Synthetic 2D Digital Mammography and Tomosynthesis: Update and Tips for Clinical Implementation

Emily F. Conant, M.D.
Professor, Chief of Breast Imaging
Hospital of the University of Pennsylvania
Philadelphia, PA

Disclosures

Consulting Fees (Reader studies): Hologic, Inc., Siemens’s Healthcare
Research Grant: NCI U54 Multi-Center PROSPR trial: Comparative Effectiveness of Digital Breast Tomosynthesis

At Penn, we have 4 clinical tomosynthesis units (Hologic)
We began screening of all patients with DBT in Sept. 2011 and all diagnostic patients with DBT in Jan. 2014.
We implemented synthetic 2D with DBT in Jan. 2015.

Outline

Part 1: Update on DBT screening outcome data
– What’s new?

Part 2: Review of synthetic imaging
– What does the data show?
– Case-based examples of synthetic imaging

Part 3: Efficiency tools for DBT interpretation
– Slabbing, CAD enhanced navigation

Update on DBT Screening Outcomes

Summary of Characteristics of DBT systems (*FDA approved)

<table>
<thead>
<tr>
<th>Industry</th>
<th>Detector</th>
<th>Pixel</th>
<th>Size (µm)</th>
<th>Beam Angle</th>
<th>Projections</th>
<th>Tube-movement</th>
<th>Reconstruction</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hologic</td>
<td>Se 50</td>
<td>15°</td>
<td>15 Continuous</td>
<td>Continuous, stationary detector</td>
<td>Non-linear FBP</td>
<td>4 Standard, 1 High res</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Ge</td>
<td>IBF 0.33</td>
<td>15°</td>
<td>15 Continuous</td>
<td>Continuous, stationary detector</td>
<td>Non-linear FBP</td>
<td>4 Standard, 1 High res</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>SenoGraph</td>
<td>Senior 3D</td>
<td>15°</td>
<td>15 Continuous</td>
<td>Continuous, stationary detector</td>
<td>Non-linear FBP</td>
<td>4 Standard, 1 High res</td>
<td>20</td>
<td></td>
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<tr>
<td>Fuji</td>
<td>µSe 50</td>
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<td>Non-linear FBP</td>
<td>4 Standard, 1 High res</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Clarity</td>
<td>90</td>
<td>15°</td>
<td>15 Continuous</td>
<td>Continuous, stationary detector</td>
<td>Non-linear FBP</td>
<td>4 Standard, 1 High res</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Siemens</td>
<td>Mammomax</td>
<td>50</td>
<td>15°</td>
<td>Continuous</td>
<td>Non-linear FBP</td>
<td>4 Standard, 1 High res</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Synthetic imaging available

Summary of DBT Screening Studies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design</th>
<th>Volumes</th>
<th>Recall Rate (%)</th>
<th>DM versus DBT</th>
<th>Cancer Rate (per/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman (2006)</td>
<td>{B}</td>
<td>12,303 multi-view</td>
<td>10.7 ± 7%</td>
<td>5% reduction</td>
<td>4.6 (p&lt;0.05)</td>
</tr>
<tr>
<td>Roe (2012)</td>
<td>{S}</td>
<td>17,624 multi-view</td>
<td>10.7 ± 7%</td>
<td>5% reduction</td>
<td>4.6 (p&lt;0.05)</td>
</tr>
<tr>
<td>Claudio (2013)</td>
<td>{S}</td>
<td>7,000 DM + DBT</td>
<td>10.7 ± 7%</td>
<td>5% reduction</td>
<td>4.6 (p&lt;0.05)</td>
</tr>
<tr>
<td>Fidow (2014)</td>
<td>{S}</td>
<td>10,714 multi-view</td>
<td>10.7 ± 7%</td>
<td>5% reduction</td>
<td>4.6 (p&lt;0.05)</td>
</tr>
<tr>
<td>Greenberg (2014)</td>
<td>C</td>
<td>10,714 multi-view</td>
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<td>5% reduction</td>
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</tr>
<tr>
<td>McCormick (2015)</td>
<td>C</td>
<td>10,714 multi-view</td>
<td>10.7 ± 7%</td>
<td>5% reduction</td>
<td>4.6 (p&lt;0.05)</td>
</tr>
<tr>
<td>Lawrence (2016)</td>
<td>C</td>
<td>10,714 multi-view</td>
<td>10.7 ± 7%</td>
<td>5% reduction</td>
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<th>Volumes</th>
<th>DM versus DBT</th>
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</thead>
<tbody>
<tr>
<td>Skaane (2013)</td>
<td>13,013</td>
<td></td>
</tr>
<tr>
<td>Rose (2013)</td>
<td>18,015</td>
<td>DM + DBT</td>
</tr>
<tr>
<td>Ciatto (2013)</td>
<td></td>
<td>Recall Rate (%)</td>
</tr>
<tr>
<td>Friedewald (2013)</td>
<td>21,299</td>
<td></td>
</tr>
<tr>
<td>Skaane (2016)</td>
<td>23,355</td>
<td></td>
</tr>
<tr>
<td>McCormy (2016)</td>
<td>25,299</td>
<td></td>
</tr>
<tr>
<td>Laurence (2016)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reduction in Recall from 15 to 37%
Change in Cancer Detection Rate from ~15 to ~33%

Sub-populations reported in Friedewald, et al.

Limitations

- Studies “first round” or “prevalent” screens
- Only two studies prospective (Oslo and Italian trials)
- In retrospective studies, majority of sites had concurrent DM screening therefore, potential for bias in screened cohorts
- There was little follow-up to determine false negatives

Additional questions regarding DBT screening?

Are the improved outcomes sustainable?
- Evaluate consecutive years of DBT screening
  - Prevalent versus incident screening
- Analysis of false negative studies:
  - Surrogate for mortality benefit
- Dose reduction with synthetic imaging – Are outcomes similar to screening with DM/DBT?

Results from Penn consecutive years of DBT screening

<table>
<thead>
<tr>
<th>Metric</th>
<th>Year 0 DM</th>
<th>Year 1 DBT</th>
<th>Year 2 DBT</th>
<th>Year 3 DBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall rate (%)</td>
<td>10.4</td>
<td>8.8</td>
<td>9.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Cancer rate/1000</td>
<td>4.6</td>
<td>5.5</td>
<td>5.8</td>
<td>6.1</td>
</tr>
<tr>
<td>PPV1</td>
<td>4.4</td>
<td>6.2</td>
<td>6.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Interval CA/1000</td>
<td>0.7</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

University of Pennsylvania Data

Method:
- Four consecutive years DBT screening
  - Population level analysis (each year of screening)
  - Patient level analysis (each round of screening)
  - Comparison with cancer registry data for false negatives

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What about first round, “Prevalence Effect”? 

Breast Cancer Research & Treatment (2016)

Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: a cohort study within the PROSPR consortium

PROSPR consortium (Brigham-Dartmouth, U.Vt. UPenn)
- Patient level data
  - 16% reduction in recall (8.7% vs 10.4%; p<0.001)
  - 34% increase in cancer detection (5.9 vs 4.4/1000; p=0.0026)
  - 27% invasive cancers
  - Trend in decrease in false negatives (0.46 vs 0.6/1000)

Cancer Detection and Recall Rate Change with DBT: Age and Density (PROSPR data)

JAMA Consortium: Outcomes by Density

What about Dose??
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Comparison of DBT Dose

- Hologic DBT increases with thicker breasts (≥ 50mm)
- Siemens DBT dose is higher than DM for all thicknesses
- GE DBT dose same as DM (has grid for both modes)

What about Dose?

- Dose measured with standard phantom*

<table>
<thead>
<tr>
<th>Exam</th>
<th>Radiation Dose per view</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFDM Hologic</td>
<td>1.2 mGy</td>
</tr>
<tr>
<td>FFDM across manufacturers**</td>
<td>1.43 mGy</td>
</tr>
<tr>
<td>FFDM plus DBT</td>
<td>2.65 mGy</td>
</tr>
<tr>
<td>s2D plus DBT</td>
<td>1.45 mGy</td>
</tr>
</tbody>
</table>

45% reduction in dose

*From FDA PMA submission by Hologic for synthetic 2D
**Collected from medical physicists' dose measurements for MQSA inspection 1-9 2012

Part 2: Synthetic 2D Imaging

Which is DM and which is s2D?

Overview of s2D Reconstruction

DBT image data used to create both 1mm slices for tomo "stack" and s2D images

Multiple, low dose images obtained and then reconstruction

Overview of s2D Reconstruction

s2D Mamm
Tomo Slices

Synthetic 2D is about more than just dose!

Need 2D images to maintain outcomes of DBT screening for efficient, high volume screening

- Global assessment of breasts:
  - BI-RADS density assessment
  - Comparison with prior images
  - Assessment of lesions – esp. calcs, asymmetries, etc.
Zuley M, et al. (Radiol 2014)

Reader study: 8 readers and 123 cases:
- 2D alone or combo with DBT comparable to DM/DBT

Skaane P, et al. (Radiol 2014)

<table>
<thead>
<tr>
<th>Study period 1 (n=12,621)</th>
<th>Study period 2 (n=12,270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM/DBT</td>
<td>2D/DBT</td>
</tr>
<tr>
<td># False-positive scores</td>
<td>670</td>
</tr>
<tr>
<td># True-positive scores*</td>
<td>101</td>
</tr>
<tr>
<td># cases recalled at arbitration</td>
<td>351</td>
</tr>
<tr>
<td># women detected with cancer</td>
<td>100</td>
</tr>
<tr>
<td>PPV(%)</td>
<td>28.5</td>
</tr>
</tbody>
</table>

*In each study period, one patient has bilateral cancers detected on DM/DBT.

ACR Phantom and Image quality

Purpose: compare ACR phantom image quality 2D vs DM

Results:
- DM > 2D overall, primarily due to "fiber" scores
- 2D > DM for med-large specks
  - However, less for small high contrast objects and all low contrast objects due to noise and overall resolution
- Did not meet the ACR requirement set for film screen
- However, did not evaluate scores of combo 2D/DBT

ACR Phantoms

Passing grade: 4 Fibers, 3 Specks, 3 Masses

Gilbert et al (Radiology 7/17/15)

- Multicenter, multireader, retrospective study, 7060 cases
  - 2D mammography
  - 2D plus DBT (DBT)
  - 2D plus sDBT (sDBT)
- Sensitivity:
  - 87% 2D
  - 89% 2D + DBT
  - 88% sDBT
- Specificity:
  - 57% 2D
  - 70% 2D + DBT
  - 72% sDBT

"s2D + DBT and 2D + DBT had better sensitivity for depicting 11-20 mm inv CA than 2D alone."

"However s2D + DBT was inferior to both 2D alone and 2D + DBT in depicting microcalcifications and 11-20mm DCIS."
Clinical Implementation of Synthetic 2D

At Penn, we introduced s2D in Sept. 2014
- Initially, s2D was behind DM in hanging protocol
- Moved s2D in front of DM – toggle for comparison
- After 2 months, removed DM from screening

Synthetic 2D with Tomosynthesis

Pathology: Ductal Carcinoma in situ (DCIS)

Synthetic Imaging: False Positive Calcifications

56 yo at screening.

Possible calcifications?
DM Magnification: No definite calcifications
Magnification at recall demonstrates no calcifications.
s2D reconstruction algorithm may make normal ligaments appear like calcifications.

Synthetic Imaging and enhanced distortion?

43 yo for baseline screen with questionable architectural distortion?

On sequential DBT slices, each component of the “lesion” is a separate structure (note localizer positions).
Normal study, no recall needed.
Synthetic 2D Outcomes at Penn

Performance outcomes being measured
- Recall rate (by lesion type)
- Cancer detection rate per 1000 screened
- PPV1 – cancers/recalled patients

Performance metrics with s2D?

<table>
<thead>
<tr>
<th>Modality</th>
<th>Overall</th>
<th>Calc</th>
<th>Masses</th>
<th>Asym.</th>
<th>Arch dist</th>
<th>Technical</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>10.4%</td>
<td>1.8%</td>
<td>2.4%</td>
<td>6.1%</td>
<td>0.7%</td>
<td>0.44%</td>
</tr>
<tr>
<td>DM+DBT</td>
<td>8.8%</td>
<td>1.6%</td>
<td>2.7%</td>
<td>4.5%</td>
<td>1.0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>s2D+DBT</td>
<td>7.1%</td>
<td>1.1%</td>
<td>2.4%</td>
<td>3.2%</td>
<td>1.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

p value (DM/DBT vs s2D/DBT) <0.001 0.02 0.31 <0.001 0.70 0.03

DBT screening dose reduced by 39%
- Maintained low recall rate (actually continues to decrease)
- Significant changes in calcs, asymmetries and technical recalls

s2D Performance metrics continued...

<table>
<thead>
<tr>
<th>Metric</th>
<th>DM/DBT</th>
<th>s2D/DBT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy rate (%)</td>
<td>2.0</td>
<td>1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Cancer/1000</td>
<td>5.45</td>
<td>5.03</td>
<td>0.732</td>
</tr>
<tr>
<td>In situ</td>
<td>1.48</td>
<td>0.9</td>
<td>0.301</td>
</tr>
<tr>
<td>Invasive</td>
<td>3.85</td>
<td>4.10</td>
<td>0.840</td>
</tr>
<tr>
<td>PPV1 (%)</td>
<td>6.2</td>
<td>7.1</td>
<td>0.548</td>
</tr>
<tr>
<td>PPV3 (%)</td>
<td>27.0</td>
<td>18.6</td>
<td>0.026</td>
</tr>
</tbody>
</table>

s2D maintains benefits of DBT:
- Increased number of cancers detected per recall (PPV1)
- Sensitivity and specificity similar, thus far...
- Slight decrease in detection of in situ cancers to be monitored

Population-level Cancer and Biopsy rates, PPV1 by year

`s2D data is based on initial 6 months of data – not powered for cancer detection..."
s2D Image Appearance varies based on Breast Density and Thickness

Very thick, fatty breast

Very thin, dense breast

Comparison of Density in s2D and DM

Fatty Scattered Heterogeneous Extremely Dense

Calcifications: 43 yo at screening.
Calcifications are best seen on s2D.
They are much more conspicuous on s2D.

Final Pathology: DCIS, high nuclear grade, associated comedo necrosis

Calcifications: 48 yo at screening.
Subtle calcifications “pop”, more distinct and brighter on s2D versus DM.
At recall, biopsy recommended.
Final pathology: DCIS

Calcifications: 62 yo at screening.
History of stable diffuse, amorphous calcs and milk of calcium

New calcifications in superior breast.
s2D reconstruction “enhances” calcifications, making them easier to detect.
Pathology: High grade DCIS
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Mass and Calcifications
68 yo with nipple retraction.

Individual calcifications retain discrete appearance on s2D. Spiculated mass better seen on s2D and DBT.

Final pathology: Invasive ductal carcinoma with extensive DCIS

False Positive Calcifications
58 yo at screening. Retroareolar calcifications seen on s2D.

s2D: possible calcs
Recall DM: no calcs
Spot Mags: no calcs

On DM and spot magnifications, calcifications do not persist.
s2D reconstruction may cause normal ligaments to appear like calcifications.

Examples of Lesions
Masses and Asymmetries

Mass: 63 yo at screening.
1 cm spiculated mass with faint calcifications in left breast.
Mass & calcifications better seen on s2D due to accentuation of spiculation and calcifications.
Final pathology: Invasive mammary carcinoma, intermediate grade

Asymmetry
54 yo at screening.

On screening, asymmetry is best seen on s2D and DBT MLO.
Additional projections demonstrate a mass in upper inner quadrant.
Final pathology: Invasive ductal carcinoma, intermediate grade

Mass: 35 yo with lump.

Patient was lactating - lesion is a galactocele.
Examples of Lesions

Architectural Distortion

Architectural Distortion

51 yo at screening.
Subtle distortion not apparent on DM but well seen on s2D.
Final pathology: Invasive ductal carcinoma

62 yo at screening.
Architectural distortion seen better on CC DBT.
Final pathology: Invasive lobular carcinoma (also a cyst)

60 yo at screening.
Architectural distortion was recalled from screening s2D. At diagnostic evaluation it was not apparent on the DM ML view but persisted on the on DBT compression.
Final pathology: Invasive ductal and lobular carcinoma

Examples of s2D Reconstruction

Metal Artifact

Metallic clips create artifact on DBT and s2D that may obscure subtle findings. A modified reconstruction algorithm reduces this artifact.
Metal Artifact

40 yo s/p mastectomy with TRAM reconstruction with palpable lump right breast.
Fat necrosis was seen in the area of patient’s palpable concern.

<table>
<thead>
<tr>
<th>Without Reconstruction Algorithm</th>
<th>With Reconstruction Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Motion Artifact

Parenchyma on s2D image appears “blurry” compared to DM. On DBT and projections images, there is significant motion.

<table>
<thead>
<tr>
<th><img src="image3.png" alt="Image" /></th>
</tr>
</thead>
</table>

Motion Artifact

Suspicious calcifications seen on s2D MLO view, localizing to lateral breast but no where to be seen on CC view. Patient recalled and mag done. Stereo biopsy yields DCIS

<table>
<thead>
<tr>
<th><img src="image4.png" alt="Image" /></th>
</tr>
</thead>
</table>

Part 3: Efficiency Tools for Tomosynthesis

Planes, Slabs, and Synthetic 2D

- Tomo-Planes (0.5mm or 1.0mm distance)
- Slab = 1 cm thick
- V-Preview Synthetic 2D image from 3D data

3 data files in BTO DICOM format

Images SenoClare by GE
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Reading Efficiency – “Slabbing”

“CAD” Driven Image Processing to improve Efficiency

Example: CC FFDM and MLO Synthetic

Example: MLO Slices and CAD-Synthetic

Synthetic Imaging with Navigation tool

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Synthetic Imaging with Navigation tool

Improved Efficiency?

RSNA abstract 2015:
• 276 cases comparing 0.5 vs 10mm slices
  – 10 mm slabs efficient work-flow without performance loss - masses, densities, arch D
  – 10X less image file size for PACs storage!

iCAD FDA PMA submission study:
• 20 radiologists reading 240 cases:
  – Approximately 29% reduction in reading time
  – Maintenance of clinical performance

“The Next big thing is whatever makes the Last big thing usable”
Blake Rose, Co-creator of Firefox

Conclusions

Synthetic 2D versus digital mammogram:
• Replacing DM with s2D significantly decreases dose
• Appearance s2D differs based on breast density, thickness, and lesion type
• Calcifications and distortion more conspicuous on s2D

Conclusions

Synthetic 2D and early screening outcomes:
• Implementing s2D results in some false positives, but overall, recall rate unchanged to slightly decreased
• Implementation of s2D+DBT maintains cancer detection achieved with DM/DBT at reduced dose

*s2D is an acceptable replacement for DM in DBT screening
Thank you!