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Past, Present, and Future of Machine Learning and Artificial Intelligence for Breast Cancer Screening

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Abstract

Breast cancer screening has evolved substantially over the past few decades because of advancements in new image acquisition systems and novel artificial intelligence (AI) algorithms. This review provides a brief overview of the history, current state, and future of AI in breast cancer screening and diagnosis along with challenges involved in the development of AI systems. Although AI has been developing for interpretation tasks associated with breast cancer screening for decades, its potential to combat the subjective nature and improve the efficiency of human image interpretation is always expanding. The rapid advancement of computational power and deep learning has increased greatly in AI research, with promising performance in detection and classification tasks across imaging modalities. Most AI systems, based on human-engineered or deep learning methods, serve as concurrent or secondary readers, that is, as aids to radiologists for a specific, well-defined task. In the future, AI may be able to perform multiple integrated tasks, making decisions at the level of or surpassing the ability of humans. Artificial intelligence may also serve as a partial primary reader to streamline ancillary tasks, triaging cases or ruling out obvious normal cases. However, before AI is used as an independent, autonomous reader, various challenges need to be addressed, including explainability and interpretability, in addition to repeatability and generalizability, to ensure that AI will provide a significant clinical benefit to breast cancer screening across all populations.

Key words: artificial intelligence; computer-aided diagnosis; breast imaging; machine learning; screening.

Introduction

Breast cancer screening has evolved substantially over the past few decades because of advancements in both image acquisition systems and novel artificial intelligence (AI) algorithms. Although AI has been developing for interpretation tasks associated with breast cancer screening for decades, its potential is greater now since newer acquisition systems yield 3D and 4D images, with the need for AI to enhance the efficiency of the interpretation. Key use cases for AI in breast imaging include risk assessment, detection, diagnosis, prognosis, and therapeutic response. This review focuses on the general topics of human engineering and deep learning, including transfer learning, as they pertain to the detection and diagnosis of breast cancer.

Globally, female breast cancer is the most commonly diagnosed cancer, and it is the greatest contributor to cancer death in women (1). Since the peak of breast cancer mortality in 1989, there has been a 42% decrease in mortality in the United States (2). In the late 1990s, the annual decline in mortality rate was more than 3%, although in recent years

Key Messages

- Artificial intelligence (AI) of medical images for use in breast cancer screening has advanced greatly over the past four decades.
- Computer outputs from AI in breast imaging are being developed for clinical use as secondary, concurrent, or primary readers.
- Prior to implementation of AI, it is important to understand the intended task, expected claim, target population, repeatability, and performance of the algorithm as well as that of the end user (ie, the radiologist).

the decline has slowed to 1% annually, possibly due to plateauing mammography rates and a slight increase in incidence rates (2). Screening mammography has played an important role in reducing breast cancer–related mortality by increasing cancer detection rates at earlier stages. As a result, cancer screening can enable less invasive and more effective treatment (3,4). However, limited contrast and overlapping tissue in the 2D projection images from mammograms is not ideal for those with dense breasts, contributing to overdiagnosis and overtreatment (4–6). To address the need for more effective screening, additional imaging modalities have been developed to augment mammography (7–9).

Digital breast tomosynthesis (DBT) has been shown to have greater cancer detection rates compared to mammography, as it can reduce false positives resulting from overlapping normal tissues (3). In addition, the nonionizing radiation imaging modalities, whole breast US and 3D MRI, have demonstrated sensitivity benefits over mammography, especially in detecting mammographically occult disease (6,10). Whole breast US has demonstrated benefits in patients with dense breasts, although it has an increased risk of false positives and limited ability for screening in the general population (3,6). MRI also offers the benefits of 3D resolution along with temporal information from dynamic contrast-enhanced MRI (DCE-MRI), and it is beneficial for use in women with dense breasts and above-average risk (6,11). Features extracted from MRI, including lesion size, shape, and texture, can serve as strong indicators for use in diagnosis (12). Therefore, DCE-MRI is being used as a supplemental screening modality in patients with high risk for cancer, determined by their family history, breast density, and/or *BRCA* mutation status. To maintain the efficiency and throughput and to increase the performance of screening MRI, abbreviated and ultrafast protocols have been developed (9,11,13). While specific guidelines vary around the world, the World Health Organization recommends mammography screening every two years for average-risk women aged 50 to 69 years old (4). The American Cancer Society recommends annual screening mammography or DBT starting at 40 years old for average-risk women and recommends annual MRI as an adjunct to screening mammography or DBT starting at 30 years old for high-risk women (3,10).

These imaging modalities provide radiologists with an abundance of data for each patient; however, it is important to note that the benefit of a medical imaging exam depends on both the quality and interpretation of the image. Inherent limits to labor-intensive human interpretation include errors due to structural noise, incomplete visual search patterns, suboptimal image quality, or fatigue (9,14–16). To effectively interpret DBT, US, or MRI data, additional expertise may be required for detection, diagnoses, and patient management. To combat the subjective nature and improve efficiency of human image interpretation, AI methods are being developed to support radiologists in their interpretation decision-making process.

Artificial intelligence refers broadly to the use of computers to learn and perform tasks typically conducted by humans. Artificial intelligence can be subcategorized by the extent of its scope or the learning ability of the system. Most AI systems available currently are limited learning or narrow AI. These systems perform a single, well-defined task such as detection, diagnosis, or segmentation, learned from a labeled set of information directly related to the task. On a broader scale, future implementations could potentially encompass AI to perform many integrated tasks at an organization or society level and to make decisions at the level of or surpassing the ability of humans.

Machine learning is a subset of AI that uses specific programs to identify patterns from an input and learns to make inferences without direct intervention from humans. Machine learning can be further categorized as supervised or unsupervised learning. In supervised learning, the data on which an algorithm is trained are labeled, and in unsupervised learning, the data are unlabeled (17). Most medical imaging tasks use supervised learning to perform classification, whereas unsupervised learning is commonly used for clustering or dimensionality reduction. Conventional methods of machine learning in medical imaging, as opposed to deep learning methods, use human-engineered radiomic features to characterize, for example, the breast lesion, extracted from images as inputs to simple classifiers (eg, random forest or support vector machines) to classify cases (18,19). Image features can be extracted from deep learning networks, a subset of machine learning that directly learns image features from pixel- or voxel-level data. However, these networks contain many learned parameters and components, necessitating large data sets for the training of the network, which are frequently difficult to obtain in medical imaging applications because of a lack of annotations and labels (18–20).

Most computer-aided diagnosis (CAD) systems/AI for breast screening fall into the categories of human-engineered or deep-learning-based AI, using radiomic and/or deep network extracted features to perform a task (Figure 1). Artificial intelligence used in assisting the end user (ie, the radiologist) has been termed CAD, which can be further divided into categories based on the specific clinical task,

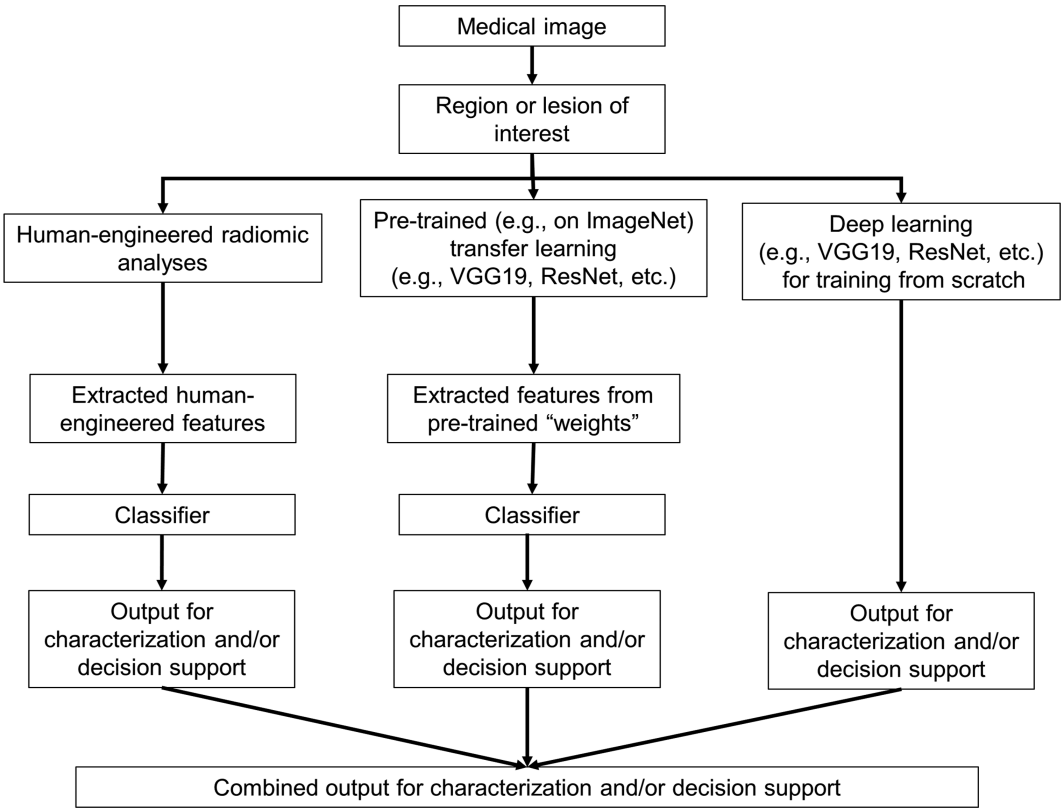

Figure 1. Commonly used AI development pipelines for image classification and decision support, as explored in Whitney et al (7). The publicly available ImageNet database may be used to train convolutional neural networks, such as VGG19 from the Visual Geometry Group and ResNet (Residual Network).

primarily computer-aided detection (CADe), computer-aided diagnosis (CADx), triage (CADt), or rule-out.

Overall, AI has the potential to improve both the efficacy and efficiency of breast cancer screening through quantitative, reproducible, and objective algorithms. Artificial intelligence techniques are capable of recognizing complex patterns that might be difficult for the human eye to notice, and they should be developed to be robust to noise and generalizable to a variety of disease representations (8,9,18). Artificial intelligence also has the potential to simultaneously interpret data from multiple streams, including images, genomics, and patient history (8). Techniques for automatic longitudinal monitoring of breast density or tissue changes could lead to personalized care decisions, particularly beneficial for high-risk screening populations. The benefits of improved detection rates, saved time, and profitability are currently challenged by the risk of increased recall rates, increasing costs, and less than favorable perceptions of AI (21). However, further advances in AI systems could enhance the role of radiologists by allowing them to focus on "value-added tasks," such as patient interactions and integrated care, rather than interpretation tasks (22).

History of AI in Breast Cancer Screening and Diagnosis

Despite the recent explosion of AI in medical imaging, facilitated by advances in deep learning networks and computing power, research in AI methods has been around for decades. The first articles on the use of computers for cancer detection from radiographic images were published in the 1950s and 1960s (23). However, computational limitations and inadequate image quality levels prevented practical use of the methods. In the late 1980s and 1990s, AI tools for detection of lung and breast cancer were revisited and developed, with the names CADe and CADx (for computer-aided detection and computer-aided diagnosis, respectively) to represent their role as an aid to the radiologist as opposed to a replacement (24,25). The first observer study to compare radiologist performance without and with CADe was published by Chan et al in 1990 (26). The first use of deep learning using a convolutional neural network (CNN) was published by Zhang et al in 1994, for detecting microcalcification clusters on mammograms, and then incorporated into CADe commercial systems (27). The first commercial CADe system was the ImageChecker M1000 (R2 Technology, now Hologic, Inc., Bedford, MA), approved by the Food and Drug Administration (FDA) in 1998 to serve as a second reader to be used after a radiologist's initial review of a case (26). By 2008, CADe was being used in 70% of mammographic screening studies at outpatient hospitals and 81% of private office screenings (28).

The late 1990s and early 2000s brought about increased research in AI for breast cancer, especially for diagnostic tasks (ie, CADx), with a focus on the use of human-engineered

(radiomic) features. In reader studies, including mammography, US, or MRI, radiologists would be presented with computer-extracted attributes, for example, features, graphical representations comparing to other cases, and machine-learning-driven lesion signatures indicating likelihoods of malignancy, leaving the final decision to the radiologist (29–31). Convolutional neural networks were also then being investigated in the task of distinguishing biopsy-proven masses from normal tissue on mammograms as well, similar to other CADx applications (32).

While the first applications of AI to breast screening focused on mammography, many of the techniques were further customized and translated to other screening modalities. As DBT emerged in the field as a promising 3D alternative to standard mammography, AI techniques were rapidly extended to DBT imaging (33–35). Additionally, CADe and CADx methods for both 2D and 3D breast US were developed in the 2000s (36,37). As MRI became an adjunct imaging modality for screening women with dense breasts, AI systems were developed for DCE-MRI. In 1998, a method for automated extraction of human-engineered radiomic features based on size, shape, and kinetics of radiologist-delineated masses was successful in distinguishing benign from malignant lesions (38). Soon after, techniques for 3D computerized lesion segmentation from DCE-MRI were introduced (39). In the early 2000s, texture analysis, morphology, and kinetics were incorporated in the development of automatic methods for lesion classification (40–44). Some of the early commercial software systems offered interactive tools for the assessment of DCE-MRI that could be integrated in the clinical workflow, providing decision support while reducing evaluation time and observer variability (42,45). The first commercial CADx system was QuantX (Quantitative Insights, now Qlarity Imaging, Chicago, IL), approved by the FDA in 2017 as a second reader to be used after a radiologist's initial review of a suspect lesion on DCE-MRI (12).

Current State of AI in Breast Cancer Screening and Diagnosis

Within the last 10 years, AI has been a dominant force in breast cancer screening research. Artificial intelligence is being implemented for a range of uses: as a second reader, as a concurrent reader, as a primary reader in rule-out, and as a triage system for the prioritization of cases for reader order (46–48). Note that AI systems are mainly an aid to the reader and are not intended to replace the breast radiologist, although future efforts may be directed toward developing methods to function autonomously. Figure 2 demonstrates the process for developing AI to serve in the different roles during the screening workflow.

Methods for the development of human-engineered techniques and deep learning algorithms for screening modalities in the past decade have shown a variety of promising advancements (19,48,52,53). In mammography and DBT,

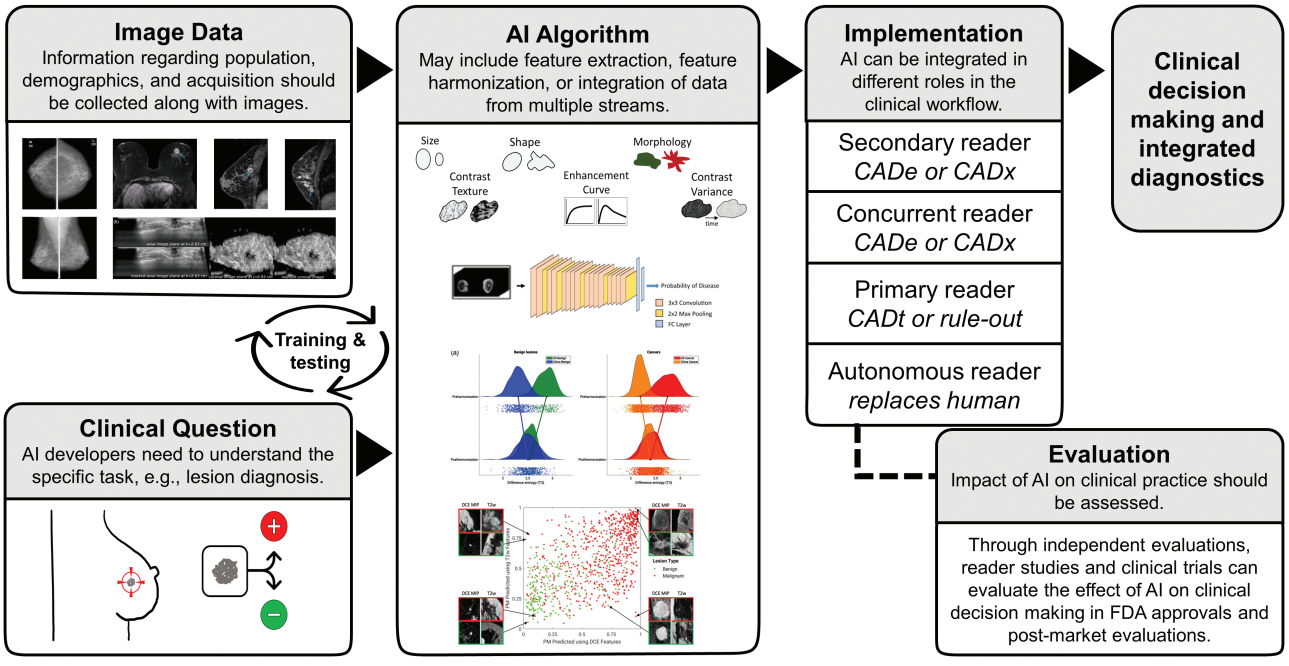

Figure 2. Schematic illustrating the components in developing an artificial intelligence (AI) algorithm for breast cancer screening (17,49–51). Specific algorithms will be trained and tested for unique tasks that are based on the data set and clinical questions. The systems can serve different roles for the end user in computer-aided detection (CADe), computer-aided diagnosis (CADx), triage (CADt), or rule-out tasks. The impact of AI on the efficacy and efficiency of the clinical interpretation and workflow may be quantified with reader studies before approval by the Food and Drug Administration (FDA).

human-engineered techniques have been expanded to include a wider selection of complex image features, and deep learning algorithms for detection and classification have been developed for faster implementation (53,54). Studies have shown that AI-assisted methods can maintain the accuracy of diagnosis while increasing the efficiency of interpretation for automated 3D breast US examinations (55,56). A number of AI techniques have also been developed to automatically detect and classify lesions based on the dynamic and morphological information contained in several MRI sequences (57–59).

Limitations in performance with deep networks due to data set size have been partially alleviated in recent years through the use of transfer learning. Transfer learning uses networks that are pretrained on other images, for example, the millions of natural images (cats, dogs, etc) in ImageNet, which can then be used directly to extract generic features from medical images or subsequently fine-tuned to produce features specific to a medical imaging data set (60–62). Both human-engineered and deep learning AI techniques have each been shown to perform well in breast lesion classification tasks; a number of publications have cited significant improvements in algorithm performances when merging human-engineered radiomic and deep learning algorithms into the machine learning decision across mammography, US, and DCE-MRI, even with modestly sized data sets (7,61,63).

In addition, modifying the image format input to deep networks in order to more efficiently incorporate volumetric and temporal information, such as postcontrast subtraction maximum intensity projection images, has been shown to further improve performance in breast tumor classification tasks (62). Further performance improvements have been reported by effectively fusing image data from multiparametric breast MRIs (DCE-MRI, T2-weighted, diffusion-weighted imaging), through either human-engineered or deep learning methods, at the pixel level, the feature level, or the classifier output level (51,64). Basically, effective development of an AI algorithm requires knowledge of the image acquisition process and the various formats of image presentation/reconstruction as well as the architecture of the radiomics/deep network itself.

As of the date of publication of this review, 21 AI algorithms for breast imaging have been cleared by the FDA (65). Of the 20 cleared algorithms, nine are for the purpose of breast density assessment, and 12 are intended to analyze breast lesion characteristics. Although the majority of cleared algorithms are for use on mammography or DBT imaging, three are based on breast US and one on breast screening MRI.

Challenges in AI in Breast Cancer Screening and Diagnosis

Explainability and Interpretability

One critical challenge in AI is the "black-box" nature of algorithms; many physicians are hesitant to accept AI output when the decision-making processes are opaque. To reach full clinical potential, technology needs to be explainable, interpretable, and user-friendly (15,17). Developers should also consider the fact that a variety of users, including clinicians, researchers, regulators, and insurance carriers, will have different interests in the system output, such as disease likelihood, pixel-level activation, data collection method, workflow efficiency, or cost (66,67). Researchers have found some potential solutions for explainability in medical imaging through the use of applications (eg, Grad-CAM) that highlight pixels within an image that are used by the algorithm in its decision making. Correlating AI outputs with human descriptions can also help in the interpretability of AI output. These applications can aid users in understanding why an AI algorithm may be failing in certain instances or populations. Nevertheless, the issue remains of how to trust and explain instances when an algorithm makes a prediction that does not align with the user's (ie, radiologist's) interpretation of an image, such as highlighting areas outside the body.

Robustness and Repeatability

Another key challenge focuses on the robustness and repeatability of AI algorithms. Because of the challenging nature of detection and diagnosis in medical images, the performance level of AI systems developed for these tasks may be very sensitive to small variations in image data. As a result, the output of such algorithms could be perturbed by many factors (eg, image acquisition parameters, segmentation selection, or biased training data). Robustness and repeatability have been issues widely documented for systems that use conventional human-engineered radiomic features, as feature definitions and calculation methods can vary widely from system to system (49,68). Deep learning AI methods are not immune to robustness challenges either, as the trained model and classifier performance can be impacted by the training data. Further, computers themselves can vary in their confidence of their output, particularly for cases that are difficult for the computer to classify. As shown in Amstutz et al (Figure 3), cases that were deemed to be clearly benign or clearly malignant by the computer demonstrated better repeatability (ie, more robust as shown by the smaller 95% confidence interval) than confusing cases that had computer outputs yielding estimates of malignancy around 50% (69). Such findings are similar to radiologists in that obvious malignant cases and obvious benign cases are easier to diagnose than confusing cases.

Generalizability, Bias, and Harmonization

Similar to the necessity for robustness and repeatability, AI algorithms also need to be generalizable to new populations and imaging systems and attempt to be free of bias (70). Given patient privacy regulations, large, well-curated data

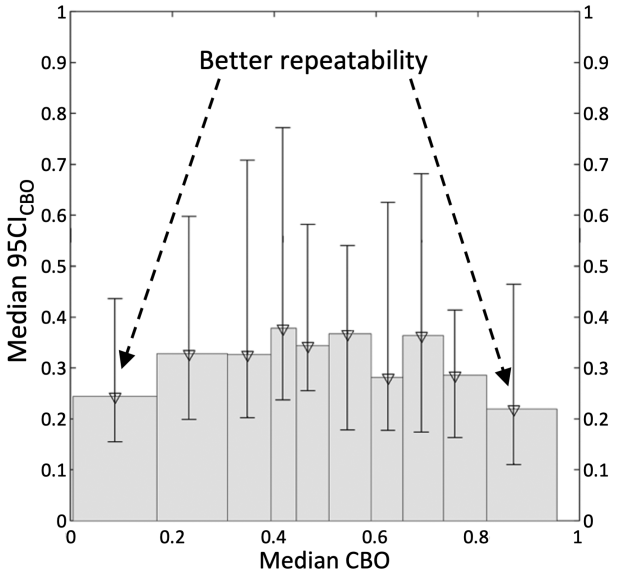

Figure 3. Case-based repeatability of radiomic features in classification of benign and malignant lesions in mammograms over 1000 iterations. The median case-based classifier output (CBO) 95% confidence interval (95CI) determined bin height, with shorter bins indicating better repeatability, and the median CBO was plotted in 10 bins in ascending order [from Amstutz et al (69); with permission].

sets are particularly difficult to obtain. As a result, many studies are based on small, single-institution data sets. For AI methods, which rely on training with available data, performance estimates can result that do not readily generalize to other populations or imaging systems. A few publicly available image repositories, including the Medical Imaging and Data Resource Center (MIDRC) and The Cancer Imaging Archive (TCIA), aim to alleviate this challenge by providing equitable access to a diverse population of imaging studies for a variety of diseases and clinical tasks (71,72). However, these resources require the initiative of researchers and clinicians to adopt an imaging sharing culture for society to truly benefit from the power of AI in medical imaging. Conversely, in order to maintain useful and trusted outputs, it may be best to develop algorithms for specific tasks, or specific acquisition systems, rather than general systems (66). Standardized training and testing protocols can be established to determine the generalizability of models, and it is important to evaluate performance of the computer algorithm as well as the end users when they are interpreting images without and with the AI system (17,66).

Ethical Implementation and Integration

Other challenges are the ethical use and integration of AI systems into the clinical setting. Ethical use of AI is a major consideration, as most AI systems are not yet approved by the FDA or are approved for a specific application. The user has the ethical obligation to implement approved algorithms only as they are intended, including using an algorithm only with appropriate images and use cases and not for "off-label" applications. Also, clinical workflows may have to be modified to account for changing from manually reading cases to reading cases with an AI aid. Clinicians and hospitals may need to construct new billing codes for this work, and future investigations should evaluate the clinical and financial impact of AI on radiologists and patients across health care systems (21).

Future of AI in Breast Cancer Screening and Diagnosis

The next generation of AI in breast cancer screening is expected to further increase the efficiency and efficacy of medical image interpretation across all modalities. One aspect of this goal is to extend AI from a second or concurrent reader (CADe, CADx) to an autonomous or partially autonomous reader (53). Recent studies have shown software that approaches or exceeds the performance of radiologists (73,74). For example, McKinney et al showed an AI detection system for screening mammography capable of outperforming six radiologists, with an average absolute margin in the area under the receiver operating characteristic curve of 11.5% between the AI system and the radiologists (73). However, limitations and challenges exist between the current state of AI and clinically applicable autonomous reading. For instance, many reports on the diagnostic accuracy of AI exist, but there is a lack of evidence on the perception and implementation of AI in actual clinical practice (21).

While the majority of AI research has focused on single interpretation tasks such as detection or diagnosis, a large area in which AI may have an impact on future breast cancer screening workflow is through the application of AI to streamline ancillary tasks. For example, AI may preprocess images or assist in the generation of standardized reporting documents (18). Image preprocessing may include image reconstruction, artifact correction, noise reduction, and user-preferred arrangement (hanging) of images.

It is important to note that according to FDA Code of Federal Regulations Title 21, computer-aided triage refers to software used to prioritize images and not to remove any from a given imaging queue (75); CAD rule-out, in contrast, would potentially remove a subset of cases from a screening queue if deemed to be below a predetermined risk threshold at which human reading in addition to computer reading is not necessary. The rule-out software would act as a truly autonomous reader for the subset of cases removed from a screening queue. Both triage and rule-out software could streamline clinical workflow, with rule-out having the potential to reduce radiologist workload without reducing screening sensitivity (76–78).

Conclusion

Over the last few decades, the development of new imaging technologies and the advancement of computational power

have contributed to an evolution of breast cancer screening practices. With the increasing use of DBT, US, and MRI in addition to mammography, the burden of image interpretation by radiologists is expanding. Fortunately, novel AI methods continue to be developed with the aim to improve the efficacy and efficiency of image interpretation. The majority of breast cancer AI systems are based on human-engineered or deep learning methods, and such AI systems serve as concurrent or secondary readers to the radiologist for detection and diagnosis. Future advances in AI will include systems that serve as primary readers to prioritize cases or streamline ancillary tasks, potentially allowing the radiologists' role to be enhanced as they integrate multimodality computer outputs with medical findings. Note that before AI may be used as an independent, autonomous reader, various challenges need to be addressed, including explainability, repeatability, and generalizability. Ultimately, the goal will be focused on AI providing a significant clinical benefit in breast cancer screening and diagnosis.

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Conflict of Interest Statement

M.L.G. is a stockholder in R2 Technology/Hologic and QView; receives royalties from Hologic, GE Medical Systems, MEDIAN Technologies, Riverain Medical, Mitsubishi, and Toshiba; and is a cofounder of Quantitative Insights (now Qlarity Imaging). Following the University of Chicago Conflict of Interest Policy, the investigators disclose publicly actual or potential significant financial interest that would reasonably appear to be directly and significantly affected by the research activities. N.B. and L.D. declare no competing interests.

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