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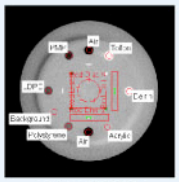

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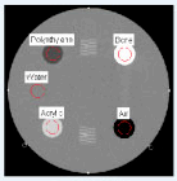

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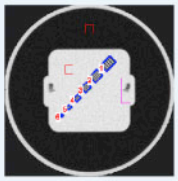

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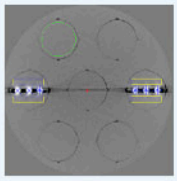

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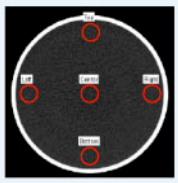

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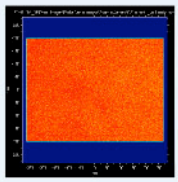

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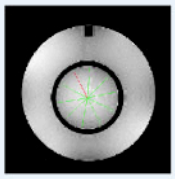

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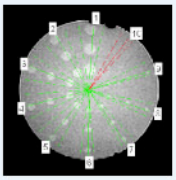

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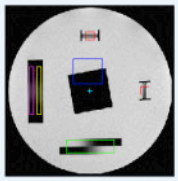

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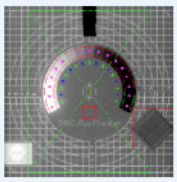

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Determinants of the reliability of ultrasound tomography sound speed estimates as a surrogate for volumetric breast density

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Purpose: High breast density, as measured by mammography, is associated with increased breast cancer risk, but standard methods of assessment have limitations including 2D representation of breast tissue, distortion due to breast compression, and use of ionizing radiation. Ultrasound tomography (UST) is a novel imaging method that averts these limitations and uses sound speed measures rather than x-ray imaging to estimate breast density. The authors evaluated the reproducibility of measures of speed of sound and changes in this parameter using UST.
Methods: One experienced and five newly trained raters measured sound speed in serial UST scans for 22 women (two scans per person) to assess inter-rater reliability. Intrarater reliability was assessed for four raters. A random effects model was used to calculate the percent variation in sound speed and change in sound speed attributable to subject, scan, rater, and repeat reads. The authors estimated the intraclass correlation coefficients (ICCs) for these measures based on data from the authors' experienced rater.
Results: Median (range) time between baseline and follow-up UST scans was five (1–13) months. Contributions of factors to sound speed variance were differences between subjects (86.0%), baseline versus follow-up scans (7.5%), inter-rater evaluations (1.1%), and intrarater reproducibility (~0%). When evaluating change in sound speed between scans, 2.7% and ~0% of variation were attributed to inter- and intrarater variation, respectively. For the experienced rater's repeat reads, agreement for sound speed was excellent (ICC = 93.4%) and for change in sound speed substantial (ICC = 70.4%), indicating very good reproducibility of these measures.
Conclusions: UST provided highly reproducible sound speed measurements, which reflect breast density, suggesting that UST has utility in sensitively assessing change in density. © *2015 American Association of Physicists in Medicine.* [http://dx.doi.org/10.1118/1.4929985]

Key words: breast density, ultrasound tomography, reliability, reproducibility, change in breast density, breast cancer

1. INTRODUCTION

Increased percent mammographic breast density is a strong independent risk factor for breast cancer.[1] Mammography uses x-ray technology to create a 2D image of the compressed breast. The interaction between x-ray and breast tissue is used to calculate an indirect measure of breast density. Breast density is typically computed from the mammographic image by dividing the radio-opaque area, corresponding to epithelial and stromal tissues, by the total breast area, which includes both dense and nondense areas, the latter reflecting adipose tissue.[2,3]

Over the past decade, calculations of breast density from mammographic images have evolved from qualitative measures [e.g., Wolfe's classification[2] and breast imaging reporting and data system (BI-RADS)[4]] to more objective measurements (e.g., visual assessment of percent breast density and computer-assisted thresholding methods).[1,5] Although methods for measuring volumetric breast density from mammography have been developed,[6,7] the 2D nature of mammographic images may represent an inherent limitation of this imaging technique.[8] In addition, variability in protocols for mammogram acquisition, including machine settings, digital or film technique, degree of breast compression, and other factors may diminish reproducibility of density measures. Particularly, comparing serial images within one woman over time is difficult, as women are unlikely to be imaged repeatedly with the same mammography machine under identical conditions.[9] Further, mammograms expose women to potentially harmful ionizing radiation, which limits the frequency with which examinations can be repeated and pose concerns about imaging young women who may be particularly susceptible.[10] Magnetic resonance imaging (MRI) is an alternative method for measuring breast density, which uses a magnetic field and radio wave energy to provide a 3D image of organs without exposure to ionizing radiation.[5,11–13] However, MRI is more expensive than mammography, not easily accessible, and requires special facilities in addition to intensive training.

Ultrasound tomography (UST), a novel imaging tool that uses sound speed measures, provides the ability to assess volumetric breast density of the uncompressed breast, similar to MRI, without many of the limitations of mammography.[3,14] Sound speed has been shown to be a surrogate to mammographic measures of breast density, with statistically significant correlations with both BI-RADS density categories and computer-assisted quantitative measures of mammographic breast density.[3,15–21] Of additional importance, UST provides the opportunity to conduct serial breast scans without the risk of ionizing radiation and to monitor changes in breast density over time.[18] Obtaining reliable estimates of density change is clinically relevant as a growing number of studies have demonstrated that changes in breast density are associated with response to some breast cancer treatments, such as tamoxifen.[22–26]

Previous studies have illustrated the technical aspects of volumetric breast density evaluation from UST sound speed images.[3,15,27] Here, we aimed to assess the rater reliability of UST sound speed estimates as a surrogate for volumetric breast density, using a prototype scanner,[14] among a subset of participants enrolled in an ongoing study monitoring breast density changes over the course of a year. Demonstrating the reproducibility of sound speed measurements in the context of this study is critical, given that detecting changes in density over brief intervals requires excellent precision.

2. MATERIALS AND METHODS

2.A. Study population

The study population included a subset of women, with at least two UST serial breast scans available, enrolled between 2011 and 2012 in the Ultrasound Study of Tamoxifen.[18] Briefly, participants 30–70 yr of age at baseline were recruited from the Barbara Ann Karmanos Cancer Institute (KCI) and Henry Ford Hospital (HFH) in Detroit, MI. Exclusion criteria included weight >250 lbs and breast diameter >20 cm (maximal allowable for scanner), pregnancy, breastfeeding, current breast implants, and active breast skin infections. Women underwent UST scans at baseline and had a second follow-up scan ranging from one month to 13 months after baseline. The contralateral breast was scanned in participants with a diagnosis of incident unilateral atypical lobular or ductal hyperplasia (ALH/ADH), ductal or lobular carcinoma *in situ* (DCIS/LCIS), or invasive breast cancer. The breast to be scanned was randomly selected in women without a diagnosis of ALH/ADH, DCIS/LCIS, or invasive breast cancer. During follow-up, study participants who developed an active breast skin infection, who had an excisional biopsy, or who had a mastectomy of the same breast scanned at baseline were excluded. The analytic population was comprised of 22 study participants who provided written informed consent. The study was approved by ethical boards at all participating institutions.

2.B. Ultrasound tomography

Participants were scanned with the Computed Ultrasound Risk Evaluation (CURE) UST prototype.[14] Briefly, UST scans were performed while a patient was in the prone position with the breast to be scanned suspended in a water bath (Fig. 1). Breasts were scanned with a 20 cm ring-shaped transducer, consisting of 256 elements that transmit and receive ultrasound pulses, which was mounted on an automated gantry that progressively captured 40–100 coronal image slices beginning at the chest wall and progressing to the nipple. Unlike conventional ultrasound, UST provides four tomographic images: high-resolution reflection, low-resolution reflection, attenuation, and sound speed images. The present analysis focused on volumetric breast density as estimated through sound speed images.

Sound speed images were processed prior to analysis using the public domain software package ImageJ.[28] To begin, the first and last image slices, comprising boundaries of the breast tissue, were identified to remove images of the chest wall, pectoralis muscle, and the water bath (i.e., extending beyond

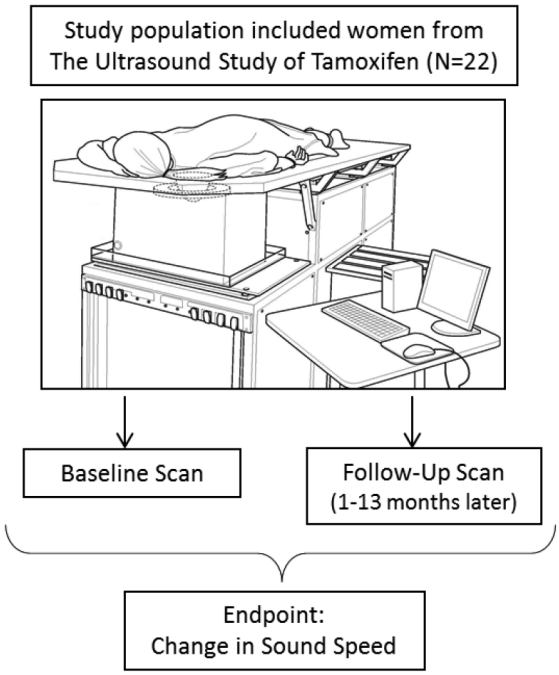

FIG. 1. Study design and depiction of the ultrasound tomography scanner, adapted from Duric *et al.* (Ref. 17).

the nipple; Fig. 2). A semiautomated method was used to differentiate the breast from the water bath as an ellipse, for each image slice, as thresholding techniques were not an option since the sound speed of the water bath falls within the expected range of the sound speed for breast tissue [Fig. 3(A)]. Next, dark ring artifacts, which were caused by slow moving surface waves when the transducer was closer to the breast (i.e., closer to the chest wall in larger breasts and specifically affecting breast tissue nearer to the skin surface) and can decrease the overall measured sound speed, were eliminated [Fig. 3(B)]. Manual removal of dark ring artifact was done in ImageJ. A large ellipse was fit to encompass the breast tissue area, allowing the pixels related to the dark ring artifact, outside of the ellipse, to be cleared and set to zero. These artifacts were seen in approximately half of images. The median percentage of voxels removed was 7%, ranging from 0.4% to 28%. To analyze change in sound speed between serial scans, image files were restricted to a common volume that was contained within both scans. For tomograms included in the common volume, the sound speed measures, in m/s, from pixel values in each tomogram, were averaged together to generate the sound speed measurement used as a proxy of breast density.

One experienced rater, who processed UST scans and recorded sound speed measures in the Ultrasound Study of Tamoxifen, trained five raters to process the UST scans. All raters, masked to subject data, performed preanalytic processing of images and recorded the measured sound speed. The baseline and repeat scans were assessed by raters sequentially for each subject to enable determination of common volumes for each pair of scans. Next, four of these raters, including the experienced rater, repeated these measurements on the same scans. For the second review, the scans were randomly reordered, but baseline and follow-up scans for each subject were still read sequentially since this was necessary to identify the common volume.

2.C. Statistical analysis

The inter- and intrarater reliabilities of sound speed measures were assessed using a random effects model containing covariates with potential sources of variation nested within one another (i.e., subject, baseline or follow-

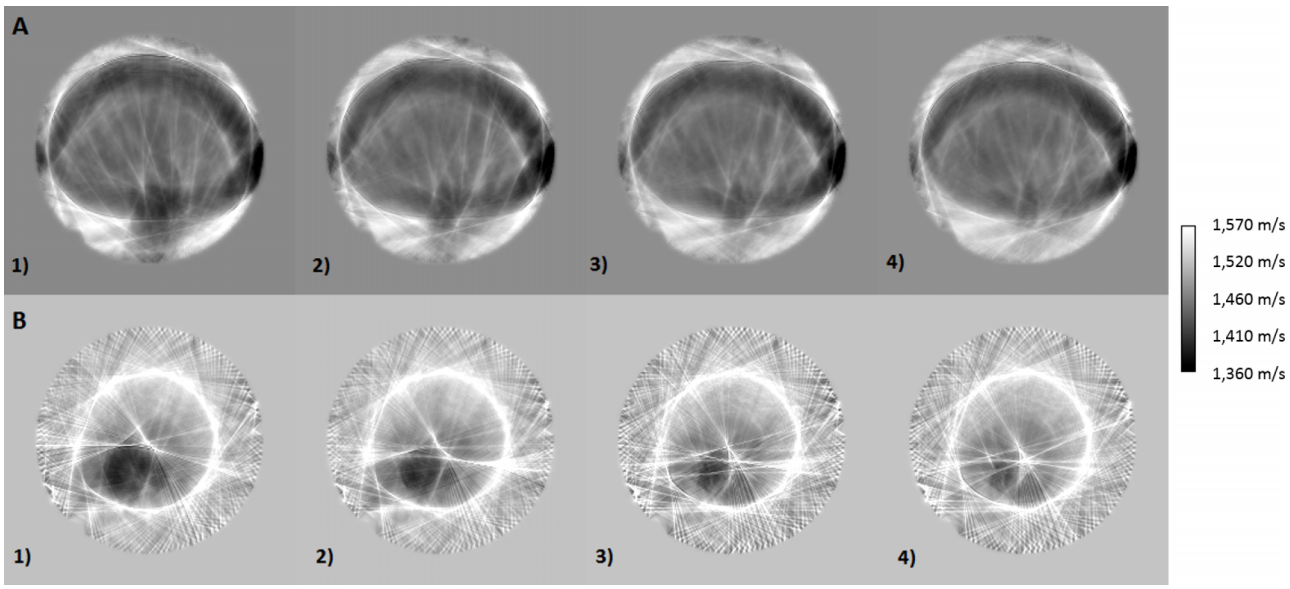

FIG. 2. (A) Selection of starting breast tissue image slice from the first four tomograms, which borders the chest wall. In this example, slice three was chosen to be the first slice without any chest wall present. Slices three and four were included in the final sound speed image stack. (B) Selection of the last breast tissue image slice, which borders the nipple. In this example, slice three was chosen to be the last slice with the nipple present. Slices one, two, and three were therefore included in the final image stack.

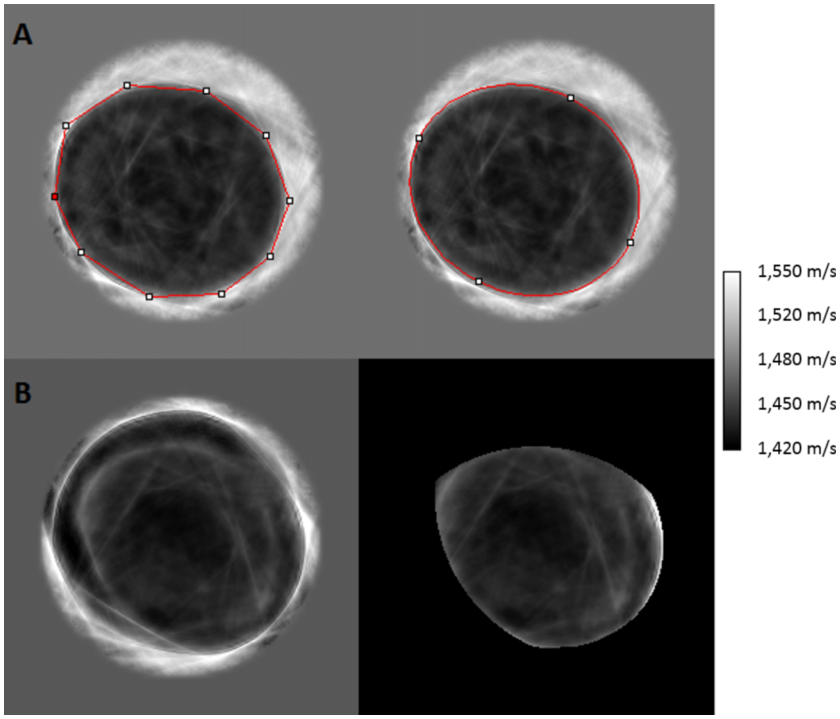

FIG. 3. (A) Depiction of the segmentation algorithm that was utilized to remove sections of each image associated with the water bath: (left) in this example using a midsection slice (free of the artifacts shown in Fig. 2), the breast/water bath interface was first manually selected using 10 points, and second (right), an ellipse was fit to the chosen points to approximate the shape of the breast in the current slice. (B) Sample sound speed image before (left) and after (right) the removal of a dark ring artifact. The images show a portion of a breast dominated by fatty tissues as indicated by dark regions inside the contour (indicating low sound speeds) while the water outside the breast has a higher sound speed and appears whiter.

up scan, rater, and repeat measurements by four of the raters; Fig. 4). An unbalanced model provided the ability to increase statistical power and fully utilize data from all raters, since only four out of the six raters had repeated reads. The percent variation in sound speed attributed to each of these covariates was calculated. Additionally, to assess the reliability of estimating changes in breast density over time, the change in sound speed between the baseline and follow-up scan was assessed. A similar random effects model was used to calculate percent variation in change in sound speed attributed to each covariate. Intraclass correlation coefficients (ICCs) for sound speed and change in sound speed were also calculated based on the experienced rater's first and second reads. ICC values for strength of agreement were interpreted as slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or excellent (0.81–1.00).[29] All analyses were conducted in SAS v9.3 using PROC GLM (2011, SAS Institute, Cary, NC).

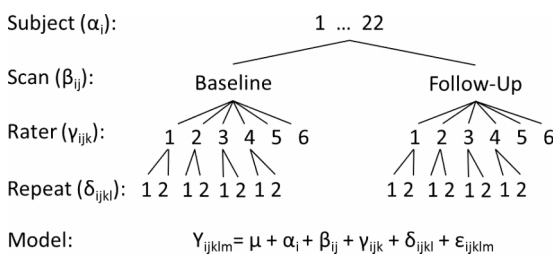

FIG. 4. Unbalanced, nested, random effects model used to calculate percent variation in sound speed attributed to each covariate.

3. RESULTS

Among participants included in this analysis ($n = 22$), the median time between baseline and follow-up scans was five months (161 days), ranging from one to 13 months (39–405 days). For both baseline and follow-up scans, the median sound speed measure was 1450 m/s (range: 1430–1480 m/s) and the median change in sound speed between scans was −4.41 m/s (range: −9.48 to 13.04 m/s; Table I). Baseline and follow-up UST sound speeds for each participant are also shown in Fig. 5.

TABLE I. Descriptive statistics for baseline and follow-up scans from UST ($N = 22$).

Measures	Median (range)
UST sound speed measures[a]	
Baseline (m/s)	1450 (1430–1480)
Follow-up (m/s)	1450 (1430–1480)
Change in baseline and follow-up (m/s)	−4.41 (−9.48 to 13.04)
Time between baseline and follow-up	
Months	5 (1–13)
Days	161 (39–405)

Note: *N*, frequency; UST, ultrasound tomography.
[a]First reads from the experienced rater.

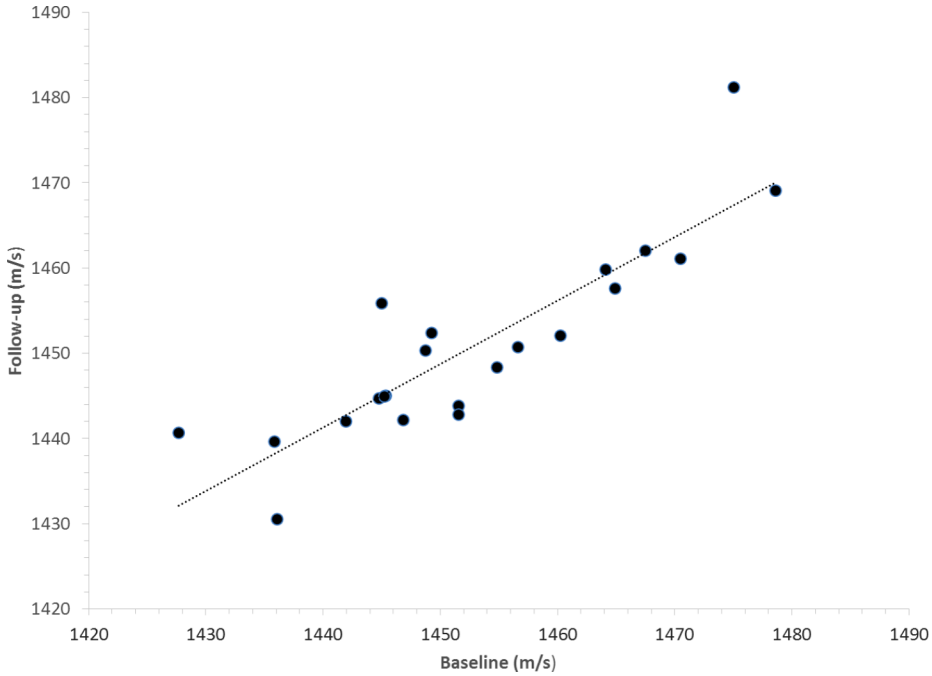

FIG. 5. Scatterplot of baseline and follow-up sound speed measures for each participant as measured by the experienced rater ($N = 22$).

Variation among participants accounted for 86% of the variation in sound speed, with additional contributors including variation between baseline and follow-up scans within subject (7.5%), and differences between the six raters [1.1%, Table II(A)]. The variation for intrarater measurements approached 0%. Results were similar when evaluating change in sound speed between baseline and follow-up scans, with most variation in sound speed due to variability between subjects (62.6%). Variation in change in sound speed estimates attributable to differences between the raters was 2.7% and within raters nearly 0%. For our experienced rater's repeat reads, we observed an excellent level of reproducibility (Fig. 6), with an ICC of 93.3%, for sound speed measures and a substantial level of reproducibility, with an ICC of 70.4%, for change in sound speed [Table II(B)].

4. DISCUSSION

Our results demonstrate that estimates of volumetric breast density, based on UST sound speed measurements, yield excellent inter- and intrarater reliabilities. Most importantly, variations in sound speed measurements were largely a reflection of differences between subjects and, to a lesser degree, changes between baseline and follow-up scans, with rater being the least likely to contribute to sound speed variations. Additionally, repeat measures performed by the experienced rater showed a high degree of reproducibility for sound speed measures and substantial reproducibility for assessment of change in sound speed between baseline and follow-up UST scans. Given that average sound speed changes within individuals were approximately 4 m/s, these data underscore the sensitivity of UST measurements. These results suggest that UST is a reliable tool for estimating breast density and sensitively detecting changes in its value within individuals over time.

Currently, clinical radiologists routinely report breast density from mammography using visual assessment according to the American College of Radiology's BI-RADS breast density classification as almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense.[4] BI-RADS density assessment has been shown to have substantial intrarater agreement (Cohen's kappa (κ) ranging from 0.64 to 0.90) and moderate inter-rater agreement (κ ranging from 0.44 to 0.77).[30–35] Most disagreements reflect imprecise separation of the two intermediate density categories, scattered fibroglandular and heterogeneously dense, which are the predominant categories in the general population,

TABLE II. (A) Percent variation in sound speed and change in sound speed attributable to covariates and (B) ICC for the experienced rater's repeat reads for sound speed and change in sound speed.

	(A) Percent variation (%)				(B) ICC (%)
Measure	Subject	Scan	Rater	Repeat	Experienced rater
Sound speed	86.0	7.5	1.1	0	93.3
Change in sound speed	62.6	—	2.7	0	70.4

Note: ICC, intraclass correlation coefficient.

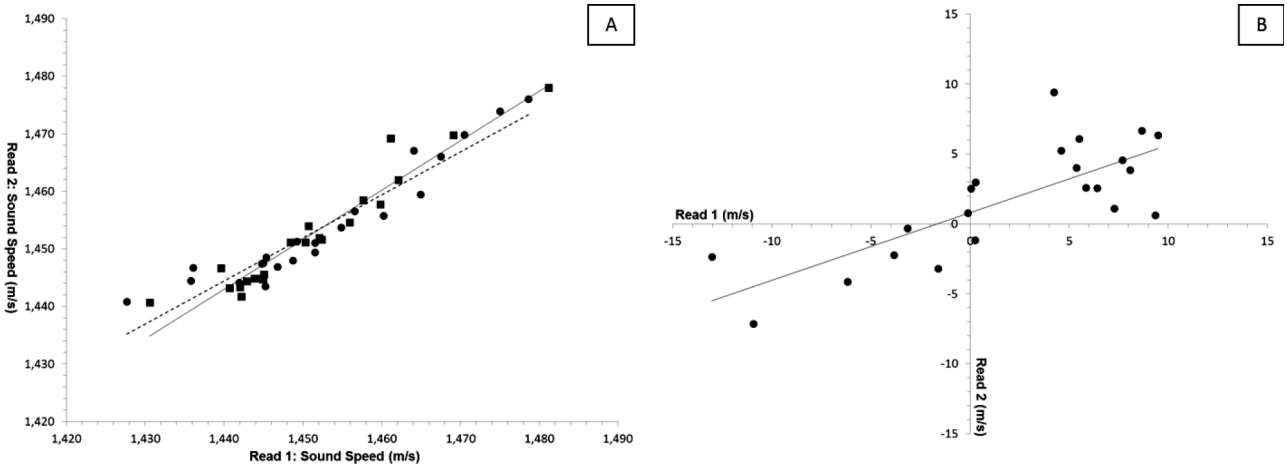

FIG. 6. Scatterplots comparing (A) the repeat reads from the experienced rater's measurements of breast density in sound speed at baseline (round symbols and dotted line) and follow-up (square symbols and solid line) and (B) the change in sound speed between the baseline and follow-up UST scan.

independent of age and menopausal status.[30,36,37] Accordingly, substantial changes in density may nonetheless represent within category changes, rendering them unapparent with BI-RADS assessment.

Other methods used to visually estimate percent density, using six categories of percent density, have previously shown moderate to high inter- (ICCs ranging from 0.68 to 0.89) and intrarater reliabilities (ICCs ranging from 0.73 to 0.96),[38–41] and high inter- (ICC = 0.94) and intrarater reliabilities (ICC = 0.96) using 21 categories.[42] Consistent with the intrarater reliability estimates we observed for sound speed measures, mammographic breast density assessment using quantitative computer-assisted interactive thresholding methods has also yielded high intrarater reliability (correlation coefficients ranging from 0.82 to 0.94).[39,41,43,44] Thus, the reproducibility of UST density measures compares favorably with other reliable methods for single determinations, especially since UST relies upon quantitative volumetric assessment of sound speed. For estimating changes in density, UST offers the possibility of improved reliability, because of the greater ability to align 3D images, the invariability of sound speed, and the constancy of machine settings, which offers the potential for achieving limited variability in sound speed measurement between scanners.

Growing evidence suggests that a reduction in breast density, among women receiving tamoxifen in either adjuvant treatment or chemoprevention, is predictive of clinical response.[22–26] The Ultrasound Study of Tamoxifen will assess whether repeated UST sound speed measurements among tamoxifen users can identify declines in density within months. The possibility of distinguishing tamoxifen responders from nonresponders quickly could provide encouragement for adherence among responders and suggest exploration of other options among nonresponders. The value of measuring change in density as a means of screening and risk assessment to predict risk of second contralateral breast cancers,[45] and to monitor patients receiving combined estrogen plus progestin hormone replacement,[46] has been studied, but data are limited and not yet conclusive.

Strengths of this analysis include access to the Ultrasound Study of Tamoxifen population, which provided the ability to assess inter- and intrarater reliabilities of UST sound speed measures and, more importantly, serial measures within subjects, affording the opportunity to assess the reliability of change in sound speed. Additionally, we used a method of randomization (i.e., subject scans were randomized, but each subject's baseline and follow-up scans were read sequentially) similar to a past analysis that found this to be a sensitive method for assessing change in breast density as measured from mammography,[47] although we did not randomize order within subject scans. Another important aspect in the feasibility of future implementation of this technology was the ease in training raters to conduct these measurements. Although results of this analysis are promising, the sample size was limited and future analyses assessing this novel surrogate of breast density are needed. To maximize statistical power, we used multiple raters to assess between ($n = 6$) and within rater ($n = 4$) reliability and analyzed all data in one efficient model. Future goals include reducing the amount of manual modifications needed to remove dark ring artifacts. Finally, whereas we assessed determinants of the reliability of sound speed estimates averaged across the total breast volume, prior studies have suggested that localized breast density measures may prove to be informative with respect to risk prediction.[48,49] Work to determine whether sound speed changes are uniform throughout the breast or show regional variation is ongoing in this study population. It is conceivable that UST imaging may permit better assessment of this process than mammography because of the possibility of 3D alignment of serial images, but the reliability of localized sound speed estimates will require future evaluation.

Serial measurement of breast density may represent a potential approach for enhancing risk assessment beyond what is achievable with single measurements. This early study suggests that UST represents a promising method for serially assessing breast density with high precision, 3D assessment without compression of the breast, and avoidance of radiation. Currently, research studies focused on determining factors

that contribute to change in breast density are limited by the existing methods of measurement. UST may represent a technique for advancing this area of research.

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