510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
INSTRUMENT ONLY

I Background Information:

A 510(k) Number

K213883

B Applicant

Hamamatsu Photonics K.K.

C Proprietary and Established Names

NanoZoomer S360MD Slide scanner system

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:

New device

B Type of Test:

Digital pathology whole slide imaging

III Intended Use/Indications for Use:

A Indication(s) for Use:

The NanoZoomer S360MD Slide scanner system ("NanoZoomer System") is an automated digital slide creation, viewing, and management system. The NanoZoomer System 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

NanoZoomer System is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens.

The NanoZoomer System comprises the NanoZoomer S360MD Slide scanner, the NZViewMD Software and the JVC Kenwood JD-C240BN01A display. The NanoZoomer 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 NanoZoomer System.

B Intended Use(s):

Same as Intended Use.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For in vitro diagnostic (IVD) use only

D Special instrument requirements:

- NanoZoomer S360MD Slide scanner which includes the NZAcquireMD image acquisition software 1.0.0
- NZViewMD Software 1.0.0
- Display (JVC Kenwood JD-C240BN01A)

IV Device/System Characteristics:

A Device Description:

The NanoZoomer S360MD Slide scanner system is comprised of the NanoZoomer S360MD Slide scanner, the NZViewMD Software and the JVC Kenwood JD-C240BN01A display. It is an automated system for creating, viewing, and managing digital slides. Digital whole slide images (WSIs) of glass slides may be viewed, stored, retrieved, annotated, and/or shared, permitting the pathologist to make a primary diagnosis based on the review of the WSIs. The NanoZoomer system does not include any automated Image Analysis Applications that would constitute computer aided detection or diagnosis.

The NanoZoomer S360MD Slide scanner (Slide scanner) creates digital whole slide images (WSIs) of conventional histological glass slides containing FFPE tissue samples. The NanoZoomer slide scanner can be loaded with a maximum of 360 glass slides placed in 12 cassettes each with 30 standard-sized slides (length 75.0–76.5 mm, width 24.7–26.5 mm, thickness 0.9–1.2 mm). Each cassette is manually loaded with slides by the operator, with the slide labels facing outward so they can still be read while the cassette is loaded into the scanner. Once the slide's position is secured, the macro camera located directly above the slide first takes a picture of the slide's barcode image as illuminated by an overhead LED, and then takes a macro image of the actual tissue trans-illuminated by a flat-panel LED underneath. The slide holder then moves to the micro imaging position for scanning. The system automatically detects

areas where tissues are present and scans a single overall rectangular area containing all detected tissues. The scanning area is automatically determined using a macro image of the slide. The NanoZoomer System uses its motorized stage, 20x objective lens, CMOS camera and LED to detect appropriate focusing points and scan the identified areas of interest. A single micro camera acquires one square image at a time and the acquired images (tiles) are stitched together to make a single composite high-resolution image. Images are automatically saved to the hard disk during scanning and may be viewed later by using the included viewing software. The NZAcquireMD software organizes all WSI tiles into a single NDPI file. Each digital image covers an entire slide and typically contains billions of image pixels. The NZAcquireMD software allows the user to operate the scanner and to store and archive digital images.

Slides can be scanned in the non-batch mode and batch mode. In non-batch mode, a user-specified slide is brought onto the slide holder and the WSI (macro image) is displayed on the monitor. The user can draw rectangular windows manually with the mouse to specify areas to be scanned. The system then scans a single overall rectangular area that contains all user-specified scan areas.

The NZViewMD software is a software component intended to be used with the display monitor (JVC Kenwood JD-C240BN01A) and runs on a separate viewing workstation PC. The NZViewMD software opens the WSI images acquired with slide scanner from the image storage attached to local network and uses the color profile to render the image data to the calibrated display monitor to deliver the image view at the appropriate magnification. It has the following functionalities: continuous panning and zooming, comparing multiple slide images simultaneously in multiple windows, creating annotations during review using annotation tools, tracking of visited areas and annotations and digital bookmarks.

The display, a JVC Kenwood JD-C240BN01A allows the slide images to be viewed. The JVC Kenwood JD-C240BN01A features an IPS LCD color display with a display area of 518.4 mm × 324.0 mm, a resolution of 1,920 × 1,200 pixels, and an aspect ratio of 16:10, illuminated by an edge LED backlight.

The NanoZoomer S360MD Slide scanner system can be connected to a server and a display monitor over a customer-provided local area network (LAN). The supporting networking hardware and software are also not part of the system and may be located in a central server room separately from the workstation, viewing software, and display monitor.

B Instrument Description Information:

1. Instrument Name:
   NanoZoomer S360MD Slide scanner system (NanoZoomer System)

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 formalin-fixed paraffin embedded (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 H&E stained. Then digital images are obtained from these glass slides using the NanoZoomer S360MD Slide scanner.

4. Calibration:
   When the system is launched (powered up), automatic system diagnosis is performed by the software using the provided calibration slides. This process evaluates the proper functioning of the light source, imaging sensor, and macro sensor and light source. When necessary, based on the automatic system diagnosis, adjustment of the shading correction and color balance correction features is performed automatically by the system. Monthly cleaning such as dusting of the scan mechanism and optical components is also performed by the user.

   System administrators and field service personnel may also complete a system check following the NZAcquireMD Instructions for Use and the NZTuneMD service software and the calibration slides. This checks correction status and acquires correction data for whole slide and scanned images.

   Additional calibration and quality control procedures are performed during field service visits following procedures provided in the NanoZoomer S360MD Maintenance Manual. These include annual testing of several critical components in the system and annual calibration of the components and the display.

5. Quality Control
   Quality control (QC) activities are performed by the user. Prior to scanning slides using the NanoZoomer S360MD Slide scanner, the user conducts QC of the slides per the laboratory's standards and professional guidelines (e.g., staining, cover-slipping, and barcode placement, etc.). After completing a scan, the user checks the image data and image quality using Quality Check (QC) mode in NZAcquireMD which includes the following steps:
   - Display the Scan Result screen by selecting a slide for which scanning has been completed.
   - Confirm scan area, focus quality, and barcode information. Confirm that the barcode information displayed above the slide image is consistent with the barcode label.
   - Check the slide image to ensure all tissue on the slide are present within the scan area.

   Manually verifying tissue block with the scanned images is also performed as needed. Slides are rescanned if necessary.

   Before reading the scanned WSIs, the pathologist should ensure that all scanned slide images have been imported for every case and the images are of acceptable quality for diagnostic purposes. The pathologist reviews scanned images from all the slides associated with a case before rendering a diagnosis.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Philips IntelliSite Pathology Solution

B Predicate 510(k) Number(s):

DEN160056

C Comparison with Predicate(s):

Device & Predicate Device(s):	K213883	DEN160056
Device Trade Name	NanoZoomer S360MD Slide scanner system	Philips IntelliSite Pathology Solution (PIPS)
General Device Characteristic Similarities		
Intended Use/Indications For Use	The NanoZoomer S360MD Slide scanner system ("NanoZoomer System") is an automated digital slide creation, viewing, and management system. The NanoZoomer System 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 NanoZoomer System is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens. The NanoZoomer System comprises the NanoZoomer S360MD Slide scanner, the NZViewMD Software and the JVC Kenwood JD-C240BN01A display. The NanoZoomer 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	The Philips IntelliSite Pathology Solution (PIPS) is an automated digital slide creation, viewing, and management system. The PIPS 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 PIPS is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens. The PIPS comprises the Image Management System (IMS), the Ultra Fast Scanner (UFS) and Display. The PIPS 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 PIPS.

	safeguards to assure the validity of the interpretation of images obtained using NanoZoomer System.	
General Device Characteristic Differences		
Slide Feeder	360 slides (12 cassettes; each holds up to 30 standard-sized slides)	300 slides (15 glass slide racks with up to 20 slides per rack)
Digital Imaging Sensor	Color CMOS	CCD (TDI line sensor)
Image Processing Software	The system's embedded image processing software is responsible for image acquisition and the processing of individual tiles prior to image composition or stitching.	Proprietary software is used for image processing during acquisition and includes autofocus and calibration.
Image Composition	A micro camera acquires one square image at a time and the acquired images (tiles) are stitched together to make a single composite high-resolution image. A macro camera image which includes the entire slide is also created. In addition, the image contains the number of planes at the Z-axis if captured.	A composite macro image, which includes the slide label and a low-power image of the entire slide, is created in addition to the high-resolution image of the scanned regions of interest.
Image File Formats	Hamamatsu's NZAcquireMD software organizes all WSI tiles into a single NDPi file, which is a proprietary file format.	Philips's proprietary format, iSyntax, is used to store and transmit the images between the UFS and the IMS.
Image Review Manipulation Software	The NZViewMD software provides the user with a continuous view across the X-Y plane of the WSI with the ability to: • View images with continuous panning and zooming • Annotate and bookmark images • Track visited areas and	A software only subsystem with functionality that includes the ability to: • View images and patient data • Organize workload • Annotate, bookmark, and/or tag images • Manually score images • Invite and join others for a shared session

	annotations • Export images to a network server • Discrete Z-axis displacement	• Send review requests • Export images and generate reports

VI Standards/Guidance Documents Referenced:

1. ISO 14971: 2019 Medical devices – Application of risk management to medical devices.
2. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. Guidance for Industry and Food and Drug Administration Staff, May 2005
3. IEC60601-1:2010, AMD1:2016, IEC61010-2-101: 2018, IEC61326-2-6:2012, and FCC 47 C.F.R. Part 15 Subpart B standards.
4. Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices. Guidance for Industry and Food and Drug Administration Staff. Document issued on: April 2016
5. Applying Human Factors and Usability Engineering to Medical Devices. Guidance for Industry and Food and Drug Administration Staff. Document issued on: February 2016

VII Performance Characteristics:

A Analytical Performance:

a. *Precision/ Reproducibility:*

The objective of the study was to evaluate the repeatability (within- and between- scanner) and reproducibility (between-site) of the NanoZoomer S360MD Slide scanner system.

The precision of the device was based on the assessment and identification of specific histopathologic “features” that are observed in FFPE H&E stained slides. Each enrolled case consisted of a single slide containing an example of a single feature, called the primary feature, that had been selected by the enrolling pathologist (EP). Each slide was then verified by a verifying enrolling pathologist (VEP). A total of 30 different primary features from 540 cases from a single site were enrolled, 10 each at three different magnifications (10x, 20x, and 40x). Of these 30 features, 21 (7 per magnification level) were chosen to be "Study" features and 9 were chosen to be "Sham" features. Sham features were used to reduce the risk of reader recall bias but the primary study endpoint for the study was only assessed based on Study feature data for all sub-studies. Additional features at a given magnification, called secondary features, were allowed to be present on the slide and did not impact the eligibility of that slide to be included in the study. A total of 3 sites were used in this study. The Primary Features enrolled are summarized in Table 1 below.

Table 1: Features/Organs Used in the Precision Study

Feature	Magnification	Organ #1	Organ #2	Organ #3
Small Artery	10X	Placenta	Kidney	Lung
Psammoma Body	10X	Lymph node (Metastatic Papillary Thyroid Cancer)	Dura	Thyroid (Papillary Thyroid Cancer)
Keratin Pearl	10X	Skin	Lung	Head/Neck/Nose
Granuloma	10X	Lung	Lymph Node	Colon
Adipose Cell	10X	Soft Tissue	Skin	Mesentery
Gland	10X	Prostate	Gastrointestinal Tract	Salivary Gland
Necrosis	10X	Skin	Prostate	Colon
Cartilage	10X	Trachea	Nasal Septum	Larynx/Nose
Duct	10X	Prostate	Pancreatic Duct	Salivary Duct
Nerve	10X	Prostate	Soft Tissue	Skin
Reed-Sternberg Cell	20X	Mediastinum	Soft Tissue	Gastrointestinal Tract
Polymorph Neutrophil	20X	Bladder	Lung	Gastrointestinal Tract
Plasma Cell	20X	Colon	Bladder	Kidney
Goblet Cell	20X	Colon	Gastroesophageal Junction	Bladder
Macrophage	20X	Lung	Kidney	Bladder
Foreign Body Giant Cell	20X	Bladder	Soft Tissue	Joint
Clear Cell of Renal Carcinoma	20X	Kidney	Bone	Lung
Myxoid Stroma	20X	Heart Valve	Kidney	Salivary Gland
Muscle Cell	20X	Soft Tissue	Bladder	Uterus
Calcification	20X	Blood Vessel	Soft Tissue	Gastrointestinal Tract
Cilia	40X	Bronchus	Nose	Fallopian Tube
Eosinophil with Granules	40X	Bladder	Colon	Nasal Sinus
Mitotic Figure	40X	Soft Tissue	Breast	Bladder
Invasive Lobular Carcinoma	40X	Breast	Stomach	Bone
Osteoid Matrix	40X	Bone	Osteoid/ Osteosarcoma	Knee
Intercellular Bridges	40X	Lung	Skin	Head/Neck
Hemosiderin	40X	Kidney	Lung	Colon
Intranuclear Inclusion	40X	Thyroid	Skin	Dura
Melanin Pigment	40X	Skin (Melanoma)	Liver	Skin (Pigmentation/ Necrosis)
Crystals	40X	Kidney	Prostate	Salivary Gland

Study Inclusion Criteria:

Glass slides were screened for the known features and were considered eligible for the study only if all of the following criteria applied:

- Slides are selected from cases in a consecutive manner starting with cases at least 1 year old since accessioning
- Slide is a glass H&E stained cover-slipped surgical pathology slide of human tissue

- Slide has the designated primary feature in the FOV, which is readily observable in its natural environment although the slide may also have one or more secondary features from the same magnification group in the FOV
- Slide is not damaged, has tissue on the slide, and the staining is not faded and otherwise passes all quality checks

Study Exclusion Criteria:
Slides were excluded from the study if any of the following criteria applied:
- Slide is unable to be scanned, contains damaged tissue or has indelible markings
- Slide comes from an active (less than 1 year old) case
- Slide is from a patient who already has a slide enrolled in the study, only 1 slide per patient to be enrolled

Slide scanning of the same set of enrolled slides was performed sequentially at all three study sites. Each slide was allowed to be scanned up to a total of five times (i.e., up to four rescans). Once the scanning was completed, the scanning technicians at each site created TIFF images from each of the original scanned WSIs. These TIFF images were called field-of-view (FOV) images because they represented the field of view that would be observed through a microscope at the appropriate magnification for the feature in question. The size of the TIFF images was standardized to be comparable to the amount of surface area seen at the magnification for the case in question. These FOV images (rather than entire WSIs) were the images read by the reading pathologists (RPs).

The scanning of the Study Sets was then further randomly assigned, depending on the sub-study, as described below:

- Within-Scanner Sub-Study (Sub-Study 1, or SS1): Study slides were scanned three (3) times each on three (3) different scanners at one study site, resulting in nine (9) unique scans for each slide (3,402 total scans). The order in which each Set was scanned on each individual scanner was randomly assigned as was the order of scanners on which each Set was scanned.

- Between-Scanner Sub-Study (Sub-Study 2, or SS2): Study slides were scanned once on three (3) different scanners, resulting in three (3) unique scans for each slide (1,134 total scans). The order in which each Set was scanned on each individual scanner was randomly assigned.

- Between-Site Sub-Study (Sub-Study 3, or SS3): Study slides were scanned once on three (3) different scanners, which were at three (3) different study sites, resulting in three (3) unique scans for each slide (1,134 total scans). The order in which each Set was scanned was randomly assigned but was the same order for each site.

A total of nine (RP participated in the study, with three participating in each sub-study. Each RP participated in only one sub-study. Each RP reviewed a series of FOV images during each reading session, with at least 14 days wash out period between sessions. The study endpoints were as follows:

- Positive and negative percentage agreements (PPA, NPA) between scans from the same scanner (intra-scanner precision)
- Positive and negative percentage agreements between scans from different scanners at the same site (inter-scanner precision)

- Positive and negative percentage agreements between scans from different scanners at different sites (between-site precision)

Within-Scanner Study:
Each RP read 432 FOVs (378 Study FOVs/54 Sham FOVs) in each of three (3) different reading Sessions for a total of 1,296 reads per RP. There were 3,888 total reads performed in the within-scanner sub-study. Excluding the sham FOV readings led to 3,402 pairwise comparisons between study FOVs. Agreement rates calculated from the cross-tabulation Table for the within-scanner sub-study are shown in Table 3 below:

Table 3: Within-Scanner Agreement Rates

System	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI	
			%	95% CI
Scanner 1	924	1134	94.3	(92.8, 95.7)
Scanner 2	934	1134	95.0	(93.5, 96.3)
Scanner 3	941	1134	94.3	(92.8, 95.7)
Total	2799	3402	94.5	(93.7, 95.3)

The data show that the study acceptance criterion of the lower limit of the 95% confidence interval of the (Average Positive Agreement) APA exceeding 85% was met.

Between-Scanner Study:
Each RP read 432 FOVs (378 Study FOVs/54 Sham FOVs) in each of three (3) different reading Sessions for a total of 1,296 reads per RP. There were 3,888 total reads performed in the inter-scanner sub-study. Excluding the sham FOV readings led to 3,402 pairwise comparisons between study FOVs. Agreement rates calculated from the cross-tabulation table for the inter-scanner sub-study are shown in Table 4 below:

Table 4: Between-Scanner Agreement Rates

Systems Compared	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI	
			%	95% CI
Scanner 1 v Scanner 2	874	1134	92.5	(90.4, 94.2)
Scanner 1 v Scanner 3	880	1134	93.1	(91.2, 94.9)
Scanner 2 v Scanner 3	861	1134	91.4	(89.3, 93.4)
Total	2615	3402	92.4	(90.7, 93.8)

The data show that the study acceptance criterion of the lower limit of the 95% confidence interval of the APA exceeding 85% was met.

Between-Site Study:
There were 1,134 total reads performed in the between-site substudy, and therefore 1,134 pairwise comparisons between study FOVs. Agreement rates calculated from the cross-tabulation table for the inter-site sub-study are shown in Table 5 below:

Table 5: Between Site Agreement Rates

Sites Compared	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI	
			%	95% CI
Site 1 vs. Site 2	309	378	93.1	(90.9, 94.9)
Site 1 vs. Site 3	308	378	93.6	(91.5, 95.4)
Site 2 vs. Site 3	310	378	93.7	(91.6, 95.5)
Total	927	1134	93.4	(91.8, 94.9)

The data show that the study acceptance criterion of the lower limit of the 95% confidence interval of the APA exceeding 85% was met.

b. Linearity:
Not applicable

c. Analytical Specificity/Interference:
Not Applicable

d. Carry-Over:
Not Applicable

e. Accuracy (Instrument):
Not Applicable

B. Technical Studies

Multiple studies were conducted to evaluate the performance of the NanoZoomer System as recommended in FDA's 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 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 LED was provided. Testing information was provided to verify the intensity and spectral variation of the LED light incident on the slide over time.

c. Imaging Optics

An Optical schematic with all optical elements identified from slide (object plane) to image sensor (micro camera) was provided. Descriptive information regarding the microscope objective and the magnification of imaging optics was provided. Testing information regarding the magnification, relative irradiance, optical distortions, and 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 was provided. Test data to determine positioning accuracy and repeatability for the X-Y and Z stages 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. Testing to measure and evaluate linearity, spatial uniformity, dark current, noise, opto-electronic conversion function, and electron conversion factor of the sensor was provided.

f. Image Processing Software

Information and specifications on the exposure control, white balance, color correction, sub-sampling, pixel-offset correction, shading (flat-field) correction, and pixel-defect correction were provided. Testing confirmed that the pixel offset correction, shading and white balance, and color correction matrix functions work correctly.

g. Image Composition

Information and specifications on the scanning method and Z-stack depth, was 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. Testing demonstrated compression specifications were met.

i. Image Review Manipulation Software

Information and specifications for continuous panning, continuous zooming, discrete Z-axis displacement, comparison of slides in multiple windows, annotation tools, image enhancement, color manipulation (not for use in diagnostic procedures), tracking of visited areas and digital bookmarks was provided. Testing demonstrated the alignment precision of Z-stack images.

j. Computer Environment

Information and specifications on the computer hardware, operating system, memory, hard disk, graphics card, graphics card driver, color management settings, color profile, display interface and network were provided.

k. Display

Information and specifications on the technological characteristics of the display device, 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 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, color calibration tools, and frequency and nature of quality-control tests was provided. Test data to verify the performance of the display was provided.

l. Color Reproducibility

Test data to quantify the accuracy and precision of the color transformation from the slide to the display monitor was provided.

m. Spatial Resolution

Test data to evaluate the spatial resolution, including the composite optical performance of all components in the image acquisition phase was provided.

n. Focusing Test

Test data to demonstrate that the focus quality is clinically acceptable for a variety of histologic preparations, including different tissue types, stain intensities, specimen thicknesses, and stain types was provided.

o. Whole Slide Tissue Coverage

Test data to demonstrate that the entire tissue specimen on the clinical slide is detected by device was provided.

p. Stitching Error

Test data to assess the quality of WSI stitching boundaries for clinical slides exhibiting a variety of histologic preparations, including different tissue types, stain intensities, specimen thicknesses, and stain types was provided.

q. Turnaround Time

Test data to evaluate the average time required to execute zooming and panning operations, and to refresh the display in response to user input was provided.

C. Human Factors Study

Human factors studies were designed around user critical tasks, and use scenarios performed by users were conducted. There were three intended users for the NanoZoomer: Scan Technicians, Pathologists and Maintenance Engineers. A total of 15 test subjects were used. For each intended user group, validation tests were conducted separately. A systematic evaluation of task-based usability including essential task as and critical tasks required for operation of the device were evaluated at multiple sites using multiple users. The NanoZoomer S360MD has been found to be reasonably safe and effective for all of the intended users (i.e., the Scan Technicians,

Pathologists and Maintenance Engineers), uses and use environments. Overall, the results of the human factors testing are acceptable.

D. Clinical Studies

A retrospective multi-center study was conducted to demonstrate that viewing, reviewing, and diagnosing digital images of surgical pathology FFPE tissue slides using the Hamamatsu NanoZoomer S360MD Slide scanner system ("WSI") is non-inferior to using conventional light microscopy ("glass") under clinical use conditions. The study consisted of reviewing archived, de-identified and previously "signed-out" slides representing main organ systems within surgical pathology. Cases included retrospective H&E stained FFPE tissue, special stains and/or immunohistochemical stains (IHC) from the pathology practice, but did not include frozen sections, or cytological and hematological cases.

A total of 2,000 cases consisting of multiple organs and tissue types were enrolled in the study at four sites (500 cases per site) including difficult and challenging cases. At each site, four pathologists read all the cases assigned to their site using both WSI and glass methods in a randomized order and with a washout period of at least four weeks between readings, resulting in a total of 8,000 planned WSI reads and 8,000 planned glass reads. After the reader pathologist completed a primary diagnosis case report form (CRF) at a site, two pathologist adjudicators reviewed the study reader's diagnosis and compared it with the original "signed out" diagnosis (reference) to determine concordance, minor discordance or major discordance between the study diagnosis (by WSI and glass methods) and original "signed out" diagnosis. A third pathologist adjudicator was used if disagreement occurred between the first two adjudicators on the classification of a "major" discordance. The original signed-out diagnosis is based on the original sign-out pathologic diagnosis rendered at the institutions using an optical (light) microscope. A major discordance was defined as a difference in diagnosis that would be associated with a clinically important difference in patient management. A minor discordance was defined as a difference in diagnosis that would not be associated with a clinically important difference in patient management.

The acceptance criteria were as follows:

- The upper bound of the two-sided 95% CI of the difference between the overall major discordance rates of WSI diagnoses and Glass diagnoses is ≤4%.
- The major discordance rate of the WSI diagnoses is ≤7%.

<u>Key Case and Slide Study Inclusion Criteria:</u>

Cases were eligible to be included in the study only if all of the following criteria applied:

- Cases originating from and that were diagnosed at that local site
- Cases are available in the site's archive
- Cases are at least 1 year old since accessioning
- Cases are selected because their primary diagnosis is consistent with the assigned target categories as specified in the study protocol
- Cases have a set of slides representative of the primary diagnosis for which it has been selected.
- Slide is obtained by surgical pathology and prepared from FFPE human tissue
- Slides must be stained with H&E and accompanying special stains and/or IHC stains

- A chosen slide must demonstrate and be representative of the primary diagnosis; 1 H&E slide selection may suffice for biopsy cases,
- For resection cases, a minimum of 5 H&E slides must be selected, which represent the primary diagnosis. If represented with less than 5 H&E slides, additional H&E slides (primary, secondary, or benign slides) from same case may be used to fulfill minimum number
- Slide is intact, has correct size/thickness, good edges, undamaged coverslip, without pen markings that can't be removed, no air bubbles, tidy labels, and fulfills the quality checks per the general clinical practice

Key Case and Slide Study Exclusion Criteria:
Cases were excluded from the study if any of the following criteria applied:
- Case does not have relevant slides or if case information necessary for the study is missing
- Case is still active (less than 1 year old) at the local site
- Cases for which the control slides for immunohistochemistry and special stains are not available
- Two cases from same individual
- Gross-only cases that have no slides
- Cases that are frozen section, cytology or hematology or immunofluorescence specimens only
- Case where the only available set of slides have evidence only of secondary or no diagnoses and not the primary diagnosis for which the case is being screened.
- Glass slide that is broken, has abnormal size/thickness, beveled edges, poor coverslip (cracks, waviness, scratches), is sticky, has many pen markings or dirt that cannot be removed, contains air bubbles and overhanging labels that can't be corrected, and if stain is severely faded.

Over all four sites, there were a total of 15,995 diagnoses (7,997 digital and 7,998 optical). The overall major discordance rate, as observed over all sites, reading pathologists and organs, was 3.5% for WSI and 3.1% for glass. The major discordance rates as estimated by a logistic model (mixed-model repeated-measures logistic regression) resulted in very similar, slightly lower proportions of 3.5% for WSI and 3.1% for glass. The WSI-glass difference in the major discordance rate was 0.4%, with a two-sided 95% Cl of [−0.10%, 1.0%] derived from a delta method approximation. The upper limit of this confidence interval was less than the pre-specified non-inferiority margin of 4%, therefore the WSI method using the Hamamatsu NanoZoomer S360MD Slide scanner system is considered non-inferior to the glass method.

Table 9: Primary Analysis of WSI Non-Inferiority to Glass

	WSI Major Discordance Rate			**Glass Major Discordance Rate**			**Difference WSI – Glass**	
	N	**%**	**95% CI**	**N**	**%**	**95% CI**	**%**	**95% CI**
Observed	7997	3.5%	-	7998	3.1%	-	0.4%	-
Modeled	7997	3.5%	2.6%, 4.7%	7998	3.1%	2.2%, 4.2%	0.4%	-0.1%, 1.0%

These results meet the two pre-specified acceptance criteria for the study. Specifically, the major discordance rate for the WSI modality, which was 3.5%, was required to be <7.0% and the upper limit of the 95% confidence interval of the difference in major discordance rate between the modalities (WSI-Glass), which was 1.0%, was required to be <4.0%.

Table 10: Major Discordance Rates by Organ

		WSI Major Discordance		Glass Major Discordance		WSI-Glass Difference
Organ		**N**	**%**	**N**	**%**	**% Difference**
Breast	Observed	1198	5.3%	1200	4.8%	0.6%
	Modeled	1198	5.2%	1200	4.6%	0.6%
Prostate	Observed	1200	1.2%	1200	1.8%	-0.7%
	Modeled	1200	1.2%	1200	1.8%	-0.7%
Respiratory*	Observed	400	10.3%	400	9.8%	0.5%
	Modeled	400	10.4%	400	9.9%	0.5%
Colorectal	Observed	600	0.7%	600	0.5%	0.2%
	Modeled	600	0.7%	600	0.5%	0.2%
GE Junction	Observed	400	6.0%	400	3.5%	2.5%
	Modeled	400	6.1%	400	3.5%	2.5%
Stomach	Observed	400	1.5%	400	0.8%	0.8%
	Modeled	400	1.5%	400	0.7%	0.7%
Skin	Observed	700	5.7%	700	4.6%	1.1%
	Modeled	700	5.7%	700	4.6%	1.1%
Lymph Node	Observed	400	1.8%	400	1.8%	0.0%
	Modeled	400	1.8%	400	1.8%	0.0%
Bladder	Observed	400	6.3%	400	4.3%	2.0%
	Modeled	400	6.2%	400	4.2%	2.0%
Gynecological	Observed	600	3.5%	600	3.5%	0.0%
	Modeled	600	3.6%	600	3.6%	-0.0%
Liver/ Bile Duct	Observed	200	2.0%	200	1.5%	0.5%
	Modeled	200	2.0%	200	1.5%	0.5%
Endocrine	Observed	400	4.5%	400	3.3%	1.3%
	Modeled	400	4.5%	400	3.3%	1.2%
Brain/Neuro	Observed	240	0.8%	240	0.4%	0.4%
	Modeled	240	0.8%	240	0.4%	0.4%
Kidney	Observed	200	0.5%	200	1.5%	-1.0%
	Modeled	200	0.5%	200	1.5%	-1.0%
Salivary Gland	Observed	200	1.0%	199	1.5%	-0.5%
	Modeled	200	1.0%	199	1.5%	-0.5%
Hernial/Peritoneal[+]	Observed	40	0.0%	40	0.0%	0.0%
Gallbladder[+]	Observed	40	0.0%	40	0.0%	0.0%
Appendix[#]	Observed	40	5.0%	40	0.0%	5.0%
Soft Tissue Tumors[#]	Observed	79	1.3%	79	0.0%	1.3%
Anus/Perianal	Observed	200	2.0%	200	3.5%	-1.5%
	Modeled	200	2.0%	200	3.5%	-1.5%
Other[+]	Observed	60	0.0%	60	0.0%	0.0%

**Includes Lung, Bronchus, Larynx, Oral Cavity, & Nasopharynx*

[+] MMRM could not be fit for organs for which no major discordances were observed: Hernial/Peritoneal, Gallbladder, and Other miscellaneous.

[#] MMRM failed to converge for Appendix and Soft Tissue Tumors

Overall, these results demonstrate that the NanoZoomer S360MD Slide scanner system is safe and effective when used by pathologists for primary diagnoses purposes.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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