DISCLOSURES

- I own shares in the following companies through mutual funds which are utilized in medical practice and/or health care. Two of these companies (*) are directly mentioned in this presentation.
  - *General Electric (GE) (0.67% of portfolio)*
  - *Hologic, Inc. (0.09% of portfolio)*
  - UnitedHealth Group Inc (0.74%)
  - Allergan (0.50%)
  - Intuitive Surgical Inc (0.48%)
  - New Link Genetics (0.26%)
  - Medtronic (0.19%)
  - McKesson (0.04%)
OVERVIEW

▸ 3D breast tomosynthesis
▸ Tumor Response Assessment
▸ Radiation dose reduction project
▸ Hemangioma…or something else?
HEMANGIOMA

- Benign tumor composed of multiple vascular channels lined by endothelial cells supported by thin fibrous stroma

- Best diagnostic clues:
  
  - On US, well-defined, uniformly hyperechoic mass. May see posterior acoustic enhancement.
  
  - On CT, peripheral nodular enhancement on arterial phase scan with slow, progressive, centripetal enhancement isodense to vessels.
  
  - On MRI: Very T2 hyper intense, with post-gadolinium nodular progressive enhancement isodense to vessels

Images from StatDx, Michael Federle, MD FACR
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HEMANGIOMA?
HEMANGIOMA?
ADVANCES IN DIAGNOSTIC IMAGING

A. Hemangioma
B. Hepatocellular carcinoma
C. Metastases from unknown primary malignancy
D. Focal nodular hyperplasia
E. Hepatic cyst
Approximately 231,840 new cases of invasive breast cancer and 40,290 breast cancer deaths expected in 2015

Mammographic screening can reduce breast cancer deaths by 30%

Digital mammography (DM) provide a two-dimensional image of a three-dimensional structure and superimposition of normal tissue can obscure masses or other important features of malignancy

DIGITAL BREAST TOMOSYNTHESIS

- DBT is a “better mammogram”
- Multiple low dose projection x-ray images are obtained along an arc¹
- X-ray tube pivots in an arc of varying degrees (15-50)¹
- 3-dimensional DBT images are reconstructed from projection images by mathematical equation (FBP or IR)¹
- In all manufacturers, multiple 2D images are created in thin 1 mm increments and available for display¹

ADVANCES IN DIAGNOSTIC IMAGING

TRADITIONAL 2D DIGITAL MAMMOGRAPHY
DIGITAL BREAST TOMOSYNTHESIS

Multiple low dose projection x-ray images are obtained along an arc.

X-ray tube pivots in an arc of varying degrees (15-50).

3-dimensional DBT images are reconstructed from projection images.
15 projection images x Filtered Back Projection (FT) = 1 mm image set through the breast.
Largest prospective trial of 12631 patients comparing digital mammography with digital breast tomosynthesis

- 15% reduction in recall rate\(^1\)
- 27% increase in cancer detection rate\(^1\)

Similar to another trial

- 15% reduction in recall rate\(^2\)
- 29% increase in cancer detection rate\(^2\)

---

Digital Breast Tomosynthesis

- Breast cancer screening; looking for mass, calcifications or architectural distortion
- Architectural distortion much better seen at DBT
- 268 BI-RADS 4 or 5 screening detected lesions with DM and DBT
- 7% (19 of 268) were occult at DM and only seen at DBT
  - 10 of 19 (53%) were invasive breast cancers
    - 7 of 10 ILC, 3 of 10 IDC

Pathology: 6 cm invasive lobular carcinoma.

Advances in Diagnostic Imaging

Digital Breast Tomosynthesis

- Quasi-three-dimensional information from DBT allows triangulation of subtle one-view-only lesions so that further targeted imaging (US>MRI) is possible.

- In a study of 115 malignant lesions, 35% were better or only seen on DBT CC view whereas only 11% were better or only seen on MLO view\textsuperscript{4}

- Another study of 34 mixed benign and malignant lesions, 15% were better seen at CC DBT\textsuperscript{5}


\textsuperscript{5} Rafferty EA, Niklason L, Jameson-Meehan L. Breast tomosynthesis: one view or two? [abstr]. In: Radiological Society of North America scientific assembly and annual meeting program. Oak Brook, Ill: RSNA, 2006; 225.
Pathology results: Intermediate grade invasive ductal carcinoma.

Pathology results: Intermediate grade invasive ductal carcinoma with DCIS.

DIGITAL BREAST TOMOSYNTHESIS

Many trials and data, but the biggest was published in 2014 in JAMA\textsuperscript{6}

Breast Cancer Screening Using Tomosynthesis in Combination with Digital Mammography

454,850 exams

Period 1: 2010-2011 (Digital mammography)

Period 2: 2011-2012 (3D breast tomosynthesis + digital mammography)

Major outcomes:

- Increased cancer detection rate: 4.2 to 5.4 per 1000
- Decreased callback rate: 107 to 91 per 1000 (ie, 10.7\% to 9.1\%)

DIGITAL BREAST TOMOSYNTHESIS

- McFarland Clinic Experience

- Compared our final year at full field digital mammography (2011) to our most recent complete year of DBT (2015) in a manner identical to the 2014 JAMA article (2011 vs 2012).

## Digital Breast Tomosynthesis - McFarland Experience

<table>
<thead>
<tr>
<th>Site</th>
<th># radiologists</th>
<th>Academic or nonacademic</th>
<th>Period 1 cases</th>
<th>Period 2 cases</th>
<th>Recall rate digital (%)</th>
<th>Recall rate DBT (%)</th>
<th>Cancer detection digital per 1000</th>
<th>Cancer detection DBT per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>3.1</td>
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<td>29948</td>
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<td>5.2</td>
<td>4.1</td>
<td>5.1</td>
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<tr>
<td>Study average</td>
<td>10.7</td>
<td>5A 8N</td>
<td>21629</td>
<td>13358</td>
<td>10.7</td>
<td>8.9</td>
<td>4.3</td>
<td>5.4</td>
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<tr>
<td>McFarland</td>
<td>8</td>
<td>N</td>
<td>16548</td>
<td>18067</td>
<td>11.6</td>
<td>7.4</td>
<td>4.3</td>
<td>5.0</td>
</tr>
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<td>5A 8N</td>
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<td>13358</td>
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<td>5.4</td>
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<td>5.0</td>
<td>11.6</td>
<td>7.4</td>
</tr>
</tbody>
</table>

+16% (+15%, +15%)  
-36% (-27%, -29%)
Figure. Combined Change in Cancer Detection Rate and Recall Rate for Each Institution After Implementation of Tomosynthesis

Lines demonstrate combined change in performance for each institution, labeled by site number. Pooled performance across all institutions is shown in blue. The model estimate is shown in orange.


1 The algorithm assumes that the clinical examination shows a focal palpable area of concern. If the clinical examination reveals less concerning findings, such as mild nodularity or a ridge of tissue, then further evaluation after negative imaging is not required.

Probable benign features include: round, oval or minimally lobular shape; circumscribed margins; and equal or low density on mammography; and homogeneously hypodense or sonolucent solid mass with circumscribed margins and lack of malignant features on US. If the mass is new on imaging, then biopsy is indicated.

Suspicious features include: irregular shape, ill-defined or spiculated margins, high density on mammography, non-parallel orientation, or posterior acoustic shadowing.
18-29 yo: Ultrasound followed by mammogram for area of palpable concern in age 18-29 if there is no corresponding abnormality found by the ultrasound after radiologist has reviewed the ultrasound.

<18 yo: Ultrasound only. Mammogram performed only if advocated for by the patient/parents/guardian after discussion with the radiologist.

MRI Abdomen without and with gadolinium from an outside institution 2/11/2016
ADVANCES IN DIAGNOSTIC IMAGING

A. Hemangioma
B. Hepatocellular carcinoma
C. Metastases from unknown primary malignancy
D. Focal nodular hyperplasia
E. Hepatic cyst
TUMOR RESPONSE ASSESSMENT

- Response Evaluation Criteria In Solid Tumors (RECIST)
- First published February 2000
- Most recently revised 2009 (RECIST 1.1)
- Standardized assessments
  - Complete response/remission (CR)
  - Partial response (PR)
  - Progression of disease (PD)
  - Stable disease (SD)

### RECIST 1.1 - HOW IT WORKS

<table>
<thead>
<tr>
<th>Lesions</th>
<th>5/2</th>
</tr>
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<tr>
<td>Measurement</td>
<td>LA ((SA_{LN}))</td>
</tr>
<tr>
<td>PD/PR</td>
<td>20%/30%</td>
</tr>
<tr>
<td>New lesions</td>
<td>PD</td>
</tr>
</tbody>
</table>

## RECIST 1.1 - HOW IT WORKS

<table>
<thead>
<tr>
<th>Target</th>
<th>Non target</th>
<th>New lesion</th>
<th>Overall</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
<td>Non PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Yes or no</td>
<td>Yes or no</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Any</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

RECIDST 1.1 - HOW IT WORKS

-30% = PR

SD = STABLE DISEASE

NADIR

+20% = PD

CR = COMPLETE REMISSION

PR = PARTIAL RESPONSE

PD = PROGRESSIVE DISEASE

SD = STABLE DISEASE

baseline follow up 1 follow up 2 follow up 3

-30% = PR

SD = + 4%

+20% = PD
## Tumor Response Assessment

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tumor/Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST 1.1</td>
<td>Most tumors</td>
</tr>
<tr>
<td>PERCIST 1.0</td>
<td>PET</td>
</tr>
<tr>
<td>Cheson</td>
<td>PET</td>
</tr>
<tr>
<td>Lugano</td>
<td>Diffuse Large B-cell Lymphoma (DLBCL)</td>
</tr>
<tr>
<td>Choi</td>
<td>GIST</td>
</tr>
<tr>
<td>NRC/Lee (New Response Criteria)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>RANO (Response Assessment in Neuro-Oncology)</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>MASS (Morphology, Attenuation, Size, Structure)</td>
<td>RCC</td>
</tr>
<tr>
<td>irRC/irRECIST</td>
<td>Melanoma</td>
</tr>
<tr>
<td>mRECIST</td>
<td>HCC</td>
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</table>
## RECIST 1.1 VS LUGANO

<table>
<thead>
<tr>
<th></th>
<th>RECIST 1.1</th>
<th>Lugano</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesions</strong></td>
<td>5/2</td>
<td>6</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td>LA or ((SA_{LN}))</td>
<td>LA x SA = (PPD)</td>
</tr>
<tr>
<td></td>
<td>(PPD_1 + PPD_2 + \text{etc} = (SPD)</td>
<td></td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>Disappearance of target &amp; &lt;10mm (LN_{SA})</td>
<td>(&lt;1.5 \text{ cm } LN_{LA}) &amp; disappearance of non-nodal dz</td>
</tr>
<tr>
<td><strong>PD/PR</strong></td>
<td>+20%/−30%</td>
<td>+50% &amp; +0.5(&lt;2cm) or +1(&gt;2cm)/−50%</td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td><strong>PET assessment</strong></td>
<td>No (PERCIST 1.0)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TUMOR RESPONSE ASSESSMENT

▸ Limitations

▸ Inconsistent measurements between readers and even with same reader

▸ Difficulty with measuring ill-defined lesions

TUMOR RESPONSE ASSESSMENT

**Limitations**

- Inconsistent measurements between readers and even with the same reader\(^1\)
- Difficulty with measuring ill-defined lesions\(^1\)

A. Hemangioma
B. Hepatocellular carcinoma
C. Metastases from unknown primary malignancy
D. Focal nodular hyperplasia
E. Hepatic cyst
RADIATION DOSE REDUCTION PROJECT

- CT abdomen and pelvis without contrast for renal colic symptoms

- Guidance from American College of Radiology states these exams should be performed with an average dose-length-product (DLP) of 200 mGy-cm (3 mSv).


- ACR Dose Registry analysis in 2013 showed significant heterogeneity nationwide regarding adoption.
What is the lowest minimum dosing that can cause harm?

100 mGy = 100 mSv

Figure 5: Graph shows number of solid cancers as a function of absorbed dose. □ = people who were not in the cities at the time of the bombing. (Data are from table 4 of reference 14.)
What is the lowest minimum dosing that can cause harm?

Figure 4: Graph shows models for extrapolating radiation-induced cancer risk to low doses (dashed line and curves). Linear no-threshold (LNT) model = dashed straight line.

0.1 Sv = 100 mSv
3000 DLP approximates 45 mSv.
964.9 DLP approximates 14.5 mSv.
400 DLP approximates 6 mSv.
200 DLP approximates 3 mSv.
Initial goal: We wanted to achieve an average of 2x the recommended ACR average (DLP=400, 6 mSv).

Red line: Average dose from 55 patients imaged on the 6 CT scanners surveyed. (DLP 964.9, approx 14.5 mSv).

Yellow line: Midwest average from 14,642 exams compiled from 2011-2013 by ACR dose registry (DLP 781, approx 11.2 mSv).

Orange line: National average from 49,903 exams compiled from 2011-2013 by ACR dose registry (DLP 746, approx 11.2 mSv).

Green line: Recommended average for these exams by ACR (DLP=200, 3 mSv).

2015 data

2016 data
A. Hemangioma

B. Hepatocellular carcinoma

C. Metastases from unknown primary malignancy

D. Focal nodular hyperplasia

E. Hepatic cyst
Hemangiomas and a breast carcinoma met - Both previously treated with Avastin