Horizons 2013: Connecting the AAPM and the NCI PS-OC Program

Clinical Applications of Physical Sciences in Breast Oncology: One Cancer Surgeon's Perspective

E. Shelley Hwang MD, MPH
Duke Comprehensive Cancer Center
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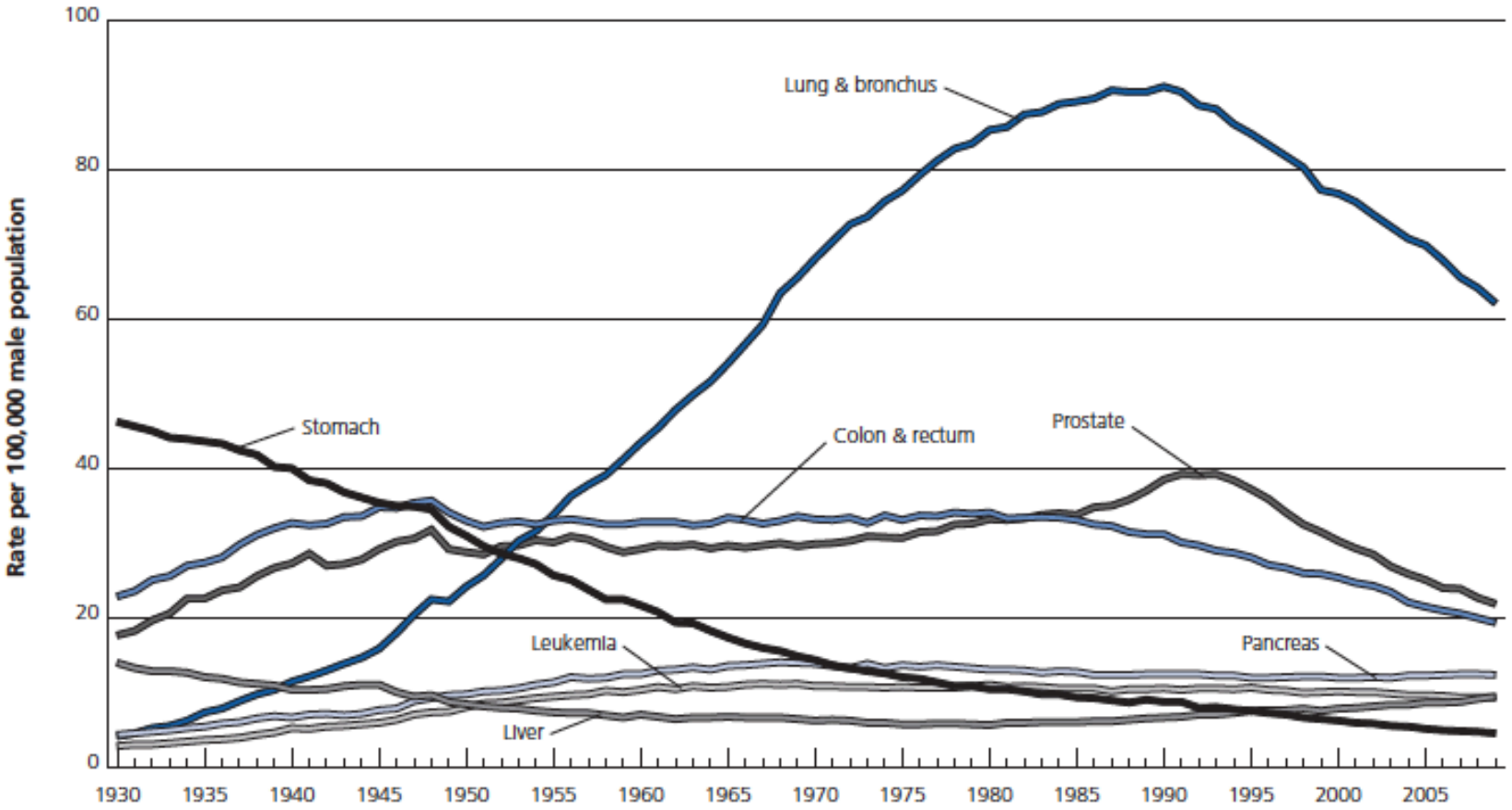
Applications of Physical Sciences in Breast Oncology

- Diagnosis
  - Breast tomosynthesis
  - 3D CT
  - Breast density
- Treatment
  - Surgery—Margin assessment
  - Radiation therapy
- Prevention/Surveillance/Prognosis (PSOC)
  - Breast Density
  - CTCs
  - Tumor heterogeneity

Age-adjusted Cancer Death Rates*, Males by Site, US, 1930-2009

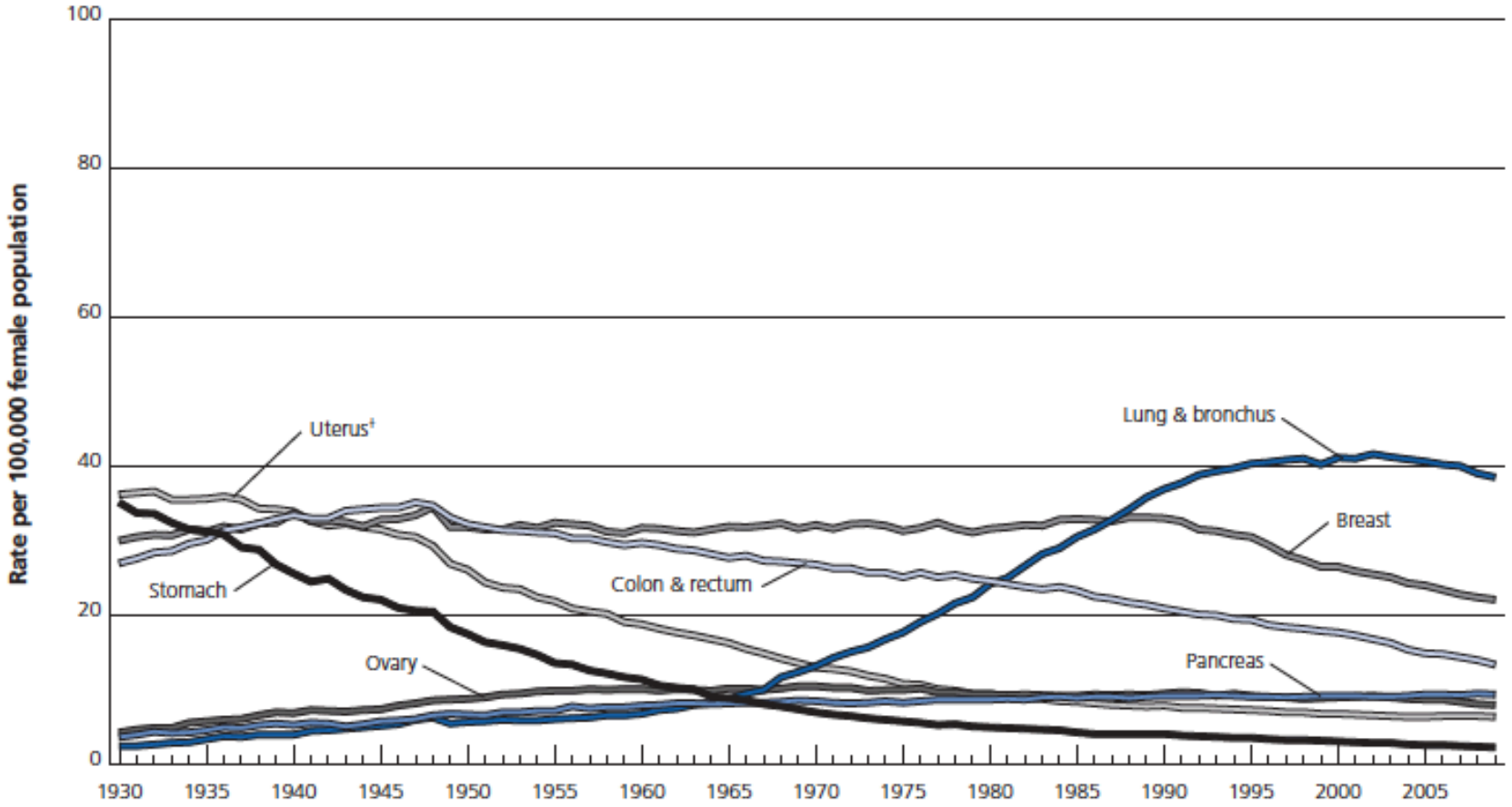


*Per 100,000, age adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2009



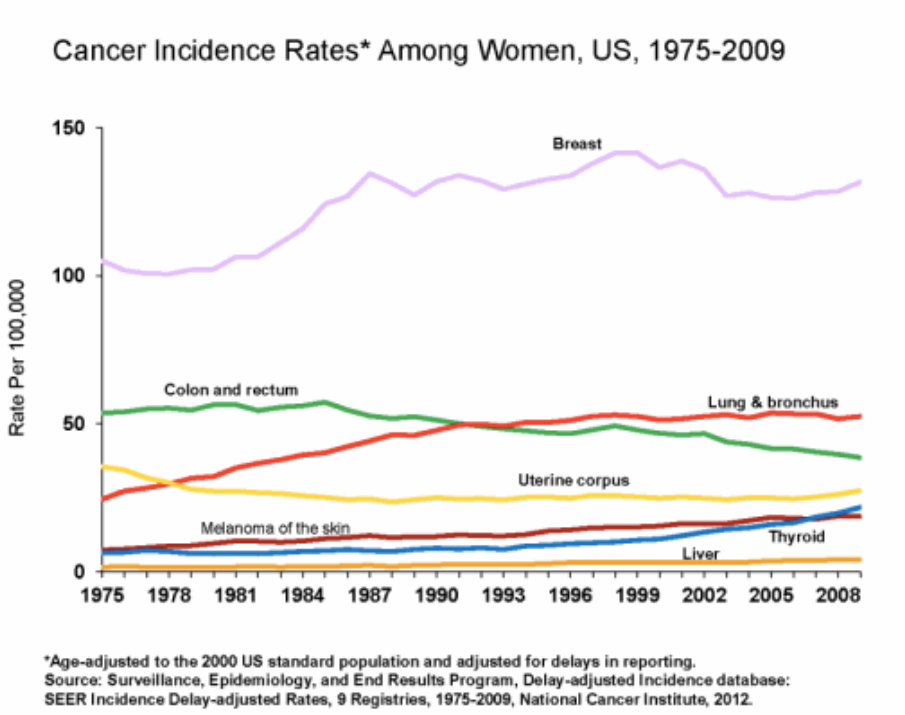
*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

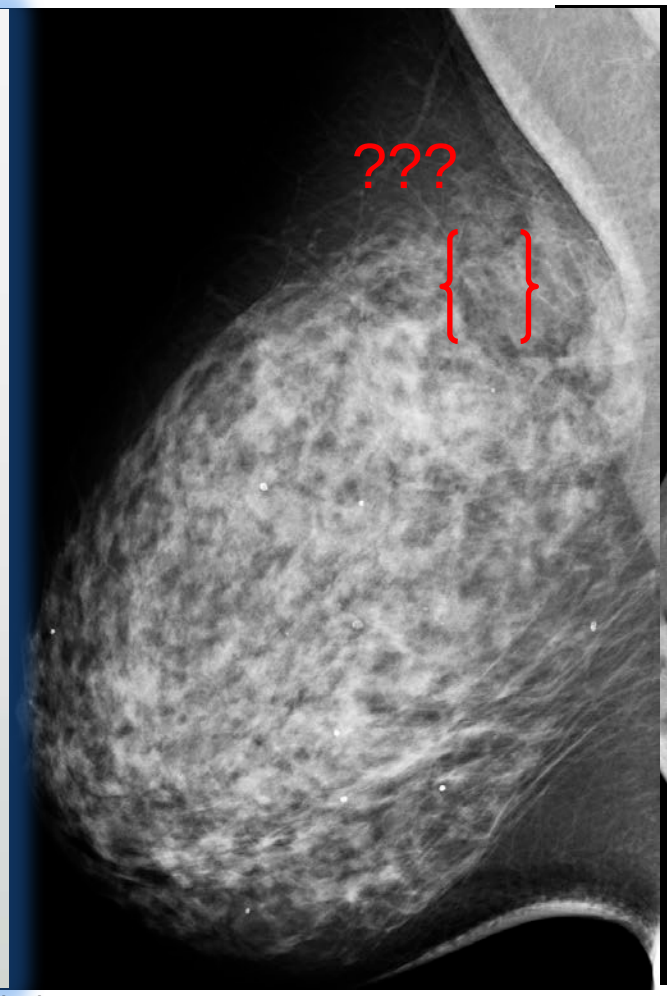
Breast Cancer Diagnosis

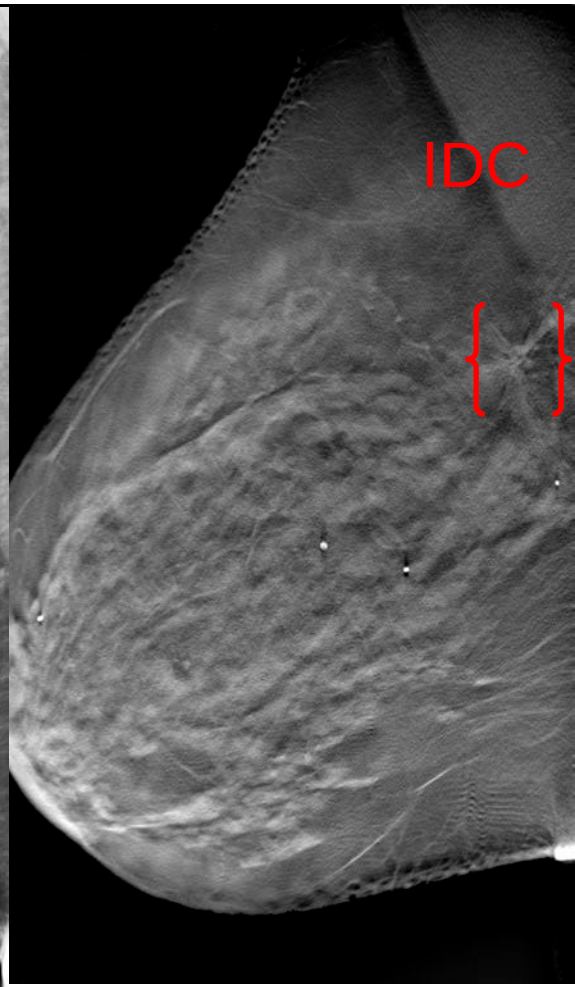
- More than 1 in 8 women in the United States will be diagnosed with breast cancer; 250,000 diagnosed annually
- Almost **40 million mammograms** are done every year—estimated cost of **$5 -7 billion**
- Mammographic screening was implemented in the 1980's
  - Only 25% >5 MMG
  - Associated with reduction in mortality
  - Guidelines controversial
- New technologies
  - **Tomosynthesis**
  - **3D breast CT**



Breast Tomosynthesis

improves mammography sensitivity and specificity



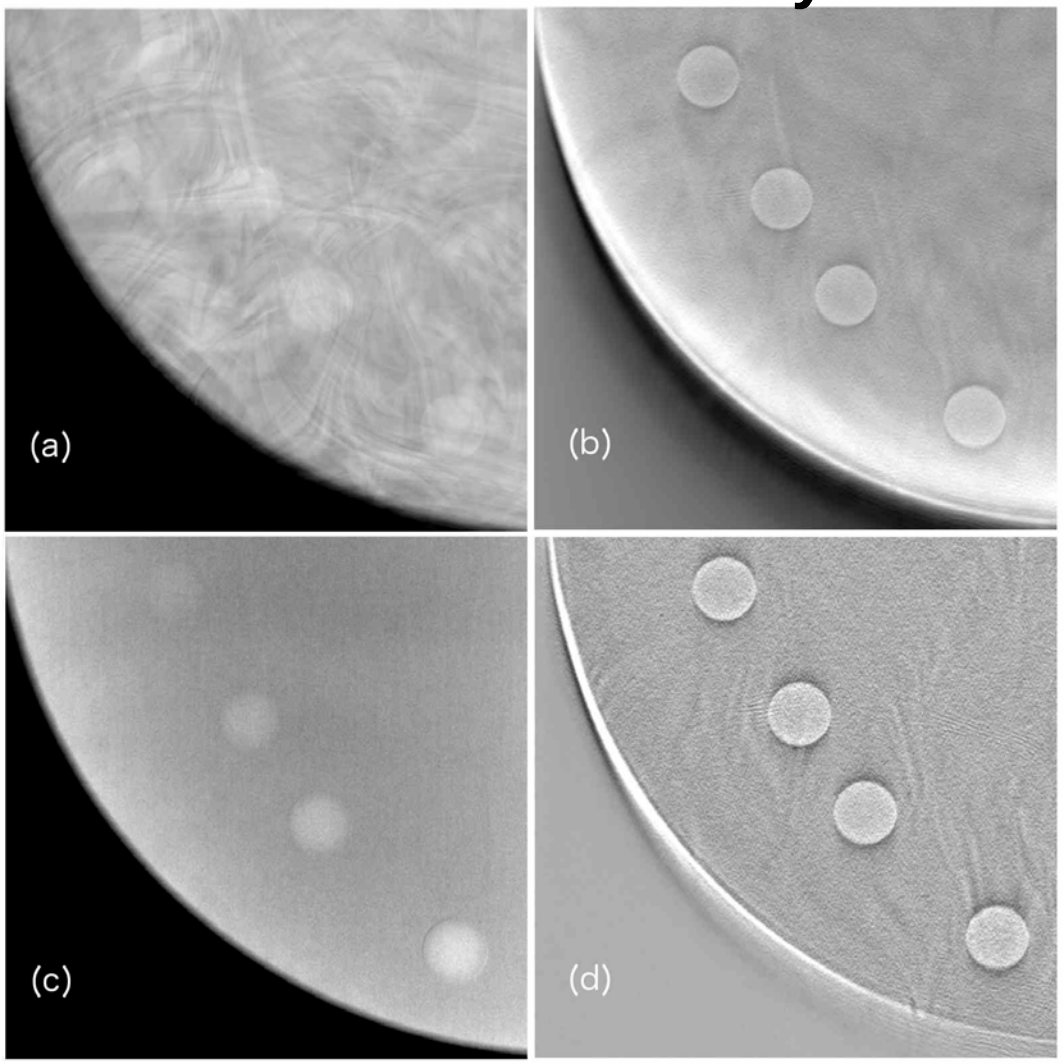


- 2D mammo (L) missed cancer, easily seen on 3D tomo slice (R)

Contrast-enhanced mammo/tomo

MMG **tomosynthesis**

Standard FFDM, lesions obscured by anatomy



Standard tomo, remove overlap w/ 3D acquisition

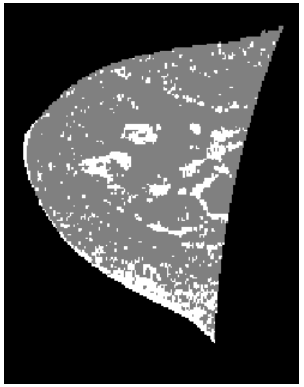
Dual energy FFDM, subtract anatomy by energy cancelation

Temporal subtraction tomo, temporal + 3D to remove anatomy

Joseph Lo, Duke University

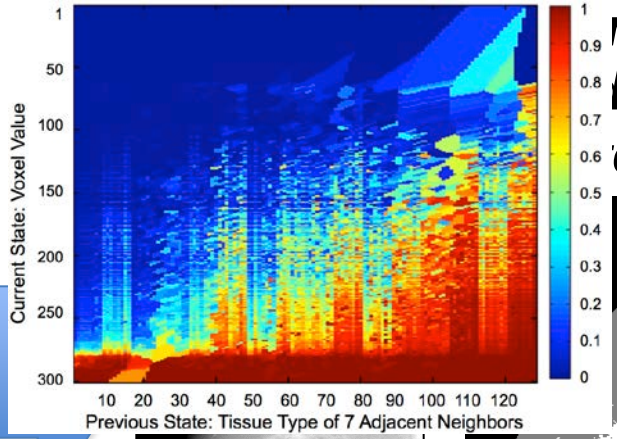
Cross-modality approach to measure breast tomosynthesis density

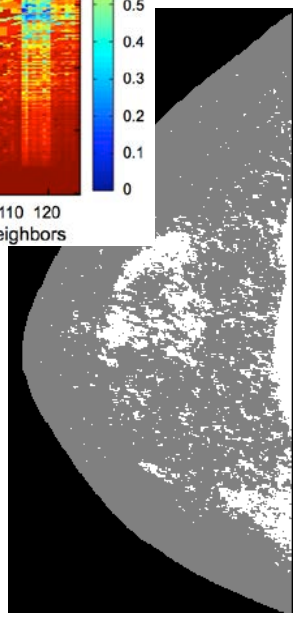
- Probabilistic model uses both anatomy and voxel values
- Train with MRI, apply cross-modality to tomo

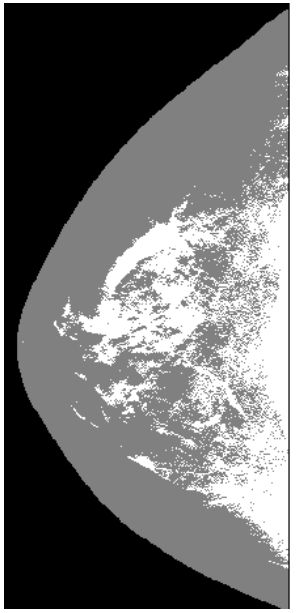


MRI: convert original image (left) to ground truth (right), which can train Hidden Markov Model to segment fibroglandular vs adipose tissue, then apply to tomo.

Tomo: original image (left), segmented much better than ling (right) that es density







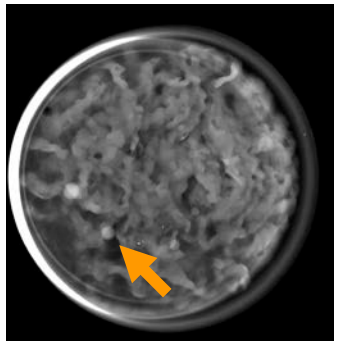
3-D Breast Computerized Tomography (CT)

- Lead-lined walls & doors
- Radiopaque & contoured patient support
- Laser positioning cross-hairs
- Fully-3D motion of x-ray & digital detector
- NO breast compression
- Images acquisition in 10-12 minutes

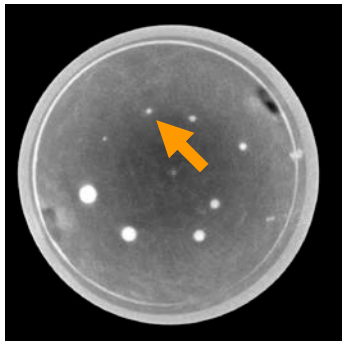
McKinley *et al*. *Proc. IWDM.* Springer-Verlag. (2012):442-449.

3D CT pilot: Reader Results

Digital Mammography



Breast 3D CT



- Preliminary studies indicate fully-3D breast CT has significant advantage over digital mammography in tumor detection
- Smallest observer detectable size in dense breast:

Digital Mammography – 7.8mm

Breast CT – 2.1mm

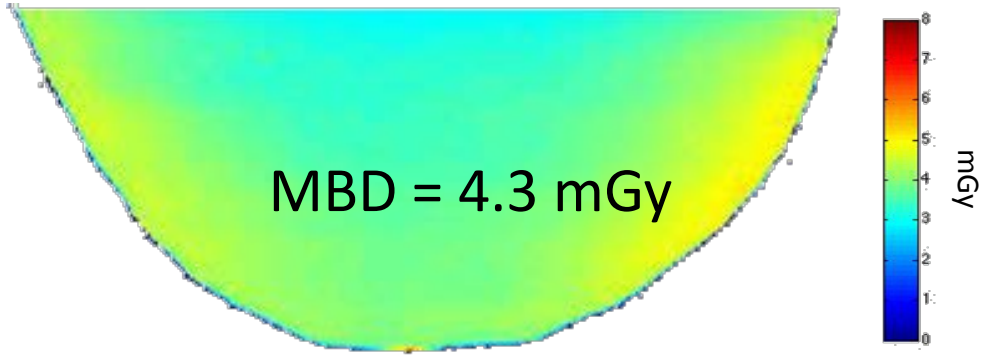
Detection sensitivity at 50X smaller volume

McKinley *et al*. *SPIE Med. Imag.* **6150**(1D):1-10, 2007.

3D CT pilot: Dosimetry Assessment

Photo of Breast Tissue

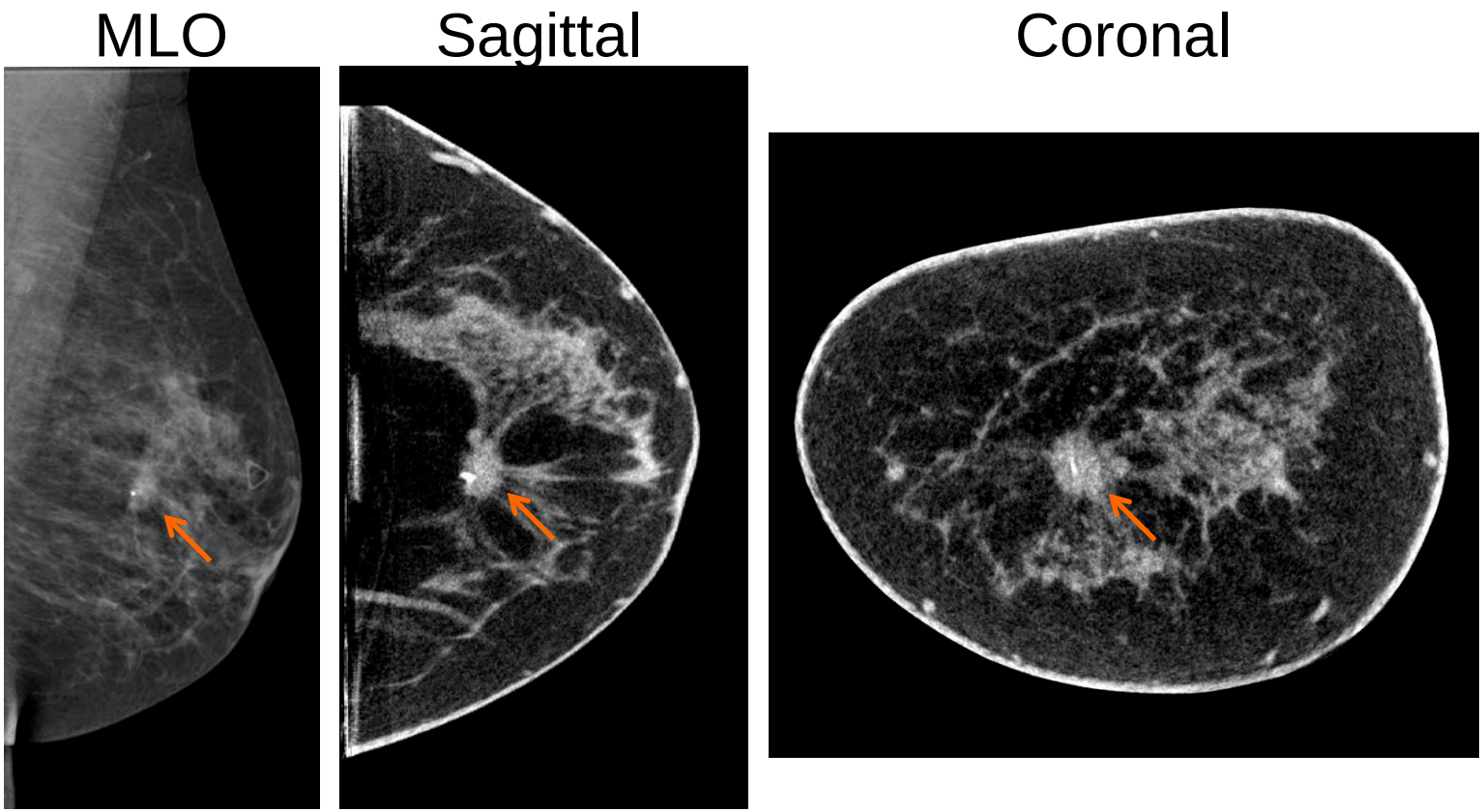
2D Dose 'Heat' Scale



- Cadaver breast measurements have Mean Breast Dose (MBD) <4.5 mGy per breast for fully-3D breast CT
- MMG dose: 3.7 mGy

Crotty *et al*. *Medical Physics* **38**(6):3232, 2011.

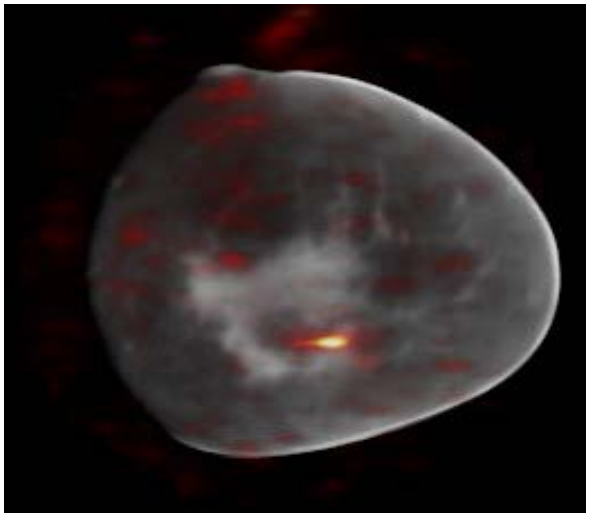
3D CT pilot: Image comparison between MMG and 3D CT



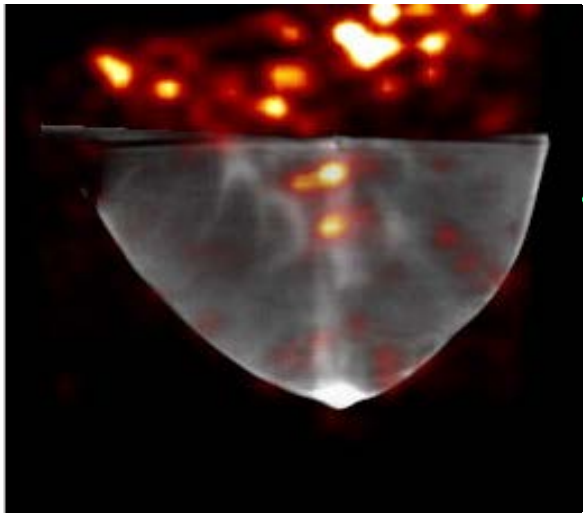
McKinley *et al*. *Proc. IWDM.* Springer-Verlag. (2012):442-449.

Functional imaging: 3D CT/PET

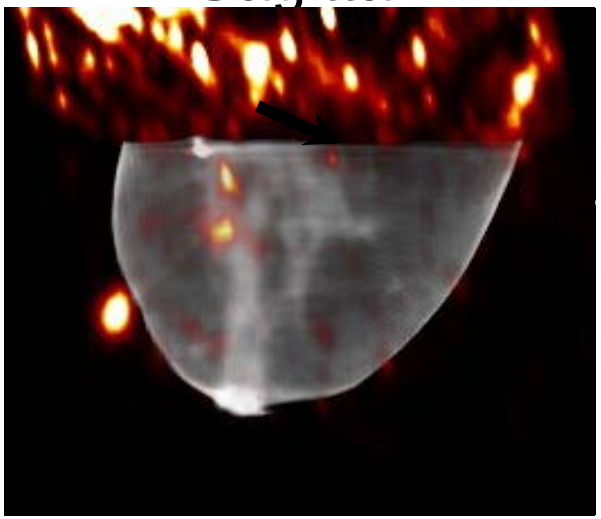
Coronal



Axial



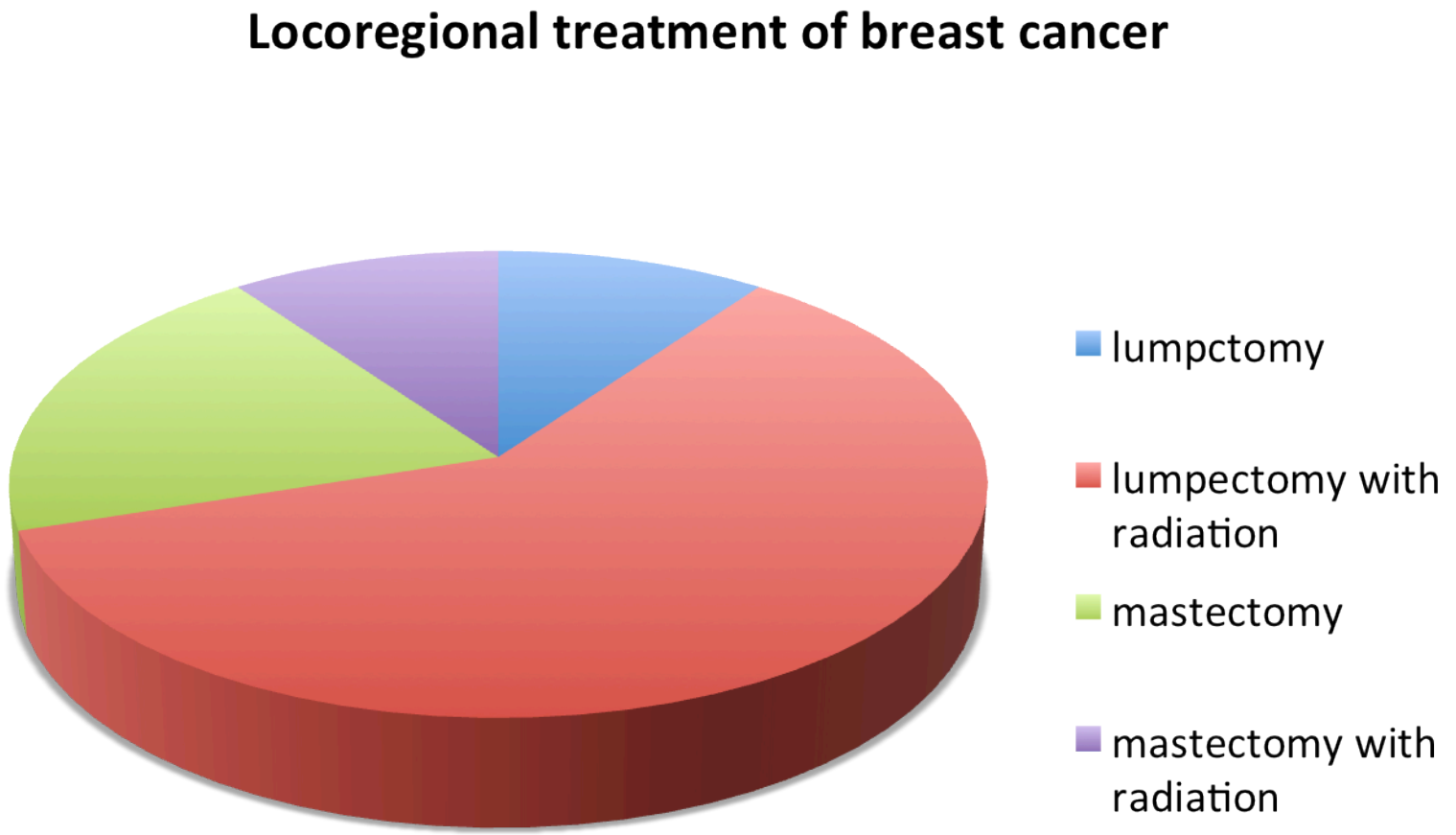
Sagittal



- Combined dedicated breast SPECT and CT at Duke
  - Systems are combined on the same gantry
  - Illustrates utility of functional SPECT information along with anatomy from bCT

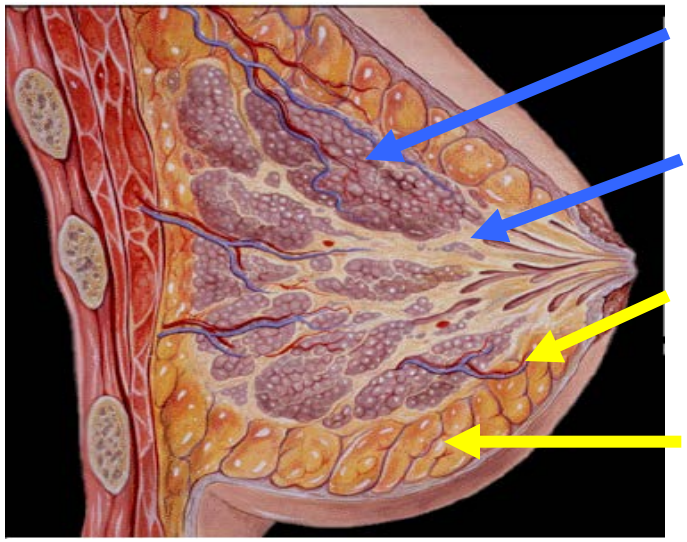
Madhav *et al*. 2007. *IEEE Conference Record NSS/MIC*, 5:3781.

Breast Cancer Treatment



Almost 40,000 women undergo at least one repeat surgery

Optical spectral mapping of reflectance spectroscopy leverages optical contrast between normal and cancer tissue

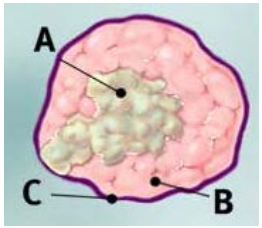


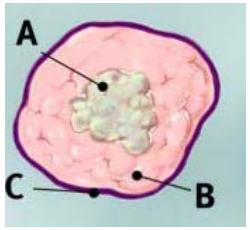
Cell scattering

Collagen scattering

Hemoglobin absorption

β-carotene absorption

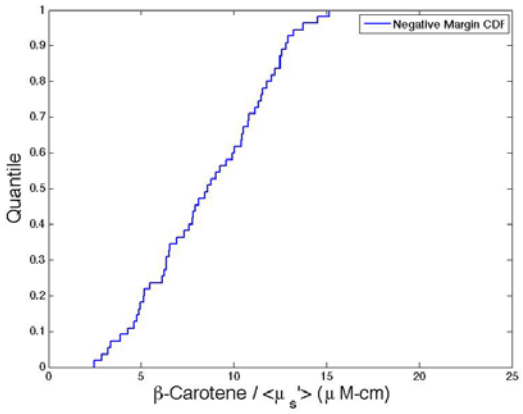




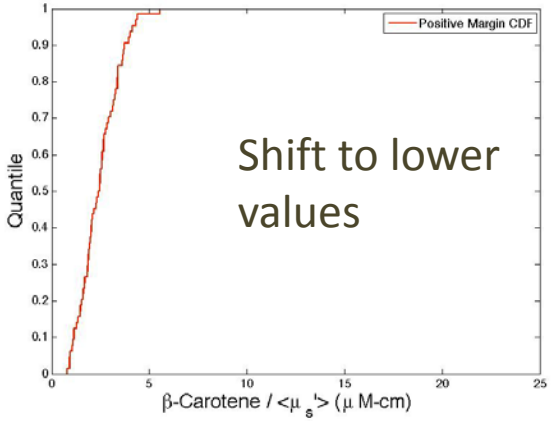
Contrast [1]

- **β-carotene** ⬇
- **Hemoglobin** ⬆
- **Scattering** ⬆

"Negative margin"



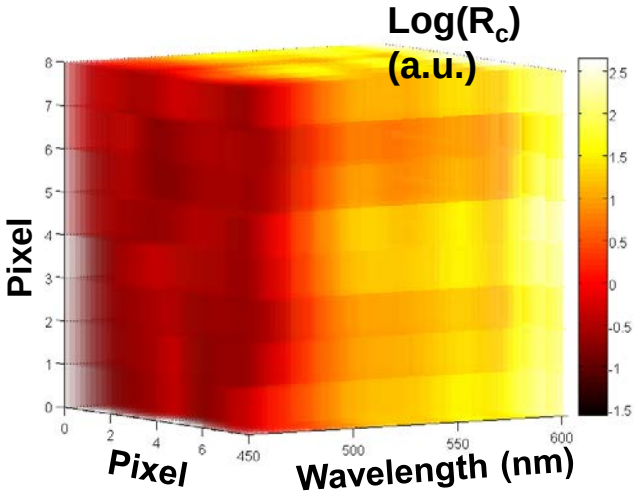
"Positive margin"

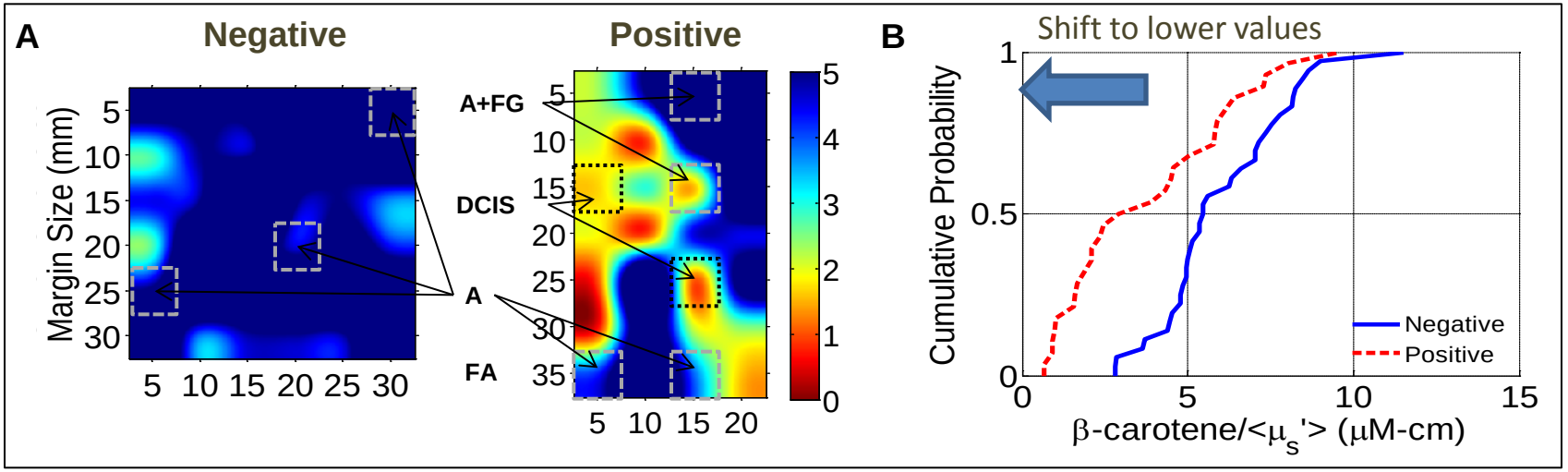


Shift to lower values

[1] Volynskaya, 2008; Zhu., 2006: Zhu, 2008; Palmer, 2006; Ghosh, 2001; Cerussi, 2006;

Rapid Surveillance of a Tumor Margin in < 30 seconds

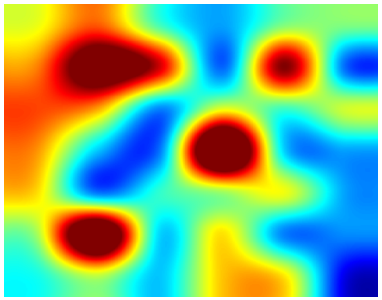




Bydlon and Brown et al, PLOS one,2013

Predictive models for margin assessment (75 patient study)

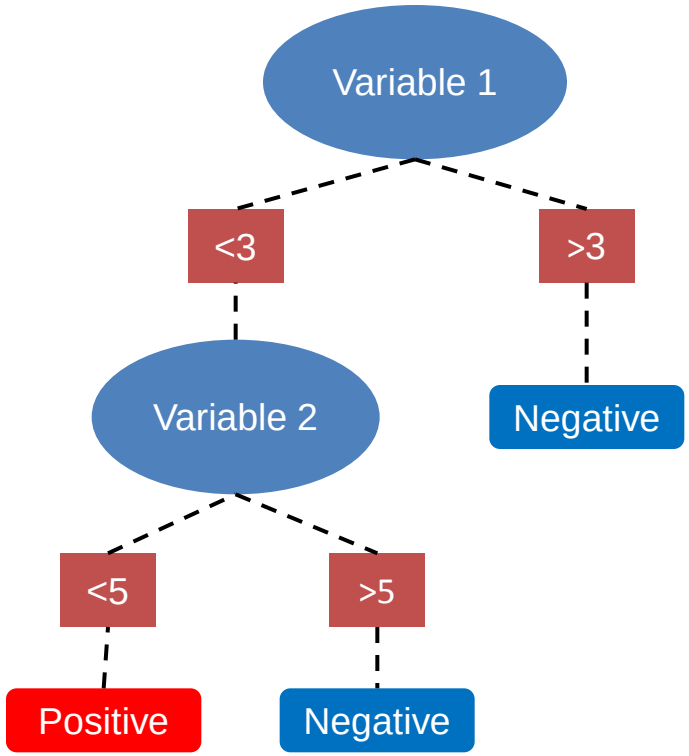
Image variables



- Median
- Quantile thresholds
- KS-statistic

Samples (n)	Se (%)	Sp (%)	PPV	NPV
All (88)	74	86	85	75
Low Density (48)	65	92	88	74
High Density (40)	83	76	83	76

Conditional Inference Tree



Bydlon and Brown, PloS One, 2013

Radiation Therapy for breast cancer: Standard Approach

- External beam radiotherapy administered daily on an outpatient basis for 4-6 weeks

- Treatment considerations:
  - Skin reactions
  - Fatigue
  - Exposure of healthy tissues (lung, heart)
  - Access to radiation
  - Cost

Novel Techniques of Administering Breast Radiation

- Hypofractionation: giving larger radiation doses over shorter time course
  - TARGIT trial
    - Intraoperative radiation
    - Given for 30 min to lumpectomy site only
    - Part of an international prospective randomized trial—endpoints recurrence, cosmesis
  - Preoperative radiosurgery

Intrabeam single-dose radiation for breast cancer

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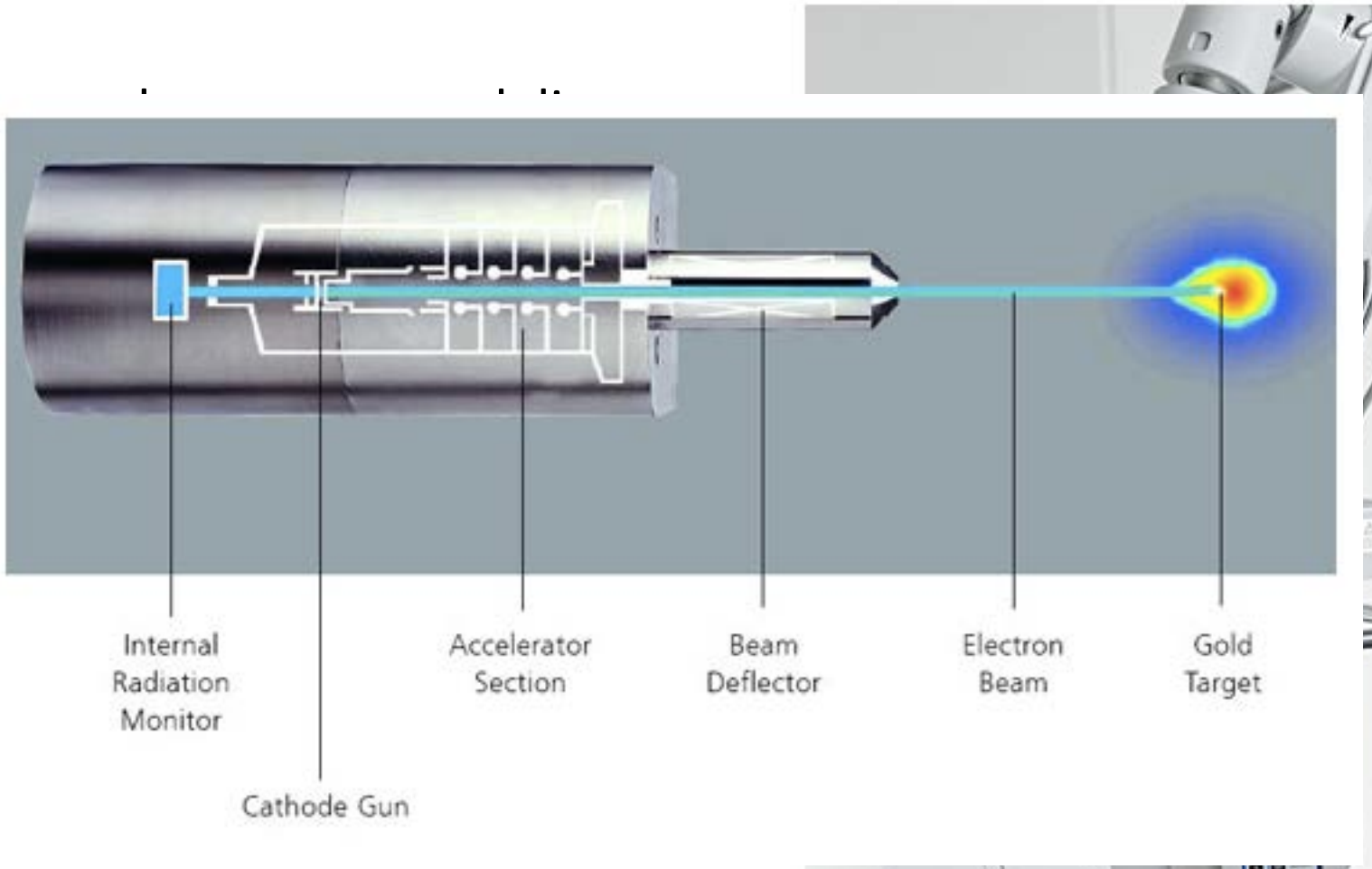
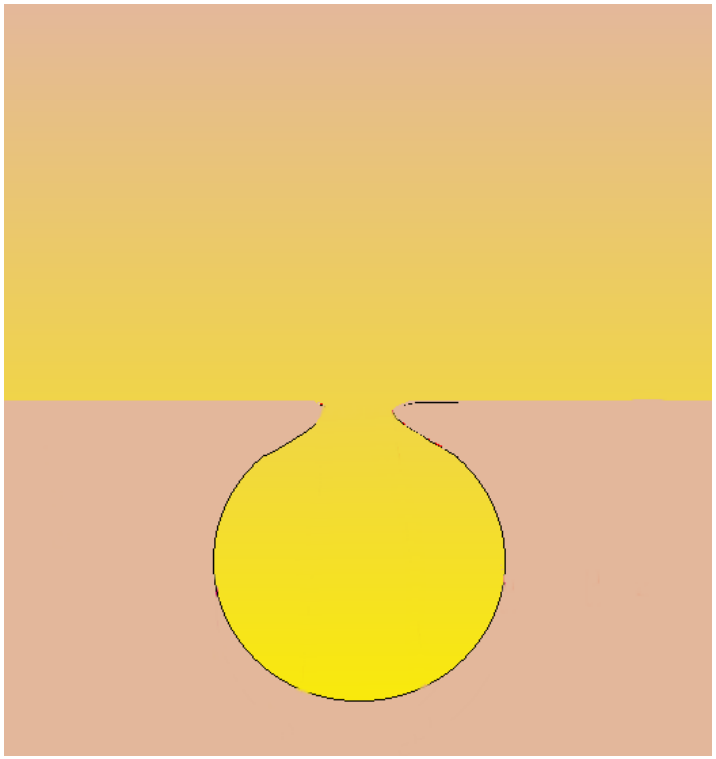
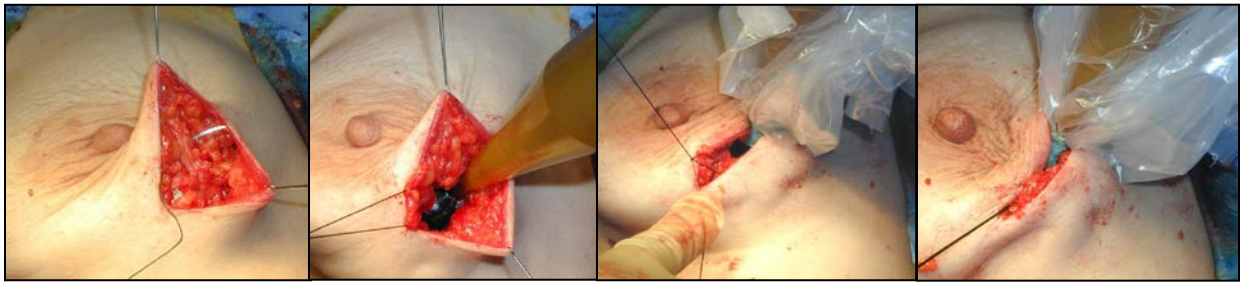


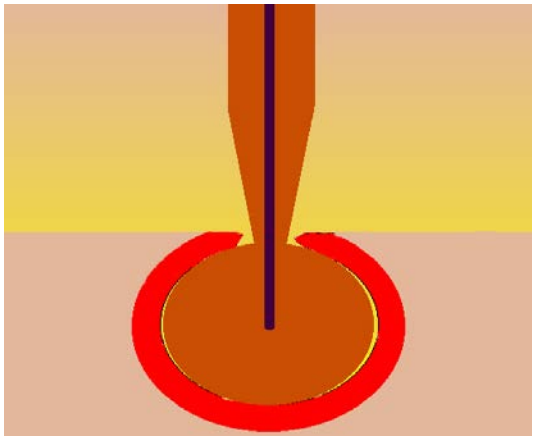
Intrabeam Radiotherapy

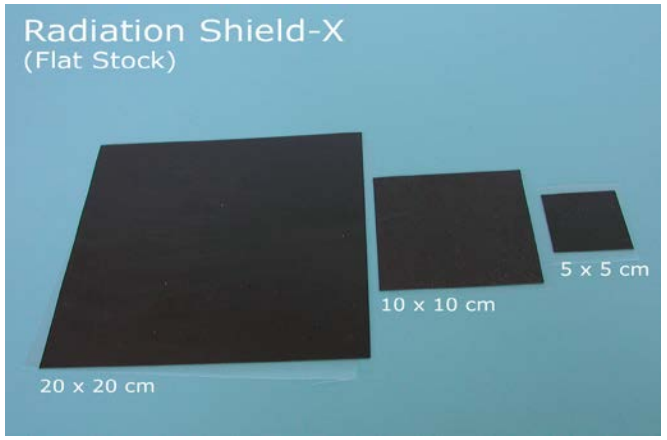


1. Surgeon performs the lumpectomy
2. Surgeon sizes the cavity for the appropriate size applicator

Intrabeam Radiotherapy





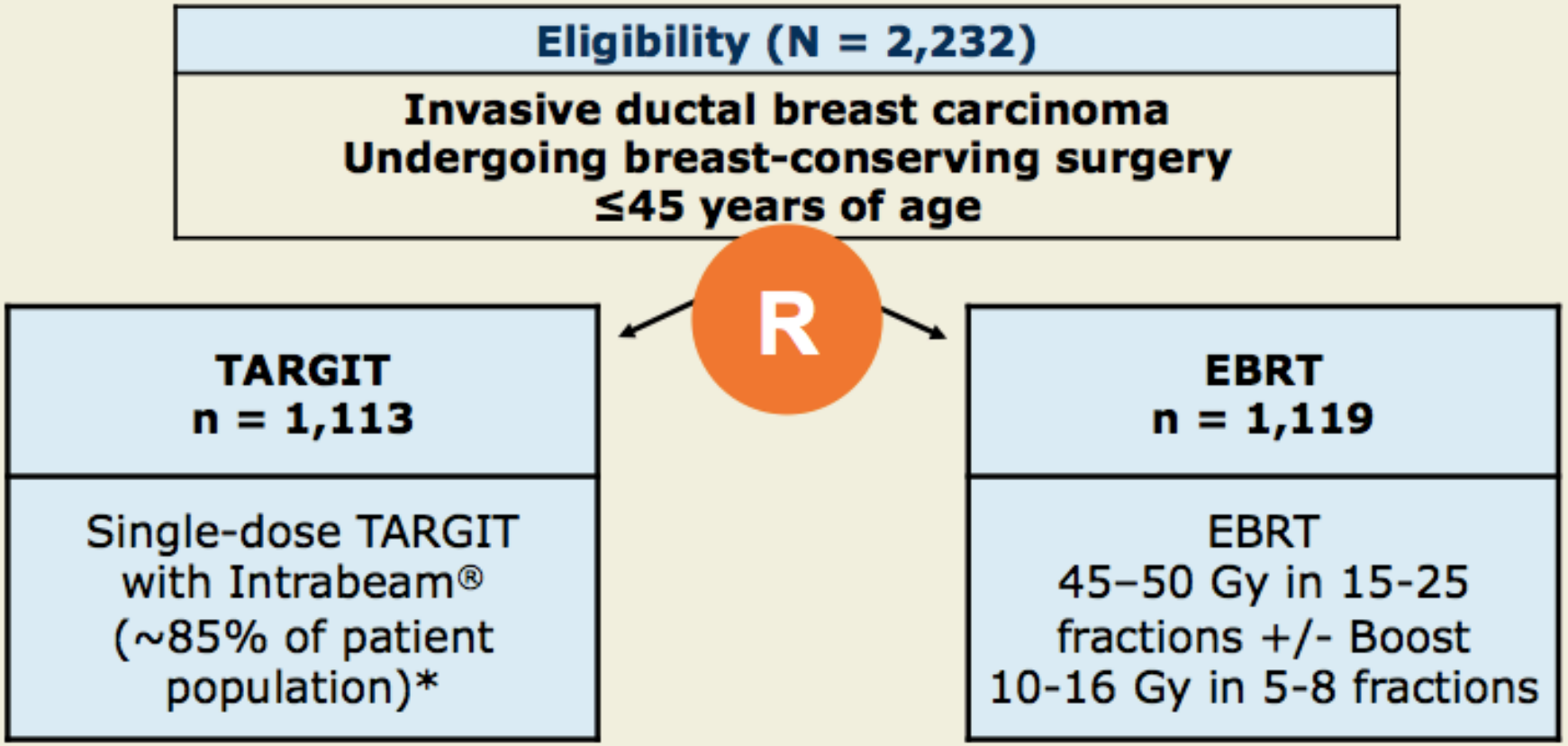


3. The Intrabeam is draped;applicator is affixed to the PRS
4. Surgeon places X-ray source and applicator inside cavity and purse string stitch is used to approximate the tissue to the applicator for even dose distribution
5. Surgeon uses sterile shields to protects delicate tissues

Intrabeam Radiotherapy

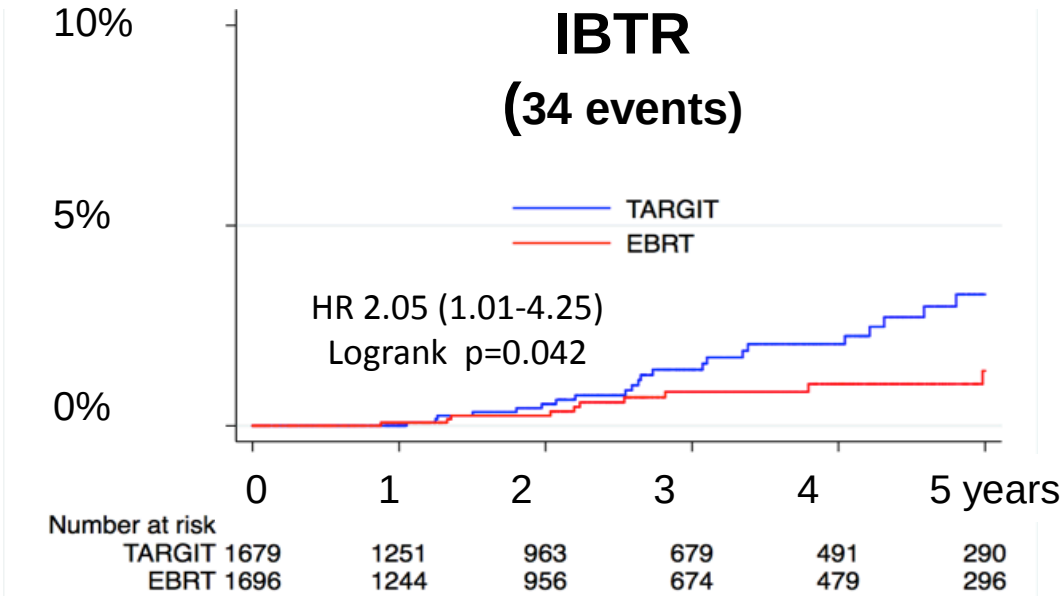
6. Radiation Oncologist sets the prescribed dose (5 gy to 1 cm) into the control console
7. Optional shielding is applied around the applicator to protect against scatter
8. Radiation treatment is delivered in 21 – 30 min.

Targeted Intraoperative Radiotherapy (TARGIT-A) Study Design

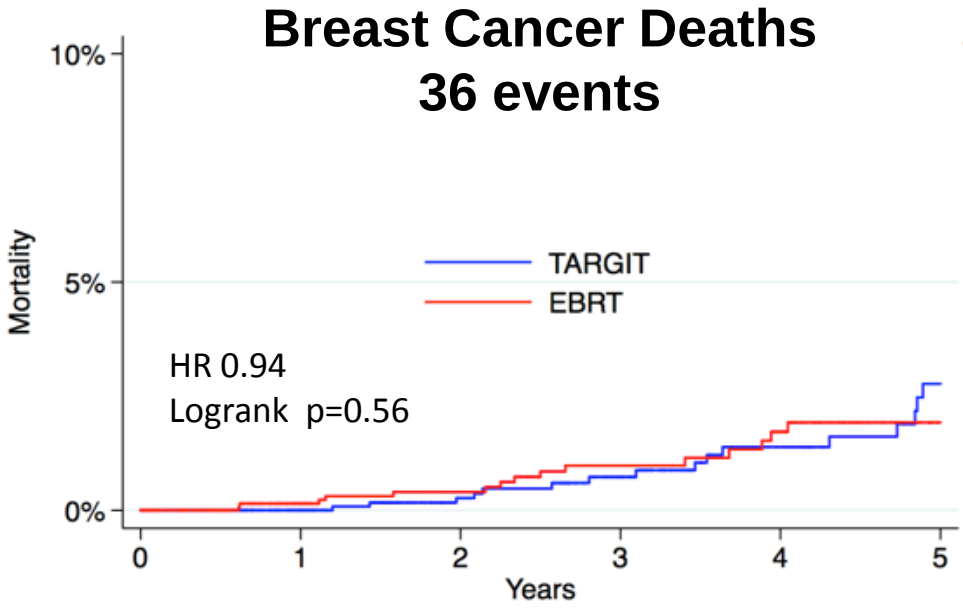


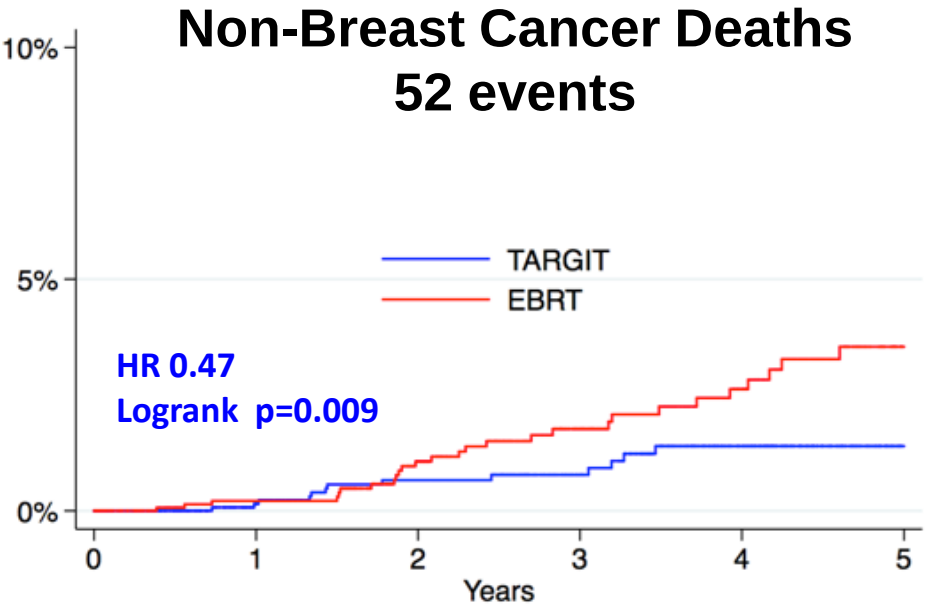
* Plus EBRT (45-50 Gy, no boost) in patients at high risk (~15%); Pre-specified criteria (unsuspected lobular carcinoma, lymphovascular invasion, etc)

Baum M et al. *Proc ASCO* 2010;Abstract LBA517; Vaidya JS et al. *Lancet* 2010;[Epub ahead of print].



Difference
2.01%
(0.32-3.7)





Vaidya JS, et al: SABCS 2012, Abstract S4-1

PREOPERATIVE PARTIAL BREAST RADIOSURGERY

cT1NoMo breast cancer

↓

Verify biopsy clip

↓

Planning MRI/CT

↓

Treatment

↓

Acute toxicity evaluation

INCLUSION CRITERIA

- T1NoMo unicentric invasive carcinoma

Screen Failures

Objectives

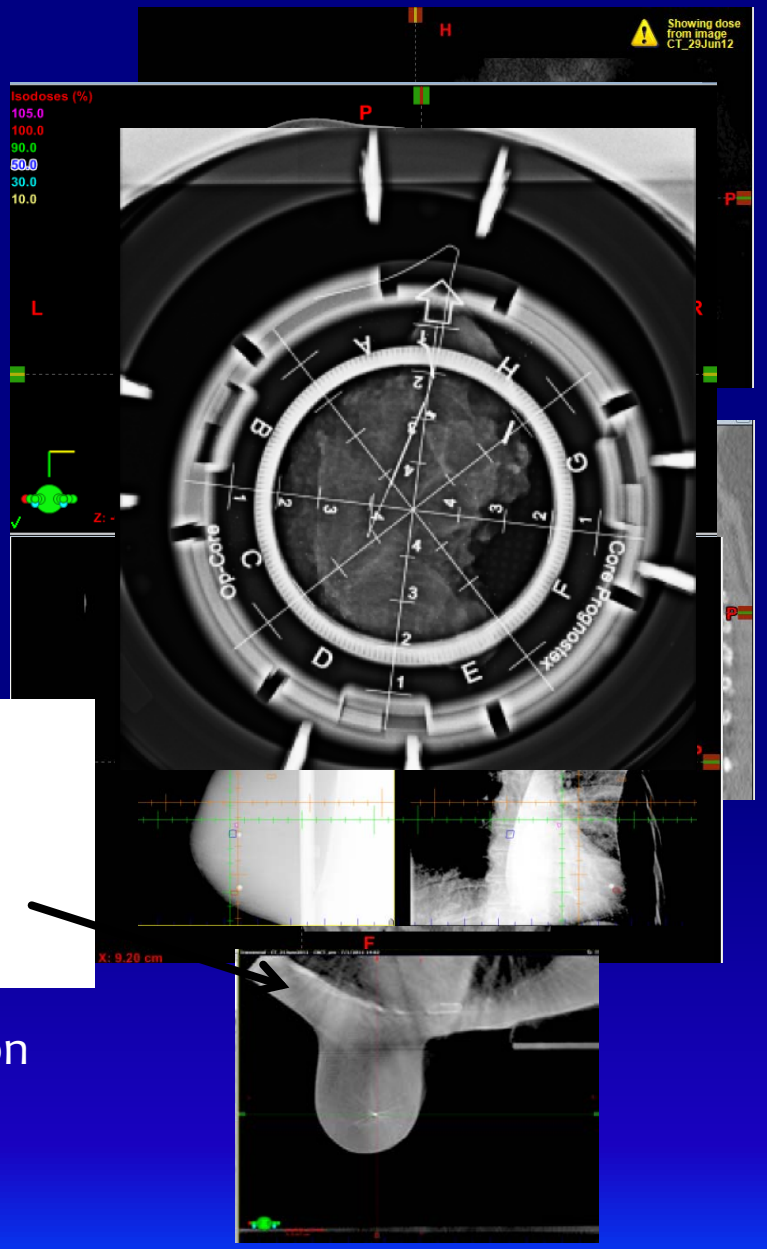
- *Determine the maximum dose*
- *Evaluate safety as measured by acute (3-4 weeks) grade 3, 4 toxicity*
- *Local control/cosmesis*
- *Paired tissue/imaging correlatives*
- *Provide standard post-operative RT for high risk features*

Level 1	15 Gy
	y
	y

Research MRI

Dose Delivery

- *Prone position*
  - *Rare supine*
- *No breast immobilization*
- *Kv/CBCT confirmation*



Horton J et al; ASTRO 2013

PREOPERATIVE PARTIAL BREAST RADIOSURGERY:

- *Phase I Outcomes*
  - *Median follow-up:*
    - *6.9 months*
  - *32 patients treated:*
    - *25 invasive*
    - *7 DCIS*
  - *No acute grade 3, 4 toxicities*
  - *No recurrences to date*

Time Point	Patient-Reported Cosmetic Outcome	Physician Reported Cosmetic Outcome
Baseline (n=32)	31 excellent/good 1 fair/poor	32 excellent/good
6 months (n=22|20)	22 excellent/good	20 excellent/good
12 months (n=11|10)	10 excellent/good 1 fair/poor	8 excellent/good *2 fair/poor
24 months (n=5)	4 excellent/good 1 fair/poor	4 excellent/good *1 fair/poor

*fair/poor outcomes both in patients receiving post-operative RT

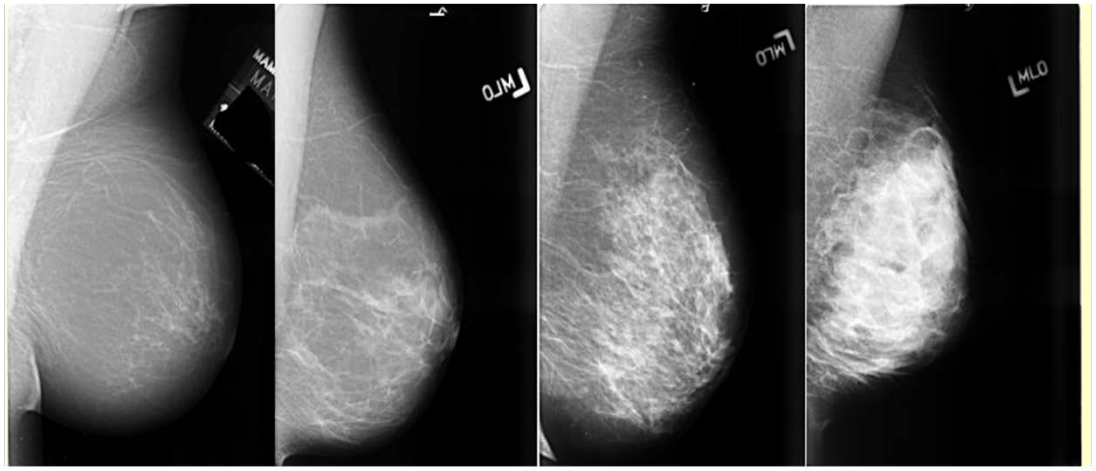
Horton J et al; ASTRO 2013

PSOC Collaborations

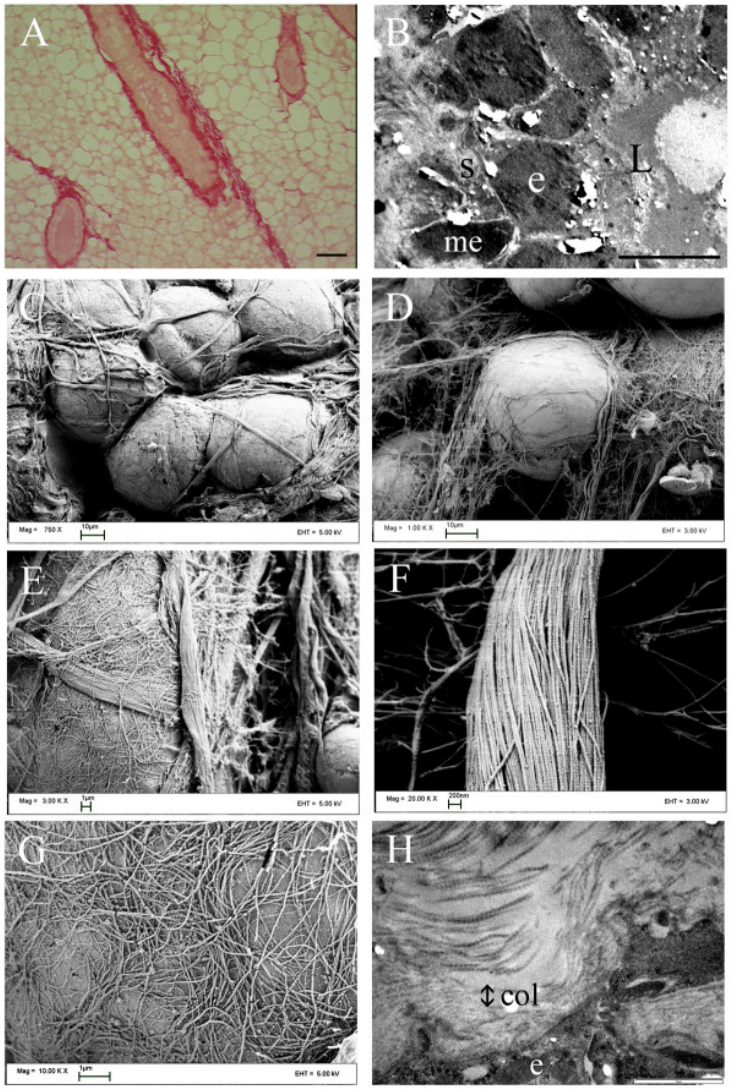
Association Between Breast Density and Breast Cancer Risk

- Breast density strongly correlated with breast cancer risk (RR 4-6)
- Heritable component (twin studies): 60%
- Responsive to changes in exogenous and endogenous hormones
  - HRT
  - Luteal phase of menstrual cycle
  - Menopause

- Lifestyle/modifiable component:
  - Late age at first birth
  - Nulliparity
  - HRT



Epithelial cells are intimately connected to surrounding collagen in the ECM



In soft tissues, type I collagen accounts for 80-90% of all extracellular matrix (ECM) proteins

general:

- maintaining structural integrity
- contributing tensile strength to tissue

more specialized role in regulation of:

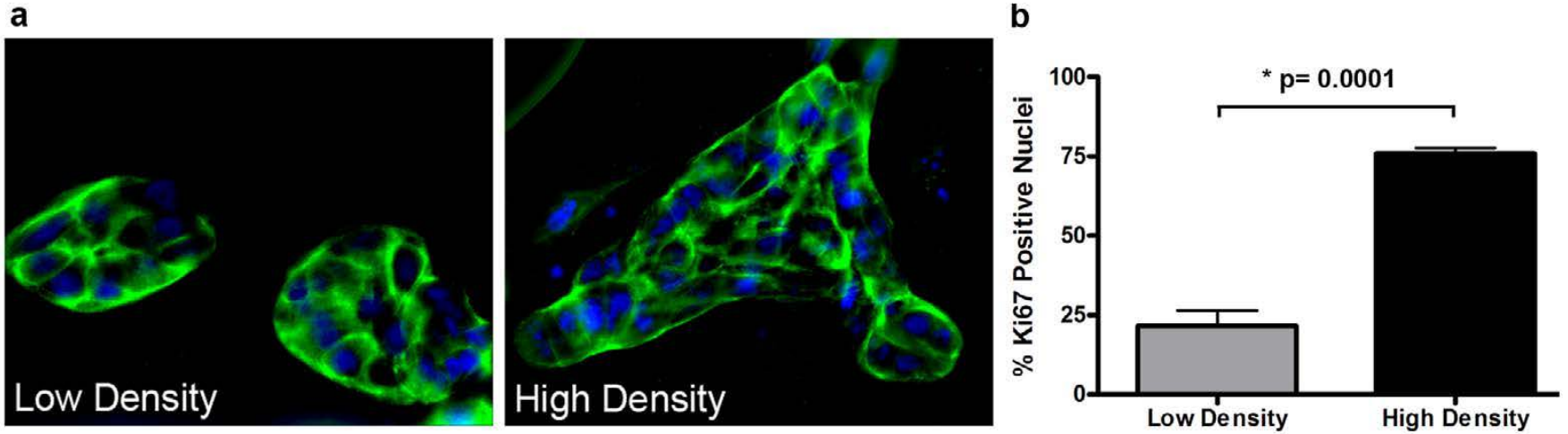
- cell polarity
- migration
- survival

Normal stroma: parallel orientation with respect to epithelium; newly synthesized peritumoral stroma loosely woven morphology and non-planar orientation

high MD associated with altered type I collagen production and altered collagen remodeling

Provenzano PP, BMC Med 2006

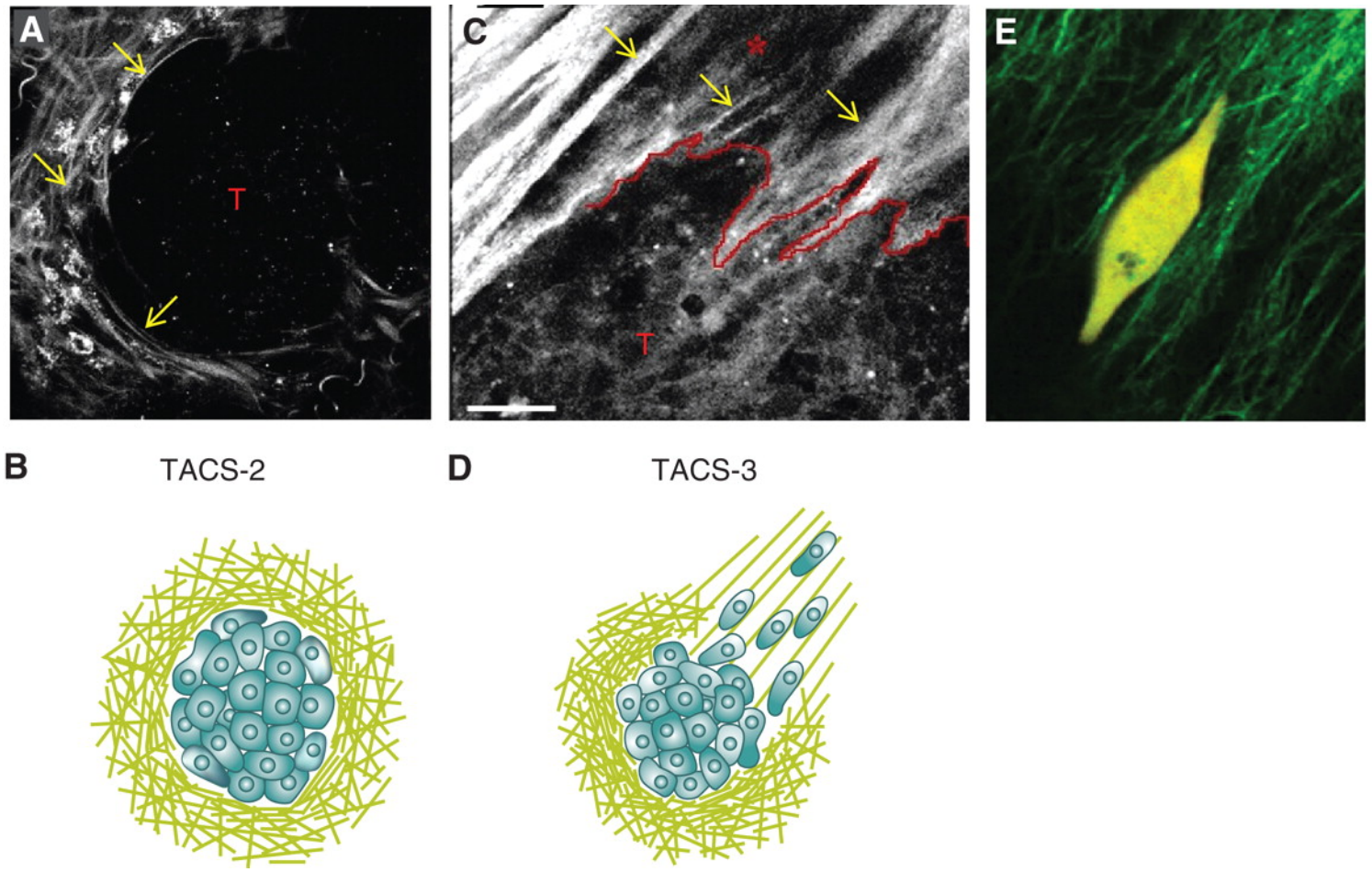
Epithelial cells respond to the stiffness of the collagen matrix



Increased collagen matrix density directly promotes epithelial cell proliferation. **(a)** Actin staining to visualize MCF10A human mammary epithelial cells cultured within low (1.3 mg/ml) and high-density (3.0 mg/ml) collagen gels for 21 days (actin, green; nuclei, blue). Left: Two well-differentiated acini structures formed in low-density matrices. Right: A single, less organized colony. **(b)** Increased proliferation of mammary epithelial cells cultured within high-density matrices, measured by increased detection of the Ki67 antigen, a marker of proliferation.

Provenzano PP, BMC Med 2008

Collagen alignment facilitates invasion



Schedin P , Keely P J Cold Spring Harb Perspect Biol 2011

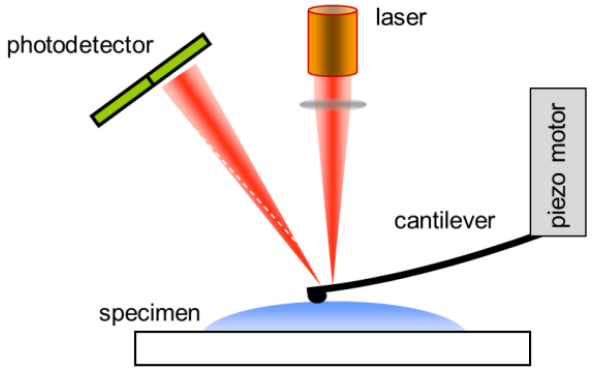
Clinical/Translational implications for human breast cancer

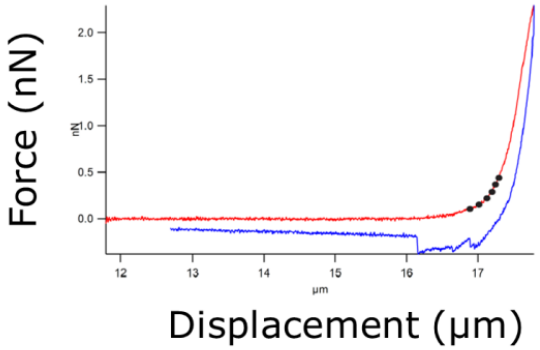
- Geospatial relationship of breast stiffness
  - within and between breasts (areas of increased risk?)
  - with proximity to tumor
- Relationship/proximity to histophenotype & molecular subtype
- Predictor of invasive potential? Metastatic potential? Treatment response?

Methods to measure the ECM mechanical properties

Stiffness

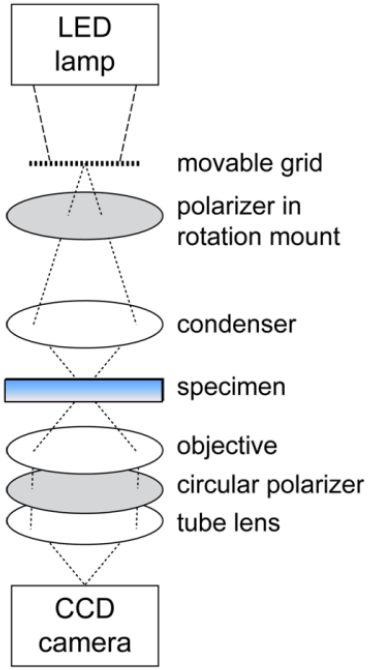
Atomic Force Microscopy stiffness measurement



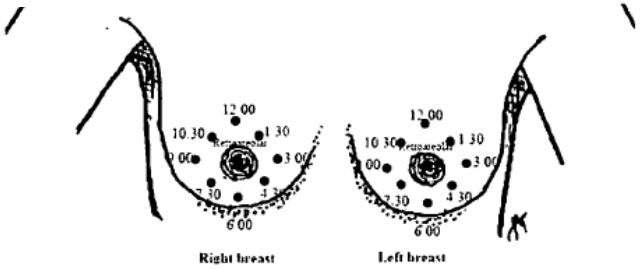


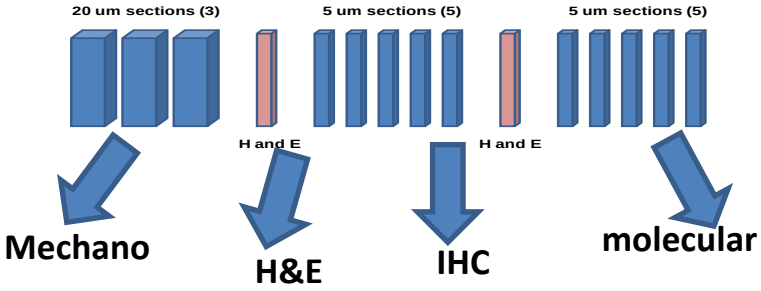
Tension

SIMPOL imaging of tension field



Courtesy of Quianming Shi, PhD
Liphardt Lab- Phyisics Department
UC Berkeley

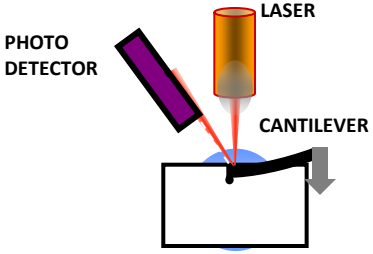




Irene Acerbi

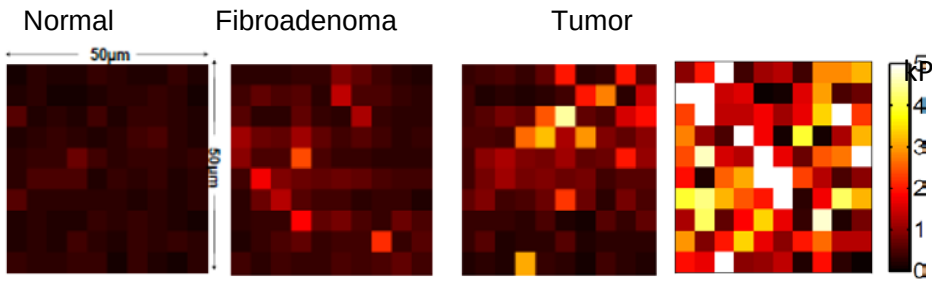
Alfred Au

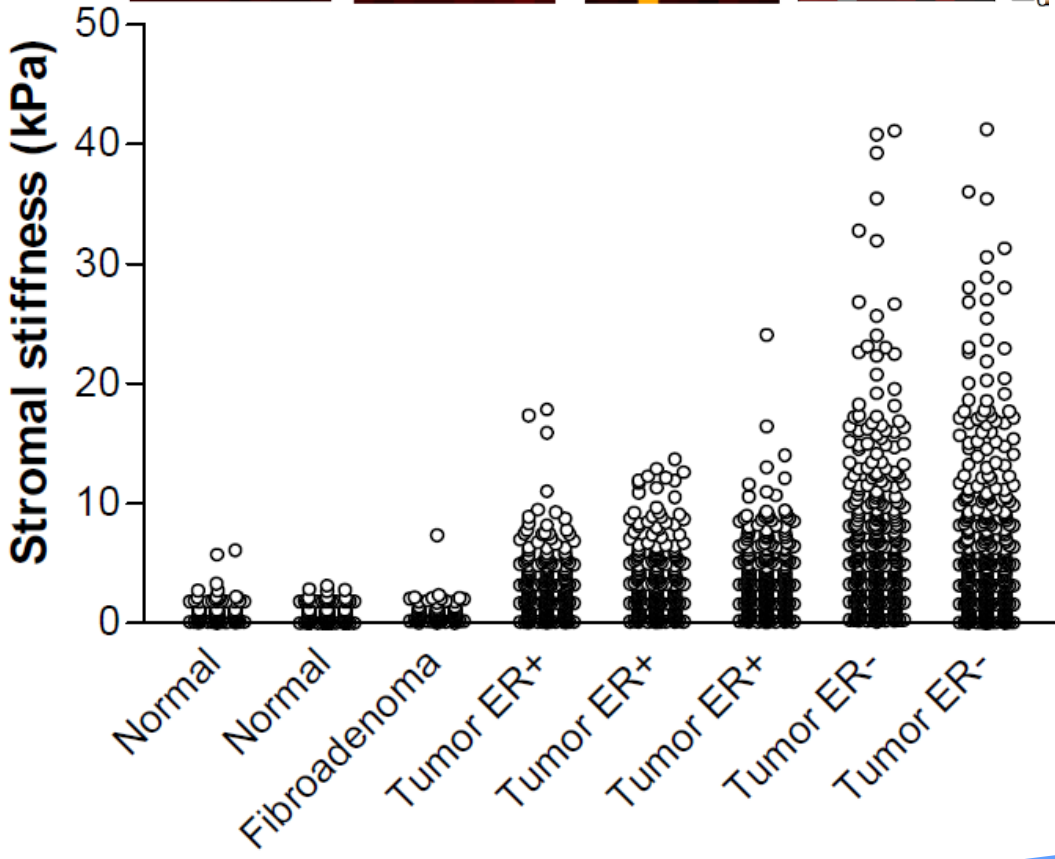
Atomic Force Microscope



Stiffness Maps

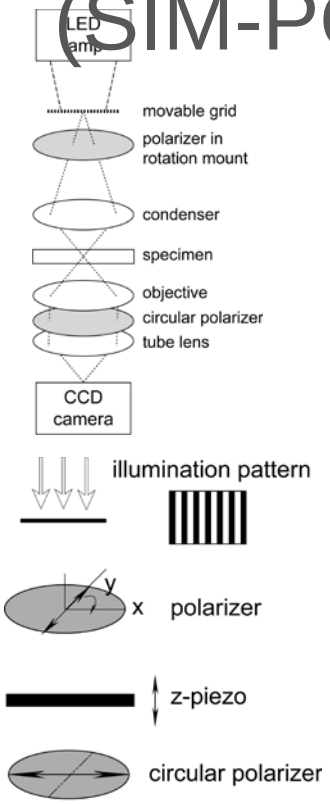
(kPa)

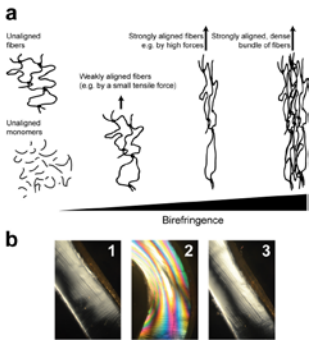


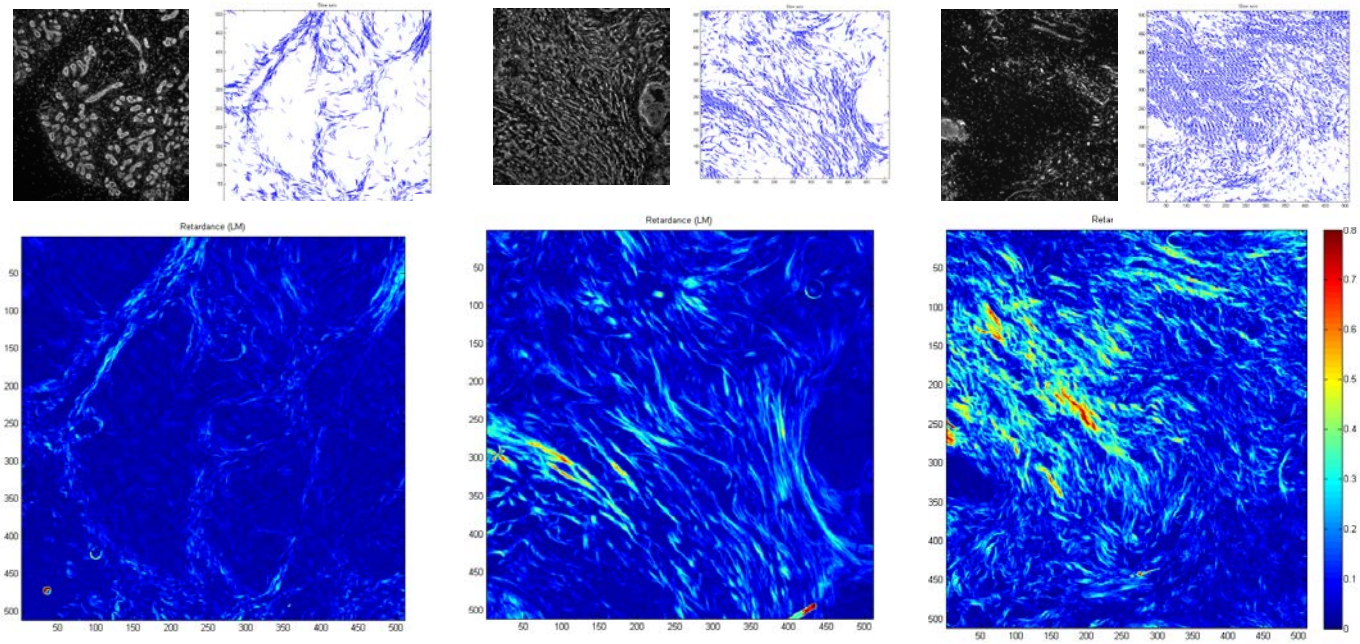


Malignant Phenotype

Structured illumination polarized microscopy (SIM-POL) imaging visualizes ECM orientation







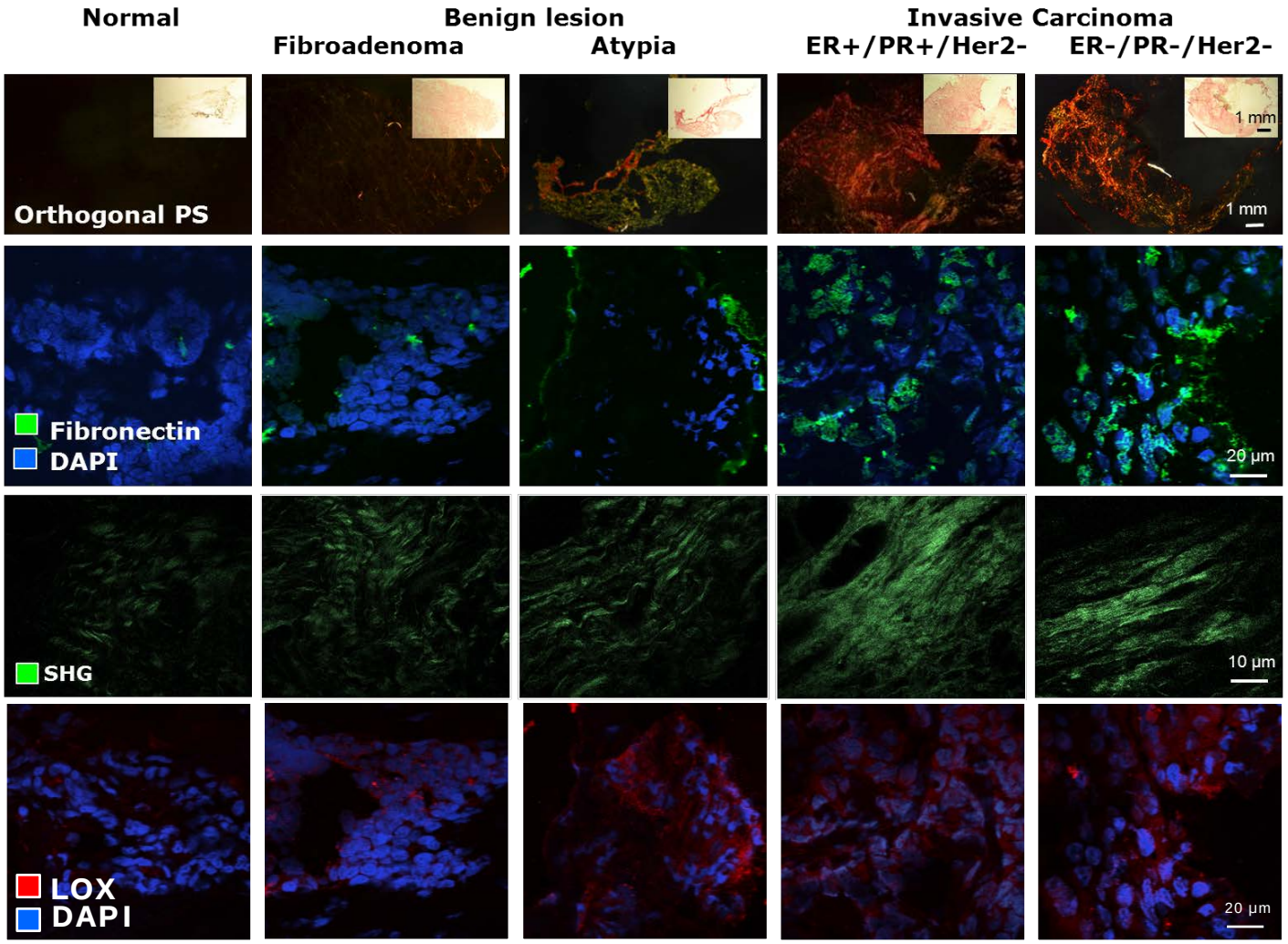
NORMAL ER+ve TUMOR ER-ve TUMOR

Malignant Phenotype

Jan Liphardt UCBerkeley

Quanming Shi

ECM remodeling and malignant phenotype



Malignant phenotype in breast tissue is associated with higher collagen content (orthogonal PS signal), higher Fibronectin deposition, higher linearization of collagen (as seen with Second Harmonics Generation) and higher collagen cross-linkling (LysilOxidase LOX) staining.

This may be changing the mechanical properties of the tissue.

Differential Gene Expression in BRCA 1(+) stroma (prophylactic mastectomy)

BRCA1 mutation leads to dominant stromal phenotype?
Enrichment analysis of the 1496 genes differentially expressed between BRCA1 group and normal regardless of cell type

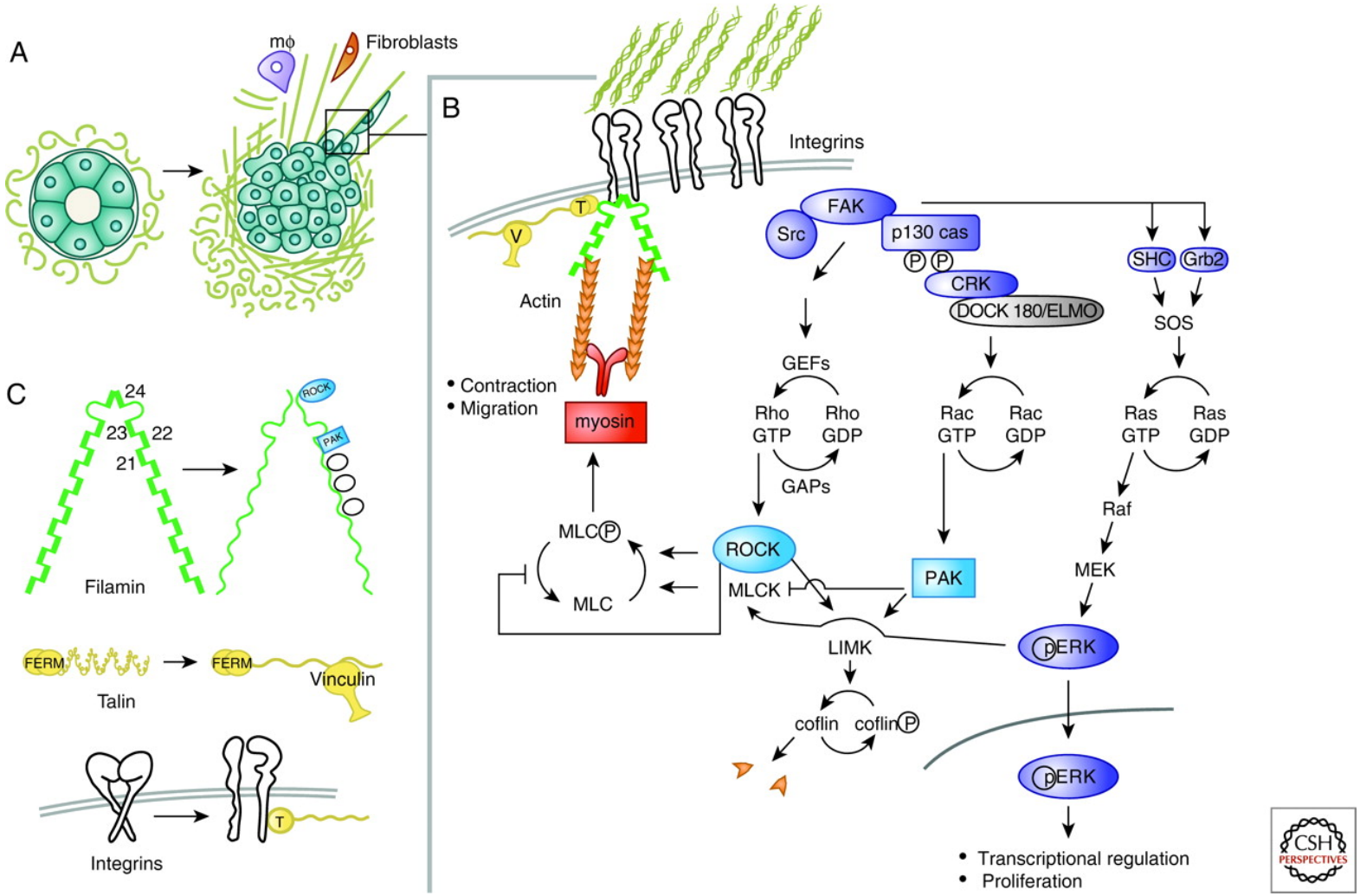
GeneGo Process Networks

Export | Export to image

#	Networks	0 0.3 0.6 0.9 1.2 1.5 1.8 2.1 -log(pValue)	pValue	Ratio
1	Immune response_Th17-derived cytokines		1.221e-3	16/98
2	Proliferation_Negative regulation of cell proliferation		4.518e-3	23/183
3	Signal Transduction_TGF-beta, GDF and Activin signaling		4.690e-3	20/152
4	Cell cycle_G1-S Growth factor regulation		4.926e-3	24/195
5	Development_ERK5 in cell proliferation and neuronal survival		5.312e-3	6/24
6	Apoptosis_Anti-Apoptosis mediated by external signals via MAPK and JAK/STAT		7.055e-3	22/179
7	Cell cycle_G2-M		9.120e-3	24/205
8	Cytoskeleton_Intermediate filaments		1.054e-2	12/81
9	Signal Transduction_BMP and GDF signaling		1.071e-2	13/91
10	Development_EMT_Regulation of epithelial-to-mesenchymal transition		1.178e-2	26/232

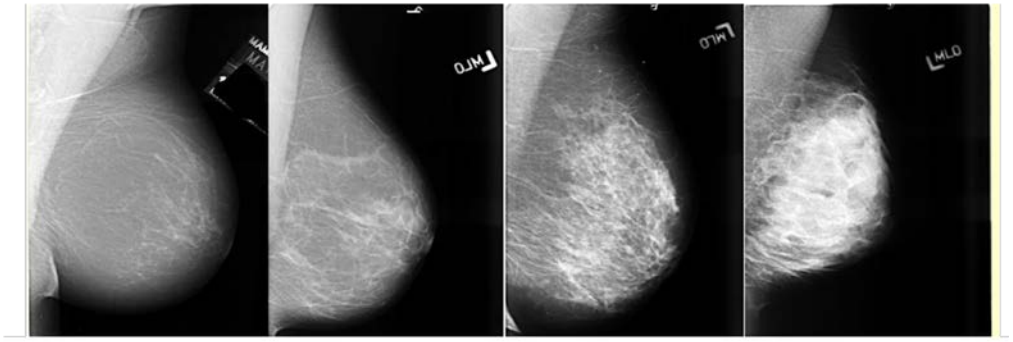
Polyak K, unpublished data

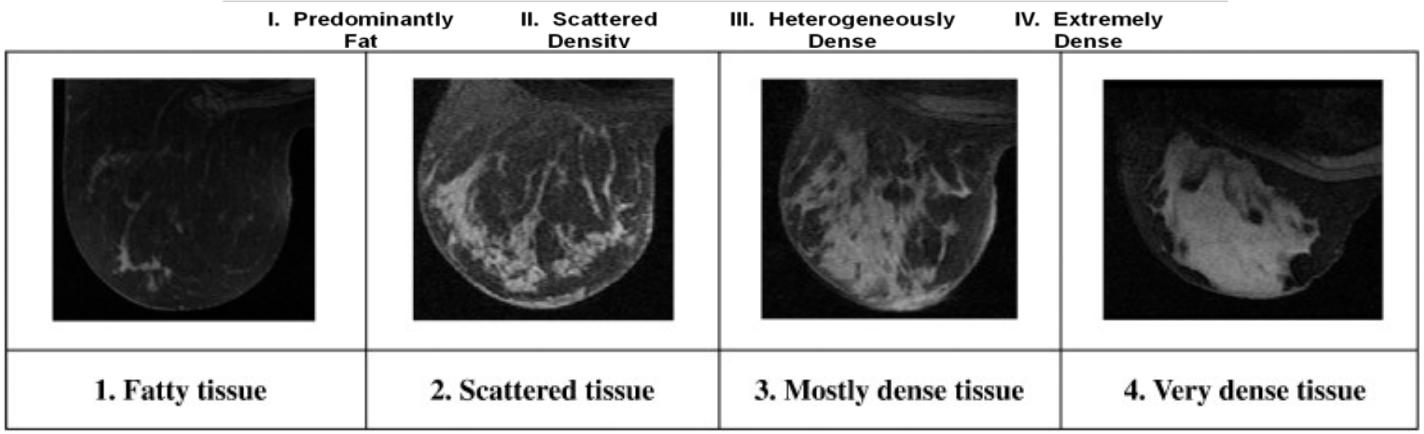
Mechanical signaling pathways



Schedin P , Keely P J Cold Spring Harb Perspect Biol 2011

Constituents of mamographic density and breast MRI differ

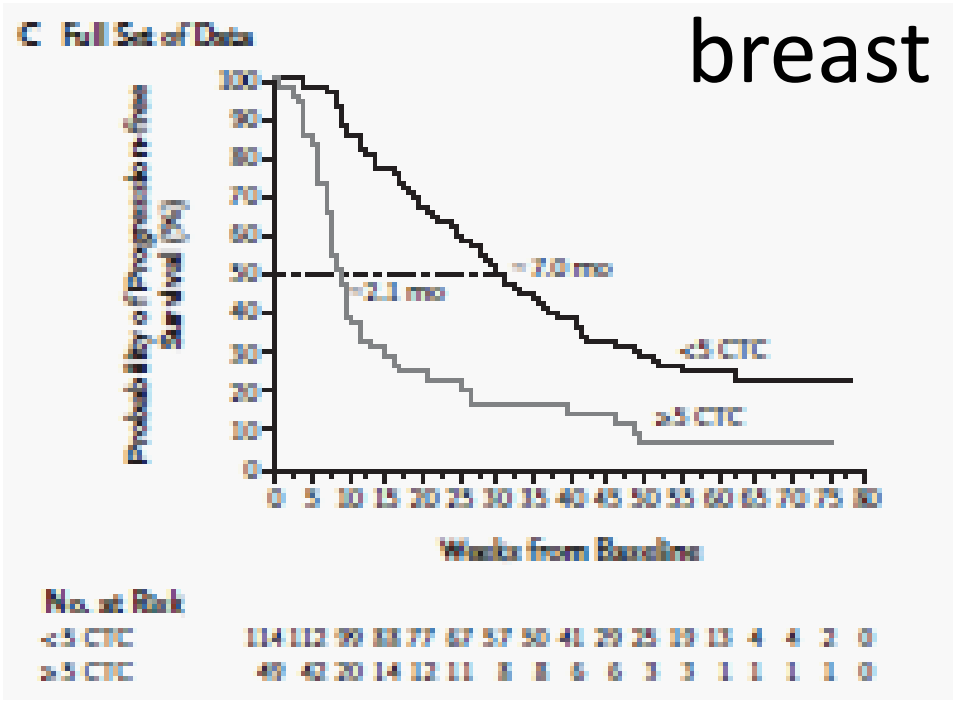


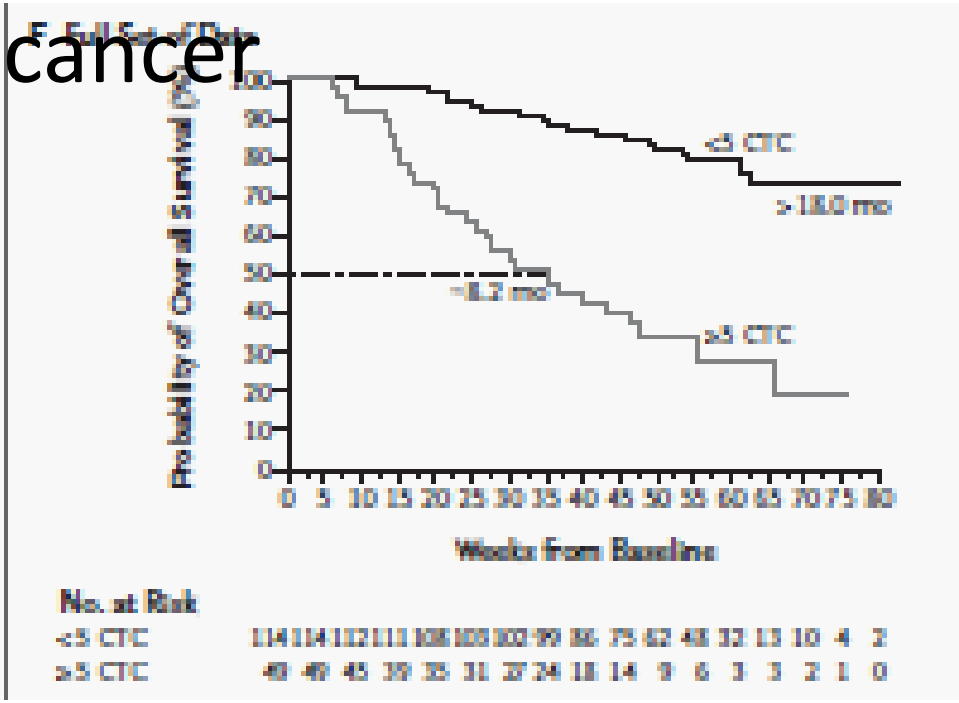


MRI technique was compared to 2-dimensional mammography and showed a moderate correlation in an unselected group (R^2=0.67) but very low correlation in patients with high breast density (R^2=0.26), suggesting that there exists a compositional component to breast MR density that does not overlap with MMG breast density

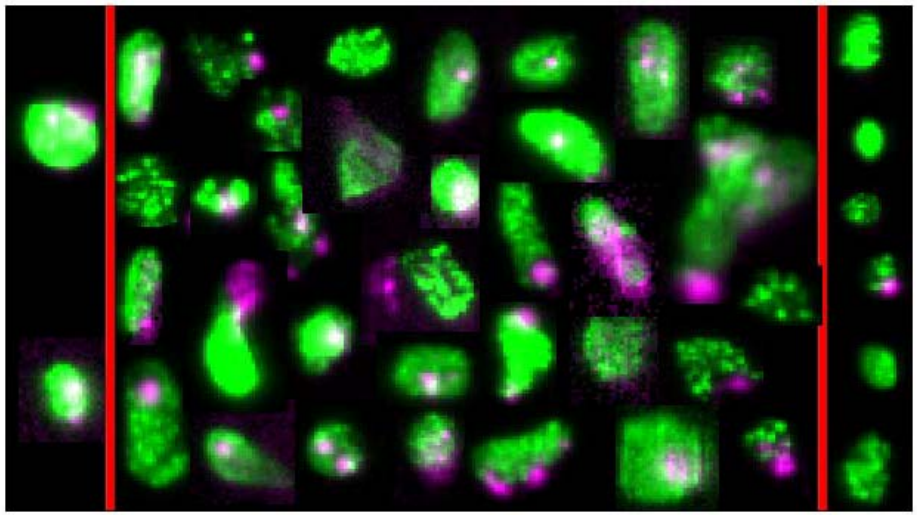
Klifa C et al, MRI 2010

CTC (CellSearch) prognostic in metastatic breast cancer





B

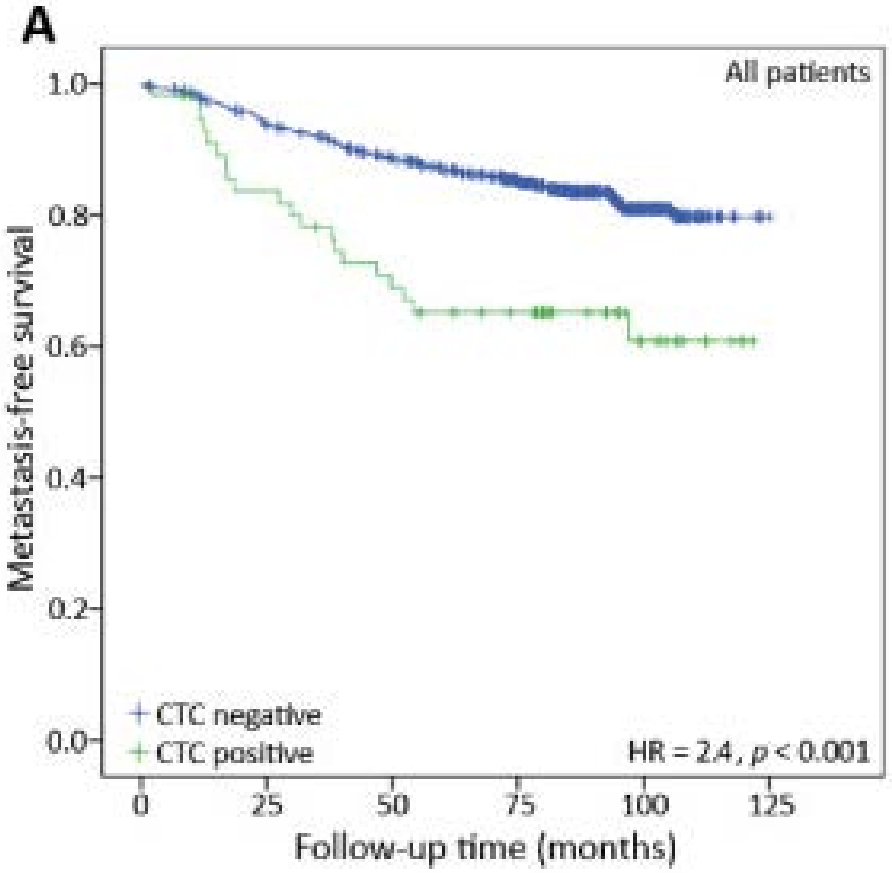


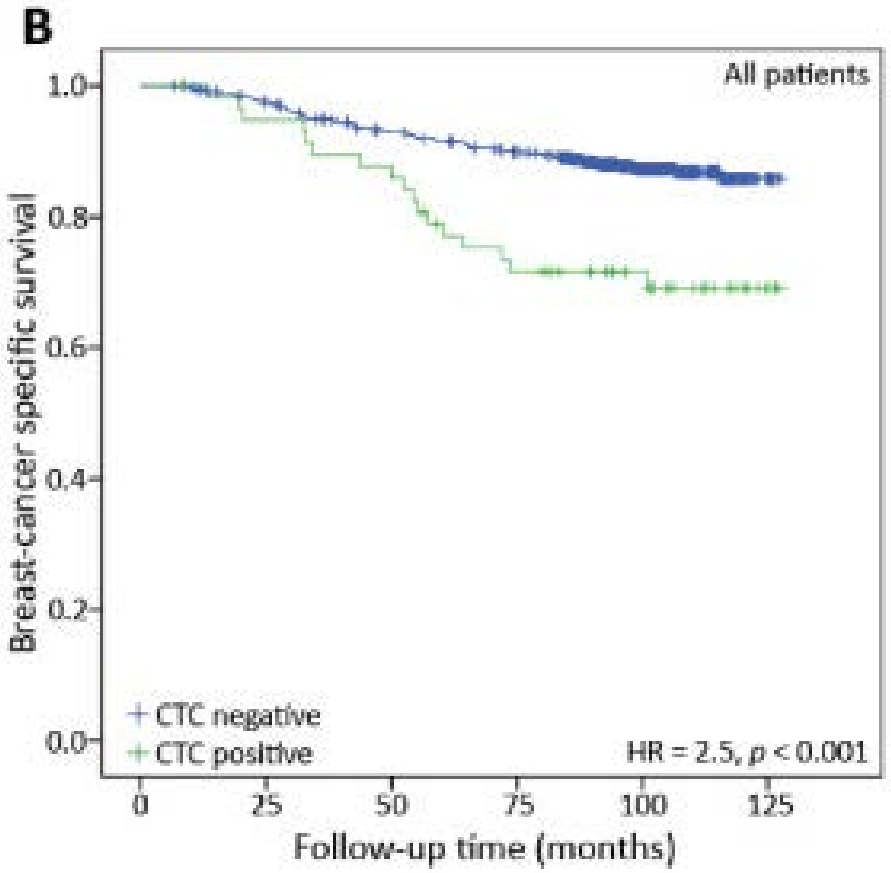
CellSearch technology

- relies on immunomagnetic bead enrichment step of EpCAM(+) cells
- Enrichment step can result in intact cells or fragmented cells
- 49% of Stage IV breast cancer CTC(+) (Cristofanilli, 2004)

Swaby R et al, BMC Medicine, 2011

CTC are prognostic in early stage invasive breast cancer





Molloy TJ, Br Ca Res 2011

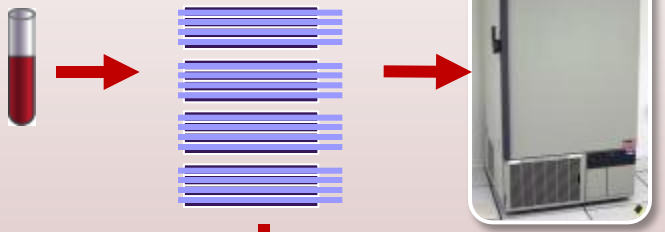
PSOC0039 –0044: HD-CTC vs. CellSearch

Cancer Type	HD-CTCs/mL	HD-CTCs/7.5 mL	CellSearch/7.5 mL
Breast #1	49.3	369	1
Breast #2	87	652	0
Breast #3	33.4	250	1
Breast #4	199.3	1494	1
Breast #5	5	37	23
Prostate #1	2.3	17	0
Prostate #2	8.4	63	3
Prostate #3	107.3	804	21
Prostate #4	1.3	9	0
Prostate #5	150.5	1128	1
Prostate #6	0	0	0
Prostate #7	1.4	10	4
Prostate #8	1.5	11	1
Prostate #9	145.3	1089	6
Prostate #10	57.6	432	0

Process for Finding HD-CTC

Centrifugation & Plating

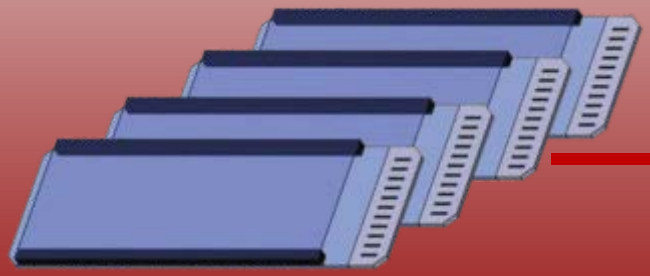
1 Prepare Cartridges



2 Store Cartridges

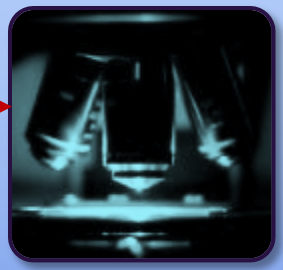
3 Thaw and process cartridges

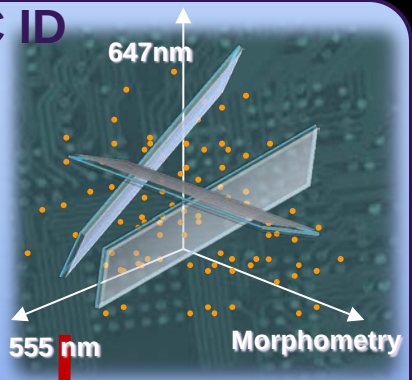
CTC Assay



CTC ID

4 Scan Cartridges





5 Run Algorithms

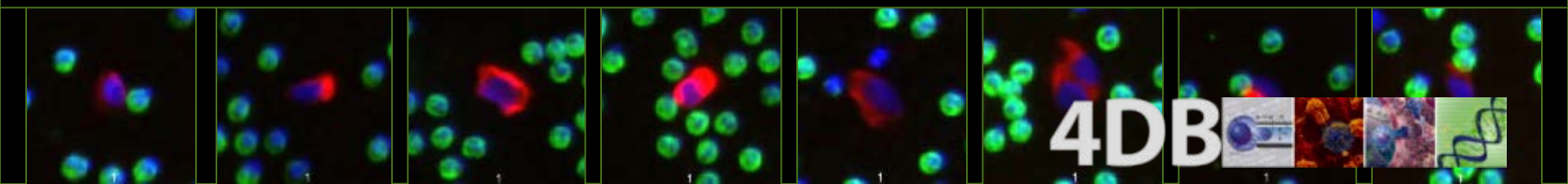
6 Technical Analysis

7 CTC Reports/
Professional Analysis

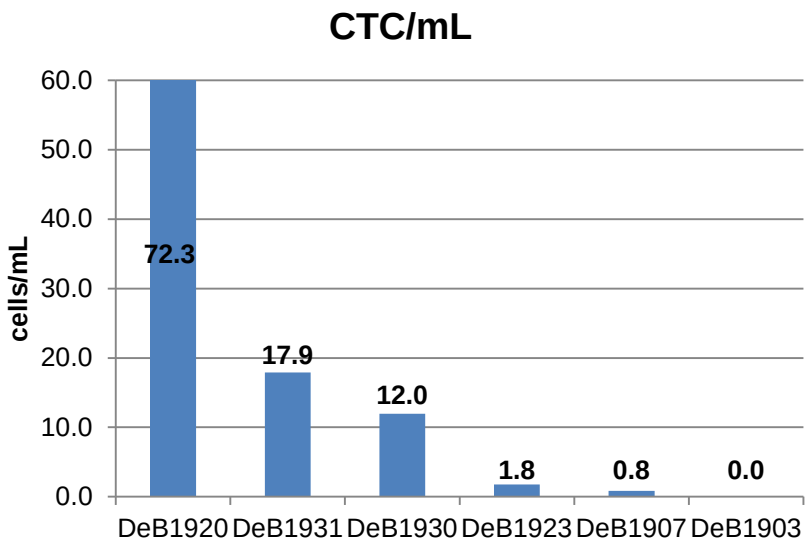
All 103 CTCs identified on 1 slide from Stage IV prostate cancer patient (Kuhn: 1129/7.5mL; CellSearch: 1/7.5mL)

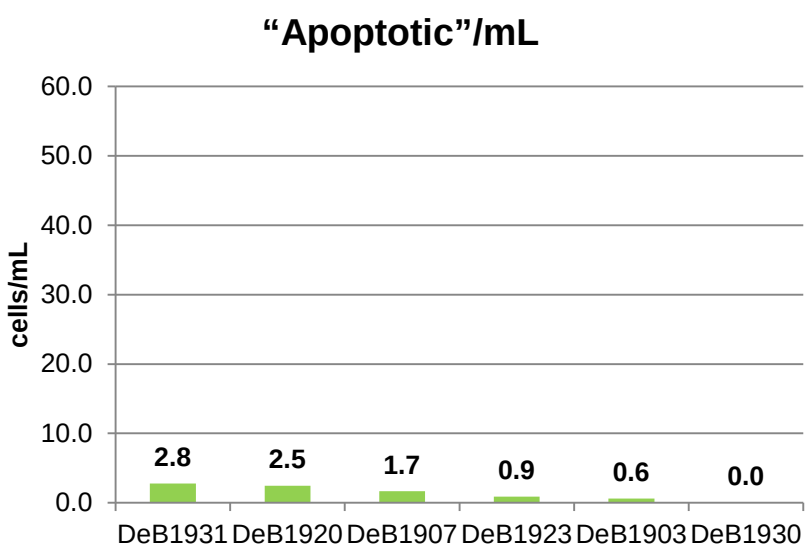
High Definition CTC = HD CTC

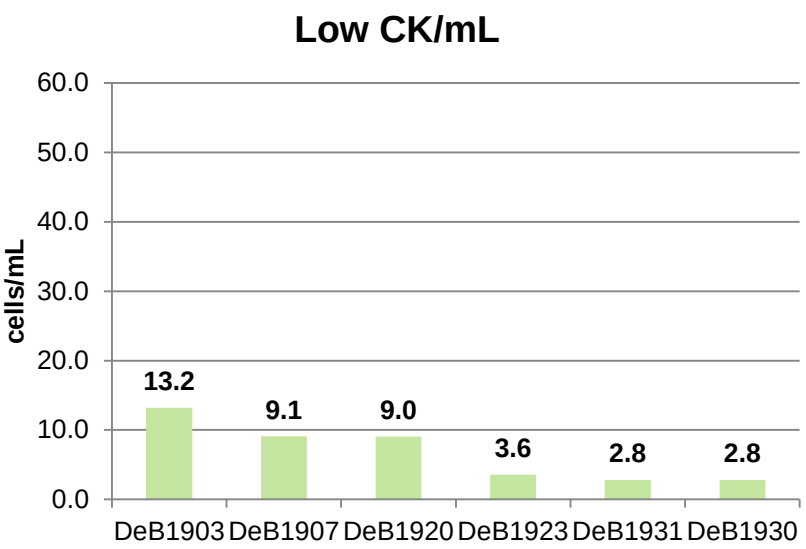
- An Event that has an intact nucleus (DAPI+)
- And has cytokeratin (tissue origin marker)
- And has NOT CD45 (leucocyte origin marker)
- And is morphologic distinct from surrounding leucocytes
- And is displayed in diagnostic pathology quality

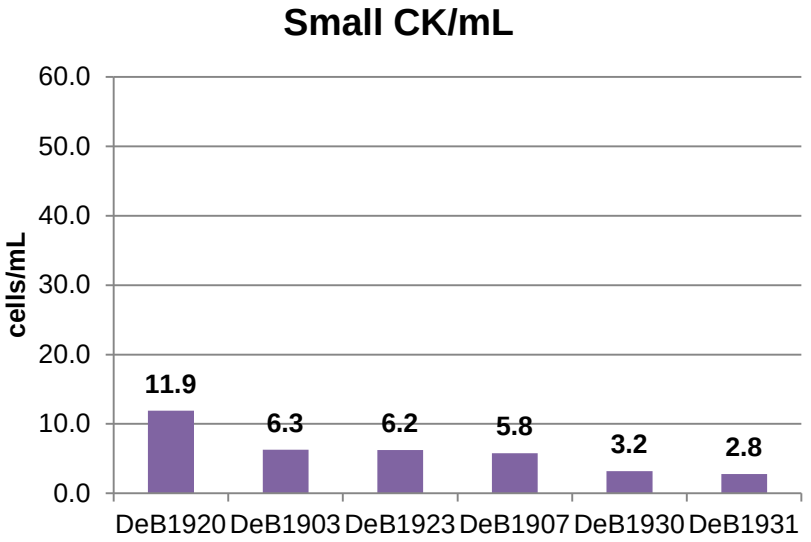


Benign Patients

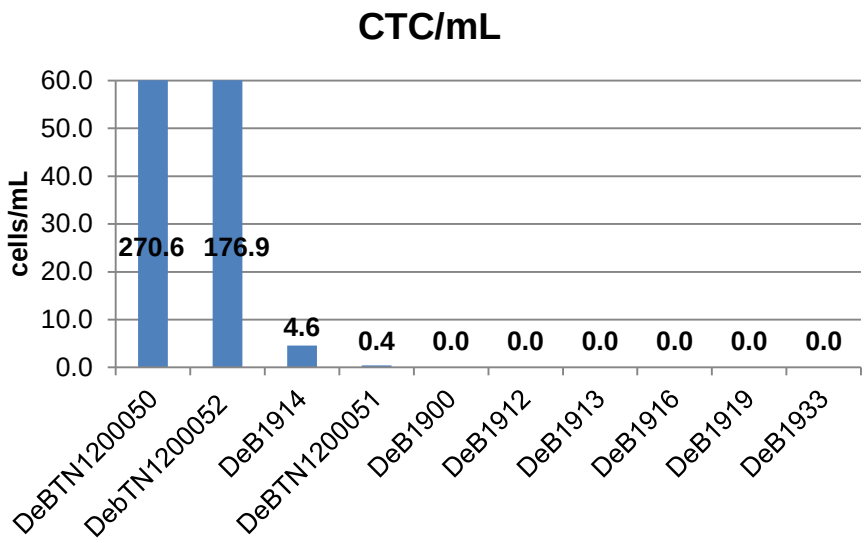


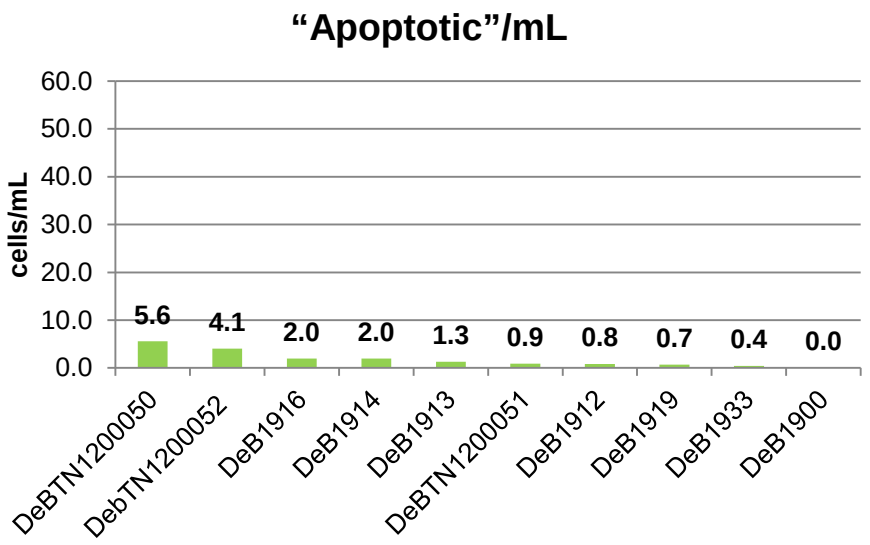


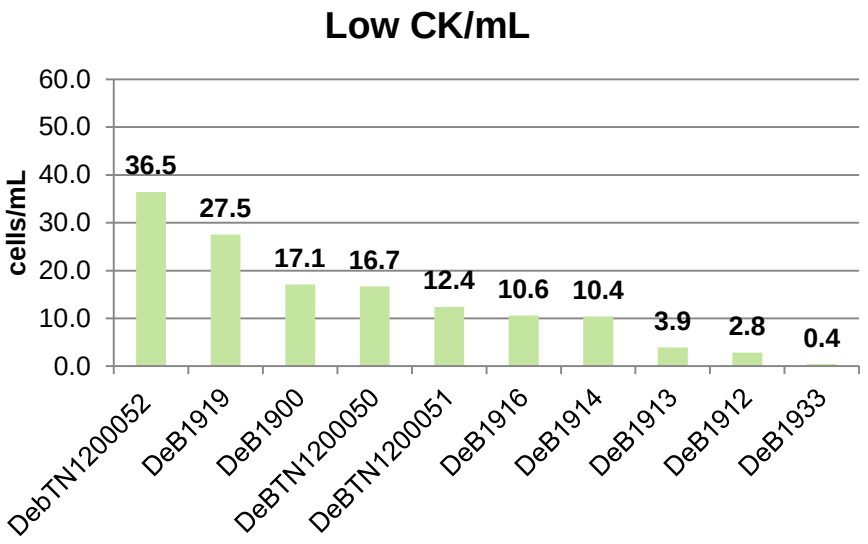


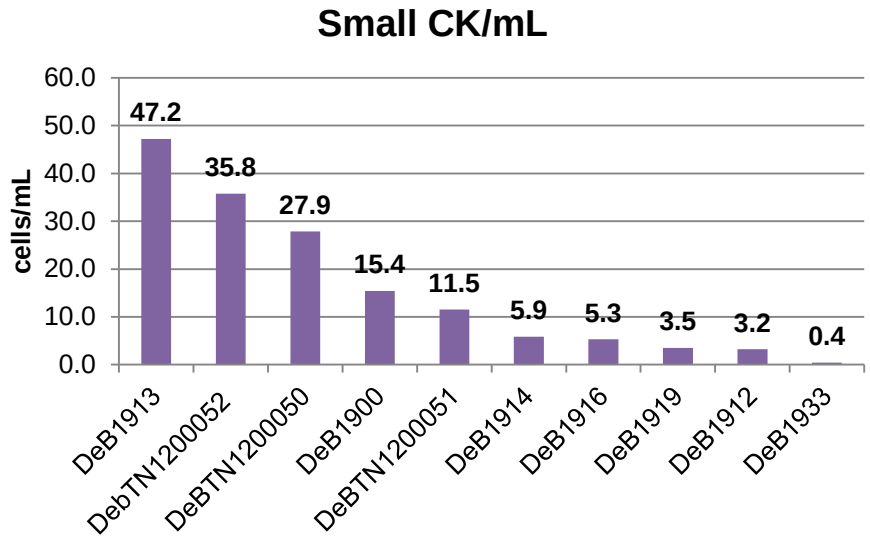


Malignant Patients

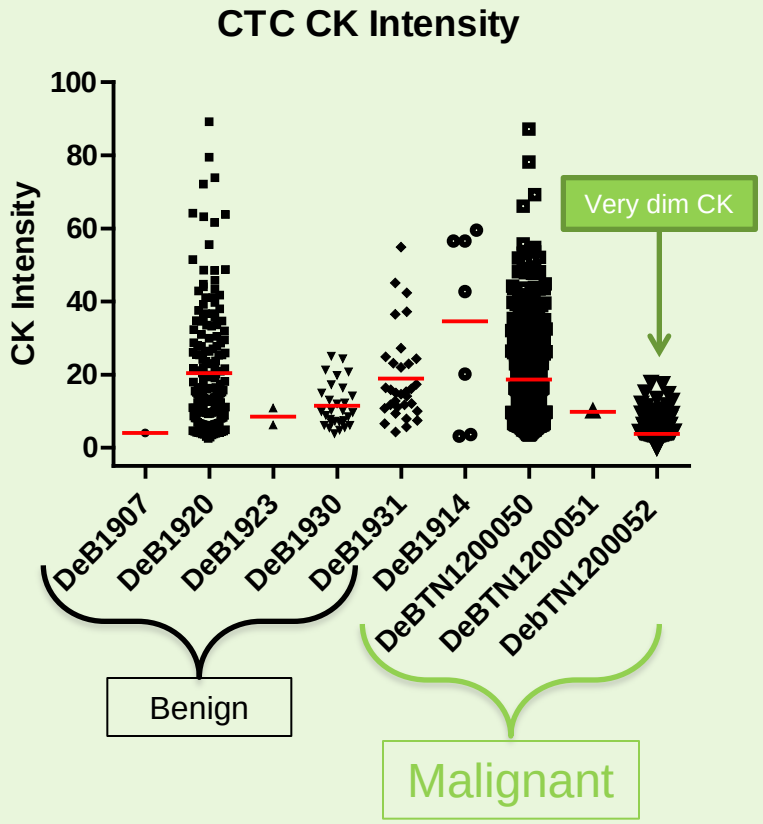


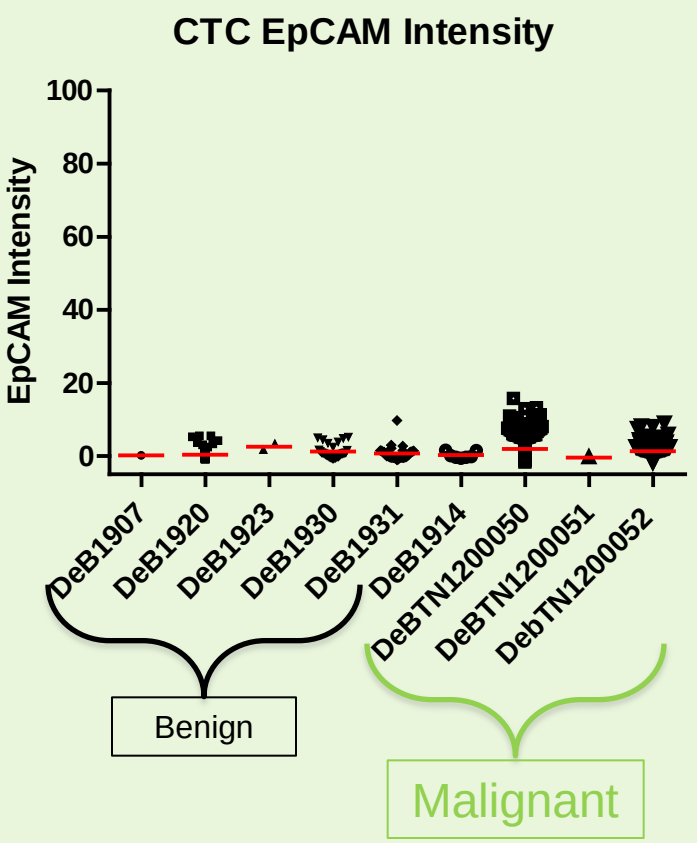






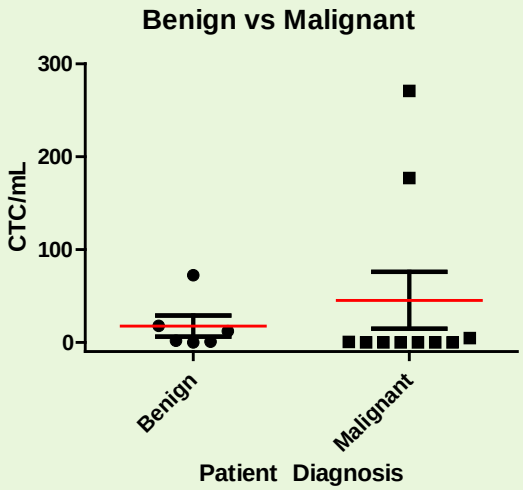
Cytokeratin and EpCAM Intensity for all CTCs

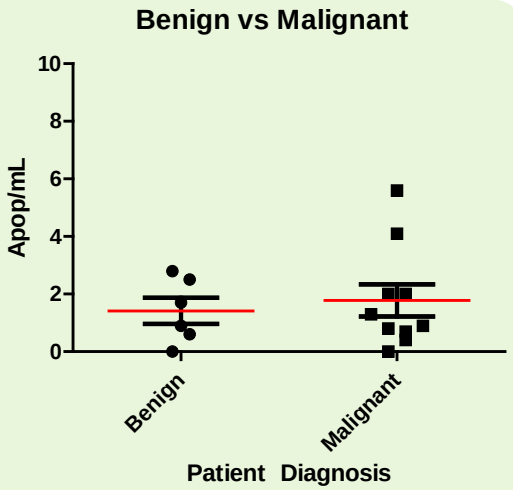


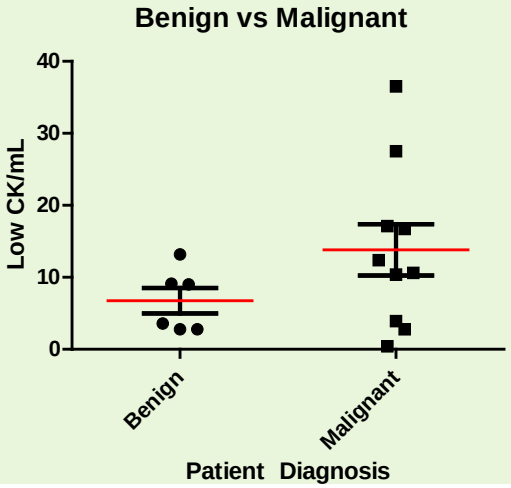


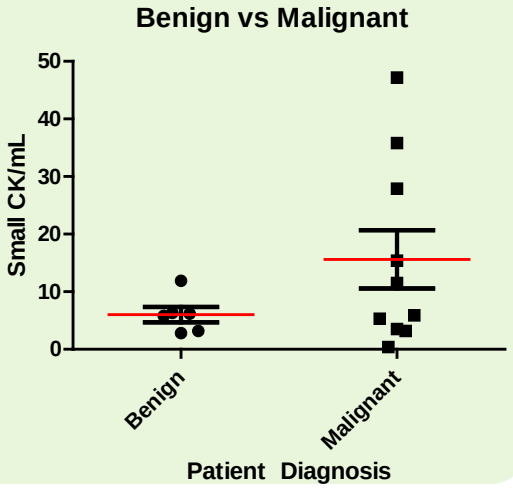
CTCs and Diagnosis

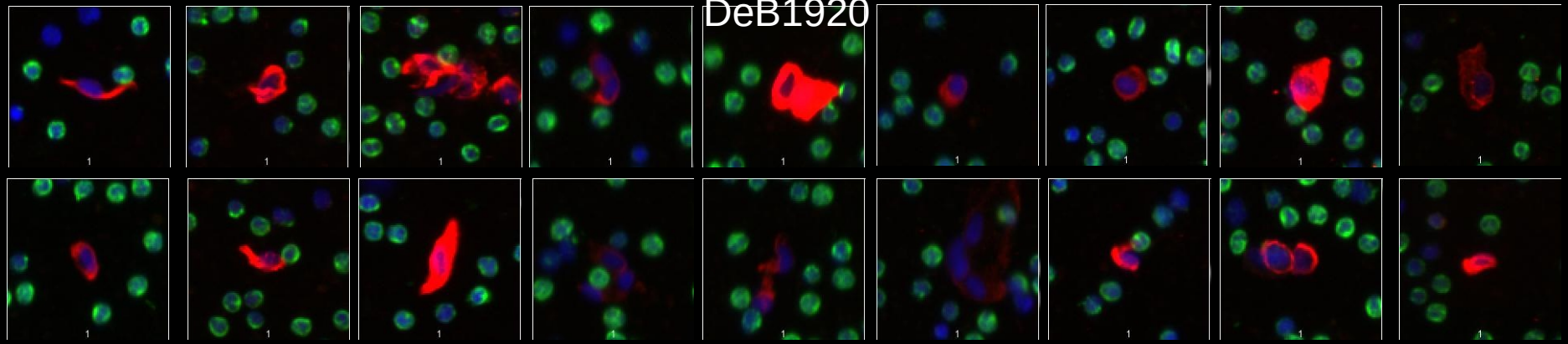
CTC	Benign	Malignant
Mean	17.47	45.25
Std. Deviation	27.8	96.65
Std. Error	11.35	30.56
Apoptotic	Benign	Malignant
Mean	1.417	1.78
Std. Deviation	1.105	1.773
Std. Error	0.4512	0.5605
Low CK	Benign	Malignant
Mean	6.75	13.83
Std. Deviation	4.32	11.28
Std. Error	1.764	3.566
Small CK	Benign	Malignant
Mean	6.033	15.61
Std. Deviation	3.257	16.01
Std. Error	1.33	5.062

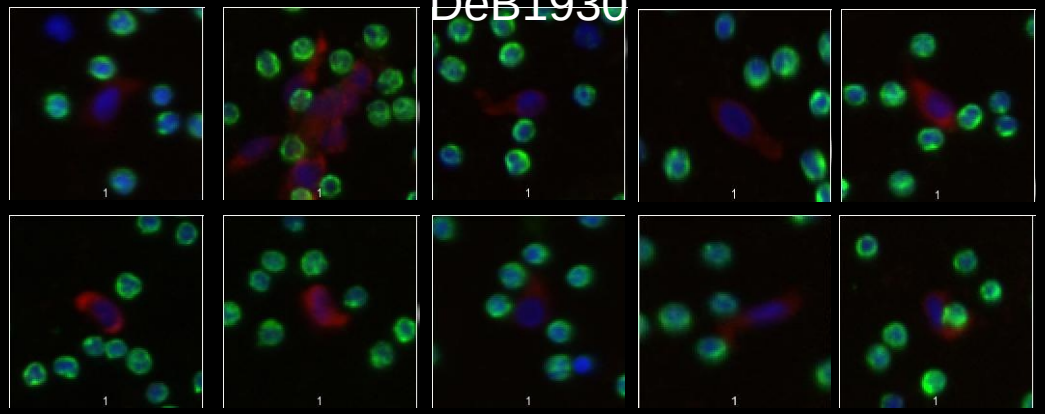




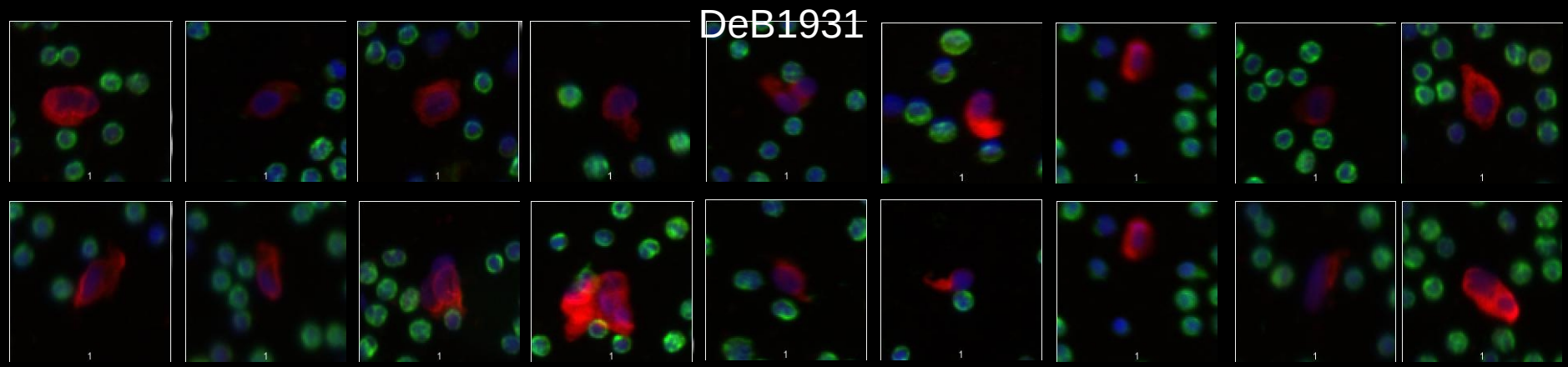




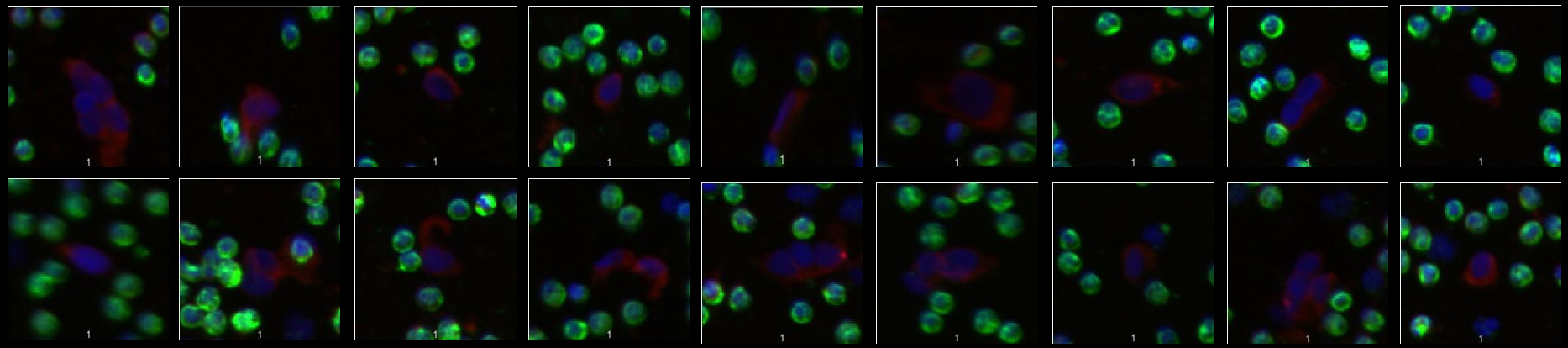




3 Benign Patients

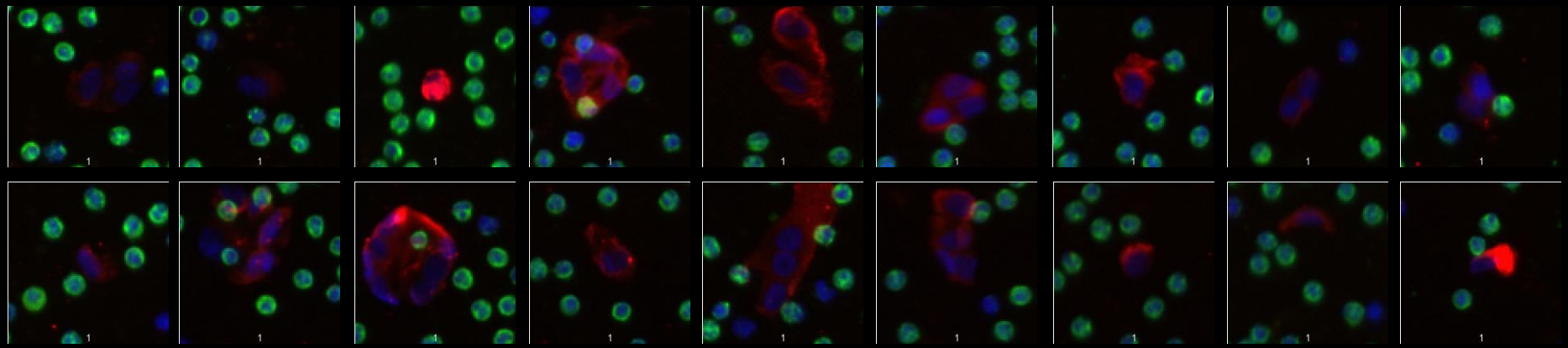


DeBTN1200052

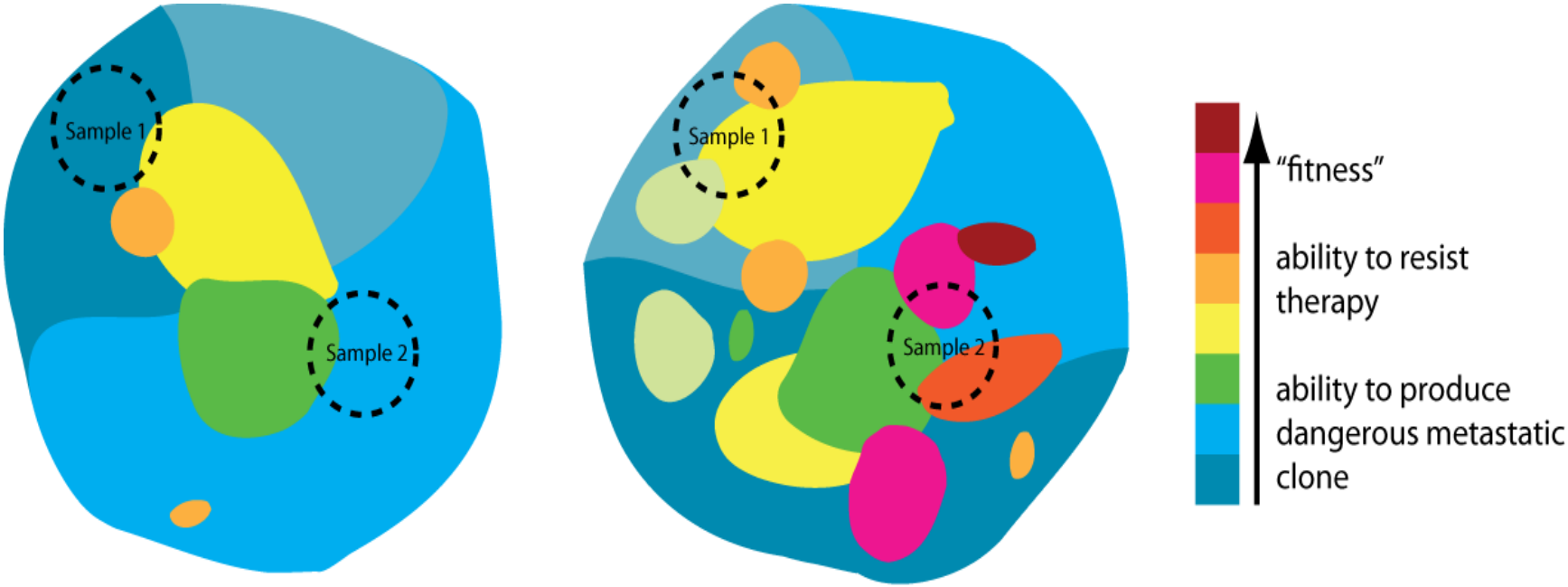


2 Malignant Patients

DeBTN1200050



Within-tumor diversity and risk of cancer progression

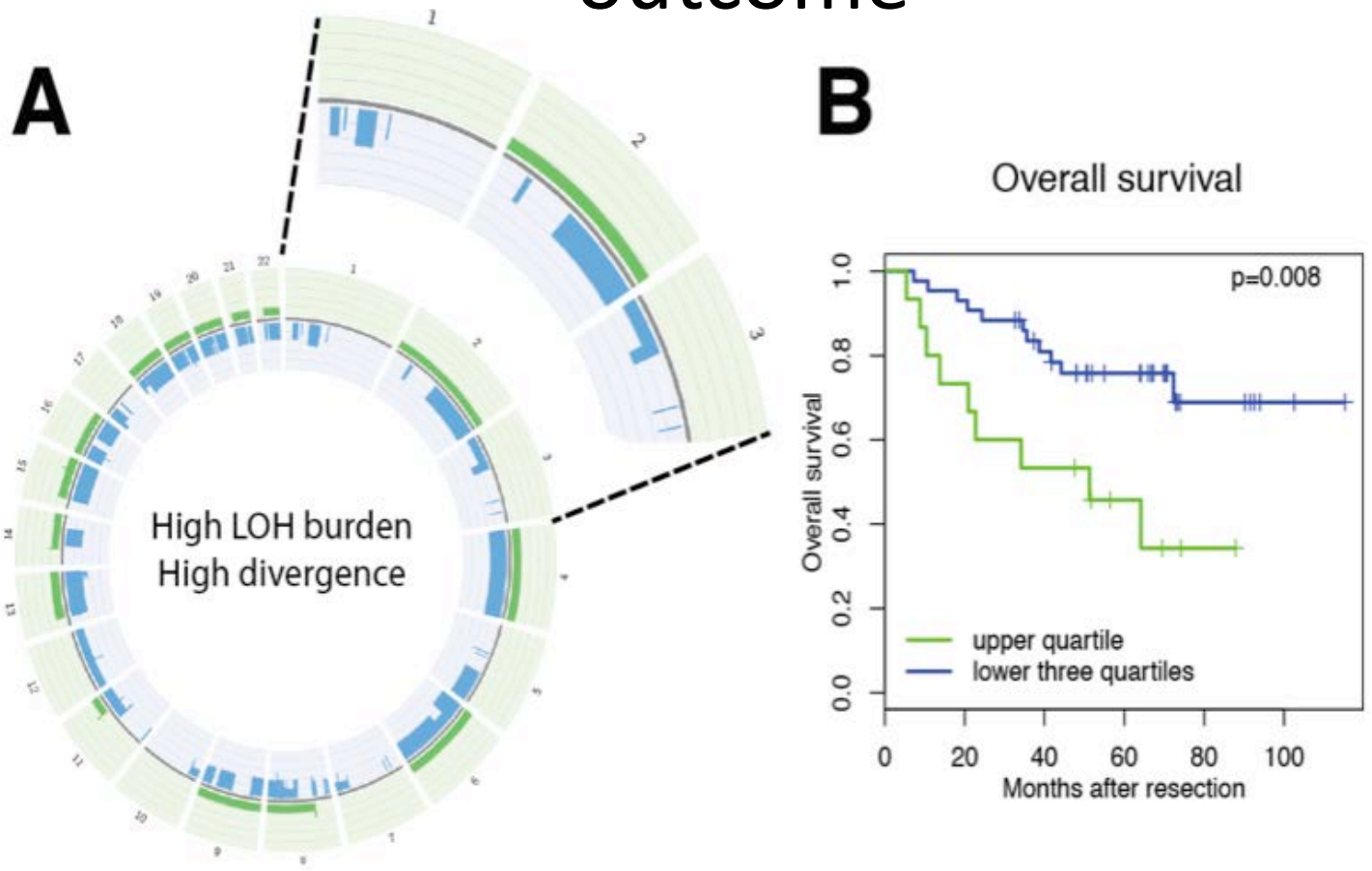


Low clonal genetic diversity:
- Few clones
- Low genetic diversity
- Tumor unlikey to contain a well adapted clone
- Good outcome

High clonal genetic diversity:
- Few clones
- Low genetic diversity
- Tumor unlikey to contain a well adapted clone
- Poor outcome

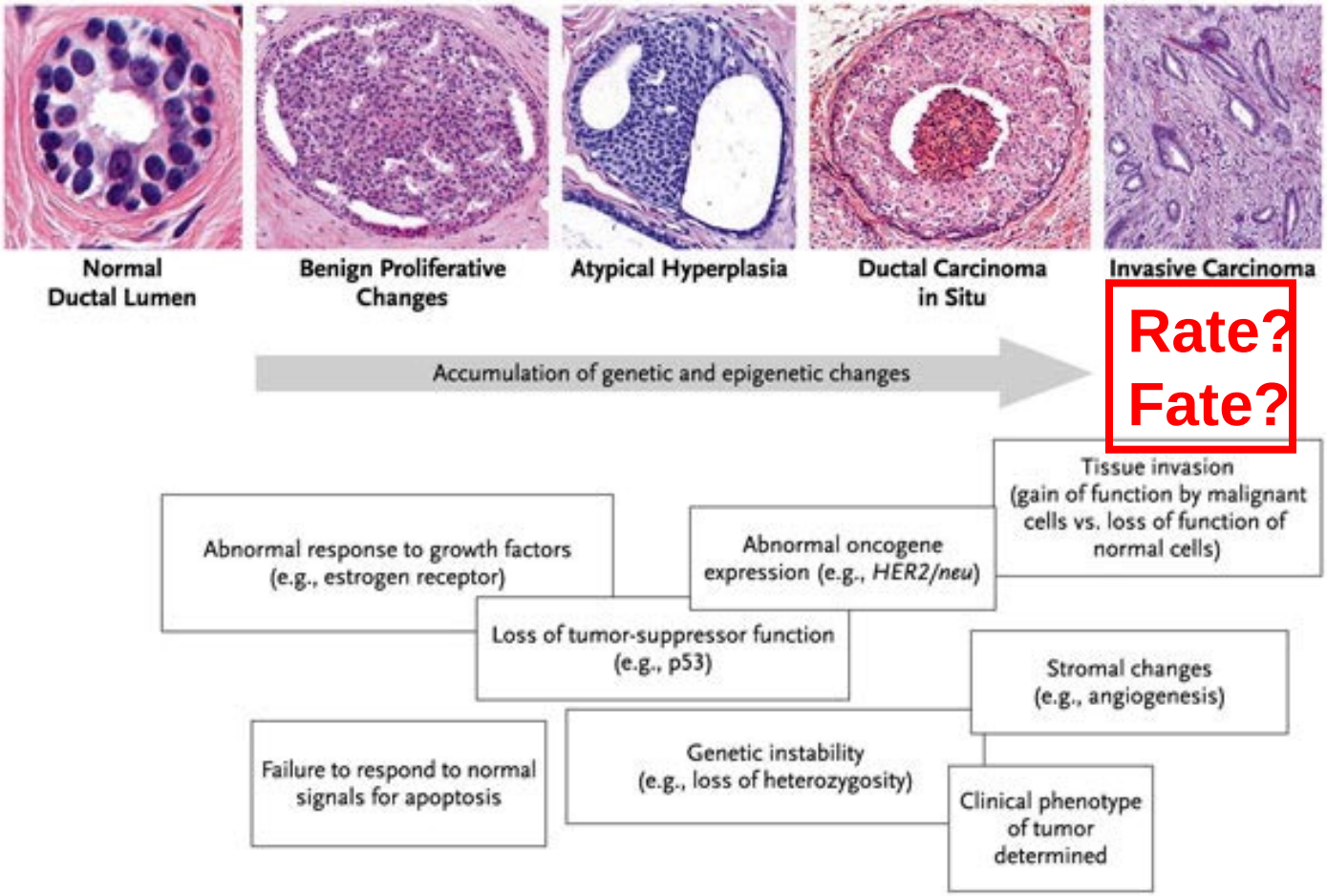
Within-tumor diversity as a predictor of cancer development risk. Tumors with low diversity (left) contain few clones and so are unlikely to contain a clone with malignant potential, that is able to adapt to the changing environment within an evolving tumor.

Heterogeneity is associated with clinical outcome



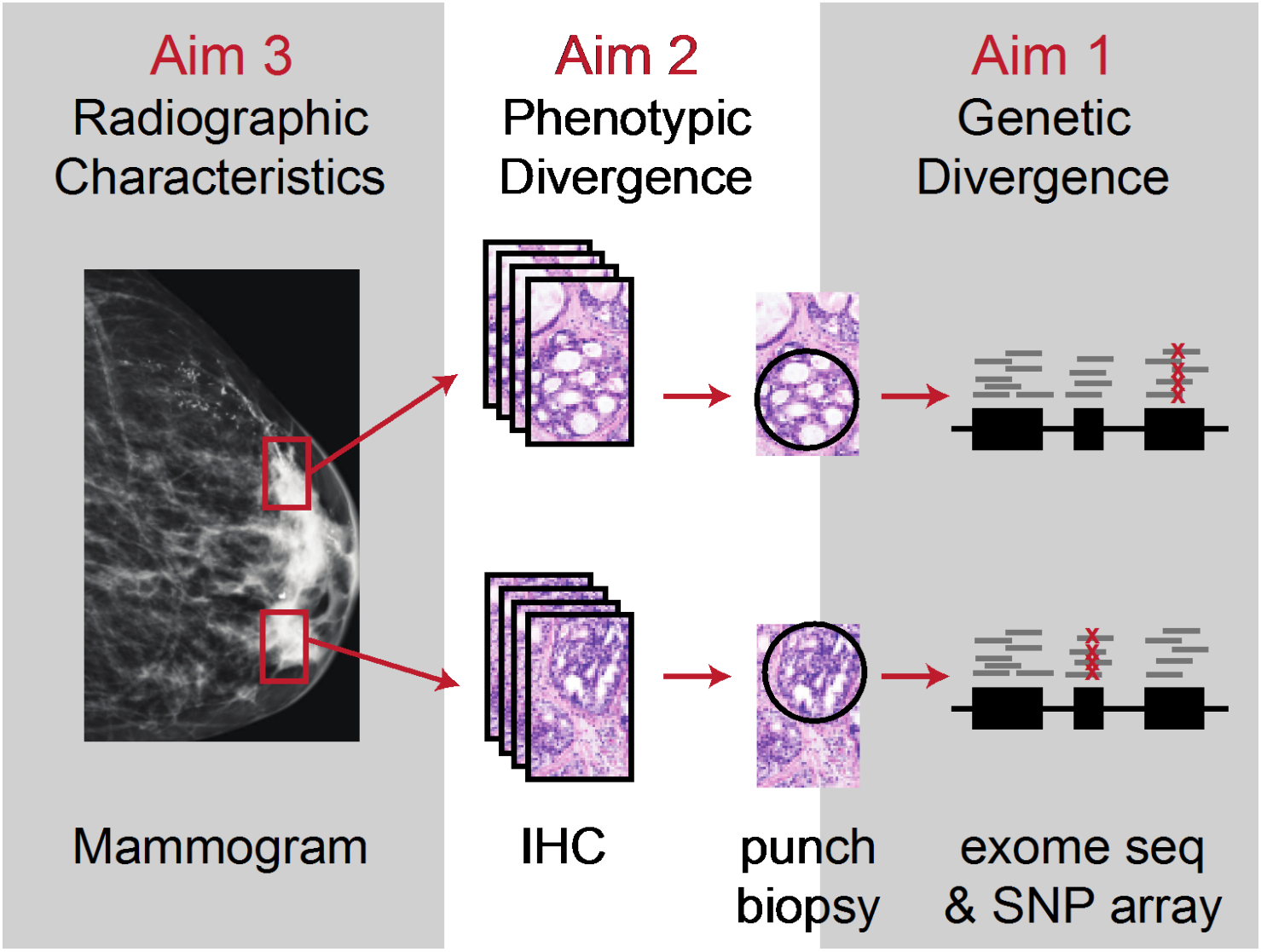
Circos plots of two samples (blue and green) from the same lung adenocarcinoma. This is an example of a patient with high levels of LOH and divergence between the two regions. Other patients had high levels of LOH but low divergence scores. B. Kaplan-Meier survival curves for all 58 lung adenocarcinoma patients included in the study, stratified by genetic divergence as measured on SNP arrays.

DCIS is Part of a Continuum of Pathologic Change



Burstein HJ, et al. *N Engl J Med*. 2004.

Compare 50 pure DCIS to 50 DCIS with invasive disease



Summary

- The physical sciences are the cornerstone of cancer diagnosis and treatment
- Advances in engineering >>> more effective therapy with less toxicity
- “wild side” of physical sciences will be the source of future advances in oncology

Collaborators

- Bay Area PSOC (Liphardt/Weaver)
- Scripps PSOC (Kuhn)
- Maley Lab (UCSF)
- UCSF Breast Oncology Program

- Funding:
  - PSOC/SAIC-F
  - Komen
  - Breast Cancer Research Foundation/TBCRC

- Duke:
  - Jeff Marks Lab
  - Joseph Lo Lab
  - Martin Tornai Lab
  - Nimmi Ramanujam Lab
  - Janet Horton and Duke Radiation Oncology Department
  - Duke Cancer Institute

- **Patients and their families who participate in research**