



Tomosynthesis and synthetic 2D images – a 3D dose-equivalent solution for screening mammography

GE Digital Breast Tomosynthesis

Digital Breast Tomosynthesis (DBT) is a three-dimensional (3D) imaging technology that uses a low-dose limited angle X-ray sweep around compressed breasts to produce 3D images that reduce image quality issues associated with overlapping structures (superimposition), a limitation in standard two-dimensional (2D) mammography.

In 2014, GE Healthcare's SenoClaire™ DBT device ("SenoClaire") was approved by the FDA with a screening protocol that consisted of 2D craniocaudal (CC) and 3D mediolateral oblique (MLO) views. Because both 2D and 3D images were still required, GE Healthcare sought extension of SenoClaire's approval to include 3D CC in the screening protocol.

To extend the screening indications and clinical performance claims of SenoClaire, GE Healthcare conducted a blinded image evaluation (BIE) study that compared the diagnostic accuracy of breast images acquired with DBT versus images acquired with 2D full-field digital mammography (FFDM). Clinical breast images were obtained from four (4) Ethics Committee-approved clinical case collection studies, where two-view (CC and MLO) FFDM and DBT images were obtained from adult, asymptomatic women undergoing digital mammography. The results of the BIE study not only clearly demonstrated that two-view (3D CC and 3D MLO) DBT provides superior diagnostic accuracy versus two-view 2D FFDM (as described in this white paper), but it also substantiated new claims for GE Healthcare's proprietary synthetic 2D image reconstruction algorithm, Volume Preview (V-Preview).

2D Images without Extra Dose

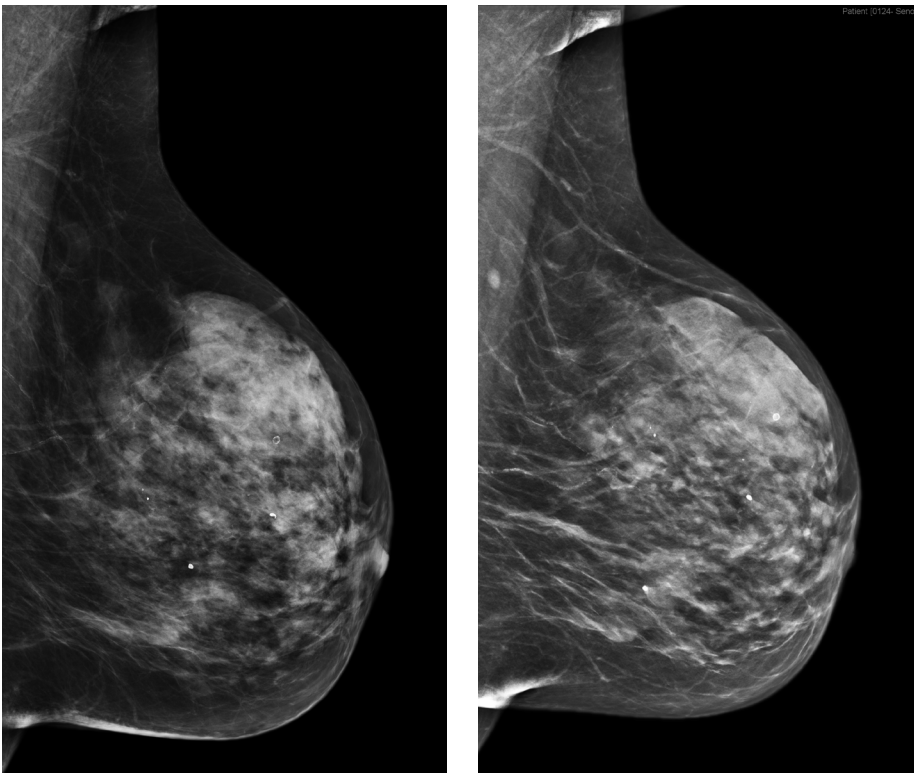
V-Preview uses raw 3D image data to reconstruct synthetic 2D images, and since the raw data are acquired during DBT acquisition, there is no need for additional radiation exposure to obtain a 2D image.

During SenoClaire's DBT acquisition, 9 low-dose projections are acquired by angulating the X-ray tube over a 25° sweep of the compressed breast. 3D image sets (planes and slabs) are produced from the 9 projections using a dedicated Adaptive Statistical Iterative Reconstruction (ASIR™) algorithm. When the X-ray beam is perpendicular to the detector, a central projection is acquired. The V-Preview 2D image is reconstructed from this central projection by incorporating information from the other 8 projections.

The BIE study discussed herein applied a new version of V-Preview (version 3, "V-Preview 3") to the raw 3D clinical image data. V-Preview 3 is an evolution of V-Preview version 1 and functions by enhancing image quality and conspicuity of the fine structures. The V-Preview 3 images, which are generated using the GE Seno Iris™ Connect, are now approved for use in the new DBT screening protocol, thus eliminating the need to obtain 2D images and the added radiation exposure of 2D image acquisitions.

Blinded Image Evaluation – 3D DBT vs. 2D FFDM

Female patients presenting for screening exams with digital mammography were enrolled into the clinical case collection studies. 3D breast images were obtained using the GE SenoClaire DBT device and 2D breast images were acquired using the GE Senographe™ Essential FFDM device. Two-views (CC and MLO) of each breast were acquired with both DBT and FFDM. De-identified images and associated data from these case collection studies were used in the subsequent BIE study.



FFDM (left) and V-Preview 3.1 (right) for same patient.

The purpose of the BIE study was to test the accuracy of two-view DBT + V-Preview 3 versus two-view FFDM for diagnosing breast cancer in an adult, asymptomatic screening population. Other tests in the study included comparing the sensitivity (i.e. abnormal findings are detected when present) and specificity (i.e., abnormal findings that are non-cancerous are differentiated from cancerous findings) of DBT versus FFDM. Radiation dose information obtained during the clinical studies was also compared between FFDM and DBT.

BIE Study Cases

Clinical DBT images and associated data were prepared for the BIE by generating synthetic V-Preview 3 3D images and pairing them with the corresponding 3D images (consisting of slabs and planes). Thus, the DBT image set for each case consisted of 3D CC and MLO views plus V-Preview 3 CC and MLO views. The 2D FFDM image sets were presented during the BIE in the same format as collected in the clinical studies.

One-hundred and seven (107) cases were included in the study analyses. Of the 107 cases, 39 were diagnosed with breast cancer, 21 were diagnosed with benign findings or lesions, and 47 were found to be normal (no findings or lesions). The BIE case set also included 32 invasive cancers, 21 cases with masses, and 9 cases with only calcifications. Cases also represented a range of breast densities, from almost entirely fatty to extremely dense.

BIE Study Paradigm

Nine (9) independent MQSA-qualified radiologists (readers) evaluated the DBT and FFDM image sets. Readers were blinded to the clinical histories and truth statuses (cancer or no cancer) for all cases during the BIE sessions. Each reader evaluated each DBT and FFDM image set on their own workstation. To avoid memory bias by the readers, DBT and FFDM image sets for each case were presented in two different BIE sessions, with approximately four (4) weeks separating the sessions (memory wash-out period). All readers evaluated all cases and participated in both BIE sessions.

For each breast in each DBT and FFDM image set, readers assigned screening BI-RADS scores and malignancy scores using a 7-point malignancy scale (**Table 1**). If applicable, readers also detailed the localization and characteristics of findings and assigned diagnostic BI-RADS scores.

Superior Diagnostic Accuracy

Diagnostic accuracy of two-view DBT + V-Preview 3 versus FFDM was measured using a receiver operating characteristic (ROC) area under the curve (AUC) of the pooled 7-point malignancy scores from each reader and the truth status of each case, as diagnosed in the clinical studies. The ROC AUC methodology is used to predict accuracy of diagnostic tests. An ROC AUC equal to 1.0 is considered a perfect diagnostic test for differentiating between disease or no disease, or in the context of the BIE study, cancer or no cancer.

The BIE study analyses showed that ROC AUCs for FFDM and DBT were 0.792 and 0.851, respectively, with an improvement of 0.059 for DBT (ROC AUCs plotted in **Figure 2**). Not only was non-inferiority established, but DBT exhibited significantly superior diagnostic accuracy compared to FFDM ($p = 0.0421$).

Malignancy Score	Definition
1	Definitely not malignant
2	Almost certainly not malignant
3	Probably not malignant
4	Possibly malignant
5	Probably malignant
6	Almost certainly malignant
7	Definitely malignant

Table 1: 7-point malignancy scale used during BIEs.

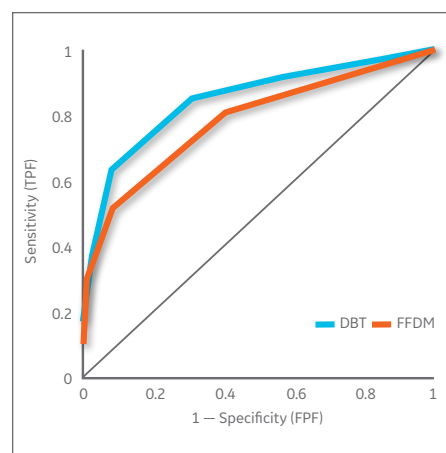


Figure 2: ROC Curves for DBT and FFDM. DBT curve (blue, solid) represents CC and MLO views of both 3D DBT images and V-Preview 3 images. FFDM curve (orange, dotted) represents CC and MLO 2D images.

Specificity and Sensitivity Results

The specificity and sensitivity analyses used the pooled case-level screening BI-RADS scores from all the readers for cases with non-cancer and cancer truth diagnoses, respectively. Specificity was calculated as the percentage of non-cancer cases (N=68) scored as screening BI-RADS 1 or 2 by the readers (i.e. evaluated as negative or benign). Sensitivity was calculated as the percentage of cancer cases (N=39) scored as screening BI-RADS 0 by the readers (i.e. evaluated as positive for suspicious finding).

Specificities for FFDM and DBT were 0.294 and 0.424, respectively, with an observed improvement of 0.129 for DBT. Not only was non-inferiority established, but **DBT exhibited significantly superior specificity compared to FFDM (p = 0.0001).**

Sensitivities for FFDM and DBT were 0.911 and 0.915, respectively, with an observed improvement of 0.004 with DBT. The BIE results confirm that **DBT is at least non-inferior to FFDM for sensitivity.**

Screening Recall Rate

Screening recall rate subgroup analysis used the pooled screening BI-RADS assessments for each reader for all cases regardless of truth status. BI-RADS scores of 0 were considered as positive for recall and BI-RADS scores of 1 or 2 were considered as negative for recall. Screening recall rate was defined as the percentage of cases that are evaluated as positive for recall.

The recall rates for FFDM and DBT were 0.779 and 0.701, respectively, with an improvement of -0.079 with DBT, clearly showing that **DBT has a superior (or lower) recall rate than FFDM (p = 0.0013).**

Radiation Dose

Average two-view (CC and MLO) glandular breast radiation doses were used to compare the FFDM and DBT doses in the BIE study. Results showed that the average FFDM and DBT doses were 2.97 mGy and 3.02 mGy, respectively, demonstrating that **radiation exposure is equivalent in DBT and FFDM screening exams.**

Conclusions

The cumulative results of the BIE study substantiate the benefits of DBT plus V-Preview 3 for the overall screening population by improving diagnostic accuracy while maintaining radiation doses equivalent to FFDM. The improved accuracy translates into significantly higher specificity and, relatedly, significantly lower recall rate.

In summary, the BIE study successfully supported extension of SenoClaire's screening indications and clinical performance claims with the following conclusions:

1. The diagnostic accuracy of 2-view DBT with V-Preview is superior to that of 2-view FFDM.
2. Reader specificity with 2-view DBT with V-Preview is superior to that of 2-view FFDM.
3. Recall rate of non-cancer cases with 2-view DBT with V-Preview is lower than that of 2-view FFDM.
4. Sensitivity of 2-view DBT with V-Preview is non-inferior to that of 2-view FFDM.
5. The GE 2-view DBT protocol operates at the same dose as a standard 2-view FFDM.
6. V-Preview can be used in conjunction with the DBT image set for screening and diagnosis of breast cancer.





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Appendix – Definition Terms

- Per protocol analysis set: group of study patients (within the full set of participants) who completely fulfilled the study protocol
- Sensitivity: percentage of detected cancers (out of all cancers in the study population); maximum value= %100
- Specificity: percentage of correctly diagnosed benign cases (out of all benign cases in the study population); maximum value= %100
- ROC (Receiver Operating Characteristic) curve: plot of sensitivity versus (-1specificity)
- (ROC) AUC: area under the (ROC) curve; maximum value=1
- Recall rate: fraction of recalled participants based on imaging out of the full set of participants
- p-value: probability to be incorrect in stating that a difference is statistically significant; $p < 0.05$ is the generally accepted threshold.

GE imagination at work