Aperio AT2 DX System Overview

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Aperio AT2 DX System Overview

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Customer Resources

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Disclaimers

- Use normal care in maintaining and using your MDDS. Interrupting network connections or turning off the MDDS while it is writing scanned images can result in data loss.
- This manual is not a substitute for the detailed operator training provided by Leica Biosystems Imaging or for other advanced instruction. Leica Biosystems Imaging Field Representatives should be contacted immediately for assistance in the event of any instrument malfunction. Installation of hardware should only be performed by a certified Leica Biosystems Imaging Service Engineer.
- Caution: Federal (U.S.) law restricts this device to sale by or on the order of an appropriately licensed healthcare practitioner.

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REF 23AT2DX

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Contents

1 Introduction

Leica Biosystems Imaging Aperio AT2 DX System enables pathologists to perform a primary diagnosis using digital microscopy.

This guide provides an overview of the Aperio AT2 DX System.

Intended Use

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 and interpret digital images of surgical pathology slides prepared from formalin-fixed paraffin embedded (FFPE) tissue. The Aperio AT2 DX System is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens.

The Aperio AT2 DX System is composed of the Aperio AT2 DX scanner, the Aperio 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.

Image Viewing Restrictions for Primary Diagnosis

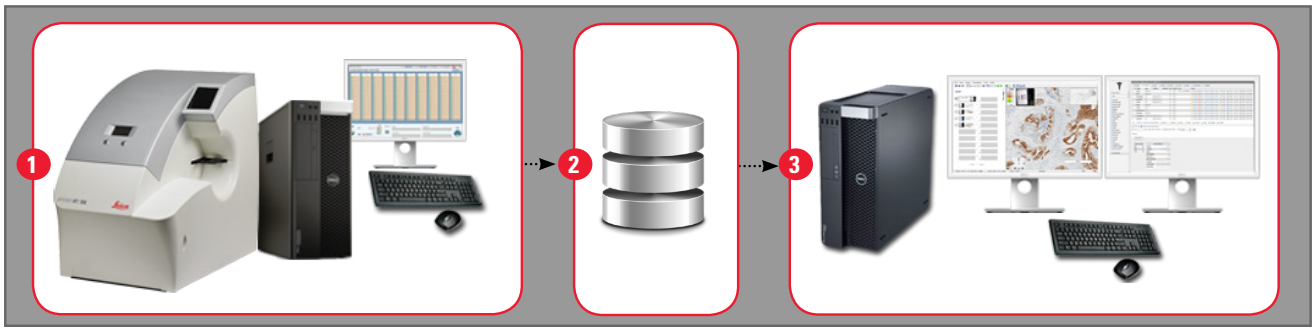
The images produced by the Aperio AT2 DX are for diagnostic use within the Aperio AT2 DX System only. Images opened outside the system with non-cleared Aperio viewers will display an error alerting the user that these images cannot be used for primary diagnosis.

Non-cleared Aperio viewers include:

- Aperio ImageScope (*all* non-DX versions)
- Aperio WebViewer
- Aperio WebScope
- Aperio ePathViewer

Aperio AT2 DX System Workflow

The arrows represent the flow of image data from one system to the next.



System Components	Workflow Steps
1 Aperio AT2 DX Scanner and local Aperio AT2 DX Viewing Station with scanner Console software.	• Scan glass slides to create digital slides. • Perform quality control.
2 MDDS (Medical Device Data System). *Your MDDS works together with the Aperio AT2 DX System, and is not provided as a part of the Aperio AT2 DX System.*	• Interface with Aperio AT2 DX scanner. • Build and store case data, including digital slides. • Interface with Aperio ImageScope DX.
3 Aperio AT2 DX Viewing Stations with Aperio ImageScope DX.	• Open digital slides from the MDDS that were created by the Aperio AT2 DX scanner. • Perform further quality control on digital slides created by the Aperio AT2 DX. • View and annotate digital slides created by the Aperio AT2 DX. • Read digital slides created by the Aperio AT2 DX for primary diagnosis.

Aperio AT2 DX System Component Overview

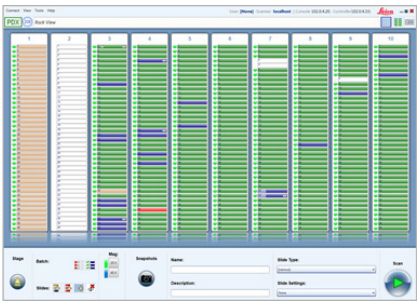
The Aperio AT2 DX System consists of the components described in the following sections.

Aperio AT2 DX

Use the Aperio AT2 DX scanner to scan glass slides for the purpose of primary diagnosis. For details about using the Aperio AT2 DX, see the *Aperio AT2 DX User's Guide*.

Aperio AT2 DX Console Scanning Software

The Aperio AT2 DX Viewing Station connected to the Aperio AT2 DX comes with the Aperio AT2 DX Console scanning software installed. You use the Console software to control the scanner. For more details, see the *Aperio AT2 DX User's Guide*.



Aperio AT2 DX Viewing Stations and Monitors

The Aperio AT2 DX System comes with a local Aperio AT2 DX Viewing Station that is connected to the Aperio AT2 DX scanner, and one or more Aperio AT2 DX Viewing Stations used to read digital slides created by the Aperio AT2 DX. Only the Aperio AT2 DX Viewing Stations and calibrated monitors that you receive as part of the Aperio AT2 DX System are supported for primary diagnosis.

You should check the display quality of your monitor every month. For instructions, see *"Perform a Monitor Quality Check" on page 16*.

CAUTION: The monitors provided with the Aperio AT2 DX System are calibrated at the factory and may require periodic re-calibration in the field by authorized Leica Biosystems technicians. Contact your Leica Biosystems Technical Services representative for information. Do not attempt to change the monitor display settings, as doing so may interfere with the monitor calibration.

For information about maintenance for the workstations and monitors that make up your Aperio AT2 DX Viewing Stations, see the manuals for those devices.

Viewing Station Specifications

The viewing station (part number 23DX-VW) includes two calibrated monitors and workstation installed with Aperio DX Viewer.

Client Workstation

Feature	Details
CPU speed	Intel Xeon W-2123 3.9GHz Turbo, 4C, 8.25M Cache, HT, (120W) DDR4-2666
Hard disk space	80GB free disk space
Memory	8GB or more recommended
Network card	1 Gigabit network card or faster
Video card	24-bit color at monitor's resolution
Operating system	Windows 10

Monitors

The monitors included in the Aperio Viewing Station are calibrated to a Leica internal specification which is specific for stain colors and optimized for digital slide viewing by pathologists.

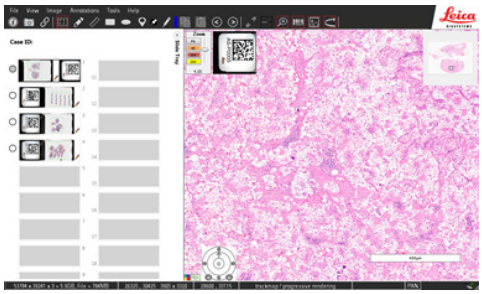
Feature	Details
Display type	LCD (flat panel)
Native screen resolution	1920(h) x 1200(v) pixels
Backlight	LED
Active screen (diagonal)	609.7 mm/24.0 inches
Color depth	16.7 million colors (8-bit RGB)
Contrast ratio (typical)	1000:1
Viewing angle	178 degrees
Luminance	• Stablization: Integrated backlight • Maximum (typical) cd/m^2: 300 • Calibrated (typical) cd/m^2: 180 • Non-uniformity: <30% on 9 points, 10%/80% luminance

Feature	Details
Connectivity	HDMI, display port
Response time (typical)	15 ms
Display mode control	VESA (MCCS), On Screen Display (OSD)
Calibrated Performance	
Supported color modes	DICOM with ICC profile
Color gamut	>100% sRGB
Color accuracy	Maximum delta-E <7
Gray tracking	+/-0.01 u'v'
Grayscale transfer function deviation (Gamma)	<10% on 18 points
Sharpness, artifacts, reflectivity	Verified with TG18-QC target (See *"Perform a Monitor Quality Check" on page 16*.)

Aperio ImageScope DX

Aperio ImageScope DX enables you to review digital slides created by the Aperio AT2 DX scanner for the purpose of performing a primary diagnosis.

For more details about using Aperio ImageScope DX, see the *Aperio ImageScope DX User's Guide*.



Supported Image Types

Aperio ImageScope DX supports only SVS files created by the Aperio AT2 DX scanner.

Optional Input Device (3-D Mouse)

You have the option of using the 3Dconnexion SpaceMouse Pro three-dimensional mouse to view and navigate digital slides in Aperio ImageScope DX.

For more details, see the "3-D Mouse Quick Reference" appendix in the *Aperio ImageScope DX User's Guide*.

Medical Device Data System

The Aperio AT2 DX System is designed to work together with your organization's medical device data system (MDDS). The patient case data, including digital slides, reside in the MDDS. Your MDDS interfaces with the Aperio AT2 DX scanner and the Aperio AT2 DX Viewing Stations.

An MDDS is a device that manages medical device data. Examples include:

- Laboratory Information System (LIS)
- Laboratory Management System (LMS)
- Laboratory Information Management System (LIMS)

See *"Chapter 3: System Security and Network Configuration" on page 19* for information on MDDS security requirements.

System Requirements

The monitors provided with the Aperio AT2 DX System have been calibrated at the factory and may require periodic re-calibration in the field by authorized Leica Biosystems technicians. Contact your Leica Biosystems Technical Services representative for information. Do not attempt to change the monitor display settings as doing so may interfere with the monitor calibration.

The Aperio AT2 DX System may only be used with the Aperio AT2 DX scanner and viewing stations and monitors supplied with that system.

- For safety instructions and maintenance information for Aperio AT2 DX Viewing Stations (including monitors), refer to the user manuals that came with that equipment.
- For safety instructions, maintenance information, and specifications for the Aperio AT2 DX scanner, refer to the *Aperio AT2 DX User's Guide*.

Network Configuration and Cybersecurity

For information on network bandwidth requirements and recommendations for protecting the Aperio AT2 DX System from cybersecurity threats, see *"Chapter 3: System Security and Network Configuration" on page 19.*

Aperio AT2 DX System Workflow and Documentation Set

The following table describes the user documentation that comes with your Aperio AT2 DX System.

This guide:	Includes information about:
Aperio AT2 DX User's Guide	• Slide preparation • Scanner preparation • Loading slides • Scanning slides using the Console • Performing quality review on digital slides • Maintenance • Troubleshooting
Aperio AT2 DX System Overview (This guide)	• The Intended Use statement for the Aperio AT2 DX System • An overview of the Aperio AT2 DX System • Using and checking the Aperio AT2 DX Viewing Station • Cybersecurity and network configuration recommendations
Aperio ImageScope DX User's Guide	• Instructions for using Aperio ImageScope DX to read, navigate, and annotate digital slides

Training

Leica Biosystems Imaging offers on-site training courses. Contact Leica Biosystems Imaging Customer Support for information about training options.

As with any change in diagnostic methodology, and especially one that relies on visual interpretation of complex images, a transition from manual microscopy to digital microscopy presents the possibility of an unintended but systematic change in diagnostic performance. Training should be undertaken to assure concordance between manual microscopy and digital microscopy before clinical adoption of the device. The laboratory is responsible for ensuring that concordance goals are reached and maintained.

2 Using and Maintaining the Aperio AT2 DX Viewing Station

This section contains use and maintenance information for the Aperio AT2 DX Viewing Station that is specific to the Aperio AT2 DX System. For general information on maintenance, operation instructions, and safety instructions, refer to the manufacturer's manuals that came with your Aperio AT2 DX Viewing Station.

Turning on the Aperio AT2 DX Viewing Station

To start the Aperio AT2 DX Viewing Station:

1. Press the power button on the front panel of the workstation.
2. When the Windows login screen appears, log in with the Windows user name and password. The first time you turn on the workstation, you will use the default user name and password (contact your administrator or Leica Biosystems Technical Services for the initial default user name and password).

   We recommend your administrator change this password as soon as the system is installed, so contact your administrator for the current password if it has changed.
3. Turn on the Aperio Viewing Station monitors.

Set Up Your Aperio AT2 DX Viewing Station

Leica Biosystems Technical Services sets up your Aperio AT2 DX Viewing Stations for optimal use when they install the Aperio AT2 DX System. However, here are some tips for making best use of this equipment after it is installed.

Ambient Lighting

Locate viewing stations in a room with normal office-level lighting.

Reflections on the Monitor

When working at the viewing station, you should not see any objects or yourself reflected in your monitor.

To check for reflections:

1. In normal office-level lighting, sit approximately 30 cm to 60 cm from the monitor.
2. Sitting directly in front of the monitor, move slowly to the left and right to view the monitor at about a 15-degree angle from either side.
3. As you are seated in front of the monitor and viewing it as described previously, check if there are reflections on the monitors. If there are reflections, make any necessary adjustments:

- If you see light from a lamp or window reflected on the monitor, move the monitors to a different location.
- If you see high-contrast objects reflected on the monitor, try reducing the ambient lighting or move the objects out of view. Some common sources of reflection include high-contrast patterns on clothing, identification badges worn on white shirts, and picture frames hanging on light-colored walls.

Cleaning Your Viewing Station Monitor

Keep your monitor clean and free from dust. Refer to the cleaning instructions that came with your monitor.

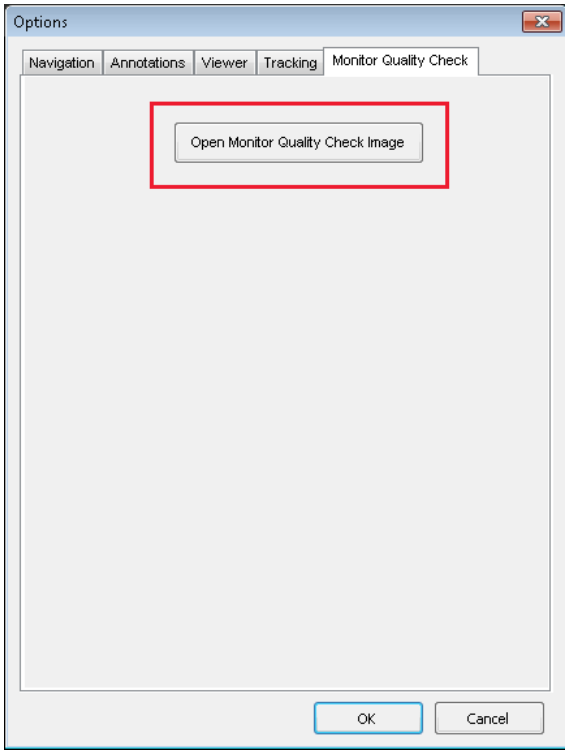
Perform a Monitor Quality Check

We recommend performing a visual quality check on your monitor once a month.

You check the monitor quality by evaluating a special test image. Familiarizing yourself with the test image when you first use the system may help you more readily identify any changes in the image in the future.

Follow these steps to evaluate the test image:

1. On your Aperio AT2 DX Viewing Station, open Aperio ImageScope DX.
2. Go to the **Tools** menu, and select **Monitor Quality Check**. The Monitor Quality Check tab opens.

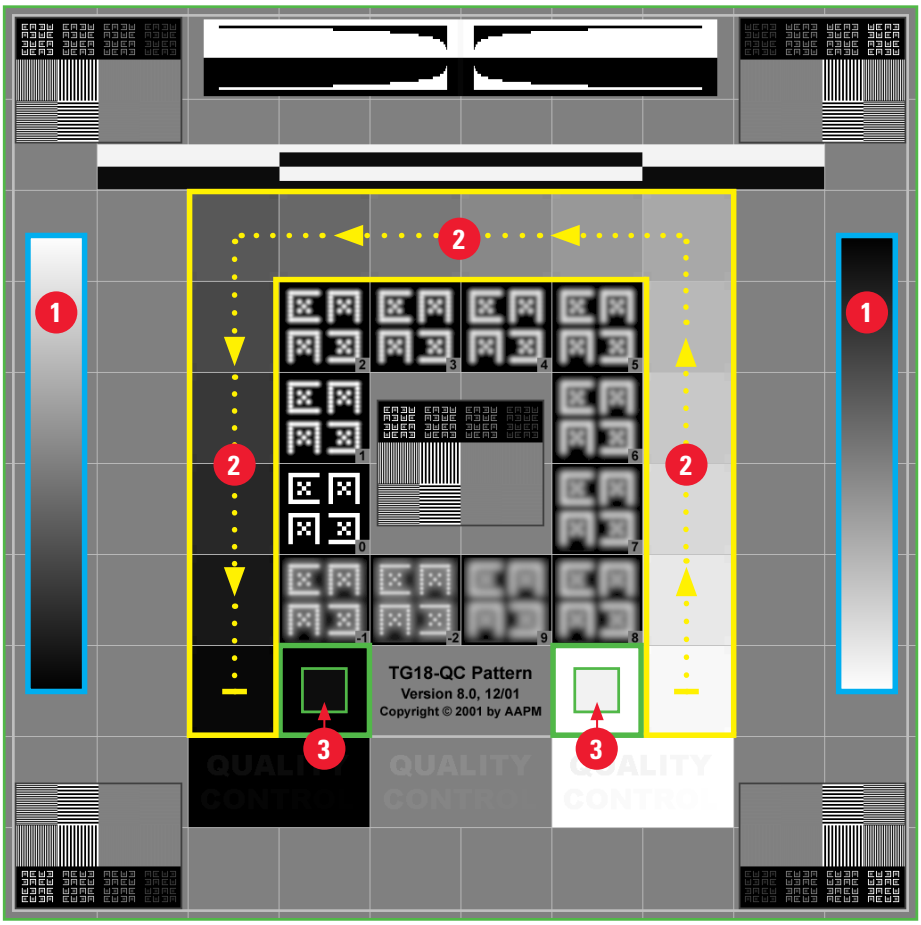


3. Click **Open Monitor Quality Check Image**.

   The test pattern image appears in your Aperio ImageScope DX window.

The test image appears on a calibrated monitor with a higher level of clarity than this example.

The colored outlines and numbers are not part of the test image. They are included here to identify the areas to evaluate.



4. Check for the following items on the test image.

Test Graphic Area:	What to Check:
1 Vertical gradient bars outlined in **Blue**.	▸ Changes in intensity are smooth and uniform over the entire range of bright to dark. ▸ There are no noticeable bands of constant intensity (solid white, gray, or black) inside or near the edges of the bars.
2 Upside down U-shape outlined in **Yellow**.	▸ Following the direction of the yellow arrows in the example (from white to black), the change in intensity from one square patch to the next increases by the same relative amount.

Test Graphic Area:	What to Check:
3 Squares outlined in **Green**.	▸ The small 95% grayscale square patch inside the black square is clearly visible at normal viewing distance (30 - 60 cm). ▸ The small 5% grayscale square patch inside the white square is clearly visible at normal viewing distance (30 - 60 cm).

5. If you notice an issue with any of the test image evaluations, contact Leica Biosystems Technical Services.
6. To close the test pattern image, go to the **File** menu and select **Close Case**.

3 System Security and Network Configuration

This chapter contains information on requirements and recommendations for ensuring the Aperio AT2 DX System and your MDDS on your network are protected from security threats and provide a good user experience. This chapter is provided for IT personnel and network administrators who are responsible for maintaining the Aperio AT2 DX System in your institution's network environment.

Protecting the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations

This section contains tips and recommendations for protecting the Aperio AT2 DX Viewing Stations (both connected directly to the Aperio AT2 DX scanner and connected to the MDDS through the Intranet) and Aperio AT2 DX Control Station from security threats. Also, see *"Protecting the MDDS" on page 21* for recommendations for your server on which patient data and images are stored.

Password, Login, and User Configuration Safeguards

After the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations are installed at your site, users are required to reset their password the first time they log in. In addition, you are required to reset the password for the Windows administrator account. The first time you turn on the control station and viewing station, you will use the default user name and password (contact your administrator or Leica Biosystems Technical Services for the initial default user name and password).

To change the user or administrator Windows password, log in as that user and press CTRL + ALT + DELETE. On the next screen select **Change a password**. Then change the password.

By default, Windows 10 on the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations is set to enforce the following password rules:

- Passwords must contain:
  - Minimum of eight characters
  - At least one non-alpha numeric character
  - At least one numeric digit
  - At least one lower case letter
- When changing a user password, you may not re-use any of the last five passwords recently used.
- Users are required to change their password every 90 days. The Windows administrator account password must also be changed every 90 days.

- After entering five invalid login attempts, the user is locked out for 30 minutes. If it is not practical to wait for 30 minutes to use the system, the user should contact the IT administrator to reset the user account.
- By default, the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations are configured to time out screen displays after 15 minutes of inactivity and users are required to log in again after that time.
- For security reasons, do not use user names *Admin*, *Administrator*, or *Demo* when adding users to the Aperio AT2 DX Control Station or Aperio Image View Stations.

Changing the Aperio Service Account Password

The Aperio service account on the AT2 DX Control Station is required for scanner operation. Although you are not required to change the Aperio service account password, changing the password periodically may be required by your institution's password policy.

For the default user name and password for the Aperio service account, contact your Leica Biosystems Services representative. After changing the password for this account, you must update the ApService service credentials. For instructions on changing the password and updating the ApService credentials, refer to the section "Change the Aperio Service Account Password and Update ApService" in the *Aperio AT2 DX User's Guide*.

Physical Safeguards

- Embedded disk encryption does not rquire a user password.
- To protect the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations from malware, viruses, data corruption, or privacy breaches, the USB ports on the stations have been physically blocked and cannot be used.
- Protect the Aperio AT2 DX Control Station and the Aperio AT2 DX Viewing Stations from unauthorized access by limiting physical access to them.

Administrative Safeguards

- The Aperio AT2 DX System supports Active Directory. We recommend using Active Directory to centralize user authentication both for security reasons and to make it easier to add and remove users from the system.
- Note that users must have administrative privileges if they are going to start and restart Aperio AT2 DX scanning services. Rather than giving all scanner users administrative privileges, you may want to create a user group on the Aperio AT2 DX Control Station that has the privileges necessary to restart scanner services, and add new users to that group.
- Set up the users of the Aperio AT2 DX System with permissions that allow them to access only the portions of the system required for their work.
- We recommend that all users working with the Aperio AT2 DX System be part of a specific Windows domain in which users or user groups have been defined with access permissions to images and other data used by this system, and that only these users and user groups have these access permissions.
- Protect the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations from unauthorized access by using standard IT techniques. For example:

  - Firewalls - By default, Windows Firewall is enabled on Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations

- Microsoft AppLocker, a Windows 10 administrative tool used to prevent unauthorized programs from running (whitelisting), has been implemented on Aperio AT2 DX Viewing Stations and the Aperio AT2 DX Control Station.
- Windows Event Viewer is configured by default on the Aperio AT2 DX Control Station to track access to patient information and images stored in these locations: Controller\macroimages, \Controller\rackstate.xml, D:\Images, and D:\Stripes. For information on using the Windows Event Viewer, consult Windows documentation.

Data Encryption

- Disk encryption keys are provided to you with the system. If you do not have your encryption keys, call Leica Biosystems Technical Services.
- In-transit and local encryption uses BitLocker AES256 (TPM 2.0) bit encryption algorithm. All data at rest and in-transit is fully encrypted.
- SMBv3 is used for encryption of local and remote data transfers on Aperio network servers.

Malware Protection

- AppLocker provides malware protection.

Update Policies

- Aperio hot fixes, patches, and software upgrades will be made available to you by Leica Biosystems Technical Services.
- By default, automatic Windows updates are disabled on the Aperio AT2 DX Control Station and Aperio AT2 DX Viewing Stations. Aperio security specialists evaluate both industry security reports and Microsoft operating system vulnerability and problem reports, and determine what actions need to be taken. If critical updates are required, Leica Biosystems Technical Services will notify affected customers.

Protecting the MDDS

The MDDS (Medical Device Data System) is the storage device that contains the scanned images. This device is your hardware that is maintained by your IT organization. Here are some recommendations for your MDDS:

- Your IT department must maintain the MDDS, applying Windows and Aperio security patches and hot fixes that may be available for that system.
- You should select an MDDS that can be configured to detect intrusion attempts such as random password attacks, automatically locking accounts used for such attacks, and notifying administrators of such events.
- Due to limitations of the operating system we cannot protect Private Health Information data in transit. Therefore, we recommend that you protect data in transit by using SSL with strong security protocols such as Transport Layer Security (TLS) version 1.2 or newer or that you use network-level encryption such as IPSec or SSH tunneling.
- We recommend implementing whitelisting on the MDDS to prevent unauthorized applications from running on it.
- If you are not using whitelisting (which prevents any virus from executing), we strongly recommend installing anti-

virus software on the MDDS. Run antivirus scans at least every 30 days.

If using antivirus software, we recommend you configure it to exclude .SVS, .SCN, .TIF, JPG file types as well as the file storage from "on access scanning" as these files can be very large and are accessed continually as they are being scanned and users are viewing the digital slides. Virus scans should be configured to run during non peak hours as they are very CPU intensive and can interfere with scanning. (In rare circumstances, third-party applications such as virus or security software may prevent Aperio software from connecting to servers or devices. If you are having this problem, contact Leica Biosystems Technical Services for assistance.)

- Periodically back up the hard disks on the MDDS.
- We recommend using a disk encryption utility to encrypt the contents of the MDDS hard disks.
- The file shares on the MDDS should be protected from unauthorized access using accepted IT practices.
- You should enable Windows Event logging on your MDDS to track user access and changes to data folders that contain patient information and images.

Digital Slide Bandwidth Requirements

The bandwidth required for different applications varies, as discussed below.

Digital Slide Viewing Requirements

The minimum network bandwidth required for a good user experience when viewing digital slides is 250KB/s per user. When it's available, our viewing software will make use of additional available bandwidth to provide the users a better viewing experience.

Actual bandwidth usage when viewing digital slides varies with the type of slide, viewing habits of the pathologist, tissue area, nature of each case, the client application and performance options in the viewer application. However, based on experience, Aperio has found that a typical viewing session requires about 25MB of data to be transferred to the end user with a variable rate of 250KB/s to 500KB/s.

When using Aperio ImageScope DX, the data for the viewing session is streamed to the end user. First the user is provided the view that has been requested, and then surrounding views are cached in anticipation that the user will request them. The ability to stream this data to end users greatly improves their viewing experience and allows multiple users to easily share even low bandwidth connections while viewing digital slides.

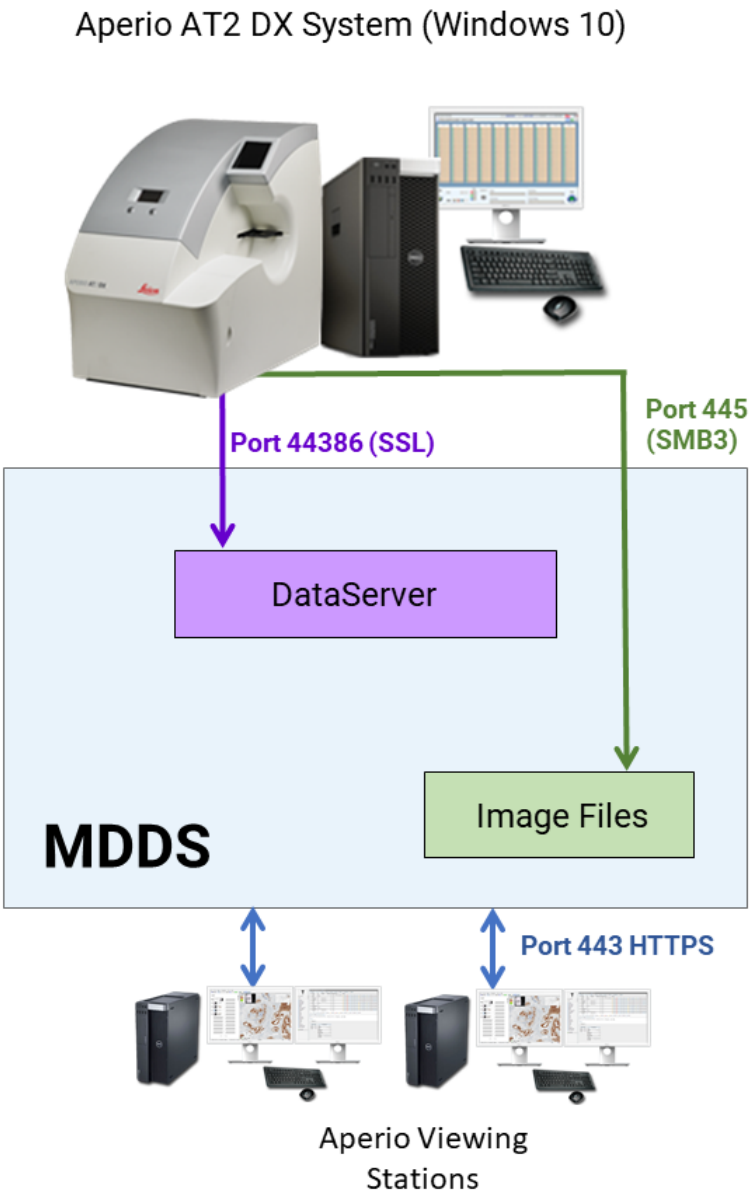
Digital Slide Capture on Aperio AT2 DX

We recommend that the connection between the scanner and scanner control station be low latency and dedicated to scanning activities. If the connection is not dedicated, scanning performance may be impacted or may impact other applications on your network.

Network Configuration

Below is a diagram showing a standard, secure configuration of the Aperio AT2 DX System.

Note that Leica Biosystems offers an MDDS product, Aperio Path DX. Contact your Leica Biosystems sales representative for information on that product.



4 Performance Characteristics

This chapter discusses the clinical studies performed using the Aperio AT2 DX System.

Precision

Three studies were conducted to assess precision within systems (Intra-System Study), between systems/sites (Inter-System/Site Study), and within and between pathologists (Intra/Inter-Pathologist Study).

The assessments were based on the study pathologists' identification (i.e., reading) of select histopathologic features (e.g., chondrocytes, fat cells) observed in images created from the scanning of the precision tissue panel. The panel was composed of 69 FFPE hematoxylin and eosin (H&E) stained tissue slides. The 69 slides included 23 unique histologic features (12 features scanned at 20x magnification and 11 scanned at 40x magnification). Each of these 23 features was represented in 3 different organ types (23 features × 3 different organ types per feature = 69 slides). Each slide contained 2 or 3 histologic features (with most slides having 3 features) that were each captured in a field of view (FOV) totaling 202 FOVs from the set of 69 slides. An additional 12 slides, presented as wild card slides, were scanned and reviewed with precision tissue panel FOVs to minimize recall bias and were excluded from the agreement analyses.

The 3 studies were conducted using the same set of 69 slides across sites, systems, and/or pathologists. The FOVs generated from multiple scans of the same feature were rotated to different orientations. There was a washout period of at least 14 days between pathologist reading sessions. Precision was assessed for each study separately by analyzing agreement within systems, between systems/sites, and within and between pathologists. Overall agreements within systems, between systems/sites, and within and between pathologists were also estimated.

Intra-System Study

In this study, 3 systems housed at 3 different sites (1 system per site) were evaluated. The set of 69 slides was divided equally and randomly between the 3 systems/sites (23 slides per system). For each system/site, the 23 slides were scanned once on each of 3 scanning sessions.

The number of FOVs obtained from a single scanning of 23 slides by each system/site was slightly unequal (67, 67, and 68 FOVs at Site 1, 2, and 3, respectively) because slides had 2 or 3 features extracted. Overall systems/sites and scanning sessions, 606 FOVs were extracted.The FOVs were reviewed by a single pathologist over 3 reading sessions (FOVs from a single scanning session [combining systems] per reading session).

For each system/site, agreements between scan 1 versus scan 2, scan 1 versus scan 3, and scan 2 versus scan 3 were analyzed (*see "Table 1. Intra-System Study: Agreement Within Systems" on page 25*). The overall intra-system precision was based on the pooled data of all 3 systems.

Table 1. Intra-System Study: Agreement Within Systems

System	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI*		
			% Agreement	Lower	Upper
System 1	193	201	96.0%	91.0%	100%
System 2	201	201	100%	98.2%	100%
System 3	199	204	97.5%	93.6%	100%
Overall	**593**	**606**	**97.9%**	**95.9%**	**99.5%**

*A bootstrap approach was used to calculate 95% CIs with the following exception. When the agreement estimate was 100%, the Arcsine (variance stabilizing transformation) approach that corrected for the continuity was used to calculate CIs (Pires and Amado, 2008).

Inter-System/Site Study

In this study, 3 systems housed at 3 different sites (1 system per site) were evaluated. The set of 69 study slides were scanned once on each system. Overall systems, 606 FOVs were extracted. The FOVs were reviewed by a single pathologist over 3 reading sessions (FOVs from a single site per reading session).

Overall systems, 606 FOVs were extracted. The FOVs were reviewed by a single pathologist over 3 reading sessions (FOVs from a single system per reading session). Agreements between system 1 versus system 2, system 1 versus system 3, and system 2 versus system 3 were analyzed (*see "Table 2. Inter-System/Site Study: Agreement Between Systems"*). The overall inter-system/site precision was based on the pooled data of all 3 systems.

Table 2. Inter-System/Site Study: Agreement Between Systems

System	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI*		
			% Agreement	Lower	Upper
System 1 vs System 2	195	202	96.5%	94.1%	99.0%
System 1 vs System 3	194	202	96.0%	93.1%	98.5%
System 2 vs System 3	193	202	95.5%	92.6%	98.0%
Overall	**582**	**606**	**96.0%**	**93.6%**	**98.2%**

*A bootstrap approach was used to calculate 95% CIs.

Intra/Inter-Pathologist Study

In this study, 1 system at 1 site was used to scan the set of 69 slides once. FOVs were extracted and each FOV was saved in 3 different orientations. Overall orientations, 606 FOVs were extracted and transferred to each of 3 study pathologists.

For the intra-pathologist evaluation, agreements between orientation 1 versus orientation 2, orientation 1 versus orientation 3, and orientation 2 versus orientation 3 were analyzed for each pathologist (*see "Table 3. Intra/Inter-Pathologist Study: Agreement Within Pathologists"*). The overall intra-pathologist precision was based on the pooled data from each pathologist.

Table 3. Intra/Inter-Pathologist Study: Agreement Within Pathologists

Pathologist	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI*		
			% Agreement	Lower	Upper
Pathologist 1	561	606	92.6%	89.6%	95.7%
Pathologist 2	595	606	98.2%	96.3%	99.7%
Pathologist 3	571	606	94.2%	91.4%	96.9%
Overall	**1727**	**1818**	**95.0%**	**92.9%**	**96.8%**

*A bootstrap approach was used to calculate 95% CIs.

For the inter-pathologist evaluation, agreements between pathologist 1 versus pathologist 2, pathologist 1 versus pathologist 3, and pathologist 2 versus pathologist 3 were analyzed (*"Table 4. Intra- and Inter-Pathologist Study: Agreement Between Pathologists"*). The overall inter-pathologist precision was based on the pooled data from each pathologist.

Table 4. Intra- and Inter-Pathologist Study: Agreement Between Pathologists

Pathologist Comparison	Number of Pairwise Agreements	Number of Comparison Pairs	Agreement Rate and 95% CI*		
			% Agreement	Lower	Upper
Pathologist 1 vs Pathologist 2	572	606	94.4%	91.6%	96.9
Pathologist 1 vs Pathologist 3	562	606	92.7%	89.9%	95.4%
Pathologist 2 vs Pathologist 3	579	606	95.5%	93.1%	97.7%
Overall	**1713**	**1818**	**94.2%**	**91.7%**	**96.4%**

*A bootstrap approach was used to calculate 95% CIs.

Clinical Study

A multicenter study was conducted to demonstrate that using the Aperio AT2 DX System to view, review, and diagnose digital images of surgical pathology formalin-fixed paraffin-embedded (FFPE) tissue slides is noninferior to using optical (light) microscopy. The primary endpoint was the difference in major discrepancy[1] (discordance) rates between whole slide image review (WSIR) and light microscope slide review (MSR) diagnosis modalities when each modality was compared to the original sign-out pathologic diagnosis (also known as reference diagnosis), which was previously decided at the sites using a light microscope.

1 A discrepancy that would be associated with a clinically importance difference in patient management.

Across 5 sites, 2045 cases (with 5849 slides) were evaluated. Cases included a diverse mixture of pathologic diagnoses and tissue/organ types. At each site, each reading pathologist (3 or 4 pathologists[2] per site) evaluated all cases from their site. The reading pathologists were provided with all representative slide(s) (or whole slide images) of a case and the ancillary clinical information. Each reading pathologist evaluated cases using both the Aperio AT2 DX System and the light microscope. At each site, half of the reading pathologists evaluated scanned images of the slides using the Aperio AT2 DX System first while the other half evaluated slides using the light microscope first. Between the first and subsequent reading of the same case, a washout period of at least 31 days was required.

At least 2 adjudication pathologists independently compared each reading pathologist's study diagnosis (WSIR or MSR diagnosis) against the reference diagnosis to determine concordance in accordance with a prespecified set of concordance rules. If the study diagnosis was not concordant with the reference diagnosis, a discrepancy that would be associated with a clinically importance difference in patient management was considered a major discrepancy. A minor discrepancy would not be associated with a clinically important difference in patient management.

For each study diagnosis, the 2 adjudication pathologists' concordance determinations were compared. Consensus was obtained when both adjudication pathologists reported diagnoses as concordant and/or minor discrepancy (consensus score = no major discrepancy), or when both adjudicators reported major discrepancies (consensus score = major discrepancy). If the concordance determinations disagreed (e.g., minor discrepancy and major discrepancy) or if 1 of the primary adjudicators deferred assigning a concordance determination, then the study diagnosis was independently reviewed by a third adjudicator. If consensus (as defined above) between 2 of 3 adjudicators was not obtained or if 2 adjudicators deferred, then the 3 adjudicators held a panel meeting to review the relevant case(s) and come to a consensus, either assigning a concordance determination (concordant, minor discrepancy, major discrepancy) or deferring the case. The consensus decision from the panel meeting was the final determination for each study diagnoses reviewed.

Major discrepancy rates were estimated for WSIR and MSR diagnoses when each modality was compared to the reference diagnosis. To demonstrate the WSIR diagnosis modality was noninferior to the MSR diagnosis modality, the difference between the major discrepancy rates of the 2 modalities was calculated. A generalized linear model was used to derive the estimates of the major discrepancy rates and the difference along with their 95% CIs.

There were 2045 cases evaluated by 3 or 4 pathologists using both modalities. Combining sites, pathologists, and organ types, 7509 WSIR and 7522 MSR diagnoses were established, had consensus scores, and were included in the statistical analyses.

Deferred diagnosis was excluded from the data analysis as missing data. *"Table 5. Overall Major Discrepancy Rates for the WSIR and MSR Modalities and the Difference Between the Overall Major Discrepancy Rates" on page 28* shows the overall major discrepancy rates for both modalities (when each is compared to the reference diagnosis) based on observed results and by the logistic regression model. The modeled overall major discrepancy rate estimates appeared to be slightly lower than the observed estimates, although the differences in overall major discrepancy rates between the 2 modalities were almost identical. The upper bound of the 95% CI for the difference of overall major discrepancy rates was 1.03%, which was smaller than the predefined acceptance limit of 4%. Thus, the primary endpoint was met.

2 3 pathologists at 1 site and 4 pathologists at the other 4 sites.

Table 5. Overall Major Discrepancy Rates for the WSIR and MSR Modalities and the Difference Between the Overall Major Discrepancy Rates

	WSIRD Major Discrepancy*			MSRD Major Discrepancy*			Difference in Major Discrepancy Rates (WSIRD minus MSRD)	
	n	Rate (%)	Model 95% CI	n	Rate (%)	Model 95% CI	%	Model 95% CI
Observed	280	3.73	—	247	3.28	—	0.45	—
Model		3.64	(3.21, 4.12)		3.20	(2.80, 3.65)	0.44	(-0.15%, 1.03%)

MSRD = MSR diagnosis, WSIRD = WSIR diagnosis

* N = 7509 for WSIR, N = 7522 for MSR

Even though the study was not powered to analyze results by organ, the observed estimates of the major discrepancy rates for the WSIR and MSR diagnoses and the difference in these rates were derived for each organ as shown in *"Table 6. Major Discrepancy Rates by Organ"* Three (3) organ types, appendix, gallbladder and hernia/peritoneal, had major discrepancy rates of 0.00% for both modalities. To test modality-by-organ interaction, data from these 3 organ types were pooled with data from other biologically relevant organ types; appendix was pooled with colorectal, gallbladder with liver/bile duct, and hernia/peritoneal with soft tissue. For all organ types, the difference in the major discrepancy rates between WSIR diagnosis and MSR diagnosis (relative to the reference diagnosis) were ≤ 2.03% in the absolute values. Thus, our data suggest that WSIR and MSR diagnoses are similar across all major tissue/organ types.

Table 6. Major Discrepancy Rates by Organ

Organ Type	Major Discrepancy Rate		Difference in Major Discrepancy Rates (WSIRD - MSRD)
	MSRD	WSIRD	
Anus/perianal	2.79%	3.95%	1.16%
Appendix	0.00%	0.00%	0.00%
Bladder	9.47%	10.40%	0.93%
Brain/neuro	2.54%	3.09%	0.55%
Breast	3.53%	4.29%	0.76%
Colorectal	2.46%	2.46%	0.00%
Endocrine	4.57%	4.04%	-0.53%
Gastroesophageal junction	3.16%	3.69%	0.54%
Gallbladder	0.00%	0.00%	0.00%
Gynecological	3.18%	4.28%	1.10%
Hernia/peritoneal	0.00%	0.00%	0.00%
Kidney	1.69%	1.14%	-0.56%
Liver/bile duct	0.53%	1.59%	1.06%
Lung	3.68%	5.24%	1.55%
Lymph node	1.87%	1.09%	-0.78%

Organ Type	Major Discrepancy Rate		Difference in Major Discrepancy Rates (WSIRD - MSRD)
Prostate	3.44%	3.00%	-0.44%
Salivary gland	1.69%	0.55%	-1.14%
Skin	2.72%	4.74%	2.03%
Soft tissue	4.83%	4.23%	-0.60%
Stomach	2.09%	3.15%	1.06%

MSRD = MSR diagnosis, WSIRD = WSIR diagnosis

The consensus scores (major discrepancy, no major discrepancy) were compared between the 2 modalities. There were 7423 pairs with adjudication outcomes for both modalities. Overall, 96.1% (7137/7423) of the consensus scores agreed. Of the 7137 pairs in agreement, 1.5% (109/7137) had major discrepancies for both modalities and 98.5% (7028/7137) had no major discrepancies for both modalities.

Although our study was not powered to specifically to investigate this issue, we compared unbalanced diagnoses from different modalities on the same cases. An unbalanced diagnosis occurred for cases for which one modality diagnosis had a major discrepancy with the reference diagnosis and the other modality diagnosis was concordant with the reference diagnosis for the same pathologist.

Unbalanced diagnoses represented a small percentage of the overall cases (0% to 4.9%) and were similar in both modalities. When the specific diagnoses were examined by tissue/organ type, there were no apparent trends in any tissue/organ type that suggested WSIR is more inherently prone to major discrepancies compared to MSR. Consistent with these observations, statistical analysis showed that the modality-by-organ interaction was not statistically significant. Similarly, none of our reading pathologists showed a tendency to have more types of specific major discrepancies with WSI as compared to MS.

5 Technical Performance Assessment Summary

This chapter gives a summary of the Aperio AT2 DX System technical performance assessment (TPA).

TPA Guidance	Test Description	Result
Slide Feeder	Slide dimensions meet ISO8037/1 Optics and Optical Instruments	Pass
	Number of slides in queue	Pass
	Electro-mechanical automation	Pass
	HW (slide loading process)	Pass
	SW (automatic slide identification	Pass
	LCD display provides user feedback (alarms, notifications, etc.)	Pass
	Failure modes and effects analysis	Pass
Light Source	Lamp component information verification	Pass
	Lamp output adjustment control	Pass
	Lamp optical filters/types	Pass
	Lamp optical filters components	Pass
	Lamp expected intra-slide intensity variation (CV = coefficient of variation as a %)	Pass
	Lamp expected daily intensity CV	Pass
	Lamp expected intra-slide spectral CV	Pass
	Lamp expected daily spectral CV	Pass
	Lamp expected lifetime spectral CV	Pass
	Lamp intensity/spectral variation tracking capabilities	Pass
	Condenser illumination format (Kohler, critical, etc)	Pass
	Condenser component info verification	Pass
	Condenser numerical aperture	Pass
	Condenser focal length	Pass
	Condenser working distance	Pass
	Light source and condenser and wavelength accuracy and spectral efficiency	Pass

TPA Guidance	Test Description	Result
Imaging	Optical schematic	Pass
	Objective lens verification	Pass
	Auxiliary lenses (TL, mag changer)	Pass
	Magnification of imaging optics per ISO 8039:2014	Pass
	Relative irradiance per ISO 13653	Pass
	Distortion per ISO 9039	Pass
	Chromatic aberrations per ISO 15795	Pass
Scanner Movement	Stage size	Pass
	Stage manufacturing and model number	Pass
	Stage material	Pass
	Single multi-axis or stacked single-axis stages	Pass
	Type of guides/ways	Pass
	Slide holder	Pass
	Movement type	Pass
	Resolution for XY axes	Pass
	Movement of Z axis	Pass
	Speed(s) of axes	Pass
	Range of travel	Pass
	Scanning area	Pass
	Localization/barcode reading	Pass
	Open/Closed loop operation	Pass
	Positional accuracy (calibration) and repeatability	Pass
	Lost motion compensation (e.g., backlash)	Pass
	Physical control for single slide, non-batch mode	Pass
	Method for selecting area to be scanned	Pass
	Failure modes and effects analysis	Pass
	Positional repeatability and accuracy per ISO 230-2:2014	Pass

TPA Guidance	Test Description	Result
Digital Imaging Sensor	Sensor type	Pass
	Number and dimension of pixels	Pass
	Configuration of color filter array	Pass
	Spectral transmittance of color filter	Pass
	Quantum efficiency vs. wavelength	Pass
	Linearity	Pass
	Spatial uniformity	Pass
	Dark current (electrons/second)	Pass
	Read noise (electrons)	Pass
	Readout rate	Pass
	Output format	Pass
	Opto-electronic conversion function per ISO 14524:2009	Pass
	Noise measurements per ISO 15739:2003	Pass
Imaging Processing Software	Exposure control	Pass
	White balance	Pass
	Color correction	Pass
	Sub-sampling	Pass
	Pixel-offset correction	Pass
	Pixel-gain or flat-field correction	Pass
	Pixel defect correction	Pass
Image Composition	Single/multiple objectives	Pass
	Scanning pattern	Pass
	Scan overlap	Pass
	Stitching algorithms	Pass
	Background correction functions	Pass
	Single slide scan time	Pass
	Number of Z planes scanned	Pass
	Images of digitized calibration slides	Pass
	Analysis of focus quality metrics	Pass
	Analysis of coverage	Pass
File Formats	Compression method	Pass
	Compression ratio	Pass
	Compression type	Pass
	File format	Pass
	DICOM compliant	Pass
	File organization/structure	Pass

TPA Guidance	Test Description	Result
Image Review Manipulation Software	Panning and pre-fetching	Pass
	Zooming (magnification)	Pass
	Discrete Z displacement	Pass
	Compare multiple images simultaneously	Pass
	Annotations	Pass
	Image enhancement (filtering)	Pass
	Color manipulation	Pass
	Annotation tools	Pass
	Tracking of visited areas	Pass
	Digital bookmarks	Pass
	Virtual "multi-head microscope"	N/A
Computer Environment	Hardware	Pass
	OS	Pass
	Graphics card	Pass
	Graphics card driver	Pass
	Color management settings	Pass
	Color profile	Pass
	Display interface	Pass
Display	User controls - Specified test settings (factory default)	Pass
	Spatial resolution	Pass
	Pixel defects	Pass
	Artifacts	Pass
	Temporal response	Pass
	Maximum luminance	Pass
	Minimum luminance	Pass
	Gamma value/gray scale display function (DICOM)	Pass
	Luminance uniformity	Pass
	Luminance stability	Pass
	Bidirectional Reflection Distribution Function (BDRF) and/or, Spectral/Diffuse Reflection Coefficients	Pass
	Gray tracking (chromaticity vs. luminance)	Pass
	Color scale (primary coordinates)	Pass
	Color gamut volume	Pass

TPA Guidance	Test Description	Result
Color Reproducibility	Input color patches	Pass
	Ground Truth: CIELAB values. Measure using colorimeter	Pass
	Output digital image file	Pass
	Calculate color differences	Pass
	CIELAB values in digital images	Pass
	Output color stimuli	Pass
MTF - Spatial Resolution	Resolution and spatial frequency response per ISO 12233:2014 (E)	Pass
Focusing Test	Focusing data required	Pass
	Focus method (auto-focus)	Pass
	Selection of manual focus points (if applicable)	Pass
	Focus evaluation metrics	Pass
	Constructing focus map from sample points	Pass
Whole Slide Coverage	Tissue coverage test method including:	Pass
	• Selection of the input slide tissue	Pass
	• Determine the complete coverage of the input tissue slide	Pass
	• Measure the actual coverage of the WSI output	Pass
	• Calculate the ratio of the actual to complete coverage	Pass
Stitching Error	Selection of the input tissue slide	Pass
	Sampling of the stitching boundaries where stitching errors might occur	Pass
	Determine the perfect stitching as the ground truth	Pass
	Evaluate quality of the actual stitching boundaries with the perfect one that does not have stitching artifacts	Pass
Turnaround Time	Typical turnaround time including test method and test conditions	Pass
User Interface	User operation options	Pass
	Information presented to the user	Pass
	Human factors report	Pass
Labeling	Labeling sufficient to satisfy 21 CFR Part 801 and 21 CFR 809.10	Pass
	Labeling and training study including timing and content	Pass
Quality Control	Frequency and test methods, responsibility and quantitative limits	Pass

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O

P

R

S

T

U

W

Symbols

- The following symbols may appear on your product label or in this user's guide:

	Consult instructions for use
	Manufacturer
	Date of manufacture (year - month - day)
	European Union Authorized Representative
	In vitro diagnostic device
	Serial number
	Catalog number
	Relative humidity range
	Biological risks
	Storage temperature range
	Electronic and electrical equipment waste disposal
	The exclamation point within an equilateral triangle is intended to alert you to the presence of important operating and maintenance (servicing) instructions.
	The lightning flash with arrowhead symbol within an equilateral triangle is intended to alert you to the presence of uninsulated "dangerous voltage" within the product's enclosure that may be of sufficient magnitude to constitute a risk of electric shock to persons.
	The flat surface with waves symbol within an equilateral triangle is intended to alert you to the presence of hot surfaces which could cause burn damage.
	The UV lamp within an equilateral triangle is intended to alert you to the presence of UV light within the product's enclosure that may be of sufficient magnitude to constitute a risk to the operator.

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