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Advances in Breast Cancer Care: The Role of Artificial Intelligence and Digital Pathology in Precision Medicine

Ayşe Hümeyra Dur Karasayar[1,2], İbrahim Kulaç[1,3,4,5], Nilgün Kapucuoğlu[5]

[1]Graduate School of Health Sciences, Koç University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Pathology, Başakşehir Çam and Sakura Hospital, İstanbul, Türkiye
[3]Koç University & İş Bank Artificial Intelligence Center, Koç University, İstanbul, Türkiye
[4]Research Center for Translational Medicine, Koç University, İstanbul, Türkiye
[5]Department of Pathology, Koç University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Artificial intelligence (AI) and digital pathology are transforming breast cancer management by addressing the limitations inherent in traditional histopathological methods. The application of machine learning algorithms has enhanced the ability of AI systems to classify breast cancer subtypes, grade tumors, and quantify key biomarkers, thereby improving diagnostic accuracy and prognostic precision. Furthermore, AI-powered image analysis has demonstrated superiority in detecting lymph node metastases, contributing to more precise staging, treatment planning, and reduced evaluation time. The ability of AI to predict molecular markers, including human epidermal growth factor receptor 2 status, *BRCA* mutations and homologus recombination deficiency, offers substantial potential for the development of personalized treatment strategies. A collaborative approach between pathologists and AI systems is essential to fully harness the potential of this technology. Although AI provides automation and objective analysis, human expertise remains indispensable for the interpretation of results and clinical decision-making. This partnership is anticipated to transform breast cancer care by enhancing patient outcomes and optimizing treatment approaches.

Keywords: Artificial intelligence; breast cancer; pathology; AI

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Key Points

- Artificial intelligence (AI) can assist pathologists in enhancing the precision of molecular assessments in breast cancer, while also reducing the time required for evaluation.
- AI has the potential to predict key molecular markers, including HER2 status, BRCA mutations, and homologous recombination deficiency, directly from Hematoxylin & Eosin (H&E) slides.
- AI is best utilized as a complementary tool, working in tandem with pathologists to optimize the diagnostic workflow and ensure the most accurate and timely care for patients.

Introduction

Breast cancer is one of the most prevalent and challenging diseases in the field of oncology. Given the diverse subtypes and variable responses to treatment, accurate diagnosis, prognosis, and prediction of treatment outcomes are vital for effective management. Microscopic examination, though reliable, is subject to known limitations, including intra- and inter-observer variability. In the era of artificial intelligence (AI), machine learning (ML) and deep learning (DL) algorithms enhance the ability of histopathologists to make more accurate and reproducible diagnoses. These technologies offer a plethora of advances, such as interpreting complex patterns in breast cancer histology, streamlining time-consuming tasks like lymph node metastasis detection, or scoring predictive immunohistocemical biomarkers faster and in a more accurate way, ultimately leading to better patient outcomes and more personalized treatment plans.

AI, encompassing ML and DL techniques, offers robust tools for analyzing complex datasets and uncovering patterns that may be imperceptible to humans. In breast cancer care, AI applications can aid in tasks ranging from automating histopathological analysis to predicting treatment outcomes. The emergence of biomarkers evaluable through immunohistochemistry (IHC) and the inclusion of parameters, such as tumor infiltrating lymphocyte (TIL) percentage and treatment effects in synoptic reports have rendered the reporting process for breast cancer increasingly detailed and labor-intensive (1, 2). The evaluation of these parameters, however, is relatively subjective,

Corresponding Author:
Nilgün Kapucuoğlu MD; kapucuoglun@gmail.com

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necessitating the development of more standardized methods and the use of objective tools to ensure consistency and reliability in reporting.

By addressing the need for reproducibility and leveraging the vast datasets generated from histological slides, AI can augment the capabilities of histopathologists and oncologists, leading to enhanced accuracy and efficiency in breast cancer management.

The aim of this review was to provide a comprehensive overview of the current state of AI in breast pathological analysis with its diagnostic, prognostic, and predictive aspects. The techniques employed, the clinical implications, and the challenges that need to be addressed for broader implementation will all be addressed in the following article.

Breast Cancer Detection and Classification

The accurate classification of breast cancer is critical, as each subtype responds differently to treatment protocols. Misclassification can lead to suboptimal treatment decisions and compromised patient outcomes. To address this challenge, a comprehensive evaluation of morphological, IHC, and molecular features is essential. These tools hold the potential to significantly reduce time required for diagnosis while increasing accuracy, allowing for quicker therapeutic decisions and high concordance (3-6). The emergence of AI in the field of breast cancer classification marks a significant departure from conventional diagnostics, making a more nuanced and comprehensive analysis of tumors possible for future discoveries.Among notable contributions to this field, Cruz-Roa et al. (5) and Fondón et al. (6) have demonstated the potential of AI in detecting invasive ductal carcinoma within the surrounding breast parenchyma. Studies such as those by Yamamoto et al. (3), Han et al. (4) and Sharma and Mehra (7) have shown how DL models can classify breast cancer with remarkable accuracy. Han et al. (4) further illustrated the ability of AI algorithms to distinguish between ductal, lobular, mucinous and papillary morphology of breast carcinoma as well as benign proliferative lesions of both stroma and epithelium. Sandbank et al. (8) have taken this a step further by developing an algorithm capable of distinguishing between low- and high-grade *in situ* ductal and lobular carcinoma, as well as differentiating *in situ* from invasive carcinoma. In addition, the algorithm was reported to be adept at differentiating atypical ductal hyperplasia from ductal carcinoma *in situ*. By distinguishing between low- and high-grade *in situ* lesions and between atypical ductal hyperplasia and ductal carcinoma *in situ*, this algorithm addresses one of the most critical challenges in histopathology - the accurate classification of early-stage lesions that carry different prognostic implications. Such precise differentiation is important for determining the appropriate treatment pathway, thereby reducing the likelihood of overtreatment or undertreatment.

Breast Cancer Grading

Cancer grading is widely recognized as the most important prognostic factor for the majority of tumor types, including breast cancer. However, intra- and inter-observer variability, coupled with the inherent subjectivity in histopathological assessment, makes histological grading far from perfect. While promising, molecular methods are often time-consuming and costly. This is where AI may again be of benefit with a transformative potential. AI algorithms, capable of stratifying tumors based on features beyond traditional morphology, offer a promising avenue for the future of cancer diagnostics.

The integration of AI in the histological grading of breast cancer marks a significant advance in pathological assessment, offering enhanced accuracy, reproducibility, and efficiency. The complexity of breast cancer diagnostics, characterized by diverse histopathological features, has historically posed challenges for consistent and reliable grading. Subsections like mitotic figure count, tubule formation, and nuclear grading are revolutionized by the AI models offering a predictive accuracy that enhances human analysis. This level of granularity in grading is not merely academic; it directly translates to more accurate patient prognoses and informs treatment efficacy. AI-driven approaches, particularly DL models, address these issues by providing objective analyses (Table 1).

Evaluation of Tubule Formation

One of the components of histological grading of breast cancer is assessment of tubule formation. Romo-Bucheli et al. (9) demonstrated the potential of DL classifiers in identifying tubule formation in estrogen receptor-positive (ER+) breast cancer whole slide images. Their findings showed a strong correlation between the tubule formation indicator and genetic risk categories, suggesting that automated quantification can offer a more consistent method for assessing tumor aggressiveness. Mantrala et al. (10) also demonstrated that AI models could accurately assess tubule formation, matching the performance of experienced pathologists and reducing inter-observer variability. This consistency is key to reliable prognostic evaluations and tailored treatment strategies.

This advance aids personalized treatment decisions by providing a reliable metric for tumor grading, opening up a new avenue for correlating histological features with genomic assays. This correlation is important as it could potentially reduce the need for costly genetic testing by substituting it with AI analysis of standard histological slides, making prognostic testing more accessible and cost-effective.

Counting Mitoses

Counting mitoses, a pivotal component of breast cancer grading, is also one of the most time-consuming processes for histopathologists from all levels of expertise. It is known to have significant inter- and intra-observer variability, yet it is directly associated with tumor aggressiveness and grading. AI has demonstrably enhanced the reliability of mitotic figure detection by removing time constraints and variability. Studies by Balkenhol et al. (11) and Li et al. (12) demonstrated the clear advantages of DL-based automated mitotic counting over traditional manual methods. Moreover, Pantanowitz et al. (13) and Nateghi et al. (14) addressed this issue by integrating an AI tool designed for mitotic figure detection. Their findings indicated significant improvements in accuracy, precision, and sensitivity in tumor proliferation rate assessment. These findings improve the consistency in grading by reducing interobserver variability, enhancing both workflow efficiency and diagnostic confidence.

Nuclear Grade Assessment

Nuclear grading, which involves assessing nuclear size, shape, and pleomorphism, can be subjective due to the variations in human interpretation. It requires expertise and, on many occasions, it is not an easy task to distinguish nuclear grade 1 from 2 or 2 from 3. Thus, grade 2 has been used as a safety net for many pathologists since this differentiation is more challenging simply due to inability to notice

Table 1. Major AI-based digital pathology applications for classification and grading of breast cancer

Year	Author(s)	Study aim	# of Patients/ patches	AI approach used	Performance metrics
2017	**Yamamoto et al. (3)**	Detection and classification of ductal carcinoma in situ	22	SVM	90.9% accuracy
2017	**Han et al. (4)**	Multi-classification of breast cancer histopathology images	82	Class structure-based deep CNN	93.2% accuracy
2017	**Cruz-Roa et al. (5)**	Invasive tumor extent evaluation	349	Class structure-based deep CNN	75.9% accuracy
2018	**Fondón et al. (6)**	Classify breast tissue samples into four malignancy levels	150	Feature vector + SVM	75.8% accuracy
2020	**Sharma and Mehra (7)**	Automatic multi-classification of breast cancer histopathological images	82	SVM	94% accuracy
2022	**Sandbank et al. (8)**	Subtypes of invasive carcinoma and TIL evaluation	436	CNN	AUC: 0.99
2016	**Romo-Bucheli et al. (9)**	Automated tubule nuclei detection and correlation with Oncotype DX	174	Deep neural network	89% accuracy
2022	**Mantrala et al. (10)**	Concordance in breast cancer grading by AI vs pathologists	137	Deep learning for semantic segmentation	65.9% accuracy
2019	**Balkenhol et al. (11)**	Deep learning-assisted mitotic counting for breast cancer	388	CNN	R = 0.810 (95% CI: 0.76–0.86)
2018	**Li et al. (12)**	Detection, verification, and segmentation for mitosis	50	Deep detection network	F-score: 0.827
2020	**Pantanowitz et al. (13)**	Accurate and efficient mitosis counting	320	R-CNN (region-based CNN)	Improved accuracy with AI
2021	**Nateghi et al. (14)**	Mitosis detection in tumor proliferation prediction	73	SVM	F-score: 0.738
2022	**Wang et al. (15)**	Improved breast cancer histological grading	>1000	CNN	AUC: 0.91 (95% CI: 0.88–0.93)
2021	**Elsharawy et al. (16)**	Improved grading for refined prognostic classification	>1000	CNN	AUC: 0.68 (95% CI: 0.65–0.71)
2021	**Zewdie et al. (17)**	Classification of breast cancer types and grades using deep learning	82	Deep CNN	96.75% accuracy

SVM: Support vector machines; CNN: Convolutional neural network; TIL: Tumor infiltrating lymphocytes; AUC: Area under curve; CI: Confidence interval, AI: Artificial intelligence

subtle differences through the human eye. This subjectivity introduces variability into the diagnostic process, which can impact both grading accuracy and prognostic evaluations.

A significant advance in breast cancer grading lies in the use of DL models to enhance the stratification of intermediate Nottingham Histological Grade (NHG) 2 cases, which historically pose challenges due to their variability and intermediate prognostic value. By analyzing whole-slide histopathology images, these models identify subtle morphological patterns that differentiate NHG 2 tumors into lower- and higher-risk groups, mirroring the characteristics of NHG 1 and NHG 3 (15). This approach offers prognostic insights comparable to molecular assays but is faster, more cost-effective, and uses routine Hematoxylin and Eosin (H&E) slides.

AI models, such as those highlighted by Elsharawy et al. (16), can standardize the grading process, reducing variability and improving prognostic evaluations. Similarly, the study by Mantrala et al. (10) confirmed that AI could match human performance in grading nuclear pleomorphism, thus mitigating inconsistencies among pathologists and providing more reliable prognostic information. Their work showed that AI could successfully detect morphological attributes of the nucleus which are key to determining tumor grade, and provide survival stratification across various patient cohorts. These AI tools are not yet designed to replace the human eye but rather to enhance the histopathologist's ability to detect the subtle changes that can significantly impact the course of treatment (10, 15, 17). This integration supports more informed clinical decision-making and facilitates personalized treatment strategies, ultimately improving patient care and outcomes.

Biomarker Quantification

ER, PR and HER2 Evaluation

Accurate and objective assessment of biomarkers plays a vital role in breast cancer diagnosis, prognosis prediction, and treatment

planning. The success of targeted therapies and endocrine therapy in breast cancer relies heavily on the precise quantification of estrogen and progesterone hormone receptors (ER and PR) and the human epidermal growth factor receptor 2 (HER2) protein. Traditional evaluation methods may be subjective and prone to errors. Fortunately, recent advances in AI and digital image analysis (DIA) offer promising solutions for achieving consistent and reliable biomarker quantification. AI algorithms were initially developed for basic IHC evaluation tasks, such as counting positive cells (i.e., DAB-stained brown cells) in manually selected tumor regions. However, with advances in tumor detection algorithms, these methods have evolved to integrate both tumor area and tumor cell detection and cell quantification. This enables not only the reliable counting of positive cells but also the assessment of their staining intensities, ultimately providing objective and consistent scores for biomarkers, including ER, PR, and Ki-67.

Recently, various groups have developed algorithms that have comparable performance to expert histopathologists, exhibiting high accuracy and consistency for the evaluation of ER, PR and Ki-67 in breast cancer (18, 19). These algorithms demonstrated strong correlation with expert decisions, indicating its feasibility in a clinical setting.

Similar results have been published for HER2 evaluation algorithms. Hartage et al. (20) validated their algorithm for HER2 IHC assessment, showing high correlation with fluorescent *in situ* hybridization results and improved consistency compared to manual scoring. Furthermore, Li et al. (21) investigated their model for HER2 IHC in predicting response to anti-HER2 neoadjuvant chemotherapy. DIA provided quantitative analysis of HER2 expression, revealing a significant correlation with pathological complete response (pCR) rates. This research suggests that DIA-based HER2 assessment can improve the prediction of treatment response, enabling more personalized treatment strategies. Notably, the assessment of HER2 status can be nuanced, with borderline cases posing a challenge for histopathologists. These findings highlight DIA's potential to streamline workflows and enhance the consistency of biomarker evaluations, especially in cases with equivocal results after manual scoring.

In conclusion, AI and DIA hold immense potential to revolutionize breast cancer diagnostics and personalized medicine approaches. By providing automated, standardized, and quantitative assessments, they can significantly improve the accuracy and consistency of biomarker analysis, leading to better diagnosis, more informed treatment decisions, and ultimately, improved patient outcomes. While further research is needed to optimize AI algorithms and ensure the generalizability of DIA methods, the integration of these technologies in objective biomarker quantification is a very promising step forward (Table 2).

Ki-67 Proliferation Assessment

Ki-67 is a well-established prognostic marker for breast cancer. Traditionally, Ki-67 assessment involves manual counting, a time-consuming and error-prone process. AI-powered Ki-67 quantification, as described by Bodén et al. (22), represents a significant advance in the field. Unlike manual counting, AI provides the option of comprehensive analysis of the entire slide, offering a more objective and robust approach (18, 22, 23). Bodén et al. (22) demonstrated that AI-based Ki-67 assessment achieved a high correlation with manual counts by histopathologists. This comprehensive Ki-67 analysis by AI could lead to more accurate prognoses and individualized treatment plans, particularly when deciding on the use of neoadjuvant therapy.

PD-L1 Scoring

AI-assisted programmed death-ligand 1 (PD-L1) scoring, particularly through the combined positive score, has garnered significant attention for its potential to standardize and enhance the accuracy of IHC-based evaluations in cancer treatment. While its application has been better established in non-small cell lung cancer (NSCLC), there is still room for improvement in other organ cancers. In NSCLC, AI tools have

Table 2. Major AI-based digital pathology applications for molecular profiling of breast cancer

Year	First author	Study aim	#of Patients/ patches	AI approach used	Performance metrics
2023	**Abele et al. (18)**	AI-assisted analysis of Ki-67 and hormone receptors	204	CNN	Agreement rates: Ki-67 (87.6%), ER/PR (89.4%).
2022	**Shafi et al. (19)**	Validation of automated digital determination of estrogen receptor status	97	Computer vision-based DIA	Pearson's $r = 0.72$
2020	**Hartage et al. (20)**	Validation of HER2 IHC digital imaging and FISH correlation	612	Computer vision-based DIA	Cohen's kappa (κ): 0.71
2020	**Li et al. (21)**	Quantitative digital imaging of HER2 IHC to predict response to therapy	153	Computer vision-Based DIA	HER2 DIA connectivity & pCR (OR = 136.08, $p = 0.002$)
2021	**Bodén et al. (22)**	Human-in-the-loop Ki-67 assessment	200	DCNN based object detection	Cohen's kappa (κ): 0.84
2024	**Dy et al. (23)**	Improved accuracy and agreement in Ki-67 assessments	420	CNN	Ki-67% error rate: 0.6%

CNN: Convolutional neural network; DIA: Digital image analysis; IHC: Immunohistochemistry; FISH: Fluorescence *in situ* hybridization; pCR: Pathological complete response; DCNN: Deep convolutional neural network; OR: Odds ratio; HER2: Human epidermal growth factor receptor 2; AI: Artificial intelligence; ER: Estrogen receptor; PR: Progesterone receptor

already demonstrated considerable success in improving interobserver concordance. Algorithms, such as the dual-scale categorization-based DL methods have shown high concordance rates when compared to histopathologists, underscoring their potential in clinical applications (24).

However, in other cancers including breast cancer, AI applications in PD-L1 scoring are in the earlier stages of research and development. Initial studies in breast cancer, especially multi-institutional studies, show promise in improving scoring consistency between histopathologists. AI-assisted models have demonstrated significant potential, boosting concordance from moderate to excellent levels (25, 26). These models aid in overcoming the subjectivity of human evaluation, especially when scoring tumor-infiltrating immune cells, which is key in determining patient eligibility for immunotherapy.

AI models for PD-L1 scoring need to be further refined and validated across various cancers. The adoption of AI in scoring systems for cancers beyond the lung, such as urothelial carcinoma and head-and-neck squamous cell carcinoma, is expected to follow suit, offering an invaluable tool for clinicians to make more reliable, data-driven treatment decisions.

AI-Powered TIL and Tumor Microenvironment Assessment

AI has transformed how TILs and the broader tumor microenvironment (TME) are assessed, particularly in breast cancer. TILs, which are key immune response markers, play a critical role in the prognosis of cancers, such as HER2-positive and triple-negative breast cancer (TNBC). Traditionally, TIL evaluation, as with other histopathological evaluations, was subjective and prone to variability. However, AI offers a standardized and objective approach, reducing this variability and providing a consistent evaluation of the immune response within the TME (27, 28). AI-powered methods can quantify the spatial organization and interactions of TILs with other immune and tumor cells, which is vital when stratifying patients for immunotherapy. Studies have shown that AI-driven analysis of H&E and multiplex IHC images enhances the ability to predict treatment responses, such as pCR to chemotherapy, especially in HER2-positive and TNBC subtypes (27).AI models developed for this purpose have demonstrated higher accuracy in predicting pCR compared to manual assessments by histopathologists, underscoring the potential of AI to guide personalized treatment strategies (11, 29). AI also plays a critical role in advancing our understanding of the TME by identifying organizations and interactions that are difficult for human observers to discern. This includes quantifying the presence and behavior of immune cells like TILs, as well as mapping their interactions with tumor cells (30). This deeper analysis provides a more comprehensive understanding of the immune landscape, which is essential for optimizing treatment plans and enhancing the precision of immunotherapies.

AI-Powered Lymph Node Metastasis Detection

The accurate detection of lymph node metastasis is a key factor in staging and treatment planning in breast cancer. However, for small occult tumor foci in lymph nodes, traditional pathological assessment can be tricky and, in some cases, requires additional IHC studies. Fortunately, recent advances in AI offer promising solutions for more precise lymph node metastasis detection, potentially removing the need for the additional IHC step, saving both time and resources (31-35).

Several studies have investigated the application of DL algorithms for lymph node metastasis detection in breast cancer. Liu et al. (36) developed such an algorithm for identifying metastatic cancer cells in sentinel lymph node biopsies. The algorithm achieved impressive performance in detecting metastases, even for small foci. The study also demonstrated the robustness of the algorithm when faced with common tissue sample variations, indicating its potential for reliable performance in diverse clinical settings. Furthermore, the algorithm demonstrated a high sensitivity with low false positives, significantly reducing missed metastases compared to traditional methods.

Steiner et al. (35) evaluated the impact of DL assistance in histopathologists' evaluations of lymph nodes for metastatic breast cancer. The AI model significantly improved diagnostic accuracy, particularly for challenging micrometastases. Using AI resulted in reduced errors and review time, while also enhancing histopathological accuracy. Building on these findings, other groups have explored integrating AI into digital pathology workflows for efficient and accurate lymph node metastasis diagnosis (31). AI models, trained on a large dataset of H&E-stained slides, demonstrated high sensitivity and specificity in detecting lymph node metastases, significantly reducing false negatives. Importantly, the model accurately identified macro- and micrometastases, leading to more precise diagnoses (33, 37).Looking beyond breast cancer, a recent study Bándi et al. (38) explored continual learning strategies for cancer-independent detection of lymph node metastases. This approach aims to develop robust AI models that can detect metastases across various cancer types without requiring cancer-specific retraining. The continual learning models demonstrated high accuracy and reliability across diverse datasets encompassing breast, colon, and head-and-neck cancers. This approach allows for continuous learning and adaptation, enhancing the model's generalizability across different clinical scenarios. By employing a cancer-independent detection strategy, these models can be more broadly applicable in clinical practice, offering a scalable solution for lymph node metastasis detection across various cancers.

Radiomics presents a promising, AI-driven approach for also improving axillary lymph node staging in breast cancer, leveraging medical imaging to create predictive models with high sensitivity, specificity and efficiency. Despite its potential to replace invasive procedures, limited validation, retrospective study designs, and lack of cost-effectiveness analyses highlight the need for robust clinical trials and meta-analyses for clinical implementation (39). When combined with advances in AI-powered lymph node metastasis detection, including DL algorithms and cancer-independent models, radiomics can integrate seamlessly into digital pathology workflows. This integration offers a scalable solution for precise diagnosis and treatment planning across diverse cancer types.

The Future: AI-Assisted Molecular Prediction

Molecular subtyping of breast cancer is becoming increasingly important. Accurate subtype determination necessitates the evaluation of each tissue block of the tumor, yet reproducibility can be challenged by the heterogeneous nature of breast cancer tumors. The application of AI extends beyond traditional histopathological analysis. Its predictive capabilities are now at the molecular level. Farahmand et al. (40) used AI to predict HER2 status using H&E sections with high accuracy, which is vital for determining eligibility for targeted therapies, like trastuzumab. Similarly, the ability of AI to predict *BRCA* mutation status from histological images, as shown by Wang et al. (41) indicates its potential in genetic risk assessment and personalized medicine.

These holds promise for identifying patients carrying *BRCA1* and *BRCA2* mutations who are at high risk for developing hereditary breast cancer and guiding preventive measures. Several studies have shown promise in detecting molecular subtypes, particularly in distinguishing the basal-like subtype from luminal-A (42, 43). The objective must be to reduce the costs associated with molecular testing and mitigate the impact of limited experience by automating this classification process.

The integration of AI into molecular prediction also includes its potential to classify tumor recurrence risks based on histological features, circumventing the need for costly molecular assays. Whitney et al. (44) demonstrated that computer-extracted nuclear morphology features from routine H&E-stained images could accurately predict Oncotype DX risk categories for ER-positive breast cancer patients. By leveraging AI-driven analysis of nuclear architecture and shape, the study achieved significant classification accuracy, with an area under the curve of up to 0.83 in distinguishing between low and high recurrence risk groups. This method not only complements molecular testing but also offers a faster, cost-effective, and nondestructive alternative. As such, AI-driven histopathological tools are paving the way for precise recurrence risk stratification and personalized treatment planning, particularly in resource-limited settings where access to molecular assays may be constrained.

AI-Enhanced Homologous Recombination Deficiency Detection

Homologous recombination deficiency (HRD) status holds a substantial potential in determining the optimal treatment course for patients with breast cancer (45, 46). Traditional molecular methods to identify HRD status, while accurate, are often time-consuming, costly, and require specialized equipment, limiting their accessibility in resource-constrained settings. To address these challenges, AI has emerged as a promising solution. AI-powered tools use H&E slides to predict HRD status directly (47). These models analyze tissue samples with a high degree of accuracy, often surpassing traditional methods in identifying patients who may benefit from targeted therapies, like platinum-based chemotherapies and PARP inhibitors. By automating the detection process, AI enables faster, more scalable, and more accessible HRD testing. Furthermore, the ability to identify a broader range of HRD-positive patients can lead to more effective treatment strategies and potentially enhance survival rates.

PIK3CA/AKT Pathway Alteration Detection

ML, and particularly DL, have shown progress in detecting actionable genetic alterations of breast cancer directly from the H&E-stained slides. These AI models can detect subtle morphological changes linked to genetic mutations, providing an innovative approach to molecular analysis (48, 49).

In TNBC, DL models have proven highly effective in predicting *PIK3CA* mutations, demonstrating their reliability in molecular diagnostics (48). Similar methods have been successfully applied across multiple cancer types, including breast cancer, with strong predictive outcomes for detecting mutations like *PIK3CA* (49). These models use convolutional neural networks to analyze thousands of image files from histopathology slides, allowing them to recognize patterns linked to genetic alterations. This method enhances real-time prediction, positioning AI as a valuable tool in advancing pathology practices.

Challenges, Risks and Practical Considerations in AI Integration for Breast Pathology

Despite its transformative potential, AI in breast histopathology presents several challenges and risks that must be carefully addressed. Algorithmic bias remains a significant concern, as AI models trained on limited datasets may not generalize well to diverse populations. This may result in disparities in diagnostic accuracy, particularly for underrepresented demographic groups. Ensuring diverse, representative, and well-annotated datasets is vital to avoid bias and ensure equitable AI-driven diagnostics across various demographics. In addition, validation in diverse clinical settings is important to ensure that AI tools perform consistently across different laboratories, imaging systems, and staining techniques. Another challenge is the potential for misdiagnoses if AI tools are improperly calibrated or misinterpreted by users. Over-reliance on AI without adequate human oversight could lead to errors in classification, particularly in borderline or equivocal cases. Therefore, robust validation, external benchmarking, and continued histopathologist involvement are essential to mitigate these risks.

Integrating AI into pathology workflows necessitates a strategic approach that accounts for multiple factors, including specialized training for histopathologists and other laboratory personnel, the financial implications of adopting AI-driven solutions, compliance with regulatory standards, and seamless interoperability with existing digital pathology systems. Foremost, training and skill development are critical, as histopathologists must become proficient in using AI-assisted tools, interpreting AI-generated insights, and understanding the limitations of these systems. Institutions must invest in educational programs and workshops to ensure a smooth transition into AI-enhanced diagnostics. Cost considerations also play a significant role in the adoption of AI in pathology departments. While AI has the potential to improve efficiency and accuracy, the initial investment in infrastructure, software licensing, and continuous updates can be substantial. Pathology laboratories will need to conduct cost-benefit analyses to determine the financial viability of AI integration and explore funding or reimbursement models to support implementation. Finally, interoperability with existing pathology systems is essential for efficient workflow integration. AI tools must be compatible with various digital pathology platforms, whole slide imaging systems, and laboratory information management systems to facilitate seamless data exchange and avoid disruptions in clinical workflows. Ensuring standardized data formats and adherence to industry-wide interoperability frameworks can help maximize the potential benefit of AI while maintaining workflow efficiency.

Importantly, regulatory compliance will be crucial, as AI-driven diagnostic tools must meet strict guidelines set by regulatory bodies such as the Food and Drug Administration, Conformite Europeenne, and CAP to ensure patient safety, reliability, and ethical use. Institutions must navigate complex approval processes and ensure that AI systems are validated for clinical use before deployment. Addressing all these factors will be essential for the successful implementation of AI in pathological assessment, allowing for improved diagnostic accuracy, streamlined workflows, and enhanced patient outcomes.

Discussion and Conclusion

The integration of AI into breast cancer pathological assessment represents a transformative advance toward achieving greater precision, standardization, and efficiency in diagnostic and prognostic assessments. AI systems enhance the capabilities of histopathologists by augmenting the accuracy of molecular-level evaluations, which is essential for personalized medicine. As AI technologies continue to evolve and are seamlessly integrated into clinical workflows, they are

poised to improve patient outcomes through rapid, reproducible, and detailed histopathological evaluation. AI algorithms, trained on annotated data provided by histopathologists, have the potential to reduce both cost and time associated with diagnostic evaluations while maintaining high-quality standards of care.The future of breast cancer pathology lies in the development of a synergistic relationship between AI and pathologists. The majority of the algorithms mentioned in this article operate as an adjunct to the pathologist, rather than a final decision maker. Human-in-the-loop systems offer an augmented diagnostic assistant or a second reader. AI technologies excel in increasing diagnostic accuracy, and detecting subtle patterns that may elude even the most trained human eye. Pathologists, with their clinical expertise and nuanced understanding of patient care, are essential for guiding the development of AI models, interpreting AI-generated insights, and ensuring that these tools are applied ethically and responsibly in clinical practice. This collaboration between AI and human expertise holds immense promise for realizing the full potential of personalized breast cancer management, leading to more effective, individualized treatment strategies and improved clinical outcomes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.H.D.K., İ.K., N.K.; Concept: A.H.D.K., İ.K., N.K.; Design: A.H.D.K., İ.K., N.K.; Data Collection or Processing: A.H.D.K.; Analysis or Interpretation A.H.D.K., İ.K.; Literature Search: A.H.D.K., İ.K., N.K.; Writing: A.H.D.K., İ.K.

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