

Genius™

**Digital Diagnostics System
with Genius Cervical AI**

Instructions for Use

Genius™ Digital Diagnostics System with Genius Cervical AI



Instructions for Use



INTENDED USE/INTENDED PURPOSE

The Genius™ Digital Diagnostics System, when used with the Genius Cervical AI algorithm, is a qualitative, *in vitro* diagnostic device indicated 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 categories, including adenocarcinoma, as defined by *The Bethesda System for Reporting Cervical Cytology*¹.

The Genius Digital Diagnostics System includes the automated Genius Digital Imager, the Genius Image Management Server (IMS), and the Genius Review Station. If using the Genius Cervical AI algorithm, it must be used alongside the other components to the Genius Digital Diagnostics System. The system is for the creation and viewing of digital images of scanned ThinPrep glass slides that would otherwise be appropriate for manual visualization by conventional light microscopy. It is the responsibility of a qualified pathologist to employ appropriate procedures and safeguards to assure the validity of the interpretation of images obtained using this system.

Patient Population

The Genius Digital Diagnostics System uses gynecological specimens from women, collected during routine screening (including initial screening and referral population) and gynecological specimens collected from women with a previous cervical abnormality.

For professional use.

SUMMARY AND EXPLANATION OF THE SYSTEM

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 the slide. The objects classified as most clinically relevant are presented in a gallery 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. 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 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 slide review. The reviewer always has the option to move and zoom through a view of the whole slide image, which provides complete freedom to move any portion of the cell spot into the field of view for examination.

The summary of safety and performance for this device may be found in the EUDAMED database at ec.europa.eu/tools/eudamed.

If any serious incident occurs related to this device or any components used with this device, report it to Hologic Technical Support and the competent authority local to the user and/or patient.

LIMITATIONS

- Only personnel who have been appropriately trained should operate the Genius Digital Imager or Review Station.
- The Genius Cervical AI algorithm is only indicated for use with the ThinPrep Pap test.
- The laboratory Technical Supervisor should establish individual workload limits for personnel using the Genius Digital Diagnostics System.
- ThinPrep microscope slides appropriate for the sample type must be used. For gynecological cases, ThinPrep Imaging System microscope slides with fiducial marks must be used.
- Slides must be stained using the ThinPrep Stain according to the applicable ThinPrep Imaging System slide staining protocol.
- Slides should be clean and free of debris before being placed on the system.
- The slide coverslip should be dry and located correctly.
- Slides that are broken or poorly coverslipped should not be used.
- Slides used with the 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 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. They are required for proper performance of the system and cannot be substituted.

WARNINGS

- For *In Vitro* Diagnostic Use

- The 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 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.
- 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.

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.

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

| Diagnostic Threshold | Sensitivity % | | | Specificity % | | |
|----------------------|-------------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|
| | 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | | | | | | | | Total |
|---------------|---------------|--------------|-------------|--------------|------------|-------------|--------------|-------------|---------------|--------------|
| | | UNSAT | NILM | ASCUS | AGC | LSIL | ASC-H | HSIL | Cancer | |
| 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 | |
| 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 | | | | | | | | Total |
|---------------|---------------|--------------|-------------|--------------|------------|-------------|--------------|-------------|---------------|--------------|
| | | UNSAT | NILM | ASCUS | AGC | LSIL | ASC-H | HSIL | Cancer | |
| 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 | |
| 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 | |
| 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 TIS 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

| Diagnostic Threshold | Sensitivity % | | | Specificity % | | |
|----------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| | 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, -0.5) |
| 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: | | | | | | |
| <i>Trichomonas vaginalis</i> | 71 | 1.2 | 70 | 1.2 | 103 | 1.8 |
| Fungal organisms consistent with <i>Candida</i> 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 <i>Actinomyces</i> 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 |

| | Manual Review | | TIS Review | | Genius Review | |
|---|---------------|-------------|-------------|-------------|---------------|-------------|
| 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.

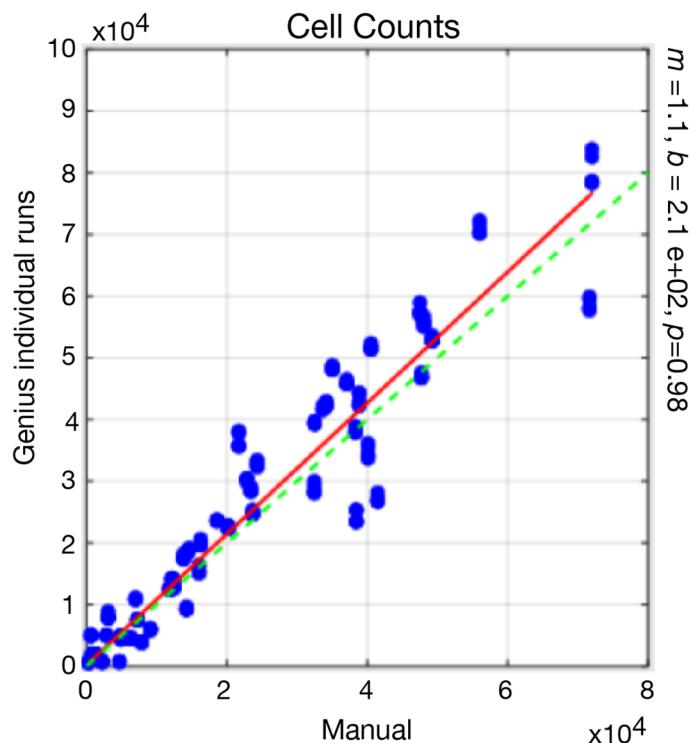
ThinPrep Pap test patient sample slides were prepared on a ThinPrep 5000 processor, stained and coverslipped. The same slides were imaged on three Genius Digital Imagers three separate times. To obtain the manual cell count for the slides in the study, a CT viewed the whole slide image presented on the 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 OOs 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 Evaluations | 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% |

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

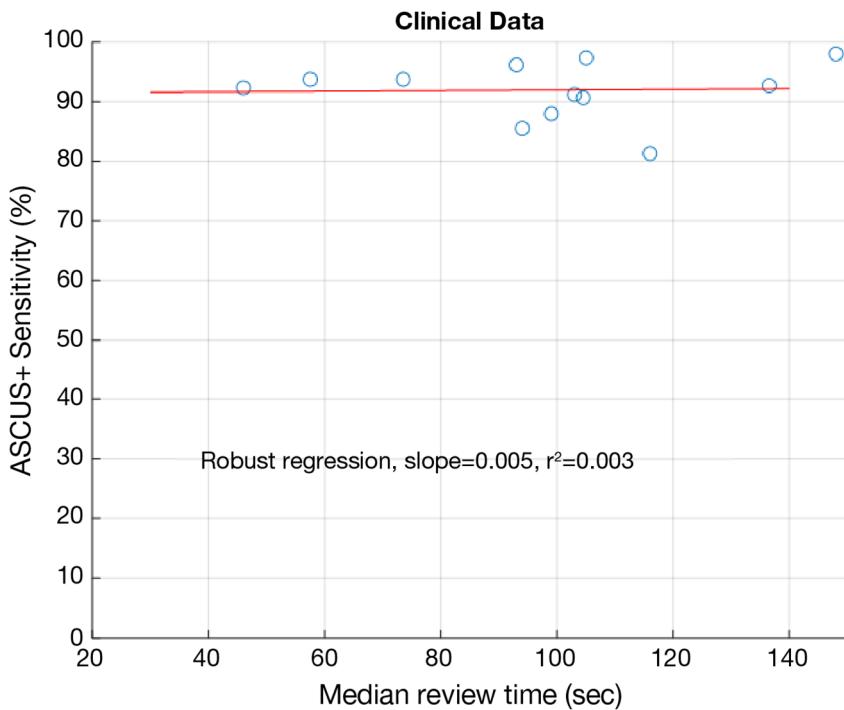
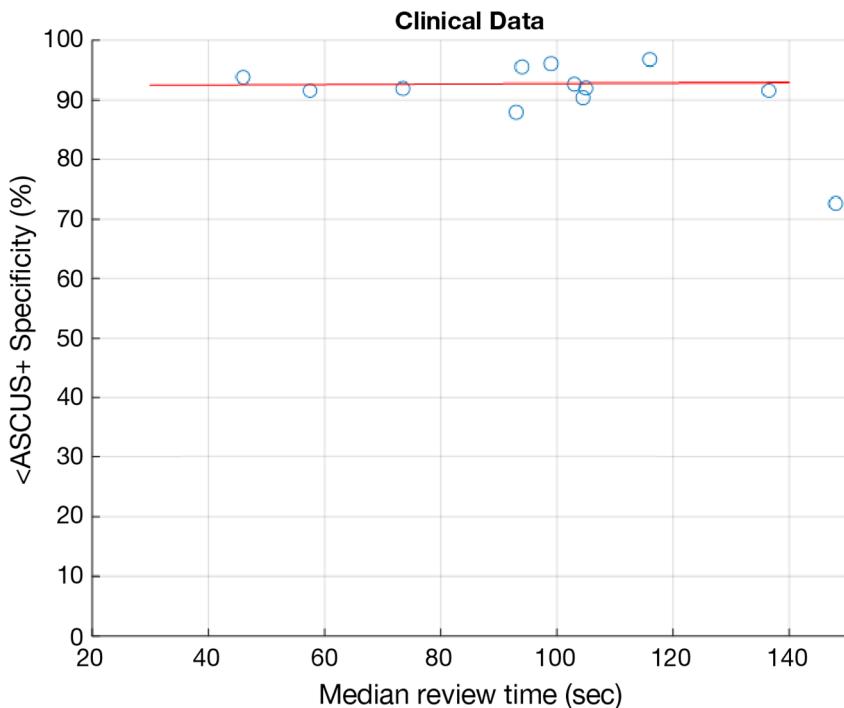


Figure 3. Specificity vs. Median Review Time



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 SCREENING RATES: WORKLOAD GUIDANCE

In the U.S., workload is defined by CLIA as a maximum of 100 cases in no less than an 8-hour workday. This refers to a full manual review of 100 glass slides using a microscope. 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.

The five fastest screening rates from the clinical study are shown in Table 27.

Table 27. Fastest Review Times from Genius Cervical AI Clinical Study

| Site ID | CT | Median Case Review Time (sec) |
|-----------------|-----------|--------------------------------------|
| 3 | 1 | 46 |
| 4 | 3 | 57 |
| 4 | 2 | 73 |
| 3 | 2 | 93 |
| 2 | 1 | 94 |
| Combined | | 70 |

The overall median screening time per slide for these five reviewers is 70 seconds.

The CLIA maximum of 100 manual reviews per 8-hour day is equivalent to 288 seconds per review. (8 hours x 60 minutes x 60 seconds/100 reviews = 288 seconds/review). The fastest CTs in the Genius Cervical AI clinical study reviewed cases in $70/288 = 0.24$ of the time limit set for manual review. This 0.24 can be rounded up slightly to 0.25, or $\frac{1}{4}$. The clinical study demonstrated that a Genius Cervical AI assisted review can be performed accurately at this rate.

Therefore, the workload guidance is to count Genius Cervical AI case reviews as 0.25 CLIA “slide equivalents”. Any slide reviewed using the glass slide and a microscope continues to count as one full CLIA slide equivalent toward the maximum workload of 100.

1 Genius Cervical AI Case = 0.25 CLIA Slide Equivalent

An example of the workload for reviewing ThinPrep Pap tests with the Genius Digital Diagnostic System:

$$200 \text{ Genius Cervical AI Case Reviews} = 50 \text{ slides}$$
$$(200 \times 0.25 = 50)$$

Total number of slides screened: 50

The maximum possible Genius Cervical AI case reviews in an 8-hour day, if no glass slide reviews are performed, is 400 cases/day.

Note: ALL laboratories should have a clear standard operating procedure for documentation of their method of workload counting and for establishing workload limits.

It is the responsibility of the Technical Supervisor to evaluate and set workload limits for individual cytologist 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 demonstrate that the Genius Digital Diagnostics System, when used with the Genius Cervical AI algorithm, is 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, including adenocarcinoma, 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 showed that screening time is reduced without adversely affecting diagnostic accuracy, contributing to a workload limit recommendation of 400 cases 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
 - Digital Imager computer
 - Slide carriers
- Genius Review Station
 - Monitor
 - Review Station computer*
- Genius Image Management Server
 - Server*
 - Network switch*
 - Monitor, keyboard, mouse for the Image Management Server (for customers using a Hologic-supplied Image Management Server)

*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 the 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 the Genius Image Management Server Dashboard User's Manual for the minimum specifications for the server and network switch.

MATERIALS REQUIRED BUT NOT PROVIDED

- Slide staining racks
- Keyboard and mouse for each Review Station (for customers not using a Hologic-supplied Review Station computer)

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, contact Hologic:

TScytology@hologic.com

And via the toll-free number below:

United Kingdom 0800 0323318

REVISION HISTORY

| Revision | Date | Description |
|-----------------------|--------|---|
| AW-32316-002 Rev. 001 | 8-2025 | Initial release with US clinical study data. Change to be exclusive to ThinPrep Pap tests using the Genius Cervical AI algorithm. |



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AW-32316-002 Rev. 001

GeniusTM Digital Diagnostics System

Instructions for Use

With Genius Cervical AI

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Patent Information
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