



TOPICAL REVIEW

Artificial intelligence in breast imaging: potentials and challenges

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Abstract

Breast cancer, which is the most common type of malignant tumor among humans, is a leading cause of death in females. Standard treatment strategies, including neoadjuvant chemotherapy, surgery, postoperative chemotherapy, targeted therapy, endocrine therapy, and radiotherapy, are tailored for individual patients. Such personalized therapies have tremendously reduced the threat of breast cancer in females. Furthermore, early imaging screening plays an important role in reducing the treatment cycle and improving breast cancer prognosis. The recent innovative revolution in artificial intelligence (AI) has aided radiologists in the early and accurate diagnosis of breast cancer. In this review, we introduce the necessity of incorporating AI into breast imaging and the applications of AI in mammography, ultrasonography, magnetic resonance imaging, and positron emission tomography/computed tomography based on published articles since 1994. Moreover, the challenges of AI in breast imaging are discussed.

Abbreviations

Abbreviation Full Term

ABVS	Automated Breast Volume Scanning
AI	Artificial Intelligence
ALN	Axillary Lymph Node
ALNM	Axillary Lymph Node Metastasis
AUC	Area Under the Curve
BI-RADS	Breast Imaging Reporting and Data System
CAD	Computer-Aided Diagnosis
CNNs	Convolutional Neural Networks
CSCO	Chinese Society of Clinical Oncology
DCE	Dynamic Contrast-Enhanced
DCIS	Ductal Carcinoma <i>in Situ</i>
DL	Deep Learning

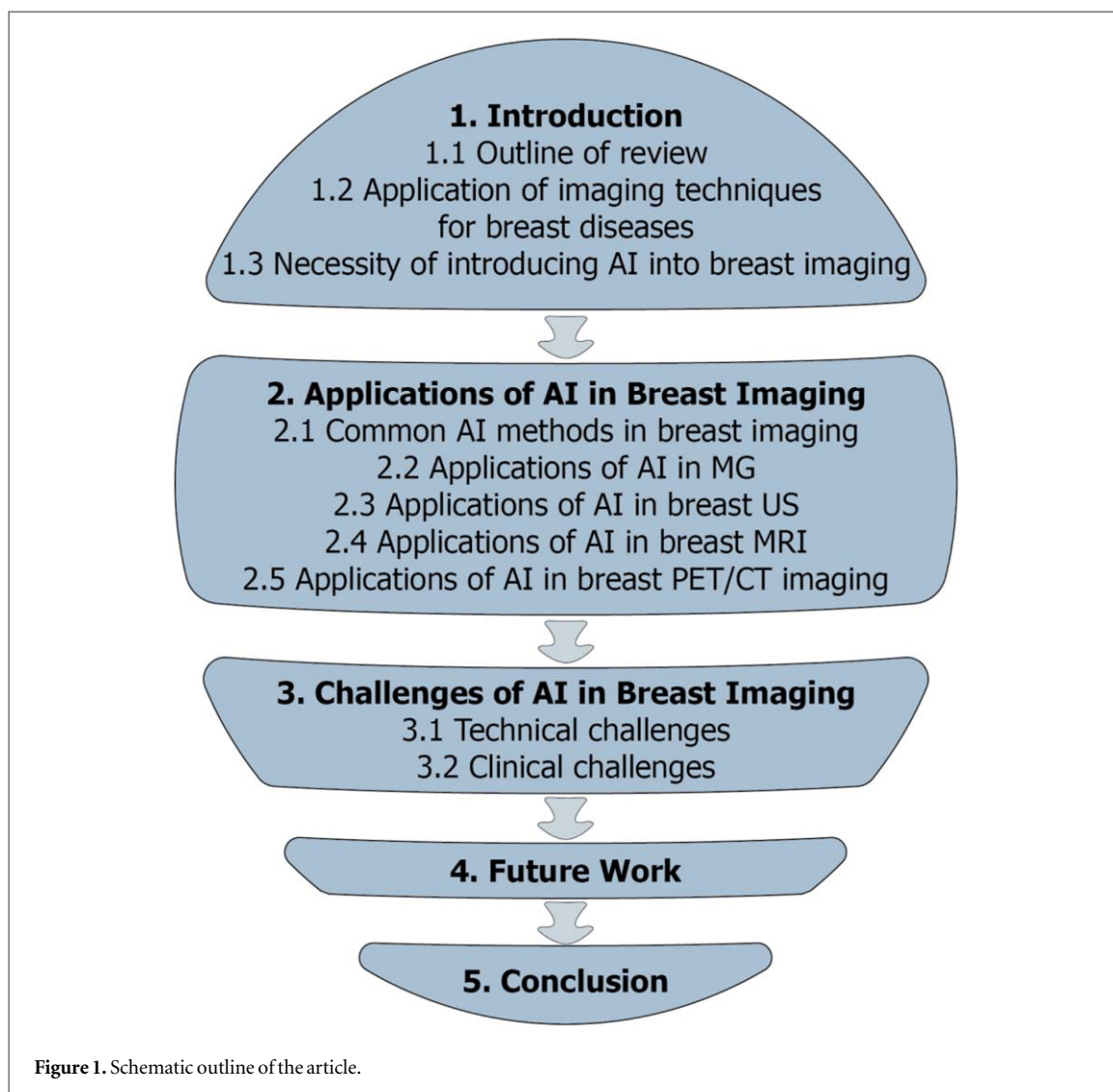
DWI	Diffusion-Weighted Image
FDA	Food and Drug Administration
FUSCC	Fudan University Shanghai Cancer Center
HER2	Human Epidermal Growth Factor 2
HR	Hormone Receptor
MG	Mammography
ML	Machine Learning
MRI	Magnetic Resonance Imaging
NAC	Neoadjuvant Chemotherapy
pCR	Pathological Complete Response
PET/CT	Positron Emission Tomography Combined with Computed Tomography
US	Ultrasonography
SUV _{max}	Maximum Standardized Uptake Value
3D	Three-Dimensional
TNBC	Triple-Negative Breast Cancer
T1WI	T1-Weighted Image
T2WI	T2-Weighted Image

1. Introduction

Breast cancer, which was previously the most common type of malignant tumor among females, has become the top-ranking malignant tumor in humans overall (Ferlay *et al* 2021). However, the mortality rate of 15.5% is much lower than the incidence rate of 24.5% among females (Ferlay *et al* 2021). The promising prognosis is a result of the efforts of scientists and breast physicians, who have worked on understanding precise subtypes and personalized therapy in the past two decades. Specialists have found that breast cancer is a disease with the prospect of precise therapy. Breast cancer can be divided into unique groups using the immunohistochemical expression profile typically based on estrogen/progesterone receptor statuses, and expression of human epidermal growth factor 2 (HER2) (Goldhirsch *et al* 2013). Each subtype exhibits specific biological tumor characteristics. The significant advancements in surgery, radiotherapy, endocrine therapy, chemotherapy, and targeted treatment of patients based on molecular subtypes have laid the foundation for the precise classification and personalized treatment of breast cancer. Despite this progress in the treatment of breast cancer, tumor heterogeneity, the diversity within the tumor and/or among different patients (Turashvili and Brogi 2017) is a non-negligible factor in determining optimal treatment strategies and prognosis of breast cancer (Coates *et al* 2015, Prat *et al* 2015, Harbeck and Gnant 2017). The luminal subtype is characterized by a high incidence of long-term recurrence (Gao and Swain 2018), the HER2 subtype is likely to be resistant to targeted therapeutic medicine (Ocaña *et al* 2020), and the triple-negative subtype has a poor prognosis within five years (Hwang *et al* 2019). In addition, according to the authors' experience, tumor heterogeneity is an obstacle to the accurate and early diagnosis of certain atypical breast tumors (Li *et al* 2018). Delayed diagnosis may inevitably affect the timely treatment of breast cancer patients.

Imaging plays an important role in breast cancer screening and diagnosis. Mammography (MG) and ultrasonography (US) are the preferred techniques for breast cancer screening and diagnosis. Magnetic resonance imaging (MRI) provides high sensitivity for breast cancer detection and diagnosis. Positron emission tomography combined with computed tomography (PET/CT) is important in the management of breast cancer patients. With the recent advancements in imaging technologies, most breast cancers can be recognized with prompt diagnosis and efficient consecutive therapies. However, as mentioned above, tumor heterogeneity is a major obstacle to the precise diagnosis of certain atypical or very early breast cancers, such as triple-negative breast cancer (TNBC) (Li *et al* 2018), mucinous breast cancers (Ginter *et al* 2020, Pintican *et al* 2020), and ductal carcinoma *in situ* (Watanabe *et al* 2017). In these cases, physician experience is of limited value, as human eyes cannot differentiate the subtle differences in the images.

To assist radiologists, scientists have been trying to introduce the intelligent algorithms that can respond in a similar manner as human beings, which is known as artificial intelligence (AI). As a branch of computer science, AI is a technological process that simulates, extends, and expands human cognitive thinking to complete a task through extracting and synthesizing abstract information. The application of AI to the medical imaging field was first proposed in the 1990s (Shen *et al* 2021b). As breast cancer is the most common malignant tumor in females,



early and precise diagnosis and treatment have a significant potential impact on patients, thereby motivating innovation in the application of AI techniques (Morgan and Mates 2021). AI has been proved to be valuable for breast cancer screening, detection, differential diagnosis, molecular subtyping, treatment response and prognosis prediction, etc, regarding to the commonly used breast imaging techniques. Recently, as summarized by Bahl, there have been about twenty AI applications that are approved by the Food and Drug Administration (FDA) for MG, breast US, and breast MRI (Bahl 2022).

In the literature, there have been a number of review articles about AI applications in breast imaging written from multiple perspectives (Le *et al* 2019, Mendelson 2019, Bahl 2020, Hickman *et al* 2021, Morgan and Mates 2021, Bitencourt *et al* 2021). Compared with previous reviews, in this article, we will address the issue of tumor heterogeneity which is one of the most important justifications for introducing AI in breast imaging. In addition, the applications of AI in breast PET/CT are summarized in the present article.

1.1. Outline of review

A schematic outline of this review is presented in figure 1. In the Introduction section, the applications of *in vivo* patient imaging techniques for breast diseases are highlighted, followed by the introduction of AI into breast imaging. Based on published articles since 1994, the following sections of the article present the applications of AI in breast imaging, which include: (1) common AI methods that are used for breast imaging, (2) applications of AI in MG, (3) applications of AI in breast US, (4) applications of AI in breast MRI, and (5) applications of AI in breast PET/CT. Subsequently, the technical and clinical challenges of AI in breast imaging are discussed, followed by an outline of future work and conclusions.

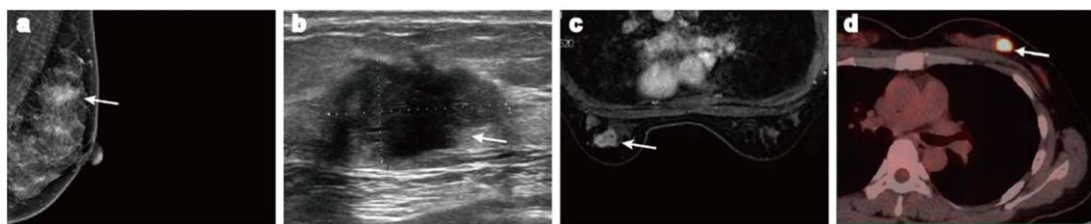


Figure 2. Digital MG, US, MRI and PET-CT scans of a 42 y old woman with an infiltrating ductal carcinoma in the left breast, indicated with the white arrows. (a): MG, (b): US, (c): MRI, (d): PET-CT.

1.2. Application of imaging techniques for breast diseases

MG and US have been recognized as the most common imaging techniques for the detection of breast cancer (Guo *et al* 2018a). MG is the primary diagnostic technique that is used in screening programs, particularly in Western countries. MG can detect microcalcifications that are invisible in US (Jackson 2004). Nevertheless, it exhibits certain limitations in the case of dense breasts, which are common in Asian women and young women. US is complementary to MG in the detection of breast cancer. In China, US is usually recommended as an effective combination with MG as the first choice for breast screening and the differential diagnosis of benign and malignant breast masses (CSCO 2021). As no radiation-related damage occurs, it is suitable for any age and physiological period of females, particularly for pregnant or lactating women. US also offers advantages in the detection of potentially malignant changes in axillary lymph nodes (Guo *et al* 2018a).

Among the available imaging modalities, MRI provides the highest sensitivity for breast cancer detection and diagnosis (Mann *et al* 2019). It is currently used as an adjunct to MG screening, especially for high-risk patients. As stratified by American Cancer Society, the risk factors for breast cancers mainly include genetic mutations, family history, and clinical risk factors such as thoracic radiotherapy, lobular neoplasia, ductal hyperplasia, and high mammographic density (Saslow *et al* 2007). Furthermore, it is an indispensable tool for assessing the preoperative stage, evaluating the treatment response, and diagnosing difficult and complicated cases (Mann *et al* 2019). MRI can provide more detailed information through a variety of scanning sequences compared to other imaging modalities. The dynamic contrast-enhanced (DCE) image and post-contrast T1-weighted image (T1WI), which provide the morphological and kinetic features of breast lesions observed after contrast material administration, form the basis for breast MRI protocols. The T2-weighted image (T2WI) enables the visualization of cysts, edema, and necrosis owing to their liquid nature, and such information is important for prognostic assessment. The diffusion-weighted image (DWI) quantifies the random movement of water molecules in tissues, which is associated with tissue microstructure and cell density (Mann *et al* 2019). However, owing to its high cost and long image acquisition time, MRI is not as popular as MG and US imaging.

PET/CT can provide three dimensional (3D) map of the activity distribution of a radioactive tracer, which in the case of ^{18}F -FDG can be used to estimate the glucose metabolism in tissues and standard metabolic parameters, including the maximum standardized uptake value (SUV_{max}), metabolic tumor volume, and total lesion glycolysis. However, compared with US, MG, and MRI, PET/CT is not suitable for breast cancer screening because of its high cost and radiation exposure. Its main applications include the staging and evaluation of the treatment response and suspected recurrence or metastasis (Fowler and Cho 2021, Kikano *et al* 2021, Sarikaya 2021).

In clinical practice, MG, US, MRI and PET-CT are applied selectively and complementarily to aid in the screening, diagnosis, treatment response monitor and prognosis prediction (figure 2). With the advancement of imaging technology, the amount of data is increasing which is time consuming for radiologists. For example, with the introduction of digital breast tomosynthesis, a stack of 2D slices of the imaged breast, although the diagnostic performance is increased, the interpretation time for radiologists almost doubles compared with MG (Skaane *et al* 2013). The similar issue also arises for automated breast volume scanning (ABVS) (Ibraheem *et al* 2022) and multi-parametric MRI imaging comprising ~ 5 imaging sequences (Mann *et al* 2019). Therefore, automated methods of interpreting these images are highly demanded to reach a balance between diagnostic performance and interpretation time. On the other hand, the performance of breast imaging is closely related to the heterogeneity of breast cancers especially for the prediction of treatment response and prognosis. Due to the heterogeneity, human interpretation without powerful computation is limited to achieve the best performance for differentiating different biological subtypes with a variety of possible treatments, predicting the response to therapy and overall survival. These noninvasive observations and predictions which are beyond traditional detection and diagnosis are important parts in the era of individualized and precision medicine. AI has been introduced in the context of advanced imaging and the demand of powerful computations.

1.3. Necessity of introducing AI into breast imaging

In 2021, the Chinese Society of Clinical Oncology guidelines stressed the important role of AI in the field of tumor diagnosis and treatment with an increasing application in clinical practice (CSCO 2021). AI is gaining attention in the diagnosis and treatment of breast cancer, the prediction of survival prognosis, and the prediction of treatment response after neoadjuvant chemotherapy (NAC) owing to its powerful computing and learning ability (Bahl 2020).

In recent years, AI-assisted imaging diagnosis has flourished with the evolution of big data and computational frameworks. The role of conventional computer-aided diagnosis (CAD) is expanding beyond screening and differential diagnosis toward applications in therapy evaluation and risk assessment (Giger 2010, Mendelson 2019). Moreover, intelligent output can be obtained from automated analysis based on images that are collected by radiologists to assist in detecting lesion, determining the lesion malignancy rate, evaluating the response to therapy, and predicting the prognosis.

AI may reduce human efforts in terms of detecting suspicious nodules or masses in US or MG images in the screening field. At the authors' institute, an US AI equipment has been developed for the automatic location of suspicious areas during US scanning which is valuable for inexperienced physicians (Hou *et al* 2022). Meanwhile, the commercial S-Detect technology has been used clinically to increase the confidence of US physicians in diagnosing breast nodules (Kim *et al* 2017, Sun *et al* 2022a).

The role of imaging has expanded from screening and diagnosis to the prediction of treatment efficacy and prognosis, considering the vast information that is hidden in the images. However, human eyes have a limited ability to achieve advanced predictions without the aid of AI such as the prediction of response to chemotherapy and prognosis of breast cancer based on imaging information (Galati *et al* 2022).

1.3.1. Tumor heterogeneity

It is well known that breast cancer is a type of heterogeneous malignant tumor comprising multiple distinct subtypes that differ on the clinical, histopathological, and genetic levels (Roulot *et al* 2016). Tumor heterogeneity is characterized by inter- and intra-tumor heterogeneity.

Inter-tumor heterogeneity has been described as the variety among different tumors, and it was extensively characterized in the 2000s owing to the development of high-throughput analyses (Zardavas *et al* 2015, Roulot *et al* 2016). Inter-tumor heterogeneity has implications for guiding the treatment of the four breast cancer subtypes (Goldhirsch *et al* 2013). Each subtype has specific biological characteristics and clinical behaviors, which provide the foundations for the precise treatment of breast cancer with a promising prognosis.

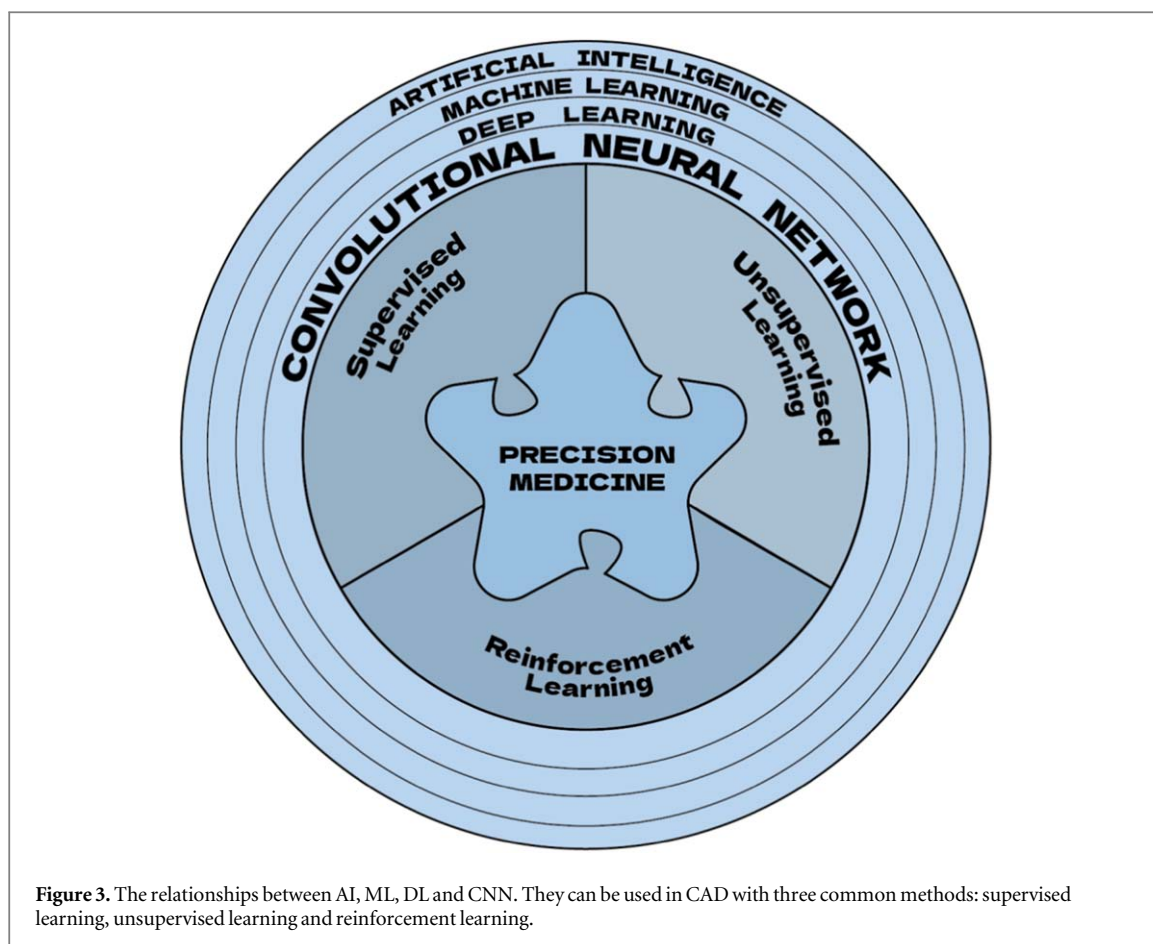
Intra-tumor heterogeneity has been identified within the different regions of the tumor (spatial heterogeneity), along with tumor progression (temporal heterogeneity). Pathological and immunohistochemical results that are obtained from a biopsy or a small portion of tumor specimens may not represent the overall tumor composition owing to the spatial heterogeneity. Therefore, it is important to recognize the spatial heterogeneity as it may be indicative of treatment effectiveness, with evidence that increases heterogeneity corresponds to a reduced likelihood of pathological complete response (pCR) (Januškevičienė and Petrikaitė 2019). Furthermore, tumors with more prominent heterogeneity may be resistant to therapy as they adapt to new microenvironmental conditions more easily (Issa-Nummer *et al* 2013, Almendro *et al* 2014).

In the era of precision medicine, it is important to capture the heterogeneity of each specific molecular subtype, as this biological variance enables such heterogeneity to be anticipated and adaptive therapeutic strategies to be sought. The imaging appearance is an integral phenotype of all proteomics and genomics (Aerts 2016). Therefore, the imaging feature of the breast mass is an important supplement to the local pathological and immunohistochemical characteristics in the development of precision medicine and personalized treatment. AI is expected to facilitate this integration because of the vast amount of information hidden in the images that it conveys.

1.3.2. Precision medicine and personalized treatment

Evidence-based medicine that results from a precise subtype of breast cancer can provide sufficient details for precision medicine in breast cancer. However, inter- and intra-tumor heterogeneity is an obstacle to the efficient treatment of all breast cancers. Thus, personalized treatment is in high demand to improve the outcome of breast cancer further (Jiang *et al* 2021d). Advanced research in multi-omics analysis and intra-tumor interaction with the microenvironment is warranted to enrich the evidence for personalized treatment.

Precision tumor medicine refers to the use of various omics detection technologies, including proteomics, transcriptomics, genomics, epigenomics, and metabolomics, to obtain tumor-related biological information for guiding tumor screening, diagnosis, and treatment (Pinker *et al* 2018, Sachdev *et al* 2019). Multigene mutation detection offers significant value for molecular subtyping, breast cancer risk prediction, and the selection of precise treatment plans. For example, the Fudan University Shanghai Cancer Center (FUSCC) subtype of TNBC has been established based on proteomics (Zhao *et al* 2020, Gong *et al* 2022), transcriptomics



(Liu *et al* 2016), genomics (Jiang *et al* 2019), and metabolomics (Gong *et al* 2021). It has been proven that the combination of AI imaging and multiple omics may achieve an FUSCC subtype more rapidly and easily (Jiang *et al* 2022a).

Precision medicine should consider the static omics of individual breast cancers as well as the dynamic omics during treatment and follow-up (Pinker *et al* 2018). Breast imaging offers the advantage of the dynamic surveillance of breast tumors throughout the whole process of screening, diagnosis and post-operative follow up. Therefore, in addition to biological omics, Pinker *et al* proposed the combination of quantitative radiomics which can extract valuable quantifiable data from digital medical images with multiple biological omics to provide dynamic surveillance for breast cancer (Pinker *et al* 2018). This approach is known as radiogenomics, which may link the complete imaging appearance with genetic information. Radiogenomics can quantify lesion characteristics to stratify benign and malignant breast tumors more effectively, thereby enabling precise diagnosis. It can also reflect the genetic information of a heterogeneous tumor and guide tailored therapy. After the therapy, radiogenomics can also incorporate imaging biomarkers with phenomics and genomics to predict recurrence risk.

2. Applications of AI in breast imaging

2.1. Common AI methods in breast imaging

The most frequently concerned AI models are machine learning (ML), deep learning (DL) and convolutional neural networks (CNNs) (Castiglioni *et al* 2021). The relationships between AI, ML, DL, and CNNs are depicted in figure 3. They are different in terms of the capability, complexity, interpretability, and the types of problems they're best suited for.

ML models primarily include support vector machines and random forests. Support vector machines group data into two or more classes through a 'hyperplane' that separates the categories as far as possible by analyzing numerous features (Kohli *et al* 2017). Random forests employ a collection of decision trees based on a random subset of features that are extracted from the training data. When a new input appears, the model makes a prediction (e.g. 'positive' or 'negative') for each tree and the voted result from all trees is considered as the best solution. These models are relatively straightforward and work well with structured, tabular data. They are less

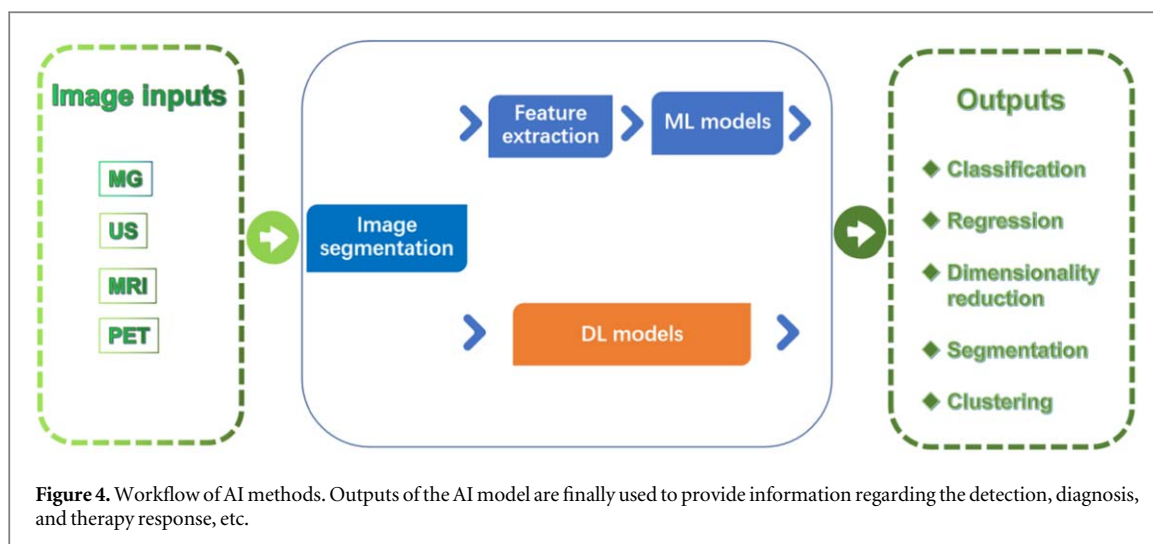


Figure 4. Workflow of AI methods. Outputs of the AI model are finally used to provide information regarding the detection, diagnosis, and therapy response, etc.

complex, easier to understand, and often provide good baseline models. However, they might not perform as well with extremely complex tasks or very large datasets. They also struggle with unstructured data, such as images or text.

DL, which is a subset of ML and offers the capability to cluster data and make predictions, uses neural networks to mimic the human brain (Tang *et al* 2018). The neural network consists of multiple layers of connected nodes, each of which receives input from other nodes with weights that are set randomly. DL models, can handle much more complex tasks and are particularly good at working with unstructured data like images, text, and audio. They can automatically learn and extract features from raw data, a process known as representation learning. However, they require large amount of data and computational resources. The complexity of DL models also makes them prone to overfitting if not properly regularized. Meanwhile, DL models are often referred to as 'black boxes' because it can be difficult to understand why they're making certain decisions. Some progress has been made in improving the interpretability of DL models (like attention mechanisms, feature visualization, etc), but it's still a significant challenge compared to traditional ML models.

As a subset of DL and the most common type of neural network, the CNN is suited to identify particular patterns in images which can occur at different locations because the convolution operation is spatially invariant (Burt *et al* 2018, Robertson *et al* 2018). In a systemic review, Nasser and Yusof found that CNN model has the most accurate performance with the most extensive application for breast cancer diagnosis (Nasser and Yusof 2023). A CNN consists of three layers: an input layer, a hidden layer (one or more hidden convolutional layers), and an output layer (Pesapane *et al* 2018). Although the performance of the CNN may improve with deeper architectures, this may result in network overfitting. An appropriate network design significantly contributes to the final performance (Abdelhafiz *et al* 2019).

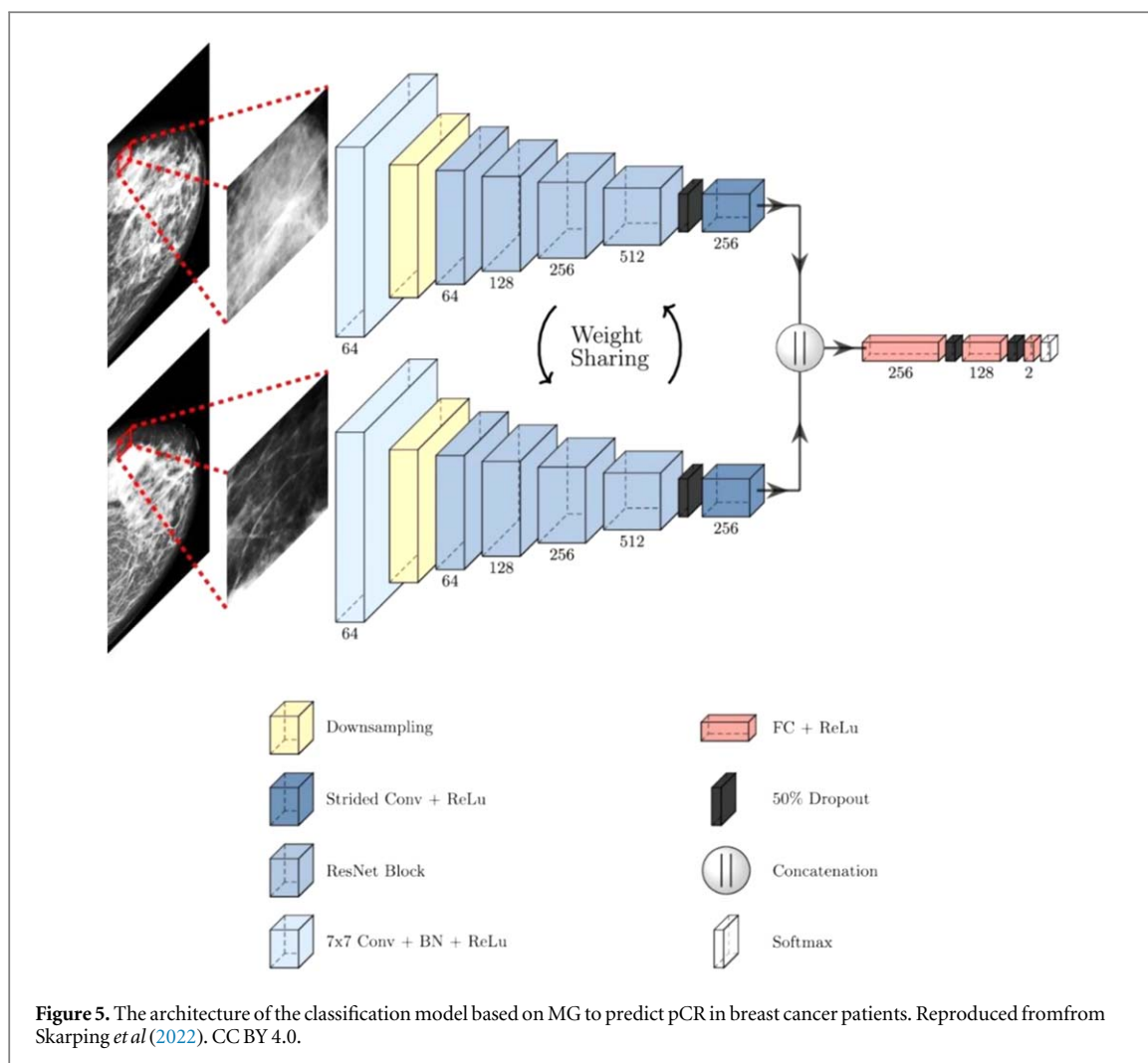
Data are indispensable for training a sophisticated model. An AI model can be trained in three manners: supervised, unsupervised, and reinforcement learning (figure 3). Supervised learning creates a model to predict the outcomes based on labeled data. Unsupervised learning determines the patterns and associations in unlabeled data to create groups and clusters. Reinforcement learning takes advantage of the reward mechanism for training feedback to achieve a desirable or undesirable state.

Figure 4 presents the workflow of AI models. Most AI models in the breast imaging literature use supervised learning; for example, benign and malignant breast tumors are differentiated with breast images that are labeled as positive or negative. ML algorithms rely on hand-engineered (or hand-designed) features based on the knowledge and experience of the clinician (such as the density or shape), whereas DL algorithms learn the features automatically. Given a sufficiently large training dataset, DL-based AI systems may be able to classify data better than methods that use hand-designed features (Chartrand *et al* 2017).

2.2. Applications of AI in MG

Two main types of lesions appear on mammograms: calcification clusters and soft tissue findings (masses, distortions, and asymmetries). The significant advantage of MG is its high sensitivity in detecting calcifications, particularly microcalcifications, which are usually invisible in other imaging modalities such as US or MRI (Jackson 2004).

The earliest research on CAD in MG was conducted in 1967 by Winsberg *et al* with the motivation of liberating radiologists from the large volume of screening mammograms in asymptomatic women (Vyborny and Giger 1994). Subsequently, numerous trials have been conducted to develop CAD for MG. These trials can



be categorized into computer-aided detection (CADe) and computer-aided diagnosis (CADx) (Sechopoulos *et al* 2021). CADe is aimed at detecting suspicious lesions in MG, which may be calcification clusters and/or soft tissue lesions. CADx algorithms estimate the pathological nature of a detected lesion as benign or malignant. These CAD algorithms have been studied intensively with promising results in clinical practice (Warren Burhenne *et al* 2000, Birdwell *et al* 2001, Freer and Ulissey 2001, Destounis *et al* 2004). However, it was proven that the expected value of CAD was overestimated with the recognition of the significant variety in MG features in studies with large sample sizes (Fenton *et al* 2007, Lehman *et al* 2015). Finally, the application of CAD in MG has not involved extensive clinical practice (Sechopoulos *et al* 2021).

Driven by the CNN model, AI has revolutionized the image interpretation of digital MG in recent years (Geras *et al* 2019). The applications thereof mainly focused on tumor screening (Kooi *et al* 2017, Al-Masni *et al* 2018, Le *et al* 2019, Rodriguez-Ruiz *et al* 2019, Kim *et al* 2020), tumor differentiation (Al-Masni *et al* 2018, Rodríguez-Ruiz *et al* 2019, Sasaki *et al* 2020), and cancer risk prediction (Arieno *et al* 2019, Yala *et al* 2019, Dembrower *et al* 2020). Skarping *et al* used DL-based method for automatic analysis of digital MG of primary breast tumors to predict pCR with an area under the curve (AUC) of 0.71. Figure 5 illustrates the use of DL to predict response to NAC based on MG (Skarping *et al* 2022). Table 1 summarizes the published studies that have evaluated the performance of CNN models in MG for breast cancer screening and detection. Moreover, several commercial products, such as Transpara™ (Rodríguez-Ruiz *et al* 2019, Rodríguez-Ruiz *et al* 2019) and MammoScreen™ (Pacilè *et al* 2020) have been incorporated with AI learning models. These above two products have been approved by the FDA.

2.3. Applications of AI in breast US

AI-assisted systems have improved the performance of US in terms of the automatic identification of breast lesions, differential diagnosis between benign and malignant breast cancers, correlation between US imaging features and histopathological characteristics, and prediction of NAC and tumor recurrence (Akkus *et al* 2019,

Table 1. CNN framework-based AI studies in MG for screening and detection of breast cancers.

References	Dataset	CNN model	Main finding	Performance
Kooi <i>et al</i> (2017)	Self-collected data	Deep CNN model	The CNN model trained on a large data set of mammographic lesions outperforms the CAD system. There was no significant difference between CNN model and certified radiologists.	The area under the curve (AUC) for CNN and CAD was 0.929 and 0.910, respectively; the AUC for CNN and radiologists was 0.852 and 0.911, respectively
Rodríguez-Ruiz <i>et al</i> (2019)	An enriched dataset with screening detected cancers	Deep CNN model	AI may help radiologists to improve the cancer detection at mammography without requiring additional reading time.	The AUC and sensitivity were higher with AI support than with unaided reading (0.89 versus 0.87 for AUC; 0.86 versus 0.83 for sensitivity)
Rodríguez-Ruiz <i>et al</i> (2019)	Multi-center data	Deep CNN model Transpara 1.4.0	The AI system has similar performance for detecting breast cancer in MG compared with an average of 101 radiologists. This finding was consistently validated in a large, heterogeneous, multi-center, multi-vendor, and cancer-enriched cohort.	The AI system had a higher AUC than the average of 101 radiologists (0.840 versus 0.814). The AI system had an AUC higher than 61.4% of the 101 radiologists
Sasaki <i>et al</i> (2020)	Self-collected data	Deep CNN model	The diagnostic performance of AI system was statistically lower than that of human readers	The AUC, sensitivity and specificity for AI were all lower than that of human readers (0.706 versus 0.816 for AUC, 0.85 versus 0.89 for sensitivity, and 0.67 versus 0.86 for specificity)
Kim <i>et al</i> (2020)	Multi-center data	CNN model ResNet-34	AI is able to detect early-stage breast cancer in MG especially in dense breast compositions. Meanwhile, the performance of radiologists was significantly improved with the aid of AI	AI had good performance on all the three datasets: South Korea dataset (AUC 0.970), USA dataset (AUC 0.953), and UK dataset (AUC 0.938) The performance of human readers was poorer than AI standalone (0.810 versus 0.940 for AUC)

Table 2. Selected AI studies in breast US regarding to tumor differentiation, biological property evaluation and prognosis prediction.

References	Application	AI model	Main finding
Shen <i>et al</i> (2021a)	Breast tumor identification	DL model	In a retrospective reader study, the AI achieves a higher AUC than the average of ten breast radiologists (0.962 versus 0.924). This indicates the potentials of using AI in breast US diagnosis
Han <i>et al</i> (2017)	Breast tumor classification	GoogLeNet CNN model	The networks showed an accuracy of about 0.90, a sensitivity of 0.86 and a specificity of 0.96. The limitation of the study is that target regions of interest need the manual selection of radiologists
Ciritsis <i>et al</i> (2019)	Breast tumor classification	Deep CNN model	To differentiate BI-RADS 2–3 versus BI-RADS 4–5 in an external dataset, the CNN model had an accuracy of 95.3% compared with the accuracy of 94.1% on human readers
Zhao <i>et al</i> (2022)	Breast tumor classification	DL model (MobileNet)	The MobileNet model had the best diagnostic performance to identify malignant tumors among BI-RADS 4A lesions with an AUC of 89.7% and an accuracy of 91.3% in the testing dataset
(Zhou <i>et al</i> 2021a)	Molecular subtyping	Assembled CNN model	The CNN model based on multiple modes of grayscale, color Doppler flow imaging, and shear-wave elastography images has good performance (AUC 0.89–0.96) to predict the four-classification breast cancer molecular subtypes
Zhou <i>et al</i> (2020)	ALNM prediction	DL CNN model (Inception V3)	The Inception V3 CNN model achieved an AUC of 0.89 in the prediction of the final clinical diagnosis of ALNM in the independent dataset
Zheng <i>et al</i> (2020)	ALNM prediction	DL radiomics model	The combination of clinical parameter and DL radiomics model yields the best diagnostic performance in predicting ALNM status with an AUC of 0.902 in the test cohort
Jiang <i>et al</i> (2021a)	Therapy response evaluation	DL radiomic nomogram	The developed model can predict the pathological complete response (pCR) status accurately with an AUC of 0.94 in the validation cohort
Yu <i>et al</i> (2021a)	Prognosis prediction	Radiomic nomogram	The radiomics nomogram performed better than the clinicopathological nomogram (0.796 versus 0.761 for C-index)

Gu and Jiang 2022). In this section, we present a comprehensive review of these applications, with selected references indicated in table 2.

2.3.1. Automatic identification and segmentation

The hand-crafted outlining of breast lesion contours is time consuming and subjective, particularly for those without distinct margins. Therefore, the automated identification of lesions is desirable for efficient AI analysis. Researchers have developed various automated AI detection models for breast lesions in US images (Marcomini *et al* 2016, Yap *et al* 2018, Cao *et al* 2019, Qi *et al* 2019, Lee *et al* 2020, Shen *et al* 2021a, Chen *et al* 2022b), including 3D breast US images (Gu *et al* 2016).

Marcomini *et al* first developed an identification model for tissue-mimicking phantoms with nodules similar to breast lesions, and subsequently applied the algorithms to clinical images (Marcomini *et al* 2016). The neural multilayer perceptron classifier achieved an accuracy of 81% for breast lesion identification in clinical practice. The most suitable AI model for a specific clinical dataset needs to be selected among the vast number of available models. Cao *et al* evaluated the performance of four training protocols for object detection (Cao *et al* 2019). Shen *et al* developed an AI system to identify breast cancer in US images using the largest dataset to date, and the accuracy thereof could reach the level of radiologists (Shen *et al* 2021a). This demonstrates the potential of AI in future clinical practice.

2.3.2. Differential diagnosis

The detection of suspicious breast lesions in US images is the first step for US physicians. However, the most important aspect is the accurate diagnosis of the pathological properties; that is, whether the nodule is benign or malignant. Many AI models have been developed to assist US physicians in the differentiation of breast lesions (Han *et al* 2017, Xiao *et al* 2018, Byra *et al* 2019, Choi *et al* 2019, Ciritsis *et al* 2019, Fujioka *et al* 2019, Hejduk *et al* 2022). The performance of AI models varies significantly as a result of the different dataset sources and algorithms that are adopted. Most studies have affirmed the auxiliary diagnostic value of AI models for US physicians. A commercial US system that incorporated an AI module was launched and exhibited promising results, which further confirmed the clinical potential of AI technology (Kim *et al* 2017, Di Segni *et al* 2018).

In the authors' view, the differential diagnosis of most breast lesions with typical malignant sonographic features is not challenging for qualified US physicians. However, AI-assisted differential diagnosis is desirable for lesions with atypical US features. The authors' group previously evaluated the value of DL models in reducing

the malignancy rate among breast imaging reporting and data system (BI-RADS) 4A lesions to achieve more accurate risk stratification (Zhao *et al* 2022). A further study is being conducted to evaluate the value of AI for diagnosing malignant breast tumors with atypical sonographic features using a large dataset from multiple centers.

2.3.3. Correlation with tumor invasive properties

Medical images were previously treated as gross anatomical images of tissues, organs, or lesions, in which the information of morphological changes was focused. However, in addition to displaying these conventional descriptive signs, medical images contain extremely large amounts of digital information that can be deeply excavated (Aerts *et al* 2014, Gillies *et al* 2016). The digital information is correlated with the molecular subtypes (Guo *et al* 2018b, Wu *et al* 2021, Zhou *et al* 2021a, Jiang *et al* 2021b), and histopathological variables (Cui *et al* 2021, Li *et al* 2022a) of breast cancer, as well as axillary lymph node metastasis (Sun *et al* 2020, Zheng *et al* 2020, Zhou *et al* 2020).

Breast cancer is a highly heterogeneous disease with four common molecular subtypes. Thus, the variety in imaging is expected to be a result of the heterogeneity of the biological properties. It has been found that sonographic radiomics can classify the molecular subtypes of both invasive breast cancer and ductal carcinoma *in situ* (Guo *et al* 2018b, Wu *et al* 2021, Zhou *et al* 2021a, Jiang *et al* 2021b). However, according to our experience, caution should be exercised in that the molecular subtypes overlap with one another in terms of the sonographic features. The classification potential of AI algorithms for molecular subtypes should be rationally examined (Shi *et al* 2021).

The axillary lymph node (ALN) status is crucial in determining the tumor stage and subsequent treatment strategy. The presence and load of ALN metastasis (ALNM) are dependent on the primary breast tumor. Therefore, the prediction of ALNM based on sonographic features using AI algorithms has been highlighted in various research articles (Yu *et al* 2019, Guo *et al* 2020, Zheng *et al* 2020, Lee *et al* 2021a, 2021b, Zhou *et al* 2021c, Jiang *et al* 2022b). Although the performance of these models is acceptable, it has been suggested that the prediction should also consider clinicopathological features to achieve satisfactory performance (Guo *et al* 2020, Zheng *et al* 2020, Lee *et al* 2021a). Meanwhile, the perineural region (Moon *et al* 2017, Sun *et al* 2020) and elastography (Jiang *et al* 2022b) are also valuable for predicting the ALNM status.

2.3.4. Prediction of treatment response and recurrence

US has traditionally been the major screening and diagnostic tool for breast cancer. However, an increasing number of studies have demonstrated that US features, particularly radiomics features, are potential imaging biomarkers for predicting the treatment response to NAC (Byra *et al* 2021, Jiang *et al* 2021a, Gu *et al* 2022) and the risk of postoperative recurrence of breast cancer (Xiong *et al* 2021, Yu *et al* 2021a, Sheng *et al* 2022). Although the studies to date have been promising, robust results that have been verified using a large dataset remain lacking. Furthermore, it should be acknowledged that imaging information is not beyond clinicopathological factors, such as the molecular subtype, metastatic load in the axilla, and NAC regimen, which should be considered when designing similar studies.

2.4. Applications of AI in breast MRI

AI techniques that aid in MRI image analysis can facilitate radiologists in clinical decision-making with enhanced diagnostic efficiency and precision. Such techniques have mainly been applied to lesion detection, risk assessment, and treatment response prediction (Sheth and Giger 2020, Bitencourt *et al*, Satake *et al* 2022). Selected articles relating to MRI-based AI studies are summarized in table 3.

2.4.1. Detection and classification

AI based on breast MRI has mainly been used to aid in classifying breast lesions as benign or malignant (Zhang *et al* 2020, Potsch *et al* 2021, Sun *et al* 2021, Jiang *et al* 2021c, Altabella *et al* 2022, Daimiel Naranjo *et al* 2022, Militello *et al* 2022). Most of these studies achieved comparable classification efficacy to radiologists using an ML model (Daimiel Naranjo *et al* 2022) or a DL CNN model (Truhn *et al* 2019, Chung *et al* 2022, Witowski *et al* 2022). Ultrafast MRI, which reduces the image acquisition and interpretation time, has attracted increasing attention in recent years (Jing *et al* 2022). The DL model can be used for the automatic identification of normal scans in ultrafast breast tissue, thereby greatly decreasing the MRI screening time and costs (Ayatollahi *et al* 2021, Jing *et al* 2022). Figure 6 shows the process of using DL to exclude lesions with ultrafast breast MRI to shorten acquisition and reading time. AI has also been used to diagnose clinically challenging lesions, such as non-mass-like lesions, sub-centimeter lesions, and lesions in patients with dense breasts (Lo Gullo *et al* 2020, Verburg *et al* 2022, Wang *et al* 2022a).

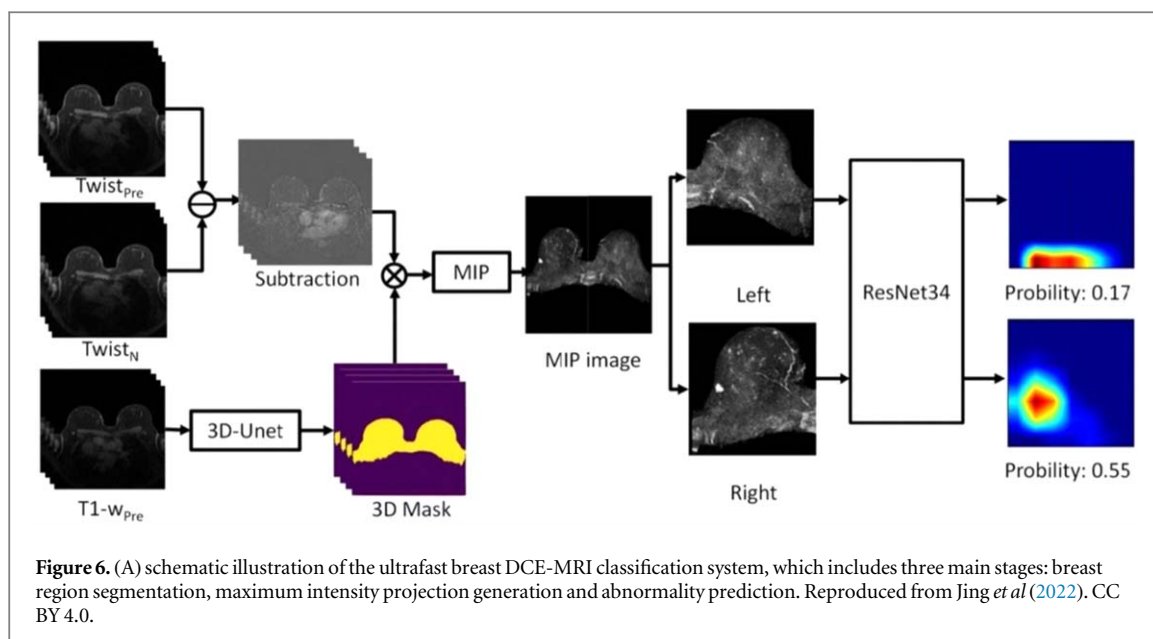


Table 3. Selected AI studies in breast MRI regarding to tumor detection, classification and prediction.

References	Application	AI model	Main finding
Ayatollahi <i>et al</i> (2021)	Breast tumor detection	A modified 3D Retina-Net DL model	The DL model can efficiently detect benign and malignant lesions on ultrafast DCE-MRI. The model can also help to detect those less visible hard-to-detect malignant breast lesions
Jiang <i>et al</i> (2021c)	Breast tumor classification	Computer-assisted diagnostic software (QuantX)	AI software for MRI can improve radiologists' performance with an average AUC of all readers improved from 0.71 to 0.76 in the task of differentiating benign and malignant breast lesions
Jiang <i>et al</i> (2022a)	Breast tumor classification and prognosis prediction	Radiomics model	Radiomics were able to identify TNBC and predict TNBC molecular subtypes. Furthermore, radiomics quantifying the heterogeneity in peritumoral regions can represent tumor metabolism and immune response patterns, and predict patient outcomes
Zhang <i>et al</i> (2021b)	Molecular subtyping	CNN model	Deep learning based on MRI can differentiate three kinds of molecular subtypes of breast cancer. The recurrent neural network has a better performance compared with conventional CNN model
Bitencourt <i>et al</i> (2020)	Prediction for biomarker and treatment response	ML radiomics model	The ML model incorporating both clinical and MRI radiomics features, can be used to assess the expression level of HER2 and can predict the possibility of pCR after NAC in HER2 overexpressing breast cancer patients
Yu <i>et al</i> (2021b)	ALNM prediction	ML radiomics model	The multiomics incorporating MRI radiomics of tumor and axillary lymph node, clinicopathologic characteristics, and molecular subtypes achieved an AUC of 0.91 to predict ALNM in the external validation cohort
Sutton <i>et al</i> (2020)	Therapy response evaluation	ML radiomics model	The combination of MRI radiomics and molecular subtype can predict the pCR after NAC with an AUC of 0.78 in the validation set
Li <i>et al</i> (2016)	Recurrence risk prediction	Radiomics model	Breast MR imaging radiomics have the potential to predict the risk of breast cancer recurrence derived from MammaPrint, Oncotype DX, and PAM50 gene assays

Another application of AI is the classification of the pathological or molecular subtypes of breast cancer. Multiclass molecular subtype differentiation is a substantially more challenging task than diagnosis. Many studies have explored the potential of radiomics or DL models to classify breast cancer subtypes (Zhang *et al* 2021b, Zhou *et al* 2021b, Lee *et al* 2022, Tsuchiya *et al* 2022, Yin *et al* 2022, Sun *et al* 2022b, Lafci *et al* 2023). In addition to the molecular subtype, MRI AI can classify the Ki-67 expression and histological grade, which are

important factors in estimating the biological behavior and treatment sensitivity (Liu *et al* 2021, Song *et al* 2021, Zhang *et al* 2022, Fan *et al* 2022b).

2.4.2. Prediction

Similar to the application of AI in breast US, many investigators have evaluated AI techniques for breast MRI in predicting the ALNM status (Yu *et al* 2020, Zhang *et al* 2021a, Yu *et al* 2021b, Gao *et al* 2022, Zhan *et al* 2022, Li *et al* 2022b, Wang *et al* 2022b, Li *et al* 2022c) as well the response to NAC (Braman *et al* 2017, Banerjee *et al* 2018, Braman *et al* 2019, Liu *et al* 2019b, Bitencourt *et al* 2020, Sutton *et al* 2020, Choudhery *et al* 2022, Massafra *et al* 2022, Caballo *et al* 2023). A recently published study explored the potential of four-dimensional (4D, 3D + time) ML radiomics based on spatiotemporal information from pretreatment DCE-MRI to identify patients who achieved pCR following NAC (Caballo *et al* 2023). Although AI techniques are unlikely to replace invasive biopsies, they offer the advantage of providing prognostic information that is derived from the entire tumor, whereas biopsy sampling only represents a small part of the tumor. This may be particularly useful for monitoring biological changes during treatment.

AI-enhanced MRI has been investigated as a noninvasive predictor of breast cancer prognosis (Eun *et al* 2021, Ma *et al* 2022, Thakran *et al* 2022, Fan *et al* 2022a, Chen *et al* 2022c). Fan *et al* found that the radiogenomic signature of the texture and morphological features was positively associated with the Oncotype DX RS, and a predicted RS that was greater than 29.9 was related to poor recurrence-free survival (Fan *et al* 2022a). In certain studies, MR images have been associated with other types of genetic testing, such as the 50-gene PAM50 and Curebest 95-gene assays, to identify radiogenomics signatures and provide alternatives for patients who did not undergo gene testing (Li *et al* 2016, Tokuda *et al* 2020). Ma *et al* developed a radiomics model using pre- and post-NAC DCE-MRI features to predict systemic recurrence in TNBC patients (Ma *et al* 2022). The radiomics achieved better predictive performance than the clinical model in predicting the recurrence risk within three years following NAC, with an AUC of 0.933. Thakran *et al* concluded that the radiomics features of parametric response maps that were derived from DCE-MRI kinetic maps achieved the best predictive performance for recurrence risk, with a C-statistic of 0.72 (Thakran *et al* 2022).

2.5. Applications of AI in breast PET/CT imaging

Breast imaging AI models based on PET/CT have also been studied in recent years (Romeo *et al* 2021, Sadaghiani *et al* 2021, Urso *et al* 2022). Applications of PET/CT include tumor staging, the evaluation of the treatment response, and suspected disease recurrence (Fowler and Cho 2021, Kikano *et al* 2021, Sarikaya 2021). Table 4 listed some elected AI studies in breast PET-CT or PET-MRI regarding to tumor detection, classification and prediction.

Krajnc *et al* established an ML model based on PET/CT to aid in the differentiation of benign and malignant tumors. Their method achieved an AUC of 0.81 for the differentiation and could identify TNBC with an AUC of 0.82 (Krajnc *et al* 2021). The PET and MRI-derived radiomic features were found to be associated with the tumor grade, overall stage, subtypes, prognosis (Huang *et al* 2018), and hormone receptors (Umutlu *et al* 2021). However, Araz *et al* found that all radiomics parameters from PET/CT failed to predict the hormone receptors (Araz *et al* 2022). PET-derived radiomics has also been applied to the prediction of other rare malignant breast cancers, such as breast lymphoma (Ou *et al* 2019).

As mentioned previously, ALNM is one of the most important clinical factors in determining treatment strategies and prognostic outcomes. PET/CT provides high specificity but relatively low sensitivity for ALNM evaluation. Advanced AI techniques have been applied to address this issue and promising results have been achieved (Li *et al* 2021, Song 2021, Chen *et al* 2022a). Chen *et al* used PET/CT radiomics to identify occult ALNM in clinically node-negative patients (Chen *et al* 2022a). The developed model improved the diagnostic performance of occult ALNM, with a mean AUC of 0.817 and mean accuracy of 0.812. With the prevalence of COVID-19 mRNA vaccinations in recent years, the correct differentiation between metastatic and reactive ALN has become a new challenge. Eifer *et al* found that the radiomics features that were extracted from PET/CT performed effectively in differentiating between breast-related ALNM and COVID-19 vaccine-related axillary lymphadenopathy (Eifer *et al* 2022).

The application of PET-based AI models for further identification of patients who may benefit from NAC at the early stage is an area of significant interest owing to the capability to quantify metabolic activity in breast tumors (Antunovic *et al* 2019, Yoon *et al* 2019, Li *et al* 2020, Roy *et al* 2022, Umutlu *et al* 2022, Yang *et al* 2022).

3. Challenges of AI in breast imaging

In addition to screening and detection, the ideal roles of AI in breast imaging include aiding radiologists in reaching the most appropriate diagnosis, assisting clinicians in creating the best treatment plan, and

Table 4. Selected AI studies in breast PET-CT or PET-MRI regarding to tumor detection, classification and prediction.

References	Application	AI model	Main finding
Krajnc <i>et al</i> (2021)	Breast tumor detection and differentiation	ML model	The ML model yielded good performance for cancer detection (80% sensitivity, 78% specificity, 80% accuracy, 0.81 AUC), and for the identification of TNBC (85% sensitivity, 78% specificity, 82% accuracy, 0.82 AUC). which is higher than the SUV(max) model (0.76 AUC in cancer detection and 0.70 AUC in predicting TNBC)
Umutlu <i>et al</i> (2021)	Molecular subtyping and tumor decoding	ML radiomics model	MR and PET data provided good prediction for hormone receptor status and proliferation rate (estrogen receptor AUC 0.87, progesterone receptor AUC 0.88, Ki-67 AUC 0.997) as well as lymphonodular (AUC 0.81) and distant metastatic spread (AUC 0.99)
Song (2021)	ALNM prediction	ML radiomics model	The ML-based 18F-FDG PET/CT radiomics model showed good performance for the prediction of ALN metastasis in the test cohorts with the sensitivity, specificity, and accuracy of 90.9%, 71.4%, and 80%, respectively
Chen <i>et al</i> (2022a)	Occult ALNM detection	ML radiomics model	Radiomics features based on the random forest model could predict the occult ALNM in infiltrative ductal carcinoma patients (mean AUC, 0.817; mean accuracy, 81.2%)
Umutlu <i>et al</i> (2022)	pCR prediction	ML radiomics model	The combined ¹⁸ F-FDG PET/MRI radiomics features enables the prediction of pCR in breast cancer patients, especially in those with HR+ /HER2- receptor status (AUC 0.94)
Yang (2022)	pCR prediction	ML radiomics model	The PET/CT-based radiomics analysis might provide efficient predictors of pCR in patients with breast cancer with the AUC ranging from 0.819 to 0.849 in the validation cohort

incorporating other clinical-pathological-immunohistochemical variables to predict the risk of recurrence or metastasis. Thus, breast imaging AI is expected to contribute to precision medicine and personalized treatment. However, various technical and clinical challenges exist in the sustainable development of breast imaging AI.

3.1. Technical challenges

First, big data forms the basis of AI in breast imaging. However, clinical breast images are not rich enough at one center. Multicenter studies are required to address this problem. Moreover, this challenge may be reinforced by the nonstandard nature of ultrasound images, e.g. deviations in the image collection, equipment, and image setting. This may be alleviated through accumulating enough data from various ultrasound equipment at different settings and developing sophisticated AI models to tolerate those interferences.

Second, the uninterpretability of current DL models that are applied to breast imaging makes it challenging to transfer the technique from research to real clinical practice despite of the applications commercial AI products. Such a challenge may be alleviated by the development of interpretable DL models in the future (Liu *et al* 2019a, Vellido 2020).

Third, as most current DL models are supervised, the model training process relies on well-defined training data. Thus, all regions of interest on the breast images should be well delineated, which requires substantial labor and is sensitive to subjective errors. The requirement of manually delineated labels in breast imaging may pose a significant challenge for a long time (Bi *et al* 2019). This challenge may be mitigated using unsupervised DL models which get rid of the delineation of labels (Chen *et al* 2023).

3.2. Clinical challenges

Although AI is a robust tool for dealing with complicated tasks, the integration of the computing resources that are required by AI necessitates human input, especially in the training stage. However, clinicians have limited time to collect massive amounts of data, which is why most related AI studies include a limited number of cases or focus on specific medical information (Nagendran *et al* 2020). Most studies evaluated the applications of AI based on one imaging modality. The combination of multiple imaging modalities is desired (Romeo *et al* 2021). Furthermore, the ethical issues relating to patient privacy and data security in breast imaging AI cannot be ignored. The protection of data security is critical when sharing data, especially in multicenter studies (Hickman *et al* 2021).

Tumor heterogeneity is a major obstacle for radiologists to give accurate diagnosis for each single case in the clinical circumstance as a result of variable imaging appearances, but also provides an opportunity for the continuous exploration of AI in breast imaging. It is difficult for radiologists to determine the pathological

nature of certain atypical breast lesions owing to the high heterogeneity of cancer. Thus, AI is desirable for aiding radiologists in reaching the most appropriate diagnosis for such breast lesions. Moreover, AI is expected to aid in evaluating the prospects, success, and failure of treatment outcomes based on learning from the successful treatment of clinical cases (Maddox *et al* 2019). However, the challenge from tumor heterogeneity also exists for AI to reach perfect computation results and agreement among different studies. An integrated model to incorporate imaging data with clinical-pathological-immunohistochemical-genetic information is desired to overcome the effect of tumor heterogeneity.

The role of AI systems in diagnosis applications has been disputed (Giger 2010). Should AI be used as the second reader or replace human readers if its standalone performance is comparable or superior to that of radiologists? Furthermore, when a controversy arises between AI and human readers, which diagnostic conclusion should be the final one? These questions need to be answered before AI can be applied extensively in clinical practice.

Breast imaging is useful for preoperative diagnosis, and its significance in guiding treatment strategies and prognosis prediction should also be explored. However, it is difficult to integrate breast imaging AI with clinical datasets without the support of clinicians. Fortunately, an increasing number of breast clinicians are focusing on the integration of imaging data and other related information into AI models to cater to personalized treatment and precision medicine (Jiang *et al* 2022a). Moreover, multi-omics studies have become a hot topic for characterizing the molecular biology of tumors, including the genomics, transcriptomics, proteomics, and metabolomics (Ponzi *et al* 2021). Current evidence suggests that the clinical transformation of most developed high-performance AI algorithms remains in the initial stages (Nagendran *et al* 2020). It is expected that all information of each specific patient will be consolidated to build a large data archive for training robust AI models at all institutions in the near future. Personalized treatment and prognosis prediction for subsequent breast cancer patients can hopefully be realized using such models.

4. Future work

Breast imaging AI is not expected to exceed radiologists for lesions with typical benign or malignant imaging features in the diagnosis of breast cancer; however, it can offer significant advantages for lesions that are difficult for radiologists to differentiate. Therefore, further studies to evaluate the performance of AI in the diagnosis of atypical breast lesions are warranted. Furthermore, the combination of multiple imaging modalities may provide beneficial reference resources for clinical decisions.

AI has also undergone rapid development in medical fields other than medical imaging in recent years. Imaging data, pathological sections, and gene sequencing of patients have become important prerequisites for the accurate diagnosis and treatment of tumors. However, most AI models that have been proposed by researchers to date are based on a single imaging system and lack model training in combination with information from other imaging methods as well as information from electronic medical records. Therefore, the integration of this information with AI models is of great importance for the development of individualized treatment strategies. To this end, AI is expected to be incorporated into clinical practice and to become routinely used by clinical workers.

5. Conclusions

In this article, we have justified the necessity of introducing AI techniques into breast imaging, reviewed the applications of AI in breast imaging modalities, and presented technical and clinical challenges in this area. The key conclusions can be summarized as follows: (1) Breast imaging AI is clinically necessary and practically feasible in the era of precision medicine and personalized treatment. (2) The expectation should be for AI to aid radiologists in dealing with difficult cases, rather than to replace radiologists, in the diagnosis of breast cancer. (3) The future integration of multiple imaging modalities as well as radiomics with clinical data and multi-omics is warranted.

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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary information files).

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Conflict of interest

None.

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