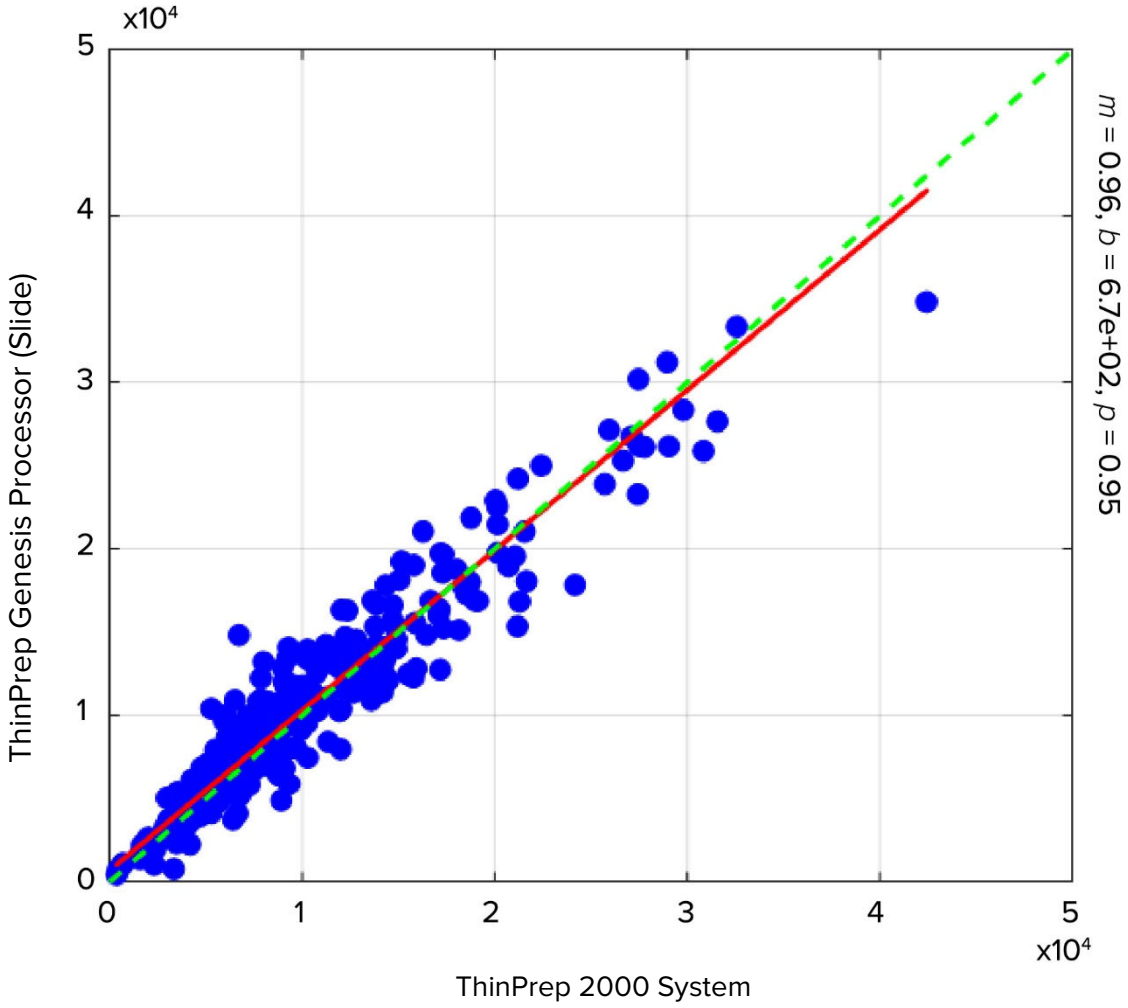
Two comparisons were made. Slides prepared on the ThinPrep Genesis processor using the "Aliquot + Slide" process were compared to slides prepared on the ThinPrep 2000 system. And, slides prepared on the ThinPrep Genesis processor using the "Slide Only" process were compared to slides prepared using the ThinPrep 2000 system.

A split-sample technique was used. A total of 300 specimens were enrolled in the study. Each specimen was split into three portions. Specimens processed by one of three methods (ThinPrep 2000, ThinPrep Genesis "Aliquot + Slide" or ThinPrep Genesis "Slide"). The slides were stained, coverslipped, and then imaged with the ThinPrep Imaging System in order to quantify the amount of cellular material on each slide. Furthermore, the slides prepared in the cell count study were reviewed by cytotechnologists and categorized according to the Bethesda System for Reporting Cervical Cytology.

Results of the Study: ThinPrep Genesis "Slide Only" Process vs. ThinPrep 2000 System

Figure 1 presents a scatter plot of cell counts and an ordinary Deming linear regression analysis.

Figure 1: ThinPrep Genesis "Slide" Process vs. ThinPrep 2000 System



Deming regression analysis was performed and the slope was 0.96 with 95%CI: (0.94; 0.99) and the intercept was 670 with 95% CI: (420; 930)

The resulting diagnosis determinates are presented in Table 44.

Table 44: Diagnostic Comparison of Slides Processed on the ThinPrep Genesis Processor ("Slide Only" Process) vs. ThinPrep 2000 System

		ThinPrep 2000 System		
		UNSAT	***ASCUS+***	**NILM**
ThinPrep Genesis Processor ("Slide Only" process)	***UNSAT***	10	0	1
	ASCUS+	0	66	13
	NILM	3	12	195

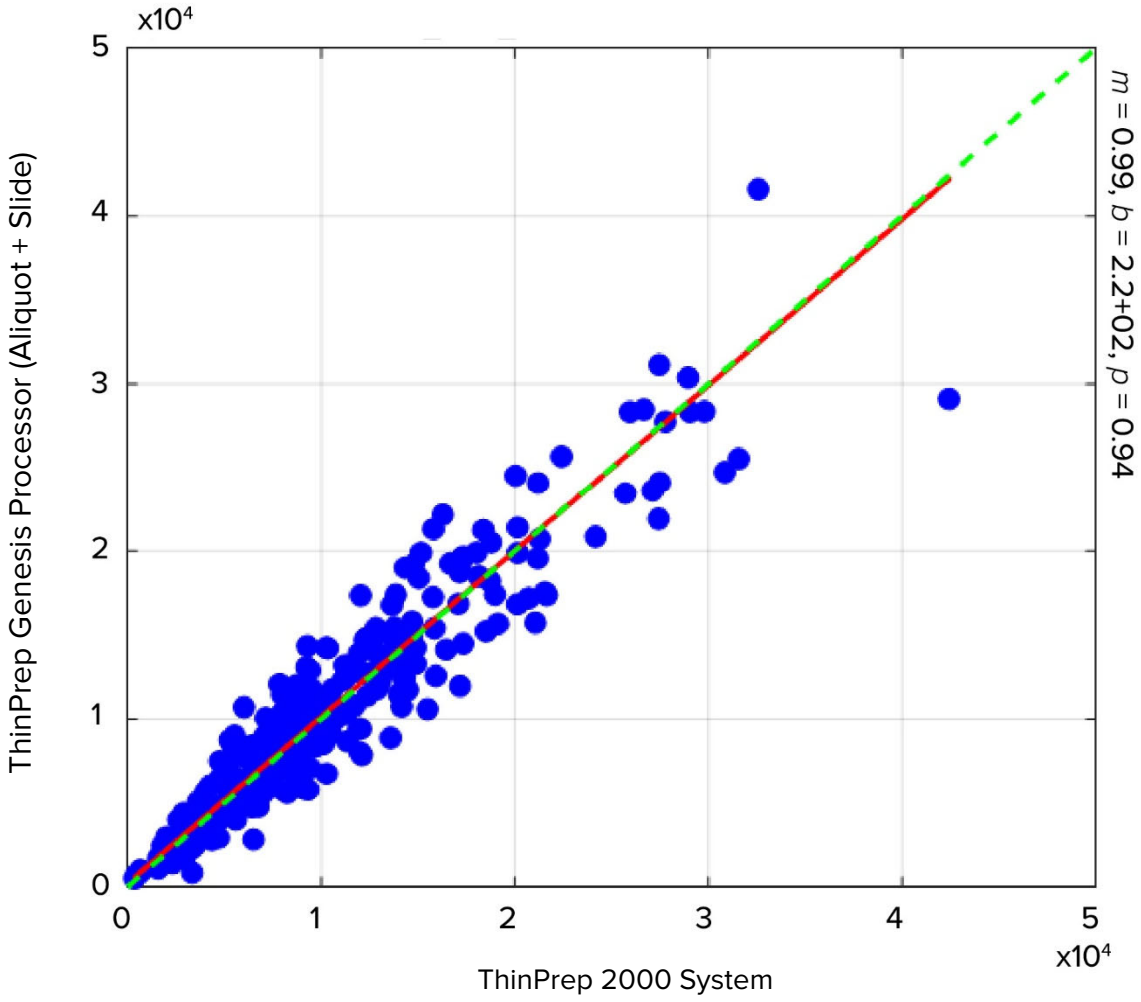
Percent of UNSAT slides were 3.7% (11/300) for ThinPrep Genesis Processor ("Slide" process) and 4.3% (13/300) for ThinPrep 2000 system; difference was -0.7%, 95%CI: (-2.6%; 1.1%). Percent for ASC-US+ slides were 27.6% (79/286) for ThinPrep Genesis Processor ("Slide Only" process) and 27.3% (78/286) for ThinPrep 2000 system; difference was 0.3% with 95%CI: (-3.2%; 3.9%).

The data demonstrate similar cell count values on the ThinPrep Genesis processor ("Slide Only" process) and ThinPrep 2000 system.

Results of the Study: ThinPrep Genesis "Aliquot+Slide" Process vs. ThinPrep 2000 System

Figure 2 presents a scatter plot of cell counts and an ordinary Deming linear regression analysis.

Figure 2: ThinPrep Genesis "Aliquot + Slide" Process vs. ThinPrep 2000 System



Deming regression analysis was performed and the slope was 0.99 with 95%CI: (0.96; 1.02) and the intercept was 220 with 95%CI: (-70;500)

The resulting diagnosis determinates are presented in Table 45.

Table 45: Diagnostic Comparison of Slides Processed on the ThinPrep Genesis Processor (Aliquot + Slide Process) vs. ThinPrep 2000 System

		ThinPrep 2000 System		
		UNSAT	***ASCUS+***	**NILM**
ThinPrep Genesis Processor ("Aliquot + Slide" process)	***UNSAT***	9	0	2
	ASCUS+	0	70	15
	NILM	4	8	192

Percent of UNSAT slides were 3.7% (11/300) for ThinPrep Genesis Processor ("Aliquot+ Slide" process) and 4.3% (13/300) for ThinPrep 2000 system; difference was -0.7%, 95%CI: (-2.8%; 1.3%). Percent for ASC-US+ slides were 29.7% (85/286) for ThinPrep Genesis Processor ("Aliquot+Slide" process) and 27.4% (78/286) for ThinPrep 2000 system; difference was 2.5% with 95%CI: (-0.9%; 5.8%).

The data demonstrate similar cell count values on the ThinPrep Genesis processor ("Aliquot+ Slide" process) and ThinPrep 2000 system.

Carry-Over Study

Cellular carry-over between slides was evaluated in a study forthe ThinPrep Genesis processor and the ThinPrep 2000 system.

On each system 350 abnormal clinical specimens were processed, alternating with 350 PreservCyt vials containing no cells ("acellular vials"). Specimens processed on the ThinPrep Genesis processor used the "Aliquot + Slide" process. After processing, slides made from the acellular vials were segregated from the cellular slides, stained and coverslipped and then reviewed by cytotechnologists. Any cells found on a slide were noted. Slides made from an acellular vial but containing at least one cell were considered to have cellular carry-over. One slide from the ThinPrep 2000 system was excluded due to operator error. Table 46 presents the results.

Table 46: Cellular Carry-Over

	ThinPrep 2000 System	ThinPrep Genesis Processor ("Aliquot+Slide" process)
Total # of Slides	349	350
# of Slides with carry-over	89	20
% of Slides with carry-over	25.5%	5.7%
Number of cells on the slides with carry-over: Median (Min, Max)	2 (1, 96)	2 (1, 43)

The study demonstrated that the cellular cross-contamination from slide to slide on the ThinPrep Genesis is not inferior to the cross-contamination on the ThinPrep 2000 system.

Aliquot Delivery Study

The ability for the ThinPrep Genesis processor to dispense an aliquot from a ThinPrep vial into an output tube was evaluated in a laboratory study. The data generated for this study demonstrate that the ThinPrep Genesis processor dispenses 1 mL ± 4% from the ThinPrep vial to an output tube.

Conclusions

The results of the study comparing the performance of the ThinPrep Genesis processor to the ThinPrep 2000 system demonstrate that the ThinPrep Genesis processor is at least as effective as the ThinPrep 2000 system for preparing slides from gynecologic specimens for the detection of atypical cells, cervical cancer including adenocarcinoma or its precursor lesions, as well as all other cytologic categories as defined by *The Bethesda System for Reporting Cervical Cytology*.

The ThinPrep® 2000 system is as effective as the conventional Pap smear in a variety of patient populations and may be used as a replacement for the conventional Pap smear method for the detection of atypical cells, cervical cancer, or its precursor lesions, as well as all other cytologic categories as defined by The Bethesda System. Since the ThinPrep Genesis processor uses similar cell collection and slide preparation technology as the ThinPrep 2000 system, the ThinPrep Genesis processor is also as effective as the conventional Pap smear in a variety of patient populations and may be used as a replacement for the conventional Pap smear method for the detection of atypical cells, cervical cancer, or its precursor lesions, as well as all other cytologic categories as defined by the Bethesda System.

The ThinPrep 2000 system is significantly more effective than the conventional Pap smear for the detection of Low-grade Squamous Intraepithelial (LSIL) and more severe lesions in a variety of patient populations. Since the ThinPrep Genesis processor uses similar cell collection and slide preparation technology as the ThinPrep 2000 system, the ThinPrep Genesis processor is also significantly more effective than the conventional Pap smear for the detection of Low-grade Squamous Intraepithelial (LSIL) and more severe lesions in a variety of patient populations.

Specimen quality with the ThinPrep 2000 system is significantly improved over that of conventional Pap smear preparation in a variety of patient populations. Since the ThinPrep Genesis processor uses similar cell collection and slide preparation technology as the ThinPrep 2000 system, the specimen quality with the ThinPrep Genesis processor is also significantly improved over that of conventional Pap smear preparation in a variety of patient populations.

MATERIALS REQUIRED

MATERIALS PROVIDED

- ThinPrep Genesis processor
- ThinPrep Genesis processor operator's manual
- Power cord
- Waste bottle assembly with tubing harness and transport cover
- Fixative baths (10)
- Pipette tip disposal cup (2)
- Absorbent pad for filter plug (4)
- Absorbent pad for filter puncture area (4)
- Pipette tip holder (2, for customers performing aliquot removal)
- Multi-channel pipette tip gripper (for customers performing aliquot removal)
- Slide printer (optional)
- Tube printer (optional)
- USB key (1)

MATERIALS REQUIRED BUT NOT PROVIDED

- 20 ml PreservCyt® Solution vial
- ThinPrep® Pap Test filter
- ThinPrep® microscope slide
- Pipette tips (conductive, disposable, plastic pipette tips with an aerosol-resistant filter, 1 mL, for customers performing aliquot removal)
- Specimen transfer tube (for customers performing aliquot removal)
- Cervical collection device
- Slide staining system and reagents
- Standard laboratory fixative
- Coverslips and mounting media

- Lint-free wipes
- Personal protective equipment
- Sodium hypochlorite solution (0.5% solution, for customers performing aliquot removal)

STORAGE

- Store PreservCyt Solution between 15°C (59°F) and 30°C (86°F). Do not use beyond the expiration date printed on the container.
- Store PreservCyt Solution with cytologic sample intended for ThinPrep Pap testing between 15°C (59°F) and 30°C (86°F) for up to 6 weeks.

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TECHNICAL SERVICE AND PRODUCT INFORMATION

For technical service and assistance related to use of the ThinPrep Genesis processor, contact Hologic:

Telephone: 1-800-442-9892

Fax: 1-508-229-2795

For international or toll-free blocked calls, please contact 1-508-263-2900.

Email: info@hologic.com

Hologic, Inc.
250 Campus Drive
Marlborough, MA 01752
1-800-442-9892
www.hologic.com