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AI in Histopathology: Automated Cancer Diagnosis to Detect Cancerous Cells and Assess Tumor Grade

Muhammad Fahad, Muhammad Umer Qayyum, Nasrullah Abbasi
Washington University of Science and Technology, Alexandria, Virginia, USA

ABSTRACT

Artificial intelligence has revolutionized the field of histopathology by making automated cancer diagnosis possible with high degrees of accuracy, especially in detecting cancerous cells from non-cancerous cells and tumor grading. Traditionally, histopathology relies on microscopic observation of stained tissue samples to identify and classify various kinds of cancers; therefore, it plays a very important role in diagnosis. However, there is an inherent limitation to manual examination such as subjectivity, variability, and a time-consuming process. The integration of AI with Machine Learning (ML) and Deep Learning (DL) algorithms introduces improvement in diagnostic accuracy and efficiency by processing whole slide images (WSIs) within histopathological diagnosis. A number of machine learning techniques, such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs), have been able to adopt automated identification of malignant features, hence improving on the grading, staging, and prognosis of cancer. Besides, the AI-based computational pathology models outperform the conventional diagnostic approach due to a minimal incidence of errors, leading to consistency in results. This review paper discusses, for a variety of cancers such as breast, lung, and prostate, the state of the art in AI applications for cancer diagnosis in histopathology. It also summarized the growing benefits of AI in enhancing workflow efficiency, reducing variability in diagnosis, and improving immunohistochemistry IHC biomarker assessments. As AI technology continues to evolve, it has the potential to alter the future of clinical decision-making and streamline cancer diagnostics.

Keywords: Artificial Intelligence (AI), Histopathology, Machine Learning (ML), Deep Learning (DL), Cancer Diagnosis, Tumor Grading, AI in Healthcare

INTRODUCTION

Histopathology, the microscopic examination of tissue specimens, has been a cornerstone in cancer diagnosis for decades. It involves analyzing cell shapes and tissue structures to detect malignant areas and assess tumor severity. While histopathological methods are highly regarded for their accuracy, they are time-consuming and prone to human error due to the subjectivity of visual assessments. The introduction of artificial intelligence (AI) into histopathology offers the potential to revolutionize cancer diagnostics. AI models, particularly machine learning (ML) and deep learning (DL) algorithms, have the ability to process vast amounts of data quickly, identifying patterns and anomalies that may be difficult for human pathologists to detect. These AI models can analyze whole slide images (WSIs) and classify cancerous tissue with greater precision than traditional methods. AI techniques such as convolutional neural networks (CNNs) have demonstrated remarkable success in automating the detection and grading of various cancers, including breast, lung, and prostate cancers. This paper aims to explore the application of AI in histopathology, particularly its role in automating cancer diagnosis, detecting malignant cells, and assessing tumor grade. By examining current AI-based approaches and their impact on clinical workflows, this study highlights the transformative potential of AI in enhancing the accuracy and efficiency of cancer diagnostics.

AI TECHNIQUES IN HISTOPATHOLOGY

AI models evolved from expert systems to typical ML, eventually DL. Expert systems depend on expert guidelines, and typical ML has to produce characteristics based on expert expertise. In contrast, DL learns directly from raw data and incorporates an output layer with several hidden layers. When compared to expert systems and hand-crafted ML techniques, DL approaches are more efficient and accurate. The advancement of algorithms such as convolutional neural network (CNN), fully convolutional network (FCN), recurrent neural network (RNN), and generative adversarial network (GAN) has resulted in numerous studies on the application of DL-based AI in pathology. The implementation of AI in pathology aids in alleviating the constraints of subjective visual assessment and combines various metrics for precise tumor therapies. AI applications in tumor pathology extend almost all forms of tumors and are used for prediction, diagnosis, classification, grading, and staging. Many ML and DL algorithms for tumor diagnosis are based on various ML approaches, including Decision Trees (DTs), Artificial Neural Networks (ANNs), K-nearest neighbor (KNN), and Support Vector Machines (SVMs). Before using machine learning methods, certain pre-processing needs to be done. For instance, when cancer locations are found in WSI, small micro patches of 256 x 256 are sampled from huge WSIs. The features are then extracted and classified as cancerous or non-cancer in every specific patch. The purpose of extracting features is to get meaningful data for machine learning applications (Komura & Ishikawa, 2018). Machine learning, a key aspect of artificial intelligence, involves algorithms that identify patterns in existing data and use them to make predictions about new data. In ML image analysis, supervised, unsupervised, semi-supervised, and multiple-instance learning approaches are used to interpret extracted features. Supervised learning algorithms, such as support vector machines, and random forests, aim to map new images to predefined categories (e.g., "cancer") based on training with labeled data. Unsupervised learning algorithms, including principal component analysis, k-means clustering, and anomaly detection, seek to uncover internal structures and similarities in images without relying on labeled reference data. Additionally, semi-supervised and multiple-instance learning methods integrate aspects of both supervised and unsupervised techniques to enhance performance and adaptability. These algorithms learn predictive models through a training phase, where an artificial neural network's parameters are adjusted. The model's accuracy is then evaluated on new, unseen data during a testing or validation phase to minimize generalization error (Xing & Yang, 2016).

The efficiency of these image analysis algorithms was enormously enhanced by the advent of DL, in precise by deep convolutional neural networks (CNNs), which consist of numerous neurons, their connections, and parameters. During training, CNNs process both positive and negative samples, allowing neurons to coordinate their operations to perform specific tasks. Due to the complexity and scale of CNNs, substantial computational power is required, typically provided by Graphics Processing Units (GPUs), to efficiently handle large datasets. Unlike traditional neural networks, CNNs feature convolutional and pooling layers that enhance their ability to extract and identify important features from images while reducing network size. This design makes CNNs particularly effective at classifying large images and capturing spatial features (Rawat et al., 2017). The Bayesian-YOLOv4 CNN-based model was developed to detect breast tumors with a scoring accuracy of more than 92% in a variety of training data sets (Ahmed et al., 2022). Artificial neural networks (ANNs) are computational models designed to emulate the human brain's neural networks. The simplest form, known as multilayer perceptron, comprises an input layer, one or more hidden layers, and an output layer. The input layer processes initial data, while the output layer generates the final result, with hidden layers performing complex computations. The number of neurons in each layer depends on the training data's size and type (Sultan et al., 2020). Recurrent neural networks (RNNs) are a type of artificial neural network that incorporate both current and previously encountered inputs. They utilize hidden layers with recurrent feedback neurons to retain and integrate past information with new data. This capability allows RNNs to leverage historical data for making informed predictions on new inputs. While convolutional neural networks (CNNs) excel in image classification, RNNs are particularly suited for multiple image sets (Sultan et al., 2020). Developing a multi-tasking AI program that works on many tumors is difficult. To acquire good results, pathologists must utilize a range of AI-based algorithms throughout the pathological investigation, in which the neoplasm ought to be identified, categorized, and staged by several models of the algorithm, and a distinct algorithm.

ACCURACY AND EFFICIENCY OF AI IN HISTOPATHOLOGY

The basic histopathology workflow encompasses fixing tissue in formalin, implementing it in paraffin, slicing sections, and staining them for microscopic evaluation. The standard H&E staining takes about 2 hours, after which the slides are secured and preserved. Conversely, fast H&E fixing and staining, which is implemented in operations to make quick decisions, includes freezing tissue and staining in 10-15 minutes. While this procedure is quicker, it generally produces lower-quality stains due to methodology and reagent concentration variations. The manual histology techniques have numerous acknowledged limitations which adversely affect patient quality of life. For instance, it is destructive and may exhaust the tissue specimen, causing further extraction of tissue (e.g., extra biopsies); also, the preparation of tissue is lengthy and laborious, particularly if specialized or complex stains are used (Dean, 2020). Cancer diagnosis differs by 20% between skilled pathologists and beginners. A recent study revealed a 75.3% disparity between individual and professional diagnoses (He et al., 2022). Moreover, DL advancements in virtual staining and stain transfer are gaining significant interest in histopathology, after two decades of efforts to explore alternative tissue imaging methods. New algorithmic approaches show promise for real-time, advanced virtual staining in intraoperative settings. These techniques can reduce processing times, standardize stain quality, cut laboratory costs, and minimize exposure to toxic chemicals. Additionally, virtual staining allows for better tissue preservation and integration with molecular analysis, enabling quicker and more accurate treatment planning (Zeng et al., 2020).

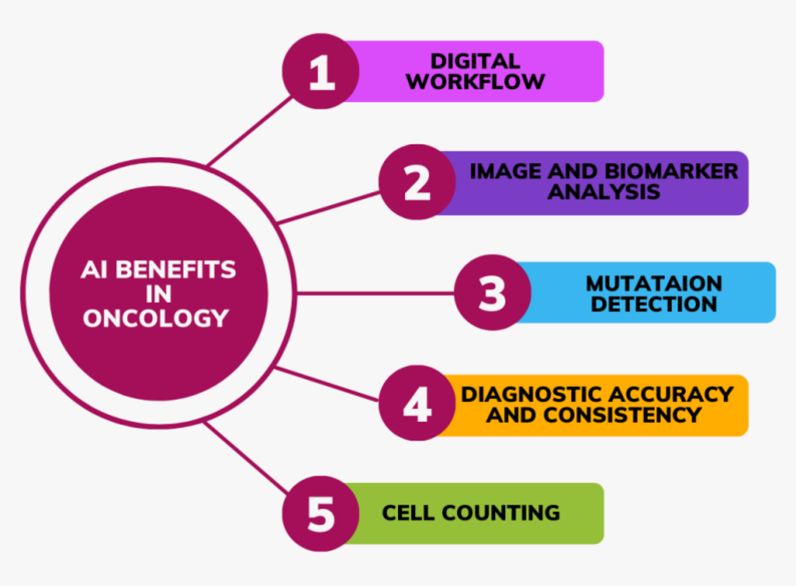
In histopathology, The Tumor Proliferation Assessment Challenge 2016 (TUPAC16) was the first attempt to automate the prediction of breast tumor proliferation scores using mitosis detection in entire slide images. In a 2017 study, CNNs utilized to analyze 646 breast tissue samples, attaining an AUC of 0.92 for identifying malignant from benign tissue, while in follow-up work, they employed context-aware layered CNNs to diagnose breast pathology in WSIs, achieving an AUC of 0.96 for binary classification and an 81% precision for classifying WSIs as normal or benign, or invasive ductal carcinoma (Bejnordi et al., 2017). Moreover, DL algorithms in oncologic histopathology are commonly validated by comparing their performance to that of professional pathologists. The Cancer Metastases in Lymph Nodes Challenge 2016 (CAMELYON16) demonstrated this technique by requiring 11 pathologists to detect breast cancer metastases from 129 whole slide images (WSIs) within a particular period. The findings showed that some deep learning algorithms surpassed pathologists in terms of both accuracy and speed for diagnosing breast cancer lymph node metastases (Bejnordi et al., 2017). DL provides advanced functionality, decision-making skills, and the ability to handle exceedingly enormous data sets along with machine learning activities. Moreover, DL techniques have significantly improved performance in basic visual computing tasks like image classification and segmentation (discriminative models). It has also demonstrated enhanced efficiency in visual processing tasks such as synthesis and rendering (generative models). Additionally, CAD systems surpass traditional visual methods in accuracy and consistency, effectively identifying key features like specific stains, tumor staging, and mitosis presence. Content-Based Image Retrieval (CBIR) systems also used in DL, which find similar images from large databases, are particularly useful for diagnosing rare cases by providing relevant histopathological references. These systems improve efficiency through techniques like feature reduction, quick search methods, and deep learning approaches such as SMILY (Similar Medical Image Like Yours) (Hegde et al., 2019; Kim et al., 2020).

Moreover, in a study by Mercan et al. (2019) CNN was developed to analyze images from 240 breast biopsies and differentiate between normal tissue, atypia, ductal carcinoma in situ (DCIS), and invasive cancer. The model's performance was evaluated against a consensus report from three pathologists and it was also compared to the diagnoses made by 87 other pathologists. The CNN achieved the same specificity (0.80) as the pathologists, but it outperformed them in accuracy (0.85 vs. 0.82) and sensitivity (0.89 vs. 0.70) for classifying invasive cancer. Recently, a decision support system for digital pathology was reported that uses a deep learning framework based on multiple instances learning to detect cancer. Their model was trained and validated on a large dataset comprising 9,894 breast metastasis slides, 9,962 skin slides, and 24,859 prostate core biopsy slides. The system achieved an area under the curve (AUC) of over 0.98 for detecting breast cancer in lymph nodes, basal cell carcinoma, and prostate cancer. Clinically, this tool could help pathologists eliminate 65–75% of slides with 100% sensitivity, streamlining their workflow. Additionally, the study showed that patient-level diagnoses could be used as training labels, avoiding the need for time-consuming pixel-level manual annotations.

BENEFITS OF AI IN AUTOMATED CANCER DIAGNOSIS

The overall perspective for AI in digital histopathology is in the developing stage, but its frequent merits encompass improved diagnostic reliability and precision, as well as enhanced workflow performance. AI can be used in a digital workflow system to provide voice detection, specimen slide bar codes, and updates automatically to the pathologist's output display. This integration has the potential to cut overall processing time by up to 40% (Ye, 2015). Diagnostic pathology frequently encounters issues of variability and subjectivity, especially in Gleason grading for prostate tumors, where artificial limits can impair recurrence. DL algorithms taught by experienced urological pathologists outperform ordinary pathologists in Gleason grading, with an area under the curve (AUC) of 0.997 for recognizing benign/ malignant specimens. These AI algorithms can improve grading uniformity and streamline diagnoses, which could lead to more accurate result prognoses. Although modern AI uses, which include prostate tumors, are mainly concerned with differentiating benign/malignant issues, progress is currently underway regarding recognizing metastatic tumors and carcinomas in various other tumors, including breast and cervical tumors (Nagpal et al., 2019; Zhang et al., 2017). Various image analysis tools are available for quantifying immunohistochemistry (IHC) biomarkers, with some FDA and CE IVD-cleared algorithms used for assessing features like ER, PR, HER-2, and Ki-67 expression in breast cancer. These tools are employed in certain medical centers and hold promise for standardizing companion diagnostic tests such as PD-L1. AI has the potential to enhance diagnostic IHC analysis and could also play a significant role in clinical trials by standardizing baseline tests and endpoints through objective image analysis rather than relying on subjective human evaluation (Koelzer et al., 2018). Accurate cell counts, which are challenging for pathologists and often given as rough estimates, are particularly valuable for assessing immune responses or tumor burden. AI's objectivity in cell counting leads to new prognostic insight and established prognostic factors. For instance, a study using a convolutional neural network (CNN) for mitosis detection found that mitotic counts in triple-negative breast cancer had minimal prognostic value. Similarly, in cancers such as colorectal, breast, and melanoma, tumor-infiltrating lymphocyte (TIL) counts are increasingly recognized for their prognostic significance, though current classifications are prone to observer variability (Fu et al., 2019).

AI can detect subtle cell changes in H&E-stained slides that are often imperceptible to pathologists, and these changes can indicate specific genetic mutations. For example, AI has been used to predict SPOP mutations in prostate cancer, BRAF mutations in melanoma, and several common mutations in lung adenocarcinoma. AI could reduce the reliance on immunohistochemistry (IHC) and provide immediate mutation predictions from H&E images, potentially streamlining genetic testing. AI has also been applied to predict consensus molecular subtypes in colorectal cancer and assess microsatellite instability (Cifci, 2022). AI holds significant promise for integrating various types of data, including radiological and histological images (radiohistomics) and genomic information (histogenomics). This integration allows for tracking the molecular evolution of cancer cells and addressing tumor heterogeneity challenges. While earlier AI methods focused on individual organs, current approaches are increasingly achieving insights across multiple tumor types, such as detecting mutation types in a pan-cancer context. Additionally, AI is being used to study tumor-infiltrating lymphocytes (TILs) across different tumor types and tissue sites, combined with genomic data, to gain a new understanding of their roles in various tumor environments (Saltz et al., 2018).



Flow chart: Benefits of AI

CHALLENGES AND LIMITATIONS

Regardless of a century of expansion, the application of AI in clinical practice remains restricted. It is because of plenty of aspects, such as legislative and validity barriers, high prices, and the requirement for substantial expenditures in digital pathology facilities. Massive, manually labeled datasets are required for efficient training in AI image processing networks, primarily those based on ANNs. Despite modest advances with weakly supervised DL, the considerable effort needed to train these devices poses an obstacle to broad clinical application. The presumptions in ANNs are a major challenge in training computational image analysis mechanisms, and it is significantly affected by the available training data. However, providing more labeled slides might help minimize bias, variables in specimen analysis, that involve tissue size, staining performance, and scanning tools, can contribute extra error. Algorithms developed on slides from a particular laboratory might respond inappropriately when presented with slides from another. AI algorithms develop conclusions based on training data, which may contain inaccurate preconceptions, including misidentifying benign tissue as cancer. To overcome these challenges, coordination through numerous research facilities to create diversified training datasets and algorithms for AI can assist in reducing bias and enhance overall precision (Moxley-Wyles et al., 2020).

The journey from developing to marketing a new AI tool is complex and lengthy. Ideally, this process involves collaboration among industry, academia, and clinicians. Development requires completing standard research steps, including ethics approval, funding, and pilot studies. Prototype tools must undergo rigorous validation to ensure clinical reliability and meet regulatory standards, which includes assessing accuracy, reproducibility, and performance, and conducting a cost-benefit analysis. Validation is best achieved through multicenter clinical trials. Currently, guidance for verifying AI tools in diagnostic settings is limited, though some publications on the topic have started to emerge. For AI tools to be used in healthcare, they must obtain regulatory clearance as medical devices, which involves extensive validation to provide evidence for their effectiveness. While the regulatory framework for AI in healthcare is not well-defined in most countries, the USA has made significant progress. Once an AI tool is approved, laboratories must implement ongoing quality control measures, including incident reporting, regular audits, and performance monitoring, to maintain accreditation (Moxley-Wyles et al., 2020). Additionally, there is a need to define and establish training requirements for pathologists and biomedical scientists to ensure they are proficient in using AI tools confidently. Interoperability in AI and digital pathology is crucial, as there is a need for standardized, open file types to enable seamless integration across different systems. Governance and ethical concerns are also significant, particularly regarding the potential future role of AI in fully replacing pathologists in the reporting process. According to the EU General Data Protection Regulations (GDPR), individuals have the right to not be subject to decisions based solely on automated processing. Public opinion emphasizes the importance of transparency and involvement in how healthcare data is used (Allen, 2019). The field of integrating histopathology with computational tools is actively evolving. The development and optimization of computer-aided analysis and diagnostic tools for high-resolution digital histological images are ongoing and continue to advance.

CONCLUSION

The application of artificial intelligence (AI) in histopathology provides a substantial improvement in cancer detection and tumor evaluation. Conventional histological techniques, particularly depending upon manual inspection of dyed tissue slides, usually lack reliability and efficacy. AI, particularly deep learning (DL) and machine learning (ML), overcomes these challenges by improving diagnostic precision, reliability, and effectiveness of workflows. AI designs, which include as convolutional neural networks (CNNs), have been discovered to be extremely successful at evaluating whole-slide images (WSIs) and recognizing minute modifications in cells that human pathologists may overlook. These approaches have demonstrated improved accuracy in carcinoma categorization, grading, and staging, as well as the recognition of unusual or challenging cases. Furthermore, automated digital staining procedures provide advantages such as shorter processing times, reduced requirement of extra biopsies, and improved tissue conservation, which simplifies diagnoses and decreases the consumption of harmful chemicals. Despite these advancements, several challenges remain. The widespread adoption of AI in histopathology is hindered by the need for large, annotated datasets, regulatory hurdles, and variability in specimen processing. Rigorous validation is required to ensure these tools' reliability and clinical effectiveness. Addressing these challenges through collaboration among researchers, clinicians, and industry stakeholders will be crucial. In summary, AI holds great promise for improving cancer diagnosis and treatment by providing more accurate and efficient methods. Continued development and careful implementation of AI technologies will likely enhance patient outcomes and transform the diagnostic workflow in histopathology.

REFERENCES

Abdeltawab, H., Khalifa, F., Ghazal, M., Cheng, L., Gondim, D., & El-Baz, A. (2021). A pyramidal deep learning pipeline for kidney whole-slide histology images classification. *Scientific reports, 11*(1), 20189.

Acs, B., Rantalainen, M., & Hartman, J. (2020). Artificial intelligence as the next step towards precision pathology. *Journal of internal medicine, 288*(1), 62-81.

Ahmed, A. A., Abouzid, M., & Kaczmarek, E. (2022). Deep learning approaches in histopathology. *Cancers, 14*(21), 5264.

Allen, T. C. (2019). Regulating artificial intelligence for a successful pathology future. *Archives of pathology & laboratory medicine*, *143*(10), 1175-1179.

Bejnordi, B. E., Lin, J., Glass, B., Mullooly, M., Gierach, G. L., Sherman, M. E., ... & Beck, A. H. (2017, April). Deep learning-based assessment of tumor-associated stroma for diagnosing breast cancer in histopathology images. In *2017 IEEE 14th international symposium on biomedical imaging (ISBI 2017)* (pp. 929-932). IEEE.

Bejnordi, B. E., Veta, M., Van Diest, P. J., Van Ginneken, B., Karssemeijer, N., Litjens, G., ... & CAMELYON16 Consortium. (2017). Diagnostic assessment of deep learning algorithms for detection of lymph node metastases in women with breast cancer. *Jama, 318*(22), 2199-2210.

Bejnordi, B. E., Zuidhof, G., Balkenhol, M., Hermsen, M., Bult, P., van Ginneken, B., ... & van der Laak, J. (2017). Context-aware stacked convolutional neural networks for classification of breast carcinomas in whole-slide histopathology images. *Journal of Medical Imaging, 4*(4), 044504-044504.

Cifci, D., Foersch, S., & Kather, J. N. (2022). Artificial intelligence to identify genetic alterations in conventional histopathology. *The Journal of Pathology, 257*(4), 430-444.

Colling, R., Pitman, H., Oien, K., Rajpoot, N., Macklin, P., CM‐Path AI in Histopathology Working Group, ... & Verrill, C. (2019). Artificial intelligence in digital pathology: a roadmap to routine use in clinical practice. *The Journal of pathology, 249*(2), 143-150.

Coudray, N., Ocampo, P. S., Sakellaropoulos, T., Narula, N., Snuderl, M., Fenyö, D., ... & Tsirigos, A. (2018). Classification and mutation prediction from non–small cell lung cancer histopathology images using deep learning. *Nature medicine, 24*(10), 1559-1567.

Dean, W. (2020). Emerging advances to transform histopathology using virtual staining. *BME frontiers, 2020*, 9647163.

Doyle, S., Hwang, M., Shah, K., Madabhushi, A., Feldman, M., & Tomaszeweski, J. (2007, April). Automated grading of prostate cancer using architectural and textural image features. In *2007 4th IEEE International Symposium on Biomedical Imaging: From Nano to Macro* (pp. 1284-1287). IEEE.

Ehteshami Bejnordi, B., Mullooly, M., Pfeiffer, R. M., Fan, S., Vacek, P. M., Weaver, D. L., ... & Sherman, M. E. (2018). Using deep convolutional neural networks to identify and classify tumor-associated stroma in diagnostic breast biopsies. *Modern Pathology, 31*(10), 1502-1512.

Fu, Q., Chen, N., Ge, C., Li, R., Li, Z., Zeng, B., ... & Li, G. (2019). Prognostic value of tumor-infiltrating lymphocytes in melanoma: a systematic review and meta-analysis. *Oncoimmunology, 8*(7), e1593806.

He, L., Long, L. R., Antani, S., & Thoma, G. R. (2012). Histology image analysis for carcinoma detection and grading. *Computer methods and programs in biomedicine, 107*(3), 538-556.

He, W., Liu, T., Han, Y., Ming, W., Du, J., Liu, Y., ... & Cao, C. (2022). A review: The detection of cancer cells in histopathology based on machine vision. *Computers in Biology and Medicine, 146*, 105636.

Hegde, N., Hipp, J. D., Liu, Y., Emmert-Buck, M., Reif, E., Smilkov, D., ... & Stumpe, M. C. (2019). Similar image search for histopathology: SMILY. *NPJ digital medicine, 2*(1), 56.

Iizuka, O., Kanavati, F., Kato, K., Rambeau, M., Arihiro, K., & Tsuneki, M. (2020). Deep learning models for histopathological classification of gastric and colonic epithelial tumours. *Scientific reports, 10*(1), 1504.

Kim, M., Yun, J., Cho, Y., Shin, K., Jang, R., Bae, H. J., & Kim, N. (2020). Deep learning in medical imaging. *Neurospine, 17*(2), 471.

Koelzer, V. H., Gisler, A., Hanhart, J. C., Griss, J., Wagner, S. N., Willi, N., ... & Mertz, K. D. (2018). Digital image analysis improves precision of PD-L1 scoring in cutaneous melanoma. *Histopathology, 73*(3), 397-406.

Komura, D., & Ishikawa, S. (2018). Machine learning methods for histopathological image analysis. *Computational and structural biotechnology journal, 16*, 34-42.

Lin, H., Chen, H., Weng, L., Shao, J., & Lin, J. (2021). Automatic detection of oral cancer in smartphone-based images using deep learning for early diagnosis. *Journal of Biomedical Optics, 26*(8), 086007-086007.

Mercan, E., Mehta, S., Bartlett, J., Shapiro, L. G., Weaver, D. L., & Elmore, J. G. (2019). Assessment of machine learning of breast pathology structures for automated differentiation of breast cancer and high-risk proliferative lesions. *JAMA network open, 2*(8), e198777-e198777.

Moxley-Wyles, B., Colling, R., & Verrill, C. (2020). Artificial intelligence in pathology: an overview. *Diagnostic Histopathology, 26*(11), 513-520.

Nagpal, K., Foote, D., Liu, Y., Chen, P. H. C., Wulczyn, E., Tan, F., ... & Stumpe, M. C. (2019). Development and validation of a deep learning algorithm for improving Gleason scoring of prostate cancer. *NPJ digital medicine, 2*(1), 48.

Rawat, W., & Wang, Z. (2017). Deep convolutional neural networks for image classification: A comprehensive review. *Neural computation, 29*(9), 2352-2449.

Saltz, J., Gupta, R., Hou, L., Kurc, T., Singh, P., Nguyen, V., ... & Danilova, L. (2018). Spatial organization and molecular correlation of tumor-infiltrating lymphocytes using deep learning on pathology images. *Cell reports, 23*(1), 181-193.

Sultan, A. S., Elgharib, M. A., Tavares, T., Jessri, M., & Basile, J. R. (2020). The use of artificial intelligence, machine learning and deep learning in oncologic histopathology. *Journal of Oral Pathology & Medicine, 49*(9), 849-856.

Xing, F., & Yang, L. (2016). Machine learning and its application in microscopic image analysis. In *Machine learning and medical imaging* (pp. 97-127). Academic Press.

Ye, J. J. (2015). Artificial intelligence for pathologists is not near—it is here: description of a prototype that can transform how we practice pathology tomorrow. *Archives of Pathology and Laboratory Medicine, 139*(7), 929-935.

Zeng, Y., & Zhang, J. (2020). A machine learning model for detecting invasive ductal carcinoma with Google Cloud AutoML Vision. *Computers in biology and medicine, 122*, 103861.

Zhang, L., Lu, L., Nogues, I., Summers, R. M., Liu, S., & Yao, J. (2017). DeepPap: deep convolutional networks for cervical cell classification. *IEEE journal of biomedical and health informatics, 21*(6), 1633-1643.