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Review article

Staying abreast of imaging – Current status of breast cancer detection in high density breast

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ABSTRACT

Objectives: The aim of this paper is to illustrate the current status of imaging in high breast density as we enter a new decade of advancing medicine and technology to diagnose breast lesions.
Key findings: Early detection of breast cancer has become the chief focus of research from governments to individuals. However, with varying breast densities across the globe, the explosion of breast density information related to imaging, phenotypes, diet, computer aided diagnosis and artificial intelligence has witnessed a dramatic shift in new screening recommendations in mammography, physical examination, screening younger women and women with comorbid conditions, screening women at high risk, and new screening technologies. Breast density is well known to be a risk factor in patients with suspected/known breast neoplasia. Extensive research in the field of qualitative and quantitative analysis on different tissue characteristics of the breast has rapidly become the chief focus of breast imaging. A summary of the available guidelines and modalities of breast imaging, as well as new emerging techniques under study that can potentially provide an augmentation or even a replacement of those currently available.
Conclusion: Despite all the advances in technology and all the research directed towards breast cancer, detection of breast cancer in dense breasts remains a dilemma.
Implications for practice: It is of utmost importance to develop highly sensitive screening modalities for early detection of breast cancer.

Introduction

Breast density is well known to be a risk factor in patients with suspected/known breast neoplasia.[1,2] Extensive research in the field of qualitative and quantitative analysis on different tissue characteristics of the breast has rapidly become the chief focus of breast imaging.[2,3] Anatomically, breast tissue consists of both fibro-glandular and adipose tissue.[4] The difference in concentration of these components determines their radiographic appearance.[5] On a mammogram, adipose tissue is radiologically lucent and appears lucent compared to epithelium and stroma which are denser and appear opaque.[6] Dense breast tissue has been proven to be a risk factor for breast cancer development and is measured as the absolute amount of dense area (epithelium and stroma) in the breast.[7,8] Women with dense breasts (75% glandular and stromal tissue) are known to have a 4–6 fold increase in risk of developing breast cancer.[9] As such, with radiologically dense breasts, lesions tend to have a masking effect due to the similar x-ray attenuation profiles as fibro-glandular tissue, resulting in their reduced detection.[10] Therefore, reporting the nature of dense breasts with mammography has become a challenge to image reporters.

From all the available breast imaging modalities, mammography, which although is inaccurate in women with dense breasts or less women than 30 years of age,[11] has been the only proven cost-beneficial method to decrease mortality of breast cancer by 40% when women are regularly screened.[12,13] The sensitivity of detecting lesions by digital mammography is currently 85% in women ages 40 to 79.[14] However, this sensitivity decreases from around 83% in fatty breasts to 23.7% in heterogenous dense breasts

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which places greater emphasis on imaging the dense breast.[11] This would spur physicians to refer patients for supplemental imaging in nonconclusive studies raising the false positive rates to 10%, 80% of which are clarified on further imaging such as ultrasound and magnetic resonance imaging (MRI) while 10% will require biopsies.[12] Additionally, false negatives can reach between 15 and 20% particularly in women with dense breast tissue.[12] Thus, the need for multiple imaging modalities that account for volume and area have been created in an attempt to better assess breast density quantitatively and qualitatively.

MRI imaging has demonstrated significantly increased sensitivity for intraductal and familial cancer detection with its sensitivity, positive predictive value, negative predictive value, and false-negative (91.5%, 90.5%, 82.1%, and 8.5% respectively).[15,16] Tomosynthesis, which is the basis for 3D mammography, where individual slices of overlapping breast tissue are created, has shown a slight increase in sensitivity of breast cancer detection.[15] As further studies are discussing breast density and evaluation techniques, it has become a critical subject for breast cancer detection. There is currently no one clear measure of breast composition for evaluation of cancer risk and management.[17] Therefore, in this review we discuss current quantitative and qualitative breast density measurement techniques alongside the benefits of imaging modalities.

Assessment of breast density

Breast density assessment is a critical component in screening for breast cancer. The current gold standard for quantifying the degree of breast tissue density is the breast imaging reporting and data systems (BI-RADS).[18] Given the fact that it is based on subjective evaluation, the need for objective measurement tools arose. As such, area and volume quantification were incorporated. Area techniques involve direct images of the breast and visual segmentation of the areas accordingly.[19,20] This method is limited by inter- and intra-reader variability. On the other hand, volumetric methods are being recently implicated for breast density measurement. This approach relies on using a software that quantifies breast density from information obtained from the x-ray modality.[21,22] It proved to be less subject to inter-reader variability[23] and therefore, results in relatively higher reproducibility as compared to measurements using area techniques.

Quantitative techniques

BI-RADS

The BI-RADS scheme is a quantitative breast density classification that was developed by the American College of Radiology (ACR) in order to provide a unified reporting system and terminology between radiologists, thus preventing confusion and providing information for risk assessment by referring clinicians.[24] BI-RADS is almost universally accepted and widely used.[25] The latest scheme was updated in February 2014, and it subjectively classified mammographic breast density based on the relative appearance of dense tissue and fat, divided into four categories (A-D) instead of (1–4) (Figs. 1 and 2), thus eliminating percentiles of glandular tissue in each breast (Table 1).[26] Description of masses, calcifications, lesion locations, and tissue composition was modified by means of terminology in order to provide flexibility in situations where the previous BIRADS has failed and corrected inconsistencies.[27] It further assessed breast malignancy from x-ray interpretation and categorized it into Category 0 to Category 6 (Table 2).[28]

Limitations included subjective assessment, 2 dimensional measure, moderate interobserver agreement, and reduced reproducibility.[7,25] In a study performed by Lee et Al.[29] agreement among expert breast radiologists was studied in reporting mammograms with BIRADS 4 or 5. Highest agreement was in mass identification with a kappa of 0.82. However, radiologists demonstrated weak agreements in identifying asymmetries and architectural distortions with a kappa of 0.09 and 0.28 respectively.[29] BI-RADS use in general has a kappa value of 0.43–0.49 which reads as moderate interobserver agreement. However, its wide use and applicability for screening has surpassed its limitations.[30–32]

Area mammographic breast density (MBD) techniques

Mammographic density (MD), classified as the percentage of breast tissue assessed by radiologist using mammogram, is reflective of the variation in composition.[8] It can be divided into three phenotypes: absolute dense area (ADA), absolute non-dense area (NDA), percent density area (PDA). These areas are quantitatively measured using 3-dimensional (3D) computer software.[33] A meta-analyses by Krishnan et al.[34] analyzed breast cancer through detection mode and tumor size using mammographic screening. They reported that ADA and PDA where both predictors of inherent risk of breast cancer. Moreover, PDA, not BMI, was the best predictor for masking of breast cancer. PDA was also a stronger risk factor for developing breast cancer than was ADA. As for NDA, it was inversely associated with breast cancer risk. Hence, careful assessment and reporting of dense versus non-dense breast by radiologists should be considered before implementation of adjunct screening strategies.[35] Area breast density measures take into account the projections rather than the absolute volume, which represents a substantial limitation to its use.[36] Limitations also include the lack of dense tissue depth and overlapping regions evaluation. Moreover, the acquisition of the image with different breast compression intensity can have different extents of breast tissue expansion, thus changing the apparent area based density.[37]

Volumetric mammographic breast density techniques

With all the limitations presented with area-based methods for MD quantification, raw information obtained from mammographic images was manipulated in order to develop volumetric based quantification methods that take into account the depth of fibroglandular tissue. Each method consisted of a different approach in volumetric assessment which was limited to quantra, volpara, and spectral density.

Quantra is an imaging system that uses an absolute physics model of 3D structure imaging parameter to quantify breast volume, fibroglandular volume and fibroglandular percentage of the right and left breast mammograms.[37] It is both accurate and reproducible in terms of accessing breast density on digital mammograms.[38] Moreover, Quantra generates pseudo-BIRADS grades for mammographic breast density (MBD) assessment on a two-grade scale (BIRADS 1–2 vs 3–4) instead of the four–grade scale (BIRADS A-D) of a clinical setting.[39] When compared to radiologists, it has demonstrated moderate agreement with a kappa of 0.46.[37]

Volpara is an automated volumetric density measure that is based on relative physics principles calculating mammographic breast density through a reference pixel of purely adipose tissue in each image and then estimating x-ray attenuation relative to that pixel for all other points in the image.[40] It has been shown to be reliable and reproducible in terms of MBD assessment and demonstrated a strong positive correlation with BIRADS.[25] However, Volpara use is limited in scattered density breasts in terms of reproducible reliability. When compared to radiologists, it has proven moderate variability with a Kappa of 0.57.[37]

MRI, considered the gold standard for evaluation of volumetric breast density estimates, was compared to Quantra and Volpara in a

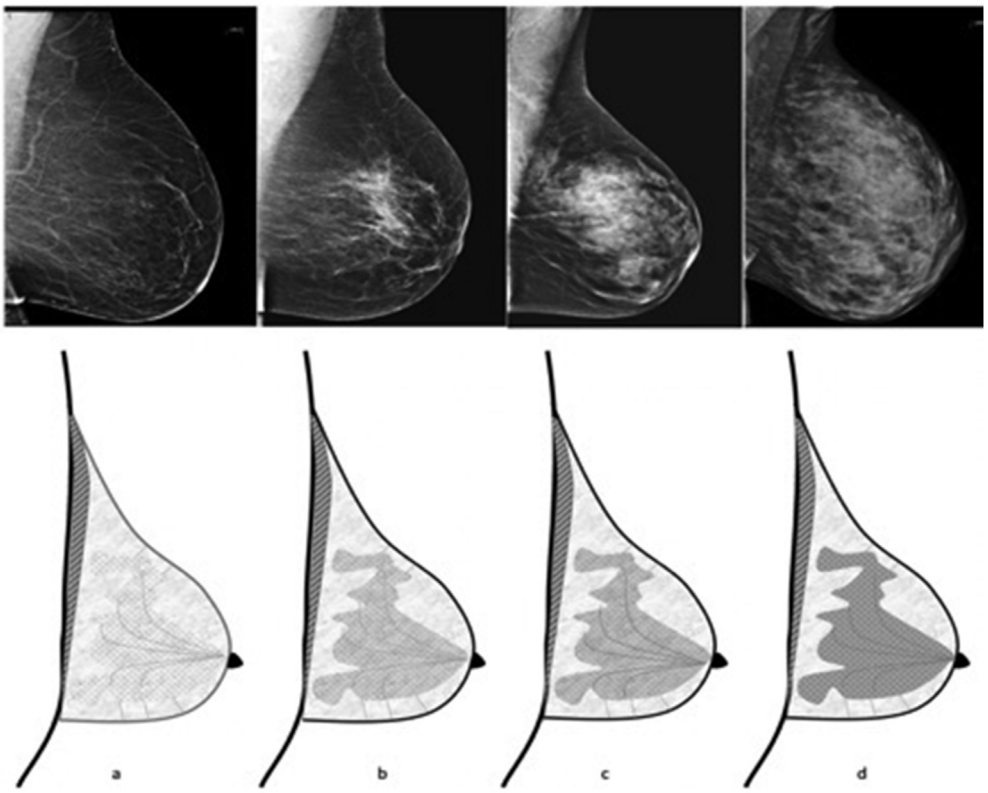

Figure 1. Different breast densities on mammogram with corresponding illustrations. (a) almost entirely fat, (b) scattered fibro-glandular tissue, (c) heterogeneously dense, (d) Extremely dense.

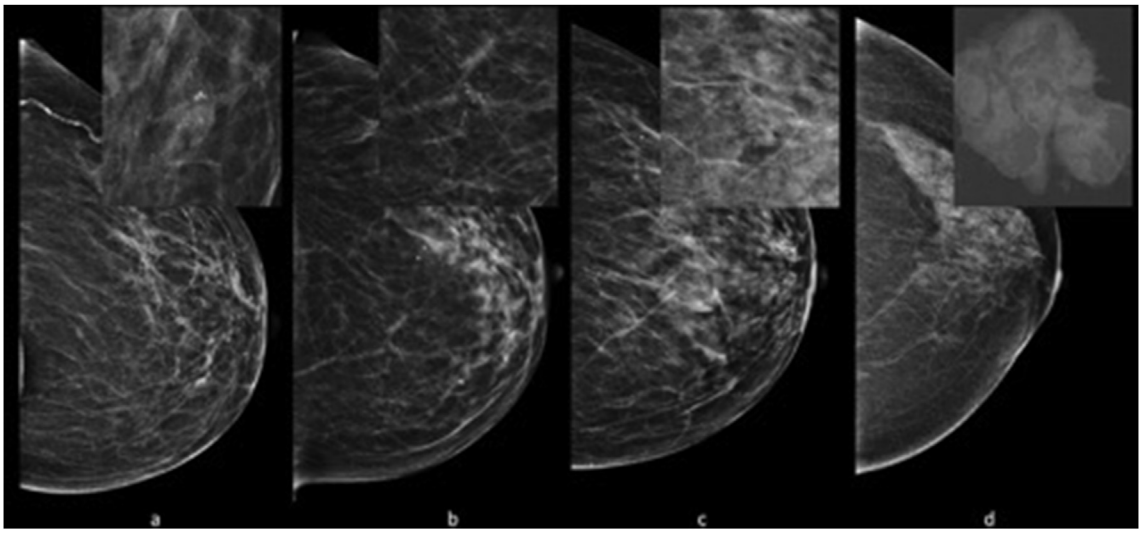

Figure 2. Ductal Carcinoma In-situ (DCS) lesions patterns with various fibro-glandular density. (a) almost entirely fat (≤25%), (b) scattered fibro-glandular densities (25–50% fibro-glandular), (c) heterogenous fibro-glandular densities (51–75% fibro-glandular) and (d) Extremely dense (>75% fibro-glandular).

study by Wang et Al.[41] Volpara demonstrated the highest correlation to MRI in dense breasts. Ekpo et al. measured the reproducibility of the different methods that assess breast density using digital breast tomosynthesis (DBT). The study concluded that Volpara and Quantra are both reliable and reproducible in terms of calculating volumetric breast density and are preferred compared to other methods. However, since they are the most common clinical methodology, they need to be adjusted to reflect the BIRADS categories.[42] Furthermore, both Volpara and Quantra have been demonstrated to assess volumetric changes in breast density in women on hormone therapy (HT), which will enable radiologists to measure the progress caused by HT on women at risk of breast cancer development.[43] Moon et al.[44] used tomosynthesis to estimate breast density and compared their results to MRI and

Table 1
Difference between 4th edition and 5th edition BI-RADS classification of breast density[27].

4th Edition	5th Edition
The breast is almost entirely fat (<25% glandular)	The breasts are almost entirely fatty
There are scattered areas of fibroglandular densities (approximately 25–50% glandular)	There are scattered areas of fibroglandular density
The breast is heterogeneously dense, which could obscure detection of small masses (approximately 51–75% glandular)	The breasts are heterogeneously dense, which may obscure small masses
The breast is extremely dense. This may lower the sensitivity of mammography (>75% glandular)	The breasts are extremely dense, which lowers the sensitivity of mammography

Table 2
Description of BI-RADS category and its risk of malignancy[22].

BI-RADS Category	Description	Risk of Malignancy
0	Incomplete	Needs additional testing
1	Negative	No/minimal risk
2	Benign	No/minimal risk
3	Probably benign	0%–2%
4	Suspicious	2%–95%
4A	Low suspicion	2%–10%
4B	Moderate suspicion	10%–50%
4C	High suspicion	50%–95%
5	Highly suspicious	95% or higher
6	Tissue confirmed cancer	Biopsy-proven malignancy

mammographic images. An automatic skin remover and an FCM(Fuzzy C Mean) classifier that separates fibro-glandular breast tissue from surrounding tissue was used that provided a useful 3 dimensional information on breast density.

Spectral Density Measurement Tool[37] is a spectral based breast density volumetric quantification tool. It uses dual energy decomposition in order to quantify adipose and fibro-glandular tissue sparing the need to use contrast as compared to the regular low dose mammogram.[45] A photon counting detector incorporated in the machine sorts photons as high or low energy, which is used to generate a “MicroDose Density Score” from output data that is comparable to the BI-RADS score. Volumetric breast density, total breast tissue and fibro-glandular volumes are also extracted. However, this method is yet to be further investigated and studied to demonstrate its applicability.

Imaging modalities

Several tools have been used to screen for breast cancer. Mammogram is commonly used to measure breast density. However, one disadvantage is the ability of the tumor to mask in highly dense breasts. This will result in a reduction of the sensitivity of the mammogram and hence further screening modalities need to be supplemented.[7]

Digital breast tomosynthesis (DBT)

Digital Breast tomosynthesis (DBT), first introduced in 1997, is an imaging technique that acquires multiple breast images from different angulations of the X-ray tube, where these images are later presented as 3D reconstructions.[46] It has emerged as a new imaging modality that decreases the masking effect in overlapping fibro-glandular tissue, hence increasing the sensitivity that was lacking in the traditional mammogram.[46] DBT is expensive and if used in conjunction with mammogram, increases radiation exposure to the women being screened.[47] However, this increased radiation is still below FDA approved limits of radiation which is 3mGy/view.[46] Skaane et al. compared between conventional mammography alone or in conjunction with DBT in 12,631 women.[48] A 27% increase in detection rate for invasive and in situ carcinoma cancers was reported when both modalities were combined, as well as a 15% decrease of false positive rate. Limited data currently exists for emphasizing its benefits or recommendations of application. Current literature suggests its use as an adjunct or in combination with mammography. As for its use as a single screening modality, DBT has proved in multiple studies that it underestimates breast density values when compared with mammography,[49] attributed to differences in positioning, compression, dose to the detector, and software algorithms.[50] Further studies need to be conducted in terms of image acquisition and interpretation, as well as clinical applications in order to better assess the use of a tool with great potential.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) has been proven to have the highest sensitivity for detecting breast cancer, especially with women at high risk of developing breast cancer.[51] Multiple malignant foci in the breast are detected with a sensitivity of less than 50% with mammography.[52] The sensitivity on the other hand with gadolinium enhanced MRI for detection of invasive cancers goes up to 94–99% and 50–80% for cancers in-situ. Specificity in MRI is approximately 65–79%[52] which makes up some of the limitations that have been associated with MRI in addition to cost and its use of gadolinium injection.[7] Limited evidence supports the regular use of screening MRI because of no improved outcome.[53] The strongest evidence exists for patients who are established to have the BRCA mutation or a strong family history.[53] As for evidence on breast density, MRI is significantly more sensitive than mammography for the detection of malignant foci in fibro-glandular, heterogenous, or extremely dense breasts, but nor more sensitive in fatty breasts.[52]

Ultrasound

Another modality that screens for breast density is ultrasound (US). US provides anatomical information of the breast, is noninvasive, inexpensive and does not involve radiation exposure. However, US has proven low specificity due to its inability to differentiate between cancer and breast lesions,[54] along with a high unacceptable rate of positives and false negatives.[55] Studies have demonstrated that the addition of US to mammogram screening increases breast cancer detection,[56] making ultrasound a supplementary imaging modality, not a primary screening tool. Supplemental US screening in dense breasts provides an additional increase in breast cancer detection rates by 1.9–4.2%, depending on the population.[57]

Molecular breast imaging (MBI)

MBI also known as breast-specific gamma imaging (BSGI), is a nuclear breast imaging technique that uses a high resolution, small field-of-view breast-specific gamma camera.[58] This technique

allows the use of radiotracers as biomarkers to image cellular activity.[59] In a cancerous cell, higher uptake of radiotracer is observed compared to normal tissue due to the increased mitochondrial density and vascularity. MBI has been proven to be highly sensitive and specific in detecting sub-centimetric breast cancer lesions, DCIS and atypical breast lesions with an overall sensitivity of 90%, independent of breast density, that decreases to 82% for sub-centimetric lesions.[58,60] However, the high radiation dose is a limitation although it would still be below natural background radiation levels.[25]

Artificial intelligence (AI) and computed aided diagnosis (CAD)

Normally the diagnosis by radiologists is affected by many factors such as low image quality, overlapping structures, visual fatigue, limited visual ability and so on. Computer Aided Diagnosis (CAD) however, has become one of the major research subjects in medical imaging and diagnostic radiology[61] that provides a computer output as a second opinion to assist radiologists' image interpretation by improving the accuracy and consistency of radiological diagnosis and also by reducing the image reading time.[61] CAD systems are normally developed using two computational techniques: computer vision and AI. Computer vision uses techniques of image processing for enhancement, segmentation and feature extraction are used. Many methods and techniques of Artificial Intelligence (AI) can be applied to quantify attributes of the structures identified to be further classified and it is very efficient for complex data analysis. However, with the variable qualitative approach to the classification of breast density according to the BIRADS system, it has variations in confidence of detection. Fatty breasts and extremely dense breasts are highly consistent, but greater variability exists in distinguishing scattered density from heterogeneously dense parenchyma especially by radiologists from different geographic regions such as the US and UK.[62]

Machine learning, a component of AI, is currently used as a programming application that automatically extracts and interprets complex data. Incorporated techniques like deep and reinforcement learning allow continuous manipulation of input data, thus affecting sequential decisions. AI algorithms are being developed that convert whole digital images into quantitative pixel level variables that are unrecognizable by the human eye; these images are clustered and associated with biopsy results which are the gold standard for diagnosing breast cancer. A recent study demonstrated that the AUC(area under the curve) was 0.9421 when the CNN-model was trained from scratch on their mammographic images, and the accuracy increased gradually along with an increased size of training samples. After removing the potentially inaccurately labeled images, AUC was increased to 0.9882 and 0.9857 for without and with the pretrained model, respectively, both significantly higher than when using the full imaging dataset; thus, showing encouraging results while using CAD and deep learning (AI) in classifying and mainly distinguishing between "scattered density" vs "heterogeneously dense" breast density categories.[63–65]

Transforming data into knowledge will have disruptions on several areas of medicine. Prognostic models nowadays are restricted to a few variables because humans enter and tally the scores. Instead, the data can be used directly from EHRs (electronic health records) or databases, allowing models to use thousands of rich predictor variables. Machine learning may also aid reporting activities by highlighting certain image findings during the reporting process that the radiologist may adopt or reject. Combined large imaging data sets with recent advances in computer vision, will cause fast improvements in performance; and machine accuracy will soon be better than that of humans. Furthermore, there is an alarming frequency of errors in diagnostics and few interventions to correct them. Machine learning will improve the diagnostic accuracy. However, this technology disruption will develop slowly, over the next years, for three reasons: first, the gold standard for diagnosis is not clear in several conditions, causing difficulty in training algorithms. Second, high-value electronic healthcare data are often stored in unstructured formats that are unreachable to algorithms without layers of preprocessing. Finally, models need to be performed and validated for each diagnosis individually (63). Moreover, allowing the data speak for themselves can cause issues.

Algorithms might "overfit" predictions to spurious correlations in the data and could produce estimates that are unstable. This can cause overly optimistic estimates of model accuracy and exaggerated claims about real-world performance. These concerns are serious and thus models must be tested on real independent validation data sets, from various populations or periods that had no role in model development (63). Also, machine learning does not solve any of the serious problems of causal inference in observational data sets. Algorithms may be good at predicting outcomes, but predictors are not causes (64). Finally, a key issue is the quantity and quality of input data. Machine learning algorithms are highly "data hungry", requiring millions of observations to have acceptable performance levels (65). In addition, biases in data collection can substantially affect both performance and generalizability. That is data fed into these systems may be wrongly reported in the first place, which raises the issue of re-interpreting these images, and associating with biopsy results. At this point, the aim is to differentiate normal fibro-glandular tissue from potential cancerous one. In the future, AI may further be used to differentiate between benign and malignant lesions,[66] what pattern of dense breast is malignant and what is benign, what needs further screening and biopsy and what does not.

Conclusion

Despite all the advances in technology and all the research directed towards breast cancer, detection of breast cancer in dense breasts remains a dilemma. It is the most common cancer in women, accounting for 25.1% of all cancers.[67] Women with high density breast tissue are faced with two challenges which are increased risk for developing breast cancer and late diagnosis of breast cancer explained by the low sensitivity of screening mammograms in this population. Complex cellular and molecular mechanisms interplay beyond our current understanding causing an increased association between breast cancer and increased breast tissue density. Thus, it is of utmost importance to develop highly sensitive screening modalities for early detection. There is still a lot of debate on how to approach imaging in the screening workup of women with high density breasts. These women should be offered a multimodal screening strategy that focuses on increased sensitivity and lowering rates of false negatives. Imaging modalities might benefit from developing a new biomarker that would aid in detecting radiologically challenging cases. We have provided a summary of the available guidelines and modalities of breast imaging, as well as the new emerging techniques under study that can potentially provide an augmentation or even a replacement of those currently available for a better diagnostic approach of cancer in dense breast tissue.

Conflict of interest statement

All authors have nothing to disclose and have no conflict of interest.

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