



## **BD FocalPoint™ GS Imaging System Product Insert**

### **A. Name and Intended Use**

The BD FocalPoint™ GS Imaging System is intended to assist in cervical cancer screening of BD SurePath™ Pap Test slides to detect evidence of squamous carcinoma, adenocarcinoma and their usual precursor conditions. These slides will be ranked according to the likelihood of abnormality, and provide relocation and visual review of up to 10 fields of view (FOVs) most likely to contain abnormal cells. Additionally, the system identifies at least 15% of all successfully processed slides with the BD FocalPoint™ Slide Profiler\* Directed QC Technology™ for a directed QC re-screen.

Intended users are trained cytology laboratory personnel operating under the direct supervision of a qualified cytology supervisor or laboratory manager/director.

\*For more information about the performance of the BD FocalPoint™ Slide Profiler, please see the product insert document No. 779-04194-02.

### **B. Summary and Explanation of the BD FocalPoint™ GS Imaging System**

The BD FocalPoint™ GS Imaging System includes the BD FocalPoint™ Slide Profiler and the BD FocalPoint™ GS Review Station. The BD FocalPoint™ Slide Profiler is an automated cytology screening device that classifies slides using a high speed video equipped microscope and image interpretation software to image and analyze the complex images on a cervical cytology slide. The BD FocalPoint™ GS Imaging System includes screening algorithms for over 100 object analysis features, including both squamous and glandular algorithms to determine potential abnormality.

The device is intended to detect slides with evidence of squamous carcinoma, adenocarcinoma and their usual precursor conditions. These abnormalities fall within the following diagnostic categories of The Bethesda System<sup>1</sup> (TBS 2001):

#### **Epithelial Cell Abnormalities:**

##### **Squamous Cell**

- Atypical squamous cells
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesions (LSIL)
- High-grade squamous intraepithelial lesions (HSIL)
- Squamous cell carcinoma

##### **Glandular Cell**

- Atypical glandular cells (endocervical, endometrial, glandular), NOS (Not Otherwise Specified) or Favor Neoplastic
- Adenocarcinoma in situ (AIS)
- Adenocarcinoma (endocervical, endometrial, extrauterine or NOS)

### **C. Description of Device**

The BD FocalPoint™ GS Imaging System combines the automated screening capability of the BD FocalPoint™ Slide Profiler (formerly the AutoPap Primary Screening System) with the precision field location capability of the BD FocalPoint™ GS Review Station. The BD FocalPoint™ GS Review Station is an accessory device to the BD FocalPoint™ Slide Profiler. The BD FocalPoint™ GS Review Station reads slide processing results data from the BD FocalPoint™ Slide Profiler and presents the results data to a cytotechnologist to assist the cytotechnologist in interpretation of the specimen on a slide. The slide results data include slide identification data, ranking and specimen quality indicators, associated cell pattern images, slide reference frame data, and processing status indications for each slide via a network connection. Additionally, the BD FocalPoint™ Slide Profiler identifies up to 11 fields of view on a slide or location coordinates (x, y), one for ease of location confirmation, and up to 10 that are most likely to contain abnormal cells. The coordinates are saved for future relocation. The No Further Review feature is disabled when the BD FocalPoint™ Slide Profiler is combined with the BD FocalPoint™ GS Review Station.

The FOV review is specifically for BD SurePath™ Pap Test slides. To enable the FOV review and reporting capabilities, one or more computer-controlled BD FocalPoint™ GS Review Stations are networked to a BD FocalPoint™ Slide Profiler(s) via a BD FocalPoint™ GS Server with a centralized database. BD FocalPoint™ GS Review Stations are equipped with commercially available microscopes and automated stages to rapidly relocate FOV (x, y) locations for the cytotechnologist review. During the FOV Review, the cytotechnologist determines if a full slide review is warranted. If no abnormality is identified during the FOV review and there are no specimen limiting conditions, the slide can be designated as negative (NILM). If abnormal cells or specimen limiting conditions are identified during the FOV review, the cytotechnologist performs a full slide review. The Full Microscopic Review is performed for the following slides:

- abnormality on FOV Review,
- adequacy reasons,
- no FOVs presented, or
- designated for QC Review.

### **D. Principles of Operation**

The BD FocalPoint™ Slide Profiler ranks slides as to their likelihood of abnormality and provides indications regarding the specimen quality parameters of squamous cellularity and presence of adequate endocervical component. Additionally, the BD FocalPoint™ Slide Profiler identifies up to 10 locations on a slide that are the most likely to contain an abnormality. Images of the cell patterns for these locations are stored by the BD FocalPoint™ Slide Profiler to aid in ensuring accurate relocation of cell regions at the BD FocalPoint™ GS Review Station.

## E. Limitations

- Only appropriately trained personnel should operate the BD FocalPoint™ Slide Profiler and BD FocalPoint™ GS Review Stations. BD Diagnostics – TriPath or its designee will train qualified laboratory personnel.
- The BD FocalPoint™ GS Imaging System is only intended for use with properly prepared BD SurePath™ Pap Test slides.
- The BD FocalPoint™ GS Imaging System designates FOVs to facilitate a rapid cytologic assessment of slides. These FOVs may not include all areas on a slide with an abnormality. Additionally, the FOVs selected may not contain the most severe examples of abnormality on the slide; therefore, in order to get the most severe diagnosis, the entire slide should be reviewed.
- The FOVs designated by the BD FocalPoint™ GS Imaging System are presented in descending order from highest likelihood of containing abnormality to lowest likelihood, as determined by the internal algorithm. However, it is possible that a cytotechnologist may rank these FOVs differently; therefore, the cytotechnologist must review all FOVs.
- The No Further Review feature is disabled when the BD FocalPoint™ Slide Profiler is combined with the BD FocalPoint™ GS Review Station.
- The performance characteristics of the BD FocalPoint™ GS Imaging System have not been established for the detection of the following diagnostic categories of The Bethesda System:
  - Endometrial cells, cytologically benign, in a postmenopausal woman or in women over 40 years old
  - Rare malignant neoplasms, such as extrauterine and metastatic carcinomas and sarcomas
- For the clinical sites and study populations tested, the BD FocalPoint™ GS Imaging System has demonstrated its effectiveness in processing BD SurePath™ Pap Test slides, although its performance may vary from laboratory to laboratory.
- The laboratory technical director should establish individual workload limits for personnel using the BD FocalPoint™ GS Imaging System.
- If laboratory personnel do not work an 8-hour day, the workload limits should be prorated accordingly.
- The BD FocalPoint™ GS Imaging System has not been proven to be safe and effective at workload levels that exceed product labeling.

- Although the BD FocalPoint™ GS Imaging System is compatible with a wide range of staining procedures currently implemented in clinical laboratories, the device may not be compatible with all staining methods currently available. BD Diagnostics – TriPath can assist the laboratory in ensuring that the staining method is compatible with the device.

## F. Warnings



### **Broken Glass Hazard when Handling Slides**

Do not drop or break slides during slide preparation and when loading and unloading slides into trays. If slides are broken, injuries may occur.



### **Moving Parts Hazard when Loading/Unloading Trays**

Remove all potentially obstructive jewelry and clothing before loading or unloading trays. After opening a hopper door, be sure all moving parts in the hopper have stopped before inserting or removing a tray. If trays are inserted before all moving parts have stopped, injuries may occur or the device may jam.



### **Shock Potential when Cleaning the Monitor**

Failure to remove power to the monitor before performing the procedure could result in an electric shock. See the Operator's Manual.



### **Electromagnetic Fields**

This is a Class A product. In a domestic environment, this product may cause radio interference with other electronic devices, such as telephones and other medical equipment, in which case the user may be required to take measures to reduce such interference.



### **Shock Potential when Power Applied Improperly**

The symbol next to the power connector indicates potential shock hazard. Ensure that the system is connected to a power receptacle that provides voltage and current within the specified rating for the system. Use of an incompatible power receptacle may produce electrical shock and fire hazards.



### **Shock Potential when Improperly Grounded**

Never use a two-prong plug adapter to connect primary power to the system. Use of a two-prong adapter disconnects the utility ground, creating a potential shock hazard. Always connect the system power cord directly to an appropriate receptacle with a functional ground.



### **Shock Potential when Cleaning with Power Applied**

Always turn off the power switch and unplug the power cord before cleaning the outer surfaces or internal components of the device to avoid a potential shock hazard.



### **Shock Potential from Spilled Liquids**

Do not place containers with liquids on the device, the workstation cart or any surface on the BD FocalPoint™ GS Review Station. Do not spill liquids on the system; fluid seepage into internal components creates a potential shock hazard. Shut down the device, disconnect from the power source, and wipe up all spills immediately. Do not operate the system if internal components have been exposed to fluid.

## **G. Precautions**

For *in vitro* diagnostic use only.

### **Bar Codes**

The BD FocalPoint™ Slide Profiler will identify each slide in the system by its unique bar code. BD Diagnostics – TriPath recommends formats Code 128 A, B, and C. Additionally, Interleaved 2 of 5, Code 39, and Code 39 Full ASCII are also acceptable. Other bar code types may be applicable. More detailed information on bar code and bar code printing specifications can be supplied by your BD Diagnostics – TriPath representative.

### **Copy Service**

Data from the BD FocalPoint™ Slide Profiler is available for 10 days from when the slides are processed.

### **Slide and Coverslip Requirements**

This device cannot be recommended for use with slides and coverslips that do not comply with the specifications provided in the Operator's Manual, particularly broken slides, dirty or marked slides, and non-standard slide or cover slip sizes.

### **Staining Procedures**

Staining procedures should be conducted carefully to ensure accurate results. See the Operator's Manual for additional information.

### **Backup Procedures**

When performing the backup procedures, BD Diagnostics – TriPath recommends that two backup media be used in rotation; each backup media would be used every other day. This will ensure minimum loss of data in the unlikely event of a workstation failure.

## Shutdown Procedures

It is important to shut down the system components in the proper order. Except in an emergency situation, such as those described in the “Warnings” section, shutting down the BD FocalPoint™ GS Imaging System should only be performed as described in the Operator’s Manual to avoid loss of data. If no emergency situation exists, consult the Operator’s Manual for the appropriate procedures or contact BD Diagnostics – TriPath or its designated representative to shut down the device.

## Replacement Fuses

Use replacement fuses with the required current rating and specification. Using improper fuses or short-circuiting the fuse holders may cause fire or damage the device.

## Installation and Service

The device should be installed only by company authorized personnel. Only technically qualified personnel, trained by BD Diagnostics – TriPath, should perform troubleshooting and service procedures on internal components.

## H. Clinical Study Characteristics

### H.1 Study Design

A multicenter, prospective, two-armed clinical study was designed to evaluate the effectiveness of the BD FocalPoint™ GS Imaging System in the screening of BD SurePath™ Pap Test slides prepared by the BD PrepStain™ System. This study was conducted at four CLIA-certified clinical lab sites in the United States from July 2006 through January 2007, evaluating 12,732 slides with a minimum of 2,500 slides per site. An additional independent institution was used as the adjudication center. The results of the BD FocalPoint™ GS Imaging Systems’ interpretations were compared with the results of the clinical sites’ Current Practice (Manual Screening) study arm, and both arms were compared with “cytology truth” as determined by the Cytology Adjudication Center or (CAC).

In addition to the sites’ prospective slides, a total of 422 slides from Sponsor-provided BD SurePath™ Pap Test samples from subjects with a history of cervical cancer and slides prepared at each site from appropriately stored BD SurePath™ pellets collected from subjects whose Pap results were determined to be abnormal were randomly seeded.

Table H.1 presents the distribution by site for all 12,732 slides assigned study slide ID numbers, detailed by prospective samples and seeded samples.

**Table H.1 Distribution of Study Slides by Site**

Site	Prospective	Seeded	Total Slides
1	2,667	125	2,792
2	3,339	178	3,517
3	2,937	75	3,012
4	3,367	44	3,411
<b>Total</b>	<b>12,310</b>	<b>422</b>	<b>12,732</b>

Personnel at the clinical laboratory site were trained to screen and evaluate BD SurePath™ Pap Test cervical cytology specimens using the BD FocalPoint™ GS Review Station. The study design included two study arms:

### **Manual Initial Screening (Control Arm)**

The laboratory's current practice, which consisted of:

- 100% manual primary screening
- At least 10% random rescreening (designated as quality control or QC)
- Handling of slides according to current laboratory policy for hierarchical review and QC

### **BD FocalPoint™ GS Imaging System (Experimental Arm)**

The experimental arm included:

- 100% BD FocalPoint™ Slide Profiler primary screening
- Review of identified FOVs on the BD FocalPoint™ GS Review Station as a screening tool
- At least 15% BD FocalPoint™ GS Directed QC Technology™ rescreening
- Handling of slides according to current laboratory policy for hierarchical review and directed QC. Rules that applied to the Control arm were also applied without deviation to the BD FocalPoint™ GS Imaging System arm.

All BD SurePath™ Pap Test samples had slides prepared using the BD PrepStain™ System. As a general guideline, subjects whose slides had an additional QC rescreen performed had prior history of additional caution in screening. Therefore, all slides that met the criteria in the Control arm of the study were also screened under the same procedures in the experimental, BD FocalPoint™ GS Imaging System arm of the study. Finally, there were no restrictions based on previous patient history in the slide types utilized in this study.

## **H.2 Slide Accountability**

Of the 12,732 slides originally assigned Study Slide ID numbers, 345 (2.7%) were excluded. These exclusions were fairly well distributed among the enrolling sites. Seventy-one (0.6%) slides were not processed through the BD FocalPoint™ Slide Profiler. After completion of the study, three additional slides, one from Site 2 and two from Site 4, were excluded due to incomplete data. This amounts to a total of 419 (3.3%) slides excluded from the study prior to statistical analysis. Once excluded slides were removed from the pool of slides, the total evaluable slides for this intended use trial numbered 12,313.

## **Site Characteristics**

The four geographically diverse clinical trial sites were all previous BD SurePath™ Pap Test laboratories. The characteristics of the study sites are summarized in Table H.2.1.

**Table H.2.1 Site Characteristics**

Site	1	2	3	4
Study ASC-US+ prevalence	2.4%	4.5%	3.2%	4.5%
Study HSIL+ prevalence	0.3%	0.9%	0.3%	0.9%
BD SurePath™ Pap Tests Per Year	48,000	122,000	38,500	35,000
Number of Cytotechnologists in Study	4	4	4	4
Number of Cytopathologists in Study	2	2	2	3

Table H.2.2 demonstrates study site prevalence rates with seeded samples included.

**Table H.2.2 Characteristics of the Clinical Study Sites (Seeded Samples Included)**

Site	1	2	3	4
Study ASC-US+ prevalence*	9.0%	11.9%	8.1%	12.8%
Study HSIL+ prevalence*	1.2%	2.1%	1.2%	2.0%

\*includes seeded samples

### **H.3 Specimen Adequacy**

The BD FocalPoint™ Slide Profiler provided information to cytotechnologists on certain characteristics of slide adequacy for all successfully processed slides. For each slide with adequate cellularity, the BD FocalPoint™ Slide Profiler provided the following: (1) presence/absence of squamous component; (2) presence/absence of endocervical component. This study used the following information for determination of slide adequacy:

#### **TBS 2001**

According to TBS 2001, a slide is “Satisfactory for evaluation” if the following apply:

- An estimated minimum of at least 5,000 well-visualized / well-preserved squamous cells are present
- Endocervical component is present or absent
- Quality Indicator mentioned if 50% – 75% of the cellular components are obscured by inflammation, blood, bacteria, mucus, or artifact that precludes cytologic interpretation of the slide

A slide is classified as “Unsatisfactory for evaluation” by TBS 2001 if any of the following apply:

- An estimated minimum of less than 5,000 well- visualized / well-preserved squamous cells are present determined by cell counts performed on representative fields
- 75% or more of the cellular components are obscured by inflammation, blood, bacteria, mucus, or artifact that precludes cytologic interpretation of the slide

- Specimen rejected/not processed (specify reason)
- Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

Slides that were determined to be abnormal or “Unsatisfactory” but had not previously gone to the CAC were forwarded to the CAC for “cytology truth” determination.

#### H.4 Endocervical Cell Component Results

A revised endocervical cell (EC) component detection algorithm was implemented to improve the BD FocalPoint™ GS Imaging System indication for the presence or absence of EC. Both this revised EC detection algorithm and the previously implemented EC detection algorithm evaluated slides in this study.

Results from these two algorithms were collated to determine the predictive value of the BD FocalPoint™ GS Imaging System’s designation of EC Sufficient/Insufficient. Truth regarding the EC status of cases is derived from the CAC “cytology truth” designation for each case. One thousand nine hundred fifty-seven slides were designated Negative (NILM) by CAC. Since no discrepancy resolution occurred for adequacy related information at CAC, only data for 1,613 NILM slides with concurrent EC results are presented below. Tables H.4.1 and H.4.2 give the results for the Prior and Revised EC detection algorithms for CAC designated NILM non-atrophic slides.

**Table H.4.1 NILM Slides Containing EC (CAC Designation)**

		Prior EC Detection Algorithm		Total
		Insufficient	Sufficient	
Revised EC Detection Algorithm	Insufficient	76	126	202
	Sufficient	363	935	1,298
Total		439	1,061	1,500

Among 1,500 NILM slides designated by CAC as “Sufficient”, Revised and Prior EC algorithms detected as “Sufficient” 86.5% (1298/1500) and 70.7% (1061/1500) slides correspondingly. Improvement was 15.8% with 95% CI: 13.0% to 18.6%.

**Table H.4.2 NILM Slides Not Containing EC (CAC Designation)**

		Prior EC Detection Algorithm		Total
		Insufficient	Sufficient	
Revised EC Detection Algorithm	Insufficient	16	38	54
	Sufficient	12	47	59
Total		28	85	113

Among 113 NILM slides designated by CAC as “Insufficient”, Revised and Prior EC algorithms detected as “Insufficient” 47.8% (54/113) and 24.8% (28/113) slides correspondingly. Improvement was 23.0% with 95% CI: 11.1% to 34.0%.

Table H.4.3 provides the predictive values for the Prior and Revised EC detection algorithms. Slides with discrepancy between experts in CAC were not included in this calculation. The comparison of prior and revised EC detection algorithms was not established for all NILM slides.

**Table H.4.3 Predictive Values – EC Detection Algorithms**

	Positive Predictive Value (Positive – Contains EC)	Negative Predictive Value (Negative – Does not contain EC)
Prior EC Detection Algorithm	92.6% (1,061/1,146)	6.0% (28/467)
Revised EC Detection Algorithm	95.7% (1,298/1,357)	21.1% (54/256)

### H.5 BD FocalPoint™ Slide Profiler Quintile Ranking

For every slide that the BD FocalPoint™ Slide Profiler determines to have sufficient cellularity, the BD FocalPoint™ Slide Profiler provides a quintile rank that corresponds to the slide’s likelihood of containing abnormality. The quintile rank is expressed as a number from 1 to 5, where quintile 1 indicates that the slide is in the set of slides most likely (top 20%) to contain abnormality. Table H.5 shows the number of abnormal slides as determined by the CAC (truth adjudication) panel with their associated quintile rank. The adjudicated Negative slides (not shown) were distributed in all five quintiles proportionately.

These data demonstrate that a high proportion of abnormal slides are ranked in quintile 1 and that progressively fewer slides containing abnormality are in the lower likelihood quintiles. Thus, the BD FocalPoint™ Slide Profiler ranking is an effective indicator of likelihood of abnormality.

**Table H.5 Abnormal Slides by Rank**

		ASC-US	ASC-H	AGC*	LSIL	HSIL**	Squamous Cancer	Adeno Cancer	Total
Quintile	1	175	17	4	343	130	26	5	700
	2	121	7	0	116	10	5	0	259
	3	89	1	2	55	7	0	0	154
	4	61	0	1	27	1	0	1	91
	5	43	0	1	26	1	0	0	71
	5***	7	1	0	8	6	11	1	34
	<b>Total</b>	496	26	8	575	155	42	7	1,309

\* Two of these cases also are ASC-US, one other case is AGC favor neoplasia

\*\* One of these cases also is AGC

\*\*\* Slides designated as “Insufficient Squamous” by the BD FocalPoint™ Slide Profiler

In the study there were 12 samples of carcinoma that were found by the device to be limited in squamous cellularity that by convention were ranked as quintile 5 with an accompanying designation that they were “Insufficient Squamous”, or low squamous cellularity cases. Slides were designated as low squamous cellularity because the

BD FocalPoint™ Slide Profiler could not locate a sufficient number of squamous epithelial cells. Pap test samples of malignant lesions, including conventional and liquid-based samples, are at significant risk for presenting with low squamous cellularity and concurrent low numbers of malignant cells.<sup>2,3,4</sup> In premenopausal patients, the low squamous cellularity and rarity of malignant cells are often attributed to excessive blood, inflammation, and necrotic debris associated with the invasive tumor. The latter elements may form the dominant components of the sample, hence diluting the number of malignant cells in the final preparation. In postmenopausal patients, squamous cellularity is often limited as a result of poor sample collection from atrophic epithelium. Regardless of the etiology, samples of low or inadequate squamous cellularity must be considered at increased risk for harboring a significant lesion, and thus deserve additional attention during the screening process. In cases with low squamous cellularity, the BD FocalPoint™ Slide Profiler may not provide FOVs for review at the BD FocalPoint™ GS Review Station resulting in triage to a manual full slide review.

## **I. Clinical Study Results**

### **I.1 Determination of Cytology Truth**

Slides diagnosed as abnormal or unsatisfactory by either or both study arms were referred to the Cytology Adjudication Center (CAC) for a reference final “cytology truth” diagnosis and adequacy determination (the total number of slides was 1,792). In addition to all abnormal or unsatisfactory slides, at least 10% of the slides from all sites diagnosed as Negative by both study arms (concordant NILMs) were also sent to the CAC for review. The CAC cytopathology panel consisted of six cytopathologists, all Diplomats of the American Board of Pathology in Anatomic and Clinical Pathology, with State of New Jersey licensure. The cytopathologists had between 20 and 32 years of experience.

Each slide was reviewed by two of the six cytopathologists participating on the panel. If the two cytopathologists rendered the same cytology diagnosis, that became the cytology truth. If the two did not render the same diagnosis, a third cytopathologist reviewed the slide. If two out of the three agreed, that diagnosis became cytology truth. If all three rendered different diagnoses, then the three reviewed the slide together under a multi-head microscope and determined the final cytology truth diagnosis.

The CAC results were used as the “Gold Standard” to define the following major “true” categories of the Bethesda System: UNSAT, Negative (or NILM), ASC-US, ASC-H, AGC, LSIL, HSIL, AIS, and Cancer.

Among 12,313 slides, 10,521 slides were diagnosed as Negative by both arms, Manual Screening and BD FocalPoint™ GS Imaging System. Among 10,521 slides with Negative results by both arms, 1,497 (14.2%) random slides were referred to the CAC for truth determination. Among these 1,497 slides, there were 80 (5.34%) slides with a true diagnosis of ASC-US, 4 (0.27%) with a true diagnosis of AGC, and 2 (0.13%) with a true diagnosis of ASC-H. The total number of slides referred to CAC was 3,289.

In this study design, the ratio of true positive rates of the BD FocalPoint™ GS Imaging System and Manual Screening, and the ratio of false positive rates of the BD FocalPoint™ GS Imaging System and Manual Screening can be estimated in an unbiased way<sup>5</sup>. For the calculation of absolute difference between sensitivities of the BD FocalPoint™ GS Imaging System and Manual Screening and the calculation of absolute difference between specificities of the BD FocalPoint™ GS Imaging System and Manual Screening along with 95% CI, a multiple imputation technique<sup>6</sup> was used because the 14.2% of slides with Negative diagnosis by both arms had verification of a true diagnosis by CAC.

## I.2 Sensitivity and Specificity for the Previously Defined Abnormal Grouping

Tables I.2.1 - I.2.5 compare the ratio of true positive rate (TPR) and ratio of false positive rate (FPR) and difference in sensitivity and specificity results for BD FocalPoint™ GS Imaging System arm versus the Manual Screening arm for slides with a CAC diagnosis of Cancer, HSIL+, LSIL+, ASC-H+, and ASC-US+.

**Table I.2.1 BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of Cancer**

“Positive” means “Cancer”. Sensitivity is a percent of “true” Cancer slides classified in either study arm as “Cancer” and specificity is a percent of “true” Non-cancer (Combined UNSAT, Neg, ASC-US, ASC-H, AGC, LSIL, HSIL, and AIS) slides classified in either study arm as non-Cancer.

Site	Sensitivity						
	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint™ GS	Number of Slides Pos by Manual	Ratio TPR <sub>GS</sub> /TPR <sub>Manual</sub>	Sensitivity BD FocalPoint™ GS	Sensitivity Manual	Difference
1	6	2	1	2.00	33.3%	16.7%	16.7%
2	9	6	5	1.20	66.7%	55.6%	11.1%
3	14	7	5	1.40	50.0%	35.7%	14.3%
4	20	19	11	1.73	95.0%	55.0%	40.0%
<b>All (95% CI)</b>	49	34	22	1.55 (1.12, 2.29)	69.4% (54.6, 81.8)	44.9% (30.7, 59.8)	24.5% (4.8, 42.2)

Site	Specificity						
	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint™ GS	Number of Slides Non-Pos by Manual	Ratio FPR <sub>GS</sub> /FPR <sub>Manual</sub>	Specificity BD FocalPoint™ GS	Specificity Manual	Difference
1	588	586	586	1.00	99.7%	99.7%	0.0%
2	995	993	995	--	99.8%	100.0%	-0.2%
3	747	747	747	--	100.0%	100.0%	0.0%
4	910	904	909	6.00	99.3%	99.9%	-0.5%
<b>All (95% CI)</b>	3240	3230	3237	3.33 (1.17, 10.00)	99.7% (99.4, 99.9)	99.9% (99.7, 100.0)	-0.2% (-0.5, -0.0)

The results presented in Table I.2.1 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 24.5% for the detection of Cancer. The range of differences in sensitivity was 11.1% to 40.0% among the sites. The Cancer specificity for all sites combined showed a slight decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -0.5% to 0.0% among the sites.

**Table I.2.2 BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of HSIL+**

“Positive” means “HSIL+”. Sensitivity is a percent of “true” HSIL+ (combined HSIL, AIS, and Cancer) slides classified in either study arm as “HSIL+” and specificity is a percent of “true” Non-HSIL+ (Combined UNSAT, Neg, ASC-US, ASC-H, AGC, and LSIL) slides classified in either study arm as non-HSIL+.

Sensitivity							
Site	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint™ GS	Number of Slides Pos by Manual	Ratio $\frac{TPR_{GS}}{TPR_{Manual}}$	Sensitivity BD FocalPoint™ GS	Sensitivity Manual	Difference
1	32	31	29	1.07	96.9%	90.6%	6.3%
2	72	58	36	1.61	80.6%	50.0%	30.6%
3	35	28	27	1.04	80.0%	77.1%	2.9%
4	65	57	42	1.36	87.7%	64.6%	23.1%
<b>All (95% CI)</b>	204	174	134	1.30 (1.18, 1.43)	85.3% (79.7, 89.9)	65.7% (58.7, 72.2)	19.6% (12.7, 26.8)

Specificity							
Site	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint™ GS	Number of Slides Non-Pos by Manual	Ratio $\frac{FPR_{GS}}{FPR_{Manual}}$	Specificity BD FocalPoint™ GS	Specificity Manual	Difference
1	562	546	551	1.45	97.2%	98.0%	-0.9%
2	932	879	920	4.42	94.3%	98.7%	-4.4%
3	726	685	691	1.17	94.4%	95.2%	-0.8%
4	865	823	851	3.00	95.1%	98.4%	-3.2%
<b>All (95% CI)</b>	3085	2933	3013	2.11 (1.71, 2.65)	95.1% (94.3, 95.8)	97.7% (97.1, 98.2)	-2.6% (-3.4, -1.9)

The results presented in Table I.2.2 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 19.6% for the detection of HSIL+. The range of differences in sensitivity was 2.9% to 30.6% among the sites. The HSIL+ specificity for all sites combined showed a decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -4.4% to -0.8% among the sites.

**Table I.2.3 BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of LSIL+**

“Positive” means “LSIL+”. Sensitivity is a percent of “true” LSIL+ (combined LSIL, HSIL, AIS, and Cancer) slides classified in either study arm as “LSIL+” and specificity is a percent of “true” Non-LSIL+ (Combined UNSAT, Neg, ASC-US, ASC-H and AGC) slides classified in either study arm as non-LSIL+.

Sensitivity							
Site	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint™ GS	Number of Slides Pos by Manual	Ratio TPR <sub>GS</sub> /TPR <sub>Manual</sub>	Sensitivity BD FocalPoint™ GS	Sensitivity Manual	Difference
1	156	133	129	1.03	85.3%	82.7%	2.6%
2	222	197	167	1.18	88.7%	75.2%	13.5%
3	131	126	129	0.98	96.2%	98.5%	-2.3%
4	270	215	170	1.27	79.6%	63.0%	16.7%
<b>All (95% CI)</b>	779	671	595	1.13 (1.09, 1.18)	86.1% (83.5, 88.5)	76.4% (73.2, 79.3)	9.8% (6.7, 12.9)

Specificity							
Site	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint™ GS	Number of Slides Non-Pos by Manual	Ratio FPR <sub>GS</sub> /FPR <sub>Manual</sub>	Specificity BD FocalPoint™ GS	Specificity Manual	Difference
1	438	408	413	1.20	93.2%	94.3%	-1.1%
2	782	704	760	3.55	90.0%	97.2%	-7.2%
3	630	539	476	0.59	85.6%	75.6%	10.0%
4	660	575	625	2.43	87.1%	94.7%	-7.6%
<b>All (95% CI)</b>	2510	2226	2274	1.20 (1.05, 1.37)	88.7% (87.4, 89.9)	90.6% (89.4, 91.7)	-1.9% (-3.3, -0.6)

The results presented in Table I.2.3 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 9.8% for the detection of LSIL+. The range of differences in sensitivity was -2.3% to 16.7% among the sites. The LSIL+ specificity for all sites combined showed a decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -7.6% to 10.0% among the sites.

**Table I.2.4 BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of ASC-H+**

“Positive” means “ASC-H+”. Sensitivity is a percent of “true” ASC-H+ (combined ASC-H, AGC, LSIL, HSIL, AIS, and Cancer) slides classified in either study arm as “ASC-H+” and specificity is a percent of “true” Non-ASC-H+ (Combined UNSAT, Neg, and ASC-US) slides classified in either study arm as non-ASC-H+.

Sensitivity							
Site	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint™ GS	Number of Slides Pos by Manual	Ratio $\frac{TPR_{GS}}{TPR_{Manual}}$	Sensitivity BD FocalPoint™ GS	Sensitivity Manual	Difference
1	160	140	137	1.02	87.5%	85.6%	1.9%
2	237	213	186	1.15	89.9%	78.5%	11.4%
3	137	130	134	0.97	94.9%	97.8%	-2.9%
4	277	224	175	1.28	80.9%	63.2%	17.7%
<b>All (95% CI)</b>	811	707	632	1.12 (1.08, 1.16)	87.2% (84.7, 89.4)	77.9% (74.9, 80.7)	9.2% (6.4, 12.2)

Specificity							
Site	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint™ GS	Number of Slides Non-Pos by Manual	Ratio $\frac{FPR_{GS}}{FPR_{Manual}}$	Specificity BD FocalPoint™ GS	Specificity Manual	Difference
1	434	400	409	1.36	92.2%	94.2%	-2.1%
2	767	681	737	2.87	88.8%	96.1%	-7.3%
3	624	526	471	0.64	84.3%	75.5%	8.8%
4	653	552	616	2.73	84.5%	94.3%	-9.8%
<b>All (95% CI)</b>	2478	2159	2233	1.30 (1.14, 1.49)	87.1% (85.7, 88.4)	90.1% (88.9, 91.3)	-3.0% (-4.5, -1.5)

The results presented in Table I.2.4 show that the BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than a manual review by 9.2% for the detection of ASC-H+. The range of differences in sensitivity was -2.9% to 17.7% among the sites. The ASC-H+ specificity for all sites combined showed a decrease for the BD FocalPoint™ GS Imaging System. The range of differences in specificity was -9.8% to 8.8% among the sites.

**Table I.2.5 BD FocalPoint™ GS Imaging System vs. Manual Screening results for the slides with CAC determination of ASC-US+**

“Positive” means “ASC-US+”. Sensitivity is a percent of “true” ASC-US+ (combined ASC-US, ASC-H, AGC, LSIL, HSIL, AIS, and Cancer) slides classified in either study arm as “ASC-US+” and specificity is a percent of “true” Non-ASC-US+ ( Combined UNSAT and Neg) slides classified in either study arm as non-ASC-US+.

Sensitivity							
Site	Number of slides Pos by CAC	Number of slides Pos by BD FocalPoint™ GS	Number of Slides Pos by Manual	Ratio $\frac{TPR_{GS}}{TPR_{Manual}}$	Sensitivity BD FocalPoint™ GS	Sensitivity Manual	Difference
1	242	198	215	0.92	81.8%	88.8%	-7.0%
2	409	328	311	1.06	80.2%	76.0%	4.2%
3	235	198	218	0.91	84.3%	92.8%	-8.5%
4	423	338	337	1.00	79.9%	79.7%	0.2%
<b>All (95% CI)</b>	1309	1062	1081	0.98 (0.95, 1.01)	81.1% (78.9, 83.2)	82.6% (80.4, 84.6)	-1.5% (-4.1, 1.2)

Specificity							
Site	Number of slides Non-Pos by CAC	Number of slides Non-Pos by BD FocalPoint™ GS	Number of Slides Non-Pos by Manual	Ratio $\frac{FPR_{GS}}{FPR_{Manual}}$	Specificity BD FocalPoint™ GS	Specificity Manual	Difference
1	352	314	311	0.93	89.2%	88.4%	0.9%
2	595	508	499	0.91	85.4%	83.9%	1.5%
3	526	431	395	0.73	81.9%	75.1%	6.8%
4	507	420	433	1.18	82.8%	85.4%	-2.6%
<b>All (95% CI)</b>	1980	1673	1638	0.90 (0.79, 1.01)	84.5% (82.8, 86.1)	82.7% (81.0, 84.4)	1.8% (-0.3, 3.8)

The results presented in Table I.2.5 show that the ASC-US+ sensitivity for all sites combined was not statistically significantly different between study arms. The range of differences in sensitivity was -8.5% to 4.2% among the sites. The ASC-US+ specificity for all sites combined was not statistically significantly different between study arms. The range of differences in specificity was -2.6% to 6.8% among the sites.

### I.3 Comparisons of Study Arm Diagnoses

Table I.3.1 compares the performance of the Manual Screening arm versus the BD FocalPoint™ GS Imaging System arm for each category of the Bethesda System.

**Table I.3.1 BD FocalPoint™ GS Imaging System Diagnosis vs. Manual Screening Diagnosis**

	Manual Screening Diagnosis										
	UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total	
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	16	11	0	0	0	0	0	0	0	27
	NEG	4	10,521	267	8	7	105	4	0	1	10,917
	ASC-US	0	175	123	3	0	39	3	0	0	343
	ASC-H	0	16	12	4	0	4	3	0	0	39
	AGC	0	19	3	1	4	4	1	0	0	32
	LSIL	0	100	121	2	0	379	27	0	0	629
	HSIL	0	26	20	13	1	93	122	0	4	279
	AIS	0	0	0	0	0	0	2	0	1	3
	CA	0	2	0	0	3	1	19	0	19	44
	Total	20	10,870	546	31	15	625	181	0	25	12,313

Tables I.3.2 – I.3.8 show the performance of the BD FocalPoint™ GS Imaging System and Manual Screening compared to the final CAC diagnosis for the following categories of the Bethesda System: Cancer, HSIL, LSIL, AGC, ASC-H, ASC-US, and Negative.

**Table I.3.2 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as Cancer**

	Manual Screening Diagnosis										
	UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total	
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	0	0	0	0	0	0	0	1	1
	ASC-US	0	0	0	0	0	0	0	0	0	0
	ASC-H	0	0	0	0	0	0	0	0	0	0
	AGC	0	0	0	0	0	0	0	0	0	0
	LSIL	0	0	0	0	0	0	0	0	0	0
	HSIL	0	0	0	0	1	0	8	0	3	12
	AIS	0	0	0	0	0	0	1	0	1	2
	CA	0	1	0	0	3	0	13	0	17	34
	Total	0	1	0	0	4	0	22	0	22	49

Among the 49 slides determined Cancer by the CAC, 34 (69.4%) slides in the BD FocalPoint™ GS Imaging System arm and 22 (44.9%) slides in the Manual Screening arm were diagnosed as Cancer. The detection of cancer was numerically higher in the BD FocalPoint™ GS Imaging System arm of the study. Of the 13 cancers undercalled but

appropriately triaged by the BD FocalPoint™ GS Imaging System, 12 were classified as HSIL\* and 1 was classified as a Negative. This “Negative” slide was indicated for a manual full slide review by the BD FocalPoint™ GS Imaging System due to a designation of “Insufficient Squamous” (low squamous cellularity) and subsequently classified as Negative during the cytology review process. In cases with low squamous cellularity, the BD FocalPoint™ Slide Profiler may not provide FOVs for review at the BD FocalPoint™ GS Review Station resulting in triage to a manual full slide review. Of the 27 cancers undercalled by Manual Screening, 22 were classified as HSIL, 4 as AGC, and 1 as Negative.

\*ASCCP guidelines recommend colposcopy with ECC assessment to manage all women with HSIL<sup>7</sup>.

**Table I.3.3 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as HSIL**

	Manual Screening Diagnosis									
	UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
UNSAT	0	0	0	0	0	0	0	0	0	0
NEG	0	0	0	0	0	3	0	0	0	3
ASC-US	0	0	1	1	0	1	0	0	0	3
ASC-H	0	0	1	0	0	0	0	0	0	1
AGC	0	0	0	0	0	0	1	0	0	1
LSIL	0	0	2	1	0	11	7	0	0	21
HSIL	0	3	3	7	0	30	72	0	1	116
AIS	0	0	0	0	0	0	1	0	0	1
CA	0	0	0	0	0	1	6	0	2	9
Total	0	3	7	9	0	46	87	0	3	155

Among the 155 slides determined HSIL by the CAC, 116 (74.8%) slides in the BD FocalPoint™ GS Imaging System arm and 87 (56.1%) slides in the Manual Screening arm were diagnosed as HSIL. Three (1.9%) slides in the BD FocalPoint™ GS Imaging System arm and 3 (1.9%) slides in the Manual Screening arm were diagnosed as Negative.

**Table I.3.4 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides  
Adjudicated as LSIL**

		Manual Screening Diagnosis									Total
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	
<b>BD FocalPoint™ GS Imaging System Diagnosis</b>	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	0	21	1	0	16	1	0	0	39
	ASC-US	0	11	26	1	0	13	0	0	0	51
	ASC-H	0	0	4	1	0	2	1	0	0	8
	AGC	0	1	0	0	0	0	0	0	0	1
	LSIL	0	22	61	1	0	288	16	0	0	388
	HSIL	0	3	6	1	0	48	30	0	0	88
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	<b>Total</b>	0	37	118	5	0	367	48	0	0	575

Among the 575 slides determined LSIL by the CAC, 388 (67.5%) slides in the BD FocalPoint™ GS Imaging System arm and 367 (63.8%) slides in the Manual Screening arm were diagnosed as LSIL. Thirty-nine (6.8%) slides in the BD FocalPoint™ GS Imaging System arm and 37 (6.4%) slides in the Manual Screening arm were diagnosed as Negative.

**Table I.3.5 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides  
Adjudicated as AGC**

		Manual Screening Diagnosis									Total
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	
<b>BD FocalPoint™ GS Imaging System Diagnosis</b>	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	4	0	0	0	0	0	0	0	4
	ASC-US	0	1	0	0	0	0	0	0	0	1
	ASC-H	0	0	0	0	0	0	0	0	0	0
	AGC	0	0	0	0	1	0	0	0	0	1
	LSIL	0	0	0	0	0	0	0	0	0	0
	HSIL	0	0	0	0	0	0	0	0	0	0
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	<b>Total</b>	0	5	0	0	1	0	0	0	0	6

Among the 6 slides determined AGC by the CAC, 1 (16.7%) slide in the BD FocalPoint™ GS Imaging System arm and 1 (16.7%) slide in the Manual Screening arm were diagnosed as AGC. Four (66.7%) slides in the BD FocalPoint™ GS Imaging System arm and 5 (83.3%) slides in the Manual Screening arm were diagnosed as Negative.

**Table I.3.6 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as ASC-H**

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	2	0	0	0	0	0	0	0	2
	ASC-US	0	0	0	0	0	0	0	0	0	0
	ASC-H	0	0	0	1	0	1	0	0	0	2
	AGC	0	0	2	1	0	1	0	0	0	4
	LSIL	0	0	2	0	0	0	2	0	0	4
	HSIL	0	0	2	3	0	4	5	0	0	14
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	Total	0	2	6	5	0	6	7	0	0	26

Among the 26 slides determined ASC-H by the CAC, 2 (7.7%) slides in the BD FocalPoint™ GS Imaging System arm and 5 (19.2%) slides in the Manual Screening arm were diagnosed as ASC-H. Two (7.7%) slides in the BD FocalPoint™ GS Imaging System arm and 2 (7.7%) slides in the Manual Screening arm were diagnosed as Negative.

**Table I.3.7 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides Adjudicated as ASC-US**

	Manual Screening Diagnosis										
		UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
BD FocalPoint™ GS Imaging System Diagnosis	UNSAT	0	0	0	0	0	0	0	0	0	0
	NEG	0	80	79	3	0	36	0	0	0	198
	ASC-US	0	52	47	1	0	15	3	0	0	118
	ASC-H	0	3	5	2	0	0	1	0	0	11
	AGC	0	2	0	0	1	2	0	0	0	5
	LSIL	0	33	36	0	0	63	2	0	0	134
	HSIL	0	10	6	1	0	9	6	0	0	32
	AIS	0	0	0	0	0	0	0	0	0	0
	CA	0	0	0	0	0	0	0	0	0	0
	Total	0	180	173	7	1	125	12	0	0	498

Among the 498 slides determined ASC-US by the CAC, 118 (23.7%) slides in the BD FocalPoint™ GS Imaging System arm and 173 (34.7%) slides in the Manual Screening arm were diagnosed as ASC-US. One hundred ninety-eight (39.8%) slides in the BD FocalPoint™ GS Imaging System arm and 180 (36.1%) slides in the Manual Screening arm were diagnosed as Negative.

**Table I.3.8 BD FocalPoint™ GS Imaging System vs. Manual Screening for Slides  
Adjudicated as Negative**

	Manual Screening Diagnosis									
	UNSAT	NEG	ASC-US	ASC-H	AGC	LSIL	HSIL	AIS	CA	Total
UNSAT	1	5	0	0	0	0	0	0	0	6
NEG	2	1,411	167	4	7	50	3	0	0	1,644
ASC-US	0	111	49	0	0	10	0	0	0	170
ASC-H	0	13	2	0	0	1	1	0	0	17
AGC	0	16	1	0	2	1	0	0	0	20
LSIL	0	45	20	0	0	17	0	0	0	82
HSIL	0	10	3	1	0	2	1	0	0	17
AIS	0	0	0	0	0	0	0	0	0	0
CA	0	1	0	0	0	0	0	0	0	1
Total	3	1,612	242	5	9	81	5	0	0	1,957

Among the 1,957 slides determined Negative by the CAC, 1,644 (84.0%) slides in the BD FocalPoint™ GS Imaging System arm and 1,612 (82.4%) slides in the Manual Screening arm were diagnosed as Negative.

#### **I.4 ASC/SIL Ratios from Manual Screening versus BD FocalPoint™ GS Imaging System**

Table I.4.1 displays the ASC/SIL ratios for the Manual Screening arm and the BD FocalPoint™ GS Imaging System arm. ASC is the sum of all ASC-US and ASC-H slides. SIL is the sum of all LSIL, HSIL and Cancer slides. The ASC/SIL ratio includes true positive and false positive slides (as compared to CAC); therefore, Tables I.2.1 - I.2.5 provide more detailed information about the ratio of true positive rate and ratio of false positive rate separately.

**Table I.4.1 ASC/SIL Ratios by Study Arm**

Site	Manual Screening Arm			BD FocalPoint™ GS Imaging System Arm		
	ASC	SIL	ASC/SIL Ratio	ASC	SIL	ASC/SIL Ratio
<b>1</b>	102	155	0.66	72	163	0.44
<b>2</b>	216	194	1.11	123	274	0.45
<b>3</b>	68	294	0.23	73	215	0.34
<b>4</b>	203	211	0.96	114	300	0.38
<b>All</b>	589	854	0.69	382	952	0.40

The data in Table I.4.1 indicate that the overall ASC/SIL ratio decreased 42% ((0.69-0.40)/0.69) in the BD FocalPoint™ GS Imaging System arm of the study compared with the Manual Screening arm of the study. This result indicates that the ASC/SIL ratio for the BD FocalPoint™ GS Imaging System is substantially lower than the ASC/SIL ratio of Manual Screening.

## I.5 Unsatisfactory Slides Analysis

Table I.5.1 displays the distribution of the 23 slides determined by the CAC truth determination process to be Unsatisfactory.

**Table I.5.1 Classification of Unsatisfactory Slides (No Adjustment)**  
Manual Screening

		Unsat (+)	Sat (-)	Total
<b>BD FocalPoint™ GS Imaging System</b>	Unsat (+)	15	6	21
	Sat (-)	2	0	2
	Total	17	6	23

The adjudicated percentage of unsatisfactory slides is 0.70% (23/3285) with 95% confidence interval (0.44%, 1.05%). The BD FocalPoint™ GS Imaging System arm correctly assessed the unsatisfactory status of slides 91.3% (21/23) of the time whereas the Manual Screening arm correctly assessed the slide as being unsatisfactory 73.9% (17/23) of the time. This resulted in a 17.4% increase in slides correctly assessed for unsatisfactory status by the BD FocalPoint™ GS Imaging System arm versus the Manual Screening arm. The increase of 17.4% was not statistically significant (95% CI: -8.3% to 42.4%).

## I.6 Benign Cellular Changes for the Manual Screening and BD FocalPoint™ GS Imaging System Arms

**Table I.6.1 Summary of NILM (Negative) or Benign Cellular Changes for the Manual Screening Arm and BD FocalPoint™ GS Imaging System Arms**

Site	Any Organism		Reactive Cellular Changes		Atrophy	
	Manual Screening	BD FocalPoint™ GS	Manual Screening	BD FocalPoint™ GS	Manual Screening	BD FocalPoint™ GS
<b>1</b>	154	124	110	70	132	122
<b>2</b>	351	359	9	8	13	27
<b>3</b>	382	391	276	281	241	254
<b>4</b>	523	514	1	8	1	25
<b>All</b>	1,410	1,388	396	367	387	428

## I.7 Specimen Adequacy for the Manual Screening and BD FocalPoint™ GS Imaging System Arms

**Table I.7.1 Summary of Specimen Adequacy for the Manual Screening Arm and BD FocalPoint™ GS Imaging System Arms**

Site	Absence of endocervical component		50%-75% of squamous epithelial cells obscured		Scant cellularity	
	Manual Screening	BD FocalPoint™ GS	Manual Screening	BD FocalPoint™ GS	Manual Screening	BD FocalPoint™ GS
<b>1</b>	220	262	3	1	9	12
<b>2</b>	288	437	46	55	0	2
<b>3</b>	347	434	0	0	12	10
<b>4</b>	135	112	66	8	0	1
<b>All</b>	990	1,245	115	64	21	25

Site	Too few epithelial cells present (less than 5000)		More than 75% of the squamous epithelial cells obscured		Unsatisfactory slide	
	Manual Screening	BD FocalPoint™ GS	Manual Screening	BD FocalPoint™ GS	Manual Screening	BD FocalPoint™ GS
<b>1</b>	9	9	0	0	8	9
<b>2</b>	2	3	2	2	6	9
<b>3</b>	0	3	0	0	0	3
<b>4</b>	6	9	1	0	6	6
<b>All</b>	17	24	3	2	20	27

## I.8 Daily Cytotechnologist Screening Rates

A workload study documenting cytotechnologist screening rates was conducted throughout the course of the BD FocalPoint™ GS Imaging System clinical trial. Workload data collection was similar for both arms and included time spent reviewing clinical information and reporting diagnostic interpretations. The clinical information available to the study participant was similar in both arms. The work environment was the same in both study arms. In the BD FocalPoint™ GS Imaging System workload study arm, five cytotechnologists worked an average of three to four hours, seven cytotechnologists worked an average of four to five hours, and none worked more than an average of five hours. See Table I.8.1.

Four cytotechnologists at each of four sites for a total of 16 cytotechnologists participated in the workload evaluation study. Pap test screening experience ranged from two to 36 years. Cytotechnologists who participated in the Manual Screening arm participated in the BD FocalPoint™ GS Imaging System arm but did not review the same slides from one arm to the next. Table I.8.1 below provides the workload statistics by study site.

**Table I.8.1 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	Mean Day	High Day
Site 1	MS	3,258	5.15	52.8	78.1	192.0
	GS	2,823	4.51	75.7	123.5	174.0
1003	MS	836	3.88	52.8	91.1	192.0
	GS	747	4.07	88.0	133.3	174.0
1004	MS	993	6.27	62.4	74.7	84.5
	GS	840	4.85	97.5	128.1	150.0
1005	MS	818	5.40	56.0	72.1	88.0
	GS	870	5.00	98.5	131.7	156.8
1006	MS	611	5.53	59.2	68.4	77.8
	GS	366	4.00	75.7	92.6	107.1
Site 2	MS	4,518	4.70	59.1	90.7	130.0
	GS	3,457	3.81	48.0	98.9	123.8
2000	MS	996	4.11	59.1	79.8	93.3
	GS	951	4.00	84.1	100.1	114.0
2001	MS	1,197	5.21	75.1	87.3	94.9
	GS	793	3.76	84.1	98.3	110.0
2002	MS	1,184	3.88	89.2	112.4	130.0
	GS	875	3.70	48.0	98.5	123.8
2003	MS	1,141	5.81	80.0	82.9	88.0
	GS	838	3.77	88.0	98.7	105.8
Site 4	MS	4,011	3.06	44.1	120.6	185.2
	GS	3,353	4.61	98.6	150.9	240.0
4003	MS	439	2.34	44.1	93.7	138.0
	GS	568	4.85	106.7	133.8	158.2
4004	MS	1,312	3.05	72.2	139.0	185.2
	GS	933	4.82	122.1	172.2	198.1
4005	MS	1,275	3.35	96.0	129.0	153.2
	GS	904	4.64	118.1	154.7	179.2
4008	MS	985	3.30	97.9	110.5	126.3
	GS	948	4.32	98.6	142.6	240.0

Table I.8.1 shows the screening rates achieved with the BD FocalPoint™ GS Imaging System. The maximum number of slides examined by an individual using the BD FocalPoint™ GS Imaging System should not exceed 170 slides in an 8-hour workday.

- It is the responsibility of the Technical Supervisor to evaluate and set workload limits for individual cytotechnologists based on laboratory clinical performance.
- According to CLIA '88, these workload limits should be reassessed every six months.
- Since limits beyond 170 slides per 8-hour work day have not been documented to be safe and effective, workload limits should not exceed the maximum limit specified within the product labeling.

The BD FocalPoint™ GS Imaging System limit of 170 slides in an 8-hour workday includes all actions to interpret and report slide results as follows:

- Review clinical history and BD FocalPoint™ Slide Profiler information,
- Location confirmation of first FOV,
- Screen up to 10 FOVs at the BD FocalPoint™ GS Review Station microscope,
- Full slide review as needed at BD FocalPoint™ GS Review Station microscope, and
- Record results and triage appropriately.

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:

$$\frac{\text{Number of hours spent screening BD SurePath™ slides using the BD FocalPoint™ GS Imaging System} \times 170}{8}$$

For any other slide type manually screened i.e. Non-GYN, refer to the CLIA '88 workload requirement to calculate daily workload per 8-hour day per 24 hour period.

**Table I.8.2 Comparison of Prevalence rates and Performance with screening rates using all work load time periods in order to permit comparison with sensitivity and specificity performance**

Site	ASC-US+ n (%)*	ASC-H+ n (%)*	LSIL+ n (%)*	HSIL+ n (%)*	Study Arm	Extrapolated Daily Rates <sup>†</sup> (8-hour workday)		
						Low	Mean	High
All	1309 (10.63)	811 (6.59)	779 (6.33)	204 (1.66)	MS	30.8	98.7	212.6
					GS	48.0	129.3	240.0

\* Prevalence rates

<sup>†</sup> These numbers are based on all slides in the study to match the table for sensitivity and specificity but included all time periods for the study both greater and less than four hours per day.

Site	Study Arm	Performance for ASC-US+ % Difference				Performance for ASC-H+ % Difference				Performance for LSIL+ % Difference				Performance for HSIL+ % Difference			
		Sensitivity		Specificity		Sensitivity		Specificity		Sensitivity		Specificity		Sensitivity		Specificity	
All	MS (%)	82.6	-1.5	82.7	+1.8	77.9	+9.2	90.1	-3.0	76.4	+9.8	90.6	-1.9	65.7	+19.6	97.7	-2.6
	GS (%)	81.1		84.5		87.2		87.1		86.1		88.7		85.3		95.1	

## J. Clinical Study Conclusions

In this clinical study:

1. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of Cancer. The Cancer sensitivity for all sites combined was 69.4% for the BD FocalPoint™ GS Imaging System arm versus 44.9% for the Manual Screening arm resulting in a statistically significant increase of 24.5% with 95% CI: 4.8% to 42.2%. The Cancer specificity for all sites combined was 99.7% for the BD FocalPoint™ GS Imaging System arm versus 99.9% for the Manual Screening arm resulting in a slight decrease of 0.2% with 95% CI: -0.5% to -0.0%.
2. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of HSIL+. The HSIL+ sensitivity for all sites combined was 85.3% for the BD FocalPoint™ GS Imaging System arm versus 65.7% for the Manual Screening arm resulting in a statistically significant increase of 19.6% with 95% CI: 12.7% to 26.8%. The HSIL+ specificity for all sites combined was 95.1% for the BD FocalPoint™ GS Imaging System arm versus 97.7% for the Manual Screening arm resulting in a decrease of 2.6% with 95% CI: -3.4% to -1.9%.
3. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of LSIL+. The LSIL+ sensitivity for all sites combined was 86.1% for the BD FocalPoint™ GS Imaging System arm versus 76.4% for the Manual Screening arm resulting in a statistically significant increase of 9.8% with 95% CI: 6.7% to 12.9%. The LSIL+ specificity for all sites combined was 88.7% for the BD FocalPoint™ GS Imaging System arm versus 90.6% for the Manual Screening arm resulting in a decrease of 1.9% with 95% CI: -3.3% to -0.6%.
4. The BD FocalPoint™ GS Imaging System sensitivity was found to be statistically higher than the manual review of BD SurePath™ Pap Test Slides for the detection of ASC-H+. The ASC-H+ sensitivity for all sites combined was 87.2% for the BD FocalPoint™ GS Imaging System arm versus 77.9% for the Manual Screening arm resulting in a statistically significant increase of 9.2% with 95% CI: 6.4% to 12.2%. The ASC-H+ specificity for all sites combined was 87.1% for the BD FocalPoint™ GS Imaging System arm versus 90.1% for the Manual Screening arm resulting in a decrease of 3.0% with 95% CI: -4.5% to -1.5%.
5. The ASC-US+ sensitivity for all sites combined was 81.1% for the BD FocalPoint™ GS Imaging System arm versus 82.6% for the Manual Screening arm resulting in a slight decrease of 1.5% (not statistically significant) with 95% CI: -4.1% to 1.2%. The ASC-US+ specificity for all sites combined was 84.5% for the BD FocalPoint™ GS Imaging System arm versus 82.7% for the Manual Screening

arm were similar (difference was 1.8%; not statistically significant) with 95% CI: -0.3% to 3.8%.

6. Based on the results from this study, the maximum daily workload limit when using the BD FocalPoint™ GS Imaging System for primary screening of BD SurePath™ Pap Test slides should not exceed 170 slides per 8-hour workday. This workload limit of 170 slides includes time spent on manual full slide review which should not supersede the CLIA requirement of 100 slides in an 8-hour workday for any type of slide requiring a manual full slide review.

For these study sites and these study populations, the data from this clinical trial demonstrate the BD FocalPoint™ GS Imaging System's safe and effective use in the primary screening of BD SurePath™ Pap Test slides in detecting cervical abnormalities for all Bethesda<sup>1</sup> categories. The results of this study support the indication that the sorting and ranking of slides by the BD FocalPoint™ Slide Profiler, in combination with the review of Field of Views (FOVs) at the BD FocalPoint™ GS Review Station, assists in the detection of ASC-US+, in a manner that is at least equivalent to Manual Screening.

In the detection of Cancer, HSIL+, LSIL+, and ASC-H+, the BD FocalPoint™ GS Imaging System sensitivity is statistically higher than Manual Screening accompanied by a concurrent increase in Pap test screening productivity.

#### **K. Storage and Operation**

- Do not expose the system to direct sunlight or temperature extremes (e.g., airflow from heating or cooling systems).
- The operating temperature range for the BD FocalPoint™ Slide Profiler is 10°– 30° C (50°– 86° F).

#### **L. Technical Service and Product Information**

For technical service and assistance related to use of the BD FocalPoint™ GS Imaging System, contact BD Diagnostics – TriPath:

- Telephone: 1-866-874-7284 (within the U.S. and Canada) or Europe at +32-2-704-43-80 (Internationally)
- Fax: (U.S.) 336-290-8333 or (Europe) +32 2 721 36 00

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