

# The Concept of Personalized Screening and Genetic Counseling

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# Personalized Screening

- Standard Screening in the U.S.
- Who is high risk?
- How do we screen them?
- How does genetic counseling play a role?



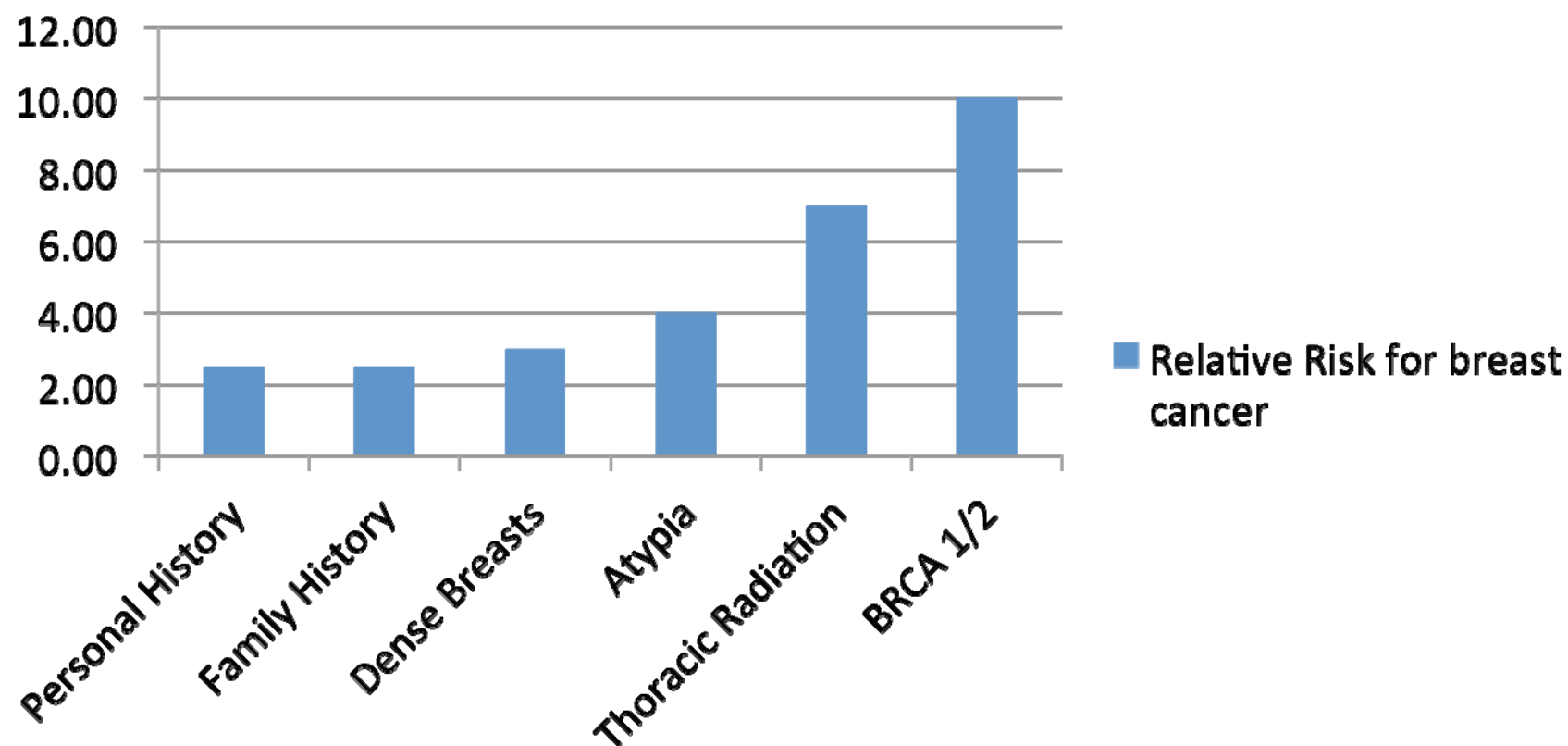
# Standard Screening

American Cancer Society	National Comprehensive Cancer Network	U.S. Preventive Services Task Force
<b>Mammography</b>		
Every year starting at age 40	Every year starting at age 40	Informed decision-making with a health care provider ages 40-49  Every 2 years ages 50-74
<b>Clinical Breast Exam</b>		
Every 3 years ages 20-39	Every 1-3 years ages 25-39	Not enough evidence to recommend for or against
Every year starting at age 40	Every year starting at age 40	



# High Risk Patients

## Relative Risk for breast cancer



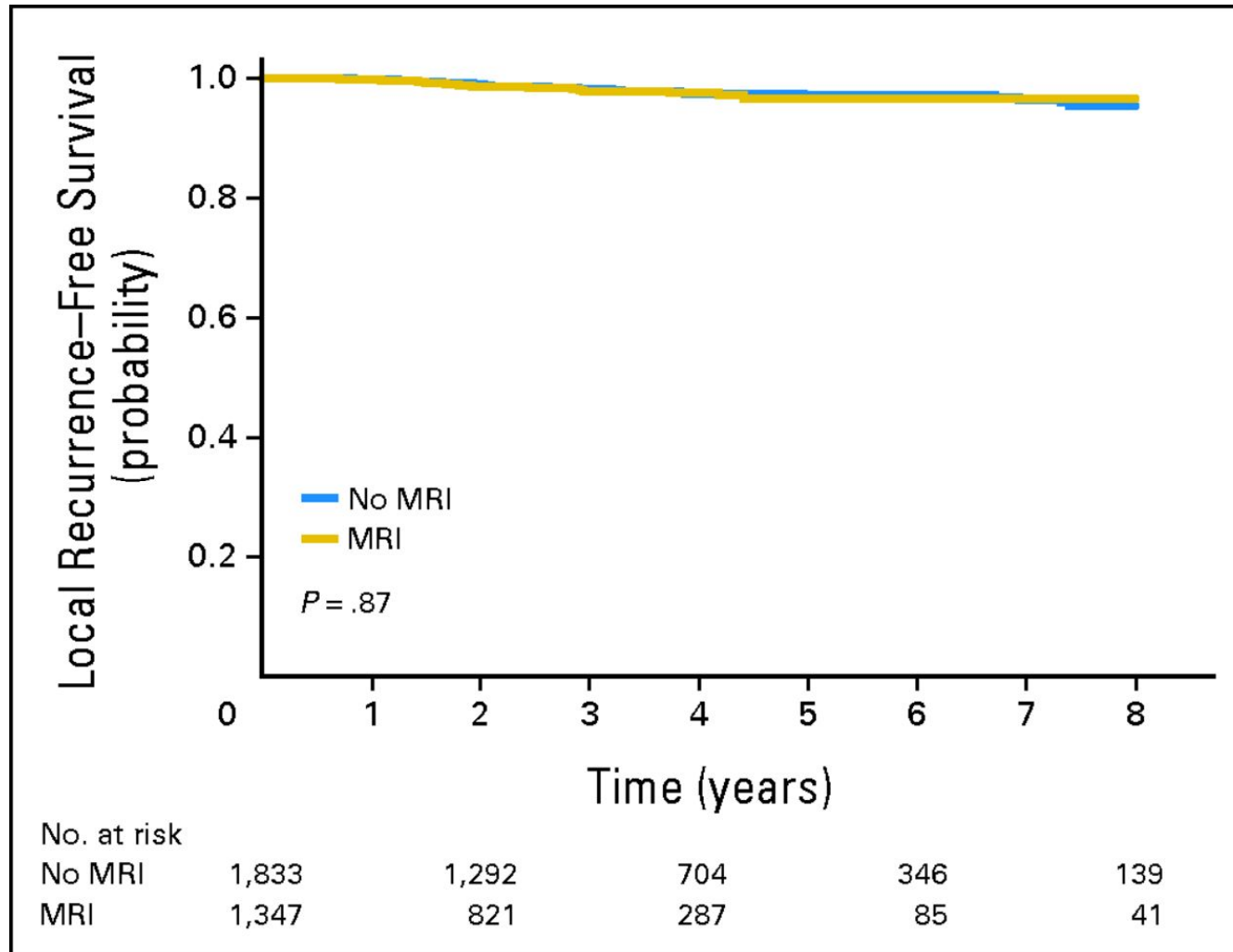
American Cancer Society, Breast Cancer Facts & Figures 2011-2012 and Cancer Facts & Figures 2013

# Personal History

- No consistent data that enhanced screening improves outcome.



**Kaplan-Meier local recurrence-free survival curves for magnetic resonance imaging (MRI) versus no MRI. P value is based on the log-rank test for equality of survival function curves.**



Houssami N et al. JCO 2014;32:392-401

# Strong Family History/Atypia

- Lifetime risk greater than 20%
- Women  $\leq 35$  with a  $>1.7\%$  5-year risk of developing breast CA

(Based on familial risk models, e.g. Claus or Gail)

- Annual MMG
- Clinical Breast Exam (CBE) every 6-12 mos
- MRI



# Strong Family History/Atypia

*Table 5. Meta-analysis of Studies\**

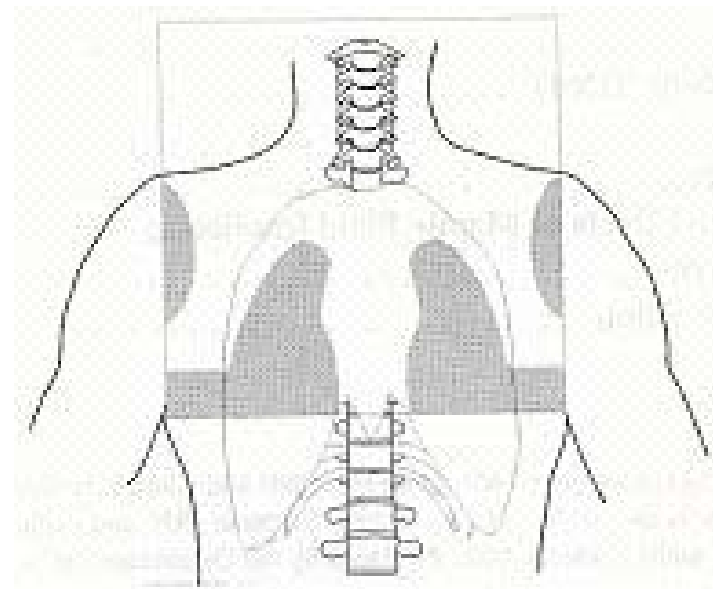
Screening Technique and BI-RADS Cutoff Value (Reference)	Studies/Screening Examinations/Tumors, n/n/n	Diagnostic Odds Ratio (95% CI)
<b>Mammography</b>		
≥3 (23, 24, 26, 31)	4/6678/108	14.7 (6.1–35.6)§
≥4 (22–24, 26, 27, 29, 30)	7/8818/178	38.5 (15.9–93.3)§
<b>MRI</b>		
≥3 (23, 24, 26, 28, 31)	5/6719/109	18.3 (11.7–28.7)
≥4 (22–24, 26–30)	8/8857/178	88.7 (34.6–227.5)§
<b>Mammography and MRI</b>		
≥3 (25, 26, 31)	3/2509/63	45.9 (17.5–120.9)
≥4 (22, 24, 26, 27, 29)	5/4272/115	124.8 (36.4–427.4)§

Ann Intern Med. 2008;148(9):671-679. doi:10.7326/0003-4819-148-9-200805060-00007

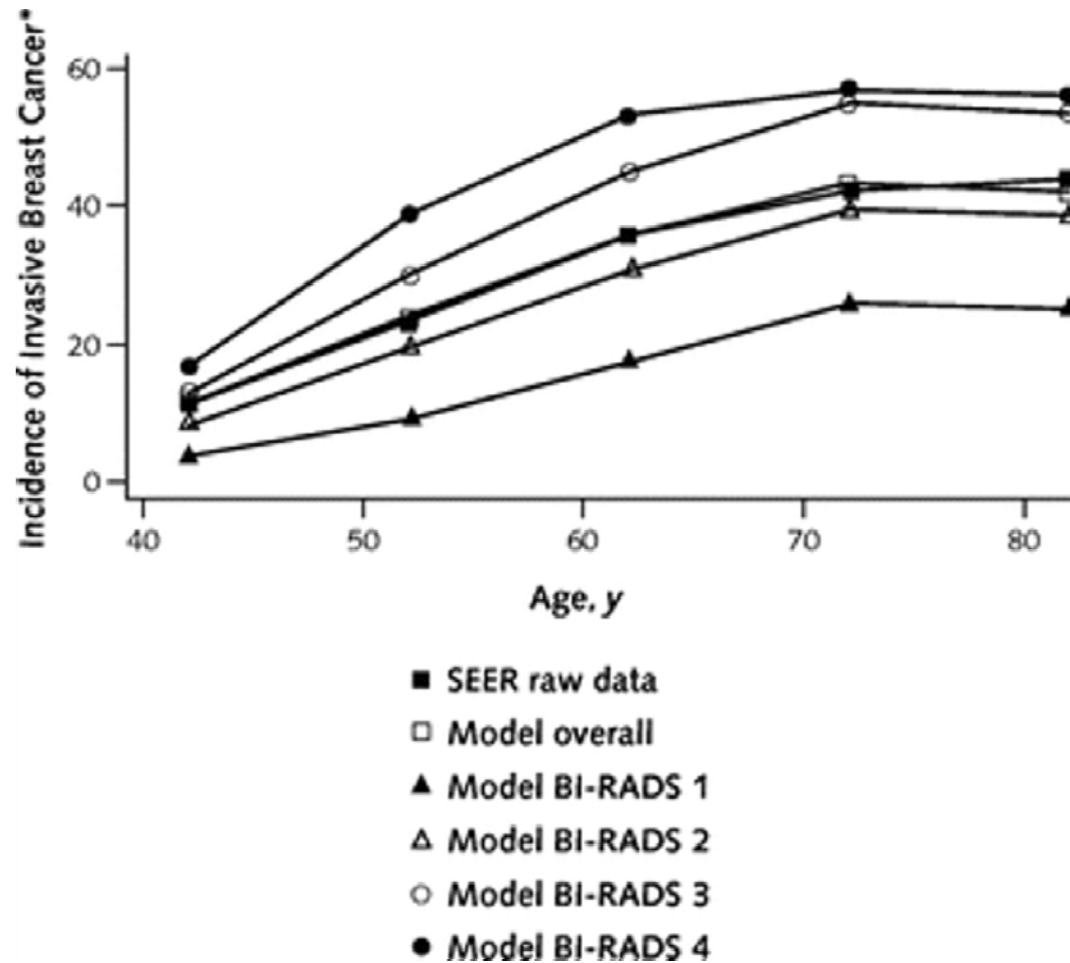
# Thoracic/Mantle Radiation

Beginning 8-10 years  
after RT or at age 25  
(whichever occurs last)

- Annual MMG
- CBE every 6-12 mos
- ?MRI

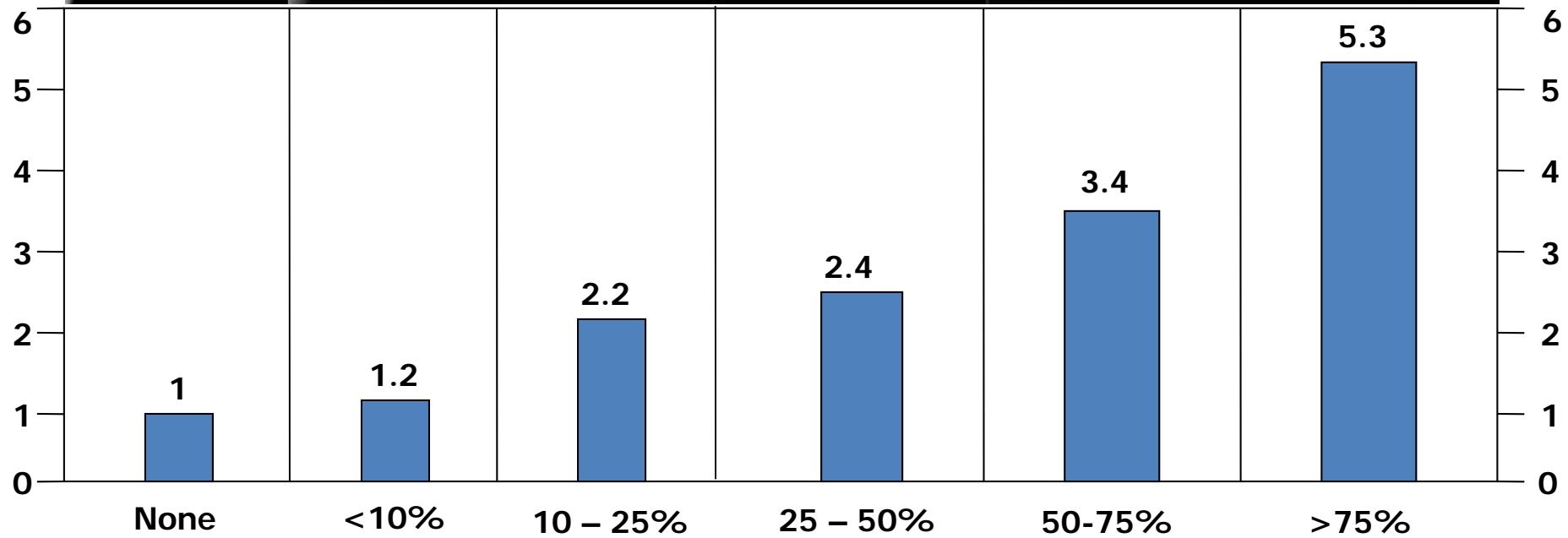
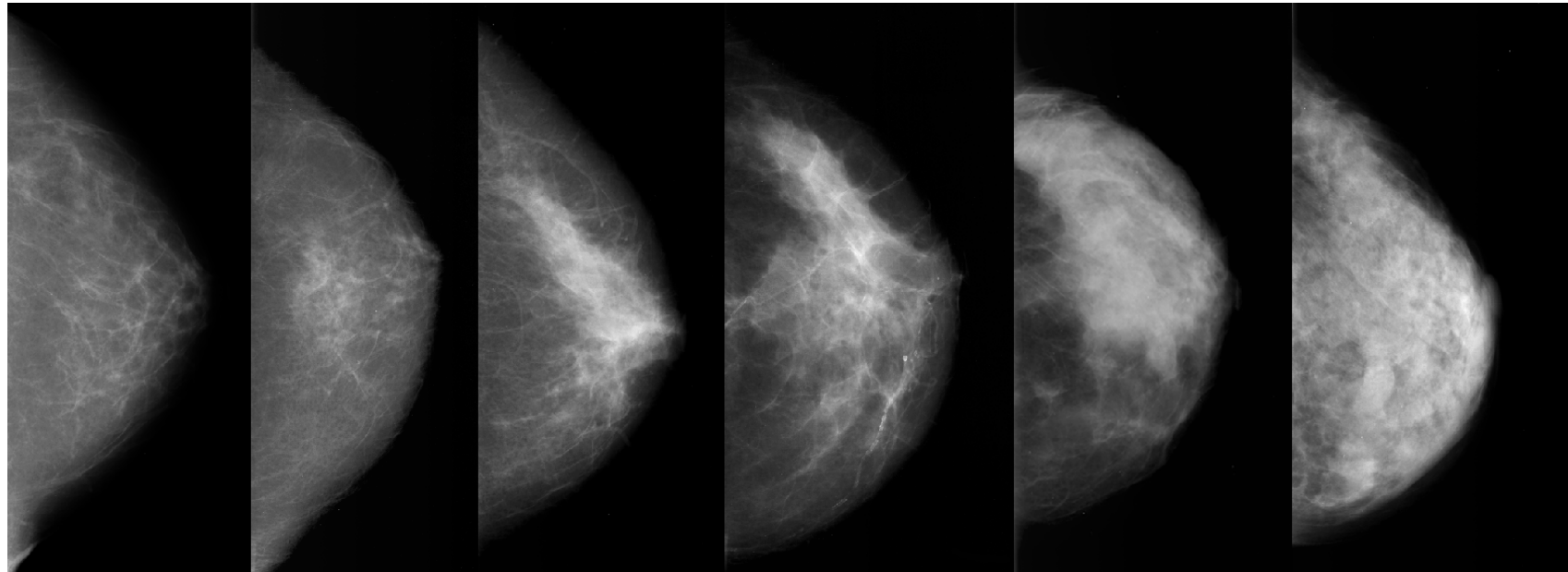


# Breast Density



Ann Intern Med. 2011;155(1):10-20. doi:10.7326/0003-4819-155-1-201107050-00003

Boyd, 1995 via J. Harvey, UVA



# Breast Density

*Table 3. Outcomes of Mammography Every 2 Years, Mammography Every 3 to 4 Years, and No Mammography in Women With No Previous Breast Biopsy or Family History of Breast Cancer*

Age and BI-RADS Category	Patients, %	10-Year Incidence of Invasive Breast Cancer, %	10-Year Incidence of False-Positive Results, %*	Mammography Frequency Comparison	Number Needed to Screen†	Cost per QALY Gained, \$
<b>40-49 y</b>						
1	4.4	0.43	17.2	3-4 y vs. none	8475	228 427
				2 y vs. 3-4 y	27 778	362 699
2	35.3	0.89	33.3	3-4 y vs. none	4870	120 113
				2 y vs. 3-4 y	12 195	140 048
3	46.8	1.38	38.9	3-4 y vs. none	4386	90 646
				2 y vs. 3-4 y	7813	87 769‡
4	13.5	1.79	38.8	3-4 y vs. none	2703	83 899
				2 y vs. none	6579	74 482‡

Ann Intern Med. 2011;155(1):10-20. doi:10.7326/0003-4819-155-1-201107050-00003

# Possible tests to add to mammography

<b>Modality vs. Mammography alone</b>	<b>Absolute ↑ Cancer Detection per 1000 screens</b>
Clinical breast exam	0.3
Double Read	1
CAD	1
Tomosynthesis	2
Ultrasound	3-4
Molecular Breast Imaging, Contrast-enhanced mammo	7-8

Courtesy of Wendie Berg, MD, PhD

# Genetically High Risk

- BRCA 1 or 2
- Rare genetic disorders (Li- Fraumeni, Cowden, Bannayan-Riley-Ruvalcaba)
- Untested 1st degree relatives of the above



# High Hereditary Risk Screening

- National Comprehensive Cancer Network (NCCN) Guidelines
  - Annual Mammography starting at age 25
  - Clinical Breast Exam every 6 to 12 months
  - Questions
    - MRI?
    - Screening Ultrasound?

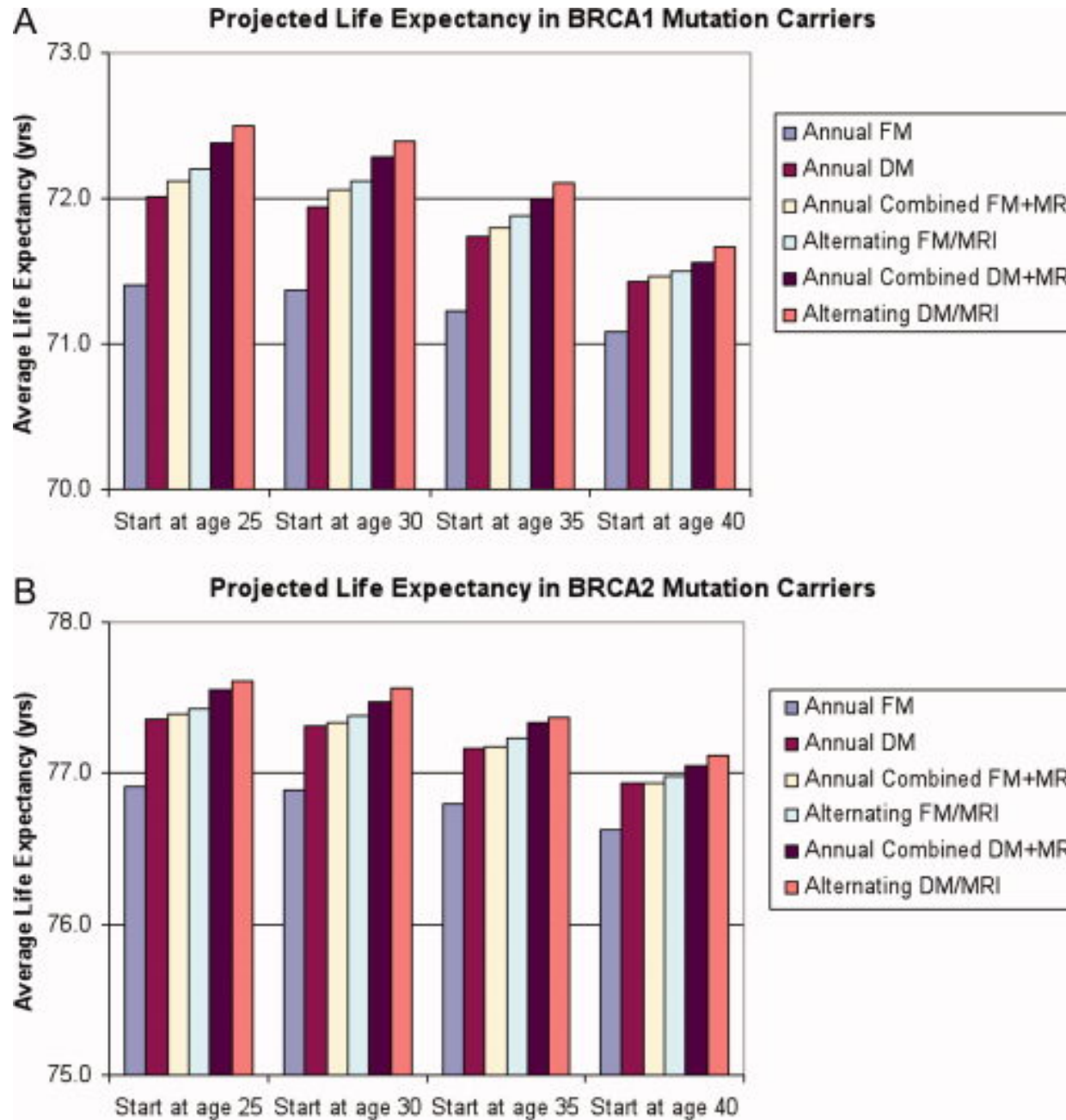


# BRCA Mutations

**Table 1: Lifetime breast cancer risk**

	Lifetime breast cancer risk	Median age of breast cancer onset (y)
General population	11%	61
<i>BRCA1</i>	65%	43
<i>BRCA2</i>	45%	41

## Annual screening strategies in *BRCA1* and *BRCA2* gene mutation carriers



# HOW DO WE SCREEN?

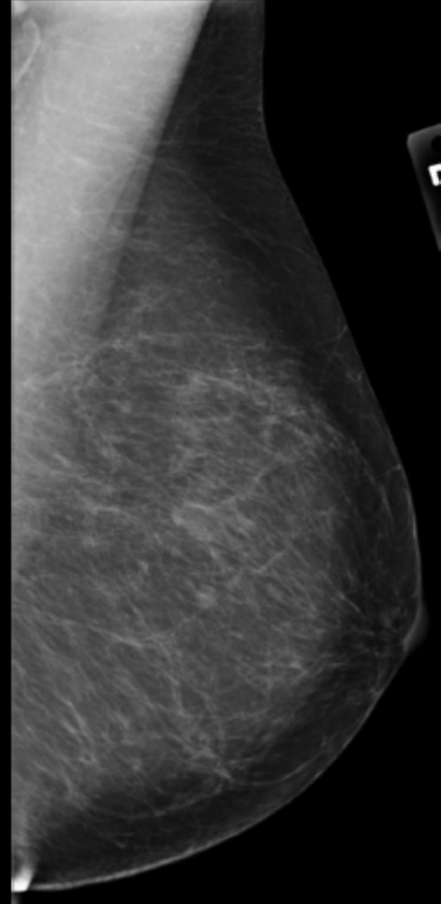
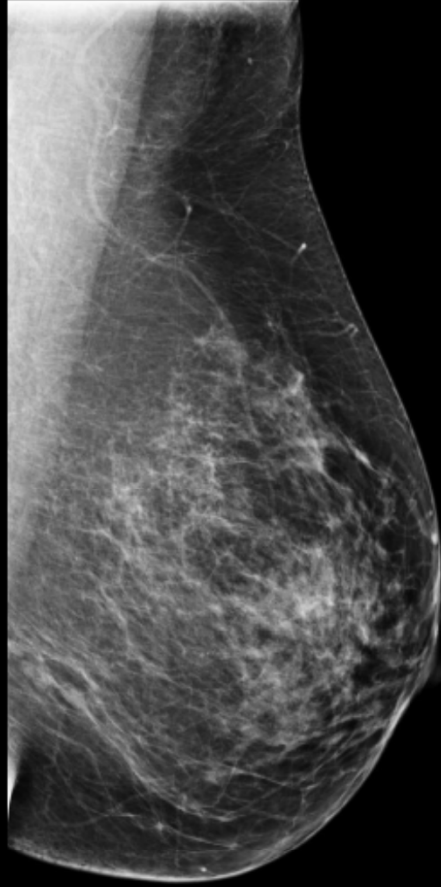
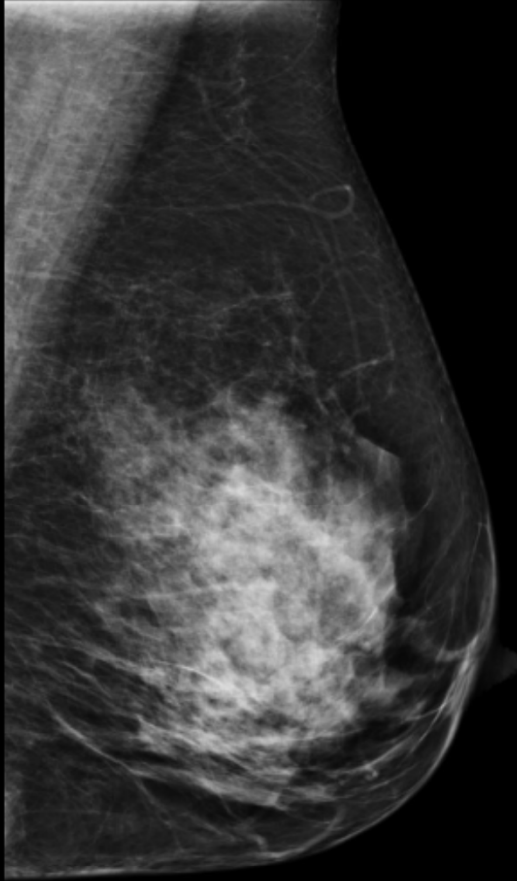
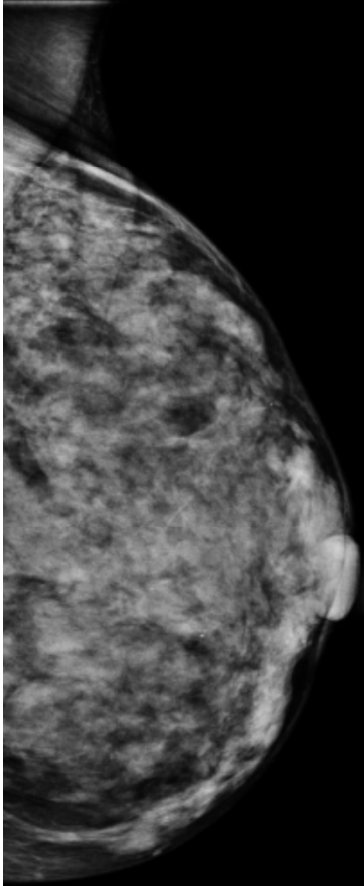


# Screening Mammography

- + Several randomized controlled trials since the 1960's
- + Reduction in mortality (25-30%)
- + Smaller and more node-negative tumors
- No normal breast across patients
- Breast tissue varies with hormonal changes
- Doesn't tell the whole story (see structure, not function)

Radiol Clin N Am 40 (2002) 395-407





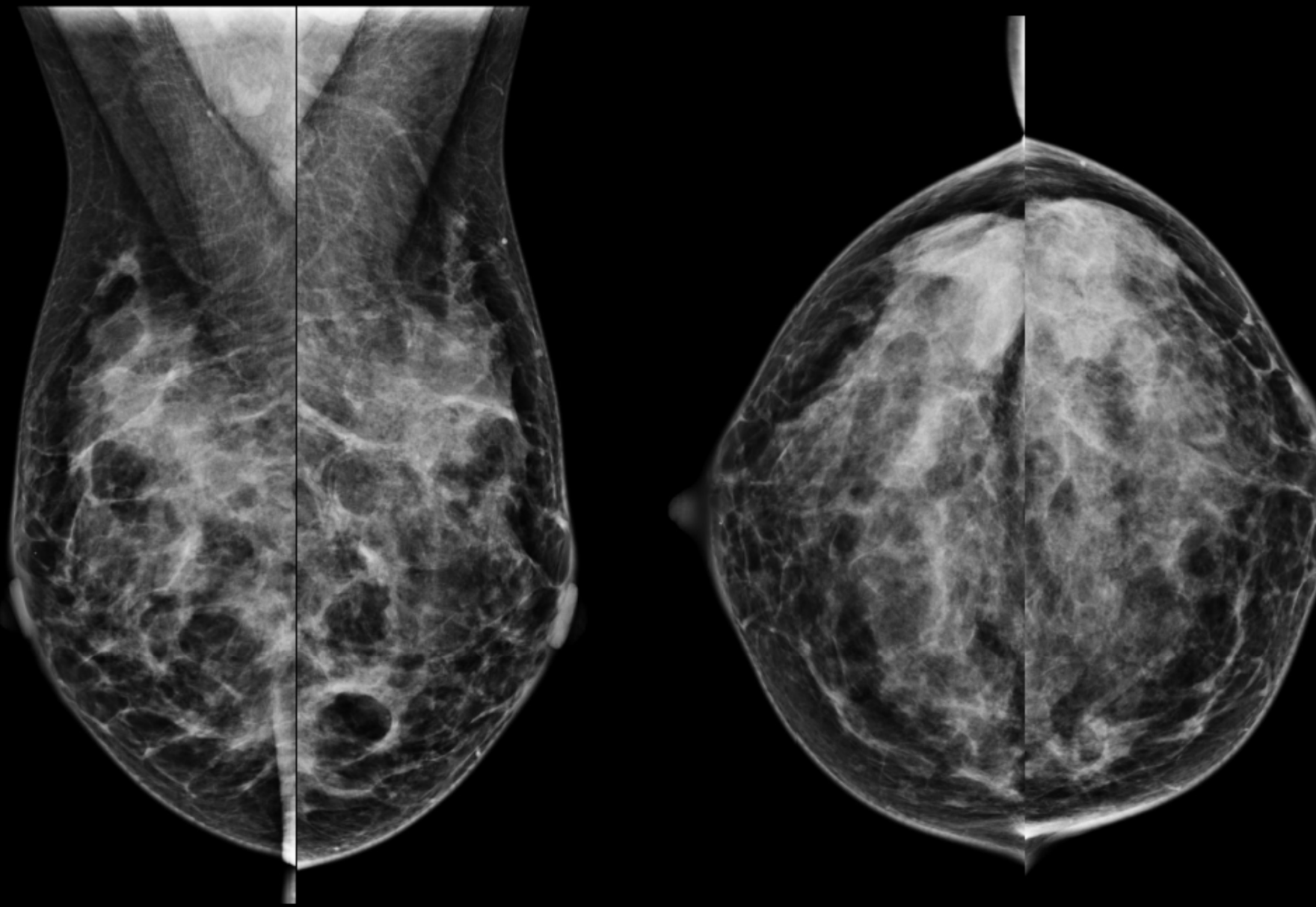
# Mammography Alone

- 35-50% cancers found between screenings
- 40-78% tumors >1cm
- 20-56% had nodal involvement



Rosen et al. J Clin Oncol 2001;19:924-30  
Brekelmans et al. J Clin Oncol 2001;19:924-30  
Komenaka et al. Cancer 2004;100:2079-83

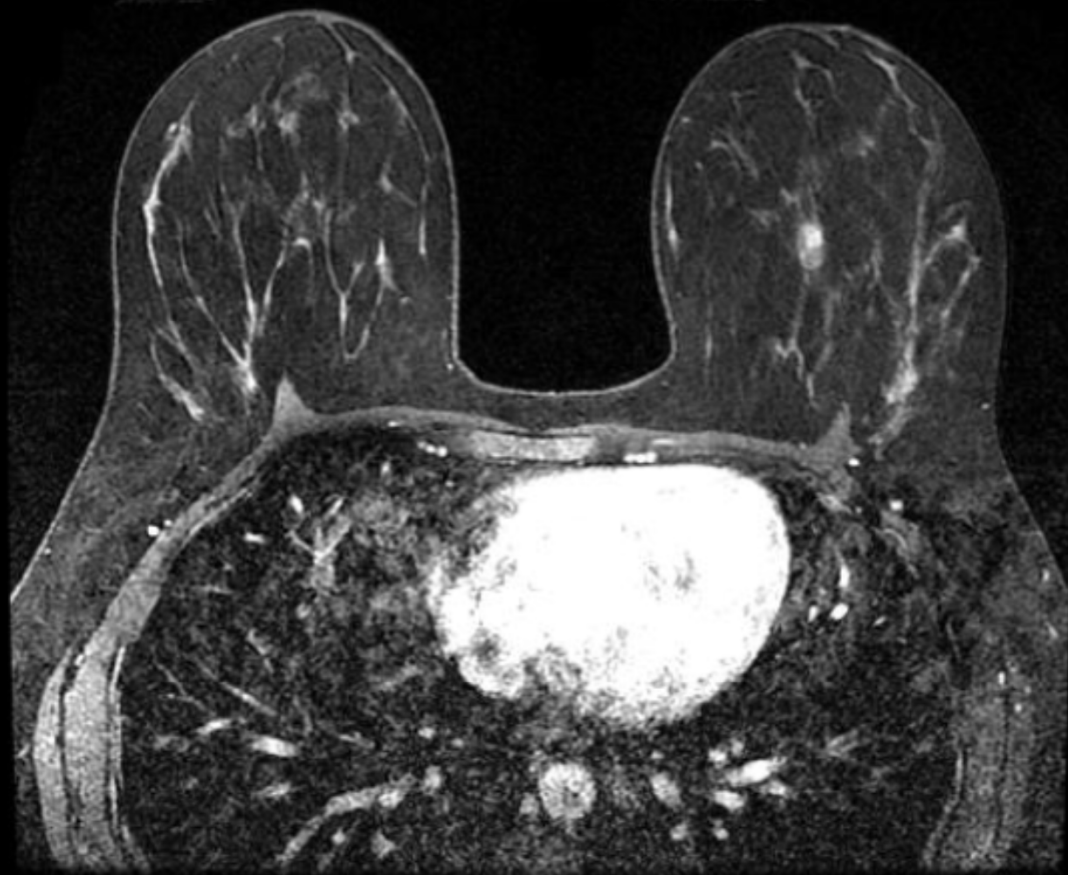
41year old BRCA1 mutation carrier for annual screening

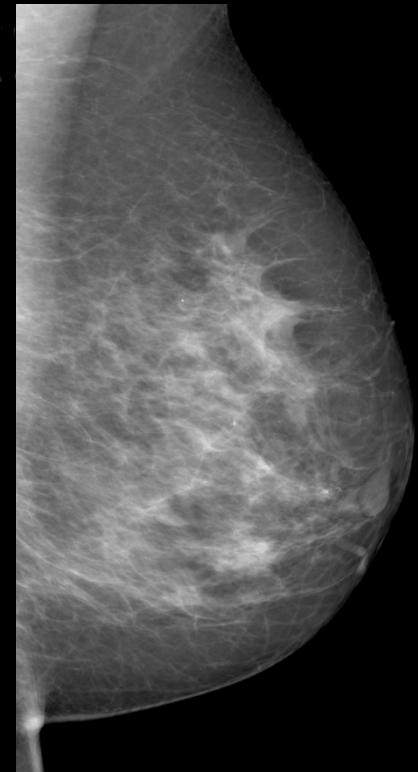
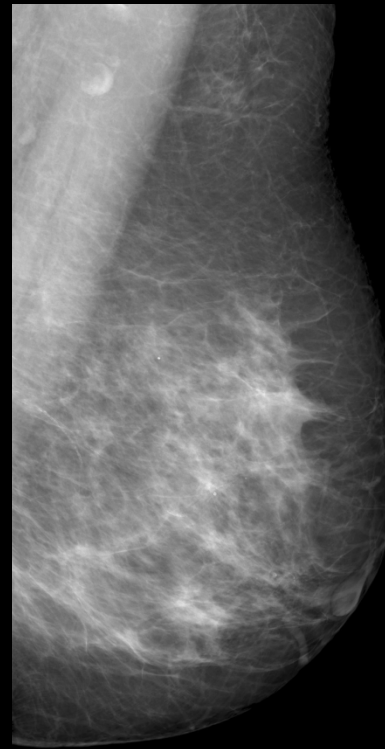
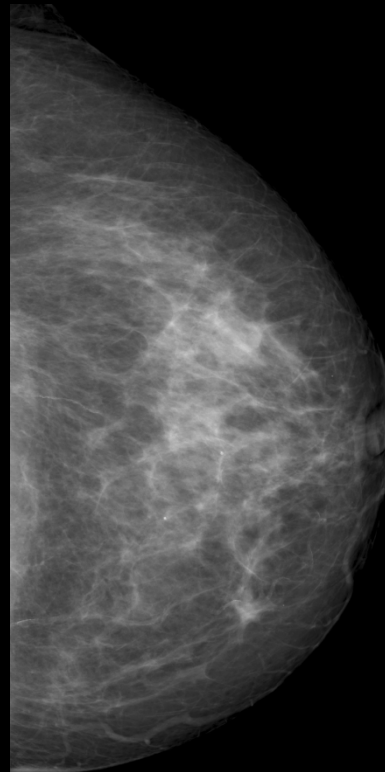
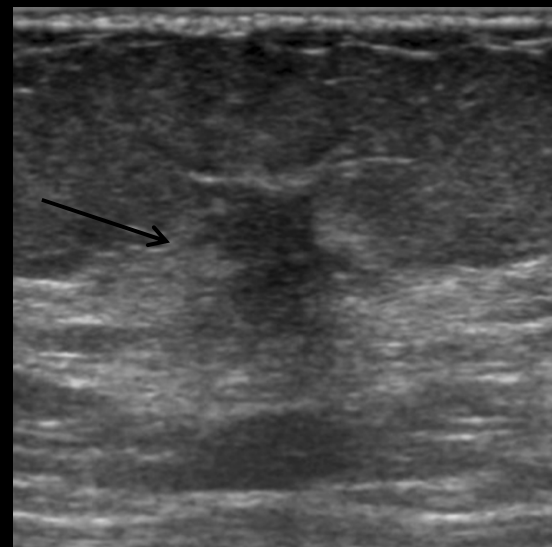
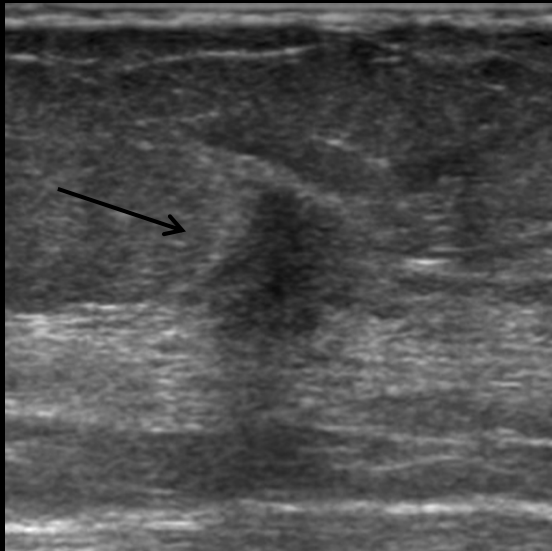




US Bx: IDC, nucl gr 2

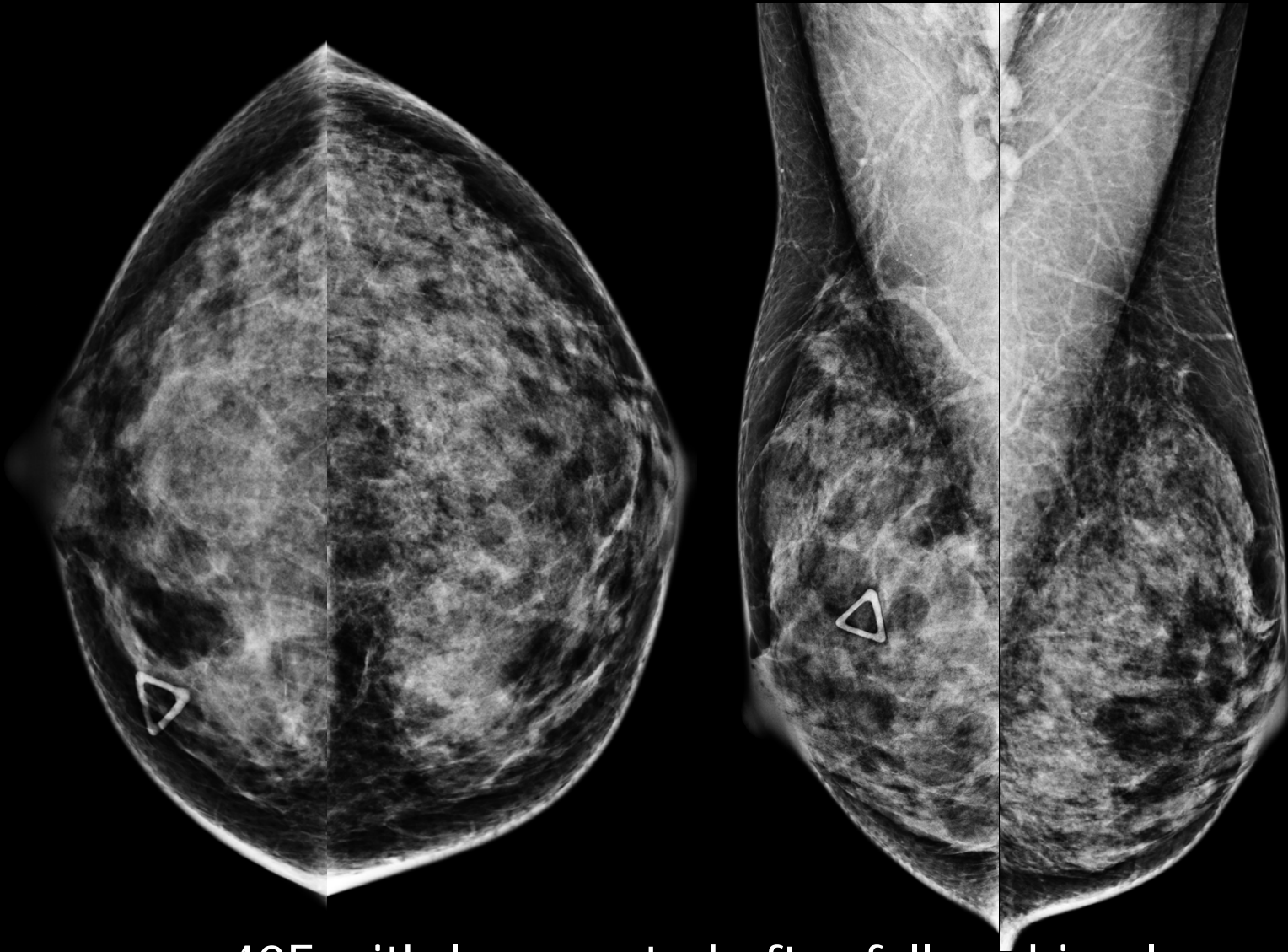






70F personal hx rt mastectomy, BRCA-1 mutation carrier  
24 mo screen US+ 19 mm grade 3 IDC-DCIS, N0

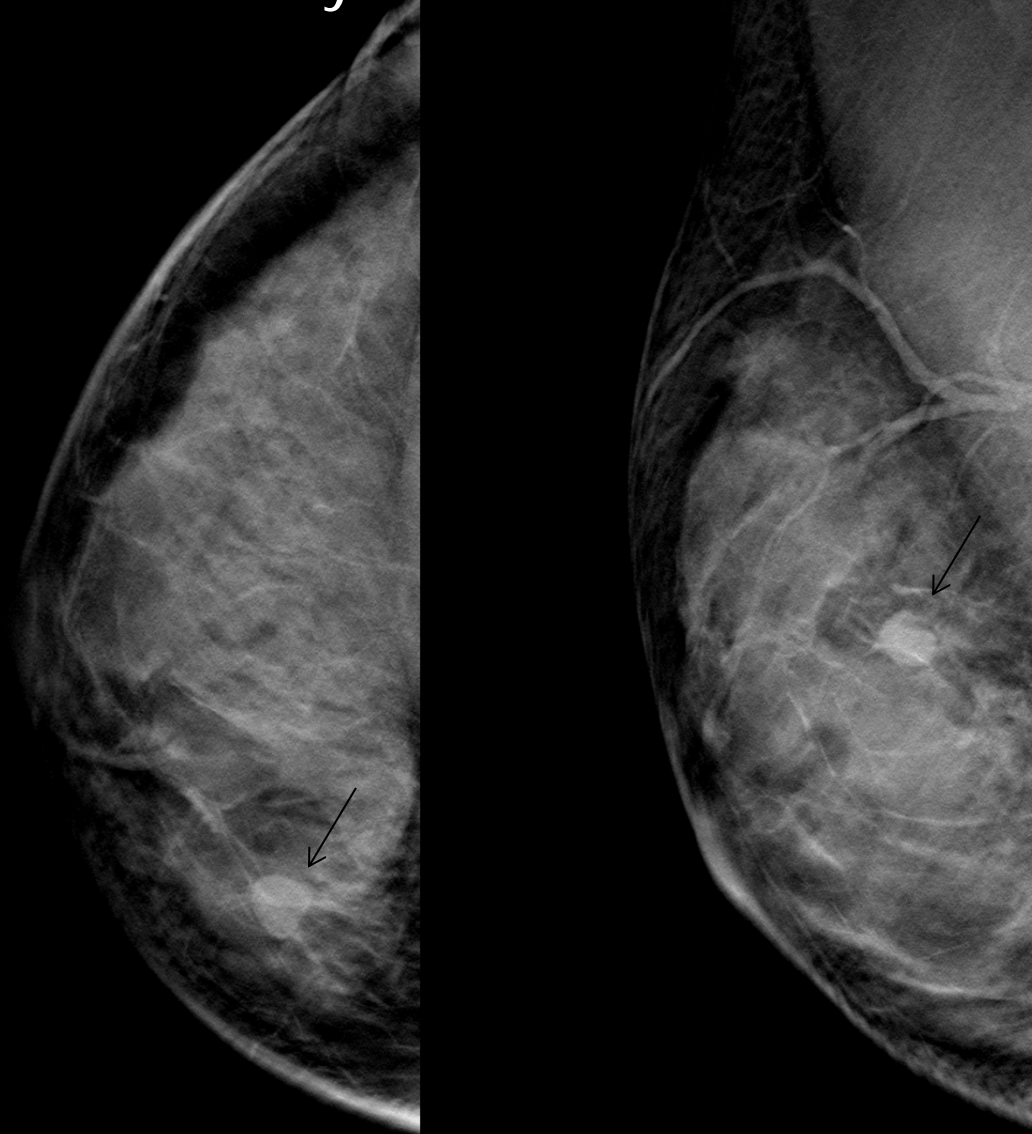
Courtesy Dr. Mary Mahoney, U Cincinnati  
& Wendie Berg, MD, PhD



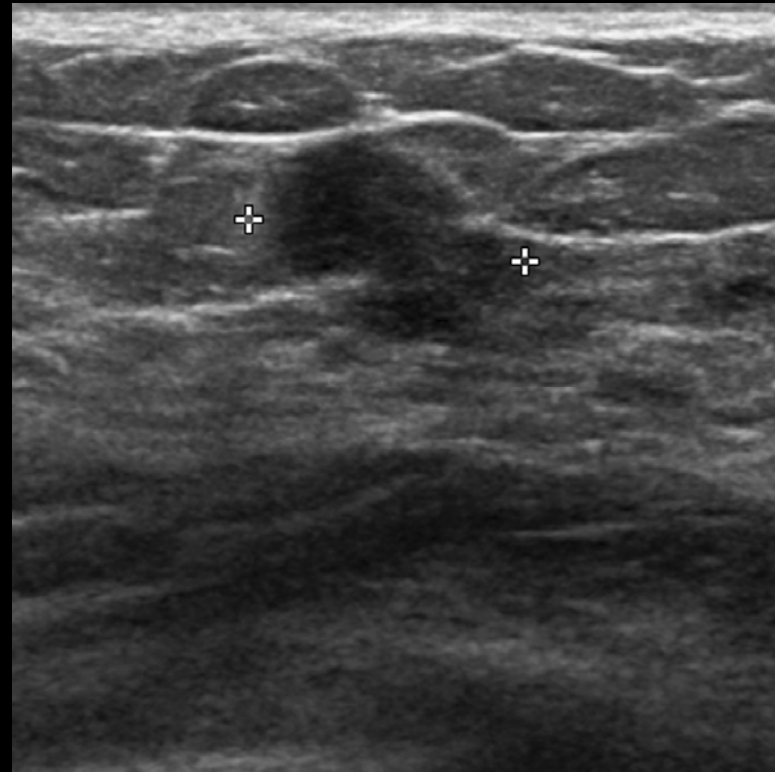
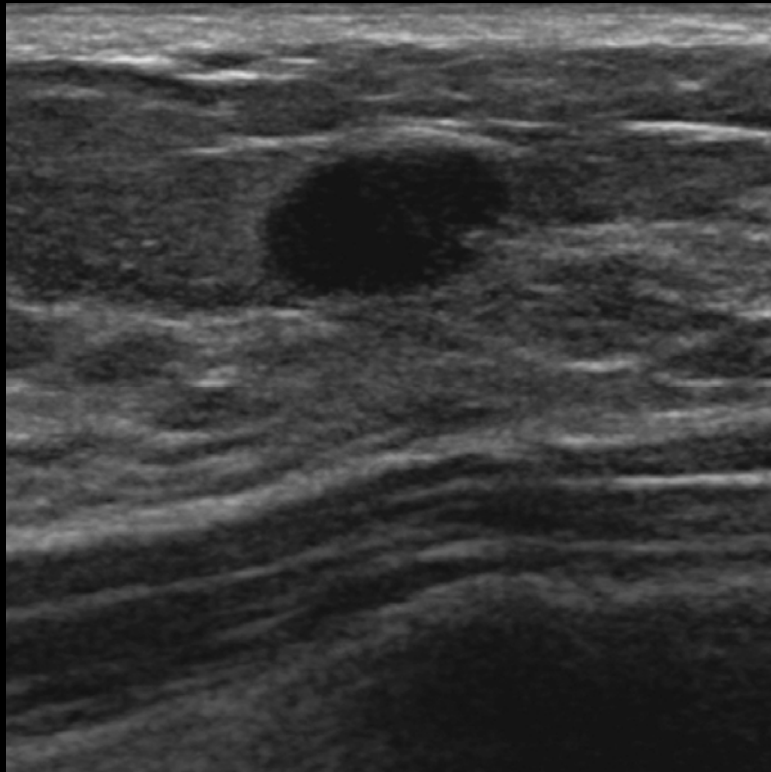
40F with lump noted after fall on bicycle

Courtesy of Wendie Berg, MD, PhD

# Single slices from tomosynthesis

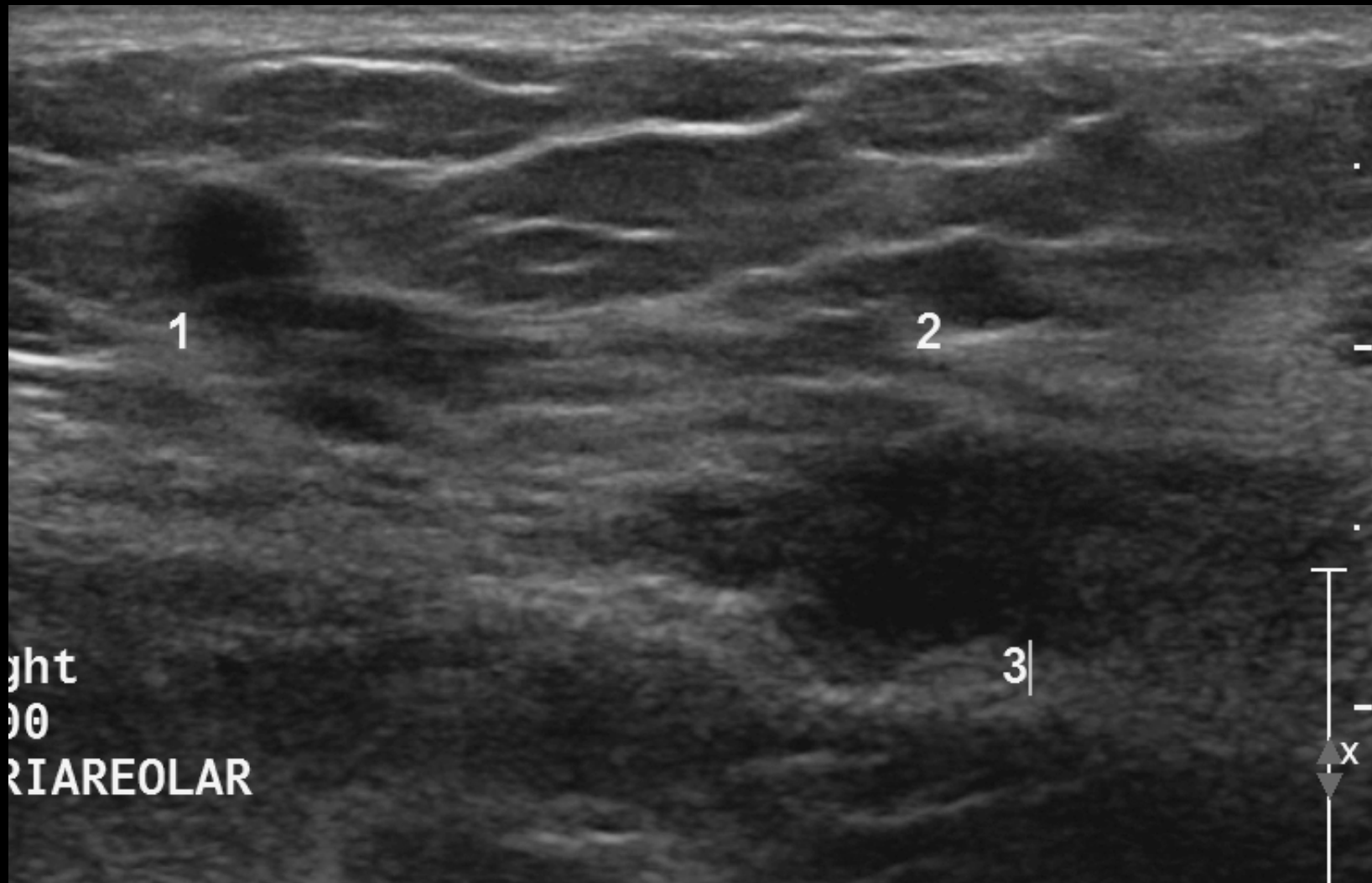


Courtesy of Wendie Berg, MD, PhD

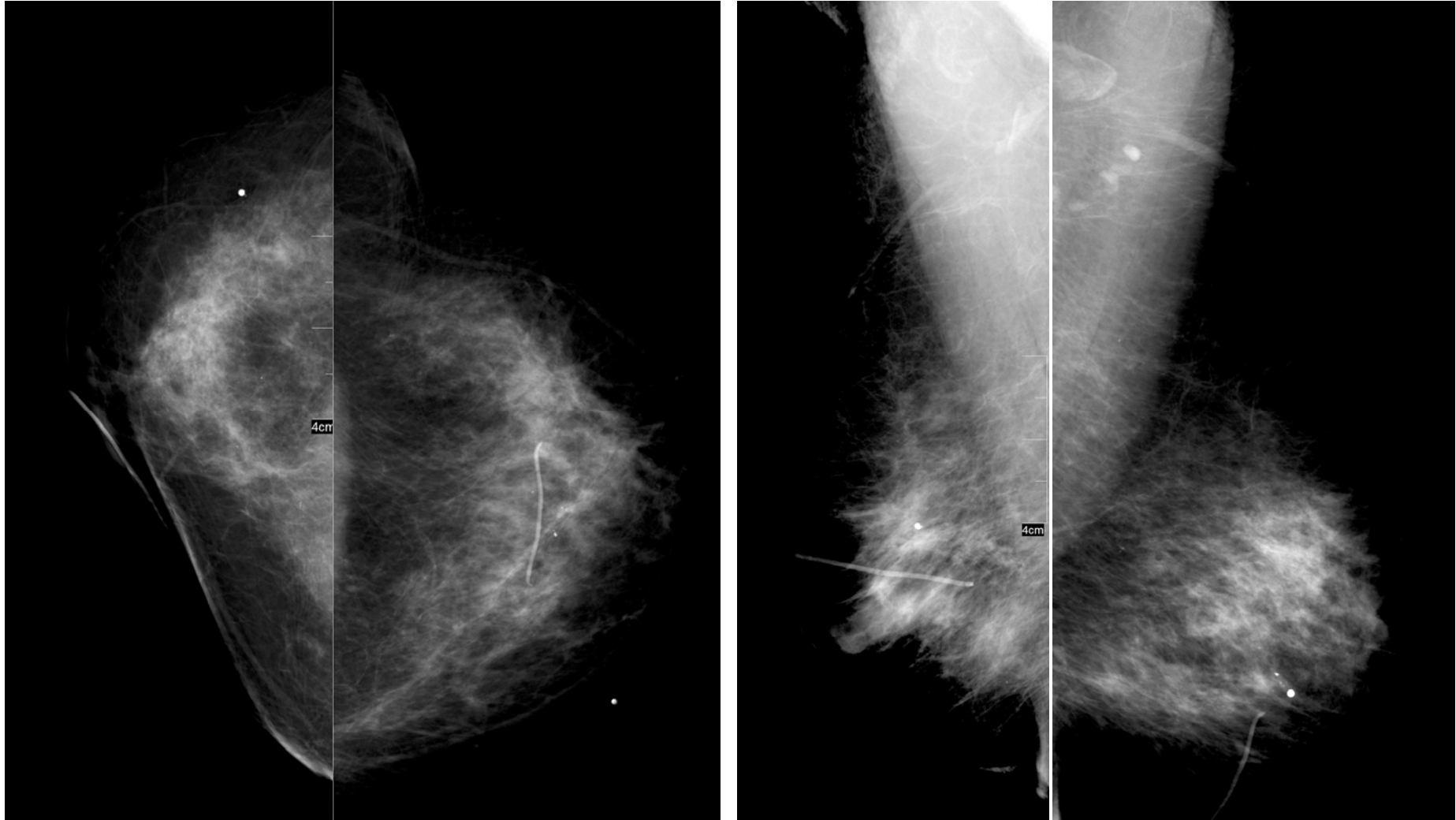


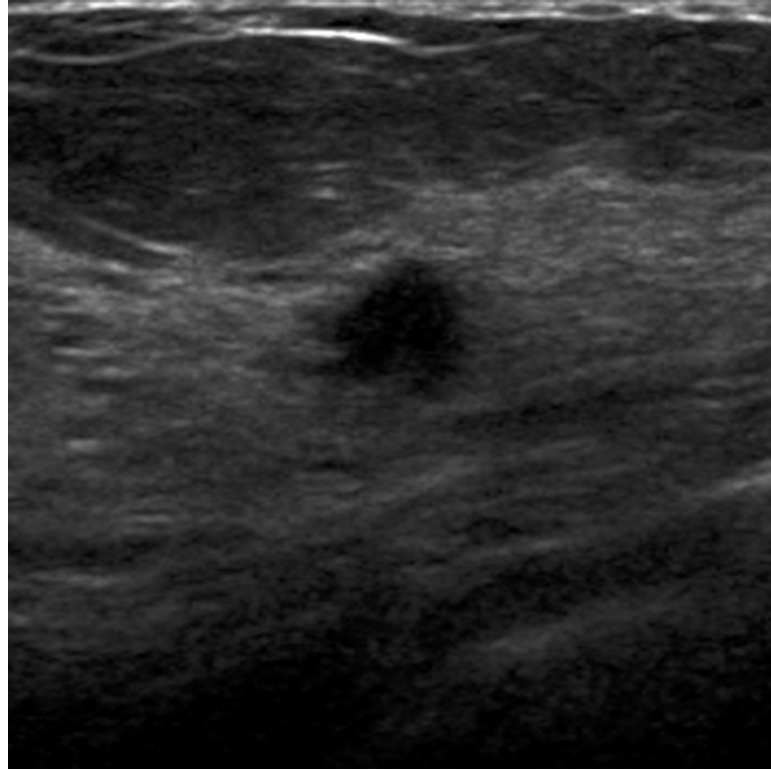
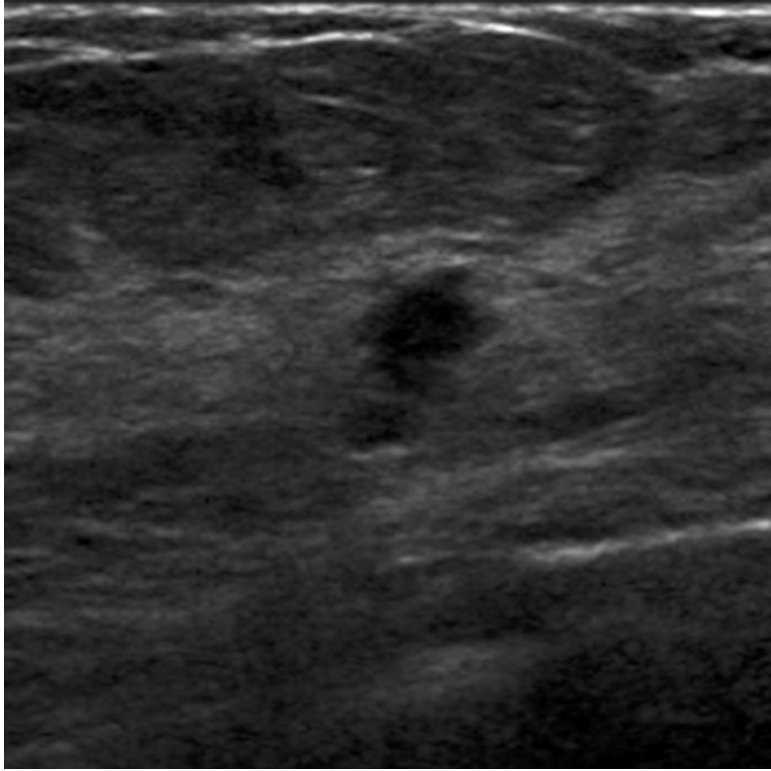
Courtesy of Wendie Berg, MD, PhD

# Multifocal grade 3 IDC (ER, PR, HER2 positive)



64F personal hx breast cancer Rt







# Screening Breast US in Women at Intermediate Elevated Risk for Breast Cancer: ACRIN 6666 Trial

- 2809 pts with elevated risk of breast cancer
- Increased density by MG
- Asymptomatic
- Annual mammogram and US each yr x 3

# Results: 3 Yr Program

111 participants with cancer in 7473 screens (1.5%)

- 59/111 (53%) with cancer by MG
  - 33/111 (30%) only by MG; (55%) invasive
- 58/111 (52%) with cancer by US
  - 32/111 (29%) only by US; (94%) of those invasive
- Both Mammography and US recommended

# Summary CDR

Screen 1000 women	# women add testing	# women found breast cancer
2D MG alone	100	2-7
2D MG plus 3D	70	4-10 (3D: 2-3)
2D MG + US	170-230	5-11 (US: 3-4)
2D MG + MRI	160-220	12-17 (MRI : 10)

Courtesy Berg MD, PhD

# GENETIC COUNSELING



University of Pittsburgh Cancer Institute



MAGEE-WOMENS RESEARCH INSTITUTE

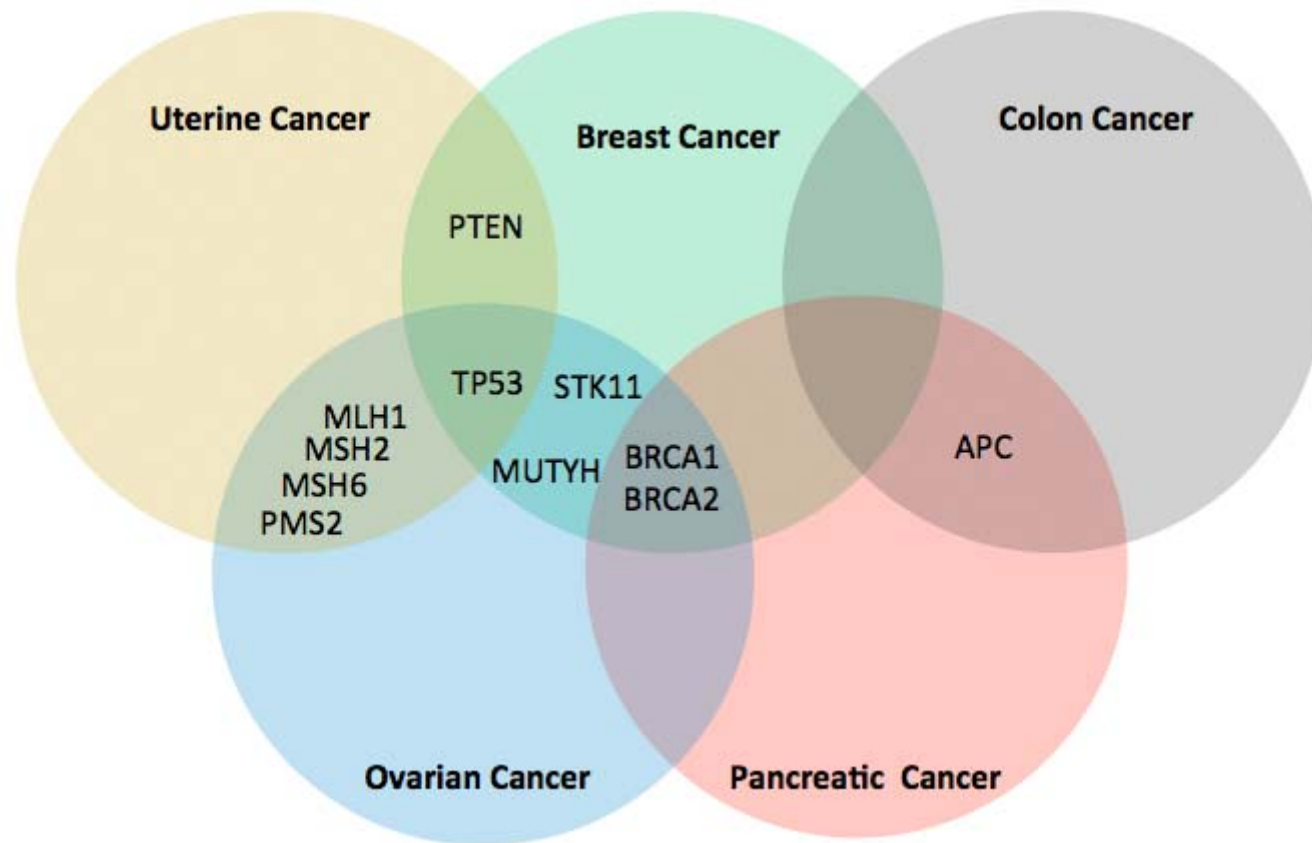
Magee-Womens Hospital of UPMC



# Eligibility - BRCA

- Many Criteria
  - Breast cancer diagnosed before age 50 years
  - Cancer in both breasts
  - Both breast and ovarian cancers
  - Multiple breast cancers
  - Two or more primary types of *BRCA1*- or *BRCA2*-related cancers in a single family member
  - Cases of male breast cancer

# Mo' Genes, Mo' Problems



# Expanded Panels - Eligibility

- Hereditary Breast and Ovarian Cancer (HBOC) syndrome
- Family history of HBOC
- Tested negative for the *BRCA1* and *BRCA2* mutations.
  - early-onset of breast cancer (i.e. <50 years)
  - ovarian cancer at any age
  - two primary breast cancers
  - multiple family members with breast cancer
  - males with breast cancer

Genes	<u>Risk of Breast Cancer</u>	
	OR	Lifetime Risk
<b>FANC-BRCA Pathway Genes</b>		
BRCA1	10-20X	50-85%
BRCA2	10-20X	50-85%
PALB2	2-4X	
BRIP1	2-4X	
RAD51C	2-4X	
BARD1	2-4X	
RAD50	2-4X	
NBN	2-4X	
MRE11A	2-4X	
<b>CHEK2 Pathway</b>		
CHEK2	2-4X	
ATM	2-4X	
TP53		80-100%



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**Genes****Risk of Breast Cancer**

OR

Lifetime Risk

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**MMR Genes**

MLH1

MSH2

PMS2

PMS1

EPCAM

**Syndromic Colon Cancers**

APC

BMPR1A

SMAD4

**Other Syndromic Genes**

CDH1

PTEN

STK11

RB1

MUTYH

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# Expanded Panels

- Pros
  - Evaluate many genes at once
  - Look for rare genes
  - Save time and \$
  - More accurately assess risk
  - Screen those who might not be eligible by standard criteria
- Cons
  - Eligibility criteria unclear
  - Predicting risk
  - Unsure of screening/management recommendations for most mutations
  - Discrimination

Thank You!

