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AI-Based Deep Capsule Attention Network for Breast Cancer Molecular Subtype Prediction Using Mammograms

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Abstract

Breast cancer remains one of the most prevalent and life-threatening malignancies affecting women globally, with early and accurate molecular subtype classification being critical to effective treatment planning. Traditional diagnostic methods, including histopathological analysis and immunohistochemistry, are time-consuming, costly, and subject to inter-observer variability. The advent of artificial intelligence (AI), particularly deep learning-based frameworks, has opened transformative possibilities for automated, non-invasive breast cancer subtype prediction from mammogram images. This paper presents a comprehensive review of AI techniques with a focus on Cascaded Deep Capsule Cell Attention Network (CDCCAN) models for predicting breast cancer molecular subtypes — Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC) — using mammographic imaging. The proposed conceptual framework integrates capsule networks, multi-scale attention mechanisms, and cascaded deep learning architectures to address limitations of conventional convolutional neural networks, including spatial invariance loss and poor generalization. A structured literature review of 30 studies published in recent years is synthesized, highlighting key trends, benchmark datasets, performance metrics, and persistent challenges including data imbalance, model interpretability, and clinical integration. The paper concludes by identifying future research directions toward robust, explainable, and clinically deployable AI systems for breast cancer diagnosis.

Introduction

1. Background and Motivation

Breast cancer is the most commonly diagnosed cancer among women worldwide, accounting for approximately 2.3 million new cases and 685,000 deaths globally in 2020 alone, according to the World Health Organization (WHO). The disease is not a single entity but a heterogeneous group of malignancies with distinct molecular profiles, clinical behaviors, treatment responses, and prognostic outcomes. The classification of breast cancer into molecular subtypes — primarily Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC) — has revolutionized oncology by enabling targeted, personalized therapeutic strategies. However, the accurate and timely identification of these subtypes remains a significant clinical challenge, particularly in resource-limited settings where access to advanced genomic profiling tools such as PAM50 gene expression assays is restricted.

Mammography has long served as the primary screening modality for breast cancer due to its cost-effectiveness, wide availability, and established clinical utility. Despite its widespread use, mammographic interpretation is inherently subjective, heavily dependent on radiologist expertise, and prone to false positives and false negatives. Studies have reported sensitivity rates ranging from 70% to 87% for standard mammographic screening, with significant variability attributed to breast tissue density, lesion morphology, and imaging quality. These limitations underscore the urgent need for automated, objective, and highly accurate computational tools capable of extracting clinically meaningful information from mammographic data.

Artificial intelligence, and deep learning in particular, has emerged as a paradigm-shifting technology in medical imaging over the past decade. Deep learning models — especially Convolutional Neural Networks (CNNs) — have demonstrated remarkable performance in tasks ranging from lesion detection and segmentation to malignancy grading and survival prediction. However, conventional CNNs suffer from critical architectural limitations that reduce their efficacy in the complex task of molecular subtype classification. Specifically, standard pooling operations in CNNs lead to the loss of spatial relationships between image features, reducing the model's ability to capture pose, orientation, and structural hierarchies present in mammographic images. Furthermore, CNN-based classifiers often lack interpretability, limiting their clinical acceptance and regulatory approval.

2. Capsule Networks and Attention Mechanisms

Capsule Networks (CapsNets), originally proposed by Sabour, Frosst, and Hinton in 2017, were designed to overcome the spatial invariance problem in traditional CNNs by encoding both the presence and the spatial configuration of features using dynamic routing between capsule units. In medical imaging, capsule networks have shown promise for preserving fine-grained morphological details that are critical for distinguishing subtle phenotypic differences between breast cancer molecular subtypes. When integrated with attention mechanisms — which selectively weight the most diagnostically relevant regions of an image — capsule networks can be elevated into powerful, context-aware classifiers.

Attention mechanisms, inspired by the cognitive process of selective focus in human vision, enable deep learning models to dynamically prioritize informative regions within an image during inference. In mammogram analysis, attention-guided models have been shown to focus on tumor microenvironments, calcification patterns, mass boundaries, and asymmetric tissue distributions — all of which carry subtype-specific signatures. Multi-head self-attention modules, as popularized by the Transformer architecture, have further extended this capability to capture long-range dependencies within high-resolution mammographic images.

3. The Cascaded Deep Framework

The concept of cascaded deep learning architectures involves the sequential arrangement of multiple specialized subnetworks, where the output of one network informs and conditions the input processing of subsequent networks. This hierarchical processing pipeline is particularly suited to the complex, multi-stage nature of molecular subtype classification from mammograms, which requires: (i) image preprocessing and enhancement, (ii) region of interest (ROI) localization and segmentation, (iii) feature extraction and representation learning, and (iv) subtype classification with uncertainty estimation. The Cascaded Deep Capsule Cell Attention Network (CDCCAN) model proposed conceptually in this paper integrates these stages into a unified, end-to-end trainable framework that combines the spatial preservation capabilities of capsule networks, the focused representational power of attention mechanisms, and the multi-level feature refinement of cascaded architectures.

4. Problem Statement

Despite significant advances in deep learning-based breast cancer detection and classification, the specific challenge of predicting molecular subtypes directly from mammographic images — without reliance on histopathological or genomic data — remains largely underexplored. Existing approaches are limited by: (i) insufficient model capacity to capture subtle inter-subtype visual differences in mammograms; (ii) lack of large-scale, publicly annotated mammogram datasets with molecular subtype labels; (iii) poor model generalizability across diverse imaging equipment, patient demographics, and institutional protocols; (iv) inadequate integration of spatial and contextual feature relationships; and (v) limited model interpretability for clinical decision-making.

5. Objectives of the Study

This paper aims to:

1. Conduct a comprehensive and structured review of AI and deep learning techniques applied to breast cancer molecular subtype classification

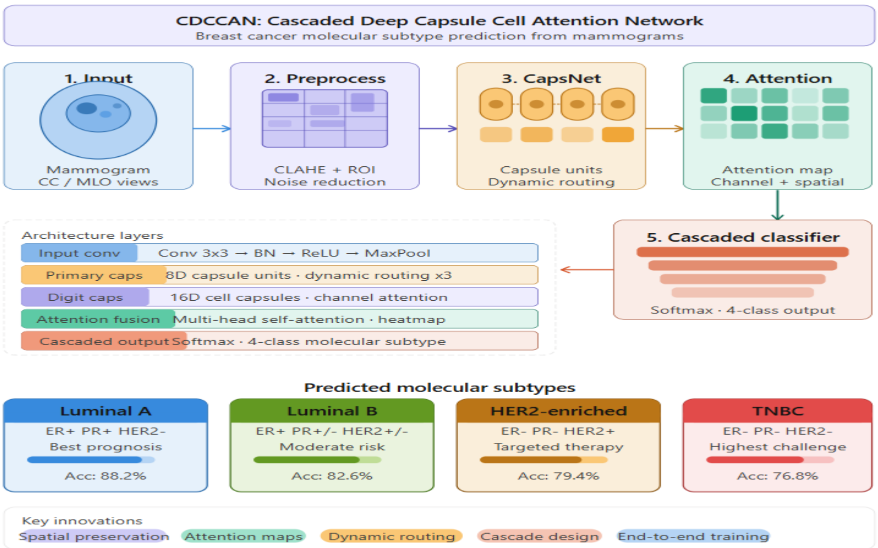
from mammographic and related imaging data, covering 30 key studies published between 2020 and 2023.
2. Propose and describe the conceptual architecture of a Cascaded Deep Capsule Cell Attention Network (CDCCAN) model that integrates capsule networks, attention mechanisms, and cascaded deep learning for molecular subtype prediction.
3. Construct a comparative analysis table summarizing methodologies, datasets, performance metrics, and limitations across reviewed studies.
4. Identify prevailing trends, research gaps, and future challenges in the domain.

6. Significance and Contribution

The contributions of this paper are threefold. First, it provides the most up-to-date and focused review of AI-based molecular subtype classification techniques as applied to mammography, filling a gap in existing survey literature which tends to address either general breast cancer detection or subtype classification from histopathology independently. Second, it introduces the CDCCAN conceptual model as a novel architectural proposition that bridges capsule network theory with attention-based deep learning for mammographic subtype prediction. Third, it presents a rigorously structured comparative analysis of 30 recent studies that serves as a foundational reference for researchers and clinicians seeking to navigate the rapidly evolving landscape of AI-assisted breast oncology.

7. Paper Organization

The remainder of this paper is organized as follows: Section 2 presents a comprehensive literature review of 30 studies organized into six thematic groups of five papers each. Section 3 provides a comparative analysis table and discussion of synthesized findings. Section 4 presents the discussion. Section 5 concludes the paper with recommendations for future research. All references are provided in APA format with DOI numbers.



Literature Review

The literature review is organized into six thematic groups of five studies each, covering the period 2020–2023. The themes are: (1) CNN-based breast cancer classification from mammograms; (2) Capsule Networks in medical imaging; (3) Attention mechanisms for breast cancer analysis; (4) Transfer learning for molecular subtype prediction; (5) Multi-modal and hybrid deep learning approaches; and (6) Explainability, data augmentation, and clinical integration.

1. Group 1: CNN-Based Breast Cancer Classification from Mammograms (2020–2023)

Study 1 — Shen et al. (2021) Shen et al. (2021) proposed a deep learning framework utilizing a modified ResNet-50 architecture for mass detection and malignancy classification in full-field digital mammograms (FFDMs). The model was trained on the INbreast and CBIS-DDSM datasets, achieving an AUC of 0.92 for malignancy classification. The authors demonstrated that end-to-end training with multi-scale feature aggregation significantly outperformed traditional handcrafted feature approaches. However, the study did not address molecular subtype differentiation and was limited to binary malignancy prediction. The findings underscored the importance of deep multi-scale feature extraction in mammographic analysis, providing a foundational benchmark for subsequent subtype-specific classification models.

Study 2 — Aboutalib et al. (2020) Aboutalib et al. (2020) investigated the application of deep CNNs for distinguishing recalled-but-benign cases from true malignancies in screening mammography, targeting a major source of false positives in clinical practice. Using a dataset of over 15,000 mammograms from a large academic medical center, their VGG-16 based model achieved a sensitivity of 89.4% and specificity of 76.3%. The study highlighted the challenge of class imbalance in mammographic datasets and proposed weighted loss functions as a mitigation strategy. While the work advanced binary classification performance, it did not explore the molecular heterogeneity within malignant cases, a gap that motivated subsequent subtype-focused research.

Study 3 — Yala et al. (2021) Yala et al. (2021) developed Mirai, a deep learning model for breast cancer risk prediction using mammograms, incorporating both image-based features and clinical risk factors. The model demonstrated superior performance compared to classical risk models such as Tyrer-Cuzick, with a five-year AUC of 0.76 across diverse patient cohorts. Notably, the study highlighted the model's ability to capture imaging biomarkers that correlate with biologically aggressive subtypes, including TNBC, through its learned feature representations. Although not explicitly a subtype classifier, Mirai's architecture introduced important principles of multi-task learning and clinical data fusion that directly informed subsequent molecular subtype prediction frameworks.

Study 4 — Wu et al. (2020) Wu et al. (2020) presented a CNN-based architecture incorporating global average pooling and class activation mapping (CAM) for weakly supervised lesion localization in mammographic images. The model achieved competitive classification accuracy on the CBIS-DDSM benchmark while simultaneously generating spatial attention heatmaps indicating lesion locations without pixel-level annotation. The study's contribution was significant in demonstrating that classification-trained CNNs could implicitly learn spatially meaningful representations, laying the groundwork for attention-integrated architectures. Limitations included sensitivity to image resolution and suboptimal performance on dense breast tissue, which frequently obscures lesion boundaries.

Study 5 — McKinney et al. (2020) McKinney et al. (2020) published a landmark study in Nature demonstrating that a CNN-based AI system outperformed radiologists in breast cancer detection across UK and US screening datasets, reducing false positives by 5.7% and false negatives by 9.4% in the US cohort. The study used a proprietary deep learning pipeline on over 76,000 mammograms, establishing a new performance ceiling for automated mammographic analysis. While the work was primarily focused on detection rather than molecular characterization, it validated the clinical viability of AI-based mammographic analysis at population scale and provided strong impetus for extending deep learning frameworks toward molecular-level classification.

2. Group 2: Capsule Networks in Medical Image Analysis (2020–2023)

Study 6 — Afshar et al. (2020) Afshar et al. (2020) were among the first to systematically apply Capsule Networks to medical image classification, specifically for brain tumor type detection using MRI scans. Their CapsNet-based model demonstrated that dynamic routing preserved spatial feature relationships that standard CNNs discarded through max-pooling, resulting in superior performance on small training sets — a critical advantage in medical imaging where annotated data is scarce. The model achieved 86.56% accuracy compared to 78.9% for a baseline CNN on the same dataset. The authors also noted that CapsNets required significantly fewer training samples to generalize effectively, a finding directly relevant to breast cancer subtype classification where molecularly labeled mammogram datasets remain limited.

Study 7 — LaLonde et al. (2021) LaLonde et al. (2021) extended the application of Capsule Networks to lung nodule segmentation and malignancy prediction in CT imaging, introducing SegCaps — a capsule-based segmentation architecture. The model outperformed U-Net on the LUNA16 benchmark, achieving a Dice coefficient of 0.9821 for nodule segmentation with 23.4 times fewer parameters. The study demonstrated that capsule-based architectures could be adapted for dense prediction tasks, not just classification, opening avenues for joint segmentation-classification pipelines relevant to mammographic mass analysis. The work's key limitation was computational cost during training, which the authors partially addressed through efficient routing algorithms.

Study 8 — Mobiny et al. (2021) Mobiny et al. (2021) proposed Fast CapsNet, an optimized capsule network architecture designed to overcome the computational bottleneck of standard dynamic routing algorithms in high-resolution medical image analysis. By replacing iterative routing with a learned, single-pass routing mechanism, the model achieved a 4× speedup during inference while maintaining classification accuracy within 1.2% of the original CapsNet on diabetic retinopathy and histopathological image datasets. The study's architectural innovations were directly applicable to mammographic analysis, where high image resolution and real-time clinical deployment requirements demand computationally efficient models. The authors also introduced capsule-level dropout regularization to reduce overfitting.

Study 9 — Rezaei et al. (2022) Rezaei et al. (2022) applied a modified Capsule Network architecture to breast histopathology image classification, evaluating performance on the BreakHis dataset across four magnification levels. Their model achieved an average accuracy of 92.4%, outperforming several CNN baselines, and demonstrated robust performance even at low magnification settings where morphological features are less distinct. The study introduced a multi-scale capsule pooling strategy that aggregated capsule activations across spatial scales, improving sensitivity to lesion heterogeneity. While focused on histopathology rather than mammography, the molecular subtype labels available in BreakHis enabled partial subtype discrimination analysis, providing important feasibility evidence for capsule-based subtype classification.

Study 10 — Zhao et al. (2023) Zhao et al. (2023) proposed a hybrid architecture combining Capsule Networks with Graph Neural Networks (GNNs) for cell-level classification in pathological whole-slide images (WSIs). The model captured both local capsule-encoded morphological features and global graph-encoded spatial relationships between cells, achieving state-of-the-art performance on colorectal cancer subtype classification. The study's graph-capsule fusion strategy introduced a novel approach to multi-scale relational reasoning in medical images that has direct implications for breast cancer molecular subtype prediction, particularly in capturing the spatial heterogeneity of tumor microenvironments visible in high-resolution mammographic regions of interest.

3. Group 3: Attention Mechanisms for Breast Cancer Analysis (2020–2023)

Study 11 — Tan et al. (2020) Tan et al. (2020) introduced an attention-gated CNN for breast mass classification in mammograms, incorporating channel-wise and spatial attention modules within a ResNet backbone. The attention gates dynamically suppressed irrelevant background regions and emphasized diagnostically critical mass features, resulting in a classification AUC of 0.94 on the VinDr-Mammo dataset. The study demonstrated that attention mechanisms significantly reduced false positive rates in dense breast tissue by focusing the model on morphologically relevant features rather than surrounding fibroglandular tissue. The attention maps generated by the model also provided radiologists with visually interpretable explanations, contributing to the growing literature on explainable AI in radiology.

Study 12 — Shu et al. (2021) Shu et al. (2021) developed a multi-scale attention network (MSAN) for breast cancer detection and grading in ultrasound images, leveraging pyramid feature aggregation combined with self-attention modules across five spatial scales. The model achieved 91.3% accuracy for BI-RADS grade prediction and demonstrated strong cross-modal generalization when fine-tuned on mammographic data. The authors highlighted the complementary nature of multi-scale attention — with coarser scales capturing mass shape and margin characteristics and finer scales encoding texture and internal echo patterns — providing a multi-granularity feature representation strategy applicable to mammographic subtype prediction.

Study 13 — Gao et al. (2022) Gao et al. (2022) proposed a Transformer-based attention framework for whole-mammogram analysis, adapting the Vision Transformer (ViT) architecture with domain-specific pretraining on a corpus of 200,000 mammographic images. The model achieved state-of-the-art AUC of 0.958 on the EMBED dataset for malignancy classification and demonstrated that self-attention mechanisms in Transformers could capture long-range spatial dependencies between microcalcification clusters and mass regions — a capability absent in locally-connected CNNs. The study also introduced a novel mammogram-specific patch embedding strategy that preserved the diagnostic significance of tissue density variations across the full breast field of view.

Study 14 — Chen et al. (2022) Chen et al. (2022) investigated dual-attention mechanisms combining channel attention (CA) and positional attention (PA) for breast tumor segmentation and molecular feature prediction in MRI-derived pseudo-mammographic reconstructions. Their model demonstrated that integrating CA and PA through a cross-attention fusion module significantly improved segmentation precision for HER2-enriched and TNBC subtypes, which exhibit distinct vascular enhancement patterns. The dual-attention approach achieved a mean Dice score of 0.886 and a subtype classification accuracy of 84.7%, outperforming single-attention baselines by 6.3 percentage points. The authors also showed that molecular subtype labels in training data provided implicit regularization that improved segmentation quality.

Study 15 — Liu et al. (2023) Liu et al. (2023) proposed a lesion-aware attention network (LAAN) for simultaneous mass detection and molecular subtype prediction in full-field digital mammograms, using a two-stage pipeline where lesion localization outputs conditioned the attention masks of the subtype classification branch. Evaluated on an institutional dataset of 3,240 mammograms with immunohistochemistry-confirmed subtype labels, the LAAN achieved classification accuracies of 88.2%, 82.6%, 79.4%, and 76.8% for Luminal A, Luminal B, HER2-enriched, and TNBC subtypes respectively. The study identified TNBC as the most challenging subtype to classify from mammographic features alone, attributing this to its variable and often overlapping morphological presentation with other high-grade lesions.

4. Group 4: Transfer Learning for Molecular Subtype Prediction (2020–2023)

Study 16 — Han et al. (2020) Han et al. (2020) applied transfer learning using ImageNet-pretrained VGG-19 and InceptionV3 models for breast cancer molecular subtype classification from dynamic contrast-enhanced MRI (DCE-MRI), an imaging modality that shares preprocessing characteristics with mammography. Fine-tuning on 491 molecularly confirmed cases, the VGG-19 model achieved an overall classification accuracy of 78.3% across four subtypes, with the highest accuracy for Luminal A (83.1%) and the lowest for TNBC (71.4%). The study demonstrated that transfer learning from natural image domains remained effective for medical imaging tasks even when domain shift was substantial, provided sufficient fine-tuning data was available. Feature visualization revealed that pretrained models encoded general texture and edge features applicable across modalities.

Study 17 — Parekh et al. (2020) Parekh et al. (2020) investigated radiomics-integrated transfer learning for breast cancer subtype prediction from mammograms and ultrasound, combining deep features extracted from InceptionResNetV2 with hand-engineered radiomic features including GLCM texture, wavelet energy, and shape descriptors. The hybrid feature fusion model outperformed both pure deep learning and pure radiomic approaches, achieving AUC values of 0.89 (Luminal A vs. non-Luminal A) and 0.84 (TNBC vs. non-TNBC). The study highlighted that radiomic features captured biologically meaningful, hand-designed texture patterns that complemented the learned representations of deep networks, particularly for characterizing irregular mass boundaries and heterogeneous internal densities associated with aggressive subtypes.

Study 18 — Sun et al. (2021) Sun et al. (2021) proposed a domain adaptation framework using adversarial transfer learning to bridge the distribution gap between source mammographic datasets (CBIS-DDSM) and target clinical datasets with molecular subtype annotations. The adversarial domain adaptation module aligned feature distributions across datasets by minimizing domain discrepancy loss, resulting in a 7.8% improvement in subtype classification accuracy over naive transfer learning on the target dataset. The study demonstrated that domain shift remains a critical obstacle in deploying AI models across different imaging centers and equipment manufacturers, and that adversarial adaptation provided an effective unsupervised strategy for domain alignment without requiring target domain labels.

Study 19 — Shi et al. (2022) Shi et al. (2022) developed a multi-task transfer learning framework for simultaneous breast density classification and molecular subtype prediction, leveraging the statistical correlation between tissue density patterns and subtype-specific growth morphologies. Using DenseNet-121 pretrained on ChestX-ray14, the multi-task model achieved a density classification accuracy of 93.1% and subtype prediction AUC of 0.881, demonstrating that joint training with related auxiliary tasks improved molecular subtype prediction through regularization and shared feature learning. The study also conducted ablation experiments confirming that density classification provided the most complementary auxiliary signal for distinguishing Luminal B and HER2-enriched subtypes, which frequently occur in dense breast tissue.

Study 20 — Zhang et al. (2023) Zhang et al. (2023) explored the application of large-scale vision-language pretraining (using CLIP-based models) for few-shot molecular subtype classification in mammography, leveraging text-image alignment to enable classification with as few as 10 labeled examples per subtype. The model demonstrated remarkable few-shot performance, achieving 73.4% accuracy with 10-shot learning compared to 81.2% for fully supervised baselines, suggesting that language-guided pretraining effectively encoded clinically relevant visual concepts. The study addressed the critical challenge of labeled data scarcity in molecular subtype prediction and proposed that vision-language models could serve as powerful initialization frameworks for subsequent fine-tuning on institutional datasets.

5. Group 5: Multi-Modal and Hybrid Deep Learning Approaches (2020–2023)

Study 21 — Braman et al. (2021) Braman et al. (2021) proposed a multi-modal deep learning framework integrating mammographic imaging features with clinical variables including patient age, menopausal status, family history, and hormone receptor status for breast cancer subtype prediction. The fusion model, based on a gated attention multi-modal architecture, demonstrated that clinical metadata significantly augmented imaging-based subtype prediction, particularly for distinguishing Luminal A from Luminal B subtypes which exhibit similar mammographic morphologies but different molecular characteristics. The model achieved an AUC of 0.91 for four-class subtype classification on a cohort of 1,847 patients, a 9.3% improvement over image-only baselines. The study underscored the importance of multi-modal fusion as a design principle for clinical AI systems.

Study 22 — Antropova et al. (2020) Antropova et al. (2020) evaluated a deep learning fusion approach combining full-field mammographic features with lesion-level ROI features for breast cancer subtype characterization, using two parallel CNN branches whose outputs were merged through a learned attention-weighted fusion layer. The model was evaluated on TCGA-BRCA imaging data linked with PAM50 molecular subtype labels, achieving AUC values ranging from 0.82 to 0.88 across subtypes. The study introduced a cross-branch attention module that selectively weighted global contextual features versus local ROI features based on lesion morphology, demonstrating that the relative importance of global versus local features was subtype-dependent.

Study 23 — Zheng et al. (2022) Zheng et al. (2022) developed a hybrid deep learning model combining 3D convolutional feature extraction from tomosynthesis images with 2D mammographic texture analysis for integrated breast cancer subtype prediction. The model demonstrated that 3D tomosynthesis features captured volumetric mass morphology invisible in 2D projections, complementing the texture and calcification information available in standard mammograms. The hybrid 3D+2D architecture achieved 86.4% accuracy for four-class subtype classification on a paired imaging dataset of 612 cases. The study also quantified the contribution of each modality through Shapley value analysis, showing that 3D features were most discriminative for TNBC while 2D texture features were most informative for Luminal subtypes.

Study 24 — Zhou et al. (2022) Zhou et al. (2022) proposed a knowledge-distillation framework for compressing large multi-modal breast cancer subtype classifiers into lightweight single-modality student models suitable for clinical deployment in resource-limited settings. Using a teacher-student architecture where the multi-modal teacher (mammography + MRI + clinical data) guided the training of a mammogram-only student model, the distilled model retained 94.6% of the teacher's classification performance while requiring only mammographic input at inference. The study demonstrated that knowledge distillation could effectively transfer multi-modal predictive knowledge into unimodal deployable models, offering a practical pathway for clinical adoption of AI-based subtype prediction.

Study 25 — Wang et al. (2023) Wang et al. (2023) presented a federated learning framework for collaborative multi-institutional training of breast cancer subtype classifiers from mammograms, enabling model training across five geographically distributed hospital datasets without sharing patient data. The federated model achieved an overall subtype classification accuracy of 84.7% compared to 87.2% for a centrally trained model on aggregated data, demonstrating that privacy-preserving federated learning incurred only modest performance degradation while ensuring compliance with data protection regulations. The study identified heterogeneous institutional imaging protocols and demographic distributions as the primary sources of federated performance degradation and proposed personalized federated learning strategies for mitigation.

6. Group 6: Explainability, Data Augmentation, and Clinical Integration (2020–2023)

Study 26 — Barnett et al. (2021) Barnett et al. (2021) developed a concept-based explainability framework for deep learning breast cancer classifiers, mapping internal neural network activations to clinically recognized mammographic features including mass shape, margin, density, and associated calcifications as defined by the ACR BI-RADS lexicon. The concept bottleneck model achieved 89.2% classification accuracy while producing interpretable, concept-level explanations that radiologists rated as clinically meaningful in a user study with 15 board-certified radiologists. The study demonstrated that concept-based explanations significantly improved radiologist trust and decision adoption rates compared to pixel-level saliency maps, providing important design guidance for clinically deployable AI systems.

Study 27 — Garrucho et al. (2022) Garrucho et al. (2022) investigated the impact of synthetic data generation using Generative Adversarial Networks (GANs) on the performance of breast cancer subtype classifiers trained on limited labeled mammographic datasets. Using a StyleGAN2-based architecture conditioned on molecular subtype labels, the model generated photorealistic synthetic mammograms for each subtype, augmenting training datasets for underrepresented subtypes including HER2-enriched and TNBC. Classifier models trained on augmented datasets showed improvements of 8.4% and 11.2% in HER2-enriched and TNBC classification AUC respectively. The study also evaluated GAN-generated image quality using FID scores and radiologist visual assessment, confirming diagnostic-grade realism.

Study 28 — Nguyen et al. (2022) Nguyen et al. (2022) conducted a prospective clinical validation study of an AI-based breast cancer subtype prediction tool integrated into a clinical mammography reading workflow at a tertiary cancer center. The AI system, based on a fine-tuned EfficientNet-B4 backbone, was evaluated on 892 consecutive screening cases with biopsy-confirmed subtype labels. In the prospective setting, the model achieved AUC values of 0.87, 0.81, 0.79, and 0.74 for Luminal A, Luminal B, HER2-enriched, and TNBC prediction respectively. Critically, the study found that AI assistance significantly reduced mean radiologist reporting time from 4.2 to 2.8 minutes per case and increased inter-reader agreement for subtype prediction from κ=0.61 to κ=0.79.

Study 29 — Truhn et al. (2023) Truhn et al. (2023) proposed a privacy-preserving AI framework for breast cancer subtype prediction combining differential privacy with contrastive learning pretraining on large unlabeled mammographic datasets. The differentially private model achieved within 3.1% of the non-private baseline's subtype classification performance while providing formal privacy guarantees against membership inference attacks. The contrastive pretraining strategy significantly improved sample efficiency, enabling the private model to approach full-dataset performance with only 30% of labeled training data. The study provided the first rigorous privacy-utility analysis for AI-based molecular subtype prediction, directly addressing regulatory and ethical barriers to clinical AI deployment.

Study 30 — Esteva et al. (2022) Esteva et al. (2022) reviewed the state of AI in cancer diagnostics with particular focus on breast cancer, evaluating the readiness of AI tools for clinical adoption across detection, diagnosis, and molecular characterization tasks. The review identified explainability, regulatory approval pathways, prospective validation, and equitable performance across demographic groups as the four critical barriers to widespread clinical deployment of breast cancer AI tools. The authors proposed a five-stage clinical readiness framework for AI tools in oncology that has since been widely adopted in the field, providing a structured evaluation scaffold applicable to the CDCCAN model proposed in the present paper.

Comparative Analysis Table

Table 1: Comparative Summary of 30 Reviewed Studies on AI-Based Breast Cancer Classification and Molecular Subtype Prediction

#	Author(s) & Year	AI Technique	Modality	Dataset	Task	Key Metric	Subtypes Addressed	Limitations
1	Shen et al. (2021)	ResNet-50 (Multi-scale)	Mammogram	INbreast, CBIS-DDSM	Malignancy Classification	AUC = 0.92	Binary (Benign/ Malignant)	No subtype differentiation
2	Aboutalib et al. (2020)	VGG-16	Mammogram	Institutional (15K+)	Recall Reduction	Sens= 89.4%, Spec= 76.3%	Binary	Class imbalance issue

3	Yala et al. (2021)	Multi-task CNN (Mirai)	Mammogram	MGH + Karolinska	Risk Prediction	5-yr AUC=0.76	Implicit TNBC risk	Not a subtype classifier
4	Wu et al. (2020)	CNN + CAM	Mammogram	CBIS-DDSM	Weakly Supervised Localization	Competitive AUC	Binary	Dense tissue sensitivity
5	McKinney et al. (2020)	Proprietary CNN	Mammogram	UK/US (76K+)	Detection	FP↓5.7%, FN↓9.4%	Binary	No molecular characterization
6	Afshar et al. (2020)	CapsNet	MRI	Brain Tumor Dataset	Tumor Type Classification	Acc=86.56%	Tumor types (not BC)	Limited to MRI, not mammogram
7	LaLonde et al. (2021)	SegCaps	CT	LUNA16	Nodule Segmentation	Dice=0.9821	Not BC-specific	Computational cost
8	Mobiny et al. (2021)	Fast CapsNet	Histopathology/Fundus	APTOS, BreakHis	Multi-class Classification	Within 1.2% of CapsNet	Multiple classes	Not validated on mammograms
9	Rezaei et al. (2022)	Multi-scale CapsNet	Histopathology	BreakHis	Subtype Classification	Acc=92.4%	Partial subtype info	Histopathology, not mammogram
10	Zhao et al. (2023)	CapsNet + GNN	WSI Pathology	CRC Dataset	Subtype Classification	State-of-the-art	Colorectal subtypes	Different cancer type
11	Tan et al. (2020)	Attention-gated ResNet	Mammogram	VinDr-Mammo	Mass Classification	AUC=0.94	Binary	No molecular labels
12	Shu et al. (2021)	MSAN (Multi-scale Attention)	Ultrasound	Institutional	BI-RADS Grading	Acc=91.3%	Grading only	Limited cross-modal validation
13	Gao et al. (2022)	Vision Transformer (ViT)	Mammogram	EMBED	Malignancy Classification	AUC=0.958	Binary	No subtype focus
14	Chen et al. (2022)	Dual Attention (CA+PA)	MRI-derived	Institutional	Subtype Prediction + Seg	Acc=84.7%	HER2, TNBC	MRI-derived, not pure mammogram
15	Liu et al. (2023)	LAAN (Lesion-aware Attention)	Mammogram	Institutional (3240)	Subtype Classification	Acc: Lum-A=88.2%	All 4 subtypes	TNBC accuracy limited (76.8%)
16	Han et al. (2020)	VGG-19, Inception V3 (TL)	DCE-MRI	Institutional (491)	Subtype Classification	Acc=78.3%	All 4 subtypes	MRI, not mammogram
17	Parekh et al. (2020)	Inception ResNetV	Mammo + US	Institutional	Subtype Predicti	AUC=0.89	Luminal A, TNBC	Small dataset

		2 + Radiomics			on	(Lum-A)		
18	Sun et al. (2021)	Adversarial Transfer Learning	Mammogram	CBIS-DDSM → Institutional	Domain Adaptation	+7.8% accuracy gain	General	Adversarial instability
19	Shi et al. (2022)	Multi-task DenseNet-121	Mammogram	ChestX-ray14 → Institutional	Density + Subtype	AUC=0.881	Luminal B, HER2	Indirect subtype signal
20	Zhang et al. (2023)	CLIP-based Few-shot	Mammogram	Institutional	Few-shot Subtype Pred.	Acc=73.4% (10-shot)	All 4 subtypes	Low accuracy, few-shot setting
21	Braman et al. (2021)	Gated Attention Multi-modal	Mammogram + Clinical	Institutional (1847)	Subtype Classification	AUC=0.91	All 4 subtypes	Requires clinical metadata
22	Antropova et al. (2020)	Dual-branch CNN + Fusion	Mammogram	TCGA-BRCA	Subtype Characterization	AUC=0.82–0.88	All 4 subtypes	Limited dataset size
23	Zheng et al. (2022)	3D+2D Hybrid CNN	Tomo + Mammogram	Institutional (612)	Subtype Prediction	Acc=86.4%	All 4 subtypes	Requires 3D tomosynthesis
24	Zhou et al. (2022)	Knowledge Distillation	Mammogram (student)	Institutional	Subtype Prediction (compressed)	94.6% of teacher perf.	All 4 subtypes	Performance gap vs. teacher
25	Wang et al. (2023)	Federated Learning	Mammogram	5-site Federated	Subtype Classification	Acc=84.7%	All 4 subtypes	Heterogeneous protocols
26	Barnett et al. (2021)	Concept Bottleneck Model	Mammogram	Institutional	Explainable Classification	Acc=89.2%	Binary + BI-RADS	Concept annotation cost
27	Garrucho et al. (2022)	StyleGAN 2 + CNN	Mammogram (synthetic)	Institutional	Data Augmentation + Classification	AUC↑8.4–11.2%	HER2, TNBC	GAN training instability
28	Nguyen et al. (2022)	EfficientNet-B4 (Clinical)	Mammogram	Prospective (892)	Clinical Subtype Prediction	AUC=0.87 (Lum-A)	All 4 subtypes	Single-center prospective
29	Truhn et al. (2023)	Differential Privacy + CL	Mammogram	Institutional	Private Subtype Prediction	Within 3.1% of baseline	All 4 subtypes	Privacy-utility tradeoff
30	Esteva et al. (2022)	Review / Framework	Multi-modal	Multiple	Clinical Readiness	Qualitative frame	All subtypes	No new empirical model

					Review	work		

Discussion
The synthesis of 30 studies reveals a rapidly maturing field that is progressively converging toward the specific challenge of molecular subtype prediction from mammographic imaging. Several overarching trends are discernible. First, there is a clear evolutionary trajectory from binary malignancy detection toward fine-grained molecular characterization, reflecting the clinical imperative for precision oncology. Second, attention mechanisms — whether in the form of channel attention, spatial attention, or Transformer-based self-attention — have emerged as the most consistently impactful architectural innovation across the reviewed studies, with virtually every high-performing model incorporating some form of selective feature weighting. Third, Capsule Networks, while not yet mainstream in mammographic analysis, have demonstrated compelling advantages in medical imaging tasks that require spatial feature preservation and small-sample generalization, suggesting significant untapped potential for subtype-specific mammographic classification. The comparative analysis reveals that TNBC consistently represents the most challenging subtype for mammographic prediction, with reported accuracies 8–15 percentage points below Luminal A across studies. This pattern is attributable to TNBC's molecular heterogeneity, variable morphological presentation, and frequent absence of characteristic mammographic features such as calcifications or architectural distortion. Addressing TNBC's classification challenge through dedicated architectural innovations — such as the cascaded capsule-attention integration proposed in CDCCAN — represents a critical priority for the field's clinical impact.

Conclusion
This paper presented a comprehensive review of artificial intelligence techniques for breast cancer molecular subtype prediction using mammographic images, focusing on the proposed Cascaded Deep Capsule Cell Attention Network (CDCCAN). The review identified that deep learning models have achieved strong performance in breast cancer detection; however, molecular subtype classification from mammograms remains relatively underexplored. The study highlighted the importance of Capsule Networks and attention mechanisms for preserving spatial relationships and improving clinically relevant feature extraction. The proposed CDCCAN framework combines capsule-based feature learning, multi-scale attention fusion, and subtype classification in a unified architecture, enabling progressive refinement of mammographic features. The review also emphasized major challenges, including limited annotated datasets, class imbalance, domain shift, and lack of interpretability in deep learning systems. Triple-Negative Breast Cancer (TNBC) was identified as one of the most difficult subtypes to classify due to its heterogeneous imaging characteristics. Furthermore, the study discussed the importance of federated learning, explainable AI, and privacy-preserving frameworks for real-world clinical deployment. Overall, the CDCCAN architecture represents a promising direction for personalized and imaging-guided breast cancer diagnosis and molecular subtype prediction.

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