Quantitative imaging phenotyping of breast cancer risk

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Nothing to Disclose
Toward Precision Cancer Screening

Shieh et al. (Nat Rev Clin Oncol. 2016)
Need for More Accurate Ways of Predicting Breast Cancer Risk

The key role of imaging phenotypes
Wolfe’s Parenchymal Patterns

NI (Lowest risk)

PI

P2

DY (Highest risk)

Wolfe AJR 1976
Breast Density & Risk

Breast Percent Density (PD%)

PD = 0%
PD < 10%
PD < 25%
PD < 50%
PD < 75%
PD < 100%

**Established, independent risk factor**
McCormack et al. *Cancer Epidemiol Biomarkers Prev.* 2006
Eng et al. *Breast Cancer Res.* 2014

**Improves risk assessment models**
Brentnall et al. *Breast Cancer Res.* 2015

**Has shared genetic basis with breast cancer susceptibility**
Stone et al. *Cancer Res.* 2015

**Predicts both inherent risk and masking risk**
Strand et al. *Int J Cancer* 2017

**Associated with tumor profile**
Bertrand et al. *Cancer Epidemiol Biomarkers Prev.* 2015


**PD = 31%**

**BIRADS = 3**

Gail 5 Yr = 0.7%

Gail Life = 3.6%

**PD = 31%**

**BIRADS = 2**

Gail 5 Yr = 7.6%

Gail Life = 20.7%
Beyond Breast Density: Texture Features for Pattern Analysis

Spatial relationship among gray levels

4 gray-level image

Gray-level co-occurrence matrix for $0^\circ$

Run-length matrix for $0^\circ$

Low contrast

High contrast
Beyond Breast Density: Texture Features for Pattern Analysis

Gray-level intensity distribution

Intrinsic patterns of image intensity (texture roughness)
Parenchymal texture patterns are indicative of genetic risk markers (BRCA1/2)

Digitized film mammograms

Huo et al. Radiology 2002
Li et al. J Med Imag. 2014

Digital mammograms
Parenchymal texture patterns are predictive of cancer-case-control status

<table>
<thead>
<tr>
<th>Texture Feature</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laws</td>
<td>1.27 (1.06, 1.54)</td>
</tr>
<tr>
<td>Markovian</td>
<td>1.26 (1.07, 1.47)</td>
</tr>
<tr>
<td>Run Length</td>
<td>1.26 (1.03, 1.54)</td>
</tr>
<tr>
<td>Wavelet</td>
<td>1.24 (1.05, 1.46)</td>
</tr>
<tr>
<td>Fourier</td>
<td>1.31 (1.08, 1.60)</td>
</tr>
<tr>
<td>Power law</td>
<td>1.32 (1.09, 1.60)</td>
</tr>
</tbody>
</table>

*Model adjusted for Age, BMI and breast PD*

Wei et al. *Radiology* 2011
Manduca et al. *Cancer Epidemiol Biomarkers Prev.* 2009

Gastounioti et al. *Breast Cancer Research* 2016 (Review)
### Table 5: Risk associated of either DCIS or invasive cancer for each feature

<table>
<thead>
<tr>
<th>Feature</th>
<th>DCIS (OR, 95% CI)</th>
<th>Invasive (OR, 95% CI)</th>
<th>p value*</th>
<th>p het**</th>
<th>ER- (OR, 95% CI)</th>
<th>p value*</th>
<th>p het**</th>
<th>ER+ (OR, 95% CI)</th>
<th>p value*</th>
<th>p het**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N case/N control</strong></td>
<td>254/1659</td>
<td>908/1659</td>
<td></td>
<td></td>
<td>116/1291</td>
<td></td>
<td></td>
<td>746/1291</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FD_TH_75</strong></td>
<td>0.87 (0.74–1.01)</td>
<td>0.87 (0.78–0.96)</td>
<td>0.010</td>
<td>0.98</td>
<td>0.84 (0.67–1.06)</td>
<td>0.048</td>
<td>0.72</td>
<td>0.88 (0.79–0.99)</td>
<td>0.048</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>0.88 (0.76–1.02)</td>
<td>0.88 (0.80–0.96)</td>
<td>0.011</td>
<td>0.93</td>
<td>0.85 (0.69–1.05)</td>
<td>0.009</td>
<td>0.90</td>
<td>0.86 (0.78–0.95)</td>
<td>0.009</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Entropy</strong></td>
<td>1.18 (1.02–1.38)</td>
<td>1.13 (1.03–1.25)</td>
<td>0.010</td>
<td>0.60</td>
<td>1.16 (0.93–1.44)</td>
<td>0.024</td>
<td>0.96</td>
<td>1.15 (1.03–1.28)</td>
<td>0.024</td>
<td>0.96</td>
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<tr>
<td><strong>FD_TH_70</strong></td>
<td>0.85 (0.72–1.00)</td>
<td>0.87 (0.79–0.97)</td>
<td>0.015</td>
<td>0.75</td>
<td>0.84 (0.67–1.06)</td>
<td>0.085</td>
<td>0.64</td>
<td>0.89 (0.79–1.00)</td>
<td>0.085</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>FD_TH_80</strong></td>
<td>0.90 (0.77–1.04)</td>
<td>0.89 (0.81–0.98)</td>
<td>0.034</td>
<td>0.90</td>
<td>0.85 (0.68–1.05)</td>
<td>0.066</td>
<td>0.64</td>
<td>0.89 (0.80–1.00)</td>
<td>0.066</td>
<td>0.64</td>
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<tr>
<td><strong>FD_TH_10</strong></td>
<td><strong>1.19 (1.04–1.38)</strong></td>
<td><strong>1.09 (0.99–1.19)</strong></td>
<td><strong>0.022</strong></td>
<td><strong>0.21</strong></td>
<td>1.03 (0.84–1.26)</td>
<td>0.479</td>
<td>0.75</td>
<td>1.06 (0.96–1.18)</td>
<td>0.479</td>
<td>0.75</td>
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<tr>
<td><strong>Kurtosis</strong></td>
<td>0.86 (0.73–1.00)</td>
<td>0.90 (0.81–0.99)</td>
<td>0.032</td>
<td>0.58</td>
<td>0.98 (0.78–1.22)</td>
<td>0.216</td>
<td>0.53</td>
<td>0.91 (0.81–1.01)</td>
<td>0.216</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>FD_TH_65</strong></td>
<td>0.84 (0.71–0.99)</td>
<td>0.89 (0.80–0.99)</td>
<td>0.049</td>
<td>0.49</td>
<td>0.83 (0.65–1.06)</td>
<td>0.170</td>
<td>0.46</td>
<td>0.91 (0.81–1.03)</td>
<td>0.170</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>FD_Minkowski</strong></td>
<td>0.90 (0.74–1.08)</td>
<td>0.86 (0.77–0.97)</td>
<td>0.042</td>
<td>0.71</td>
<td>0.77 (0.59–1.01)</td>
<td>0.063</td>
<td>0.32</td>
<td>0.89 (0.78–1.01)</td>
<td>0.063</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Busyness</strong></td>
<td>1.15 (1.00–1.33)</td>
<td>1.09 (1.00–1.19)</td>
<td>0.053</td>
<td>0.46</td>
<td>0.92 (0.75–1.14)</td>
<td>0.128</td>
<td>0.12</td>
<td>1.09 (0.99–1.21)</td>
<td>0.128</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Homogeneity</strong></td>
<td><strong>1.05 (0.90–1.22)</strong></td>
<td><strong>1.13 (1.03–1.24)</strong></td>
<td><strong>0.042</strong></td>
<td><strong>0.36</strong></td>
<td><strong>1.06 (0.86–1.31)</strong></td>
<td><strong>1.12 (1.01–1.24)</strong></td>
<td><strong>0.091</strong></td>
<td><strong>0.62</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dissimilarity</strong></td>
<td><strong>0.96 (0.83–1.12)</strong></td>
<td>0.89 (0.81–0.98)</td>
<td><strong>0.057</strong></td>
<td><strong>0.35</strong></td>
<td><strong>0.95 (0.77–1.17)</strong></td>
<td><strong>0.89 (0.81–0.99)</strong></td>
<td><strong>0.110</strong></td>
<td><strong>0.61</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FD_TH_60</strong></td>
<td>0.85 (0.71–1.02)</td>
<td>0.9 (0.81–1.01)</td>
<td>0.077</td>
<td>0.56</td>
<td>0.9 (0.69–1.15)</td>
<td>0.348</td>
<td>0.85</td>
<td>0.92 (0.81–1.04)</td>
<td>0.348</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>FD_TH_85</strong></td>
<td>0.92 (0.79–1.06)</td>
<td>0.91 (0.83–1)</td>
<td>0.130</td>
<td>0.98</td>
<td>0.89 (0.72–1.09)</td>
<td>0.173</td>
<td>0.77</td>
<td>0.91 (0.82–1.01)</td>
<td>0.173</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>FD_TH_15</strong></td>
<td>1.2 (1.04–1.39)</td>
<td>1.06 (0.97–1.16)</td>
<td>0.034</td>
<td>0.09</td>
<td>0.96 (0.78–1.18)</td>
<td>0.572</td>
<td>0.43</td>
<td>1.05 (0.95–1.16)</td>
<td>0.572</td>
<td>0.43</td>
</tr>
</tbody>
</table>
Lattice-based Parenchymal Texture Analysis

Spatial Lattice Windows

Fractal dimension

Entropy

Histogram 95th mean

Run-length Emphasis

Limitations

Film versus digital mammography

Non standardized way for feature extraction:
- breast sampling
- feature parameterization

Effects of image acquisition settings
- vendor
- image format
- kVp, mAs, etc.

Lack of anatomical correspondences
Are there differences between image-derived measures from raw and processed digital mammograms?
Automated Quantitative Measurements

2 Density Measures (LIBRA)

\[ DA = A_{\text{dense tissue}} \]

\[ PD = \frac{A_{\text{dense tissue}}}{A_{\text{breast}}} \]

29 Texture Features (histogram, co-occurrence, run-length, structural)

Gastounioti et al. Medical Physics 2016
Study Population

8,458 Pairs of MLO-view Raw and Processed Digital Mammograms
GE Senographe Essential/Hologic Selenia Dimensions

 Entire 1 Yr screening cohort
(Sept. 2010 - Aug. 2011)
No history of breast cancer

10,739 women

MLO images available
in both formats

4,389 women

4,278 women

Unilateral or Bilateral
breast images available

Exclude image artifacts

MLO: medio-lateral oblique

Feature measurements are significantly different, yet strongly or moderately correlated, between raw and processed images.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Vendor 1 (N = 2903 image pairs)</th>
<th>Vendor 2 (N = 5555 image pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LME model (Intercept) b (CI)</td>
<td>LME model (Intercept) b (CI)</td>
</tr>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>Density</td>
<td>Density</td>
<td>Density</td>
</tr>
<tr>
<td>DA</td>
<td>(13.84) 0.70 [*] [0.67 0.74]</td>
<td>(12.48) 0.41 [*] [0.38 0.43]</td>
</tr>
<tr>
<td>PD</td>
<td>(10.71) 0.63 [*] [0.60 0.66]</td>
<td>(3.96) 0.67 [*] [0.64 0.69]</td>
</tr>
<tr>
<td>Texture</td>
<td>Textures</td>
<td>Textures</td>
</tr>
<tr>
<td>T1</td>
<td>(0.30) 0.86 [*] [0.85 0.88]</td>
<td>(0.12) 0.89 [*] [0.87 0.91]</td>
</tr>
<tr>
<td>T2</td>
<td>(0.67) 0.87 [*] [0.85 0.88]</td>
<td>(1.20) 0.74 [*] [0.72 0.75]</td>
</tr>
<tr>
<td>T3</td>
<td>(−1.601.11) 0.74 [*] [0.62 0.86]</td>
<td>(7.749.71) 2.43 [*] [2.27 2.60]</td>
</tr>
<tr>
<td>T4</td>
<td>(0.00) 0.60 [*] [0.58 0.62]</td>
<td>(0.00) 0.05 [*] [0.04 0.05]</td>
</tr>
<tr>
<td>T5</td>
<td>(0.00) 0.59 [*] [0.55 0.63]</td>
<td>(0.00) 0.09 [*] [0.08 0.10]</td>
</tr>
<tr>
<td>T6</td>
<td>(−4.02) 0.53 [*] [0.51 0.55]</td>
<td>(9.92) (−0.01 [*] [−0.02 0.00]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T22</td>
<td>(29.22) 0.68 [*] [0.65 0.71]</td>
<td>(41.52) 0.24 [*] [0.23 0.26]</td>
</tr>
<tr>
<td>T23</td>
<td>(164.73) 1.07 [*] [1.04 1.10]</td>
<td>(1.248.74) 0.48 [*] [0.46 0.51]</td>
</tr>
<tr>
<td>T24</td>
<td>(0.80) 0.20 [*] [0.19 0.22]</td>
<td>(1.04) (−0.04 [*] [−0.08 0.00]</td>
</tr>
<tr>
<td>T25</td>
<td>(0.00) 0.17 [*] [0.15 0.18]</td>
<td>(0.00) 0.22 [*] [0.18 0.25]</td>
</tr>
</tbody>
</table>
Differences depend on the feature, the vendor, and image acquisition settings.

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<tr>
<th>Feature</th>
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<tr>
<td></td>
<td>LME model</td>
<td>LME model</td>
</tr>
<tr>
<td>Density</td>
<td>(Intercept) $b$ (CI) $R^2$ $r$</td>
<td>(Intercept) $b$ (CI) $R^2$ $r$</td>
</tr>
<tr>
<td>DA</td>
<td>(13.84) 0.70* [0.67 0.74] 0.68</td>
<td>(12.48) 0.41* [0.38 0.43] 0.50</td>
</tr>
<tr>
<td>PD</td>
<td>(10.71) 0.63* [0.60 0.66] 0.83</td>
<td>(3.96) 0.67* [0.64 0.69] 0.68</td>
</tr>
<tr>
<td>Texture</td>
<td>T1 (0.30) 0.86* [0.85 0.88] 0.87</td>
<td>(0.12) 0.89* [0.87 0.91] 0.56</td>
</tr>
<tr>
<td></td>
<td>T2 (0.67) 0.87* [0.85 0.88] 0.75</td>
<td>(1.20) 0.74* [0.72 0.75] 0.51</td>
</tr>
<tr>
<td></td>
<td>T3 (1.601) 0.74* [0.62 0.86] 0.08</td>
<td>(7.749) 2.43* [2.27 2.60] 0.17</td>
</tr>
<tr>
<td></td>
<td>T4 (0.00) 0.60* [0.58 0.62] 0.65</td>
<td>(0.00) 0.05* [0.04 0.05] 0.30</td>
</tr>
<tr>
<td></td>
<td>T5 (0.00) 0.59* [0.55 0.63] 0.34</td>
<td>(0.00) 0.09* [0.08 0.10] 0.07</td>
</tr>
<tr>
<td></td>
<td>T6 (4.02) 0.53* [0.51 0.55] 0.56</td>
<td>(9.92) −0.01* [−0.02 0.00] 0.01</td>
</tr>
<tr>
<td></td>
<td>T7 (1.183) 0.35* [0.34 0.37] 0.64</td>
<td>(13 080) 1.64* [1.56 1.71] 0.42</td>
</tr>
<tr>
<td></td>
<td>T8 (28.68) 0.68* [0.66 0.69] 0.79</td>
<td>(251.56) 1.27* [1.20 1.34] 0.29</td>
</tr>
<tr>
<td></td>
<td>T9 (0.08) 0.57* [0.54 0.59] 0.56</td>
<td>(0.06) 0.14* [0.13 0.16] 0.22</td>
</tr>
<tr>
<td></td>
<td>T22 (29.22) 0.68* [0.65 0.71] 0.48</td>
<td>(41.52) 0.24* [0.23 0.26] 0.36</td>
</tr>
<tr>
<td></td>
<td>T23 (164.73) 1.07* [1.04 1.10] 0.73</td>
<td>(1.248) 0.48* [0.46 0.51] 0.31</td>
</tr>
<tr>
<td></td>
<td>T24 (0.80) 0.20* [0.19 0.22] 0.37</td>
<td>(1.04) −0.04* [−0.08 0.00] 0.00</td>
</tr>
<tr>
<td></td>
<td>T25 (0.00) 0.17* [0.15 0.18] 0.23</td>
<td>(0.00) 0.22* [0.18 0.25] 0.01</td>
</tr>
</tbody>
</table>

Differences depend on the feature, the vendor, and image acquisition settings.

Modification of the linear model slope by woman- and system-specific factors.
Differences depend on the feature, the vendor, and image acquisition settings.

Modification of the linear model slope by woman- and system-specific factors
Potential Implications of Such Differences

Feature correlations for raw images

Vendor 1

Feature correlations for processed images

Vendor 2

Gastounioti et al. Medical Physics 2016
Potential Implications of Such Differences

Bilateral feature symmetry for processed images

Bilateral feature symmetry for raw images

Identifying Robust Texture Features

Fractal dimension

Local binary pattern

Histogram skewness

✓ Strongly correlated
✓ Slight modification of the linear model slope by woman- and system-specific factors
Texture Analysis: The value of considering breast anatomy.
Largely Variable Breast Morphology
Is inherent risk uniformly expressed in the breast parenchyma?

CBA: central breast area
UOA: upper-inner area

Breast-anatomy-driven texture analysis

- Dense vs. fatty tissue segmentation
- Breast landmarks and sub-regions
- Anatomically-oriented texture feature extraction
- Anatomical Weight
- Weighted texture feature summarization

Gastounioti et al. SPIE Medical Imaging 2017, RSNA 2016
Anatomically-oriented polar grid
Each region is assigned a different weight

Weighted Texture Signature

Texture Feature Maps
Preliminary Evaluation in a Cancer-case-Control Dataset

Raw (“For Processing”) MLO-view Digital Mammograms of 424 women
GE Healthcare Senographe 2000D / Senographe DS

106 cancer cases
1:3 age & side-matched
Unaffected breasts of women diagnosed with unilateral breast cancer

318 controls
Women with negative screening mammograms and confirmed negative 1-year follow-up

MLO: medio-lateral oblique

Gastounioti et al. SPIE Medical Imaging 2017, RSNA 2016
Comparisons against simpler texture analysis which does not incorporate the notion of breast anatomy*

Regular grid to sample the breast

Equal weights in texture feature summarization


Gastounioti et al. SPIE Medical Imaging 2017, RSNA 2016
Incorporating breast anatomy enhances texture associations with breast cancer.

Breast-anatomy-driven approach  

\[ \text{AUC } = 0.87 \]
\[ 95\% \text{ CI [0.79 0.94]} \]

\[ \text{AUC } = 0.80 \]
\[ 95\% \text{ CI [0.71 0.85]} \]

DeLong’s test \( p = 0.041 \)

17\% of cases correctly reclassified upwards
4\% of controls correctly reclassified downwards
Intrinsic radiomic phenotypes of breast parenchymal complexity and their associations to breast density
Radiomic Analysis: Parenchymal Complexity Measurements

29 Texture Features
(histogram, co-occurrence, run-length, structural)

Work in progress
Phenotype Identification via Unsupervised Clustering

Optimal number of clusters (k):
- Stability (Consensus clustering)
- Statistical significance (SigClust)

Work in progress
Phenotype Identification via Unsupervised Clustering

Test set

Clusters Reproducibility

- Statistical significance (SigClust)

- Min Euclidean Distance

Cluster 1: x centroid
Cluster 2: x centroid
Cluster 3: x centroid
Cluster 4: x centroid

Work in progress
4 Distinct Phenotypes Identified Based on Radiomic Analysis

Training set

4 distinct clusters identified
SigClust, p<0.0001

Work in progress
Associations of Phenotypes with Risk Factors

Work in progress
Intrinsic phenotypes for mammographic parenchymal complexity capture different information than conventional breast density.

$R^2 = 0.24$ for linear association

$$CS = a + b \times PD$$

Work in progress
Intrinsic phenotypes for mammographic parenchymal complexity capture different information than conventional breast density.
Next Generation Technologies:
Deep imaging phenotyping of breast cancer risk
Deep Learning

- Remarkable impact on medical image analysis.
- Recent studies show potential in breast cancer risk prediction.


Geras et al. 2017 (arXiv:1703.07047)
Convolutional Neural Networks (ConvNets)

Layer 1
Convolution
Pooling

Layer 2
Convolution
Pooling

Layer N
Convolution
Pooling

Fully-connected MLP Layer
Classifier

Hidden layers

Classification

…
ConvNets as a Feature Fusion Approach

Step 1: Lattice-based Texture Analysis

Step 2: 3D ConvNet
Preliminary Evaluation in a Cancer-case-Control Dataset

Raw ("For Processing") MLO-view Digital Mammograms of 424 women
GE Healthcare Senographe 2000D / Senographe DS

106 cancer cases

1:3 age & side-matched

318 controls

Unaffected breasts of women diagnosed with unilateral breast cancer

Women with negative screening mammograms and confirmed negative 1-year follow-up

MLO: medio-lateral oblique
Informative interactions between localized motifs exist in mammographic texture feature maps, and can be extracted and summarized via deep learning.

For each woman:

1. Preprocessed Mammogram
2. Logistic Regression
3. Conv. Layer 1
4. Pool. Layer 1
5. Conv. Layer 2
6. Pool. Layer 2
7. Conv. Layer 3
8. Pool. Layer 3
9. Conv. Layer 4
10. Pool. Layer 4
11. Conv. Layer 5
12. Pool. Layer 5
13. MLP 1
14. MLP 2
15. Sigmoid Classifier

AUC_{Hybrid} = 0.90
AUC_{Texture} = 0.79
AUC_{2D ConvNet} = 0.63
The Challenge of Transition to Digital Breast Tomosynthesis
Digital Breast Tomosynthesis (DBT)

- Tube Rotation
- X-rays
- Compression Plate
- Breast
- Detector
- 3D Reconstruction

Courtesy of Dr. Carton
Research & Technical Challenges of DBT

- Optimization of existing pipelines for 2D image analysis
  - DBT slices
  - Synthetic Mammograms
- Extensions to 3D for image volumes
  - Voxel anisotropy
  - Computational cost
- Evaluation of prediction capacity of DBT features
  - Large datasets
  - Involve multiple screening centers
  - Prospectively collected data
- Employing deep learning technologies
  - Supervised/Unsupervised tools
  - Visualization of deep learned features
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Funding
NIH/NCI (R01, U54, R21)
American Cancer Society
Susan G. Komen for the Cure
Basser Research Center
Penn ITMAT, CBICA
Thank You!

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