White paper

Superior Diagnostic Accuracy with Digital Breast Tomosynthesis plus Synthetic Mammograms

Key findings of the clinical Premarket Approval study on the MAMMOMAT Revelation with Tomosynthesis Option

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Daan Hellingman, PhD
Clinical Excellence & Cooperations,
Siemens Healthcare GmbH

Nancy A. Obuchowski, PhD
Quantitative Health Science,
Cleveland Clinic Foundation

Agnieszka Lazar
Research and Development,
Siemens Healthcare GmbH

Mathias D. Hoernig
X-ray Physics and Systems,
Siemens Healthcare GmbH

Axel Hebecker, PhD
Clinical Excellence & Cooperations,
Siemens Healthcare GmbH

SIEMENS Healthineers

Introduction

The aim of this white paper is to summarize the results of a multi-reader multi-case (MRMC) study on the MAMMOMAT Revelation with Tomosynthesis Option that laid the groundwork for its Premarket Approval (PMA) by the Food and Drug Administration (FDA) [1].
Part of these results contributed to the assessment of the safety and effectiveness of 2-view 50° wide-angle digital breast tomosynthesis (DBT) plus synthetic mammograms for breast cancer screening and diagnosis in the United States.

Rationale, objective and study design

Siemens Healthineers has been the first vendor that received FDA approval for the use of 2-view DBT alone in breast cancer screening [2]. Although 2-view wide-angle DBT has been proven to have a superior diagnostic accuracy as compared to 2-view full-field digital mammography (FFDM) alone [3,4], additional 2D mammograms are often acquired in clinical practice that serve as overview images and enable comparison with prior 2D mammograms. Unfortunately, combining DBT and FFDM results in a longer acquisition and breast compression time for the patient. More importantly, FFDM as an adjunct to DBT generates a higher radiation dose. To overcome these challenges, the so-called 2D synthetic mammogram (Insight 2D) was developed.

Insight 2D is reconstructed from a DBT data set using special algorithms. The soft tissue contrast in the synthetic mammograms has been optimized so that the overall image impression of Insight 2D[1] is very similar to FFDM (see Figure 1).

The primary objective of this MRMC reader study was to demonstrate the superiority of 50° wide-angle DBT plus synthetic mammograms in terms of the diagnostic accuracy in detecting and characterizing breast lesions as compared to FFDM alone.

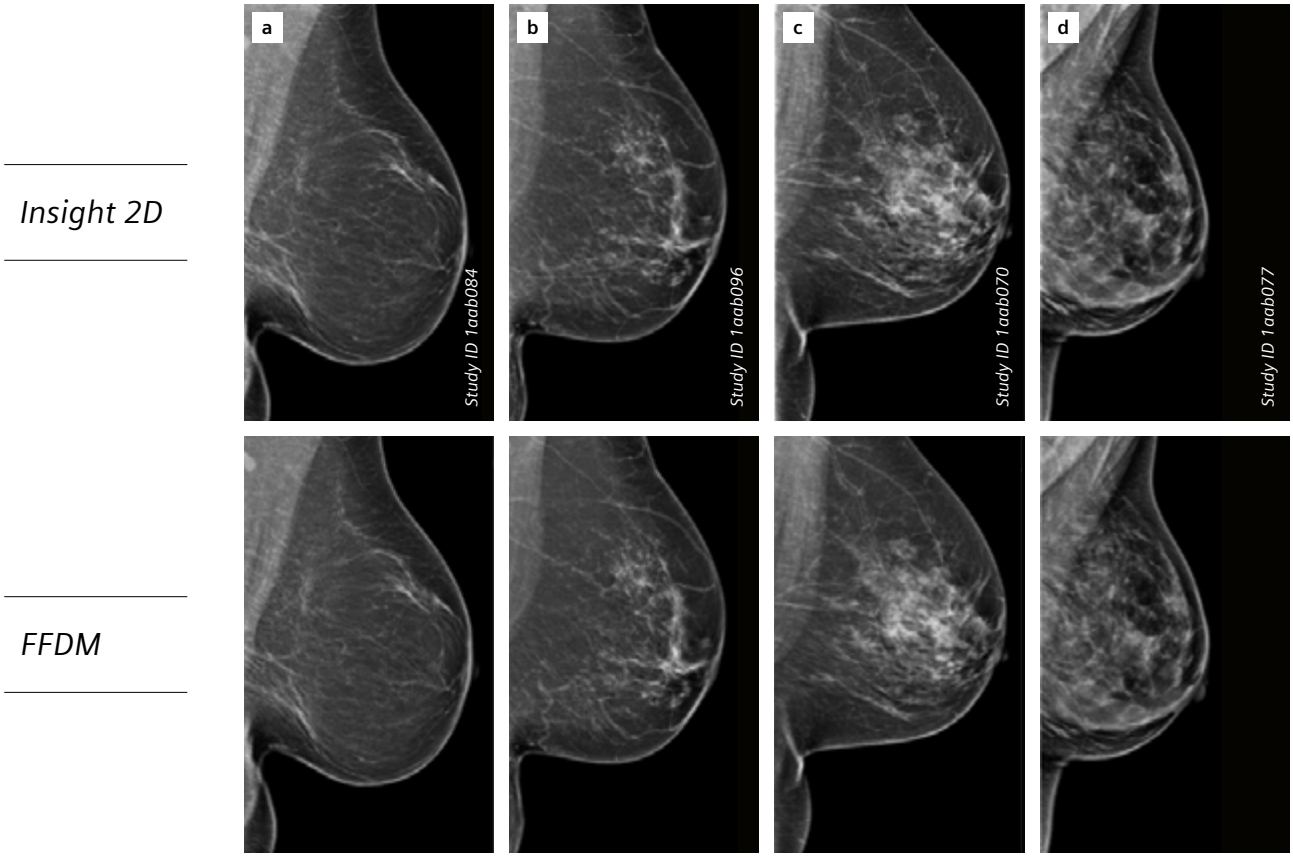

Figure 1: Comparison of Insight 2D and FFDM for different breast densities

[1] *Software version VC20 or higher*

Library of images

This study is based on a library of images specifically collected for this and previous DBT PMA studies. A total of 764 subjects (54.9 ± 9.8 years) were enrolled between May 2011 and April 2014 from seven United States clinical sites:

- Duke University, Durham, NC;
- SUNY, Stonybrook, NY;
- Brigham & Women's Hospital, Boston, MA;
- Cleveland Clinic, Cleveland, OH;
- NYU, New York, NY;
- St. Luke's Episcopal Hospital, Houston, TX; and
- Miami Baptist Hospital, Miami, FL.

The library included FFDM images and DBT images. All images were collected prospectively through a written informed consent process with approval from local institutional review boards prior to enrolling participants in image collection.

The FFDM images were acquired according to the standard of care using a number of commercially available FFDM systems. In addition to these clinically indicated screening mammograms, the DBT images were acquired solely on Siemens Healthineers systems. All breasts were imaged in craniocaudal (CC) as well as mediolateral oblique (MLO) positioning.

For malignant lesions, the ground truth for the type and location of the lesions was 1) based on the mammography findings described by the radiologist at the clinical site and based on the standard of care and 2) confirmed by the radiology and pathology reports after biopsy. For cases with a biopsy-confirmed benign finding, follow-up examinations were performed after 6 or 12 months. For normal findings, follow-up was performed after 12 months to confirm the non-cancer status.

MRMC study population

A subset of cases was randomly selected from the library of images (Table 1). Specific mammographic features like breast density and lesion type were included in order to obtain a distribution of cases similar to that seen in a screening population.

Table 1: Subject characteristics

2-view DBT + Insight 2D | 2-view FFDM

Subjects selected: 350

- 111 with cancer
- 90 with benign findings[1]
- 149 normal[1]

Breast density

- Almost entirely fat: 6.9%
- Scattered fibroglandular: 38.4%
- Heterogeneously dense: 47.1%
- Extremely dense: 7.5%
- Missing data: 1.1%

Malignant lesion type

- Mass: 64.8%
- Calcification: 21.1%
- Architectural distortion: 9.2%
- Asymmetric density: 4.9%

Cancer type

- Invasive cancer: 81%
- Ductal carcinoma *in situ*: 19%

[1] *23 breasts in 19 subjects (10 with benign and 9 with normal findings) had unknown ground-truth due to missing follow-up or BI-RADS 3 at follow-up imaging. Subjects were included to prevent selection bias. Statistical analysis shows that the results with imputation of the unverified breasts are consistent with the results based on only verified breasts.*

Reading and image interpretation

A total of 20 Mammography Quality Standards Act (MQSA) – qualified radiologists (“readers”) reviewed and scored the clinical images. All readers were trained to read Siemens Healthineers wide-angle DBT + synthetic mammograms. Each reader participated in two reading sessions separated by a wash-out period of at least 6 weeks. During each reading session, half of the cases were interpreted using FFDM alone (MLO and CC). The other half of the cases were interpreted using DBT (CC and MLO) + Insight 2D (CC and MLO). After the wash-out period, the readers interpreted the opposite modality for each case. Cases were randomized to be read with either FFDM or DBT + Insight 2D first and the reading order within each group was randomly assigned. Readers assigned a screening BI-RADS score to each breast (0, 1, or 2). Readers were also asked to identify all suspicious lesions and assign a probability of malignancy score to each.

MRMC study results

Significant improvement in diagnostic accuracy

Table 2 summarizes the main results that were observed in terms of diagnostic accuracy. To calculate sensitivity and specificity, a BI-RADS score of 1 or 2 was considered a negative finding, and a BI-RADS score of 0 was considered a positive finding.

The diagnostic accuracy in detecting and characterizing breast lesions was described by referring to the area under the receiver operating characteristic curve (AUC ROC). The probability of malignancy score was used to construct the ROC curves. The readers' average area under the ROC curve was calculated to summarize the diagnostic accuracy of all readers together. The average AUC ROC was significantly higher (+0.056) with DBT + Insight 2D compared to FFDM alone (Figure 2). Nineteen readers (95%) improved their accuracy in detecting and diagnosing cancers when reading 50° wide-angle DBT + Insight 2D compared to FFDM alone (Figure 3).

These results demonstrate the **superior diagnostic accuracy** of Siemens Healthineers' 50° wide-angle DBT plus Insight 2D compared to FFDM alone.

Table 2: Significant improvement in diagnostic accuracy

2-view DBT + Insight 2D | 2-view FFDM

Average AUC ROC:

- 2-view FFDM: 0.837
- 2-view DBT + Insight 2D: 0.893
- $\Delta_{AUC\ ROC}$: 0.056
- p-value: < 0.0001

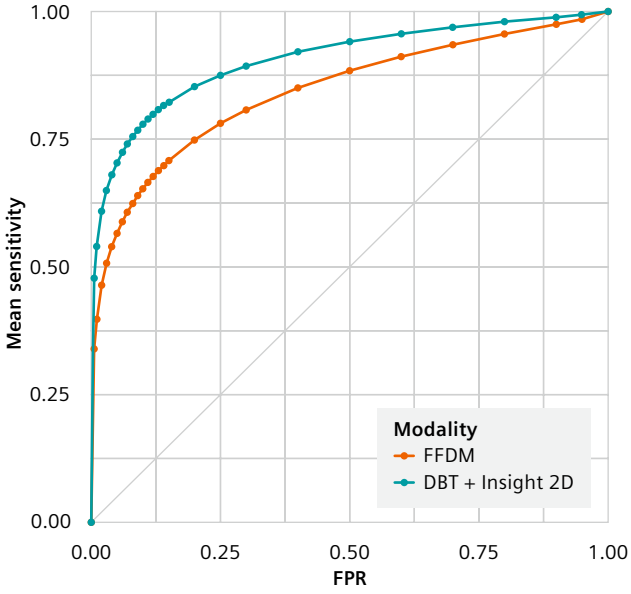

Figure 2: Average reader breast-level ROC curves for 2-view FFDM (orange) and 2-view DBT + Insight 2D (petrol). Calculation based on ratings of 20 readers.

Figure 3: Readers' estimated breast-level AUCs with FFDM sorted by lowest to highest (orange) and the estimated increase (petrol) or decrease (grey) with DBT + Insight 2D.

Significant improvement in sensitivity

The sensitivity in detecting breast cancers was calculated at the breast-level. Among breasts with cancer, a BI-RADS score of 0 assigned to the breast was considered a true-positive finding.

The readers' average sensitivity was significantly higher with DBT + Insight 2D compared to FFDM alone (Table 3). The average relative increase in sensitivity at the subject-level was 5.8%. Eighteen readers (90%) improved their sensitivity when reading 50° wide-angle tomosynthesis with Insight 2D compared to FFDM alone.

This demonstrates the **superior sensitivity** of Siemens Healthineers' 50° wide-angle DBT plus Insight 2D compared to FFDM alone.

Significant reduction in the non-cancer recall rate

All women with a BI-RADS 0 during screening will be recalled for further diagnostic work-up. This group consists of true and false positives, the latter receiving unnecessary follow-up procedures like ultrasound or biopsy. The non-cancer recall rate was calculated at the subject-level and describes the number of women with false positive findings as a proportion of all women without cancer.

The readers' average non-cancer recall rate was significantly lower with DBT + Insight 2D compared to FFDM alone (Table 4). The average relative reduction in non-cancer recall rate at the subject-level was 27.4%. Nineteen readers (95%) reduced their non-cancer recall rate when reading 50° wide-angle tomosynthesis with Insight 2D compared to FFDM alone.

This demonstrates the **increased diagnostic confidence** obtained using Siemens Healthineers' 50° wide-angle DBT plus Insight 2D compared to FFDM alone.

Table 3: Significant improvement in sensitivity

2-view DBT + Insight 2D | 2-view FFDM

Readers' average sensitivity:

- 2-view FFDM: 0.8047
- 2-view DBT + Insight 2D: 0.8517
- $\Delta_{sensitivity}$: 0.047
- p-value: 0.0430
- Relative increase: 5.8%

Table 4: Significant reduction in the non-cancer recall rate

2-view DBT + Insight 2D | 2-view FFDM

Readers' average non-cancer recall rate:

- 2-view FFDM: 0.4729
- 2-view DBT + Insight 2D: 0.3435
- $\Delta_{Non\text{-}cancer\ recall\ rate}$: -0.1294
- p-value: < 0.0001
- Relative decrease: 27.4%

Trends in specific breast cancer subgroups

Supplemental analyses were performed to observe trends in different breast cancer subgroups. Table 5 summarizes the differences in average reader breast-level AUCs, as measure of diagnostic accuracy, between wide-angle DBT plus Insight 2D and FFDM.

Table 5: Average reader breast-level AUCs for specific breast cancer subgroups

	 DBT + Insight 2D (STD)	 FFDM (STD)	Δ_{AUC}
Dense breasts (c/d)	0.8754 (0.0229)	0.8295 (0.0255)	+0.0459
Non-dense breasts (a/b)	0.9088 (0.0208)	0.8391 (0.0259)	+0.0697
Mass	0.9363 (0.0145)	0.8714 (0.0198)	+0.0649
Calcification	0.8094 (0.0367)	0.8159 (0.0360)	-0.0064
Architectural distortion	0.9298 (0.0313)	0.8414 (0.0421)	+0.0884
Invasive cancer	0.9273 (0.0147)	0.8535 (0.0120)	+0.0739

Summary

This white paper describes a clinical study using Siemens Healthineers' wide-angle DBT system plus synthetic mammograms (Insight 2D) which supported the Premarket Approval by the Food and Drug Administration. The MRMC study demonstrated a superior diagnostic accuracy, sensitivity, and a reduced non-cancer recall rate using Siemens Healthineers' 50° wide-angle DBT plus Insight 2D as compared to FFDM alone. These results provide evidence that Siemens Healthineers' 50° wide-angle DBT plus Insight 2D can be used with a high level of confidence in breast cancer screening and diagnosis.

Abbreviations

AUC ROC	Area under the ROC curve
BI-RADS	Breast Imaging Reporting and Data System
CC	Craniocaudal
DBT	Digital Breast Tomosynthesis
FFDM	Full-Field Digital Mammography
MLO	Mediolateral oblique
MRMC	Multi-Reader Multi-Case
MQSA	Mammography Quality Standards Act and Program
PMA	Premarket Approval
ROC	Receiver Operating Characteristic
STD	Standard Deviation

References

[1] Siemens Medical Solutions USA Inc. (2020) PMA P140011/S007

[2] Siemens Medical Solutions USA Inc. (2016) PMA P140011/S001

[3] Georgian-Smith D, Obuchowski NA, Lo JY, Brem RF, Baker JA, Fisher PR, Rim A, Zhao W, Fajardo LL, Mertelmeier T. Can Digital Breast Tomosynthesis Replace Full-Field Digital Mammography? A Multireader, Multicase Study of Wide-Angle Tomosynthesis. AJR Am J Roentgenol. 2019:1-7

[4] Nalleweg N, Mertelmeier T, Korporaal JG, Hebecker A (2016) Superior Diagnostic Accuracy with Additional Digital Breast Tomosynthesis: Main findings of the clinical study for Premarket Approval of Mammomat Inspiration with Tomosynthesis Option. Siemens White Paper

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Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

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