Genius™ Digital Diagnostics System with the Genius™ Cervical AI Algorithm

Instructions for Use

℞ only

IVD

INTENDED USE

The Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm includes the Genius™ Digital Imager, Genius™ Image Management Server (IMS), the Genius™ Review Station, and the Genius™ Cervical AI algorithm. The Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm is intended for the creation and viewing of digital images of scanned ThinPrep® Pap Test glass slides. Objects of interest selected by the Genius™ Cervical AI algorithm from the scanned digital image are presented in a gallery format, next to the image of the whole cell spot on the Genius™ Review Station, for review and interpretation. The Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm is intended to aid in cervical cancer screening 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 cytological categories as defined by The Bethesda System for Reporting Cervical Cytology[1].

After digital review with the Genius™ Cervical AI algorithm, if there is uncertainty in the diagnosis, then direct examination of the glass slide by light microscopy should be performed. Digital images from the Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm should be interpreted by qualified cytologists and pathologists in conjunction with the patient's screening history, other risk factors, and professional guidelines which guide patient management.

SUMMARY AND EXPLANATION OF THE SYSTEM

The Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm uses Pap test slides prepared from gynecologic (cervical/vaginal) samples obtained from women for screening, diagnosis and management.

Slides that have been prepared for screening using the ThinPrep® 2000 system, the ThinPrep® 5000 processor, or the ThinPrep® Genesis™ processor and stained with ThinPrep® stain (Papanicolaou stain) are loaded into slide carriers which are placed into the Digital Imager. The operator uses a touch screen on the Digital Imager to interact with the instrument via a graphic, menu-driven interface.

A slide ID reader scans the slide's accession ID and locates the position of the cell spot. Then, the Digital Imager scans the entire ThinPrep cell spot, creating an in-focus, whole slide image.

For ThinPrep® Pap test patient sample slides, the Genius™ Cervical AI algorithm identifies objects of interest found on a digital image of the slide. The objects classified as most clinically relevant are presented to a cytologist (CT) or pathologist for review in a gallery of images. The slide image data, the slide ID and its associated data record are transmitted to the Image Management Server, and the slide is returned to its slide carrier.

The Image Management Server acts as the central data manager for the Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm. As slides are imaged by the Digital Imager and reviewed at the Review Station, the server stores, retrieves and transmits information based on the case ID.

The CT or pathologist reviews cases at the Review Station. The Review Station is a dedicated computer running a Review Station software application, with a monitor suitable for diagnostic review of objects of interest and/or whole slide images. The Review Station is connected to a keyboard and mouse. When a valid case accession ID has been identified at the Review Station, the server sends the images for that ID. The CT or pathologist is presented with a gallery of images of objects of interest for that slide.

When any image is being reviewed, the CT or pathologist has the option to electronically mark objects of interest and include the marks in the case review. The reviewer, in addition to reviewing the gallery images, has the option to move to any portion of the cell spot for examination.

LIMITATIONS

- Performance characteristics of the Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm are based on using Genius Cervical AI tools, including the entire gallery, to assist in diagnosing a case and should be used accordingly. The performance of the Genius Digital Diagnostics System with the Genius™ Cervical AI algorithm using only a digital review of the entire cell spot has not been evaluated.
- There is no priority or ranking in the order with which the objects of interest are displayed in the gallery and therefore, the user must review all objects in the gallery.
- After review of the entire gallery of images provided by the Genius Cervical AI algorithm, if there is uncertainty in diagnosis, then direct examination of the glass slide by light microscopy should be performed.
- Only personnel who have been trained in the use of the Genius Digital Imager, Review Station and Genius Cervical AI algorithm should operate the system.
- ThinPrep Imaging System microscope slides with fiducial marks must be used.
- The Genius Digital Diagnostics System with the Genius™ Cervical AI algorithm is indicated for use only with the slides prepared using a ThinPrep 2000 system, ThinPrep 5000 processor or ThinPrep Genesis processor and stained with ThinPrep stain. The Genius Digital Diagnostics System with the Genius Cervical AI algorithm is not indicated for the ThinPrep Pap test slides prepared with any other cytology processor including the ThinPrep® 3000 processor.
- The laboratory Technical Supervisor should establish individual workload limits for personnel using the Genius Digital Diagnostics System with the Genius Cervical AI algorithm. Please also see section on “Cytologist Workload Determination”.

- Gynecological slides must be stained using the ThinPrep stain (Papanicolaou 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 cover slipped should not be used.
- Slides should be imaged by the Genius Digital Imager in a timely manner, according to normal laboratory practices.
- Slides used with the Genius Digital Imager must contain properly formatted accession number identification information as described in the operator's manual.
- The performance of the Genius Digital Diagnostics System with the Genius™ Cervical AI algorithm using slides prepared from reprocessed sample vials has not been evaluated.
- The monitor and graphics card for the Review Station are those supplied by Hologic specifically for the Genius Digital Diagnostics System with the Genius™ Cervical AI algorithm. They are required for proper performance of the system and cannot be substituted.

WARNINGS

- For *In Vitro* Diagnostic Use
- The Genius™ Digital Imager generates, uses, and can radiate radio frequency energy and may cause interference to radio communications.
- The Genius™ Digital Imager uses glass microscope slides, which may have sharp edges. In addition, the slides may be broken in their storage packaging or on the instrument. Use caution when handling glass slides and when cleaning the instrument.
- 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 per CLIA regulation 42 CFR 493.1257 to ensure proper use and selection of appropriate workload limits.
- Users should employ appropriate cybersecurity measures when the device is used for remote review.
- Service Installation Only. The system must be installed by trained Hologic personnel only.
- For professional use only.

PRECAUTIONS

- Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the Digital Imager, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.

- Care should be taken to assure that slides are correctly oriented in the Digital Imager slide carrier to prevent rejection by the system.
- The Digital Imager should be placed on a flat, sturdy surface away from any vibrating machinery to assure proper operation.

TRAINING AND QUALITY CONTROL

- Evaluation of cases should be performed only by cytologists and pathologists who have been trained, by Hologic or organizations designated by Hologic, to evaluate digital images of scanned ThinPrep® Pap Test glass slides using Genius Cervical AI.
- For Cytologists who begin clinical use of the device, labs should consider additional training policies and procedures, as needed, such as re-review of a lab-determined number of cases.
- If a product malfunction occurs, which caused, or could lead to an adverse event, the device user should consider filing a Medical Device Report (MDR) to US FDA using MedWatch Form 3500 (https://www.fda.gov/media/76299/download) for voluntary reporting.

PERFORMANCE CHARACTERISTICS

GENIUS™ DIGITAL DIAGNOSTICS SYSTEM WITH THE GENIUS™ CERVICAL AI ALGORITHM COMPARED TO GLASS SLIDE MANUAL REVIEW

A multi-center Genius Cervical AI Clinical Study was performed within the United States. The objective of the study was to show that routine screening of ThinPrep Pap test slides using the Genius Digital Diagnostics System with the Genius Cervical AI algorithm was comparable to the approved method of screening using glass slides with a light microscope.

The study included 1994 slides and four (4) clinical sites (laboratories). Slides were prepared from residual material after the clinical sites signed out the case, from women who were screened for cervical cancer using the ThinPrep Pap test. Samples that were enrolled were processed on the ThinPrep® 2000 system, the ThinPrep® 5000 processor, or the ThinPrep® Genesis™ processor. At each of four (4) clinical sites, three (3) independent teams consisting of one (1) cytologist (CT) and one (1) pathologist at each site (CT/Pathologist teams) reviewed all cases at their site. All cases at the corresponding site were reviewed independently by the three teams at that particular site and, therefore, the number of reviews at the site were 3 x the number of slides at the site. Site CT/Pathologist teams screened cases in 3 review phases as follows: manual review of glass slides with a light microscope without the assistance of the ThinPrep Imaging System (TIS) (Manual review), review of glass slides with the ThinPrep Imaging System (TIS review), and review of digital images with the Genius Digital Diagnostics System with the Genius Cervical AI algorithm (Genius Cervical AI review), in that order. Cases with an ASCUS, AGC, LSIL, ASC-H, HSIL, Cancer

or unsatisfactory for evaluation (UNSAT) result by the CT were also reviewed by the pathologist. A minimum 14-day washout period occurred between each review phase. The cases were randomized prior to each review phase. Cytological diagnoses and specimen adequacy were determined in accordance with the Bethesda System criteria.

An adjudicated diagnosis was used as a “gold standard” (“reference” or “ground truth”). Cases were screened by an adjudication panel, composed of three (3) adjudication CT/Pathologist teams, consisting of one (1) CT and one (1) pathologist each (adjudication CT/Pathologist teams). Slides were reviewed independently by the three teams. All cases, regardless of result, were reviewed by CTs and pathologists. For each case, results from each adjudication CT/Pathologist team were used to obtain a consensus result, defined as the result for which there was majority agreement (by at least two of the three adjudication CT/Pathologist teams). If a consensus result was not obtained initially, these cases underwent review by the three adjudication pathologists simultaneously using a multi-headed microscope (multi-head review). The reference result was based on either the consensus result (if met initially) or the multi-head review result (if consensus was not obtained initially). Cytological diagnoses and specimen adequacy were determined in accordance with the Bethesda System criteria: NILM, ASCUS, AGC, LSIL, ASC-H, HSIL, Cancer and UNSAT.

Laboratory and Patient Characteristics

The cytology laboratories participating in the study were comprised of four (4) sites. All sites selected had extensive experience in the processing and evaluation of gynecologic ThinPrep Pap test slides and were trained in the use of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm.

There were 1995 slides that were eligible for the study. Of these, 1994 slides were included in the study and one (1) was excluded from the study because the slide failed the quality audit due to a scratched coverslip, an exclusion criterion. The total number of reviews was 5,982 (3 x 1994 slides). Thirty-four (34) cases (102 reviews) had adjudication results of UNSAT and the remaining 1960 cases (5,880 reviews) were Satisfactory (SAT) for evaluation and had reference adjudication diagnoses. Table 1 provides characteristics of the participating clinical sites. Table 2 describes the patient populations with SAT slides, at each of the study sites.

Table 1. Site Characteristics

Site	1	2	3	4
ThinPrep Pap Tests Per Year	48,000	239,750	329,500	4,500
Number of Cytologists in Study	3	3	3	3
Number of Pathologists in Study	3	3	3	3

Table 2. Site Demographics

Site Number	Total number	Median Age (yrs)	# Hysterectomy (% of enrolled)	# Postmenopausal (% of enrolled)
1	488	33.0	18 (3.7)	37 (7.6)
2	494	36.0	6 (1.2)	24 (4.9)
3	490	35.0	22 (4.5)	43 (8.8)
4	488	37.0	6 (1.2)	41 (8.4)
Overall	1960	35.0	52 (2.6)	141 (7.4)

Eligibility Criteria

Cases were eligible to be included in the study if they met the following criteria: ThinPrep slides of known diagnoses generated from residual cytological specimens (within 6 weeks from date of collection) in the approximate number from the following enrollment diagnostic categories:

- NILM: 1060 cases
- ASCUS: 225 cases
- AGC: 20 cases
- LSIL: 225 cases
- ASC–H: 225 cases
- HSIL: 225 cases
- Cancers: 20 cases (squamous and/or adenocarcinoma)
- UNSAT 20 cases

Cases were excluded from the study if any of the following criteria applies:

- Any slides deemed not adequate, (if slide is broken, dilute, or is otherwise unreadable).

Objective of the Clinical Study

The primary objectives of this study included comparing the sensitivity and specificity when diagnosing cases imaged and reviewed on the Genius Digital Diagnostics System with the Genius Cervical AI algorithm with the sensitivity and specificity of Manual review and also with TIS review. An adjudicated diagnosis was used as a “gold standard” (“reference” or “ground

truth"). The comparison of sensitivities and specificities was performed at the following thresholds (described in Table 3 below): ASCUS+, LSIL+, ASC-H+, HSIL+, Cancer.

Table 3. Category Partitions

Threshold	Negative	Positive
ASCUS+	NILM	ASCUS, AGC, LSIL, ASC-H, HSIL, Cancer
LSIL+	NILM, ASCUS, AGC	LSIL, ASC-H, HSIL, Cancer
ASC-H+	NILM, ASCUS, AGC, LSIL	ASC-H, HSIL, Cancer
HSIL+	NILM, ASCUS, AGC, LSIL, ASC-H	HSIL, Cancer
Cancer	NILM, ASCUS, AGC, LSIL, ASC-H, HSIL	Cancer
Abbreviations for Diagnostic Thresholds: NILM: negative for intraepithelial lesion or malignancy; ASCUS: atypical squamous cells of undetermined significance; AGC: atypical glandular cells; LSIL: low grade squamous intraepithelial lesion; ASC-H: atypical squamous cells – cannot exclude HSIL; HSIL: High grade squamous intraepithelial lesion		

Sensitivity and specificity of each review type (Genius Cervical AI review, Manual review and TIS review) were calculated on all cases with a satisfactory reference result at the ASCUS+, LSIL+, ASC-H+, HSIL+ and Cancer diagnostic thresholds. Of these cases, UNSAT Genius Cervical AI, Manual, or TIS review results were considered positive at each diagnostic threshold.

Sensitivity was separately calculated on all cases with an UNSAT reference result, where sensitivity was defined as the proportion of Genius Cervical AI, Manual, or TIS review results of UNSAT or ASCUS+. Specificity was also calculated, where specificity was defined as the proportion of satisfactory Genius Cervical AI, Manual, or TIS review results on all cases with a satisfactory reference result.

Differences in sensitivities and differences in specificities were calculated along with two-sided 95% confidence intervals (95% CI).

A) GENIUS CERVICAL AI REVIEW COMPARED WITH MANUAL REVIEW

A.1 Performance of Genius Cervical AI Review and Manual Review

Table 4.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Compared to Adjudicated Diagnosis

	Sensitivity %			Specificity %		
Diagnostic Threshold	**Genius (95% CI)**	**Manual (95% CI)**	**Difference (Genius – Manual) (95% CI)**	**Genius (95% CI)**	**Manual (95% CI)**	**Difference (Genius – Manual) (95% CI)**
ASCUS+	91.7 [1950/2127] (90.1, 93.3)	90.1 [1917/2127] (88.7, 91.8)	1.6 [33/2127] (-0.1, 3.2)	91.0 [3414/3753] (89.7, 92.1)	92.2 [3461/3753] (91.1, 93.2)	-1.3 [-47/3753] (-2.3, -0.2)
LSIL+	89.1 [1467/1647] (87.2, 91.0)	84.7 [1395/1647] (82.3, 86.8)	4.4 [72/1647] (2.1, 6.7)	91.7 [3883/4233] (90.5, 92.9)	94.1 [3984/4233] (93.1, 95.0)	-2.4 [-101/4233] (-3.5, -1.4)
ASC-H+	87.8 [938/1068] (84.8, 90.2)	79.6 [850/1068] (76.3, 82.5)	8.2 [88/1068] (4.8, 11.6)	94.2 [4531/4812] (93.2, 95.1)	97.0 [4669/4812] (96.4, 97.7)	-2.9 [-138/4812] (-3.8, -1.9)
HSIL+	81.5 [699/858] (78.5, 84.4)	74.0 [635/858] (70.1, 77.5)	7.5 [64/858] (4.0, 11.4)	94.8 [4763/5022] (94.0, 95.6)	97.2 [4882/5022] (96.6, 97.8)	-2.4 [-119/5022] (-3.0, -1.7)

The sensitivity of the Genius Cervical AI was statistically significantly higher for LSIL+, ASC-H+ and HSIL+. Increase in sensitivity was 4.4%, 8.2% and 7.5% for LSIL+, ASC-H+ and HSIL+, respectively. There were statistically significant decreases in specificity for ASCUS+, LSIL+, ASC-H+, and HSIL+ diagnostic thresholds. The decrease in specificity was 1.3%, 2.4%, 2.9% and 2.4% for ASCUS+, LSIL+, ASC-H+, and HSIL+, respectively.

A.2 Genius Cervical AI Review vs. Manual Review Stratified by Site

ASCUS+

Sensitivity is a percent of "reference" ASCUS+ cases classified in Genius Cervical AI reviews or in Manual reviews as ASCUS+ or UNSAT, and specificity is a percent of "reference" NILM cases classified in either review as NILM.

Table 5.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Stratified by Site at ASCUS+

Sites	Number of Cases	Sensitivity (95%CI)			Specificity (95%CI)		
		Genius	Manual	Difference	Genius	Manual	Difference
Site 1	488	93.4 [538/576] (90.0, 96.1)	87.8 [506/576] (83.9, 91.3)	5.6 [32/576] (1.7, 8.7)	91.7 [814/888] (88.6, 94.1)	95.6 [849/888] (93.6, 97.3)	-3.9 [-35/888] (-6.3, -1.7)
Site 2	494	87.7 [479/546] (83.6, 90.9)	93.2 [509/546] (90.0, 95.8)	-5.5 [-30/546] (-9.0, -2.0)	93.3 [873/936] (91.2, 95.2)	90.9 [851/936] (88.4, 93.5)	2.4 [22/936] (0.3, 4.7)
Site 3	490	92.2 [506/549] (88.9, 95.0)	88.7 [487/549] (85.4, 92.0)	3.5 [19/549] (0.4, 6.1)	92.6 [853/921] (90.1, 94.9)	92.0 [847/921] (89.9, 93.8)	0.7 [6/921] (-1.9, 2.8)
Site 4	488	93.6 [427/456] (90.8, 96.1)	91.0 [415/456] (87.3, 94.7)	2.6 [12/546] (-0.6, 5.8)	86.7 [874/1008] (83.9, 89.4)	90.7 [914/1008] (88.1, 93.0)	-4.0 [-40/1008] (-6.2, -1.6)
Total	1960	91.7 [1950/2127] (90.1, 93.3)	90.1 [1917/2127] (88.7, 91.8)	1.6 [33/2127] (-0.1, 3.2)	91.0 [3414/3753] (89.7, 92.1)	92.2 [3461/3753] (91.1, 93.2)	-1.3 [-47/3753] (-2.3, -0.2)

LSIL+

Sensitivity is a percent of "reference" LSIL+ cases classified in Genius Cervical AI reviews or in Manual reviews as LSIL+ or UNSAT, and specificity is a percent of "reference" (NILM or ASCUS or AGC) cases classified in either review as NILM or ASCUS or AGC.

Table 6.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Stratified by Site at LSIL+

Sites	Number of Cases	Sensitivity (95%CI)			Specificity (95%CI)		
		Genius	Manual	Difference	Genius	Manual	Difference
Site 1	488	88.5 [401/453] (84.2, 92.2)	83.7 [379/453] (78.9, 87.8)	4.9 [22/453] (0.5, 9.5)	91.0 [920/1011] (88.2, 93.8)	94.3 [953/1011] (92.3, 96.4)	-3.3 [-33/1011] (-5.6, -1.1)
Site 2	494	85.9 [348/405] (81.0, 89.8)	93.1 [377/405] (89.7, 96.2)	-7.2 [-29/405] (-11.1, -3.3)	92.9 [1000/1077] (90.8, 94.8)	92.3 [994/1077] (89.8, 94.5)	0.6 [6/1077] (-1.5, 2.7)
Site 3	490	89.7 [390/435] (86.2, 93.0)	72.6 [316/435] (66.9, 77.6)	17.0 [74/435] (12.2, 22.3)	92.4 [956/1035] (89.9, 94.5)	97.1 [1005/1035] (95.9, 98.3)	-4.7 [-49/1035] (-7.1, -2.9)
Site 4	488	92.7 [328/354] (89.5, 95.1)	91.2 [323/354] (87.2, 94.6)	1.4 [5/354] (-2.7, 5.9)	90.7 [1007/1110] (88.4, 92.9)	93.0 [1032/1110] (90.8, 94.9)	-2.3 [-25/1110] (-4.1, 0.1)
Total	1960	89.1 [1467/1647] (87.2, 91.0)	84.7 [1395/1647] (82.3, 86.8)	4.4 [72/1647] (2.1, 6.7)	91.7 [3883/4233] (90.5, 92.9)	94.1 [3984/4233] (93.1, 95.0)	-2.4 [-101/4233] (-3.5, -1.4)

ASC-H+

Sensitivity is a percent of "reference" ASC-H+ cases classified in Genius reviews or in Manual reviews as ASC-H+ or UNSAT, and specificity is a percent of "reference" (NILM or ASCUS or AGC or LSIL) cases classified in either review as NILM or ASCUS or AGC or LSIL.

Table 7.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Stratified by Site at ASC-H+

Sites	Number of Cases	Sensitivity (95%CI)			Specificity (95%CI)		
		Genius	Manual	Difference	Genius	Manual	Difference
Site 1	488	85.7 [257/300] (80.0, 90.4)	80.0 [240/300] (74.1, 85.3)	5.7 [17/300] (0.0, 11.8)	92.4 [1075/1164] (89.7, 94.6)	96.1 [1119/1164] (94.5, 97.7)	-3.8 [-44/1164] (-5.6, -2.0)
Site 2	494	83.3 [230/276] (77.3, 88.7)	90.9 [251/276] (86.1, 95.4)	-7.6 [-21/276] (-13.4, -2.7)	96.5 [1164/1206] (94.9, 97.9)	96.0 [1158/1206] (94.5, 97.5)	0.5 [6/1206] (-1.0, 2.1)
Site 3	490	92.3 [241/261] (87.8, 95.9)	69.7 [182/261] (62.6, 77.2)	22.6 [59/261] (15.6, 28.9)	94.5 [1143/1209] (92.5, 96.4)	98.5 [1191/1209] (97.7, 99.2)	-4.0 [-48/1209] (-5.7, -2.3)
Site 4	488	90.9 [210/231] (87.0, 94.4)	76.6 [177/231] (68.8, 84.0)	14.3 [33/231] (6.3, 22.8)	93.2 [1149/1233] (91.2, 95.1)	97.4 [1201/1233] (96.3, 98.5)	-4.2 [-52/1233] (-6.2, -2.4)
Total	1960	87.8 [938/1068] (84.8, 90.2)	79.6 [850/1068] (76.3, 82.5)	8.2 [88/1068] (4.8, 11.6)	94.2 [4531/4812] (93.2, 95.1)	97.0 [4669/4812] (96.4, 97.7)	-2.9 [-138/4812] (-3.8, -1.9)

HSIL+

Sensitivity is a percent of "reference" HSIL+ cases classified in Genius reviews or in Manual reviews as HSIL+ or UNSAT, and specificity is a percent of "reference" (NILM or ASCUS or AGC or LSIL or ASC-H) cases classified in either review as NILM or ASCUS or AGC or LSIL or ASC-H.

Table 8.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Stratified by Site at HSIL+

Sites	Number of Cases	Sensitivity (95%CI)			Specificity (95%CI)		
		Genius	Manual	Difference	Genius	Manual	Difference
Site 1	488	79.4 [193/243] (72.4, 86.3)	74.5 [181/243] (68.4, 81.0)	4.9 [12/243] (-2.4, 12.3)	93.5 [1142/1221] (91.1, 95.4)	95.7 [1169/1221] (94.0, 97.2)	-2.2 [-27/1221] (-3.9, -0.9)
Site 2	494	77.5 [179/231] (70.3, 84.6)	87.4 [202/231] (80.3, 93.3)	-10.0 [-23/231] (-17.0, -4.1)	96.8 [1211/1251] (95.5, 97.9)	96.8 [1211/1251] (95.4, 98.0)	0.0 [0/1251] (-1.1, 1.0)
Site 3	490	83.8 [171/204] (77.8, 89.5)	54.4 [111/204] (45.7, 62.9)	29.4 [60/204] (22.4, 37.5)	95.6 [1210/1266] (94.0, 97.0)	99.4 [1259/1266] (98.9, 99.8)	-3.9 [-49/1266] (-5.3, -2.5)
Site 4	488	86.7 [156/180] (82.1, 91.3)	78.3 [141/180] (70.7, 86.8)	8.3 [15/180] (0.0, 15.7)	93.5 [1200/1284] (91.8, 95.1)	96.8 [1243/1284] (95.5, 98.0)	-3.3 [-43/1284] (-4.9, -1.7)
Total	1960	81.5 [699/858] (78.5, 84.4)	74.0 [635/858] (70.1, 77.5)	7.5 [64/858] (4.0, 11.4)	94.8 [4763/5022] (94.0, 95.6)	97.2 [4882/5022] (96.6, 97.8)	-2.4 [-119/5022] (-3.0, -1.7)

Cancer

Sensitivity is a percent of "reference" Cancer cases classified in Genius Cervical AI reviews or in Manual reviews as Cancer or UNSAT, and specificity is a percent of "reference" (NILM or ASCUS or AGC or LSIL or ASC-H or HSIL) cases classified in either review as NILM or ASCUS or AGC or LSIL or ASC-H or HSIL.

Table 9.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Stratified by Site at Cancer

Sites	Number of Cases	Sensitivity (95%CI)			Specificity (95%CI)		
		Genius	Manual	Difference	Genius	Manual	Difference
Site 1	488	66.7 [14/21] (25.0, 100.0)	76.2 [16/21] (50.0, 100.0)	-9.5 [-2/21] (-33.3, 11.1)	98.3 [1418/1443] (97.0, 99.2)	98.6 [1423/1443] (97.7, 99.3)	-0.3 [-5/1443] (-1.1, 0.3)
Site 2	494	66.7 [14/21] (20.8, 100.0)	85.7 [18/21] (63.0, 100.0)	-19.0 [-4/21] (-44.4, 0.0)	98.6 [1440/1461] (97.8, 99.3)	97.7 [1428/1461] (96.5, 98.8)	0.8 [12/1461] (0.1, 1.6)
Site 3	490	60.6 [20/33] (33.3, 84.6)	39.4 [13/33] (16.7, 66.7)	21.2 [7/33] (3.7, 40.0)	98.9 [1421/1437] (98.2, 99.5)	99.4 [1429/1437] (98.8, 99.9)	-0.6 [-8/1437] (-1.3, 0.1)
Site 4	488	76.2 [16/21] (44.4, 100.0)	81.0 [17/21] (55.6, 100.0)	-4.8 [-1/21] (-22.2, 13.3)	98.4 [1420/1443] (97.6, 99.1)	98.4 [1420/1443] (97.6, 99.2)	0.0 [0/1443] (-0.8, 0.8)
Total	1960	66.7 [64/96] (51.7, 80.6)	66.7 [64/96] (54.3, 79.0)	0.0 [0/96] (-9.8, 11.1)	98.5 [5699/5784] (98.0, 98.9)	98.5 [5700/5784] (98.1, 98.9)	-0.0 [-1/5784] (-0.4, 0.4)

UNSAT

Sensitivity is a percent of "reference" UNSAT cases classified in Genius reviews or in Manual reviews as UNSAT or ASCUS+, and specificity is a percent of "reference" Satisfactory (SAT) slides classified in either review as SAT.

Table 10.
Sensitivity and Specificity of Genius Cervical AI Review and Manual Review Stratified by Site at UNSAT

Sites	Number of Cases	Sensitivity (95%CI)			Specificity (95%CI)		
		Genius	Manual	Difference	Genius	Manual	Difference
Site 1	503	86.7 [39/45] (71.1, 100)	51.1 [23/45] (26.7, 73.3)	35.6 [16/45] (11.1, 57.8)	99.6 [1458/1464] (98.9, 100)	99.9 [1463/1464] (99.8, 100)	-0.3 [-5/1464] (-1.0, 0.1)
Site 2	500	77.8 [14/18] (55.6, 94.4)	77.8 [14/18] (55.6, 100)	0.0 [0/18] (-16.7, 16.7)	99.6 [1476/1482] (99.1, 100)	99.7 [1478/1482] (99.3, 100)	-0.1 [-2/1482] (-0.5, 0.1)
Site 3	495	80.0 [12/15] (40.0, 100)	53.3 [8/15] (26.7, 66.7)	26.7 [-4/15] (13.3, 33.3)	99.7 [1465/1470] (99.2, 100)	99.9 [1468/1470] (99.7, 100)	-0.2 [-3/1470] (-0.6, 0.1)
Site 4	496	70.8 [17/24] (37.5, 95.8)	75.0 [18/24] (50.0, 95.8)	-4.2 [-1/24] (-29.2, 25.0)	100 [1464/1464] (100, 100)	99.3 [1454/1464] (98.8, 99.8)	0.7 [10/1464] (0.2, 1.2)
Total	1994	80.4 [82/102] (67.6, 91.2)	61.8 [63/102] (50.0, 72.5)	18.6 [19/102] (5.9, 31.4)	99.7 [5863/5880] (99.5, 99.9)	99.7 [5863/5880] (99.5, 99.9)	0.0 [0/5880] (-0.2, 0.2)

A.3: Tables of performance of each Bethesda Category

Table 11 through Table 18 summarize results from Genius Cervical AI review and Manual review for each of the major descriptive diagnosis classifications of the Bethesda System as determined by the adjudication diagnosis: NILM, ASCUS, AGC, LSIL, ASC-H, HSIL, Cancer, and the diagnostic category UNSAT.

Table 11. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of NILM

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	3	10	1	0	0	0	0	0	14
	NILM	10	3250	113	12	8	19	2	0	3414
	ASCUS	0	122	43	0	7	4	1	0	177
	AGC	1	19	1	0	0	2	2	0	25
	LSIL	0	16	22	0	4	0	0	0	42
	ASC-H	1	30	10	0	1	5	1	1	49
	HSIL	1	10	6	0	3	2	5	0	27
	Cancer	0	4	0	1	0	0	0	0	5
	Total	16	3461	196	13	23	32	11	1	3753

Among the 3753 reviews determined by the adjudication panel to be NILM, 3414 (91.0%) reviews in the Genius Cervical AI Review and 3461 (92.2%) reviews in the Manual Review were diagnosed as NILM, and 81 (2.2%) reviews in the Genius Cervical AI Review and 44 (1.2%) reviews in the Manual Review were diagnosed as ASC-H+, including 5 (0.13%) reviews in Genius Cervical AI Review and 1 (0.03%) review in the Manual Review that were diagnosed as Cancer.

Table 12. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of ASCUS

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	0	2	1	0	0	0	0	0	3
	NILM	0	49	40	0	16	6	2	0	113
	ASCUS	0	35	70	1	32	1	3	0	142
	AGC	0	0	0	0	0	0	0	0	0
	LSIL	0	20	51	0	48	2	0	0	121
	ASC-H	0	11	15	0	10	8	3	0	47
	HSIL	0	1	8	0	11	3	6	0	29
	Cancer	0	0	2	0	0	1	0	1	4
	Total	0	118	187	1	117	21	14	1	459

Among the 459 reviews determined by the adjudication panel to be ASCUS, 142 (30.9%) reviews in the Genius Cervical AI Review and 187 (40.7%) reviews in the Manual Review were diagnosed as ASCUS, and 113 (24.6%) reviews in the Genius Cervical AI Review and 118 (25.7%) reviews in the Manual Review were diagnosed as NILM.

Table 13. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of AGC

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	0	0	0	0	0	0	0	0	0
	NILM	0	5	0	0	0	1	0	1	7
	ASCUS	0	0	0	0	0	0	0	0	0
	AGC	0	1	0	1	0	0	0	3	5
	LSIL	0	0	0	0	0	0	0	0	0
	ASC-H	0	1	0	0	0	0	0	0	1
	HSIL	0	0	0	0	0	0	0	0	0
	Cancer	0	0	0	0	0	0	1	7	8
	Total	0	7	0	1	0	1	1	11	21

Among the 21 reviews determined by the adjudication panel to be AGC, 5 (23.8%) reviews in the Genius Cervical AI Review and 1 (4.8%) review in the Manual Review were diagnosed as AGC, and 7 (33.3%) reviews in the Genius Cervical AI Review and 7 (33.3%) reviews in the Manual Review were diagnosed as NILM.

Table 14. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of LSIL

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	0	0	0	0	0	0	0	0	0
	NILM	0	2	6	0	2	0	1	0	11
	ASCUS	0	10	17	0	35	1	1	0	64
	AGC	0	0	0	0	0	0	0	0	0
	LSIL	0	18	35	0	351	2	4	0	410
	ASC-H	0	0	8	0	16	1	1	0	26
	HSIL	0	1	3	0	39	7	15	1	66
	Cancer	0	0	1	0	1	0	0	0	2
	Total	0	31	70	0	444	11	22	1	579

Among the 579 reviews determined by the adjudication panel to be LSIL, 410 (70.8%) reviews in the Genius Cervical AI Review and 444 (76.7%) reviews in the Manual Review were diagnosed as LSIL, and 11 (1.9%) reviews in the Genius Cervical AI Review and 31 (5.4%) reviews in the Manual Review were diagnosed as NILM.

Table 15. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of ASC-H

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	0	0	0	0	0	0	0	0	0
	NILM	0	9	0	0	0	5	5	0	19
	ASCUS	0	4	4	1	2	4	5	0	20
	AGC	0	1	1	0	0	1	0	0	3
	LSIL	0	0	0	0	3	1	2	0	6
	ASC-H	0	6	14	0	8	23	10	0	61
	HSIL	0	10	20	0	10	21	33	1	95
	Cancer	0	0	0	0	0	0	1	5	6
	Total	0	30	39	1	23	55	56	6	210

Among the 210 reviews determined by the adjudication panel to be ASC-H, 61 (29.0%) reviews in the Genius Cervical AI Review and 55 (26.2%) reviews in the Manual Review were diagnosed as ASC-H, and 19 (9.0%) reviews in the Genius Cervical AI Review and 30 (14.3%) reviews in the Manual Review were diagnosed as NILM.

Table 16. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of HSIL

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	0	0	0	0	0	0	0	0	0
	NILM	0	1	1	1	0	5	11	4	23
	ASCUS	0	0	3	0	0	7	9	0	19
	AGC	0	1	1	0	0	2	6	1	11
	LSIL	0	0	0	0	12	0	7	0	19
	ASC-H	0	3	9	1	8	18	34	2	75
	HSIL	1	18	21	8	23	62	418	21	572
	Cancer	0	0	1	1	1	1	20	19	43
	Total	1	23	36	11	44	95	505	47	762

Among the 762 reviews determined by the adjudication panel to be HSIL, 572 (75.1%) reviews in the Genius Cervical AI Review and 505 (66.3%) reviews in the Manual Review were diagnosed as HSIL, and 23 (3.0%) reviews in the Genius Cervical AI Review and 23 (3.0%) reviews in the Manual Review were diagnosed as NILM.

Table 17. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of Cancer

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	0	0	0	0	0	0	0	0	0
	NILM	0	1	0	0	0	0	1	2	4
	ASCUS	0	0	0	0	0	0	1	0	1
	AGC	0	0	1	1	0	0	0	3	5
	LSIL	0	0	0	0	0	0	0	0	0
	ASC-H	0	0	0	0	0	1	0	1	2
	HSIL	0	0	1	1	0	1	13	4	20
	Cancer	0	0	1	5	0	1	3	54	64
	Total	0	1	3	7	0	3	18	64	96

Among the 96 reviews determined by the adjudication panel to be Cancer, 64 (66.7%) reviews in the Genius Cervical AI Review and 64 (66.7%) reviews in the Manual Review were diagnosed as Cancer, and 4 (4.2%) reviews in the Genius Cervical AI Review and 1 (1.0%) review in the Manual Review were diagnosed as NILM.

Table 18. Genius Cervical AI Review and Manual Review Results for All Diagnostic Categories in Slides with Adjudicated Results of UNSAT

		Manual								
		UNSAT	**NILM**	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	**UNSAT**	50	22	0	0	0	0	0	0	72
	NILM	6	14	0	0	0	0	0	0	20
	ASCUS	2	1	0	0	0	0	0	0	3
	AGC	0	1	1	0	0	0	0	0	2
	LSIL	0	0	0	0	0	0	0	0	0
	ASC-H	1	0	1	1	0	1	0	0	4
	HSIL	0	0	0	0	0	0	0	0	0
	Cancer	0	1	0	0	0	0	0	0	1
	Total	59	39	2	1	0	1	0	0	102

Among the 102 reviews determined by the adjudication panel to be UNSAT, 72 (70.6%) reviews in the Genius Cervical AI Review and 59 (57.8%) reviews in the Manual Review were diagnosed as UNSAT, and 20 (19.6%) reviews in the Genius Cervical AI Review and 39 (38.2%) reviews in the Manual Review were diagnosed as NILM.

For slides diagnosed as UNSAT by adjudication, the Genius Digital Diagnostics System with the Genius Cervical AI algorithm correctly identified 18.6% more slides than Manual as UNSAT or ASCUS+.

In summary, comparison of the performances of Genius Digital Diagnostic System with the Genius Cervical AI algorithm and Manual reviews with regard to false NILM results is presented in Table 19 below.

Table 19. Summary of False NILM results for Genius Cervical AI Review and Manual Review

Review Type	Reference results by Adjudication						
% False NILM	**ASCUS**	**AGC**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Overall**
Genius	24.6% (113/459)	33.3% (7/21)	1.9% (11/579)	9.0% (19/210)	3.0% (23/762)	4.2% (4/96)	8.3% (177/2127)
Manual	25.7% (118/459)	33.3% (7/21)	5.4% (31/579)	14.3% (30/210)	3.0% (23/762)	1.0% (1/96)	9.9% (210/2127)
Genius–Manual	-1.1% (-5/459)	0.0% (0/21)	-3.5% (-20/579)	-5.2% (-11/210)	0.0% (0/762)	3.1% (3/96)	-1.6% (-33/2127)

Comparison of the performances of Genius Digital Diagnostic System with the Genius Cervical AI algorithm and Manual reviews with regard to false LSIL+ for the cases with NILM reference results by adjudication is presented in Table 20 below.

Table 20. Summary of False positive results for Genius Cervical AI Review and Manual Review

Percent of LSIL, ASC-H, HSIL and Cancer for cases with NILM reference results by Adjudication					
Review Type	**LSIL**	**ASC-H**	**HSIL**	**Cancer**	**Total**
Genius	1.12% (42/3753)	1.31% (49/3753)	0.72% (27/3753)	0.13% (5/3753)	3.28% (123/3753)
Manual	0.61% (23/3753)	0.85% (32/3753)	0.29% (11/3753)	0.03% (1/3753)	1.79% (67/3753)
Genius–Manual	0.51% (19/3753)	0.45% (17/3753)	0.43% (16/3753)	0.11% (4/3753)	1.49% (56/3753)

B. GENIUS CERVICAL AI REVIEW COMPARED WITH TIS REVIEW

Performance of Genius Cervical AI Review and Manual Review

The study also compared the performance of ThinPrep slides reviewed on the Genius Digital Diagnostic System with the Genius Cervical AI algorithm with ThinPrep slides reviewed on the ThinPrep Imaging System (TIS). The results for the Genius Cervical AI review versus TIS review are presented in Table 21.

Table 21. Sensitivity and Specificity of Genius Cervical AI Review and TIS Review Compared to Adjudicated Diagnosis

	Sensitivity %			Specificity %		
Diagnostic Threshold	**Genius (95% CI)**	**TIS (95% CI)**	**Difference (Genius – TIS) (95% CI)**	**Genius (95% CI)**	**TIS (95% CI)**	**Difference (Genius – TIS) (95% CI)**
ASCUS+	91.7 [1950/2127] (90.1, 93.3)	91.6 [1948/2127] (90.0, 93.0)	0.1 [-2/2127] (-1.6, 1.5)	91.0 [3414/3753] (89.7, 92.1)	92.6 [3474/3753] (91.5, 93.6)	-1.6 [-60/3753] (-2.8, -0.6)
LSIL+	89.1 [1467/1647] (87.2, 91.0)	87.7 [1444/1647] (85.6, 89.8)	1.4 [23/1647] (-0.6, 3.6)	91.7 [3883/4233] (90.5, 92.9)	93.3 [3950/4233] (92.2, 94.4)	-1.6 [-67/4233] (-2.6, -20.5)
ASC-H+	87.8 [938/1068] (84.8, 90.2)	84.3 [900/1068] (80.9, 87.0)	3.6 [38/1068] (0.6, 6.6)	94.2 [4531/4812] (93.2, 95.1)	96.4 [4639/4812] (95.6, 97.2)	-2.2 [-108/4812] (-3.1, -1.3)
HSIL+	81.5 [699/858] (78.5, 84.4)	77.9 [668/858] (74.0, 81.5)	3.6 [31/858] (0.0, 7.4)	94.8 [4763/5022] (94.0, 95.6)	96.6 [4850/5022] (95.9, 97.3)	-1.7 [-87/5022] (-2.4, -1.0)

The observed sensitivity of the Genius Cervical AI was greater than TIS at the ASCUS+, LSIL+, ASC-H+, and HSIL+ thresholds. The increase in sensitivity was 3.6% for both ASC-H+ and HSIL+ and statistically significant. There were statistically significant decreases in specificity for the ASCUS+, LSIL+, ASC-H+, and HSIL+ diagnostic thresholds. The decrease in specificity was 1.6%, 1.6%, 2.2% and 1.7% for ASCUS+, LSIL+, ASC-H+, and HSIL+, respectively.

C. DESCRIPTIVE DIAGNOSIS FOR BENIGN CELLULAR CHANGES

Table 22 shows the descriptive diagnosis marginal frequencies for benign cellular changes and other non-neoplastic findings for all sites combined. Each case was read by each of 3 site CT/Pathologist teams. Each case was read first by a cytologist; non-NILM slides (as determined by the cytologist) were read by a pathologist from the same site CT/Pathologist team.

Table 22. Unadjudicated Marginal Frequencies – Summary of Descriptive Diagnosis for Benign Cellular Changes

	Manual Review		**TIS Review**		**Genius Review**	
Number of Reviews	5880		5880		5880	
Descriptive Diagnosis	**N**	**%**	**N**	**%**	**N**	**%**
Benign Cellular Changes	**721**	**12.3**	**686**	**11.7**	**1035**	**17.6**
Organisms:						
Trichomonas vaginalis	71	1.2	70	1.2	103	1.8
Fungal organisms consistent with *Candida* spp.	261	4.4	222	3.8	312	5.3
Shift in flora s/o bacterial vaginosis	371	6.3	373	6.3	562	9.6
Bacteria consistent with *Actinomyces* spp.	16	0.3	19	0.3	54	0.9
Cellular changes consistent with Herpes virus	2	0	2	0	3	0.1
Other infection	0	0	0	0	1	0
Other Non-Neoplastic Findings	**440**	**7.5**	**346**	**5.9**	**513**	**8.7**
Reactive cellular changes associated with inflammation	227	3.9	160	2.7	279	4.7
Atrophy	191	3.2	168	2.9	198	3.4
Reactive cellular changes associated with radiation	1	0	0	0	0	0
Reactive cellular changes associated with IUD	0	0	1	0	0	0
Glandular cells status post hysterectomy	0	0	0	0	2	0
Endometrial cells in a woman ≥45 yrs of age	21	0.4	17	0.3	34	0.6

Presence of Endocervical Component	**4387**	**74.6**	**4239**	**72.1**	**4602**	**78.3**

A higher percentage of infectious organisms/vaginal infections (17.6% [1035/5880] vs 12.3% [721/5880]) and non-neoplastic findings (8.7% [513/5880] vs 7.5% [440/5880]) was observed using Genius Cervical AI review compared to Manual review, respectively. A higher percentage of infectious organisms/vaginal infections (17.6% [1035/5880] vs 11.7% [686/5880]) and non-neoplastic findings (8.7% [513/5880] vs 5.9% [346/5880]) was also observed using Genius Cervical AI review compared to TIS review, respectively.

ANALYTICAL PERFORMANCE OF THE GENIUS DIGITAL DIAGNOSTICS SYSTEM WITH THE GENIUS CERVICAL AI ALGORITHM

CELL COUNT STUDY

A study was conducted to evaluate the performance of the cell count metric produced by the Genius Cervical AI algorithm compared to a manual cell count.

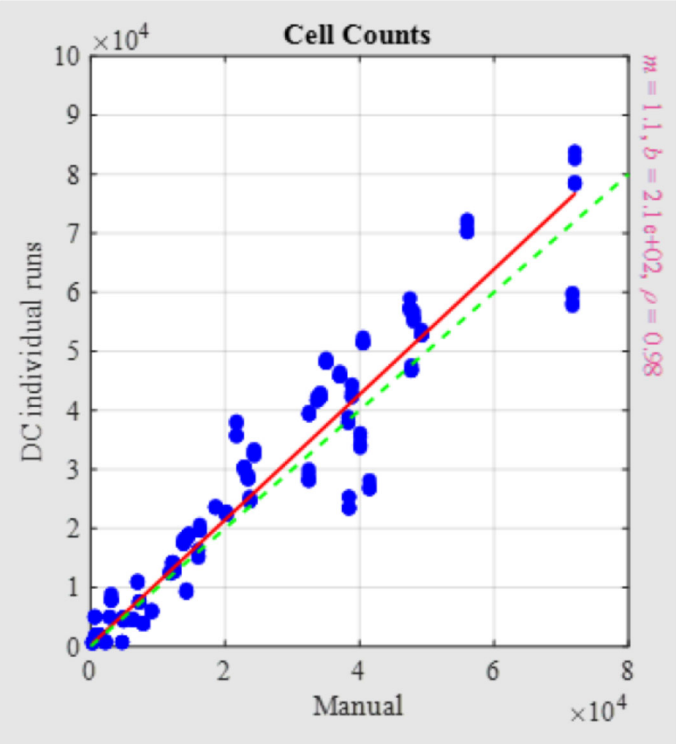
ThinPrep Pap test patient sample slides were prepared on a ThinPrep 5000 processor, stained and coverslipped. The same slides were imaged on three Genius Digital Imagers three separate times. To obtain the manual cell count for the slides in the study, a CT viewed the whole slide image presented on the Genius Review Station, counted the cells presented in a portion of the cell spot image, and estimated the total number of cells based on the portion, similar to the normal process for counting cells on slides viewed on a microscope. The cell counts derived on each Digital Imager by the algorithm in the Genius Digital Diagnostics System were compared to the manual cell count estimate.

A total of 50 specimens, including at least 8 slides with counts near the clinically important threshold of 5000 cells, were enrolled in the study. The slides covered a range of cellularity typical of a clinical environment.

Using this study data, the within-imager precision %CV was 0.6% and between-imager %CV was 2.7%.

Figure 1 compares the cell counts between the Genius Cervical AI algorithm and a manual cell count method for each specimen.

Figure 1. Scatter Plot of Digital Result versus Manual Result



The appropriate linear regression analysis was performed, and slope was 1.06 with 95% CI: (1.01; 1.11) and the intercept of 213 with 95% CI: (28; 398). The relative systematic difference between digital review and manual review counts at 5,000 cells was 10% with 95% CI: (4%; 17%).

The results of the Cell Count Study were acceptable.

OBJECTS OF INTEREST (OOI) REPRODUCIBILITY STUDY

A study was conducted to demonstrate that the Genius Cervical AI algorithm accurately and reproducibly selects Objects of Interest (OOI), at one site. An OOI is a cell or cluster of cells on a glass slide scanned by the Genius Diagnostics System with the Genius Cervical AI algorithm that most likely contains clinically relevant information for diagnostic purposes. The study compared OOIs selected by the Genius Cervical AI algorithm to the reference diagnosis by adjudication for the slide. The study evaluated the performance of the Genius Cervical AI algorithm to present images suitable for diagnosing abnormal cervical cases. The study also measured reproducibility of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm.

In the study, 37 ThinPrep Pap test slides were enrolled, selected from slides used in the clinical study for the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, covering the full range of abnormal diagnostic categories as defined in *The Bethesda System for Reporting Cervical Cytology*. These slides were made on the ThinPrep 2000 system, ThinPrep 5000 processor, and ThinPrep Genesis processor. The slides were imaged three times on three different Genius Digital Imagers.

Three CTs independently reviewed the nine runs of each case on the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, blinded as to the reference diagnosis for the case. In each review on the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, the CT recorded what the CT observed in every tile in the gallery for the case on the Review Station.

The accuracy and reproducibility of the algorithm were measured by comparison to the adjudicated reference diagnoses determined during the clinical study.

OOI Study Results

Table 23. OOI Summary by Reference Category (all CTs)

Reference Dx	# Slides	# of Evalua-tions	Proportion Abnormal OOIs	Median # Abnormal OOIs	Range of Number Abnormal OOIs (Min; Max)	Proportion Category+ OOIs	Median # Category+ OOIs	Range of Number Cat+ OOIs (Min; Max)
UNSAT	2	54	31%	0	0 ; 5			
NILM	5	135	16%	0	0 ; 4			
ASCUS	5	135	100%	6	2 ; 17	100%	6	2 ; 17
LSIL	5	135	100%	10	3 ; 23	96%	5	0 ; 23
ASC-H	5	135	100%	13	4 ; 22	100%	11	3 ; 19
AGC	5	135	100%	12	3 ; 24	100%	12	3 ; 24
HSIL	5	135	100%	18	12 ; 25	100%	9	2 ; 21
CANCER	5	135	100%	14	5 ; 20	92%	6	0 ; 14
All Abnormal	30	810	100%	13	3 ; 25	98%	8	0 ; 24

OOI Summary by Reference Category Table Key:

- # of evaluations = (total valid runs) * (# of CTs for the given diagnosis subset of slides)
- Proportion abnormal = the fraction of evaluations for which at least one abnormal OOI was observed
- Median # abnormal = the median number of abnormal OOIs in the evaluations
- Proportion category+ = the fraction of evaluations for which at least one OOI that is equal or greater than the reference diagnosis observed.

Reference Dx	"Category+" OOI labels
ASCUS	ASCUS, LSIL, ASC-H, AGC, HSIL, Cancer
LSIL	LSIL, ASC-H, HSIL, Cancer
ASC-H	ASC-H, HSIL, Cancer
HSIL	HSIL, Cancer
Cancer	Cancer

- Median # category+ = the median number of OOIs that are category+ in the evaluations

Note that, for the reference cancer slide reviews, while 100% had OOIs marked by the CTs as ASCUS+, 92% had OOIs marked as cancer.

Agreement Rates by Threshold

Table 24 below shows the positive agreement rate of the OOIs at various abnormal thresholds. For example, there were 20 LSIL+ slides (combined LSIL, ASC-H, HSIL, and CANCER), evaluated by 3 CTs over 9 imaging runs for a total of 540 evaluations. Of those, 530 had LSIL OOIs or higher for an agreement rate of 530/540 = 98%.

Table 24. Agreement rates by Reference Threshold

Threshold	# of Evaluations	Agreement Rate
ASCUS+	810	100%
LSIL+	540	98%
ASC-H+	405	99%
HSIL+	270	99%
CANCER	135	92%

OOI Reproducibility

Table 25 below shows the between-instrument and within-instrument agreement rates for the presence of Category+ OOIs.

Table 25. OOI Reproducibility

	# of Pairs	% Agreement
Between-instrument	999	96%
Within-instrument	999	99%

TECHNICAL PERFORMANCE CHARACTERISTICS

Multiple studies were conducted to evaluate the performance of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm.

Study Name	Study Description	Results
Slide Feeder	Evaluate the configuration of the slide feeder mechanism, user interaction with the slide feeder, including hardware, software, feedback mechanisms, and Failure Mode and Effects Analysis (FMEA).	Performance met the defined criteria
Light Source	Verify the intensity and spectral variation of the LED light source at various time intervals.	Performance met the defined criteria
Imaging Optics	Test magnification, relative irradiance, optical distortions, and chromatics aberrations.	Performance met the defined criteria
Mechanical Scanner Movement	Test positioning accuracy and repeatability for the X-Y and Z stages.	Performance met the defined criteria
Digital Imaging Sensor	Measure and evaluate linearity, spatial uniformity, dark current, noise, opto-electronic conversion function, and electron conversion factor of the sensor.	Performance met the defined criteria
Image Processing Software	Test image processing for the Genius Digital Diagnostics System with the Genius Cervical AI algorithm.	Performance met the defined criteria
Image Composition	Test specifications on the scanning method.	Performance met the defined criteria

Image File Format	Test compression method, compression ratio, file format, and file organization.	Performance met the defined criteria
Image Review Manipulation Software	Test continuous panning, continuous zooming, and digital bookmarks.	Performance met the defined criteria
Computer Environment	Test computer hardware, operating system, memory, hard disk, graphics card, graphics card driver, color management settings, color profile, display interface and network specification.	Performance met the defined criteria
Display	Test to verify the performance of the display including color-calibration tools and quality-control.	Performance met the defined criteria
Structural Similarity Index Measurement (SSIM)	Assessment of the SSIM that combines measurements of luminance, contrast, and structure at the pixel level across multiple runs, instruments, and calibration cycles.	Performance met the defined criteria
Color Reproducibility	Test to quantify the accuracy and precision of the color transformation from the slide to the display monitor.	Performance met the defined criteria
Spatial Resolution	Test to evaluate the spatial resolution, including the composite optical performance of all components in the image acquisition phase.	Performance met the defined criteria
Focus Test	Test to demonstrate the focus quality of the whole slide images produced by the Genius Digital Imager.	Performance met the defined criteria
Whole Slide Tissue Coverage	Test to demonstrate that the entire specimen on the clinical slide is detected by the device.	Performance met the defined criteria
Stitching Error	Test to assess the quality and accuracy of stitching image swaths in the Genius Digital Imager.	Performance met the defined criteria
Turnaround Time	Test to evaluate the average time required to execute zooming and panning operations, and to refresh the display in response to user input.	Performance met the defined criteria

User Interface	Human Factors Engineering or Usability Engineering testing regarding user interactions with the Genius Digital Imager and Genius Review Station.	Performance met the defined criteria

CYTOLOGIST SCREENING TIME STUDY

As part of the Genius Cervical AI Clinical Study, Hologic collected cytologist screening time data and calculated accuracy.

The study data includes the case review times for a total of 12 cytologists, screening a total of 1994 digital cytology cases in a clinical setting, although the review periods varied as cytologists were not fully dedicated to the clinical study. The study measured the diagnostic performance results of each CT compared to adjudicated (ADJ) diagnoses.

The results are summarized below in Table 26 which shows the median case review time for the 12 CTs compared to the sensitivity and specificity results at the ASCUS + threshold, as compared to adjudicated results.

Table 26. CT Review Times and ASCUS+ Sensitivity / Specificity

Site ID	Number of Cases	% ASCUS+	CT	Median Case Review Time (sec)	Range of Case Review Time (sec) (5^{th} ; 95^{th} percentile)	ASCUS+ Sensitivity	ASCUS+ Specificity
1	488	39.3 (192/488)	1	104	41 ; 644	90.7%	90.4%
			2	116	48 ; 479	81.3%	96.8%
			3	103	48 ; 416	91.2%	92.6%
2	494	36.8 (182/494)	1	94	49 ; 348	85.5%	95.5%
			2	148	82 ; 363	98.0%	72.6%
			3	105	66 ; 249	97.4%	92.0%
3	490	37.3 (183/490)	1	46	25 ; 120	92.3%	93.8%
			2	93	44 ; 263	96.2%	87.9%
			3	99	46 ; 284	88.0%	96.1%
4	488	31.1 (152/488)	1	136	72 ; 290	92.7%	91.6%
			2	73	42 ; 259	93.8%	91.9%
			3	57	31 ; 232	93.8%	91.6%

Figures 2 and 3 show scatterplots for the sensitivity and specificity results, respectively, as well as the resulting regression coefficients.

Figure 2. Sensitivity vs. Median Review Time

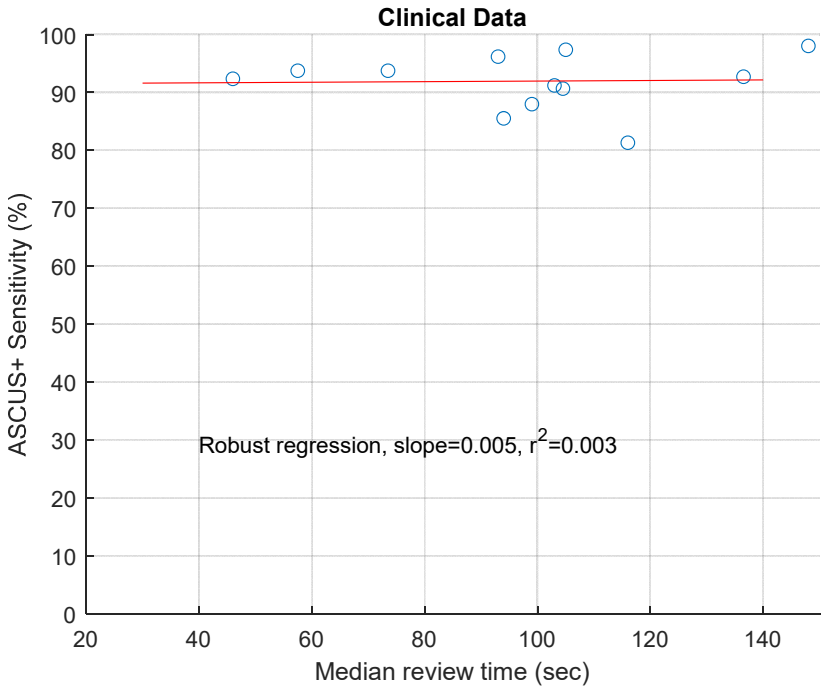
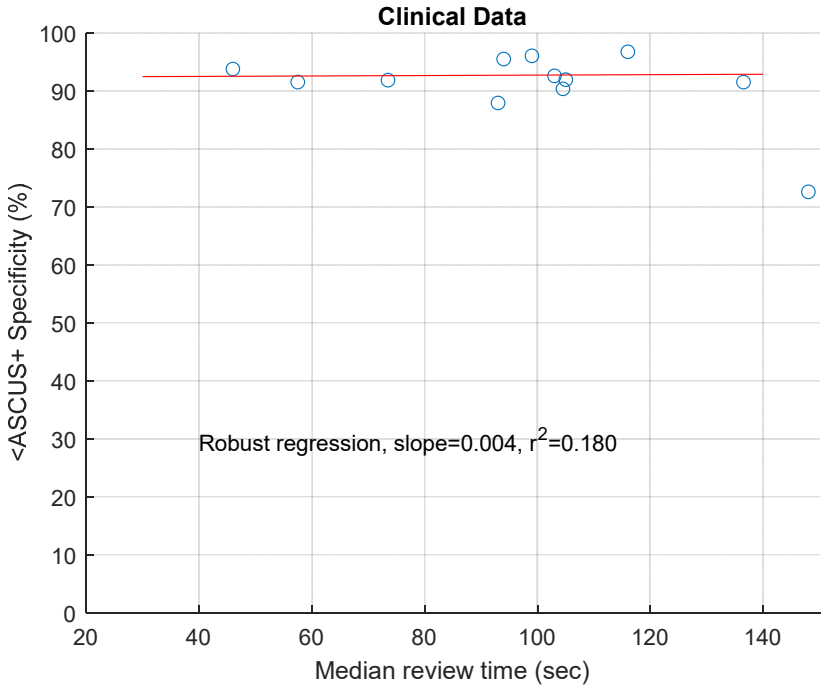


Figure 3. Specificity vs. Median Review Time



Regression analysis based on performance of 12 CTs showed that correlation coefficients for both the sensitivity and specificity analyses are low (0.003 and 0.180, respectively), indicating minimal dependence between performance and review time.

The data based on performance of 12 CTs in this study did not find that the CT case review time impacted the diagnostic performance at the ASCUS+ threshold.

CYTOLOGIST WORKLOAD DETERMINATION

Workload is defined by CLIA as a maximum of 100 slides in no less than an 8-hour workday. This refers to a full manual review (FMR) of 100 slides on a microscope. All cases diagnosed from the Genius Digital Diagnostics System with the Genius Cervical AI algorithm count as 0.5 or ½ CLIA slide equivalent. In the Genius Cervical AI clinical study, CTs accurately diagnosed cases using digital images presented by the system more efficiently than with a full manual review of a case.

Use the below method to calculate workload, which cannot exceed the CLIA maximum limit of 100 slides (or 100 CLIA slide equivalents) in no less than an 8-hour workday:

- All Genius Cervical AI (GCAI) case reviews count as 0.5 slide (½ CLIA slide equivalent)
- All full manual reviews of the glass slide count as 1 slide (1 CLIA slide equivalent)
- A full manual review of the glass slide in addition to a GCAI review counts as 1.5 slides (1.5 CLIA slide equivalents)

0.5*GCAI + 1.5*(GCAI + FMR)+ 1*FMR ≤ 100 CLIA slide equivalents

Example 1 - workload for reviewing ThinPrep Pap tests with the Genius Digital Diagnostic System with the Genius Cervical AI algorithm:

200 Genius Cervical AI Case Reviews = 100 CLIA slide equivalents
(200 * 0.5 = 100)

Total number of CLIA slide equivalents screened: 100

Example 2 - workload for reviewing ThinPrep Pap tests with the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, when some cases were reviewed both digitally and on glass:

180 Genius Cervical AI Case Reviews = 90 CLIA slide equivalents [180 * 0.5 = 90]

6 Genius Cervical AI Case Reviews + FMR = 9 CLIA slide equivalents [(6 * 0.5)+(6 * 1) = 9]

Total number of CLIA slide equivalents screened: 99 (90 + 9)

Notes:

- ALL laboratories should have a clear standard operating procedure for documentation of workload counting and for establishing workload limits.
- It is the responsibility of the Technical Supervisor to evaluate and set workload limits for individual cytologists based on laboratory clinical performance.
- According to CLIA '88, these workload limits should be reassessed every six months.

CYBERSECURITY

Medical device security is a shared responsibility between stakeholders, including healthcare facilities, patients, providers, and manufacturers of medical devices.

The Genius Digital Diagnostics System with the Genius Cervical AI algorithm is designed for security using a layered architecture approach to cybersecurity. Risks have been reduced as far as possible, and Hologic continually evaluates security patches, software updates including off-the-shelf (OTS), and the effectiveness of controls in the layered security architecture. Hologic applies critical security updates immediately after validation and applies non-critical security patches during regular scheduled maintenance periods.

Refer to and follow the Security instructions in the Genius Digital Imager Operator's Manual, the Genius Review Station Operator's Manual and the Genius IMS User's Manual.

CONCLUSIONS

The data from the studies conducted on the Genius Digital Diagnostics System with the Genius Cervical AI algorithm demonstrate that the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, is safe and effective for assisting in 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 cytological criteria as defined *by The Bethesda System for Reporting Cervical Cytology*[1].

- In the Genius Cervical AI Clinical Study, for all sites combined for ASCUS+, there was an observed improvement in sensitivity of the Genius Digital Diagnostics System with Genius Cervical AI review method over the Manual Review method. This increase of 1.6% was not statistically significant, with a 95% confidence interval of -0.1% to 3.2%.

- For LSIL+, ASC-H+ and HSIL+, the improvement in sensitivity of the Genius Digital Diagnostics System with Genius Cervical AI method over the Manual Review method was statistically significant and was as follows-

- For LSIL+: 4.4% with a confidence interval of 2.1% to 6.7%
- For ASC-H+: 8.2% with a confidence interval of 4.8% to 11.6%
- For HSIL+: 7.5% with a confidence interval of 4.0% to 11.4%. With regard to false negative (less than HSIL) rate for HSIL+, the 7.5% increase in HSIL + sensitivity means a decrease in Manual false negative rate of 26.0% to 18.5% false negative rate by the Genius Digital Diagnostics System with the Genius Cervical AI algorithm resulted in 28.8% reduction in the number false negative reviews (28.8% = (26.0%-18.5%)/26.0%).

- For Cancer, the observed sensitivities of the Genius Digital Diagnostics System with Genius Cervical AI method and Manual Review method were the same, with a confidence interval of -9.8% to 11.1%.

The data from the studies conducted on the Genius Digital Diagnostics System with the Genius Cervical AI algorithm showed that screening time is reduced without affecting diagnostic performance when compared to the manual review. The workload limit for the Genius Digital Diagnostic System with the Genius Cervical AI algorithm was established at 200 case reviews in no less than an 8-hour workday, if there were no cases reviewed with FMR and is not to exceed 100 CLIA equivalent slides in no less than an 8-hour workday.

Specimen adequacy as described in Bethesda 2014 can be determined using Genius Digital Diagnostics System with the Genius Cervical AI algorithm. Unsatisfactory rates between manual and Genius Cervical AI-assisted review were similar in the clinical study. Estimated cell count was found to be comparable between manual and Genius Cervical AI-assisted review as well. Additionally, endocervical component was similar using Genius Cervical AI-assisted review compared to manual review.

For the clinical sites and the study populations tested, the data from the clinical study demonstrates that the use of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm 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.

MATERIALS REQUIRED

MATERIALS PROVIDED

- Genius Digital Imager
    - Digital Imager (PRD-05815)
    - Digital Imager computer (CMP-01687)
    - Slide carriers (ASY-14299)
- Genius Review Station
    - Monitor (CMP-01669)
    - Review Station computer*
- Genius Image Management Server
    - Server*
    - Network switch*

*In some configurations of the system, the laboratory may supply the Review Station computer into which Hologic installs a Hologic-supplied graphics card. Refer to Genius Review Station Operator's Manual for the minimum specifications for the computer. In some configurations of the system, a laboratory may supply the server hardware and network switch. Refer to Genius IMS user's manual for the minimum specifications for the server and network switch.

- Complete instructions for operating the components in the system are also required and provided by Hologic:
    - Genius Digital Imager Operator's Manual: MAN-08469-001
    - Genius Review Station Operator's Manual: MAN-08467-001
    - Genius Image Management Server User's Manual: MAN-08468-001

MATERIALS REQUIRED BUT NOT PROVIDED

- Slide staining racks
- Monitor, keyboard, mouse for the Image Management Server
- Keyboard and mouse for each Review Station

STORAGE

- Refer to the Technical Specifications included in the Digital Imager operator's manual.
- Additional storage requirements may apply. Refer to the documentation provided with the server, monitors and computers.

BIBLIOGRAPHY

1. Nayar R, Wilbur DC. (eds), *The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes.* 3rd ed. Cham, Switzerland: Springer: 2015

TECHNICAL SERVICE AND PRODUCT INFORMATION

For technical service and assistance related to use of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, contact Hologic:

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