# CARL E. RAVIN ADVANCED IMAGING LABORATORIES

## Technique Optimization in Digital Mammography

Nicole T. Ranger, M.Sc.

NicoleTRangerMSc@gmail.com

Carl E. Ravin Advanced Imaging Labs
Department of Radiology
Duke University Medical Center

#### Index

- 1. Introduction to Optimization in Mammography
- 2. Characteristics of S/F vs. Digital Mammography
- 3. Technique Optimization Methodology
- 4. What does this mean to me in the Clinic?

#### Part 1

# Introduction to Technique Optimization in Mammography

## Technique Acquisition Parameters

#### 1. X-RAY BEAM SPECTRUM

- target material
- filter material and thickness
- tube kilovoltage (kVp)

#### 2. EXPOSURE LEVEL

- beam current x time (mAs)

### Optimization

"Any process or procedure which ensures that doses due to appropriate medical exposure for radiological purposes are kept as low as reasonably achievable (ALARA) consistent with obtaining the required diagnostic information .."

IAEA-TECDOC-1447 May 2005"

## Implications

A mammography image of adequate to superior image quality is NOT acquired using an optimal technique if the dose to the patient was higher than necessary to yield a diagnostic image.

Must find optimum balance between dose & image quality



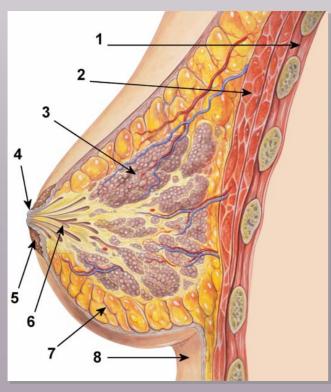
## Optimization in Mammography

"In mammography, the objective is to produce images that provide maximum visualization of breast anatomy and the signs of disease without subjecting the patient to unnecessary radiation"

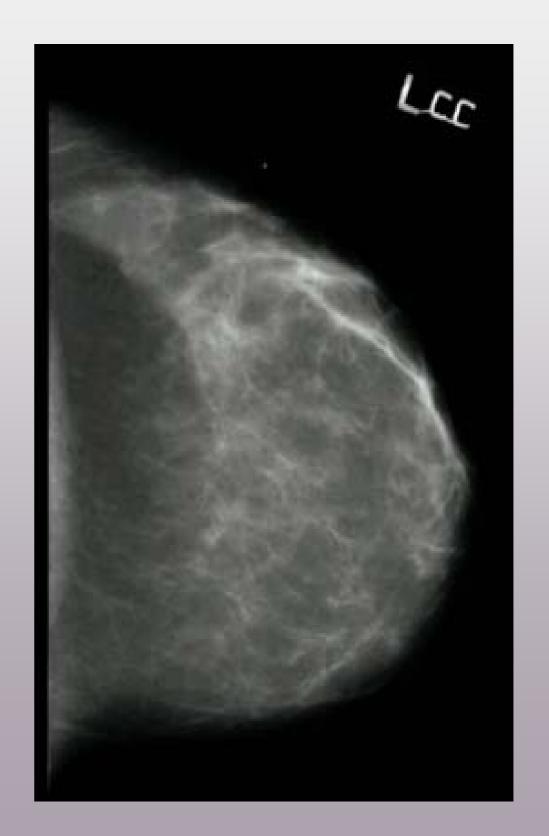
- IAFA

## Normal Breast Anatomy

- 1. Chest wall
- 2. Pectoralis muscles
- 3. Lobules
- 4. Nipple
- 5. Areola
- 6. Duct
- 7. Fatty tissue
- 8. Skin



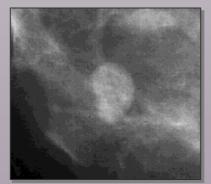
www.wikipedia.com

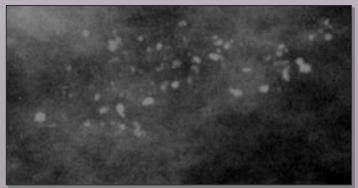


## Features of Breast Cancer in Mammography Imaging

- Increased Density (relative to prior exam)
- Architectural Distortion
- Micro-calcifications
- Masses







#### 1. DIAGNOSTIC OBJECTIVES

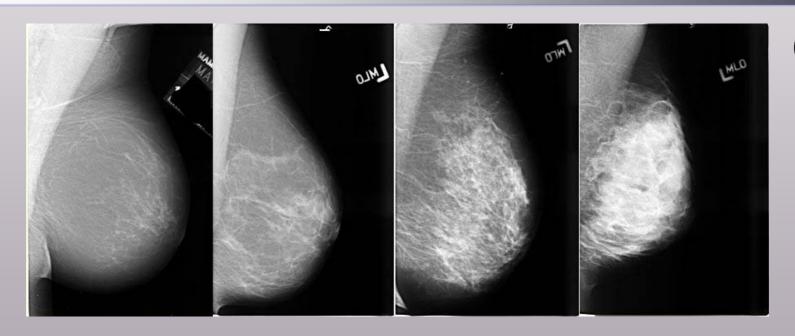
- Detect and characterize microcalcification cluster patterns and morphology
- Visualize breast parenchyma and subtle architectural distortions
- Detect soft tissue masses and assess shape, size, degree of local invasion

#### II. CHALLENGES

#### A. NORMAL BREAST DENSITY VARIATIONS

- Age, Genetics, Menstrual cycle (premenopausal women)

**ADIPOSE** 



**GLANDULAR** 

Source: McGill University Department of Medicine Online Mammography Tutorial

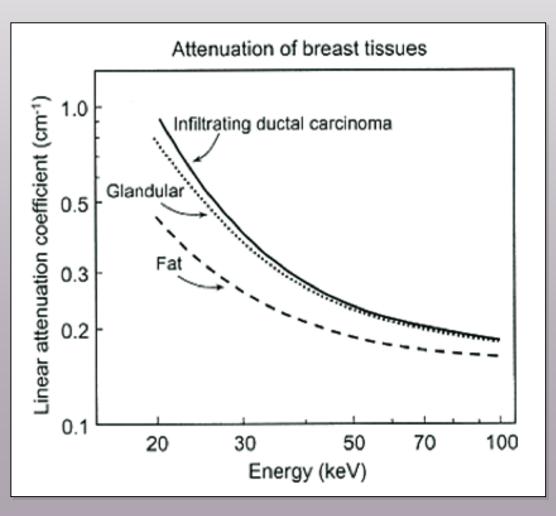
For adequate SNR<sup>2</sup> choice of radiographic technique must be patient- and context-specific

#### II. CHALLENGES

#### B. HIGH TISSUE CONTRAST RESOLUTION REQUIRED

Fibro-glandular and tumor tissue have similar attenuation properties

Optimize beam quality to maximize differential absorption and ...



Source: Bushberg, The Essential Physics of Medical Imaging

#### **Use COMPRESSION**

### Craniocaudal Mediolateral Oblique

(CC)

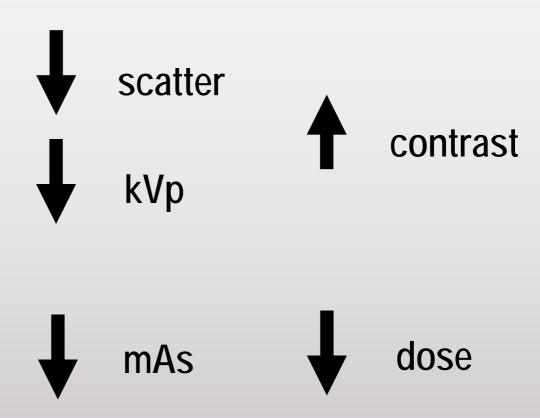
(MLO)





Source: Basset LW, Imaging the Breast, Cancer Medicine, 6<sup>th</sup> ed

Breast Thicknesses: 2 cm - 8 cm



#### **Scatter Fraction:**

0.8 – 1.0

0.4 - 0.5

uncompressed compressed





Source: Bushberg, The Essential Physics of Medical Imaging

#### II. CHALLENGES

#### C. NEED FOR DEVICE-SPECIFIC OPTIMIZATION

Different:

- Technology, i.e. Receptor Sensitivity
- Target/Filter options
- Exposure and other controls
- Image Processing

May require different imaging protocols & techniques for different technologies & systems, i.e. SF versus CR, CR versus DR, Direct DR versus Indirect DR, etc...

#### III. IMAGING SYSTEM REQUIREMENTS

- High Receptor Sensitivity
- **↓** DOSE

- High Spatial Resolution
- High Contrast Resolution
- Low Noise
- Reproducibility
  - Consistent image quality & exposure

#### IV. PRIMARY QUALITY FACTORS

RESOLUTION Focal Spot Size & Blur

Magnification,

Pixel Pitch

**Patient Motion Blur** 

CONTRAST Tissue Density, Thickness

X-Ray Beam Quality (Target/Filter/kVP)

NOISE Receptor Sensitivity

mAs / Exposure

#### V. TECHNIQUE FACTORS

Target (Anode): Molybdenum (Mo)

Rhodium (Rh)

Tungsten (W)

Filter: Mo, Rh, Al, Ag

Tube Voltage: kVp

Exposure: mAs

CONTRAST

NOISE

#### VI. BREAST DOSIMETRY

#### Mean or Average Glandular Dose (MGD/AGD)

$$MGD = D_gN \times E$$

D<sub>g</sub>N: Exposure normalized glandular dose

(abs. dose / unit exposure)

E: Entrance surface exposure

~ 2.0 mGy (3.0 mGy ACR limit)

TABLE 8-6. DgN CONVERSION FACTOR (mRAD PER ROENTGEN) AS A FUNCTION OF HVL AND kVp FOR Mo TARGET/FILTER: 4.5-CM BREAST THICKNESS OF 50% GLANDULAR AND 50% ADIPOSE BREAST TISSUE COMPOSITION\*

	kVp							
HVL (mm)	25	26	27	28	29	30	31	32
0.25	122							
0.26	126	128						
0.27	130	132	134					
0.28	134	136	138	139				
0.29	139	141	142	143	144			
0.30	143	145	146	147	148	149		
0.31	147	149	150	151	152	153	154	
0.32	151	153	154	155	156	158	159	160
0.33	155	157	158	159	160	162	163	164
0.34	160	161	162	163	164	166	167	168
0.35	164	166	167	168	169	170	171	172
0.36	168	170	171	172	173	174	175	176
0.37		174	175	176	177	178	178	179
0.38			179	180	181	182	182	183
0.39				184	185	186	186	187
0.40					189	190	191	192

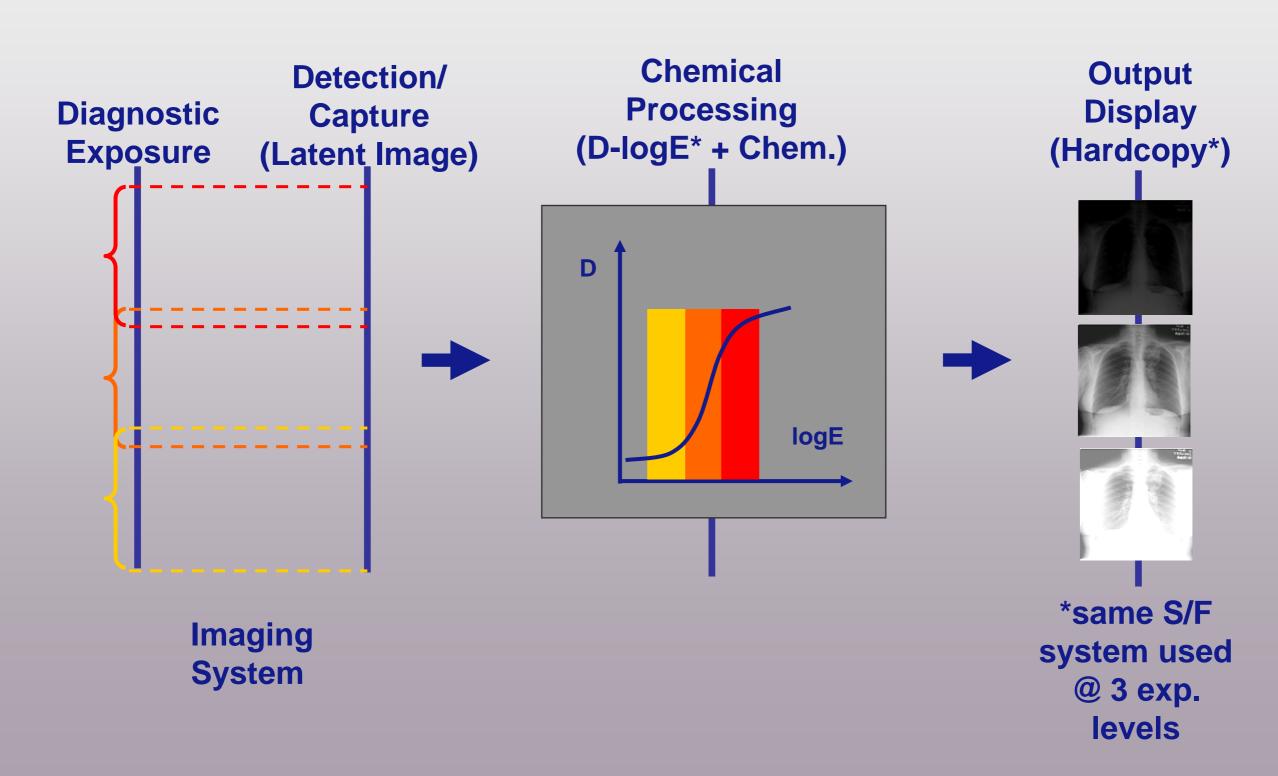
<sup>\*</sup>Adapted from ACR QC Manual, 1999.

Source: Bushberg, The Essential Physics of Medical Imaging

#### Part 2

## The Advantages of Digital Mammography

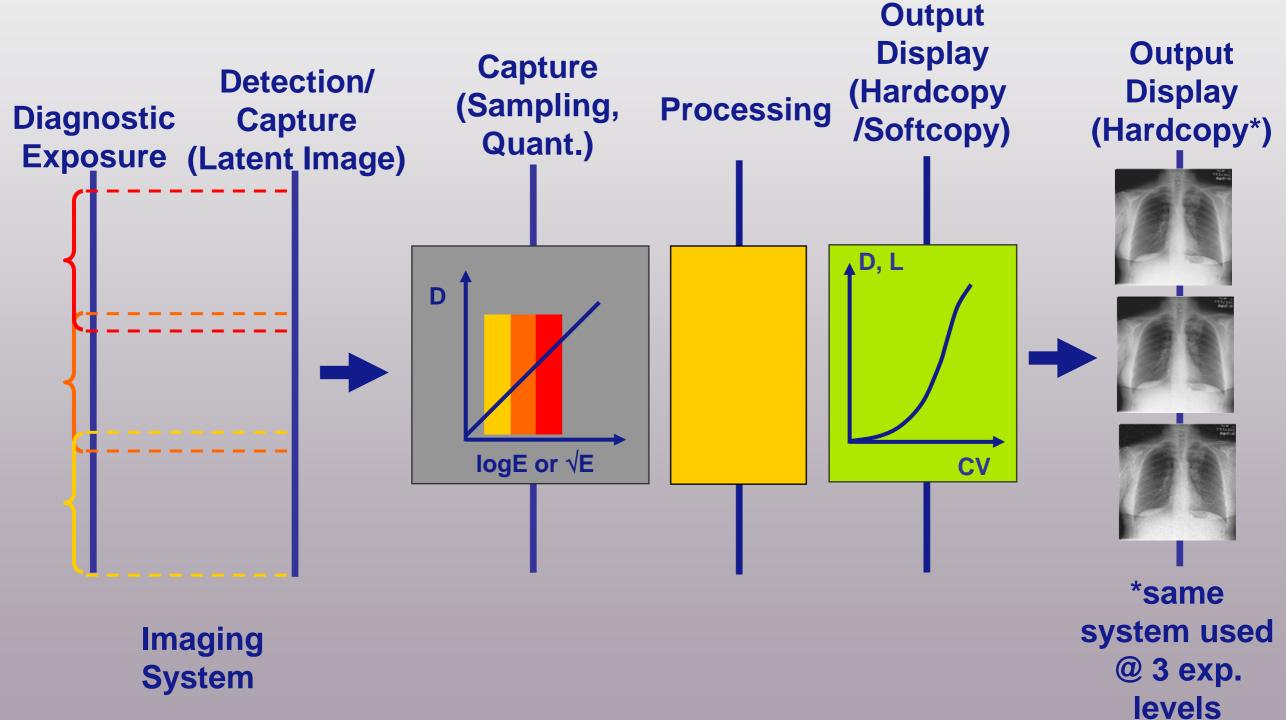
## Analog Imaging Chain (Screen-Film)



### Technique Optimization Screen-Film

- Optimization criteria based on film density
- Typical Target/Filter: Mo/Mo or Mo/Rh
- Dependent on film processor performance
- Impacted by speed and latitude of film
- Film is capture, display and storage medium

## Digital Imaging Chain (CR, DR)



## Technique Optimization Digital Mammography

- Optimization criteria can be subjective, semiobjective or objective, e.g. based on a computed figure-of-merit (FOM)
- Prerequisite: Detector calibration & QC
- Typical Target/Filter: W/Rh
- Acquisition, processing and display can and should be optimized separately

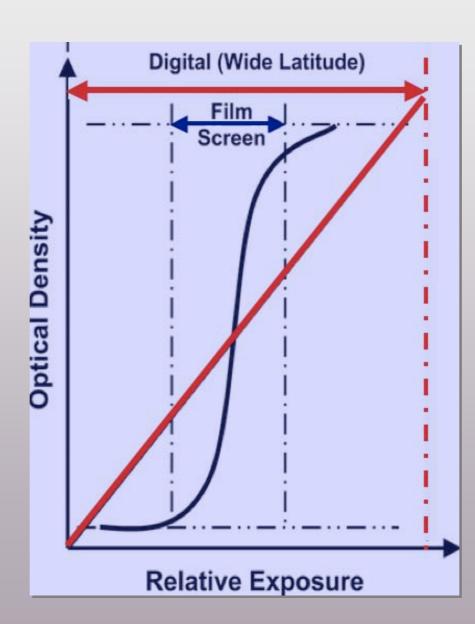
### Latitude: S/F vs DR

SF

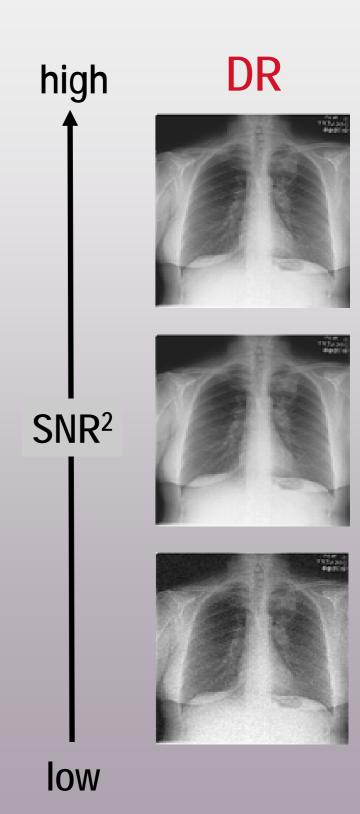








Adapted from: Mahesh M., Radiographics (2004)



#### CR SYSTEM COMPARISONS

CLASS	TYPE /PHOSPHOR*	MODEL	MANUFAC- TURER	PIXEL PITCH* (mm)	ACTIVE AREA (cm²)	TARGET/ FILTER
CR	PSP BaSrFBrl:Eu	CR35-X CR85-X	AGFA	0.050	18 x 24 24 x 30	?
CR	PSP BaFBrl:Eu	ASPIRE CLEARVIEW	FUJIFILM	0.050	18 x 24 24 x 30	?
CR	PSP BaFBr:Eu	DIRECTVIEW	CARESTREAM	0.0485	18 x 24 24 x 30	?
CR	PSP BaFI:Eu	REGIUS 190	KONICA- MINOLTA	0.04375	18 x 24 24 x 30	?

<sup>\*</sup> Source: NHS Report 06047 Computed Radiography (CR) Systems for Mammography (2006)

DR SYSTEM COMPARISONS

DI SISILIM COMPANISONS							
CLASS	TYPE	MODEL	VENDOR	PIXEL PITCH (mm)	ACTIVE RECEPTOR AREA (cm <sup>2</sup> )	TARGET/ FILTER	
DR	Indirect CsI Slot-scan CCD	Senoscan	FISCHER/ HOLOGIC	0.054 (0.027)	21 x 29	Mo/Mo Mo/Rh Rh/Rh W/Al	
DR	Direct aSe	Aspire HD* (Amulet)	FUJIFILM	0.050	18 x 24 24 x 30	Mo/Mo Mo/Rh Rh/Rh	

LORAD/

HOLOGIC

**PLANMED** 

0.070

0.085

25 x 29

17 x 24

24 x 30

Mo/Mo

Mo/Rh

W/Ag

W/Rh

Direct aSe

Indirect

aSi:Csl

Selenia

Nuance

Nuance Excel

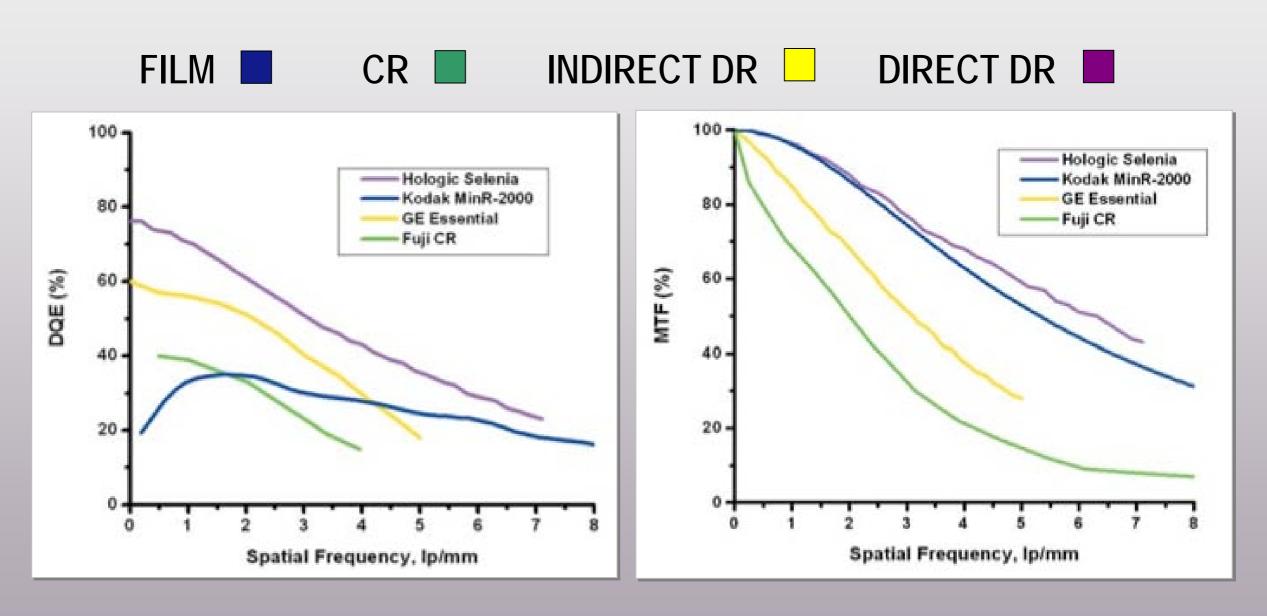
DR

DR

#### DR SYSTEM COMPARISONS

CLASS	TYPE	MODEL	VENDOR	PIXEL PITCH (mm)	ACTIVE RECEPTOR AREA (cm <sup>2</sup> )	TARGET /FILTER
DR	Direct aSe	Novation DR Novation S Inspiration	SIEMENS	0.070 0.070 0.085	18 x 23 24 x 29 24 x 30	Mo/Mo Mo/Rh W/Rh
DR	Indirect aSi:CsI Flat Panel	2000D, DS Essential Senographe	GE	0.100 0.100 0.100	19.2 x 23 19.2 x 23 24 x 30.7	Mo/Mo Mo/Rh Rh/Rh

#### IMAGING PERFORMANCE COMPARISONS

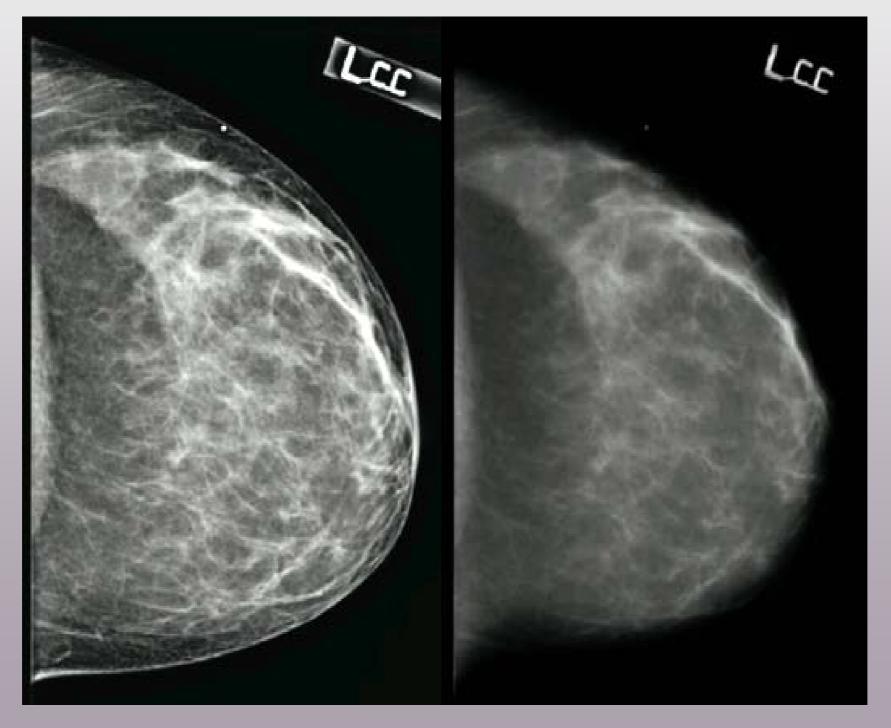


As a class DR systems typically have lower resolution than screen/film

## Why go Digital?

DIGITAL

**SCREEN-FILM** 



### Advantages of Digital

- Increased throughput
- Increased sensitivity
- Increased latitude
- Better contrast resolution
- Contrast adjustment

- Image processing
- Advanced applications
- Decreased dose
- Indefinite archival
- Simultaneous access

#### But ...

Lower spatial resolution (generally)

## Digital is the Future

As of 12/2009:

59% of MQSA certified facilities had 1 or more FFDM units

60% of all MQSA certified units were FFDM

New mammography unit sales in US almost exclusively digital

Source: MQSA website

#### Part 3

## Technique Optimization Methodology

## Technique Optimization Methods

- Spectral Simulation using Monte Carlo methods
- Experimental Studies using Objective Criteria (Figures-of-Merit)
- Clinically-Relevant Task Based Observer Studies
- Prospective or Retrospective Clinical Studies
- Subjective Evaluation of Image Quality Phantom Data

### Example

### Technique Optimization Protocol

- objective figure of merit (FOM)
- quotient of SdNR<sup>2</sup> to MGD
- computed for masses and calcs

## Technique Optimization Protocol

#### Physical Setup

#### **Siemens Mammomat Novation DR**

Mo/Mo vs W/Rh kVp: 23, 25, 27, 29, 31, 33, 35



Ranger et al, Med Phys 37 (2010



### Technique Optimization Protocol

#### FIGURE - OF - MERIT

$$FOM = \frac{SdNR^2}{MGD} \qquad \leftarrow \text{ Quality}$$

$$Dose$$

SdNR<sup>2</sup>: Signal Difference to Noise Ratio Squared

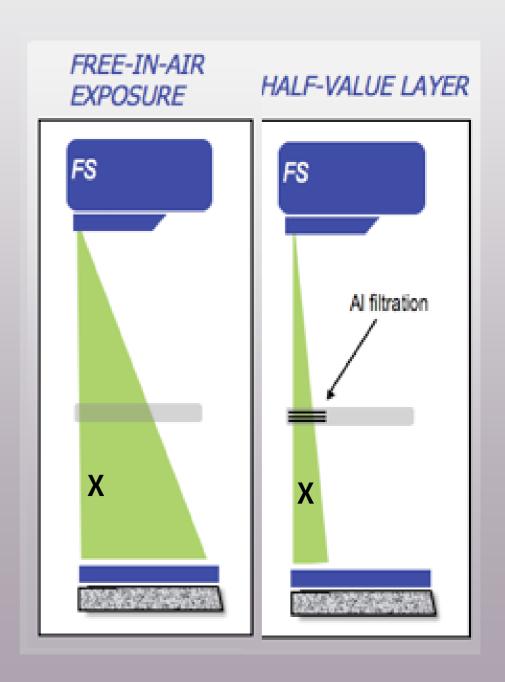
MGD: Mean Glandular Dose (computed from spectral estimates using Spectra\*)

### Characterizing the Beam Quality & Exposure

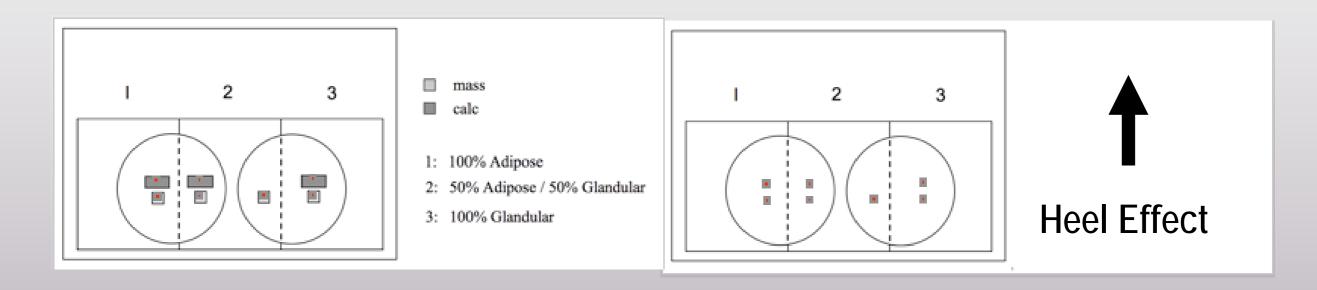
Measure free-in-air exposure at each beam quality: target/filter & kVp

Extrapolate to phantom surface using inverse square law

Measure HVL at each beam quality using narrow beam geometry and calibrated ion chamber fitted with a Mammo probe.



### Computation of SdNR<sup>2</sup>



### With Inclusions

### Without Inclusions

S<sub>i</sub>: mean signal in ROI overlying inclusion

S<sub>b</sub>: mean signal in ROI in background (same location)

### FOM Results



10.0000

50% Gland

100% Gland

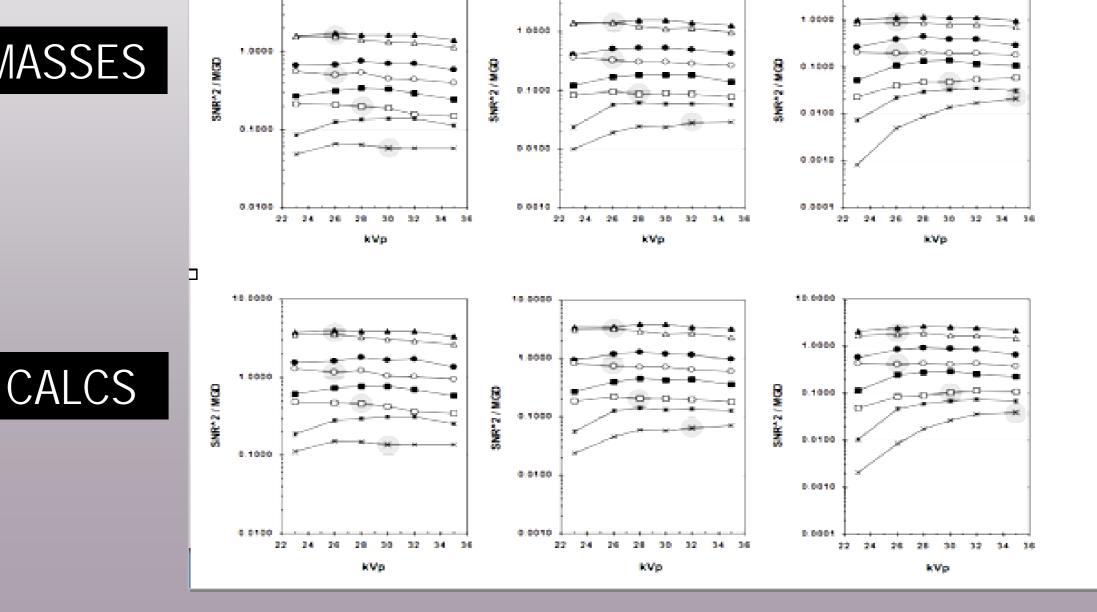
— W/Rh 2 cm -/-- Mo/Mo 2 cm W/Rh 4 cm.

-○- Mo/Mo 4 cm W/Rh 6 cm →□ Mo/Mo 6 cm

—×— W/Rh 8 cm. -X= Mo/Mo 8 cm

10.0000

MASSES

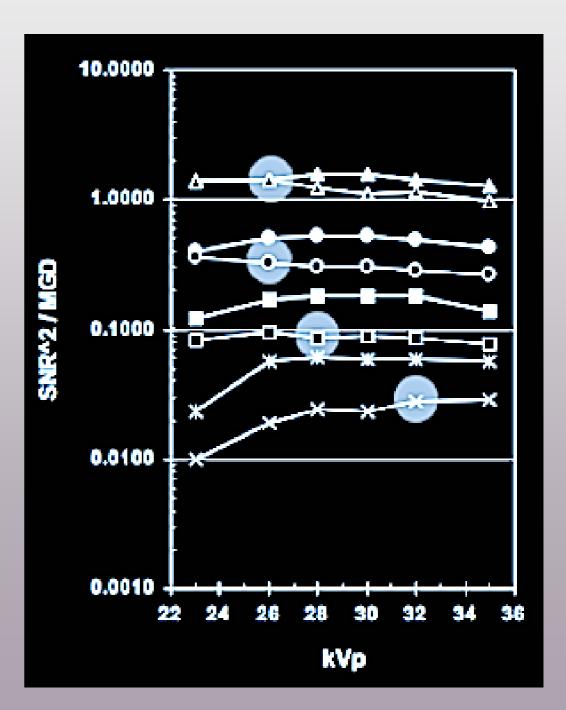


### Computation of the FOMR and Dose Savings

Relative FOM (FOM<sup>R</sup>) gives the image quality improvement at the new technique (W/Rh) in comparison to the optimized reference technique (Mo/Mo ) for the equivalent glandular dose

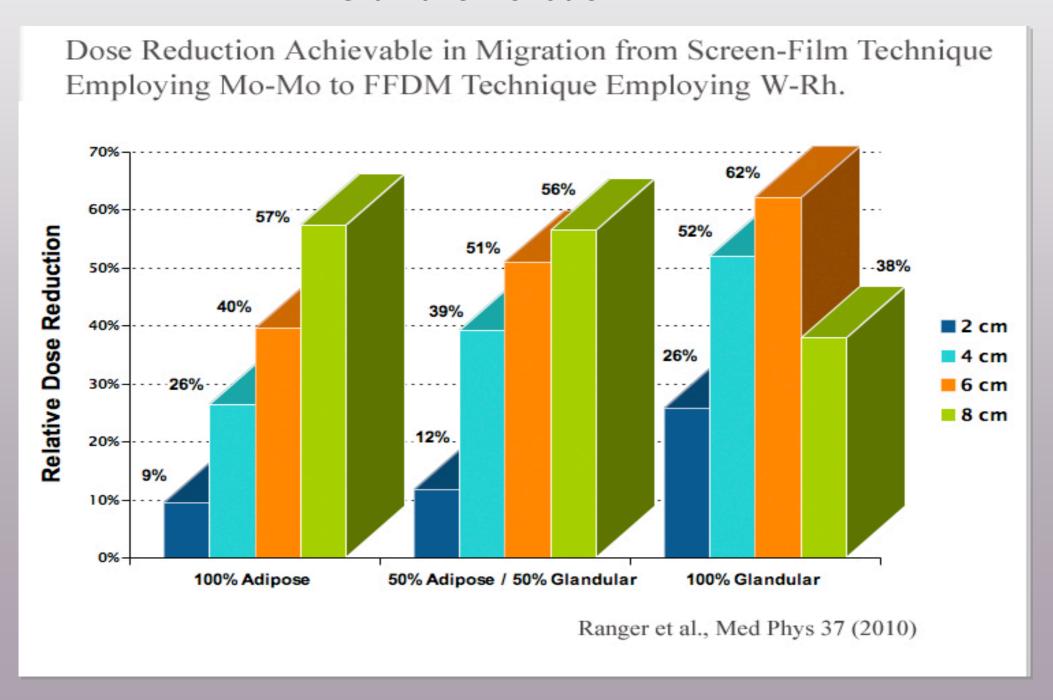
$$FOM^{R} = \frac{FOM_{EVAL}}{FOM_{REF}}$$

RELATIVE
$$DOSE \longrightarrow (FOM^R)^{-1}$$
SAVINGS



### Relative Dose Savings

### **Siemens Novation DR**



# Dose savings likely to be much more conservative ....

WHY?

# Breast Density: What is typical or average?

# Common misconception that average breast density is 50% adipose tissue to 50% fibroglandular or "50-50"

### The myth of the 50-50 breast

M. J. Yaffe<sup>a)</sup>

Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario M4N 3M5, Canada

J. M. Boone and N. Packard

UC Davis Medical Center, University of California-Davis, Sacramento, California 95817

O. Alonzo-Proulx

Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario M4N 3M5, Canada

S.-Y. Huand

UC Davis Medical Center, University of California-Davis, Sacramento, California 95817

C. L. Peressotti

Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario M4N 3M5, Canada

A. Al-Mayah and K. Brock

University Health Network, University of Toronto, Toronto, Ontario M5G 2M9, Canada

(Received 30 April 2009; revised 23 September 2009; accepted for publication 29 September 2009; published 5 November 2009)

Ref: Yaffe et al, The Myth of the 50-50 Breast

## Normal Density Variations

ACR BI-RADS BREAST DENSITY CLASSIFICATION SCHEME

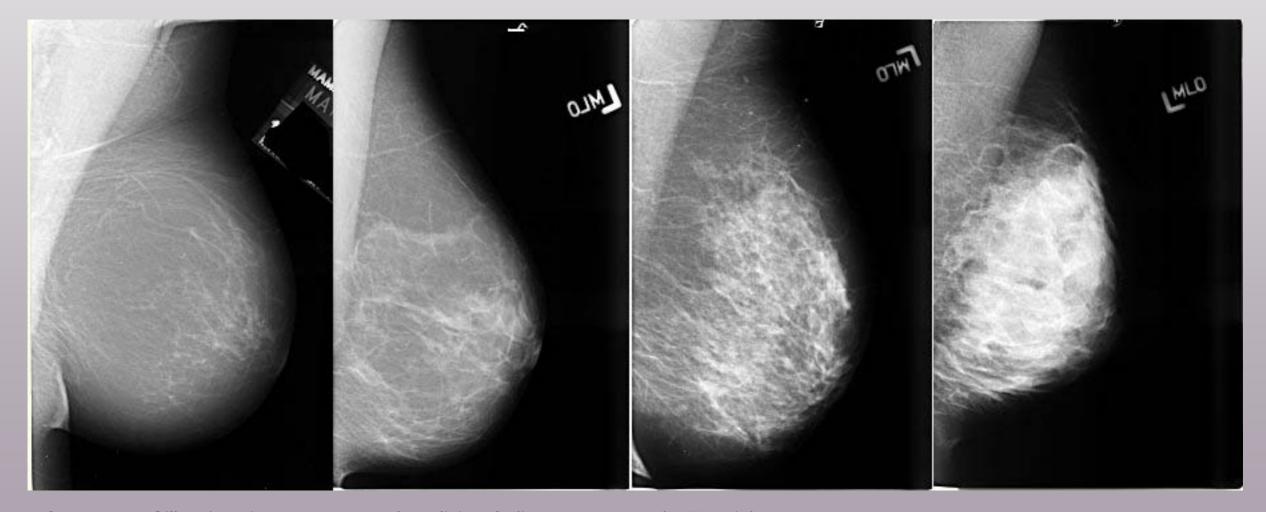
Category 1

Category 2

Category 3

Category 4

### ADIPOSE GLANDULAR



Source: McGill University Department of Medicine Online Mammography Tutorial

### Part 4

# What does all this mean in the clinic?

# Summary Key Concepts

Image quality must be optimized in the context of the COST (RISK) associated with the patient's EXPOSURE (DOSE) and that is accomplished via Technique Optimization

- Tradeoff between QUALITY and DOSE
- Optimization must be patient- and applicationspecific, i.e. tailored to patient size, exam type and other relevant factors

### Recommendations

- Automatic exposure (and other controls, e.g. automatic kVp, Target-Filter selection, etc..) controls should be verified as part of routine acceptance testing and checked on a routine basis.
- 2. AEC cells in conventional mammo units are located beneath the grid. CR cassette structure/sensitivity varies from vendor to vendor. Must calibrate the AEC for the intended CR casette type and only use those cassettes
- 3. Newer FFDM systems employ a virtual AEC in conjunction with a short prescan to determine the exposure termination conditions. Make sure it works as intended

### Recommendations

- 4. An imaging QA program must include monitoring of the system in the context of its intended clinical use a PROPERLY OPERATING imaging system is NOT the same as one OPERATED PROPERLY
  - Validate vendor-recommended techniques/protocols
  - Establish written imaging protocols and SOPs
  - Mandate ongoing staff training and in-services
  - Conduct routine audits to ensure compliance

### **ACKNOWLEDGMENTS**

### Information or Assistance Provided by:

DUKE

Joseph Y. Lo, PhD

Ehsan Samei, PhD

Jay A. Baker, MD

Anne Jarvis

SIEMENS

Thomas M. Mertelmeier, PhD

OTHER

Eric Gingold, PhD

Which of the following is NOT an advantage of digital mammography over screen film mammography:

20%	a)	improved throughput
20%	b)	improved latitude
20%	c)	higher spatial resolution
20%	d)	decreased dose for comparable image quality
20%	e)	image processing and digital archival

Which of the following is NOT an advantage of digital mammography over screen film mammography:

- (a) improved throughput
- (b) improved latitude
- (c) higher spatial resolution
- (d) decreased dose for comparable image quality
- (e) image processing and digital archival

Answer: (c)

Ref: Williams, M.B., Fajardo L.L., Digital Mammography: Performance Considerations and Current Detector Designs, Acad Radiol 3:429-437 (1996)

The technique factor that has the strongest impact on digital mammography image quality as reflected in a Figure-of-Merit (FOM) computed from the ratio of CNR2 or SdNR2 to MGD is:

```
20% a) focal spot size

20% b) mAs

20% c) field size

20% d) kVp

20% e) target / filter combination
```

The technique factor that has the strongest impact on digital mammography image quality as reflected in a Figure-of-Merit (FOM) computed from the ratio of SNR<sup>2</sup> or SdNR<sup>2</sup> to MGD is:

- (a) focal spot size
- (b) mAs
- (c) field size
- (d) kVp
- (e) target / filter combination

### Answer: (e)

Ref1: "Optimization of Exposure Factors in Full Field Digital Mammography", Williams et al, Med. Phys. 35: 2414-23 (2009)

Ref2: "A Technique Optimization Protocol and the Potential for Dose Reduction in Digital Mammography", Ranger NT, Lo JY, Samei E, Med. Phys. 37: 962-9 (2010)

In digital mammography, the approximate Mean Glandular Dose (MGD) for a 5 cm thick average density breast imaged using automatic exposure control with a W/Rh target/filter combination would be closest to:

20%	a) 0.02 mGy	
20%	b) 0.2 mGy	
20%	c) 2.0 mGy	
20%	d) 20.0 mGy	
20%	e) 200.0 mGy	

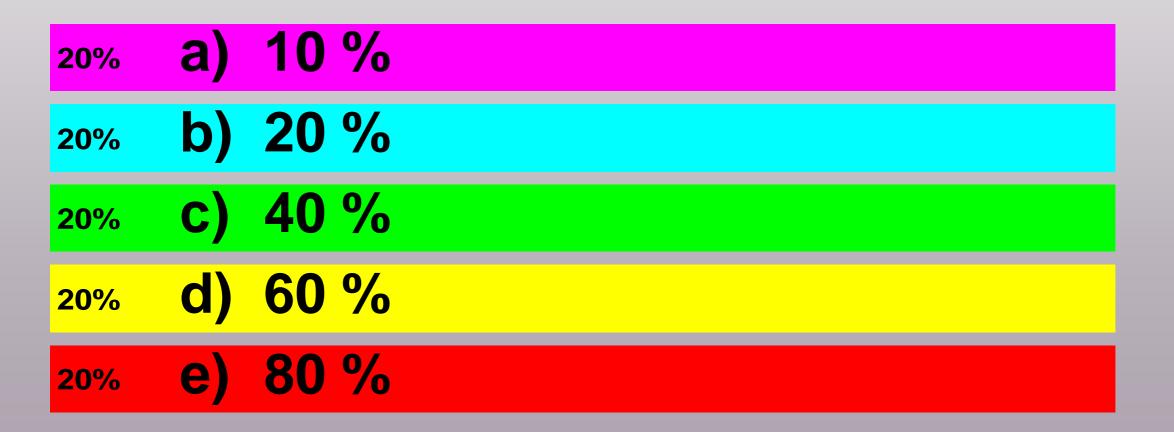
In digital mammography, the approximate Mean Glandular Dose (MGD) for a 5 cm thick average density breast imaged using automatic exposure control with a W/Rh target/filter combination would be closest to:

- (a) 0.02 mGy
- (b) 0.2 mGy
- (c) 2.0 mGy
- (d) 20.0 mGy
- (e) 200.0 mGy

Answer: (c)

Ref: "Comparison of Acquisition Parameters and Breast Dose in Digital Mammography and Screen-film Mammography in the American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial", Hendrick RE, Pisano E, Averbukh A, Moran C, Berns EA, Yaffe MJ, Herman B, Acharyya S, Gatsonis C, AJR 194: 362-369 (2010)

For a 4 cm breast with a composition ratio of 50% glandular to 50% adipose, the magnitude of dose reduction achievable for comparable image quality in the transition from screen/film to digital mammography is approximately:



For a 4 cm breast with a composition ratio of 50% glandular to 50% adipose, the magnitude of dose reduction achievable for comparable image quality in the transition from screen/film to digital mammography is approximately:

- (a) 10 %
- (b) 20 %
- (c) 40 %
- (d) 60 %
- (e) 80 %

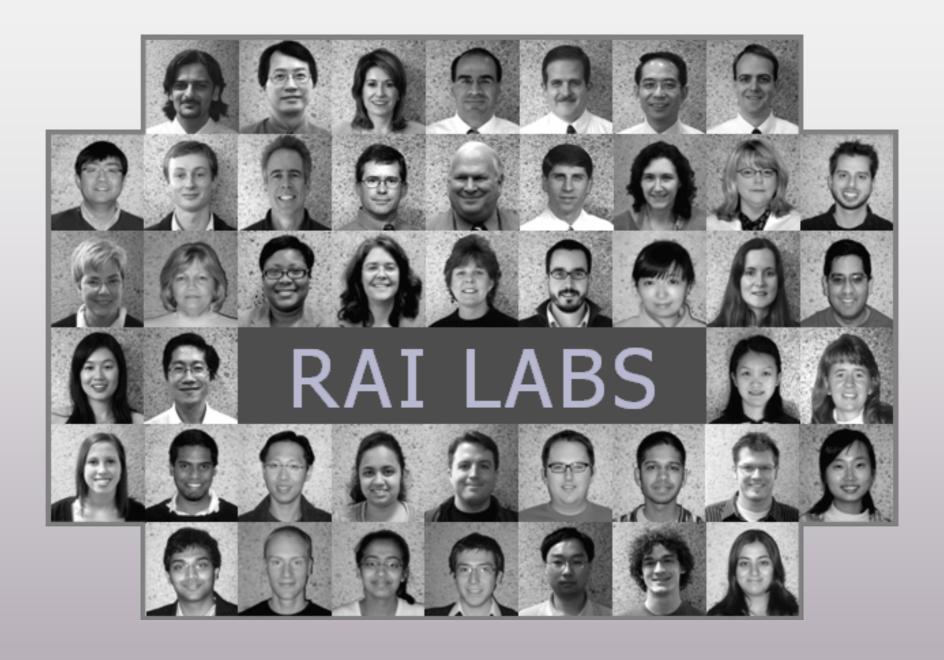
57

### Answer: (c)

Ref: "A Technique Optimization Protocol and the Potential for Dose Reduction in Digital Mammography", Ranger NT, Lo JY, Samei E, Med. Phys. 37: 962-9 (2010)

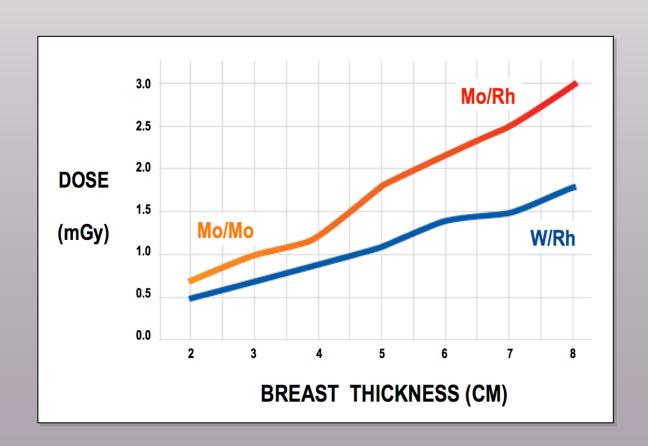
# **LABORATORIES**

### Thank you for your attention.



Email: NicoleTRangerMSc@gmail.com

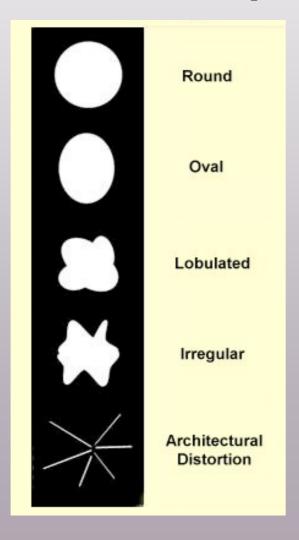
# **OLD SLIDES**



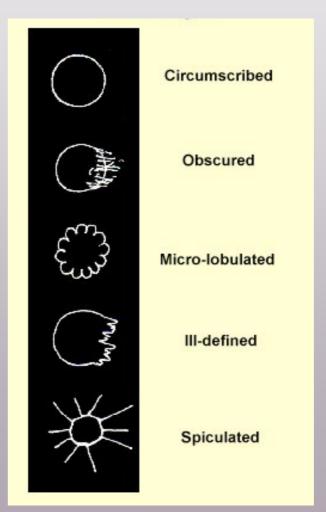
Source: IMS Giotto 3D brochure

# Characterizing Breast Masses

### Mass Shape



### Mass Margins



# Characterizing Microcalcifications

### Low Probability or Typically Benign

Skin calcifications, lucent, polygonal shape Vascular calcifications
Coarse, larger calcifications

### Intermediate Probability

Indistinct or amorphous microcalcifications

### **High Probability**

Clusters of heterogeneous or pleomorphic calcifications, irregular size & shape & < 0.5 mm diameter are suspicious

Fine linear or branching calcifications < 1 mm in with are associated with necrotic cancer cells

NEED EXAMPLE IMAGES/FIGURES

# Need a image quality- & dosesensitive metric to objectively assess optimization

# Typical Calibrations (DR)

### Correction for bad detector elements (dels)

### Flat-field correction

Correction for radiation field non-uniformity (i.e. Heel Effect)

Gain and offset correction for each del

Correction for velocity variation during scan (CR)

### Correction for geometric distortion \*

<sup>\*</sup> Primarily in CCD lens-based imaging systems

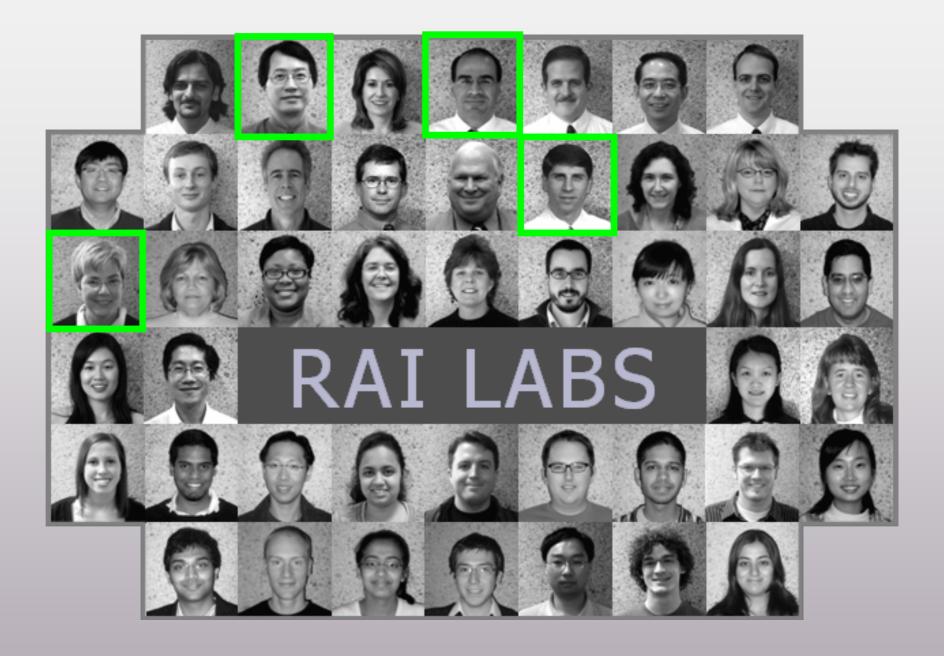
study published in September 2005 in the New England Journal of Medicine compareddigital mammograms to film mammograms. The study involved 49,000 women in North America with no known signs of breast cancer. The women were screened using both digital and film mammograms at the beginning of the study and again one year later. Breast cancer was found in 335 of the women. The researchers determined that digital mammograms were superior to film mammograms for three groups:women under 50 years of agewomen with dense breastswomen who have not yet gone through menopause, or who have been in menopause less than one year. Digital mammograms did not prove to be more beneficial for post-menopausal women over age 50 that do not have dense breasts. Additionally, both forms of mammogram had the same rate of false positives.

### Recommendations

- Take advantage of the free resources available
- Invest in a high quality IEC-compliant edge device
- Use lower purity "legacy" Al not the ≥ 99.9% purity Al specified by the standard (test Al before use)
- Review the fundamentals of DQE physics
- Study the body of literature on DQE testing
- Obtain the IEC standards for reference
- Recruit a "DQE Mentor"

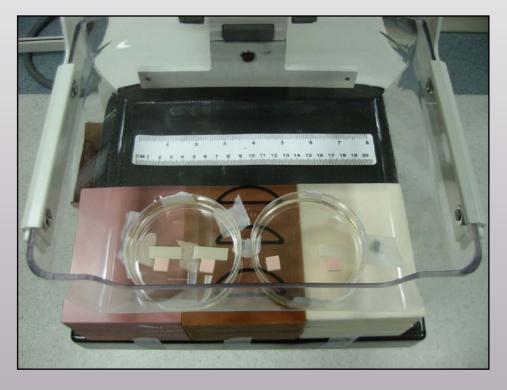
# **LABORATORIES**

### Thank you for your attention.



Email: nicole.ranger@duke.edu

## **EXTRA STUFF**





### **ACKNOWLEDGMENTS**

## Information &/or Assistance Provided by:

DUKE .

Joseph Y. Lo, PhD

Ehsan Samei, PhD

Jay A. Baker, MD

**Anne Jarvis** 

SIEMENS

Thomas M. Mertelmeier, PhD

# Introduction

#### CONTEXT

1 in 8 women (13%) will be diagnosed with breast cancer in their lifetime

In 2006, 191,410 new breast cancer cases

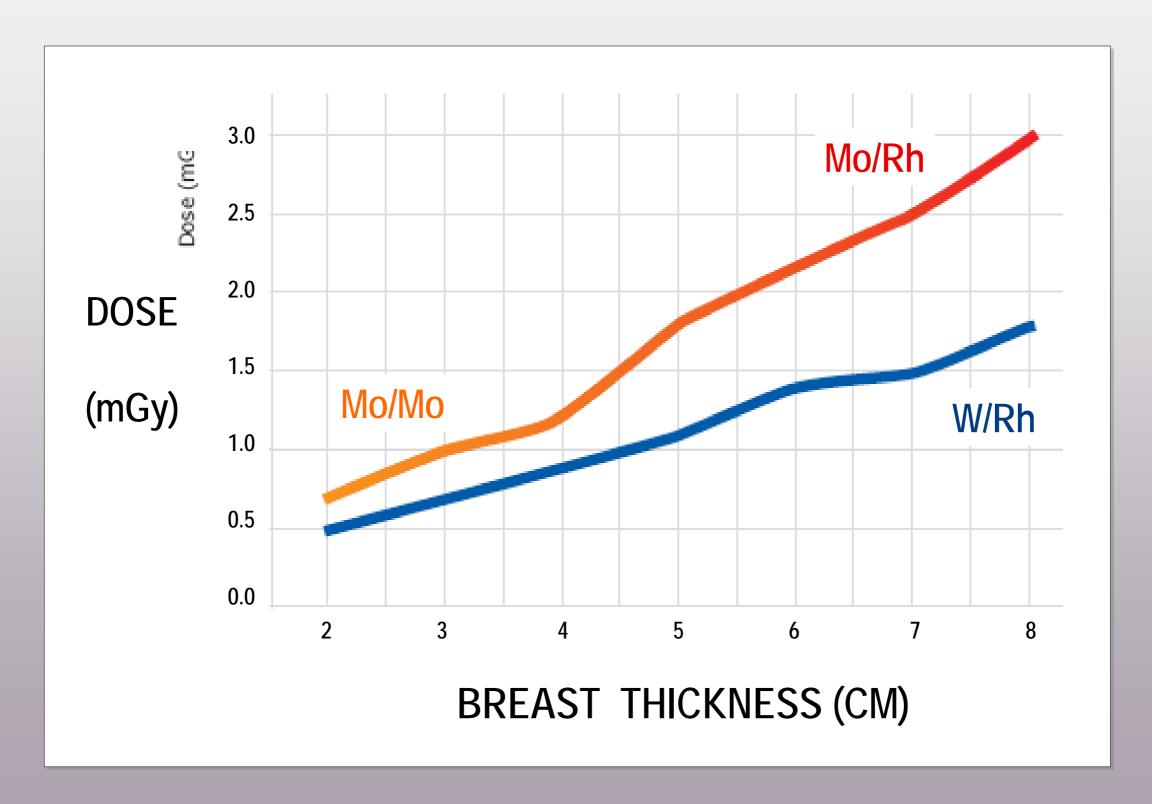
In 20\_\_\_, \_\_ screening mammography exams were conducted in the US and \_\_\_% were performed using a digital mammography imaging system

#### **Characteristic Photons:**

Moly: 17.9, 19.5

Rhodium: 20.2, 22.7

Best spectra with kVp set 5-10 kVp above K-edge



Source: IMS Giotto 3D brochure

# Radiographic Characteristics of Breast Tissue

Tissue Type	Density	Atomic #
Adipose		
Glandular		
Calcification		

# **Breast Imaging Statistics**

Breast cancer #\_\_\_ cause of death in women aged XX-YY Lifetime risk: 1 in 8 women will be diagnosed In 2006, \_\_\_\_ new cases of breast cancer were diagnosed; approx. half of which were diagnosed as a result of screening mammography Risk of inducing a breast cancer as a result of exposures associated with lifetime of screening mammography: \_\_\_\_\_ In 20\_\_\_, \_\_\_\_ screening mammography exams were conducted in the US and \_\_\_\_% of those studies were performed using a digital mammography imaging system

Sources: http://apps.nccd.cdc.gov/uscs/

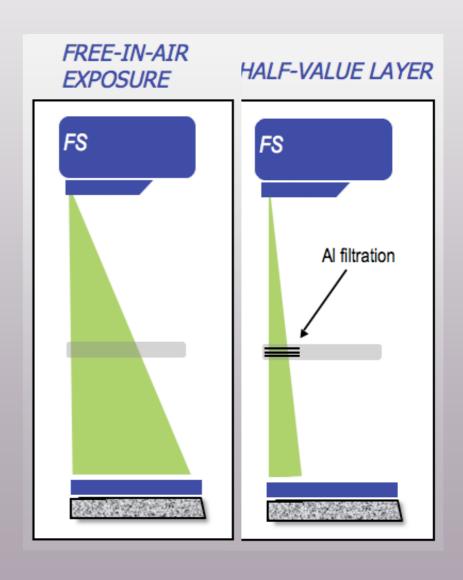
# Technique Optimization Protocol

# Characterizing the Beam Quality & Exposure

Measure free-in-air exposure at each beam quality: target/filter & kVp

Extrapolate to phantom surface using inverse square law

Measure HVL at each beam quality using narrow beam geometry and calibrated ion chamber fitted with a Mammo probe

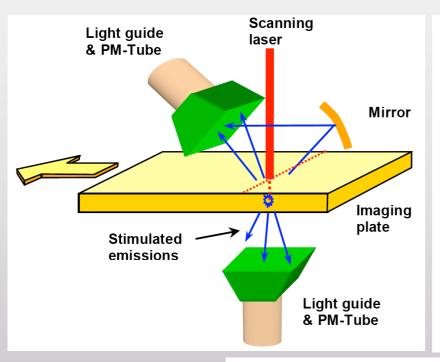


#### **GE Senographe**

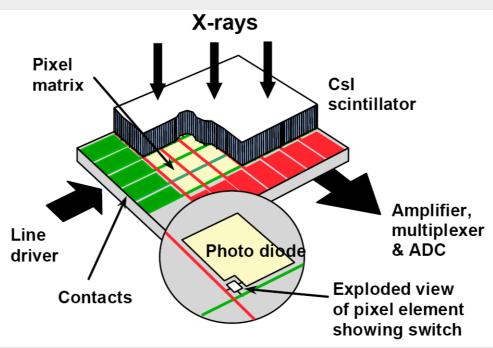
Indirect DR: Cs(I) TFT

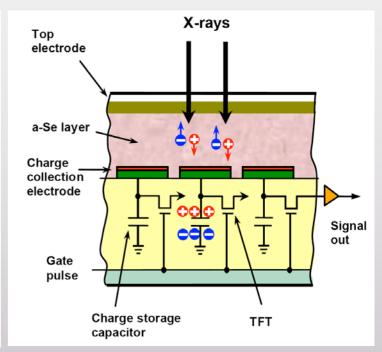
# Hologic Selenia

Direct DR: aSe TFT



CR: PSP





#### Indirect vs. Direct Detection ➤Indirect: scintillator converts x-rays to light photons → causes scattering/image blur → "smooth" image ➤ Direct: no scintillator → detector converts x-rays to electrons directly - no intermediate steps → "sharper", "edge enhanced" Screen-Film Direct Digital Indirect Digital X-ray photon X-ray photon X-ray photon Csl . Phosphor Selenium Scintillator Layer Semiconductor TFT array or CCD TFT array Film

#### **Indirect Conversion**

**GE Senographe** 

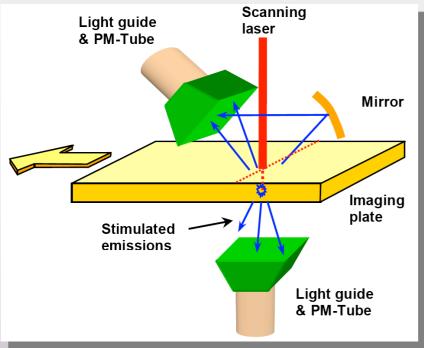
Selenia

#### **GE** Senographe

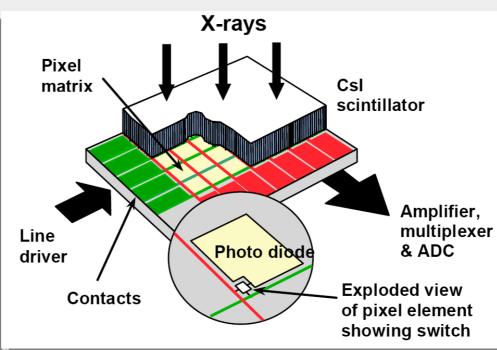
Indirect DR: Cs(I) TFT

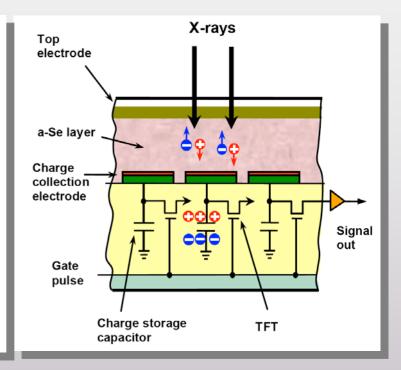
Hologic Selenia

Direct DR: aSe TFT



CR: PSP

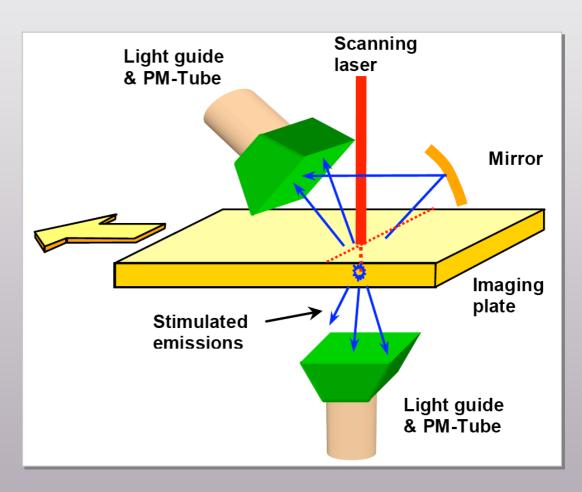






**DIRECT DETECTION** 

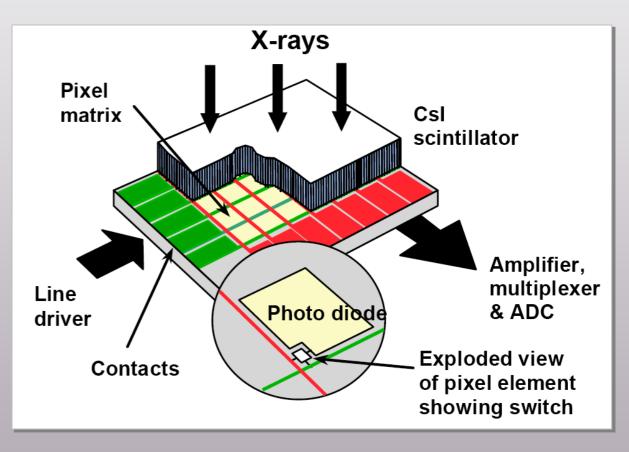
# Computed Radiography



Source: Basset LW, Imaging the Breast, Cancer Medicine, 6th ed

# Indirect DR

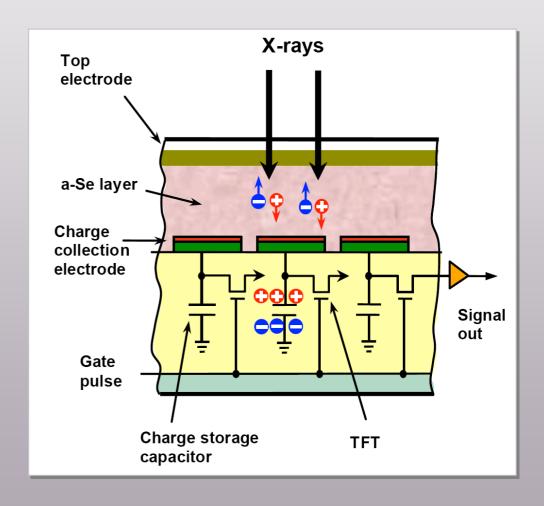
#### Cs(I) TFT Array



Source: Basset LW, Imaging the Breast, Cancer Medicine, 6th ed

# Direct DR

## aSi TFT Array



Source: Basset LW, Imaging the Breast, Cancer Medicine, 6th ed