510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

I Background Information:

A 510(k) Number

K232202

B Applicant

Leica Biosystems Imaging, Inc.

C Proprietary and Established Names

Aperio GT 450 DX

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
PSY	Class II	21 CFR 864.3700	88-Pathology

II Submission/Device Overview:

A Purpose for Submission:

1. New device
2. Add 3 additional specific displays intended to be used with the new device

B Type of Test:

Digital pathology whole slide imaging

III Intended Use/Indications for Use:

A Intended Use(s):

The Aperio GT 450 DX is an automated digital slide creation and viewing system. The Aperio GT450 DX is intended for in vitro diagnostic use as an aid to the pathologist to review and interpret digital images of surgical pathology slides prepared from formalin-fixed paraffin embedded (FFPE) tissue. The Aperio GT 450 DX is for creation and viewing of digital images of

scanned glass slides that would otherwise be appropriate for manual visualization by conventional light microscopy.

Aperio GT 450 DX is comprised of the Aperio GT 450 DX scanner, which generates images in the Digital Imaging and Communications in Medicine (DICOM) and in the ScanScope Virtual Slide (SVS) file formats, the Aperio WebViewer DX viewer, and the displays. The Aperio GT 450 DX is intended to be used with the interoperable components specified in Table 1.

Table 1: Interoperable components of Aperio GT 450 DX

Scanner Hardware	Scanner Output file format	Interoperable Viewing Software	Interoperable Displays
Aperio GT 450 DX scanner	SVS	Aperio WebViewer DX	Barco MDPC-8127 Dell UP3017 Dell U3023E Dell U3223QE
Aperio GT 450 DX scanner	SVS	Sectra Digital Pathology Module (3.3)	Dell U3223QE
Aperio GT 450 DX scanner	DICOM	Sectra Digital Pathology Module (3.3)	Dell U3223QE

The Aperio GT 450 DX is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens. 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 the Aperio GT 450 DX.

B Indication(s) for Use:

Same as Intended Use.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only
For In vitro diagnostic (IVD) use only

IV Device/System Characteristics:

A Device Description:

The Aperio GT 450 DX is a Whole Slide Imaging (WSI) system which includes the following components.

- Aperio GT 450 DX digital slide scanner which includes the corresponding scanner configuration software, Aperio GT 450 Scanner Administration Manager DX (SAM DX)

- Viewing Workstation executing Aperio WebViewer DX image viewing software (version 1.0.0.5033)
- Display

The Aperio GT 450 DX scanner is a semi-automated benchtop brightfield WSI scanner which includes the scanner configuration software and Aperio GT 450 Scanner Administration Manager DX (SAM DX) and is intended to scan surgical pathology glass slides prepared from FFPE tissue. The scanner supports continuous glass-slide loading of up to 15 racks with a total of 450-slide capacity, priority rack scanning, and automated image quality checks during image acquisition. The Aperio GT 450 DX scanner detects the racks once loaded in the scanner and automatically loads each slide in the batch to the stage and scans the glass slide to generate the WSI image. It can achieve a scan speed of 32 seconds at the 40x scanning magnification for a 15 mm x 15 mm area. Users operate the scanner via a touchscreen interface.

The Aperio GT 450 DX scanner can save digital images in a unique Aperio ScanScope Virtual Slide (SVS) image format or Digital Imaging and Communications in Medicine (DICOM) image format. SVS images displayed in Aperio WebViewer DX are compressed to 94% of the source SVS file, or JPEG Q = 94. After acquiring the scanned digital images, they are sent to end-user-provided image storage attached to the scanner's local network, where they can be cataloged in image storage software including Image Management System (IMS), such as Aperio eSlide Manager or a Picture Archiving and Communication System (PACS).

Aperio GT 450 SAM DX is centralized scanner management software external to the connected scanner(s). This software application enables configuration, monitoring, and service access of multiple scanners from a single desktop client location. Aperio GT 450 SAM DX is installed on a customer-provided server that resides on the same network as the scanner(s) for image management.

The Aperio WebViewer DX image viewing software is a web-based image viewer that enables users to perform quality control of images and to review and annotate digital images acquired from the Aperio GT450 DX scanner for pathology primary diagnosis. The Aperio WebViewer DX also incorporates monitor display image validation checks, which provide the user with the ability to ensure the digital slide images are displayed as intended on their monitor, and that browser updates have not inadvertently affected the image display quality. Aperio WebViewer DX is installed on a server and accessed from an IMS (e.g., Aperio eSlide Manager) or a customer's Laboratory Information System (LIS) using compatible browsers.

The display allows the slide images to be viewed. The interoperable displays are thin-film transistor, in-plane switching (TFT), color liquid crystal displays (TFT-LCD/IPS) calibrated to the sRGB color space. Their specifications are listed in Table 8 below.

Instrument Description Information:

1. Instrument Name:
   Aperio GT 450 DX

2. Specimen Identification:
Glass slides and scanned images are identified based on the previously assigned specimen identifiers such as patient identifiers, barcodes, etc. Digital images of surgical pathology slides prepared from FFPE tissue.

3. Specimen Sampling and Handling:
Specimen sampling and handling are performed upstream and independent of the use of the subject device. Specimen sampling includes surgical pathology specimens such as biopsy or resection specimens which are processed using standard histology techniques. The FFPE tissue sections are stained using the Hematoxylin and Eosin (H&E) staining procedure. Then digital images are obtained from these glass slides using the Aperio GT 450 DX scanner.

4. Calibration:
The Aperio GT 450 DX scanner performs essential image calibrations at the time the scanner is powered on. No additional calibration is needed for regular use. There is no calibration for Aperio GT 450 DX software.

5. Quality Control:
Quality control (QC) activities are performed by the user per the laboratory standards and professional guidelines (e.g., staining, cover-slipping, barcode placement) prior to loading the slides into the Aperio GT 450 DX scanner. After completing a scan, the lab technician checks image data and image quality as per the instructions for use. Before review, the pathologist performs quality control on the WSI images of the slide per instructions for use.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Aperio AT2 DX System

B Predicate 510(k) Number(s):

K190332

C Comparison with Predicate(s):

Device & Predicate Device(s):	**K232202** Aperio GT 450 DX	**K190332** Aperio AT2 DX System
General Device Characteristics: Similarities		
Intended Use	The Aperio GT 450 DX is an automated digital slide creation and viewing system. The Aperio GT 450 DX is intended for in vitro diagnostic use as an aid to the pathologist to review and interpret digital images of surgical pathology slides prepared from formalin-fixed paraffin embedded (FFPE) tissue. The Aperio	The Aperio AT2 DX System is an automated digital slide creation and viewing system. The Aperio AT2 DX System is intended for *in vitro* diagnostic use as an aid to the pathologist to review

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The Aperio AT2 DX System is composed of the AperioAT2 DX scanner, the ImageScope DX review application and Display. The Aperio AT2 DX System is for creation and viewing of digital images of scanned 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 the Aperio AT2 DX System</td></tr>
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Device & Predicate Device(s):	**K232202** Aperio GT 450 DX	**K190332** Aperio AT2 DX System
Principle of Operation	The Aperio GT 450 DX is a WSI system. The technician places the slides into the Aperio GT 450 DX scanner. The Aperio GT 450 DX scanner automatically loads the slides, takes the micro images, finds the tissues, and scans the slides. The scanner also automatically performs quality control (QC) and notifies the user of any image quality issue during the image acquisition. The image data is sent to end-user-provided image storage attached to the local network. During the review, the pathologist opens WSI images acquired with the WSI scanner from the image storage, performs further QC, and reads WSI images of the slides to make a diagnosis.	Same
Device Components	WSI scanner (Aperio GT450 DX scanner), Image Management System (Aperio WebViewer DX image viewing software) and color monitor display	WSI scanner (Aperio AT2 DX scanner), Image Management System (ImageScope DX application) and color monitor display
Image Storage	Images are stored in the end-user- provided image storage attached to the local network.	Same
General Device Characteristic: Differences		
Scanning Magnification	40x	40x 20x
Slide Loading Method	Automatic	Automatic and Manual
Continuous Slide Loading	Yes	No
Throughput (includes slide handling) at 40x	81 slides per hour	20 slides per hour
Scan Speed at 40x	< 32 sec/slide, 15 x 15 mm	< 2 min 35 sec/slide, 15 x
Scan Output Image Format	SVS and DICOM	SVS
Compatible Display (Monitor)	DELL UP3017 Dell U3023E Dell U3223QE Barco MDPC-8127	Dell MR2416

VI Standards/Guidance Documents Referenced:

1. FDA Guidance "Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices" dated April 20, 2016.
2. Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food and Drug Administration Staff February 3, 2016.
3. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. Guidance for Industry and Food and Drug Administration Staff, May 2005.
4. IEC/EN 61010-1:2010/AMD1: 2016, Safety requirements for electrical equipment for measurement, control, and laboratory use – Part 1: General requirements.
5. IEC/EN 61010-2-101: 2018, Safety requirements for electrical equipment for measurement, control, and laboratory use – Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment.
6. FDA Guidance "Electromagnetic Compatibility (EMC) of Medical Devices (June 6, 2022).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The objective of this study was to evaluate the repeatability (within- and between- system) and reproducibility (between-site) of the Aperio GT 450 DX.

The precision of the device was based on 5 reading pathologists' assessments and identification of specific histopathologic "features" that are observed in FFPE H&E stained slides. Twenty-three (23) primary features were selected for the analytical studies. The selected primary features were evaluated at their relevant magnifications -12 primary features evaluated at 20x magnification level and 11 primary features evaluated at 40x magnification level.

The Precision Panel Slide Curator (curator) identified study slides by conducting a Lab Information System (LIS) search and reviewing the microscope slides from consecutive cases that potentially contain the study features (Table 1). A representative H&E stained slide or a re-cut slide containing the feature(s) of interest was obtained from each case. After the curator selected and marked the study features on the slides, the slides were scanned at magnification levels designated to the study features, either 20x or 40x magnification. The curator reviewed the glass slides through the microscope while reviewing the WSI images on the monitor to extract Field of Views (FOVs) containing the study features from the WSI images using a lossless compression type. For each subsequent WSI images of the same slide, the annotations were manually replicated by a technician using the image viewing software to extract and randomly rotate the FOVs by 90, 180 or 270 degrees to minimize recall bias. A trained study personnel verified the FOV filenames and also that the FOV extraction areas were correct and enrolled the FOVs in the study. During precision study, the extracted FOV images were restricted for both the area of tissue visible to the reading pathologists and for the viewing magnification. The reading pathologists were not allowed to navigate the WSI image or change magnification or get access to any clinical information associated with the study slides. Additional slides that may or may not include any of the study features were included as "wild card" slides to reduce recall

bias. The "wild card" FOVs were extracted by following the same procedures as the study FOVs. As shown in Table 1, each primary study feature was represented in 3 FFPE sections of different organ types. From each slide, 2 or 3 FOVs containing either one primary study feature, or a primary study feature and secondary study feature(s) in each FOV were selected. A total of 202 FOVs were selected from 69 glass slides. Out of 202 FOVs, 46 FOVs (from 24 slides) contained multiple histologic features and 156 FOVs (from 62 slides) contained one primary histologic feature. In addition, 36 wild card FOVs were selected from 12 glass slides. There was a minimum washout period of 14 days between pathologist reading sessions.

Table 1: Primary Histologic Study Features in Precision Study

Feature	Specimen Source/Organ Type
FOV Magnification – 20x	
Chondrocytes	Toe
	Femoral Head
	Osteosarcoma of humerus
Fat cells (adipocytes)	Axillary lymph node
	Femoral head
	Prostate
Foreign body giant cells	Knee synovium
	Shoulder
	Sigmoid colon
Goblet cells in intestinal mucosa or intestinal metaplasia	Gastroesophageal junction
	Sigmoid colon
	Tubular adenoma (intestine)
Granulomas	Colon
	Iliac crest (bone)
	Cervical lymph node
Infiltrating or metastatic lobular carcinoma	Iliac crest (bone)
	Jejunum
	Breast
Intraglandular necrosis	Lung
	Liver
	Right colon
Osteoclasts	Sacrum
	Toe
	Paget's disease of spine
Osteocytes	Foot
	Maxilla
	Osteosarcoma of femur
Pleomorphic nucleus of malignant cell	11^{th} rib
	Sacrum
	Vertebra

Feature	Specimen Source/Organ Type
Serrated intestinal epithelium (for example sessile serrated polyp)	Appendix
	Ascending colon polyp
	Sigmoid colon
Skeletal muscle fibers	Lower leg
	Shoulder
	Spine
FOV Magnification – 40x	
Asteroid bodies	Axillary lymph node
	Liver
	Synovium
Clear cells (renal cell carcinoma)	Humerus
	Retroperitoneal lymph node
	Right kidney
Foreign bodies (for example plant material or foreign debris)	Distal femur
	Foot
	Wrist
Hemosiderin (pigment)	Knee synovium
	Liver
	Osteosarcoma of femur
Megakaryocytes	Cervical Spine
	Femur (margin of sarcoma)
	Tibia
Necrosis	Femoral head
	Para-aortic lymph node
	Right leg
Nerve cell bodies (for example ganglion cells)	Ganglioneuroma
	Small bowel
	Stomach
Nuclear grooves	Cervical lymph node (papillary thyroid carcinoma)
	Iliac crest (bone) (Langerhan's cell granuloma)
	Ovary (Brenner tumor)
Osteoid matrix	Femur
	Humerus
	Lung
Psammoma bodies	Cervical lymph node (metastatic papillary carcinoma of thyroid)
	Fallopian tube (papillary ovarian carcinoma)
	Left ventral cranial region (meningioma)
Reed-Sternberg cell	Axillary lymph node

Feature	Specimen Source/Organ Type
	Neck mass
	Spleen

The precision of the Aperio GT 450 DX was assessed in 3 sub-studies:

- Within-system precision was assessed using 3 independent systems. Overall within-system precision was also assessed.
- Between-system/site precision, was assessed 3 independent systems at 3 different sites. Overall between systems/sites precision was also assessed.
- Within- and between-pathologist precision was assessed using images generated from a single system. Overall within-pathologists and overall between-pathologists precision were also assessed.

The precision was considered acceptable if the lower bounds of the 2-sided 95% confidence interval (CI) of the overall agreements for each precision component (within-system, between-system/site, within-pathologist, and between-pathologist) were ≥ 85%

Within-System Precision

This study evaluated the agreement between the 3 scans from the same system/site. The panel of 69 study slides was split equally among the three (3) sites (i.e., each site scanned a separate subset of slides). Each site has a single scanning system. For each system, 23 slides were scanned once on each of three (3) days, producing three (3) sets of scans for each slide. FOVs were extracted from scanned WSI images. The FOVs from three scanning sessions were evaluated by one reading pathologist over three different reading sessions with at least a two-week washout period in between the reading sessions. In each reading session, the reading pathologist evaluated all 202 study FOVs from each of three scanning sessions (across three scanning systems), plus unique "wild card" FOVs to assist in preventing recall bias between reading sessions.

For each system, agreements between scan 1 versus scan 2, scan 1 versus scan 3 and scan 2 versus scan 3 were analyzed. The overall within-system precision was based on the pooled data of all three systems. A bootstrap approach was used to calculate 95% Confidence Intervals (CIs).

Table 2. Within Systems Precision Study Results

			Agreement Rate and 95% CI		
System/Site	**Number of Pairwise Agreements**	**Number of Comparison Pairs**	**% Agreement**	**Lower**	**Upper**
System 1 /Site1	255	261	97.7	95.7%	99.3%
System 2 /Site2	270	276	97.8	95.9%	99.3%
System 3	212	222	95.5	92.5%	98.1%

/Site3					
Overall	737	759	97.1	95.8%	98.3%

Between-System/Between-Site Precision

At each of three study sites, a study technician scanned the entire set of 69 study slides once. FOVs from three scanning sessions (resulting from one session from each of the three sites) were extracted. From all the scanning systems, 606 FOVs were transferred to a single reading pathologist for evaluation in three separate reading sessions. In each reading session, the reading pathologist evaluated all 202 study FOVs from a single site, plus unique "wild card" FOVs to assist in preventing recall bias between reading sessions. Agreements between systems at Site 1 versus Site 2, systems at Site 1 versus Site 3 and systems at Site 2 versus Site 3 were analyzed. The overall inter-system/inter-site precision is based on the pooled data from each system-to-system comparison. A bootstrap approach was used to calculate 95% CIs.

Table 3. Between Systems Precision Study Results

			Agreement Rate and 95% CI		
System	**Number of Pairwise Agreements**	**Number of Comparison Pairs**	**% Agreement**	**Lower**	**Upper**
System 1 vs System 2	241	253	95.3	92.5%	97.7%
System 1 vs System 3	246	253	97.2	95.0%	99.2%
System 2 vs System 3	244	253	96.4	94.0%	98.5%
Overall	731	759	96.3	94.9%	97.6%

Within-Site/Within-Pathologist and Between-Pathologist Precision

The entire set of 69 slides were scanned once at one site. FOVs were extracted and saved in three different orientations. From all the orientations, 606 FOVs were presented to each of three reading pathologists for evaluation in three reading sessions. In each reading session, each reading pathologist evaluated all 202 study FOVs plus unique "wild card" FOVs to assist in preventing recall bias between reading sessions. For within-pathologist precision, agreements between FOVs in orientation 1 versus orientation 2, orientation 1versus orientation 3, and orientation 2 versus orientation 3 were analyzed for each reading pathologist. The overall within-pathologist precision was based on the pooled data from each reading pathologist. A bootstrap approach was used to calculate 95% CIs.

Table 4. Within-Pathologists Precision Study Results

			Agreement Rate and 95% CI		
Pathologist	**Number of Pairwise Agreements**	**Number of Comparison Pairs**	**% Agreement**	**Lower**	**Upper**
Pathologist 1	729	759	96.0	94.7%	97.3%
Pathologist 2	677	759	89.2	86.8%	91.3%
Pathologist 3	723	759	95.3	93.7%	96.7%
Overall	2129	2277	93.5	92.4%	94.5%

For between-pathologist precision, agreements between pathologist 1 versus pathologist 2, pathologist 1 versus pathologist 3, and pathologist 2 versus pathologist 3 were analyzed. The overall between-pathologist precision was based on the pooled data from each reading pathologist. A bootstrap approach was used to calculate 95% CIs.

Table 5. Between-Pathologist Precision Study Results:

			Agreement Rate and 95% CI		
Pathologist	**Number of Pairwise Agreements**	**Number of Comparison Pairs**	**% Agreement**	**Lower**	**Upper**
Pathologist 1 vs Pathologist 2	686	759	90.4	88.2%	92.4%
Pathologist 1 vs Pathologist 3	727	759	95.8	94.3%	97.2%
Pathologist 2 vs Pathologist 3	676	759	89.1	86.9%	91.2%
Overall	2089	2277	91.7	90.6%	92.8%

2. *Linearity:*

   Not applicable

3. *Analytical Specificity/Interference:*

   Not applicable

4. *Accuracy (Instrument):*

   Not applicable

5. *Carry-Over:*

   Not applicable

B. Technical Studies:

Multiple studies were conducted to evaluate the performance of the Aperio GT 450 DX as recommended in FDA Guidance, *Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices.*

a. Slide Feeder

Information was provided on the configuration of the slide feed mechanism, including a physical description of the slide, the number of slides in the queue (carrier), and the class of automation. Information was provided on the user interaction with the slide feeder, including hardware, software, feedback mechanisms, and Failure Mode and Effects Analysis (FMEA).

b. Light source

Descriptive information associated with the lamp and the condenser was provided. Testing information was provided to verify the spectral distribution of the light source as part of the color reproduction capability of the Aperio GT 450 DX scanner.

c. Imaging optics

An optical schematic with all optical elements identified from the slide (object plane) to the digital image sensor (image plane) was provided. Descriptive information regarding the microscope objective, the auxiliary lenses, and the magnification of imaging optics was provided. Testing information regarding the relative irradiance, optical distortions, and lateral chromatics aberrations was provided.

d. Mechanical scanner movement

Information and specifications on the configuration of the stage, method of movement, control of movement of the stage, and FMEA were provided. Test data to verify the repeatability of the stage movement and verify the mechanism that the stage movement stays within limits during operations was provided.

e. Digital imaging sensor

Information and specifications on the sensor type, pixel information, responsivity specifications, noise specifications, readout rate, and digital output format were provided. Test data to determine the correct functioning of the digital image sensor was provided. The digital image sensor converts slides' optical signals to digital signals. The digital signals consist of a set of numerical values corresponding to the brightness and color at each point in the optical image.

f. Image processing software

Information and specifications on exposure control, white balance, color correction, sub-sampling, pixel-offset correction, pixel-gain or flat-field correction, and pixel-defect correction were provided.

g. Image composition

Information and specifications on the scanning method, the scanning speed, and the number of planes at the Z-axis to be digitized were provided. Test data to analyze the image composition performance was provided.

h. *Image files format*
Information and specifications on the compression method, compression ratio, file format, and file organization were provided.

i. *Image review manipulation software*
Information and specifications on continuous panning and pre-fetching, continuous zooming, discrete Z-axis displacement, the ability to compare multiple slides simultaneously on multiple windows, image enhancement and sharpening functions, color manipulation, annotation tools, and digital bookmarks were provided.

j. *Computer environment*
Information and specifications on the computer hardware, operating system, graphics card, graphics card driver, color management settings, color profile, and display interface were provided.

k. *Display*
Information and specifications on the technological characteristics of the display device, the physical size of the viewable area and aspect ratio, backlight type and properties, frame rate and refresh rate, a pixel array, pitch, pixel aperture ratio, and subpixel matrix scheme, subpixel driving to improve grayscale resolution, supported color spaces, display interface, user controls of brightness, contrast, gamma, color space, power-saving options, etc., via the on-screen display menu, ambient light adaptation, touchscreen technology, color calibration tools, and frequency and nature of quality-control tests were provided. Test data to verify the performance of the display was provided.

l. *Color reproducibility*
Test data to evaluate the color reproducibility of the system was provided.

m. *Spatial resolution*
Test data to evaluate the composite optical performance of all components in the image acquisition phase was provided.

n. *Focusing test*
Test data to evaluate the technical focus quality of the system was provided.

o. *Whole slide tissue coverage*
Test data to demonstrate that the entire tissue specimen on the glass slide is detected by the tissue detection algorithms and that all the tissue specimens are included in the digital image file was provided.

p. *Stitching error*
Test data to evaluate the stitching errors and artifacts in the reconstructed image was provided.

q. *Turnaround time*
Test data to evaluate the turnaround time of the system was provided.

C. Clinical studies:

A multi-center study was conducted to demonstrate that viewing, reviewing, and diagnosing

digital images of surgical pathology FFPE tissue slides using the Aperio GT 450 DX System is non-inferior to using optical (light) microscopy. The primary endpoint was the difference in major discordance rates between WSI review modality (WSIR) and microscope slide review modality (MSR) when compared to the reference (main) diagnosis, which is based on the original sign-out pathologic diagnosis rendered at the institutions, using an optical (light) microscope. The study cases were selected from the previous Aperio AT2 DX System clinical study (K190332). In order to ensure cases met the selection criteria and that selected slides were representative of the primary diagnosis the case curation process and the study inclusion and exclusion criteria in the previous study were as follows: The case curation pathologist reviewed the sign-out diagnosis and supporting documentation available at the time of the diagnosis (i.e., pathology report). By reviewing the microscopic slides used to make the sign-out diagnosis, the slide(s) that were representative of the sign-out diagnosis for the case were identified. The selected slides included H&E, immunohistochemistry (IHC), special stains and any slides that were not critical to diagnosis but supported the final surgical pathology report (e.g., margins, lymph node status, vascular and neural invasion), and any slides representing required elements of the College of American Pathologists (CAP) applicable cancer protocols. In the case of IHCs and special stains, the inclusion of control slides was required to fulfill the quality checks according to general clinical practice. The site's curation verification pathologist verified that the selected slide(s) reflected the main diagnosis for the case as well as the required ancillary information for cancer cases met all inclusion criteria and none of the exclusion criteria stated below before the case was enrolled in the study.

Inclusion criteria:

- All glass slides with human tissue obtained via surgical pathology of the original case were available.
- The original sign-out diagnosis and ancillary supporting information were available.
- The selected slide(s) for the main diagnosis and the control slide(s) (e.g., controls for IHC stained slides) matched the study requested organ type and fulfilled the quality checks according to general clinical practice.
- For cases with multiple diagnoses in a single sign-out pathology report, only the main diagnosis and ancillary information were included.

Exclusion criteria:

- H&E stained slides that were used for the original sign-out diagnosis were not available at the site and re-cuts were not available.
- If applicable, the IHC or special stain slides that were used for the original sign out diagnosis were not available at the site or had unacceptable artifacts. Control slides for IHC or special stain were not available.
- Cases for which slides needed to support the original sign-out diagnosis required either a special light source (e.g., a mercury lamp for fluorescence microscopy) or special filters (e.g., for polarized light).
- Cases with slides containing unremovable markings or were damaged.
- Cases that contained frozen sections or gross specimens only.
- Cases that were missing significant clinical and ancillary information that was available at the time the case was originally interpreted (e.g., X-rays).
- Cases that were signed out less than one year prior to the date of curation.
- Only one case could be enrolled per patient.

A total of 1161 cases were selected to be enrolled in the current study and included a diverse

mixture of pathologic diagnoses and tissue/organ types. There was a total of 3 study sites.

At each site of the 3 study sites, technician(s) scanned slides from cases identified at their sites using the Aperio GT 450 DX. Each reading pathologist at each site (3 pathologists at each of sites 1 and 2 and 4 pathologists at Site 3) evaluated all study cases from their site using the Aperio GT 450 DX, as well as the case ancillary information to determine WSIR diagnosis. For each reading pathologist, approximately 50% of cases were reviewed from the site's local server (local access) and approximately 50% of cases were reviewed from the LBS image web hosting site (remote access). If the WSIR diagnosis could not be determined, the reading pathologist could defer the diagnosis. The reason(s) for deferring a diagnosis was documented.

There was a total of 3709 case reads performed by WSIR: (Site 1: 399 cases × 3 pathologists) + (Site 2: 500 cases × 3 pathologists) + (Site 3: 253 × 4 pathologists). There were 1883 case reads (1883/3709, 50.8%) performed at the local viewing station (local cohort) and 1826 number of cases reads (1826/3709, 49.2%) performed at the remote viewing station (remote cohort). For MSR diagnosis, the consensus scores generated during the previous Aperio AT2 DX System clinical study (K190332) were used for this study to estimate MSR diagnosis major discordance rate.

A minimum of 2 adjudication pathologists (also known as adjudicators) independently assessed concordance (concordant, minor discordance, major discordance) of the WSIR diagnosis against the sign-out diagnosis (reference diagnosis) using predefined rules. A major discordance was defined as a difference in diagnosis that resulted in a clinically important difference in patient management, while a minor discordance would not be associated with a clinically important difference in patient management. The concordance score for the same case between the 2 adjudicators were compared to determine a consensus score for major discordance status. If consensus was not reached between the first 2 adjudicators, a third adjudicator reviewed the study diagnosis against the reference diagnosis. If consensus between 2 of 3 adjudicators was still not reached, then the 3 adjudicators convened as a panel to come to a consensus for the major discordant status. WSIR diagnosis consensus scores were used to estimate WSIR diagnosis major discordant rate.

Major discordance rates were estimated for WSIR diagnosis and MSR diagnosis (relative to the reference diagnosis), as well as the difference in overall major discordance rates between the 2 modalities. For the primary objective of demonstrating the WSIR major discordance rate to be non-inferior to the MSR major discordance rate, a Generalized Linear Mixed Model (GLIMMIX) logistic regression was conducted. For each reading result the dependent variable was the major discordance status and independent variables included modality as a fixed effect (WSIR vs. MSR) and site, reader, and case as random effects. A two-sided 95% CI for the modality effect, i.e., the overall major discordance rate difference (WSIR minus MSR), was constructed from this analysis. If the upper bound of the 95% CI was less than the non-inferiority margin of 4%, WSIR would be considered non-inferior to MSR shows the overall major discordance rates of the full cohort for both modalities (relative to the reference diagnosis) based on observed results and by the generalized linear model.

Thirty-six (36) WSIR case reads from 1 pathologist at Site 2 were excluded due to incorrectly assigned diagnoses (14 case reads from the local cohort and 22 case reads from the remote cohort). One case read (remote cohort) from 1 pathologist at Site 2 was excluded from both modalities due to an absence of MSR data from previous Aperio AT2 DX System Accuracy Study. Therefore, 3672 and 3708 cases read were performed by WSIR (local cohort: 1869 case reads; remote cohort: 1803 case reads) and MSR, respectively.

Excluding the 122 (3.3%, 122/3672) WSIR and 77 (2.1%, 77/3708) MSR deferred diagnoses (cases for which no study diagnoses was assigned and were not sent for adjudication), 3550 WSIR and 3631 MSR diagnoses were generated by the reading pathologists and sent for adjudication. Of the 122 WSIR deferred diagnoses, 62 (62/122, 50.1%) were from the local cohort and 60 (60/122, 49.2%) were from the remote cohort, resulting in 1807 and 1743 diagnoses for the local and remote cohorts, respectively. Note: MSR diagnoses were generated during the previous Aperio AT2 DX System clinical study (K190332).

One WSIR diagnosis (local cohort) was deferred by the adjudicators. Therefore, 3549 WSIR diagnoses were included in the statistical analyses (1806 from the local cohort and 1743 from the remote cohort). For MSR, 3631 diagnoses had consensus scores (from the previous Aperio AT2 DX System clinical study) and were included in the statistical analyses. analyses.

Study Results

The overall observed major discordance rate for WSIR diagnosis was 6.14% (218/3549) and for MSR diagnosis was 3.66% (133/3631). The overall major discordance rates estimated by the generalized linear model were 5.84% (95% CI: 5.01% to 6.80%) for the WSIR diagnosis and 3.44% (95% CI: 2.84 to 4.17%) for the MSR diagnosis. The estimated difference in major discordance rates (WSIR diagnosis minus MSR diagnosis) was 2.40% (95% CI: 1.40% to 3.39%). The upper bound of the 95% CI of the estimated difference in major discordance rates was 3.39% which met the predefined acceptance criteria of ≤4%.

The secondary endpoint was to demonstrate that the overall major discordant rate between the WSIR diagnosis and the reference diagnosis did not exceed 7%; the upper bound of the 95% CI for the overall major discordant rate of WSIR diagnosis was 6.80%, which met the predefined acceptance criteria of ≤7%. Thus, the study met the primary objective. Study results are shown in the table below.

Table 6: Clinical Study Results Based on Major Discordance Rates

	Whole Slide Imaging Review (WSIR)			**Light Microscope Slide Review (MSR)**			**Difference (WSIR – MSR)**	
	Total Reads	% discordant	95% CI	Total Reads	% discordant	95% CI	% discordant	95% CI
Observed	3549	6.14%	-	3631	3.66%	-		-
Model		5.84%	(5.01%, 6.80%)		3.44%	(2.84, 4.17)	2.40%	(1.40%,3.39 %)

The differences in major discordance rates by organ types for the full cohort between WSIR and MSR are shown in the table below.

Table 7: Major Discordance Rates by Organ

Organ Type	**Major Discordance Rate**		**Difference in Major Discordance Rates (WSIRD minus MSRD)**
	WSIRD (n=3549)	**MSRD (n=3631)**	
Anus/Perianal	7.26%	3.23%	4.03%
Appendix	0.00%	0.00%	0.00%

Organ Type	Major Discordance Rate		Difference in Major Discordance Rates (WSIRD minus MSRD)
	WSIRD (n=3549)	MSRD (n=3631)	
Bladder	14.79%	12.87%	1.93%
Brain/Neuro	2.90%	6.02%	-3.13%
Breast	7.62%	3.61%	4.01%
Colorectal	2.18%	1.42%	0.76%
Endocrine	6.47%	3.53%	2.94%
GE Junction	2.91%	4.65%	-1.74%
Gallbladder	0.00%	0.00%	0.00%
Gyn	5.22%	4.69%	0.53%
Hernial/Peritoneal	0.00%	0.00%	0.00%
Kidney, Neoplastic	3.13%	1.03%	2.09%
Liver/BD	4.55%	1.39%	3.16%
Lung	7.11%	2.02%	5.09%
Lymph Node	2.76%	2.27%	0.49%
Prostate	6.80%	4.03%	2.76%
Salivary gland	1.43%	1.37%	0.06%
Skin	10.57%	2.87%	7.70%
Soft Tissue Tumor	6.90%	3.41%	3.49%
Stomach	3.97%	3.27%	0.71%

The observed estimates for the major discordance rates for the WSIR and MSR diagnoses (relative to the reference diagnosis) and the difference between the two modalities (WSIR major discordance rate minus MSR major discordance rate) for each organ for the full cohort, local cohort and remote cohort are as follows: Three (3) organ types (appendix, gallbladder, and hernial/peritoneal) had observed major discordance rates of 0.00% for both modalities in the full cohort. For the local cohort, there were an additional 2 organ types [kidney (neoplastic) and salivary gland] that had major discordance rates of 0.00% for both modalities. Excluding these organs from the respective cohorts, the difference in major discordance rates (WSIR diagnosis minus MSR diagnosis) ranged from -3.13% (brain/neuro) to 7.70% (skin) for the full cohort, -6.52% (brain/neuro) to 8.88% (skin) for the local cohort and -3.49% (GE junction) to 9.38% (liver/BD) for the remote cohort. The clinical study was not powered to analyze results by individual organ site or diagnosis. The performance of Aperio GT 450 DX was determined by the overall difference in major discordance rate between WSIR and MSR.

Please see K232208 [Sectra Digital Pathology Module (3.3)] for performance data to support viewing of images in the DICOM format generated by Aperio GT 450 DX.

D. Testing Performed for Addition of other Specific Displays:
Technical testing and the results as specified in the table below was performed to validate additional specific displays intended to be used with the Aperio GT 450 DX as interoperable components.

Table 8. Display Equivalency Test

Test Name	Unit	Display			
		Dell U3023E	**Dell U3223QE**	**Barco MDPC-8127**	**Dell UP3017 (Comparator)**
1. Specifications	Display technology	TFT-LCD/IPS	TFT-LCD/IPS	TFT-LCD/IPS	TFT-LCD/IPS
	Screen diagonal	30 inch	31.5 inch	27 inch	30 inch
	Pixel count	2560(h) x 1600(v)	3840(h) x 2160(v)	3840(h) x 2160(v)	2560(h) x 1600(v)
	Color space	sRGB	sRGB	sRGB	sRGB
	Display interface	Display Port	Display Port	Display Port	Display Port
2. Pixel defects	Visual	None	None	None	None
3. Artifacts	TG18-QC	Passed	Passed	Passed	Passed
4. Maximum luminance and contrast ratio	cd/m^2 contrast ratio	Lmax = 237 Contrast = 1568	Lmax = 235 Contrast = 2426	Lmax = 435 Contrast = 1046	Lmax = 265 Contrast = 1031
5. Luminance uniformity	Max Non-uniformity	11.16%	12.58%	1.74%	16.74%
6. Grayscale	ΔL/L	1.69%	6.72%	4.15%	4.81%
7. Gray tracking	Max Δ|u', v'|	0.0034	0.0021	0.005	0.004
8. Color difference	Max ΔE	1.608	2.1815	1.5161	4.8135
9. Color gamut volume	sRGB	100%	100%	132%	99%
10. Temporal response	ms	8	5	8	8

E. Human Factor Study:

Human factors studies for Aperio GT 450 DX were conducted. The studies were designed around critical user tasks and use scenarios performed by representative users from histotechnicians and pathologists. The information included a list of all critical user tasks and a description of the process used to identify them. A systematic evaluation involving simulated use by representative users performing all tasks (including critical tasks) required for the operation of the device and a subjective assessment of failure was provided. All participants were able to perform all tasks (including the critical tasks) and no critical task failures were observed. There were several occasional difficulties, which was attributed to non-familiarity associated with first-time use of the new software and instrument. The learnability and ease of use were acceptable and there were no difficulties or failures observed on tasks that could lead to patient harm. In all instances, both pathologists and histotechnicians were able to identify cases and ensure that the case presentation was complete in the user interface.

VIII Proposed Labeling:

The labeling is sufficient, and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable, and the special controls for this device type under 21 CFR 864.3700.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.