

Personalized Breast Cancer Detection

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Nothing to Disclose

History

- Mammography only imaging test globally recommended for breast cancer screening
- 7 RCT have shown substantial reduction in mortality
- Certain sub-populations have poor outcomes
- Certain populations at higher risk & may benefit from additional screening

Tabar: Lancet 2003

Screening

- Purpose to alter the history of an otherwise debilitating or fatal disease through early detection
- 76% of image detected cancers are Stage 0 or 1
- >50% of clinically detected cancers are Stage 2 or greater
- 71% deaths from breast cancer occur in women not regularly screened

Screening Concerns

- **Overdiagnosis:** Cancer never would have become clinically evident or slow growth & patient dies of another cause
- **False positives:** no cancer diagnosis within 1 year of additional testing. Costs for imaging, biopsy, anxiety
- **False negative:** Interval cancer becomes clinically evident before next annual screen after negative mammogram

Screening Exams

- Should not increase identification of low & intermediate grade DCIS (**over diagnosis**)
- Should decrease the incidence of advanced stage breast cancer (**false negative**)
- Should result in fewer interval cancers (**false negative**)

MRI Guidelines: Low Risk

- **<15% lifetime risk:** Annual mammography
- No indication for breast MRI

Saslow: Ca Cancer J Clin, 2007

www.cancer.gov/bcrisktool.com

MRI Guidelines: Intermediate Risk

- **15-20% lifetime:** Annual mammography & discuss risks & benefits of MRI
- Personal history of DCIS or invasive breast cancer, LCIS, ADH or ALH
- Extremely or heterogeneously **dense breast tissue** on mammography

Saslow: Ca Cancer J Clin, 2007

www.cancer.gov/bcrisktool.com

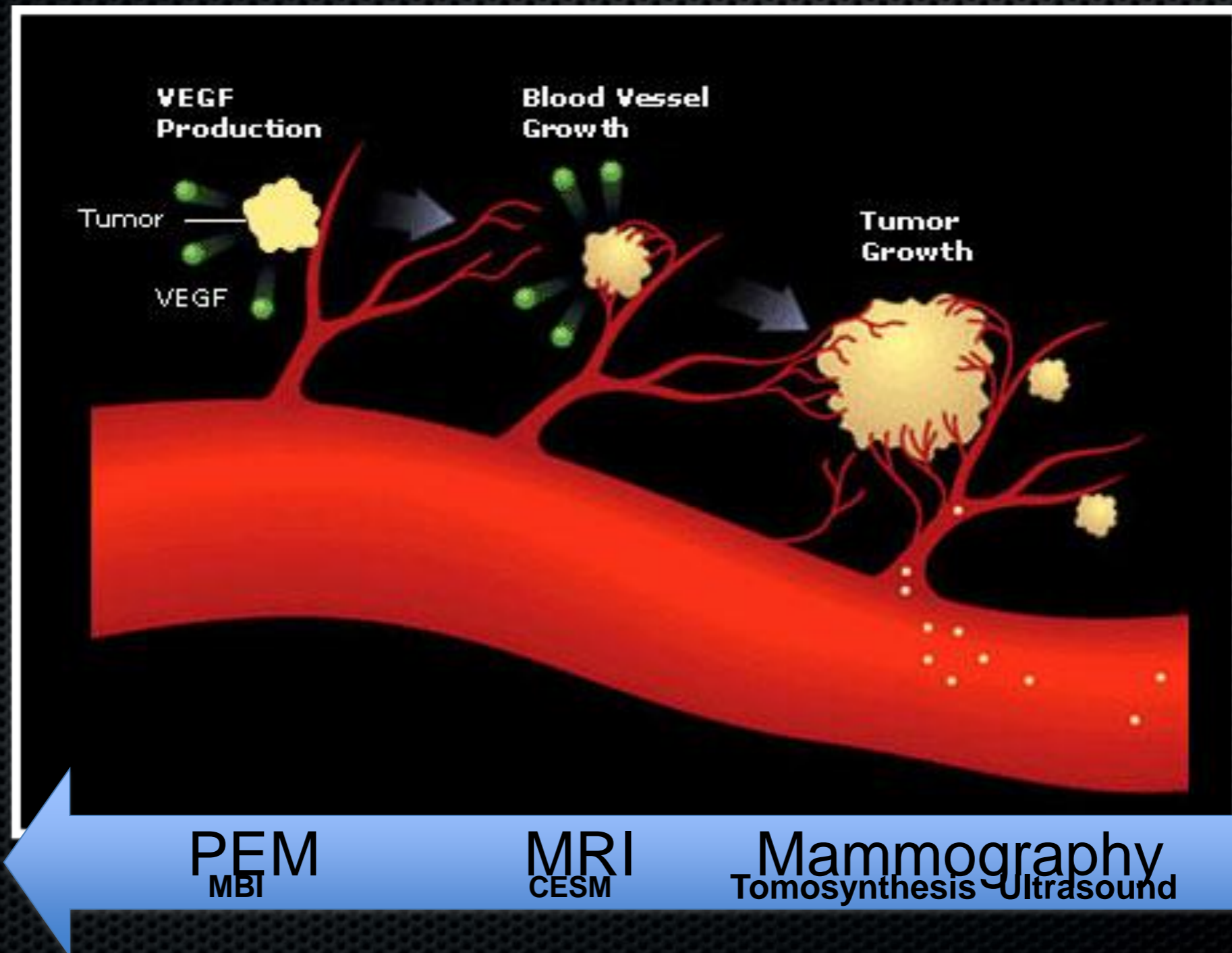
MRI Guidelines: High Risk

- **>20% lifetime risk:** Annual mammography & MRI
- BRCA or 1st degree relative of BRCA but not tested
- RT to chest ages 10-30
- Rare syndromes with high breast cancer risk

Saslow: Ca Cancer J Clin, 2007

www.cancer.gov/bcrisktool.com

Tumor Growth & Detection





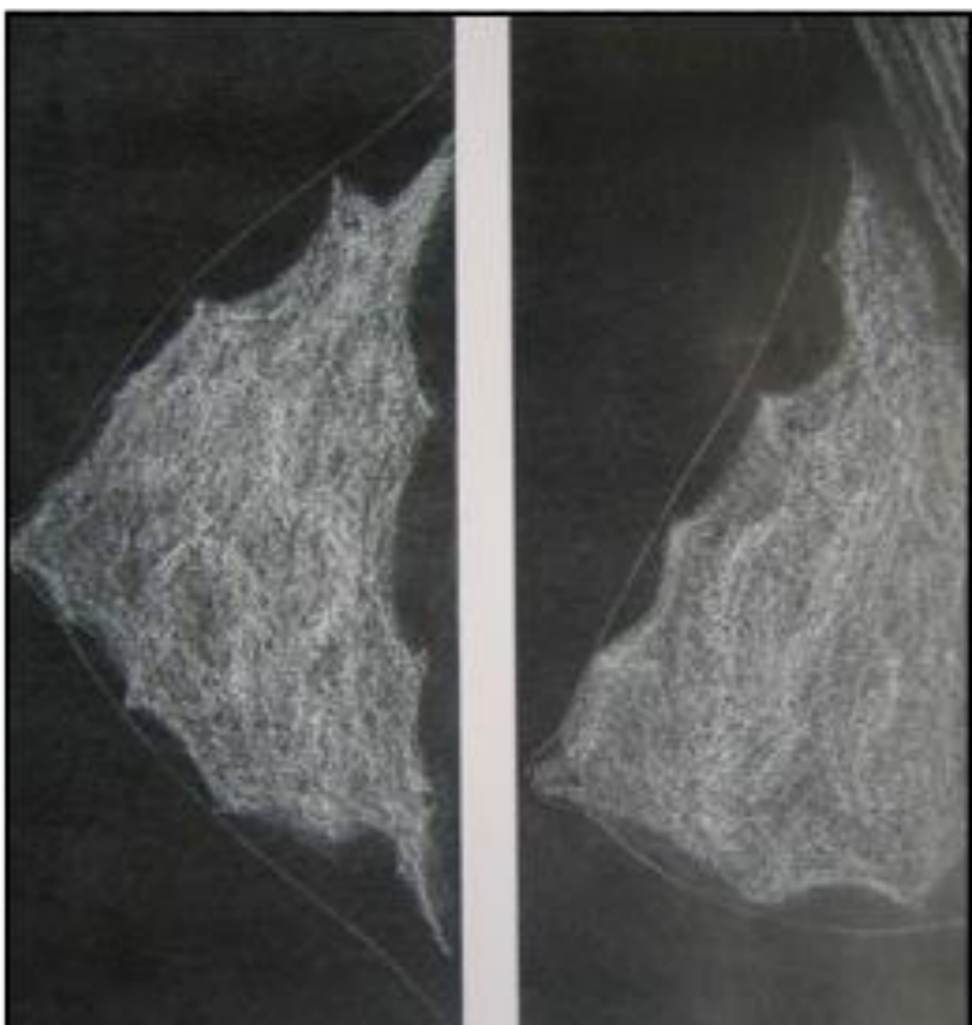
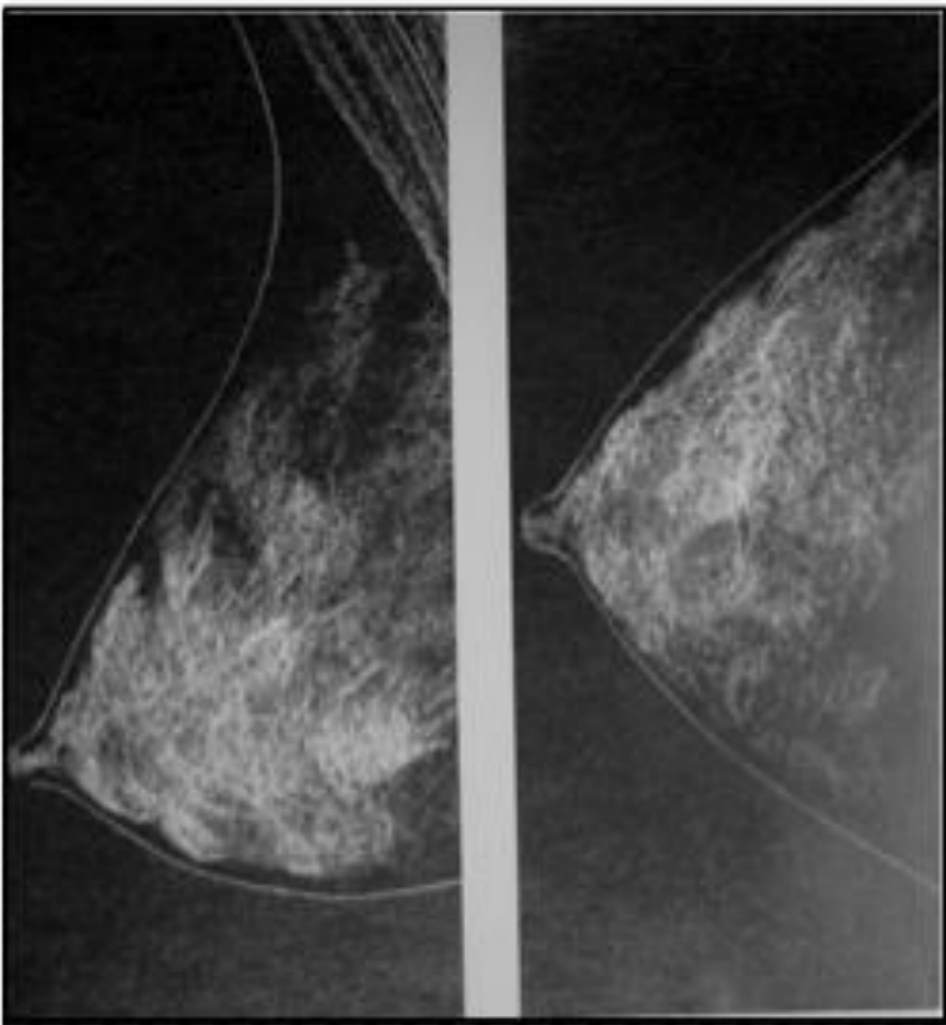
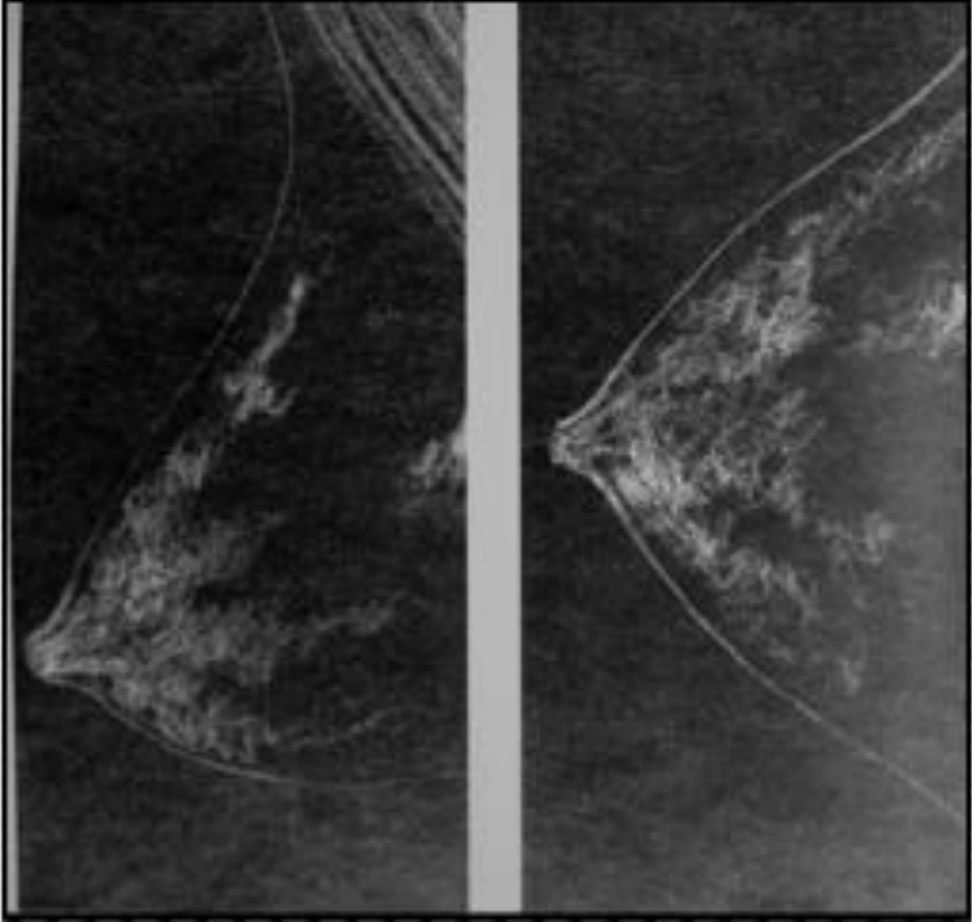
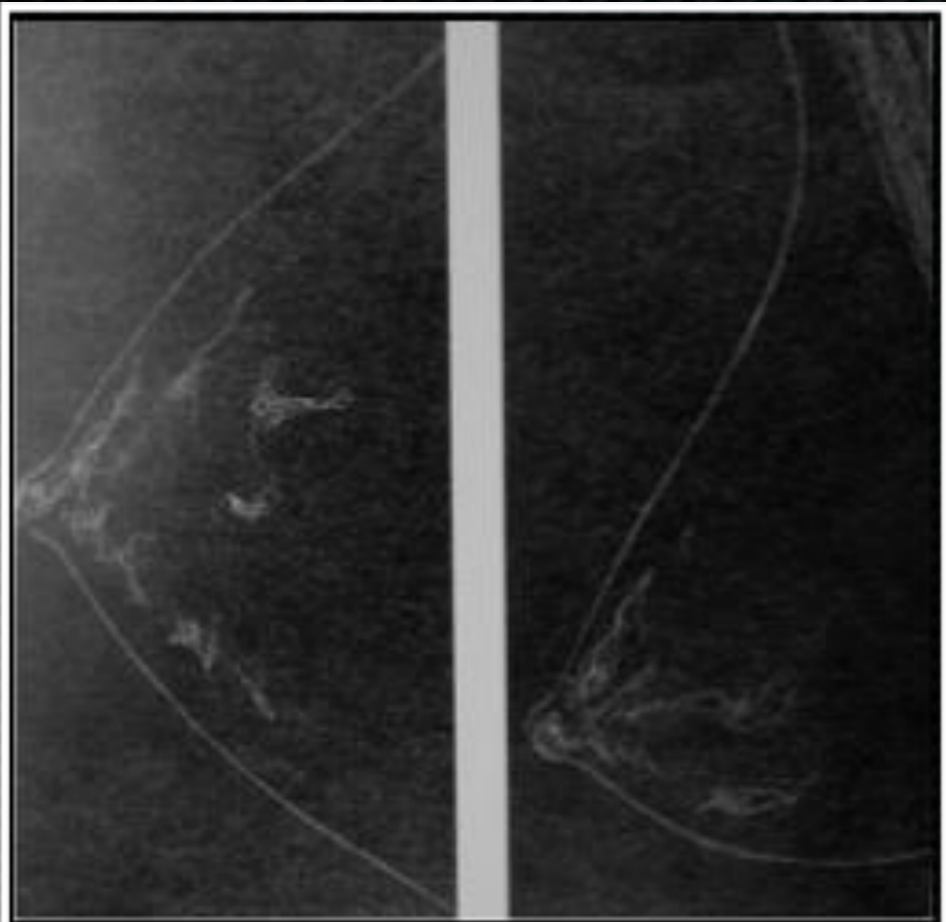
DMIST

- 49,000 women with both analog & digital screening
- **Sensitivity:** 40-50 year old with high breast density
- Analog: **27%**
- Digital: **59%**

Pisano: NEJM 2005

Density: BIRADS Definition

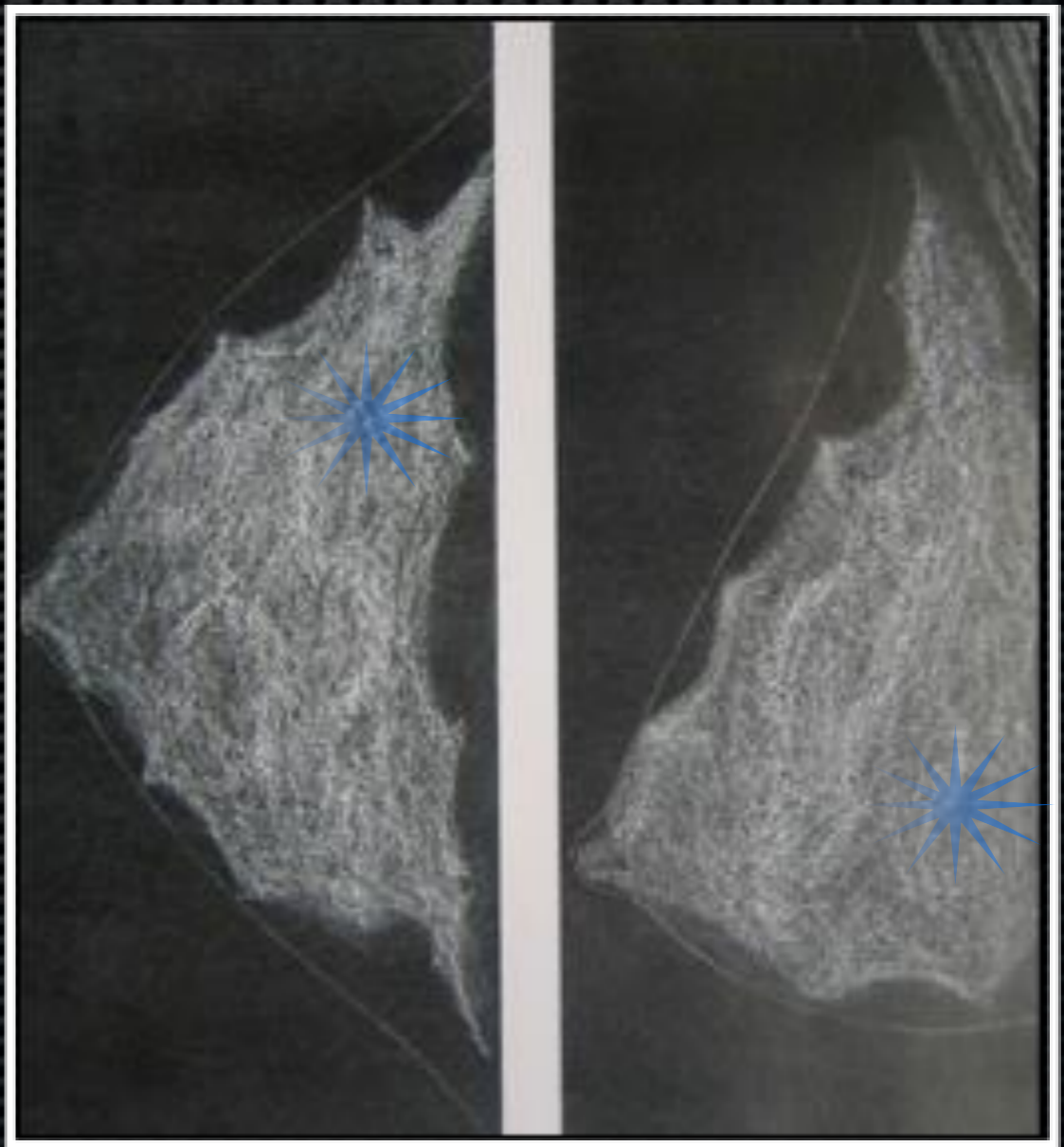
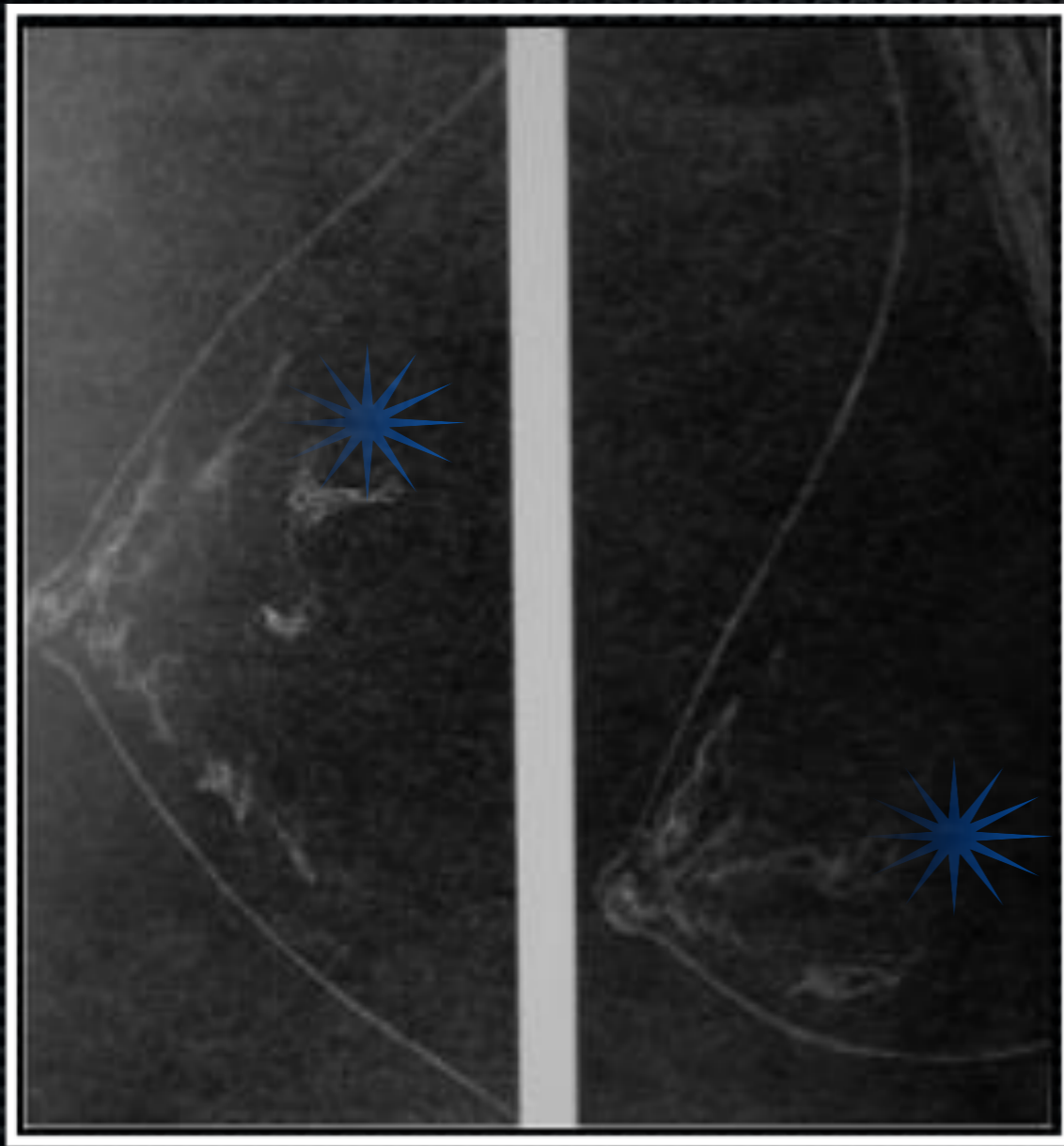
- BIRADS A: fatty breast density
- BIRADS B: scattered fibroglandular densities
- **BIRADS C**: heterogeneously dense 
- **BIRADS D**: extremely dense 

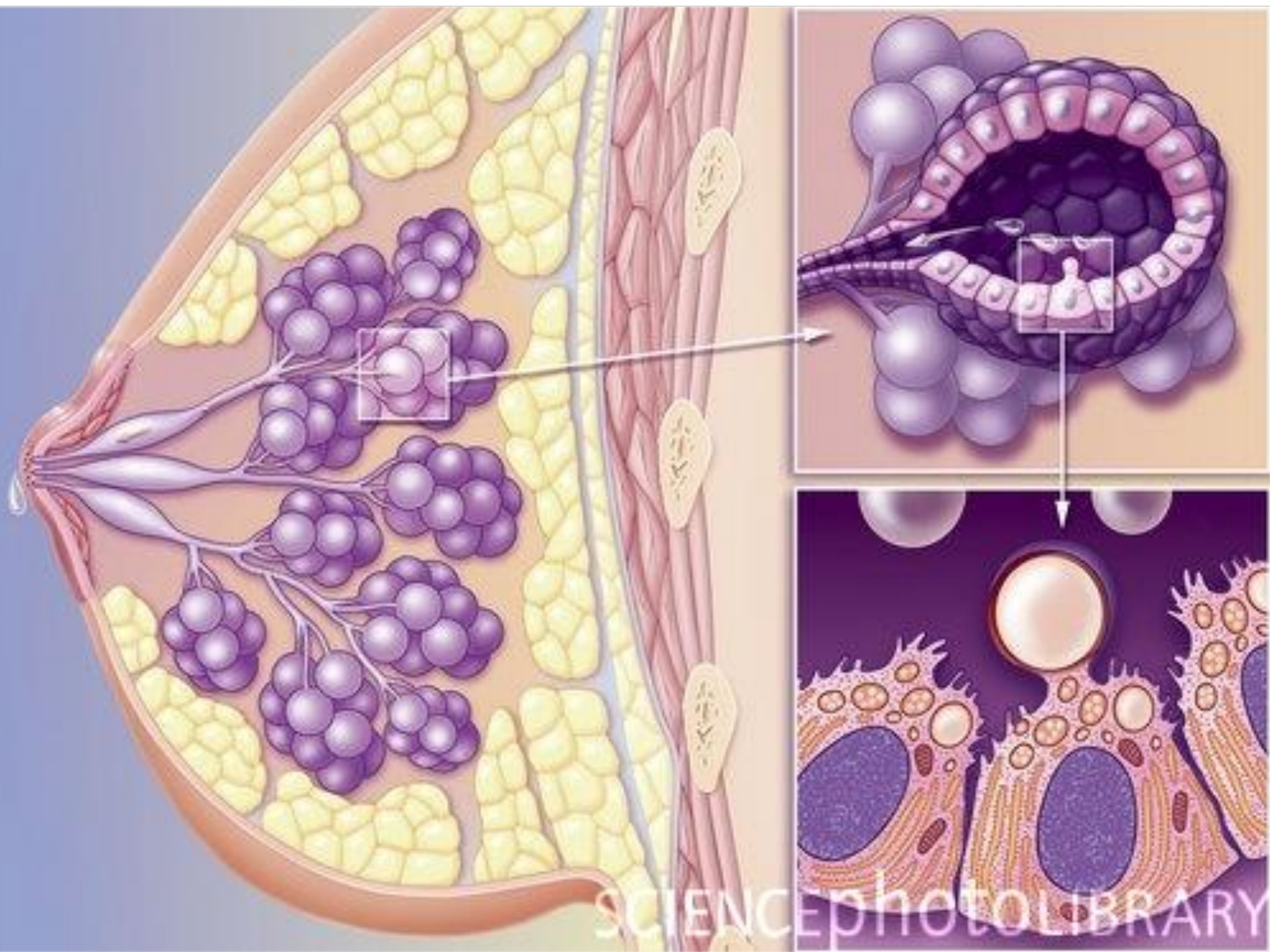


Breast Density

- Association of density with delayed detection due to lower sensitivity of mammography: **masking**
- More pathologic elements & growth factors which have the potential to induce cancer
“A seed in fertile soil”

Masking





Cancer in Dense Breasts

- Higher grade
- Larger size
- Hormone receptor negative
- Interval disease

Interval Cancer Rate & Density

Breast Density	Sensitivity	% Interval CA
Fatty	80%	9%
Heterogeneously Dense	59%	25%
Extremely Dense	30%	59%

Invasive Cancer Survival

- **Screening Goal:**

Find invasive cancer <1 cm in size

Node negative

Interval cancer rate $<10\%$

Tabar: Rad Clin N Amer 2000

Smith: Rad Clin N Amer 2004

Ultrasound Screening Trials

Author	Prevalence
Gordon: 1995	44/12,706 (3.5/1000)
Buchberger: 2000	32/8103 (3.9/1000)
Kaplan:2001	6/1862 (3.0/1000)
Kolb:2002	37/13,546 (2.7/1000)
Chrystal:2003	7/1515 (4.6/1000)
LeConte: 2003	16/4236 (3.8/1000)
	150/42,838 (3.5/1000)

Cancer Types: n=150

- 94% invasive
- 70% node negative
- 91% Stage 0 or 1

Clinical Trials: ACRIN 6666

- MD performed US in patients at increased risk & high breast density
- N = 2809
- Diagnostic yield mammo 7.6/1000 increased to 11.8/1000 with US (55% increase yield)
- 92% invasive, median 10mm, 89% node negative

ACRIN 6666: Cases/1000

Year	Mammo	Mammo & US	Add'l Yield
1	7.5	12.8	5.3
2	6.4	10.0	3.6
3	9.9	13.8	3.9

ACRIN 6666

Year	# CA	# Interval	Rate (%)
1	36	2	5.6%
2	29	4	14%
3	46	3	6.5%
Total	111	9	8.1%

Ultrasound Benefits

- Finds invasive breast cancer
- Reduces interval cancer rate
- Well tolerated without radiation
- Automated devices improve efficiency



GE Invenia

Ultrasound Challenges

- User dependent
- Few qualified technologists
- PPV3 of biopsy is low: BIRADS lexicon, ancillary techniques: Doppler & SWE

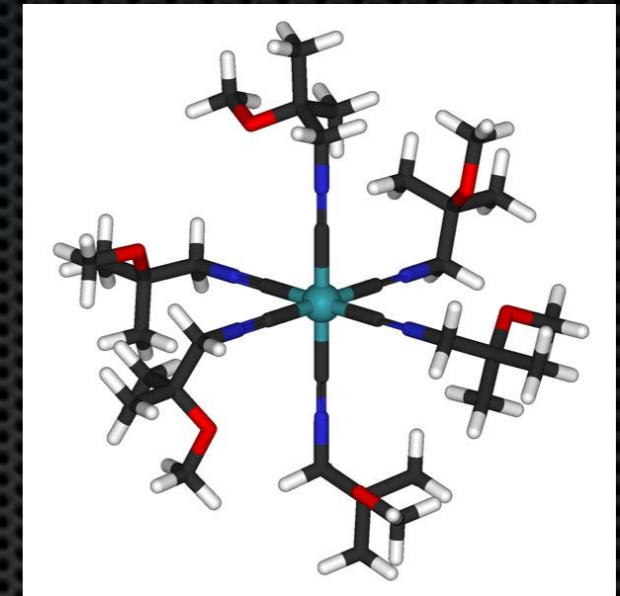
Molecular Breast Imaging: History

- Tc Sestamibi myocardial perfusion agent found to accumulate in breast lesions
- 1997: FDA approval for breast imaging
- Nondedicated gamma camera
- Sensitivity for lesions <1cm 35-65%

Scintimammography



Tc Sestamibi



- Passive diffusion across cell membrane
- Sequestered in cytoplasm (mitochondria)
- **Functional Imaging**: uptake proportional to blood flow & mitotic activity
- Rapid uptake: image immediately

MBI Imaging Protocol

- Day 7-14 of menstrual cycle
- 3-4 hour fast
- Warm blanket around torso
- 8mCi Tc sestamibi
- Wait 5 minutes
- Standard CC & MLO views @ 10min/view

GE Discovery 750B



Radiation Dose

- 8mCi TcSestamibi delivers 2.4 mSv effective whole body dose (digital mammogram 0.8 mSv)
- Equivalent to 1 year background dose
- Dose cleared by biliary system through intestine
- Weigh benefit to risk to patient

Mayo Clinic Experience

- 936 asymptomatic high risk patients with dense breasts
- **11** cancers found:
 - 1 mammo only (5mm DCIS)
 - 7** MBI only
 - 2 both
 - 1 neither, found at follow up

Rhodes: Radiology 2011

Diagnostic Yield

Mammography	3.2/1000 screened
MBI	9.6/1000 screened
Combined	10.7/1000 screened

Sensitivity

	Overall	Invasive CA	Non-Invasive CA
Mammo	27%	29%	25%
MBI	82%	100%	50%
Combined	91%	100%	75%

MBI Clinical Indications

- Screening the patient at increased risk
- Local staging of breast cancer
- Indeterminant finding: nipple dc, BIRADS 3, palpable with no imaging finding, multiple imaging findings, unknown primary, one view finding, distortion, lesion seen on MRI
- Technically difficult imaging: dense, implants, silicone or paraffin injections
- Breast MRI indicated with contraindications

Workup Algorithm

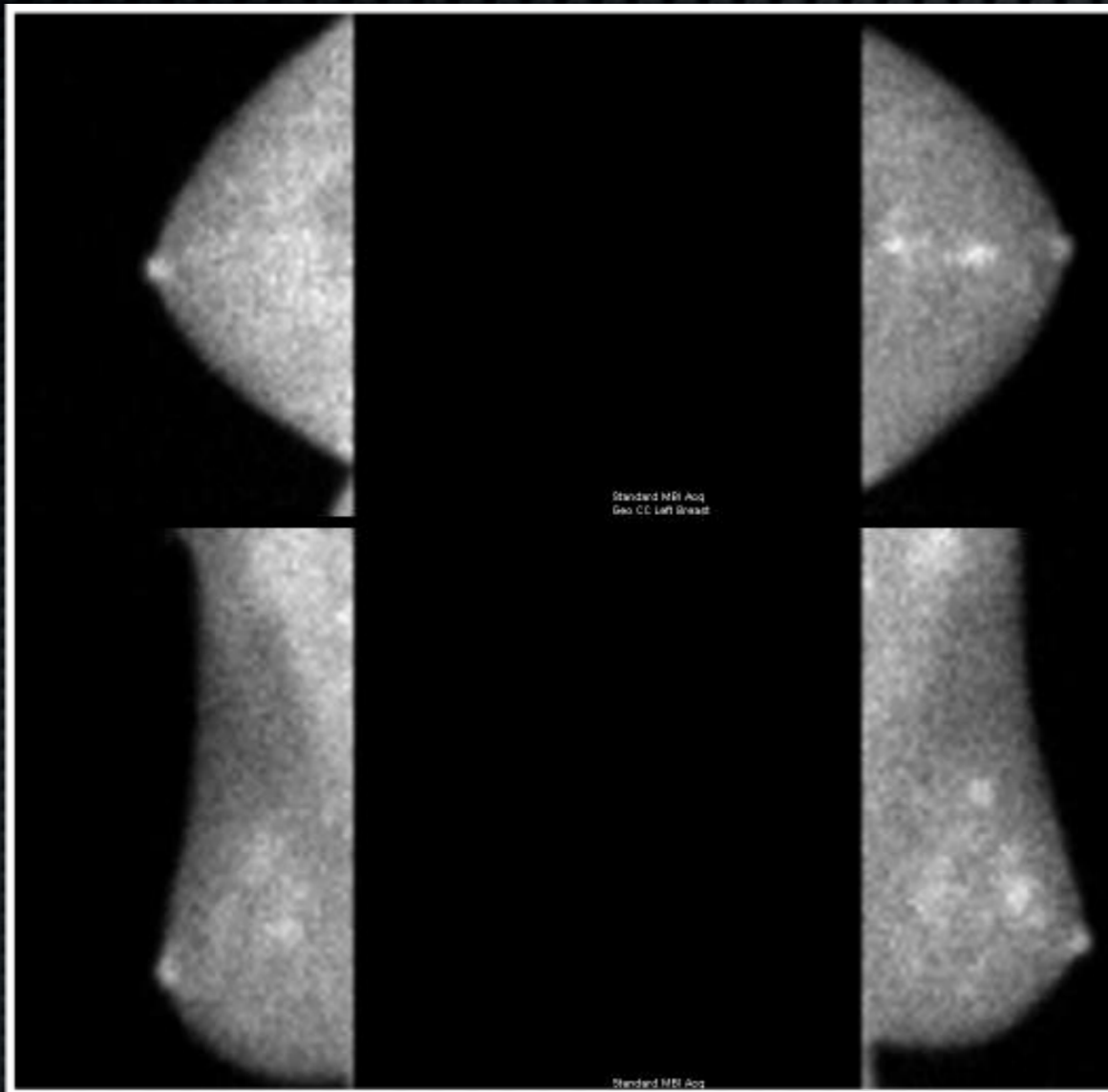
- BIRADS 3, 4 or 5
- Diagnostic mammogram & US
- BIRADS 3: nothing seen, 6 month follow up MBI
- BIRADS 4 or 5: biopsy, MRI



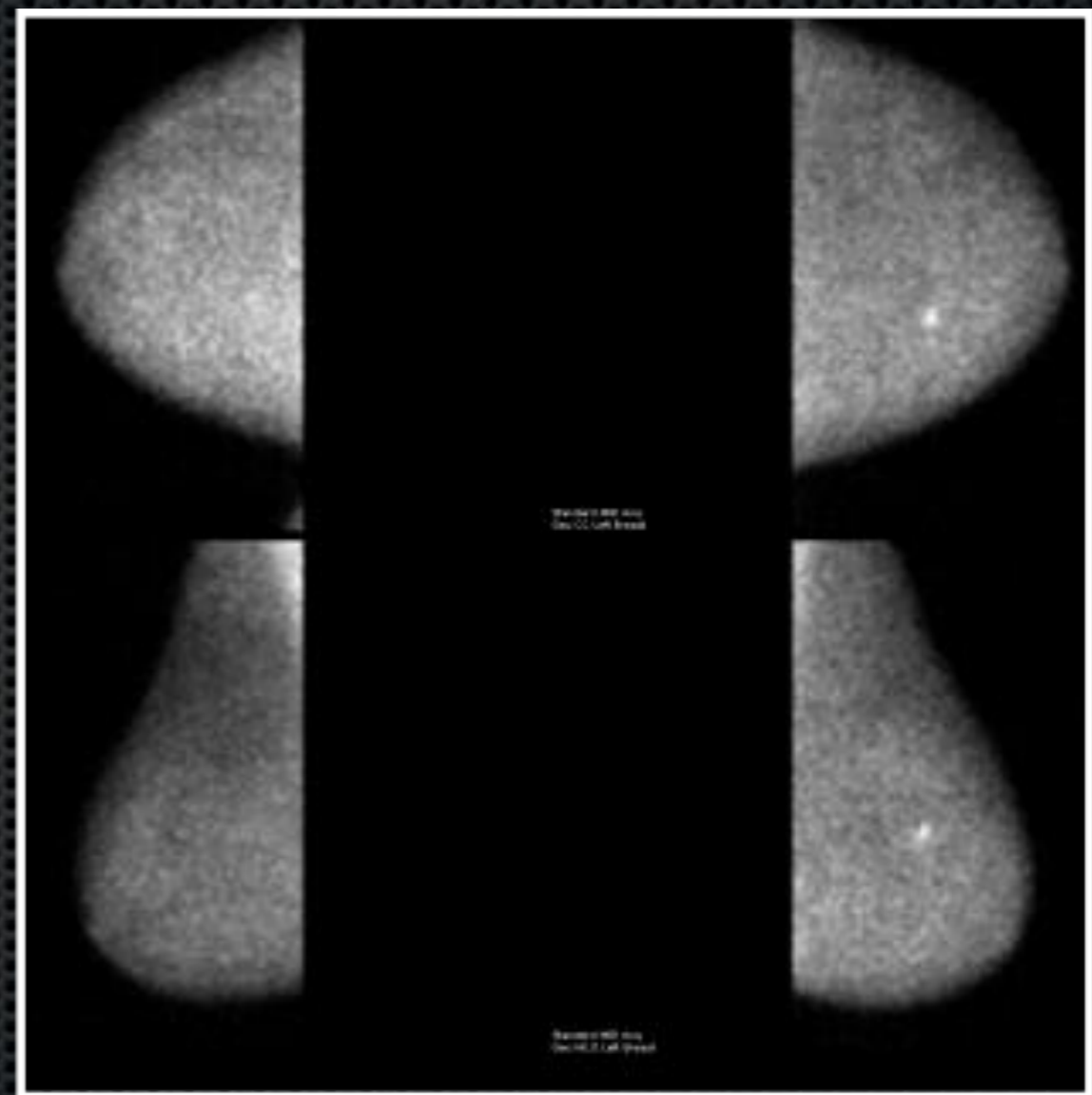
Cancers Detected: N=8

Cancer	Type	Grade	Size cm	Nodes
1	IDC	3	1.2	Neg
2	IDC	2	2.2	Neg
3a	IDC	1	1.0	Neg
3b	DCIS	2	1.1	Neg
4	DCIS	1	1.2	Neg
5	IDC	2	0.5	Neg
6	IDC	1-2	0.5	Neg
7	IDC	1-2	0.8	Neg

Malignant Findings

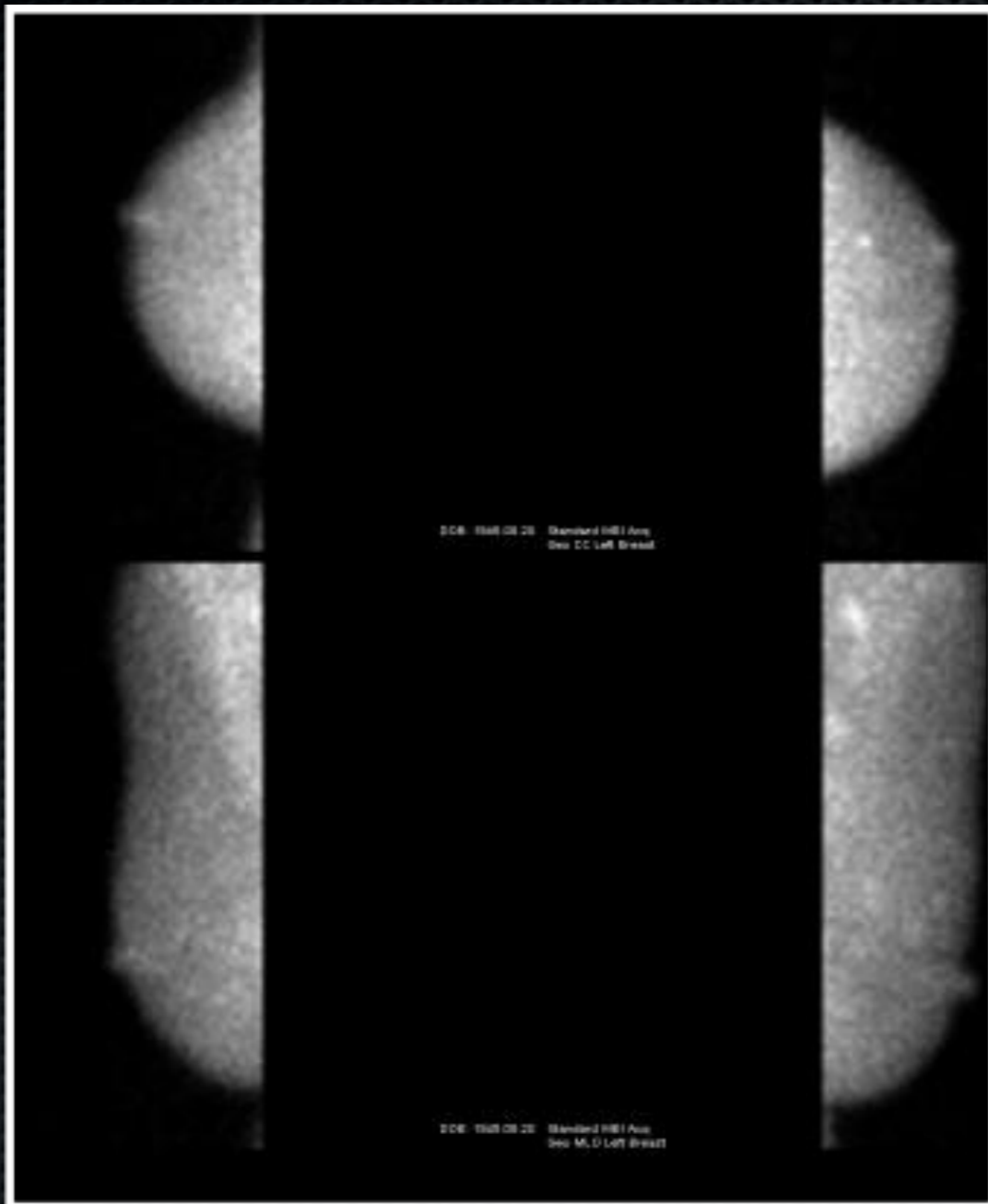


48 year old women at high risk with negative dense mammogram. 2 areas of uptake on the left. Negative US. MRI and MRI biopsy found multifocal invasive ductal carcinoma^{x1}

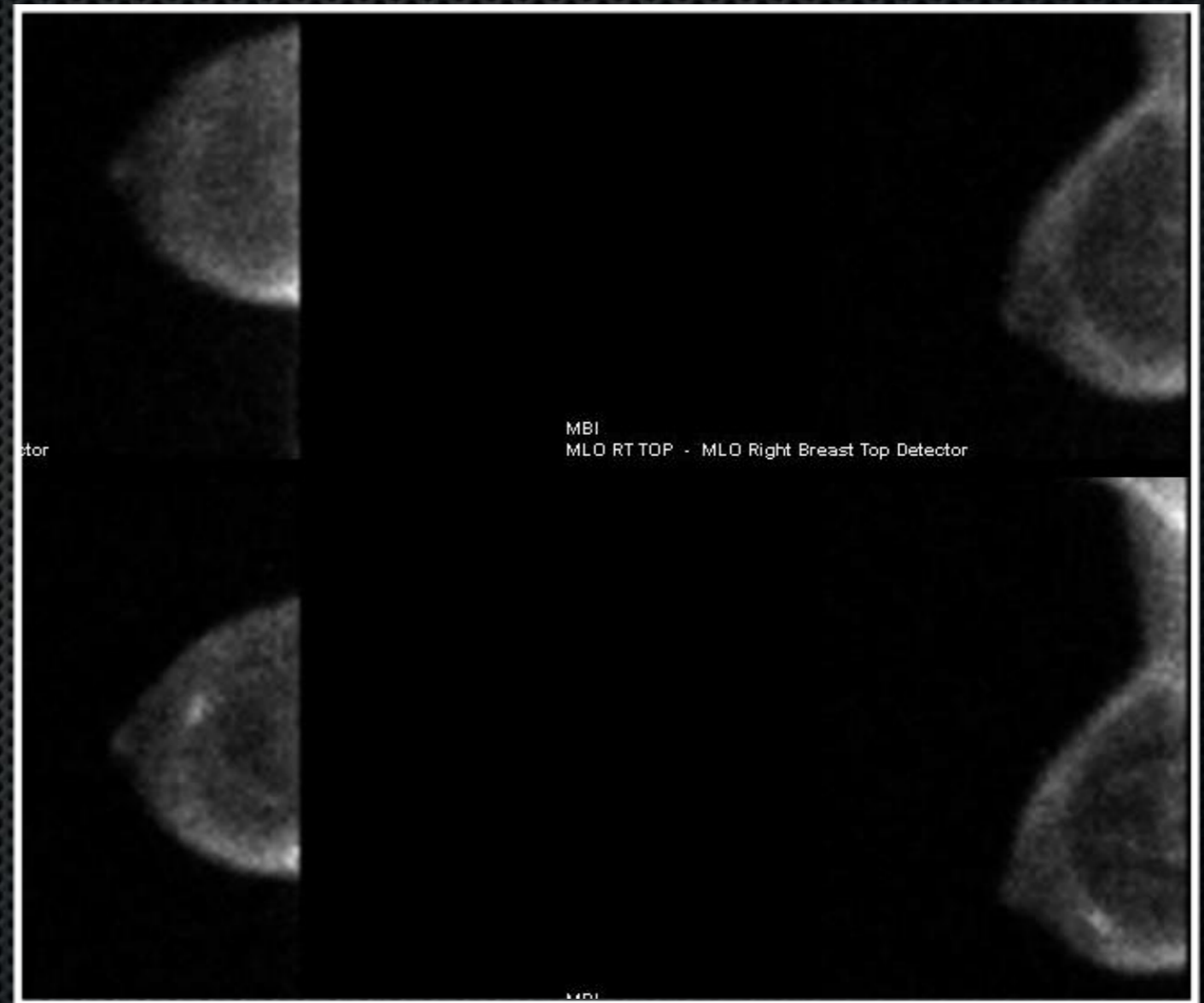


68 year old woman with indeterminant mammogram found to have 6mm invasive ductal carcinoma on the left

Malignant Findings

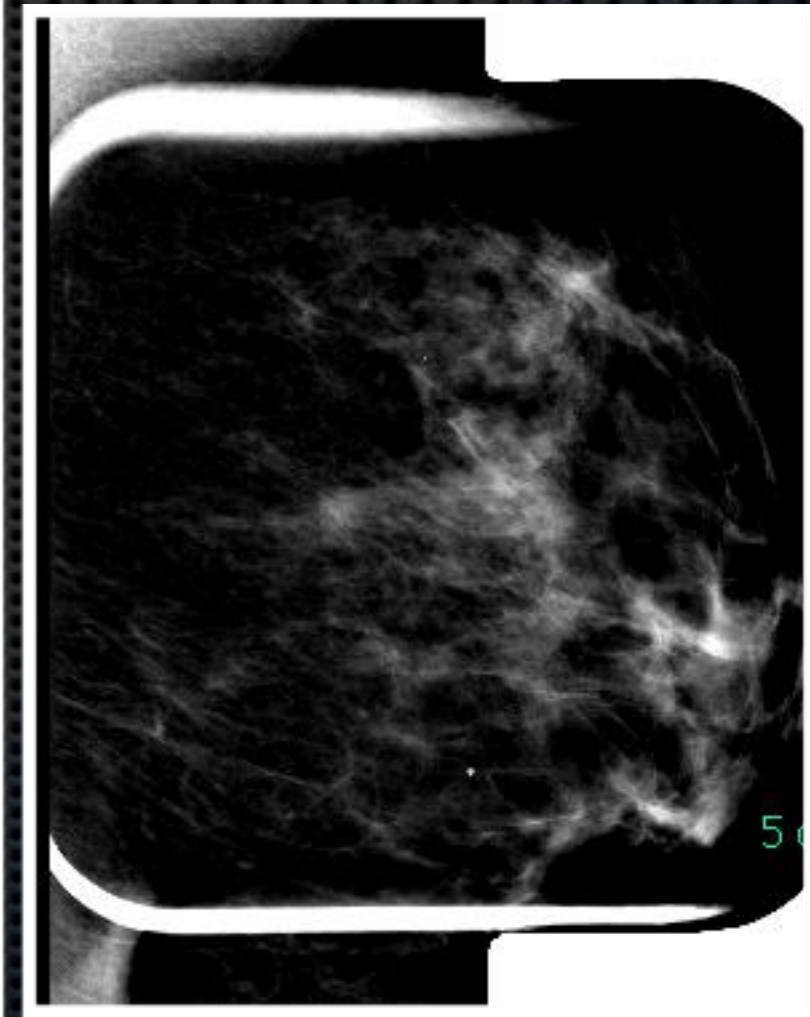
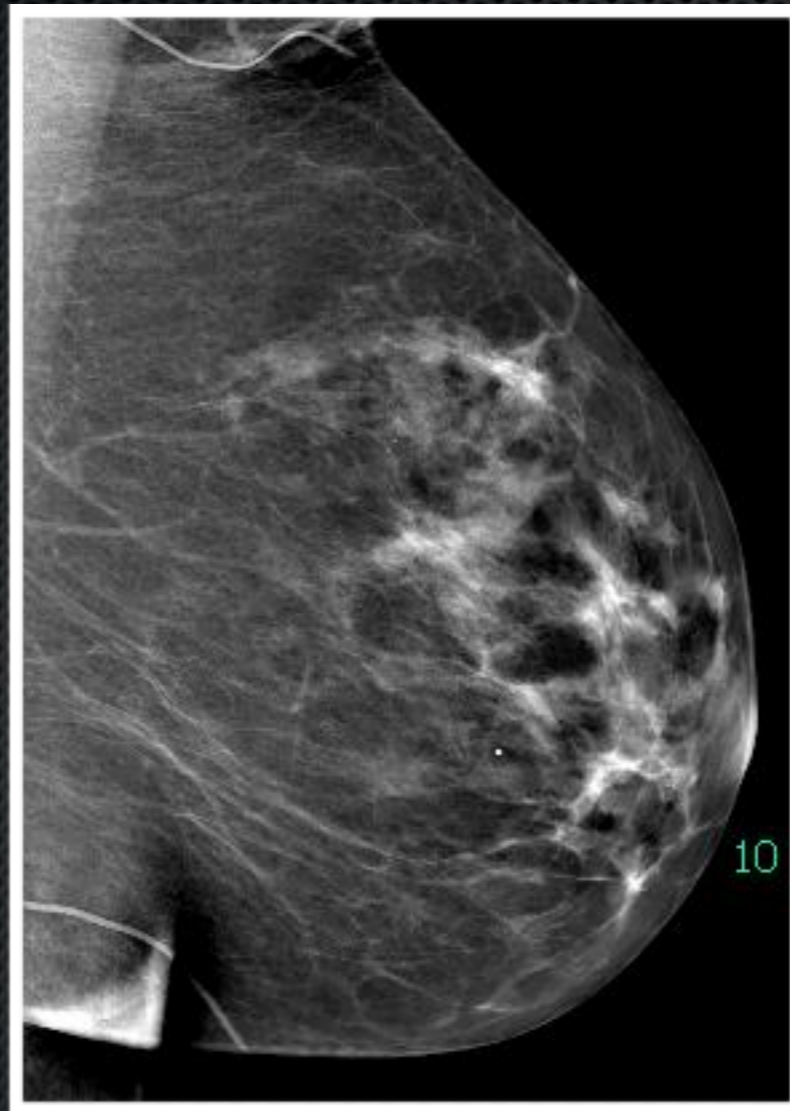
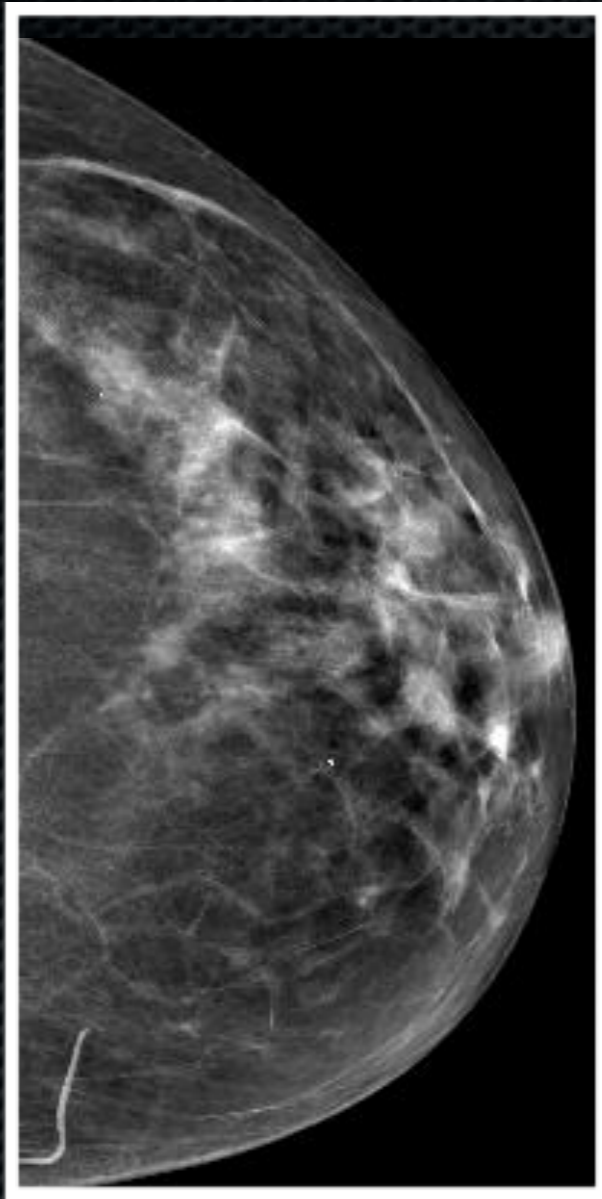


62 year old woman at high risk found to have a small solitary focus of activity laterally on the left. DCIS found at excisional biopsy

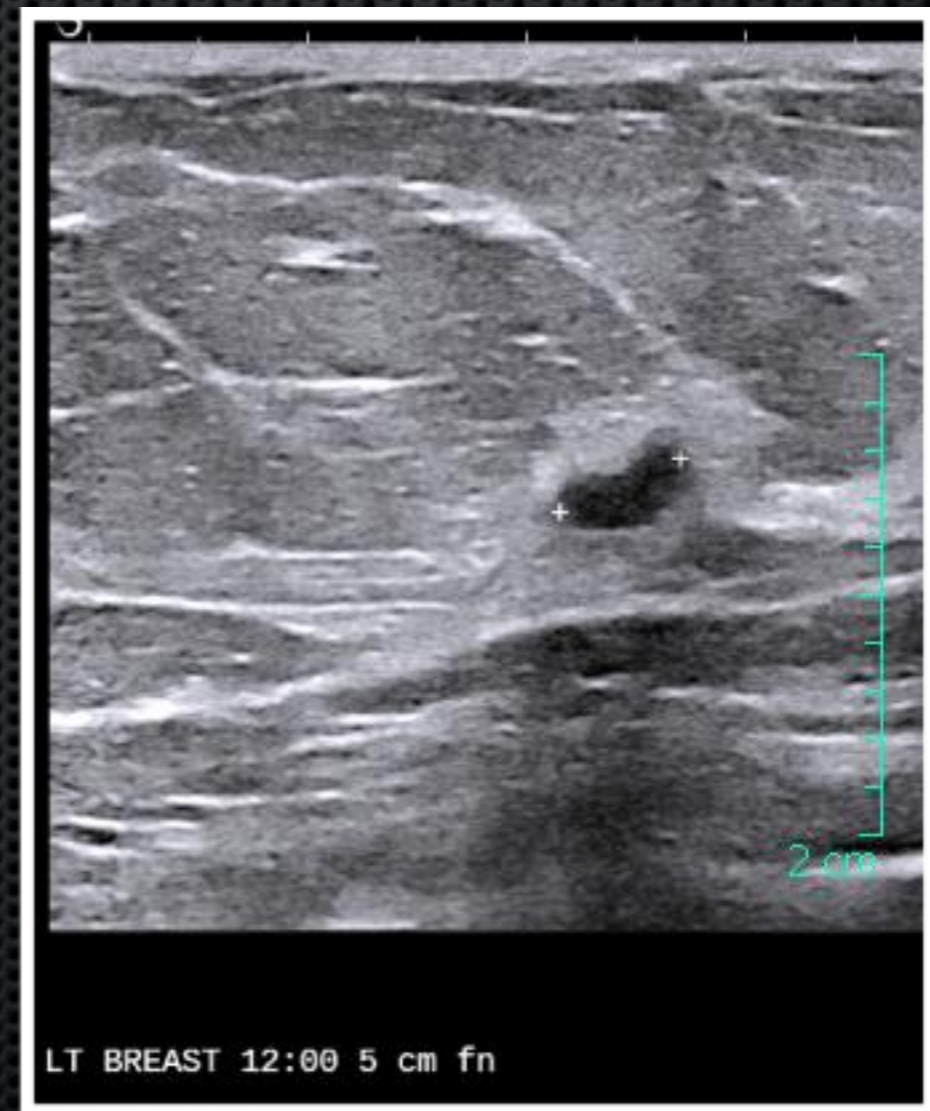
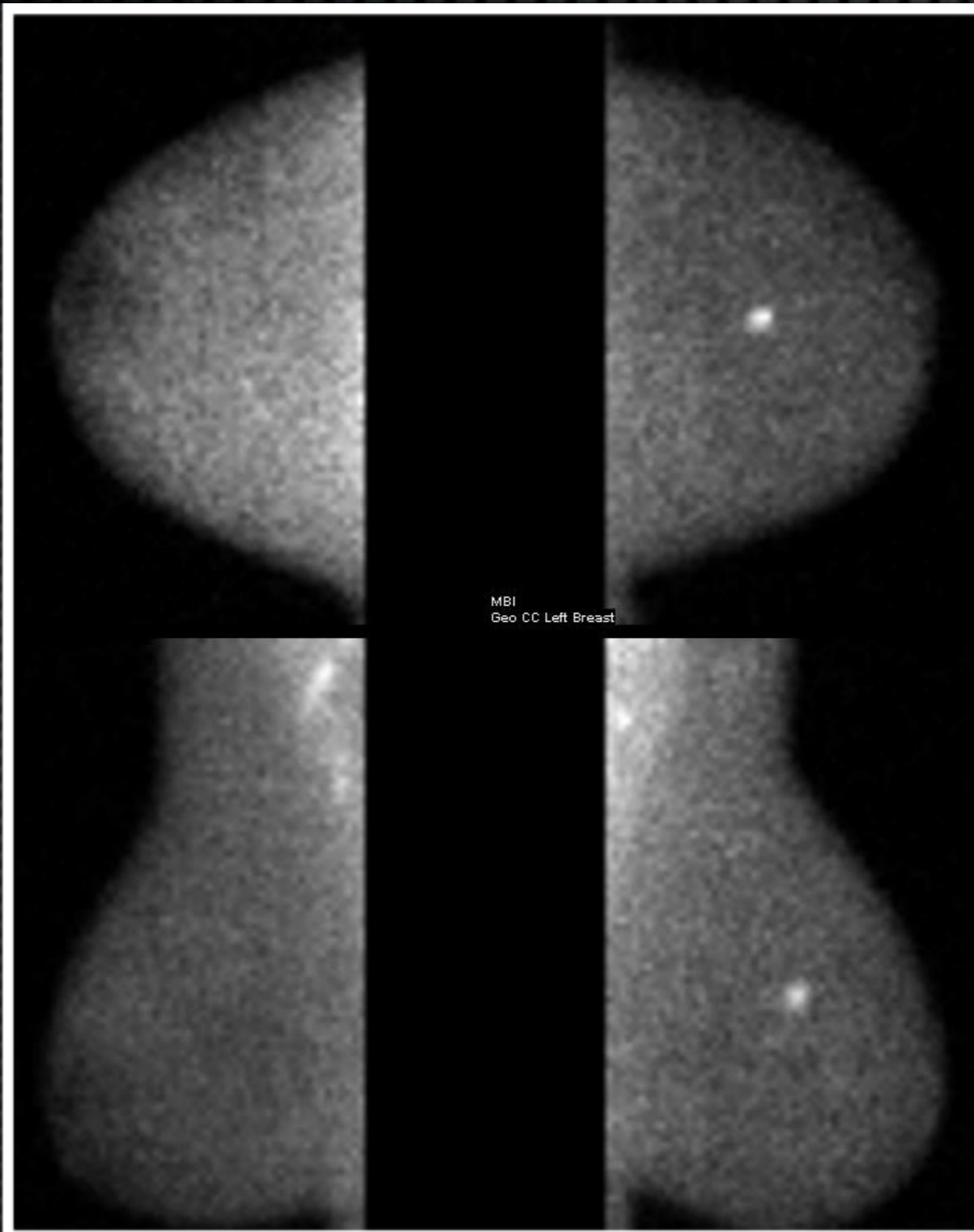


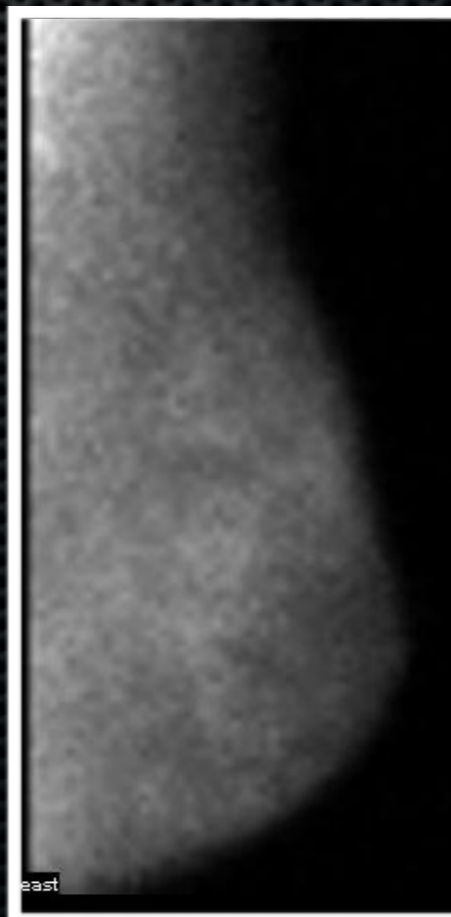
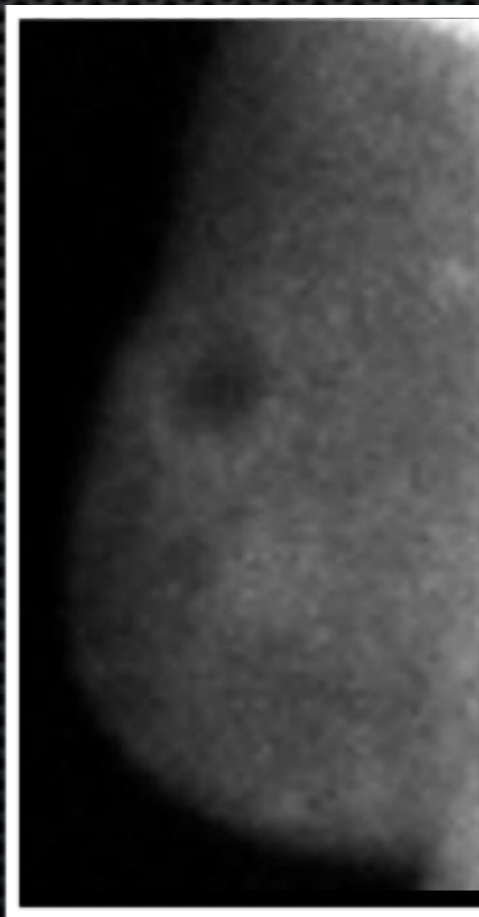
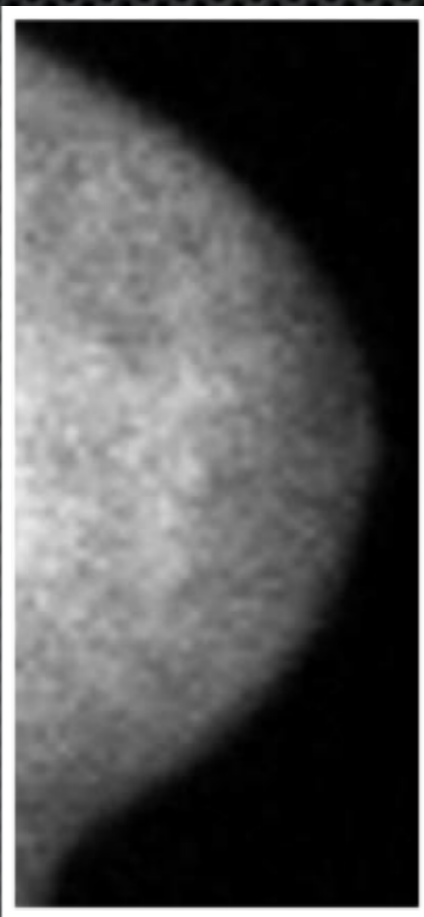
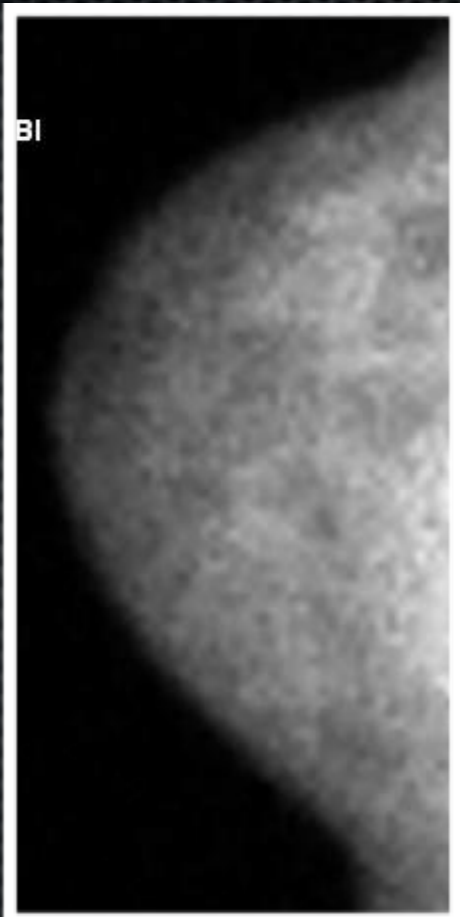
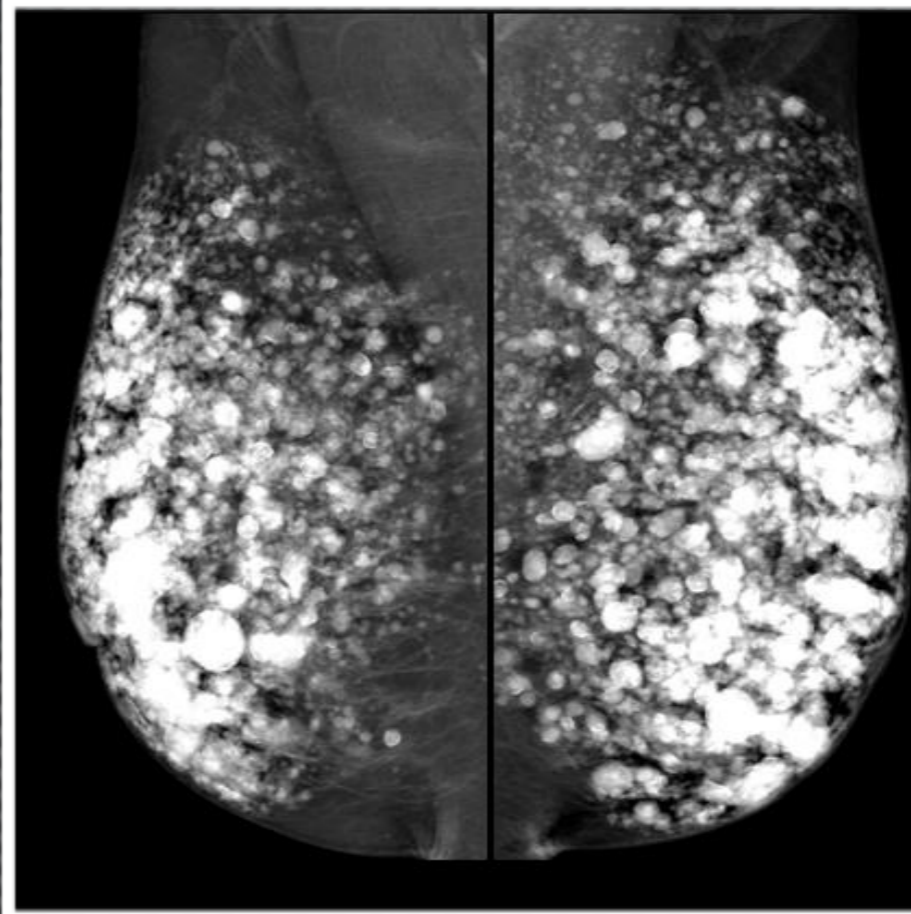
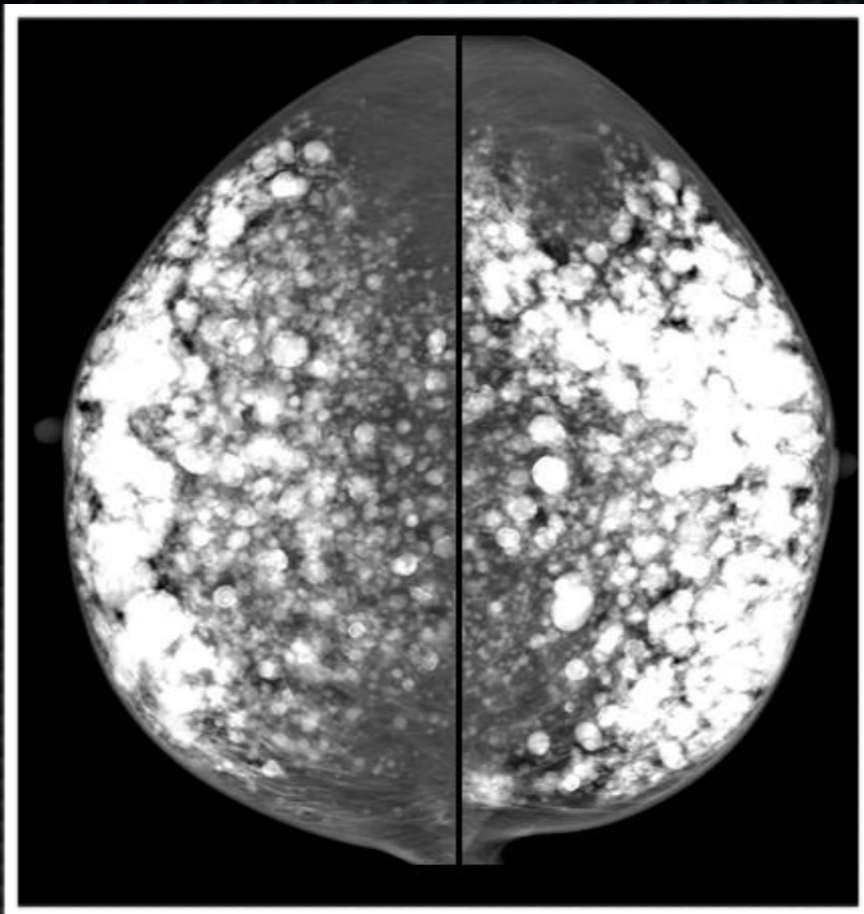
52 year old woman with BRCA gene found to have an abnormal area of activity abutting an implant on the right. Invasive ductal carcinoma

Mammogram



MBI & Ultrasound



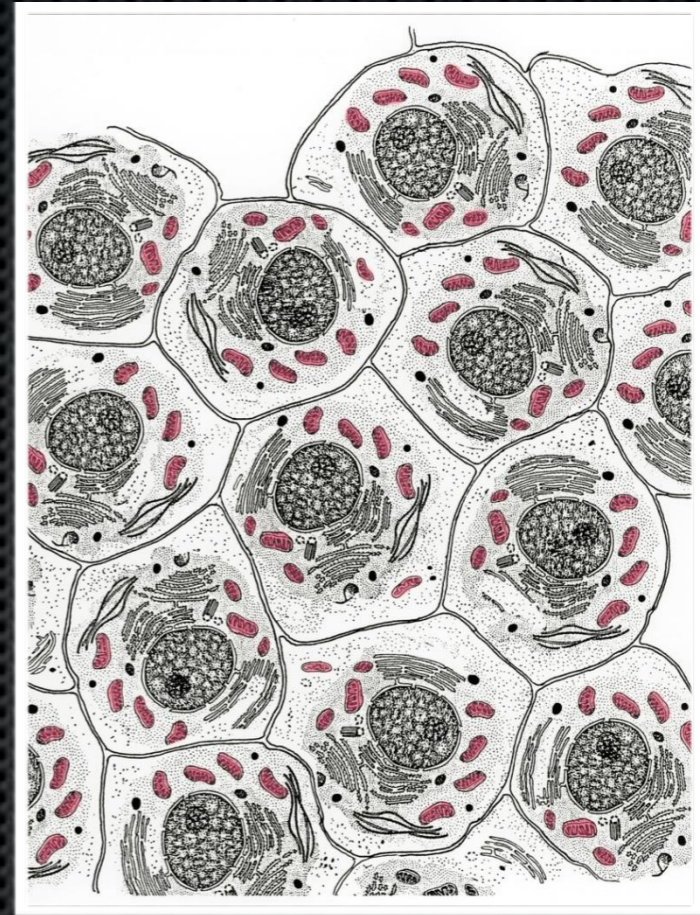


MBI Advantages

- Screening & other indications
- No wait time
- Radiotracer readily available
- Mammographic views

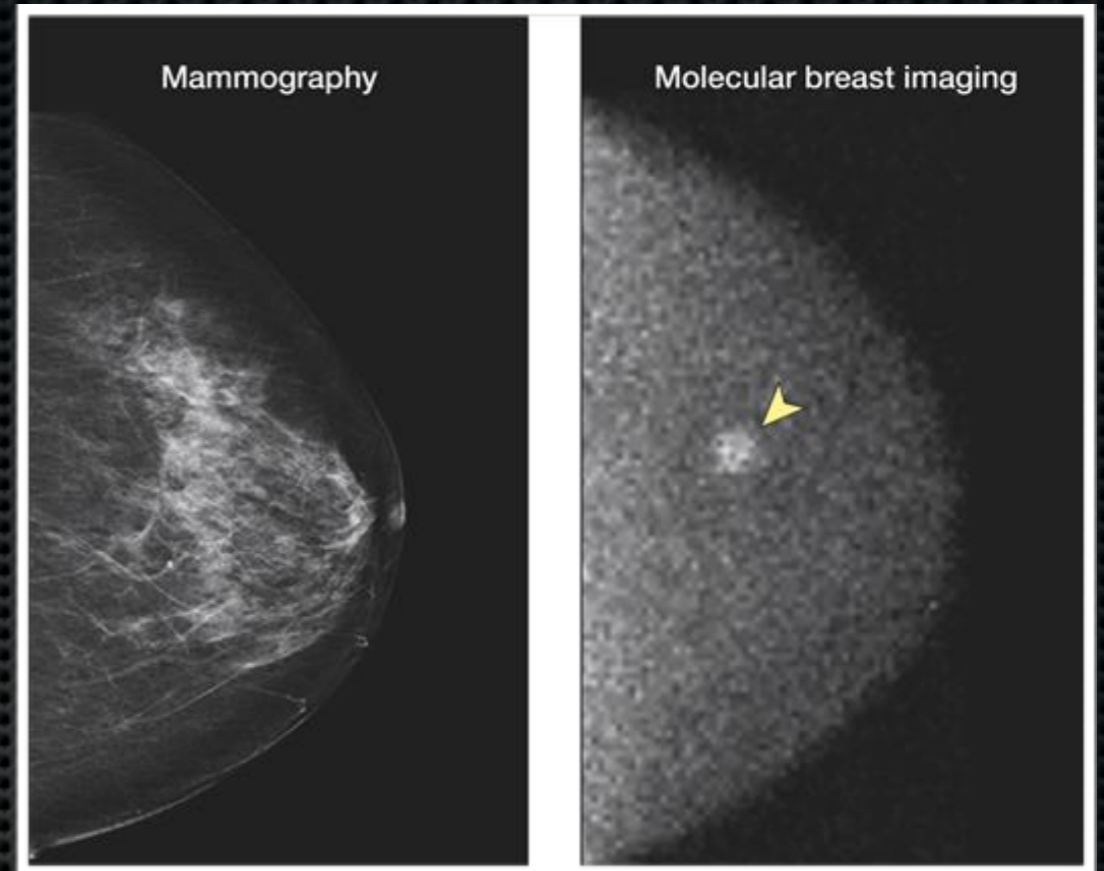


MBI Benefits



- Sensitive to invasive disease
- Less compression than mammography
- Less expensive than MRI (1/3 cost)

MBI Challenges



- Injection
- Radiation exposure to whole body
- Longer imaging time than mammography
- Biopsy capability in development

Contrast Enhanced

Spectral

Mammography

- Anatomic & functional imaging of tumor neo-vascularity
- Low dose digital mammography @ 2 energy levels
- Low energy 26-30 kvp: filter Mo/Rh: **Anatomy**
- High energy 45-49 kvp: Cu filter: **Function**
- 20% higher dose than 2D mammography
- Small added expense of Iodine and disposables

MSK CESM Experience

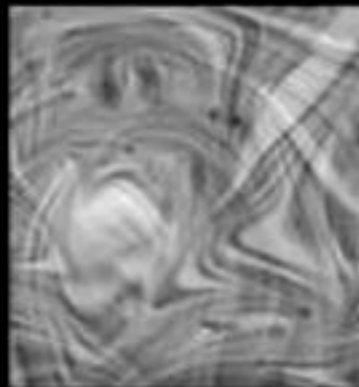
- 72 women with known cancer had DM, MRI & CESM for staging of disease
- **Index lesion sensitivity:** DM 81%, MRI & CESM 96%
- **False positive findings:** MRI 25%, CESM 4%
- Additional ipsilateral malignant finding: MRI 88%, CESM 56%

CESM

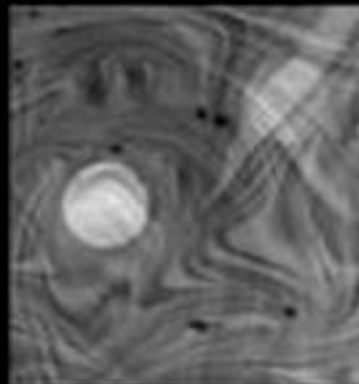
- IV access for injection of iodine bolus & flush
- Image after 2 minute circulation
- 4 pairs of images in 5 minutes
- Same mammography equipment, room, technologist
- Morphologic & functional information as with MRI

Dual Energy Technique

Low energy
image (a)



High energy
image (b)



Iodine
image (c)



Low energy 26-30 kVp
with Mo or Rh filter

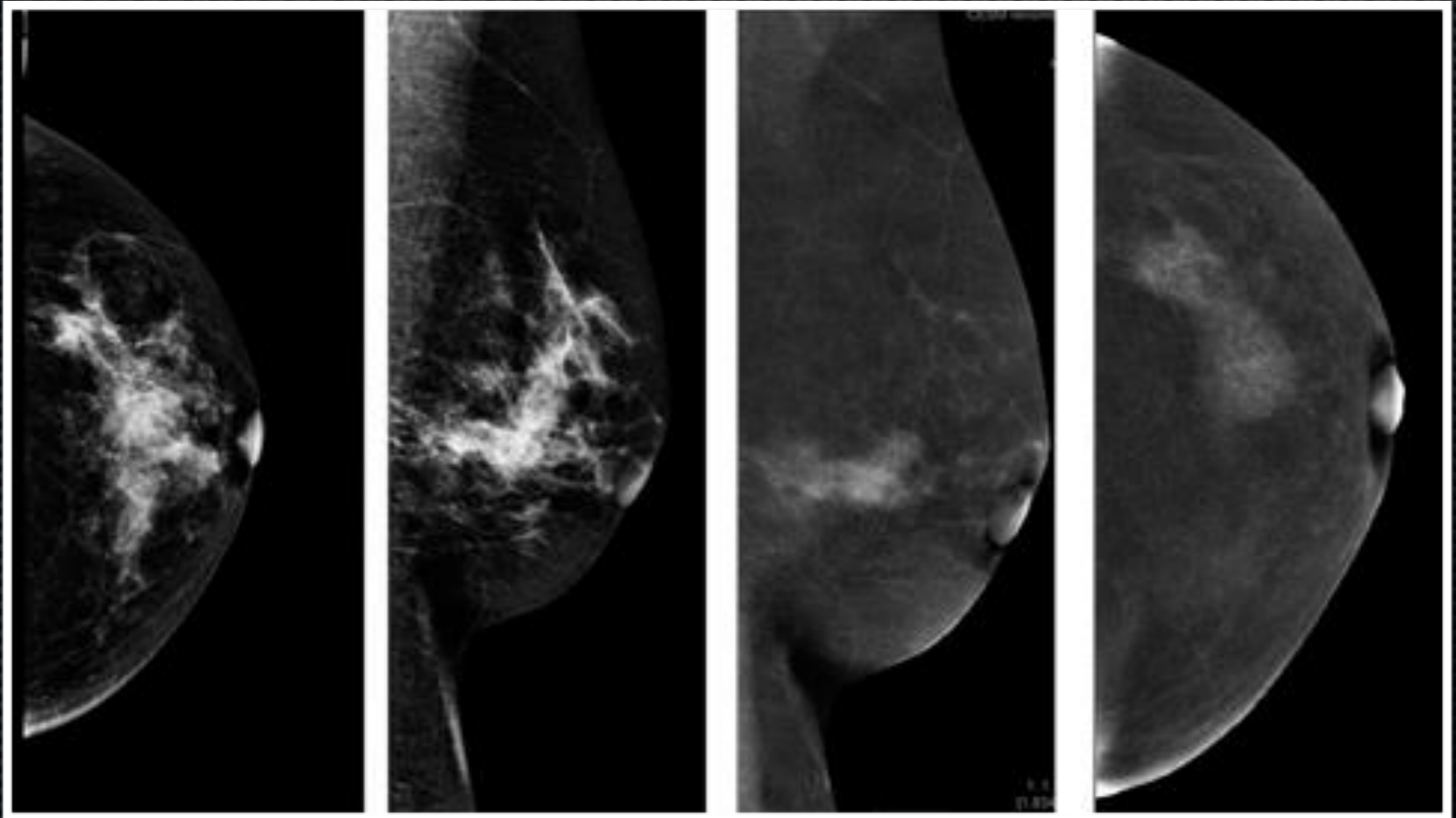
Anatomic

High energy 45-49 kVp
Cu filter

Functional

Difference between
suppresses background so
Iodine is seen

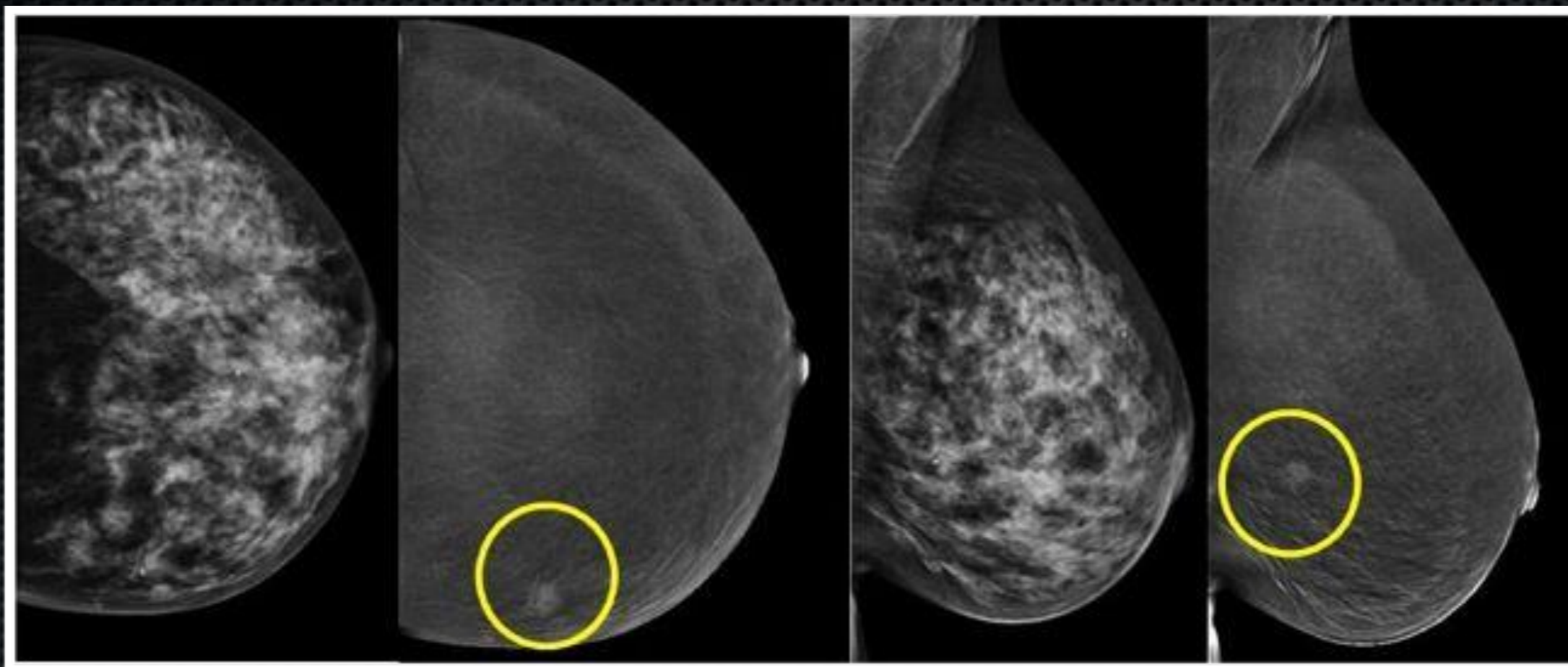
CESM Cancer

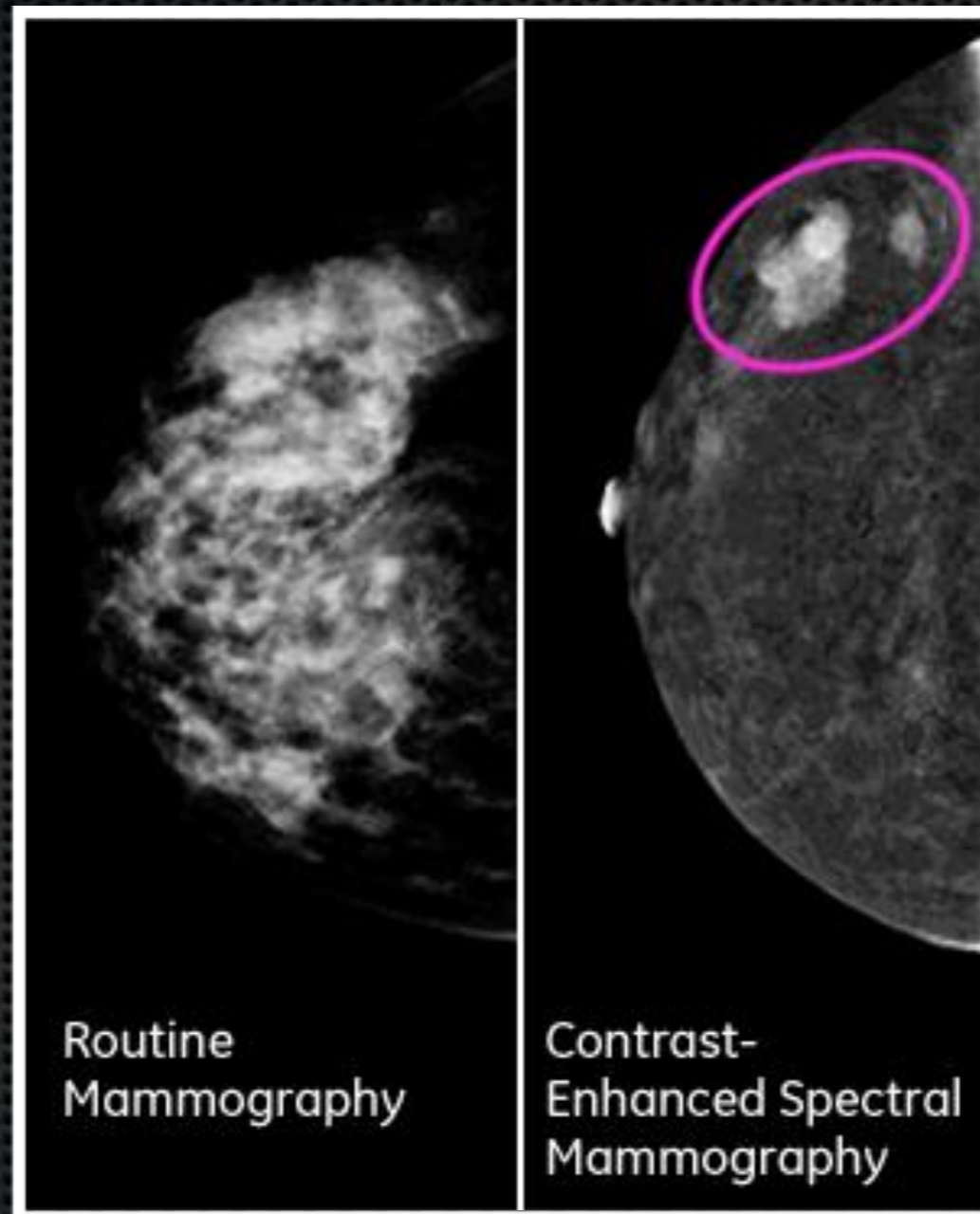


Anatomic

Functional

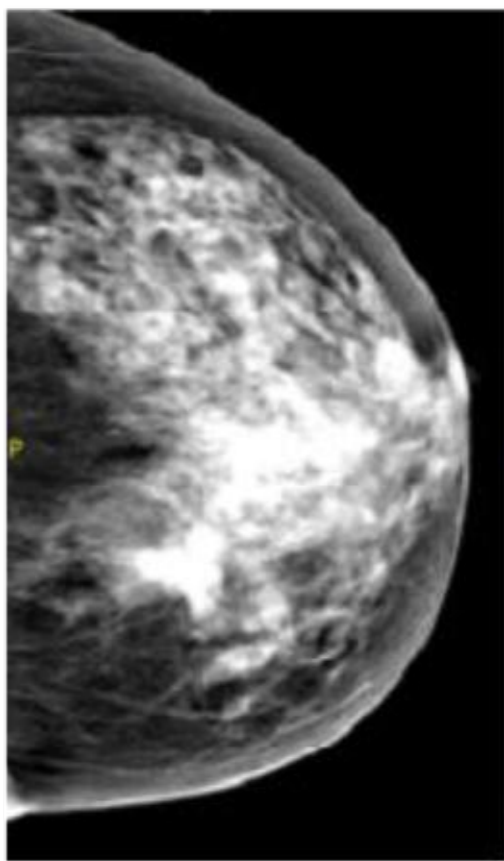
CESM Malignancy



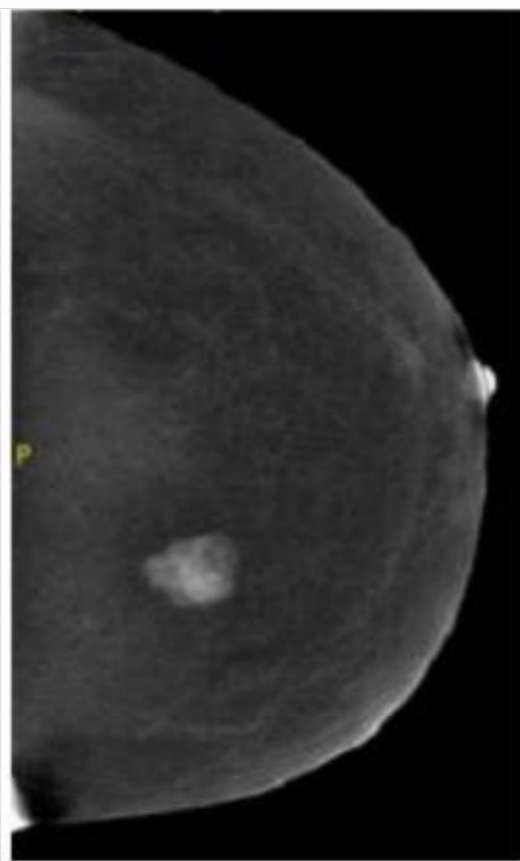


Routine
Mammography

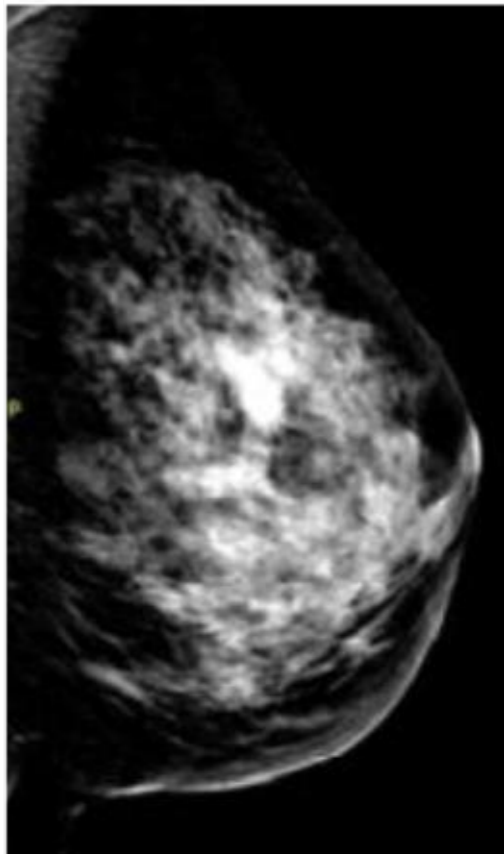
Contrast-
Enhanced Spectral
Mammography



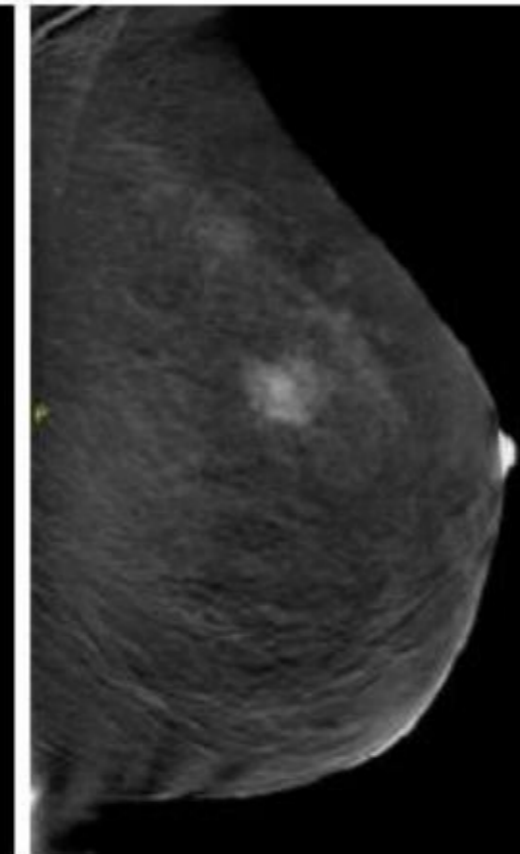
a)



b)



c)



d)

Solitary Malignancy

CESM Benefits

- Low cost
- Low radiation dose to breast only
- Anatomic & functional information
- High sensitivity

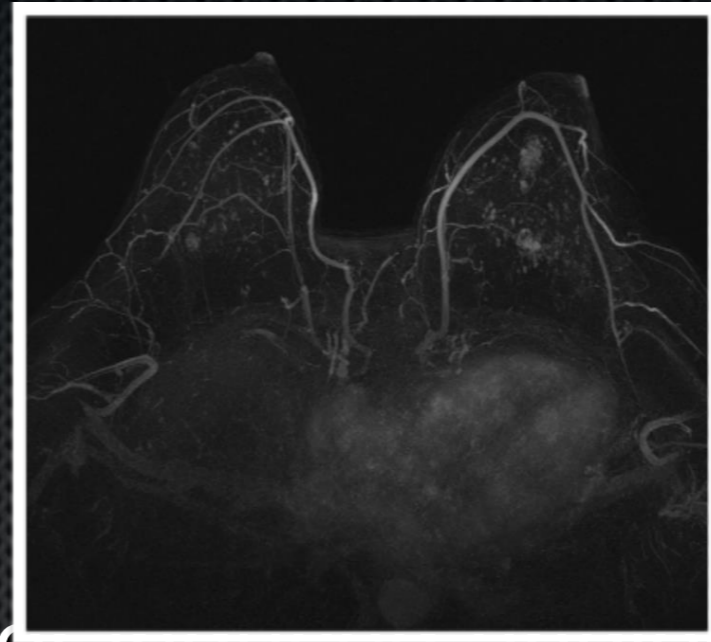
CESM Challenges

- Iodine contrast injection
- Role in screening & diagnostics not yet defined

BRRH CESM Protocol

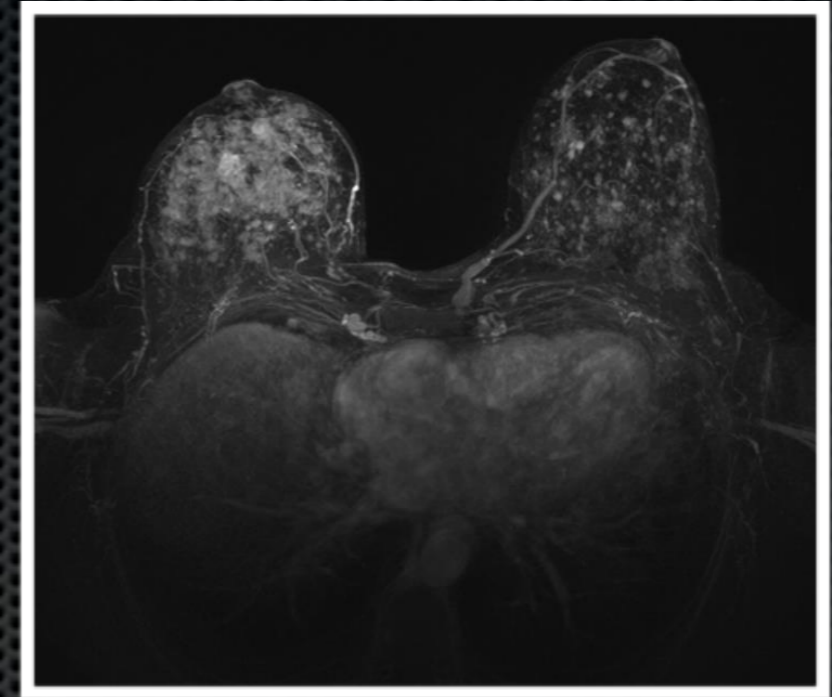
- Highest risk patients followed for 24 months
- Annual MRI & biannual CESM
- Evaluate outcomes & patient satisfaction
- Pilot program of 15 patients

MRI



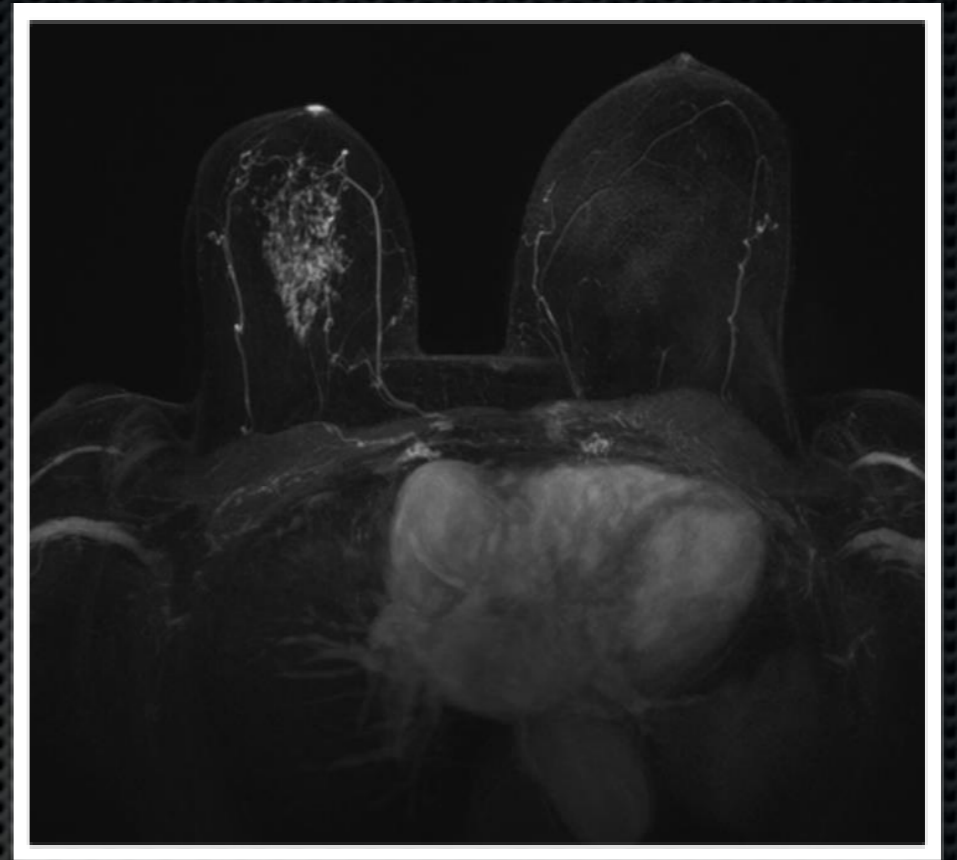
- Identifies cancer due to tumor induced angiogenesis
- Evaluate lesions for morphology & kinetics pattern
- High sensitivity for invasive & noninvasive cancer
- No compromise with breast density, scar, RT, implants
- False Negative: rare when performed/interpreted OK

MRI Specificity



- As low as 30%
- Results in unnecessary tests & biopsies
- Delays surgery
- Increases patient anxiety
- Increases medical costs
- Increases election of prophylactic mastectomy

MRI Indications



- High risk screening lifetime risk >20%
- Staging & restaging of breast cancer
- Problem solving clinical or imaging indeterminant lesions

MRI Benefits

- Most sensitive study
- Superior anatomic detail

MRI Challenges

- Lack of standardized acquisition & interpretation
- Low specificity with high false positive rate: BIRADS 3 or 4 lesions not uncommon
- Poor patient acceptance: lengthy & uncomfortable
- Hormonal influence: day 7-14 menstrual cycle

LWHWI 2015

- Inform patients of high or low density & lifetime risk
- Invite **high density or risk** for assessment/education
- Comprehensive risk assessment recommendations for follow-up surveillance
- Educate about risks & benefits of additional exams

Low Risk Surveillance

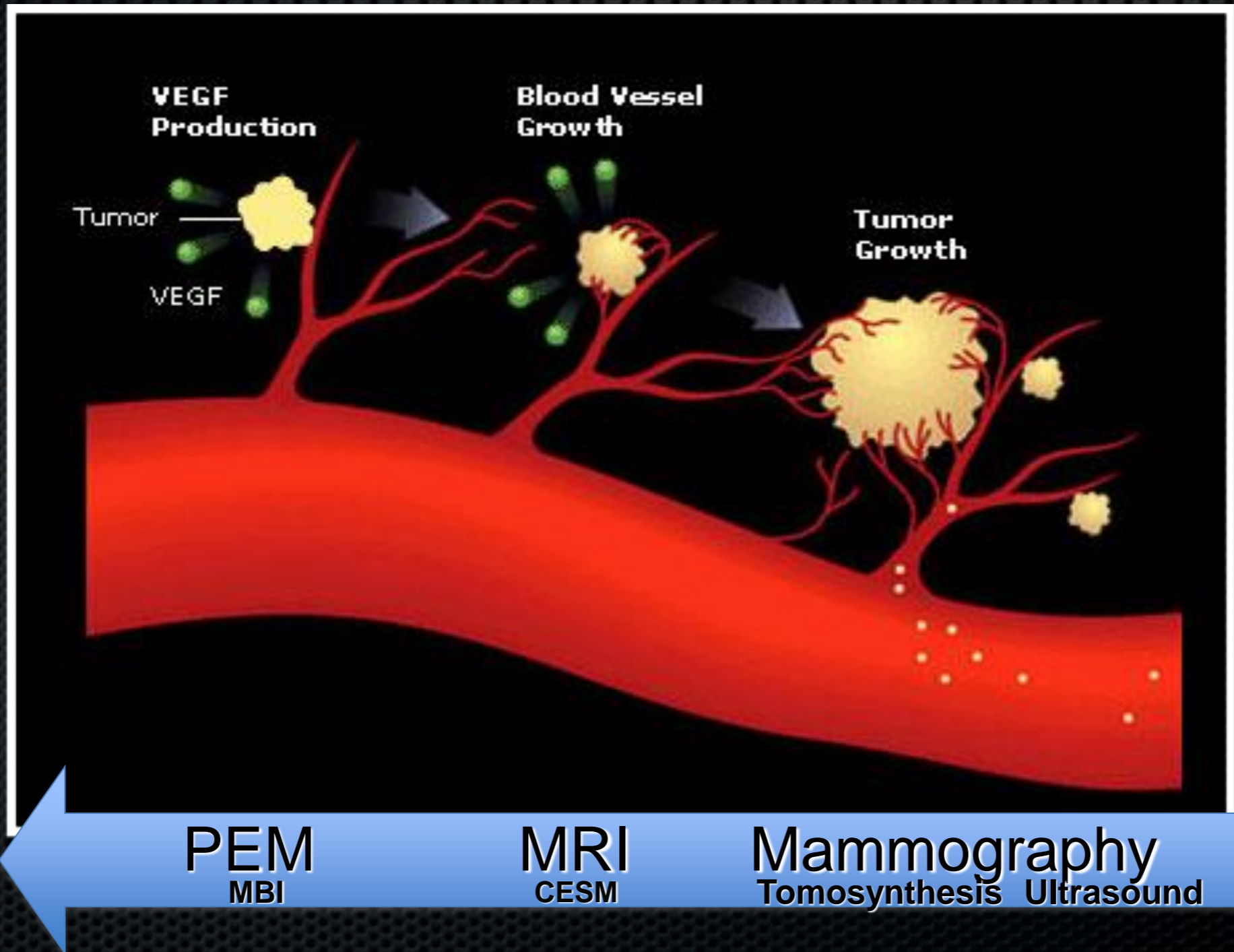
- **<15% lifetime risk**
- Annual mammography 2D or 3D at age 40
- **Dense breasts**: consider bilateral ultrasound
- High anxiety consider CESM

Intermediate Risk Surveillance

- **15-20% lifetime**
- Annual mammography 2D or 3D after 40
- Consider bilateral **ultrasound, MBI or CESM**

High Risk Surveillance

- **>20% lifetime risk**
- Annual mammography 2D or 3D beginning at 30
- Annual breast **MRI**
- Consider **CESM** @ 6mo interval between MRI



Supplemental Cancer Yield

<u>Exam</u>	<u>Detection Rate</u>
2D Mammo	4-7/1000
3D Mammo	2/1000
Double read	1/1000
CAD	1/1000
US	3-4/1000
MBI	7.5/1000
MRI	7-20/1000

Conclusion

- **Risk stratification** is important to optimize breast cancer detection. Achieved at screening & formal risk evaluation
- Multiple tools to include **anatomic & functional imaging** is important to maximize cancer detection
- **Personalized care** is the future of breast cancer detection