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Utilization of Artificial Intelligence in Breast Pathology: An Overview

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ABSTRACT

In the last decade, artificial intelligence (AI) has been increasingly used in various fields of medicine. Recently, the advent of whole slide images (WSI) or digitized slides has paved the way for AI-based anatomic pathology. This paper set out to review the potential integration of AI algorithms in the workflow, and the utilization of AI in the practice of breast pathology.

Key words: AI algorithm, anatomic pathology, artificial intelligence, breast cancer, digitized slides, whole slide images

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INTRODUCTION

The World Health Organization (WHO) has reported that there were 2.3 million women diagnosed with breast cancer, and 685,000 deaths globally in 2020.[1] Surprisingly, the Philippines has the highest incidence rate of breast cancer in Asia. Approximately 7% (1/13) of Filipino women will develop breast cancer in their lifetime and 25% (1/4) who were diagnosed with breast cancer die within the first 5 years.[2] Breast examination, mammogram, ultrasound, magnetic resonance imaging (MRI), and biopsy are some of the tests used to diagnose breast cancer.[3]

The recent and ongoing advances in artificial intelligence (AI), machine learning (ML), and deep learning (DL), have paved the way for the development of AI algorithms not just in pathology, but in the practice of medicine in general.[4] For a pathologist, these ML and DL approaches offer the potential to significantly improve workflow, reduce turnaround time, and increase diagnostic accuracy. In 2022, Sandbank and colleagues conducted a validation and real-world clinical application of an AI algorithm for breast cancer detection in biopsies. Their study focused on 4 main steps: (1) development of an AI algorithm for breast cancer detection using digitized slides; (2) algorithm internal testing; (3) blinded algorithm validation using an independent dataset and (4) algorithm deployment in routine clinical use. Galen™ Breast was used for the algorithm's internal testing and external validation. Based on the results of the study, it has been observed that the area under the curve (AUC) for invasive breast cancer detection was 0.990 (95% CI 0.984-0.997) with a sensitivity and specificity of 95.51% and 93.57%, respectively. On the other hand, the AUC for ductal carcinoma in situ (DCIS) detection was 0.980 (95% CI 0.967-0.993) with a sensitivity and specificity of 93.79% and 93.20%, respectively. The diagnostic performance for tumor-infiltrating lymphocytes (TILs) was remarkable with an AUC of 0.965.[5] Overall, based on this study, the deployment of an AI algorithm in the clinical setting was proven to be useful for breast cancer detection in biopsies.

KNOWING THE PAST TO UNDERSTAND THE PRESENT

In the 1950s, enzyme histochemistry was used to apply specific reactions on tissue sections with the aid of chemical dyes. In 1956, the term artificial intelligence was coined by John McCarthy. Three years later, machine learning was introduced by Arthur Samuel. Then in the 1960s, electron microscopy (EM) was first used to assist in the diagnosis of kidney diseases and neuropathies. In 1965, computerized image analysis of cells and chromosomes was introduced by Judith Prewitt and Mortimer Mendelsohn. Eventually in the 1980s, immunohistochemistry (IHC) became a major part of diagnosis for various malignancies. The term deep learning was coined by Rina Dechter in 1986 and two years later, the convolutional neural network (CNN) model was invented by Yann LeCun. In 1990, a whole slide scanner was introduced. In the 2000s, molecular diagnostics has been widely used for assessing diagnostic and therapeutic biomarkers. Examples of biomarkers used in clinical practice to guide diagnosis and therapeutic decisions for breast cancer include but are not limited to breast cancer gene (BRCA), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PI3KCA), Oncotype DX, MammaPrint Test, and immunohistochemical 4 (IHC4). In 2013, a photoacoustic microscopy (PAM) imaging technique was developed. The following year, the generative adversarial network (GAN) was introduced by Ian Goodfellow. In 2016, microscopy with ultraviolet surface excitation (MUSE) microscopy was invented and the year after, Philips received approval for a digital pathology whole-slide scanning solution.[6-10]

COMPUTATIONAL PATHOLOGY

Machine learning is a subset of AI and is largely classified into 3 categories namely supervised learning, unsupervised learning, and semi-supervised learning. Examples of supervised learning include artificial neural networks (ANN), decision trees, k-nearest neighbors, and linear regression. Deep learning is a subset of ML and the commonly used model in anatomic pathology is supervised learning based on the convolutional neural network (CNN).[11] Training of neutral networks begins by dividing each whole slide image (WSI) into smaller patches. The reason for this is that the number of pixels for WSI is about 10^5 x 10^5 which is too big for processing. Each patch then goes through multiple convolutional kernels or filters, and the convolved patches are flattened and used as input. The weights and biases are adjusted, and the model is trained.[4] Examples of training goals and datasets using the CNN model are shown in Table 1.[12-21] Meanwhile, unsupervised learning is an ML method that takes unlabeled input data to form and generate patterns. Examples of unsupervised learning techniques include cluster analysis and principal component analysis.[11]

VALIDATING DIGITIZED SLIDES

Digital pathology has played an important role in the development and application of WSI. This technology utilized an automated scanner capable of digitizing the whole slide using state-of-the-art software. Validation of WSI is essential to ensure that diagnostic performance and quality assurance are in place. Hence, the College of American Pathologists (CAP) has set forth guidelines for validating WSI for diagnostic purposes.[22]

1. All pathology laboratories implementing WSI technology for clinical diagnostic purposes should carry out their own validation studies.
2. Validation should be appropriate for and applicable to the intended clinical use and clinical setting of the application in which WSI will be employed; Validation of WSI systems should involve specimen preparation types relevant to the intended use (e.g., formalin-fixed paraffin-embedded tissue, frozen tissue, immunohistochemical stains, cytology slides, hematology blood smears).
3. The validation study should closely emulate the real-world clinical environment in which the technology will be used.
4. The validation study should encompass the entire WSI system.
5. Revalidation is required whenever a significant change is made to any component of the WSI system.
6. A pathologist adequately trained to use the WSI system must be involved in the validation process.
7. The validation process should include a sample set of at least 60 cases for one application (e.g., hematoxylin-eosin-stained sections of fixed tissue, frozen sections, cytology, hematology) that reflects the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine practice.
8. The validation study should establish diagnostic concordance between digital and glass slides for the same observer (i.e., intraobserver variability).
9. Digital and glass slides can be evaluated in random or nonrandom order (as to which is examined first and second) during the validation process.
10. A washout period of at least 2 weeks should occur between viewing digital and glass slides.

Table 1. Examples of training goals and datasets using CNN model

DL	Input	Training goal	Dataset	Authors
CNN	WSI	Diagnosis of breast cancer	Private	Mi et al., 2021
CNN	WSI	Genomic correlation of breast cancer	TCGA	Lu et al., 2021
CNN	WSI	Diagnosis of brain tumor	Private	Im et al., 2021
CNN	WSI	Diagnosis of gastric cancer	Private	Hu et al., 2021
CNN	WSI	Screening of cervical cancer	Private	Cheng et al., 2021
CNN	WSI	Diagnosis of ovarian cancer	TCGA	Shin et al., 2021
CNN	WSI	Classification of colon cancer	TCGA	Zhou et al., 2021
CNN	WSI	Segmentation of prostate gland	Private	Salvi et al., 2021
CNN	WSI	Classification of transplant kidney	Private	Kers et al., 2022
CNN	WSI	Prognosis of lung cancer	Private	Shim et al., 2021

CNN: convolutional neural network; DL: deep learning; TCGA: The Cancer Genome Atlas; WSI: whole slide image

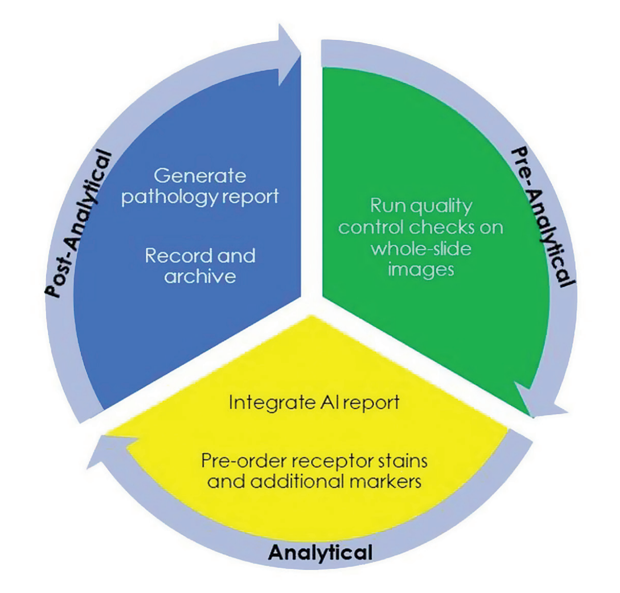

Figure 1. The three phases of laboratory testing.

11. The validation process should confirm that all the material present on a glass slide to be scanned is included in the digital image.
12. Documentation should be maintained recording the method, measurements, and final approval of validation for the WSI system to be used in the clinical laboratory.

EMBEDDING AI ALGORITHM IN THE WORKFLOW

The integration of AI into the workflow of anatomic pathology has many advantages and opens more opportunities in clinical practice. First, it can perform quality control in the 3 phases of the laboratory work processes namely, the pre-analytical phase, the analytical phase, and the post-analytical phase. Specifically, the AI algorithm can run quality control checks on the digitized slides using either frozen sections or formalin-fixed paraffin-embedded (FFPE) tissue blocks (Figure 1). After which, integrated diagnosis can be achieved through consolidation and correlation of clinical information, laboratory findings, and AI reports.[23] Furthermore, pertinent radiologic images and omics studies (e.g., genomics, transcriptomics, proteomics) may be integrated into the clinical data and would offer a wider perspective. Lastly, personalized patient-centric analysis and interpretation of the case, as well as the generation of a final pathology report and archiving can be incorporated into the workflow.

Whole slide images using hematoxylin and eosin (H&E)-stained slides can be easily scanned. The glass slides are usually scanned at 40x magnification with a resolution of 0.23 to 0.25 μm/pixel.[24-26] Some of the commonly used scanners that are now available in the market include IntelliSite (Philipps Digital Pathology Solutions, Netherlands); Aperio (Leica Biosystems, Germany); NanoZoomer (Hamamatsu, Japan); and Axioscan (Zeiss, Oberkochen, Germany). This has accelerated the deployment of WSI for clinical use mostly in developed countries. In particular, the IntelliSite has been approved for diagnostic purposes in the United States (US) and is licensed for in-vitro diagnostics (IVD) in the European Union (EU), Canada, Japan, Singapore, Korea, and the Middle East. These scanners can produce automated, high-speed, and high-resolution digitized slides.

The AI algorithm can help in the practice of breast pathology by:

1. Providing efficient workflow and improved turnaround time. This means that pathology cases can be prioritized in terms of diagnosis. Immunohistochemistry stains such as ER, PR, and HER2 can be pre-ordered. Additional levels such as calcifications can also be pre-ordered.
2. Detecting invasive cancers and DCIS with an AUC close to 1.0 as demonstrated by Sandbank and colleagues;
3. Distinguishing different subtypes of cancer. In particular, the AI algorithm can separate ductal and lobular cancers. This would then help the physician identify patients who are unlikely to respond to neoadjuvant therapies;
4. Detecting a special type of cancer of favorable prognosis. An example of this is the detection of tubular and mucinous carcinoma;.
5. Detecting metaplastic carcinomas;[5]
6. Detecting lymph nodes for metastasis;[27]
7. Quantitating various markers such as antigen Kiel 67 (Ki-67), programmed cell death ligand 1 (PD-L1), and TILs.[28]

HOW WILL AI ENHANCE THE PRACTICE OF BREAST PATHOLOGY?

AI has already been shown to be of value in prostate cancer and can be used as a critical adjunct to anatomic pathology.[29,30] The pathologist who used AI has these to offer:

1. Increase diagnostic accuracy through notification and alert system;
2. Improve interobserver concordance;
3. Provide an additional layer of quality control and improve patient safety.

CHALLENGES TO THE IMPLEMENTATION OF AI

The challenges for the implementation of AI in anatomic pathology include but are not limited to the following: algorithm validation and generalizability; digitalizing slides and storage of WSI requires huge and expensive data storage facilities; ethical issues; integration of other pertinent data such as radiology images and omics (e.g., genomics, transcriptomics, proteomics); regulatory considerations and technological infrastructure. Here, there is a need for laboratories to invest and develop the technological infrastructure to support whole-slide imaging using AI algorithms.

WILL AI REPLACE THE PATHOLOGISTS?

Charles Darwin, known for his theory of evolution by natural selection, published his landmark book on the Origin of Species in 1859. According to him, *it is not the strongest of the species that survives nor the most intelligent that* *survives. It is the one that is adaptable to change.*[31] This means that AI will not replace the pathologists but instead, AI will enhance the practice of anatomic pathology. In other words, AI is the perfect companion for breast cancer detection in biopsies. This is in line with the perspective of a seasoned pathologist, Dr. Stuart J. Schnitt, Chief of Breast Oncologic Pathology, Dana-Farber Brigham Cancer Center, and Professor of Pathology, at Harvard Medical School. According to him, *instead of pathologists being replaced by AI, pathologists who use AI will replace those who don't use AI.*[32] Taken together, the integration of AI in the practice of breast pathology can significantly improve diagnostic accuracy and efficiency.

CONCLUSION

AI algorithms have been developed and validated for detecting breast cancer in biopsies. This offers the potential to increase accuracy, improve patient safety, and eventually help in providing better care and patient outcomes. Given the limited number of pathologists and the increasing caseloads, AI-based systems may ease the pressure on anatomic pathologists, reduce interobserver variability, and improve total turnaround time. Indeed, AI is increasingly a maturing technology, however, further evaluation in the clinical setting, as well as a demonstration of the clinical utility of AI in anatomic pathology is crucial to widespread adoption.

STATEMENT OF AUTHORSHIP

The author certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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