



The Role of Automation and Robotics in Improving Laboratory Efficiency and Accuracy

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Background – One of the goals of pathology is to standardize laboratory practices to increase the precision and effectiveness of diagnostic testing, which will ultimately enhance patient care and results. Standardization is crucial in the domains of tissue processing, analysis, and reporting.

Aim of Work – To enhance diagnostic testing through the adoption of innovative technologies and to describe the state-of-the-art of automation in pathology laboratories.

Methods – Innovative technologies are being created and put into use, focusing on digital pathology and artificial intelligence. However, challenges such as algorithm training and data privacy issues still need to be resolved.

Results – Digital pathology and artificial intelligence are emerging in a structured manner, leading to advancements in laboratory practices.

Conclusion – For the field of pathology to advance and for patient care to be improved, standard laboratory practices and innovative technologies must be adopted. By anticipating laboratory needs and demands, the aim is to inspire innovation tools and processes as positively transformative support for operators, organizations, and patients

Keywords – Pathology, Standardization, Diagnostic Testing, Digital Pathology, Artificial Intelligence, Automation..

Introduction:

In recent decades, significant efforts have been undertaken to standardize surgical pathology laboratory techniques and reduce the need for manual labor. The objective is to enhance diagnosis accuracy and ultimately improve patient care outcomes. Vigilant handling of anatomic pathology samples is essential, since any misplacement or inadequate storage may lead to substantial diagnostic, legal, and ethical repercussions. For paraffin-embedded blocks, the ideal storage conditions include controlled temperature and

humidity, whereas glass slides should be preserved in secure and traceable systems [1, 2].

These issues have been heavily emphasised in the Guidelines published by the Superior Health Council of the Italian Ministry of Health [3]. The establishment and maintenance of a secure and controlled chain of custody for biological samples from collection to storage are crucial in ensuring quality, traceability, and proper conservation. Achieving compliance and operational efficiency requires the implementation of solutions that automate and optimize the activities of labeling,

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archiving, and searching. Automation, the use of technology to replace or improve human labor in a production process, is of utmost importance.

Establishing uniformity in tissue processing, analysis, and reporting is a fundamental goal in surgical pathology. This ensures that diagnostic findings are accurate and consistent, and that diagnostic reporting is transparent. Advancements in technology, such as digital pathology systems and artificial intelligence approaches, are being investigated and used to enhance scientific accuracy in diagnosis. Nevertheless, the adoption of these technologies has been sluggish due to concerns pertaining to data privacy, financial implications, and interoperability. Moreover, molecular pathology requires the use of proven analytical techniques to provide accurate results [6-8]. In this specific setting, quality assurance and control systems play a crucial role by serving as supplementary measures to ensure the accuracy and reliability of results [9-11].

The precise surveillance, storage, and preservation of specimens are crucial since they directly impact diagnostic accuracy, patient care, and scientific investigation. Utilizing state-of-the-art technology and standardized processes is crucial for the advancement of surgical pathology and patient care. The present essay presents a comprehensive summary of the recent progress in the automation of pathology laboratories. The primary aim is to foster the development of cutting-edge technologies and processes that should support operators, organizations, and, most importantly, patients.

The pre-analytical phase of tissue processing includes all the processes from collection of tissue samples to submission of histopathology slides for interpretation [1]. The potential areas of automation in the pre-analytical phase of pathology include the acquisition and surveillance of specimens, their manipulation, embedding, sectioning, and staining (Figure 1).

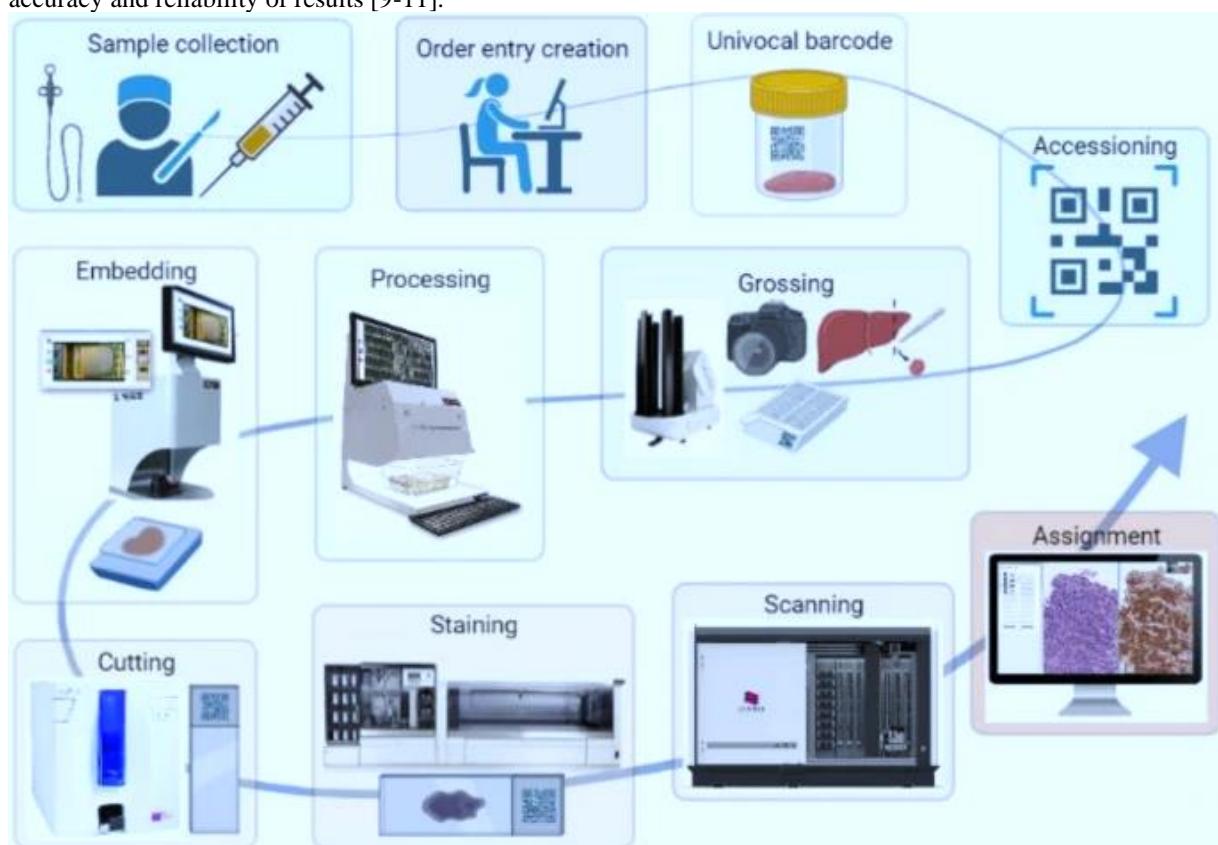


Figure 1. Implementation of automated workflow in the pre-analytical procedures.

Sample tracking

Due to the rising volume of specimens received, it is essential to establish automated systems that can assist in overseeing and managing the workflow of the specimens. Barcode scanning technology and laboratory information management software (LIMS) are utilized to track the location,

status, and processing stage of each specimen [12, 13]. The implementation of robotic automation in the workflow process for specimens within laboratories has the potential to minimize human errors and enhance the efficiency of turnaround times for diagnostic procedures.

Automated software possesses the ability to generate barcode labels that can be attached to the specimen container, thereby enhancing tracking and notifying laboratory personnel upon the receipt of a specimen. To modify the location and status of the sample in the LIMS, please scan the barcode as it advances through each operational step. The laboratory personnel can effectively monitor the status of each specimen, identify any delays or issues requiring attention, and ascertain the identity and timing of individuals involved in particular operations with the specimen. PathTracker™, developed by SPOT Diagnostic imaging in Sterling Heights, MI, USA, is a sophisticated laboratory system tailored for mass barcode scanning. It employs cutting-edge technology to collect, manage, analyze, and save all barcodes within the field of view. The stated scanning duration for a 150-cassette processing basket is 30 seconds. Broken or poorly printed barcodes are identified, and PathTracker™ provides a variety of repair tools to address these issues, either automatically or manually, ensuring seamless production continuity.

The FinderFLEX robot, produced by Logibiotech in Alseno, Italy, is engineered for the manipulation and electronic scanning of cytohistological samples. The FinderFLEX robot features a multi-articulated mechanical arm designed for the automatic and secure handling and insertion of slides, macrosection slides, biopsy cassettes, super mega cassettes, and vials into designated racks. The operator is required to power on the device and authenticate their identity to facilitate the inclusion of any future samples for storage. Utilizing an advanced barcode scanner, FinderFLEX effectively scans barcodes, QR codes, and Data Matrix 2D codes, facilitating direct communication with the LIS to ensure a systematic and traceable sample management and handling process. FinderFLEX streamlines the identification and management of samples directly from their standard racks and containers, leading to a significant decrease in handling times. The automated transmission of the gripper fingers enables this functionality. Additionally, the device is equipped with straightforward and intuitive software along with a touchscreen interface, allowing the user to operate it safely during emergencies.

Biomedical tissue processing

The importance of uniformity in tissue processing within the realm of anatomic pathology is paramount. It ensures consistency by reducing discrepancies and confirming that any variations are due to the specimens themselves. The implementation of this standardized method enhances quality control, enabling the detection and treatment of issues, including the presence of impurities [14]. Moreover, it enhances the precision of diagnostic tests by preventing alterations in tissue structure or structure that could affect subsequent

analytical processes. Ultimately, it enhances laboratory operations, increasing efficiency and optimizing resource use.

Traditionally, pathologists and technicians invested significant time in the physical preparation of tissue samples for diagnostic analysis. The development of automated methods and instruments has facilitated a rapid, precise, and minimally human-involved approach to tissue fixation and processing. The Tissue-Tek Xpress® × 120 tissue processor, produced by Sakura Finetek in Tokyo, Japan, facilitates the efficient and consistent processing of histology workflows through the use of vacuum infiltration. This processor ensures an even distribution of cases and minimizes workloads, enabling the processing of extensive tissue specimens in only 2.5 hours. The HistoCore PEGASUS Plus tissue processor (Leica Biosystems, Wetzlar, Germany) enables the simultaneous execution of multiple protocols on a single device. This integrated system facilitates the individual documentation of cassette ID, quantity, and color, along with basket ID, user ID, and reagent details.

Automated tissue fixation and extraction offer numerous benefits over manual methods. Initially, the meticulous control of all procedures by the computer minimizes the chances of mistakes and unpredictability in tissue processing through automation. This could result in more precise and reliable diagnostic outcomes, enhancing patient care and results. One more benefit of automation is the possibility of accelerated processing times, as the computer can manage the timing of each phase to enhance efficiency. Ultimately, automation enables laboratory personnel to concentrate on essential tasks like quality control.

Implementation of automated tissue embedding

Embedding is an essential step in the histology process, conducted manually following tissue processing and necessitating careful training and expertise. Accurate alignment of the tissue within the paraffin is essential, as a misoriented specimen can yield an uninformative slice and may result in tissue loss during the cutting process, potentially leading to negative outcomes for the patient. The technologist carefully inserts surgical specimens and biopsies one by one, ensuring their accurate placement, a process that can be both challenging and time intensive. Highly skilled professionals with exceptional manual dexterity are needed to ensure optimal conditions for the cutting segment of this process.

Automated embedding systems offer numerous benefits over manual embedding, such as improved efficiency, consistent processing, and reduced dependence on human labor. The Synergy system automates tissue embedding within the processing procedures, eliminating the necessity for manual reopening of cassettes and adjustments of tissue positioning. The Synergy technology system

consists of specified molds, pads, and a meticulously designed rack. The implementation of a unified tissue processing and embedding technique allows the sponges utilized for the pads to maintain proper specimen alignment, facilitating optimal cutting during the microtome stage.

The Tissue-Tek AutoTEC® a120, in conjunction with Tissue-Tek® Paraform® cassettes and Tissue-Tek® Paraform® Tissue Orientation Gels, constitutes an integral component of Sakura's SMART automation system, aimed at optimizing manual tasks and ensuring a smooth workflow within the biomedical laboratory. These gels are engineered to securely hold and preserve the alignment of small tissue samples. Once the tissue is properly oriented during grossing, the Tissue-Tek® Paraform® Sectionable Cassette System provides an efficient solution for automating cassette embedding, achieving a throughput of up to 120 cassettes per hour. This technique effectively secures the specimen during the processing and embedding stages, thereby minimizing tissue loss and eliminating the necessity for specimen reconfiguration.

The automated embedding methods demonstrated in this study outperform manual embedding, especially regarding productivity and consistency. The implementation of automated embedding has the potential to improve the accuracy and reliability of diagnostic tests by minimizing the chances of human error and variability. It is essential to recognize that tissues can display considerable differences in size, shape, and consistency, and not all structures may be suitable for automated embedding. For specific delicate or uniquely shaped samples, manual embedding may be required to ensure proper alignment and preservation.

Automated microtome

Since the eighteenth century, microtomes have served as essential instruments in pathology laboratories, transforming tissue analysis by producing extremely thin sections for detailed examination of cellular architecture and investigation of disease mechanisms. While crucial, the operation of a microtome remains a demanding task that necessitates skilled handling and precise calibration. To ensure reliable and consistent results, it is essential to employ innovative techniques and advanced automation to tackle the critical challenges of section thickness variation and tissue distortion. The automated microtome operates by utilizing a motorized cutting blade to precisely slice the tissue specimen into thin sections. The instrument's control panel allows for the production of tissue sections at varying thicknesses by adjusting the designated thickness settings. The automation of the instrument guarantees consistent tissue segment thickness, thereby minimizing the potential for errors and enhancing the accuracy of diagnostic results.

The AS-410M automated microtome, developed by Dainippon Seiki in Nagaokakyo, Japan, is engineered to produce precise and high-quality histological cuts automatically, adhering to predetermined criteria for each specific instance or tissue type. Following the incision, the specimen is positioned onto a slide and carefully stretched. The slide is subsequently placed in a drying chamber for future collection. The resulting slices exhibit remarkable uniformity and demonstrate superior quality. Additionally, the equipment includes roughing modules, cut quality tracking, slide printing, and integration with the Laboratory Data System to ensure comprehensive traceability of the samples.

The projected output is 250 blocks over a 7-hour work shift, with the capability to operate continuously for 24 hours a day. Sakura's Tissue-Tek AutoSection® Automated Microtome offers a wide array of integrated safety features, along with one-touch trimming and customizable sectioning capabilities. This mechanism ensures the block is aligned with the blade edge, thereby providing precise XYZ alignment. This technique guarantees consistent alignment of blocks, regardless of prior trimming or sectioning on various microtomes, thereby safeguarding both tissue integrity and the efforts of the operator. There are certain limitations in utilizing this technology, particularly regarding the challenge of effectively cutting through hard or delicate materials. Additionally, a limited number of biopsies may still require human expertise to ensure the preservation of valuable tissue.

Advancements in automated slide staining and cover slipping

The implementation of automated staining technologies has streamlined the processing of substantial sample volumes, concurrently minimizing human error, enhancing uniformity, and improving the efficiency as well as the accuracy of staining techniques. The importance of hematoxylin and eosin (H&E)-stained slides in morphological evaluation is paramount. The automation of every step of the procedure can result in improved reproducibility, accuracy, and reliability. Research indicates that employing automated individual staining protocols, rather than batch-stained slides, could offer greater benefits for digital pathology [16]. The Ventana HE 600, produced by Roche Diagnostics in Basel, Switzerland, serves as an outstanding instance of a dedicated slide staining system.

Immunohistochemistry (IHC) is an advanced diagnostic method in pathology that employs tagged antibodies to accurately detect specific antigens in tissue sections. Automation has greatly enhanced the efficiency of IHC staining through the optimization of incubation times, ranges of temperatures, and reagent concentrations, all of

which are crucial for ensuring accurate antigen-antibody reactivity. Moreover, the automated techniques significantly reduce background noise and non-specific staining, thereby improving the signal-to-noise ratio and the general appearance of the stained slides. Numerous companies have developed contemporary computerized staining systems to meet the varied needs of pathology laboratories.

The VENTANA BenchMark series of automated slide stainers, produced by Roche Diagnostics in Basel, Switzerland, provides extensive solutions for immunohistochemistry (IHC) and *in situ* hybridization (ISH) staining. The BOND-PRIME automated staining platform, created by Leica Biosystems in Wetzlar, Germany, is designed to meet diverse workflow needs, including batch, continuous, single slide, or STAT instances, as well as combinations of these, for both immunohistochemistry (IHC) and immunofluorescence (ISH). The Tissue-Tek Genie® system, created by Sakura Finetek in Tokyo, Japan, is a fully automated, random access stainer specifically designed for immunohistochemistry (IHC) and *in situ* hybridization (ISH). The facility is equipped with distinct staining stations that facilitate the simultaneous and unrestricted processing of slides with diverse antibodies and probes.

Coverslipping represents a critical step in the preparation of a high-quality histology glass slide. The quality of coverslipping is essential, as the presence of air bubbles, improper amounts of mounting media, and dry-mounted slides can impede the diagnostic process. Three distinct coverslipping techniques exist: the traditional glass coverslip, the liquid approach, and the film method. The film technique stands out as the most efficient automated method, demonstrating significantly fewer air bubbles and staining alterations when compared to the other two techniques [17]. As a result, this represents the most effective method for producing glass slides intended for digital scanners.

Collaborative robotics

The computerization of manual procedures presents considerable challenges in various situations. Devices, even those from the same manufacturer, frequently exhibit insufficient coordination to enable the smooth flow of materials. The movement of sections across rack structures is a common laboratory activity, exemplified by the transfer of samples from a staining structure to coverslipping equipment [18]. The technique can be demanding and may result in material waste due to the possibility of components falling or breaking.

There exists considerable opportunity to enhance manufacturing efficiency and to effectively

integrate various stages, alongside the necessity for additional process innovations. The rise of collaborative robotics has resulted in an increased application of robotic systems for material transfer across manufacturing processes. Collaborative robots, often referred to as "cobots," are designed with sensors that facilitate smooth interaction between humans and robots without requiring protective barriers. Additionally, the implementation of adaptable, camera-supported grasping mechanisms improves the operational effectiveness of these types of systems.

The Tissue-Tek SmartConnect® from Sakura represents a cutting-edge advancement in laboratory automation, effectively connecting human expertise with streamlined and reliable processes. This collaborative robot has been meticulously designed to function seamlessly alongside laboratory personnel, offering assistance in various procedures while improving precision and efficiency. The initiation of automated tissue processing occurs exclusively upon the loading of the Tissue-Tek Xpress® × 120 through SmartConnect. Subsequently, SmartConnect independently transmits the magazines to the Tissue-Tek AutoTEC® a120 embedder. SmartConnect delivers uniform, high-quality embedded blocks tailored for seamless microtomy integration. Implementing a system in laboratories optimizes workflow, reduces human error, and enhances overall efficiency.

Moreover, the incorporation of advanced technology into these systems, including machine learning and artificial intelligence, could result in more precise and accurate sample handling, thus enhancing the overall outcomes. The laboratory could benefit from the implementation of such robots. The aim is to minimize both human errors and unintentional mistakes, along with contamination risks.

Optimizing repetitive tasks and improving processes and managerial systems; Improving productivity and efficiency. Ensuring accurate tracking and traceability of the specimens to guarantee their quality. Enhancing the efficiency of repetitive manual tasks performed by healthcare staff, thereby enabling a greater allocation of time to strategic tasks that deliver substantial added value, enhancing patient satisfaction and, ultimately, ensuring patient safety.

Analytical procedures

During the analytical phase of pathology, automation is applied across various domains, including data input templates, digital pathology, synoptic reporting, and computational pathology algorithms for the analytical process (Figure 2).

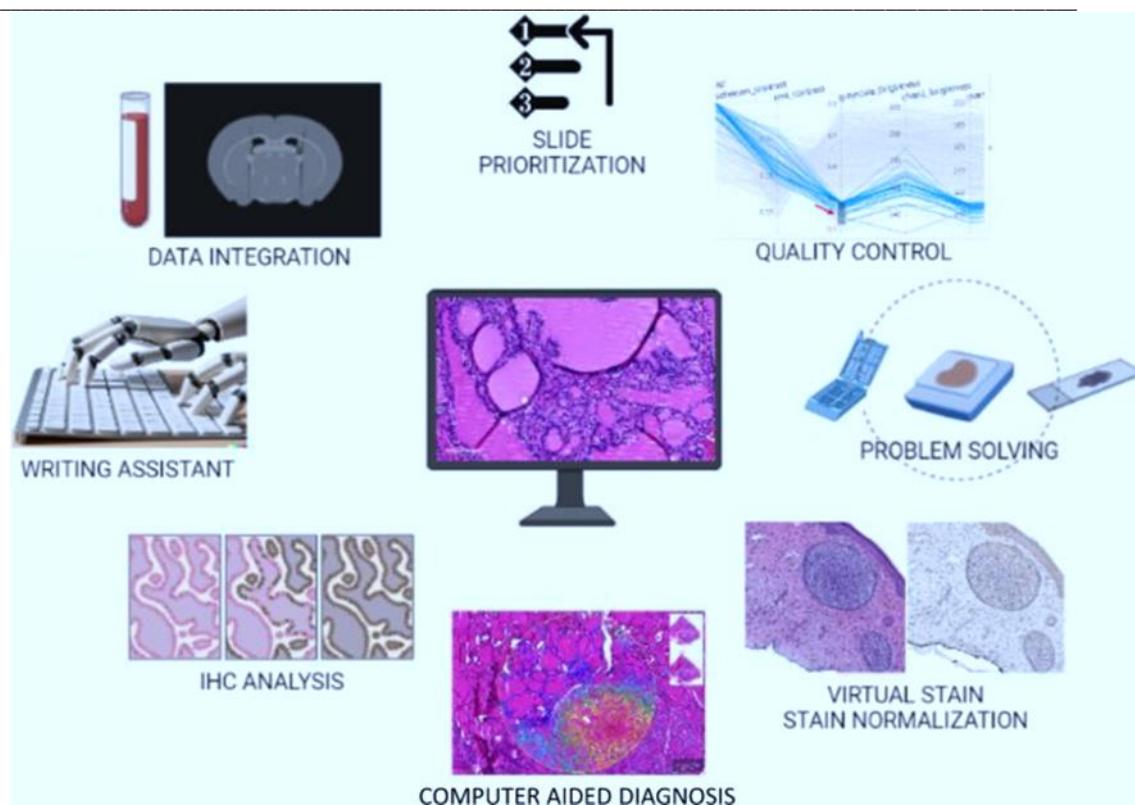


Figure 2. The automated workflow associated with the analytical activities.

In modern diagnostic medicine, the critical areas of digital pathology and computational pathology are significantly altering the methods by which physicians analyze, diagnose, and treat diseases [7]. The introduction of pathology glass slide scanners has revolutionized the domain of digital pathology by enabling the conversion of histological samples on glass slides into high-resolution digital images. The enhanced accessibility, storage, and exchange of information have fostered global collaboration among health care providers. Throughout the years, these scanners have significantly improved in speed, resolution, and overall capabilities.

Notable products currently offered in the market consist of the NanoZoomer series produced by Hamamatsu in Hamamatsu City, Japan; Aperio by Leica Biosystems in Wetzlar, Germany; IntelliSite by Philips in Eindhoven, the Netherlands; Pannoramic series by 3DHISTECH in Budapest, Hungary; and Axioscan by Zeiss in Oberkochen, Germany. Each of these devices delivers exceptional picture quality, processing speed, and capacity, meticulously crafted to fulfill the diverse needs of diagnostic laboratories and research institutions.

The digitization of glass slides through whole slide imaging, often referred to as digital pathology, allows pathologists to view, analyze, and share high-resolution digital images of histological and cytological specimens. This technology allows pathologists to collaborate remotely, consult with

experts globally, improve diagnostic accuracy, and accelerate patient treatment [19]. The domain of computational pathology emphasizes the advancement and application of machine learning algorithms and artificial intelligence (AI) to assess digital slides. This approach enables the extraction of measurable data from digitized slides, allowing for the identification of distinct patterns and biomarkers. This, in turn, enhances diagnostic precision and supports informed decisions in personalized medicine [6].

The convergence of numerous advancements in whole slide imaging techniques, enhanced processing capabilities, and the accessibility of extensive annotated datasets has collectively propelled the growth of digital and computational pathology. The growing demand for diagnostic solutions that are efficient, precise, and cost-effective has led to an increase in investment and research in these areas. The primary application of digital and computational pathology is in the identification and detection of cancer. In the context of automated diagnosis and classification of various tumor types, including breast, lung, and prostate cancer, machine learning algorithms have demonstrated significant efficiency. The algorithms possess the ability to analyze digital histopathology images to identify neoplastic cells, differentiate between benign and malignant tumors, and even classify the subtypes and grades of the malignancies [20-23].

In this context, the implementation of this technology can alleviate the workload for pathologists, reduce variability among observers, and enhance the reliability and accuracy of diagnoses through the automation of these processes [24]. Heinz et al. conducted an anonymous online poll to identify potential beneficial applications of AI in pathology, involving 75 specialists in computational pathology from both academic and industry sectors [25]. The survey findings revealed that the most promising potential application is the direct prediction of treatment response from standard pathology slides. Digital pathology is currently the focus of extensive research in translational medicine, serving as a tool to predict drug responses and pinpoint patients who are most likely to benefit from therapy.

The identification of patients who may derive the greatest benefit from immune checkpoint inhibitor-based therapy, such as PD-1/PD-L1 inhibition, represents a significant and ongoing challenge in the field of immuno-oncology [26]. Importantly, alongside the expression of PD-L1 on tumor and immune cells, the immunological environment represented by tumor-infiltrating lymphocytes (TILs) has demonstrated considerable predictive potential [27].

Park et al. have developed a novel AI-based algorithm designed to analyze and quantify tumor-infiltrating lymphocytes (TILs) within the tumor microenvironment. This system can differentiate among three immune phenotypes (IP): inflamed, immunological-excluded, and immune-desert [28]. The authors have demonstrated that patients with inflamed tumors exhibit a more favorable prognosis regarding overall survival (OS) and progression-free survival (PFS). Patients with inflamed neoplasms and elevated PD-L1 expression demonstrate a significant improvement in survival rates when compared to those with high PD-L1 expression in non-inflamed tumors.

These findings highlight that employing image analysis enhances precision and effectiveness by automatically assessing specific characteristics that cannot be captured through visual observation. In addition to tumor pathology, computational pathology is being explored and utilized in essential yet frequently neglected domains, including transplantation pathology. This specialized field examines post-transplant graft biopsy results to assess rejection or graft damage, evaluates organ donor biopsies for organ allocation, and addresses various functional and non-neoplastic pathology contexts.

In the current landscape of extensive data, it is clear that digital and computational pathology offer significant methodologies for managing and analyzing vast amounts of information sourced from various domains, including genomics, proteomics, and clinical data. The application of machine

learning algorithms facilitates data analysis integration, improves understanding of disease etiology, and reveals new avenues for analysis, prediction, and treatment.

Administrators perceive that a significant obstacle to the integration of digital pathology into clinical practice is its cost. Ho and colleagues developed a financial prediction regarding the introduction of digital pathology at a large health care institution to evaluate potential reductions in operating costs [32]. The projected cost savings stem from two key benefits associated with the adoption of digital pathology: potential improvements in workflow and productivity, along with the streamlining of laboratory operations; and reduced treatment costs due to lower rates of interpretation errors by general pathologists who are not subspecialists. The authors projected that the total cost savings over a span of 5 years could approach \$18 million. The findings suggest that if the costs related to acquiring and implementing digital pathology remain below this threshold, the investment's profitability becomes attractive to hospital administration.

Currently, numerous integrated digital pathology systems are being implemented worldwide, showcasing the feasibility of adopting digital pathology workflows in both small and large pathology departments that serve extensive and diverse healthcare organizations with complex patient demographic profiles. Furthermore, official guidelines have been issued. The importance of digital pathology in the education of anatomic pathology is clear, as evidenced by the growing accessibility of resources like digital pathology atlases. The use of such materials enhances proficiency in essential skills including feature identification, differential diagnosis, annotation, photography, description, and presentation. The utilization of these materials appears to be critically significant in tackling the reluctance to embrace digital technologies among specific learners. The regular integration of these materials into various case discussions, instructional collections, and tutorials can greatly improve and accelerate the learning process [37].

Digital and computational pathology, while having made significant advancements and showcasing potential applications, continues to encounter numerous unresolved challenges. Due to the sensitive nature of medical data and the necessity for professionals to share photographs and information, there have been raised concerns regarding privacy and security. Standardizing digital imaging techniques, data formats, and annotation protocols is crucial for ensuring consistency and compatibility across various systems and organizations. The incorporation of machine learning algorithms into clinical processes necessitates thorough validation and testing to guarantee their

reliability and clinical applicability. Furthermore, developing strategies to reduce model accuracy degradation in the presence of artifacts is crucial.

We recommend that the next group of pathologists should have comprehensive training in anatomic pathology, while also integrating essential concepts of computational pathology and image analysis into their skill set. This will enable the integration of medicine, computer science, and data analytics, thereby bridging the cultural divide. While pathologists may not be required to become hybrid professionals, they will certainly need the ability to collaborate with computer scientists to understand and address the potential limitations of emerging technological methods, and importantly, to take a central role in this significant transformation.

Despite these challenges, the future of digital and computational pathology appears bright. Integrating advanced imaging techniques with machine learning algorithms will significantly improve diagnostic accuracy and offer patients a more thorough understanding of disease processes.

Conclusion

Automation in surgical pathology has demonstrated considerable potential in enhancing precision, productivity, and the overall standard of patient care worldwide. Pathology laboratories can improve efficiency, streamline processes, and expedite diagnostic procedures through the implementation of advanced technologies such as robotics, artificial intelligence, and machine learning. As scientific advancements continue to evolve, it is essential for the medical field to embrace and adapt to these changes while addressing any ethical and legal challenges that may arise. The evolution of automation is undeniably linked to the future of surgical pathology, resulting in enhanced diagnostic accuracy, improved patient outcomes, and a greater understanding of diseases.

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