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Quality Management System in Clinical Digital Pathology Operations at a Tertiary Cancer Center

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Abstract

Digital pathology workflows can improve pathology operations by allowing reliable and fast retrieval of digital images, digitally reviewing pathology slides, enabling remote work and telepathology, use of computer aided tools, and sharing of digital images for research and educational purposes. The need for quality systems is a prerequisite for successful clinical grade digital pathology adoption and patient safety.

In this work, we describe the development of a structured digital pathology laboratory quality management system (QMS) for the clinical digital pathology operations at Memorial Sloan Kettering Cancer Center (MSK). This digital pathology specific QMS development stemmed from the gaps that were identified when MSK integrated digital pathology into its clinical practice.

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The Digital Scan Team in conjunction with the Department of Pathology and Laboratory Medicine Quality Team developed a QMS tailored to the scanning operation to support departmental and institutional needs. As a first step, systemic mapping of the digital pathology operations identified the pre-scan, scan, and post-scan processes, instrumentation, and staffing involved in the digital pathology operation. Next, gaps identified in quality control and quality assurance measures led to the development of standard operating procedures and training material for the different roles and workflows in the process. All digital pathology related documents were subject to regulatory review and approval by Departmental leadership.

The quality essentials were developed into an extensive Digital Pathology Quality Essentials (DPQE) framework to specifically address the needs of the growing clinical use of digital pathology technologies. Using the unique digital experience gained at MSK, we present our recommendations for QMS for large scale digital pathology operations in clinical settings.

Introduction

The field of pathology is undergoing a digital transformation with scanning, reviewing, and storing of pathology slides in a digital format. Digital workflows have demonstrated many benefits to pathologists and healthcare systems. These include reliable and fast retrieval of digital images, ability to digitally review and compare prior pathology slides at any time, enable remote work and telepathology, allow the use of computational aided tools, as well as the sharing of digital images for research and educational purposes [1–7].

Memorial Sloan Kettering Cancer Center (MSK) Department of Pathology and Laboratory Medicine (DPLM) was an early adopter of digital pathology systems. Initial explorations began in 2006 and gradual onboarding of technologies led to the creation of an infrastructure to enable a large-scale high throughput whole slide imaging operation. While quality management systems are well known to pathology laboratory operations, they have not been well described for clinically deployed digital pathology systems.

The Joint Commission (TJC) formalized action to address medical errors by issuing patient safety goals starting in 2004 [8]. An important goal is improved accuracy of patient identification, while another is improved effectiveness of communication among caregivers. Both of these goals have implications in the practice of pathology and laboratory medicine, and indeed, have been recognized before these formal declarations [9].

A laboratory Quality Management System (QMS) is a systematic, integrated set of activities to establish and control the work processes from pre-analytical through post-analytical phases, manage resources, conduct evaluations, and make continual improvements to ensure consistent quality results. The World Health Organization Quality Management Handbook serves as a guide for the quality essentials for the QMS[10]. QMS have been described by the International Organization for Standardization (ISO) and the Clinical Laboratory Standards Institute (CLSI) as “coordinated activities to direct and control an organization with regard to quality” [11,12]. In the U.S., a QMS is a Clinical Laboratory Improvement Amendments (CLIA) requirement for all clinical laboratories that test human specimens for health assessment or to diagnose, prevent, or manage disease. Implementing a QMS is

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critical to providing quality reliable results for clinical decision-making for all laboratory operations [13].

In 2013 the College of American Pathologists (CAP) published a guideline on whole slide imaging (WSI) validation for diagnostic purposes[14] with an updated guideline that was published in 2021[15]. Another publication from the European Society for digital and Integrative Pathology detailed guidelines that included histology quality checkpoints for clinical digital pathology workflows[16].

MSK was the first institution to receive New York State Department of Health (NYSDOH) approval for clinical use in reviewing patient slides with digital pathology systems [17]. Soon after the integration of digital pathology into the clinical operations, a gap analysis followed by actions to address them were made to construct an internal QMS for holistic digital pathology system operations and to develop quality standards and protocols to ensure clinical laboratory quality processes are maintained.

This paper details the internal MSK development of a structured digital pathology laboratory QMS implemented for the specific needs of the institution's operations, from accessioning, specimen processing, glass slide generation, whole slide scanning, data transmission, storage, and integration into the laboratory information system (LIS). This homegrown QMS could be used as a blueprint and tailored for institutions that are integrating digital pathology systems into their pathology operations.

Methods

Scanning Operation (Hardware and Software)

In 2020, the Department of Pathology and Laboratory Medicine (then known as the Department of Pathology) at MSK had 26 whole slide scanners including Leica Aperio AT2 and GT450 (Leica Biosystems, Buffalo Grove, Illinois); 3DHistech Pannoramic 1000, and Philips Ultra-Fast Scanner (Philips, Amsterdam, the Netherlands). The whole slide scanners predominantly used for the clinical operation during the time of developing the QMS were the AT2 and GT450 scanners. The number of GT450 scanners has grown from one in May 2020 to 16 to date. All scanners were located in either the histology laboratory or adjacent space on the same floor of the laboratory. Temperature and humidity monitoring in scanning spaces is tracked remotely using NetBotz (APC, West Kingston, Rhode Island).

Glass slides including H&E, Immunohistochemistry (IHC), special stains, and frozen section slides, are scanned routinely at ×40 equivalent resolution (0.25 μm/pixel); however, ×20 equivalent resolution (0.5 μm/pixel or 0.16 μm/pixel). Scans were also performed for retrospective scanning (e.g. slides from cases already clinically reported) in approximately 10% of the slides scanned. The whole slide images are transferred and stored in the institution's data center. The Department supports a network connection of 1 gigabit/second for each computer workstation and whole slide scanner. The whole slide scanners share a 10 gigabit/second connection to the institutional data center that is located off-site of the main campus. Studies detailing the technical network infrastructure of the digital pathology operation have been previously published [18,19]. The advanced barcoding and tracking

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module implemented at our institution uses 2D barcodes that are decoded by the whole slide scanners, and interface to the vendor supported database with the PicsPlus module of the LIS (Cerner CoPathPlus, Cerner Corporation, Kansas City, Missouri). Pathologists can launch whole slide images from within the LIS or the custom developed MSK Pathology Digital Worklist and are viewed in a separate WSI viewer application web-based MSK Slide Viewer that has been clinically validated[17,20].

Data analysis of MSK's digital pathology operations including archive scan volumes from the LIS were performed. Scanner capital acquisitions, preventive maintenance and service contract records were obtained and analyzed from the department's accounting records. Turnaround times were calculated for cases with digitally scanned slides to evaluate any potential delays in slide distribution or case sign out. Staffing records were obtained from our enterprise human resources system. The Department's standard operating procedures (SOPs) and laboratory protocols, as well as global standards such as CLSI guidelines were reviewed and evaluated to be adapted towards inclusion of the validated digital pathology system.

QMS design

The Digital Scan Team in conjunction with the Quality Team at DPLM developed a QMS tailored to the scanning operation to support departmental needs at MSK. A systemic identification and review of the histology laboratory Quality Assurance (QA) essentials as defined by a QMS was conducted in our department. Gaps identified in Quality Control (QC) measures and the required digital pathology QA measures led to the development of SOPs and training material for the different roles and workflows built for clinical use of digital pathology systems. As with other laboratory policies and procedures, all digital pathology related documents were subject to regulatory review and approval by Departmental leadership.

Quality and performance metrics were needed to monitor the daily digital pathology operations. Monitoring these metrics allows for detection of unforeseen test system drift, identifying areas of improvement, and confirmation of a stable testing system [11]. Action is taken when the information from the quality and performance metrics demonstrates unacceptable performance or a trend in that direction. The digital pathology QA plan outlines the quality and performance metrics specific to those processes and all data is available to departmental stakeholders.

Results

Key QMS practices include periodic audits and quality monitors to assess compliance with regulatory related requirements and laboratory defined expectations. Quality practices and metrics are in place to ensure quality throughout the pre-analytic, analytic, and post-analytic phases of testing. The QMS includes measures to identify and evaluate errors, defects, incidents, and other problems that may interfere with patient care services.

Whole slide imaging incorporates three processes: (1) the pre-scan glass slide generation; (2) glass slide digitization; and (3) image review of digital slide. The pre-scan steps include

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histology laboratory processes similar to conventional analog pathology specimens, with the goal of producing high quality microscopy slides with centered, closely embedded, uniformly sectioned tissue to allow the generation of the best quality slide. This is followed by staining and coverslipping of the glass slides. These steps were already covered under existing MSK histology laboratory QMS. The additional WSI steps required the development of QMS for these novel processes.

The MSK teams developed QA essentials for digital pathology following the World Health Organization Laboratory Quality Management System: Handbook [10,21] and the Clinical and Laboratory Standards Institute model [11]. These were used to guide the Digital Pathology Quality Essentials (DPQE) for our digital pathology operations and are summarized in Table 1.

SOPs are documents that include instructions and describe how to perform a clinical activity. SOPs enable laboratories to document, validate, share, and optimize their laboratory procedures. Each laboratory has the primary responsibility for developing and implementing its own SOPs and QMS. All digital scan team staff have the responsibility of following approved SOPs and are encouraged to review and suggest procedural updates to laboratory leadership when opportunities for improvement to standard operating procedures are identified.

The QMS prompts staff to document defects when expected scanning activities outcomes do not occur. This is an identified ongoing process, and as the QMS matures with expansion and growth of the scope of the digital scanning activities, new and revised SOPs are linked to additional policies, instructions, and other appendices. The DPQE quality measures were developed, outlined, reviewed, and are detailed below.

Digital Pathology Quality Essentials (DPQE)

1. **Organization and leadership—**Organization and leadership QA essential describes the key leadership responsibilities that are integral to a laboratory's success in achieving and maintaining a systematic approach to quality and meeting regulatory, accreditation, customer, and internal requirements [21].

The digital pathology operations team currently provides scanning services and support (e.g., clinical-prospective, clinical-retrospective, archival, research and education use scanning) for surgical pathology, cytopathology, hematopathology, molecular pathology, research, biobank, and experimental pathology, at DPLM. The Department consists of 123 faculty and 1300 staff. Future scanning support will include clinical pathology subspecialties.

Pathology organizational charts illustrate the reporting relationships among the laboratory management, the laboratory director, section director(s)/technical supervisor(s) and supervisor(s)/general supervisor(s), and technical/non-technical staff. DPLM's digital pathology operations team consists of a director, manager, and imaging technicians. The digital scan team organization chart is approved by leadership, and all departmental organization charts are stored and available for review, with periodic updates as needed.

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The laboratory assesses gaps in actual and projected staffing based on changes in projected volumes from clinical services, staffing variance reports, and laboratory staffing schedules. Staffing is adjusted based on work prioritization, need for reassignment to cover other work areas and overtime need to complete pending work.

2. Customer focus—Customer focus emphasizes the need to meet the expectations set forth by the digital scan team and laboratory customers. It also describes methods for seeking customer input to confirm that expectations are continually met [21]. Establishing policies for customer service results in processes and procedures to identify the satisfaction and evolving needs of digital scan team's customers. Based on customer feedback and needs, scanning workflows can be re-designed to meet expectations.

The digital scan team interacts with multiple teams with different needs and priorities both internally and externally. An effort was made to identify the customers (Figure 1) and have processes in place to assess the different customer needs (e.g., hardware and software solutions, data availability requirements and turnaround times). The internal MSK customers are ordering physicians, trainees, pathologists, pathologist office coordinators, laboratorians, biobank staff, researchers, legal staff, and administration. External customers include consulting pathologists, support staff, legal firms, vendors and research collaborators.

Each customer's priorities and needs require different communication modes, data transfer solutions, information technology (IT) resources and reporting capabilities. Processes were put in place to ensure effective communication and timely customer service while securing patient data and conforming to institutional and departmental guidelines.

Goals for achieving and maintaining customer and personnel satisfaction were defined, and progress was regularly reviewed. Feedback and satisfaction data are reported to management for evaluation of improvement opportunities. Complaints are promptly forwarded to the DPLM Quality team for investigation as to root cause and corrective actions needed.

One of the major efforts performed during the initial implementation of digital scanning was to ensure the DPLM pathologists were familiar and comfortable in using the digital pathology workflows and clinical sign out. This included establishing the reliability and trust in the extra scanning steps of our operations and avoidance of delays in the availability of slides to the pathologists for their dedicated review. Two surveys distributed to the pathologists in 2018 and 2020 showed an increase in comfortability and familiarity in providing primary diagnosis using WSI, even if glass slides would not be made available [2,17]. The digital scan team continues to request feedback from pathologists and trainees using direct communication and annual surveys as well as feedback from internal and external staff and administration.

Based on gaps identified in customer service communications between the different stakeholders involved in the clinical digital scanning activities, the digital scan team added the following improvements to the daily workflows: 1) Communication with the histology laboratory was established with team dedicated email listservs and telephone lines; 2) Designated online forms were designed for the different scan requests including internal

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and external scan requests for clinical, educational, and research needs, 3) Processes for communications with vendors and administration were established and resulted in scheduled recurring meetings with all stakeholders; 4) An updated internal website with information regarding the digital scan team, services, and capabilities is being revamped to reflect these communication improvements.

3. **Facilities and safety—**Facilities and safety category provides information about the maintenance and safety programs needed to support the laboratory. The laboratory needs to establish and maintain a facility that provides adequate space, workflow, and environmental conditions to support the quality of work and safety for all staff, in compliance with published regulations [21]. For digital scanning this requires the identification of appropriate, ventilated space, free of excessive vibrations, dust accumulation, and other environmental considerations to prevent instrument failures.

DPLM is committed to providing a safe work environment for patients and staff by providing adequate and well-maintained facilities, equipment and utility systems needed to carry out quality laboratory testing. The digital scan team works closely with additional departments within MSK including Facilities Management, Biomedical Physics & Engineering, Environmental Health & Safety, Information Systems, and Employee Health and Wellness Service to minimize the risk of injury or illness to laboratory staff and to ensure facilities and environment are maintained and safe for the provision of necessary services.

The integration of whole slide scanners to the pathology operations required additional monitoring of scanning related spaces to ensure suitability of environment for the tasks being performed in that space. Laboratory space was rearranged, and scanners were distributed to allow for more streamlined operations taking into account the location of the glass slide production and case collation to minimize glass slide transfers and unnecessary foot traffic by the imaging technicians. Digital scan team leadership considers changes in scanner type and throughput, scanners, workflow processes, and feedback from personnel when considering new space or potential renovations to existing space. Staff from the department meets periodically to discuss space planning, design, and operational issues as they relate to digital pathology functions (i.e., space planning meetings, IT meetings, laboratory managers meetings). Team leadership works with institutional leadership and facilities management, for planning digital pathology needs for current/future, and new/renovated space needs.

The scanning activities are located in a low-foot traffic area within the department that is proximal to the glass slide preparation and case collation workspace. Most whole slide scanners function within an environmental temperature range of 15°C to 28°C and humidity range of 20% to 80%. Temperature and humidity monitoring units were added to the scan rooms, and a monthly log of all temperature and humidity readings is reviewed, signed, and maintained in digital scan team folders. When temperature and humidity values extend beyond acceptable ranges, the non-conformance is investigated and addressed.

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In an effort to maintain the continuity and quality of whole slide imaging during instances of power loss or electrical current fluctuations, all scanning related instrumentation is connected to emergency power outlets that provide back-up power during loss. The emergency power system is maintained and monitored. All scanners are also connected to uninterruptible power supply units (UPS) to assure they have adequate electrical power management.

The laboratory measures to ensure facility and safety QMS goals are met include: 1) Daily and monthly environmental monitoring (i.e., temperature, humidity) via remote systems; 2) Quarterly biosafety audits performed by laboratory staff (i.e., to assess compliance with fire safety, biohazard, waste management, personnel protective equipment (PPE), and hand hygiene requirements); 3) Periodic safety walkthroughs performed by the Environmental Health & Safety and local Fire Department; 4) Daily and monthly review of digital scanning QC worksheets and environmental monitoring documentation; 5) Annual internal audit.

4. Personnel Management—The personnel management category describes obtaining and retaining an adequate number of qualified, well-trained, and competent laboratory staff to perform and manage the activities of the laboratory, training and competency, orientation, etc. [21]. Training for staff may vary based on position and includes staff with photography expertise, prior laboratory or digital imaging experience, or entry level staff who can be trained during on-boarding.

DPLM created a digital scan team to address the staffing needed to perform the tasks associated with digital scanning operations. Duties included initial slide handling, QC activities, slide preparation prior to loading the scanner, post-scan image review, equipment operation, documentation and record keeping and other administrative tasks (e.g., addressing stat requests, responding to customer service inquiries, troubleshooting misplaced slides, environmental monitoring, and training of faculty and staff).

In the early implementation phase of investigating and building up the disruptive digital scanning technologies and workflows, internal pathology photographers were approached to be part of the digital scan team based on their prior work experience (i.e., experience with gross pathology photography, image analysis of pathology digital images for the purposes of publication and presentations and customer service). As the department's scanning volume increased and with the introduction of prospective scanning prior to slide distribution in 2020 [17], laboratory aides were identified to assist with prospective slide scanning of slides within the histology laboratory post-slide preparation.

With appropriate training, identified personnel were found to be competent to perform the duties associated with the pre-scan and post-scan digital operations. Job descriptions for imaging technicians were formalized. Job qualifications included data entry experience in a laboratory environment, experience in pathology accessioning or slide library or administrative work experience in the health care environment. Applicable skills and abilities included in the job description included written communication skills, effective problem-solving and troubleshooting skills, customer service skills and ability to work with tight timeframes and meet strict deadlines.

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Educational material used for training includes a hybrid of internally developed modules and hardware vendor provided educational material. In 2018, the National Society for Histotechnology (NSH) and Digital Pathology Association (DPA) developed an online self-paced digital pathology certificate program in response to a lack of formal educational opportunities and standards for clinical practice within the digital pathology environment[22]. The program consists of seven learning modules covering the history of digital pathology, technology basics, uses for digital pathology, considerations for selecting, implementing digital pathology, workflow considerations and best practices, image analysis, validation, and regulatory requirements. The online program also includes intermittent knowledge checks and a final examination. This certification represents a tool to standardize the minimum level of training and competency for digital pathology staff. DPLM is currently encouraging the completion of this program by all its digital pathology staff.

Additionally, an organizational chart was developed to identify the reporting structure for staff to an administrative manager who oversaw the overall digital pathology operations. The digital pathology manager is responsible for overseeing the day-to-day operations including ensuring appropriate staffing levels, monitoring turnaround time, identifying opportunities for improvement and staff management. The digital pathology manager oversees training, competency assessment and performance assessment of digital pathology staff to ensure they are knowledgeable and competent in their job responsibilities. Ongoing education is also provided to staff as digital pathology technology continues to evolve and opportunities for improvement are identified and implemented. The digital pathology manager is also responsible maintaining and retaining personnel records as required by laboratory regulations.

5. Supplier and inventory Management—Purchasing and inventory details procurement and service agreements that the laboratory has with customers and outside vendors to ensure that specified requirements for critical supplies and services are consistently met [21].

Procurement of slide scanning equipment mirrors the hospital purchasing and inventory requirements followed by other MSK laboratory sections. The reliability and qualifications of any equipment vendor is verified by hospital procurement staff, including review of purchase agreements as well as service level agreements, delivery, and installation timelines. In addition, records of receiving, inspecting, installing, testing, and handling of the WSI instrument are maintained by the digital scan team staff. It is important to note that the purchasing and inventory of WSI is not different than that of other hospital networked biomedical equipment with the needs for LIS integration and compatibility with MSK middleware solutions and image storage servers.

Digitization of pathology glass slides requires the use of additional laboratory supplies such as ethanol 190 proof, gauze, and razor blades for the pre-analytic steps of glass slide(s) preparation for scanning, as well as office supplies for the various team activities. These supplies are tracked, kept in the inventory, and are ordered as any other laboratory consumable.

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6. Equipment—Equipment essential in the QMS describes selection and installation of equipment, equipment maintenance and calibration, documentation of equipment-related problems, and record maintenance [21].

Proper management of the equipment in the laboratory is necessary to ensure accurate, reliable and timely testing [10]. For the digital scan team this translates to scanner selection, onboarding, instrument validation, scanner preventative maintenance (PM) and function checks.

Scanners are selected based on criteria including their technical features and suitability for our different use cases [3,4,23]. Digital scanner selection criteria to be considered before instrument purchase and onboarding include features such as scanner capacity, image quality continuous/ batch load options, glass slide size, magnification, brightfield/ fluorescence needs, scan speed and time for image availability, file format and viewer, ergonomics, cost, lab footprint, expected downtime, reliability, and availability of vendor service.

Vendors are vetted based on institutional experience and the availabilty of reliable services that they can provide to support the digital pathology continuous operation.

Following the selection of potential scanners, a rigorous no commitment onsite evaluation by the digital scan team is required before any new scanner model purchase to ensure that the scanner performance, such as image quality, scanning speed, ergonomics and operating cost, matches the intended use case and expectations of our operation. This evaluation also includes a review of a comprehensive set of digital slides representing routine departmental cases using the following image quality metrics: 1) Out of focus regions; 2) Tissue detection capture completeness (tissue outside coverslip, under coverslip, or no tissue detected); 3) Barcode failure: scanner level, LIS level, missing slides; 4) Other quality issues: banding, pixelated areas.

The overall performance of the scanner and the suitability for departmental needs will influence the decision to recommend purchase of the evaluated scanner model.

Once an instrument is purchased, the vendor is responsible for supplying the install requirements and for coordinating the delivery and install with the internal team. After onsite installation and calibration, the vendor is responsible for training the internal staff and ensuring that the scanner is performing as anticipated and integrated into our different systems. All purchase and installation documentation are saved and available as part of the laboratory's QMS document and records management. The scanner is also added to MSKs biomedical asset/equipment management system.

The scanner goes through a development phase in which functional testing is conducted using a variety of representative glass slide scans, ensuring scan profiles are available before proceeding to instrument validation and clinical use. The validation includes scanning identical glass slides on the evaluated and existing validated scanners and ensuring that the resulting images and metrics are comparable.

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The digital scan team receives initial training to understand the scanner mechanics, its limitations and intended use in our operations.

PM ensures performance and functionality of departmental scanners to prevent scanner failures (Figure 2). Scanner PMs include external contractual vendor scheduled visits but also internally developed MSK PM activities for quality maintenance.

The external PM varies by the vendor but includes preventive checkups, re-calibrations, repairs, replacement of worn parts, scanner updates and further hardware related interventions. These onsite visits are documented and list the service(s) that were completed and are scheduled twice per year or per the vendor's recommendation. Scanners go through function checks and performance verification by the digital scan team following the service.

Internal weekly PM includes cleaning of optical and slide handling parts before image quality degrades as residue accumulation results in buildup of glass shards, mounting media and dust on the objective and the slide stage and handlers. Management incorporated procedures for weekly cleaning of our scanners once we realized that many of our failures were derived from these residues and this resulted in improvement in the image quality and decline in scanner failures. The weekly PM requires several minutes of digital scan team technician time per scanner.

The contractual annual vendor service agreements cover timely service and repair solutions. Troubleshooting procedures were developed internally to minimize downtime of scanners, with assigned responsibilities to all digital scan team members. These allow immediate attention and troubleshooting of failures in a timely manner without the need to involve and wait for the vendors' technical teams. Once the digital pathology system is clinically validated, the technology is considered a clinical system, similar to other laboratory instruments (e.g., stainer, coverslipper). In addition, the digital pathology manager has oversight of all the equipment, maintains scanner purchase and maintenance records and instrument specific SOPs. This team member also serves as a senior contact for the vendor technical services and follows vendor specific service notification protocols to minimize scanner downtimes and compromised turnaround times (TAT).

To ensure comparable instrument quality of the different scanners, the laboratory performs an interinstrument analysis every 6 months. This analysis is done by running 30 routine laboratory slides on all validated scanners and comparing run time and image failures that require re-scan.

7. **Process management—**Process management describes oversight of processes directly and indirectly related to the laboratory's path of workflow to achieve laboratory-defined requirements including efficient use of resources, [3,4,21,24] maintaining slide and image quality standards, and ensuring the availability of quality images for downstream clinical, educational, research and other uses.

The glass slide digitization effort includes a step wise approach for obtaining a high-quality glass slide prior to scanning and then after the digitization, a high-quality digital image. Five

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different checkpoints were identified that resulted in new SOPs to detail the processes to follow for each of these checkpoints.

Figure 3 summarizes the quality pre-analytic and analytic phase checkpoints that are followed during the slide production and digitization process.

The first QC step is to ensure glass slides are free of laboratory histology artifacts such as air bubbles, ink markings on the coverslip (especially for glass slides received from outside laboratories for pathology consultation), overhanging slide labels and coverslips [4,18,24,25]. The pre-scanning QC process requires careful macro-evaluation of slide artifacts that have to be resolved before scanning. Some institutions also have demonstrated the value of checking the block and tissue present on the glass slide [26].

The second QC step requires careful visual examination of each slide for uniform staining, fully dry slides and slides free of visible breaks or cracks, visible fingerprints, ink markings and dust particles. If the tissue section extends underneath the edge of the slide label or to the edges of glass slide, the tissue present past those areas will not be scanned in focus. Coverslips are checked such that there are no overhanging edges beyond the edges of the glass slide or air bubbles. The slide label with the patient information should be legible and on the appropriate up-facing surface, firmly adhered to the glass slide without extending past the slide edges. The barcode on the label should be legible (not cut off or smeared). This QC step is especially important for glass slides processed and submitted from outside laboratories as multiple barcode labels present on the glass slide could lead to barcode errors during scanning and cause the digitized slide not to be linked or available within the LIS. Imaging technicians check slide labels with available hand-held barcode scanners to ensure readability of the barcode prior to placing the slide on the whole slide scanner. Including a barcode tracking station to scan each glass slide in all pre-scanning work areas ensures each barcode is readable by handheld barcode readers and can also be configured to track the glass slide in the LIS as scanned or marked for scanning. Glass slides without barcodes, or barcodes that failed reading by the handheld bar code reader, require the creation of new MSK bar-coded slide labels that are affixed on the glass slide prior to scanning. Training is needed for accessioning staff and imaging technicians to apply barcoded slide labels in appropriate areas of the slide to ensure essential data (i.e., patient identifiers, outside accession number, stain name, etc.) remains visible on WSI.

Major quality differences are found between slides produced directly from the MSK laboratory (e.g., in-house), and slides processed and submitted by outside laboratories as consultation cases (e.g., domestic and international). The processing and prepping of these slides are external to that of the laboratory produced slides and cannot be controlled by MSK. These slides require additional steps of inspection, cleaning and relabeling before they can be loaded on scanner racks.

The third QC checkpoint is the real time thumbnail review (e.g. macro image) of all images on the scanner[27]. There are multiple slide scanning error codes that most scanners can provide, such as barcode detection failure, image quality errors or if no tissue was identified on the slide (i.e., usually slides with scant tissue, fatty tissue or faint immunohistochemical

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stains). Based on these errors, the scanner operator can address scanning issues without removing slides from the scanner. Most modern scanners provide internal QC procedures to ensure a high scan quality, but these QC processes are not sufficient. As a result, incorrect focus points, scanning and glass slide artifacts or missing tissue are not always detected by the different scanners.

The 4th QC workflow is to ensure the digital slide is of adequate quality and is transmitted successfully and accessible within the LIS. This QC process involves investigation of the digital pathology system vendor's database or within the LIS to review quality evaluation for typical WSI artifacts (i.e., tissue detection, out of focus, horizontal striping, color quality, etc.). The digital scan team notifies the laboratory and slides requiring a rescan are included in the subsequent batch of slides or can be manually scanned in real-time. It is the responsibility of the laboratory staff and digital scan team to ensure quality scanning operations and minimize WSI defects prior to reaching the pathologist for diagnostic review, but not all digital slides get reviewed by imaging technicians prior to pathologist's review.

This process requires coordination of the timing for the availability of quality images and the pathologist's sign out schedules and required an adjustment of the imaging technicians' schedules to avoid delays in image availability to the pathologists. All errors and troubleshooting get recorded and monitored to maintain quality metrics and identify further training opportunities for staff. Automated software may be used in the future to notify staff of slides that need to be rescanned.

The 5th QC of the WSI at diagnostic review is the last and definitive QC step of the digital image. When viewing a digital slide in the WSI viewer software, pathologists may identify poor quality digital slides and request prompt rescanning of the glass slide or defer review of the glass slide for final diagnosis. The documentation for this additional QC step has been implemented within the MSK Viewer. A link to the accession number and slide is automatically generated and sent to the digital scan team via email with reason of the report, such that the slide can quickly be rescanned [18]

Reviewing of the images by the digital scan team requires the calculated effort of 1 FTE for every 3–4 high throughput scanners. Imaging technicians use the vendor imaging tools to open images and look for out of focus regions, banding, barcode errors and any other defects that will require a rescan of the slide. This is a process that is time sensitive as any slides requiring rescan at this point in the clinical journey will delay glass slide distribution to trainees/pathologists and pathology results reporting.

Tracking of the first-time scan quality error rate and the type of errors detected in the post scan review began soon after starting the prospective scanning of biopsy slides in the laboratory. The data is used for QC, training and for future improvements of the operation. Figure 4a summarizes scan errors derived from MSKs digital scan team from January-December 2021.

The error type is tracked, and a typical distribution of all errors can be seen in Figure 4B. Errors have been grouped into 4 categories: Barcode errors, missing tissue, out of focus

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regions, and horizontal lines/banding. The error rate is due to missing scanned tissue in the digital slide, followed by barcode errors and blurry/out of focus images.

Missing tissue that is detected in the post review could be minimized with careful QC immediately after a slide is scanned before it is removed from the scanner. This can be quickly done via a thumbnail review prior to removing the completed rack from the device. Some of the quality issues were scanner dependent issues and required vendor interventions. Periodic spikes in barcode errors suggest that it might be related to a label printer issue that can be avoided by retraining the staff involved in the printing and labeling of slides. Ensuring these label printers are functioning properly and print readable barcodes resulted in a decrease in barcode read failures and relabeling of slides. Understanding the cause of these error peaks and minimizing the human error that is involved in these scans is a top priority and will greatly improve the operations in the laboratory and the overall turnaround time (TAT).

The laboratory's error tracking is currently a manual and a time-consuming process. Efforts are being made to replace the current process with an automated dashboard to enhance timely recognition and remediation of issues by involved staff.

Tracking of the image errors demonstrated differences in the error numbers of the different scanners (data not shown). Once adjusted for total slides scanned, we were able to track the percent of rescans for each of our scanners. The total scan error rate is less than 1.5% for the prospective scans.

Modifying workflows and training for staff was required to minimize delays in TAT. Downtime periods where slides were traditionally being collated with their respective cases or awaiting review overnight were used for digital scanning efforts to maintain slide distribution or case reporting turnaround time. As a result, laboratory aides were trained to load and operate basic functionality on the high throughput whole slide scanners and the digital scan team was tasked with troubleshooting and technical support, in addition to both teams providing QC checks on the glass slides and whole slide images. The staff was trained to improve first time scan success rates, with minor modifications such as centering of tissue during embedding and sectioning and allowing time for racks to fully dry before being loaded into the whole slide scanners. Additional coverage of digital scan team members was needed at night for troubleshooting and post review of the scanned slides. To accommodate for these needs the team started to work 24 hours a day.

Monitoring TAT is essential in order to identify and prevent delays in slide availability for pathologist reporting particularly following the introduction of prospective scanning in the laboratory. Prospective scanning of biopsy glass slides started in August 2020 and included overnight surgical pathology routine biopsies that are cut and stained in the laboratory prior to 8 am. Figure 5 is an example of the TAT data tracking from January 2020 to December 2021 of laboratory biopsy scanning. These values were compared to median turnaround time that was measured for the first months of 2020.

The median turnaround time for case accession to last slide of case available for distribution has not changed significantly in the 17 months following the adoption of prospective

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scanning. TAT values remained acceptable even when biopsy specimen numbers exceeded those of the pre-pandemic levels in March 2021. The analysis demonstrates there was no significant delay in the time from case accession to the distribution of the first available case slide from the laboratory baseline as compared to after prospective clinical scanning. Even though not all cases were reported digitally, this data shows that prospective scanning of glass slides does not alter turnaround times despite the added scanning workflow steps.

8. Documents and Records Management—Documents and records management DPQE describes the creation, management, and retention of the policy, process, and procedure documents for the DPQEs and path of workflow [21].

As digital pathology operations were introduced to the pathology operations, a need was identified for internal documentation by the digital scan team. These include digital copies of the DPQE plan, validation records, equipment service and maintenance records, applicable SOPs, all relevant digital scanning forms and logs, in addition to personnel records. The digital scan team utilized the DPLM's document management platform that includes a repository for documents and allows retrieval and tracking of all digital scanning documents and their different versions. Versions are locked for editing and only changeable by authorized individuals in the pathology department. A record of staff who are required to read laboratory documents is also documented within the platform.

Regulations require retention of laboratory records for certain time frames. Digital pathology operation related records should likewise be retained. As of July 2023, there are no federal regulatory requirements defining retention timeframes for digital images [28]. The College of American Pathologists (CAP) 2022 guidance for digital images used for primary diagnosis, required 10 year retention if the original glass slides are not available, and stated that there is no retention requirement for images of glass slide preparations when the source slides remain readable for the required retention period [29]. New York State (NYS), a CLIA exempt state, requires NYS permitted laboratories to retain histology slides or electronic images that allow re-evaluation of the entire slide(s) used for reporting results for 20 years [30].

9. Information management—The information management essential provides guidance for managing the information generated and entered into laboratory record keeping systems (e.g., patient demographics, examination results and reports, interpretations) [21].

The WSI experience in our department follows all information technology record keeping requirements in the laboratory. Access and retrieval of digital data is controlled using existing SOPs. Image data is managed by different hospital and pathology teams. Key pre-requisites to deployment of a digital pathology system are barcoding and tracking as well as LIS integration. These solutions support the technical gateway for the glass slide to be digitized, maintained, and visualized in the LIS. Digital and glass slide storage management improvements were made at MSK after deployment of the digital pathology system. As glass slide retrievals from older accessions were mitigated by the digital slide availability, they could be moved to a less expensive, more distant location for retention mandates. Similarly, digital storage requirements increased as the scanning efforts expanded in scale and are included in budgetary discussions annually.

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The addition of WSI experience in the clinical workflow resulted in the identification of gaps in available tools and initiated the development of new software tools for the improved quality of the operations. These software developments were built in conjunction with the enterprise informatics division of the institution with a goal of effectively leveraging the digital data. One of the first software tools developed, originated from a need identified during the public health emergency as remote pathologists did not have easy access to their clinical cases, let alone know which cases were assigned to them. After developing wireframes and iterating with the development team, a Pathology Digital Worklist was developed to enable a user-friendly view of case assignments with access to digitally scanned clinical requisition documents, as well as interface with the MSK Viewer for reviewing of whole slide images.

The Worklist was also integrated into our clinical systems to ultimately consolidate various silos of information and display them in one view (e.g., access to clinical history through the electronic medical record, gross examination, intraoperative consultation reports, specimen tracking information, radiology PACS, prior patient accessions, etc.). Additional notification systems were also developed to provide alerts to pathologists for laboratory ordered (glass) slide stain completion and also for newly scanned (digital) slides. Upon the successful deployment of the Worklist, further operational improvements through dashboards were developed. These operational dashboards help provide up to date information regarding digital scan volumes, velocity, variety, and their respective value for clinical, research, and educational purposes. These dashboards provide visualizations to also track error management and remediate QC issues in a proactive manner. These improvements to the digital workflow provide tremendous value in layering digital solutions to enhance the quality digital operation at our institution.

10. Nonconforming event management: Nonconforming event management refers to processes for detecting and documenting nonconformances, classifying nonconformances for analysis, and correcting the problems they represent [21].

Tracking non-conformances associated with digital pathology operations involves a coordinated effort between several teams and multiple hardware and software solutions. The goal is to maximize quality and minimize failures in the different steps of the digital workflow process. Correcting digital pathology process errors requires timely identification and reporting of non-conformances (e.g., image errors, equipment failure, bar code errors). The digital scan team management tracks all nonconformance events in a spreadsheet (Table 2). Occurrences get logged on paper and are transcribed in electronic forms maintained in a departmental shared folder. Nonconformances are investigated, tracked, and analyzed for their root cause in order to identify opportunities for improvement, including modifying workflows and SOPs. To streamline reviews, digital pathology management is exploring the use of dashboards for non-conformance management.

11. Assessments—Assessments DPQE describes the use of external and internal monitoring and evaluation to verify that laboratory processes meet requirements and to determine how well those processes are functioning [21].

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The DPLM demonstrates its commitment to quality laboratory practices through enrollment in mandatory and/or voluntary external accreditation assessment and inspection programs. The DPLM also facilitates external accreditation assessment events and is subject to unannounced inspections. The team reviews guidelines from professional societies in order to identify and integrate evolving digital pathology practices into MSK's digital operations.

The laboratory verifies the accuracy and reliability of each laboratory examination and specimen type through enrollment, participation, and management of an external proficiency testing (PT) program. When no formal PT program is available, the laboratory maintains an alternative process (internal PT) for verifying examination method accuracy and reliability. DPLM's *Proficiency Testing* policy outlines departmental policies regarding proficiency testing including enrollment if CMS/NYSDOH-approved proficiency testing programs or alternative assessments of examination procedures' performance for non-regulated analytes. CAP offers a HistoQIP Whole Slide Imaging Quality Improvement Program (HQWSI) that MSK participates in [31]. The program provides the laboratories that are using whole slide imaging for clinical applications to upload images from their scanners to the CAP designated server. Participating laboratories receive feedback on the different aspects of the image as well as the quality of digital pathology workflow. Participants are also expected to investigate, respond to and document non-conformances identified through this assessment process similar to other PT events.

Internal and external assessments inform the laboratory as to whether the laboratory is complying with regulatory requirements and responsive to customers' needs and expectations. The digital pathology operation is included in DPLM's annual internal audit for the surgical pathology service.

12. Continual improvement—Continual improvement describes mechanisms for identifying opportunities for improvement and developing a strategy to continue this improvement [21]. Digital pathology is a relatively new technology, with workflows that were established at MSK in 2020. Based on the concept of W. Edwards Deming that continual improvement is the primary goal of a QMS [32], we identified the need for ongoing, constant improvement of current digital pathology processes. This includes the adoption of new workflows, technologies, multi-team process improvements and constant search for better, leaner operations. There are defined departmental strategies for continual improvement, and these include identifying improvement opportunities, selecting opportunities, generating and implementing solutions, and then evaluating the effect of those solutions. They are followed by integrating and sustaining these improvements. The innovative nature of digital scanning offers multiple opportunities for improvements with new technologies, solutions and operational data obtained by MSK and other institutions. The digital scan team management also keeps abreast of the scientific literature and emerging commercial products to identify improvement opportunities for DPLM scan operations.

The improvement process starts with the analysis of current operations, identification of process bottlenecks and inefficiencies, as well as defining quality and performance metrics for current operations. The digitization process including the pathology teams involved, scanning instrumentation and available scan capacity were identified and charted. Table

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3 is an example of potential quality and performance metrics that were identified in the analytical workflow process for the digital pathology operation.

An analysis of nonconformances is used for root cause analysis by the team, and findings are used for education and SOP modification. A summary of weekly quality metrics is displayed for all departmental stakeholders to review. All the quality improvement activities, progress, and findings are included in the digital scan team quality reports to leadership and the Department for Quality and Safety for review.

The experience in our department has led to the identification of gaps in available tools, and the development of new software tools for the improved quality of the operations. As the industry matures, we anticipate the onboarding and adoption of additional commercially available hardware and software tools to provide solutions for our pathology workflows. Continual improvement and adoption of digital pathology technologies also requires change management procedures that involve all the stakeholders and the different teams affected by the new digital scanning workflows and digital image availability.

Discussion

The WHO defines quality as “accuracy, reliability and timeliness of reported test results” and states that the laboratory results must be as accurate as possible, all aspects of the laboratory operations must be reliable, and reporting must be timely in order to be useful in a clinical or public health setting.”[10].

Clinical digital pathology operations require a careful analysis of workflows and the development of measures to ensure quality operations. The need for quality systems is a prerequisite for successful clinical grade digital pathology adoption. Using the unique digital experience gained at MSK we present our guideline for QMS for large scale digital pathology operations in clinical settings as was developed and tested in our pathology laboratory from 2020 to date. These findings can be utilized, adopted, and reproduced at other institutions.

This digital pathology specific QMS development stemmed from the gaps that were identified when MSK integrated digital pathology into its clinical systems following the public health COVID-19 emergency in 2020 [17,33]. The WHO Quality management Handbook [10] served as a guide for the quality essentials for the QMS. These twelve quality essentials (Table 1) were developed into an extensive DPQE framework to specifically address the needs of the growing clinical use of digital pathology technologies.

MSK has a quality team who guides and coordinates the different QMS activities and reports to hospital leadership. This team oversees the implementation of the QMS by all teams and staff members, manages an audit program, identifies critical QC issues and preventive measures, monitors procedure verification, equipment inventories, and prioritizes risk management and staff training.

The need for establishing new quality measures for digital pathology has been documented by other early adopters of digital pathology [14–16,34–36]. The need for a digital pathology

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QMS is not different than that of any other laboratory operation, with the goals of monitoring and evaluating all relevant data, promoting accuracy and safety, and mitigating risk to patients and employees while reducing waste and controlling costs.

As more healthcare systems and laboratories are adopting digital pathology workflows and integrating those into their clinical operations, the framework used by MSK can be modified and applied to additional institutions based on their specific needs. Each digital pathology laboratory will need to evaluate their regulatory requirement, proposed and existing use cases and potential risk. For example, a research laboratory will have different documentation needs than a clinical laboratory currently integrating digital pathology as part of the clinical systems. This 12 quality essential framework is not intended to replace the need to follow ISO15189 or Good Laboratory Practice (GLP) licensing requirements for manufacturing laboratories that require this certification [37]. The extent of these WHO based DPQE will vary based on the size of the operation and the resources that are involved or are anticipated. The framework allows flexibility for periodic adaptations based on the changing technologies and quality requirements in the laboratory.

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Data Availability Statement:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Fig. 1:
Identified MSK digital scan team customers.

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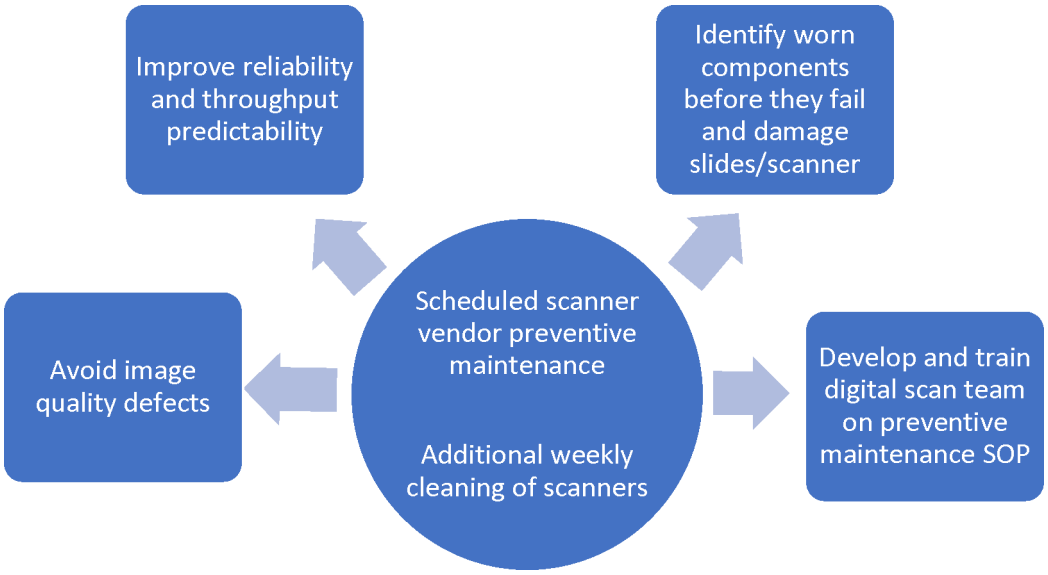

Fig. 2:
Preventive maintenance benefits for the digital scanning operations.

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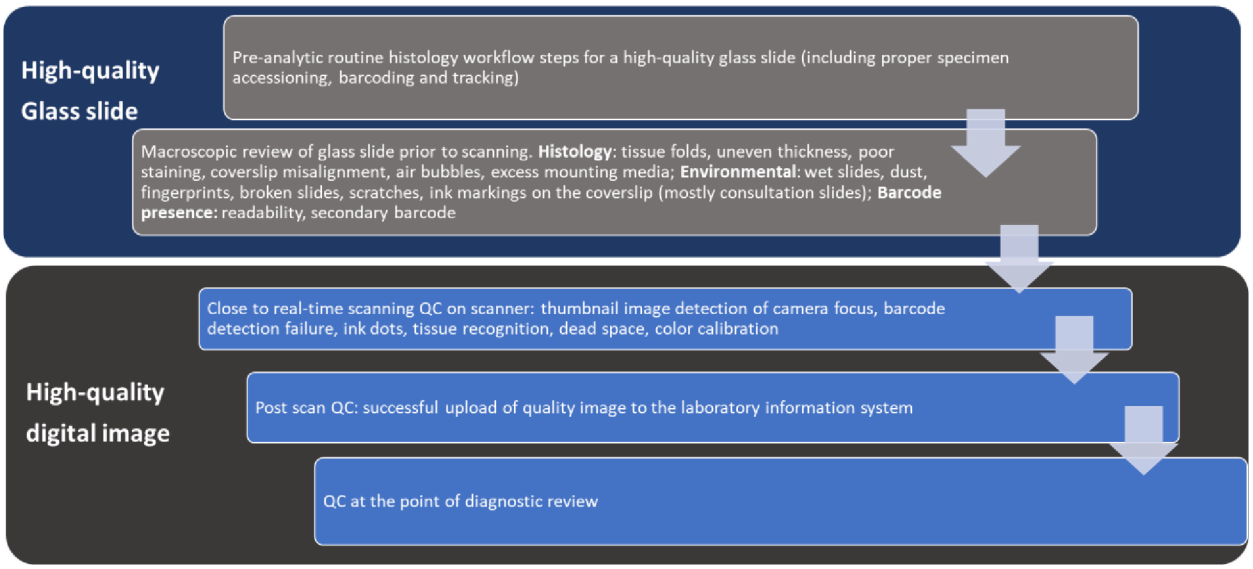

Fig. 3:

Digital scan team slide and image quality checkpoints introduced in the pre-analytic and analytic phases of whole slide imaging.

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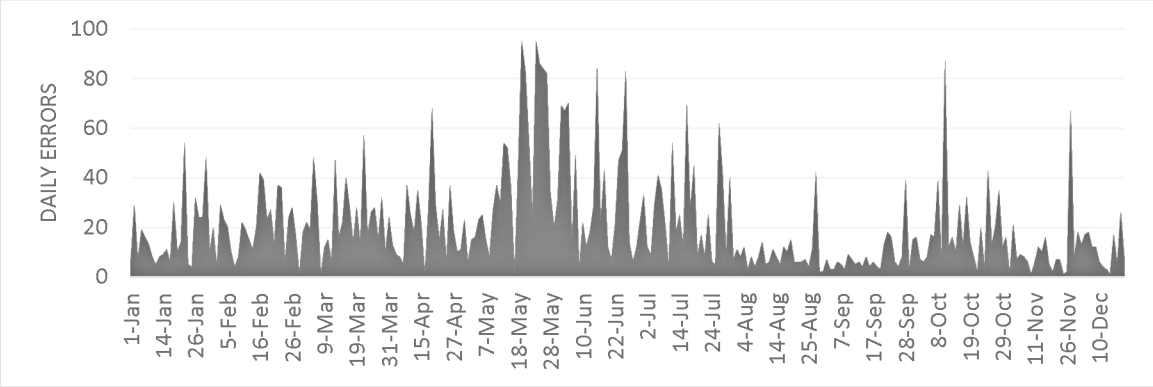
A



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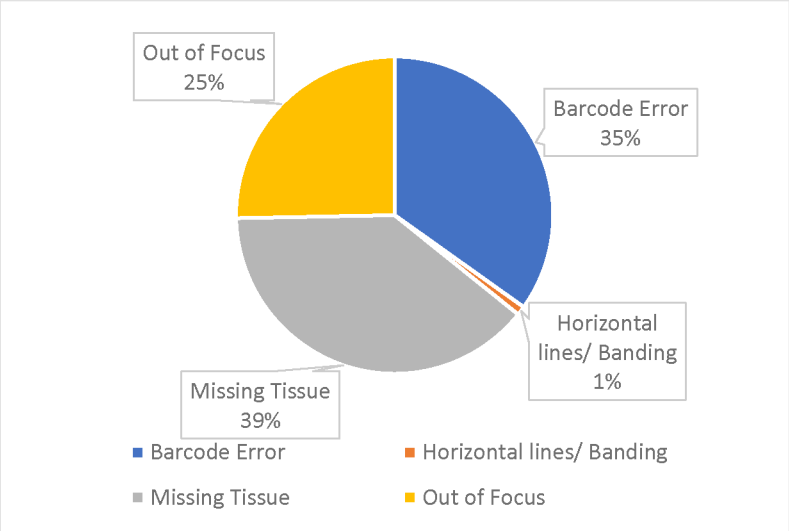

Fig. 4:

Scan errors for the years 2020– 2021. A, Daily pattern of scanned image errors as reported by the digital scan team image reviewers; B, Scanned image error type (n=5714).

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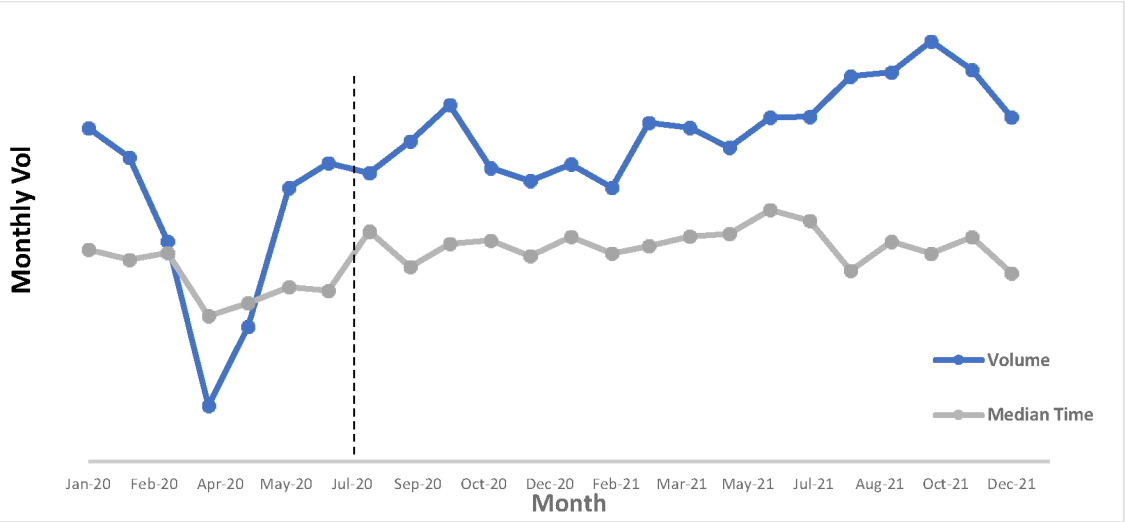

Fig. 5:

Example of TAT monitoring for scanned biopsy slides. Trends of biopsy slide volume (blue) and slide turnaround time (grey) from accessioning to laboratory verification (Jan 2020-Dec 2021). The dotted line represents the start of the added prospective WSI step in the laboratory before case distribution to pathologists.

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Table 1:

Summary of Digital Pathology Quality Management System (QMS), detailing the Digital Pathology Quality Essentials (DPQE) at MSK and their digital pathology specific measures

Digital Pathology Quality Essential (DPQE)	Digital Pathology Measures
Organization and Leadership	Organization chart, roles and responsibilities, job descriptions, laboratory goals, communication, succession planning
Customer Focus	Identification of digital pathology customers, determination of expectations and satisfaction of pathologists, patients, administration
Facilities and Safety Management	Space allocation and needs, access control, engineering controls, environment monitoring (i.e., temperature, humidity), safety procedures
Personnel Management	Orientation, training and competency, continuing education, performance evaluations
Supplier and Inventory management	Efficient process of obtaining equipment and digital pathology required supplies including equipment receipt procedure and inventory management of all digital pathology assets
Equipment management	Scanner qualification, inventory, scanner specific protocols, preventative maintenance and performance management
Process management	Establishment of digitization workflows, documentation of workflows, monitoring slide and image quality
Documents and Records Management	Establishment, maintenance and updating of controlled documents, maintenance of flowcharts, scanning standard operating procedures, policies, validations related to digital pathology operation
Information management	Information technology security, access and retrieval, upload of images to the lab information system, data storage management
Occurrence (non-conformance)	Identification and reporting of digital pathology occurrences, documentation and investigations of non-conforming events, image errors, equipment failure, tracking and monitoring corrective actions of digital pathology operations
Assessments	Internal digital scanning related audits, quality assurance reports, inspections, proficiency testing (Internal and external)
Quality/Continual improvement	Identification and assessment of improvement opportunities for digital pathology operations, solutions for error analysis and problem resolution, integration of improvements in digital pathology operations

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Table 2:

Example of a non-conformance log spreadsheet used by the digital scan team to log scan errors

Digital Scanning Team Error Log							
Date of Error	**Type of Error *(examples)***	**Staff**	**Phase Error Occurred**	**Cases #s Impacted**	**Corrective Action *(examples)***	**Date of Corrective Action**	**Supervisor Review**
	QC Fail		Pre-Scan		Repeated Slide Prep		
	Software error		Scan		Rebooted computer		
	Artifacts obstruct view		Post-Scan		Informed Pathologist		
	Failed to decode barcode		Scan		Repeated scan		
	Failed to transfer WSI over network		Scan		Contacted network analyst		
	Missing tissue		Scan		Repeated scan		

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Table 3:

Recommended quality and performance metrics for the analytical and post analytical phases of a digital pathology operation.

Digital Pathology Workflow Phase	Metric	Rationale
Slides loaded into racks and into scanner and scan run	✓ Number of cases, slides and type of slides scanned ✓ Quality defects of slides ✓ Timing of scanner loading ✓ Scanner specific errors ✓ Time for successful scan of slides	✓ Scanner capacity and turnaround time requirements ✓ Instrument reliability and performance ✓ Pre-analytic specimen quality issues ✓ Laboratory production and scanning capacity
Image review	✓ Qualitative and quantitative metrics of all image errors ✓ Tracking of all nonconformance events	✓ Repeat scan needed to prevent delays in TAT ✓ Monitoring image quality errors for process improvement ✓ Understanding nonconformance events for education and training
Image upload into the LIS	✓ Post scan metrics: quantify image size and timing of image upload	✓ Monitor if storage of digital images becomes a constriction of operations. ✓ Ability to correlate digital scan input to populating in the LIS
Case review by pathologist	✓ Time to open image, quality errors	✓ Monitoring servers and network performance ✓ Use data to maintain expected image quality and TAT needs