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Double reading of automated breast ultrasound with digital mammography or digital breast tomosynthesis for breast cancer screening

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ABSTRACT

Purpose: To evaluate the impact of double reading automated breast ultrasound (ABUS) when added to full field digital mammography (FFDM) or digital breast tomosynthesis (DBT) for breast cancer screening.

Methods: From April 2014 to June 2015, 124 women with dense breasts and intermediate to high breast cancer risk were recruited for screening with FFDM, DBT, and ABUS. Readers used FFDM and DBT in clinical practice and received ABUS training prior to study initiation. FFDM or DBT were first interpreted alone by two independent readers and then with ABUS. All recalled women underwent diagnostic workup with at least one year of follow-up. Recall rates were compared using the sign test; differences in outcomes were evaluated using Fisher's exact test.

Results: Of 121 women with complete follow-up, all had family (35.5%) or personal (20.7%) history of breast cancer, or both (43.8%). Twenty-four women (19.8%) were recalled by at least one modality. Recalls increased from 5.0% to 13.2% ($p = 0.002$) when ABUS was added to FFDM and from 3.3% to 10.7% ($p = 0.004$) when ABUS was added to DBT. Findings recalled by both readers were more likely to result in a recommendation for short term follow-up imaging or tissue biopsy compared to findings recalled by only one reader (100% vs. 42.1%, $p = 0.041$). The cancer detection rate was 8.3 per 1000 screens (1/121); mode of detection: FFDM and DBT.

Conclusions: Adding ABUS significantly increased the recall rate of both FFDM and DBT screening. Double reading of ABUS during early phase adoption may reduce false positive recalls.

1. Introduction

Breast density is a known factor that moderately increases breast cancer risk and has a masking effect that reduces breast cancer detection on film-screen mammography [1,2]. Technologic advances for mammography, including full field digital mammography (FFDM) and digital breast tomosynthesis (DBT), and supplemental screening methods such as whole breast ultrasound aim to improve early cancer detection.

To increase patient awareness of the issues related to breast density and breast cancer screening in the United States, 34 states have passed legislation mandating that women receive information regarding breast density with their screening mammography results [3]. While specific requirements regarding who is informed, whether specific language is mandated, and whether supplemental screening tests are mentioned vary by state [4,5], enactment of breast density notification laws have led to increased utilization of supplemental screening modalities [6,7].

Whole breast ultrasound is commonly used as a supplemental screening method given that it is widely available and does not require ionizing radiation or use of intravenous contrast. The two forms – handheld ultrasound (HHUS) and the more recently developed automated breast ultrasound (ABUS) – possess excellent agreement in terms of lesion visualization and characterization [8], and both have been demonstrated to increase breast cancer detection in women with dense breasts [9–12]. However, as a modality, whole breast ultrasound screening is also limited by low specificity, positive predictive value, and therefore risk of false positives [13].

One way to address these limitations may be to double read screening whole breast ultrasounds. Unfortunately, HHUS precludes this approach due to the real time nature of visualizing the entire volume of breast tissue and operator dependency on obtaining a selective and limited number of images of areas of interest. In contrast, ABUS

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allows evaluation of the whole volume of breast tissue uncoupled from the time of image acquisition, enabling a double reading approach [14]. Despite this capability, the benefit of double reading ABUS remains unknown.

To address this knowledge gap, we conducted this study to evaluate the diagnostic impact of adding ABUS, via single and double reading, to FFDM or DBT for breast cancer screening.

2. Material and methods

Between April 2014 and June 2015, we enrolled women in a prospective, institutional review board-approved, Health Insurance Portability and Accountability Act compliant, single-site, non-randomized, blinded-reader, crossover study of ABUS, FFDM, and DBT for breast cancer screening (ClinicalTrials.gov Identifier: BLINDED). GE Healthcare provided financial support for data collection and analysis by study team members. In addition, GE Healthcare provided the ABUS system (Invenia) on loan for the duration of the study and a research DBT unit (GE SenoClaire DBT with Volume-Preview Synthetic 2D Mammography) from April 2014 to April 2015. From May 2015 onward, study participants received DBT examinations on clinical DBT units. The study investigators had full control of the data and information submitted for publication. All participants provided written informed consent.

2.1. Study population

Eligible women were age 18 and older with dense breasts and intermediate to high breast cancer risk. Breast density was determined by prior mammogram assignment of heterogeneously dense or extremely dense breasts. Intermediate to high breast cancer risk was based on meeting one or more of the American Cancer Society criteria [15]: BRCA1 or BRCA2 gene mutation; first-degree relative with BRCA1 or BRCA2 gene mutation self-reported by subjects without prior genetic testing; prior radiation therapy to the chest between ages 10 and 30 years; Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, or one of these syndromes in a first-degree relative; or previous diagnosis of breast cancer, ductal carcinoma in situ, lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia. Women were excluded if they were screened for breast cancer with any breast imaging modality within one year prior to enrollment, exhibited signs or symptoms of breast cancer, or were diagnosed with breast cancer within one year prior to enrollment. Women with bilateral breast implants and women who were pregnant or lactating at the time of the study were also excluded.

2.2. Image acquisition

Women enrolled in the study underwent breast cancer screening with FFDM, DBT, and ABUS. All FFDM and DBT images were obtained using a FFDM and DBT system. FFDM images and then DBT images of each breast were acquired in the standard craniocaudal and mediolateral oblique views by a trained technologist. DBT images were post-processed and reconstructed for viewing and included synthetic 2D images for each view. All ABUS images were obtained by a trained technologist. Transverse images of each breast were obtained with an automated 15.3 cm 6–15 MHz transducer in three transversely oriented "sweeps" over the central, lateral, and medial breast. A hypoallergenic acoustic coupling lotion was applied before each view was obtained. Each view took approximately 30 s to acquire, and total examination time was generally < 15 min. Images were reconstructed for viewing in the axial, sagittal, and coronal planes on a dedicated ABUS workstation.

2.3. Pilot phase

Fifty women were enrolled in a pre-study pilot phase to ensure consistent acquisition and interpretation of ABUS images. Pilot phase ABUS images were not included in the study analysis and were not used to direct clinical care.

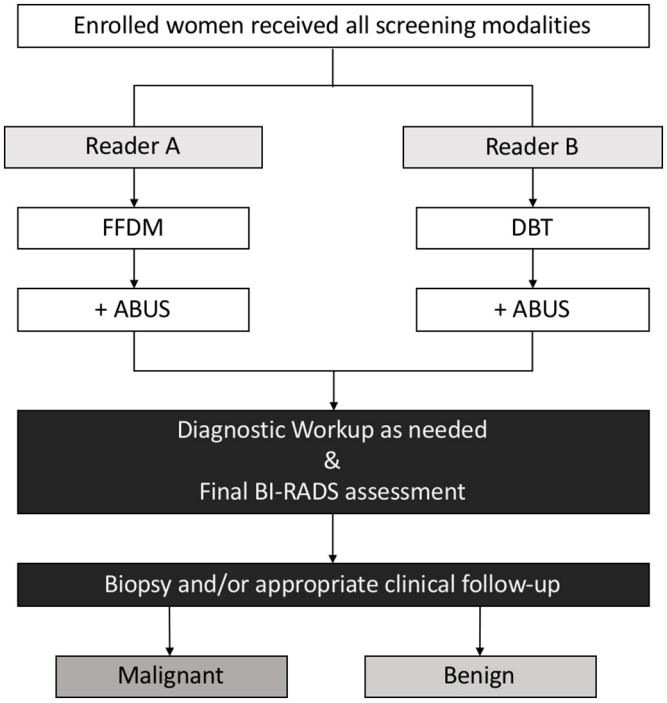

Fig. 1. Study schema. First screening assessment given by Reader A for FFDM alone and by Reader B for DBT with synthetic 2D alone. Second screening assessment given by Reader A for FFDM + ABUS and by Reader B for DBT + ABUS. Neither reader had access to FFDM + DBT combination.

2.4. Reader study design

All six readers were fellowship-trained breast imaging radiologists with experience using FFDM and DBT in clinical practice. Readers had experience using HHUS in the diagnostic setting, but not for whole breast screening. All readers participated in the pilot phase and underwent training in ABUS interpretation prior to study initiation with a 4-hour case-based review of anonymized FFDM and ABUS cases.

Enrolled women underwent imaging with all three modalities: FFDM, DBT with synthetic 2D images, and ABUS (Fig. 1). For each patient, FFDM and DBT were first interpreted without the ABUS examination. "Reader A" interpreted the FFDM images and "Reader B", a different radiologist, independently interpreted the DBT images. Reader A and Reader B were blinded to results of the other mammographic modality. Combined FFDM and DBT images were not available to either reader. Prior examinations were available to both readers. An initial BI-RADS assessment (0, 1, or 2) was recorded by each reader. Both readers were then shown the ABUS examination and asked to provide a combined BI-RADS assessment (FFDM + ABUS for Reader A, DBT with synthetic 2D + ABUS for Reader B). Any of the six radiologists served as Reader A or Reader B, but could not be both for the same patient. Because the study was designed to evaluate different alternative screening processes, either FFDM without and then with ABUS, or DBT without and then with ABUS, no consensus/arbitration process was included in the study protocol.

2.5. Subject follow-up

All subjects with an abnormal screening interpretation (BI-RADS 0 assessment) were recalled for standard of care diagnostic imaging evaluation with additional mammographic views and/or targeted

handheld ultrasound examination at the discretion of the interpreting radiologist in clinic on the day of diagnostic evaluation, with no requirement for the radiologist issuing the recall to complete the diagnostic workup. Diagnostic examination results and final BI-RADS assessments were recorded. All women were followed up for at least 12 months. For diagnostic examinations with a BI-RADS 3 final assessment, short term follow-up imaging was recommended at intervals of 6, 12, and 24 months. For diagnostic examinations with BI-RADS 4 (suspicious) or 5 (highly suspicious) final assessments, image-guided percutaneous core biopsy was pursued. Subsequent cancer diagnoses were tracked using our institutional Consortium Oncology Data Integration (CODI) database with linkage to the Cancer Surveillance System [16], part of the Surveillance Epidemiology and End Results program of the National Cancer Institute, which collects population-based data on cancer incidence and survival in 13 counties of western Washington state.

2.6. Statistical analysis

Recall rates for FFDM and DBT, with or without ABUS, were compared using the sign test. Inter-reader agreement for recall between Reader A (FFDM) and Reader B (DBT) with or without ABUS, was summarized using percent agreement and Cohen's kappa. Fisher's exact test was used to compare rates of recommendation for short-term follow-up imaging or biopsy between women recalled by only one reader and women recalled by both readers. Clopper-Pearson exact 95% confidence intervals were calculated for the changes in recall rates after adding ABUS and for the cancer detection rate. All statistical calculations were conducted with the statistical computing language R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-sided tests were used, with statistical significance defined as $p < 0.05$.

3. Results

Of 124 women enrolled in the study, one decided not to undergo the ABUS examination and two were lost to follow up. All 121 women with complete follow-up had family (35.5%) or personal (20.7%) history of breast cancer, or both (43.8%) (Table 1). The majority were non-Hispanic Caucasian (85.1%), < 60 years of age (68.6%), and post-menopausal (61.2%).

Table 1
Study population characteristics (N = 121).

Characteristic	N (%)*
Age (years)	
18–39	12 (9.9%)
40–49	28 (23.1%)
50–59	43 (35.5%)
60–69	30 (24.8%)
≥70	8 (6.6%)
Race/ethnicity	
White, non-Hispanic	103 (85.1%)
Black, non-Hispanic	3 (2.5%)
Hispanic	0 (0.0%)
Asian	5 (4.1%)
American Indian/Alaskan Native	1 (0.8%)
Unknown	9 (7.4%)
Family history[a] and personal history of breast cancer	
Family history only	43 (35.5%)
Personal history only	25 (20.7%)
Family history and personal history	53 (43.8%)
Menopausal status[b]	
Pre-menopausal	45 (37.2%)
Peri-menopausal	2 (1.7%)
Post-menopausal	74 (61.2%)

* Percent values may not add up to 100% due to rounding.
[a] Family history defined as having at least one 1st degree family member or two 2nd degree family members diagnosed with breast cancer.
[b] Determined by medical record or patient report at time of consent.

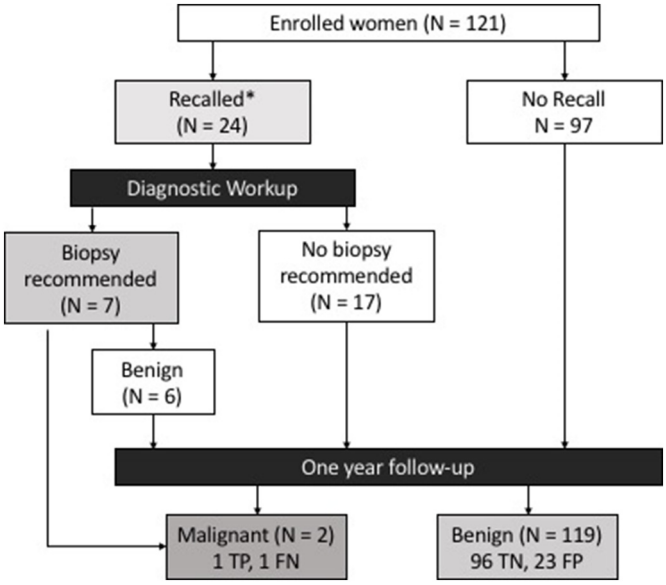

Fig. 2. Screening results and outcomes. *Either reader, any modality.

Twenty-four (19.8%) women had at least one abnormal screening examination and were recalled for additional diagnostic imaging (Fig. 2). The recall rates for FFDM alone and DBT alone were 5.0% (6/121, 95% CI: 1.8–10.5%) and 3.3% (4/121, 95% CI: 0.9–8.2%), respectively ($p = 0.69$ for the difference) (Fig. 3). With the addition of ABUS to FFDM, the recall rate increased by 8.3% (10/121, 95% CI: 4.0–14.7%, $p = 0.002$) to 13.2% (16/121, 95% CI: 7.8–20.6%) compared to FFDM alone. Similarly, the recall rate increased by 7.4% (9/121, 95% CI: 3.5–13.7%, $p = 0.004$) to 10.7% (13/121, 95% CI: 5.8–17.7%) when adding ABUS to DBT. There was no significant difference in the recall rate of FFDM with ABUS compared to DBT with ABUS ($p = 0.65$). Sixteen of the 24 recalls (66.7%) were for findings identified only by ABUS.

Five women were recalled by both readers, two for calcifications

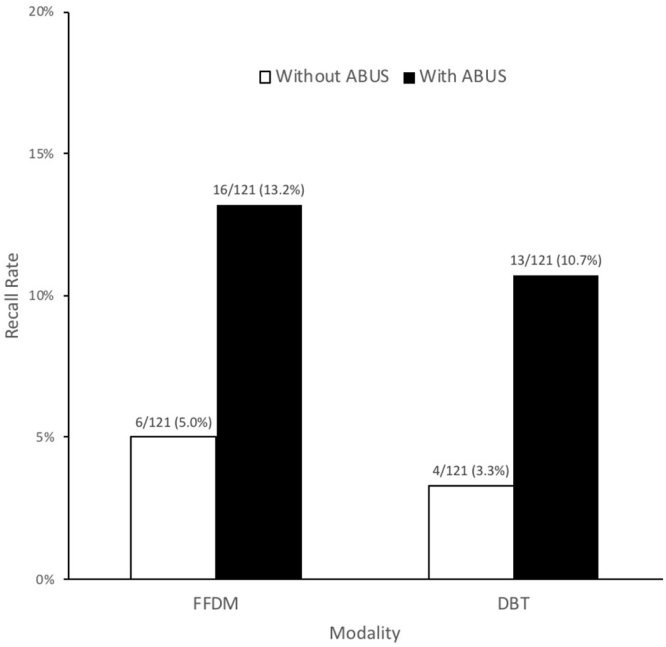

Fig. 3. Recall rates for FFDM vs. DBT, without and with ABUS.

Table 2
Lesion characteristics and outcome after recall (N = 24 women).

Study ID	Screen findings				Diagnostic finding	Final BIRADS	Outcome	Additional details
	Reader A		Reader B					
	FFDM	+ABUS	DBT	+ABUS				
Two reader recalls N = 5								
2	Calcs		Calcs		Calcs	4	Benign	Pseudoangiomatous fibrous stroma with associated stromal microcalcifications
81	Calcs		Calcs		Calcs	4	Malignant	High risk lesion, excisional biopsy revealed DCIS
56		Mass		Mass	Mass	4	Benign	Fibrocystic changes, including cyst wall, dense stromal fibrosis and sclerosis
61		Mass		Mass	Mass	3	Benign	Stability with two-year imaging follow-up
63		Mass		Mass	Mass	3	Benign	Stability with two-year imaging follow-up
One reader recalls N = 19								
20	Calcs				Calcs	3	Benign	Stability with two-year imaging follow-up
21	Calcs				Calcs	2	Benign	
116	Calcs				Calcs	4	Benign	Benign microcalcifications
86	FA	Mass			Mass	4	Benign	Fibroadenoma
93			AD		No finding	2	Benign	
122			AS		Stable AS	1	Negative	
13		Mass vs. artifact			No finding	2	Benign	
30		Mass			No finding	1	Negative	
42		Mass			Cyst	2	Benign	
43		Mass			Dermal mass	2	Benign	
64		Mass			No finding	1	Negative	
94		Mass			Mass	4	Benign	Fibroadenoma
120		Mass			No finding	2	Benign	
9				Mass	Cyst	2	Benign	
34				Mass	Cyst	2	Benign	
36				Mass	Mass	3	Benign	No malignant pathology in CODI database
74				Mass	Mass	3	Benign	Fibroadenoma[a]
82				Mass	Complex mass versus complicated cyst	4	Benign	Cyst aspiration - brownish/clear fluid was obtained and discarded
124				Mass	Mass	3	Benign	Stability with two-year imaging follow-up

Abbreviations: Calcs = calcifications, FA = focal asymmetry AD = architectural distortion, AS = asymmetry.
[a] Patient #74 was not recommended biopsy (BI-RADS 3), however patient requested biopsy.

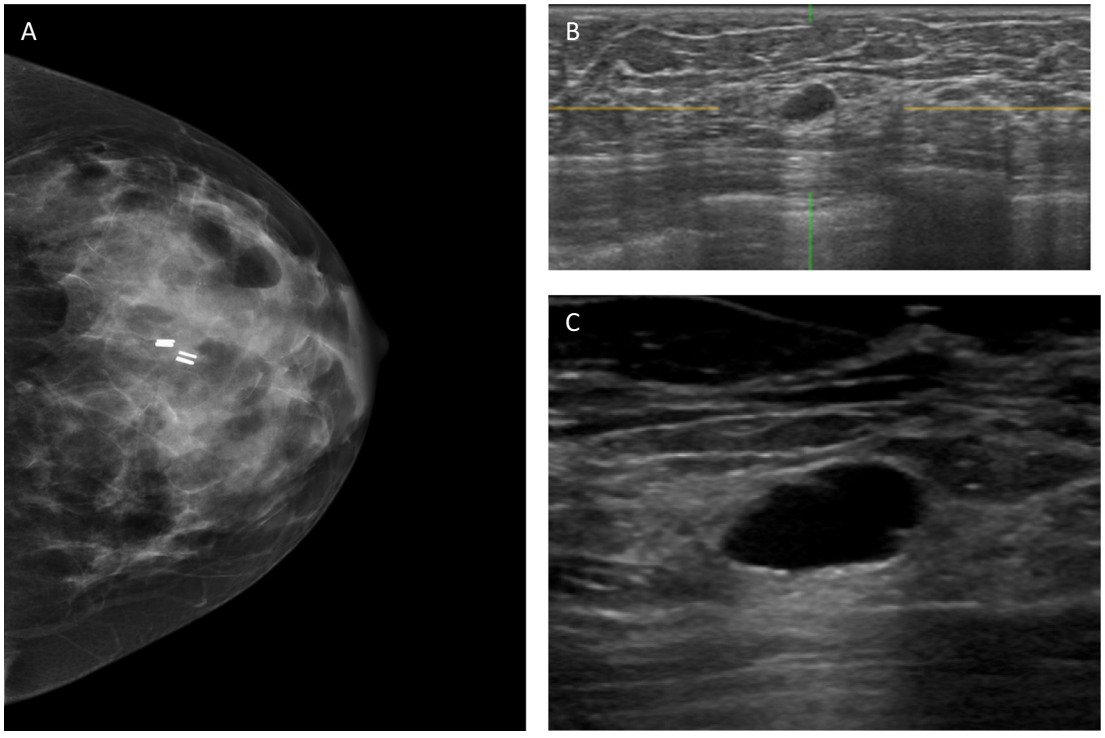

Fig. 4. ABUS-only finding recalled with benign final assessment (patient 9). A) FFDM craniocaudal mammogram of the left breast. The breast is heterogeneously dense. There are clips from prior biopsy. No suspicious mass or calcifications. B) ABUS of the left breast showed an oval hypoechoic mass at 2:00. C) Targeted ultrasound of the left breast at 2:00 showed a lobulated simple anechoic cyst with an internal septation.

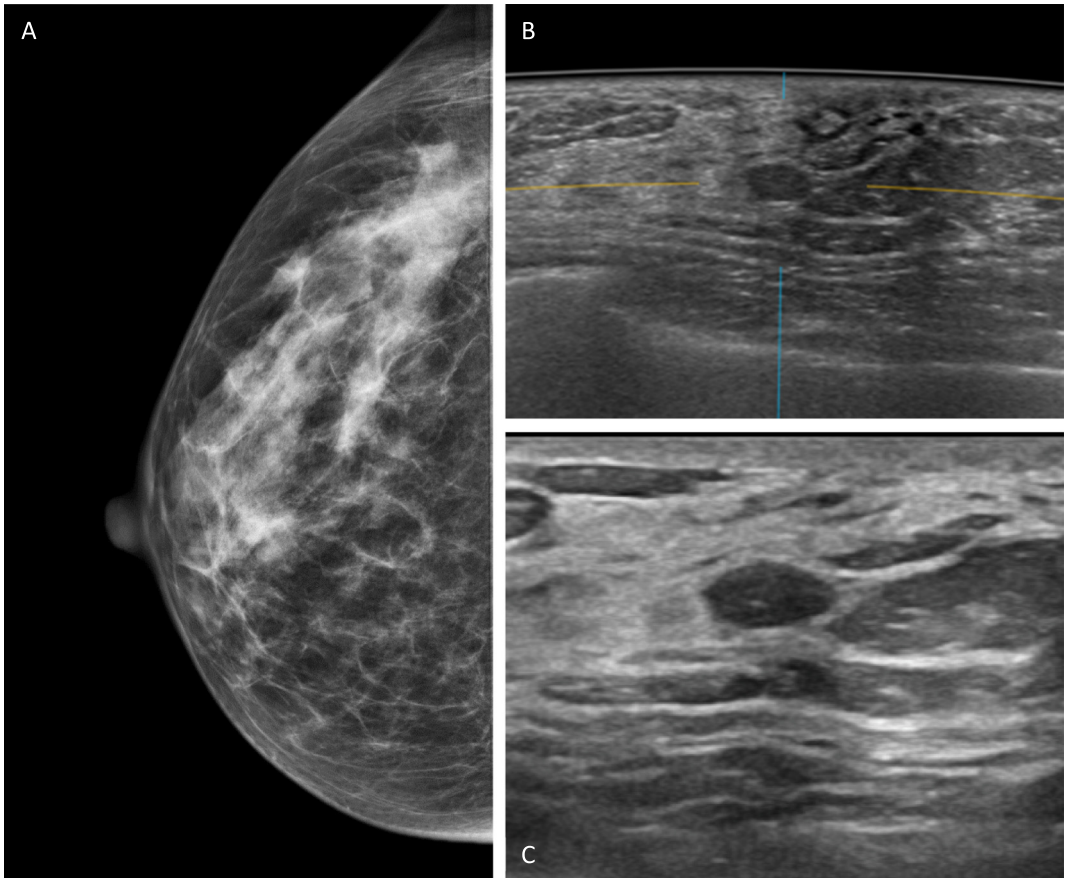

Fig. 5. ABUS-only finding recalled with probably benign final assessment (patient 74). A) FFDM craniocaudal view of the right breast. The breast is heterogeneously dense. There are no suspicious masses or calcifications. B) ABUS of the right breast showed an oval hypoechoic mass at 7:00. C) Targeted ultrasound of the right breast at 7:00 showed an oval circumscribed solid mass, likely a fibroadenoma. BI-RADS 3 final assessment was issued but patient elected to undergo biopsy. Pathology revealed a fibroadenoma.

identified only by FFDM and DBT, and three for masses identified only by ABUS (Table 2). Nineteen women were recalled by only one reader, one for a finding identified on both FFDM and ABUS and the rest for findings identified by a single modality. Inter-reader percent agreement for recall without ABUS was 95.0% (115/121), with a corresponding Cohen's kappa = 0.38 (95% CI: −0.02–0.77). Inter-reader percent agreement with ABUS was 84.3% (102/121) with corresponding Cohen's kappa = 0.26 (95% CI: 0.02–0.50). After diagnostic imaging evaluation, 11 of the 24 recalls (45.8%) were issued final BI-RADS 1 or 2 (Fig. 4), 6 (25%) were issued BI-RADS 3, and 7 (29.2%) were issued BI-RADS 4 assessments. One woman who was given a BI-RADS 3 final assessment requested tissue biopsy, with a resulting benign and concordant pathology result (Fig. 5). The five remaining BI-RADS 3 cases demonstrated stability with two-year imaging follow up and/or no subsequent cancer diagnosis in the CODI database.

Considering all modalities, findings recalled by both readers were more likely to result in a recommendation for short term follow-up imaging or tissue biopsy when compared to findings recalled by one reader (100% [5/5] vs. 42.1% [8/19], p = 0.041). All biopsy recommendations for findings recalled by only one reader (n = 4) resulted in benign pathology. Of the three biopsy recommendations for lesions recalled by both readers, one revealed ductal carcinoma in situ. This malignancy presented as calcifications that were recalled on both FFDM and DBT but was not visualized on ABUS. This constituted the only screen-detected cancer in the trial, resulting in an overall cancer detection rate of 8.3 per 1000 women screened (95% CI: 0.2–45.2). After one year follow up, there was one malignancy in a woman who returned for annual screening prior to 365 days, with positive results leading to breast cancer diagnosis. The study subject was a 56 year old female with a personal history of breast cancer diagnosed in 1995 and treated with mastectomy. She received screening of the contralateral breast in this study, with a result of BI-RADS 2 (Benign) for prior benign percutaneous biopsy. She subsequently returned for screening on day 364 of the follow up period. The follow-up mammogram was also issued a BI-RADS 2 assessment. She also received targeted ultrasound of a palpable mass in the axilla on the same side as the mastectomy. A suspicious mass was identified, and same-day biopsy revealed an axillary recurrence. While this finding was not visualized on the study examinations, it was counted as a false negative per the study protocol specifying any breast cancer diagnosed within the 365 day follow up period.

4. Discussion

Our study evaluated single versus double reading of ABUS for supplemental breast cancer screening among readers new to the technology and has two major findings. Our results add to prior studies evaluating the addition of ABUS to FFDM [17–20] by demonstrating that ABUS significantly increased the recall rate when added to FFDM or DBT with synthetic 2D as a primary screening modality. Synthetic 2D was approved by the Food and Drug Administration in May 2013 as an alternative to FFDM in DBT screening, which reduces the radiation dose for DBT screening since synthetic 2D images are reconstructed from the DBT acquisition and a separate FFDM image is not obtained [21,22]. Early studies have shown that this yields comparable outcomes to screening with FFDM alone and with DBT in combination with FFDM

[21,23–25]. The use of combined FFDM and DBT screening is likely to decrease as practices adopt the DBT with synthetic 2D format to reduce radiation exposure while preserving diagnostic outcomes. While prior work has demonstrated the benefit of adding ABUS to FFDM, it is also important to understand its incremental benefit when added to DBT with synthetic 2D as an increasingly widespread screening technology. In this study with a small sample size, the incremental cancer detection rate was zero, with no additional cancers detected by ABUS.

In addition, our study demonstrates the value of double reading ABUS. Compared to double reader recalls, we found that single reader recalls were more frequently resolved by diagnostic imaging (final BI-RADS 1 or 2). This suggests that double reading of ABUS, especially during the early adoption period when readers are new to the technology, may increase the "yield" of diagnostic evaluation and reduce false-positive recalls. Prior work has demonstrated that double reading can result in improved sensitivity [14] and that single reader recall rates for ABUS decrease over time in the early adoption phase [26], presumably as radiologist familiarity with the modality increases. While our study protocol did not require that the radiologist issuing the recall perform the subsequent diagnostic evaluation, it was possible for a radiologist to further evaluate a lesion that he or she recalled, offering an opportunity for feedback and learning. As more practices begin to offer ABUS for supplemental screening, double reading during the early adoption phase may help offset unnecessary downstream diagnostic evaluations. However, integration of double reading into clinical workflows was beyond the scope of our study. Assessment of additional interpretation time from two independent radiologists was not included in our study design, nor was assessment of an additional arbitration to achieve consensus on interpretation. It is possible that an arbitration step might be needed to achieve reduction in recall rates while preserving cancer detection and should be evaluated in future studies.

Limitations of our study include a cohort consisting of patients with dense breasts who were also at intermediate to high risk for future development of breast cancer based on genetic or personal history, which may have impacted the complexity of ABUS findings and resulting recall rates. It is possible that double reading would have had a different impact on ABUS recall rates among women with no other risk factors beyond dense breasts. While recall rates under double reading may in part reflect the lack of HHUS screening experience in our practice, our results remain applicable to the many practices choosing to implement ABUS without previously offering HHUS screening. In addition, the detection of a single breast cancer in our study cohort is associated with wide 95% confidence intervals in estimating the incremental cancer detection rate with supplemental ABUS screening. However, our observed incremental recall rates using FFDM + ABUS are consistent with those in the published literature [17–20], suggesting a similar added cancer yield may have been observed if the study had been performed in a larger patient population. Finally, our study population had low proportions of certain sub-groups, such as racial/ethnic minorities, which may limit generalizability.

Additional research is needed in several areas. Future prospective randomized trials evaluating ABUS as a supplemental imaging technology to both FFDM and DBT with synthetic 2D will be important as its use is likely to increase with the increasing passage of breast density notification laws. As new screening technologies emerge, such as those that aim to combine DBT and ABUS into a single device [27], studies should continue to assess their impact on diagnostic performance and outcomes. ABUS has comparable performance to HHUS with the added benefits of standardized image acquisition, decreased operator dependency, and the ability to review the entire volume of breast tissue, conduct temporal comparisons, and pursue double reading [14]. Given the importance of the early adoption phase, future studies should evaluate the amount of time required for single reader recall rates to reach a steady state and the optimal time over which double reading could be used to maximize the yield of diagnostic evaluations. Finally, supplemental imaging with HHUS does not appear cost-effective compared to mammography. Cost-effectiveness was only approached if HHUS test performance exceeded that of mammography [28], which has not yet been achieved with current technology. Therefore, despite ABUS being relatively easy to use and less time consuming than HHUS, future cost-effectiveness analysis of ABUS as an adjunct to the current standard of care is needed.

5. Conclusions

Recall rates increased substantially when supplemental ABUS screening was added to standard-of-care FFDM and DBT examinations, but double reading may represent a potential way to increase the "yield" of diagnostic evaluation and mitigate false-positive recalls in the early adoption phase of new technology use. Given trends in breast density notification legislation, this topic is likely to grow in importance, and our study provides important insights on optimal workflow and training for radiologists considering or beginning to supplement FFDM or DBT screening with ABUS.

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