FDA U.S. FOOD & DRUG ADMINISTRATION

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR

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

DECISION SUMMARY

I Background Information:

A De Novo Number

DEN210035

B Applicant

Hologic Inc.

C Proprietary and Established Names

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

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QYV	Digital cervical cytology slide imaging system with artificial intelligence algorithm	21 CFR 864.3900	Pathology

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the Hologic's Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm.

B Measurand:

Not applicable

C Type of Test:

Digital cytology whole slide imaging system with AI algorithm to assist in review of digital images of ThinPrep Pap test slides.

III Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

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

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

C Special Conditions for Use Statement(s):

For *in vitro* diagnostic (IVD) use only
For prescription use only

D Special Instrument Requirements:

- Genius Digital Imager
- Genius Image Management Server (IMS)
- Genius Review Station
- Genius Cervical AI algorithm

IV Device/System Characteristics:

A. Device Description:

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

The Genius Digital Diagnostics System includes, Genius Digital Imager, Genius Image Management Server, Genius Review Station(s), and Genius Cervical AI algorithm, as shown in Figure 1 below.

Figure 1. The Genius Digital Diagnostics System

Genius Digital Imager (Digital Imager)

The Genius Digital Imager digitally scans ThinPrep® Pap test slides that have been prepared using the ThinPrep 2000 system, ThinPrep 5000 processor or ThinPrep Genesis processor, stained with the ThinPrep stain (Papanicolaou-based stain) and cover slipped. The Digital Imager is operated using the user interface which is a menu-driven, graphical display touch screen. The Digital Imager consists of the following:

- Digital Imager processor which images the slides, one at a time.
- Digital Imager computer which captures the images and controls the electromechanical components of the system.
- Image Management Server which stores the slide ID and pertinent image data. The Digital Imager requires a connection to the Image Management Server.

Genius Image Management Server (IMS)

The Genius IMS subsystem is responsible for data management and includes a database, an image repository, and an imager web service, which is a HTTPS server for interfacing with the Digital Imager. The IMS hosts web applications for the review station.
Information stored on the IMS's database subsystem is tracked by unique accession IDs, which are read from the microscope slide labels when they are scanned on the Digital Imager. The Digital Imager, IMS, and Review Stations are connected by a local area network. The IMS stores whole slide images in the image repository, (a physical structure of the files on a local storage disk), along with associated information from the review of the slides in a SQL database to facilitate the display of images for cytologist (CTs) and pathologists (PTs) to review. In addition to the network connection between the Digital Imager, IMS and Review Station, another network connection is required for accessing an optional archive storage system. The minimum computer requirements for the IMS are listed in the Table 1.

Table 1. Genius Image Management Server (IMS) Minimum Requirements

Server Hardware	Dual Intel Xeon Silver 4214 2.20 GHz processor 64 GB memory 240 GB SSD for OS (boot) RAID 10 Array configuration 30 TB configured storage capacity Two 10 GB Ethernet ports 3 USB 2.0 (or faster) ports Display interface (HDMI or Display Port) Dual, hot plug, redundant power supply (1+1), 750 W or greater
Operating System	Windows 64-bit minimum; Windows Server 2016 recommended
Display	A minimum resolution of 1366 by 768 pixels

Genius Review Station

The Genius Review Station includes a dedicated computer running the IMS client software and the Barco MDPC-8127 display which is a high-resolution display that has been validated for diagnostic review of objects of interest (OOIs) or whole cell spot images. The Review Station is used by CTs and PTs to screen the ThinPrep® Pap Test slides that have been imaged using the Digital Imager. The minimum specifications for the dedicated computer and specifications of the high-resolution display are listed in Tables 2 and 3.

Table 2. Review Station Computer Minimum Requirements

Hardware	• x86 processor, Intel® Core i7 2.4Ghz (4C, 8T) • 16 GB DDR4 Memory or greater • 256 GB Drive or greater • 1Gb or faster network connection • Barco MXRT display control card • PCIe Gen3 x 16 slot for the display control card • A keyboard and a mouse
Operating System	Windows 10, 64-bit
Browser	Google Chrome, Version 85 (1.3.35.451) or greater
Environmental	• Operating temperature range: 16-32ºC • Non- Operating temperature range: -28ºC to 50ºC • Operating humidity range: 20-80% RH, noncondensing • Non- operating humidity range: 15-95% RH, noncondensing

Table 3. Specifications of the Barco Display

Manufacturer	Barco
Model number	MDPC-8127
Hologic part number	CMP-01669
Screen technology	IPS LED
Active screen size (diagonal)	684 mm (27")
Active screen size (H x V)	569 x 335 mm (22.4 x 13.2")
Aspect ratio (H:V)	16:9
Resolution	8 MP (3840 x 2160 pixels @ 120 Hz)
Pixel pitch	0.155 mm
Color imaging	Yes
Power rating	100-240 Vac, 50/60 Hz, 3.6-1.6 A
Power consumption	75 W (nominal) @ calibrated luminance of 450 cd/m² < 0.5 W (hibernate) < 0.5 W (standby)
Operating temperature	0 °C to 35 °C (20 °C to 30 °C within specs)

Genius Cervical AI algorithm

The Genius Cervical AI algorithm is a software algorithm which is pre-loaded on the Genius Digital Imager. The Genius Cervical AI algorithm uses Convolutional Neural Network (CNN) technology to analyze ThinPrep® Pap Test whole slide images scanned using the Genius Digital Imager and selects OOIs to be displayed for review by a CT or PT. The Genius Cervical AI algorithm software is separate with its own software subsystem. The user selects the appropriate specimen type [i.e., GYN (Pap test slide)] to be scanned before initiating the scanning process. The analysis of the image is performed automatically by the Genius Cervical AI algorithm after the scanned digital image is generated by the Genius Digital Imager. A typical input image is a high-resolution color scan of a ThinPrep cell spot, containing over $6x10^9$ pixels, from 5,000 to 100,000 cells. The output of the algorithm is a set of OOIs, organized into rows and designed to provide information for the reviewer to determine the diagnostic category for that particular image (case) per The Bethesda System for Reporting Cervical Cytology. There are 5 rows of OOIs and 6 primary OOIs per row. There are an additional 6 secondary OOIs available per row that the user can review, as needed. The OOIs are grouped into rows of particular diagnostic categories. Priority is given to abnormal cells when populating the first four rows, followed by cell types needed for assessing specimen adequacy (Endocervical cells and Squamous Metaplasia). The final row shows infectious organisms when present. The algorithm also provides a total count of squamous cells on the slide. This count may be used by the reviewer in assessing specimen adequacy. The cells and cell clusters presented in a gallery format on the Genius Review

Station, as shown in Figure 2 below, allows the reviewer to view all OOIs presented by the algorithm. The CT or PT can digitally mark OOIs for subsequent review.

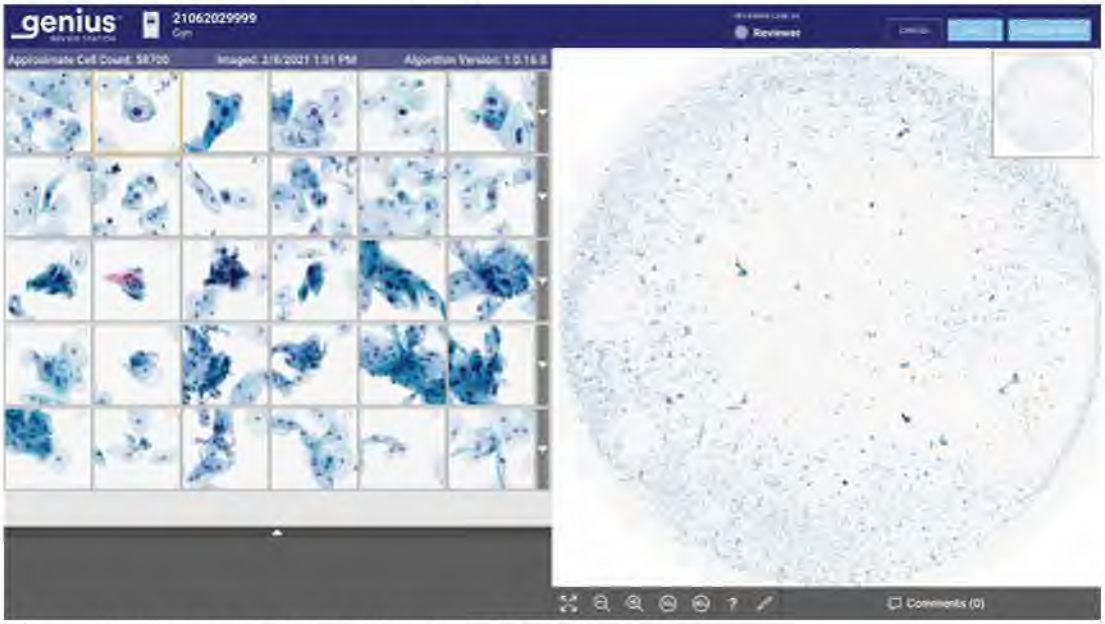

Figure 2. Example Review Screen with OOI Gallery

B. Principle of Operation

The Genius Digital Diagnostics System is designed for scanning and generating digital images of ThinPrep® Pap test slides. The process is displayed in Figure 3. These digitized images can then be reviewed and interpreted by CTs and PTs for the purposes of reporting Pap test results per The Bethesda System for Reporting Cervical Cytology. Stained ThinPrep® Pap-test slides 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. The slide ID reader scans the case's accession ID and locates the position of the cell spot. The Digital Imager contains slide handling robotics and digital imaging components to scan the entire ThinPrep cell spot to create an in-focus whole slide image. For ThinPrep® Pap test slides, the Genius Cervical AI algorithm identifies OOIs found on the digital image of the slide. The objects classified as most clinically relevant are presented in a gallery to the CT and PT for review. The slide image data, the slide ID, are transmitted to the IMS, and the slide is returned to its slide carrier. The IMS functions as the central data manager for the Genius Digital Diagnostics System. As slides are imaged by the Digital Imager and reviewed by the CT or PT at the Review Station, the IMS stores, retrieves, and transmits information based on the case ID. The Review Station is a dedicated computer running the Review Station software application, with a display validated for diagnostic review of OOIs and/or whole cell spot images. The Review Station is connected to a keyboard and a mouse. When a valid case accession ID has been identified at the Review Station, the server sends the images for that case ID to the user. The CT or PT is presented with a gallery of images of OOIs for that slide for review. When any image is being reviewed, the CT or PT has the option to digitally mark objects of interest and include the marks in the case review. The reviewer can move and zoom into any area of interest to evaluate details of the cell spot using a mouse or arrow keys for examination. The reviewer is responsible for

ensuring the validity of the interpretation of the digital images created by the Genius Digital Diagnostics System.

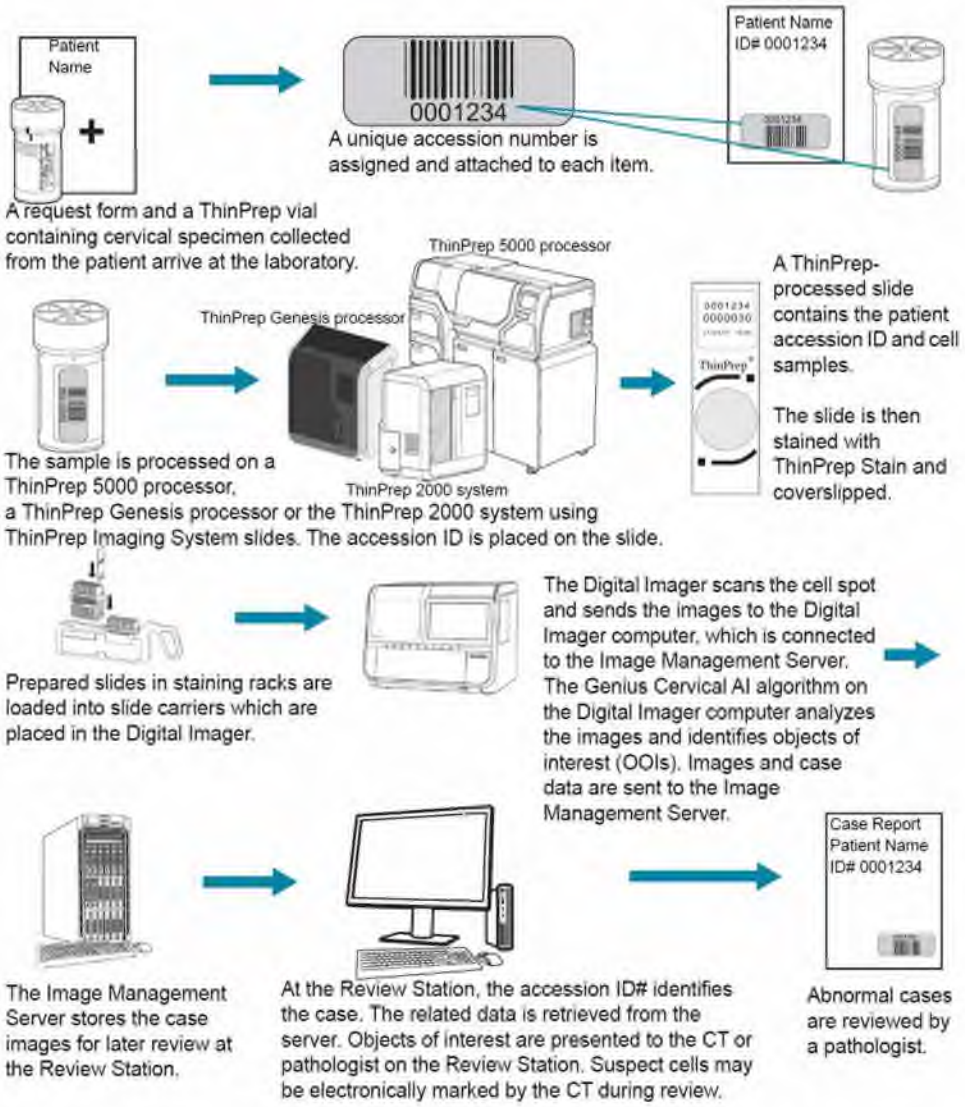

Figure 3. Genius Digital Diagnostics System: Laboratory Workflow for Cervical Cancer Screening (Lab Workflow for ThinPrep® Pap Test Cases)

C. Interpretation of Results

The Genius Cervical AI algorithm presents a gallery of images of clinically relevant objects. After reviewing the entire gallery and the digital images, the CT and/or PT provide an interpretation and diagnosis of the image per The Bethesda System for Reporting Cervical Cytology. It is the responsibility of qualified CTs and PTs to employ appropriate procedures and safeguards to assure the validity of the interpretation of images obtained using this system. The Genius Digital Diagnostics System should be used in conjunction with the standard of care

evaluation of the slide image, including professional screening and management guidelines to guide patient care. Users must always review the entire gallery prior to rendering an interpretation to minimize interpretive errors. After review of the digital images with the Genius Cervical AI algorithm, if there is uncertainty in the diagnosis, then direct examination of the glass slide by light microscopy is performed.

D. Software

The Genius™ Digital Diagnostics System with the Genius™ Cervical AI software was identified to have a moderate level of concern as defined in FDA's Guidance for the Content of Premarket Submission for Software Contained in Medical Devices (May 11, 2005). Software Verification and Validation (V&V) testing was performed to demonstrate that the software conforms to user needs, intended uses, and that design outputs meet design requirements. The verification plan included test coverage for hardware specifications, software specifications and error diagnostics specification.

i. Software Description: Hologic Inc. provided a general description of the features in the software documentation and in the device description. The description of the software is consistent with the device functionality described in the device description.

ii. Device Hazard Analysis: Hologic Inc. provided separate analyses of the device and cybersecurity concerns. The content of the hazard analysis is sufficient and assesses pre- and post-mitigation risks. The device hazard analysis includes:
   - Identification of the hazard
   - Cause of the hazard (hazardous situation)
   - Probability of the hazard
   - Severity of the hazard
   - Method of control or mitigation
   - Corrective measures taken, including an explanation of the aspects of the device design/requirements, that eliminate, reduce, or warn of a hazardous event verification of the control implementation, which is traceable through the enumerated traceability matrix.

iii. Software Requirement Specifications (SRS): The SRS includes user, engineering, algorithmic, cybersecurity, and various other types of requirements that give a full description of the functionality of the device. The SRS is consistent with the device description and software description.

iv. Architecture Design Chart: Hologic Inc. provided the software overview and included flow diagrams representative of process flow for various features of the Genius™ Digital Diagnostics System with the Genius™ Cervical AI algorithm.

v. Software Design Specification (SDS): The SDS is traceable to the SRS and demonstrates how individual requirements are implemented in the software design and includes appropriate linkages to predefined verification testing.

vi. Traceability Analysis/Matrix: Hologic Inc. provided traceability between all documents including the SRS, SDS, and subsequent verification and validation. Hazard mitigations are traceable throughout all documents.

vii. Software Development Environment: Hologic Inc. outlined the software development environment and the processes/procedures used for medical device software development. The content is consistent with expected quality system norms.

viii. Verification and Validation Testing: The validation and system level verifications procedures are based upon the requirements with clearly defined test procedures and pass/fail criteria. All tests passed. Unit level test procedures, actual, and expected results are included for all design specifications.

ix. Revision Level History: System Software Version (v) 1.1.0 was released prior to its use in all the performance studies, including analytical (standalone and precision) and clinical reader study. The Genius Cervical AI algorithm v1.0.16.0 will remain locked for use with the authorized device and will not be continually trained and improved with each cohort analyzed in clinical practice, after marketing authorization.

x. Unresolved Anomalies: There are no unresolved anomalies.

xi. Cybersecurity: The cybersecurity documentation is consistent with the recommendations for information that should be included in premarket submissions outlined in the FDA guidance document "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices: Guidance for Industry and Food and Drug Administration Staff" (issued October 2, 2014). Information related to cybersecurity reviewed included:

- Hazard analysis related to cybersecurity risks,
- Traceability documentation linking cybersecurity controls to risks considered,
- Summary plan for validating software updates and patches throughout the lifecycle of the medical device,
- Summary describing controls in place to ensure that the medical device will maintain its integrity, and
- Device instructions for use and product specifications related to recommended cybersecurity controls appropriate for the intended use of the device.

xii. Remote Use: Hologic provided information about the device environment and risks such as connection method and requirements, optimal connection speed, network requirements, minimum network specifications, image quality, etc., with respect to remote use. A network speed value of at least 100 MBps is recommended for optimal speed in loading images and case data. Users must contact network administrator if the speed test value is below this threshold. Users who choose to remotely connect the Genius Review Station to the Genius Image Management Server are responsible for the maintenance of their network's cybersecurity.

V Standards/Guidance Documents Referenced:

Standard Number	Title
EN ISO 14971:2019	Medical Devices – Application of risk management to medical devices
EN 61010-1:3rd edition	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 1: General Requirements
IEC 61010-1:3rd edition	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 1: General Requirements
CSA C22.2 #61010-1-12:3rd edition	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 1: General Requirements

Standard Number	Title
EN 61010-2-101:2nd Edition	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for IVD medical equipment
IEC 61010-2-101:2nd Edition	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for IVD medical equipment
CSA C22.2 # 61010-2-101:2nd edition	Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for IVD medical equipment
IEC 60601-1-2:4th Edition	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance — Collateral Standard: Electromagnetic disturbances —Requirements and tests
IEC TR 62366-2	Medical Devices-Part 2: Guidance on the application of usability engineering to medical devices
EN 60601-1-2:4th edition	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance — Collateral Standard: Electromagnetic disturbances —Requirements and tests
EN 61326-2-6:2nd edition	Electrical equipment for measurement, control and laboratory use-EMC requirements-Part 2-6 Particular requirements-IVD medical equipment
IEC 61326-2-6:2nd Edition	Electrical equipment for measurement, control and laboratory use-EMC requirements-Part 2-6 Particular requirements-IVD medical equipment
IEC 61326-1:2nd edition	Electrical equipment for measurement, control and laboratory use – EMC requirements – Part 1: General requirements
EN 61326-1:2nd edition	Electrical equipment for measurement, control and laboratory use – EMC requirements – Part 1: General requirements
EN ISO 13485:2016	Medical Devices – Quality management systems-requirements for regulatory purposes
EN 13612:2002	Performance evaluation of IVD medical devices
ASTM D4169-16:2016	Standard Practice for Performance Testing of Shipping Containers and Systems
EN ISO 18113-1:2011	In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) Part 1: Terms, definitions and general requirements
EN ISO 18113-3:2011	In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) Part 3: In vitro instruments for professional use
EN 62304:2015	Medical Device Software – Software life cycle processes

Standard Number	Title
EN 62366-1:2015	Medical Devices – Application of usability engineering to medical devices
ISO 15223-1:2016	Medical devices- symbols to be used with medical device labels, labelling and information to be supplied-Part 1 General requirements
FDA Guidance: 2016	Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices
FDA Guidance: May 2005	Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
FDA Guidance September 2019	Guidance for Off-the-Shelf Software Use in Medical Devices
FDA Guidance: February 2016	Applying Human Factors and Usability Engineering to Medical Devices

VI Performance Characteristics:

A. Technical Performance Assessment

Multiple studies were performed to verify that the Genius Digital Diagnostic System with the Genius Cervical AI algorithm met all product specification and performance requirements for safe and effective use of the device. Detailed descriptions of the device components and bench testing results were provided for the following:

- Slide Feeder: Information was provided on the slide feed mechanism, slide configuration, class of automation, user interaction, and failure mode and effects analysis.
- Light Source: Information and specifications on the light source (bulb type, manufacturer and model, wattage, spectral power distribution, expected lifetime, and output adjustment control) and the condenser (illumination format, manufacturer and model, numeric aperture, and working distance) were provided. The expected variation of intensity and spectra was evaluated for three periods:
    - Duration of a single scan
    - Duration of a single workday
    - Lifetime of the device
    - Information on capability of tracking intensity and spectral degradation with lifetime was provided. Spectral distribution of the light incident on the slide was measured.
- Imaging Optics: Information and specifications on the optical elements, including optical schematic, microscope objective, auxiliary lens, and magnification, were provided. The imaging optical system was validated with the following tests:
    - Relative irradiance
    - Distortion
    - Lateral chromatic aberrations
    - Longitudinal chromatic aberrations

- Z-focal plane acquisition method: Information on the volumetric imaging method was provided.
- Mechanical Scanner Movement: Information and specifications on the imaging robotics were provided. The stage position and camera trigger signal are synchronized by utilizing position monitoring and close-loop control.
- Digital Imaging Sensor: Information and specifications on the digital imaging sensor, including sensor type, sensor manufacturer, number of pixels, dimension of pixel, configuration of color filter array, spectral transmission of color filter mask, relative response versus wavelength, linearity, spatial uniformity, dark current level, read noise, readout rate, and digital output format, were provided.
- Image Processing and Composition: The whole slide image creation was validated with the following tests:
    - Exposure control
    - White balance
    - Color correction
    - Sub-sampling and pixel offset correction
    - Flat-field correction
    - Pixel defect correction
    - Scanning method
    - Stitching and merging
    - Scanning speed
    - Number of planes
- Image Files Format: Information and specifications on the full-resolution TIFF file and pyramid TIFF file were provided.
- Image Review Manipulation Software: Information and specifications on continuous panning, continuous zooming, tracking of visited objects, and digital marking were provided.
- Computer Environment: Information and specifications on the computer hardware, operating system, graphics card and driver, color management settings, color profile, and display interfaces were provided.
- Display: Information and specifications on the display device (Barco MDPC-8127, CMP-01669) were provided, including the technology characteristics, physical size of the viewable area and aspect ratio, backlight type and properties, frame rate and refresh rate, pixel array, pitch, pixel aperture ratio and subpixel matrix scheme, subpixel driving for greyscale, display interface, ambient light adaptation, color calibration tools, and frequency and nature of quality-control tests.

Technical performance assessments at a system level were performed for the following:

- Coverage of Z-depth to represent the 3D aspects of the cytological sample:
  The volumetric imaging method was validated with bench tests using a Ronchi pattern and compared with a conventional microscope. The acquired Z-depth was ≥ 24 microns.
- Color Reproducibility: Accuracy and precision of the colors displayed on the Genius Review Station Computer were validated with the following tests:
    - Reproducibility of Imager calibration across multiple Sierra slides
    - Reproducibility of Imager calibration across multiple Imagers

- Reproducibility of calibration across multiple displays
- Overall system accuracy, displayed color compared to the intended color

The colors displayed on the Genius Review Stations for scans taken using the Genius Digital Imager meets the acceptance criteria specified.

- Structural Similarity Index Measurement (SSIM) Study: Test data to assess the reproducibility of image capture across multiple imagers, multiple runs on a single imager, and over the calibration cycles of the imager was provided. A set of 18 Pap test slides were imaged using the Genius Digital Diagnostics System with the Genius Cervical AI algorithm, as listed in Table 4.

Table 4. Bethesda Diagnostic Category Slide Distribution

Category Name	Quantity
NILM	3
ASCUS / AGUS	3
LSIL	3
ASC-H	3
HSIL	3
CANCER	3

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.

Three separate Genius Digital Imagers were used for imaging slides. Between-imager reproducibility was evaluated by imaging slides once on 3 separate Genius Digital Imagers. Within-imager reproducibility was evaluated by imaging the slides 3 times on a single Genius Digital Imager. Imaging Stability was evaluated by imaging the slides 3 times on a single system with an instrument auto-calibration performed between each run. The study evaluation was based on assessing the structural similarity index metric (SSIM) which combines measurements of luminance, contrast, and structure at the pixel level. The acceptance criteria of SSIM above 0.9 was set. Study results showed all SSIM were greater than the 0.9. Performance met the defined criteria.

- Spatial Resolution: The spatial resolution of the optics in the Digital Imager was validated with the following tests:
  - Edge-based spatial frequency response data including horizontal and vertical targets
  - Edge-based spatial frequency response data including 45-degree target
  - Sinusoidal spatial frequency response data including Siemens Star target

  The spatial resolution of the optics in the digital cytology imager meets the pre-specified acceptance criteria.
- Focusing Testing: The focus quality of whole slide images was validated with the following tests:
  - Tallying the fraction of slides where there are quality control (QC) focus errors
  - Manual review of slides for out of focus region identification
  - Estimate sensitivity of the QC focus error check

The focus quality of whole slide images produced by the Digital Diagnostics system meets the acceptance criteria specified.

- Whole Cell-Spot Coverage: A set of 223 slides were imaged, and then analyzed to determine whether the entire cell spot was included within the image. An in-house software tool was created to analyze the swath scan pattern and the presence of cells in each swath for a human review. The Genius Digital Imager scanned the entire cell spot of the slide and the cell spot coverage was determined to be acceptable based on visual inspection.
- Stitching Error: A set of slides was imaged and the swath data before and after stitching were captured. The stitched image was compared with an unstitched image of the same material using the multi-scale structural similarity metric (MS-SSIM). The stitching of image swaths in the Genius Digital Imager met the pre-specified acceptance criteria.
- Turnaround Time: A stopwatch was used to determine the time required to complete the following operations:
    - View the whole slide image and the OOI gallery
    - Display initial images when a new slide review is selected
    - Pan to the left on the whole slide image
    - Zoom in 40x on the whole slide image
    - Zoom out 10x on the whole slide image
    - Pan up in full screen and view the whole slide image
    - Select an OOI from the gallery and view the whole slide image once the complete image is zoomed in
    - Select an OOI from the more/like row in the gallery and view the whole slide image once the complete image is zoomed in.

  The turnaround time used in the Genius Digital Imager was determined to be acceptable.

B. Analytical Performance:

1. Objects of Interest (OOI) Reproducibility

A single site study was conducted to demonstrate that the Genius Cervical AI algorithm accurately and reproducibly selects OOIs. An OOI is a cell or cluster of cells on a glass slide scanned by the Genius Diagnostics System that most likely contains clinically relevant information for diagnostic purposes. In the study, thirty-seven ThinPrep Pap test slides were enrolled which were selected from slides used in the Genius Digital Diagnostics System with the Genius Cervical AI algorithm clinical study. The selected slides covered the full range of abnormal diagnostic categories as defined in The Bethesda System for Reporting Cervical Cytology. These slides were prepared 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, blinded to the reference diagnosis for the case. A minimum of a

two-week washout period was used between the review of the images from each run. During each review on the Genius Digital Diagnostics System with Genius Cervical AI algorithm, the CT recorded the observation in every tile in the gallery for the case on the Genius Review Station. The study compared OOIs selected by the Genius Cervical AI algorithm to the reference diagnosis which was the adjudicated diagnosis for the slide that was determined during the clinical study (See clinical study section below for details of the method used to determine the reference diagnosis for each slide). The accuracy and reproducibility of the Genius Digital Diagnostics System with Genius Cervical AI algorithm was measured by comparison to the adjudicated reference diagnoses. The study evaluated the performance of the Genius Cervical AI algorithm in presenting images suitable for diagnosing Pap test cases. The study also measured reproducibility of the Genius Digital Diagnostics System, as a whole. A summary of the performance data is shown in Table 5 below.

Table 5. OOI Summary by Reference Category (all CTs)

Reference Dx	# Slides	# of Evalua-tions	Proportion of Abnormal OOIs	Median # of Abnormal OOIs	Range of # of Abnormal OOIs (Min;Max)	Proportion Category+ OOIs	Median # Category+ OOIs	Range of # of Category+ 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

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.

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

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

Agreement Rates by Threshold

Table 6 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 6. Agreement rates by Reference Threshold

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

OOI Reproducibility

Table 7 below shows the between-instrument and within-instrument agreement rates for the presence of Category+ OOIs.

Table 7. OOI Reproducibility

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

2. 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. A total of 50 ThinPrep Pap test slides including at least 8 slides with counts near the clinically important threshold of 5000 cells, were enrolled in the study (described in Table 8 below). These slides were prepared on a ThinPrep 5000 processor, stained and cover slipped. 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.

Table 8: Diagnostic category of slides used in the Cell Count Study

Category	# of Slides
AGUS	4
ASC-H	3
HSIL	12
LSIL	5
NILM	23

CANCER	3
Grand Total	**50**

Within-imager reproducibility was evaluated by imaging the slides 3 times on a single Genius Digital Imager and comparing cell count results. Between-imager reproducibility was evaluated by imaging slides once on 3 separate Genius Digital Imagers and comparing cell count results. Cell count accuracy was evaluated by comparing the Genius Cervical AI derived cell counts to the cytologist manual count estimate for each slide. The reproducibility was compared across three runs on one instrument (between-instrument) and across one run on three instruments (within-instrument) and the mean cell count and %CV were calculated. Data showed that the within-imager precision %CV was 0.6% and between-imager %CV was 2.7%. Figure 4 compares the cell counts between the Genius Cervical AI algorithm and a manual cell count method for each specimen.

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 the cell count determined by the CT during the review of glass slides to the Genius Cervical AI algorithm derived cell counts at 5,000 cells was 10% with 95% CI: (4%; 17%).

The results of the cell count study were acceptable. Scatter plot of agreement is shown in Figure 4.

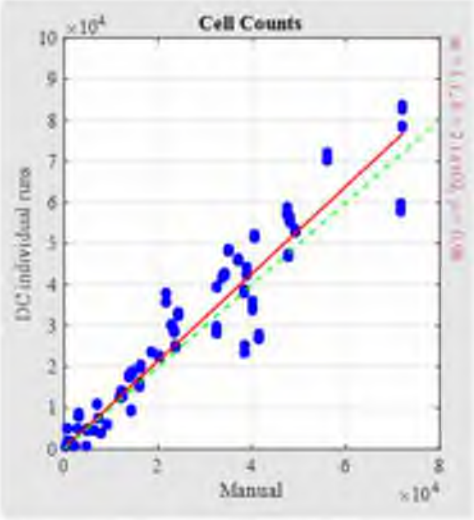

Figure 4. Scatter Plot of Agreement between Interpretations Using Genius Cervical AI algorithm Review versus Manual Glass Slide Review

C. Clinical Studies:

Genius Digital Diagnostics System with the Genius Cervical AI algorithm Review (Genius Cervical AI Clinical Study) Compared to Manual Microscope Review of Glass Slides

A multi-center Genius Cervical AI Algorithm Clinical Study was performed within the United States. The objective of the study was to show that routine screening of ThinPrep Pap test slide images 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, which is the current standard of care.

The study included 1994 slides and 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 4 clinical sites, 3 independent teams consisting of 1 CT and 1 PT at each (site CT/PT 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 times the number of slides at the site. Site CT/PT 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 Genius Cervical AI algorithm (Genius Cervical AI review/Digital 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 PT. 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 3 adjudication CT/PT teams, consisting of 1 CT and 1 PT each (adjudication CT/PT team). Slides were reviewed independently by the three teams. All cases, regardless of result, were reviewed by CTs and PTs. For each case, results from each adjudication CT/PT 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/PT teams). If a consensus result was not obtained initially, these cases underwent review by the three adjudication PTs 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 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 9 provides characteristics of the participating clinical sites. Table 10 describes the patient populations with SAT slides, at each of the study sites.

Table 9. 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 10. 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). The approximate number of slides from the Bethesda System diagnostic categories that were enrolled in the study are as follows:

- 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 slide was deemed not adequate due to broken slide, dilute specimen or slide 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 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 11 below): ASCUS+, LSIL+, ASC-H+, HSIL+, Cancer.

Table 11. Bethesda System Diagnostic 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

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 algorithm 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 calculated separately 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).

C.1.1 Performance of Genius Cervical AI Review and Manual Glass Slide Review

Table 12. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Compared to Adjudicated Diagnosis

	Sensitivity %			Specificity %		
Diagnostic Threshold	**Genius (95% CI)**	**Manual (95% CI)**	**Difference (Genius – Manual) (95% CI)[1]**	**Genius (95% CI)**	**Manual (95% CI)**	**Difference (Genius – Manual) (95% CI)[1]**
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 (described in Table 12 above).

C.1.2 Genius Cervical AI Algorithm Review vs. Manual Glass Slide 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 (described in Table 13 below).

Table 13. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) 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 algorithm 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, (described in Table 14 below).

Table 14. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) 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, (described in Table 15 below).

Table 15. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) 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, (described in Table 16 below).

Table 16. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) 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 algorithm 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, (described in Table 17 below).

Table 17. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) 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, (described in Table 18 below).

Table 18. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) 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)

C.1.3 Tables of performance of each Bethesda Category

Table 19 through Table 26 summarize results from Genius Cervical AI algorithm-assisted 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 19. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of NILM

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

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

Table 20. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of ASCUS

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

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

Table 21. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of AGC

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

Among the 21 reviews determined by the adjudication panel to be AGC, 5 (23.8%) reviews in the Genius Cervical AI Algorithm 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 22. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of LSIL

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

Among the 579 reviews determined by the adjudication panel to be LSIL, 410 (70.8%) reviews in the Genius Cervical AI Algorithm 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 23. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of ASC-H

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

Among the 210 reviews determined by the adjudication panel to be ASC-H, 61 (29.0%) reviews in the Genius Cervical AI Algorithm 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 24. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of HSIL

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

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

Table 25. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Diagnoses of Cancer

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

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

Table 26. Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Results for All Diagnostic Categories in Slides with Adjudicated Results of UNSAT

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

Among the 102 reviews determined by the adjudication panel to be UNSAT, 72 (70.6%) reviews in the Genius Cervical AI Algorithm Review and 59 (57.8%) reviews in the Manual Review were diagnosed as UNSAT, and 20 (19.6%) reviews in the Genius Cervical AI Algorithm 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 the Genius Digital Diagnostic System with the Genius Cervical AI algorithm and Manual reviews with regard to false NILM results is presented in Table 27 below.

Table 27. Summary of False NILM results for Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (Manual) Review

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

Numbers in light grey colored cells in the above table indicate the reduction in the number of false NILM results using the Genius Cervical AI algorithm-based image review compared to manual glass slide review. Number in dark grey colored cell in the above table indicates the increase in the number of false NILM results using the Genius Cervical AI algorithm-based image review compared to manual glass slide review.

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 28 below.

Table 28. Summary of False positive results for Genius Cervical AI Algorithm Review (Genius) and Manual Glass Slide Review (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)

C.2 Genius Digital Diagnostics System with the Genius Cervical AI Algorithm Review compared with TIS Review

Performance of Genius Cervical AI Algorithm Review and TIS Review

The study also compared the performance of ThinPrep slides reviewed on the Genius Digital Diagnostic System with Genius Cervical AI Algorithm with ThinPrep slides reviewed on the ThinPrep Imaging System (TIS). The results for the Genius Cervical AI Algorithm review versus TIS review are presented in Table 29.

Table 29. Sensitivity and Specificity of Genius Cervical AI Algorithm Review (Genius) and TIS Review (TIS) Compared to Adjudicated Diagnosis

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

The observed sensitivity of the Genius Cervical AI Algorithm 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.3 Descriptive diagnosis for benign cellular changes

Table 30 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/PT teams. Each case was read first by a cytologist; non-NILM slides (as determined by the cytologist) were read by a PT from the same site CT/ PT team.

Table 30. Unadjudicated Marginal Frequencies –Summary of Descriptive Diagnosis for Benign Cellular Changes

	Manual Glass Slide Based Review		TIS Based Review		Genius Based Review	
Number of Reviews	5880		5880		5880	
Descriptive Diagnosis	**N**	**%**	**N**	**%**	**N**	**%**
Benign Cellular Changes	**721**	**12.3**	**686**	**11.7**	**1035**	**17.6**
Organisms:						
Trichomonas vaginalis	71	1.2	70	1.2	103	1.8
Fungal organisms consistent with *Candida* spp.	261	4.4	222	3.8	312	5.3
Shift in flora s/o bacterial vaginosis	371	6.3	373	6.3	562	9.6
Bacteria consistent with *Actinomyces* spp.	16	0.3	19	0.3	54	0.9
Cellular changes consistent with Herpes virus	2	0	2	0	3	0.1
Other infection	0	0	0	0	1	0
Other Non-Neoplastic Findings	**440**	**7.5**	**346**	**5.9**	**513**	**8.7**
Reactive cellular changes associated with inflammation	227	3.9	160	2.7	279	4.7
Atrophy	191	3.2	168	2.9	198	3.4
Reactive cellular changes associated with radiation	1	0	0	0	0	0
Reactive cellular changes associated with IUD	0	0	1	0	0	0
Glandular cells status post hysterectomy	0	0	0	0	2	0
Endometrial cells in a woman ≥45 yrs of age	21	0.4	17	0.3	34	0.6
Presence of Endocervical Component	**4387**	**74.6**	**4239**	**72.1**	**4602**	**78.3**

A higher percentage of infectious organisms (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 Glass Slide review, respectively. A higher percentage of infectious organisms (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 algorithm review compared to TIS review, respectively.

VII Cytologist Screening Time Study

As part of the Genius Cervical AI Clinical Study, Hologic also collected cytologist screening time data. 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. 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 31 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 31. 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 5 and 6 show scatterplots for the sensitivity and specificity results, respectively, as well as the resulting regression coefficients.

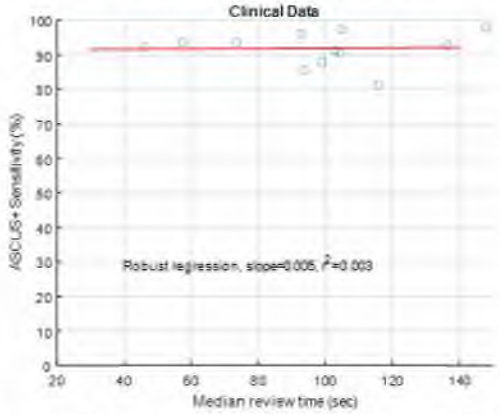

Figure 5. Sensitivity vs. Median Review Time

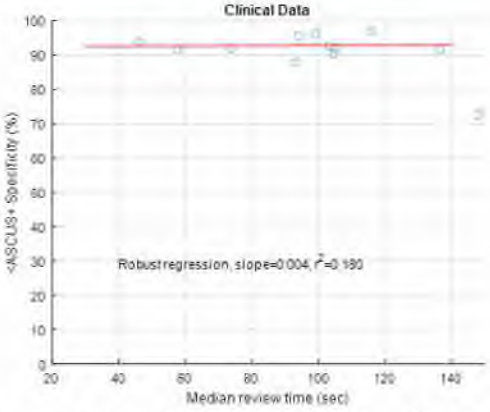

Figure 6. Specificity vs. Median Review Time

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 indicate that the CT case review time impacted the diagnostic performance at the ASCUS+ threshold.

Cytologist Workload Determination

Workload is defined by Clinical Laboratory Improvement Amendments of 1988 (CLIA) as a maximum limit of 100 slides in no less than an 8-hour workday (Clinical Laboratory Improvement Amendments of 1988; Final Rule. Federal Register. Feb. 28 1992; 57: 493.1483.). This refers to a full manual review of 100 slides. Based on the clinical study, the cytologist workload limit for the Genius Digital Diagnostics System with the Genius Cervical AI algorithm is as follows:

All cases diagnosed from the Genius Digital Diagnostics System with Genius Cervical AI algorithm count as 0.5 or ½ CLIA slide equivalent. In the Genius Cervical AI clinical study, CTs accurately diagnosed cases using digital images presented by the system more efficiently than with a full manual review of a case.

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

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

$$0.5*GCAI + 1.5*(GCAI + FMR) + 1*FMR \leq 100 \text{ CLIA slide equivalents}$$

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

200 Genius Cervical AI Case Reviews = 100 CLIA slide equivalents
(200 x 0.5 = 100)
Total number of CLIA slide equivalents screened: 100

Example 2 - workload for reviewing ThinPrep Pap tests with the Genius Digital Diagnostics System with the Genius Cervical AI algorithm device when some cases were reviewed both digitally and on glass:
180 Genius Cervical AI Case Reviews = 90 CLIA slide equivalents [180 x 0.5 = 90]
6 Genius Cervical AI Case Reviews + FMR = 9 CLIA slide equivalents [(6 x 0.5) + (6 x 1) = 9]
Total number of CLIA slide equivalents screened: 99 (90 + 9)

Notes:

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

VIII Human Factors Studies

Formative and Summative Studies were performed for the Genius Digital Diagnostic System with the Genius Cervical AI algorithm. A study was conducted to evaluate the usability and user experience of the Genius Review Station with 15 representative users. Study methodology is based on the HFE process, usability testing, and risk management guidance provided in the FDA 2016 human factors guidance documents and additional technical reports and standards identified in the table in section J above.

Study personnel conducted the testing under simulated-use conditions. Participants went through task scenarios that involved interaction with the Genius Review Station and the review of imaged slides that were selected prior to the session. The simulated use conditions were sufficient to confirm that intended users could use the Genius Review Station safely and to test the effectiveness of risk mitigations associated with highly rated risks. All critical tasks were assessed under the simulated-use conditions and post-test interviews were conducted to determine the root cause of any observed or unobserved use error or problem.

IX Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

X Identified Risks and Mitigations:

Risks to Health	Mitigation Measures
False negative and false positive results due to device errors in presenting abnormal cells in the digital image gallery	Certain design verification and validation, including certain studies and risk mitigation analysis. Certain labeling information, including limitations, device descriptions, methodology and protocols, and performance information.
False negative and false positive results due to incorrect interpretation of digital images or incorrect operation of the device by the user	Certain design verification and validation, including certain studies and risk mitigation analysis. Certain labeling information, including limitations, user training, device descriptions, methodology and protocols, and performance information.

XI Benefit/Risk Assessment:

A Summary of the Assessment of Benefit:

The Genius Digital Diagnostics System with Genius Cervical AI algorithm has probable benefits of aiding in cervical cancer screening for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions) and carcinoma, as well as all other cytological categories as defined by The Bethesda System for Reporting Cervical Cytology.

In the Genius Cervical AI Algorithm 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 Algorithm 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 the Genius Cervical AI algorithm 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% 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% -18.5%) / 26%).
- For Cancer, the observed sensitivities of the Genius Digital Diagnostics System with the Genius Cervical AI algorithm method and Manual Review method were the same, with a confidence interval of -9.8% to 11.1%.

B Summary of the Assessment of Risk:

False positive and false negative results from the use of this device can have a range of consequences ranging from minimal effect to serious consequences such as delay in cancer diagnosis and treatment. False-positive test results may lead to unnecessary follow-up procedures. The workup for an abnormal Pap test typically includes invasive follow-up procedures such as colposcopy and biopsy that can cause discomfort. False negative results may occur due to misclassification of an abnormal slide as normal resulting in no further diagnostic workup for the patient, which may lead to increased morbidity and mortality. Detailed descriptions of the intended user(s) and recommended training for safe use of the device as indicated in the special control and labeling mitigate the risk associated with the use of the device.

C Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

D Summary of the Assessment of Benefit-Risk:

Genius Digital Diagnostics System with the Genius Cervical AI algorithm device provides a reasonable assurance of safety and effectiveness for diagnostic use by its intended users after taking into consideration the special controls. The clinical and analytical studies have shown that the risk of accuracy loss resulting in a false positive or false negative diagnosis, is outweighed by the probable benefits, including new findings that would contribute to the correct diagnosis. This is contingent on the device being used according to the approved labeling, particularly that the end user must be fully aware of how to interpret and apply the device output.

The risks of false positive or negative results due to device or user error are mitigated by required design verification and validation, including certain studies and risk analysis to help ensure device performance and proper use. The risks are further mitigated by certain safety measures, such as user training (digital images from the Genius Digital Diagnostics System with the Genius™ Cervical AI algorithm should be interpreted by qualified cytologists and pathologists who have undergone further training specifically in the use of the device) and certain labeling information, such as limiting statements, performance information, and detailed descriptions of methodology and protocols.

The probable clinical benefits outweigh the risks for the Genius Digital Diagnostics System with the Genius Cervical AI algorithm device. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

XII Conclusion:

The De Novo request is granted, and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): QYV
Device Type: Digital cervical cytology slide imaging system with artificial intelligence algorithm
Class: II
Regulation: 21 CFR 864.3900