

A211102

Testing for Atypia in Random Periareolar Fine Needle
Aspiration (RPFNA) Cytology after 12 months
Metformin Chemoprevention versus Placebo Control



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Duke University

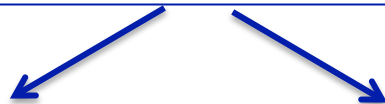
Pre-registration

- BMI > 25
- Premenopausal
- High-risk
>20% Gail, biopsy atypia, DCIS, LCIS
BRCA mutation



RPFNA t=0

Atypia, Masood Cytology ≥ 14



Metformin

850 po bid

(ramp up)

Can back down to 850 qd

Placebo

850 po bid

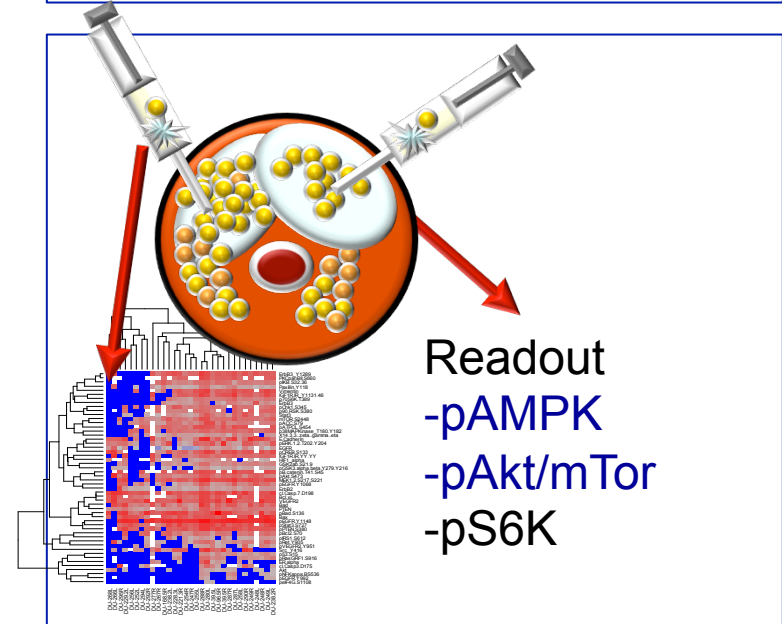
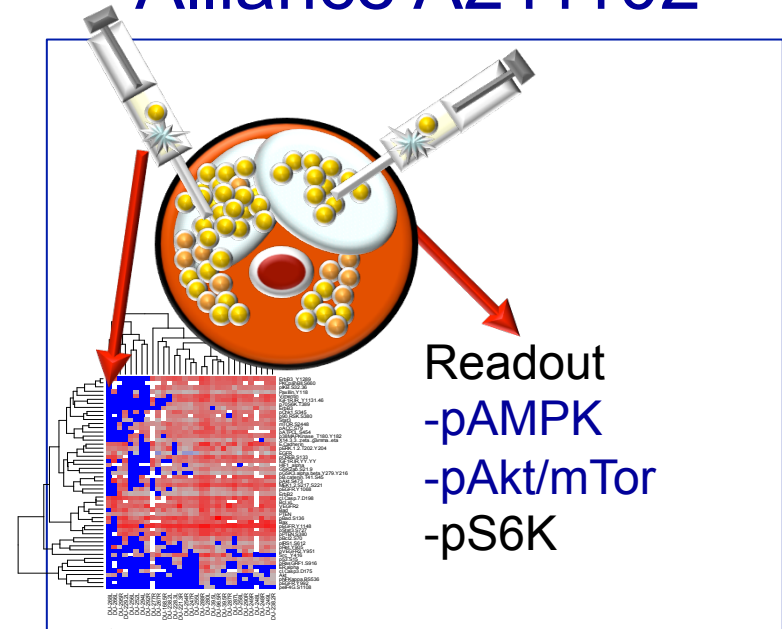
Unblinded at 12 mos

Can opt for drug



RPFNA t=12 months

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Inclusion:

Increased risk for breast cancer

Gail > 1.6 five year

Biopsy atypia, DCIS/LCIS

Family history breast and/or ovarian cancer

Atypia on RPFNA in non-excised breast tissue (Masood 14-17).

Subjects may have a **new** diagnosis of DCIS or LCIS, however, in subjects with DCIS only the nonradiated breast can be aspirated.

Premenopausal

Age 25 to 55.

BMI \geq 25

Mammogram within the last 3 months.

At least one year from pregnancy, lactation or chemotherapy.

Exclusions:

Metastatic malignancy of any kind.

Subjects on warfarin or other anticoagulants.

Bilateral breast implants or tram flap reconstruction.

Radiation to both breasts.

Elevated Cr.

Primary Outcomes

Test for the presence or absence of atypia in RPFNA after 12, and 24 months Metformin versus placebo control.

Secondary Outcomes

Test the reproducibility of RPPM in duplicate RPPM determination from single RPFNA specimen.

RPPM analysis of the initial RPFNA cytology in women with disappearance of atypia versus persistent atypia after 12, and 24 mos Metformin.

Determine the change in percent breast density from prior to the initiation of metformin or placebo treatment through one year of therapy in subjects.

Correlative Research

Surrogate biomarkers of breast cancer risk:

Atypia - surrogate endpoint biomarker/risk biomarker

Mammographic density – surrogate/risk biomarker

Phosphoprotein expression – exploratory biomarker

Circulating insulin growth factor and other cytokines -
surrogate biomarker and risk biomarker

Markers of obesity and insulin resistance:

Waist to hip ratio

Fasting serum insulin, fasting serum glucose

Circulating Homeostatic Model Assessment (HOMA)

Other Measures:

Tissue/serum Metformin levels – exploratory

Estrogen/Progesterone – exploratory biomarker.

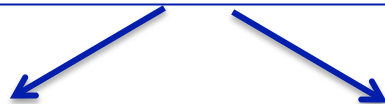
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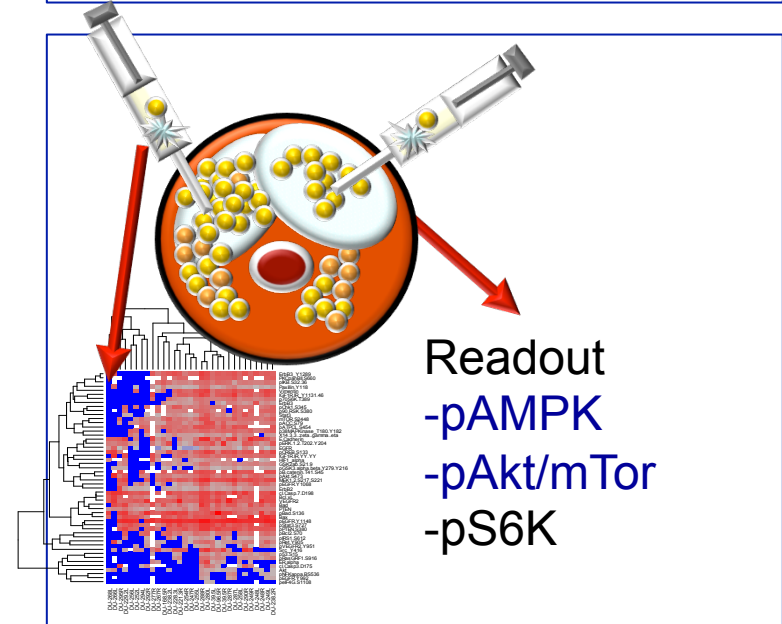
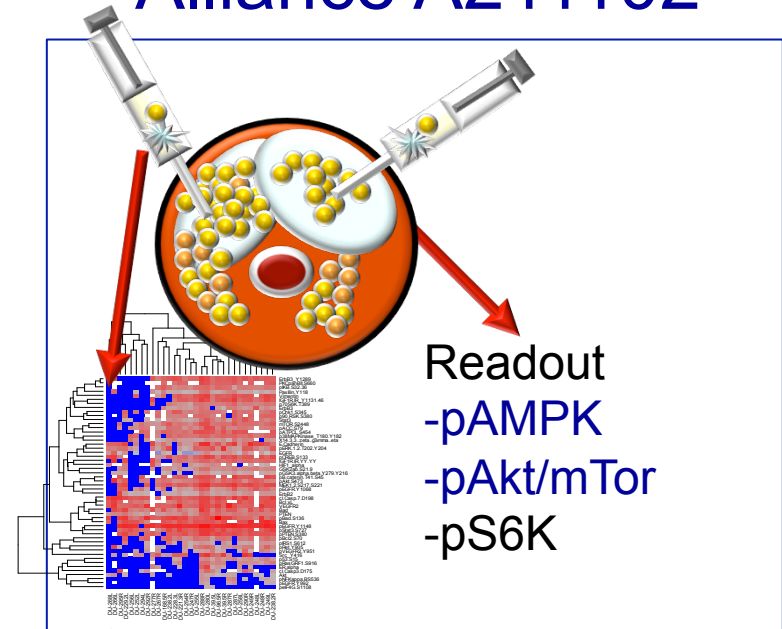
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RPFNA t=12 months

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Contact Victoria Seewaldt, M.D. for RPFNA training
seewa001@mc.duke.edu
subject line “RPFNA TRAINING”

Training options

- Skype
- Visit Duke – we can make this easy

Best patient – aspirate in OR during DCIS surgery:
35-45 years old, pre-menopausal, BMI 25-30

Contralateral breast – biopsy proven DCIS
and low suspicion for invasive cancer

Aspirate contralateral breast - >90% chance atypia

Has to refuse tamoxifen or not be eligible

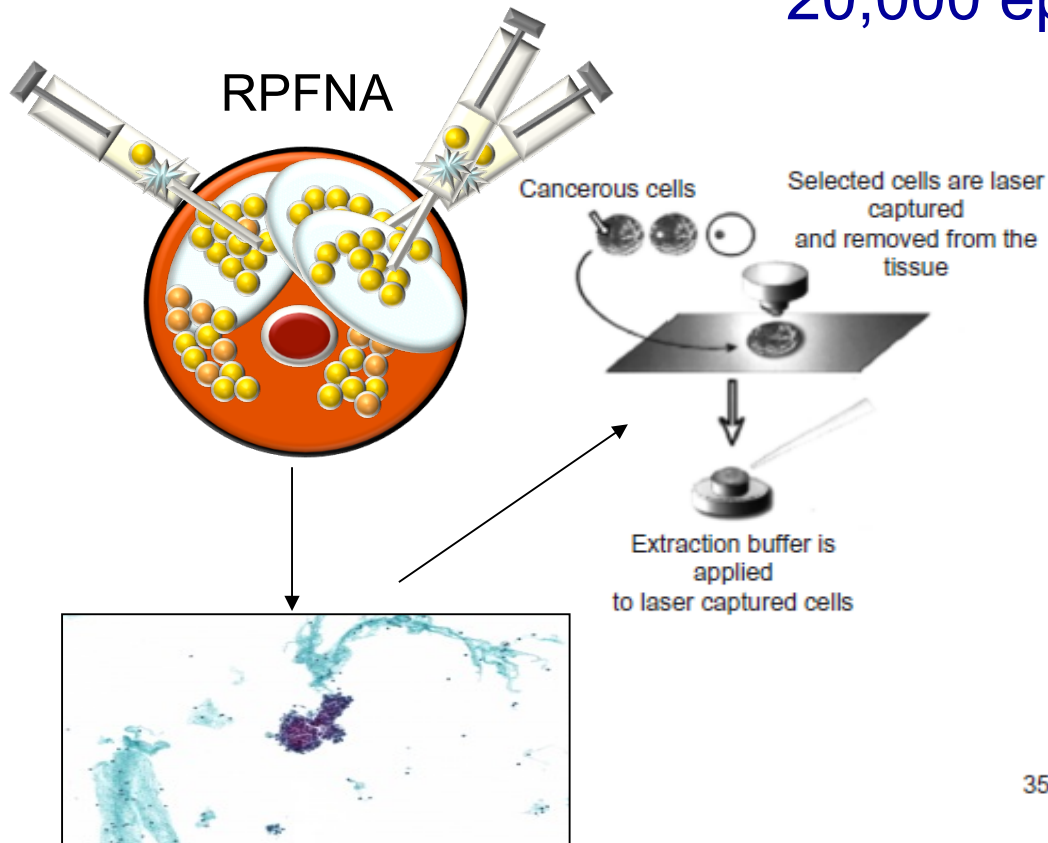
Can be BRCA mutation carrier

Phosphoprotein analysis of RPFNA cytology

50 proteins in triplicate
20,000 epithelial cells

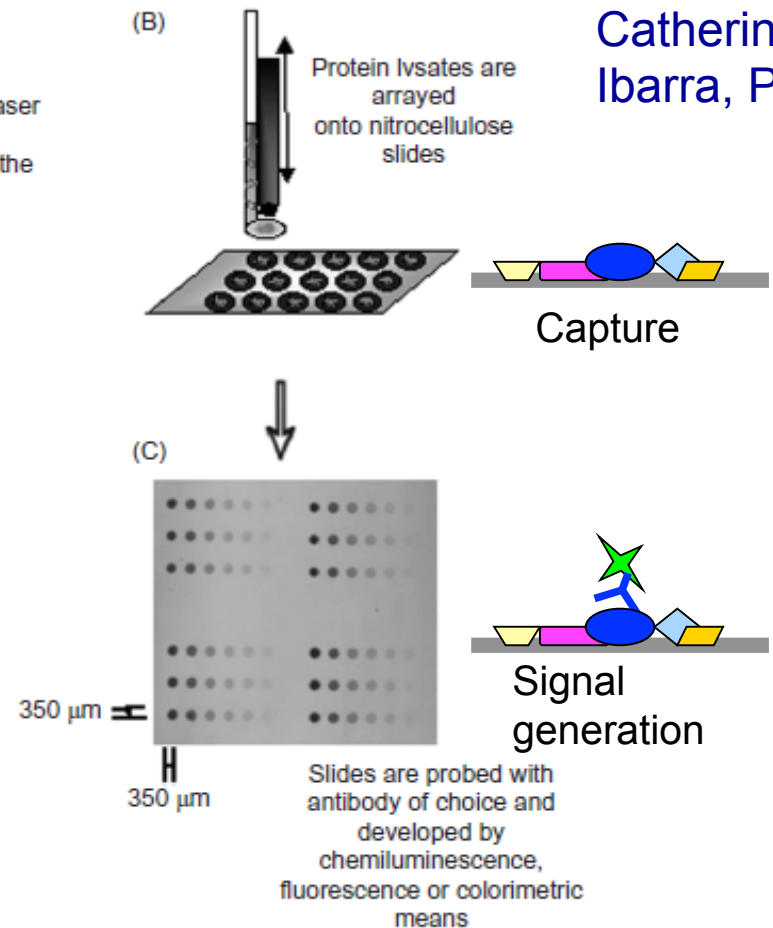


Catherine Ibarra, PhD

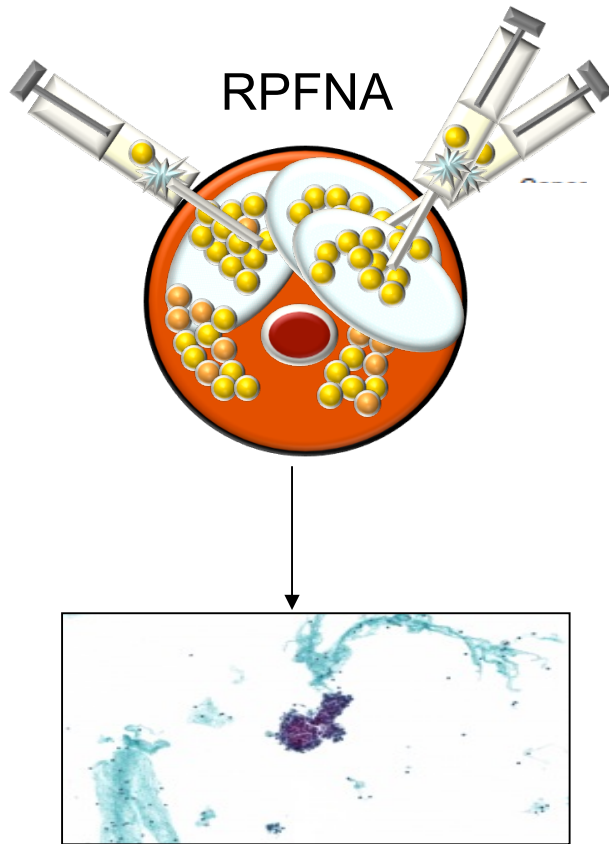


Cytospin.

Microdissection of epithelium and stroma



Cytological Sampling of High-Risk women using Random Periarolar FNA

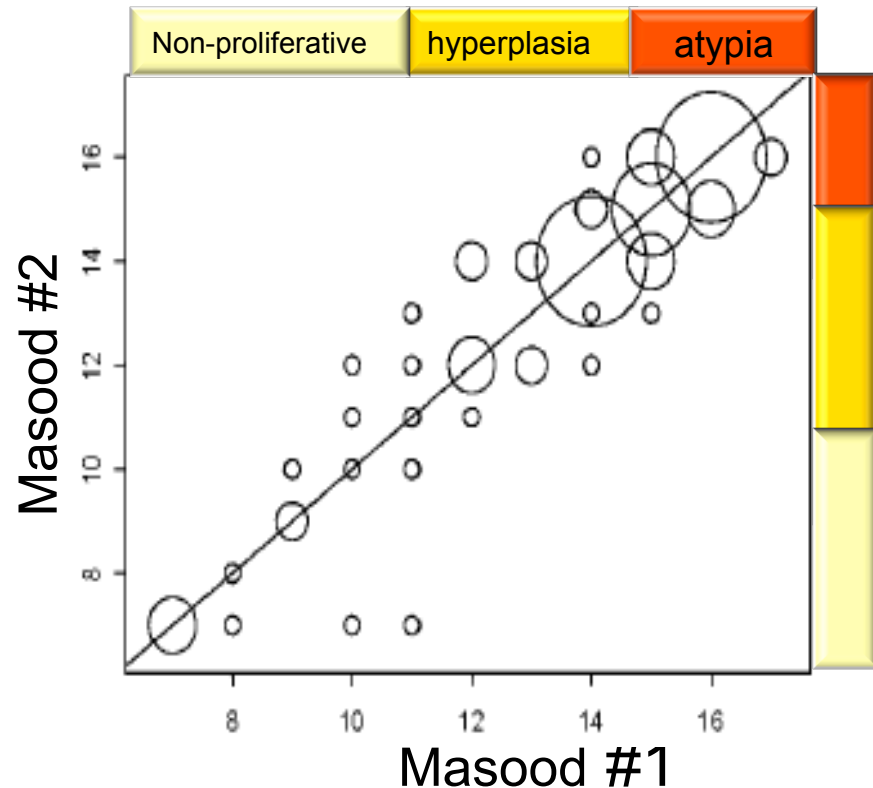


Cytospin.

Microdissection of epithelium and stroma

5 institutions, n=78;

Not affected by: Age $p=0.249$, BMI $p=0.115$, Gail $p=0.938$, BRCA $p=0.2151$, 1° family $p=0.4022$.



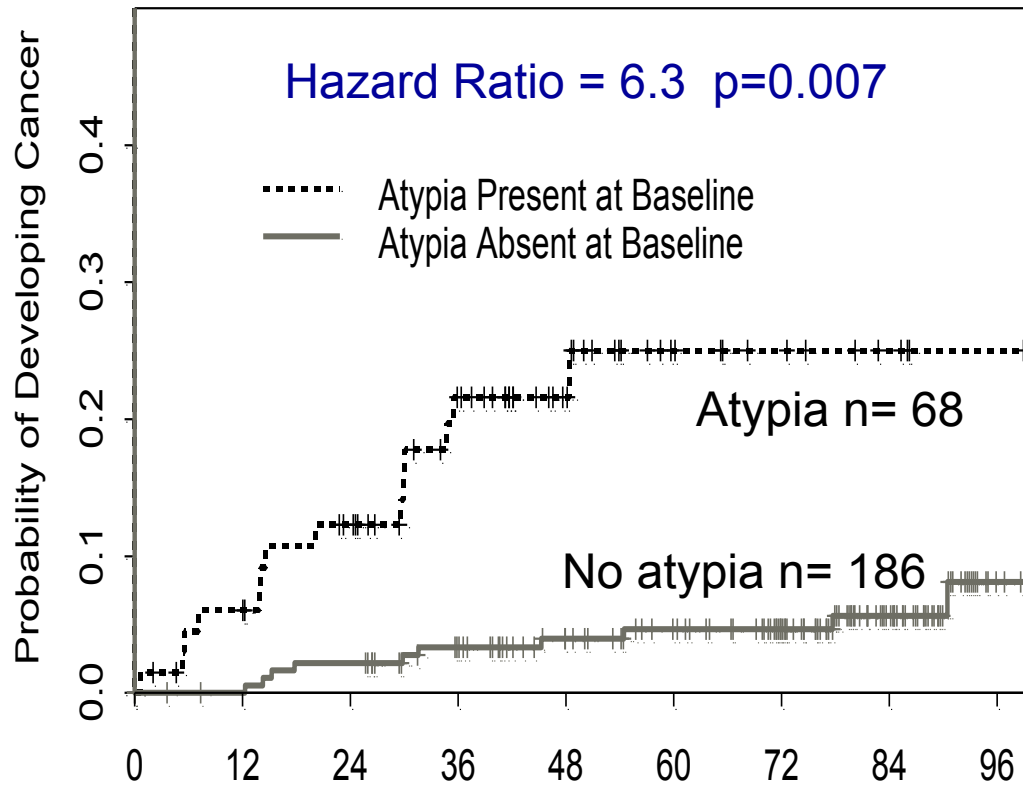
Atypia in RPFNA predicts risk for progression to cancer in women from non-BRCA high-risk families

Atypia n= 68
 No Atypia n= 186
 Total n= 254 15% African American
 (34% AA entire cohort)

		Atypia		
		Y	N	
Cancer	Y	20	4	24
	N	48	182	210
		68	186	

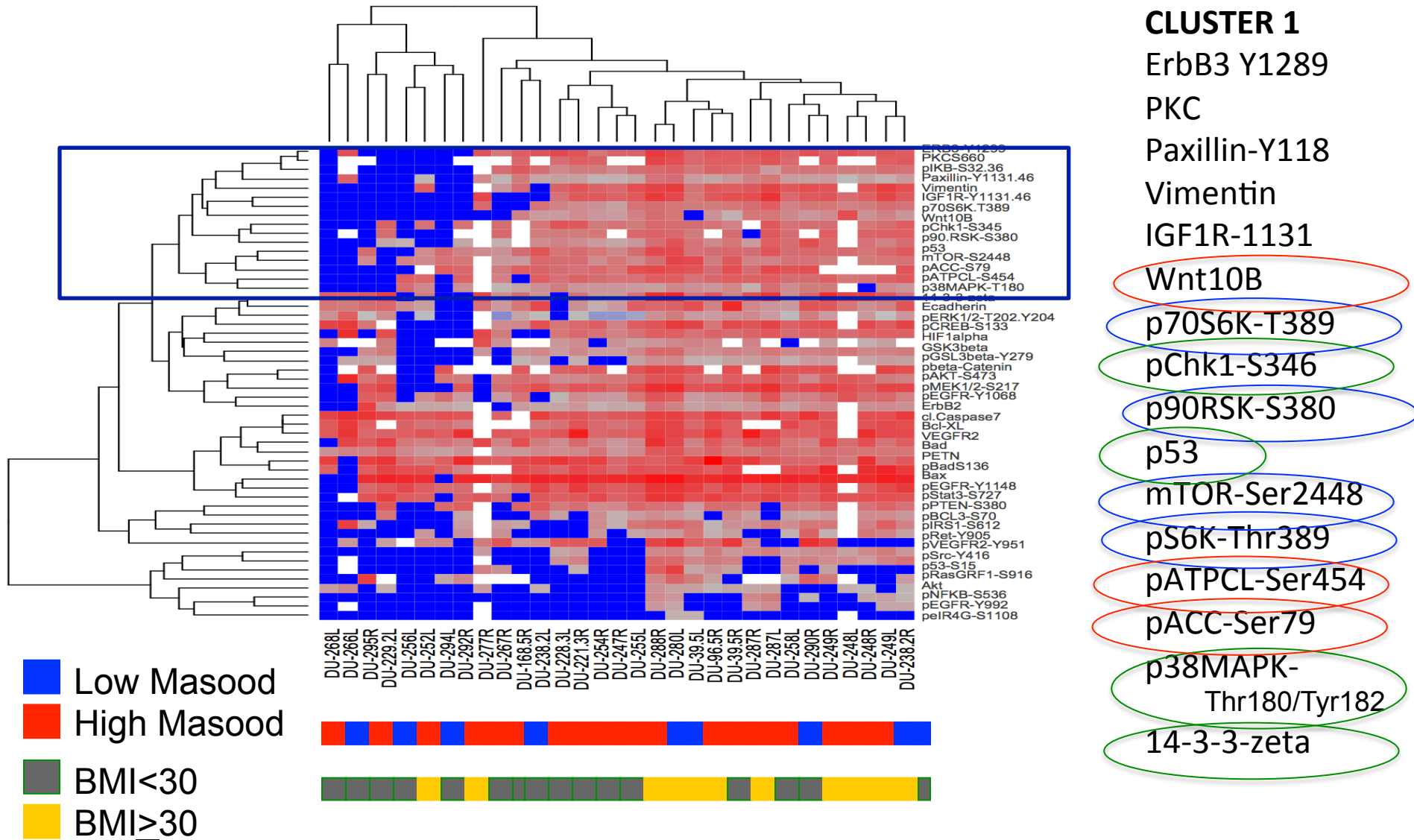
15 Invasive cancer
 9 DCIS

24 Total cancers



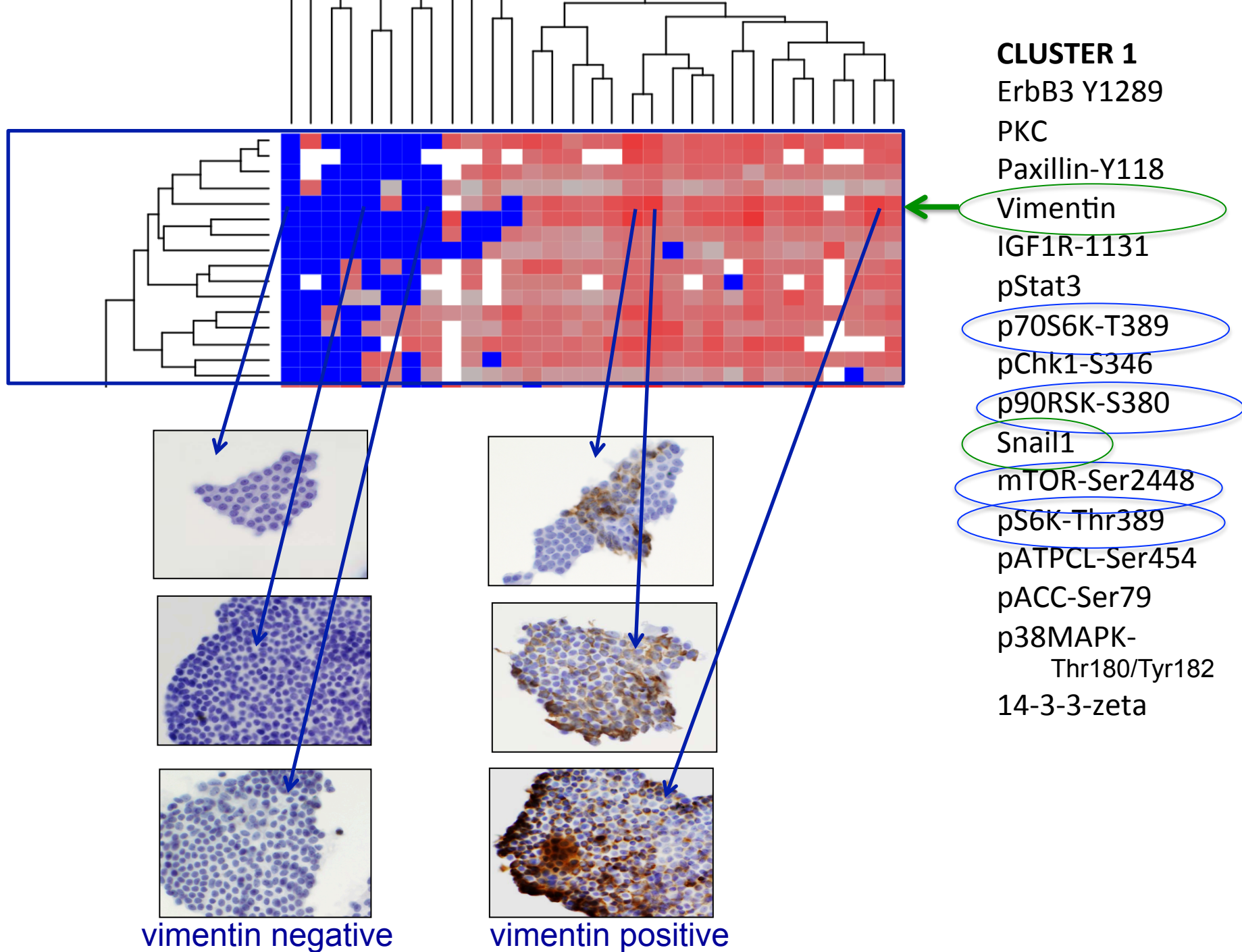
Atypia Cluster 1 – 31 high risk AA women

Akt/mTor, p53/stress, Wnt/AMPK



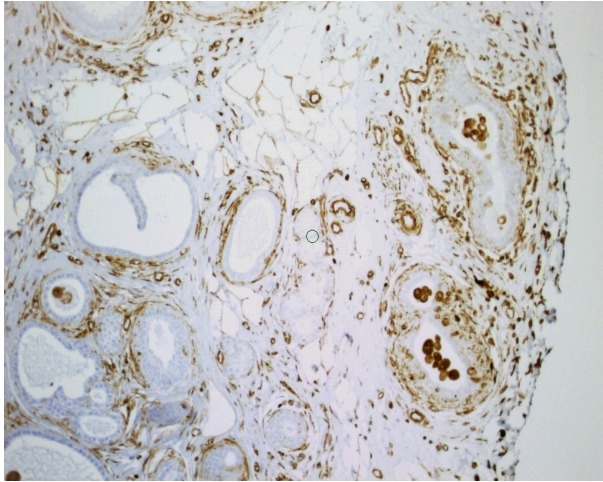
Lopez-Contreras... Fernandez-Capetillo

a allele Chk1 limits oncogene replicative stress and promotes transformation *JEM*, 2012

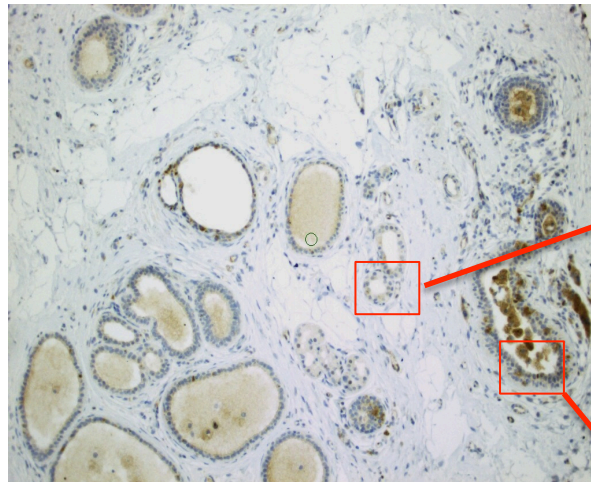


DU-368 – Markers of EMT

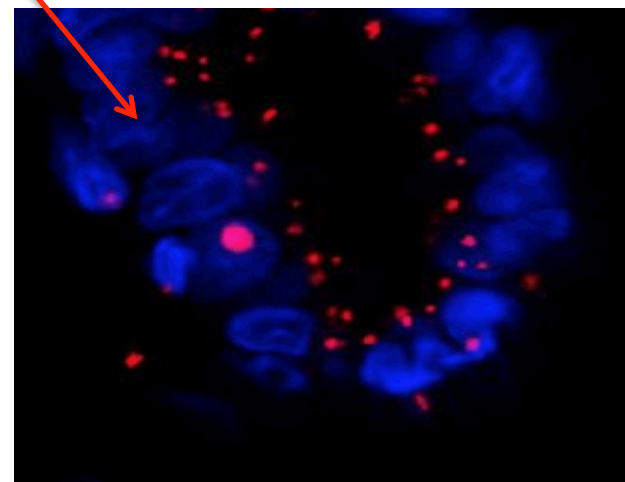
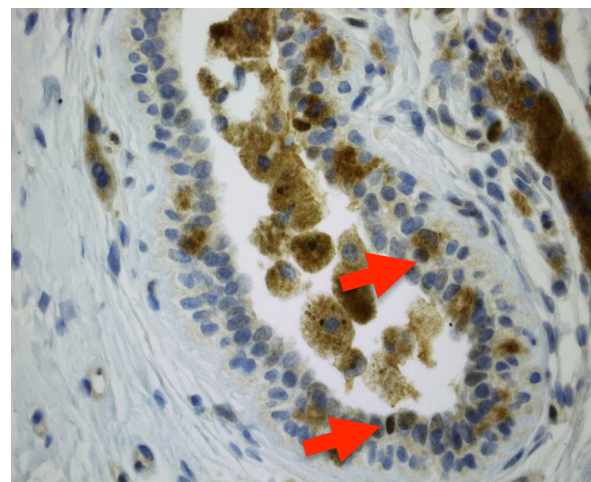
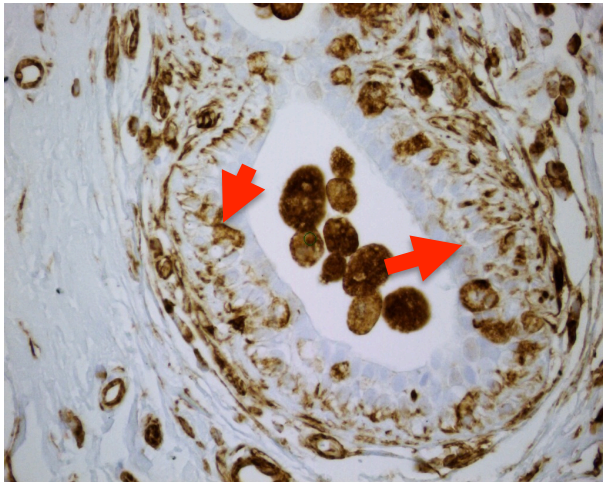
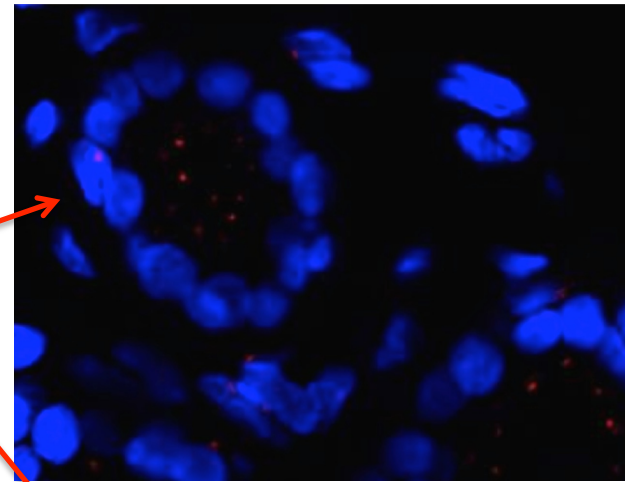
vimentin(+)



snail1(+)

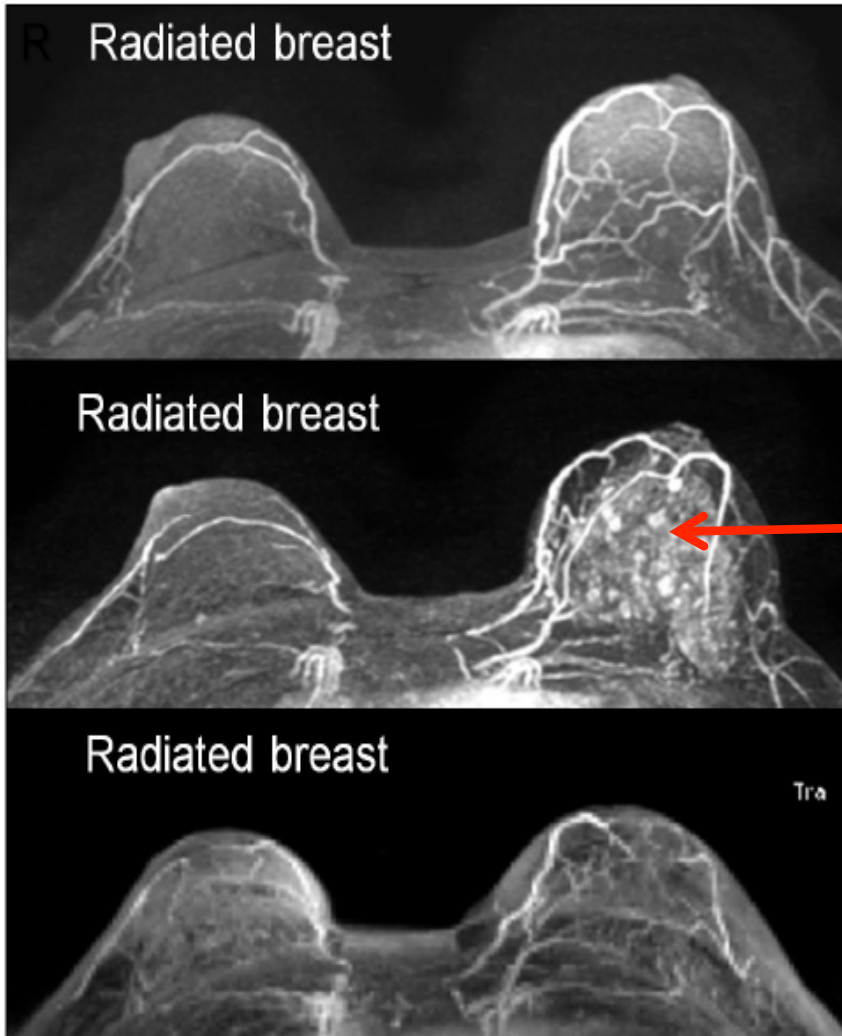


pericentrin



Non-BRCA1 mutation carrier

40 yr old woman. First pregnancy age 37, breast cancer R found after weaning.



Masood=11
Masood=12
Masood=10
Masood=10

Atypia/one
foci DCIS

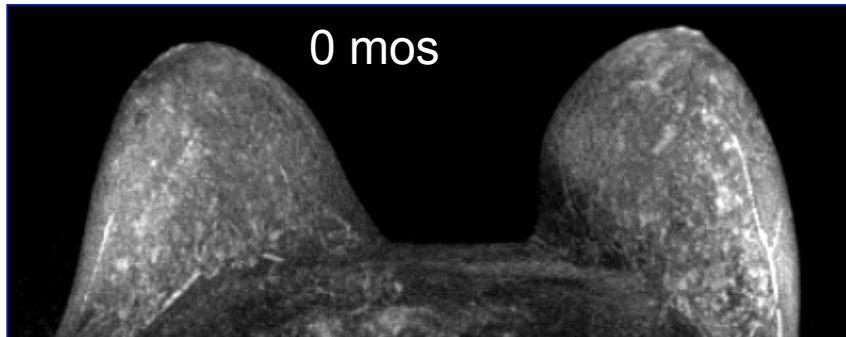
Masood=16
Masood=17

Arimidex

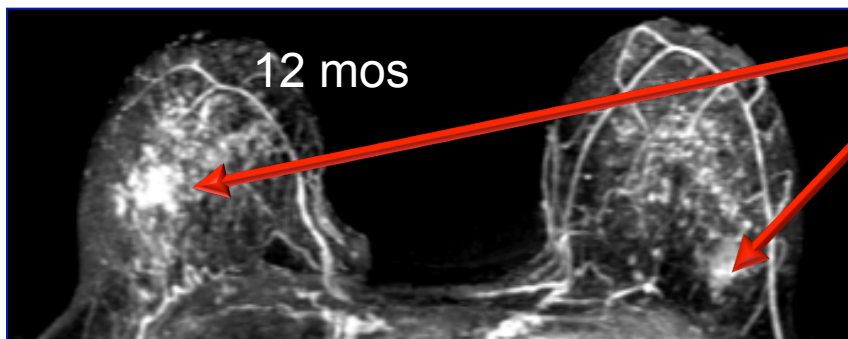
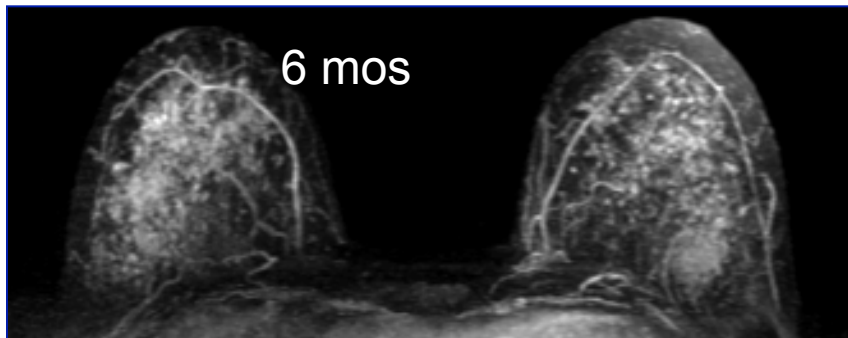
Masood=10

Breast MRI in High-Risk Women

42 yr old woman. Sister died metastatic TNBC breast cancer (normal mammogram). No BRCA mutation.



R Masood=14
L Masood=12



ER/PR-
Her2-
T1N0

R Masood=16
L Masood=17