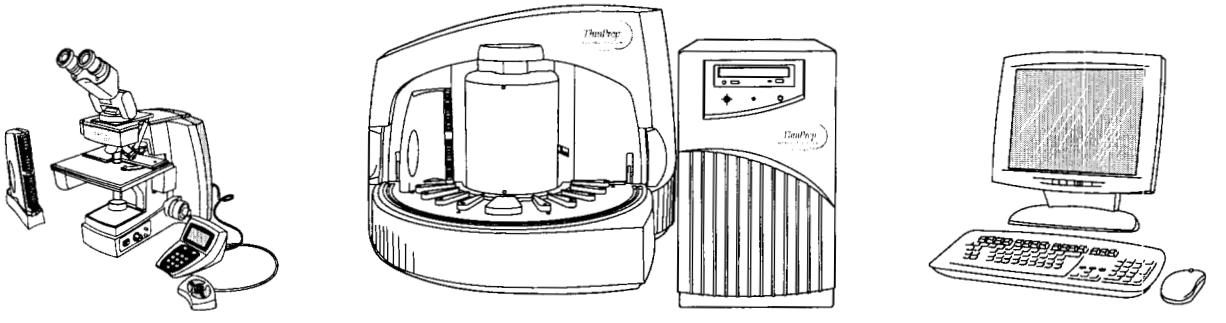
ThinPrep®
IMAGING SYSTEM

Operation Summary and Clinical Information



The ThinPrep® Imaging System

CYTYC

A. INTENDED USE

The Cytyc Corporation ThinPrep® Imaging System (Imager) is a device that uses computer imaging technology to assist in primary cervical cancer screening of ThinPrep® Pap Test slides for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), and carcinoma as well as all other cytologic criteria as defined by 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology [1].

B. SUMMARY AND EXPLANATION OF THE SYSTEM

The ThinPrep Imaging System is an automated imaging and review system for use with ThinPrep Pap Test slides. It combines imaging technology to identify microscopic fields of diagnostic interest with automated stage movement of a microscope in order to locate these fields. In routine use, the ThinPrep Imaging System selects 22 fields of view for a Cytotechnologist to review. Following review of these fields, the Cytotechnologist will either complete the diagnosis if no abnormalities are identified or review the entire slide if any abnormalities are identified. The ThinPrep Imaging System also allows the physical marking of locations of interest for the Cytopathologist.

C. PRINCIPLES OF OPERATION

The ThinPrep Imaging System consists of an Image Processor and one, or more, Review Scopes. The system makes use of computer imaging to select fields of view for presentation to a Cytotechnologist on a Review Scope. Slides used with this system must first be prepared on a ThinPrep® 2000 or 3000 Processor, and stained with ThinPrep® Stain.

The Imaging Processor acquires and processes image data from the slides to identify diagnostically relevant cells or cell groups based on an imaging algorithm that considers cellular features and nuclear darkness. During slide imaging, the alphanumeric slide accession identifier is recorded and the *x* and *y* coordinates of 22 fields of interest are stored in the computer database. This computer also coordinates the communication of information between the Image Processor and the Review Scopes.

After image processing, slides are distributed to Cytotechnologists for review utilizing the Review Scopes. The Review Scope is a microscope with an automated stage to facilitate the locating of the 22 fields containing the cells of interest. Additionally, the Review Scope provides a method for automated marking of objects for further review. Slides are individually loaded onto the Review Scope stage, the alphanumeric slide accession identifier is automatically scanned and the stored *x* and *y* coordinates representing fields of interest for that slide are electronically downloaded from the computer to the Review Scope. The Cytotechnologist then uses a keypad to step through each of the fields of interest (Autolocate). If the Cytotechnologist identifies any of these fields as containing abnormal objects, that field may be marked electronically. The Review Scope will guide the Cytotechnologist to conduct a review of the entire cell spot for any slide that has had fields electronically marked (Autoscan). The Cytotechnologist determines specimen adequacy and the presence of infections during the review of the 22 fields of view presented by the ThinPrep Imaging System. Either of two methods can be used to determine specimen adequacy. The first method is to count cells and determine the average number of cells in the 22 fields of view presented by the Imager. The second method is to count and determine the average number of cells in 10 fields of view across the diameter of the cell spot. Either method will enable the Cytotechnologist to determine if the minimum cells, as recommended by Bethesda System 2001 criteria, are present on the slide. At the conclusion of the slide review electronically marked objects are automatically ink marked. Any *x* and *y* coordinates representing marked locations along with a slide completion status are then electronically transmitted back to the computer for storage.

D. LIMITATIONS

- Only personnel who have been appropriately trained should operate the ThinPrep Imaging System Image Processor or Review Scope.
- All slides that undergo primary automated screening with the Image Processor require manual rescreening of the selected fields of view by a Cytotechnologist using a Review Scope.
- The ThinPrep Imaging System is only indicated for use with the ThinPrep Pap Test.
- The laboratory Technical Supervisor should establish individual workload limits for personnel using the ThinPrep Imaging System.
- The ThinPrep Imaging System has not been proven to be safe or effective at workload levels which exceed product labeling.
- ThinPrep slides with fiducial marks must be used.
- Slides must be stained using the ThinPrep Stain according to the applicable ThinPrep Imaging System slide staining protocol.
- Slides should be clean and free of debris before being placed on the system.
- The slide coverslip should be dry and located correctly.
- Slides that are broken or poorly coverslipped should not be used.
- Slides used with the ThinPrep Imaging System must contain properly formatted accession number identification information as described in the operator's manual.
- Slides once successfully imaged on the Image Processor cannot be imaged again.

E. WARNINGS

- The Imager generates, uses, and can radiate radio frequency energy and may cause interference to radio communications.
- A Cytyc authorized service representative must install the ThinPrep Imaging System.

F. PRECAUTIONS

- Caution should be used when loading and unloading glass slides on the ThinPrep Imaging System to prevent slide breakage and/or injury.
- Care should be taken to assure that slides are correctly oriented in the ThinPrep Imaging System cassettes to prevent rejection by the system.
- Partially processed slide cassettes should not be removed from the Image Processor, as data may be lost.
- The Image Processor should be placed on a flat, sturdy surface away from any vibrating machinery to assure proper operation.

G. PERFORMANCE CHARACTERISTICS

A multi-center, two-armed clinical study was performed over an eleven (11) month period at four (4) cytology laboratory sites within the United States. The objective of the study entitled "Multi-Center Trial Evaluating the Primary Screening Capability of the ThinPrep Imaging System" was to show that routine screening of ThinPrep Pap Test slides using the ThinPrep Imaging System is equivalent to a manual review of ThinPrep slides for all categories used for cytologic diagnosis (specimen adequacy and descriptive diagnosis) as defined by the Bethesda System criteria[2].

The two-arm study approach allowed a comparison of the cytologic interpretation (descriptive diagnosis and specimen adequacy) from a single ThinPrep prepared slide, screened first using standard laboratory cervical cytology practices (*Manual Review*) and then after a 48 day time lag were screened with the assistance of the ThinPrep Imaging System (*Imager Review*). A subset of slides from the study were reviewed and adjudicated by a panel of three (3) independent Cytopathologists to determine a consensus diagnosis. The consensus diagnosis was used as a "gold standard" for truth to evaluate the results of the study.

G.1 LABORATORY AND PATIENT CHARACTERISTICS

Of the 10,359 subjects in the study, 9,550 met the requirements for inclusion in the descriptive diagnosis analysis. During the study, 7.1% (732/10,359) slides could not be read on the Imager and required a manual review during the *Imager Review* arm. Excessive number of air bubbles on the slides was the leading contributor. Additional factors included focus problems, slide density, slide identification read failures, slides detected out of position, multiple slides seated within a cassette slot and slides that had already been imaged. The cytology laboratories participating in the study were comprised of four centers. All sites selected had extensive experience in the processing and evaluation of gynecologic ThinPrep slides, and were trained in the use of the ThinPrep Imaging System. The study population represented diverse geographic regions and subject populations of women who would undergo cervical screening with the ThinPrep Imaging System in normal clinical use. These sites included both women being routinely screened (screening population) and patients with a recent previous cervical abnormality (referral population). The characteristics of the study sites are summarized in *Table 1*.

Table 1: Site Characteristics

Site	1	2	3	4
Low Risk Population	88%	82%	90%	94%
High Risk Population	12%	18%	10%	6%
HSIL+ prevalence	1.1%	0.7%	0.4%	0.6%
ThinPrep Pap Tests Per Year	120,000	70,200	280,000	105,000
Number of Cytotechnologists	14	9	32	11
Number of Cytotechnologists in Study	2	2	2	2
Number of Cytopathologists	6	5	6	14
Number of Cytopathologists in Study	1	2	1	2

G.2 DESCRIPTIVE DIAGNOSIS SENSITIVITY AND SPECIFICITY ESTIMATES

A panel of three independent Cytopathologists adjudicated slides from all discordant (one-grade or higher cytologic difference) descriptive diagnosis cases (639), all concordant positive cases (355) and a random 5% subset of the 8550 negative concordant cases (428). The Cytopathologists on the adjudication panel were board-certified, all of whom had a subspecialty certification in Cytopathology. Their experience levels in Cytopathology ranged from 6 to 12 years. Two of the adjudicators were from university practices and one adjudicator was from a private medical center. The volumes for the adjudicator's institutions ranged from 12,000 to 30,000 ThinPrep Pap Tests annually.

A consensus diagnosis was defined as agreement by at least 2 of 3 Cytopathologists. All slides sent to the panel of Cytopathologists were not identified by site nor ordered in any fashion. When a consensus diagnosis could not be obtained by at least 2 of 3 Cytopathologists, the full panel of Cytopathologists reviewed each case simultaneously using a multi-headed microscope to determine a consensus diagnosis.

The adjudicated results were used as a "gold standard" to define the following major "true" descriptive diagnosis classifications of the Bethesda System: Negative, ASCUS, AGUS, LSIL, HSIL, Squamous Cell Carcinoma (SQ CA) and Glandular Cell Carcinoma (GL CA). Estimates of sensitivity and specificity together with 95% confidence intervals were calculated for the *Manual Review* and *Imager Review* arms of the study. The differences in sensitivity and specificity between the two arms, together with their 95% confidence intervals were also calculated. Among the random 5% subset of 8,550 cases (428 slides) that were found to be negative by both arms and adjudicated, there were 425 "true" negative and 3 "true" ASCUS slides. A multiple imputation technique was used to adjust the numbers of true positives and true negatives for the 8,550 negative concordant cases based on the 5% of cases that were adjudicated[3].

Tables 2-4 below summarize the descriptive diagnosis sensitivity and specificity estimates with 95% confidence intervals for each of the four sites and all sites combined for "true" ASCUS+, LSIL+ and HSIL+.

Table 2: Adjudicated Review Versus Imager And Manual Reviews ASCUS+ Descriptive Diagnosis Summary.

Sensitivity is a percent of "true" ASCUS+ (combined ASCUS, AGUS, LSIL, HSIL, SQ CA and GL CA) slides classified in either study arm as ASCUS+ and specificity is a percent of "true" Negative slides classified in either study arm as Negative.

Sensitivity				Specificity			
Site/ Number Cases	Manual	Imager	Difference	Site/ Number Cases	Manual	Imager	Difference
Site 1	77.2%	78.3%	+1.1%	Site 1	98.7%	99.2%	+0.4%
180	(70.4, 83.1)	(71.6, 84.1)	(-5.8, 8.0)	2132	(98.1, 99.1)	(98.7, 99.5)	(-0.1, 1.0)
Site 2	63.1%	77.5%	+14.4%	Site 2	95.8%	96.1%	+0.3%
230	(56.5, 69.3)	(71.4, 82.6)	(8.2, 20.5)	2210	(94.9, 96.6)	(95.2, 96.9)	(-0.7, 1.3)
Site 3	80.6%	94.2%	+13.6%	Site 3	98.5%	98.8%	+0.4%
103	(71.6, 87.7)	(87.8, 97.8)	(4.3, 22.9)	2196	(97.9, 99.0)	(98.3, 99.2)	(-0.3, 1.0)
Site 4	87.2%	84.4%	-2.8%	Site 4	97.3%	97.0%	-0.3%
179	(81.4, 91.7)	(78.2, 89.4)	(-10.6, 5.0)	2313	(96.6, 97.9)	(96.2, 97.7)	(-1.1, 0.5)
All	75.6%	82.0%	+6.4%	All	97.6%	97.8%	+0.2%
692	(72.2, 78.8)	(78.8, 84.8)	(2.6, 10.0)	8851	(97.2, 97.9)	(97.4, 98.1)	(-0.2, 0.6)

Numbers in parentheses represent 95% confidence intervals.

The results presented in *Table 2* show that for ASCUS+, the increase in sensitivity of the *Imager Review* over the *Manual Review* was statistically significant with the lower limit of the 95% confidence interval being 2.6% for all sites combined. The observed difference between sensitivities for ASCUS+ varied among the sites from –2.8% with a 95% confidence interval of (–10.6%; 5.0%) to +14.4% with a 95% confidence interval of (8.2%; 20.5%). The difference in

specificity results between the *Imager Review* and the *Manual Review* was not statistically significant with a 95% confidence interval of -0.2% to +0.6%. The observed differences between specificities varied among the sites from –0.3% to +0.4%.

Table 3: Adjudicated Review Versus Imager Review LSIL+ Descriptive Diagnosis Summary for Each Site and All Sites Combined.

Sensitivity is a percent of "true" LSIL+ (combined LSIL, HSIL, SQ CA and GL CA) slides classified in either study arm as LSIL+ and specificity is a percent of "true" Non-LSIL+ (combined Negative, ASCUS, AGUS) slides classified in either study arm as Non-LSIL+.

Sensitivity				Specificity			
Site/ Number Cases	Manual	Imager	Difference	Site/ Number Cases	Manual	Imager	Difference
Site 1	84.6%	82.7%	-1.9%	Site 1	98.7%	99.3%	+0.6%
104	(76.2, 90.9)	(74.0, 89.4)	(-9.5, 5.6)	2208	(98.1, 99.1)	(98.9, 99.6)	(0.1, 1.0)
Site 2	70.4%	72.4%	+2.0%	Site 2	99.3%	98.9%	-0.4%
98	(60.3, 79.2)	(62.5, 81.0)	(-6.9, 11.0)	2342	(98.8, 99.6)	(98.4, 99.3)	(-0.8, .001)
Site 3	77.4%	85.5%	+8.1%	Site 3	99.2%	99.5%	+0.3%
62	(65.0, 87.1)	(74.2, 93.1)	(-4.0, 20.1)	2237	(98.7, 99.5)	(99.1, 99.8)	(-0.1, 0.6)
Site 4	84.7%	78.4%	-6.3%	Site 4	98.7%	98.7%	-0.08%
111	(98.1, 99.1)	(76.6, 90.8)	(-14.7, 2.1)	2381	(98.2, .99.2)	(98.1, 99.1)	(-0.6, 0.4)
All	79.7%	79.2%	-0.5%	All	99.0%	99.1%	+0.09%
375	(75.3, 83.7)	(74.7, 83.2)	(-5.0, 4.0)	9168	(98.8, 99.2)	(98.9, 99.3)	(-0.1, 0.3)

Numbers in parentheses represent 95% confidence intervals.

The results presented in *Table 3* show that the difference between sensitivities of the *Imager Review* and *Manual Review* arms for LSIL+ for all sites combined was not statistically significant with a 95% confidence interval of –5.0% to +4.0%. The observed difference between sensitivities for LSIL+ varied among the sites from –6.3% with a 95% confidence interval of (–14.7%; 2.1%) to +8.1% with a 95% confidence interval of (–4.0%; 20.1%). The difference in specificity results between the *Imager Review* and the *Manual Review* was not statistically significant with a 95% confidence interval of -0.1% to +0.3%. The observed differences between specificities varied among the sites from –0.4% to +0.6%.

Table 4: Adjudicated Review Versus Imager Review HSIL+ Descriptive Diagnosis Summary for Each Site and All Sites Combined.

Sensitivity is a percent of "true" HSIL+ (combined HSIL, SQ CA and GL CA) slides classified in either study arm as HSIL+ and specificity is a percent of "true" Non-HSIL+ (combined Negative, ASCUS, AGUS, LSIL) slides classified in either study arm as Non-HSIL+.

Sensitivity				Specificity			
Site/ Number Cases	Manual	Imager	Difference	Site/ Number Cases	Manual	Imager	Difference
Site 1	89.5%	92.1%	2.6%	Site 1	98.8%	99.5%	+0.7%
38	(75.2, 97.1)	(78.6, 98.3)	(-8.9, 14.1)	2274	(98.3, 99.2)	(99.1, 99.8)	(0.2, 1.2)
Site 2	72.5%	70.0%	-2.5%	Site 2	99.8%	99.6%	-0.1%
40	(56.1, 85.4)	(53.4, 83.4)	(-15.4, 10.4)	2400	(99.5, 99.9)	(99.2, 99.8)	(-0.3, .09)
Site 3	72.7%	86.4%	+13.6%	Site 3	99.7%	99.7%	0%
22	(49.8, 89.3)	(65.1, 97.1)	(-0.7, 28.0)	2277	(99.4, 99.9)	(99.4, 99.9)	(-0.2, 0.2)
Site 4	61.5%	74.4%	+12.8%	Site 4	99.5%	99.8%	+0.3%
39	(44.6, 76.6)	(57.9, 87.0)	(-1.7, 27.4)	2453	(99.2, 99.8)	(99.5, 99.9)	(-0.003, 0.6)
All	74.1%	79.9%	+5.8%	All	99.4 %	99.6%	+0.2%
139	(66.0, 81.2)	(72.2, 86.2)	(-1.1, 12.6)	9404	(99.2, 99.6)	(99.5, 99.7)	(0.06, 0.4)

Numbers in parentheses represent 95% confidence intervals.

The results presented in *Table 4* show that the difference between sensitivities of the *Imager Review* and *Manual Review* arms for HSIL+ for all sites combined was not statistically significant with a 95% confidence interval of -1.1% to +12.6%. The observed difference between sensitivities for HSIL+ varied among the sites from –2.5% with a 95% confidence interval of (–15.4%; 10.4%) to +13.6% with a 95% confidence interval of (–0.7%; 28.0%). The increase in specificity of the Imager Review over the Manual Review was statistically significant with a 95% confidence interval of +0.06% to +0.4%. The observed differences between specificities varied among the sites from –0.1% to +0.7%.

Tables 5-9 show the performance of the *Imager Review* and *Manual Review* compared to the final consensus diagnosis made by the adjudication panel (truth) for the following major descriptive diagnosis classifications of the Bethesda System: Negative, ASCUS, AGUS, LSIL, HSIL, Cancer* (CA)

*Includes SQ CA and GL CA.

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 5: 6x6 "True Negative" Contingency Table For All Sites Combined

All 786 Cases Determined To Be Negative By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	425	138	6	10	6	2	587
ASCUS	130	39	1	3	-	-	173
AGUS	5	-	-	-	-	-	5
LSIL	9	5	-	2	-	-	16
HSIL	1	1	-	-	3	-	5
CA	-	-	-	-	-	-	0
TOTAL	570	183	7	15	9	2	786

Among the 786 cases determined by the adjudication panel to be Negative, 587 (74.7%) cases in the *Imager Review* arm and 570 (72.5%) cases in the *Manual Review* arm were diagnosed as Negative and 21 (2.7%) cases in the *Imager Review* arm and 26 (3.3%) cases in the *Manual Review* arm were diagnosed as LSIL+.

Table 6: 6x6 "True ASCUS" Contingency Table For All Sites Combined

All 251 Cases Determined To Be ASCUS By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	3	32	-	7	3	-	45
ASCUS	70	47	1	20	4	-	142
AGUS	1	-	-	-	-	-	2
LSIL	6	21	-	16	7	-	50
HSIL	2	3	-	5	1	1	12
CA	1	-	-	-	-	-	1
TOTAL	83	103	1	48	15	1	251

Among the 251 cases determined by the adjudication panel to be ASCUS, 142 (56.6%) cases in the *Imager Review* arm and 103 (41.0%) cases in the *Manual Review* arm were diagnosed as ASCUS and 45 (17.9%) cases in the *Imager Review* arm and 83 (33.1%) cases in the *Manual Review* arm were diagnosed as Negative.

Table 7: 6x6 "True AGUS" Contingency Table For All Sites Combined

All 10 Cases Determined To Be AGUS By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	-	2	1	-	1	-	4
ASCUS	-	-	1	-	-	-	1
AGUS	2	-	1	-	-	1	4
LSIL	-	-	-	-	-	-	0
HSIL	-	-	-	-	-	-	0
CA	-	-	-	-	-	1	1
TOTAL	2	2	3	0	1	2	10

Among the 10 cases determined by the adjudication panel to be AGUS, 4 (40.0%) cases in the *Imager Review* arm and 3 (30.0%) cases in the *Manual Review* arm were diagnosed as AGUS and 4 (40.0%) cases in the *Imager Review* arm and 2 (20.0%) cases in the *Manual Review* arm were diagnosed as Negative.

Table 8: 6x6 "True LSIL" Contingency Table For All Sites Combined

All 236 Cases Determined To Be LSIL By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	-	4	-	12	1	-	17
ASCUS	13	16	-	20	1	-	50
AGUS	-	-	-	-	-	-	0
LSIL	8	20	-	115	12	-	155
HSIL	-	-	-	5	9	-	14
CA	-	-	-	-	-	-	0
TOTAL	21	40	0	152	23	0	236

Among the 236 cases determined by the adjudication panel to be LSIL, 155 (65.6%) cases in the *Imager Review* arm and 152 (64.4%) cases in the *Manual Review* arm were diagnosed as LSIL and 17 (7.2%) cases in the *Imager Review* arm and 21 (8.9%) cases in the *Manual Review* arm were diagnosed as Negative.

Table 9: 6x6 "True HSIL" Contingency Table For All Sites Combined

All 138 Cases Determined To Be HSIL By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	-	1	-	-	1	-	2
ASCUS	2	4	-	2	1	-	9
AGUS	-	-	-	-	-	-	0
LSIL	1	-	-	10	6	-	17
HSIL	3	3	1	9	91	1	108
CA	-	-	-	-	1	1	2
TOTAL	6	8	1	21	100	2	138

Among the 138 cases determined by the adjudication panel to be HSIL, 108 (78.3%) cases in the *Imager Review* arm and 100 (72.5%) cases in the *Manual Review* arm were diagnosed as HSIL and 2 (1.4%) cases in the *Imager Review* arm and 6 (4.3%) cases in the *Manual Review* arm were diagnosed as Negative.

There was one (1) squamous cell carcinoma (SQ CA) case resulting from adjudication. It was diagnosed as HSIL in the *Imager Review* arm and SQ CA in the *Manual Review* arm.

Table 10 shows the study subjects unadjudicated descriptive diagnosis marginal frequencies for benign cellular changes for all sites combined.

Table 10: Unadjudicated Marginal Frequencies Summary of Descriptive Diagnosis for Benign Cellular Changes – All Sites Combined.

	Manual Review		Imager Review	
Number of Patients:	9550		9550	
Descriptive Diagnosis	**N**	**%**	**N**	**%**
Benign Cellular Changes:	**405**	**4.2**	**293**	**3.1**
Infection:				
Trichomonas Vaginalis	8	0.1	8	0.1
Fungal organisms consistent with Candida spp.	47	0.5	31	0.3
Predominance of coccobacilli	71	0.7	60	0.6
Bacteria consistent with Actinomyces spp.	1	0.0	1	0.0
Cellular Changes associated with Herpes virus	1	0.0	1	0.0
Other Infection	1	0.0	0	0.0
Reactive Cellular Changes Associated with:				
Inflammation	218	2.3	156	1.6
Atrophic with inflammation (atrophic vaginitis)	68	0.7	46	0.5
Radiation	0	0.0	0	0.0
Intrauterine contraceptive device (IUD)	0	0.0	0	0.0
Other Reactive Cellular Change	34	0.4	14	0.1

Note: Some patients had more than one diagnostic subcategory.

The *Manual Review* showed a higher rate of Benign Cellular Changes (405) than the *Imager Review* cases (293).

G.3 ANALYTICAL PERFORMANCE OF THINPREP IMAGING SYSTEM FOR DETECTION OF CERVICAL CANCER USING THINPREP® PAP TEST SLIDES FRESHLY PREPARED FROM ARCHIVAL SAMPLES

This analytical study was conducted to compare the Bethesda System 2001 results, obtained by a Cytotechnologist and a Cytopathologist, when their review was limited to 22 fields that were selected by the ThinPrep® Imaging System, to their diagnostic results obtained from their independent blinded review of the entire cell spot on the ThinPrep Pap Test slides. All of the reviews were performed in an independent and blinded manner. The test materials consisted of 33 archival PreservCyt-preserved cervical samples that had been previously diagnosed as AGUS or cancer. One ThinPrep Pap Test slide was freshly prepared from each of the 33 original PreservCyt vials. All of the ThinPrep® slides used in the study were made on the TP-2000 processor and stained with ThinPrep Stain. Based on the current cervical cancer prevalence rate in the United States, 33 cases of cervical cancer would represent the number of invasive cervical cancer cases in a population of approximately 275,000 women[4].

Initially, a board-certified Cytopathologist manually reviewed all of the fields on the ThinPrep Pap Test slides and identified and recorded the number of individual cancer cells and clusters of cancer cells that were present. For this part of the study, the Cytopathologist was not required to record any other cells with other Bethesda System 2001 diagnoses. The 33 cases included slides that represented both rare numbers of cancer cells (5-20 per slide), and numerous cancer cells (>20/slide). Cancer cells were categorized according to Bethesda System 2001 criteria for Glandular Cancer, Adenocarcinoma-in-situ and Squamous Cell Cancer. Each slide was then processed on a ThinPrep® Imaging System. The Cytotechnologist then reviewed *only* the 22 fields of view presented by the Autolocate mode of the Review Scope. No review outside of the selected 22 fields of view was permitted. For each field

of view, the Cytotechnologist counted and recorded all abnormal cell types based on the following seven Bethesda System classifications: ASCUS, LSIL, HSIL, AGUS, Glandular Cancer, Squamous Cell Carcinoma and Adenocarcinoma-In-Situ.

Finally, the same Cytopathologist who had conducted the manual review of the entire ThinPrep Pap Test slide, independently re-reviewed the slides using the identical method used by the Cytotechnologists. The Cytopathologist was blinded from the original manual review results. For each of the 22 fields of view selected by the ThinPrep Imaging System, the Cytopathologist verified and recorded the number of individual cancer cells, clusters of cancer cells, and any other abnormalities present. *Table 11* summarizes the results from this study:

Table 11: Summary of Results From Restricted Analytical Cancer Study

Cytopathologist Full Manual Review	Cytotechnologist Review of Imager Identified 22 Fields of View *	Cytopathologist Review of Imager Identified 22 Fields of View **
10 Glandular Cancer	5 Glandular Carcinoma 1 Squamous Cell Carcinoma 1 Adenocarcinoma In-situ 2 HSIL/AGUS 1 ASC-H/ASC-US	7 Glandular Carcinoma 1 Squamous Cell Carcinoma 1 AGUS 1 HSIL
1 Adenocarcinoma In-situ	1 Adenocarcinoma In-Situ	1 Adenocarcinoma In-Situ
22 Squamous Cell Carcinoma	3 Glandular Carcinoma 12 Squamous Cell Carcinoma 1 Squamous/Glandular Carcinoma 2 Adenocarcinoma In-situ 4 HSIL	21 Squamous Cell Carcinoma 1 Adenocarcinoma In-situ
Total = 33	Total = 33	Total = 33

** In the intended use of the ThinPrep® Imaging System (Imager), the Cytotechnologist would perform a full manual slide review of each of these cases and pass them on to a Cytopathologist for further review.*

** *In the intended use of the ThinPrep® Imaging System (Imager), the Cytopathologist would perform a full manual slide review of each of these cases.*

The results in *Table 11* demonstrate the ability of the ThinPrep Imaging System to successfully identify abnormalities in the 22 fields of view presented during the Autolocate mode of slide review. In all 33 cases in this study, the ThinPrep® Imaging System identified and presented cells among the 22 fields of view that were categorized as Cancer, HSIL, AGUS or ASCUS. In addition, the Cytopathologists' confirming review of the identical 22 fields of view showed consistent, but slightly improved results with all cases being categorized as Cancer, HSIL or AGUS. Consistent with the intended use of the ThinPrep Imaging System, the Cytotechnologists' diagnoses in every one of these 33 cases would have invoked the full slide Autoscan mode that would require a Cytotechnologist to screen the entire slide before making a final diagnosis. The results of this study indicate that ThinPrep Imaging System will accurately lead to a full manual slide review for the detection of cervical cancer or its precursor lesions.

G.4 SPECIMEN ADEQUACY STUDY

Of the 10,359 subjects in the study, 9627 met the requirements for inclusion in the specimen adequacy analysis.

Table 12: Unadjudicated Marginal Frequencies Summary of Specimen Adequacy Results – All Sites Combined.

	Manual Review		Imager Review	
Number of Patients:	9627		9627	
Descriptive Diagnosis	**N**	**%**	**N**	**%**
Satisfactory for Evaluation	7375	76.6	7346	76.3
Satisfactory but Limited by	2186	22.7	2252	23.4
Endocervical Component Absent	1196	12.4	1397	14.5
Scant Squamous Epithelial Component	92	1.0	102	1.1
Obscuring Blood	45	0.5	17	0.2
Obscuring Inflammation	69	0.7	68	0.7
No Clinical History	982	10.2	933	9.7
Cytolysis	4	0.0	2	0.0
Other	6	0.1	33	0.3
Unsatisfactory for Evaluation	66	0.7	29	0.3
Endocervical Component Absent	6	0.1	0	0.0
Scant Squamous Epithelial Component	35	0.4	22	0.2
Obscuring Blood	17	0.2	2	0.0
Obscuring Inflammation	8	0.1	5	0.1
No Clinical History	2	0.0	2	0.0
Cytolysis	0	0.0	0	0.0
Other	2	0.0	0	0.0

Note: Some patients had more than one diagnostic subcategory.

For SAT cases, there was agreement between the *Manual Review* cases (7375) and the *Imager Review* cases (7346). For SBLB cases, there is agreement between the *Manual Review* cases (2186) and the *Imager Review* cases (2252). Unsatisfactory cases were greater in the *Manual Review* cases (66) versus the *Imager Review* cases (29).

The adjudicated results were used as a "gold standard" to define "true" specimen adequacy classifications of the Bethesda System: SAT/SBLB and UNSAT. There were 58 "true" UNSAT cases and 9569 "true" SAT/SBLB cases.

Table 13 below summarizes specimen adequacy performance for the Imager Review and Manual Review arms for all four sites and all sites combined using the Bethesda System 1991 criteria.

Table 13: Adjudicated Review Versus Imager Review Specimen Adequacy Summary for All Sites and All Sites Combined.

Sensitivity is a percent of "true" UNSAT slides classified in either study arm as UNSAT and specificity is a percent of "true" SAT/SBLB slides classified in either study arm as SAT/SBLB.

Sensitivity				Specificity			
Site/ Number Cases	**Manual**	**Imager**	**Difference**	**Site/ Number Cases**	**Manual**	**Imager**	**Difference**
Site 1 **21**	**0%** (0/21)	**0%** (0/21)	**0.0%** (0/21)	**Site 1** **2292**	**100%** (2292/2292)	**100%** (2292/2292)	**0.0%** (0/2292)
Site 2 **6**	**100%** (6/6)	**16.7%** (1/6)	**-83.3%** (-5/6)	**Site 2** **2476**	**98.9%** (2449/2476)	**99.6%** (2465/2476)	**+0.6%** (16/2476)
Site 3 **5**	**80.0%** (4/5)	**60.0%** (3/5)	**-20.0%** (-1/5)	**Site 3** **2323**	**99.2%** (2304/2323)	**99.7%** (2315/2323)	**+0.5%** (11/2323)
Site 4 **26**	**30.8%** (8/26)	**19.2%** (5/26)	**-11.5%** (-3/26)	**Site 4** **2478**	**99.9%** (2475/2478)	**99.9%** (2476/2478)	**+0.04%** (1/2478)
All **58** **CI***	**29.3%** (17/58) (18.1, 42.7)	**13.8%** (8/58) (6.1, 25.4)	**-15.5%** (-9/58) (-25.9, -5.0)	**All** **9569** **CI***	**99.5%** (9520/9569) (99.3, 99.6)	**99.8%** (9548/9569) (99.7, 99.9)	**+0.3%** (28/9569) (0.2, 0.4)

*95% Confidence Interval

All ThinPrep slides that produced discordant unsatisfactory determinations (*Manual Review* arm vs. *Imager Review* arm) during the clinical study were assessed in an additional clinical support study to compare the method used for specimen adequacy in the clinical study with a control cell count of the slides and 3 different methods as follows: (1) Manual assessment of specimen adequacy on the entire microscope slide based on ThinPrep Bethesda System 1991 criteria; (2) Using the "diameter" method of Bethesda System 2001, which requires that the Cytotechnologist counts cells in 10 fields of view along the diameter of the cell spot and calculate the number of cells on the slide; (3) Having the Cytotechnologist count the cells in the 22 fields of view presented by the system and calculate the number of cells on the slide.

This additional support study demonstrated that the Bethesda System 1991 estimation methods, including the method used in the clinical study, do not generate similar specimen adequacy determinations when compared against each other or with the control method. Therefore, the recommended methods for determining specimen adequacy on the ThinPrep Imaging System are (1) the Bethesda System 2001 count of fields along a diagonal of the cell spot or (2) counting the cells in the 22 fields-of-view selected by the ThinPrep Imager System. Refer to the ThinPrep Imaging System Review Scope Operator's Manual for instructions on the proper use of these methods.

G.5 CYTOTECHNOLOGIST SCREENING RATES

Daily Cytotechnologist screening rates were recorded throughout the duration of the clinical study. The study was conducted in a manner designed to reproduce actual clinical conditions. Eight (8) Cytotechnologists participated in the study; two (2) at each clinical site. The experience levels of the Cytotechnologists ranged from 5 to 23 years. During the study the Cytotechnologist's screening times for the *Imager Review* arm included automated screening of the 22 fields of view with subsequent full side review of abnormal slides. A full slide review consists of approximately 120 fields of view. The number of hours each Cytotechnologist screened slides per day varied due to logistical issues and scheduling. With the ThinPrep Imaging System, Cytotechnologist screening rates were uniformly faster than the *Manual Review* method.

Table 14 summarizes the Cytotechnologist screening rates for both the *Imager Review* and the *Manual Review* methods. The total number of slides reviewed in the study and the average number of hours screened per day are presented for each Cytotechnologist and site. Screening rates (extrapolated to an 8 hour workday) are presented as the low, average and high daily screening rates achieved by each Cytotechnologist and site. The low and high daily rates were selected from the lowest and highest daily hourly rates, respectively, and are extrapolated to 8 hours.

Table 14: Cytotechnologist Screening Rates

Site/CT	Review Methods	Total Number of Slides Evaluated	Average Number of Hours Screened Per Day	Extrapolated Daily Rates (8-hour workday)		
				Low Day	Average Day	High Day
Site 1	Manual	2568	7.4	49	69	94
	Imager	2297	6.0	107	153	206
1-1	Manual	1284	7.5	49	60	72
	Imager	1168	6.1	117	153	182
1-2	Manual	1284	7.3	70	78	94
	Imager	1129	5.9	107	154	206
Site 2	Manual	2686	7.7	40	68	80
	Imager	2665	7.8	69	109	131
2-1	Manual	1348	7.6	40	71	80
	Imager	1309	7.9	97	110	118
2-2	Manual	1338	7.8	55	66	75
	Imager	1356	7.7	69	109	131
Site 3	Manual	2738	7.9	20	80	101
	Imager	2726	4.5	148	204	320
3-1	Manual	1368	7.9	63	82	91
	Imager	1460	4.2	167	230	320
3-2	Manual	1370	7.8	20	78	101
	Imager	1266	4.7	148	178	212
Site 4	Manual	2612	7.6	42	69	94
	Imager	2524	5.1	86	138	198
4-1	Manual	1305	8.2	59	75	84
	Imager	1252	5.1	86	150	190
4-2	Manual	1307	6.9	42	63	94
	Imager	1272	5.0	109	126	198

Table 15 summarizes the *Manual Review* versus the *Imager Review* for ASCUS+ and HSIL+ sensitivity and specificity by site. The table also presents the prevalence of ASCUS+, LSIL+, and HSIL+ among the reviewed slides and the respective screening daily rates of each review method. The daily screening rates are extrapolated to an 8-hour workday and are presented as the low, average and high daily screening rates by site.

Table 15: Screening Rates, Prevalence of ASCUS+, LSIL+, HSIL+, and Respective Performance for ASCUS+ and HSIL+.

Site	% of ASCUS+	% of LSIL+	% of HSIL+	Review Methods	Extrapolated Daily Rates (8-hour workday)			Performance for ASCUS+				Performance for HSIL+			
					Low Day	Average Day	High Day	Sensitivity		Specificity		Sensitivity		Specificity	
Site 1	7.7%	4.5%	1.6%	Manual	49	69	94	77.2%	+1.1%	98.7%	+0.4%	89.5%	+2.6%	98.8%	+0.7%
				Imager	107	153	206	78.3%		99.2%		92.1%		99.5%	
Site2	9.2%	4.0%	1.6%	Manual	40	68	80	63.1%	+14.4%	95.8%	+0.3%	72.5%	-2.5%	99.8%	-0.1%
				Imager	69	109	131	77.7%		96.1%		70.0%		99.6%	
Site 3	4.4%	2.7%	1.0%	Manual	20	80	101	80.6%	+13.6%	98.5%	+0.4%	64.3%	+13.6%	99.7%	0%
				Imager	148	204	320	94.2%		98.8%		78.6%		99.7%	
Site 4	7.2%	4.5%	1.6%	Manual	42	69	94	87.2%	-2.8%	97.3%	-0.3%	61.5%	+12.8%	99.5%	+0.3%
				Imager	86	138	198	84.4%		97.0%		74.4%		99.8%	

The clinical study data show that the screening rates achieved with the ThinPrep Imaging System resulted in sensitivity or specificity values that fall within acceptable limits. The maximum number of slides examined by an individual using the ThinPrep Imaging System should not exceed 200 slides in a 24-hour period. This maximum number of 200 slides is to be reviewed in no less than an 8-hour workday. For less than an 8-hour workday, the following formula must be applied to

determine the maximum number of slides to be reviewed during that workday:

$$\frac{\text{Number of hours examining slide with the ThinPrep Imaging System X 200}}{8}$$

The ThinPrep Imaging System limit of 200 slides includes the following:

- Slides where only 22 Fields of View are reviewed
- Slides that require full manual review using the Autoscan feature

The manual workload limit does not supercede the CLIA requirement of 100 slides in no less than an 8-hour day. Manual review includes the following types of slides:

- Slides reviewed on the ThinPrep Imaging System using the Autoscan feature
- Slides reviewed without the ThinPrep Imaging System
- Non–gynecologic slides.

When conducting manual review, refer to the CLIA requirements for calculating workload limits.

H. Clinical Investigation Conclusions

- For all sites combined for ASCUS+, the improvement in sensitivity of the *Imager Review* method over the *Manual Review* method is statistically significant. This increase is 6.4% with a 95% confidence interval of 2.6% to 10.0% for all sites combined. The differences in sensitivity varied among the sites from –2.8% to +14.4%. For LSIL+ and HSIL+ the sensitivity of the *Imager Review* method is equivalent to the *Manual Review* method.
- For all sites combined for HSIL+, the improvement in specificity of the *Imager Review* method over the *Manual Review* method is statistically significant. This increase is 0.2% with a 95% confidence interval of 0.06% to 0.4% for all sites combined. The differences in specificity varied among the sites from –0.1% to +0.7%. For ASCUS+ and LSIL+ the specificity of the *Imager Review* method is equivalent to the *Manual Review* method.
- Specimen adequacy can be determined using the method described in Bethesda System 2001 or by having the Cytotechnologist count the cells in the 22 fields of view presented by the Imager.
- The workload limit for the ThinPrep Imaging System has been established at 200 slides in no less than an 8-hour workday. This workload limit of 200 slides includes the time spent for manual review of slides that is not to exceed 100 slides in an 8 hour workday.

For these clinical sites and these study populations, the data from the clinical trial and clinical support studies demonstrate that the use of the ThinPrep Imaging System to assist during primary screening of ThinPrep Pap Test slides for all cytologic interpretations, as defined by the Bethesda System, is safe and effective for the detection of cervical abnormalities.

Performance may vary from site to site as a result of differences in patient populations and reading practices. As a result each laboratory using this device should employ quality assurance and control systems to ensure proper use and selection of appropriate workload limits.

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