# Study Protocol

**Official Title:** Assessment of Periodic Screening of Women With Denser Breast Using WBUS and DBT (Also Known as "DBTUST-Dense Breast Tomosynthesis / Ultrasound Screening Trial")

**ClinicalTrials.gov ID (NCT number):** NCT02643966

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## Scientific Background

Despite significant advancements in detection, diagnosis, and treatment, breast cancer remains one of the leading causes of death in women over the age of 40 [1, 2]. Across multiple randomized controlled trials (RCTs), mammography has been shown to reduce deaths due to breast cancer in women aged 40 to 74 [3]. There are subsets of women, however, where mammography is less effective. Invasive breast cancers are recognizable primarily as masses, areas of architectural distortion, and/or calcifications. Because masses are often similar in density to the breast parenchyma itself, dense breast tissue can mask cancer detection, with mammographic sensitivity of only approximately 50% in dense breasts [4-6]. Periodic mammography screening results in earlier detection of breast cancers and in the last two decades both mortality and, for many reasons including but not limited to earlier detection, morbidity of breast cancer has been steadily declining [7 -10]. However, there remains a serious and credible controversy as to the attributable benefit from mammography screening to this overall decline [11, 12]. Visually searching for and detecting breast abnormalities on any modality, but in mammography in particular, is difficult and time-consuming for radiologists due to the large volume of examinations and the low yield of detected cancers in the screening environment, in particular as related to mammograms of younger women with dense breasts. Therefore, a substantial fraction (>30%) of "detectable" breast abnormalities, including cancers that are retrospectively judged to be "visible" on mammograms, are initially completely missed (omission) or actually detected but unreported (commission) by radiologists [13-15]. The specificity of mammography is also relatively low for screening in that approximately 10% of women are recalled for additional imaging procedures and only a small fraction (15%-30%) of biopsies proves to be positive [16; 17]. Recall rates are even higher among younger women with dense breast tissue and for those women receiving their initial screening examination before a comparison to prior findings can be made [4; 5; 18-22]. To address reduced mammographic sensitivity in dense breasts, several imaging tests have been proposed as a replacement and/or for supplemental screening. Magnetic resonance imaging (MRI) has been recommended for supplemental screening in women at high risk because of genetic or familial history or prior radiation therapy to the chest before age 30 [23]. While MRI detects more cancers than even the combination of mammography plus ultrasound [6; 24-26], MRI is not well tolerated [27] or cost effective in broader populations [28], and there is currently "insufficient evidence" for or against its use in women at intermediate risk for reasons including breast density [23].

Large area size full-field digital detectors with high-resolution and wide latitude [29] enabled the development of advanced digital imaging techniques, such as digital breast tomosynthesis (DBT) [30] and breast computed tomography (CT) [31], that improve conspicuity of breast lesions by enabling the enhancement of lesion contrast and/or the provision of 3D non-overlapped tissue information at comparable radiation dose levels. Currently, several leading manufacturers are marketing and/or testing DBT systems. The DBT systems available to us are manufactured by Hologic Inc (Bedford, MA). The system acquires initially 15 low dose projection images (frames) and generates mathematically / reconstructs between 50 and 120 tomographic type slices with a non-isotropic voxel size of 125μm × 125μm × 1mm depending on the breast thickness during compression. DBT has been shown to improve performance substantially over FFDM in all breast densities, but, in particular, in women with density BIRADS 2 and 3 [32]. Interestingly, the vast majority of these improvements are in reducing recall rates while increasing the detection of invasive cancers [33-37]. With recent investigations on and approval of synthesized 2D reconstruction (C-View), the issue of added radiation dose when implementing a FFDM+DBT

screening practice is largely eliminated as the resulting procedure uses radiation exposure that is like that used in conventional FFDM. Hence, DBT is clearly a candidate for both baseline screening procedures, as well as for supplementary imaging, in particular as operationally the procedure is virtually identical to FFDM from a technologist's and a woman's perspective. The only meaningful operational difference is the increased time to interpretation (as compared with conventional FFDM based practice), which can be expected because of the large number of additional images generated by the procedure [38; 39]; however, it decreases substantially with experience [40]. Recent data on the performance of C-View alone has been published demonstrating comparable diagnostic performance to FFDM alone, as well as in conjunction with DBT [135, 136]. This comparable performance results in reducing radiation exposure to the screening population by approximately 45%, and allows for a DBT practice to be performed at comparable radiation dose to a conventional FFDM based practice.

Ultrasound is another test which has been considered for supplemental screening to FFDM of women with dense breasts [41]. Across eight single-center studies [5; 42-48] and three prospective multicenter trials [6; 49; 50], encompassing over 64,000 examinations, the supplemental cancer detection rate of ultrasound has consistently been approximately 2 to 4 per 1000. Across those series, over 90% of cancers seen only on ultrasound were invasive, with median size of ~10 mm. Among invasive cancers, where detailed [5; 6; 42; 43; 46; 49; 50], over 85% of invasive cancers seen only on ultrasound were node negative. While MRI will detect more cancers than ultrasound, the interval cancer rate with mammography plus ultrasound was only 8% after three years of screening mammography and ultrasound in the ACRIN 6666 study [6]; this rate compares favorably to those observed with mammography alone in fatty breasts [4; 51], where mammographic performance is close to being optimal. This suggests that, while additional cancers could be detected using MRI, the combination of ultrasound and mammography is sufficient. Importantly, 94% of cancers detected only with ultrasound were invasive,(96% of those were node negative, with a median size of ~10 mm [6]). The primary issues related to WBUS in large volumes are the needed professional resources (i.e., ,training, cost and practice complexity) and increasing recall rates [6; 22; 52]. In support of the aims of this proposal, at the recent Radiological Society of North America (RSNA) meeting a very preliminary report on the analysis of DBT supplemented by WBUS in the first cycle of WBUS was presented [139] and the results from 1039 examinations in a non-controlled environment confirmed that, as expected, WBUS detected approximately two additional cancers per 1000 examinations during this first WBUS cycle. There are no data available on repeat screening of this type of practice. Although there are little data on the performance of using WBUS alone for primary screening, this approach is being explored (primarily abroad) and is being assessed very preliminarily in this country as well [140]. Other recent published reports focus on comparing classification performance of DBT versus US of known abnormalities and/or include a very small number of cases [141-143]. Additional important supporting data are provided in the Preliminary Studies section later in the proposal.

There is currently a great interest in exploring practices that would increase screening efficacy in women with denser breasts who constitute a very large fraction of the screening population. WBUS and DBT are likely the most feasible approaches to replace and/or supplement screening in a large volume of women with denser breasts, because these approaches do not require injection of contrast and/or radioactive material. The objective is to demonstrate that using these technologies will increase screening efficacy in these women either by reducing recall rates or by improving cancer detection rates. Most important for future screening practices which are criticized for over-diagnosis is to increase the detection of those cancers who left alone would impact life expectancy

of the woman (as well as lifetime management cost). In this regard ultrasound seems to be doing significantly better than DBT, therefore, despite its higher recall rate, it may eventually prove to be either, as if not more efficacious than DBT as the primary screening modality in these women constituting approximately 45-50 percent of all screened women. Hence, assessing clinical utility of WBUS as either a supplementary modality or a primary screening modality is of utmost importance.

## Study Objectives

The overriding objective is to perform a clinical study that would allow for assessing the performance of DBT alone versus DBT plus WBUS, and potentially WBUS serving as a primary screening modality.

## Study Design & Methods

1) We will recruit sequentially approximately 6,200 women with known heterogeneously dense and/or primarily dense breast tissue (from a prior mammogram) who are scheduled to undergo routine mammography screening that includes a DBT examination.
2) Consenting women will undergo a DBT examination as part of their clinical exam and a WBUS examination.
3) DBT, WBUS, and a combination of both, will be independently reviewed and interpreted (Breast Imaging, Reporting and Data System rated) by experienced and specifically trained radiologists in a cross balanced (cases by mode and by reader) study design.
4) Using the results of the interpretations in a slightly modified "LOGICAL OR" mode, namely, the highest rating determines the recommendation/need for follow up, we will perform diagnostic work ups as needed (i.e., resulting from the "arbitration step").
5) We will compare cancers and other benign abnormalities detected with DBT only to those detected with WBUS. We will compare rates of false positives as a result of interpreting DBT vs. WBUS vs. a combination of both, including recall for additional testing, short-interval follow-up rates and biopsy rates. We will assess positive predictive values (PPVs) and negative predictive values (NPVs). For marginal value assessment when utilizing both modalities, we will also assess the type of abnormalities detected by each modality, assuming that a larger study will be required to assess cancer detection rates by specific types.
6) We will analyze the impact of double reading DBT on cancer detection and false positive rates. We expect to show that double reading DBT+synthetic 2D will significantly improve cancer detection compared to single reading. We hope to show that this can be achieved with minimal increase in false positives.

## Eligibility Criteria

Women aged 40 to 75 years of age with heterogeneously dense or extremely dense parenchyma by prior digital mammography report (i.e., “dense breasts”), presenting for routine annual mammography with digital breast tomosynthesis. For women who have not had any prior mammography (i.e. this is their first, baseline, mammogram), the breast tissue must be dense (heterogeneously dense or extremely dense) on the current mammogram.

## Statistical Considerations

We will primarily compare rates of true positive and false positives findings induced by DBT vs. ABUS, including recall for additional testing, short-interval follow-up rates, biopsy rates. For marginal value assessment when utilizing both modalities, we will also assess the type of abnormalities detected by each modality, assuming that a larger study will be required to assess cancer detection rates by specific types.

Our secondary analysis will compare cancer detection and recall rates from single reading DBT vs. optimal double reading DBT (best pairs). We will compare the added cancer detection from double reading to that achieved with addition of screening ultrasound.

With over 12,000 examinations that had been double read and an expected yield of approximately 80 cancers, the limiting factor will be the assessment of cancer detection as a result of the double reading with arbitration. With an expected agreement rate of 50% we estimate that we will have a power of 78% to detect an increase of 15% or more in cancer detection rate in the experimental (double reading set) as compared with single readings.The analysis for changes in recall rates will have higher power because of the substantially larger number of cases being recalled (~1200).

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