Future Practices of Breast Pathology Using Digital and Computational Pathology

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Abstract: Pathology clinical practice has evolved by adopting technological advancements initially regarded as potentially disruptive, such as electron microscopy, immunohistochemistry, and genomic sequencing. Breast pathology has a critical role as a medical domain, where the patient's pathology diagnosis has significant implications for prognostication and treatment of diseases. The advent of digital and computational pathology has brought about significant advancements in the field, offering new possibilities for enhancing diagnostic accuracy and improving patient care. Digital slide scanning enables to conversion of glass slides into high-fidelity digital images, supporting the review of cases in a digital workflow. Digitization offers the capability to render specimen diagnoses, digital archival of patient specimens, collaboration, and telepathology. Integration of image analysis and machine learning–based systems layered atop the high-resolution digital images offers novel workflows to assist breast pathologists in their clinical, educational, and research endeavors. Decision support tools may improve the detection and classification of breast lesions and the quantification of immunohistochemical studies. Computational biomarkers may help to contribute to patient management or outcomes. Furthermore, using digital and computational pathology may increase standardization and quality assurance, especially in areas with high interobserver variability. This review explores the current landscape and possible future applications of digital and computational techniques in the field of breast pathology.

Keywords: digital pathology, computational pathology, breast, image analysis, machine learning, artificial intelligence

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INTRODUCTION TO DIGITAL AND COMPUTATIONAL PATHOLOGY

The accurate and timely pathologic diagnosis of breast lesions is fundamental to patient care. The integration of whole slide imaging and digital workflows in routine pathology practice enables the implementation of computational pathology systems. Digital and computational pathology can contribute to improve patient care. Machine learning systems show promise in analyzing histology images and detecting and classifying breast lesions, quantifying biomarkers, and predicting treatment response. This review critically examines the breast pathology landscape on the future practices and applications in digital and computational pathology. This review aims to discuss how these tools can assist in improving diagnosis, grading, and biomarker quantification, focusing on diagnostic and prognostic applications.

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TECHNOLOGY ADOPTION CURVE

With the introduction of any new technology, the adoption lifecycle (eg, diffusion of innovation) is a function of how individuals and organizations embrace emerging technologies. It typically follows a bell-shaped curve, starting with innovators who eagerly embrace new technologies, followed by early adopters who are influential leaders, who quickly follow suit, recognizing the need for change and readily adopt new ideas. As the technology gains momentum, the next group of adopters are the early majority, representing a pragmatic larger cohort who embrace the technology once its value and benefits are proven. The late majority is more skeptical and adopts the technology only after it has been proven successful by the early majority. Last, laggards or skeptics who are resistant to change, may or may not adopt the new technology, typically requiring significant evidence and pressure from prior adopters. When it comes to digital pathology, early adopters have implemented the technology gradually as it matured, based on evolving use cases and the technology's advancement. The approach to adopting new medical technologies depends on factors such as specific use cases, organizational processes, and the risk aversion levels of individuals within the clinical organization, with the ultimate goal of improving patient care. To date, the use of computational pathology has mostly been innovating in the research arena with early adopters using the computational pathology workflows in clinical care. The cycle reflects the diffusion of innovation, with each group influencing the next, and successful adoption often relies on effective communication, education, and addressing concerns and barriers to each specific subsequent group.

DIGITIZATION WORKFLOW

The digitization of pathology assets (eg, glass slides) begins with the same standard histology procedures similar to all surgical pathology breast specimens. Once sectioning, staining, and coverslipping are complete, the prepared glass slides are loaded onto a digital pathology scanner (eg, whole slide scanner) equipped with a robotic stage, high-resolution camera, and optical system. The scanner captures high-resolution images of the tissue present on the glass slide by scanning it in a raster pattern and stitching together adjacent images to create a high-fidelity digital representation of the glass slide. The acquired images may undergo image processing techniques to enhance clarity, color accuracy, and overall image quality. Relevant metadata, such as patient information and pathology specimen details, may be associated with the digital image for proper clinical integration using advanced barcoding and tracking solutions present within the laboratory information system, predominantly by decoding barcodes present on the glass slide label area by the camera sensor within the whole slide scanner.

The resulting digital images, known as whole slide images (eg, digital slides), are digitally stored and accessible in an image management system. Pathologists can view these digital slides using specialized digital pathology software, allowing the ability to navigate and review the whole slide images similar to that of a brightfield microscope to facilitate low, medium, and high magnification tissue review, as well as perform various diagnostic and analytical tasks. Studies have shown noninferiority to reviewing whole slide images (eg, digital slides) in comparison to glass slides, and the Food and Drug Administration has approved several industry platforms for primary diagnosis.[1,2] Furthermore, the College of American Pathologists have published validation guidelines for laboratories to implement these technologies in clinical use for patient care.[3,4] Validation studies specific to breast pathology have demonstrated the equivalence in performance and ability to diagnostically evaluate patient tissue in a digital format to ensure safe and efficacious patient care.[5–7] Digital pathology enables primary diagnostics workflows, telepathology and remote consultations, collaboration, and efficient archiving of digital slides, facilitating enhanced accessibility, accuracy, and potential integration with computational pathology techniques for (semi)automated analysis.

IMAGE ANALYSIS AND MACHINE LEARNING

Computational pathology (eg, image analysis, machine learning) techniques are emerging as powerful tools that have the potential to revolutionize breast pathology. Through image analysis algorithms, digital pathology images can be processed, segmented, and quantified to extract relevant features and patterns in the data. Machine learning models can then be trained on similar extracted features to predict narrow, specific tasks in pathology. These tools are used in an adjunctive fashion as a virtual pathology assistant in assessing pathology digital images. In addition, machine learning systems may also assist in prognostication, predicting outcomes, and guiding patient management. With sufficient data, machine learning systems can facilitate the discovery of computational biomarkers by uncovering unbeknownst relationships within the datasets. As the field of breast pathology continues to embrace image analysis and machine learning, the potential for enhanced precision, consistency, and data-driven decision-making in diagnostic pathology is poised to grow exponentially. These technologies can drive decision-making in pathology to move from a qualitative to a quantitative diagnostic discipline. One key principle is emerging from medical professional societies to encourage the use of "AI" machine learning systems as assistive workflows under "augmented intelligence" instead of "artificial intelligence" (AI) where the nature of the system does not replace pathologists, nor act on behalf of an expert trained pathologist, but rather intend to collaboratively strengthen the role of the pathologist for specific directed tasks.[8,9] Tasks for the digital and augmented workflows in breast pathology offer capabilities to increase accuracy, improve productivity, and enable discovery.

ACCURACY

The use of decision support tools in breast pathology can enhance the detection, classification, and quantification of breast lesions, and bolster patient safety. AI is not intended to replace pathologists or health care professionals but to augment their expertise. AI tools can assist in decision-making, enhance accuracy, and improve patient care by providing additional information and insights. Pathologists remain essential for validating AI-generated results, considering clinical context, and making the final diagnostic decisions.

Detection

Machine learning–based models can aid in screening the digital slides and detecting suspicious and/or abnormal regions. Some of these models have been trained on sufficiently large expert-level datasets, whereby they can assist pathologists in identifying abnormalities in the breast specimens, and prompt focused evaluation. In other systems, machine learning has been enhanced with annotations of specific lesions by dedicated pathologists. These tools can identify potential areas for directed review in digitized histopathology slides, such as malignancies (eg, in situ and invasive carcinoma), atypical epithelial proliferations (eg, atypical ductal hyperplasia), or non-neoplastic findings such as adenosis, usual hyperplasia, or microcalcifications. The literature shows investigators developing machine learning–based models for detection, localization, and segmentation of various mammary lesions. Detection of in situ and invasive carcinoma has been documented with high accuracy.[10–18] Hanna et al evaluated a dataset of 9751 anatomical specimens (biopsy, 6289; excision, 3462) comprising total of 40,637 slides to train a convoluted neural network. The system was validated on whole slide images generated from 3742 breast specimens (biopsy, 2250; excision, 1492) comprising 13,601 digital slides that were not included in the training of the convolutional neural network model. Results showed high sensitivity of detection, with area under the receiver operating characteristic curve (AUC) of 0.98, 0.98, 0.97, 0.95, and 0.92, for invasive carcinoma, ductal carcinoma in situ (DCIS), lobular carcinoma in situ, atypical lobular hyperplasia, and atypical ductal hyperplasia, respectively[18] (Fig. 1). Breast cytology is also an area of active investigation, where small but promising studies have shown high performant models in detection of breast carcinoma.[19–22] In addition to detection, machine learning models have also been developed to segment breast pathology of interest.[10,23] Segmentation involves highlighting the specific pixels of interest for a given label (eg, ductal carcinoma in situ). Investigators have also tried to replicate machine learning models similar to how pathologists typically evaluate histopathology slides, training multimagnification neural networks to detect and segment various breast tissue compartments including carcinoma, necrosis, adipose tissue, stroma, and benign breast parenchyma.[23] These tools offer an unprecedented opportunity for quality assurance, where pathologists can now be aided in using detection systems as a second read, or virtual consult for all patients. This level of detection can provide a paradigm shift in patient safety without increasing pathologists' workloads, and no substantial delay on turnaround time compared with current practices, where secondary pathologist review for every patient in the existing analog workflow is currently time prohibitive and increases the pathologist's workload. For decision support tools that may detect the presence of carcinoma, these systems can provide supportive workflows for pathologists, especially for breast specimens with small volume of disease. Overall, using machine learning–based systems for detection of clinically meaningful lesions in breast pathology is equivalent to promoting significant patient safety measures, without increasing turnaround time or case workload.

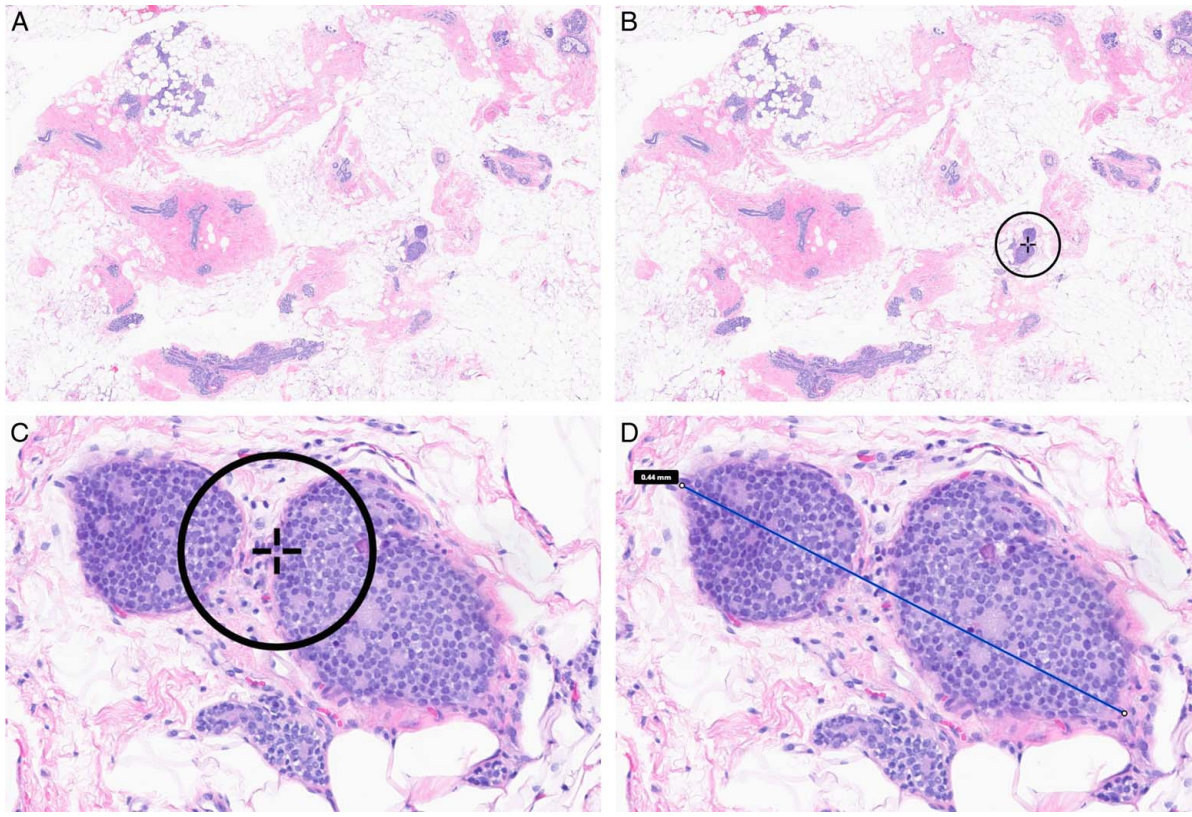

FIGURE 1. Representative breast detection of atypical ductal hyperplasia on whole slide image. Visualization of machine learning model trained to detect lesions in breast pathology. A, Low magnification image of hematoxylin and eosin slide with atypical ductal hyperplasia (ADH); B, Low magnification image of hematoxylin and eosin slide showing ADH detection by machine learning model with crosshair visualization; C, High magnification image of hematoxylin and eosin slide with ADH detection by machine learning model with crosshair visualization; D, with ruler measurement.

Classification

Accurate classification of breast lesions is paramount to ensuring appropriate patient management, especially during breast screening applications. Instead of binary detection models, many clinical applications in breast pathology use classification systems. These systems can learn to identify specific features and patterns associated with different subtypes of breast cancer. Decision support systems that provide classifications of lesions in breast pathology have been shown to determine the histologic subtype, nuclear grade, presence of mitoses, tumor grade, and analyze the tumor microenvironment.

Based on the previously published work of the BreakHis dataset, He et al[24] showed high performance in classifying adenopathy, fibroadenoma, tubular adenoma, phyllodes tumor, invasive ductal carcinoma, invasive lobular carcinoma, mucinous carcinoma, and papillary carcinoma. Mercan et al[25] showed the development of a computer vision method to classify benign, atypical, in situ, and invasive breast lesions with moderate to high performance, with highest classification performance of discriminating between atypical hyperplasia and DCIS, compared with pathologists. Although most of the published literature documents research work not implemented in clinical practice yet, a recent clinical validation of a breast classification model showed high performance with area under the AUC ranging from 0.92 to 0.99 in discriminating between atypical ductal hyperplasia versus ductal carcinoma in situ, and detection of ductal carcinoma in situ and invasive ductal carcinoma, respectively.[26]

In addition, subtyping of breast lesions is important to provide clinical context and appropriate morphologic assessment. Sandbank et al[26] reported distinguishing between invasive ductal and lobular carcinoma with an AUC of 0.97. Pathologists also routinely grade carcinoma present in breast specimens, where automated classification can support pathologist workflows. Grading of invasive carcinoma is based on the degree of nuclear atypia, tubule formation, and mitotic score, while DCIS is graded based only on nuclear atypia. Machine learning models to support grading of breast cancer have shown "pathologist-level" performance for the classification of nuclear grade.[27–31] Mercan et al[27] hypothesized grading nuclear atypia as a continuous variable instead of the traditional stepwise grading as low, intermediate, and high-grade nuclear score, and the developed model showed, on average, the highest agreement out of 10 pathologists. Other investigators have reported the development of machine learning models to support pathologists grading of breast cancer.[28,32,33] The accurate assessment of mitotic count, however, is most challenging, as cell debris and poor nuclear detail may mimic the dense chromatin of dividing cells.[34]

Multiclass models have also been shown to evaluate the tumor microenvironment by classifying immune cells, tumor cells, and their respective relationships. A machine learning

system developed to classify nuclei in a hematoxylin and eosin (H&E) image into lymphocytes, tumor cells, or fibroblasts reported a high Spearman correlation ($R = 0.73$) for computer-assisted tumor-infiltrating lymphocytes (TILs) compared with pathologist consensus, greater than the reported interpathologist correlation ($R = 0.66$).[35] Zhang et al[36] reported accuracies of up to 0.90 and 0.80 for lymphocyte detection and segmentation, respectively. In a dataset of intermediate to high-grade DCIS compared with DCIS with adjacent invasive carcinoma, the pure DCIS cases had more TILs compared with DCIS with adjacent invasive carcinoma. In addition, colocalization of TILs with DCIS was higher in DCIS with adjacent invasive carcinoma, suggesting that the microenvironment associated with breast ducts with DCIS is more inflamed than the microenvironment associated with invasive carcinoma.[37] This technology has the potential to automate the analysis of morphology and immune ecology of breast lesions. Whereby, this information can aid pathologists in accurately classifying tumors, providing valuable insights for treatment planning and prognostic assessment.

Quantification

Many routine tasks in breast pathology require semi-quantification. Machine learning systems may be best suited to quantify various findings and support pathologists' workflows. Breast biomarkers can be quantified manually or using computer-assisted image analysis tools (Fig. 2). Many image analysis systems have received Food and Drug Administration for several immunohistochemical stains [eg, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki-67, programmed death-ligand 1 (PD-L1)][38] (Table 1). In this setting, pathologists identify regions of interest using the software systems, then the image analysis software computes the positive to negative tumor cell ratios and provides a digital visualization to the pathologist who can review it and approve if he/she deems it correct. Sequential "Zero-click" models are now available that can identify the tumor areas on a given slide and use the same area for quantification of tumor cell expression of a given protein detected with immunohistochemical stain. Computer-assisted quantification of breast biomarkers with image analysis software demonstrated noninferior performance to the current standard of care.[39] All digital image analysis methods outperformed manual quantification concordance and Cohen κ agreement when compared with the PAM50 gene expression assays. Quantification of staining in tumor cells intensity and completeness of circumferential membranous staining of HER2 is also documented.[40] The College of American Pathologists published validation guidelines for digital quantitative image analysis of HER2 to support pathologist validation efforts using these tools[41] (Fig. 3). Brightfield chromogenic, and darkfield fluorescent in situ hybridization probe quantification is also possible and has been reported to show high concordance with manual quantification.[42–48] Quantification of mitotic figures based on overall high-power field tissue areas is another possible application of digital technologies. Transitioning from a circular field of view in a brightfield microscope to a digital workflow with

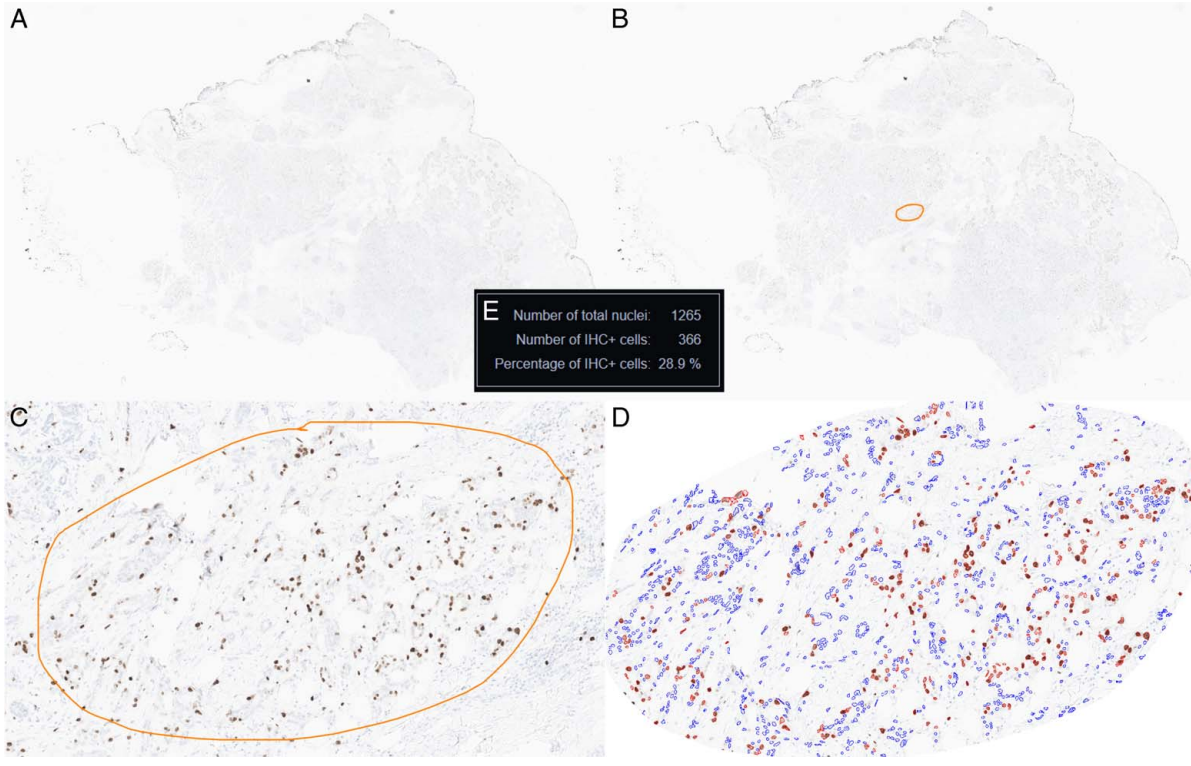

FIGURE 2. Computer aided quantification of immunohistochemical nuclear stains. A, Digital image of Ki-67 immunohistochemical stain showing whole slide image and; B, pathologist annotated region of interest; C, x 20 magnification of Ki-67 immunohistochemical stain with D, corresponding segmentation of the nuclear quantification image analysis tool; E, Cell count quantification by image analysis tool. Please see this image in color online.

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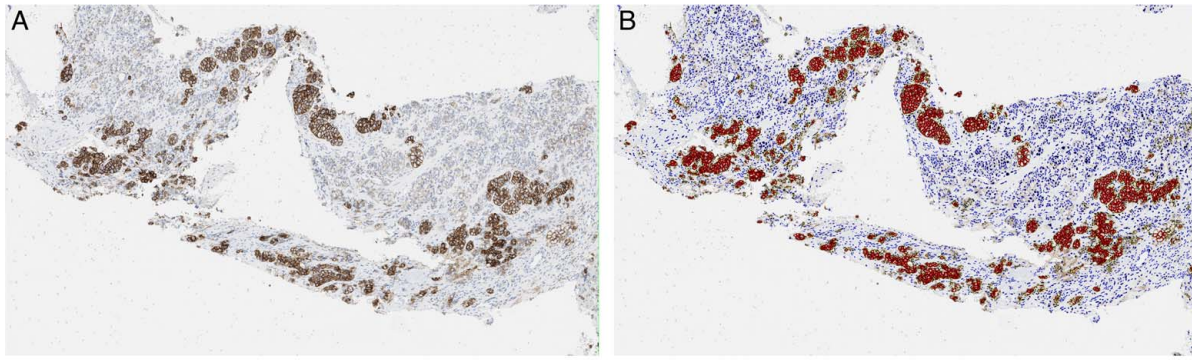
TABLE 1. Commercially Available Image Analysis Tools for Breast Biomarker Quantification

Biomarker	Company (alphabetical)	Product	Regulatory status/510K if US cleared
ER	Aperio Technologies (Leica)	Scanscope XT System	K073677
	Aperio Technologies (Leica)	Aperio ePathology eIHC IVD System (Scanscope CS, AT Turbo)	K141109
	Applied Imaging Corp.	Applied Imaging Arial	K033200
	Applied Spectral Imaging Ltd	Genasis HiPath IHC Family	K140957
	Cell Analysis Inc.	QCA (Version 3.1)	K031363
	Chromavision Medical Systems Inc.	Automated Cellular Imaging System (ACIS)	K012138
	Tripath Imaging Inc.	Ventana Image Analysis System (VIAS)	K050012
	Ventana Medical Systems Inc.	Virtuoso System for IHC (iScan Corea scanner)	K130515, K140465
	Mindpeak	Mindpeak Breast ER/PR	RUO
	Visiopharm	ER, Breast Cancer, AI	RUO
	aiforia	Clinical AI Model for Breast Cancer: ER	RUO
	Panakeia	PANProfiler	RUO
PR	Applied Imaging Corp.	Applied Imaging Arial™	K033200
	Aperio Technologies (Leica)	Scanscope XT System	K073677, K080254
	Aperio Technologies (Leica)	Aperio ePathology elHC IVD System (Scanscope CS, AT Turbo)	K141109
	Applied Spectral Imaging Ltd	Genasis HiPath IHC Family	K140957
	Tripath Imaging Inc.	Ventana Image Analysis System (VIAS)	K050012
	Ventana Medical Systems Inc.	Virtuoso System for IHC (iScan Corea)	K111869, K122143
	Ventana Medical Systems Inc.	Virtuoso System for IHC (iScan HT)	K142965
	Mindpeak	Mindpeak Breast ER/PR	RUO
	Visiopharm	PR, Breast Cancer, AI	RUO
	aiforia	Clinical AI Model for Breast Cancer: PR	RUO
HER2	Applied Imaging Corp.	Applied Imaging Arial	K031715
	Aperio Technologies (Leica)	Scanscope XT System	K071128, K071671, K080564
	Aperio Technologies (Leica)	Aperio ePathology eIHC IVD System (Scanscope CS, AT Turbo)	K141109
	Applied Spectral Imaging Ltd	Genasis HiPath IHC Family	K140957
	Bioimagene Inc. (Roche)	Pathiam Imaging Software	K062756
	Bioimagene Inc. (Ventana)	Pathiam System (iScan scanner)	K080910
	Chromavision Medical Systems Inc.	Automated Cellular Imaging System (ACIS)	K032113
	Chromavision Medical Systems Inc.	Automated Cellular Imaging System (ACIS)	K012138
	Olympus America Inc.	Virtual Slide System Olympus VS800 System	K111914
	Omnyx LLC	Omnyx IDP (VL4 scanner)	K131140
	Philips Medical Systems	Philips Herceptest Digital Score (UFS scanner)	K130021
	Tripath Imaging Inc.	Ventana Image Analysis System (VIAS)	K051282
	Ventana Medical Systems Inc.	Virtuoso System for IHC (iScan Corea scanner)	K111543, K121516
	Mindpeak	Mindpeak Breast HER2	RUO
	Visiopharm	HER2, Breast Cancer	RUO
	Visiopharm	HER2-FISH, Breast Cancer	RUO
	Visiopharm	HER2-SISH, Breast Cancer	RUO
	Visiopharm	HER2-CISH, Breast Cancer	RUO
Ki-67	Applied Spectral Imaging Ltd.	Genasis HiPath IHC Family	K140957
	Bioimagene Inc. (Ventana)	Pathiam Imaging System (iScan scanner)	K092333
	Tripath Imaging Inc.	Ventana Image Analysis System (VIAS)	K053520, K061613
	Ventana Medical Systems Inc.	Virtuoso System for IHC (iScan Corea scanner)	K111755, K121033
	Mindpeak	Mindpeak Breast Ki-67	RUO
	Visiopharm	Ki-67, Breast Cancer, AI	RUO
	Aiforia	Clinical AI Model for Breast Cancer: Ki-67	RUO
p53	Bioimagene Inc. (Ventana)	Pathiam System (iScan scanner)	K092333
	Tripath Imaging Inc.	Ventana Image Analysis System (VIAS)	K062428
	Ventana Medical Systems Inc.	Virtuoso System for IHC (iScan Corea scanner)	K111872, K121350

ER indicates estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

rectangular displays requires new methods for quantification as a digital high-power field may not be equivalent to a microscopic high-power field on a brightfield microscope.[49] Novel methods may automate quantification in ways where current standards may no longer be applicable in a digital workflow (ie, automated mitotic figure quantification and ratio of mitoses per tissue area or per number of tumor cells).[50] Mitotic figures can be subjective in analog detection workflows for pathologists.[51] Computational methodologies support screening and quantification of mitotic figures with high interrater κ coefficients. Grand challenges have been organized to provide public datasets for organizations to use and train machine learning–based models, including for mitotic figure detection.[52] Tellez et al[53] used phosphohistone-H3 immunohistochemical stains, a mitotic figure-specific marker, to train a neural network model for the quantification of mitoses. The authors reported an average κ correlation of 0.72 between manual and automated counting



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Attribute	Value
Her2 Score	3.
(3+) Percent Cells	21.24
(2+) Percent Cells	0.6155
(1+) Percent Cells	16.98
(0+) Percent Cells	61.16
Percent Complete	21.86
Membrane Intensity (Average)	74.94
(3+) Cells	2692
(2+) Cells	78
(1+) Cells	2152
(0+) Cells	7750
Cells (Total)	12672
Complete Cells	2770

FIGURE 3. Computer aided quantification of immunohistochemical membranous stains. A, Digital image of HER2 immunohistochemical stain showing whole slide image with heterogenous HER2 staining and; B, corresponding segmentation and classification of the membranous staining quantification by the image analysis tool; C, Cell count quantification by image analysis tool. Please see this image in color online.

on predefined hotspots with an F1 score of 0.65.[53,54] The study concluded that counting mitoses in a digital format is achievable with sufficient resolution on the whole slide images, and furthermore, that semiautomated quantification using a machine learning model is feasible without introducing significant bias or variability. By automating these quantification tasks, AI can reduce interobserver variability and provide consistent and reliable measurements, ensuring more accurate staging and treatment decisions.

Standardization

AI can contribute to standardizing breast pathology practices by minimizing interobserver variability and improving consistency in diagnosis. Pathologists may have variations in interpreting challenging or borderline diagnoses.[55] Machine learning–based systems can predict patterns from expert annotations and historical data to establish standardized criteria for diagnosis, reducing discrepancies and enhancing the overall quality of breast pathology assessments. This standardization can lead to improved patient outcomes and more reliable comparisons in research studies. Furthermore, in all the considered areas of detection, classification, and quantification—these decision support tools provide newfound methodologies for standardization across the practice of breast pathology. In a world where computer-aided diagnostic systems provide augmented assistance in the detection, classification, and quantification of breast pathology, evidence adopted from other decision support tools in pathology suggests improved interpathologist agreement related to tumor grading.[56] Further monitoring is needed to ensure the performance of the pathologist does not converge with the performance of the decision support system, however, for diagnostic challenges with conventionally high interobserver variability, these tools may promote an increase in pathologist agreement. Pathologists are still required to verify and validate machine learning–based systems before patient testing, and this analysis will determine the performance characteristics across the model's intended use. Standardization and quality assurance are improved through established workflows, automated quality control measures, and structured reporting templates offered by digital pathology platforms. These advances promote interobserver agreement, reduce errors, and contribute to overall quality improvement in breast pathology.

AI Priority	Accession	Patient	Specimen	Pathologist
High Invasive carcinoma	S001	A, A	Breast, biopsy	Brogi
Low Benign breast tissue	S002	B, B	Breast, mammoplasty	Hanna
High Metastatic carcinoma	S003	C, C	Axilla, Lymph node biopsy	Hanna
Medium Fibroadenoma	S004	D, D	Breast, lumpectomy	Brogi
Low Fibrocystic changes	S005	E, E	Breast, biopsy	Brogi

FIGURE 4. Pathology triage workflow in patient case management worklist. Clinical digital worklist showing patient case level predictions based on machine learning models computed on whole slide images of patient cases. Please see this image in color online.

PRODUCTIVITY

Pathologists using digital workflows and decision support tools have the foundation to enable productivity gains based on various practices. Digital transformation of pathology includes use of digital workflows where pathologists are

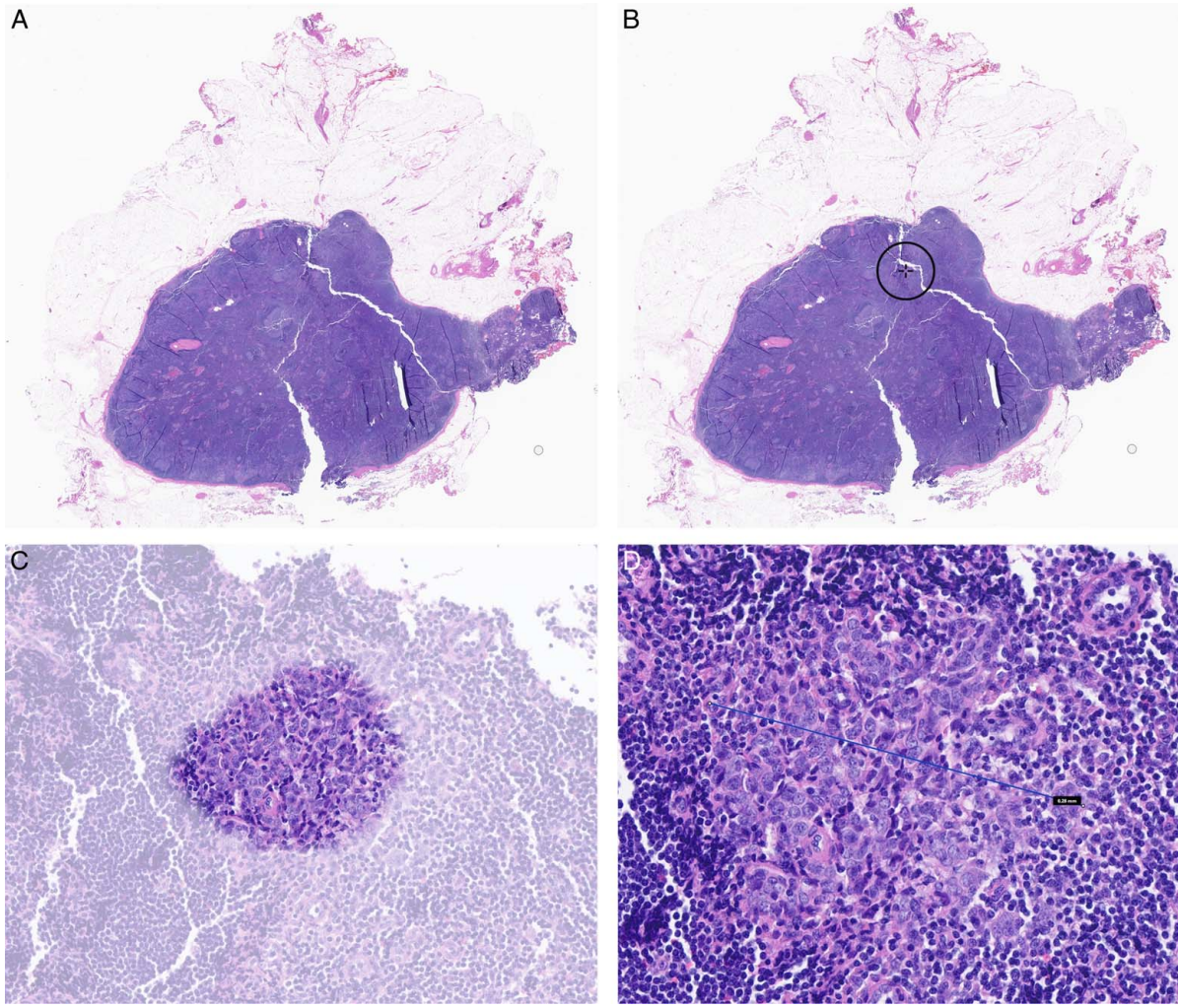

FIGURE 5. Representative metastatic breast carcinoma detection of micrometastasis on whole slide image. Visualization of machine learning model trained to detect metastatic breast cancer in lymph node tissue. A, Low magnification image of hematoxylin and eosin stained lymph node tissue; B, Low magnification image of hematoxylin and eosin stained lymph node tissue showing detection by machine learning model with crosshair visualization; C, High magnification image of hematoxylin and eosin slide with metastatic carcinoma detection by machine learning model with opacity visualization; D, with ruler measurement. Please see this image in color online.

using computer monitors and input devices to navigate digital slides akin to glass slides on a microscope. Pathologists using high-resolution monitors can review more tissue in a given field of view compared with standard-definition monitors.[49,57] Digital workflows also provide the capabilities of digital worklists enabled to provide relevant data for patient triage (Fig. 4). Having the appropriate metadata available to the pathologist can prioritize patients based on breast surgery postoperative appointments or machine learning outputs (eg, invasive carcinoma detection). Pathologists can use this information to more appropriately review their patient case assignments, as well as order breast biomarkers sooner compared with conventional workflows.[26]

Use of machine learning systems for screening and diagnostic review are available for narrow tasks in breast pathology. Machine learning–based systems are available to detect clinically meaningful breast lesions (eg, atypia, in situ, and invasive carcinoma). Furthermore, certain systems also provide visualization of microcalcifications and metastatic carcinoma to lymph nodes. Sandbank et al[26] also shows classification of microcalcifications, which can be clinically useful for screening of stereotactic breast biopsies. Time to detection of microcalcifications can be delayed if calcifications are focal, or if deeper tissue sections are needed to evaluate and compare calcifications on the specimen radiograph. Automated screening systems such as detection and visualization of microcalcifications could enable pathologists reviewing breast specimens targeted for calcifications an optimized workflow. Regarding automated detection of mitotic figures, Pantanowitz et al[58] published an average of 27.8% increase in efficiency to detecting mitotic figures when using computer-aided workflow compared with glass slide review. Other screening tasks include detection of small foci of tumor, or tumor metastases in axillary lymph nodes[59–64] (Fig. 5). One study describes improvement in time to detect micrometastases up to 48%.[65] Detection systems identifying metastatic carcinoma should be properly evaluated to ensure appropriate performance in various subgroups such

as patients who received neoadjuvant chemotherapy, carcinoma subtype (ductal vs. lobular), and small tumor burden in the lymph nodes (eg, isolated tumor cells).[61] Intraoperative consultations or frozen sections are another area where decision support systems could be implemented for decreasing turnaround time to reporting of sentinel lymph nodes in breast pathology, or margin assessment. In addition, semi or automated breast cancer grading could help decrease a portion of the time to appropriately grade carcinoma. Similar productivity can be demonstrated for breast biomarker quantification.

As these machine learning–based systems are being trained on large, high-quality datasets, the potential for democratization of pathology expert knowledge can also expand global outreach. Patients and pathologists in rural areas or in resource-restricted countries can benefit from a virtual pathology consult from a machine learning model trained using expert-level data. The combined pathologist workforce limitations could be alleviated by potential productivity improvements.[66,67] The current pathology consultation process requires shipment of glass slides and is reliant on courier transportation. Several manual tasks as well as the risk of glass slide damage would be alleviated by the immediate transmission of digital slides.

DISCOVERY

Machine learning systems have the potential to provide novel diagnostic and prognostic predictions for patients with breast disease. These systems may also use nonpathology metadata (eg, demographics, survival, comorbidities, radiology) for prognostic outputs, to combine additional covariates for quality training data. Breast cancers are associated with genetic aberrations and require biomarker testing (eg, ER, PR, and HER2). Furthermore, as novel computational biomarkers become available, training data including hormone receptor status or molecular status has been researched to be respectively predicted. In some instances, machine learning–based systems could be used in screening applications with high negative predictive value to rule out the possibility of a given mutation and avoid the need for unnecessary molecular testing. Alternatively, machine learning–based systems with positive predictive values approaching 100% may be used as a replacement for molecular tests or hormone receptor status prediction. Machine learning systems have been shown to predict breast biomarker status, molecular classification, and recurrence risk based on the morphology present in the H&E whole slide image alone.[31] Shamai et al[68] also developed a deep learning model that predicted ER expression solely from H&E-stained breast pathology images with noninferior accuracy to standard immunohistochemical studies. Similar principles have been used to predict HER2 status from tumor morphology on H&E digital slides.[69,70] Tests using machine learning must be extensively validated for such results, as the performance for a test with treatment management decision implications remains quite high. In the early testing phases, it may be prudent to use machine learning decision support systems as an adjunct to molecular testing to validate their performance.

The ideal biomarker in pathology should correlate to patient outcomes. Some existing genomic tests provide results that estimate response to therapy and other outcomes in patients with ER-positive breast cancer.[71–74] Investigators demonstrated independent risk prediction using morphologic features on H&E digital images (eg, nuclear shape, texture, and architecture) to assess predicted risk of recurrence and overall survival in patients with ER-positive breast cancers with accuracies ranging from 75% to 86%.[75–77] BCR-Net, a machine learning network recently developed to predict breast cancer recurrence from histopathology images achieved an overall AUC of 0.775 using H&E digital slides.[78] Image-based Risk Score (IbRiS), a machine learning model using breast pathology whole slide images, was developed to serve as an alternative to genomic testing and demonstrated a mean accuracy of 84% in distinguishing low-risk from high-risk patients.[79,80] In addition, computational biomarkers measuring the spatial arrangement and architecture of breast tissue elements such as TILs within the tumor have been described to predict patient survival and recurrence risk.[81,82]

For future discovery of machine learning–based systems in breast pathology, one of the highest potentials for scientific breakthroughs involves uncovering features in the breast pathology data that have yet to be described. Breast pathology has been thoroughly defined by morphologic features, graded by differentiation, and well-documented staging criteria. However, computational biomarkers may discern patterns in breast pathology data that have yet to be discovered. For instance, breast carcinoma nuclear orientation and intensity patterns (eg, consistency of nuclear intensity vs. diversity of nuclear intensity) was shown to provide prognostic importance.[83,84] Some described features may be synonymous with what is described in pathology textbooks, such as the maximal blue pixel value for atypical nuclei being akin to hyperchromasia, a hallmark of neoplasia, however, the ability to quantify these foundational tenants of disease is critical to transforming the field of breast pathology.

The fundamental principle of training machine learning models using breast pathology whole slide images to predict patient outcomes was well demonstrated. Wulczyn et al,[85] developed a deep learning system in conjunction with clinical metadata to predict low, medium, and high risk in relation to survival probability for various malignancies, including breast cancer. The integration of multimodal data in machine learning can provide several benefits in the field of breast pathology and its advancement. Multimodal data refers to a combination of data obtained with different techniques, such as histopathology whole slide images, clinical data, radiology, or genomic data. Training of machine learning systems on multimodal data can improve the accuracy of breast cancer diagnosis and classification. Integrating whole slide images and DNA sequencing data of the same tissue can provide a more comprehensive understanding of the disease, allowing for more precise subtyping of breast tumors. Multimodal datasets can be used to develop predictive models that can assist in prognosis and treatment decisions and better predict patient outcomes, such as survival rates or response to specific treatments. In a recent article by The Mahmood Lab, coupling histopathology and genomic information was superior to either alone.[86] In another study, multimodal data including patient clinical data, and pathologic (ER status, HER2 status, Nottingham grade, tumor size, and nodal status), molecular and staging features of the carcinoma, was used to train a machine learning model to predict the response to neoadjuvant chemotherapy with the best-performing model demonstrating an AUC of 0.88.[87] These models can contribute to the development of personalized medicine for

breast cancer patients, especially for patients with a family history of breast cancer or BRCA germline mutation carriers.[88]

The integration of pathology imaging and clinical data with biomarker and molecular testing techniques allows for the correlation of histopathological features with molecular data, enabling personalized treatment decisions and prognostication. Furthermore, the accumulation of large-scale pathology datasets paves the way for big data analytics, facilitating research into breast cancer etiology, biomarker discovery, and therapeutic targets.

LIMITATIONS AND ERRORS

The application of machine learning models to breast pathology has limitations and potential sources of error. The available training data are limited, as acquiring large, high-quality annotated datasets can be challenging. The use of large well-annotated datasets may also lead to poor performance and lack of generalizability when applying a machine learning model to other patient data. Breast detection models trained on curated datasets may not be generalizable to real-world data with a range of preanalytic artifacts due to air bubbles, tissue folds, ink markings, fingerprints, etc.[89] In addition, evidence in other areas of pathology and machine learning show biased training data can lead to inaccurate predictions and perpetuate biases in the decision support system.[90–93] If the training data contains a disproportionate representation of patient demographics or specific types of breast lesions, the model may show poor performance and lower accuracy in underrepresented diagnoses. For instance, a decision support tool trained using a set with an overrepresentation of invasive ductal carcinomas may not perform as well in detecting invasive lobular carcinoma or rare breast cancer subtypes (eg, adenoid cystic carcinoma). Furthermore, the intended use of the model is critical to be aware of. If only carcinomas were used in the training data, and other diagnoses of interest are not represented, the model may not recognize other clinically meaningful entities (eg, malignant phyllodes tumors). Model explainability is also important to allow increased trust and confidence in the system. Visualizations such as heatmaps can allow pathologists to better understand the model's predictions. Proper validation is required before implementing any decision support tool in clinical practice. As these tools become increasingly available and are adopted, continued research to qualify and avert these limitations is needed to improve the performance and reliability of machine learning models in breast pathology.

Errors in machine learning may occur in an imaging workflow based on challenges surrounding generalizability across different training, tuning, and evaluation datasets. Lack of generalizability may occur across changes in image properties, whole slide scanners, and image analysis software. Pantanowitz et al[94] expanded on the limits of serially changing a single image's brightness, contrast, blur, and compression of an image of invasive ductal carcinoma, HER2-positive immunohistochemical stain. By serially changing the image properties of the same image, the same image analysis software output was effected, changing from 0 to 3+, and vice versa. While some of these changes may not correlate with real scenarios in routine practice, they help understand how changes in image properties may affect image analysis and machine learning decision support systems aiding to evaluate breast pathology. In addition, staining protocols and scanner variability may also introduce bias into patient's digital slides. Leo et al[95] introduced a preparation-induced instability score that evaluates similarities between preanalytic slide generations, and a latent instability score, to quantify feature instability across and within datasets. One of the hopes for machine learning in pathology is to support the quantification of immunohistochemical stains, however, Combrinck et al analyzed ER, PR, HER2, and Ki-67 immunohistochemical staining of the same 20 tissue samples across 2 different image analysis software. Half of the ER results showed results with discrepancies over 20% between the 2 image analysis software, and Ki-67 results showed discrepancies over 20% in 60% of the samples.[96]

FUTURE CONSIDERATIONS

Breast pathology has evolved as new technologies have become available. Many of these advancements came with the advent of the light microscope, followed by immunohistochemical staining, and then molecular testing. Adoption of decision support tools using machine learning–based systems will supply pathologists with capabilities that are not available in an analog workflow. Natural language processing (NLP) techniques have provided solutions for text extraction and generation. Other future technologies that constitute an innovative area of digital imaging include multispectral imaging and multiphoton microscopy.

NATURAL LANGUAGE PROCESSING

NLP is a wide-encompassing field of techniques and methodologies aimed at enabling computers to interact with and understand human language (eg, language understanding, semantics, and syntax, sentiment analysis, machine translation, and text summarization). Recently, large language models (LLM) built using NLP and deep learning techniques, have become popularized and are developed within the NLP framework to enhance text generation capabilities. NLP has been used to extract information from pathology reports and other enterprise information systems (ie, electronic medical records, and laboratory information systems), but also has capabilities to summarize, translate, or generate data based on pathology reports or other patient clinical metadata. For example, CancerBERT, a cancer-related corpus of breast cancer patients was trained to extract cancer phenotypes from clinical notes and pathology reports, which achieved up to an F1 score of 0.9.[97] Buckley et al[98] demonstrated an NLP system to extract clinical data from pathology reports, with sensitivity and specificity of 99.1% and 96.5%, respectively when compared with expert human coders. NLP systems were also developed to be used as a clinical decision support system for radiology-pathology correlation when comparing mammographic imaging features and breast cancer subtype.[99] LLM have also been used to evaluate the performance of ChatGPT as a clinical decision support tool in patient management of breast tumor board decisions. One study showed the LLM provided similar clinical recommendations with those of the tumor board members in 70% of cases.[100] These technologies will continue to mature and evolve how breast pathology is practiced by facilitating data collection for research and providing newfound methods for pathology education to practitioners and patients.

Multispectral imaging (eg, multiplex microscopy) enables the characterization of breast tissue beyond the

traditional H&E stain. By detecting and quantifying multiple biomarkers in a single tissue sample, pathologists can gain deeper insights into cellular heterogeneity, tumor microenvironment interactions, and varying permutations of biomarker profiles of disease of the breast. These techniques allow for simultaneously assessing multiple biomarkers on the same specimen and can be further quantified.[101,102] With digitized images, evaluating breast tissue with varying antibodies on a single specimen enables discovery of patient prognostication based on cellular profiles and spatial arrangement. Hou et al[103] analyzed breast tissue with multiplex immunohistochemistry and found all patients with intratumoral $CD8^+$ cells without PD-L1 expression achieved pathologic complete response. In addition, multivariate analysis showed that PR negativity and HER2/chromosome 17 centromere ratio were significantly associated with pathologic complete response. These novel cellular profiling and imaging methods have emerged as powerful tools for analyzing breast tissue. They enable simultaneous assessment of multiple biomarkers, preservation of spatial context, and digital image analysis, introducing new avenues for diagnostic, research, and educational applications in breast pathology.

Nondestructive direct imaging of breast tissue, such as multiphoton microscopy, can generate high-resolution images of breast tissue structures and cellular features without the need for conventional histology laboratory processing and staining. These advanced imaging modalities use nonlinear optical techniques to generate images at cellular and subcellular levels, including tubules, nuclei, and mitoses, which can aid in the assessment of tumor biology and prognosis. One significant advantage of multiphoton microscopy is its ability to provide almost real-time evaluation of breast tissue specimens. This technology is nondestructive allowing pathologists the ability to examine the tissue while preserving its integrity and allowing use of it for downstream biomarker or molecular testing.[104–108] Li et al[109] conducted a study to analyze the efficacy of multiphoton microscopy in detecting changes in breast cancer to the response of neoadjuvant chemotherapy. Using image analysis the authors report significant differences in the cell nucleus area and content of collagen fibers between the neoadjuvant and posttreatment breast carcinoma tissues. The investigators also demonstrated visualization of lymphovascular invasion using multiphoton microscopy.[110] In diagnostic evaluation of breast tissue, multiphoton microscopy was shown to have accuracies ranging from of 87.5% to 94% in rendering a breast pathology diagnosis from multiphoton images.[111,112] These techniques generate images of the tissue in a relatively short time (eg, seconds to minutes) and would be amenable to intraoperative consultation workflows, and could contribute to identify suspicious foci and expedite the evaluation and reporting of margin or sentinel lymph node status in the context of intraoperative frozen section workflows.[108] Furthermore, multiphoton microscopy can be combined with other imaging modalities and molecular testing to enhance its diagnostic capabilities. It can be integrated with fluorescence imaging techniques to visualize specific molecular targets within breast tissue, such as tumor biomarkers or fluorescently labeled antibodies. This approach enables comprehensive and detailed characterization of breast lesions at both the cellular and molecular levels. These novel imaging technologies can be also combined with machine learning systems to enhance the accuracy of pathologists using these tools.

Despite its potential, there are substantial limitations to the application of multiphoton microscopy in breast pathology, as it requires specialized equipment and expertise to perform the imaging and analyze the complex datasets generated. The imaging data also require significant digital storage, orders of magnitude larger than whole slide images. These requirements may limit the widespread adoption of multiphoton microscopy in routine clinical practice. In addition, the imaging depth is relatively shallow, typically limited to a few hundred micrometers, which may restrict the visualization of deeper tissue structures. While direct breast tissue imaging using multiphoton microscopy offers exciting prospects for improving the understanding and diagnosis of breast pathologies, the ongoing research will need to be clinically realized.

CONCLUSIONS

The future of breast pathology lies in the hands of pathologists to properly implement and validate these emerging technologies. Digital and computational pathology tools complement existing pathology workflows and provide a means to enhance the diagnostic and prognostication of patients. However, their implementation necessitates careful validation, regulatory compliance, and ongoing training of pathologists. Using such tools, pathologists have the potential to enhance diagnostic accuracy, enable personalized medicine, and drive research to advance our current understanding of breast pathology. With any new technology, continued research, proper validation, and collaboration among pathologists, technologists, and researchers will be instrumental in realizing the full potential of digital and computational pathology systems in breast pathology practice. Embracing these novel technologies as complementary tools that can augment the expertise of pathologists and enhance their critical role in diagnosis and patient care is fundamental to the evolving practice of pathology.

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