Deep Learning-Based Artificial Intelligence for Mammography

Jung Hyun Yoon¹, Eun-Kyung Kim²

¹Department of Radiology, Severance Hospital, Research Institute of Radiological Science, Seoul, Korea; ²Department of Radiology, Yongin Severance Hospital, Yonsei University, College of Medicine, Yongin, Korea

During the past decade, researchers have investigated the use of computer-aided mammography interpretation. With the application of deep learning technology, artificial intelligence (AI)-based algorithms for mammography have shown promising results in the quantitative assessment of parenchymal density, detection and diagnosis of breast cancer, and prediction of breast cancer risk, enabling more precise patient management. AI-based algorithms may also enhance the efficiency of the interpretation workflow by reducing both the workload and interpretation time. However, more in-depth investigation is required to conclusively prove the effectiveness of AI-based algorithms. This review article discusses how AI algorithms can be applied to mammography interpretation as well as the current challenges in its implementation in real-world practice.

Keywords: Breast cancer; Mammography; Computer-aided diagnosis; Artificial intelligence; Deep learning

MAMMOGRAPHY FOR BREAST CANCER SCREENING

Currently, breast cancer is the most commonly diagnosed cancer in women worldwide as well as the leading cause of their mortality [1]. The annual incidence of breast cancers was an estimated 1.68 million in 2012 and has continuously risen with a 30% increase estimated in 2025 [1]. Screening programs using mammography have been implemented in several countries for the early detection and treatment of breast cancer, with the aim to mitigate mortality and other serious consequences. Mammography screening seems to have an impact on mortality; randomized controlled trials have shown an approximately 20% reduction in breast cancer-related mortality after mammography was included in breast cancer screening [2]. Based on these results, several countries formulated national recommendations or guidelines that included mammography in breast cancer screening. Although mammography screening has proven effective, the potential drawbacks of this technique have also been acknowledged: 1) false-positive recalls leading to additional imaging studies or biopsies, which in turn increase medical expenses and emotional stress for the patient; 2) false-negatives when breast cancers are either not detectable on mammography or if interpretation errors occur, ultimately delaying diagnosis; 3) radiation exposure; and 4) overdiagnosis of cancers that may not be life-threatening such as low risk ductal carcinoma in situ [3].

In the last decade, considerable improvements have been made to overcome these pitfalls of mammographic screening by adding readers, increasing screening frequencies, or adding supplementary imaging modalities to conventional mammography. For instance, the European guidelines for quality assurance in breast cancer screening and diagnosis recommend ‘double reading’, i.e., mammograms are read independently by two radiologists to enhance sensitivity and reduce unnecessary recalls [4]. Other imaging modalities such as digital breast tomosynthesis (DBT), ultrasonography (US), or magnetic resonance imaging (MRI) have been added to conventional four-view mammography to enhance breast cancer screening outcomes. Although intensifying screening practices and using supplementary...
imaging modalities may improve breast cancer detection, ensuring sufficient resources may be problematic because the burden of mammography interpretation for radiologists will increase in a double reading setting, along with an inevitable increase in medical expenses as more sensitive and advanced equipment is used [3,5]. Among additional imaging modalities, DBT has been associated with issues such as increased radiation exposure, while there is insufficient evidence to show that it can actually reduce mortality [1,3]. Lastly, as population-based breast cancer screening programs have become commonplace, daily demands for breast cancer screening and the subsequent volume of related tests have continued to rise. However, medical resources remain limited. Therefore, it is critical that current screening workflows are optimized and streamlined [6].

**INTRODUCTION OF AUTOMATED DECISION SUPPORT FOR MAMMOGRAPHY INTERPRETATION**

Advances in technology and computer programming as well as an urgent need for improved efficiency and accuracy of imaging interpretation workflows have piqued interest in computer-automated analyses of medical images. The main objectives of using computer programs to assist image interpretation are: 1) the automated detection of lesions focusing on the localization of suspicious abnormalities in an image, which is known as computer-aided detection (CADe); and/or 2) characterization of abnormalities detected by either the radiologist or the computer, which is known as computer-aided diagnosis (CADx). Based on the CADe/CADx analysis, the interpreting radiologist determines the clinical significance of the detected abnormality and whether it warrants further investigation. Although the term ‘CAD’ refers to ‘diagnosis’ using computers, CAD can be used for purposes other than diagnosis depending on the need of the radiologist. Computer programs can also provide quantitative imaging parameters such as breast parenchymal density that traditionally have been subjectively assessed by the human eye. There are certain time points in the overall workflow of mammography interpretation at which computer assistance is considered most beneficial (Fig. 1); these areas have been discussed in depth in this review.

**MAMMOGRAPHY INTERPRETATION USING CONVENTIONAL CAD**

Initial CAD programs, termed as ‘conventional CAD’...
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throughout this review, were based on mathematical models that identified patterns associated with breast cancer and displayed areas with these specific patterns as ‘marks’ on mammograms [7]. Briefly, these marked areas indicated the spots that the radiologist needed to investigate after screening [8]. When used as a ‘spell check’ type of system, initial studies showed promising results with CAD for the accurate marking of abnormalities that were later proven to be cancerous [9]. After approval by the U.S. Food and Drug Administration in June 1998 [7,10], the Centers for Medicare and Medicaid Services increased reimbursement for CAD in mammography interpretation, which subsequently led to increased CAD usage starting from 5% in 2003, then rapidly increasing to 74% in 2008 and 83% in 2012 [11].

With the exponential increase in the usage of conventional CAD, several studies have evaluated the outcomes of implementing CAD in actual clinical practice; the screening settings used in these studies have been summarized in Table 1. Although there were variations among screening environments studied in previous studies, the majority of these were able to show that using conventional CAD either resulted in higher or similar cancer detection rates at the expense of consistently higher recall rates compared to interpretations without CAD. Conventional CAD programs are biased towards high sensitivity as they are constructed to detect potential malignancies. Sensitivity was reported to be 90.0% for overall cancers, 98.2% for microcalcifications, and 88.7% for suspicious masses [12,13], which may explain the high recall rates. In addition, higher sensitivity resulted in a trade-off with decreased specificity (87.2% from 90.2%) and increased biopsy rates (up by 19.7%) after implementation of conventional CAD [14]. None of the screening performance metrics were improved with CAD in digital mammography (DM), using the data from the Breast Cancer Surveillance Consortium [11] or the Digital Mammography Imaging Screening Trial (DMIST) [15]. Both the high sensitivity and low specificity seen with conventional CAD result in a loss of reliability because the investigation of excessive marks on images may be tiresome for the radiologist. This was apparent from a previous study, wherein radiologists dismissed approximately 97.4% of the marks drawn by conventional CAD (Fig. 2) [8].

ARTIFICIAL INTELLIGENCE IN MEDICAL IMAGING

The past decade can be marked as an era of ‘artificial intelligence (AI)’ owing to massive technological advances that have enabled easy access, processing, and storage of huge amounts of data. AI is a branch of computer science dedicated to developing algorithms that accomplish tasks that are traditionally associated with human intelligence [16], and AI is already being applied to simpler technical tasks such as speech and text recognition, language processing, object detection, and classification [17-19]. AI has brought about both excitement and concern because it is expected to increase the value and efficiency of medical imaging [20].

Computer-extracted features can serve as input to ‘machine learning’ algorithms, a subset of AI that use complicated statistical techniques to enable machines to improve at certain tasks by learning data patterns [18]. Further, ‘deep learning’ (DL) is a sub-classification of machine learning, wherein multiple layered neural networks are used to assess complex patterns within the input data. After the introduction of the 2012 ImageNet Large Scale Visual Recognition Challenge [21], deep convolutional neural networks (dCNNs) are now the technique of choice for computer visualizations and are used in various fields of image classification including breast imaging. When provided with raw data, dCNNs discover features or combinations of features that are associated with or predictive of a specific outcome (in this case, ‘breast cancer detection’ or ‘breast cancer diagnosis’) instead of requiring them to be delicately crafted by humans, which is referred to as representation learning; thereby the software trains itself to perform the task as long as sufficient quality and quantity of data are provided [18,22].

APPLICATION OF AI-CAD TO MAMMOGRAPHY INTERPRETATION

Several AI-based algorithms have been developed for mammography, and the results clearly show that their use has considerably narrowed the gap between the diagnostic performances of computers and humans (Table 2). Majority of the in-house AI-algorithms show high performance in breast cancer detection; in some studies, the performance of AI-CAD is similar to or even superior to those of radiologists. Moreover, even the stand-alone performance of AI-CAD has been significantly higher than the average performance of radiologists [23-25]. In a study comparing the predictions of AI algorithms and readers using representative screening data from the United Kingdom (UK, double reading) and the United States (USA, single reading)
| References          | Study Population                                      | Study Design                          | Imaging          | CAD System            | Cancer Detection          | Sensitivity                  | Recall Rates                |
|---------------------|-------------------------------------------------------|---------------------------------------|------------------|------------------------|---------------------------|------------------------------|------------------------------|
| Gur et al. 2004 [82] | Screening, 115751 mammograms, 2000–2002, USA        | Mammograms interpreted without CAD vs. with CAD | Film mammography | R2 Technology          | 3.49 per 1000, similar to 3.61 interpreted without CAD | -                            | 11.05%, similar to interpretation without CAD 11.62% |
| Birdwell et al. 2005 [9] | Screening, 8682 mammograms, 2001–2002, USA    | Radiologist vs. CAD vs. radiologist + CAD | Film mammography | ImageChecker V2.2; R2 Technology | 7.4% increase by CAD alone (2 of 27 cancers) | -                            | ↑ 8.2% by CAD |
| Gilbert et al. 2006 [83] | Screening, 10267 mammograms, 2 centers, 1996, UK | Single reading + CAD vs. double reading | Film mammography | ImageChecker M1000 V5.0; R2 Technology | 6.5% more cancers in single reading + CAD than double reading | -                            | 8.6% in single reading + CAD, significantly higher than 6.5% in double reading |
| Morton et al. 2006 [84] | Screening, 21349 mammograms, 2001–2002, USA     | Pre-CAD vs. CAD interpretations       | Film mammography | ImageChecker M1000 V2.2; R2 Technology | 7.62% increase in breast cancer detection | -                            | 10.77%, increased from 9.84% of radiologist alone |
| Gilbert et al. 2008 [85] | Screening, 28204 women in 3 centers, 2006–2007, UK, CADET II trial | Single reading + CAD vs. double reading | Film mammography | ImageChecker DMax V8.1; R2 Technology | 7.02 in single reading + CAD, similar to 7.06 per 1000 in double reading | 87.2% in single reading + CAD, similar to 87.7% in double reading | 3.9% for single reading + CAD, significantly higher than 3.5% in double reading |
| Fenton et al. 2011 [10] | Screening, > 1.6 million mammograms at 90 facilities in the BCSC, 1998–2006, USA | Facilities using CAD, ‘CAD group’ vs. facilities without CAD, ‘non-CAD group’ | Film mammography | Not specified | 3.2, significantly decreased from 3.6 per 1000 before CAD | 81.1%, no significant differences from 79.7% before CAD | 8.9%, significantly higher than 8.4% before CAD |
| Lehman et al. 2015 [11] | Screening, 323973 women in 66 facilities of the BCSC, 2003–2009, USA | Mammography interpreted with CAD vs. interpreted without CAD | Film + digital mammography | Not specified | 4.1 per 1000, no significant differences to 4.1 in no CAD | 85.3%, no significant differences to 87.3% in no CAD | 8.7%, no significant differences to 9.7% in no CAD |

BCSC = Breast Cancer Surveillance Consortium, CAD = computer-aided detection/diagnosis, CADET II = Computer-Aided Detection Evaluation Trial II, UK = United Kingdom, USA = United States
In addition to the stand-alone results, two studies using commercially available deep-learning CAD algorithms for mammography interpretation showed that interpretation with AI-based CAD improved the diagnostic performance of radiologists compared to interpretation without AI-CAD; the area under the receiving operator characteristics curve (AUC) of radiologists alone improved after using AI-CAD from 0.810 to 0.881 \((p < 0.001)\) [23] and from 0.87 to 0.89 \((p = 0.002)\) [26]. AI-CAD showed superior performance in detecting cancers that presented as masses, distortions, asymmetries, were early stage, node-negative invasive cancers, or cancers in mammographically dense breasts [23], indicating that AI-CAD could overcome major difficulties in breast cancer detection using mammography.

Such promising results have increased expectations regarding the role of AI-CAD in screening [27]. Most recent studies on AI algorithms are from cancer-enriched populations (Table 2), with the exception of one study (1.1\%, conventional CAD vs. CNN) [28], wherein the cancer proportion ranges from 7.7–50\%. The results of the DM Dialog on Reverse Assessment and Methods (DM DREAM) Challenge may give us an idea of how AI-CAD will perform in screening settings: 144231 screening mammograms including 952 (0.7\%) cancers were used for algorithm training/validation and tested on a second independent validation cohort of 166578 examinations including 780 (0.5\%) cancers [29]. This study showed that while no single AI algorithm outperformed the radiologists, the combination of AI with radiologists resulted in a higher AUC of 0.942, significantly improving specificity and overall accuracy [29]. In another study that conducted an external evaluation of three commercially available AI-CAD
### Table 2. Diagnostic Performances of AI-CAD When Applied to Digital Mammography Interpretation

| References | Purpose | Cancer Proportion | AI Category | External Validation* | AUC | Sensitivity | Specificity | Accuracy |
|------------|---------|-------------------|-------------|-----------------------|-----|-------------|-------------|----------|
| Kooi et al. 2017 [28] | Compare between mammography CAD vs. CNN (271 annotated cancers in 18182 images) for test set; CNN: 0.886, radiologists: 0.911 | 1.5% | No, 30% saved for validation | CAD 0.910 vs. CNN 0.929, test set: CNN 0.878, radiologists 0.974 | 0.910 | 80.4% | 84.2% | 0.908 |
| Becker et al. 2017 [86] | Evaluate diagnostic accuracy of deep learning-based software | 7.7% | No, 10% for validation | DANN 0.840, AI 0.835, CNN 0.894 | 0.840 | 88.2% | 83.0% | 0.862 |
| Al-Masni et al. 2018 [87] | Detection and classification of masses on DM (300 of 600 cases) | 50.0% | No | ROI-based CNN 0.877 | 0.877 | 93.2% | 78.0% | 85.5% |
| Bandeira Diniz et al. 2018 [88] | Detection of mass/non-mass regions in non-dense and dense breast (2482 images from 1241 women) | - | No, 20% saved as test set | Deep CNN 0.840 (experienced readers: 0.890, inexperienced readers: 0.790) | 0.840 | 84.2% | 80.4% | 80.4% |
| Chougrad et al. 2018 [90] | Deep learning CAD to aid radiologists to classify mammography mass lesions (160 cancers of 320 examinations) | 51.0% | Yes, MIAS database | Deep CNN 0.98, DDSM 0.97, INbreast 0.97, BCDR 0.96, MIAS 0.96, 50.0% | 0.980 | 93.2% | 78.0% | 85.5% |
| Rodriguez-Ruiz et al. 2019 [25] | Compare the stand-alone performances of AI system (Transpara 1.4.0, Screenpoint Medical) vs. 101 radiologists | 24.6% | No | Faster-R-CNN 0.950 | 0.950 | 84.2% | 83.0% | 84.2% |
| Rodriguez-Ruiz et al. 2019 [26] | With AI: 0.89 higher than without AI: 0.87 | 20.1% | No | CNN 0.940, AI 0.910 | 0.940 | 88.2% | 83.0% | 88.2% |
| McKinney et al. 2020 [24] | With independent test set. AI = artificial intelligence, AUC = area under the receiving operator characteristics curve, BCDR = Breast Cancer Digital Repository, CAD = computer-aided detection/diagnosis, CNN = convolutional neural network, dANN = deep artificial neural networks, DDSM = Digital Database of Screening Mammography, DM = digital mammography, MIAS = Mammographic Image Analysis Society, ROI = region-of-interest, UK = United Kingdom, USA = United States | 1.6% | No | Deep learning AI model | 0.940 | 88.2% | 83.0% | 88.2% |
| Kim et al. 2020 [23] | Evaluate whether the AI algorithm for mammography can improve accuracy of breast cancer diagnosis | 50.0% | No | Deep learning AI model | 0.940 | 88.2% | 83.0% | 88.2% |

*With independent test set. AI = artificial intelligence, AUC = area under the receiving operator characteristics curve, BCDR = Breast Cancer Digital Repository, CAD = computer-aided detection/diagnosis, CNN = convolutional neural network, dANN = deep artificial neural networks, DDSM = Digital Database of Screening Mammography, DM = digital mammography, MIAS = Mammographic Image Analysis Society, ROI = region-of-interest, UK = United Kingdom, USA = United States
algorithms as independent mammography readers, high AUC values ranging from 0.920–0.956 with high sensitivities of 67.0–81.9% (77.4% for the first reader radiologist and 80.1% for the second reader radiologist) were achieved at the same specificity [30]. These findings support that AI-CAD can indeed contribute to improving performance in a real-world screening environment. However, these results need to be validated in future prospective studies.

DEEP LEARNING APPLIED TO DIGITAL BREAST TOMOSYNTHESIS

DBT provides multiple low-dose projection images of the breast that can be used to reconstruct a three-dimensional dataset of mammography images [31]. This in turn reduces the negative effect of overlapping breast tissues. Studies have proven the efficacy of DBT over full-field DM when used for breast cancer screening, with several reports of increased cancer detection rates and decreased recall rates [32-34]. Although DBT may show superior performance, its acquisition time is longer and its interpretation time is reported to be almost twice the time needed for DM [35-37], a factor that may critically impact the workload of radiologists.

Even with the superior performance of DBT over DM, perception or interpretation errors still occur [38]. Compared to the single images used to interpret each plane in DM, for DBT interpretation, radiologists have to scroll through stacked images for each mammographic projection, where the number of images per stack is proportional to the breast thickness under compression. More images mean a heavier workload, and this is the main reason for longer interpretation time and radiologists’ fatigue with DBT. Automated detection of abnormalities among multiple projection images could help clinicians localize and assess the clinical significance of a detected abnormality. Commercial or in-house softwares have been developed to assist DBT interpretation, for which initial studies commonly report a reduction in reading time while maintaining reader performance (Table 3) [39-41]. The results were more promising when an AI-based algorithm was applied to DBT interpretation [35], with the reading time being reduced by 52.7% (64.1 to 30.4 seconds) along with improvements in all diagnostic metrics such as increased sensitivity (77.0% to 85.0%), specificity (62.7% to 69.6%), AUC (0.795 to 0.852), and decreased recall rates (38.0% to 30.9%).

| References | No. of Readers | No. of DBT Exams | Software Used | Reading Time | AUC | Sensitivity (%) | Specificity (%) | Recall Rates (%) |
|------------|----------------|------------------|---------------|--------------|-----|----------------|-----------------|-----------------|
| Without CAD | With CAD       | Without CAD      | With CAD      | Without CAD  | With CAD |
| Without CAD | With CAD       | Without CAD      | With CAD      | Without CAD  | With CAD |
| Without CAD | With CAD       | Without CAD      | With CAD      | Without CAD  | With CAD |
| Without CAD | With CAD       | Without CAD      | With CAD      | Without CAD  | With CAD |
| Without CAD | With CAD       | Without CAD      | With CAD      | Without CAD  | With CAD |
| Without CAD | With CAD       | Without CAD      | With CAD      | Without CAD  | With CAD |

Table 3. Summary of Studies Using AI-CAD for DBT Interpretation

*CAD system focuses on detecting soft tissue lesions and does not detect calcifications. With statistical significance. AI = artificial intelligence, AUC = area under the receiving operator characteristics curve, CAD = computer-aided detection/diagnosis, DBT = digital breast tomosynthesis.
IMPROVING MAMMOGRAPHY INTERPRETATION WORKFLOW WITH AI-CAD

In addition to improving breast cancer detection, studies have evaluated AI-CAD for triaging mammography examinations, which is critical for screening because the majority of screening exams are negative. If AI-CAD can accurately identify cases that require less time and fewer resources without endangering the patient, we can reduce the workload of radiologists, and more time can be spent on images with suspicious features and on any subsequent diagnostic workup. Three recent studies have used AI-CAD to triage mammography examinations in this way [42-44]. In an initial study, the probability of malignancy score (scale of 0–10) generated by a commercially available AI-CAD was used to predesignate cancer-free examinations as ‘normal’ so that they were not listed as cases that needed further interpretation by radiologists. In this study, setting the threshold at an AI score of 5 resulted in approximately 50% workload reduction with 7% of cancers being interpreted as false-negatives, whereas setting the threshold at an AI score of 2 resulted in a 17% workload reduction with 1% of cancers being interpreted as false-negatives [43]. Preselection of examinations according to the AI score did not change the average AUC of radiologists, except for when the AI score was 9. This finding indicated that triaging with AI-CAD maintains radiologist performance even as it reduces the workload. In the other two studies, DL algorithms were constructed to triage mammography examinations as cancer-free using either imaging features [44] or imaging features combined with non-imaging features and pathologic outcomes [42]. These recent results corroborate previous studies that reported a workload reduction of approximately 20–34% to 91% (in a screening setting) albeit with non-inferior levels of sensitivity, negative predictive values, and improved specificity.

Triaging mammography examinations offers two advantages: First, triaging negative examinations can spare the radiologists’ time and effort, thereby reducing their overall workload, as previously mentioned. Second, by identifying cancers that have been missed by radiologists, AI can act as a final consultant (Fig. 3). A simulation study performed with this in mind reported that AI can reduce the radiologists’ workload by more than half [45]. Further, by using AI scores for women with negative double readings it also increases early detection of interval cancers by 14–59%, depending on which AI score is used as the cutoff. In this study, AI scores showed higher accuracy for predicting future interval cancers and next-round screen-detected cancers than mammographic density, and the researchers speculated that this difference was due to AI algorithms detecting subtle unidentified tumor features, whereas mammographic density was associated with tumor masking. These results suggest that AI may have another potential role in supplementary screening for women after negative findings on the mammograph. The role of AI in breast cancer risk prediction has been discussed in depth in the next section.

ASSESSMENT OF MAMMOGRAPHIC PARENCHYMAL DENSITY USING DEEP LEARNING

Breast parenchymal density is important in two aspects: 1) an increased proportion of fibroglandular tissues has been associated with a four-to six-fold increased risk for breast cancer [46-48]; and 2) the detection sensitivity of mammography can be severely affected by increased parenchymal density or ‘dense breast’ as breast masses can be potentially masked, leading to increased rates of interval cancers [47,49,50], which is why additional screening modalities such as US or MRI are used. Legislation on breast density notification was first passed in Connecticut, USA in 2009, and then in more than 30 states of the USA. Radiologists are now required to notify women on their breast density after they are screened with mammography and they also need to discuss the possibility of missed cancers in dense breasts [51,52]. Based on this requirement, we need to report parenchymal density on mammography using quantitative and objective analysis, but the qualitative four-tiered density categories of the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) [53] depend solely on the radiologist’s subjective interpretation and vary widely, with a κ = 0.40–0.87 reported in literature [54-56]. Currently, several commercially-available automated volumetric density measurement programs (Volpara, Volpara Solutions; Quantra, Hologic) enable the quantification of parenchymal data by calculating the ratio of fibroglandular tissue to the total breast volume in percentages [57].

Even with automation, inconsistencies between measurements made by radiologists and current softwares remains an issue. Studies have reported differences of 14–22.3% and fair to moderate agreement (κ = 0.32–0.61)
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Fig. 3. Diagram of various workflows using AI-CAD for mammography interpretation.

Before applying AI-CAD to mammography interpretation, the following aspects should be considered: **A.** The impact of AI-CAD differs depending on whether the radiologists are exposed to the analytic results, i.e., sequential reading, wherein the AI-CAD result is provided after the radiologist has reached a conclusion vs. independent reading, wherein the AI-CAD result is provided with the mammography images before the radiologist has reached a conclusive interpretation.

**B.** The impact of AI-CAD also differs according to the reading environment, i.e., single reading vs. double reading, wherein AI-CAD may not only assist radiologists, but even has the potential to replace a second reader or serve as a final consultant in cases where a consensus among multiple readers is required.

**C.** If AI-CAD can be considered for stand-alone reading, its analytic results can be used for workload triage such that examinations with ‘negative’ results on AI-CAD will not be interpreted by radiologists.

AI = artificial intelligence, CAD = computer-aided detection/diagnosis
between radiologists and commercially-available softwares in density classification [57,58]. To narrow the gap between computers and radiologists in density assessment, DL algorithms have been constructed and applied in several recent studies. In experimental settings, several state-of-the-art DL models showed strong similarity or agreement with the BI-RADS density assessments made by radiologists [59-63]. When implemented in routine clinical practice, a DL algorithm showed excellent agreement with radiologists with \( \kappa = 0.85 \). Further, 94% of the assessments made by the DL algorithm were accepted by the radiologists in binary categorization of non-dense or dense breasts [64]. Although DL models are in the early stages of development, they show potential for providing consistent and reliable data for breast density, which is both useful and important, especially against the backdrop of breast density legislation. Consistent and objective data are required to predict breast cancer risk and to discuss the need for supplementary studies and future management plans with the patient, which is why we expect DL algorithms to have a greater role in the assessment of parenchymal density in the future.

**ASSESSMENT OF BREAST CANCER RISK USING DEEP LEARNING**

Starting with the publication of the Gail model [65], various risk models have been developed during the past decade using multiple risk factors related to hormonal and genetic information to predict breast cancer risk [66-68]. Until recently, image-related information was not incorporated into the risk prediction models, but now mammographic breast density is a well-acknowledged risk factor [47]. Previous studies have shown that the AUC for predicting breast cancer risk has significantly improved by adding subjective mammographic parenchymal density as a risk factor [68,69]. As mentioned in our discussion on mammographic breast density, DL models have been introduced to enable more objective and quantitative density assessment. Not only do DL algorithms provide consistent assessments of density, they are also thought to provide more accurate breast cancer risk predictions based on pixel-based information embedded in mammographic images that are not perceptible to the human eye. This hypothesis has been supported in several recent publications: DL CNN using mammography for a pixel-based prediction of breast cancer risk had greater predictive potential than using breast density assessments by radiologists (odds ratio 4.42 vs. 1.67) with an overall accuracy of 72% [70]. Similarly, risk scores generated by a DL network allowed more accurate predictions of future breast cancer risk with lower false-negative rates for more aggressive cancers when compared to density-based models [71].

As the amount of readily available data has increased with corresponding advances in processing abilities, attempts have been made to use computer-analyzed imaging data as input in the DL models and combine it with traditional risk factors obtained from medical records to predict breast cancer risk with promising results. By using computerized image analysis to extract features of parenchymal texture, radiomic phenotypes resulted in significantly higher discrimination performance when added to a breast cancer risk model that included breast density and body mass index as risk factors (AUC 0.84 vs. 0.80) [72]. Similarly, a hybrid DL model using both traditional risk factors and mammograms showed the highest diagnostic performance (AUC 0.70) compared to a clinical risk-factor-based model (AUC 0.62–0.67) or image-only DL model (AUC 0.68) [73]. By using a DL model with a broader range of input data extracted from electronic health records linked to mammographic data, the algorithm showed the potential to assess breast cancers at levels comparable to radiologists (AUC 0.91, sensitivity 87%, specificity 77.3%), and detected 48% of false-negative mammography interpretations [74]. These recent studies indicate that image-based DL models show promise for more accurate breast cancer risk prediction and that we can expect more from these models in the future including personalized management for women. This is thought to be especially relevant to clinical practice as the passing of the breast density notification legislation in the USA brought about increased medical costs and workload burdens for breast cancer screening [75,76]. The applications of DL algorithms for breast cancer risk prediction are still in the early stages of development, and we anticipate studies evaluating the effect of DL algorithms when selecting women for intense breast cancer screening in the near future.

**CHALLENGES TO OVERCOME BEFORE CLINICAL APPLICATION**

Even with rapid progress, more investigation is required to prove the utility of AI in aiding radiologists with mammography in real-world settings. First, proper external validation is required [17]; while various machine learning
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techniques have been used to develop CAD algorithms for breast imaging modalities during the last few years [77], very few have been commercially utilized for clinical use, mostly due to the lack of clinical validation. We need studies that demonstrate how AI will work in the real world while considering generalizability, efficiency, user variability, and ways to optimize algorithms for consistent outcomes [78]. A recent study by Salim et al. [30] performed an external evaluation of currently released, commercially-available AI-CAD algorithms as independent readers of mammography and also in combination with radiologists. They found that commercially available AI-CAD algorithms can assess screening mammograms with sufficient diagnostic performance to be evaluated as an independent reader in future prospective studies, and more positive cases were detected when combining AI with radiologists than double reading with only radiologists. This study focused on the external validation of AI, and we hope to see more similar studies that will evaluate AI algorithms based on the features they are supposed to analyze.

Second, feasibility testing should be conducted while considering certain clinical aspects such as the incorporation of AI-CAD in clinical practice with comparisons of screening vs. diagnostic settings, single reading vs. double reading, or for reading sequences etc (Fig. 3). In addition, the methodology for estimating the true performance of an AI algorithm needs to be refined. As its name implies, the role of conventional CAD is to ‘assist’ the radiologist who can either choose to follow the CAD prompts or to neglect them when reaching a final diagnosis. Typically, final diagnoses are made by radiologists with the CAD results also taken into consideration. When assessing the performance of CAD under these circumstances—circumstances reflecting real-world practice since radiologists are the ones legally responsible for their interpretation, not CAD—the gain achieved by using a good AI-CAD may be underestimated [79]. In addition, although it is difficult to estimate related data, we need to consider how to measure the time and resources invested into interpretation to evaluate whether integrating the AI algorithm improves the efficiency of interpretation workflows.

Third, there are more technical issues to consider when developing AI algorithms for DBT than DM. Since most of the current DL algorithms have been built using two-dimensional mammography, transfer learning has been adapted through the application of a pre-trained CNN to build algorithms for DBT interpretation [80]. Furthermore, poor spatial resolution per image limits the detection accuracy of tomosynthesis, and consequently we would expect lower performance for DL algorithms with DBT compared to DM. In addition, DBTs acquired from different vendors have different angular ranges, acquisition techniques, pixel binning, and reconstruction techniques that affect mammography images [81].

Finally, there are ethical or legal issues to consider before incorporating AI into our interpretation workflow. Should AI be considered as an independent reader? Should the analytic data provided by AI-CAD algorithms be reported in medical records? As of now, the interpreting radiologist is legally responsible for his or her image interpretation regardless of whether they choose to use the AI marks, but the legal ramifications of using AI data and the degree of its use should be discussed in depth. If AI-CAD truly becomes part of everyday practice, an ethical or legal framework for the application of AI algorithms will be required, and this framework must reflect a consensus of all participants in a real-world mammography setting, from patients to radiologists. In addition, we need to be prepared for the unintended consequences of incorporating AI algorithms such as the detection of many in situ cancers rather than invasive cancers and the regression of interpretive skills due to radiologists’ overdependence on AI [5,19].

CONCLUSION

Recent advances in technology have enabled the application of AI to mammography, with stand-alone diagnostic performances comparable to those of radiologists, improvements in sensitivity or specificity in breast cancer diagnosis, and the potential reduction in the workflow or interpretation time. Although the current results for several AI algorithms in mammography seem quite positive, clinical validation is required to guarantee generalizability, efficiency, and consistency. Social consensus is also required for the role AI algorithms will play in mammography interpretation, along with ethical and legal considerations. Although AI is still in the preliminary stages of validation, there is increasing demand for its application in the medical field, and more effort is being put into implementing AI technology in actual clinical settings. Moreover, with the initiative towards prospective clinical validation studies, we need to be prepared to accept AI in clinical practice and to be aware of the impact it may have on the future of breast imaging.
Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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Conceptualization: Eun-Kyung Kim. Project administration: Eun-Kyung Kim. Resources: Jung Hyun Yoon. Supervision: Eun-Kyung Kim. Writing—original draft: Jung Hyun Yoon. Writing—review & editing: all authors.

ORCID iDs
Jung Hyun Yoon
https://orcid.org/0000-0002-2100-3513
Eun-Kyung Kim
https://orcid.org/0000-0002-3368-5013

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