HOLOGIC®

Genius™ Digital Diagnostics System with Genius™ Cervical AI

Instructions for Use

genius™ DIGITAL DIAGNOSTICS

Genius™ Digital Diagnostics System

Instructions for Use

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IVD

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 can also be used with ThinPrep® non-gynecological microscope slides and ThinPrep® UroCyte® microscope slides as an aid to the pathologist to review and interpret digital images.

The Genius Digital Diagnostics System includes the automated Genius™ Digital Imager, the Genius™ Image Management Server (IMS), and the Genius™ Review Station. 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. Non-gynecological specimens for use on the Genius™ Digital Diagnostics System may be acquired from any patient population.

For professional use.

SUMMARY AND EXPLANATION OF THE SYSTEM

Slides that have been prepared for screening 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 cytotechnologist (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.
- 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.
- Glass. The Digital Imager uses 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.
- 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

OBJECTS OF INTEREST (OOI) STUDY

A laboratory study was conducted to demonstrate that the Genius Cervical AI algorithm accurately selects OOIs. An OOI is a cell or cluster of cells on a slide preparation that most likely contains clinically relevant information for diagnostic purposes. The study compared OOIs selected by the GeniusCervical AI algorithm to the same samples imaged and reviewed by CTs using the ThinPrep Imaging System (TIS-assisted review). The study evaluated the performance of the Genius Cervical AI algorithm to present images suitable for diagnosing abnormal cervical cases, for detecting the presence of common infectious organisms in a case, and for detecting the presence of endocervical component (ECC) in a normal case. The study also measured reproducibility of the Genius Digital Diagnostics System.

In the study, 260 ThinPrep slides were enrolled, made from individual residual ThinPrep Pap test specimens, covering the full range of abnormal diagnostic categories as defined in *The Bethesda System for Reporting Cervical Cytology*. The slides were imaged once on the ThinPrep Imaging System, and the same slides were imaged three times on three different Genius Digital Imagers.

Slides were reviewed by CTs using the ThinPrep Imaging System (TIS-assisted review), and, after a washout period, the same CT reviewed the nine runs of that same case on the Genius Digital Diagnostics System. In each review on the Genius Digital Diagnostics System, the CT recorded what the CT observed in every tile in the gallery for the case on the Review Station. The CT reviews were conducted per standard laboratory procedure, recording the diagnostic result, the presences or absence of endocervical component (ECC) and the presence of any infectious organisms, such as trichomonas, candida, coccobacillus, for the TIS-assisted review.

The accuracy and reproducibility of the algorithm were measured by comparison to the TIS-assisted diagnoses. The average and standard deviation across runs leading to the same diagnosis or higher was the metric used.

OOI Study: Specimen Enrollment

Table 1 shows the nominal enrollment diagnoses (base on donor lab results) for the slides in the study. In this study there was no independent truth standard, so the study did not measure absolute accuracy; the study compared TIS-assisted review with the OOIs on the Genius Digital Diagnostics System.

Table 1. Slides Enrolled in the OOI Study

Category	# of slides
NILM	99
ASCUS	6
LSIL	60
ASC-H	8
AGUS	10
HSIL	60
CANCER	16

Study Results: Cervical Cytology Diagnostic Categories

The highest OOI category for any case across the nine runs of the case on the Genius Digital Diagnostics System was compared to the diagnostic category for the same slide in the TIS-assisted review. Table 2 shows the relationship between the Genius Digital Diagnostic System results and the TIS-assisted results.

Table 2. TIS-assisted Results vs. Genius Digital Diagnostic System OOIs

		TIS								
		UNSAT	NILM	ASCUS	LSIL	ASC-H	AGUS	HSIL	CANCER	Total
OOI	NILM	2	83	4	0	0	2	0	0	91
	ASCUS	0	10	6	3	1	0	0	0	20
	LSIL	0	0	5	27	0	0	1	0	33
	ASC-H	0	1	5	11	2	0	7	0	26
	AGUS	0	2	0	0	0	5	1	1	9
	HSIL	0	0	2	2	2	1	49	5	61
	CANCER	0	0	0	0	1	1	6	9	17
		2	96	22	43	6	9	64	15	

The study showed an average of 6.8 OOIs in tiles per case on the Genius Digital Diagnostic System matched the TIS-assisted diagnosis. The standard deviation was 1.3. These results demonstrate that the Genius Digital Diagnostic System accurately selects OOIs of most interest for diagnosis. And, the results are repeatable across multiple instruments and multiple runs.

Study Results: ECC Detection on Normal Cases

Endocervical component (ECC) presence is noted during slide review to confirm adequate cellular sampling. ECC consists of either endocervical or squamous metaplastic cells. Because the Genius Digital Diagnostics cervical cancer algorithm prioritizes the presentation of abnormal cells when they are present, ECC detection was assessed in this study on the subset of slides deemed normal (NILM) by TIS-assisted review.

Table 3 shows the relationship of ECC presence on TIS-assisted versus OOI gallery review. In each case, the "+" or "-" corresponds to ECC present or absent, respectively. The count of slides in each category is shown in the table.

Table 3. ECC Detection on Normal Cases:
Agreement between TIS-assisted Review and OOI Study Results

ECC		TIS	
		-	+
OOI	-	4	2
	+	31	59
Agreement Rates	**PPA**	97%	(89%, 99%)
	NPA	11%	(5%, 26%)
Detection Rates	**TIS**	64%	(54%, 72%)
	OOI	94%	(89%, 99%)
	(Diff)	-30%	(-40%, -20%)

The positive and negative percent agreement (PPA and NPA) were calculated with reference to the TIS-assisted result. In addition, the detection rates and difference have also been provided. Confidence intervals for the proportions are calculated using the Newcombe score method and account for correlation between the matched pairs.

The ECC detection rate for OOI review was 94%, compared to 64% for TIS-assisted review. There were 31 NILM slides for which ECC was marked as present in the OOI gallery but not noted in TIS-assisted review. Upon further inspection of those cases, the ECC consisted of rare squamous metaplastic cells, which were not noted during the TIS-assisted review.

Infectious Organism Detection

The presence of infectious organisms is noted as part of slide review to help in the clinical assessment of the case. In this study, slides were enrolled that included three classes of organism: Trichomonas, Candida, and Coccobacilli. The tables below compare the detection of each organism on TIS-assisted review and review of OOIs in the gallery of a Genius Digital Diagnostic Review Station. For each table, the positive and negative agreement rates with reference to the TIS-assisted result are provided. The overall detection rate for each organism and the difference in detection rates (TIS – OOI) are also included.

Table 4. Trichomonas Detection:
Agreement between TIS-assisted Review and OOI Study Results

TRICH		**TIS**	
		-	**+**
OOI	**-**	246	1
	+	2	8
Agreement Rates	**PPA**	89%	(57%, 98%)
	NPA	99%	(97%, 100%)
Detection Rates	**TIS**	3.5%	(1.9%, 6.5%)
	OOI	3.9%	(2.1%, 7.0%)
	(Diff)	-0.4%	(-2.5%, 1.6%)

The detection rate for Trichomonas for the Genius Digital Diagnostics System was 3.9%, compared to 3.5% for TIS-assisted review.

Table 5. Candida Detection:
Agreement between TIS-assisted Review and OOI Study Results

CAND		TIS	
		-	+
OOI	-	232	5
	+	3	17
Agreement Rates	**PPA**	77%	(57%, 90%)
	NPA	99%	(96%, 100%)
Detection Rates	**TIS**	8.6%	(5.7%, 12.6%)
	OOI	7.8%	(5.1%, 11.7%)
	(Diff)	0.8%	(-1.8%, 3.4%)

The detection rate for Candida for the Genius Digital Diagnostics System was 7.8%, compared to 8.6% for TIS-assisted review.

Table 6. Coccobacilli Detection:
Agreement between TIS-assisted Review and OOI Study Results

COCCO		TIS	
		-	+
OOI	-	203	5
	+	21	28

Agreement Rates	**PPA**	85%	(69%, 93%)
	NPA	91%	(86%, 94%)
Detection Rates	**TIS**	12.8%	(9.3%, 17.5%)
	OOI	19.1%	(14.7%, 24.3%)
	(Diff)	-6.2%	(-10.3%, -2.3%)

The detection rate for Coccobacilli for the Genius Digital Diagnostics System was 19.1%, compared to 12.8% for TIS-assisted review. Further inspection of these cases indicated that bacteria were indeed present in moderate quantities on some cells. In this study, the CTs were required to mark the type of each OOI presented, so Coccobacilli would be noted if any normal cells with bacteria overlaid were presented in the gallery. During a TIS-assisted review, and in clinical practice, bacterial infection is typically noted only when it is considered of possible clinical significance (so-called “clue” cells or a large number of infected cells). The difference in detection rates in the study is due to this difference in counting methodology and would not necessarily be reflected in clinical practice.

Overall, the presentation of infectious organisms by the algorithm is equivalent or higher than with TIS-assisted review.

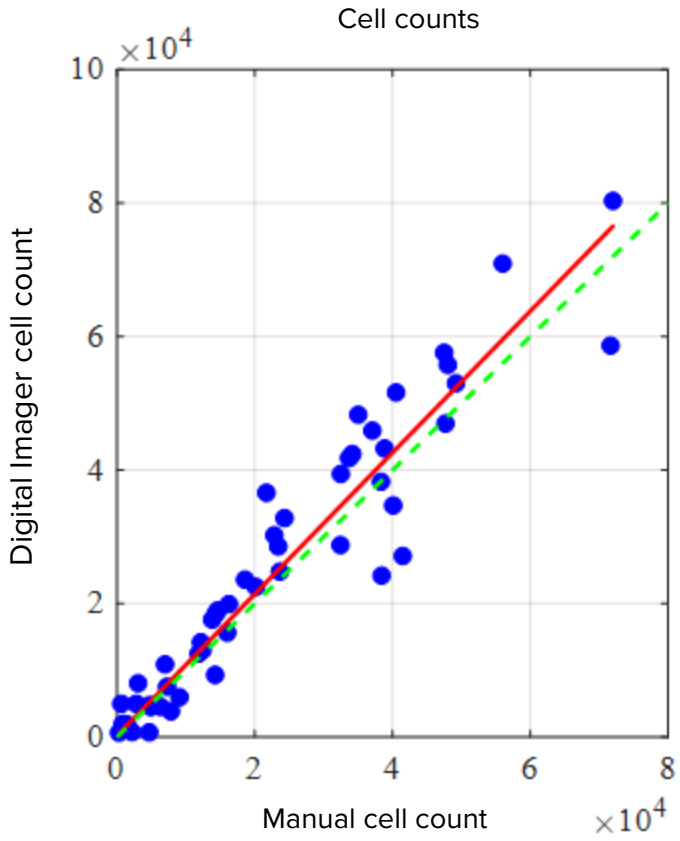
CELL COUNT STUDY

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 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 critical threshold of 5000 cells, were enrolled in the study. The slides covered a range of cellularity typical of a clinical environment. Figure 1 compares the cell counts between the Genius Cervical AI algorithm and a manual cell count method for each specimen.

Figure 1: Deming Regression
Cell Count: Digital Imager vs. Manual



The study calculated the average cell count generated by the Genius Cervical AI algorithm for each case across the three runs on each of the three Digital Imagers in the study. The intra-instrument %CV in the study was 0.6%. The inter-instrument %CV in the study was 2.7%.

The study also estimated the systematic bias of the cell count generated by the Genius Cervical AI algorithm as compared to the manual count, at a count of 5000 cells, the clinical threshold for diagnosis. In the Bethesda System[1], specimens with fewer than 5000 cells are considered unsatisfactory for screening. The count bias in the study was 528, with a 95% CI of -323 to 1379.

The results of the study demonstrate that the cell counts generated by the Genius Cervical AI algorithm are comparable to a manual cell count performed by a cytotechnologist.

GENIUS™ DIGITAL DIAGNOSTICS SYSTEM COMPARED TO MANUAL REVIEW (GENIUS CERVICAL AI CLINICAL STUDY)

A multi-center study was performed at four (4) sites within the United States. The objective of the study was to show that routine screening of ThinPrep Pap Test slides prepared on the ThinPrep® 2000 System, the ThinPrep® 5000 processor, or the ThinPrep® Genesis™ processor using the Genius Digital Diagnostics System with Genius Cervical AI is non-inferior at the ASCUS+ threshold for all categories used for cytologic diagnosis (specimen adequacy and descriptive diagnosis) as defined by the Bethesda System criteria.

The study approach allowed for a comparison of the cytologic interpretation (descriptive diagnosis and specimen adequacy) from a single ThinPrep-prepared slide (of known diagnosis), screened first using manual review and then screened with the assistance of the Genius Digital Diagnostics System. The adjudicated diagnosis for each case was used as a reference standard for truth to evaluate the results of the study.

Slides utilized in this study were processed on the ThinPrep® processors. All cases were reviewed independently. Each case in the study was screened using standard laboratory cervical cytology practices (manual review), the ThinPrep Imaging System (“TIS” review), pathologist adjudication consensus (“ADJ” review), and finally with the Genius Digital Diagnostics System. A minimum 14-day washout period occurred between each review phase. The slides were randomized prior to case review in each review phase. Cytological diagnoses and specimen adequacy were determined in accordance with the Bethesda System criteria.

Study slides prepared from a previous study were used, and additional slides were prepared specifically for this study.

Laboratory and Patient Characteristics

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

A total of 2020 cases, with 1 slide from each patient (505 cases at each site), were evaluated in this study. Each case was reviewed independently three (3) times at each site, by three (3) separate pairs of cytotechnologists and pathologists using normal laboratory and clinical procedures. Of the 2020 enrolled cases, 1995 (98.8%) cases met the requirements for inclusion in the evaluable population. Twenty-five (25) slides that were damaged, unreadable, excluded during a previous study, or processed outside the 6-week window from the collection date were excluded from all analyses. Forty-one (41) cases with UNSAT results from manual review, digital review, or adjudication were excluded from the performance analyses only. Table 7 describes the patient populations at each of the study sites.

Table 7. Clinical Study Characteristics

Site Number	Age (yrs) Median	# Hysterectomy (% of enrolled)	# Postmenopausal (% of enrolled)
1	33.0	20 (4.0)	40 (8.0)
2	36.5	6 (1.2)	25 (5.0)
3	35.0	22 (4.4)	44 (8.9)
4	37.0	7 (1.4)	42 (8.5)
Overall	35.0	55 (2.8)	151 (7.6)

Main Eligibility Criteria

Inclusion Criteria

Study slides were produced, reviewed, and adjudicated during the execution of the current study and two previous studies. The ThinPrep Pap Test slides from four sites included the following enrollment diagnoses:

- NILM: 266 cases
- ASC-US: 56 cases
- LSIL: 56 cases
- ASC-H: 56 cases
- AGUS: 5 cases
- HSIL: 56 cases
- Cancers: 5 cases

- UNSAT: 5 cases

Exclusion Criteria

Slides that were broken or rendered unreadable for the purposes of this study were excluded from the study.

Criteria for Evaluation

The primary objective of this study was to estimate the sensitivity and specificity when diagnosing cases imaged and reviewed on the Genius Digital Diagnostics System compared with manual review at the ASCUS+ threshold. The reference standard for the cases in this study was pathologist adjudication consensus diagnosis.

Descriptive Diagnosis Sensitivity and Specificity Estimates

Abbreviations for Diagnostic Thresholds:

Category Partitions

Threshold	Negative	Positive
ASCUS+	NILM	ASCUS, AGUS, LSIL, ASC-H, HSIL, Cancer
LSIL+	NILM, ASCUS, AGUS	LSIL, ASC-H, HSIL, Cancer
ASC-H+	NILM, ASCUS, AGUS, LSIL	ASC-H, HSIL, Cancer
HSIL+	NILM, ASCUS, AGUS, LSIL, ASC-H	HSIL, Cancer

The study results are presented in Table 8. In all abnormal categories, the sensitivity and specificity for the Genius Digital Diagnostics System were non-inferior to that of manual review. Superiority for the Genius Digital Diagnostics System as compared to manual review was also evident at the LSIL+, ASC-H+, and HSIL+ diagnostic thresholds for sensitivity.

Table 8. Adjudicated Review vs. Manual Review and Genius Digital Diagnostics System Review, Descriptive Diagnosis Summary (All Cases)

	Sensitivity %			Specificity %		
Diagnostic Threshold	**Manual (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**	**Manual (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**
ASCUS+	76.8 (75.8, 77.6%)	76.3 (75.1, 77.6)	0.50 (-0.87, 1.87)	93.0 (92.2, 93.7)	90.1 (89.1, 91.2)	2.83 (1.76, 3.89)
LSIL+	78.8 (77.8, 79.9)	80.9 (79.2, 82.6)	-2.04 (-3.39, -0.69)	95.3 (95.1, 95.5)	91.9 (91.2, 92.6)	3.38 (2.74, 4.03)
ASC-H+	79.1 (77.5, 80.6)	83.7 (82.6, 84.8)	-4.58 (-6.51, -2.65)	96.0 (95.7, 96.3)	92.3 (91.7, 92.8)	3.73 (3.06, 4.41)
HSIL+	72.7 (70.8, 74.5)	78.4 (76.2, 80.6)	-5.69 (-8.51, -2.88)	97.4 (97.1, 97.7)	94.7 (94.0, 95.4)	2.69 (2.04, 3.35)

There was a decrease in false negative HSIL+ diagnoses for the Genius Digital Diagnostic System as compared to manual review. The agreement of HSIL+ diagnoses for manual review with adjudicated review is 72.7%, or a false negative rate of 27.3%. The agreement of HSIL+ cases on the Genius Digital Diagnostics System with adjudicated review is 78.4%, or a false negative rate of 21.6%. This represents a 20.9% reduction in false negative diagnoses for HSIL+.

The study also compared the performance of the Genius Digital Diagnostic System with ThinPrep slides reviewed on the ThinPrep Imaging System (TIS). The results for the Genius Digital Diagnostics System versus TIS review are presented in Table 9.

Table 9. Adjudicated Review vs. TIS Review and Genius Digital Diagnostics System Review (Genius), Descriptive Diagnosis Summary (All Cases)

	Sensitivity %			Specificity %		
Diagnostic Threshold	**TIS (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**	**TIS (95% CI)**	**Genius (95% CI)**	**Difference (95% CI)**
ASCUS+	76.1 (75.0, 77.2%)	76.4 (75.1, 77.6)	-0.24 (-1.18, 0.69)	91.9 (91.2, 92.5)	90.1 (89.1, 91.2)	1.77 (0.83, 2.71)
LSIL+	80.9 (79.7, 82.0)	80.9 (79.2, 82.6)	-0.05 (-1.67, 1.57)	94.2 (93.7, 94.6)	91.9 (91.2, 92.6)	2.27 (1.74, 2.80)
ASC-H+	82.2 (80.8, 83.6)	83.8 (82.8, 84.9)	-1.63 (-3.46, 0.20)	95.0 (94.7, 95.4)	92.3 (91.7, 92.8)	2.75 (2.18, 3.32)
HSIL+	76.9 (74.9, 78.9)	78.5 (76.3, 80.7)	-1.62 (-4.57, 1.33)	96.9 (96.6, 97.1)	94.7 (94.0, 95.4)	2.17 (1.56, 2.79)

Table 10 through Table 17 show the performance of Genius Digital Diagnostics System review and manual review for the following major descriptive diagnosis classifications of the Bethesda System: NILM, ASCUS, LSIL, ASC-H, AGUS, HSIL, Cancer, and UNSAT, as determined by the adjudication panel.

Table 10. "True Negative" (NILM) Contingency Table (for all Sites Combined)
Overall Adjudicated NILM
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	8	16	0	0	0	0	0	0
	NILM	7	2881	59	10	3	13	0	3
	ASCUS	0	94	24	1	1	1	2	0
	AGUS	0	18	2	0	0	0	1	0
	LSIL	0	16	17	0	15	1	0	0
	ASC-H	1	34	16	0	2	11	5	0
	HSIL	1	16	13	0	3	10	10	0
	Cancer	0	3	1	3	0	1	0	4

Table 11. "True ASCUS" Contingency Table (for all Sites Combined)
Overall Adjudicated ASCUS
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	2	2	0	0	0	0	0	0
	NILM	1	346	62	1	8	9	2	0
	ASCUS	0	52	52	0	15	4	1	0
	AGUS	1	2	0	0	0	0	0	0
	LSIL	0	14	32	0	22	1	0	0
	ASC-H	0	8	12	1	6	7	0	0
	HSIL	0	6	8	0	7	3	7	0
	Cancer	0	0	1	0	0	0	1	0

Table 12. "True AGUS" Contingency Table (for all Sites Combined)
Overall Adjudicated AGUS
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	1	2	0	0	0	0	0	0
	NILM	0	16	2	0	0	2	1	0
	ASCUS	0	1	1	0	0	0	1	0
	AGUS	0	0	0	0	0	1	0	3
	LSIL	0	0	2	0	0	0	0	0
	ASC-H	0	0	0	0	0	0	0	0
	HSIL	0	2	0	0	1	0	1	0
	Cancer	0	0	0	2	0	0	0	0

Table 13. "True LSIL" Contingency Table (for all Sites Combined)
Overall Adjudicated LSIL
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	0	0	0	0	0	0	0	0
	NILM	0	31	31	0	15	0	1	0
	ASCUS	0	21	56	0	58	4	0	0
	AGUS	0	0	0	0	0	0	0	0
	LSIL	0	23	56	0	360	2	7	0
	ASC-H	0	2	10	0	21	10	4	0
	HSIL	0	1	12	0	49	11	45	1
	Cancer	0	0	0	0	1	0	1	1

Table 14. "True ASC-H" Contingency Table (for all Sites Combined)
Overall Adjudicated ASC-H
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	0	0	1	0	0	0	0	0
	NILM	1	27	4	0	0	5	4	0
	ASCUS	0	1	1	0	1	3	2	0
	AGUS	0	1	1	0	0	1	0	0
	LSIL	0	1	1	0	3	0	0	0
	ASC-H	0	5	9	1	3	10	3	0
	HSIL	1	4	7	2	1	4	14	0
	Cancer	0	0	0	1	1	0	1	4

Table 15. "True HSIL" Contingency Table (for all Sites Combined)
Overall Adjudicated HSIL
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	0	0	1	0	0	0	0	0
	NILM	0	8	1	2	0	7	14	1
	ASCUS	0	2	3	1	1	5	14	0
	AGUS	0	1	2	1	0	3	4	0
	LSIL	0	0	0	0	18	1	6	0
	ASC-H	0	2	8	0	10	17	37	4
	HSIL	0	11	19	7	25	66	396	25
	Cancer	0	1	3	0	0	1	17	8

Table 16. "True Cancer" Contingency Table (for all Sites Combined)
Overall Adjudicated Cancer
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	0	0	0	0	0	0	0	0
	NILM	0	0	0	0	0	0	0	3
	ASCUS	0	0	0	0	0	0	0	0
	AGUS	0	1	0	1	0	0	1	4
	LSIL	0	0	0	0	0	0	0	0
	ASC-H	0	0	1	0	1	1	0	0
	HSIL	0	0	0	0	0	2	16	1
	Cancer	0	0	0	1	0	1	5	69

Table 17. "True UNSAT" Contingency Table (for all Sites Combined)
Overall Adjudicated UNSAT
Genius Digital Diagnostics System vs. Manual Review

		Manual							
		UNSAT	**NILM**	**ASCUS**	**AGUS**	**LSIL**	**ASC-H**	**HSIL**	**Cancer**
Genius	**UNSAT**	42	14	0	0	0	0	0	0
	NILM	7	25	1	0	0	0	0	0
	ASCUS	2	1	0	0	0	0	0	0
	AGUS	0	0	0	0	0	0	2	0
	LSIL	0	0	0	0	0	0	0	0
	ASC-H	1	0	1	0	0	1	0	0
	HSIL	0	0	0	0	0	0	1	0
	Cancer	0	1	0	0	0	0	0	0

Table 18 shows the performance of Genius Digital Diagnostics System review and manual review compared to adjudicated diagnostic threshold made by the adjudication panel for the following major descriptive diagnostic thresholds: ASCUS+, LSIL+, ASC-H+, and HSIL+.

Table 18. Contingency Table (for all Sites Combined)
Overall Adjudicated vs. Manual Review and Genius Digital Diagnostics System

Overall Adjudication		**Manual Review**		**Genius Review**	
Diagnostic Threshold		**Positive**	**Negative**	**Positive**	**Negative**
ASCUS+	Positive	1956	232	1943	325
	Negative	590	3062	603	2969
LSIL+	Positive	1435	189	1472	325
	Negative	385	3831	348	3695
ASC-H+	Positive	780	193	825	374
	Negative	206	4661	161	4480
HSIL+	Positive	625	130	674	264
	Negative	235	4850	186	4716

Table 19 shows the descriptive diagnosis marginal frequencies for benign cellular changes and other non-neoplastic findings for all sites combined. Each slide was read by a CT/pathologist pair three times. Each slide was read first by a cytotechnologist and then by a pathologist.

Table 19. Unadjudicated Marginal Frequencies –
Summary of Descriptive Diagnosis for Benign Cellular Changes (for all Sites Combined)

	Manual Review		**Genius Review**	
Number of Slides	5985		5985	
Descriptive Diagnosis	**N**	**%**	**N**	**%**
Benign Cellular Changes	**721**	**12.0%**	**1035**	**17.3%**
Organisms:				
Trichomonas vaginalis	71	1.2%	103	1.7%
Fungal organisms consistent with *Candida* spp.	261	4.4%	312	5.2%
Shift in flora s/o bacterial vaginosis	371	6.2%	562	9.4%
Bacteria consistent with *Actinomyces* spp.	16	0.3%	54	0.9%

Cellular changes consistent with Herpes virus	2	0.0%	3	0.1%
Other infection	0	0.0%	1	0.0%
Other Non-Neoplastic Findings	**451**	**7.5%**	**522**	**8.7%**
Reactive cellular changes associated with inflammation	229	3.8%	280	4.7%
Atrophy	199	3.3%	206	3.4%
Reactive cellular changes associated with radiation	1	0.0%	0	0.0%
Reactive cellular changes associated with IUD	0	0.0%	0	0.0%
Glandular cells status post hysterectomy	1	0.0%	2	0.0%
Endometrial cells in a woman ≥45 yrs of age	21	0.4%	34	0.6%

The Genius Digital Diagnostics System showed a slightly higher rate of detection of infectious organisms (17.3% vs 12.0%) and other non-neoplastic findings (8.7% vs 7.5%) than Manual review; the differences in the detection of infectious organisms and non-neoplastic findings were statistically significant (P-value <0.001).

Cytotechnologist Review Rates in the Clinical Study

As part of the clinical study, the amount of time each CT spent reviewing each case was recorded. The median amount of time per case as well as the minimum time and the maximum time are shown in Table 20. In the study, the review time started when the CT clicked on the accession ID until the CT clicked the Complete Review button.

Table 20. CT Review Rates, Time per Case Genius Cervical AI Clinical Study

Site	Reviewer	Median Review Time per Case (minutes:seconds)	Minimum Review Time per Case (minutes:seconds)	Maximum Review Time per Case (hours:minutes:seconds)*
Site 1	CT-1	01:59	00:37	10:27
	CT-2	01:03	00:12	42:57
	CT-3	00:46	00:06	27:18
Site 2	CT-1	01:14	00:15	1:10:36
	CT-2	01:46	00:18	29:28
	CT-3	01:39	00:06	32:15
Site 3	CT-1	00:28	00:07	26:25
	CT-2	01:28	00:22	14:55
	CT-3	01:32	00:24	13:31
Site 4	CT-1	01:25	00:20	16:09
	CT-2	01:58	00:29	10:41
	CT-3	01:15	00:32	26:38
Combined		**01:20**	00:06	1:10:36

*CT activity was not specifically monitored in the clinical setting. Review times are case-open through case-close time stamps and may include time away from the Review Station.

Conclusion

The sensitivity and specificity of the Genius Digital Diagnostics System for review of slides processed on ThinPrep systems are non-inferior to the sensitivity and specificity of the manual review of the same slides. The sensitivity of the Genius Digital Diagnostics System is superior to the sensitivity of the manual review for the detection of abnormal cells at the LSIL+, ASC-H+, and HSIL+ diagnostic thresholds.

CYTOTECHNOLOGIST SCREENING TIME STUDY (INTERNAL STUDY)

Hologic conducted an internal study to characterize screening volumes for cytotechnologists (CTs) on the Genius Digital Diagnostics System when presented with gynecological clinical specimens of varying diagnoses. The study also intended to characterize the accuracy of screening for these cytotechnologists based on the adjudicated result of manual review of these slides.

Seventeen-hundred, forty-four (1744) slides produced from clinical specimens were available for review by CTs using the Genius Review Station in this study. Slides were imaged using two Genius Digital Imagers. Ten cytotechnologists each reviewed the resulting case images over the course of five days, working up to 8 hours per day. Case images were introduced to the cytotechnologists in a pre-randomized order throughout the 5-day work schedule. All ten cytotechnologists shared the same case randomization order. Diagnostic results were recorded into an electronic Case Report Form (CRF), and CT review times were captured by the Genius Digital Diagnostics System software for use in assessing screening volume.

This study demonstrated that CT review rates of approximately 1 minute per case are achieved when screening with the Genius Digital Diagnostics System and that screening rates did not have any effect on diagnostic accuracy.

Results of this study are presented in Table 21 through Table 23.

Table 21 shows the time spent by each of the CTs in the internal study reviewing each of the cases in the study. The median amount of time per case as well as the minimum and maximum CT review times are shown. The listed CT review times reflect the time between opening and closing of the case as recorded on the Genius Review Stations. Per the instructions of the study, this includes the time to record the diagnosis in an electronic Case Report Form.

Table 21. CT Review Rates, Time Per Case
Internal Study

Reviewer	Median Review Time per Case (minutes:seconds)	Minimum Review Time per Case (minutes:seconds)	Maximum Review Time per Case (minutes:seconds)
CT-1	01:03	00:17	07:04
CT-2	01:03	00:16	06:44
CT-3	01:02	00:19	05:41
CT-4	00:56	00:18	07:27
CT-5	00:51	00:28	04:42
CT-6	00:56	00:11	10:29
CT-7	01:02	00:18	05:16
CT-8	00:47	00:06	13:32
CT-9	00:51	00:09	14:14
CT-10	00:44	00:13	07:21
Combined	**00:55**	00:06	14:14

Diagnostic results were collected from each cytotechnologist's completed CT Review Record. Diagnostic results were applied to three clinically relevant thresholds of ASCUS+/-, LSIL+/-, or ASC-H+/-, according to the Bethesda System. Table 22 presents the sensitivity and specificity results for each CT compared to adjudicated "truth" with respect to each of the thresholds. Diagnostic "truth" is defined according to the adjudicated results obtained in the Genius Cervical AI Clinical Study.

Table 22. Sensitivity and Specificity Summary for all CTs vs. Clinical Thresholds (internal study)

CT	Median Review Time per Case (minutes:seconds)	Sensitivity			Specificity		
		ASCUS +/-	LSIL +/-	ASC-H +/-	ASCUS +/-	LSIL +/-	ASC-H +/-
CT-1	01:03	77.0%	81.0%	80.1%	92.5%	92.6%	93.2%
CT-2	01:03	79.0%	86.0%	85.1%	89.9%	87.6%	90.8%
CT-3	01:02	83.5%	84.2%	88.1%	88.4%	89.9%	91.2%
CT-4	00:56	78.8%	85.8%	92.3%	90.1%	88.6%	87.2%
CT-5	00:51	52.2%	49.7%	33.8%	97.6%	97.7%	98.9%
CT-6	00:56	80.1%	85.7%	88.1%	88.7%	88.1%	87.7%
CT-7	01:02	67.4%	75.1%	77.9%	94.1%	93.8%	94.7%
CT-8	00:47	80.4%	86.4%	86.4%	88.9%	89.9%	91.1%
CT-9	00:51	78.2%	82.1%	83.5%	88.2%	87.2%	89.7%
CT-10	00:44	64.0%	72.3%	71.5%	94.7%	93.6%	95.0%

Note: Slides which were deemed unsatisfactory for review by either the CT or the adjudication results were not included in the sensitivity and specificity results in this table.

Figure 2 shows a graphical representation of the relationship between median case review time and diagnostic performance at the ASCUS +/- threshold.

Figure 2. CT Case Review Time vs. Sensitivity / Specificity (internal study)

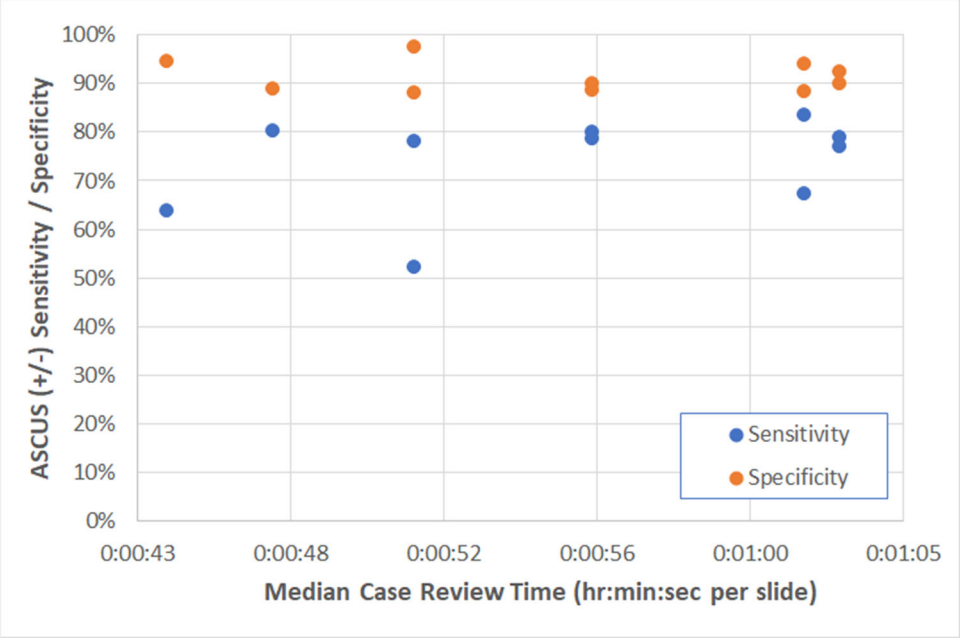
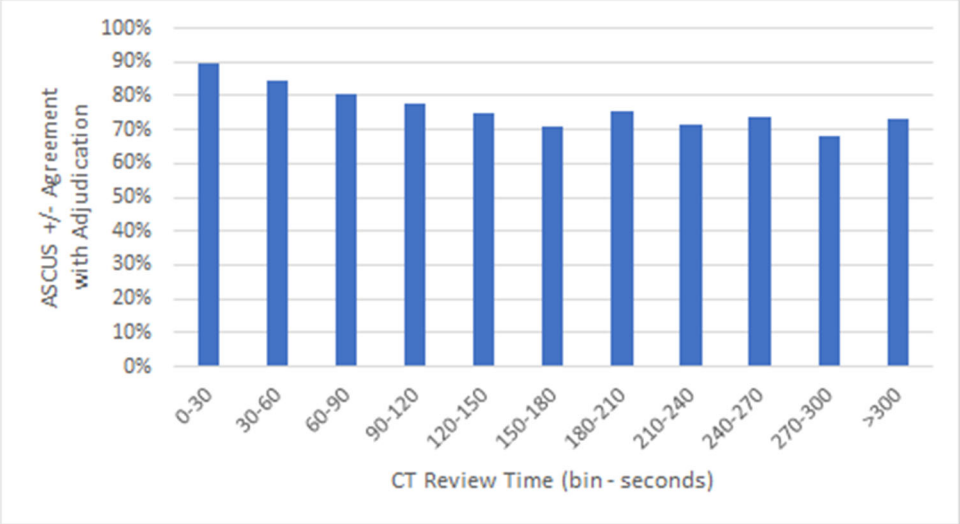


Figure 3 shows the diagnostic agreement with adjudicated truth at the ASCUS +/- threshold as a function of individual CT case review times across all CTs in this study.

Figure 3. Agreement with Adjudicated "Truth" vs. CT Review Time (internal study)



The adequacy results for the cases in the study for all ten CTs were compared to the adjudicated adequacy results. Table 23 presents the results of the comparison.

Table 23. Case Adequacy Contingency Table – Results from all 10 CTs Combined (internal study)

		Adjudicated Result	
		Satisfactory	Unsatisfactory
Genius Digital Diagnostics System Result	Satisfactory	15772	113
	Unsatisfactory	105	81

The results show a 98.6% agreement across all results between the Genius Digital Diagnostics System adequacy reviews versus adjudicated adequacy results, and unsatisfactory rates of 1.2% for both the Genius Digital Diagnostics System and adjudicated results.

This study showed that the CT review rates for Genius Digital Diagnostics System case image review are higher than rates achieved with other review methods, such as manual review or review using the ThinPrep Imaging System (TIS).

CTs showed median case review rates of approximately 1 minute per case (minimum of 44 seconds and maximum of 63 seconds per case).

The study rates are expected to be an underestimation of real-world review rates, as the clinical population in this study was highly challenging (approximately 50% abnormal rate). Analysis of per-case review times showed that reviews were longer for abnormal (ASCUS+) compared to normal (ASCUS-) cases with 1:09 (one minute, nine seconds) and 0:46 (forty-six seconds) median review times, respectively.

Specimen adequacy results showed a high agreement rate between the adjudicated adequacy results and the Genius Digital Diagnostics System adequacy results for each CT and all CTs combined (98.6% agreement). Unsatisfactory rates were also at expected levels (approximately 1.2% overall) between adjudicated and Genius Digital Diagnostics System review results.

CYTOTECHNOLOGIST SCREENING RATES: WORKLOAD GUIDANCE

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 cases. In the Genius Cervical AI clinical study and in the internal CT screening time study, CTs accurately diagnosed cases using digital images presented by the system more efficiently than with a full manual review of a case.

Figure 4 compares the median CT review rates from both the clinical study and the internal study to the sensitivity of diagnostic agreement with adjudicated truth at the ASCUS+/- threshold.

Figure 4. CT Case Review Time vs. Sensitivity (Clinical Study and Internal Study)

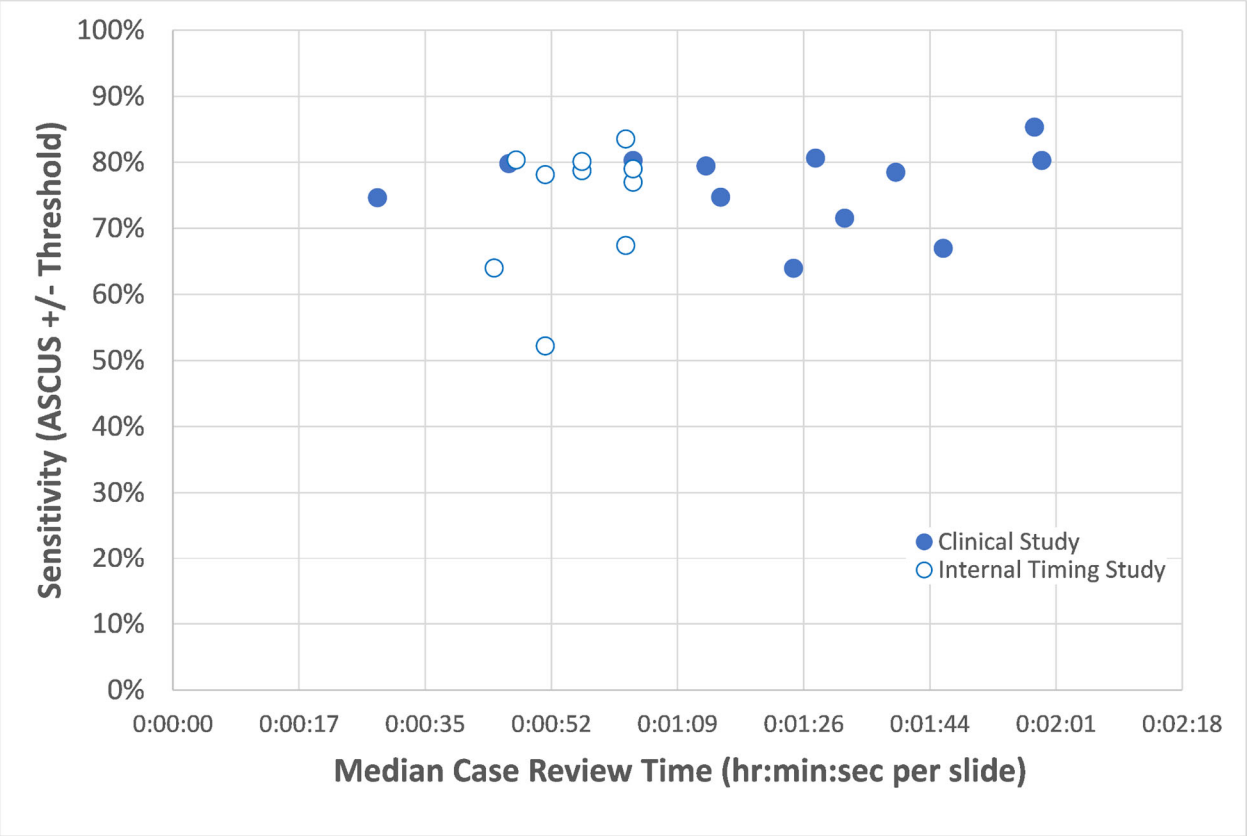
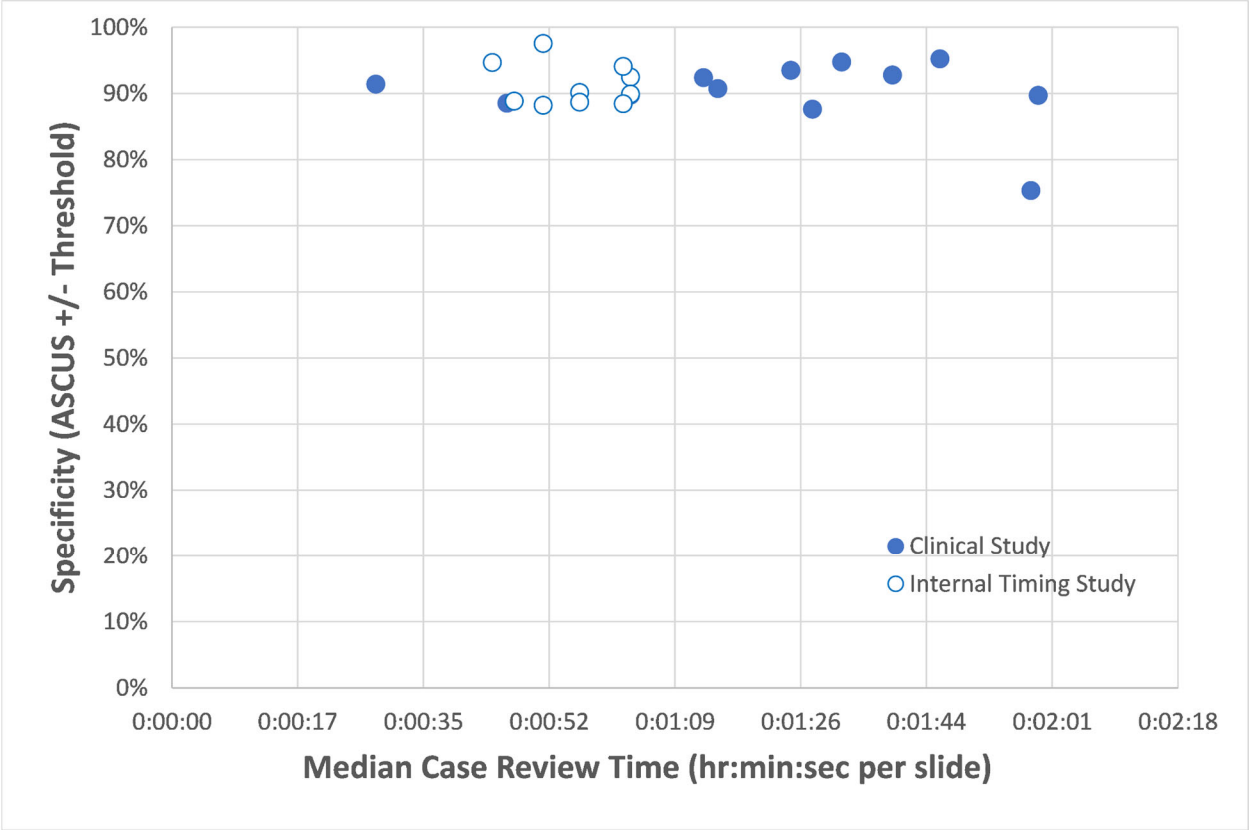


Figure 5 compares the median CT review rates from both the clinical study and the internal study to the specificity of diagnostic agreement with adjudicated truth at the ASCUS+/- threshold.

Figure 5. CT Case Review Time vs. Specificity (Clinical Study and Internal Study)



In both studies, the amount of time spent by the CT to review a case on the Genius Digital Diagnostics System did not change the rate of agreement with the adjudicated diagnostic result at the ASCUS +/- threshold.

A “slide equivalent” factor was calculated from the review rates by CTs in the clinical study (Table 20) and in the internal CT screening time study (Table 22).

The CLIA limit of 100 cases per day with Full Manual Review (FMR) is equivalent to 4.8 minutes/slide in an 8-hour day.

In the case review data collected from the studies with the Genius Digital Diagnostics System, the median rate of review for each CT ranged from 28 seconds (0.5 minute) to 1 minute, 59 seconds (2 minutes). Based on the case review data collected in the studies, the observed median rate of review was 1 minute, 20 seconds (1.33 minutes) per slide in the clinical study and 55 seconds (0.92 minutes) per slide in the internal study.

Taken together, the CT review rate can be assumed to be approximately 1.2 minutes per slide, or one-quarter of the time required for full manual review (FMR) using a microscope. A resulting “slide equivalent” recommendation for case review with the Genius Digital Diagnostics System is therefore:

1 Genius Digital Diagnostics System Case = 0.25 CLIA Slide Equivalent

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

200 Genius Digital Case Reviews = 50 slides
(200 x 0.25 = 50)

Total number of slides screened: 50

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 cytotechnologists based on laboratory clinical performance. According to CLIA '88, these workload limits should be reassessed every six months.

NON-GYNECOLOGICAL SPECIMEN STUDY

A laboratory study was conducted to demonstrate that the Genius Digital Diagnostics System presents images of non-gynecological cases for slides that would otherwise be appropriate for manual visualization by conventional light microscopy. The study compared results from cases reviewed by a CT using the Genius Digital Diagnostics System to the results of CT review of the same case slides on a microscope (manual review).

Four hundred (400) ThinPrep slides, including a range of non-gynecological specimen types, were enrolled in the study. The study included the following types of specimens: anal Pap, fluids, FNA, respiratory/mucoid, and urine. The specimens were a mix of normal, abnormal, and non-diagnostic cases, according to their donor lab results. The slides were evaluated using a manual microscope as a control. The slides were imaged on a Genius Digital Imager. After a two-week washout period to minimize recognition bias, the case images were evaluated using the Genius Review Station.

Non-gynecological Study Results

Table 24 provides the overall results of the diagnostic screening of the specimens.

Table 24. Matched-Pair Diagnostic Categories, Non-Gynecological Specimens

		Manual		
		Abnormal	**Normal**	**Non-Diagnostic**
Genius	**Abnormal**	147	23	0
	Normal	11	196	8
	Non-Diagnostic	0	0	14

Further analysis of the study data was performed to compare the diagnoses from the Genius case review versus the manual review of the glass slides for slides where a diagnosis was possible. The results are presented in Table 25.

Table 25. Proportions of Diagnoses of Abnormal Cases, Non-Gynecological Specimens

	Proportion	95% confidence interval
Manual Review	0.419	[0.370 , 0.470]
Genius Digital Review	0.451	[0.401 , 0.501]
Difference, Genius - Manual	0.032	[-0.004 , 0.062]

The study data show that the proportions of abnormal cases in a mix of non-gynecological specimens are equivalent when evaluated with the Genius Digital Diagnostics System and evaluated with manual review. Therefore, non-gynecological cytology specimens may be reliably reviewed for diagnostic evaluation using the Genius Digital Diagnostics System.

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].

The data from the studies conducted on the Genius Digital Diagnostics System showed greater sensitivity with the Genius Digital Diagnostics System with the Genius Cervical AI algorithm than with manual review in cases with a diagnosis of HSIL+ and more severe lesions. The increase in sensitivity for HSIL+ cases is 5.7% for all sites combined. The data showed a reduction of 20% in false negatives in cases with a diagnosis of HSIL+ and more severe lesions.

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.

The data from internal studies demonstrate that the Genius Digital Diagnostics System provides images that may be reliably reviewed for diagnostic evaluation of non-gynecological cytology specimens.

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

*In some configurations of the system, the laboratory may supply the Review Station computer into which Hologic installs a Hologic-supplied graphics card. In some configurations of the system, a laboratory may supply the server hardware.

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, contact Hologic:

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

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REVISION HISTORY

Revision	Date	Description
AW-24823-001 Rev. 001	8-2021	Replace CE mark. Add clinical study data. Add instructions regarding reporting serious incidents.
AW-24823-001 Rev. 002	3-2023	Clarify intended purpose.
AW-24823-001 Rev. 003	3-2024	Use part number MAN-11010-001.
AW-24823-001 Rev. 004	5-2024	Add Australian Sponsor information.

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AW-24823-001 Rev. 004

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