CIBC 2019

Chicago International Breast Course
The Westin Chicago River North
November 1-3, 2019

THE UNIVERSITY OF CHICAGO PRITZKER SCHOOL OF MEDICINE | NorthShore University HealthSystem

TOOLS FOR QUANTITATING BREAST DENSITY AND BREAST CANCER RISK

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DISCLOSURES

- GE Healthcare- research funding, consultant
- Hologic- Scientific advisory board
- Densitas- Advisory Board

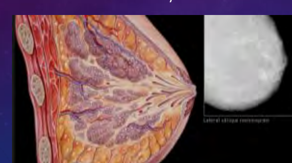
PATIENT ADVOCACY AND BREAST DENSITY NOTIFICATION LEGISLATION

- The late Dr. Nancy Cappello
  - Diagnosed with advanced stage breast cancer in 2004
  - Founded Areyoudense.org
  - Advocacy efforts helped pass the nation's first breast density notification law in 2009 in CT
- 38 states have dense breast notification laws
- Federal legislation in process
- 8 states and DC have supplemental screening reimbursement laws
  - IL, IN, LA, CT, NJ, VT, AR, DC, CO

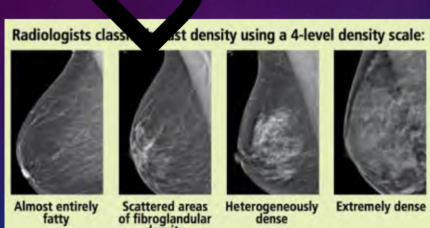
Advocacy and breast density inform legislation emphasize the importance of addressing implication[illegible] breast den[illegible]cer detection

"BREAST DENSITY"

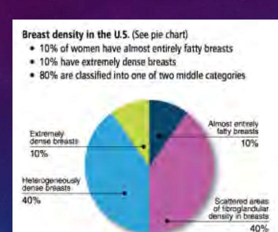
- Describes amount of fibrous, epithelial and glandular tissue in the breast relative to the amount of fatty breast tissue **on mammography**



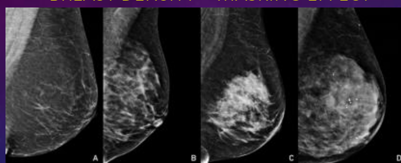
BI-RADS BREAST DENSITY CLASSIFICATION



BREAST DENSITY PREVALENCE



BREAST DENSITY – MASKING EFFECT

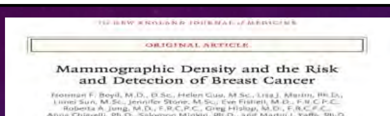


87%	Sensitivity	63%
97%	Specificity	89%

Carney PA. Ann Int Med 2003

"BREAST DENSITY" POSES RISK FOR DEVELOPING BREAST CANCER

- Increases risk of developing breast cancer
- Results in higher interval cancer rates → worse prognosis
  - Higher grade, later stage at diagnosis
- Mechanisms for this are not fully understood
- Density reflects the proportion of epithelial and stromal tissue in the breast compared to non-dense fatty tissue
- Since breast cancers originate in epithelial cells, greater areas of fibroglandular tissue reflect greater number ... of carcinogenesis



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mammographic Density and the Risk and Detection of Breast Cancer

- Women with density of 75% or more had an INCREASED risk of breast cancer
  - Compared to women with density in <10% of mammogram
- Increased risk was greater in younger than in older women
- For women < median age of 56,
  - 26% of all breast cancers and 50% of interval cancers (cancers detected less than ... months after a negative screening test) were attributable to density (BIRADS density ...)

CANCER IN DENSE BREASTS
EFFECT ON PROGNOSIS?

- Higher rate of interval cancers → worse prognosis → worse outcome
  - Majority are ER NEGATIVE, HIGHER TUMOR GRADE AND LARGER IN SIZE
- Why?
  - Hypotheses: Growth factors
    - Breast stroma produces growth factors
    - More rapid tumor growth in dense tissue

Roubidoux MA. Invasive Cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. Radiology; 2004

INTERVAL CANCERS AND BREAST DENSITY

Density	Odds Ratio	95% CI
<10%	1.0	-
10-24%	2.1	(0.9, 5.2)
25-49%	3.6	(1.5, 8.7)
50-74%	5.6	(2.1, 15.3)
>75%	17.8	(4.8, 65.9)

P<0.001

Higher rates of interval cancers → Worse prognosis

Boyd, NF et al. NEJM 2007; 356:227-36

HOW DO WE ASSESS BREAST DENSITY: TOOLS

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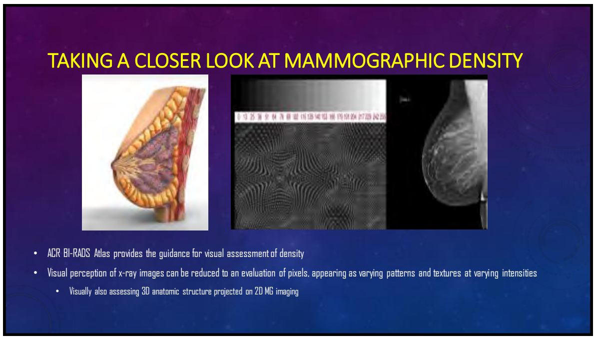

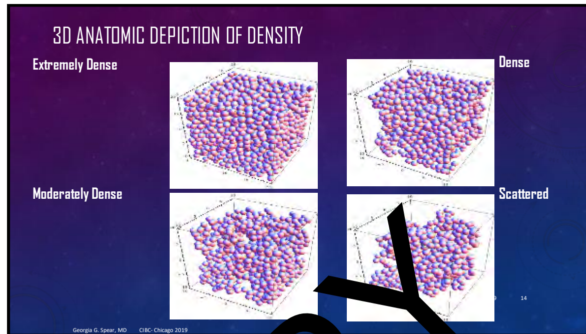

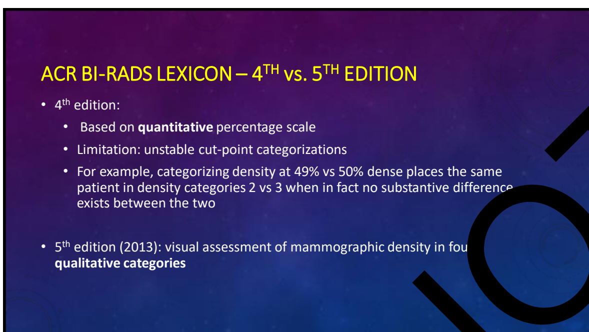

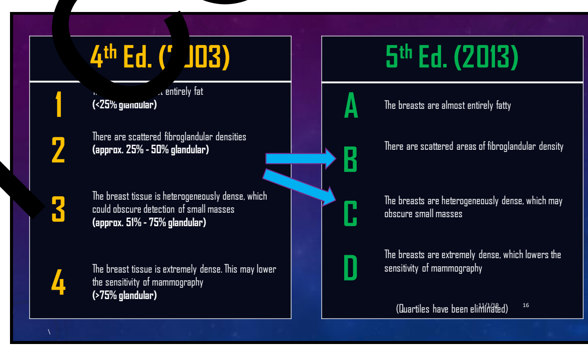

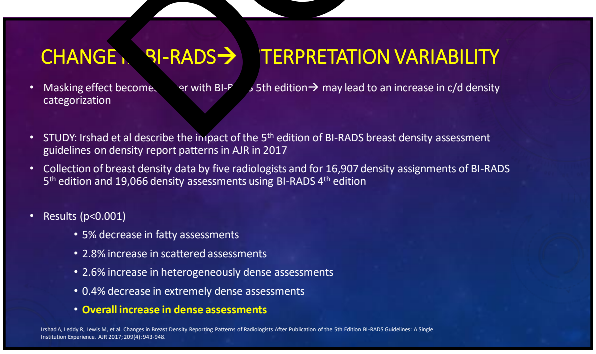

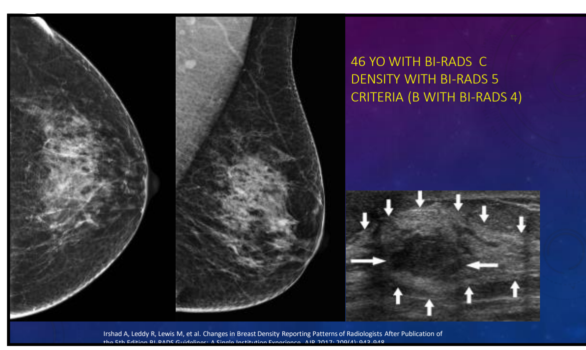

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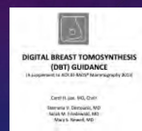
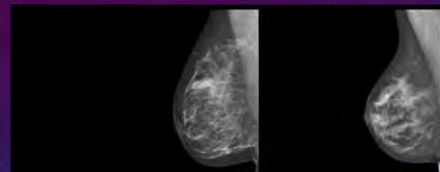
DIFFERING MAMMOGRAPHIC TECHNIQUES --> INTERPRETATION VARIABILITY

- DBT – warranted new BI-RADS
  - Breast density should be assessed on standard DM or synthesized MG, NOT on tomosynthesis slices
  - As with DM, if the two breasts differ in density, classification should be based on the more dense breast
- DBT (3D) imaging may result in a decrease in c/d categorization
  - Retrospective study of 24736 women screened with DBT versus digital mammography alone had **lower likelihood of categorization of high density breasts**
  - DBT vs digital: odds ratio, 0.69 (p<0.001); Synthetic and DBT vs digital: odds ratio, 0.43 (p<0.001)
  - Lower likelihood to categorize high density breasts with synthetic and DBT compared to digital and DBT: odds ratio, 0.62 (p<0.001)



Gastounioti A, McCarthy AM, Pantalone L, Synnestvedt M, Kontos D, Conant EF. Effect of Mammographic Screening Modality on Breast Density Assessment: Digital Mammography versus Digital Breast Tomosynthesis. Radiology 2019; 291(2): 320-327



% Density	44%	48%
4th Ed. Category	2	2
5th Ed. Category	B	C

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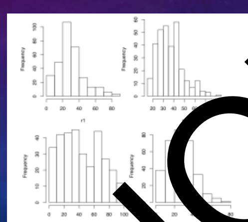
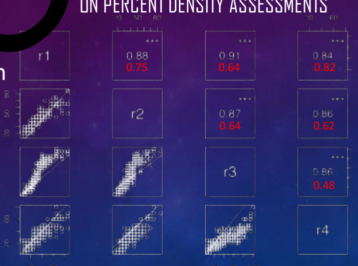
VARIABILITY IN VISUAL ASSESSMENT OF PERCENT DENSITY[4]

- 4 radiologists
- 300 mammograms
- % density- x-axis
- Ranges vary and distribution varies
- For ex, Rads 3 and 4, PBD 65% with wide variability in density assessment categorization



PAIRWISE COMPARISONS OF RADIOLOGISTS ON PERCENT DENSITY ASSESSMENTS

Good Correlation



Poor Agreement

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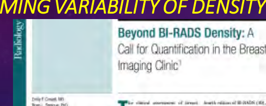
VARIABILITY IN DENSITY CATEGORIZATION

- Density assessment evaluated in practice of 83 breast radiologists in NCI's Population-Based Research Optimizing Screening through Personalized Regimens or PROSPR network
  - Rate of assignment of "dense" category (3/4) ranged from 6.3% of screening exams to up to 84.5%
  - Statistical adjustment for patient variables: age, body mass index, race and ethnicity had little effect on variability
  - Among women with consecutive mammograms interpreted by different radiologists through an average span of 1.2 years, there was 17.2% discordance in dense vs non-dense category assignments and women shifted in both directions

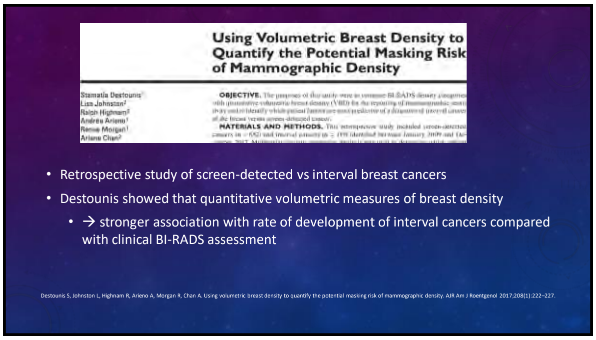
Sprague BL, Conant EF, Onega T et al. Variation in mammographic breast density assessments among radiologists in clinical practice: a multicenter observational study. **Ann Intern Med** 2016;165(7):457–464

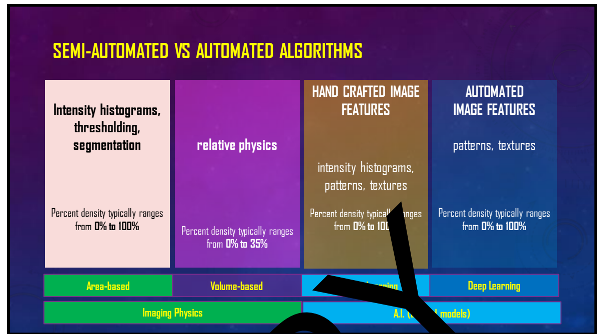
TECHNOLOGIC ADVANCEMENTS: OVERCOMING VARIABILITY OF DENSITY ASSESSMENT

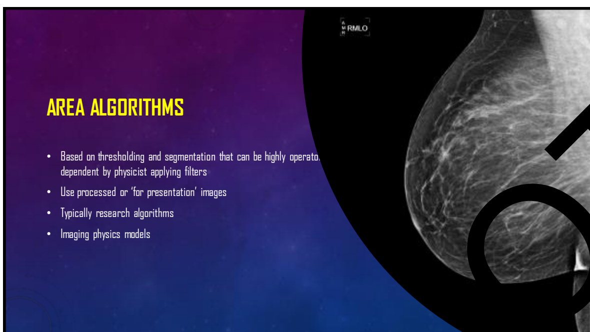


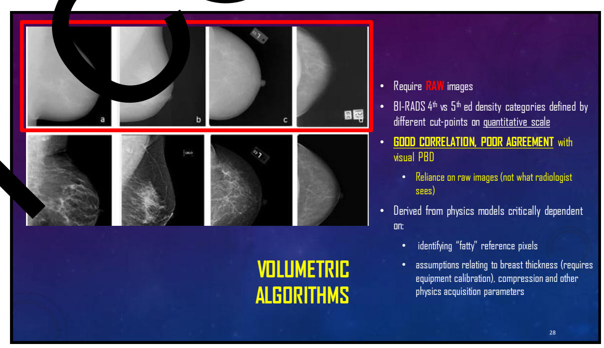
AUTOMATED vs SEMI-AUTOMATED ALGORITHMS
- Created to overcome subjective visual BI-RADS assessment and produce reproducible qualitative methods
- Area vs volumetric
- Reproducible, quantitative metrics and a continuous density score aid in more granular density-based risk stratification

Conant EF, Sprague BL, Kontos D. Beyond BI-RADS Density: A Call for Quantification in the Breast Imaging Clinic. Radiology 2018; 286(2): 401-404.


Using Volumetric Breast Density to Quantify the Potential Masking Risk of Mammographic Density
Retrospective study of screen-detected vs interval breast cancers
Destounis showed that quantitative volumetric measures of breast density
→ stronger association with rate of development of interval cancers compared with clinical BI-RADS assessment
Destounis S, Johnston L, Highnam R, Arieno A, Morgan R, Chan A. Using volumetric breast density to quantify the potential masking risk of mammographic density. AJR Am J Roentgenol 2017;208(1):222–227.


SEMI-AUTOMATED VS AUTOMATED ALGORITHMS
Intensity histograms, thresholding, segmentation
Percent density typically ranges from 0% to 100%
relative physics
Percent density typically ranges from 0% to 35%
HAND CRAFTED IMAGE FEATURES
intensity histograms, patterns, textures
AUTOMATED IMAGE FEATURES
patterns, textures
Percent density typically ranges from 0% to 100%
Area-based
Volume-based
Deep Learning
Imaging Physics


AREA ALGORITHMS
Based on thresholding and segmentation that can be highly operator dependent by physicist applying filters
Use processed or 'for presentation' images
Typically research algorithms
Imaging physics models


Require RAW images
BI-RADS 4th vs 5th ed density categories defined by different cut-points on quantitative scale
GOOD CORRELATION, POOR AGREEMENT with visual PBD
Reliance on raw images (not what radiologist sees)
Derived from physics models critically dependent on:
identifying "fatty" reference pixels
assumptions relating to breast thickness (requires equipment calibration), compression and other physics acquisition parameters
VOLUMETRIC ALGORITHMS
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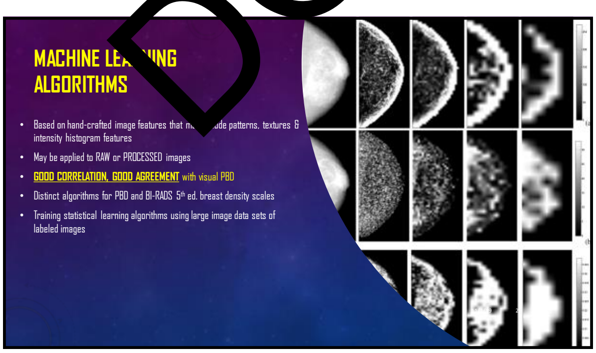
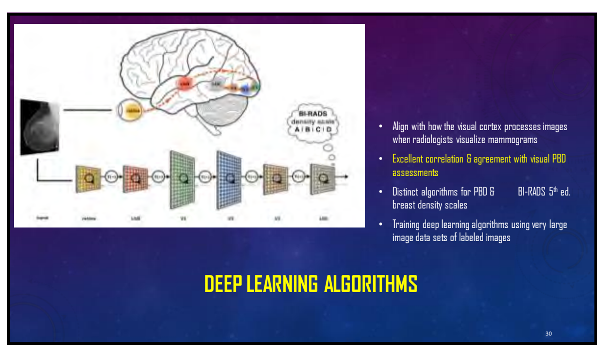

ALGORITHMS
intensity histogram features
May be applied to RAW or PROCESSED images
GOOD CORRELATION, GOOD AGREEMENT with visual PBD
Distinct algorithms for PBD and BI-RADS 5th ed. breast density scales
Training statistical learning algorithms using large image data sets of labeled images


Align with how the visual cortex processes images when radiologists visualize mammograms
Excellent correlation & agreement with visual PBD assessments
Distinct algorithms for PBD & BI-RADS 5th ed. breast density scales
Training deep learning algorithms using very large image data sets of labeled images
DEEP LEARNING ALGORITHMS
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COMMERCIALIZED ALGORITHMS

Method	Type	Algorithm	Regulatory Clearance	STANDARD DICOM	MULTI-VENDOR
Physics Models	Volumetric	Spectral Density	Y	N	N
	relative physics	VolparaDensity	Y	N	Y
		Quantra	Y	N	Y
Machine Learning	Hand Crafted Image Features	Densitas	Y	Y	Y
	patterns; textures	DenSeeMammo	Y	Y	N
		iReveal	Y	N	Y
		Quantra	Y	N	Y
Deep Learning	Automated Image Features	Densitas	*	Y	Y
	patterns; textures				

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BREAST DENSITY AND BREAST CANCER RISK

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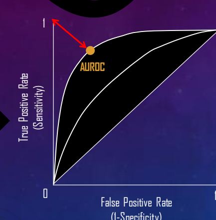
BREAST DENSITY & BREAST CANCER RISK

- Visually assessed mammographic density is strongly associated with breast cancer risk
  - 25 years of peer reviewed literature
- **The association between breast density and breast cancer risk is a KEY validation point for any breast density algorithm**
- Mammographic breast density is **one of the strongest** breast cancer risk factors.[10]
- Many risk models now incorporate breast density as a risk factor: Gail, Tyrer-Cuzick, BCSC (Breast Cancer Surveillance [illegible]sortium) risk calculator.

AU[illegible]C CURVE

Each po[illegible]e curve represents a sensiti[illegible]pecificity pair



Optimal sensitivity and specificity
→ point in the upper left corner

↑ AUC = ↑ discrimination between individuals with and without disease

A perfect model has AUC of 1 (high spec and high sens);
A useless model has an AUC of 0.5.

∴ AUROC curve can be used to demonstrate the ability of the model to predict breast cancers

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BREAST CANCER [illegible]K MODELS & [illegible]AMMOGRAPHIC DENSITY

Addition of mammographic density to both the Tyrer-Cuzick v6 and the Gail model improved the predictive performance[11]

AUC	Model	Density	Model + Density
Tyrer-Cuzick v6	0.57	0.59	0.61
Gail	0.55	0.59	0.59

- **Density alone performed as well as Gail + Density**

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BREAST CANCER RISK MODELS

Predict 5- and 10-year risk of developing breast cancer[12-16]

	Gail	Tyrer-Cuzick v8	BCSC	BRCAPRO	Claus 1993
Age	✓	✓	✓	✓	✓
BMI	✗	✓	✗	✗	✗
Menarche	✓	✓	✗	✗	✗
Menopause	✗	✓	✗	✗	✗
HRT	✗	✓	✗	✗	✗
Biopsy / ADH	✓	✓	✓	✗	✗
1° FHx Breast CA	✓	✓	✓	✓	✓
2° FHx Breast CA	✗	✓	✗	✓	✓
1° & 2° FHx Ovarian CA	✗	✓	✗	✓	✗
Breast Density	✓	✓	✓	✗	✗

- Age and family history are common to all risk models.

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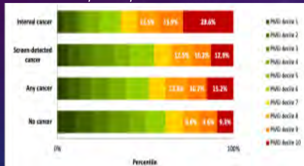
MASKING EFFECT

- Sensitivity in fatty breasts can be higher than 90%
- Sensitivity in very dense breasts can be as low as 50%



N=7700[17]

- 28.6% of interval detected cancers are in the top density decile
- 12.9% of screen-detected cancers were in the top decile
- 9.3% of controls were in the top density decile

AUTOMATED BREAST DENSITY AND RISK

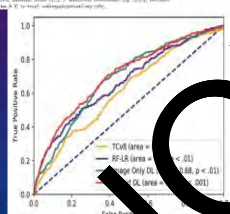
- Astley et al.[18], compared five different methods (visual analogue scale (VAS), Cumulas, Densitas, Quantra and Volpara) of breast density assessment and their relation to breast cancer risk.
  - various density measures were included with the Tyrer-Cuzick (v.6) risk score in a logistic regression analysis to evaluate breast cancer risk.
  - VAS strongest predictor of screen-detected cancers
  - Quantra – no significant association
  - Researchers concluded Densitas® and Volpara® measures had a strong association with breast cancer risk, providing a practical automated method for risk-based stratification for breast screening

Radiology — ORIGINAL RESEARCH • BREAST IMAGING

A Deep Learning Mammography-based Model for Improved Breast Cancer Risk Prediction

Adam Yala, MEng • Constance Lehman, MD, PhD • Tal Schuster, MS • Tally Portnoi, BS • Regina Barzilay, PhD

- **TCv8**: breast density + RF
  - Overall: AUROC = 0.62
  - **White**: AUROC = **0.62**
  - **African American**: AUROC = **0.45**
- **Hybrid**: Deep Learning + RF
  - Overall AUROC = 0.70
  - **White**: AUROC = **0.71**
  - **African American**: AUROC = **0.71**



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AU[illegible] DENSITY ALGORITHMS TO PREDICT RISK

- Puliti et al. volumetric breast density and risk of advanced cancers after negative screening episode: a cohort study. Breast Cancer research (2018) 20: 95
  - Risk of advanced cancer is 4X increased for extremely dense compared to non extremely dense using an automated breast density measurement
- Destounis S, Johnston L, Highnam R, Arieno A, Morgan R, Chan A. Using Volumetric Breast Density to Quantify the Potential Masking Risk of Mammographic Density. AJR 2017; 208: 1-6.
  - Highest breast density category associated with highest risk
  - Breast density is only risk factor associated with diagnosis of interval cancer versus screen-detected cancer
  - Highest density 3.6 fold more likely to have interval cancer diagnosis compared with other categories

[illegible]IMELINE

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HOW CAN WE BRING PRECISION MEDICINE INTO CLINICAL CARE?

- Deliver personalized screening on the basis of breast cancer risk
- Providing reproducible estimates of risk can lead to more effective delivery of personalized screening to improve patient outcomes
- **Breast density assessment can be used to deliver *personalized/precision screening based on risk***

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HOW CAN WE BRING PRECISION MEDICINE INTO CLINICAL CARE?

- Breast cancer risk varies widely from woman to woman in a general screening population
  - 11.6% (average woman) to 85% (germline mutations) lifetime risk
- Cookie-cutter approach to risk estimation using crude criteria based on ad-hoc categorization of risk factors leads to imprecision and either unnecessary or excessive follow-up and treatment
- Tailored screening protocols based on individual risk can[5-9]
  - Inform targeted breast cancer prevention strategies
  - Improve clinical outcomes
  - Ration resources
  - Reduce harms

CONCLUSION

- Breast density is an important risk factor for breast cancer and it is important to understand for appropriate breast cancer screening
- Reliable assessment of breast density is crucial in accurate assessment of breast cancer risk
- Reliance on clinically proven methods to address breast density and breast cancer risk is essential in providing excellent patient care
- Earlier qualitative methods are limited
- Automated methods help move us to standardizing assessment with consistency and reproducibility
- Increasing interest in this area will continue to provide information and guidance on application in a large scale breast cancer screening program

CONCLUSION

- In summary, technology's mission in today's world of breast imaging is to seek specificity without loss of sensitivity
- Safe to say that Breast Imaging is NOT a one size fits all solution
- Continued research in this arena is important to identify the best solution
- *Personalized screening is THE FUTURE*

THANK YOU

- Acknowledgements: M. Abdolell, Dalhousie University, Densitas Inc.