

A Systematic Benchmark of Advanced Architectures for Automated Multi-Class Classification in Digital Pathology

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ABSTRACT Histopathological assessment of tissue biopsies is the main way to diagnose breast cancer. The current truth is that interpreting histopathological images is subjective and typically requires a great deal of effort by busy pathologists. Deep learning has transformed the practice of Digital Pathology, but at this moment, there is no universal agreement on which architecture gives the best performance for multi-class tissue recognition. The goal of this work is to analyze and compare the traditional Convolutional Neural Network (CNN), ResNet-101 and DenseNet-169, to the recently developed Transformer architecture, the Vision Transformer (ViT), by using a systematic benchmarking approach. Our approach involved using a balanced dataset with images from four classes (Benign, InSitu, Invasive, and Normal) and included preparation of images to a standardized input size of 224x224, transfer learning, and standard augmentations. Experimental results indicated that DenseNet-169 performs significantly greater than ResNet-101 (75% accuracy) with an improved accuracy of 96.25% and F1-score of 0.9628 at comparatively low levels of computational power (67.169 GFLOPs). DeiT Base is also an effective diagnostic adjunct, but due to its extensive number of parameters (85.80M) and computational cost, there are clear advantages in using optimized dense CNN architectures in limited clinical resources.

KEYWORDS
Convolutional neural networks
Vision transformers
Multi-class classification
Comparative study
Computer-aided diagnosis
Deep learning
Histopathology
Breast cancer

INTRODUCTION

Breast cancers rank among the major healthcare issues across the globe, and they contribute to a large percentage of cancer-related deaths among women (Ma *et al.* 2024; Akbari *et al.* 2026; Alkhafaji *et al.* 2026). The present scenario regarding breast cancers, as depicted above, has continued to pose significant healthcare threats to women across the world, and their comprehensive and accurate identification still remains a challenge. Presently, for accurate identification of cancers, the "Gold Standard Test," or properly referred to, still remains the Histopathological examination of tissue biopsies. The pathologists, after careful observation of these slides, are able to differentiate the tissue patterns, viz., Benign,

InSitu, Invasive, and Normal, and so on. But this needs to be done manually and hence is time-taking, to say the least, and still tends to be a challenge due to possible variations (Yan *et al.* 2025; Jahan *et al.* 2025).

In recent years, with the introduction of deep learning into digital pathology, there was a major change in thinking and how pathway classification would be handled. Convolutional Neural Networks (CNNs) have been the dominant force in this area, due mainly to their ability to extract spatial hierarchies and local features from high-resolution digital medical imaging (Yu *et al.* 2024; Rahman *et al.* 2025; Irmak and Saygılı 2025). A variety of CNN architectures, including ResNet-101 and DenseNet-169, have provided many examples of strong benchmark architectures, addressing the problem of gradient degradation, and promoting the concept of feature reuse. With the continued development of digital pathology comes the introduction of Vision Transformers (ViTs) as well as hybrid architectures, such as the newly developed Data-efficient Image Transformer (DeiT). ViTs and DeiT also allows for

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the integration of global context into classification models and, in particular, enable the recognition of small levels of pathologic change across an entire slide (Hasan *et al.* 2025; Sumitha and Isaac 2025).

Despite such advances, an important issue is still remaining, which is a balance between high detection performance and efficient computation (Maurya *et al.* 2024; Singh and Patnaik 2026; Ahmed 2025). Although more advanced yet complex models could achieve even superior performance, their applicability in a practical environment, such as a hospital where hardware or computational capacity could be more restricted, would still include a careful consideration of parameters and GFLOPs (Kansal *et al.* 2025). Moreover, previous research works are mostly concentrating on a binary classification problem, like malignancy versus benign cases, although, in reality, a more appropriate classification is needed for multi-class problems that are commonly experienced by a human pathologist on a daily basis. There is an obvious gap between existing research works concerning a benchmark of multi-class BC using traditional CNN models and more contemporary models like transformers (Singh and Patnaik 2025; Zhang *et al.* 2025). This study is intended to address this shortcoming by presenting an overall assessment of multiple SOTA models, including DeiT Base, DenseNet-169, and ResNet-101, which have been tested with a carefully curated set of four histopathological classifications. They were evaluated based on precision, recall, f1 score, and computational burden.

RELATED WORKS

Computational Intelligence has transformed the experience of digital pathology from one of subjectively evaluating using a visual microscope to one of objective, high Throughput Diagnostic Systems for all cancers. The greatest complication in classifying breast cancer automatically is the great differences in morphology within tissue samples as benign and malignant cell types typically contain similar cellular characteristics. CNNs have historically been utilized to extract spatial features from tissue samples today there are increasing developments toward hybrid systems, frequency domain analysis and explainable A.I. (XAI) which makes A.I. more interpretable and efficient while still enabling high levels of Predictive Performance.

The study by Liu *et al.* (2024) discussed the limitations of existing methods used for feature representation in digital pathology. Liu *et al.* proposed a novel method for adaptive threshold selection which can be applied to histopathological images processed in the frequency domain using discrete wavelet transform. This adaptive thresholding process removes unnecessary noise and enhances the relevant textural features of histopathological images that are critical for producing high-resolution histopathological images. The results from their study show that adding threshold selection as part of the model's training improves convergence on complex tissue structures.

According to Gu *et al.* (2024), deep learning has been systematically evaluated to assess the role of deep learning for automating breast cancer diagnosis using automated systems. The authors highlight the value of improving the quality of preprocessing and optimising hyperparameters to achieve the most accurate diagnoses possible from these systems. The authors denote that although new architectures have value, they also suggest that utilising existing networks with strong augmentation techniques provide opportunities for diagnostic accuracy results that are comparable or superior to those achieved by newer architectures or complex tailored architectures. This research supports the need for

standardisation of digital pathology workflow processes in order to reproduce results in multiple clinical environments.

In a supervised contrastive learning framework (CHistNet) proposed by Rahaman *et al.* (2024), the authors aim to increase the ability for distinguishing features in multi-class histopathology. This is accomplished through the clustering of related pathologies in latent space while maximizing separation of unrelated classes. This method is highly effective at alleviating class imbalances that exist in breast oncology. Their research demonstrates how contrasting the results from using contrastive strategies produces a more optimal representation of the features than training using only traditional cross-entropy methods.

The researchers (Krishnappa and Reddy 2024) developed a new kind of deep ensemble graph network (DEGN) that treats the spatial organization of tissues as a series of related nodes instead of a two-dimensional pixel grid. This allows the DEGN to better represent long-range spatial relationships in a tissue sample and therefore produce a more complete understanding of the tissue microenvironment. The authors also demonstrated that an ensemble method outperforms standard CNNs at distinguishing between small architectural differences in breast tissues.

In a study conducted by Singh *et al.* (2024), colleagues explored how effective transfer learning is for classifying digital histopathological images. They specifically sought to address the limitations of relying on limited amounts of annotated digital histopathology images. Specifically, through fine-tuning a large number of pre-trained deep learning models specifically designed for histopathology tasks, they demonstrated that they could accurately distinguish between multiple grades of breast tumour types (defined by the World Health Organisation) while decreasing the time it took to train these neural networks substantially. Singh's team's work demonstrated that transfer learning represents a model that is easily scalable for implementing AI-based diagnostics in low-resource healthcare settings.

Yilmaz *et al.* (2025) Concluded through an extensive review (n = 30) of advanced neural network architectures (CNNs and ViTs) focusing on the detection of breast cancer from ultrasound and histological images. They found that although multi-scale ViTs such as MViTv2-Base are able to exploit large context globally, they are most efficient when combined with lightweight CNNs (MobileNetV3). When choosing the correct architecture, this benchmark provides guidance based on the various imaging modalities and the appropriate diagnostic need.

To overcome the issue of interpreting results from Deep Learning methods, the authors (Ukwuoma *et al.* 2025) proposed a classification strategy based on Explainable AI (XAI) using LIME and SHAP technologies to demonstrate how their algorithm provides a reliable explanation of tissue types. The framework accurately classifies the tissue types and also produces a visual explanation of how the algorithm arrived at its decision by providing a clear visual representation of the nuclear or stromal features that influenced the predictive process of the algorithm. The development of the framework helps fill the gap between the predictions made by algorithms and the reasoning that is understandable by humans, creating a bridge to building confidence in AI-assisted diagnostic devices within clinical practice and obtaining the requisite regulatory approvals for the use of AI-based diagnostic tools within clinical practice.

MATERIALS AND METHODS

Dataset and Data Preprocessing

In our research, we employed a broad histopathology dataset, which comprises four types of tissue and covers the most difficult cases in diagnosing breast cancers, namely, Benign, InSitu, Invasive, and Normal. These categories, as depicted in Figure 1, are very varying in cell structures, density, and organization, and it is essential for the multi-class problem that these aspects are well picked up by the model. To ensure a balance in the training environment and avoid the overfitting issue by giving preference to a certain class, the dataset was selected to be well-represented by an equal number of 100 images for each class, resulting in a well-prepared set of 400 high-quality images. The level of complexity, as depicted in Figure 1, necessitates the needs for the advanced model to well-capture not only the local features but also the global features ([Dataset 2025](#)).

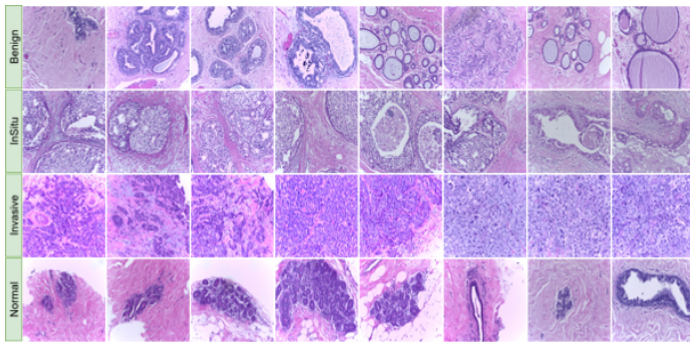


Figure 1 Sample images from the breast histopathology classes in the dataset.

We implemented a consistent preprocessing procedure for all the data, before using it in the deep learning (DL) algorithms. A primary aspect of this process was that all the patches of the histopathology were resized to the same 224×224 pixels. These particular dimensions were selected to align with the input requirements of the existing architectures (e.g., DenseNet-169, DeiT Base). Thus they are suited for direct comparisons. The partitioning of each set into training, validation, and testing subsets (70/10/20 as illustrated in Table 1) allows models to train on sufficient data while maintaining a dedicated test set to accurately assess generalization capabilities on novel pathological patterns.

Foundational Principles of Deep Learning Models (CNNs and ViTs)

Two different architectural philosophies have significantly impacted the development of automated histopathology: CNNs and ViTs. While CNNs primarily focus on local morphology with their spatial hierarchies, ViTs allow for a type of global understanding which has become increasingly important for identifying complex tissue architectures within the context of breast cancer diagnosis.

For more than 10 years, CNNs have been the standard for medical image analysis because of their unique ability to represent the local spatial correlation of histopathological slides. In this evaluation, we focus on two major advances in the architecture of CNNs to help mitigate the weaknesses of both ResNet-101 ([He et al. 2025](#)) and DenseNet-169 ([Huang et al. 2025](#)). ResNet-101 introduced the "skip connection" or residual learning concept that allows CNN's to avoid the vanishing gradient problem and learn the identity mapping across 101 layers, therefore maintaining important elements

in the image. Alternatively, DenseNet-169 proposes that every layer in a block is connected; this allows the features from previous layers to be reused as much as possible while also reducing the number of parameters, thus still maintaining the interpretation power of Deep Learning. Therefore, CNNs, as a technique in Digital Pathology, can easily detect subtle changes in cells or nuclear pleomorphism in Benign or Invasive tissue patches.

Though CNNs use localized kernels, with the advent of ViTs, there is a paradigm shift towards understanding images in a more holistic manner. Unlike previous models, where an image is treated as a patch, in ViTs, an image is treated as a set of patches, and to understand their relevance, there is the use of the "self-attention" technique, where the relevance of each patch is measured in relation to another. Though conventional ViTs are very efficient, their main bottleneck in medical imaging is their requirement for huge quantities of data. To counter this, this work uses DeiT Base ([Touvron et al. 2025](#)). This model reduces the requirement for huge quantities of data with the help of its unique teacher-student distillation technique using distillation tokening, ensuring small quantities of data (as explained in Table 1) are efficiently utilized without sacrificing its global receptive width, making it the best-suited model for multi-classification problems where the positioning of the stroma and epithelium regions plays an important role in diagnosing whether the cell is of type InSitu or Normal.

Transfer Learning and Data Augmentation

The lack of sufficient annotated examples in histopathology continues to be an obstacle in developing effective medical imaging datasets. To overcome this and achieve strong convergence in deep learning models, we used a Transfer Learning approach where instead of using resources to build our own networks from scratch (a process that would have been extremely costly compared to developing a dataset this size; see Table 1.), we took advantage of networks that were already trained on ImageNet-1K. This allowed us to use a large number of diverse features that were learned in advance by the networks to enable the models to concentrate on adjusting only the higher level portions of their architecture to identify the more specific characteristics of breast tissue, like the way that the structure of invasive carcinoma is different than the structure of breast tissue from in situ lesions.

For our Data Augmentation pipeline, we leveraged timm, a popular PyTorch Image Models library, where we utilized their standard stochastic transformations and avoided building an entirely new augmentation space from scratch. We took advantage of timm's "default" settings, which have demonstrated successful performance across modern deep learning benchmark tests. For example, the default settings incorporate key geometric and color-space perturbations, including random resized cropping, horizontal flipping, and basic color jittering, that affect a model's ability to generalize well to changes in scale or orientation (invariance). By using these standard default parameters, we ensured that any training environment we created for comparing the models (i.e., CNN vs. ViT) was repeatable and free from bias, allowing our analysis to focus primarily on the characteristics of each architecture ([Wang et al. 2024](#); [Mumuni et al. 2024](#)).

Metrics for Performance Assessment

To evaluate the effectiveness of the proposed DL models in the multi-class classification of breast cancer histopathology images, several standard quantitative metrics were employed to provide a rigorous assessment of their diagnostic performance. Accuracy was first utilized to offer a general measure of the models' abil-

■ **Table 1** Dataset Distribution by Class

Class	Train (70%)	Val (10%)	Test (20%)	Total
Benign	70	10	20	100
InSitu	70	10	20	100
Invasive	70	10	20	100
Normal	70	10	20	100
Total	280	40	80	400

ity to correctly identify the four tissue categories, Benign, InSitu, Invasive, and Normal, across the entire dataset, as defined in Eq. (1). However, given the clinical significance of misclassification in medical imaging, we further assessed the diagnostic precision and sensitivity of the architectures to ensure a more granular analysis. Precision was used to quantify the exactness of the models, representing the ratio of correctly predicted positive cases to the total predicted positives, as shown in Eq. (2). Complementary to this, Recall, also known as sensitivity, was calculated to measure the models' ability to detect all relevant positive instances, which is particularly critical in oncology to ensure that malignant tissue types are not overlooked, as formulated in Eq. (3). Finally, the F1-Score was calculated as the harmonic mean of precision and recall to provide a robust and balanced performance indicator that accounts for both false positives and false negatives, as described in Eq. (4).

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$\text{Precision} = \frac{TP}{TP + FP} \quad (2)$$

$$\text{Recall} = \frac{TP}{TP + FN} \quad (3)$$

$$\text{F1-score} = 2 \cdot \frac{\text{Precision} \cdot \text{Recall}}{\text{Precision} + \text{Recall}} \quad (4)$$

RESULTS AND DISCUSSION

The experimental results obtained from the multi-class classification of breast histopathology images demonstrate a significant variance in performance across the different architectural paradigms. By evaluating traditional CNNs alongside modern ViTs, we assessed not only the predictive accuracy of each model but also their practical feasibility for clinical deployment through the lens of computational complexity. As evidenced by the quantitative outcomes summarized in Table 2, the choice of architecture fundamentally influences the model's ability to distinguish between subtle morphological features in tissue patches.

Among the evaluated models, DenseNet-169 emerged as the superior architecture, achieving the highest accuracy of 0.9625 and an F1-score of 0.9628. Remarkably, DenseNet-169 managed to outperform its counterparts while maintaining the most efficient computational profile, utilizing only 12.49 million parameters and 67.169 GFLOPs. This high performance-to-efficiency ratio is largely attributable to its dense connectivity pattern, which maximizes feature reuse and ensures a robust gradient flow. The confusion matrix for DenseNet-169, illustrated in Figure 2, further confirms its reliability, showing perfect classification (20/20) for the Invasive

class and only minor misclassifications in other categories. For instance, only one InSitu sample was incorrectly labeled as Invasive, and a single Normal case was misidentified as Benign, indicating that the model captures the primary pathological indicators with high precision.

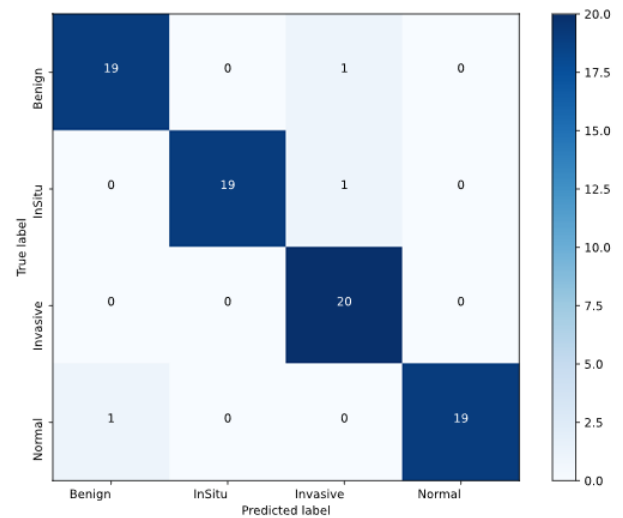


Figure 2 Confusion Matrix of the DenseNet-169 Model.

In comparison, the DeiT Base model demonstrated competitive diagnostic capabilities with an accuracy of 0.9375, yet it required significantly higher computational resources. With 85.80 million parameters and 336.955 GFLOPs, DeiT is the most demanding architecture in this study, reflecting the inherent trade-offs when using transformer-based models on smaller datasets, despite the use of distillation techniques. Conversely, ResNet-101 performed notably poor in this specific multi-class task, yielding an accuracy of only 0.75. This suggests that for this particular histopathological dataset, the standard residual blocks may not be as effective as the dense connections of DenseNet or the global attention mechanisms of DeiT in resolving the complex cellular overlaps. These findings underscore that while transformers offer powerful global context, optimized CNN architectures like DenseNet-169 currently provide a more balanced solution for high-precision, resource-efficient medical image analysis.

Table 2 Comparison of Performance Metrics and Computational Complexity of the Models

Models	Accuracy	Precision	Recall	F1-score	Params	GFLOPs
DeiT Base	0.9375	0.9410	0.9375	0.9370	85.80M	336.955
DenseNet-169	0.9625	0.9648	0.9625	0.9628	12.49M	67.169
ResNet-101	0.7500	0.7602	0.7500	0.7487	42.51M	157.288

CONCLUSION

This research has presented a comprehensive comparative analysis of CNN and transformer-based architectures for the multi-class classification of breast cancer histopathology images. By benchmarking DenseNet-169, DeiT Base, and ResNet-101, we have identified that architectural design plays a critical role in capturing the subtle morphological nuances required for accurate tissue differentiation. Our results identify DenseNet-169 as the most effective model, combining exceptional diagnostic accuracy (96.25%) with the most efficient computational profile. While ViTs like DeiT offer promising global contextual awareness, their elevated computational demands and data requirements remain significant barriers compared to the feature-reuse capabilities of dense convolutional networks. These insights underscore the potential for optimized CNNs to be integrated into real-time clinical workflows to alleviate pathologist workload and reduce diagnostic variability. Future work focuses on integrating these models into broader whole-slide imaging pipelines and exploring hybrid architecture to further bridge the gap between local tissue analysis and global architectural interpretation.

Ethical standard

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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