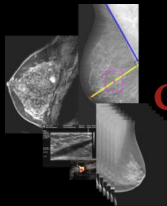


Breast Density and Beyond: *Prediction and Risk Assessment in Breast Imaging*



CBIG
Computational Breast
Imaging Group

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Vice Chair of Faculty Development
Department of Radiology
University of Pennsylvania



Perelman
School of Medicine
UNIVERSITY OF PENNSYLVANIA

Outline

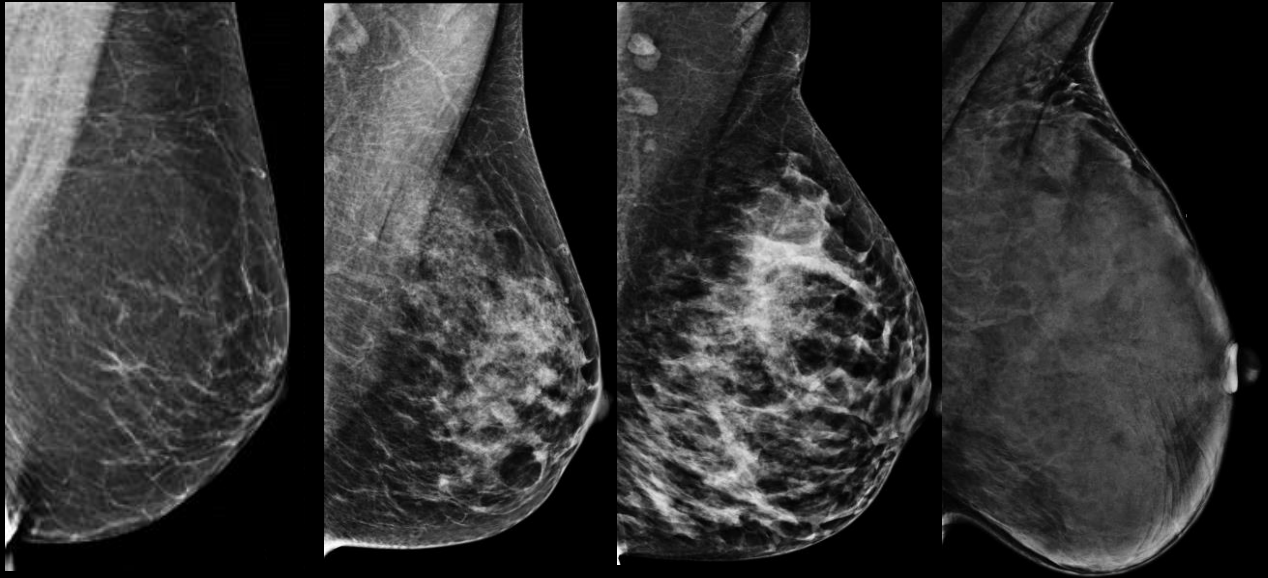
Risk Assessment in Breast Imaging:

–What's all the fuss about Breast Density?

- Implications for screening
- How to measure? Limitations?

–Beyond Breast Density - “*Breast Phenotyping*”

Breast Density: BI-RADS categories



Increasing Density: Increasing Risk of Developing Cancer

Increasing Density: Decreasing Mammography Performance

Dense Breasts May Obscure Mammogram Results

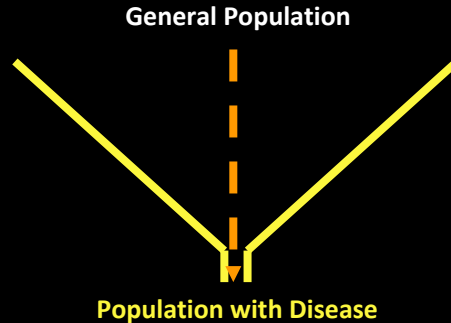
By RONI CARYN RABIN JUNE 16, 2014 4:54 PM 134 Comments



Dense tissue can make a mammogram seem like "looking through a window with snow on it." Damian Dovarganes/Associated Press

- **Breast Density Notification Legislation:**
 - >50% U.S. states, dense breasts consider supplemental screening
 - not risk based, screening modality not specified
- **Now Federal government charged with making uniform statement**

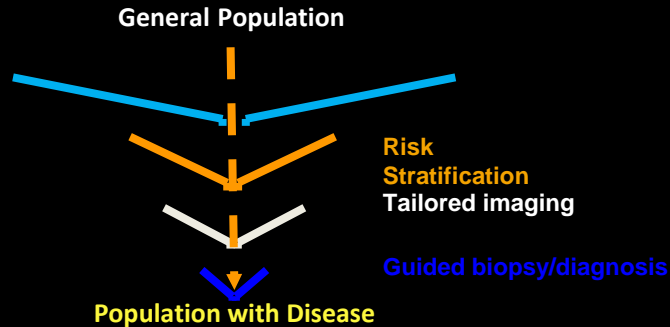
How to Risk Stratify in Breast Imaging?



Two-part Risk:

- The individual risk of developing breast cancer
 - Gail, Claus risk assessment models, BRCA $\frac{1}{2}$, etc.
- The masking risk (false-negative) and risk for a false-positive outcome
 - Unnecessary call-backs, biopsies, or missed cancer

How to Risk Stratify in Breast Imaging?



Two-part Risk:

- The individual risk of developing breast cancer
 - Gail, Claus risk assessment models, BRCA $\frac{1}{2}$, etc.
- The masking risk (false-negative) and risk for a false-positive outcome
 - Unnecessary call-backs, biopsies, or missed cancer

Imaging Phenotypes

How can we use imaging data to help guide personalized screening?

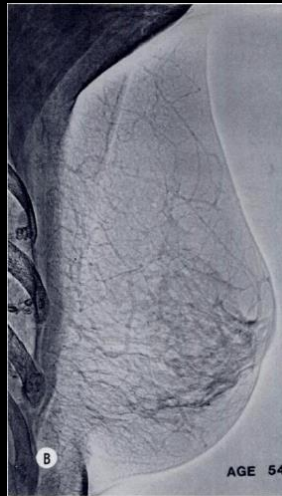
What's all the fuss about "breast density"???

Imaging in Risk Assessment

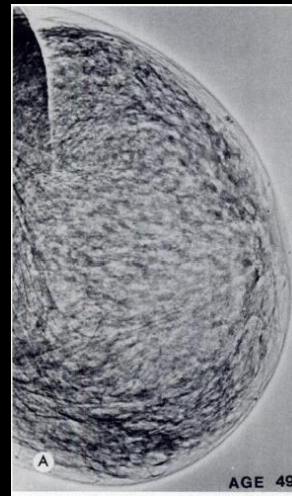


N1

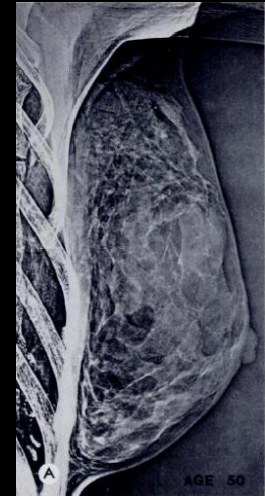
Lowest risk



P1



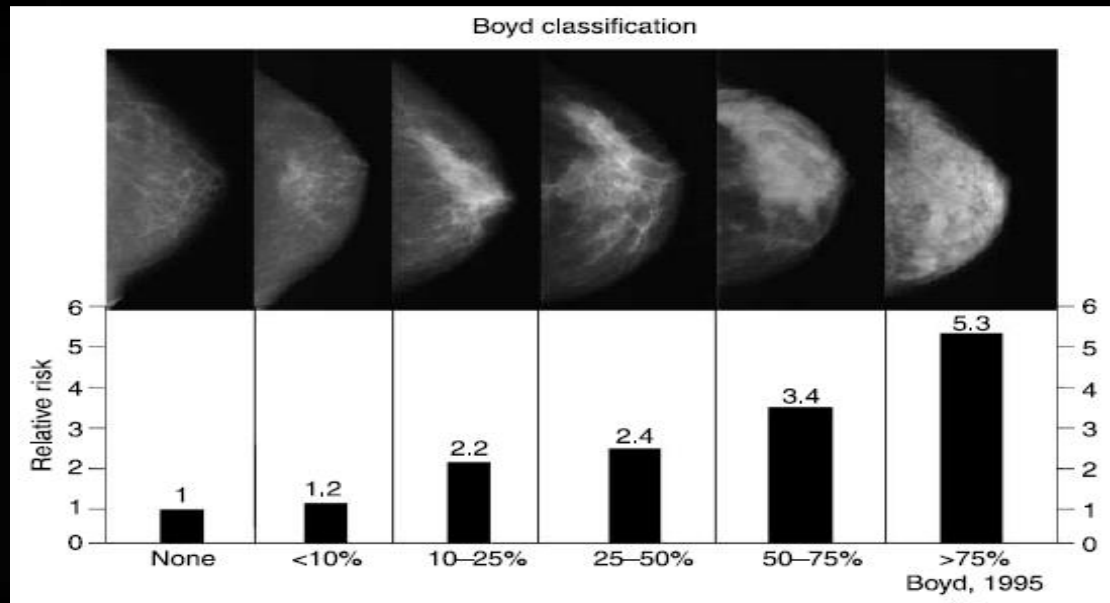
P2



DY

Highest risk

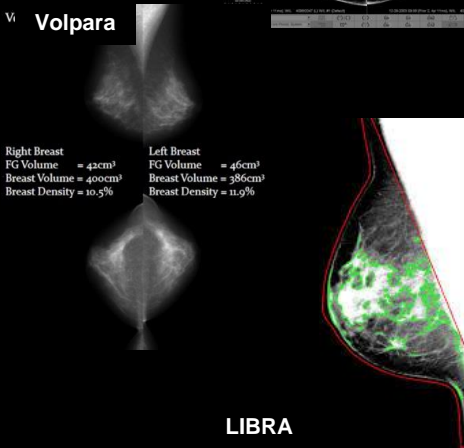
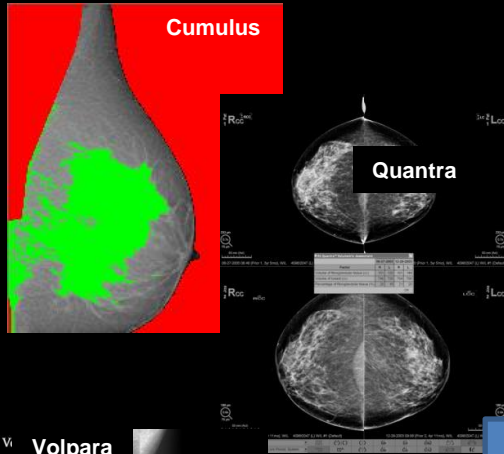
Wolfe's Parenchymal Classifications



Women with >50% dense breasts are at a 3- to 5X greater risk for breast cancer than when lowest density ²

- Partially due to lower sensitivity with increased density (masking)
- Partially due to Biology - dense tissue is rich in epithelium/stroma

Breast Density & Risk



Established, independent risk factor

McCormack et al. *Cancer Epidemiol Biomarkers Prev.* 2006

Eng et al. *Breast Cancer Res.* 2014

Sherratt et al. *Breast Cancer Res.* 2016

Improves risk assessment models

Brentnall et al. *Breast Cancer Res.* 2015

Tice et al. *Ann Intern Med.* 2008

Has shared genetic basis with breast cancer susceptibility

Stone et al. *Cancer Res.* 2015

Lindström et al. *Nat Commun.* 2014

Predicts both inherent risk and masking risk

Krishnan et al. *Breast Cancer Res.* 2016

Strand et al. *Int J Cancer* 2017

Associated with tumor profile

Bertrand et al. *Cancer Epidemiol Biomarkers Prev.* 2015

Biology and Breast Density

- Breast cancers tend to arise in dense tissue¹...
- Breast density and cancers have shared genetic²
 - SNP and BRCA data
- Some risk factors mediated thru breast density^{3,4}
 - Aromatase/Estrogen levels, chemoprevention

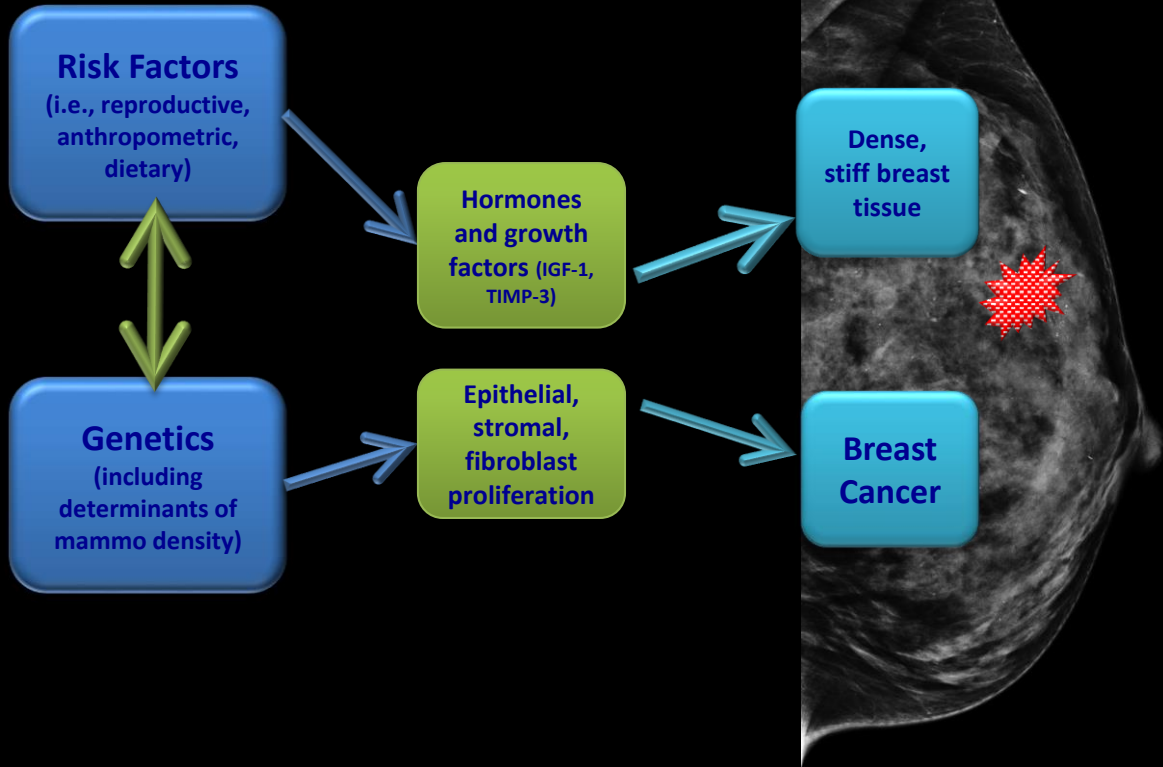
¹Pereira SM et al. SM CEBP 2011 1718-25

²Varghese JA et al. Cancer Res 2012;72; 1478-84

³Cuzick J et al. JNCI 2011;103;744-52.

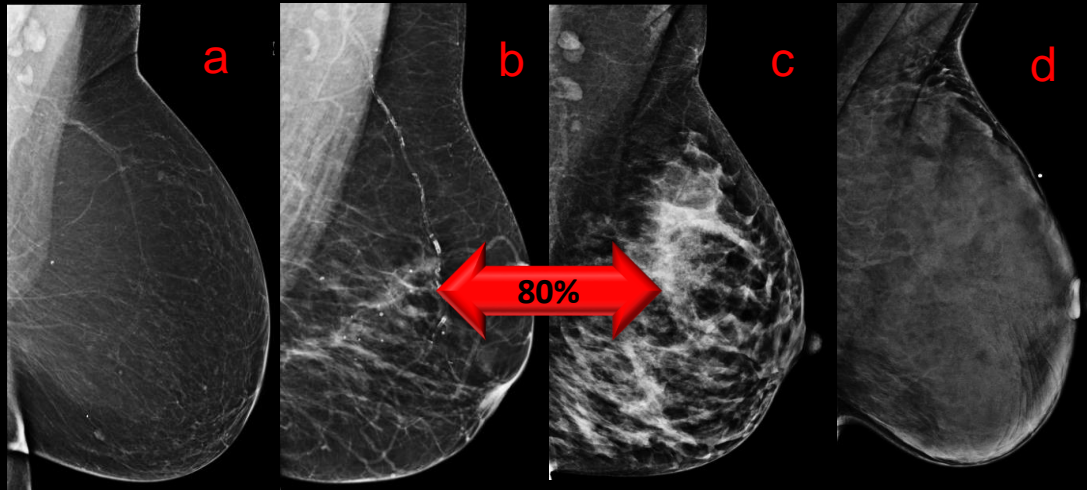
⁴Greendale GA et al. JNCI 20013;95;30-37.

Biological Hypothesis:



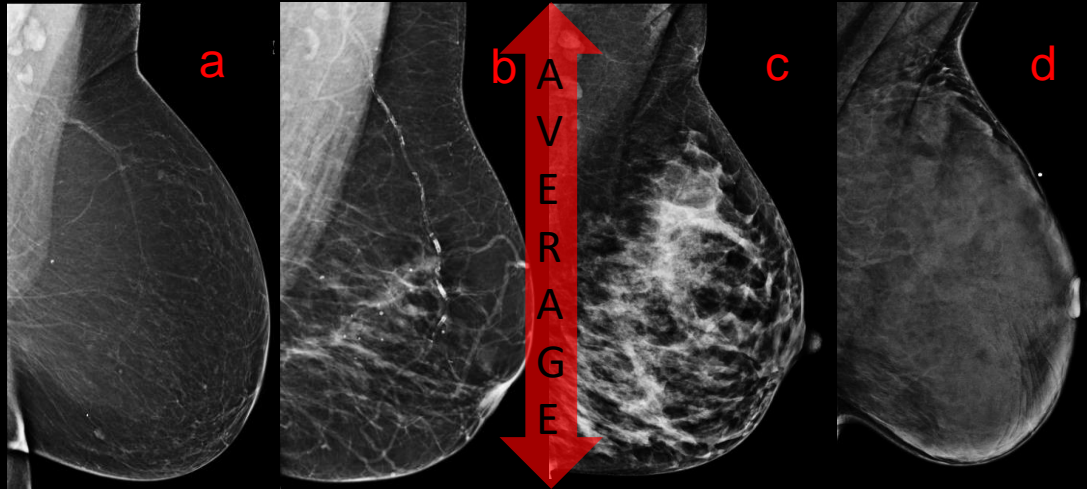
How do we measure
“Breast Density”?

First: How to Measure Breast Density?



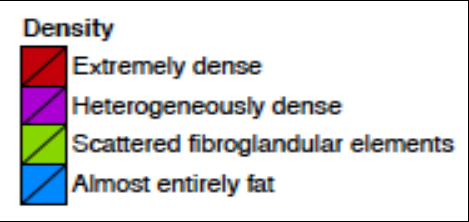
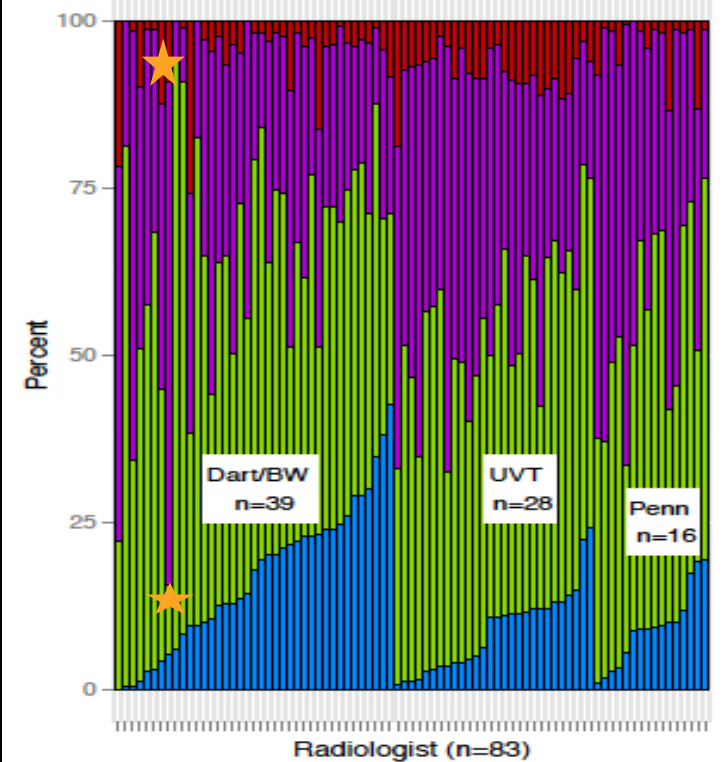
- **BI-RADS: Inter and intra-reader variability**
 - Between readers only $K=0.56$
- **Relative risk (RR) for density d vs a ~ 3-5x**
 - 80% of screened women are density b or c

First: How to Measure Breast Density?



- RR for density c vs b = <1.5
 - Average density at screen is between b-c
- RR for density c vs “average” ~ 1.2
- RR for density d vs “average” ~ 2.1

What about Inter-reader variability with BI-RADS?



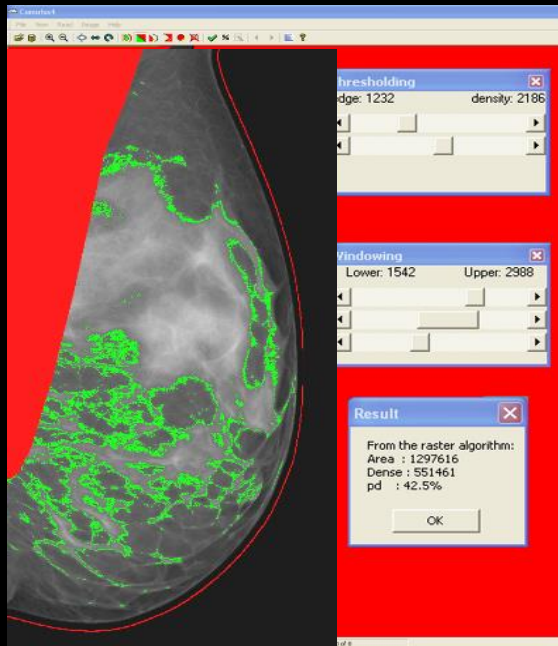
BI-RADS Breast Density

BI-RADS 4 th Edition	BI-RADS 5 th Edition
1 - Almost Entirely Fatty (<25%)	a – The breasts are almost entirely fatty
2 - Scattered Fibroglandular (25-50%)	b- There are scattered areas of fibroglandular density
3 - Heterogeneously Dense (51-<75%)	c – The breasts are heterogeneously dense, which may obscure small masses
4 - Extremely Dense (>75%)	d – The breasts are extremely dense, which lowers the sensitivity of mammography

Issues to Consider:

- *New categories without % - category now based on “densest area”*
- *What are “small masses”???*

Semi-automated Measure of Area Percent Density (PD)

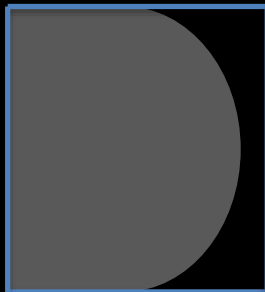
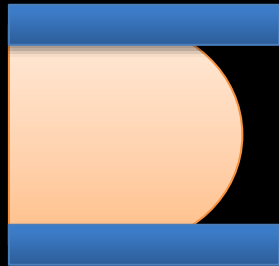


Cumulus (Univ. Toronto)

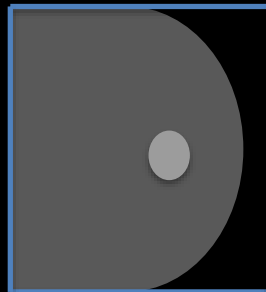
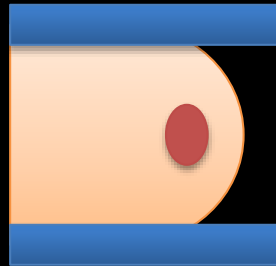
$$PD = \frac{\sum_{i=i_{DY}}^{i_{MAX}} h_i}{A} \times 100\%$$

Issues with Area-based Measurements?

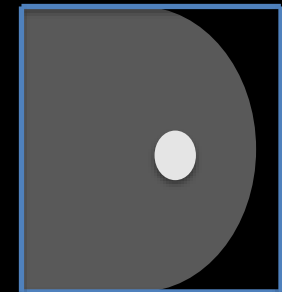
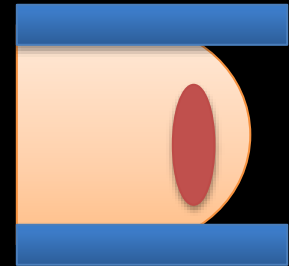
Breast in compression in CC view:



Area PD= 0%
Volume PD=0%



Area PD=5%
Volume PD=5%



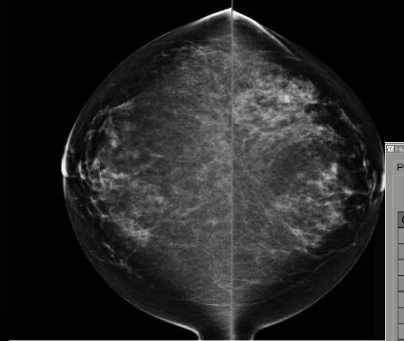
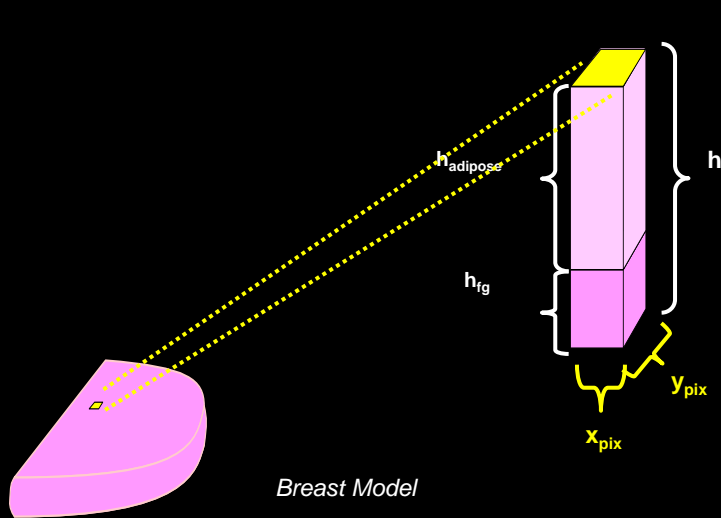
Area PD=5%
Volume PD=13%

Limitations in using Mammography to measure Percent Density

- Most methods based on a dichotomous threshold
 - “Dense or not dense” (*not many shades of grey!*)
- Different image acquisition effect results
- Most methods don’t consider breast thickness
- Significant inter and intra-reader variability!!!!!!

*How should we measure
Breast Density???*

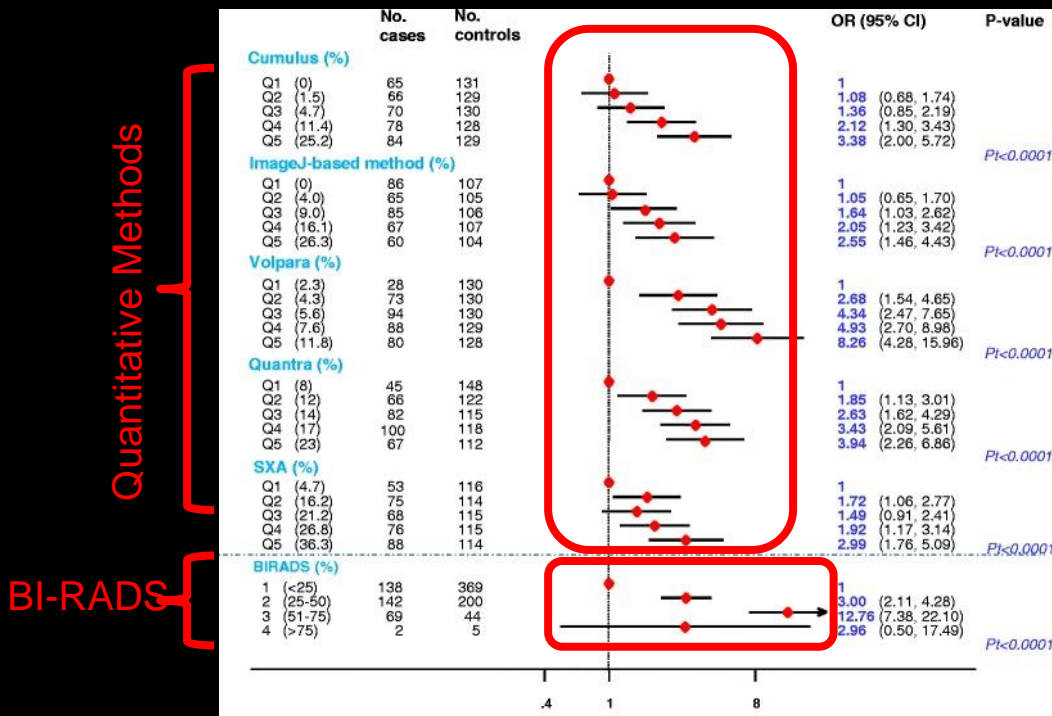
Automated Volumetric Analysis



1. Breast volume (cc)
2. Dense-tissue volume (cc)
3. Volumetric Percent Density (VPD%)

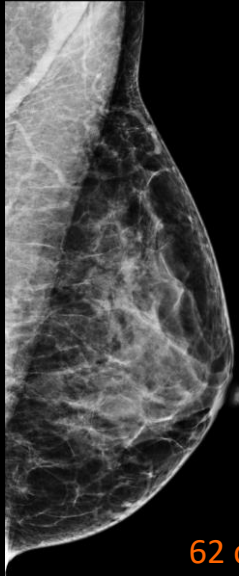
Per Subject	Per Breast	Per Image
2009-06-26		
	R	L
Quantra		
Vfg (cm3)	202	191
Vb (cm3)	671	686
Vbd (%)	30	27
Abd (%)	60	46
Vbd-score	1.62569	1.43653
Vfg-score	1.244335	1.203905
Q_abd	4	4
ri_abd	3.74234	3.68197

Risk Prediction varies by method used...

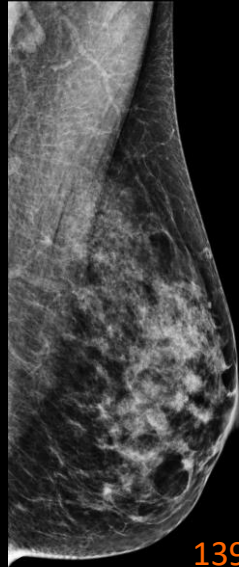


Is it Percent (%) or Absolute Volume?

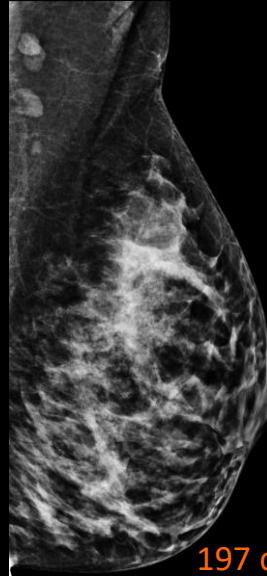
Four women with ~ 25% fibro-glandular VOLUME (FGV)



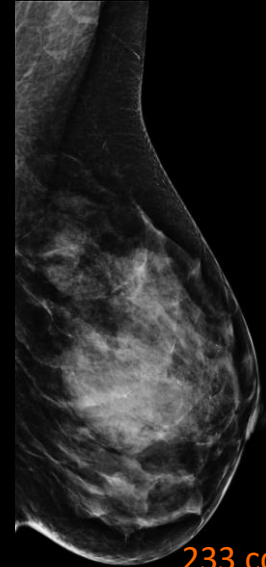
62 cc



139 cc



197 cc

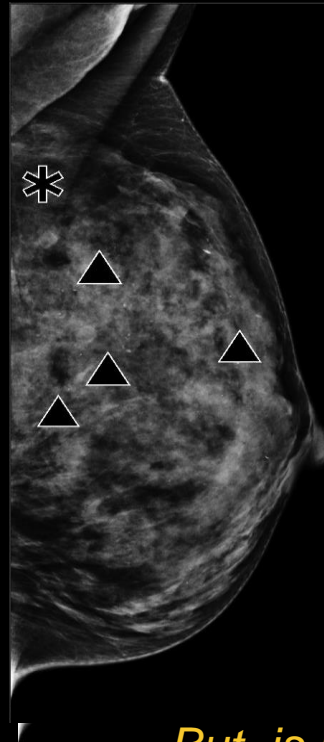
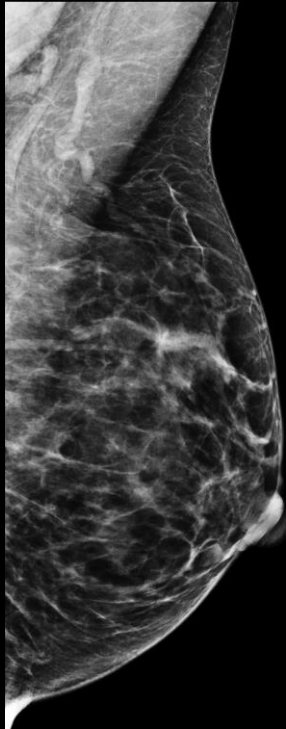


233 cc

Which is a more accurate predictor of "risk"?

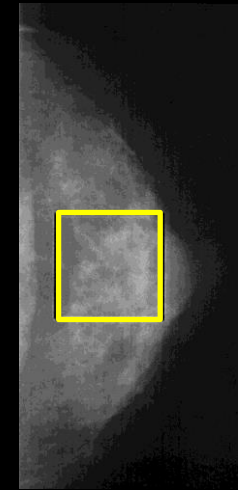
What about other imaging Biomarkers?

Breast “Complexity” confounds diagnosis...

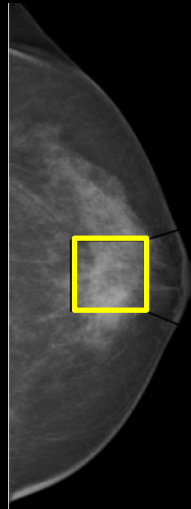
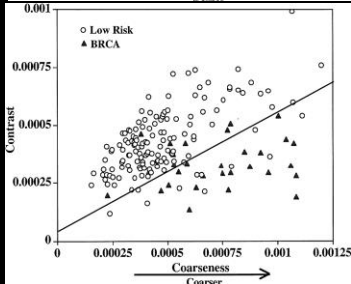
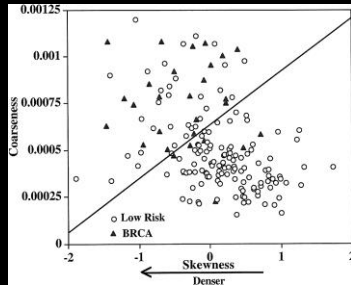


But, is it related to risk?

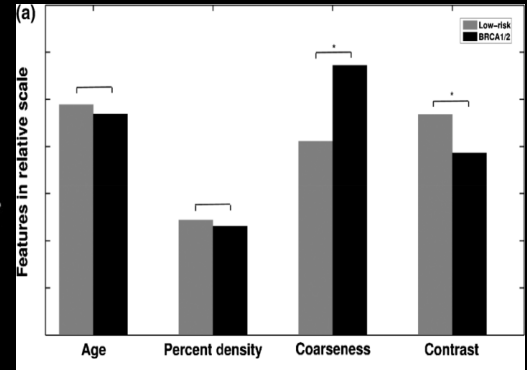
Parenchymal Texture Indicative of Genetic Risk Markers (BRCA1/2)



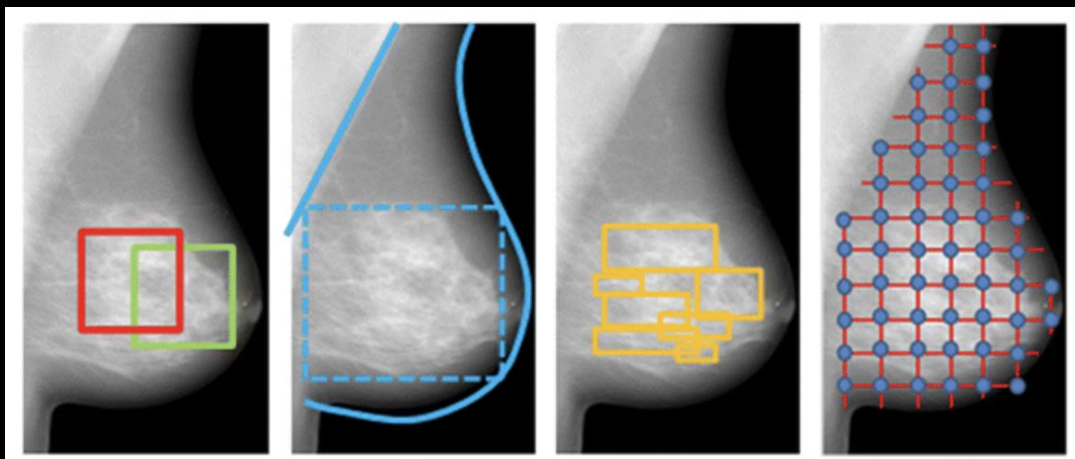
Digitized film mammograms



Digital mammograms



Texture Analysis with Varying Regions of Interest

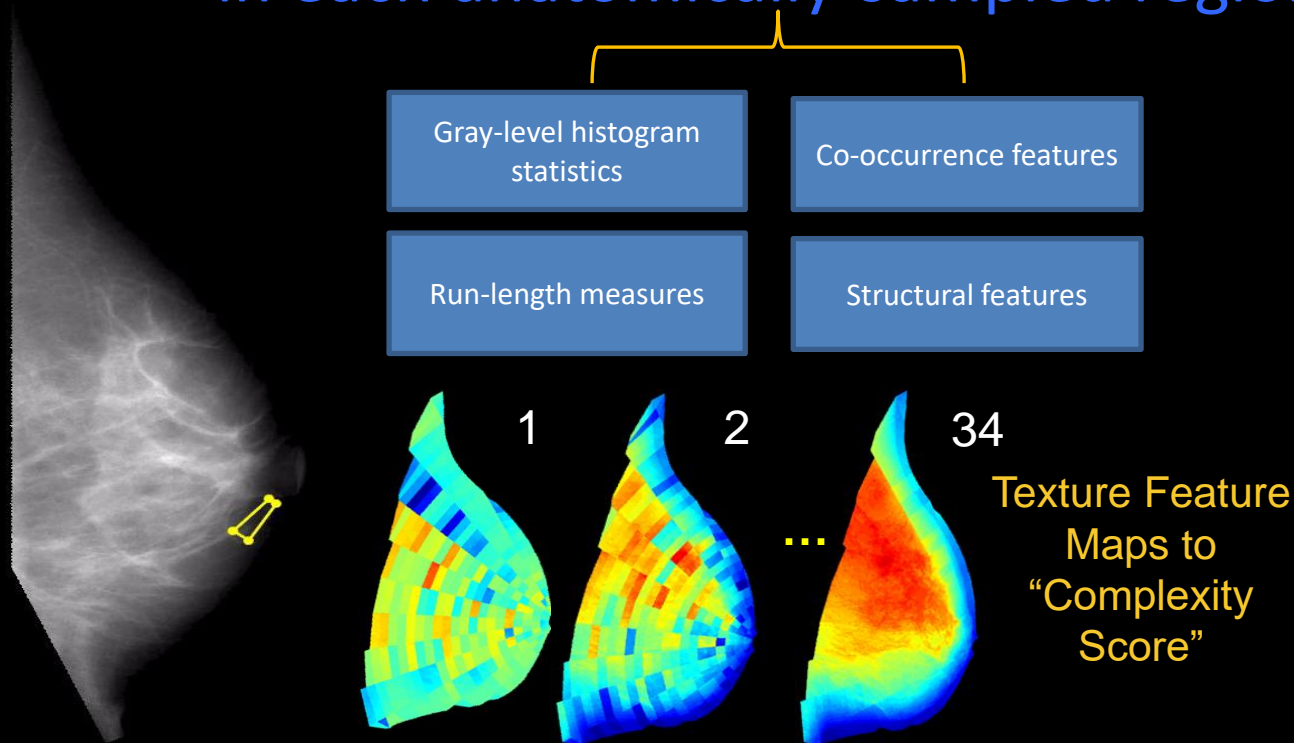


- **Increasing sampling variation increases discrimination**
 - Using gray-scale intensity features
 - Co-occurrence descriptors
 - Run-length features
 - Structural/pattern measures
 - Spectral features

Next Generation Technologies:

Deep Imaging Phenotyping of
Breast Cancer Risk

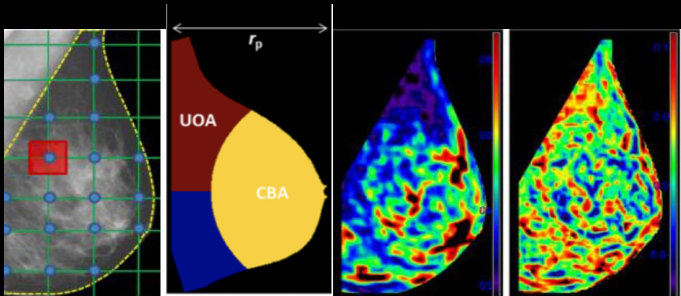
Texture descriptors extracted in each anatomically-sampled region



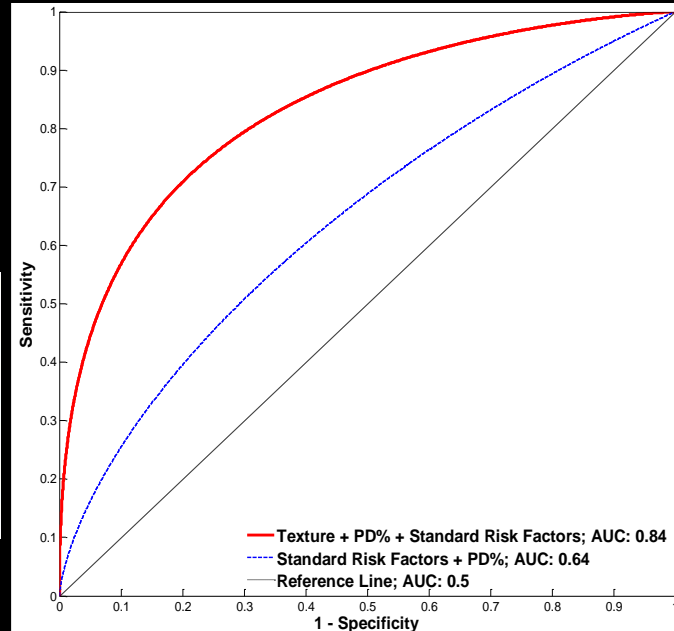
Density and Texture: Complementary Risk Factors

- **Case-control Study:**
 - 424 Women (106 cancers)
 - Age-matched 1:3; 5yr intervals

- **Risk Factors:**
 - Demographics, Breast Density (PD%)
 - Multi-Parametric Texture Features



- **All independently predictive of cancer in a combined model:**
 - Significantly better together than alone (Delong's test: $p < 0.05$).



Phenotypes of parenchymal complexity capture different information than conventional breast density



CS = 0.72
PD = 14.3%

CS = -0.68
PD = 7.9%

Non-Dense



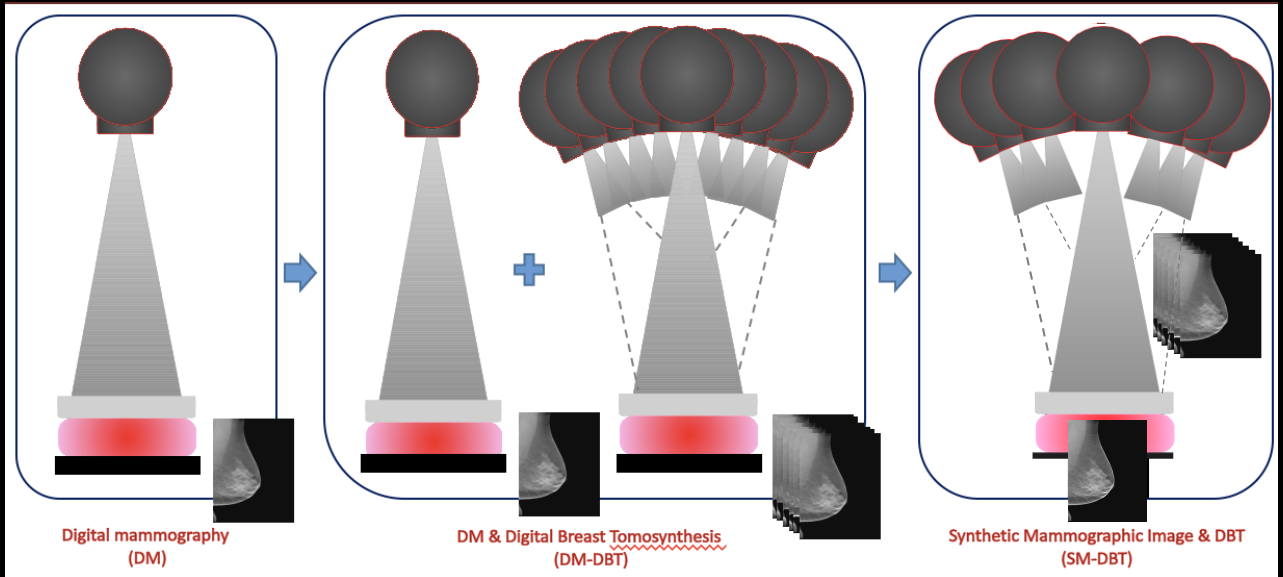
CS = 0.64
PD = 41.7%

CS = -0.65
PD = 42.5%

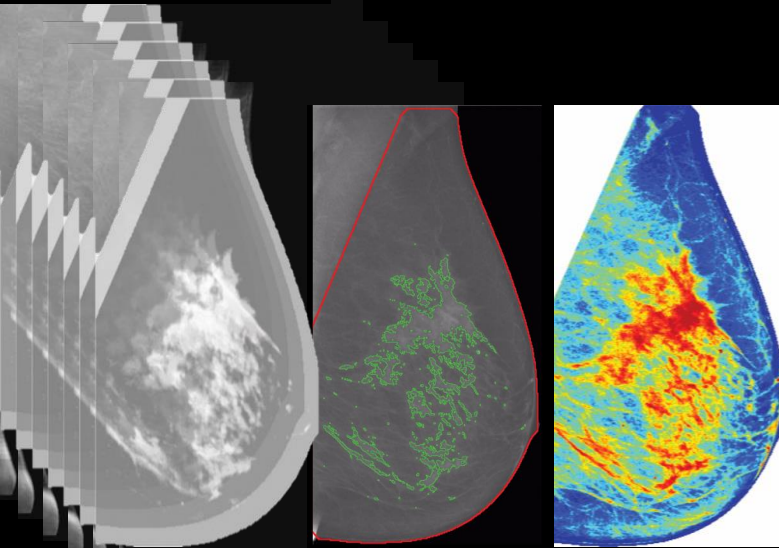
Dense

What about Digital Breast
Tomosynthesis?

Evolution of mammographic screening



Research & Technical Challenges of DBT



3D image volume

Synthetic 2D
mammogram

Automated ML
texture & density

Optimization of existing 2D pipelines:

- DBT slices
- Synthetic Mammograms

Extensions to 3D for image volumes

- Voxel anisotropy
- Computational cost

Evaluate prediction capacity DBT features

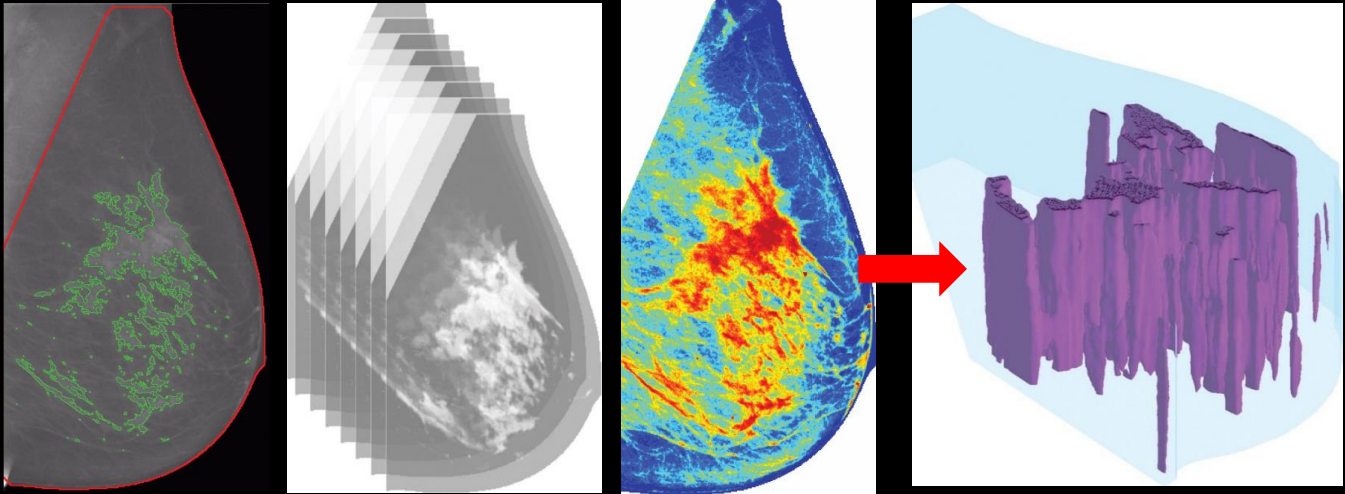
- Large, multi site/vendor prospective datasets

Employ deep learning (DL) technologies

- Supervised/Unsupervised tools
- Visualization of DL features

Transition to Tomosynthesis:

Fully-automated breast density estimation using machine learning



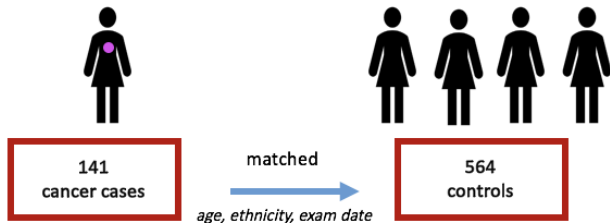
Volumetric Breast density assessment
from Digital Breast Tomosynthesis

Absolute dense volume (DV)
Volumetric percent density (VPD)

Transition to Tomosynthesis: Fully-automated breast density estimation using machine learning

Women with unilateral breast cancer
(screening studies at dx)

Women with confirmed negative
>1-year follow-up



Screened with DM-DBT at the Hospital of UPenn (Jul. 2012 – Dec. 2014)
Bilateral image acquisition (Selenia Dimensions, Hologic Inc.)

- Volumetric breast density can result in larger case-control discriminatory capacity than area-based density measures.
- Associations with breast cancer can potentially further improve when volumetric density evaluation is performed with the DBT reconstructed breast volume compared to physics-based models applied to DM.

			OR [95% CI]	AUC [95% CI]
Volumetric density measures				
<i>Quantra</i>	DV	Raw DM	1.87 [1.36, 2.56]	0.61 [0.56, 0.66]
	VPD	Raw DM	1.78 [1.23, 2.57]	0.59 [0.54, 0.65]
<i>LIBRA</i>	DV	DBT	2.40 [1.61, 3.56]	0.63 [0.58, 0.68]
	VPD	DBT	1.55 [1.08, 2.23]	0.59 [0.54, 0.65]
Area-based density measures				
<i>Quantra</i>	APD	Raw DM	1.32 [1.13, 1.56]	0.58 [0.55, 0.65]
<i>LIBRA</i>	DA	Raw DM	1.91 [1.31, 2.79]	0.59 [0.55, 0.65]
	APD	Raw DM	1.48 [1.03, 2.11]	0.57 [0.53, 0.63]
	DA	Processed DM	1.53 [1.08, 2.16]	0.57 [0.52, 0.62]
	APD	Processed DM	1.24 [0.91, 1.68]	0.57 [0.52, 0.61]

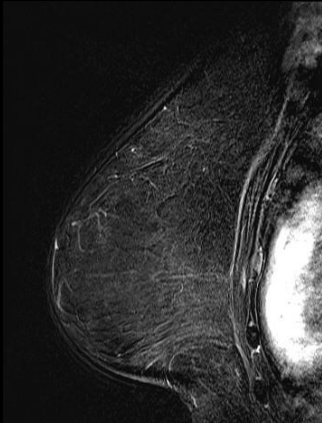
t-test
p < 0.05

Models adjusted for age and BMI.

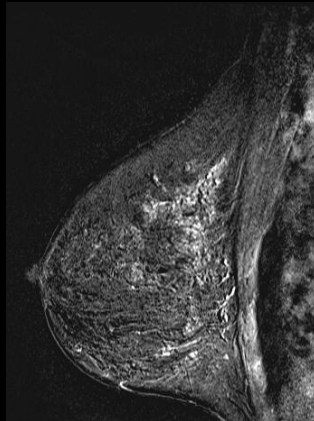
OR: Odds ratio per standard deviation increase in breast density; AUC: Area under the ROC curve.

What about MR Breast
Parenchymal Enhancement in
Risk Predictor?

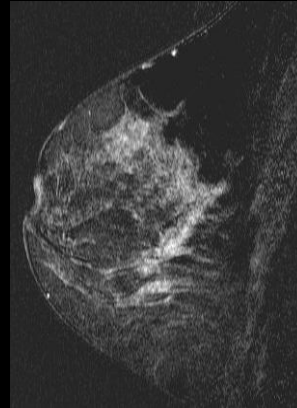
MR Background Parenchymal Enhancement*



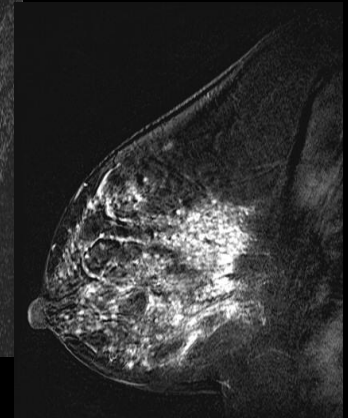
Minimal
< 25%



Mild
25-50%



Moderate
50-75%



Marked
>75%

* generally measured on first MIP post Gd
% of fibroglandular tissue that enhances

What about BPE as Risk Marker?

BPE has been shown to be predictor of risk¹

- **MR allows 3D volumetric measures**
 - Fibroglandular tissue and physiology of glandular enhancement
- **Few studies, most based on BI-RADs categories**
 - Minimal, mild, moderate, marked
 - Reader variability, decreases with training²
 - Variable across magnetic fields (1.5T vs 3T)³

¹King V. Radiology 2011

²Melsaether A et al. AJR 2014

³Giess CS et al. Radiographics 2014

DCE-MRI: Enhancement vs. Risk

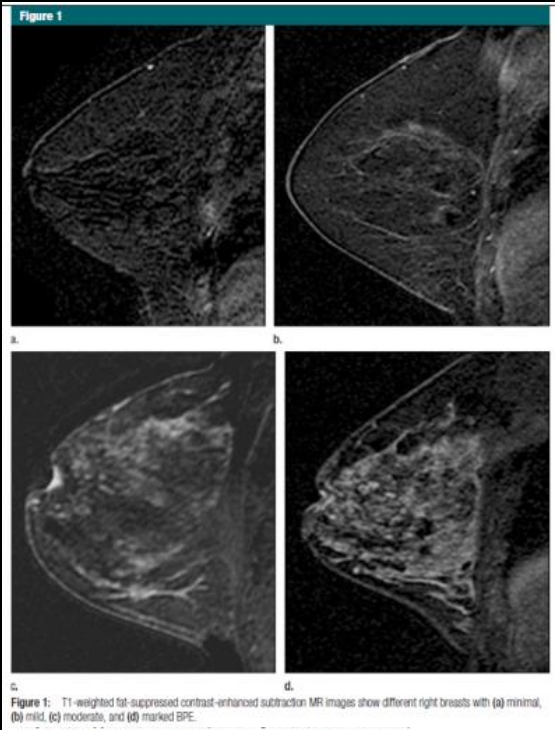


Table 4

ORs of Breast Cancer according to FGT Amount: Breast Cancer Cases vs Normal Controls

FGT Amount	Breast Cancer Cases*	Normal Controls*	OR†	P Value
Test for trend				
Reader 1				
Fatty or scattered	7/39 (18)	26/78 (33)	1.0	.061
Heterogeneously dense	19/39 (49)	35/78 (45)	2.0 (0.7, 6.0)	
Dense	13/39 (33)	17/78 (22)	3.2 (0.9, 11.2)	
Reader 2				
Fatty or scattered	5/39 (13)	29/78 (37)	1.0	.032
Heterogeneously dense	19/39 (49)	26/78 (33)	5.5 (1.4, 20.9)	
Dense	15/39 (38)	23/78 (30)	4.8 (1.2, 18.5)	

FGT

Table 3

ORs of Breast Cancer according to BPE Level: Breast Cancer Cases vs Normal Controls

BPE Level	Breast Cancer Cases*	Normal Controls*	OR†	P Value
Test for trend				
Reader 1				
Minimal or mild	16/39 (41)	63/78 (81)	1.0	<.001
Moderate	15/39 (38)	12/78 (15)	8.2 (2.2, 30.5)	
Marked	8/39 (21)	3/78 (4)	18.2 (2.8, 116.3)	
Reader 2				
Minimal or mild	13/39 (33)	48/78 (62)	1.0	.002
Moderate	16/39 (41)	23/78 (30)	2.9 (1.1, 7.5)	
Marked	10/39 (26)	7/78 (9)	7.5 (1.8, 32.2)	

BPE

DCE-MRI: Effect of Treatment

Table 4

Change in BPE Observed with Anastrozole Treatment

Baseline BPE	All Women		Exclusion of Chemotherapy Users	
	No. of Women	Decrease in BPE	No. of Women	Decrease in BPE
Minimal	17 (15.6)	0 (0)	8 (15)	0 (0)
Mild	64 (58.7)	17 (27)	32 (62)	9 (28)
Moderate	27 (24.8)	19 (70)	12 (23)	10 (83)
Marked	1 (0.9)	1 (100)	0 (0)	...
Total	109	37 (33.9)	52	19 (37)

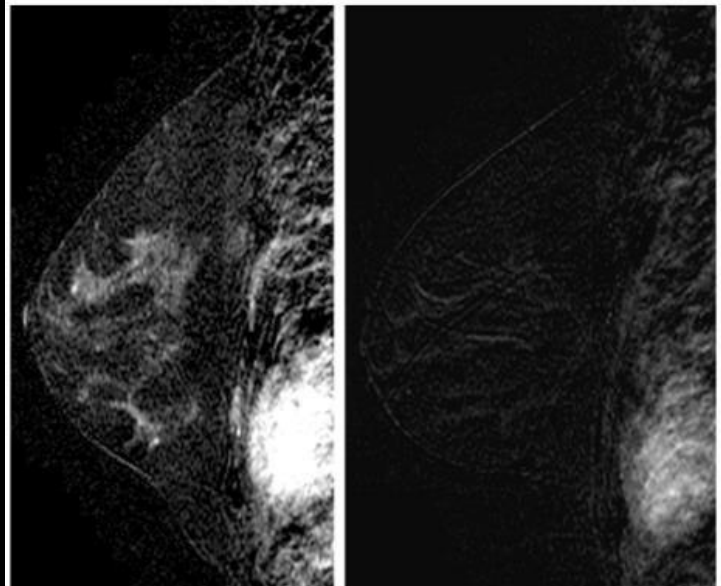
Note.—Data are numbers of women, with percentages in parentheses. *P* is less than .0001 for the number of women (all women and excluding chemotherapy users) with a decrease in BPE during treatment with anastrozole (sign test).

Table 5

Change in FGT Observed with Anastrozole Treatment

Baseline FGT	All Women		Exclusion of Chemotherapy Users	
	No. of Women	Decrease in FGT	No. of Women	Decrease in FGT
Fatty	15 (13.8)	0 (0)	5 (10)	0 (0)
Scattered	44 (40.4)	3 (7)	26 (50)	1 (4)
Heterogeneously dense	35 (32.1)	3 (9)	15 (29)	0 (0)
Dense	15 (13.8)	0 (0)	6 (12)	0 (0)
Total	109	6 (5.5)	52	1 (2)

Note.—Data are numbers of women, with percentages in parentheses. Percentages may not add up to 100% because of rounding. *P* is .031 for the number of women with a decrease in FGT during treatment with anastrozole, including all women, and *P* is greater than .05 with the exclusion of chemotherapy users (sign test).

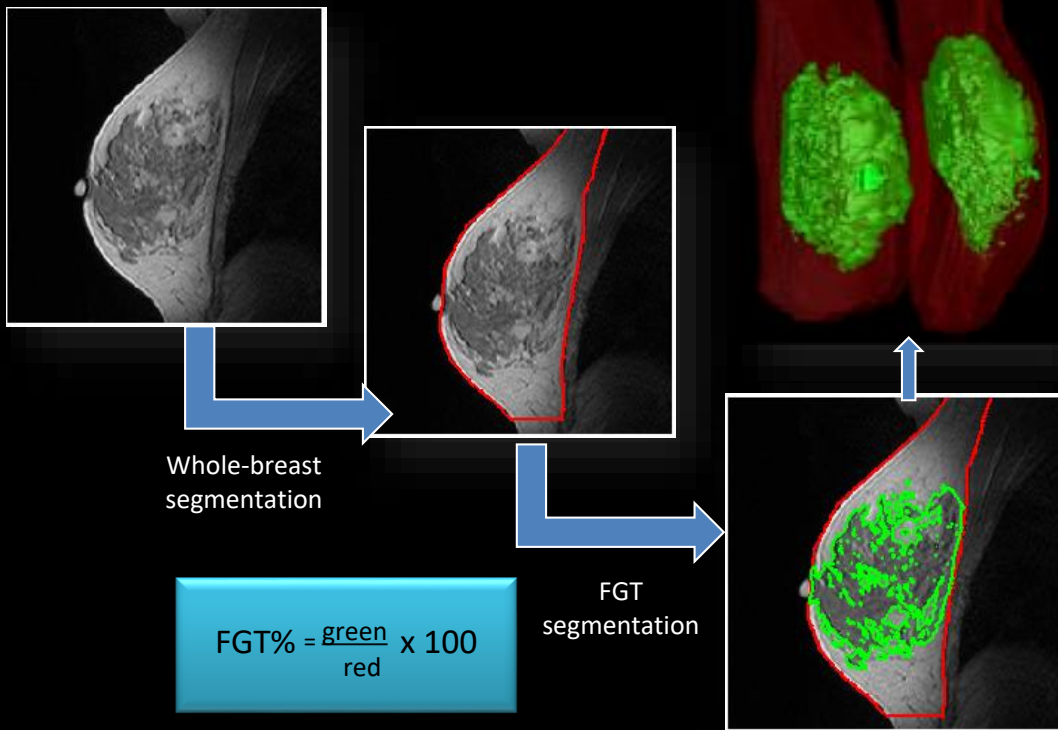


a.

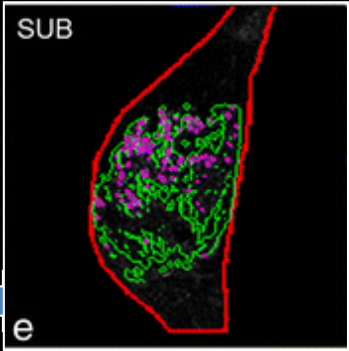
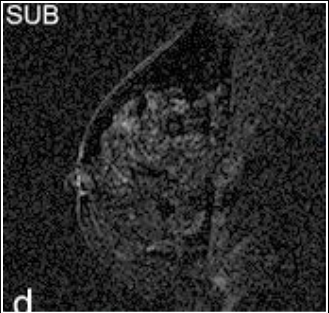
d.

(**a, b**) Sagittal contrast-enhanced T1-weighted fat-suppressed subtraction maximum intensity projection and (**c, d**) original subtraction MR images in 57-year-old woman treated for contralateral invasive lobular carcinoma. (**a, c**) Baseline images before treatment with anastrozole show moderate BPE and (**b, d**) MR images during 8 months of treatment with anastrozole show a decrease to mild BPE.

CE-MRI FGT% Estimation



CE-MRI BPE% Estimation



$$\text{BPE\%} = \frac{\text{pink}}{\text{green}} \times 100$$

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Deep Learning Model to Assess Cancer Risk on the Basis of a Breast MR Image Alone



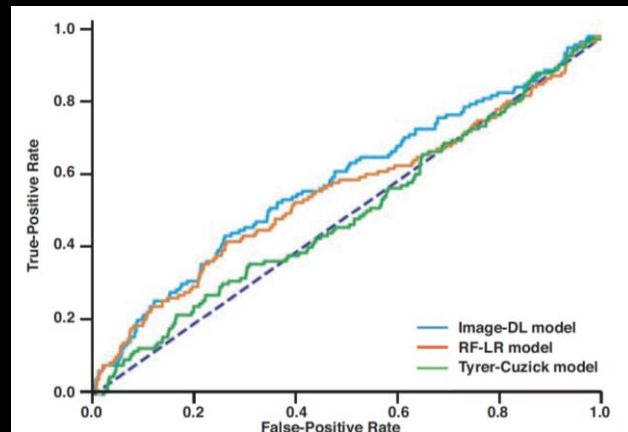
5-yr risk: 1656 MR screens, 1183 HR women

• Compared Image-Deep Learning (DL) to:

- Tyrer Cuzick (TR)
- Logistic Regression (LR) models

• AUC's:

- TK: 0.493
- RF-LR: 0.558
- *Image DL: 0.638*



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Susan Weinstein¹

**Breast MRI Fibroglandular
Volume and Parenchymal
Enhancement in *BRCA1* and *BRCA2*
Mutation Carriers Before and
Immediately After Risk-Reducing
Salpingo-Oophorectomy**



Penn data: 50 BRCA1/2 carriers:

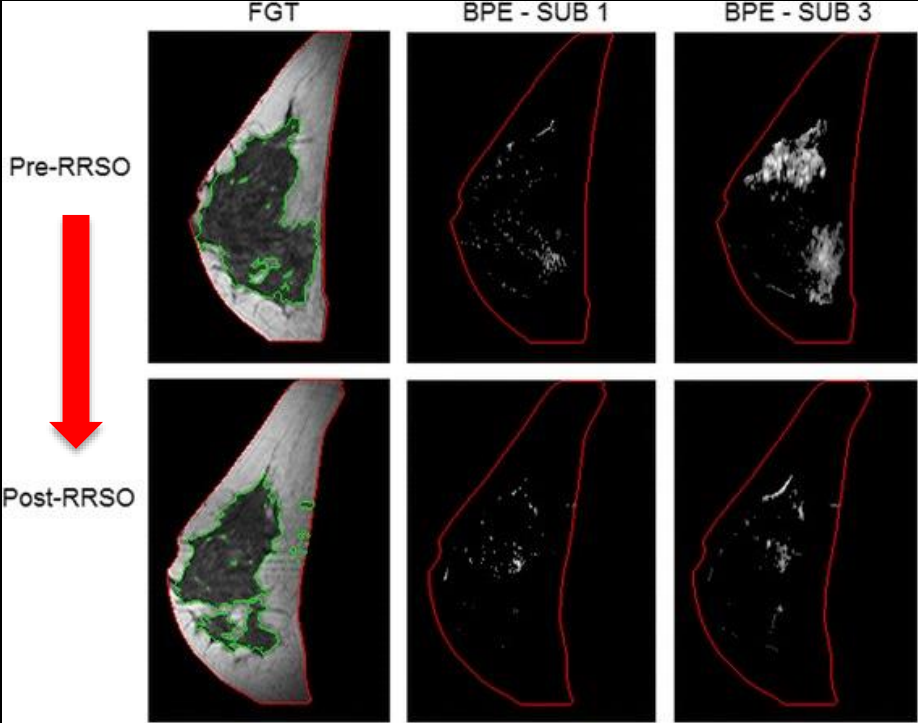
- Absolute, relative measures of BPE/FGT pre and post risk reduction salpingo-oophorectomy (RRSO)
- 44 pts with no cancer – showed signif change in BPE
- 6 pts developed cancer – no change in BPE/FGT

Average BI-RADS scores to calculate mean FGT and BPE before and after RRSO

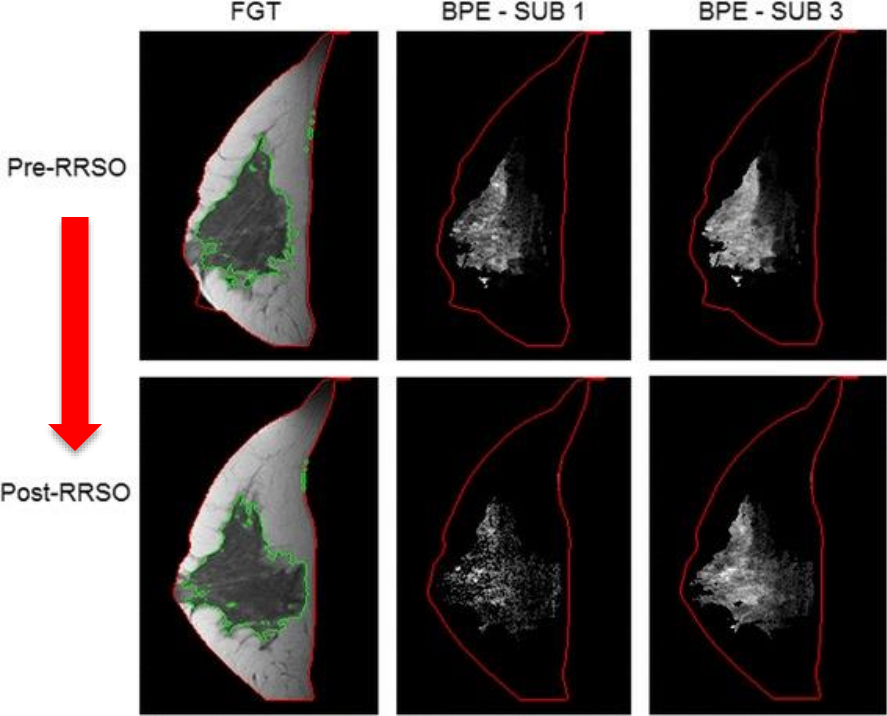
	Pre-RRSO	Post-RRSO ¹	p-value
FGV	2.63±0.78	2.58±0.75	p=0.622
BPE	2.45±0.93	1.87±0.81	p=0.0001 ✓

¹ Mean time to post-RRSO MRI = 8.3 months ± 7 months

Patient without cancer....



Patient that developed cancer...



Breast Parenchymal Enhancement

- ↑BPE more strongly associated with risk than FGT on CE-MRI¹
- ↑BPE associated with increased breast cancer risk in both pre- and post menopausal women¹
- BPE changes associated with effectiveness of risk reduction interventions²

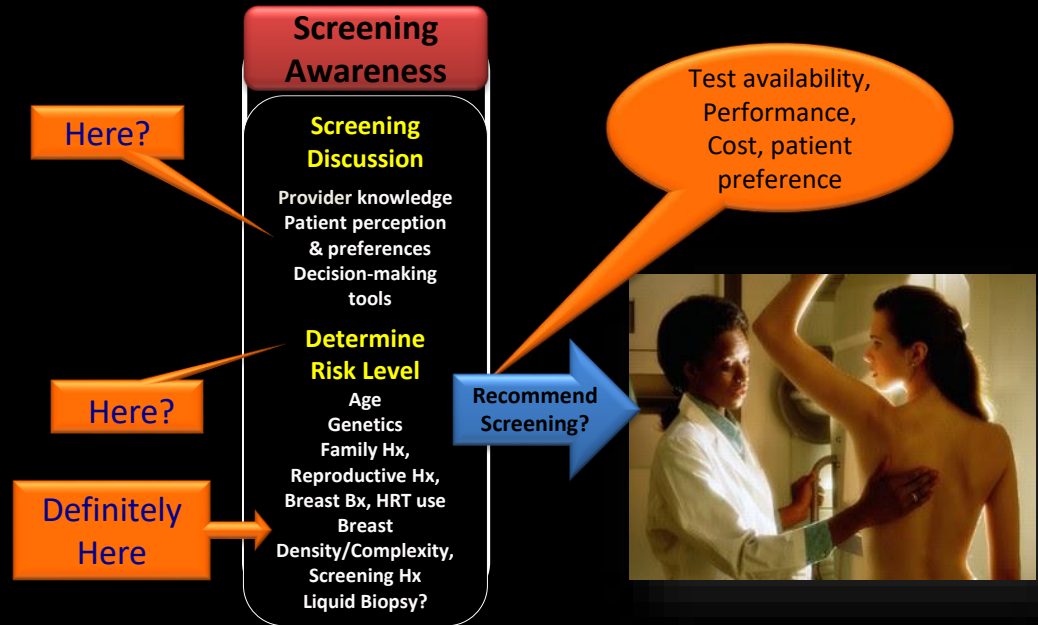
¹King et al. Radiol 2011; 260(1):50-60.

²DeLeo et al. AJR 2015;204(3):699-73.

The Future of Precision Screening:

Optimizing choices to maximize benefit, minimize harm and ensure access

Where does the Radiologist fit in?



Summary

Breast Density, Complexity and CE-MR BPE:

- **When added to risk models, improves risk estimation**
 - Developing breast cancer, risk of false positives, false negatives
- **Have use in guiding personalized screening**
 - Appropriate screening intervals and use of supplemental screening
- **Are predictors of risk reduction strategies**
 - One of the few, modifiable risk factors

Need robust, reproducible measures translated into clinics!!



Thank you!

Cybele, the Goddess of Fertility by Mihail Chemiakin

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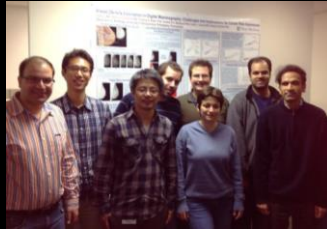
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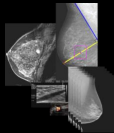
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