

HOLOGIC®

Genius™ Digital Diagnostics System



Instructions for Use

CE

IVD

INTENDED USE

The Genius™ Digital Diagnostics System, when used with the Genius™ Cervical AI algorithm, is 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 to provide a digital image of the whole cell spot for screening.

The Genius Digital Diagnostics System includes the 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.

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

When any image is being reviewed, the CT or pathologist has the option to electronically mark objects of interest and include the marks in the 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.

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 OOI 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 OOI

		TIS							Total	
		UNSAT	NILM	ASCUS	LSIL	ASC-H	AGUS	HSIL		CANCER
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 OOI 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 OOI 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.

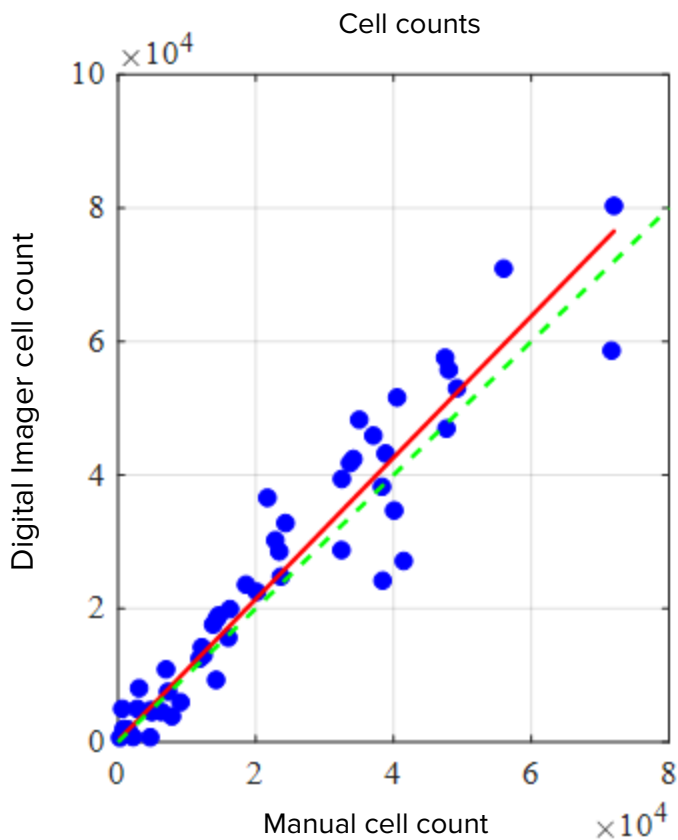
CELL COUNT STUDY

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 System¹, 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.

CONCLUSIONS

- 89.3% of abnormal slides have OOI matching or exceeding the TIS-assisted review result.
- On average, there are 6.8 OOIs that match or exceed the TIS-assisted result for abnormal slides.
- The standard deviation of number of matching OOIs is 1.3, for abnormal slides.
- Endocervical component (ECC) is detected in the OOI gallery at an equal or higher rate than in TIS-assisted reviews.
- Trichomonas is detected in the OOI gallery at an equal or higher rate than in TIS-assisted reviews.
- Candida is detected in the OOI gallery at an equal or higher rate than in TIS-assisted reviews.
- Coccobacilli are detected in the OOI gallery at an equal or higher rate than in TIS-assisted reviews.
- The Genius Digital Diagnostics System provides cell counts adequate for determining if specimen adequacy is sufficient for evaluating patient cases.

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, imaged on the Genius Digital Imager 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.

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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